

THE BURDEN OF SERIOUS ADVERSE DRUG REACTIONS IN SOUTH AFRICA

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Thesis Presented for the Degree of

DOCTOR OF PHILOSOPHY

in the Department of Medicine

UNIVERSITY OF CAPE TOWN

January 2022

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1. Mouton JP, Jobanputra N, Tatz G, Cohen K. Serious adverse drug reactions in sub-Saharan Africa in the era of antiretroviral treatment: a systematic review. *Pharmacology Research & Perspectives*. 2021;9(6):e00875. doi: 10.1002/prp2.875 **(Chapter 2 / Appendix i)**
2. Mouton JP, Mehta U, Rossiter DP, Maartens G, Cohen K. Interrater agreement of two adverse drug reaction causality assessment methods: A randomised comparison of the Liverpool Adverse Drug Reaction Causality Assessment Tool and the World Health Organization-Uppsala Monitoring Centre system. *PLOS One*. 2017;12(2):e0172830. doi: 10.1371/journal.pone.0172830 **(Chapter 3 / Appendix ii)**
3. Mouton JP, Mehta U, Parrish AG, *et al.* Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. *British Journal of Clinical Pharmacology*. 2015;80(4):818-826. doi: 10.1111/bcp.12567 **(Chapter 4 / Appendix iii)**
4. Mouton JP, Njuguna C, Kramer N, *et al.* Adverse Drug Reactions Causing Admission to Medical Wards: A Cross-Sectional Survey at 4 Hospitals in South

Africa. *Medicine (Baltimore)*. 2016;95(19):e3437. doi:

10.1097/MD.00000000000003437 **(Chapter 5 / Appendix iv)**

5. Mouton JP, Fortuin-de Smidt MC, Jobanputra N, *et al*. Serious adverse drug reactions at two children's hospitals in South Africa. *BMC Pediatrics*.

2020;20(1):3. doi: 10.1186/s12887-019-1892-x **(Chapter 6 / Appendix v)**

Together with my supervisors, I developed the independent concepts for the projects presented in this PhD thesis. I led data collection teams, prepared the datasets for analysis, conducted all analyses, and was the lead author of the manuscripts. The contributions of my co-authors are outlined in the preamble to each of Chapters 2 to 6. My supervisors have confirmed to the University of Cape Town Doctoral Degrees Board that the included papers all overwhelmingly reflect my own scientific work.

Johannes P. Mouton

MTNJOH007

31 January 2022

Abstract

Background The burden of serious adverse drug reactions (ADRs) in South Africa (SA) is not well characterised, and may be influenced by the high HIV prevalence. This thesis aims to describe this burden, by reporting findings of three hospital-based surveys of (1) ADRs causing death among adult medical inpatients, (2) ADRs causing admission of adults to medical wards, and (3) serious ADRs causing admission, prolongation of existing admission, or death among paediatric medical inpatients. Survey findings are contextualised in a systematic review of studies characterising serious ADR burden in sub-Saharan Africa (SSA).

Methods In each of the three surveys, folder review with the assistance of trigger tools was used to identify potential serious ADRs. Multidisciplinary teams assessed causality, preventability, and seriousness of these events using published criteria. The World Health Organization-Uppsala Monitoring Centre system for standardised case causality assessment was used. This choice was informed by a study using a sample of cases from one of our adult surveys, which demonstrated its higher interrater agreement compared with the Liverpool ADR Causality Assessment Tool. Multivariable logistic regression was used to explore associations between demographic and clinical factors and the occurrence of serious ADRs.

Results Among adult medical inpatients 56 of 357 deaths (16%) and 164 of 1951 admissions (8.4%) were ADR-related, and 43% and 45% respectively of these serious ADRs were preventable. Drugs used in the management of HIV and tuberculosis were frequently implicated. Among paediatric inpatients 3.8 serious ADRs occurred per 100 drug-exposed admissions, of which 23% were preventable and 20% fatal or near-fatal. A broad range of drugs was implicated in these serious paediatric ADRs. HIV positive status was independently associated with an increased risk of ADRs in every survey. Fifteen studies contributed to the systematic review. The median proportion of

admissions attributed to ADRs was 6.4% [IQR 4.0% to 8.4%] among nine active surveillance studies in adults in SSA, with antiretroviral and antituberculosis drugs often implicated in serious ADRs.

Conclusions Fatal, near-fatal, and hospitalising ADRs occurred frequently in South African hospitals. Many of these serious ADRs, particularly in adults, were preventable. Serious ADRs should be addressed in patient and health worker education, and safety monitoring systems improved. In SA and SSA the high HIV prevalence appears to be a driver of serious ADRs.

Acknowledgements

I deeply appreciate the extensive input of my supervisors, Associate Professor Karen Cohen and Professor Gary Maartens, without whom this thesis would not have come to fruition.

I appreciate the work of multiple colleagues, whose contributions as co-authors of specific Chapters are mentioned in the preamble to each Chapter. To Dr Ushma Mehta, on whose expertise and experience I leaned heavily, I want to extend a special word of thanks.

I am grateful for the assistance of several colleagues and acquaintances who, despite not being co-authors, assisted me when I needed them: Professor Karen Barnes for insights in the development of the PhD proposal, Professor Helen McIlleron, Professor Alex Welte (University of Stellenbosch), Associate Professor Maia Lesosky, and Associate Professor Michael Schomaker for biostatistical and epidemiological advice, librarians Mary Shelton and Wendy Smith for assistance in developing the systematic search strategy and obtaining full-text study reports described in Chapter 2, Professor Andrew Boulle and Nicky Maxwell for executing the data linkage described in Chapter 5, and Dr Gary Reubenson (University of Witwatersrand) for comments on Chapter 6.

Prior peer review of individual Chapters has definitely improved this thesis. I am grateful to Associate Professor Dong In Suh (Seoul National University), Professor Michael Rieder (University of Western Ontario), Professor Elisangela da Costa Lima (Federal University of Rio de Janeiro), Professor Sir Munir Pirmohamed (University of Liverpool), and other anonymous reviewers, each of whom has contributed in some way to this thesis.

To the patients whose data are described here, and to their families and caregivers, as well as to the clinicians, nurses, administrators and managers at the hospitals where we conducted the surveys, I want to express my profound gratitude.

Funding to conduct most of this research was awarded to my supervisors by the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under the terms of Cooperative Agreement Number GGH000371. I appreciate this generosity of taxpayers in the United States.

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Chapter 1 Introduction

1.1. The importance of pharmacovigilance and pharmacoepidemiology

All medicines have the potential to cause harm: safe, rational use of a medicine requires weighing its risk of harm against its potential of benefit. These risk-benefit decisions are taken daily on the individual level by clinicians and patients when deciding whether or not to use a medicine. The individual-level decision-making process is however informed by the measured risks of harm and potential of benefit as determined on the population level in clinical trials and in observational research studies. In addition to assisting with individual-level risk-benefit decisions, population-level risk-benefit evidence is utilised in policy-making decisions.

Pharmacovigilance is defined by the World Health Organisation as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”¹. Much of the detection and assessment of adverse outcomes in pharmacovigilance occur on the individual level when patients and health care workers report adverse outcomes through systems set up for this specific purpose, often relying on spontaneous reporting.

Pharmacoepidemiology has been defined as the study of the use and the effects of drugs in large numbers of people²; under this definition pharmacovigilance is considered a subfield of pharmacoepidemiology. However, pharmacoepidemiologists typically concern themselves less with the detection and assessment of adverse outcomes in individual patients, but more with finding patterns in large sets of data regarding medicine use, benefits, and harms, and in detecting associations between these factors. Pharmacoepidemiological studies often make use of secondary data, that is data sets collected for some other reason, but which is then repurposed for detecting drug utilisation, drug benefit, and drug harm.

Both the individual-level data typically collected in pharmacovigilance surveillance and research, and the population-level data typically collected in pharmacoepidemiological surveillance and research are critical in fully understanding the risks associated with medicines. In this way, the disciplines of pharmacovigilance and pharmacoepidemiology both contribute to patient care and safety, as well as to public health and safety.

1.2. Approaches to pharmacovigilance

The responsibility for safe, rational medicine use is shared by manufacturers and marketers of medicines (“industry”), regulatory authorities, academia, health programme managers, health care professionals, and patients.

Many countries require industry to investigate and report adverse drug reactions (ADRs) and/or to implement measures to limit the risk of harm as conditions of marketing authorisation. Although the requirement to report potential safety concerns to the regulator is compulsory, in most instances safety issues are reported to marketing authorisation holders on a voluntary basis by health care workers and patients, and are not systematically elicited. This therefore effectively constitutes a spontaneous ADR reporting system. Industry's compulsory safety reports to the regulatory authority may be supplemented by spontaneous ADR reports from health care workers and patients directly to the regulator. In South Africa, in terms of the Medicines Act³ and accompanying Regulations⁴, industry is compelled to report safety concerns including ADRs to the regulator, while health care workers “should” also report suspected ADRs to the regulator. ADR reporting guidelines for industry⁵ and health care workers⁶ have been published.

While the strength of these spontaneous reporting systems lies in their ability to detect rare and unusual events and to generate hypotheses, they cannot be used to calculate risks of harm. Spontaneous reporting systems universally suffer from underreporting of

ADRs (and may potentially also suffer from skewed reporting), meaning that numerators collected in these systems are not trustworthy, and they lack denominators, that is to say the size of the population at risk of harm is unknown¹.

Accurate rates at which harm occurs can only be obtained when both numerators and denominators are known. This may be achieved within a programmatic roll-out if accurate drug utilisation data is maintained for obtaining a trusted denominator, and if compulsory ADR reporting is achieved for obtaining a trusted numerator. Compulsory ADR reporting may however prove counter-productive due to reporting fatigue, and therefore programmatic pharmacovigilance surveillance is usually restricted to sentinel sites where additional resources can be allocated to it. By way of example, in 2007-2008, a compulsory antiretroviral adverse reaction reporting system was implemented in South Africa's KwaZulu-Natal province which found that approximately 2.6 ADRs (of any level of seriousness) were reported per 100 persons on antiretroviral therapy⁷.

More often, the numerators and denominators to calculate rates at which drug-related harm occurs will be provided by observational research studies. A new cohort may be specifically set up for the purpose of prospective safety monitoring after exposure to a drug ("cohort event monitoring"), or a virtual patient cohort may be constructed retrospectively or prospectively from routine data collected for another purpose. Examples of findings from cohort studies from South Africa which looked at safety questions associated with antiretroviral therapy include:

- In adults commencing first-line antiretroviral therapy, the cumulative incidence of drug discontinuations within three years was 30% for stavudine, 2% for tenofovir, and 1.3% for efavirenz⁸. Compared to zidovudine, stavudine was associated with more ADRs and tenofovir with fewer ADRs (hazard ratios of 4.9 [95% CI 3.7 to 6.4] and 0.4 [95% CI 0.2 to 0.7], respectively.)⁹

- In adults commencing second-line antiretroviral therapy, an adverse event of any seriousness (causal relationship to the drug was not necessarily established) occurred at an incidence of 367 per 1000 person-years¹⁰.
- In children, the incidence of treatment-limiting toxicity was 51 per 1000 person-years for stavudine, and 1.6, 2.0, and 1.3 per 1000 person-years for abacavir, efavirenz, and lopinavir/ritonavir, respectively¹¹.

A second observational approach to obtaining numerator and denominator data is a cross-sectional ADR prevalence study, which is typically conducted in the hospital setting. These studies are well-suited to detect serious ADRs, specifically those causing admission into hospital and prolonging existing admissions, and can also, to some extent, detect ADRs resulting in death (although they clearly cannot detect ADR-related deaths occurring outside of the hospital).

One of the earliest hospital-based ADR surveillance studies was conducted in 1965-1966 by Hurwitz in Belfast, Northern Ireland¹²⁻¹⁴, introducing methodology after which many later studies were modelled. This includes surveying several hospital wards but prioritising adult medical wards, where an investigator (or team) makes daily visits to all admitted patients and collects demographic and clinical details for every newly admitted patient regardless of cause of admission. Through review of records (with or without additional interview of the patient, their family, or caregivers, or sourcing additional information elsewhere), suspected ADRs are identified and in those patients with suspected ADRs, more detailed drug histories are recorded. The data collected for suspected ADR cases are subsequently formally assessed for causality (what Hurwitz called “probability assessment”), severity or seriousness, and preventability, often by a multidisciplinary team of experts. Data are analysed and presented descriptively; comparing patients with ADRs to those without ADRs allows for the identification of risk factors. (It is acknowledged that Hurwitz’s studies were not the first in the field, and that she seemingly modelled her studies after those conducted earlier in the 1960s at

Johns Hopkins University in Baltimore.^{15,16} The Johns Hopkins studies were however of a less rigorous design and all of the methodologic steps elucidated by Hurwitz had not yet been incorporated.)

Within three years of Hurwitz's publication, the first hospital-based ADR surveillance study in sub-Saharan Africa was being conducted in Lagos, Nigeria¹⁷. In this early Nigerian study, ADRs were found to have occurred among 47/360 (13.1%) admitted patients and were considered to be the cause of admission among 10/360 (2.8%), including four cases of haemolytic jaundice and four of haemorrhage¹⁷.

1.3. Overarching methodological considerations in drug safety studies

1.3.1. ADR definitions and conceptual frameworks

The term “adverse drug reaction” has been defined in a variety of ways, without any one definition gaining widespread acceptance above others. One widely used definition of ADR is that in use by the World Health Organization since at least 1969: “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”¹⁸. Several authors have discussed problems with this definition, including that adverse events occurring at doses other than those described, or which may not necessarily be “noxious”, or may be caused by excipients in the medicinal product rather than by the active ingredient itself, also ought to be included in the definition. Aronson and Ferner instead proposed as definition: “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”¹⁹ This is the definition used for the purposes of this thesis.

Part of the reason for the existence of different definitions of the term “ADR” lies in the different conceptual frameworks within which drug safety studies are conducted. In one framework, frequently encountered in the disciplines of pharmacy practice and patient safety, ADRs are defined in terms of *preventability*, as the subset of adverse drug events which are considered not preventable²⁰. However, under the framework used in this thesis ADRs are defined in terms of *causality*, as a subset of adverse drug events in which a causal association has been established between the drug and the event^{19,21-23}.

1.3.2. ADR causality assessment

At the heart of pharmacovigilance, and central to the ADR definition used in this thesis, is the question whether the relationship between the drug of interest and the event of interest is causal or not. ADRs are namely those adverse events which have been causally linked to the suspected medicine, as opposed to those events that merely occur coincidentally during treatment with a medicine. However, causality can be assigned with certainty only in the event that the counterfactual outcome is known²⁴ (i.e., in the absence of using this medicine, keeping all other factors unchanged, did the outcome still occur?) In randomised controlled trials this counterfactual outcome is represented by the control arm, while statistical causal inference methods such as weighting according to propensity scores may be applied to non-randomised observational data to construct a hypothetical treatment group with a counterfactual outcome. However, on the individual level, counterfactual outcomes are impossible to know. Causality between the drug and the event is therefore subjectively assigned, usually into a likelihood category, such as being “possibly” related, “probably” related, “definitely related”, or “not related” (see discussion below).

Hill famously described nine factors that should be considered when assessing the likelihood of a causal relationship in observational data in 1965²⁵. Howick²⁶ categorises and revises Hill's criteria as providing direct, mechanistic, or parallel evidence of

causation. Applying these categories of evidence to the field of pharmacovigilance, direct evidence of a causal association would include whether the event is temporo-spatially consistent with the known absorption, distribution, metabolism, and elimination (ADME) of the drug; whether the dose-response relationship, including what was observed during repeat exposures and during drug withdrawal, is consistent with the known ADME of the drug; and whether the size of the effect is unlikely to be due to confounding, which would most likely be the use of other drugs, or the presence of disease, which may result in the same or similar events. Mechanistic evidence of causation would include consideration about the biological plausibility that the event could occur with the use of the drug, and whether the observation coheres with the current state of scientific knowledge. Parallel evidence of causation includes similarity, such as situations where the observed effect is known to be causally associated with other drugs in the same class, and replicability, where the event is observed repeatedly.

Several methods have been proposed to standardise the assessment of the likelihood that an observed drug-event combination is a causally-related ADR: a 2008 systematic review found 34 different causality assessment methodologies described in the literature²⁷. These have been classified into three major groups: those methods assigning an outcome on the basis of “global introspection” (i.e., through unstructured clinical judgement), those arriving at a causality outcome after applying an algorithm, and those assigning likelihood of causality after applying a Bayesian statistical method²⁷. Global introspection methods have been criticised for not being reproducible, yet they tend to be widely used by medicines regulators and industry²⁴. Bayesian methodologies have been criticised for being too complicated for routine use, and for requiring vast quantities of data to establish realistic pre-test likelihoods²⁴. For their supposed ease of use, and apparent reproducibility, algorithmic approaches have been popular²⁴, particularly in publications of case reports and case series.

As mentioned, most methods end up assigning the likelihood of a causal association to one of several likelihood categories. However, categories are not standardised across different methods in use, and category borders are vaguely defined, or left to the user's subjective interpretation of the linguistic terms. Notwithstanding, it is important to keep in mind that what is being assigned by a causality tool is not an intrinsic quality of the event or the drug or the relationship between the two. Rather, assigning a causal category is a summary measure of several factors: in addition to the direct, mechanistic, and parallel evidence of causation described by Hill and Howick^{25,26}, these include the quality of the evidence (for example, the quality of the drug history included), the rigour with which alternative (confounding) explanations were sought, the expertise and biases of the person applying the causality assessment tool, and the notoriety of the drug-event combination.

An example of a global introspection method is the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) methodology for standardised causality assessment, promoted in the WHO International Drug Monitoring Programme (Table 1.1)²⁸. Among the algorithmic methods, Naranjo's algorithm, dating back to 1981, is the most widely used (Table 1.2)²⁹.

Table 1.1. World Health Organization-Uppsala Monitoring Centre Causality Assessment Categories

Causality term	Assessment criteria (all points should be reasonably complied with)
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Source: WHO-UMC²⁸

Table 1.2. ADR probability scale described by Naranjo

	Yes	No	Do not know
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

ADR is assigned to a probability category from the total score as follows: definite ≥ 9 , probable 5 to 8, possible 1 to 4, doubtful ≤ 0 .

Source: Naranjo²⁹

Investigators conducting a paediatric hospital surveillance study in the UK³⁰ criticised the Naranjo causality assessment tool and redesigned it into a flowchart, called the Liverpool Causality Assessment Tool (LCAT, Figure 3.1)³¹. The LCAT developers found it to have good interrater agreement, to result in an even distribution of causality categories and to be easy to use³¹. In designing our surveillance studies, we therefore considered using the LCAT to assign causality to the potential ADR cases we were to identify. However, since the LCAT had never been used outside of the setting in which it was developed, we wanted to first establish whether it was transferable to our setting before applying it to our cases. In assessing the transferability and usefulness of the new tool, it is important to note that no gold standard exists against which to measure its sensitivity or specificity, typical measures of diagnostic accuracy. Instead, we decided to measure the LCAT's interrater agreement, postulating that a tool with higher

interrater agreement is a better tool since the outcomes assigned by the tool would depend less on the raters' subjective application of it and more on the intrinsic characteristics of the tool or the case details. We designed a study to measure the interrater agreement obtained with the LCAT and directly compare it to the interrater agreement among the same raters when assigning causality using another tool (for the comparison, we selected the WHO-UMC methodology²⁸) using a sample of cases collected during our adult admission surveillance study. We decided to use the outcome of this study in the main surveillance studies: whichever tool showed the higher interrater agreement would be the one we would use to assign causality likelihood to the potential ADR cases we identified in the surveillance studies.

1.3.3. ADR preventability assessment

Similar to the assessment of causality, the assessment of the preventability of ADRs (also referred to as their “avoidability”) can be conducted using a multitude of frameworks and definitions, none of which has been universally accepted as a “gold standard”. These different methodologies have been grouped in a systematic review by Ferner and Aronson into eight groups³²; however, it is possible to collapse these to just three categories: ADRs may be called preventable because of the way the terms “ADR” and “preventable” are defined, or because the quality of medicine use resulting in the ADR is judged implicitly, or explicitly against some standard. (Ferner and Aronson's additional groups relate more to the concept of *who* performs the judgment – individual experts, expert groups reaching a consensus, or computer code – than to the conceptual methodology being applied.) As an example of methods considering ADRs preventable by definition, some authors have proposed that all ADRs classified as Type A in the Rawlins classification³³, that is, ADRs which are predictable from the known pharmacological action of the drug, should be considered preventable³². As an example of adjudicating preventability implicitly, reviewers were asked to rate the preventability of adverse events on a Likert scale from “virtually no evidence of

preventability” to “virtually certain evidence of preventability” in one study³⁴. Most often, however, preventability of ADRs have been assigned using methods relying on an explicit judgement of the quality of drug use resulting in the ADR. The widely used preventability method described by Hallas (Table 1.3) is an example of a method judging the quality of drug use against the standard of “good medical practice”.³⁵

Table 1.3. Preventability assessment described by Hallas

Preventability assignment	Description
Definitely avoidable	The drug event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account.
Possibly avoidable	The prescription was not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands.
Not avoidable	The drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice.
Unevaluable	The data for rating could not be obtained or the evidence was conflicting

Source: Hallas³⁵

For the purpose of this thesis our choice of preventability assessment method was Schumock and Thornton's seven preventability questions, an explicit judgement of the quality of drug use against a range of factors including adherence to its regulatory authorisation, to some straightforward aspects of standard of care, and to the presence or absence of errors.³⁶ Notably, this method is fairly well known, reasonably easy to apply, does not require deep subject matter expertise to judge the appropriateness of treatment against the standard of care, and allows some localisation in respect of measuring the quality of drug use against the local regulatory documentation.

Table 1.4. Preventability assessment described by Schumock and Thornton

Was the drug involved in the ADR <i>not</i> considered appropriate for the patient's clinical condition?
Was the dose, route, and frequency of administration <i>not</i> appropriate for the patient's age, weight, and disease state?
Was required therapeutic drug monitoring or other necessary laboratory test <i>not</i> performed?
Was there a history of allergy or previous reactions to the drug?
Was a drug interaction involved in the reaction?
Was a toxic serum drug level documented?
Was poor compliance involved in the reaction?

Answering “yes” to one or more of the questions suggest that the ADR in question may indeed have been preventable.

Source: Schumock and Thornton³⁶

1.3.4. ADR seriousness assessment

A “serious” ADR, in the widely accepted definition of the International Conference on Harmonisation³⁷ and the Council for International Organizations of Medical Sciences³⁸ is one that: results in death, is life-threatening at the time, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. In this thesis, three of these categories of serious ADRs are investigated: ADRs causing or prolonging admission, life-threatening ADRs associated with hospital admissions, and ADRs resulting in death in hospital. In our cross-sectional study design we were not able to investigate ADRs resulting in disability or congenital abnormalities, which requires longitudinal data.

1.4. Drug safety in sub-Saharan Africa

1.4.1. Conditions predisposing to ADRs

Conditions exist in sub-Saharan Africa which may be conducive to the occurrence of drug-related harm, including ADRs. In this region, expertise is thinly spread out and severe resource limitations exist, meaning that tasks are often delegated to lower-level health care workers, who may struggle to recognise and manage drug-related harm^{39,40}. In addition, overburdened health workers and health systems may lead to harm through errors⁴¹. Large public health programmes target regionally prevalent infectious diseases such as HIV, tuberculosis, and malaria⁴²⁻⁴⁵. Despite the fact that drugs used in the management of these three infectious diseases are notoriously known to cause drug-drug interactions, these large public health programmes provide limited scope for personalised medicine, and pharmacovigilance is not prioritised in them – or may not be incorporated at all. In parallel to the infectious disease burden, the prevalence of non-communicable diseases is increasing in sub-Saharan Africa as the population is aging^{45,46}, leading to increased use of chronic medicines to control

chronic diseases including cardiovascular and metabolic diseases, leading to even more potential for drug-drug interactions and other harms. Moreover, many medicines regulatory authorities in the region are immature, and borders are porous, allowing for falsified and substandard medicines to penetrate markets⁴⁷. The immaturity of regulators together with low public health literacy yield further challenges in communicating medicine safety issues and in developing a culture of drug safety and of reporting ADRs⁴⁸. Finally, sub-Saharan Africans show high genetic variability, and this genetic variation may affect drug metabolism which may potentially lead to harms⁴⁹. These genetically predisposed harms may not be picked up during drug development unless it specifically includes sub-Saharan African populations, with the result that these harms are only becoming noticeable after drugs have been authorised to enter the market⁴⁹.

For these reasons, pharmacovigilance and pharmacoepidemiology in sub-Saharan Africa requires strengthening⁵⁰, and the work described in this thesis was nested within one such project aiming to strengthen antiretroviral pharmacovigilance in South Africa. Compared with the rest of sub-Saharan Africa, South Africa may be less prone to the factors predisposing to harm described in the preceding paragraph, because of its relatively more mature regulatory authority, its relatively more frequent involvement in drug development trials, and its relatively higher availability of resources. However, these factors are to a large part offset by the country's aging population with high non-communicable disease burden, and the prevalence of HIV and tuberculosis which is among the world's highest^{44,45}, resulting in widespread use of antiretroviral and antituberculosis therapy. The larger project to strengthen antiretroviral pharmacovigilance in South Africa within which this thesis project is nested included a study of pharmacovigilance gaps in South Africa⁵¹, a project to describe antiretroviral ADR queries made to a medicines information centre⁵², and ongoing work supporting safety studies in cohort analyses^{8,11,53,54}.

The gap analysis study mentioned above found that despite the existence of regulatory, programmatic, and institutional pharmacovigilance systems in South Africa, these are not well-coordinated, and suffer from poor communication and poor translation into policymaking⁵¹. A second group of authors, focusing on the regulatory pharmacovigilance system in the country, found similar gaps⁵⁵. Analyses of South African health care workers' knowledge, attitudes, and practices around drug safety have found either low levels of knowledge^{39,40,56} and/or issues putting knowledge into practice^{39,40,56-58}.

1.4.2. Prior hospital-based drug safety surveillance studies in South Africa

Three previous hospital-based drug safety surveillance studies have been published from South Africa. The oldest of these, published during Apartheid in 1985, was conducted among 300 white patients consecutively admitted to a hospital in Durban. Among the 300 admissions, 4.6% were attributed to ADRs; no deaths were attributed to ADRs. Most of the ADRs occurred among elderly patients; common presentations were bleeds and dysrhythmias whereas warfarin, non-steroidal anti-inflammatories, and digoxin were the most commonly implicated drugs. Half of these ADRs were considered to have been preventable⁵⁹.

A 2005 study at Groote Schuur Hospital, an academic centre in Cape Town, prospectively surveyed elderly persons presenting to the emergency unit, using an outcome definition of adverse drug *events* (ADEs). ADEs were identified in 20% of 517 presentations, and were mostly attributed to cardiovascular drugs, anticoagulants, analgesics, and antidiabetic agents⁶⁰.

Around the same time, at a regional hospital in Cape Town (New Somerset Hospital), Mehta and colleagues conducted a prospective surveillance study specifically aimed at determining the role HIV plays in the burden of serious ADRs⁶¹. In this study, 41/665 (6.2%) admissions were the direct result of an ADR, while another 41 patients

developed ADRs during their hospital admissions. Being HIV-infected doubled the odds for experiencing an ADR-related admission, while taking antiretroviral therapy increased the odds for an ADR-related admission ten-fold. Common ADRs seen in this survey included stavudine-associated lactic acidosis, hypoglycaemia, drug-induced liver injury attributed to antituberculosis therapy, and peripheral neuropathy. Again roughly half of these ADRs, 46%, were considered preventable⁶¹.

1.4.3. Knowledge gaps

The three previous South African hospital-based surveillance studies are outdated⁵⁹ and/or poorly representative of the general South African population in terms of race⁵⁹ and age⁶⁰. While HIV is undoubtedly the country's most pressing health burden, only one of these studies was focused on the role played by HIV and the drugs used in its management. This study was, however, conducted in a single centre in one of the best-resourced provinces of South Africa, and in the early antiretroviral treatment era⁶¹; therefore, this study is no longer representative of current antiretroviral treatment and ADR patterns, and may never have been representative of the situation in other regions of South Africa. Outside of these three studies, which were conducted in very specific settings, populations, and times, the burden of serious ADRs in South African hospitals is not well-described. Some of the questions remaining to be answered are:

- How often do serious ADRs occur, what are the most common clinical presentations of serious ADRs, and which drugs are involved in these?
- What can be done to prevent serious ADRs, or to limit the harm they cause?
- How does HIV and the widespread use of ARVs influence the occurrence of serious ADRs in South Africa?
- Are methodologies developed for use in drug safety studies elsewhere transferable to the local situation?
- How does the burden of ADRs in SA compare to the rest of the world, or to other settings in sub-Saharan Africa?

1.5. Filling the knowledge gap

1.5.1. Overall aim of this thesis

The overall aim of this thesis is to provide high-quality descriptive data on the burden of serious ADRs in South Africa. Such data can be used to inform training programmes and policy decisions in the country, and may also influence such decisions in other low-/ middle-income countries, particularly those with disease burdens similar to South Africa's.

1.5.2. Specific objectives of this thesis

The specific objectives of this thesis are:

Objective 1

To compare the interrater agreement of two ADR causality assessment tools (the Liverpool ADR Causality Assessment Tool (LCAT) and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment Methodology) in the South African setting, with the result of this comparison informing the choice of causality assessment tool to be used in further studies included in this thesis (Objective 2).

Objective 2

To describe the burden of serious ADRs in adult and paediatric medical wards of selected hospitals in South Africa, including determining and describing:

- The proportion of admissions to adult medical wards attributable to ADRs,
- The proportion of deaths in adult medical wards attributable to ADRs,
- The proportion of admissions to paediatric medical wards attributable to ADRs, and the proportion of paediatric medical inpatients who develop ADRs during

their hospital stay which result in death or prolongation of the hospitalisation, and

- For each of the categories of serious ADR mentioned above, the clinical presentations involved, the drugs implicated, the preventability of the ADRs, and risk factors for the development thereof, specifically the role of HIV and antiretroviral treatment.

Objective 3

To conduct a systematic review of the literature on the burden of serious ADRs in sub-Saharan Africa, including the results from our own surveys (Objective 2), in order to contextualise our findings.

1.5.3. Structure of remainder of this thesis

A study to achieve Objective 1 is described in Chapter 3 of this thesis. In this study, we tested which one of the LCAT or the WHO-UMC method of causality assessment yielded the higher interrater agreement, using a sample of potential ADR cases collected during our adult ADR admission survey (described in Chapter 5). On the basis of the findings of this study we selected the WHO-UMC methodology for the causality assessment of all potential ADRs identified during the surveys described in Chapters 4 to 6.

We conducted a series of three hospital-based surveys to fulfil the second objective of this thesis. These studies, modelled after earlier examples of hospital-based ADR surveillance studies, collected drug utilisation and adverse event data in a cross-sectional manner at four adult and two paediatric hospitals. While survey sites were not randomly chosen, but rather were nested within existing research collaborations where we identified interested collaborators, we purposely selected sites in four different provinces, thereby increasing the representativeness of our data. Moreover, since we were interested in investigating the potential risk factor of HIV infection, the

inclusion of sites in areas of high HIV prevalence strengthened the studies. Each potential case was assessed by a multidisciplinary panel for seriousness, preventability, and causality.

Three thesis chapters describe these three surveys:

- In Chapter 4 we describe the proportion of deaths among adult medical inpatients in four hospitals in which an ADR was assessed to have played a causative role, either directly or indirectly. We describe the preventability of these fatal ADRs, the clinical presentations involved, the implicated drugs, and the apparent role played by HIV infection and other risk factors.
- In Chapter 5 we describe the proportion of admissions to the adult medical wards of four hospitals which were directly attributed to ADRs. We again describe the preventability of these hospitalising ADRs, the clinical presentations involved, the implicated drugs, and the risk factors involved.
- In Chapter 6 we describe serious ADRs occurring among paediatric patients admitted to the medical wards of two hospitals, including those ADRs which caused admission, those which developed during hospitalisation and prolonged it, and those which resulted in death. Again, we describe the preventability of these serious ADRs, the clinical presentations and the implicated drugs, and risk factors identified for the occurrence of serious ADRs.

Objective 3 is addressed in Chapter 2, which describes a systematic review of serious ADRs as described in hospital-based surveys conducted in sub-Saharan Africa since 2002, which represents the period during which antiretroviral therapy had been more widely available in the region. The three surveys described in Chapter 4 to 6 are included in this systematic review, allowing our studies to be read in the context of the findings of similar studies conducted elsewhere in sub-Saharan Africa, where the burden of HIV is high.

Each of chapters 2 to 6 has been published as a journal article (original publications are included as Appendix i to Appendix v, respectively) and the Doctoral Degrees Board of UCT permitted the inclusion of these publications in the thesis. Co-authors of these articles granted their permission for including these papers in this thesis, and where applicable, copyright holders similarly granted permission for including these publications in the thesis. Table numbers, figure numbers, and references have been changed to run continuously and supplementary materials to the original articles are included as appendices to the thesis. Each Chapter / publication describes the specific objectives relevant to that Chapter / publication, methodology and results relevant to that Chapter / publication, and some conclusions drawn from that.

Chapter 7 of the thesis provides an overall discussion and conclusion.

1.6. Ethical considerations

This PhD project was granted approval by UCT's Human Research Ethics Committee under protocol number 828/2015. The hospital-based surveillance studies were separately granted ethics approval by UCT's Human Research Ethics Committee under protocol number 576/2011 and by the University of Witwatersrand's Human Research Ethics Committee under clearance number M140707.

Chapter 2 Serious adverse drug reactions in sub-Saharan Africa in the era of antiretroviral treatment: a systematic review

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Co-author contributions

Supervision: KC

Screened studies for inclusion: KC, NJ, GT

Extracted study data: GT

Assessed study quality: GT

Critical review of manuscript: KC, NJ, GT

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Citation

Mouton JP, Jobanputra N, Tatz G, Cohen K. Serious adverse drug reactions in sub-Saharan Africa in the era of antiretroviral treatment: a systematic review. *Pharmacology Research & Perspectives*. 2021;9(6):e00875.

DOI: 10.1002/prp2.875

The original publication is included as Appendix i. Supplementary materials are included from Appendix vi to Appendix xxxii.

2.1 Abstract

We aimed to summarise and describe the burden of serious adverse drug reactions (ADRs) in sub-Saharan Africa (SSA) in the era of antiretroviral therapy. We searched Medline, CINAHL, Africa-Wide Information, Scopus, and Web of Science, without language restriction up to March 2021. We hand-searched reference lists, conference abstracts, and dissertation databases. We included studies reporting proportions of admissions attributed to ADRs, admissions prolonged by ADRs, or in-hospital deaths attributed to ADRs. Two reviewers independently screened studies, reviewed study quality using a previously published tool, and extracted data. We tested for heterogeneity using I^2 -statistics and summarised study results using medians and interquartile ranges. Subgroup analyses summarised results by study quality, setting, methodology, and population. From 1005 unique references identified, we included 15 studies. Median study quality was 7/10; heterogeneity was very high. Median [IQR] proportion of admissions attributed to ADRs was 4.8% [1.5% to 7.0%] (14 studies), and 6.4% [4.0% to 8.4%] in nine active surveillance studies in adults. Two paediatric studies reported the proportion of admissions prolonged by ADRs (0.29% and 0.99%). Three studies reported the proportion of in-hospital deaths attributed to ADRs (2.5%, 13%, and 16%). Antiretroviral and antituberculosis drugs were often implicated in serious ADRs. Evidence of the burden of serious ADRs in SSA is patchy and heterogeneous. A few high-quality studies suggest the burden is considerable, and that it reflects the regional impact of the HIV pandemic. Further characterisation of this burden is required, ideally in studies of standardised methodology.

2.2 Introduction

The burden of adverse drug reactions (ADRs) in low- and middle-income countries (LMICs) may differ from that in high-income settings for a variety of reasons, including differences in disease burden, differences in drug utilisation patterns, a potential lack of effective drug quality control, and the high risk for prescribing and dispensing errors that occur in overburdened healthcare systems. Previous systematic reviews summarising the global burden of ADRs⁶²⁻⁶⁷ included only a few surveys from LMICs, which limits the generalisability of their results to LMIC settings.

In sub-Saharan Africa (SSA), an epidemiological transition is taking place, with high prevalence of both non-communicable disease and infectious disease, particularly HIV. The World Health Organization (WHO) first introduced guidelines for scaling up antiretroviral therapy (ART) in resource-limited settings in 2002⁶⁸. Large national ART programmes in SSA could potentially contribute significantly to the burden of ADRs in this region.

Serious ADRs are those that result in death, are life-threatening, result in hospital admission or prolong an existing hospital admission, result in persistent or significant disability or incapacity, or result in a congenital anomaly or cancer^{22,38}. This systematic review aims to summarise and describe data on the burden of serious ADRs in SSA in the era of ART. We specifically focus on ADRs that cause hospital admission, prolong an existing hospital admission, or cause in-hospital death, as these three categories of serious ADRs are the ones most frequently measured by surveys, are reasonably easy to verify, are not subjectively judged, and do not require longitudinal data.

The specific objectives of this systematic review are:

Primary objective

- To summarise the proportions of hospital admissions attributable to ADRs, hospital admissions prolonged by ADRs, and in-hospital deaths attributable to ADRs in SSA in the ART era.

Secondary objectives

- To summarise the proportions of hospital admissions attributable to preventable ADRs, hospital admissions prolonged by preventable ADRs, and in-hospital deaths attributable to preventable ADRs in SSA in the ART era.
- To describe common clinical presentations of serious ADRs, and drugs commonly implicated in serious ADRs, in SSA in the ART era.
- To explore the contribution of HIV and ART to the burden of serious ADRs in SSA in the ART era.
- To explore methodological and quality issues in ADR surveys conducted in SSA in the ART era.

2.3 Methods

2.3.1 Criteria for considering studies for this review

We reviewed observational studies from SSA, published since 2002 (the year of the first WHO ART guideline for resource-constrained settings⁶⁸), which reported any of the following proportions:

- the proportion of hospital admissions attributable to ADRs,
- the proportion of hospital admissions prolonged by ADRs, or
- the proportion of in-hospital deaths attributable to ADRs.

Prospective or retrospective cohort studies, cross-sectional studies, as well as data collected in the baseline survey / control arm of trials were eligible for inclusion. Forty-

eight countries, listed in Appendix vi, were defined as SSA countries in accordance with the World Bank's use of the term. We used original study authors' definitions of "ADR", "hospital", and "admission", but we specifically did not consider attendance at an emergency unit to be a hospital admission. We only included studies conducted in unselected hospital populations. No restrictions were applied in terms of publication language or type; we included studies available as abstracts only. No restrictions were applied in terms of study population age groups.

2.3.2 Search methods for identification of studies

We searched five databases (Medline, CINAHL, Africa-Wide Information, Scopus, and Web of Science) for relevant journal articles.

The primary search strategy, developed with the help of a medical librarian, was based on a combination of free text and index term searches for searching Medline through EBSCOhost. Terms identifying SSA were derived from a recommendation by the University of North Carolina Libraries⁶⁹, and terms to identify ADRs were derived from a recommendation by the Cochrane Collaboration⁷⁰ and from terms used in a previous systematic review⁷¹. In addition to an "SSA concept" and an "ADR concept", we included two more search concepts, relating to the "seriousness" and the "prevalence" of ADRs. Search strategies for all databases are included in Appendix vii to Appendix xi.

Database searches were most recently conducted on 02 March 2021. Results were uploaded to an electronic deduplication and screening tool.

Database searches for journal articles were supplemented by hand-searches conducted by one reviewer (JPM), including reference lists and lists of excluded studies of 30 previous review articles on various medicine safety topics^{62-67,71-94}, reference lists of articles included in the current review, abstract books of the 2002 to 2020 annual meetings of the International Society of Pharmacovigilance and the

International Society of Pharmacoepidemiology, and theses and dissertations via five databases, detailed in Appendix xii. Potentially relevant reports were added to the electronic deduplication and screening tool.

2.3.3 Screening of title/abstracts

After removing duplicates, two reviewers (JPM, and either NJ or GT) independently screened all reports on title and abstract. Reports were excluded if both reviewers agreed to exclude it; reasons for exclusion at this stage were not documented. Where no English-language abstract was available, we used an online translator (Google Translate) to assess the potential relevance of the report.

2.3.4 Obtaining full-text articles

We were able to obtain full-texts of all the reports not excluded on title and abstract screening through the University of Cape Town Libraries; we did not need to contact authors for full-texts. Where multiple reports were found to relate to one study, we combined the reports into one study at this point.

2.3.5 Full-text screening

Full-text studies were reviewed for inclusion independently by two reviewers (JPM, and NJ, GT, or KC). Studies in languages other than English were translated through an online translator (Google Translate). Disagreement over inclusion was resolved through discussion between the two reviewers, and a third reviewer could arbitrate. A reason for exclusion of the study was documented.

2.3.6 Quality assessment

Included studies were independently assessed for quality by two reviewers (JPM and GT) using a slightly modified version of a quality-assessment tool developed specifically for ADR surveys⁷¹. Our modification replaced the term 'severity' in the tool with the terms 'seriousness or severity'. We calculated a quality score for each study as

the total number of 'yes' responses out of tool's ten questions. Disagreement was resolved through discussion between the two reviewers, and a third reviewer could arbitrate.

2.3.7 Data extraction

Two reviewers (JPM and GT) independently extracted data on study characteristics, the study setting, the study population, the study methodology, and study findings. (The data extraction form is included in Appendix xiii). Disagreement was resolved through discussion between the two reviewers, and a third reviewer (KC) could arbitrate. We did not contact study authors with data extraction queries.

2.3.8 Data synthesis

Studies were grouped according to the data they contained relevant to this systematic review's three co-primary objectives. Group 1 studies reported the proportion of hospital admissions attributed to ADRs, group 2 studies reported the proportion of hospital admissions prolonged by ADRs, and group 3 studies reported the proportion of in-hospital deaths attributable to ADRs; a study could be included in more than one group. Since findings could be reported on the level of the patient or on the level of the admission (i.e., allowing for re-admissions), we decided to use admission-level data if reported, and patient-level data if no admission-level data were reported.

In the primary analysis, we pooled data from all studies in each group, regardless of study quality, study setting, methodological considerations, or study populations. We tested for heterogeneity using I^2 statistics to decide whether to conduct meta-analysis: in the presence of heterogeneity, we would summarise the proportions mentioned above as medians and interquartile ranges; in the absence of heterogeneity, we would conduct random-effects meta-analysis, calculating the pooled estimate proportion after Freeman-Tukey double arcsine transformation to stabilise the variances.

We explored the proportions mentioned above by subgroups relating to study quality, study setting, methodological considerations, and study populations. Depending on heterogeneity within each subgroup (using I^2 statistics) we would proceed to synthesise the data as above.

A similar approach was followed for the secondary objectives, where we summarised serious preventable ADRs. For the remainder of the secondary and explorative objectives, we narratively summarised clinical presentations commonly reported, drugs commonly implicated, and the contribution of HIV, ART, and methodological and quality issues.

2.4 Results

Our electronic search yielded 1183 references and our hand search three more; after deduplication 1005 references remained. We excluded 964 references as irrelevant on title/abstract screening and assessed 41 studies for eligibility on full text. We excluded 26, listed in Appendix xiv with reasons. The most common reason for excluding studies on full text was that no disaggregated numerator was reported. These included studies that did not distinguish between serious and non-serious ADRs, as well as studies of “umbrella topics”, such as drug-related harm, which did not report ADRs separately. Fifteen studies^{61,95-111} were included in this systematic review (Figure 2.1).

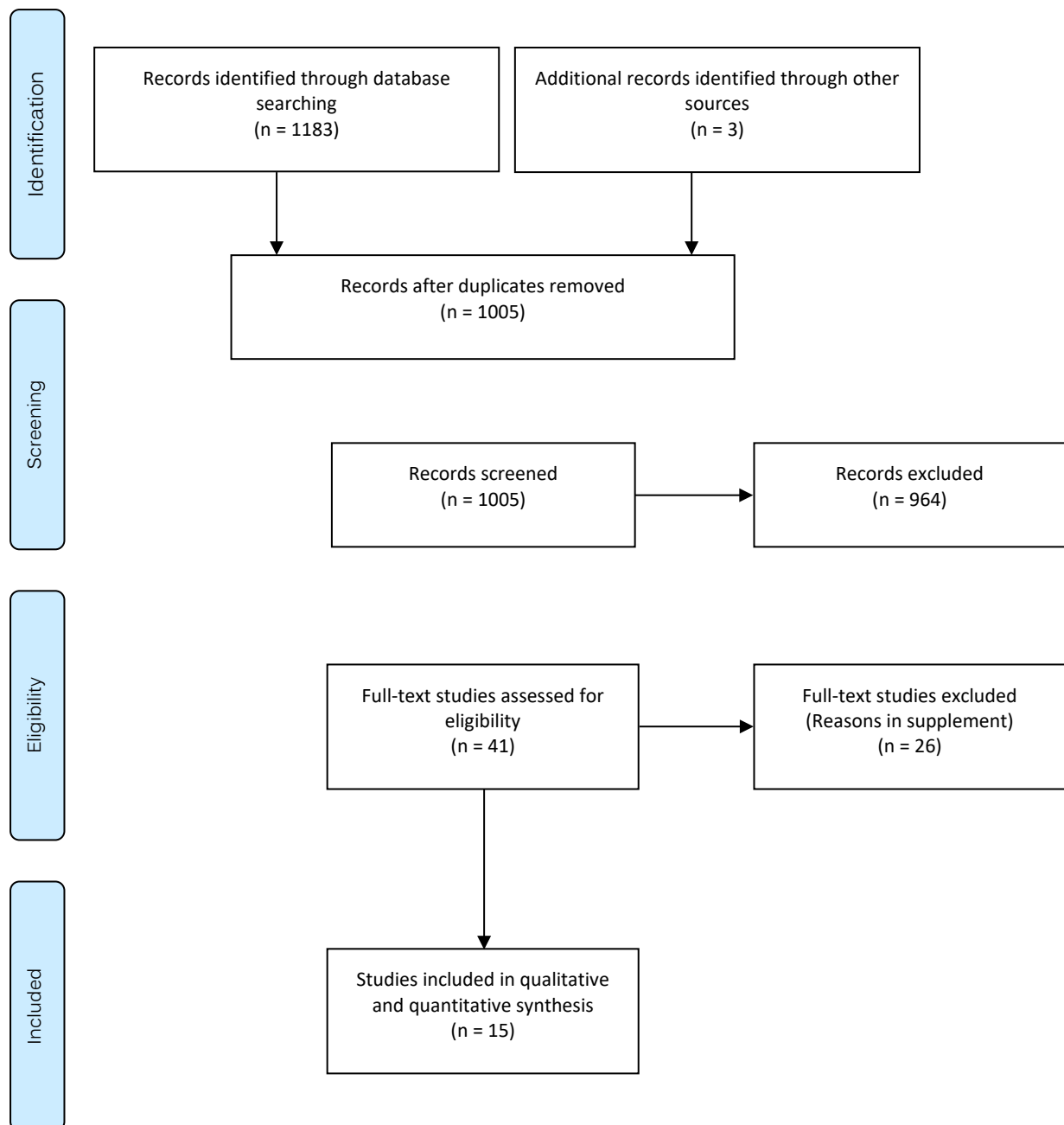


Figure 2.1. PRISMA diagram

Quality scores ranged from 1/10 (in one study) to 10/10 (in four studies). Median [IQR] quality score was 7 [3 to 10]. All studies clearly reported the study design (Table 2.1), and most also clearly described data collection methods. In general, studies reported using standard methods for assessing causality, preventability, and seriousness/severity; however, details of the processes applying these methods (for example, the people performing the assessments, solving disagreements, etc.) were

less well reported. The study characteristic reported least often was the process of establishing seriousness.

Table 2.1. Quality assessment of 15 studies included in the systematic review

Quality question	Number (proportion) 'yes'
01 Was study design clear?	15 (100%)
02 Were methods used to identify ADRs described in detail?	7 (47%)
03 Were data collection methods clearly described?	12 (80%)
04 Were the individuals who identified ADRs clearly described?	10 (67%)
05 Was the process of establishing the causal relationship described in detail?	8 (53%)
06 Were standard methods used in causality assessment?	13 (87%)
07 Was the process of establishing avoidability described in detail?	7 (47%)
08 Were standard methods used in avoidability assessment?	7 (47%)
09 Was the process of establishing seriousness or severity described in detail?	5 (33%)
10 Were standard methods used in seriousness or severity assessment?	8 (53%)

Source: adapted from Smyth et al⁷¹

Table 2.2 summarises the characteristics of studies included in this review.

Table 2.2. Characteristics of included studies

Study ID	Group *	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
Oshikoya 2007 ⁹⁵	1,2	36 months ending 2006, paediatric wards of single secondary/tertiary hospital in Nigeria	All paediatric patients admitted	Prospective and retrospective augmented folder review by multidisciplinary team	WHO definition ¹⁸ , with specific inclusion: herbal / traditional medicines	Done according to Jones method ¹¹² . Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done. Criteria not reported
Mehta 2008 ⁶¹	1,3	3 months in 2005, medical wards of single secondary/tertiary hospital in South Africa	Non-random sample of adult patients (>16 years) admitted: 1% excluded for missing records. All deaths of adult patients admitted.	Prospective folder review by multidisciplinary team	WHO definition ¹⁸ , with specific exclusions: intentional overdose and poor adherence; specific inclusion: accidental overdose	Done by multidisciplinary team (different from ADE surveillance team), according to WHO-UMC method ²⁸ . Numerator includes cases rated definite, probable, and possible	Done by multidisciplinary team (different from ADE surveillance team), according to Temple criteria ¹¹³	Done by multidisciplinary team (different from ADE surveillance team), according to Schumock criteria ³⁶
Soukho-Kaya 2010 ^{96,97}	1	12 months ending 2006, medical wards of single secondary/tertiary hospital in Mali	Non-random sample of adult patients admitted: 4% excluded for receiving cancer chemotherapy	Prospective folder review	WHO definition ¹⁸	Done according to French method ¹¹⁴ . Numerator includes cases rated definite and probable.	Implied (study reported serious outcomes)	Not done
Oshikoya 2011 ⁹⁸	1	18 months ending 2007, paediatric wards of single secondary/tertiary hospital in Nigeria	Non-random sample of paediatric patients admitted: unknown number excluded for admission < 24 hours or repeat	Prospective augmented folder review by multidisciplinary team	Edwards and Aronson ²²	Done by same investigators who conducted ADE surveillance, according to Jones method ¹¹² . Not reported which categories were	Implied (study reported serious outcomes)	Done by same investigators who conducted ADE surveillance, according to Schumock criteria ³⁶

Study ID	Group *	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
			admission or missing records			included in numerator.		
Tumwikirize 2011 ⁹⁹	1	6 months in 2005, medical wards of multiple hospitals (primary and secondary/tertiary) in Uganda	Non-random sample of adult patients (>13 years) admitted: 35% excluded for no consent or too ill to cooperate	Prospective folder review by multidisciplinary team	WHO definition ¹⁸ , with specific exclusion: herbal / traditional medicines	Done by multidisciplinary team (different from ADE surveillance team), according to Naranjo method ²⁹ . Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done according to Schumock criteria ³⁶
Kauffman 2014 ¹⁰⁰	1	6 months in 2012, single secondary/tertiary hospital in Malawi (wards not reported)	Non-random sample of adult patients (>18 years) admitted: 84% excluded for missing records	Retrospective folder review	Not defined	Done by multidisciplinary team (different from ADE surveillance team), according to Naranjo method ²⁹ . Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Not done
Aderemi- Williams 2015 ¹⁰¹	1	12 months ending 2009, medical wards of single secondary/tertiary hospital in Nigeria	Non-random sample of adult patients admitted: 96% excluded for unclear reasons	Retrospective folder review	WHO definition ¹⁸ , with specific exclusions: intentional overdose, accidental overdose, and poor adherence	Not done	Implied (study reported serious outcomes)	Not done
Ayetoro 2015 ^{102,103}	1	12 months ending 2014, medical wards of single secondary/tertiary hospital in Nigeria	Not applicable	Spontaneous reporting	Not defined	Not reported or unclear	Implied (study reported serious outcomes)	Not reported or unclear

Study ID	Group *	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
Mouton 2015 ¹⁰⁴	3	1 month in 2013, medical wards and intensive care units of multiple secondary/tertiary hospitals in South Africa	All deaths of adult patients admitted	Retrospective folder review by single investigator	Aronson and Ferner ¹⁹ , with specific exclusion: intentional overdose	Done by multidisciplinary team (different from ADE surveillance team), according to WHO-UMC method ²⁸ . Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done by multidisciplinary team (different from ADE surveillance team), according to Schumock criteria ³⁶
Mouton 2016 ¹⁰⁵	1	1 month in 2013, medical wards and intensive care units of multiple secondary/tertiary hospitals in South Africa	All admissions of adult patients	Prospective folder review by multidisciplinary team	Aronson and Ferner ¹⁹ , with specific exclusions: intentional overdose and therapeutic failure	Done by multidisciplinary team (different from ADE surveillance team), according to WHO-UMC method ²⁸ . Numerator includes cases rated definite, probable, and possible	Done by multidisciplinary team (different from ADE surveillance team), according to Temple criteria ¹¹³	Done by multidisciplinary team (different from ADE surveillance team), according to Schumock criteria ³⁶
Russom 2017 ¹⁰⁶	1	5 months in 2014, all hospitals (primary and secondary/tertiary) in Eritrea (wards not reported)	Non-random sample of adult and paediatric patients admitted: unknown number excluded for age < 30 days or no consent or admitted for delivery	Prospective surveillance by multidisciplinary team.	WHO definition ¹⁸	Done by investigators different from ADE surveillance team, according to Naranjo method ²⁹ . Numerator includes cases rated definite, probable, and possible	Done according to ICH/CIOMS criteria ³⁸	Done according to P-method ¹¹⁵
Angamo 2018 ^{107,108}	1,3	16 months ending 2016, medical wards of single	Non-random sample of adult patients (>18	Prospective augmented folder	WHO definition ¹⁸ , with specific exclusions:	Done by multidisciplinary team (different from ADE	Done by same investigators who conducted ADE	Done. Criteria not clear

Study ID	Group *	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
		secondary/tertiary hospital in Ethiopia	years) admitted: 69% excluded for no consent or missing records or no drug exposure or not interviewed due to health or other reasons. All deaths of adult patients admitted.	review by single investigator	intentional overdose, accidental overdose, drug abuse, and therapeutic failure	surveillance team), according to Naranjo method ²⁹ . Numerator includes cases rated definite and probable	surveillance. Criteria not reported	
Makiwane 2019 ¹⁰⁹	1	3 months in 2016, paediatric wards of single secondary/tertiary hospital in South Africa	Non-random sample of paediatric patients (<16 years) admitted: unknown number excluded for admission <24 hours or no consent	Prospective folder review by single investigator	WHO definition ¹⁸ , with specific inclusion: herbal / traditional medicines	Done according to Naranjo method ²⁹ . Numerator includes cases rated definite, probable, and possible	Done according to ICH/CIOMS criteria ³⁸	Not done
Adedapo 2020 ¹¹⁰	1	12 months ending 2013, medical wards of single secondary/tertiary hospital in Nigeria	Non-random sample of adult patients admitted: 57% excluded for no consent or existing admissions or repeat admissions or very ill	Prospective augmented folder review	WHO definition ¹⁸ , with specific inclusions: herbal / traditional medicines, medication errors	Done according to WHO-UMC method ²⁸ . Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done according to Wolfe criteria ⁹⁴
Mouton 2020 ¹¹¹	1,2	1 month in 2015, paediatric wards and intensive care units of multiple	Non-random sample of admissions of paediatric patients:	Prospective and retrospective folder review by multidisciplinary team	Aronson and Ferner ¹⁹ , with specific exclusions: herbal	Done by multidisciplinary team (different from ADE surveillance team),	Done by multidisciplinary team (different from ADE	Done by multidisciplinary team (different from ADE surveillance

Study ID	Group *	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
		secondary/tertiary hospitals in South Africa	unknown number excluded for elective admissions, rehydration therapy, postnatal stays		/ traditional medicines, intentional overdose, poor adherence, medication errors without harm, therapeutic failure	according to WHO- UMC method ²⁸ . Numerator includes cases rated definite, probable, and possible	surveillance team), according to Temple criteria ¹¹³	team), according to Schumock criteria ³⁶

* Group 1 studies report proportion of admissions attributed to ADRs. Group 2 studies report the proportion of admissions prolonged by ADRs. Group 3 studies report the proportion of in-hospital deaths attributed to ADRs.

2.4.1 Group 1 (studies reporting the proportion of hospital admissions attributed to ADRs)

Fourteen studies^{61,95-103,105-111} reported as outcome the proportion of admissions attributed to ADRs. To estimate the summary proportion of admissions attributed to ADRs, we first pooled all group 1 studies and tested for heterogeneity. Since very high heterogeneity was found ($I^2 = 98.2\%$), no meta-analysis was performed. The median [IQR] proportion of admissions attributed to ADRs among the 14 studies was 4.8% [1.5% to 7.0%] (Figure 2.2).

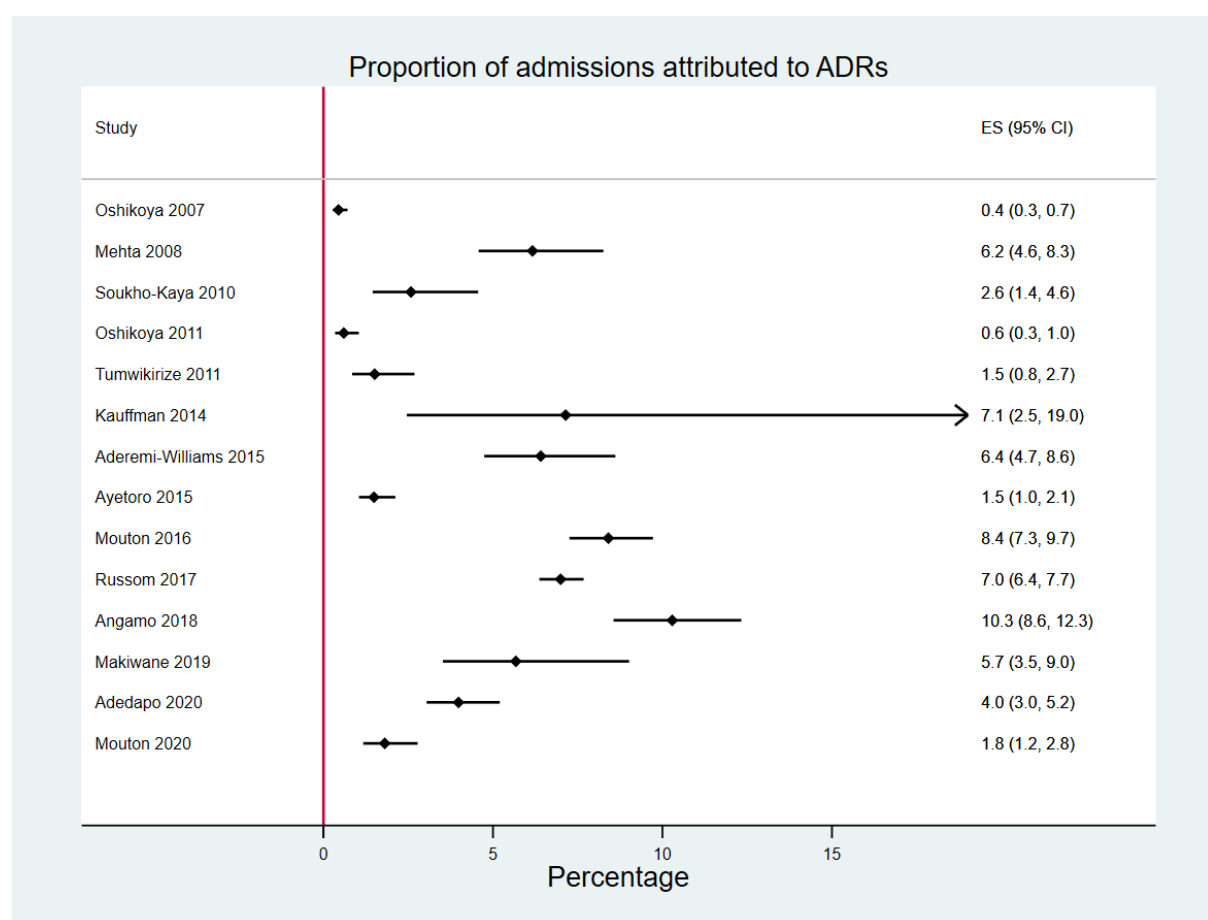


Figure 2.2. Forest plot of studies reporting proportion of admissions attributed to ADRs

ES: estimate size

We investigated heterogeneity among subgroups based on study quality, study setting, study methodology, and study population. Since there was very high heterogeneity in

each subgroup, no meta-analysis by subgroup was performed. Heterogeneity and summary proportions, by subgroup, are presented in Appendix xv to Appendix xxx.

One study, reported only in two conference abstracts^{102,103}, was a low-quality report of a spontaneous ADR reporting system in the medical wards of a Nigerian hospital, where 30/2012 (1.5%) patients were reported to have had an ADR-related admission.

The remaining thirteen studies were all conducted as active surveillance studies, eight of which were in adults^{61,96,97,99-101,105,107,108,110}, four in children^{95,98,109,111}, and one in a mixed adult and paediatric population¹⁰⁶. As this latter study presented data for adults and children separately, we could extract separate adult and paediatric datasets from it.

Key results from Group 1 studies, grouped by the ADR detection method (spontaneous reporting vs active surveillance) and study population (adults vs children) are presented in Table 2.3.

Table 2.3. Key results from studies reporting the proportion of admissions attributed to ADRs (Group 1 studies). Studies grouped by ADR detection method and population studied

Study	Proportion of admissions attributed to ADRs / Proportion of patients with admissions attributed to ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of patients with admissions attributed to ADRs who are PLWH
Spontaneous Reporting				
Ayetoro 2015 ^{102,103}	30/2012 (1.5%) patients.	NR	NR	NR
Active Surveillance, Adults				
Mehta 2008 ⁶¹	41/665 (6.2%) patients.	Metabolic (16), endocrine (10), hepatic (8) and neuropsychiatric (8)	Cardiovascular (22), antiretrovirals (17), oral hypoglycaemic agents (7), non-steroidal anti-inflammatories (7)	38% PLWH
Soukho-Kaya 2010 ^{96,97}	11/426 (2.6%) patients.	Hypoglycaemia (5)	NR	NR
Tumwikirize 2011 ⁹⁹	11/728 (1.5%) patients.	NR	NR	NR
Kauffman 2014 ¹⁰⁰	3/42 (7.1%) patients.	Anaemia (1), hyperlactataemia (1), GIT distress (1)	Stavudine (2), metronidazole (1)	3/3 PLWH

Study	Proportion of admissions attributed to ADRs / Proportion of patients with admissions attributed to ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of patients with admissions attributed to ADRs who are PLWH
Aderemi-Williams 2015 ¹⁰¹	40/624 (6.4%) patients.	Not clear	Not clear	NR
Mouton 2016 ¹⁰⁵	164/1951 (8.4%) admissions.	Renal impairment (24), hypoglycaemia (22), DILI (20), haemorrhage (19), blood dyscrasias (14)	Rifampicin (17), enalapril (13), insulin (14), tenofovir (14), warfarin (13)	64/164 (38%) in PLWH
Russom 2017 ¹⁰⁶ (adults)	295/3415 (8.6%) patients.	NR	NR	NR
Angamo 2018 ^{107,108}	103/1001 (10%) patients.	Hepatotoxicity (35), acute kidney injury (27), skin reactions (8), hypokalaemia (7), gastrointestinal bleed/gastritis (7)	Isoniazid (23), furosemide (19), pyrazinamide (18), tenofovir (9), acetylsalicylic acid (9)	29/103 (28%) PLWH and on ART
Adedapo 2020 ¹¹⁰	51/1280 (4.0%) patients.	NR	NR	NR
Active surveillance, children				
Oshikoya 2007 ⁹⁵	17/3821 (0.44%) patients.	Erythema multiforme (12)	Ampicillin (7), sulfadoxine / pyrimethamine (5), co-trimoxazole (5), phenobarbitone (3), herbs (2)	NR
Oshikoya 2011 ⁹⁸	12/2004 (0.60%) patients.	Erythema multiforme (5), Stevens-Johnson syndrome (2), macular and morbidiform rash (2)	Cotrimoxazole (6), ampicillin (4), sulfadoxine / pyrimethamine (3)	NR
Russom 2017 ¹⁰⁶ (children)	114/2433 (4.7%) patients.	NR	NR	NR
Makiwane 2019 ¹⁰⁹	16/282 (5.7%) patients.	NR	NR	NR
Mouton 2020 ¹¹¹	20/1106 (1.8%) admissions.	Urticaria (2), dystonia (2)	Prednisone (2), metoclopramide (2)	3/20 (15%) PLWH

NR: not reported; PLWH: people living with HIV

2.4.1.1 Adult active surveillance studies

Nine active surveillance studies contributed adult data (Table 2.3). All were available as English full-text reports, except one Malian study reported in both a French-language article⁹⁷ and a French-language thesis⁹⁶ with English abstracts. An Ethiopian study was

reported in two complementary articles^{107,108}. Median quality score was 7/10, ranging from 2/10 to 10/10. Studies were conducted in South Africa (two studies^{61,105}, both high quality), Nigeria (two studies^{101,110}), and in Eritrea¹⁰⁶, Ethiopia^{107,108}, Malawi¹⁰⁰, Mali^{96,97}, and Uganda⁹⁹. Study duration ranged from 1 month to 16 months, for a median of 6 months. Six studies were single-centre studies at secondary- / tertiary-level hospitals^{61,96,97,100,101,107,108,110}, while three were conducted in multiple hospitals^{99,105,106}, including primary-level hospitals in two^{99,106}. Where reported, all studies were conducted in medical wards^{61,96,97,99,101,105,107,108,110}, additionally including intensive care units in one¹⁰⁵. Only one study reported universal sampling of all patients admitted to the study wards¹⁰⁵; non-random sampling of admitted patients was described in the remainder. In these studies, large numbers of potential participants were often excluded (35%⁹⁹, 57%¹¹⁰, 69%^{107,108}, 84%¹⁰⁰, and 96%¹⁰¹ in five studies, but only 1%⁶¹ and 4%^{96,97} in two others). Reasons for excluding potential participants included no consent^{99,106-108,110}, missing records^{61,100,107,108}, being too ill to cooperate^{99,107,108,110}, admissions for cancer chemotherapy^{96,97} or delivery¹⁰⁶, readmissions¹¹⁰, no drug exposure^{107,108}, or unclear reasons¹⁰¹.

Most studies^{61,96,97,99,105-108,110} used prospective folder review as surveillance methodology, but only four^{61,99,105,106} reported this to have been conducted by multidisciplinary team. ADRs were mostly defined according to the WHO definition^{61,96,97,99,101,106-108,110}. Five studies^{61,99,100,105,107,108} reported a clear two-step method, with causality assessment conducted by a multidisciplinary team other than the surveillance team. Naranjo's causality assessment method (in 4 studies^{99,100,106-108}) and the WHO-UMC method (in three studies^{61,105,110}) were mostly used. Six studies reported assessing the preventability of ADRs, using Schumock and Thornton criteria in three studies^{61,99,105} and unreported, unclear, or other methods in three studies^{106-108,110}.

Apart from summary demographic statistics, the population included in studies' denominator was generally poorly described. Mean or median age ranged from 36 to

50 years (reported in six studies^{61,96,97,99,105,107,108,110}), and the proportion of females from 42% to 56% (reported in seven studies^{61,96,97,99,101,105,107,108,110}). Only two studies reported the proportion of patients included in the denominator that were exposed to drugs before their admission^{105,107,108}. Only two studies described the most common reason for admission, being malaria⁹⁹ and cardiovascular disease¹⁰⁵ respectively. HIV prevalence among patients included in the denominator was only reported in the South African studies, being 32% in the earlier⁶¹ and 29% in the later¹⁰⁵ study. The proportion of patients in the denominator who were taking ART increased in the interval between these two studies from 5.2%⁶¹ to 14%¹⁰⁵, and was 11% in the Ethiopian study^{107,108}.

Among the nine active surveillance studies in adult populations, the median [IQR] proportion of admissions attributed to ADRs was 6.4% [4.0% to 8.4%]. Although more studies assessed the preventability of ADRs, only one study, from South Africa, reported the proportion of admissions attributed to preventable ADRs, which was 3.7%¹⁰⁵.

Four studies reported the drugs or drug classes implicated in ADRs causing admission to hospital^{61,100,105,107,108}, with striking similarities: antiretroviral agents, antituberculosis therapy, cardiovascular drugs and hypoglycaemic drugs predominated. Common clinical presentations of these ADRs, as reported in five studies^{61,96,97,100,105,107,108}, mostly related to their hepatotoxic and nephrotoxic effects, and hypoglycaemia. Bleeds from non-steroidal anti-inflammatories and antithrombotic agents were less frequently reported.^{105,107,108}

Four studies reported HIV prevalence among patients who were admitted to hospital for ADRs. This was 38% in both South African studies^{61,105}, 28% in the Ethiopian study^{107,108}, and 3/3 in the Malawian study.¹⁰⁰

2.4.1.2 Paediatric active surveillance studies

Five active surveillance studies contributed paediatric data (Table 2.3), including two from Nigeria^{95,98}, two from South Africa^{109,111}, and one from Eritrea¹⁰⁶. All were available as English full-text articles, with median quality score 5/10, although two studies^{98,111} scored 10/10. Study duration ranged from 1 month to 36 months. Three studies were single-centre studies at secondary- / tertiary-level hospitals^{95,98,109} while two were conducted in multiple hospitals^{106,111}, including primary-level hospitals in one¹⁰⁶. One study¹¹¹ surveyed patients admitted to intensive care units in addition to those admitted to paediatric wards. Only one study reported universal sampling of all patients admitted to the study wards⁹⁵; non-random sampling of admitted patients was described in the remainder. In these studies, unknown numbers of potential participants were excluded for reasons including no consent^{106,109}, missing records⁹⁸, short duration admissions^{98,109}, admissions for rehydration¹¹¹, repeat admissions⁹⁸, elective admissions¹¹¹, or neonatal admissions^{106,111}.

Four studies reported that multidisciplinary teams conducted the surveillance^{95,98,106,111}. Three studies^{95,98,106} defined ADRs according to the WHO definition. All studies included an assessment of causality, and four^{95,98,106,111} included an assessment of preventability, although precise methods varied.

Only one study reported the proportion of patients included in the denominator that were exposed to drugs before their admission¹¹¹. Infectious diseases were frequently reported as the reason for admission^{95,98,109,111}. The proportion of children in the denominator population who had HIV infection was only reported in the two South African studies^{109,111}.

The proportion of admissions attributed to ADRs ranged from 0.4% to 5.7%, median [IQR] 1.8% [0.6% to 4.7%]. At the low end of the range were the two large Nigerian studies which seemingly included older children, with one study reporting the mean

age among all admissions being 6.4 years⁹⁸. In contrast, the South African studies' populations were younger (median age 1.4 years¹⁰⁹ and 0.9 years¹¹¹). Hypersensitivity reactions, including erythema multiforme, Stevens Johnson syndrome, urticaria, and rashes were reported as the most common presentations, and antimicrobial medicines were most commonly implicated. Two studies reported the proportion of admissions attributed to preventable ADRs, which were 0.1%⁹⁸ and 0.5%¹¹¹ respectively. Only one study, conducted in South Africa, reported HIV prevalence among children admitted for ADRs, being 15%.¹¹¹

2.4.2 Group 2 (studies reporting the proportion of hospital admissions prolonged by ADRs)

We found no study conducted in adult populations reporting the proportion of hospital admissions prolonged by ADRs. Two paediatric studies, one from Nigeria⁹⁵ and one from South Africa¹¹¹ reported this proportion (Table 2.4). In the Nigerian study⁹⁵ 0.29% children experienced ADR-related prolongation of their hospital admission. ADR preventability, presentations, implicated drugs, and HIV exposure were not reported. In the South African study¹¹¹ 0.99% admissions were prolonged by ADRs. Most prolongations were for antibiotic-associated diarrhoea, although a variety of other admission-prolonging ADRs occurred, including ADRs attributed to corticosteroids and immunosuppressants. Only one study reported the proportion of admissions prolonged by preventable ADRs, being 2/1106 (0.19%)¹¹¹. Only one study, conducted in South Africa, reported HIV prevalence among children whose hospital stays were prolonged by ADRs, being 18%.¹¹¹

Table 2.4. Key results from studies reporting the proportion of admissions prolonged by ADRs (Group 2 studies)

Study	Proportion of admissions prolonged by ADRs / Proportion of patients with admissions prolonged by ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of patients with admissions prolonged by ADRs who are PLWH
Oshikoya 2007 ⁹⁵	11/3821 (0.29%) patients.	NR	NR	NR
Mouton 2020 ¹¹¹	11/1106 (0.99%) admissions.	Diarrhoea (4), bicytopenia (2)	Prednisone (3), methylprednisolone (3), tacrolimus (2), mycophenolic acid (2), amoxicillin (2)	2/11 (18%) PLWH

NR: not reported; PLWH: people living with HIV

2.4.3 Group 3 (studies reporting the proportion of in-hospital deaths attributable to ADRs)

Three high-quality adult studies, two from South Africa^{61,104} and one from Ethiopia^{107,108}, reported the proportion of in-hospital deaths to which ADRs contributed (Table 2.5). All three studies were conducted among adults in secondary / tertiary hospitals, with one¹⁰⁴ also including patients in the intensive care unit. In two studies^{104,107,108} the proportion of deaths attributed to ADRs was the primary outcome measure, while the third⁶¹ mentioned the proportion of deaths attributed to ADRs as an additional outcome. The Ethiopian survey^{107,108} only considered deaths from ADRs already present at time of admission, and not deaths from ADRs that developed during the hospital stay, and thus may have underestimated the deaths attributable to ADRs.

Table 2.5. Key results from studies reporting the proportion of in-hospital deaths attributed to ADRs (Group 3 studies)

Study	Proportion of in-hospital deaths attributed to ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of people whose in-hospital deaths were attributed to ADRs who were PLWH
Mehta 2008 ⁶¹	2/80 (2.5%) deaths.	Acute renal failure (1), intracranial bleed (1)	Gentamycin (1), warfarin (1)	NR
Mouton 2015 ¹⁰⁴	56/357 (16%) deaths.	Renal failure (23), drug-induced liver injury (10)	Tenofovir (14), rifampicin (9), co-trimoxazole (7), furosemide (5), insulin (4)	31/56 (55%) PLWH

Study	Proportion of in-hospital deaths attributed to ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of people whose in-hospital deaths were attributed to ADRs who were PLWH
Angamo 2018 ^{107,108}	15/116 (13%) deaths.	Hepatotoxicity (7), kidney injury (4)	Isoniazid (6), pyrazinamide (3), tenofovir (2), efavirenz (2), enalapril (2), furosemide (2)	6/15 (40%) PLWH

NR: not reported; PLWH: people living with HIV

The three studies respectively found 2/80 (2.5%)⁶¹, 56/357 (16%)¹⁰⁴, and 15/116 (13%)^{107,108} deaths were ADR-related.

The proportion of deaths attributed to preventable ADRs was reported in two studies: 28/357 (7.8%) in South Africa¹⁰⁴ and 14/116 (12%) in Ethiopia^{107,108} respectively.

These two studies also reported the proportion of ADR-related deaths in which decedents were people living with HIV (PLWH): 31/56 (55%)¹⁰⁴ and 6/15 (40%)^{107,108} respectively. In both studies, renal failure and drug-induced liver injury were the most common ADRs resulting in death, and both studies listed antiretrovirals and antituberculosis drugs as the drugs most commonly implicated in ADR-related deaths.

Multivariable logistic regression in one study¹⁰⁴ identified HIV-infection with antiretroviral treatment, higher drug count, and higher comorbidity score as independent risk factors for ADR-related death. Unadjusted bivariate analyses in the other^{107,108} also showed associations between ADR-related death and exposure to antiretroviral treatment, higher drug count, and higher comorbidity score, as well as pre-existing liver disease, a history of prior ADR, low body-mass index, and exposure to antituberculosis drugs.

In addition to the three studies included in this group, fatal ADR outcomes were reported by nine other studies included in this review^{95-98,100,102,103,106,109-111}. However,

these nine studies did not report the proportion of ADR-related deaths against a denominator of all in-hospital deaths.

A Nigerian study¹¹⁰ reported seven deaths attributed to ADRs among 67 adults with serious and non-serious ADRs. These included three cases of Stevens Johnson Syndrome or toxic epidermal necrolysis with co-trimoxazole and phenytoin, two cases of haemorrhage with heparin and diclofenac, and two cases of hepatotoxicity with anti-tuberculosis therapy and herbal medicine. Two of the deaths occurred in PLWH. Among other adult studies, the Malawian study¹⁰⁰ reported one fatal outcome (hyperlactatemia with stavudine) among their three patients with serious ADRs; the Malian study^{96,97} reported three fatal outcomes (hypoglycaemia, and “colchicine-induced vomiting”) among 39 patients with 47 serious and non-serious ADRs; and the spontaneous reporting study^{102,103} reported no fatal outcomes among 30 patients with serious ADRs.

Paediatric studies generally reported low absolute numbers of fatalities. However, fatal outcomes were reported to occur in a relatively high proportion of serious ADRs: 2/17 serious ADRs were fatal (Stevens-Johnson syndrome and hepatotoxicity) in one Nigerian study⁹⁵, 2/12 (Stevens-Johnson syndrome) in the other⁹⁸, and 1/40 in a South African study¹¹¹. No fatal outcomes were reported among 61 serious and non-serious ADRs in the other South African paediatric study¹⁰⁹.

In the country-wide Eritrean survey 48 fatal ADRs were reported among 5,848 patients admitted¹⁰⁶. The two most common ADRs resulting in death were anaemia (attributed to various drugs, including zidovudine) and hepatotoxicity (mostly attributed to antituberculosis therapy). Drugs used in the management of HIV, TB, and opportunistic infections appear to have been implicated in 17 deaths.

2.5 Discussion

A small number of relatively high-quality studies report that serious ADRs contribute significantly to the burden of morbidity and mortality in SSA hospitals. Fourteen studies included in this review reported that a median 4.8% (IQR 1.5% to 7.0%) of admissions were attributed to ADRs; three studies reported that between 2.5% and 16% of in-hospital deaths were attributed to ADRs.

This systematic review demonstrated the paucity of drug safety data from hospital settings in sub-Saharan Africa, and echoes the paucity of drug safety data contributed from Africa to the global spontaneous reporting database described by others¹¹⁶. Only fifteen studies fulfilled the inclusion criteria, despite the fact that we searched databases focused on Africa as well as grey literature, and despite searching without language restrictions. Even given the overall low number of studies included, there were regional and population differences: two-thirds of the included studies came from just two countries, South Africa and Nigeria, and none from a Central African country; few studies were conducted in paediatric settings, and none specifically in older adults. These are populations to be covered in future ADR surveillance activities.

Study quality, as measured by the tool we applied, was generally high. Nevertheless, to fully comprehend the context within which ADRs occur, and the risk for their occurrence, it is essential to understand the denominator study population, including their diseases and their drug exposures¹¹⁷. Many studies included in this review did not clearly describe the denominator study population, and had this been included as a factor in the quality assessment, we may have reported lower quality overall. A further quality concern among nearly all studies included in this review is the high proportion of potential participants excluded from the surveillance activity. Non-participation was often over 50% and as high as 96% in one study, which may have resulted in a biased

sample. Again, although this is a serious quality concern, it is not reflected in the quality assessment tool we used in this review.

We found very high heterogeneity among the study results, which can be attributed to high variability in study designs as described in Table 2.2, and also to high variability in the study settings and populations, potentially including some unreported differences. It is well established that the reported prevalence of medication-related hospital admissions depends on the setting, studied population, specific outcome investigated, and surveillance method⁸⁹. Unfortunately, calls for greater standardisation in the methodology of medicine safety studies^{19,22,117} have largely gone unheeded.

Because of this high heterogeneity we did not conduct meta-analysis of studies, but reported a median 4.8% (IQR 1.5% to 7.0%) as the proportion of admissions attributed to ADRs. This estimate agrees with the results of six earlier systematic reviews of ADR-related admissions⁶²⁻⁶⁷, which estimated the proportion of admissions attributable to ADRs to range between 3.1% and 6.3% (some in sub-group analyses).

A 2018 systematic review of African studies of adverse drug events or medication errors in hospitals⁹² differed from the current review as it included only peer-reviewed publications, included studies from North Africa and studies predating the ART era, and only distinguished between serious and non-serious events in some ADE cases.

Moreover, despite defining ADRs as a subset of ADEs, the authors of that systematic review reported “overlooking” this factor⁹², in the end pooling studies reporting an outcome of ADRs together with those reporting an outcome of ADEs. In view of the methodological differences between the two systematic reviews, it is not surprising that there is little overlap in the studies included, and a very different result. For the comparable outcome we described in our Group 1 studies (proportion of admissions attributable to ADRs, n = 14 studies, median proportion 4.8%) and the earlier review’s outcome of proportion of admissions as a direct result of ADEs (n = 11 studies, median proportion 2.8%)⁹², only six studies were included in both reviews.

Another previous systematic review, published in 2016, aimed to compare adult ADR burdens in high-income countries and LMICs⁷⁵. The authors found the median proportion of admissions attributed to ADRs to be lower in LMICs (5.5%) than in high-income countries (6.3%)⁷⁵. However, this review included only three studies from SSA among the 13 LMIC studies⁷⁵. Our comparable estimate (median 6.4% among nine adult active surveillance studies) is probably more representative, and read together with the results from other systematic reviews mentioned above⁶²⁻⁶⁷ probably dispels the idea that the burden of ADR-related admissions in SSA is lower than in high-income countries.

The proportion of in-hospital deaths attributed to ADRs in Europe was the topic of a 2021 systematic review. Six studies contributed 657 drug-related deaths out of 7578 in-hospital deaths, with the meta-analytic estimated proportion being 7.3% (95% CI 4.1% to 12.5%)¹¹⁸. This estimate appears to agree with an earlier population-based study using linked databases in Sweden, in which 6.4% of in-hospital deaths were attributed to ADRs¹¹⁹. We identified only three studies conducted in SSA to report this particular outcome, and these reported 2.5%, 13%, and 16% of deaths in adult medical wards were attributed to ADRs. The low number of SSA studies reporting this proportion as an outcome precludes any meaningful interpretation of this proportion. However, it is notable that in two of the studies a large proportion of the deaths were associated with preventable ADRs. In addition, it is notable that most deaths were due to renal and liver injuries, with ART and antituberculosis therapy most often implicated. This stands in contrast to studies from Europe, which found haemorrhages to be most common fatal ADRs.^{118,119}

For several of our study objectives, we found limited data. Only two studies reported on admissions prolonged by ADRs, and there were minimal reports on admissions caused by or prolonged by preventable ADRs. These are knowledge gaps to be filled by future research.

Another exploratory objective yielding little data was describing the role played by HIV and ART in the serious ADR burden in SSA. Although rarely reported, it was consistently reported that HIV prevalence among patients with serious ADRs was higher than HIV prevalence among the denominator population^{61,104,105,107,108,111}. This imbalance was most pronounced for the outcome of ADR-related deaths. However, this finding should be interpreted with care. Where antiretroviral therapy was implicated in causing ADRs, these were often older antiretrovirals, including stavudine and efavirenz, and the ADRs were often unpredictable and unavoidable events. ART programmes in SSA are continuously improving and introducing newer drugs with fewer toxicities: stavudine has been phased out as first-line ART option in the period 2006 to 2011¹²⁰, and efavirenz is currently being phased out in favour of dolutegravir. Tenofovir alafenamide has better renal safety than tenofovir disoproxil fumarate¹²¹ and may in future replace it in ART programmes.

2.6 Conclusion

We have shown that evidence of the burden of serious ADRs in SSA is patchy and highly heterogeneous. Nevertheless, a few high-quality studies suggest that the burden is considerable. A unique feature of the ADR burden in this region is the frequency at which people living with HIV appear affected, and the frequency with which ART and medicines used in the management of opportunistic infections are implicated in this burden. However, the risk of ADRs should be considered against the risks associated with non-treatment¹¹⁷, and there is no doubt that the benefit of these medicines massively outweigh their risk of harm. Further characterisation of the serious ADR burden in SSA is required, particularly in paediatric and elderly populations, and in countries other than South Africa and Nigeria. This should ideally be performed by conducting studies of standardised methodology. As a first step towards limiting the risk of harm caused by medicines, the focus should be on avoiding preventable ADRs, which are often caused by errors. Investing in support

systems that catch errors before harm occurs is required, particularly in under-resourced and overburdened health care settings such as those in SSA.

Chapter 3 Interrater agreement of two adverse drug reaction causality assessment methods: a randomised comparison of the Liverpool Adverse Drug Reaction Causality Assessment Tool and the World Health Organization-Uppsala Monitoring Centre system

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Critical review of manuscript: KC, GM, UM, DR

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Citation

Mouton JP, Mehta U, Rossiter DP, Maartens G, Cohen K. Interrater agreement of two adverse drug reaction causality assessment methods: A randomised comparison of the Liverpool Adverse Drug Reaction Causality Assessment Tool and the World Health Organization-Uppsala Monitoring Centre system. PLOS One. 2017;12(2):e0172830.

DOI: 10.1371/journal.pone.0172830

The original publication is included as Appendix ii. Supplementary materials are included from Appendix xxxiii to Appendix xxxviii.

3.1 Abstract

Introduction A new method to assess causality of suspected adverse drug reactions, the Liverpool Adverse Drug Reaction Causality Assessment Tool (LCAT), showed high interrater agreement when used by its developers. Our aim was to compare the interrater agreement achieved by LCAT to that achieved by another causality assessment method, the World Health Organization-Uppsala Monitoring Centre system for standardised case causality assessment (WHO-UMC system), in our setting.

Methods Four raters independently assessed adverse drug reaction causality of 48 drug-event pairs, identified during a hospital-based survey. A randomised design ensured that no washout period was required between assessments with the two methods. We compared the methods' interrater agreement by calculating agreement proportions, kappa statistics, and the intraclass correlation coefficient. We identified potentially problematic questions in the LCAT by comparing raters' responses to individual questions.

Results Overall unweighted kappa was 0.61 (95% CI 0.43 to 0.80) on the WHO-UMC system and 0.27 (95% CI 0.074 to 0.46) on the LCAT. Pairwise unweighted Cohen kappa ranged from 0.33 to 1.0 on the WHO-UMC system and from 0.094 to 0.71 on the LCAT. The intraclass correlation coefficient was 0.86 (95% CI 0.74 to 0.92) on the WHO-UMC system and 0.61 (95% CI 0.39 to 0.77) on the LCAT. Two LCAT questions were identified as significant points of disagreement.

Discussion We were unable to replicate the high interrater agreement achieved by the LCAT developers and instead found its interrater agreement to be lower than that achieved when using the WHO-UMC system. We identified potential reasons for this and recommend priority areas for improving the LCAT.

3.2 Introduction

Causality assessment of suspected adverse drug reactions (ADRs) is routinely performed in regulatory pharmacovigilance and in epidemiological ADR surveys. Nevertheless, there is no agreement on the best method for assessing causality of suspected ADRs. A 2008 systematic review identified 34 methods to assess ADR causality and grouped these as reaching a decision by global introspection, by following an algorithm, or by methods based on Bayesian probabilistics²⁷. Two methods in frequent use are the WHO-UMC system²⁸, which is an example of a global introspection method, and the algorithm published by Naranjo in 1981²⁹.

The WHO-UMC system asks the rater to judge the likelihood of ADR causality into one of six outcome categories, being 'certain', 'probable/likely', 'possible', 'unlikely', 'conditional/unclassified' (a temporary outcome category, while further information is sought), or 'unassessable/unclassifiable'. Guidelines have been published to assist the rater, but these are intentionally non-explicit²⁸. The Naranjo algorithm consists of ten questions to which a rater responds 'yes', 'no', or 'unknown'. Each response is allocated a score, and the sum of scores to the ten questions is usually converted into one of four outcome categories, namely 'definite', 'probable', 'possible', or 'doubtful'.

The Naranjo algorithm was adapted into a new assessment algorithm, the Liverpool ADR Causality Assessment Tool (LCAT)³¹ by researchers involved in the Adverse Drug Reactions in Children project [5]. The LCAT arranges ten modified questions with their dichotomous responses into a flowchart to arrive at one of four outcome categories: 'definite', 'probable', 'possible', or 'unlikely' (Figure 3.1). The developers of the LCAT found it to result in a more even distribution of outcomes than the Naranjo algorithm, which yielded few 'definite' ADRs, and found that the LCAT had higher interrater agreement (IRA) than the Naranjo algorithm, as measured by the kappa statistic³¹.

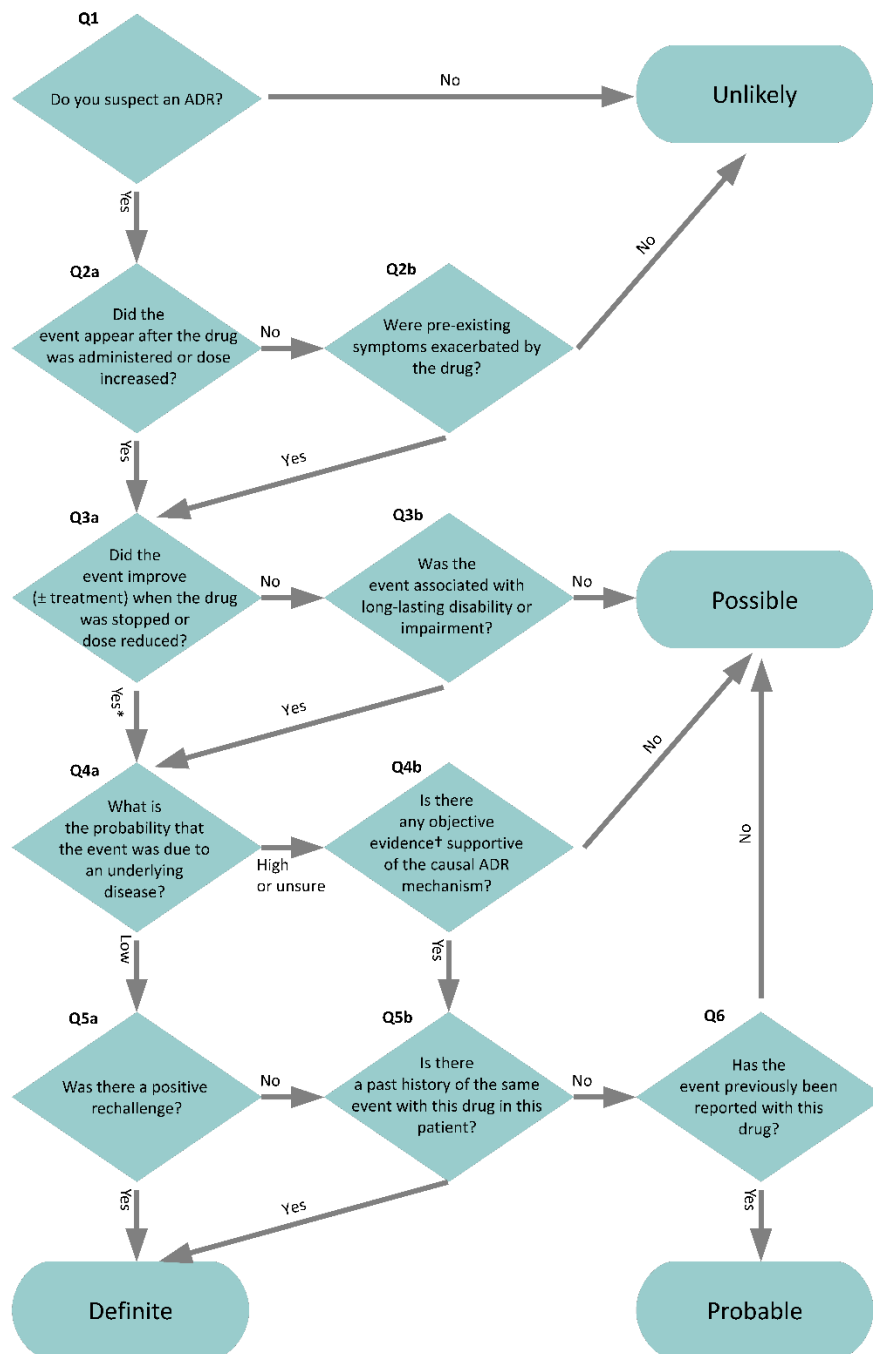


Figure 3.1. The Liverpool ADR Causality Assessment Tool

Numbering of questions as used in this chapter. *Yes or unassessable. Unassessable refers to situations where the medicine is administered on one occasion (e.g. vaccine), the patient receives intermittent therapy (e.g. chemotherapy), or is on medication which cannot be stopped (e.g. immunosuppressants). †Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient. LCAT reproduced under a Creative Commons Attribution License. Source: Gallagher³¹

As the LCAT showed early promise of ease of use and high IRA, we considered its use in a prospective survey of ADRs resulting in admission to the medical wards of four hospitals in South Africa, which we have since published¹⁰⁵. In order to make an informed choice of causality assessment methodology to use in the survey¹⁰⁵, we compared the IRA obtained with the LCAT with that obtained with the WHO-UMC system in a sample of cases from our survey¹⁰⁵. Secondary aims were to describe the distribution of outcomes achieved with each method, and to investigate whether disagreements on the LCAT outcome could be traced back to specific decision points in the algorithm.

3.3 Methods

3.3.1 Design

This study was a two-arm IRA study, using a sample of cases identified as suspected ADR-related admissions during our hospital-based survey. In one arm of the study, we measured the IRA achieved when raters used the WHO-UMC, and we measured the IRA achieved when raters used the LCAT on the same cases in the second arm of the study. A novel aspect of our study design was to eliminate the need for a washout period between the two arms by using an incomplete, randomised design. Instead of having each rater assess each case by each method, our design used block randomisation to randomly allocate causality assessment methods to cases and raters, such that each case was assessed by a new random half of raters using one method and by the remaining raters using the second method.

In our survey, we reviewed the folders of all adults admitted to the medical wards of four South African hospitals over a 30-day period¹⁰⁵. We identified suspected ADR-related admissions with the aid of a screening tool adapted from Rozich¹²². We defined an ADR according to the definition by Aronson and Ferner¹⁹. We did not regard cases of intentional drug overdose as ADRs. We recorded data from patients' clinical hospital

records; we did not augment missing data from primary care sources. We received ethical approval from the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (reference numbers 576/2011 and 828/2015.) The research constituted non-interventional, anonymised chart review of information documented during routine clinical practice, and did not elicit any information directly from patients. We did not seek individual patient consent. This was approved by the Human Research Ethics Committee.

Four raters were purposefully chosen from our Department to perform the causality assessments. They were a physician/internist ('Rater 1'), two clinical pharmacists ('Rater 2' and 'Rater 3'), and a clinical pharmacologist ('Rater 4'), all with extensive experience in various pharmacovigilance roles.

We drew a random sample of ten cases from the 289 admissions flagged as suspected ADR-related admissions in our survey (total 1,951 admissions). We used these ten cases in a self-guided training session on the use of the LCAT and the WHO-UMC system. None of the raters had experience in using the LCAT prior to the training session, but all were familiar with ADR causality assessment by global introspection, although not necessarily with the WHO-UMC system.

We drew a second random sample of 48 cases after excluding the ten cases used in training. We allowed only one randomly selected admission per patient into the sample to avoid clustering of patients re-admitted. Similarly, when more than one drug was suspected to have caused an ADR, one of the suspect drugs was selected at random. Thus, we ended up with 48 unclustered drug-event pairs as samples for this analysis.

Each of the four raters performed causality assessment on the case from a standardised case printout of summary demographic, clinical, laboratory and drug history information in our database. The order of assessment was randomised for each

rater to minimise the effect of learning. Communication between raters about the cases was not allowed, but raters were not blinded as to the purpose of their assessments and were allowed unrestricted access to reference sources. All assessments were recorded on a paper case assessment sheet. Raters were requested to trace the path of their assessment process when using the LCAT and to note any problems encountered in order to identify potentially problematic decision points on the LCAT flowchart.

In case no outcome category was achieved on the LCAT (e.g. the rater 'got stuck' in the flowchart due to a lack of information to answer a question), or a rater indicated they were unable to choose between two outcome categories, the outcome was coded as 'unassessable'. We requested raters not to use the 'conditional' outcome category on the WHO-UMC system. As a result of these factors, both methods yielded outcomes over five categories: 'definite' (the term 'certain' was considered equivalent), 'probable', 'possible', 'unlikely', and 'unassessable'.

3.3.2 Analysis

We generated a visual representation of each rater's distribution of outcomes against the mean distribution of outcomes, for each method, as a crude indicator whether our raters exhibited cognitive bias in selecting outcome categories.

To compare the methods' IRA, we calculated agreement proportions, kappa statistics, and the intraclass correlation coefficient as follows:

1. We defined exact agreement to exist between two raters using the same method if they assessed the case to the same outcome category (including both raters considering the case to be 'unassessable'), while extreme disagreement was defined to exist if they assessed the case to non-adjacent outcome categories (i.e. one 'probable' and the other 'unlikely', or one 'definite' and the other 'possible', or one 'definite' and the other 'unlikely'). Extreme

disagreement was also defined to exist where one rater considered the case to be unassessable while the other did not. We calculated the proportion of exact agreement and extreme disagreement between each rater-pair, and we calculated the proportion of specific agreement on each outcome category^{123,124}.

2. We calculated pairwise Cohen's kappas among each of the six pairs of raters in an unweighted and a linearly weighted version, for each method. We tested for marginal homogeneity among each rater-pair's assessments by performing the Stuart-Maxwell chi-square statistic on a cross-tabulation of the two raters' assessments. We also calculated an overall ('global') kappa, for each method, in an unweighted and a linearly weighted version, with 95% confidence intervals constructed by a jackknife technique, using methodology proposed by Abaira¹²⁵ suitable for incomplete study designs such as ours. For the weighted kappa calculations, we excluded all cases where one or both raters considered the case to be 'unassessable'; the weight matrix was thus a 4x4 matrix.
3. We also calculated an intraclass correlation coefficient on each method, using a one-way absolute-agreement single-measures random-effects model (ICC1,1 in the classification of Shrout and Fleiss¹²⁶). We again excluded cases where one or both raters considered the case to be 'unassessable' from this calculation.
4. In a sensitivity analysis, we investigated for variability in agreement outcomes when considering 'unassessable' ratings as missing data.

To identify potentially problematic decision-making nodes on the LCAT flowchart, we cross-tabulated raters' total number of positive and negative responses to each question. We also grouped raters into two groups (pharmacists versus clinicians) and cross-tabulated the groups' total number of positive and negative responses to each question. To interpret these cross-tabulations, we calculated chi-square statistics or performed Fisher's exact test, as appropriate. Lastly, for each of the LCAT questions we

calculated the proportion of specific agreement achieved case-wise between the two raters¹²³.

Data analysis was performed in Stata version 13.1 (Stata Corporation, College Station, Texas, USA), including the macro 'kappa2'¹²⁷ to calculate the Abairra kappa and its confidence intervals. We considered p-values <0.05 as significant.

3.4 Results

3.4.1 Subject characteristics

The 48 sampled patients had a median age of 51.5 years (interquartile range 33.5 to 62.5 years) and 30/48 (63%) were female. 24/48 (50%) were known HIV-infected, and 5/48 (10%) were on treatment for tuberculosis. The sampled drug suspects included antiretrovirals (lamivudine, tenofovir, zidovudine, efavirenz, emtricitabine, and stavudine, totalling 18 cases), cardiac agents (furosemide, hydrochlorothiazide, spironolactone, enalapril, perindopril, and nifedipine, totalling 8 cases), hypoglycaemic agents (5 cases), antituberculosis agents (4 cases), and warfarin (4 cases).

3.4.2 Distribution of outcomes and investigation for cognitive bias

The 48 cases sampled yielded 96 outcomes on each method. The WHO-UMC system resulted in 8 'definite', 11 'probable', 30 'possible', 34 'unlikely', and 13 'unassessable' outcomes. The LCAT resulted in 3 'definite', 29 'probable', 25 'possible', 32 'unlikely', and 7 'unassessable' outcomes. Individual raters' distribution of outcomes is given in Appendix xxxiii. Appendix xxxiv plots the difference between each rater's individual distribution of outcomes and the four raters' mean distribution of outcomes when using the WHO-UMC system; Appendix xxxv shows identical plots when raters used the LCAT. These plots suggest that, regardless of the causality assessment method used, Rater 2 preferentially assessed cases as 'probable', Rater 3 preferentially assessed cases as 'possible' and Rater 4 preferentially assessed cases as 'unlikely'.

3.4.3 Interrater agreement

Table 3.1 shows rater-pairs' cross-tabulated outcomes when using the WHO-UMC system and Table 3.2 shows their outcomes when using the LCAT.

Table 3.1. Pairwise distribution of outcomes, when using the WHO-UMC system

	Definite	Probable	Possible	Unlikely	Unassessable
Unassessable	0	1	1	1	5
Unlikely	0	0	7	13	
Possible	0	4	9		
Probable	0	3			
Definite	4				

Table 3.2. Pairwise distribution of outcomes, when using the LCAT

	Definite	Probable	Possible	Unlikely	Unassessable
Unassessable	0	1	1	3	1
Unlikely	0	2	9	9	
Possible	0	9	3		
Probable	1	8			
Definite	1				

Using the WHO-UMC system, exact agreement between the two raters occurred in 34 of 48 cases (0.71, range 0.50 to 1.0 among the six rater-pairs). Two rater-pairs (the pair of clinicians and one of the internist-clinical pharmacist pairs) obtained exact agreement on all cases. Using the LCAT, exact agreement occurred in 22 of 48 cases (0.46, range 0.25 to 0.80 among the six rater-pairs, highest for the pair of clinicians). The difference in exact agreement was 0.25 (95% CI 0.025 to 0.47, McNemar's chi-square $p = 0.023$). Extreme disagreement occurred with the WHO-UMC system in 3 of 48 cases (0.063) and with the LCAT in 7 of 48 cases (0.15) (Table 3.3).

Table 3.3. Exact agreement (EA), extreme disagreement (ED), unweighted pairwise Cohen kappa (κ) and linearly-weighted pairwise Cohen kappa (κ_w) for each of six rater-pairs, using two different causality assessment methods

Rater-pair	WHO-UMC					LCAT				
	<i>n</i>	EA	ED	κ	κ_w	<i>n</i>	EA	ED	κ	κ_w
Raters 1 and 2	7	1.0	0	1.0	1.0	8	0.25	0.13	0.094	0.22
Raters 1 and 3	8	0.50	0	0.35	0.53	9	0.33	0	0.13	0.077
Raters 1 and 4	6	1.0	0	1.0	1.0	10	0.80	0.10	0.71	0.88
Raters 2 and 3	10	0.60	0.10	0.49	0.67	6	0.33	0.17	0.14	0.35
Raters 2 and 4	9	0.56	0.11	0.33	0.52	8	0.50	0.13	0.27	0.55
Raters 3 and 4	8	0.75	0.13	0.60	0.77	7	0.43	0.43	0.32	0.55

All cross-tabulations were marginally homogeneous, measured by Stuart-Maxwell chi-square statistic. EA: exact agreement. ED: extreme disagreement. κ : unweighted pairwise Cohen kappa. κ_w : linearly-weighted pairwise Cohen kappa.

The proportion of specific agreement for each outcome category when using the WHO-UMC system was: for 'definite' 1.0, for 'probable' 0.55, for 'possible' 0.60, for 'unlikely' 0.76, and for 'unassessable' 0.77. The proportion of specific agreement for each outcome category when using the LCAT was: for 'definite' 0.67, for 'probable' 0.55, for 'possible' 0.24, for 'unlikely' 0.56, and for 'unassessable' 0.29.

Unweighted pairwise Cohen kappas (Table 3.3) on the WHO-UMC system ranged from 0.33 to 1.0 (mean 0.63, 95% CI 0.31 to 0.95) and on the LCAT from 0.094 to 0.71 (mean 0.28, 95% CI 0.037 to 0.52). The difference in means was 0.35 (95% CI 0.047 to 0.65) and non-zero at $p = 0.031$. Linearly weighted pairwise Cohen kappas (Table 3.3) ranged from 0.52 to 1.0 on the WHO-UMC system (mean 0.74, 95% CI 0.51 to 0.98), and from 0.077 to 0.88 on the LCAT (mean 0.44, 95% CI 0.14 to 0.74). The difference in means was 0.31 (95% CI 0.011 to 0.60) and non-zero at $p = 0.045$.

The overall unweighted Abaira kappa on the WHO-UMC system was 0.61 (95% CI 0.43 to 0.80) and the linearly weighted Abaira kappa 0.73 (95% CI 0.57 to 0.91). On the LCAT, overall unweighted Abaira kappa was 0.27 (95% CI 0.074 to 0.46) and linearly weighted Abaira kappa 0.45 (95% CI 0.25 to 0.67).

The ICC_{1,1} was 0.86 (95% CI 0.74 to 0.92) on the WHO-UMC system and 0.61 (95% CI 0.39 to 0.77) on the LCAT.

The results of the sensitivity analysis (Appendix xxxvi) were similar to those of the main analysis.

3.4.4 Investigation for potentially problematic questions on the LCAT

We observed only 13 out of the 36 'paths' theoretically possible on the LCAT flowchart among our results. The top three traces occurred 31 times, 21 times, and 20 times, respectively (Appendix xxxvii). On two cases raters disagreed on responses to the LCAT questions yet still arrived at the same outcome. Of 59 traces which proceeded beyond Q1 (see Figure 3.1 for our numbering of the LCAT questions), 35/59 (59%) did not reach Q5a, 29/59 (49%) did not reach Q6, and 27/59 (46%) did not reach Q5b.

Cross-tabulating raters' positive and negative responses to each question on the LCAT (Table 3.4), we found disproportionate responses to two questions, Q4a and Q4b. The odds ratio for a positive response on Q4a from a clinician, compared to a pharmacist, was 5.1 (95% CI 1.6 to 16, $p = 0.006$). Q4b had 22 negative responses and 9 positive responses. Seven of the positive responses came from one pharmacist rater, and there were no positive responses from either clinician rater.

Table 3.4. Distribution of raters' responses to LCAT questions

Question ^a	Negative response ^b				Positive response ^c				p-value ^d
	Rater 1	Rater 2	Rater 3	Rater 4	Rater 1	Rater 2	Rater 3	Rater 4	
1	9	8	4	10	16	14	14	15	0.66
2a	0	0	0	1	16	14	14	14	0.73
2b	0	0	0	1	0	0	0	0	
3a	2	3	1	2	14	11	13	11	0.79
3b	1	0	0	1	1	3	1	1	0.57
4a	6	8	13	4	9	6	1	8	0.008
4b	6	1	11	4	0	7	2	0	<0.001
5a	9	6	1	7	0	0	0	1	0.63
5b	8	13	2	7	1	0	1	0	0.15
6	0	1	0	0	8	12	2	7	1.00

^a See Figure 3.1 for our numbering of questions on the LCAT flowchart. ^b Negative responses: 'High/Unsure' on question 4a, 'No' on all other questions. ^c Positive responses: 'Yes/Unassessable' on question 3a, 'Low' on question 4a, 'Yes' on all other questions. ^d Chi-square or Fisher's exact test, as appropriate.

The proportions of specific agreement for each of the LCAT questions are given in Appendix xxxviii. Q4a showed the worst agreement (among questions with more than

10 paired responses), with the proportion of both positive and negative agreement on this question lower than 0.70.

Subjectively, our raters commented that they were unclear how to proceed on the LCAT flowchart in situations where (a) the drug was not withdrawn (as opposed to 'cannot be withdrawn'), (b) the patient died, (c) the patient's outcome (improved / deteriorated) was different than that of the event being considered, (d) there was a second potential drug cause (the LCAT gives no instruction on dealing with situations when combinations of drugs are implicated in one ADR, and only refers to drugs in the singular), and (e) laboratory results were not available. All four raters also independently reported being 'channelled' by the LCAT towards a 'probable' outcome when they intuitively considered a case to be 'definite'. There were three cases (a case of warfarin-associated haematuria, a case of isoniazid-associated liver injury, and a case of insulin-associated hypoglycaemia) where both raters using the WHO-UMC system assessed the case as 'definite', while both raters using the LCAT assessed the case as 'probable'.

3.5 Discussion

We were unable to replicate the high IRA, or the high proportion of 'definite' outcomes, reported by the developers of the LCAT. Instead, we found the LCAT's IRA, and its proportion of 'definite' outcomes, to be lower than those achieved by a method of global introspection. We identified potential explanations for the finding of lower IRA by tracing raters' decisional process on the LCAT flowchart.

To our knowledge, this is the first study which measured the IRA of the LCAT since its development. Previous studies have reported the LCAT's sensitivity and specificity (against a 'gold standard' of consensual expert judgement) as identical to that of the Naranjo algorithm¹²⁸; its distribution of outcomes (in a paediatric hospital-based survey) as similar to that of the Naranjo algorithm¹²⁹; and the exact agreement

obtained on the LCAT (between trainee specialists and a predefined 'correct' assessment by multidisciplinary panel) as ranging from 20% to 65%¹³⁰.

Expert clinical pharmacologists independently assessing ADR case reports by global introspection have been shown to disagree on ADR causality assessment, as well as the presence of drug-drug interactions, the contribution of the ADR to patients' admission and duration of hospitalisation, the presence of severe morbidity and ADR-related sequelae, and the contribution of the ADR to death¹³¹. As a result, global introspection has been criticised as 'neither reproducible, valid, nor accountable'¹³², and it seems intuitive that an explicit, algorithmic method should result in higher IRA than an implicit, subjective method such as global introspection. This, in fact, had been shown by Naranjo *et al.* in the original publication on the development of their method, which used published case reports to determine IRA: on only an implicit ADR causality assessment comparable to the WHO-UMC system, pairwise unweighted kappa ranged from 0.21 to 0.37, but by applying the Naranjo algorithm, pairwise unweighted kappa improved to range from 0.69 to 0.86²⁹.

Since the development of the Naranjo algorithm, however, two studies have compared its IRA to the IRA achieved on a method of global introspection and failed to replicate the higher IRA the Naranjo developers showed. First, in a routine hospital-based ADR surveillance programme, three paediatric clinical pharmacologists achieved similar IRA whether using implicit causality categories or the Naranjo algorithm¹³³. A more recent study from the Liverpool group also found similar IRA whether using the WHO-UMC system or the Naranjo algorithm¹³⁴. These studies raised the question whether the Naranjo algorithm is transferable to settings where users are unfamiliar with it or information is less complete than in published case reports.

Similar to the above two studies, which failed to replicate IRA reported by the Naranjo algorithm's developers, we were unable to replicate the IRA reported by the LCAT developers³¹. Whereas its developers found the LCAT's linearly weighted pairwise

kappas to range from 0.50 to 0.85 and its 'global' unweighted kappa to be 0.60 (95% CI 0.54 to 0.67)³¹, we found its linearly weighted pairwise kappas to range from 0.077 to 0.88 and its 'global' unweighted kappa to be 0.27 (95% CI 0.074 to 0.46).

We found the LCAT's IRA to be lower than that of the WHO-UMC system using a range of measures. The LCAT's calculated kappa statistics could be considered 'fair' to 'moderate' in terms of the frequently-used Landis and Koch interpretation¹³⁵, a category lower than WHO-UMC system's kappa statistics, which were 'moderate' to 'substantial'. Similarly, the LCAT's ICC (0.61) was a category lower than that of the WHO-UMC system (0.86) in the interpretation of Cicchetti¹³⁶ ('good' versus 'excellent'). Moreover, proportions of exact agreement and extreme disagreement among individual rater-pairs, and proportions of specific agreement on each category were consistently higher for the WHO-UMC system than the LCAT.

A possible explanation for the WHO-UMC system's higher IRA could be the LCAT's potential for disregarding information that may have otherwise contributed to the decision-making process. Loss of information can firstly occur in any algorithm designed with the potential to bypass some decision-making nodes. As pointed out previously, the LCAT flowchart is structured in such a way that some questions cannot be reached under certain circumstances¹²⁸. We found that potential information on rechallenge and on previous ADRs to the drug was only taken into account in about half of assessments on the LCAT, as those specific questions were simply not reached by raters. Secondly, loss of information can occur in an algorithm when the rater makes a pragmatic choice when 'the true answer may be somewhere in-between' the options offered by the algorithm¹³⁷. Our study was not designed to measure how often this may have happened, although our raters anecdotally reported some such instances.

In our study, both causality assessment methods resulted in assessments across all outcome categories. However, the WHO-UMC system resulted in proportionally more

'definite' and 'unassessable' outcomes, while the LCAT resulted in relatively more 'probable' outcomes. This contrasts with the LCAT developers' finding that 'definite' outcomes were most common³¹.

The LCAT's 'channelling' towards 'probable' outcomes has previously been discussed¹²⁸. It was pointed out that when a rater is unsure about the likelihood that an underlying disease caused the event, she is forced to disregard information about a positive rechallenge (which is generally considered to be a strong indicator of drug causation), as she is steered away from that question in the LCAT flowchart¹²⁸. It was also pointed out that the design of the LCAT requires either a positive rechallenge or a past history of the same event with the same drug in the same patient in order to arrive at a 'definite' outcome, and that those conditions are seldom met in routine clinical practice¹²⁸.

It would appear that the LCAT, though designed to yield more 'definite' outcomes than the Naranjo algorithm, is unlikely to achieve this when using available routine clinical data as was the case in our study design. Nevertheless, in the absence of a gold standard, it remains unclear whether a method with a predilection for 'probable' outcomes or one with a predilection for 'definite' outcomes should be regarded as preferable.

We postulate some reasons for the differences between our findings and those of the LCAT developers³¹. First, although both studies' data came from prospective hospital-based ADR surveys, our study population were adults while theirs were children. A number of their patients presented with repeated episodes of febrile neutropenia attributed to cancer chemotherapy; our survey excluded oncology wards but included a large proportion of patients infected by HIV, and antiretroviral therapy was frequently suspected of causing ADRs. Second, there were differences between the raters in the two studies: we used only four raters versus the LCAT developers' seven, and our raters had a smaller spectrum of expertise. Our raters were not involved in the

development of the LCAT, nor were they, before a training session, familiar with its use, and the LCAT developers had shown that IRA on the LCAT increased as their raters' familiarity with the method grew. Third, our assessments were based on available clinical case data summarised and captured onto a database, and not on raw case data in patient folders or data specifically collected for study purposes. Together with our use of a sensitive but non-specific trigger tool for case identification, this resulted in a high frequency of suspected ADRs ultimately assessed 'unlikely' and 'unassessable', unlike the LCAT developers' distribution of outcomes.

In addition to the methodological differences between the studies, we identified two questions in the LCAT flowchart as points of significant divergence. These were Q4a ('What is the probability that the event was due to an underlying disease?') and Q4b ('Is there any objective evidence supportive of the causal ADR mechanism?'). Answering these two questions requires some clinical judgement, and our pharmacist-raters answered these questions differently from our clinician-raters. This is not a novel finding: Naranjo *et al.* reported in their original paper that a question on alternative causes of the purported ADR resulted in most disagreement between their raters, with pharmacists answering the question differently to physicians²⁹. Another early study tracing two raters' decision-making process on the Kramer algorithm¹³⁸ also found that decision nodes requiring raters to express some form of subjective judgement resulted in disagreement more frequently than decision nodes with 'factual' questions¹³⁹.

A modification of the LCAT was recently published, in which the modified tool was used in a pharmacogenetic study to phenotypically link one ADR (pancreatitis) to one class of drugs (thiopurines)¹⁴⁰. This modification *inter alia* discarded four questions, including Q4b, rephrased four questions, including Q4a, and swapped the order of Q5a and Q4a. While the authors of the modification provided neither a justification for the modification, nor evidence of the modified tool's validity, and while it is debatable whether the modified tool would be useful outside such a restricted setting, it is

tempting to speculate that they may have been faced with some of the same problems on Q4a and Q4b we have found.

We would suggest that improvements to the LCAT may be warranted. Such improvements should aim to reduce the tool's potential for loss of information, should focus on maximising agreement on the two 'subjective' questions identified as sources of disagreement, and should provide guidance on how to answer questions in ambiguous situations.

Limitations of our study include that case summaries may have lacked detailed information, that raters had prior familiarity with global introspection as a methodology but not with the LCAT, and that raters were aware of the purpose of their assessments. We conducted self-guided training in the use of the LCAT, which was not standardised; a training module¹³⁰ is still under development by the authors of the LCAT. We used a small convenience sample of raters, limiting the generalizability of our results. It appears that bias existed in raters' preference for certain outcome categories, which may have influenced our overall kappa estimates and ICC. However, bias was not present when calculating pairwise Cohen kappas (cross-tabulations were marginally homogeneous in all instances). For these reasons further interrater (and intra-rater) agreement studies would be essential to investigate the LCAT's usefulness, as well as that of any modifications to it.

3.6 Conclusion

Causality assessment of ADRs is an expression of the rater's uncertainty in assessing the strength of evidence in favour of drug causation, rather than an expression of any inherent quality of the ADR itself. Maximising IRA has therefore been criticised for 'suppressing' disagreement, when disagreement *per se* is valuable information¹⁴¹. Nevertheless, IRA remains a widely used way to quantify a method's repeatability. Our study suggests that causality assessment using the LCAT is less repeatable than a

method of global introspection, when it is used outside of the setting in which it was developed.

Chapter 4 Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey

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Citation

Mouton JP, Mehta U, Parrish AG, *et al.* Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. *British Journal of Clinical Pharmacology*. 2015;80(4):818-826.

DOI: 10.1111/bcp.12567

The original publication is included as Appendix iii. Supplementary materials are included from Appendix xxxix to Appendix xl.

4.1 Abstract

Aims Fatal adverse drug reactions (ADRs) are important causes of death, but data from resource-limited settings are scarce. We determined the proportion of deaths in South African medical inpatients attributable to ADRs, and their preventability, stratified by human immunodeficiency virus (HIV) status.

Methods We reviewed the folders of all patients who died over a 30-day period in the medical wards of four hospitals. We identified ADR-related deaths (deaths where an ADR was 'possible', 'probable' or 'certain' using WHO-UMC criteria and where the ADR contributed to death). We determined preventability according to previously published criteria.

Results ADRs contributed to the death of 2.9% of medical admissions and 56 of 357 deaths (16%) were ADR-related. Tenofovir, rifampicin and co-trimoxazole were the most commonly implicated drugs. 43% of ADRs were considered preventable. The following factors were independently associated with ADR-related death: HIV-infected patients on antiretroviral therapy (adjusted odds ratio (aOR) 4.4, 95% confidence interval (CI) 1.6, 12), exposure to more than seven drugs (aOR 2.5, 95% CI 1.3, 4.8) and increasing comorbidity score (aOR 1.3, 95% CI 1.1, 1.7).

Conclusions In our setting, where HIV and tuberculosis are highly prevalent, fatal in-hospital ADRs were more common than reported in high income settings. Most deaths were attributed to drugs used in managing HIV and tuberculosis. A large proportion of the ADRs were preventable, highlighting the need to strengthen systems for health care worker training and support.

4.2 Introduction

Adverse drug reactions (ADRs) that result in death, particularly those considered to have been preventable, are of major public health interest. A population-based study in three Swedish counties found that 3% of all deaths were suspected to be due to ADRs, making ADRs the seventh most common cause of death¹¹⁹. This figure agrees with a systematic review⁶⁴ which ranked ADRs among the top six causes of death in the USA.

Most epidemiological data on ADR-related deaths come from hospital-based studies. Depending on the definitions and methods used, ADRs have been implicated in 2.5–18% of in-hospital deaths^{61,142-145}. However, there are limited data on mortality associated with ADRs from resource-limited settings, in particular from settings with high human immunodeficiency virus (HIV) and tuberculosis prevalence. South Africa has implemented the world's largest roll-out of antiretroviral therapy (ART), with just over 2 million people on ART in 2012¹⁴⁶, and has among the highest tuberculosis incidence globally, estimated to be 1000 new cases per 100 000 persons per year in 2012¹⁴⁷.

A previous survey performed by our group at a secondary level hospital in South Africa in 2005⁶¹, showed that HIV-infected persons were twice as likely to be admitted with an ADR compared with persons who were HIV negative or whose HIV status was unknown. In that survey, antiretroviral drugs (ARVs) and drugs used to treat opportunistic infections were frequently implicated as causing ADRs, albeit that the survey was performed early in the ART era, when more toxic ARVs were in use. Thus, there is a need for larger studies to determine the current impact of ADRs on morbidity and mortality in our setting.

We performed a cross-sectional survey in the medical wards of four hospitals in South Africa to determine the mortality attributable to ADRs, to identify the drugs implicated in these ADR-related deaths, to determine the proportion of fatal ADRs that were

preventable and to explore the effect of patients' HIV status on mortality attributed to ADRs.

4.3 Methods

4.3.1 Study design and setting

Between April and September 2013, we identified all patients who died in the medical wards of Groote Schuur Hospital, Edendale Hospital, Cecilia Makiwane Hospital and Frere Hospital, over a 30-day period at each site, by daily scrutiny of ward and/or mortuary administrative records. A description of the sites is included in Appendix xxxix. We included all patients where a decision to admit had been made by the medical team, including those who died in the emergency unit while awaiting transfer to the ward.

4.3.2 Identification of suspected ADRs and causality assessment

We defined an ADR according to the definition of Aronson & Ferner¹⁹, but we did not regard intentional overdoses or cases of immune reconstitution syndrome as ADRs. The assessment process flow is shown in Figure 4.1. Between October 2013 and April 2014, one author (JPM) reviewed each patient's medical notes, medication exposure over the 30 days prior to admission, prescription charts related to the admission, as well as the patient's laboratory data, using a trigger tool¹²² to flag the deaths suspected to be related to ADRs, and additionally flagging all cases where the cause of death was unclear. We did not attempt to augment incomplete data from other sources. For each flagged case, JPM prepared a narrative summary of events, as well as a detailed summary of drug use (codified to five level ATC codes), investigative results and clinical problems (codified to ICD-10 codes).

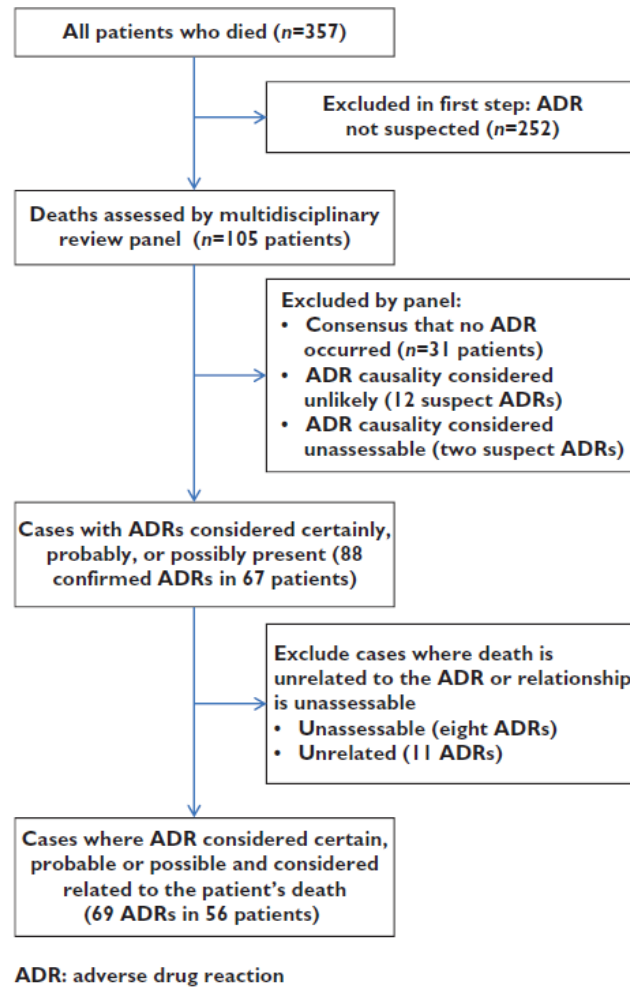


Figure 4.1. Flowchart describing the assessment process

A multidisciplinary review panel consisting of a clinical pharmacologist, a clinical pharmacist, and at least one but up to three physicians/internists met to assess each of the flagged cases for the presence of an ADR and its preventability. Each panellist was provided with the prepared case summaries and an electronic, anonymized copy of the hospital records. For each suspected ADR that was identified by one or more members of the review panel, the panel discussed its causality using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment²⁸, until consensus was reached. For ADRs categorized as ‘possible’, ‘probable’ or ‘certain’, the panel assessed the relationship between the ADR and the death of the patient. We categorized the relationship between ADR and death into one of four categories: (i) the ADR was a major contributor to the death of the

patient, (ii) the ADR contributed to the patient's death, but was not the major contributor, (iii) the ADR was unrelated to the patient's death or (iv) the relationship between ADR and death could not be determined. The panel also decided on the preventability of the ADR using the criteria of Schumock & Thornton³⁶. Where the panel could not reach consensus on the causality or preventability of an ADR, or on its relationship to the patient's death, the majority decision was recorded. In one case, where the panel consisted of four members who were evenly split in opinion over the presence/absence of an ADR, the third physician's opinion was sought following the panel meeting, to obtain a majority decision.

We defined an ADR-related death as a death where the panel held (either in consensus, or in majority) that, firstly, an ADR was 'possible', 'probable' or 'certain', according to the WHO-UMC methodology and that, secondly, the ADR was a major contributor or a contributor to the patient's death. An ADR was considered preventable if any one or more of the Schumock & Thornton criteria was answered in the affirmative.

For every patient who died, we calculated a comorbidity score modified from the Charlson comorbidity score¹⁴⁸. As the original Charlson comorbidity score assigns a score for HIV infection that is probably inappropriately high in the era of ART¹⁴⁹ and as we wanted to explore the independent effect of HIV-infected status with and without antiretroviral therapy, we excluded a diagnosis of HIV/AIDS from the calculation of the modified Charlson comorbidity score. We also calculated a drug count for every patient by counting each drug to which the patient was documented to have been exposed in the period starting three weeks prior to the date of admission and ending on the day of death, excluding vitamin and mineral supplements. For fixed drug combinations, we counted each component drug individually.

4.3.3 Data entry and analysis

Data were entered into a Microsoft Access 2010 database and analyzed using Stata 13.1 (Stata Corporation, College Station, Texas, USA). Continuous variables were summarized using medians and interquartile ranges, as they were non-normally distributed. We explored univariate associations for binary and categorical variables by cross-tabulation, and calculated chi-square statistics or performed Fisher's exact test as appropriate. As data were non-normally distributed, we used the Wilcoxon rank-sum test for between group comparisons of continuous and ordinal variables.

We constructed a multivariate logistic regression model exploring independent associations with ADR-related death. Variables were included in the model based on an a priori decision. We included the following variables in the model: age, sex, comorbidity score, drug count (using a binary variable by cutting the data at the median), HIV infection and antiretroviral treatment status (using a three category variable: HIV-negative or unknown status, HIV-infected and not on ART, HIV-infected on ART), and whether or not patients were being treated for tuberculosis. Assumptions of linearity were checked in the final model. We constructed a similar model, with the addition of the most recent CD4 count, in an analysis restricted to patients known to be HIV-infected. We used a significance level of 0.05.

4.3.4 Ethics

This study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (Reference no. 576/2011). Permission to conduct the research was granted by the respective hospitals' management and/or provincial Departments of Health.

4.4 Results

There were 1951 admissions and 357 deaths during the survey period, for a crude mortality rate of 18 deaths per 100 admissions. At the first level of review, 252 cases were assessed as having no suspected ADRs (Figure 4.1). The multidisciplinary panel reviewed the remaining 105 cases, and concluded that ADR-related causes contributed to the deaths of 56 of the 357 (16%) patients, which represents 2.9% of the 1951 patients admitted over the study period.

Sixty-nine different ADRs (four 'certain', 10 'probable' and 55 'possible', according to the WHO-UMC method) were identified to have contributed to the death of these 56 patients. Of the 56 patients, four had at least one 'certain' ADR, eight at least one 'probable' ADR and the remaining 44 had 'possible' ADRs contributing to death. In 51 cases, the panel reached consensus over the ADRs and contribution to death, while in the remaining five cases the majority of the panel agreed on the ADR, with some dissent. Patient characteristics are summarized in Table 4.1. Appendix xl lists individual patients' characteristics and details of the ADRs.

Table 4.1. Characteristics of patients whose deaths were considered ADR-related, versus patients whose deaths were not considered ADR-related

	All deaths	ADR-related deaths	Other deaths	p-value
All patients: n	357	56	301	
Females: n (%)	184 (52%)	30 (54%)	154 (51%)	p=0.741
Age: median [IQR]	53 [38, 70]	52.5 [33, 65.5]	53 [39, 72]	p=0.2209
Known HIV infected (%)	135 (38%)	31 (55%)	104 (35%)	p=0.003
On treatment for TB (%)	55 (15%)	14 (25%)	41 (14%)	p=0.030
Number of drugs exposed to: median [IQR]	7 [5, 11]	9 [7, 11]	7 [4, 11]	p=0.0008
Modified Charlson co-morbidity score: median [IQR]	2 [0, 3]	2 [1, 3]	2 [0, 3]	p=0.0246
Time from admission to death in days: median [IQR]	5 [3, 10]	6.5 [3, 11.5]	5 [3, 10]	p=0.3478
HIV-infected patients only: n	135	31	104	
Females: n (%)	61 (45%)	15 (48%)	46 (44%)	p=0.683
Age: median [IQR]	37 [30, 44]	37 [31, 52]	37 [30, 43]	p=0.3393
CD4-count: median [IQR] *	52 [19, 167]	126 [32, 299]	41 [19, 109]	p=0.0509
On ART (%)	66 (49%)	20 (65%)	46 (44%)	p=0.047
On treatment for TB (%)	45 (33%)	12 (39%)	33 (32%)	p=0.469
Number of drugs exposed to: median [IQR]	9 [6, 12]	9 [7, 10]	9 [6, 12]	p=0.8053

Modified Charlson co-morbidity score: median [IQR]	0 [0, 2]	2 [0, 2]	0 [0, 2]	p=0.0579
Time from admission to death in days: median [IQR]	5 [3, 8]	4 [2, 7]	5.5 [3, 8.5]	p=0.2082

* 20 patients missing data

ADR: adverse drug reaction, HIV: human immunodeficiency virus, ART: antiretroviral therapy, IQR: interquartile range

Thirty of the 69 ADRs (43%) were considered preventable according to the Schumock & Thornton criteria³⁶. Most often, this was because the drug was not considered appropriate for the patient, or because laboratory monitoring was inadequate (Table 4.2). In 28 of the 56 deaths (50%), at least one ADR was considered preventable.

Table 4.2. Frequency at which various preventability factors were observed amongst 69 ADRs considered to have contributed to the death of 56 patients

Schumock and Thornton criterion	No of occurrences
Was the drug involved in the ADR not considered appropriate for the patient's clinical condition based on published guidelines, clinical studies, abstracts, case reports, case series?	16
Was the dose, route and frequency of administration not appropriate for the patient's age, weight, or disease state (e.g. renal/hepatic function) based on published literature (e.g. South African Medicines Formulary, MIMS)	5
Was required therapeutic drug monitoring or other laboratory test not performed?	11
Was there a history of allergy or previous reaction to the drug?	0
Was a drug interaction involved in the reaction?	4
Was the serum drug concentration above the therapeutic range documented in adults?	0
Did compliance possibly contribute to the reaction?	2

ADR: adverse drug reaction

Of the 357 deaths, 135 patients (38%) were known to be HIV-infected, 39 (11%) were known to be HIV-negative and 183 (51%) had no HIV serology result. In the 135 HIV-infected patients, a higher proportion of patients who died from ADR-related causes were taking ARV therapy: 20/31 (65%) vs. 46/104 (44%). Of 55 patients on treatment for tuberculosis, 45 (82%) were co-infected with HIV.

Amongst the 56 patients with ADR-related deaths, 31 were HIV-infected, four were HIV-seronegative and the HIV status of 21 patients was unknown. When comparing the 31 HIV-infected patients to the 25 patients with negative or unknown HIV serology status, we found that ADR-related deaths in HIV-infected persons occurred at a significantly

younger age (median [IQR] years 37 [31, 52] vs. 66 [55, 79], $P < 0.00005$), and in persons with a lower comorbidity score (median [IQR] score 2 [0, 2] vs. 3 [2, 4], $P = 0.0010$).

There was no significant difference in the drug count (median [IQR] count 9 [7, 10] vs. 9 [7, 13], $P = 0.5071$), proportion female (48% vs. 60%, $P = 0.386$) or in the proportion of cases with at least one preventable ADR (48% vs. 52%, $P = 0.788$).

We constructed a multivariate logistic regression model to identify independent associations with ADR-related death (Table 4.3). HIV-infected patients on ART had increased odds of ADR-related death (adjusted odds ratio (aOR) 4.4, 95% confidence interval (CI) 1.6, 12). However, the odds of ADR-related death in HIV-infected patients not on ART was not significantly different from the reference group (adjusted OR 2.4, 95% CI 0.78, 7.1). Exposure to more than seven medicines prior to death was independently associated with increased odds of ADR-related death (aOR 2.5, 95% CI 1.3, 4.8). Increasing modified Charlson comorbidity score was associated with increased odds of ADR-related death (aOR 1.3, 95% CI 1.1, 1.7, for a one unit increase in score). Treatment for tuberculosis was associated with ADR-related death on univariate, but not on multivariate analysis. Age and sex were not associated with ADR-related death.

Table 4.3. Multivariate logistic regression model for the association between risk factors and ADR-related death (n=357)

Variable	Patients, n (%)	Crude Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)	Wald test p-value
Sex	357			
Male	173 (48%)	1	1	
Female	184 (52%)	1.1 (0.62 to 2.0)	1.2 (0.64 to 2.2)	0.581
Age*	357	0.91 (0.78 to 1.1)	1.1 (0.83 to 1.3)	0.644
HIV group	357			
HIV serology negative or unknown	222 (62%)	1	1	
HIV-infected and not on ART	69 (19%)	1.5 (0.69 to 3.2)	2.4 (0.78 to 7.1)	0.127
HIV-infected and on ART	66 (18%)	3.4 (1.8 to 6.7)	4.4 (1.6 to 12)	0.003
TB infection status	357			
Not on treatment for TB	302 (85%)	1	1	
On treatment for TB	55 (15%)	2.1 (1.1 to 4.2)	1.2 (0.53 to 2.6)	0.689
Drug count	357			

≤ 7 drugs	181 (51%)	1	1	
> 7 drugs	176 (49%)	3.4 (1.8 to 6.3)	2.5 (1.3 to 4.8)	0.009
Modified Charlson comorbidity score†	357	1.2 (1.0 to 1.5)	1.3 (1.1 to 1.7)	0.009

* Included in the model as a continuous variable. The odds ratio is for a ten-year increase in age.

† The odds ratio is for a one-unit increase in the comorbidity score.

ADR: adverse drug reaction, ART: antiretroviral therapy, TB: tuberculosis

To explore independent predictors of ADR-related death in HIV-infected patients, we constructed a second multivariate model restricted to the 115 patients known to be HIV-infected with complete data for all variables in the model (Table 4.4), including the variables above and CD4 count. After adjustment for age, sex, CD4 count, ART, tuberculosis treatment and modified Charlson score, only exposure to more than seven medicines prior to death remained significantly associated with increased odds of ADR-related death (aOR 3.6, 95% CI 1.1, 12). ART and CD4 count were associated with ADR-related death on univariate, but not on multivariate analysis (which may be due to lack of power).

Table 4.4. Multivariate logistic regression model for the association between risk factors and ADR-related death in HIV-infected persons (n=115)

Variable	Patients, n (%)	Crude Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)	Wald test p-value
Sex	115			
Male	61 (53%)	1	1	
Female	54 (47%)	1.4 (0.59 to 3.4)	1.2 (0.47 to 3.2)	0.664
Age*	115	1.3 (0.88 to 2.0)	1.3 (0.80 to 2.0)	0.305
CD4-count †	115	1.1 (1.0 to 1.3)	1.1 (0.98 to 1.3)	0.088
Antiretroviral therapy	115			
Not on ART	58 (50%)	1	1	
On ART	57 (50%)	2.9 (1.1 to 7.3)	2.4 (0.86 to 6.6)	0.096
TB infection status	115			
Not on treatment for TB	75 (65%)	1	1	
On treatment for TB	40 (35%)	1.5 (0.62 to 3.7)	1.1 (0.42 to 3.1)	0.802
Drug count	115			
≤ 7 drugs	41 (36%)	1	1	
> 7 drugs	74 (64%)	3.9 (1.2 to 12)	3.6 (1.1 to 12)	0.041
Modified Charlson comorbidity score ‡	115	1.3 (0.95 to 1.9)	1.2 (0.84 to 1.8)	0.281

* Included in the model as a continuous variable. The odds ratio is for a ten-year increase in age.

† Included in the model as a continuous variable. The odds ratio is for an increase of 50 cells / mm³.

‡ The odds ratio is for a one-unit increase in the comorbidity score.

ADR: adverse drug reaction, ART: antiretroviral therapy, TB: tuberculosis

The drugs implicated in ADR-related deaths are listed in Table 4.5. The two most common ADRs contributing to death were renal failure and drug-induced liver injury. Drug-induced renal failure occurred in 23 patients, with tenofovir implicated as the cause in 14 (61%) of these. In all 14 of these cases, renal failure was considered 'possibly' related to tenofovir, mostly because of concomitant drug-related causes (four cases) or concomitant disease-related causes (eight cases). Other causal drugs identified (alone or in combination) were co-trimoxazole (three cases), rifampicin (two cases), furosemide (two cases), co-amoxiclavulanic acid (two cases) and ibuprofen, enalapril, spironolactone, ciprofloxacin, aciclovir and indometacin (one case each). In 12 of these 23 cases (52%), the ADR was considered preventable, because of inadequate laboratory monitoring (seven cases), inappropriate use of the drug (five cases) and/or inappropriate dosing (two cases). Drug-induced liver injury occurred in 10 patients. In seven cases the causal drug was assessed to be an antituberculosis agent (rifampicin, isoniazid and/or pyrazinamide), and in three cases co-trimoxazole was implicated (alone or in combination with other drugs). Fluconazole, erythromycin and sodium valproate were each implicated once. In two of these 10 cases the ADR was considered to have been preventable. On both occasions use of the drug was not considered appropriate.

Table 4.5. Drugs implicated in ADR-related deaths, grouped according to ATC drug classes

Second-level ATC Drug Class*	Drugs*
A06 Drugs for constipation (1)	sodium sulfate / polyethylene glycol (1)
A10 Drugs used in diabetes (5)	insulin (4); metformin (1)
B01 Antithrombotic agents (7)	warfarin (2); heparin (1); enoxaparin (1); aspirin (3)
B05 Blood substitutes and perfusion solutions (1)	sodium chloride (1)
C02 Antihypertensives (2)	prazosin (1); hydralazine (1)
C03 Diuretics (9)	hydrochlorothiazide (2); furosemide (5); spironolactone (2)
C07 Beta blocking agents (2)	atenolol (2)
C08 Calcium channel blockers (2)	amlodipine (2)
C09 Agents acting on the renin-angiotensin system (3)	enalapril (2); perindopril (1)
H02 Corticosteroids for systemic use (3)	prednisone (3)
J01 Antibacterials for systemic use (11)	co-amoxiclavulanic acid (2); co-trimoxazole (7) ; erythromycin (1); ciprofloxacin (1)
J02 Antimycotics for systemic use (1)	fluconazole (1)
J04 Antimycobacterials (15)	rifampicin (9) ; isoniazid (3); pyrazinamide (3)
J05 Antivirals for systemic use (19)	aciclovir (1); lopinavir/ritonavir (1); stavudine (3); tenofovir (14)

L01 Antineoplastic agents (1)	chlorambucil (1)
L04 Immunosuppressants (1)	tacrolimus (1)
M01 Antiinflammatory and antirheumatic products (3)	indometacin (1); ibuprofen (2)
M04 Antigout preparations (2)	allopurinol (1); colchicine (1)
N02 Analgesics (3)	codeine (2); tramadol (1)
N03 Antiepileptics (2)	clonazepam (1); valproate (1)
N05 Psycholeptics (1)	haloperidol (1)
N06 Psychoanaleptics (1)	amitriptyline (1)
R03 Drugs for obstructive airway diseases (1)	theophylline (1)
V03 Other therapeutic products (1)	polystyrene sulfonate (1)

* The number of times each drug and drug class was implicated in an ADR-related death appears in brackets. The three most-commonly implicated drugs appear in bold.

ADR: adverse drug reaction. ATC: anatomical therapeutic chemical

Stavudine was assessed as causing lactic acidosis contributing to the death of two patients and as causing neutropaenia contributing to the death of another. Lopinavir-ritonavir and rifampicin caused diarrhoea in two patients, thereby contributing to their death, and co-trimoxazole contributed to the death of two patients through bone marrow suppression.

Seven cases of drug-associated haemorrhage resulting in death occurred, five intracranial bleeds and two gastrointestinal bleeds. Drugs implicated in the intracranial haemorrhages were warfarin (two cases), aspirin (two cases) and heparin (one case), whereas one gastrointestinal bleed was attributed to a combination of colchicine, enoxaparin and aspirin, and the other to prednisone. Cardiovascular agents were implicated in 11 deaths, with diuretics the most common subclass of agents amongst these, implicated in eight deaths.

Table 4.6 lists the causes of death and the frequency of each cause among the 301 deaths where an ADR was not considered to contribute to the death. Mortality in this group of patients was mostly attributed to tuberculosis, respiratory infections and cerebrovascular disease.

Table 4.6. Causes of death in cases where an ADR did not contribute to death

Cause of death	Frequency
Tuberculosis (confirmed or suspected)	56 (19%)
Cerebrovascular disease	44 (15%)

Respiratory infections	43 (14%)
Malignancies	25 (8%)
Infections (other*)	19 (6%)
Chronic obstructive airways disease	17 (6%)
Renal failure	13 (4%)
Cardiac failure and cardiomyopathy	11 (4%)
Meningo-encephalitis	11 (4%)
Liver failure	5 (2%)
Myocardial infarction	2 (1%)
Other† and unclear	55 (18%)
Total	301 (100%)

* Infections other than tuberculosis, respiratory infections and meningo-encephalitis.

† Causes of death identified in one patient each: diabetic ketoacidosis, pulmonary embolism, asbestosis, obstructive hydrocephalus, myelitis, aplastic anaemia, and pulmonary interstitial fibrosis.

4.5 Discussion

We found that ADRs contributed to the death of 2.9% of patients admitted to the adult medical wards of four geographically diverse hospitals in South Africa. The overall mortality rate in our study wards was 18 per 100 admissions and 16% of these deaths were ADR-related. Factors independently associated with ADR-related deaths were exposure to more than seven drugs, HIV-infected patients on ART and higher non-HIV co-morbidity score. ARVs, antituberculosis drugs and co-trimoxazole (which is virtually exclusively prescribed for the prevention and treatment of opportunistic infections in HIV-infected patients) were the most commonly implicated drugs in ADR-related deaths.

Our ADR-related inpatient mortality rate is considerably higher than has been reported in studies from high income countries. Norwegian researchers who used a broad definition of adverse drug events (including intoxications and medication errors) and conducted extensive pre- and post-mortem serum drug concentration measurements and autopsies, reported mortality attributable to drugs at 0.95% of all admissions in medical patients (18.2% of in-hospital deaths)^{142,143}. In a Finnish university hospital, deaths in 0.05% of admissions (5% of in-hospital deaths) were attributed to ADRs¹⁴⁴. In a large study from the UK, 0.15% of patients admitted to two hospitals died from an ADR present on admission¹⁵⁰. In another UK study, an ADR that developed in hospital

was considered to have contributed to the deaths of 0.4% of the patients admitted (8.2% of in-hospital deaths)¹⁴⁵. A study in three Swiss teaching hospitals reported an ADR-related mortality rate of 0.05% of admissions¹⁵¹.

There are scanty data on the mortality rate of ADRs in low- to middle-income countries. A recent study at a tertiary hospital in China reported no deaths amongst 2739 patients who experienced an ADR during their admission¹⁵², while two studies from hospitals in Brazil^{153,154} report zero and one death, respectively, amongst 81 and 212 patients with identified ADRs. Zargarzadeh *et al.*¹⁵⁵ found the mortality rate attributable to drug-related problems (including ADRs and therapeutic failures) to be 0.9% of all the admissions to three Iranian teaching hospitals. An Indian study reported an ADR-related mortality rate of 0.24% of all admissions¹⁵⁶, while another Indian study reported no ADR-related deaths amongst 1221 medical admissions¹⁵⁷. In the previous ADR survey by our group, we found two ADR-related deaths out of 80 deaths occurring over a 3-month period in 2005 (i.e. 2.5%) in the medical wards of a secondary hospital in Cape Town⁶¹. There were 665 admissions included in the analysis, giving a mortality rate of 0.3% of admissions.

As already alluded to, the ADR definition used, and specifically the question whether ADRs considered 'possible' should be counted as ADRs or not, will influence the reported rate of ADRs. We decided *a priori* to include 'possible' ADRs in our analysis, but if we had limited our analyses only to those cases where an ADR was considered 'certain' or 'probable', we would have shown a mortality rate of 12/1951 admissions (0.61%), which is still in the upper range of rates previously reported (0.05% to 0.95%) or 12/357 deaths (3.4%).

Studies conducted in high income countries^{119,142-144,150,151} report that the most frequent fatal ADRs are gastrointestinal and intracranial haemorrhages attributed to warfarin, non-steroidal anti-inflammatory drugs, heparins, antiplatelet agents, corticosteroids and/or selective serotonin re-uptake inhibitors. We found that antiretrovirals,

antituberculosis agents and/or co-trimoxazole were implicated in 27 ADR-related deaths, nearly half of all the ADR-related deaths identified, reflecting the very high burden of HIV and tuberculosis in our region.

Our multivariate regression analysis identified HIV infection and treatment with ART as an independent risk factor for ADR-related death. While stavudine is no longer recommended as a first line drug due to its toxicity¹⁵⁸, it was still associated with the death of three patients in our series. In our survey, tenofovir, which has replaced stavudine due to its lower toxicity, was the single drug most commonly implicated in ADR-related deaths. Tenofovir can cause acute or chronic renal failure, but both are uncommon¹⁵⁹. An additional insult, e.g. dehydration due to acute gastroenteritis, was present in many of the fatal cases of tenofovir-associated renal failure we identified. Dialysis facilities are limited in our region, even for acute renal failure, and many cases of severe renal failure have a fatal outcome.

Co-trimoxazole and/or anti-tuberculosis therapy was implicated in most cases of drug-induced liver injury (DILI) in our survey. In keeping with the idiosyncratic nature of most DILIs, we only identified a preventable ADR in 20% of the DILI cases, lower than the overall figure of 50% among all the deaths.

Known risk factors for the development of ADRs include multi-morbidity and polypharmacy^{142,143,145,153}, and, in some but not all studies, advancing age^{64,145,150,155}. In our survey, more severe co-morbidity as measured by the modified Charlson comorbidity score, and exposure to a higher number of drugs before and during hospitalization, but not age, were associated with ADR-related death. This did not, however, hold true for the subgroup of HIV-infected persons, in whom the only independent predictor of ADR-related death was exposure to a higher number of drugs.

Forty-three per cent of the ADRs contributing to death in our survey were considered preventable. While methodological differences make it difficult to compare this figure with other studies, our proportion is in a similar range to figures previously described in South Africa (53% of community acquired ADRs and 33% of hospital acquired ADRs)⁶¹ and in the UK (72% of community acquired¹⁵⁰ and 53% of hospital acquired¹⁴⁵ ADRs) and did not differ in the HIV-infected subgroup. Considering the preventability factors identified, training of health care workers should focus on avoiding inappropriate drug prescribing and on the importance of routine laboratory monitoring, particularly monitoring renal function.

Our study was limited by its design as a retrospective chart review of hospital data. Moreover, assessing ADR causation is always subjective, as is ascertaining the cause of death by means of folder review. However, the two-step assessment process, including the use of a trigger tool followed by the discussion of each case by a multi-disciplinary panel of experts offset the inherent subjectivity of the process to some extent. A strength of our study, increasing its generalizability, is that we included hospitals from three of South Africa's nine provinces, providing a mixture of secondary and tertiary level care, thereby increasing the survey's representativeness.

In conclusion, a larger proportion of in-hospital deaths were ADR-related in our survey than has previously been described in high income settings. Moreover, unlike the pattern in high-income countries, the drugs implicated in ADR-related deaths in our survey were mostly drugs used in the treatment of HIV and tuberculosis. The major contribution of antiretrovirals to ADR-related mortality in our setting reflects our high HIV disease burden rather than a high incidence of toxicity due to the ARV drugs used. It is concerning to note that more than half of the HIV-infected patients who died during our survey were not on antiretroviral therapy, despite having advanced HIV disease. There is a need for more studies in low- to middle-income countries

characterizing ADR-related deaths and exploring appropriate systems to improve healthcare worker prescribing in order to minimize preventable drug-related harm.

Chapter 5 Adverse drug reactions causing admission to medical wards: a cross-sectional survey at four hospitals in South Africa

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Citation

Mouton JP, Njuguna C, Kramer N, *et al.* Adverse Drug Reactions Causing Admission to Medical Wards: A Cross-Sectional Survey at 4 Hospitals in South Africa. *Medicine* (Baltimore). 2016;95(19):e3437.

DOI: 10.1097/MD.0000000000003437

The original publication is included as Appendix iv. Supplementary materials are included from Appendix xli to Appendix lviii.

5.1 Abstract

Background Limited data exist on the burden of serious adverse drug reactions (ADRs) in sub-Saharan Africa, which has high HIV and tuberculosis prevalence. We determined the proportion of adult admissions attributable to ADRs at four hospitals in South Africa. We characterized drugs implicated in, risk factors for, and the preventability of ADR-related admissions.

Methods We prospectively followed patients admitted to four hospitals' medical wards over sequential 30-day periods in 2013 and identified suspected ADRs with the aid of a trigger tool. A multidisciplinary team performed causality, preventability, and severity assessment using published criteria. We categorised an admission as ADR-related if the ADR was the primary reason for admission.

Results There were 1951 admissions involving 1904 patients: median age was 50 years (interquartile range 34 to 65), 1057/1904 (56%) were female, 559/1904 (29%) were HIV-infected, and 183/1904 (10%) were on antituberculosis therapy (ATT). There were 164/1951 (8.4%) ADR-related admissions. After adjustment for age and ATT, ADR-related admission was independently associated ($P \leq .02$) with female sex (adjusted odds ratio (aOR) 1.51, 95% confidence interval (95% CI) 1.06 to 2.14), increasing drug count (aOR 1.14 per additional drug, 95% CI 1.09 to 1.20), increasing comorbidity score (aOR 1.23 per additional point, 95% CI 1.07 to 1.41), and use of antiretroviral therapy (ART) if HIV-infected (aOR 1.92 compared with HIV-negative/unknown, 95% CI 1.17 to 3.14). The most common ADRs were renal impairment, hypoglycaemia, liver injury, and haemorrhage. Tenofovir disoproxil fumarate (TDF), insulin, rifampicin, and warfarin were most commonly implicated, respectively, in these four ADRs. ART, ATT, and/or co-trimoxazole were implicated in 56/164 (34%) ADR-related admissions. 73/164 (45%) ADRs were assessed as preventable.

Conclusion In our survey, approximately one in 12 admissions was due to an ADR. The range of ADRs and implicated drugs reflect South Africa's high HIV and tuberculosis burden. Identification and management of these ADRs should be considered in HIV and tuberculosis care and treatment programs and should be emphasized in health care worker training programmes.

5.2 Introduction

Data on the burden of serious adverse drug reactions (ADRs) in sub-Saharan Africa are limited. In this region, colliding epidemics of infectious and non-communicable diseases^{43-46,160}, prevalent pharmacogenetic variants associated with increased risk of ADRs¹⁶¹⁻¹⁶⁴, widespread concomitant use of traditional remedies^{163,165,166}, and overburdened health care systems^{42,45,163,167,168} potentially contribute to the burden of drug-related harm.

In South Africa, an estimated 6.8 million people were HIV-infected by 2014, with approximately 2.9 million receiving antiretroviral therapy (ART)¹⁶⁹. Moreover, in 2013 the country's tuberculosis incidence was estimated at 860 new cases per 100,000 population, and 62% of tuberculosis patients were HIV-co-infected¹⁷⁰. A 2005 South African hospital survey found that HIV infection was a risk factor for serious ADRs, especially in those patients on ART⁶¹. Subsequently, as with other sub-Saharan African countries, there has been massive scale-up of the ART programme with earlier initiation and use of less toxic first-line ART regimens^{158,171}.

We prospectively assessed medical admissions at four South African hospitals to determine the burden of ADRs resulting in hospital admission, to identify common serious ADRs, to identify the drugs implicated in these ADRs, to evaluate whether these ADRs were preventable, and to determine the influence of HIV infection on ADR burden and pattern.

5.3 Methods

5.3.1 Setting and study design

We conducted a cross-sectional survey during 2013 in the adult medical wards of four hospitals. We prospectively reviewed all admissions over sequential 30-day periods at the sites. The survey sites represent three different provinces of South Africa and are a

mixture of tertiary and regional hospitals. (See Appendix xli for a detailed description of the four hospitals).

We conducted this survey in parallel with a survey of ADR-related deaths, which has previously been published¹⁰⁴. The sample size was calculated to ensure adequate power for the mortality survey¹⁰⁴: we calculated that a sample size of 2000 would be needed to detect a mortality rate due to ADR of 0.3%, with a 95% confidence interval of 0.1% to 0.7% (using exact confidence interval method of Clopper-Pearson). (See Appendix xlii which demonstrates the extent of overlap between the two surveys' participants).

5.3.2 Processes and study team

One medical doctor and two pharmacists collected the data. For every admission, we recorded demographic information, drug exposure history, and diagnoses. From the admission records and investigation results we identified the reason for the admission and flagged those where it was potentially related to an ADR, with the aid of a trigger tool (see Appendix xliii for the trigger tool used), adapted from Rozich¹²². For flagged cases we collected more detailed data, including laboratory results, and a more detailed drug history, which included start and stop dates, dosage regimens, and indications. We performed an exit clinical record review at patients' discharge, death, or approximately one week after the end of the survey period for those still in hospital at survey end, to verify and augment data and to add information on the management and outcome of potential ADRs. Clinicians and nursing staff were aware of the survey, but did not actively report potential ADRs to the study team. When the data collection team identified information of direct potential benefit to the patient, this was communicated to the hospital clinical team.

Admissions identified as potentially ADR-related were assessed by a multidisciplinary case review panel for ADR causality, preventability, and severity. The panel reached its

assessment through consensus discussion. (See Appendix xli which describes details of the panel composition, case identification, and case assessment procedures).

5.3.3 Record linkage to identify all-cause mortality

We identified in-hospital deaths from hospital administrative records. We performed linkage to the national population register, using South African personal identity numbers, to identify deaths occurring within 30 days of discharge from hospital.

5.3.4 Definitions and taxonomies used

We recorded drug exposure for the 30 days before admission. We identified patients documented to have zero drug exposure, and distinguished those from patients in whom no drug history was documented in the medical records. We coded drugs according to the Anatomic Therapeutic Chemical (ATC) Classification System of the World Health Organization Collaborating Centre for Drug Statistics Methodology¹⁷², with a few exceptions and assumptions (see Appendix xli for an exposition of the exceptions and assumptions used in drug coding). We defined the drug count as the number of drugs with unique ATC codes over the 28 days before admission, excluding topical preparations, vitamins, and mineral supplements. We defined first-line ART as two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a non-nucleoside reverse transcriptase inhibitor, and second-line ART as two NRTIs in combination with a ritonavir-boosted protease inhibitor, as per South African adult ART guidelines¹⁷³.

We recorded patients' diagnoses or clinical problems according to the International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10) codes. We calculated a comorbidity score for each admission, modified from the Charlson comorbidity score¹⁴⁸. Our modification did not allocate points for a diagnosis of HIV/AIDS, as the HIV score assigned by the original Charlson method is probably

inappropriately high in the era of ART¹⁴⁹, and as we wanted to explore the independent effect of HIV infection on ADR-related admissions.

We performed causality assessment of suspected ADRs using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardised case causality assessment²⁸. We defined an ADR according to the definition of Aronson and Ferner¹⁹. We did not include intentional drug overdose, therapeutic failure, or cases of ART-associated immune reconstitution syndrome as ADRs. We coded ADRs to 'preferred terms' contained in version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA®, MedDRA Maintenance and Support Services Organization, McLean, Virginia, USA).

We considered a case to be an ADR-related admission if the multidisciplinary case review panel assessed the ADR as 'possible', 'probable', or 'certain' according to WHO-UMC criteria, and the ADR was the main reason for the admission.

We considered ADRs to be preventable if the case review panel held that one or more of the Schumock and Thornton criteria³⁶ was present. We assessed ADR severity according to guidance from Temple *et al.*¹¹³ as causing (1) temporary harm, (2) permanent harm, (3) near-death (including anaphylaxis and cardiorespiratory arrest), or (4) death. We classified ADRs as type A (predictable from the pharmacological action of the drug) or type B (idiosyncratic) according to the Rawlins and Thompson classification³³ and used this classification to inform our assessment of causality and preventability in the event of more than one drug suspected in the ADR. For type B reactions with more than one drug suspect, we assessed causality and preventability for each drug suspect separately. However, for type A reactions we assessed causality and preventability attributable to the combined action of all drug suspects. When a combination of type A and type B mechanisms were considered to have caused the ADR, we classified the ADR as type B.

5.3.5 Data entry and statistical analysis

We entered data into an Access 2010 database (Microsoft Corporation, Redmond, Washington, USA), and analysed data using Stata 13.1 (Stata Corporation, College Station, Texas, USA). We used cross-tabulation and chi-square statistics to explore associations between binary and categorical variables. We summarised continuous variables using medians and interquartile ranges, due to their non-normal distribution, and used the Wilcoxon rank-sum test for between-group comparisons of continuous variables. A *P* value of <.05 was taken to indicate significant difference.

We constructed a generalized estimation equation model, with admissions clustered on the patient level for those with readmissions, to explore independent associations between ADR-related admission and age, sex, HIV infection, ART, ATT, drug count, and modified comorbidity score. Variables were selected for inclusion in the model *a priori*, at the time of study design. To categorise HIV infection and ART exposure we constructed a three-category variable: (1) HIV-negative/unknown; (2) HIV-infected and not on ART; or (3) HIV-infected and on ART. In the main model, we excluded admissions where patients were documented as not exposed to any drugs before the admission, but included those in whom no drug history was recorded. In sensitivity analyses, we constructed two additional models, the first including all admissions, and the second excluding patients with missing drug histories as well as patients with documented zero drug exposure.

5.3.6 Ethics

The Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town approved this study (reference no 576/2011). We received permission to conduct the research by the respective hospitals' management and/or provincial Departments of Health.

5.4 Results

5.4.1 Description of the cohort: all admissions

During the survey period, 1904 patients were admitted on 1951 occasions (1858 patients were each admitted once, 45 patients were each admitted twice, and one patient was admitted three times). In 242/1951 (12%) admissions drug histories were not recorded in the medical records. Linkage with the population register was possible for only 866/1904 (45%) patients, due to missing personal identity numbers.

Patient characteristics at the time of their first admission are given in Table 5.1. HIV-infected patients were younger than HIV-negative/unknown patients (median age 36 years (interquartile range (IQR): 30 to 44 years) versus median age 58 years (IQR: 43 to 70 years), $P<.001$). Of the HIV-infected patients, 251/559 (45%) were not on ART, 253/559 (45%) were on first-line ART, 18/559 (3.2%) on second-line ART, 3/559 (0.54%) on other ART combinations, 33/559 (5.9%) on unspecified ART, and 1/559 (0.18%) on zidovudine monotherapy for prevention of mother-to-child-transmission. The drugs most commonly included in ART regimens were efavirenz (240), lamivudine (213), and TDF (207). The median CD4 count was 142.5 cells / mm³ (IQR: 42 to 328) in the 494 HIV-infected patients with CD4 cell counts available. 128/559 (23%) HIV-infected patients were on treatment for tuberculosis at the time of first admission, versus 54/1345 (4.0%) HIV-negative/unknown patients, $P<.001$.

Table 5.1. Characteristics of patients at their first admission to the medical wards of four hospitals in South Africa, 2013 (n=1904)

	All patients (n=1904)	Patients with an ADR- related admission (n=162)	Patients without an ADR-related admission (n=1742)
Age			
Median and [IQR] (years)	50 [34 to 65]	53 [36 to 65]	50 [33 to 65]
Sex			
Female	1057 ^a (56%)	108 (67%)	949 (55%)
HIV status			
Infected	559 (29%)	63 (39%)	496 (28%)
Negative	350 (18%)	19 (12%)	331 (19%)
Unknown	995 (52%)	80 (49%)	915 (53%)

ATT status at time of admission			
On ATT	182 (9.6%)	29 (18%)	153 (8.8%)
On isoniazid prophylaxis	9 (0.47%)	3 (1.9%)	6 (0.34%)
Neither on ATT nor on isoniazid prophylaxis	1713 (90%)	130 (80%)	1583 (91%)
Modified Charlson comorbidity score			
Median and [IQR]	0 [0 to 1]	1 [0 to 2]	0 [0 to 1]
Range	0 to 7	0 to 5	0 to 7
Comorbidity score = 0	1045 (55%)	63 (39%)	982 (56%)
Comorbidity score = 1 or 2	664 (35%)	71 (44%)	593 (34%)
Comorbidity score ≥ 3	195 (10%)	28 (17%)	167 (9.6%)
Drug count, n=1663^b			
Median and [IQR]	3 [1 to 5]	5 [4 to 7]	3 [1 to 5]
Range	0 to 20	1 to 17	0 to 20
Drug count = 0	239 (14%)	0 (0%)	239 (16%)
Drug count ≥ 5	571 (34%)	94 (58%)	477 (32%)

(a) Of whom 15/1057 (1.4%) were known to be pregnant. None of the pregnant females were admitted for ADR-related reasons.

(b) No drug history recorded in clinical records of 241/1904 (13%) patients.

ADR: adverse drug reaction, ATT: antituberculosis therapy, IQR: interquartile range.

Other common comorbidities included cardiovascular disease in 44% of patients, endocrine / metabolic disease in 31%, renal failure in 17%, and chronic lower respiratory disease in 8.8%. Forty percent of patients were exposed to cardiac agents before their first admission (including 29% to diuretics, 20% to angiotensin converting enzyme (ACE) inhibitors / angiotensin receptor blockers, 13% to calcium channel blockers, 12% to 'statins'), 16% to antithrombotic agents (including 13% to aspirin), and 17% to blood-glucose lowering agents (including 6.8% to insulin). 239/1904 (13%) patients were documented to have had zero drug exposure before their first admission.

The most common reasons for admission were cardiovascular disease (496/1951 (25%) admissions), respiratory disease (313/1951 (16%)), and infectious / parasitic disease (285/1951 (15%)). (See Appendix xlv, Appendix xlvAppendix xlv, and Appendix xlv which describe the prevalence of comorbidities, patients' exposure to drugs before admission, and the cause of admission, respectively).

5.4.2 ADR-related admissions: presentations and implicated drugs

We identified 164 ADR-related admissions, which represented 8.4% of all admissions (95% CI 7.2% to 9.7%). These 164 ADRs occurred in 162 patients, two of whom were each admitted twice for ADR-related reasons during the survey period.

Drugs used in the management of HIV and tuberculosis (ART, ATT, and co-trimoxazole) were implicated in 56/164 (34%) ADR-related admissions, and 63/164 (38%) ADR-related admissions occurred in HIV-infected patients.

The five most common ADRs resulting in admission were renal impairment (24 cases), hypoglycaemia (22 cases), drug-induced liver injury (DILI) (20 cases), haemorrhage (19 cases), and blood dyscrasias (14 cases). These cases are summarised in Table 5.2. (Also see Appendix xlvii, Appendix xlviii, Appendix xlix, Appendix l, and Appendix li for patient-level detail regarding each of the five most common presentations). Renal impairment, DILI, and blood dyscrasias predominantly occurred in HIV-infected and younger patients, while hypoglycaemia and haemorrhage predominantly occurred in HIV-negative/unknown and older patients.

Table 5.2. Summary of characteristics of the five most common adverse drug reactions that caused admission to the medical wards of four hospitals in South Africa, 2013

	Renal impairment	Hypoglycaemia	Drug-induced liver injury	Haemorrhage	Blood dyscrasias
Number of ADR-related admissions	24 ^a	22	20	19	14
Clinical presentation	4/24 had overlapping DILI.	18/22 had renal impairment.	12 cholestatic, 6 hepatocellular, 2 mixed. 4/20 had overlapping renal impairment.	7 GI bleed, 3 CNS bleed, 3 haemoptysis, 2 menorrhagia, 1 epistaxis, 1 haematuria, 1 haemarthrosis, 1 retroperitoneal bleed	5 anaemia, 5 thrombocytopaenia, 3 leukopaenia, 1 pancytopenia
Females <i>n</i> (%)	11/24 (46%)	15/22 (68%)	12/20 (60%)	18/19 (95%)	6/14 (43%)
Median age in years [IQR]	40.5 [32.5 to 48.5]	60.5 [56 to 74]	35 [29.5 to 41.5]	67 [53 to 79]	40.5 [31 to 60]
HIV-infected <i>n</i> (%)	17/24 (71%)	1/22 (4.5%)	18/20 (90%)	3/19 (16%)	11/14 (79%)
Median drug count [IQR]	5 [4 to 7]	5.5 [5 to 8]	4.5 [4 to 7]	5 [4 to 9]	5.5 [3 to 7]
Median comorbidity score [IQR]	1 [0 to 2]	3 [1 to 3]	0 [0 to 1]	1 [0 to 2]	0.5 [0 to 2]
Drugs associated with the ADR	11 cases: TDF (alone, or in combinations with co-trimoxazole, aciclovir, indometacin, co-amoxiclav), 9 cases: ACE-inhibitor (alone or in combinations with aspirin, furosemide, spironolactone, HCTZ, amlodipine, atenolol, hydralazine, valsartan, rifampicin) 2 cases: co-trimoxazole, 1 case: rifampicin, 1 case: co-amoxiclav & ibuprofen.	9 cases: insulin only, 1 case: insulin & metformin, 3 cases: insulin & sulfonylurea & metformin, 1 case: insulin & unspecified oral hypoglycaemic agents, 2 cases: sulfonylurea only; 6 cases: sulfonylurea & metformin.	8 cases: rifampicin only, 3 cases: efavirenz only, 2 cases: co-trimoxazole only, 1 case: enalapril, 6 cases: various combinations of ATT, NNRTIs, co-trimoxazole, erythromycin)	13 cases: warfarin, 3 cases: acetylsalicylic acid, 2 cases: unspecified NSAIDs, 1 case: diclofenac	4 cases: co-trimoxazole, 3 cases: zidovudine only, 1 case: zidovudine & lamivudine, 1 case: stavudine, 1 case: methotrexate & chloroquine, 1 case: allopurinol & colchicine, 1 case: rifampicin & isoniazid, 1 case: rifampicin & amoxicillin 1 case: valproic acid
ADR classification	Type A	15/24 (63%)	22/22 (100%)	0/20 (0%)	19/19 (100%)
					10/14 (71%)

	Type B	9/24 (38%), with 16 drug-ADR associations	0/22 (0%)	20/20 (100%), with 30 drug-ADR associations	0/19 (0%)	4/14 (29%), with 7 drug-ADR associations
Proportion preventable	Type A	9/15 (60%)	17/22 (77%)	—	11/19 (58%)	3/10 (30%)
	Type B	2/16 (13%)	—	4/30 (13%)	—	0/7 (0%)
Reasons for preventability (case-wise, at least one implicated drug-ADR association was preventable for this reason)	Inappropriate drug	7/24 (29%)	7/22 (32%)	2/20 (10%)	0/19 (0%)	0/14 (0%)
	Inappropriate dose	1/24 (4.2%)	4/22 (18%)	0/20 (0%)	4/19 (21%)	2/14 (0%)
	Inadequate monitoring	4/24 (17%)	8/22 (36%)	0/20 (0%)	5/19 (26%)	1/14 (7.1%)
	History of ADR	0/24 (0%)	4/22 (18%)	1/20 (5.0%)	4/19 (21%)	0/14 (0%)
	Interaction	0/24 (0%)	1/22 (4.6%)	0/20 (0%)	5/19 (26%)	0/14 (0%)
	Drug concentration	0/24 (0%)	0/22 (0%)	0/20 (0%)	0/19 (0%)	0/14 (0%)
	Compliance	0/24 (0%)	3/22 (14%)	0/20 (0%)	0/19 (0%)	0/14 (0%)
Combined all-cause mortality^b		12/24 (50%)	4/22 (18%)	7/20 (35%)	3/19 (16%)	3/14 (21%)
Median length of hospital stay if known to have left hospital alive: days [IQR]		9 [8 to 13.5]	6 [3 to 10]	10 [7 to 25]	6 [4 to 8.5]	6 [5 to 15]

(a) Count excludes two cases of proximal tubular dysfunction without renal impairment.

(b) All-cause mortality in-hospital and within 30 days of discharge.

ACE: angiotensin converting enzyme; ADR: adverse drug reaction, ART: antiretroviral therapy, ATT: antituberculosis therapy, CNS: central nervous system, DILI: drug-induced liver injury, GI: gastrointestinal, HCTZ: hydrochlorothiazide, IQR: interquartile range, NNRTI: non-nucleoside reverse transcriptase inhibitor, TDF: tenofovir disoproxil fumarate

Other common ADRs resulting in admission included cardiac failure (9 cases), confusion (8 cases), electrolyte disturbances (7 cases), antineoplastic-, corticosteroid-, and immunosuppressant-associated pneumonia (4 cases), hypotension (4 cases), drug reaction with eosinophilia and systemic symptoms (DRESS) (4 cases), and ataxia (3 cases). (See Appendix lii (Type A ADRs) and Appendix liii (Type B ADRs) for patient-level details of these ADR-related admissions. Also see Appendix liv which maps the 164 ADRs to the multi-level MedDRA® taxonomy).

Drugs and drug classes most commonly implicated in ADRs were NRTIs (23 times in 21 cases, with TDF implicated in 14, zidovudine in 4, stavudine in 3, and lamivudine in 2), rifampicin in 17, ACE-inhibitors in 15, insulin in 14, and warfarin in 13 cases. (See Appendix lv for a full list of drugs implicated in ADR-related admissions). Figure 5.1 plots the proportion of ADRs in which the drug was implicated against the drug's frequency of use, for the 19 drugs implicated in four or more ADR-related admissions. Warfarin, phenytoin, and co-trimoxazole were the three drugs most frequently implicated in ADR-related admissions, relative to their frequency of use.

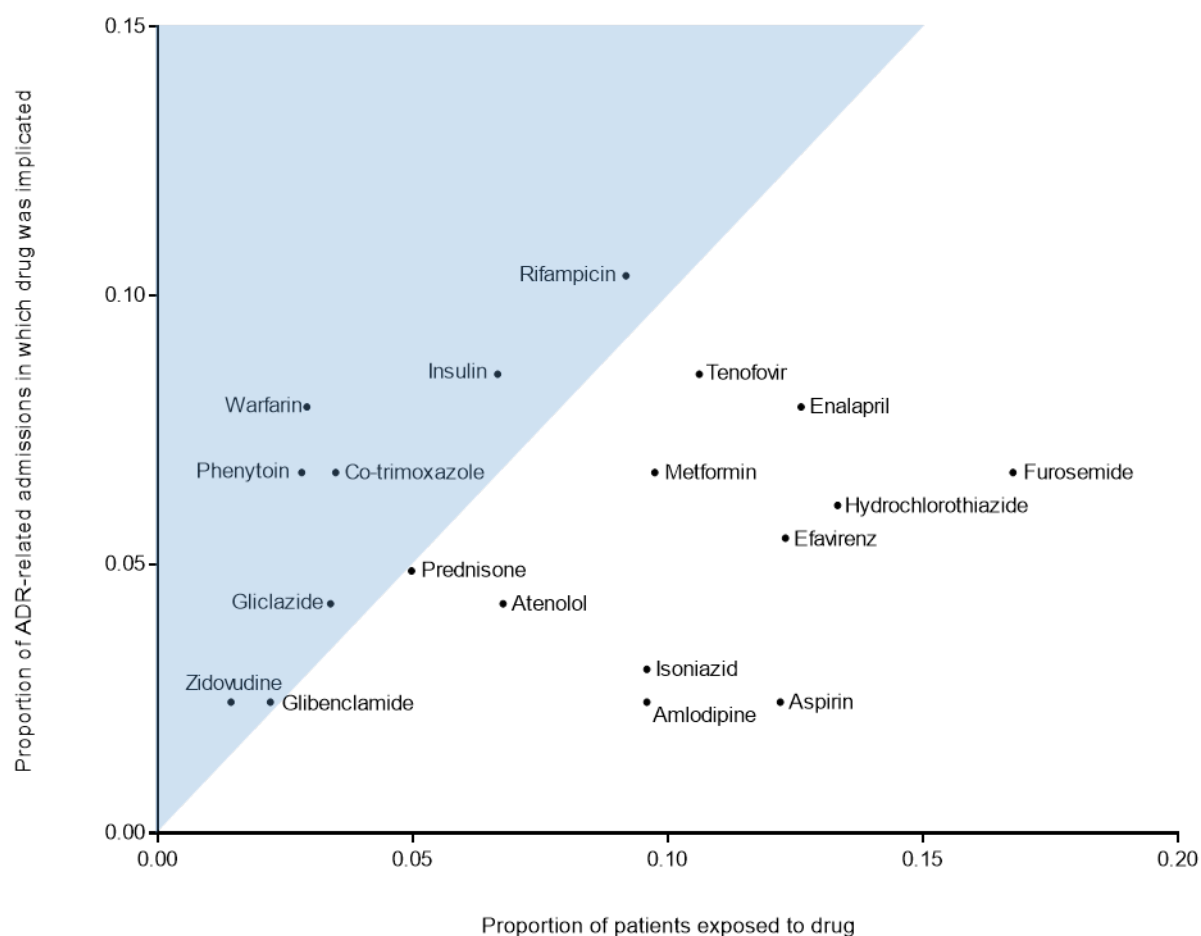


Figure 5.1. Scatterplot of 19 drugs implicated in at least 4 ADR-related admissions.

This figure shows the proportion of patients exposed to the drug before their first admission versus the proportion of ADR-related admissions in which the drug was implicated. The shaded area represents those cases where the proportion of ADRs in which the drug was implicated was higher than the proportion of patients exposed to the drug.

5.4.3 ADR-related admissions: associations

Results of the generalized equation estimation model (excluding patients who were not exposed to drugs over the 30 days before admission) are presented in Table 5.3. ADR-related admission was independently associated with female sex, higher drug count, higher comorbidity score, and HIV-infection with ART. We did not find an association between ADR-related admission and age. Associations were similar in the sensitivity analyses. (See Appendix Ivi for an alternative model including patients documented to have had zero drug exposure, and Appendix Ivii for an alternative

model excluding patients in whom no drug history was recorded in the medical records).

Table 5.3. Generalized estimation equation model of associations with adverse drug reaction-related admission (n=1711 admissions in 1669 patients), excluding patients documented to have had zero drug exposure before admission.

	n	Crude			Adjusted ^d		
		OR	(95% CI)	Wald <i>P</i> value	OR	(95% CI)	Wald <i>P</i> value
Sex							
Male (referent)	724	1.00			1.00		
Female	987	1.54	(1.09 to 2.17)	.01	1.51	(1.06 to 2.14)	.02
Age^a	1711	1.04	(0.95 to 1.13)	.39	1.02	(0.91 to 1.14)	.73
HIV and ART							
HIV-negative/unknown (referent)	1211	1.00			1.00		
HIV-infected, not on ART	186	0.85	(0.46 to 1.55)	.59	1.15	(0.59 to 2.22)	.68
HIV-infected, on ART	314	2.11	(1.46 to 3.04)	<.001	1.92	(1.17 to 3.14)	.009
Anti-tuberculosis therapy							
Not on ATT (referent)	1524	1.00			1.00		
On ATT	187	2.05	(1.33 to 3.17)	.001	1.22	(0.73 to 2.06)	.45
Drug count^b	1711	1.20	(1.15 to 1.25)	<.001	1.14	(1.09 to 1.20)	<.001
Comorbidity score^c	1711	1.29	(1.15 to 1.45)	<.001	1.23	(1.07 to 1.41)	.004

(a) Included in the model as a continuous variable. The reported odds ratio is for each 10-year increment.

(b) Included in the model as a continuous variable. The reported odds ratio is for each additional drug.

(c) Included in the model as a continuous variable. The reported odds ratio is for each additional point on the modified Charlson comorbidity score.

(d) Adjusted for other factors in the model.

ART: antiretroviral therapy, ATT: antituberculosis therapy, CI: confidence interval, OR: odds ratio.

5.4.4 ADR-related admissions: ADR classification, causality, preventability and severity

126/164 (77%) ADRs were classified as type A, and 38/164 (23%) as type B. 36/63 (57%) ADRs in HIV-infected patients were type A and 27/63 (43%) type B. This differed significantly from HIV negative/unknown patients in whom 90/101 (89%) ADRs were type A and 11/101 (11%) type B ($P<.001$). The causality assessment of ADRs, stratified by ADR type and HIV status, is described in Table 5.4.

Table 5.4. Causality assessment of adverse drug reactions, stratified by type of adverse drug reaction and by human immunodeficiency virus infection status

ADR type	Causality rating	All patients	HIV-infected	HIV-negative/unknown
Type A	Certain	41/126 (33%)	6/36 (17%)	35/90 (39%)
	Probable	26/126 (21%)	7/36 (19%)	19/90 (21%)
	Possible	59/126 (47%)	23/36 (64%)	36/90 (40%)
Type B ^a	Certain	4/61 ^b (6.6%)	1/44 ^c (2.3%)	3/17 ^d (18%)
	Probable	6/61 ^b (9.8%)	5/44 ^c (11%)	1/17 ^d (5.9%)
	Possible	51/61 ^b (84%)	38/44 ^c (86%)	13/17 ^d (76%)

(a) For type B ADRs with more than one drug suspect, causality assessment was performed on the level of the individual drug.

(b) There were 38 type B ADRs, with 61 drugs implicated.

(c) Among HIV-infected patients, there were 27 type B ADRs, with 44 drugs implicated.

(d) Among HIV-negative/unknown patients, there were 11 type B ADRs, with 17 drugs implicated.

73/164 (45%) ADRs resulting in admission were assessed as preventable. The drugs most commonly implicated in preventable ADRs were warfarin (11), insulin (10), phenytoin (9), furosemide (8) and metformin (8). 69/126 (55%) type A ADRs were assessed as preventable versus 4/38 (11%) type B ADRs ($P<.001$). In 24/126 (19%) type A ADRs the drug was inappropriate; in 14/126 (11%) the dose, route, or frequency was inappropriate; in 25/126 (20%) monitoring was insufficient; in 11/126 (8.7%) the patient previously had an ADR to the drug; in 13/126 (10%) a drug interaction played a role; in 9/126 (7.1%) a supratherapeutic drug concentration was found; and in 4/126 (3.2%) adherence played a role. In 3/38 (7.9%) type B ADRs at least one implicated drug was inappropriate for the patient, and in 1/38 (2.6%) the patient had a previous ADR to an implicated drug.

Only 20/63 (32%) ADRs in HIV-infected patients were preventable versus 53/101 (52%) in patients who were HIV-negative/unknown, $P=.009$. In 10 of these 20 cases, the ADR was assessed as preventable because the implicated drug was considered inappropriate.

We assessed 126/164 (77%) ADRs to have resulted in temporary harm, 6/126 (3.7%) to have resulted in permanent harm, 3/126 (1.8%) to have resulted in near-death, and

29/164 (18%) to have resulted in death. Table 5.5 shows that there was no association between the severity of ADRs and their preventability ($P=.71$).

Table 5.5. Severity and preventability of adverse drug reactions resulting in admission

Severity category	n	Preventable	Not preventable
Temporary harm	126	56 (44%)	70 (56%)
Permanent harm	6	4 (67%)	2 (33%)
Near-death	3	1 (33%)	2 (67%)
Death	29	12 (41%)	17 (59%)
Total	164	73 (45%)	91 (55%)

5.4.5 ADR-related admissions: patient outcomes

The median length of stay was 7 days (IQR: 4 to 11 days) in the 1528 admissions where the patient exited the hospital alive, and did not differ between admissions for ADRs (median 7 days, IQR: 4 to 10 days) and admissions for other reasons (median 7 days, IQR: 4 to 11 days, $P=.87$).

Combined all-cause mortality (in-hospital death or death within 30 days of discharge) among patients with an ADR-related admission was 38/162 (23%). This was no different from combined all-cause mortality in patients admitted for other reasons (362/1742 (21%), $P=.42$). However, combined all-cause mortality was significantly worse in HIV-infected patients with an ADR-related admission (24/63 (38%)) versus HIV-infected patients admitted for other reasons (117/496 (24%), $P=.01$).

5.5 Discussion

We found that 8.4% of admissions to adult medical wards of four hospitals in three provinces of South Africa were directly attributable to ADRs, with drugs used in the management of tuberculosis and HIV implicated in a third of these admissions. ADRs in HIV-infected patients were more likely to be severe type B ADRs, were less likely to be preventable, and were associated with higher all-cause mortality. Nearly half of ADRs resulting in admission were preventable.

Six systematic reviews, of studies with a design comparable to ours, have estimated the proportion of adult medical admissions attributable to ADRs to range between 3.1% and 6.3%⁶²⁻⁶⁷. (See Appendix Iviii for a summary of these six reviews). Studies from low- and middle-income countries (LMICs) are notably underrepresented in these reviews. Previous LMIC hospital-based surveys found the proportion of adult medical admissions attributable to ADRs to be 19% in Argentina¹⁷⁴, 7.0% in Lebanon¹⁷⁵, and 6.8% in India¹⁷⁶. ADR burden data from sub-Saharan Africa, a setting of high HIV and tuberculosis prevalence, are scarce. In a previous South African survey 6.3% of adult medical admissions were found to have been ADR-related⁶¹. While these differences may be due to variations in study design, they may also, when combined with our figure of 8.4%, suggest that ADRs may result in proportionally more medical admissions in LMICs than is the case in high income countries.

The different burden and pattern of ADR-related admissions we observed may be explained as an effect of the colliding epidemics of infectious and non-communicable diseases in South Africa. In our study, a group of mostly elderly patients with multi-morbidity presented with type A ADRs such as hypoglycaemia, haemorrhages, and hypotension, which is not unlike typical ADR presentations seen in studies from high-income settings. A second group of patients in our survey were younger, with a burden of chronic infectious diseases (which is not allocated a score on the original or modified Charlson comorbidity score), and presented with more type B ADRs including DILI and blood dyscrasias. HIV-infected patients are known to be at increased risk for drug hypersensitivity reactions, particularly to co-trimoxazole^{177,178} and ATT¹⁷⁷⁻¹⁷⁹, but the pathophysiology is not fully understood and likely to be multifactorial^{177,178}.

A meta-analysis of six observational studies found a decline in creatinine clearance attributable to TDF¹⁵⁹ that was approximately ten times the rate of normal age-related decline¹⁸⁰, which was significantly greater than that seen in randomized controlled trials^{159,180} and probably reflects the 'real-life' situation^{159,180,181}. TDF-associated renal

impairment is not uncommon in sub-Saharan Africa^{182,183}, and our survey identified eleven cases with high mortality. In all of our cases of TDF-associated renal impairment, causality was assessed as 'possible', due to the presence of concomitant diseases and/or nephrotoxic drugs. TDF use in acutely ill patients with renal dysfunction in this region is of concern, particularly when TDF is co-prescribed with other potentially nephrotoxic drugs, as there are limited facilities for renal replacement therapy in sub-Saharan Africa.

All of the patients admitted due to DILI in our survey were HIV-infected and/or taking tuberculosis treatment. A very high incidence (15%) of DILI was reported in Ethiopians on ART, ATT, and cotrimoxazole¹⁸⁴. Most of our patients with DILI showed a cholestatic liver enzyme pattern, which is similar to the Ethiopian study, and which often implicated rifampicin rather than isoniazid or pyrazinamide as the causative agent. Combined all-cause mortality among our DILI patients was 35%, which is considerably worse than the mortality rates of 5.2% to 11.5% reported in four observational studies from high-income settings¹⁸⁵.

We identified a large number of ADR admissions for hypoglycaemia. In the majority of our cases insulin was implicated and many patients had concomitant renal impairment. Most of the admissions for hypoglycaemia were assessed as preventable, mostly because of insufficient blood glucose monitoring. Insufficient blood glucose monitoring was identified as a major problem in a rural setting in South Africa, where 48% of diabetics had no blood glucose value recorded in their clinic records over the previous year¹⁸⁶.

Our finding that 45% of ADRs resulting in admission were preventable is in keeping with a 2012 meta-analysis which estimated that 52% (95% CI: 42% to 62%) of ADR-related admissions are due to preventable ADRs⁷⁹.

Our study has a number of limitations. First, we relied on clinical data recorded in hospital clinical records and we did not have access to patients' primary care medical records. Despite educating clinicians about our study, one in eight folders had no drug history recorded, and the documented drug exposure before admission suggests there may have been poor documentation of contraceptives, over-the-counter agents, topical agents, and herbal remedies, which may have resulted in under-ascertainment of ADR-related admissions. Second, linkage with the South African population register was not possible for the majority of the patients included in our survey, as accurate personal identity numbers were not routinely documented at all sites, and thus we have under-ascertained post-discharge death. Third, assessment of ADR causality, severity, and preventability is subjective and assessment by expert judgement has previously been criticised^{131,187,188}. We used a two-step process, applying a sensitive screening instrument followed by a multidisciplinary panel discussion of screened cases, to help mitigate the subjectivity associated with expert assessments.

Our study findings have limited generalizability outside secondary and tertiary settings in South Africa. Rather, it emphasizes how the local disease burden and drug use pattern influences the ADRs occurring in our setting. Public health programmes should factor in anticipated risks, including ADRs, and should incorporate risk-reduction measures. Our study demonstrates the feasibility of generating locally relevant pharmaco-epidemiological data in a resource-limited setting, and the methodology we used is suited to be periodically repeated, scaled up, and/or transferred elsewhere. The key risk drivers that an approach such as this identifies can be turned into opportunities to improve quality of care.

Chapter 6 Serious adverse drug reactions at two children's hospitals in South Africa

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Served on expert panel developing the trigger tool: KC, UM, RdW, KT, AA, CS

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Data collection and initial case review: NJ

Data management: AS

Site oversight: KT, CS

Critical review of manuscript: KC, MF-dS, NJ, UM, AS, RdW, KT, AA, MK, CS

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Citation

Mouton JP, Fortuin-de Smidt MC, Jobanputra N, *et al*. Serious adverse drug reactions at two children's hospitals in South Africa. BMC Pediatrics. 2020;20(1):3.

DOI: 10.1186/s12887-019-1892-x

The original publication is included as Appendix v. Supplementary materials are included from Appendix lix to Appendix lxxi.

6.1 Abstract

Background The high HIV prevalence in South Africa may potentially be shaping the local adverse drug reaction (ADR) burden. We aimed to describe the prevalence and characteristics of serious ADRs at admission, and during admission, to two South African children's hospitals.

Methods We reviewed the folders of children admitted over sequential 30-day periods in 2015 to the medical wards and intensive care units of each hospital. We identified potential ADRs using a trigger tool developed for this study. A multidisciplinary team assessed ADR causality, type, seriousness, and preventability through consensus discussion. We used multivariate logistic regression to explore associations with serious ADRs.

Results Among 1050 patients (median age 11 months, 56% male, 2.8% HIV-infected) with 1106 admissions we found 40 serious ADRs (3.8 per 100 drug-exposed admissions), including 9/40 (23%) preventable serious ADRs, and 8/40 (20%) fatal or near-fatal serious ADRs. Antibacterials, corticosteroids, psycholeptics, immunosuppressants, and antivirals were the most commonly implicated drug classes. Preterm neonates and children in middle childhood (6 to 11 years) were at increased risk of serious ADRs compared to infants (under 1 year) and term neonates: adjusted odds ratio (aOR) 5.97 (95% confidence interval 1.30 to 27.3) and aOR 3.63 (1.24 to 10.6) respectively. Other risk factors for serious ADRs were HIV infection (aOR 3.87 (1.14 to 13.2) versus HIV-negative) and increasing drug count (aOR 1.08 (1.04 to 1.12) per additional drug).

Conclusions Serious ADR prevalence in our survey was similar to the prevalence found elsewhere. In our setting, serious ADRs were associated with HIV-infection and the antiviral drug class was one of the most commonly implicated. Similar to other

sub-Saharan African studies, a large proportion of serious ADRs were fatal or near-fatal. Many serious ADRs were preventable.

6.2 Background

Patient safety is of central importance to all fields of medicine. However, in paediatric medicine, clinicians are faced with the reality that pre-registration drug safety data are often very limited, and that extrapolation from adult drug safety data may be inappropriate in view of children's physiological development. As such, post-marketing surveillance is critical in the ongoing safety appraisal of drugs given to children¹⁸⁹.

South Africa was home to an estimated 280,000 children living with HIV in 2017, of which an estimated 58% were on antiretroviral treatment (ART)¹⁹⁰. Despite this high prevalence of HIV, and despite ART's notorious potential to cause adverse drug reactions (ADRs) and drug-drug interactions, drug safety is a relatively understudied field in South Africa. Local paediatric drug safety data could potentially contribute to clinical decision-making and health programme policymaking.

Our main aim with this survey was to describe the prevalence of serious ADRs in two paediatric hospitals in South Africa, including the prevalence of serious ADRs at the time of admission and the prevalence of serious ADRs occurring during the admission. Further aims were to describe serious ADR manifestations and the drugs implicated in serious ADRs, to describe the preventability of serious ADRs, to describe the prevalence and manifestations of non-serious ADRs in this setting, and to explore the influence of HIV on ADRs occurring in this patient population.

6.3 Methods

6.3.1 Design and setting

We conducted this observational study through folder review of data documented during routine clinical care of patients at two hospitals in South Africa: Red Cross War Memorial Children's Hospital (RCWMCH), situated in Cape Town, Western Cape province, and Rahima Moosa Mother and Child Hospital (RMMCH), situated in

Johannesburg, Gauteng province. We selected these sites based on existing research collaborations. Both sites have paediatric ART clinics.

At RCWMCH, we surveyed all patients admitted electively and non-electively over a 30-day period in April and May 2015 to the general and specialist medical wards, to high-care beds in the medical wards, to the combined paediatric intensive care unit, and to the general section (but not the rehydration section) of the short-stay ward. We excluded admissions to surgical or oncology wards if the entire stay was spent in the surgical and oncology wards, but included those portions of surgical and oncology patients' admissions spent in the paediatric intensive care unit. The hospital provides limited neonatal services. Admission trends to RCWMCH have previously been described¹⁹¹. At RMMCH, we surveyed all patients admitted non-electively over a 30-day period in June and July 2015 to the medical wards and to the combined intensive care / high-care unit. Although RMMCH provides neonatology services, we only surveyed those neonates admitted to the intensive care / high-care unit, and not those admitted to the postnatal wards. Elective admissions to RMMCH, which were excluded from our survey, consisted mostly of children admitted as day patients for minor surgical procedures.

6.3.2 Sample size considerations

We calculated that a sample of 514 patients would detect a prevalence of serious ADRs present at admission of 2.9% (based on a previous systematic review⁷¹) with a 95% confidence interval (CI) of 1.6 to 4.8%, using the exact CI method of Clopper-Pearson¹⁹². Based on historic admission trends at the sites and specific wards included in the survey, we were confident that we would survey at least 514 admissions during the planned study duration.

6.3.3 Study processes

We consulted hospital administrative records every weekday during the 30-day survey period to identify all new admissions. The survey team (a general practitioner and a pharmacist) reviewed each patient's clinical notes, medication prescription charts, and laboratory results as soon as possible after admission and approximately every second day thereafter until the patient's discharge or death, or until study closure, seven days after the end of the 30-day survey entry period. At the time of the patient's discharge, the survey team specifically reviewed the discharge summary prepared by the clinical team to verify and augment data already collected. For patients admitted to the RCWMCH short-stay ward, we conducted folder reviews retrospectively approximately five months following the admission, and not prospectively as described above, as piloting showed it to be too resource-intensive to survey admissions prospectively in this ward.

We abstracted demographic and clinical data (including medication histories) from all patients using electronic case report forms. The survey team identified potential ADRs during the folder review with the help of a trigger tool (Table 6.1, development described below). For cases flagged by the trigger tool, we abstracted a more detailed dataset, including relevant laboratory results, and details on the management and outcome of the potential ADR. In a second stage of ADR identification and assessment, a multidisciplinary team (the survey team, together with a paediatrician, a paediatrician highly experienced in neonatology, a clinical pharmacologist, and a clinical pharmacist) discussed flagged cases' abstracted data to reach consensus on causality (thereby determining whether the potential ADR was actually an ADR), ADR type, seriousness, and preventability, using definitions described below.

Table 6.1. Trigger list used to assist in identifying potential adverse drug reactions

Category	Trigger
Use of these drugs (antidotes) suggests	Naloxone
	Methadone
	Flumazenil

Category	Trigger
a potential ADR occurred	Digoxin immune fab ("Digibind")
	Protamine sulphate
	Activated charcoal
	Biperiden / promethazine / diazepam
	Sodium polystyrene ("Kayexalate")
	Insulin with glucose
	Calcium gluconate
	Dextrose 10%
	Adrenaline (epinephrine)
	Systemic corticosteroid
	Diphenhydramine, prochlorperazine, promethazine, or any new antihistamine
	Antiemetics
	Oral vancomycin
	Granulocyte colony-stimulating factor
Supratherapeutic drug concentration suggests a potential ADR occurred	Digoxin > 1.5 nmol/L
	Theophylline > 110 µmol/L
	Lidocaine > 5 µg/L
	Phenytoin > 80 µmol/L
	Carbamazepine > 51 µmol/L
	Phenobarbital > 172 µmol/L
	Valproic acid > 700 µmol/L
	Gentamicin or tobramycin peak > 10 mg/L or 24 h trough > 2 mg/L
	Amikacin peak > 30 mg/L or 24 h trough > 2 mg/L
	Vancomycin trough > 25 mg/L or > 30 mg/L during continuous infusion
	Any other drug concentration reported as supratherapeutic
	Paracetamol concentration done (regardless of result)
Laboratory result (other than TDM) suggests a potential ADR occurred	Partial thromboplastin time (PTT) > 100 seconds
	International normalised ratio (INR) > 5
	Anti-factor Xa ≥ 1.5 IU/mL
	Platelet count < 50 x 10 ⁹ /L
	White cell count < 3 x 10 ⁹ /L
	Haemoglobin < 8 g/dL
	Pancytopenia
	<i>Clostridium difficile</i> positive stool after exposure to antibiotics
	Creatinine rising to above-normal range
	Hyponatremia or Hypernatremia
	Potassium < 3.5 mmol/L, in the absence of diarrhoea
	Potassium > 5.5 mmol/L
	Alanine transaminase (ALT) > three times upper limit of normal (ULN = 40 IU/L) in the presence of negative viral hepatitis screening test results
	Bilirubin > two times upper limit of normal (ULN = 21 µmol/L); if in a neonate, the neonate should also be on drugs
	Serum glucose <3 mmol/L, outside the perinatal period
	Hyperlactatemia on antiretroviral therapy
Clinical event suggests a potential ADR occurred	Angioedema or lip swelling
	Rash or ulceration
	Mucositis or mucosal ulceration
	Pruritus
	Sudden onset wheezing
	Jaundice, new onset
	Dystonia, ataxia, torticollis, dyskinesia
	Retinopathy in premature infant on oxygen
	Hearing disturbance or hearing loss
	Seizure(s)

Category	Trigger
	Oversedation, lethargy, falls
	Decreased level of consciousness or pressure sores
	Delirium
	Fracture or osteoporosis
	Upper gastrointestinal bleed
	Arrhythmia, new
	Hypertension
	Nausea reported by parents / documented in file
	Constipation
	Biopsy of bone marrow, kidney, or liver
	Withdrawal symptoms
	Any other event suspected to be drug-related by doctor or nurse
	Unexplained medication stop
	Readmission to acute care unit within 14 days of discharge
	Readmission to intensive care unit within 48 hours of transfer or discharge
	Require resuscitation in ward
	Death

6.3.4 Definitions, classifications, and taxonomies

We defined ADRs according to the 2005 Aronson and Ferner definition¹⁹. We performed causality assessment according to the World Health Organization (WHO)-Uppsala Monitoring Centre system for standardised case causality assessment²⁸. Those potential ADRs where drug causation was assessed as certain, probable, or possible were counted as ADRs. We specifically did not consider the following scenarios to be ADRs: intentional drug overdose, poisoning by or ingestion of nonmedicinal products, poisoning by herbal or traditional remedies, therapeutic failures, complications associated with poor adherence, and medication errors which were not associated with any harm. We codified ADRs to 'preferred terms' in version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA®, MedDRA Maintenance and Support Services Organization, McLean, VA, USA). We classified ADRs as preventable if at least one of the Schumock and Thornton preventability questions³⁶ were answered affirmatively by the multidisciplinary team. We classified ADRs in accordance with the Rawlins and Thompson classification as type A or type B¹⁹³. We used this classification to decide the level at which we conducted causality and preventability assessment in the event that multiple drugs were implicated in the ADR, as described in a previous

paper by our group¹⁰⁵. If multiple drug suspects were implicated in a type A ADR, we assessed causality and preventability based on the combined action of all the drug suspects. If multiple drug suspects were implicated in a type B ADR, we assessed causality and preventability for each drug suspect–ADR pair separately. We categorised the seriousness of ADRs as per Temple¹¹³, as causing: (i) increased monitoring but no harm; (ii) temporary harm, requiring treatment intervention; (iii) initial / prolonged hospitalization; (iv) permanent harm; (v) near-death; or (vi) death. We defined serious ADRs as those ADRs resulting in hospital admission, or prolonging hospital admission, or causing permanent harm, near-death, or death.

We recorded drugs by generic names only and codified these according to the World Health Organization's Anatomical Therapeutic Chemical Classification System (ATC)¹⁷². We defined the total drug count as the number of unique ATC codes to which the patient was exposed over the 30-day period before the admission and during their observed hospital stay. We similarly calculated a background drug count (over the 30-day period before the admission) and an in-hospital drug count for each admission. When determining drug counts, we excluded drugs applied topically to the skin, eyes, ears, nose, throat, or mouth.

We categorised age according to National Institute of Child Health and Human Development Pediatric Terminology as follows: preterm neonate, born before 37 completed weeks' gestation; term neonate, from birth to 27 days; infancy, 28 days to 12 months; toddler, 13 months to 24 months; early childhood, 25 months to 5 years; middle childhood, 6 years to 11 years; early adolescence, 12 years to 18 years¹⁹⁴. We used the admission weight to calculate a weight-for-age z-score using standards developed in the WHO Multicentre Growth Reference Study¹⁹⁵ for infants, toddlers, and children in early childhood years. We abstracted HIV status as infected, negative, or unknown, and perinatal HIV exposure status in children < 18 months old as exposed, unexposed, or unknown. We combined HIV status and perinatal HIV exposure into a

single stratified variable as follows: (1) HIV-infected; (2) HIV-negative, consisting of children < 18 months who were not perinatally exposed, children ≥ 18 months who were serologically negative, and children ≥ 18 months in whom HIV testing was not clinically indicated; and (3) an indeterminate group of children < 18 months, who were or may have been perinatally exposed to HIV but whose HIV infection status was not yet confirmed.

6.3.5 Trigger tool development

We conducted a literature review to identify previous studies that used triggers to detect potential ADRs or harm in children, or potential ADRs in adults. We combined all the drug-related triggers from these various tools. A multidisciplinary panel of seven experts (a clinical pharmacist, a clinical pharmacologist, two paediatricians, a paediatric HIV clinician, and two research medical officers) then decided on the inclusion of each trigger in a two-round modified Delphi method. In round 1, each expert independently rated the inclusion of the trigger on a 5-point Likert scale (5 = strongly agree that the trigger should be included on the trigger tool; 1 = strongly disagree that the trigger should be included on the trigger tool). We calculated the median score, first (Q1), and third (Q3) quartiles for each trigger. We defined agreement to include each potential trigger as a median score ≥ 4 and $Q1 \geq 4$, and agreement to exclude each potential trigger as a median score ≤ 2 and $Q3 \leq 2$. Additionally, experts were asked to add potential triggers to the list during round 1. In round 2, experts met to discuss triggers without agreement to include or exclude, as well as all the potential triggers added during round 1. Experts then re-scored, or in the case of newly added triggers scored, these triggers independently on the same scale. We again defined agreement to include each potential trigger as a median score ≥ 4 and $Q1 \geq 4$. Triggers with agreement to include in the first or second round were included in the final trigger list.

6.3.6 Data management and statistical analysis

We entered data into a purpose-built Access 2013 database (Microsoft Corporation, Redmond, WA). We analysed data using Stata 13.1 (Stata Corporation, College Station, TX), including the macro igrowup_restricted.ado (version 3.2.2, January 2011)¹⁹⁶ to calculate weight-for-age z-scores.

We summarised continuous variables by means and standard deviations, or by medians and interquartile ranges (IQR), depending on their distribution. We explored associations between binary and categorical variables through cross-tabulation and chi-square statistics, and we conducted between-group comparisons of continuous variables using the Wilcoxon rank-sum test or Student's t test, depending on the distribution. A P value of < 0.05 was taken to indicate statistically significant difference.

We conducted multivariate analysis of associations with serious ADRs by constructing a logistic regression model. We limited this model to children documented to have been exposed to at least one drug before and /or during their admission, and to first admissions only in the event of multiple admissions per patient. Variables which were selected *a priori* for inclusion in the model as predictor variables were age category, sex, hospital site, the summary HIV infection / exposure category described above, and total drug count. In the subgroup of patients for whom weight-for-age z-scores could be calculated, we conducted an explorative analysis adding this variable to the model.

6.3.7 Ethical issues

Our study received ethical approval from the Human Research Ethics Committees of the University of Cape Town (approval number 576/2011) and the University of the Witwatersrand (clearance certificate number M140707). We received permission to conduct the research from both hospitals. We did not request individual patients' or caregivers' consent, as this study was a non-interventional review of medical records, and this was approved by the ethics committees. We shared anonymised study

findings with the South African National Adverse Drug Event Monitoring Centre, which collects spontaneous reports on behalf of the national medicines regulator. Partial, provisional results were shared at the 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management and were published as an abstract¹⁹⁷.

6.4 Results

6.4.1 Trigger tool development

Our literature search yielded 31 articles. We compiled a list of 110 triggers from 16 included studies (see Appendix Ix). In round 1 of the modified Delphi method, we agreed to include 37 triggers and agreed to exclude one. In round 2, 74 triggers (72 from round 1 and two newly proposed triggers) were discussed. We agreed to include a further 35; the final trigger list consisted of 72 triggers (Table 6.1). Seventeen triggers refer to drugs used as antidotes (e.g. naloxone) or in the management of adverse events, 12 describe laboratory evidence of high drug concentrations, 16 refer to other abnormal laboratory values, and 27 relate to clinical events suggesting adverse drug events (e.g. unexplained medication stop.)

6.4.2 Sample description

There were 1050 patients and 1106 admissions (range one to four admissions per patient). Patient characteristics are described in Table 6.2, and admission characteristics in Table 6.3. Respiratory infections were the most common reason for admission, forming one-third of admission diagnoses (Appendix Ix). Beta-adrenergic inhalants, antipyretics, and penicillins and other beta-lactam antibiotics were the most common drugs to which children were exposed prior to their admission (Appendix Ixi), although one in five folders did not contain a pre-admission drug exposure history. The

same drug classes, together with vitamin and mineral supplements, were also the most commonly used drugs during admissions (Appendix Ixii).

Table 6.2. Patient characteristics (n=1050) at first admission to two children's hospitals, South Africa, 2015

	All patients (n=1050)	Patients with ADR(s) (any seriousness) (n=119)	Patients without ADR(s) (n=931)	P-value
Age				
Median (IQR) months	11 (2 to 41)	20 (5 to 68)	10 (2 to 37)	P=0.0010 ^e
Age categories ^a				
Preterm neonates	32 (3.1%) ^{b, c}	6 (5.0%)	26 (2.8%)	P=0.002 ^f
Term neonates	96 (9.1%) ^c	2 (1.7%)	94 (10%)	
Infants	421 (40%)	42 (35%)	379 (41%)	
Toddlers	139 (13%)	13 (11%)	126 (14%)	
Early childhood	198 (19%)	30 (25%)	168 (18%)	
Middle childhood	123 (12%)	18 (15%)	105 (11%)	
Early adolescence	41 (3.9%)	8 (6.7%)	33 (3.5%)	
Weight-for-age z-score mean (SD)				
Infants	-1.3 (2.0) (n=418)	-2.4 (2.2) (n=42)	-1.2 (2.0) (n=376)	P = 0.0002 ^g
Toddlers	-0.45 (1.5) (n=137)	-0.78 (1.2) (n=13)	-0.41 (1.5) (n=124)	P=0.3870 ^g
Early childhood	-0.54 (1.6) (n=165)	-0.54 (1.7) (n=24)	-0.54 (1.5) (n=141)	P=0.9969 ^g
Sex				
Male	590 (56%)	69 (58%)	521 (56%)	P=0.676 ^h
Female	460 (44%)	50 (42%)	410 (44%)	
HIV infection / exposure status				
HIV negative	887 (84%)	91 (76%)	796 (86%)	P=0.003 ^f
HIV indeterminate	134 (13%)	19 (16%)	115 (12%)	
HIV infected	29 (2.8%) ^d	9 (7.6%)	20 (2.1%)	
Number of admissions				
One	1001 (95%)	109 (92%)	892 (96%)	P=0.134 ^f
Two	43 (4.1%)	9 (7.6%)	34 (3.7%)	
Three	5 (0.48%)	1 (0.84%)	4 (0.43%)	
Four	1 (0.10%)	0 (0%)	1 (0.11%)	

^a Preterm neonate, born before 37 completed weeks' gestation; term neonate, from birth to 27 days; infancy, 28 days to 12 months; toddler, 13 months to 24 months; early childhood, 25 months to 5 years; middle childhood, 6 years to 11 years; early adolescence, 12 years to 18 years. ^b Preterm neonates included 16/32 (50%) moderate to late preterm (32 to <37 weeks' gestation), 12/32 (38%) very preterm (28 to <32 weeks' gestation), and 4/32 (13%) extremely preterm (<28 weeks' gestation) neonates. ^c Among all neonates (n=128): 93/128 (73%) normal or high birth weight (≥ 2500 g), 18/128 (14%) low birth weight (1500 to 2499 g), 11/128 (8.6 %) very low birth weight (1000 to 1499 g), and 6/128 (4.7%) extremely low birth weight (≤ 999 g). ^d Of whom 5/29 (17%) not yet on ART, and 24/29 (83%) on ART before and during admission. ART regimens were: 15/24 (63%) on abacavir (ABC) + lamivudine (3TC) + ritonavir-boosted lopinavir (LPV/r), 3/24 (13%) on ABC + 3TC + efavirenz (EFV), 2/24 (8.3%) on zidovudine (AZT) + 3TC + LPV/r, 1/24 (4.2%) on stavudine (D4T) + 3TC + LPV/r, 1/24 (4.2%) on AZT + 3TC + nevirapine (NVP), 1/24 (4.2%) on AZT + 3TC + EFV, and 1/24 (4.2%) on an unknown ART regimen. ^e Wilcoxon rank-sum test. ^f Fisher's exact test. ^g Student's t test. ^h Chi-square test. ADR: adverse drug reaction; IQR: interquartile range; SD: standard deviation

Table 6.3. Admission characteristics (n=1106) at two children's hospitals in South Africa, 2015

	All admissions (n=1106)	Admissions with ADR(s) (any seriousness) (n=120)	Admissions without ADR(s) (n=986)	P-value
Hospital				
RCWMCH	886 (80%)	100 (83%)	786 (80%)	P=0.349 ^c
RMMCH	220 (20%)	20 (17%)	200 (20%)	
Type of admission				
Acute admission	998 (90%)	113 (94%)	885 (90%)	P=0.124 ^c
Elective admission	108 (9.8%)	7 (5.8%)	101 (10%)	
Admission ward				
Short-stay ward only	514 (46%)	28 (23%)	486 (49%)	P<0.001 ^c
Medical wards, not ICU ^a	459 (42%)	60 (50%)	399 (40%)	
Any time spent in ICU	133 (12%)	32 (27%)	101 (10%)	
Duration of stay observed (censored at study end) (n=1105)^b				
1 day	72 (6.5%)	2 (1.7%)	70 (7.1%)	P<0.001 ^c
2 to 3 days	541 (49%)	27 (23%)	514 (52%)	
4 to 6 days	229 (21%)	20 (17%)	209 (21%)	
≥ 7 days	263 (24%)	71 (59%)	192 (19%)	
Median (days)	3	8	3	P <0.0001 ^e
Interquartile range (days)	2 to 6	4 to 13	2 to 5	
Range (days)	1 to 34	1 to 34	1 to 34	
Total stay observed (patient-days)	5744	1198	4546	
Type of exit (n=1105)^b				
Discharged / transferred out	1038 (94%)	100 (83%)	938 (95%)	P<0.001 ^d
Died	13 (1.2%)	2 (1.7%)	11 (1.1%)	
Censored (remained in-hospital by end of observation period)	54 (4.9%)	18 (15%)	36 (3.7%)	
Drug exposure over 30-day period before admission				
No drug history documented in folder	226 (20%)	12 (10%)	214 (22%)	P<0.001 ^c
No drugs	130 (12%)	7 (5.8%)	123 (12%)	
Had ≥ 1 drug(s)	750 (68%)	101 (84%)	649 (66%)	
Median background drug count	2 (n = 880)	4 (n=108)	2 (n=772)	P<0.0001 ^e
Interquartile range	1 to 4	2 to 7	1 to 4	
Range	0 to 47	0 to 42	0 to 47	
Drug exposure during admission (n=1105)^b				
No drugs	69 (6.2%)	2 (1.7%)	67 (6.8%)	P=0.028 ^c
Had ≥ 1 drug(s)	1036 (94%)	118 (98%)	918 (93%)	
Median in-hospital drug count	4 (n=1105)	11 (n=120)	4 (n=985)	P<0.0001 ^e
Interquartile range	3 to 9	7 to 19	2 to 7	
Range	0 to 46	0 to 46	0 to 36	
Median daily drug count	5 (n=5744 patient-days)	9 (n=1198 patient-days)	4 (n=4546 patient-days)	
Interquartile range	3 to 8	5 to 13	2 to 7	
Range	0 to 29	0 to 29	0 to 23	
Total drug exposure (before and during admission)				
No drugs	49 (4.4%)	0 (0%)	49 (5.0%)	P=0.012 ^c
Had ≥ 1 drug(s)	1057 (96%)	120 (100%)	937 (95%)	
Median total drug count	6	12	5	P<0.0001 ^e
Interquartile range	3 to 10	8 to 21	3 to 9	
Range	0 to 52	2 to 47	0 to 52	

^a May have moved from short-stay to medical ward; may have included a high-care stay during the admission. ^b Duration of stay, drug exposure during admission, and type of exit missing for one admission (an admission without an

ADR). ^c Chi-square test. ^d Fisher's exact test. ^e Wilcoxon rank-sum test. ADR: adverse drug reaction; ICU: intensive care unit; RCWMCH: Red Cross War Memorial Children's Hospital; RMMCH: Rahima Moosa Mother and Child Hospital

There were 29/1050 (2.8%) HIV-infected children: 24 were on ART before the admission, while five were newly diagnosed during the index admission and referred to start ART after discharge. Most (19/24, 79%) were on a regimen of ritonavir-boosted lopinavir and two nucleoside reverse transcriptase inhibitors (NRTIs), while 4/24 (17%) were on a regimen of a non-nucleoside reverse transcriptase inhibitor and two NRTIs, and 1/24 (4.2%) on an unknown regimen. The NRTIs in use were lamivudine in all 23 children, abacavir in 18, zidovudine in 4, and stavudine in 1. Fifty-one children were exposed to nevirapine for the prevention of mother-to-child HIV transmission (PMTCT) before and/or during their admissions, with additional zidovudine in 12 children.

6.4.3 Serious ADRs

The multidisciplinary panel confirmed the diagnosis of 160 ADRs, 40 of which were serious (18 caused admission, 14 prolonged admission, 7 were near-fatal, and one resulted in death). Twenty serious ADRs were present at the time of admission (Appendix lxiii), and 20 occurred during admission (Appendix lxiv). The crude prevalence of serious ADRs was 3.8 per 100 drug-exposed admissions, consisting of 2.7 serious ADRs present at admission per 100 drug-exposed admissions and 1.9 serious ADRs occurring during the admission per 100 drug-exposed admissions. Alternative ways of expressing the ADR prevalence are given in Appendix lxv.

Thirty of 40 serious ADRs were classified as type A reactions; causality assessment rated seven type A ADRs as certain, six as probable, and 17 as possible. Ten of 40 serious ADRs were classified as type B reactions or were classified as a mixture of type A and B mechanisms. There were 17 drug-ADR pairs implicated in these ten ADRs, and causality assessment rated 2 pairs as certain, 5 as probable, and 10 as possible.

Serious ADR manifestations encountered more than once were: four cases of diarrhoea prolonging the admission, two cases of near-fatal respiratory depression, two cases of near-fatal hyperkalaemia, two cases of dystonia causing admission, two cases of urticaria causing admission, and two cases of bicytopenia prolonging the admission.

Individual drugs most commonly implicated in serious ADRs were: prednisone (H02AB07, 5 times), methylprednisolone (H02AB04, 3 times), amoxicillin (J01CA04, 3 times), mycophenolic acid (L04AA06, 3 times), and tacrolimus (L04AD02, 3 times). Drug classes most commonly implicated in serious ADRs were (by second-level ATC code): systemic antibacterials (J01) in 12 serious ADRs, systemic corticosteroids (H02) in 6 serious ADRs, psycholeptics (N05) in 4 serious ADRs, immunosuppressants (L04) in 4 serious ADRs, direct-acting antivirals (J05) in 4 serious ADRs, and analgesics (N02) in 3 serious ADRs (Table 6.4). Relative to the frequency of exposure to these drug classes, immunosuppressants (L04) were disproportionately frequently implicated (Appendix lxvi).

Table 6.4. Drug classes commonly implicated in serious ADRs and the associated ADR manifestations

Drug class	Serious ADRs
Systemic antibacterials (J01), implicated in 12 serious ADRs	• Diarrhoea with amoxicillin (2 cases) and with clarithromycin (1 case), prolonging the admissions • Urticaria with phenoxymethylpenicillin (1 case) and with ceftriaxone (1 case), causing the admissions • Maculo-papular rash with flucloxacillin, prolonging the admission • Respiratory arrest with intravenous benzathine benzylpenicillin (medication error), fatal • Red-man syndrome with vancomycin, near-fatal • Thrombocytopenia with amoxicillin, causing the admission • Agranulocytosis with co-trimoxazole (and zidovudine), causing the admission • Bicytopenia with ceftriaxone, co-trimoxazole (and ganciclovir), prolonging the admission • Metabolic acidosis with amikacin (and penicillin), causing the admission
Systemic corticosteroids (H02), implicated in 6 serious ADRs	• Lower respiratory tract infection with prednisone, causing the admission • Upper respiratory tract infection with prednisone, causing the admission • <i>Pneumocystis jirovecii</i> pneumonia with prednisone and methylprednisolone, prolonging the admission • Salmonellosis with prednisone (and mycophenolic acid), prolonging the admission • Pancreatitis with prednisone and methylprednisolone, prolonging the admission • Sepsis with methylprednisolone (and mycophenolic acid and tacrolimus), prolonging the admission

Psycholeptics (N05), implicated in 4 serious ADRs	• Respiratory depression with chlorpromazine, lorazepam and diazepam (and phenobarbital), near-fatal • Respiratory depression with diazepam (and morphine and phenobarbital), near-fatal • Apnoea with midazolam, near-fatal • Delirium with clozapine, causing the admission
Immunosuppressants (L04), implicated in 4 serious ADRs	• Macrocytic anaemia with mycophenolic acid and tacrolimus, causing the admission • Neutropaenic sepsis with tacrolimus, prolonging the admission • Sepsis with mycophenolic acid and tacrolimus (and methylprednisolone), prolonging the admission • Salmonellosis with mycophenolic acid (and prednisone), prolonging the admission
Direct-acting antivirals (J05), implicated in 4 serious ADRs	• Agranulocytosis with zidovudine (and co-trimoxazole), causing the admission • Diarrhoea with lopinavir-ritonavir, prolonging the admission • Increased transaminases with efavirenz, prolonging the admission • Bicytopenia with ganciclovir (and ceftriaxone and co-trimoxazole), prolonging the admission
Analgesics (N02), implicated in 3 serious ADRs	• Respiratory depression with morphine (and diazepam and phenobarbital), near-fatal • Metabolic acidosis with paracetamol (and amikacin), causing the admission • Increased paracetamol plasma concentration, prolonging the admission

ADR: adverse drug reaction

Five of 30 (17%) type A serious ADRs and 4/17 (24%) type B serious ADR drug-event pairs were preventable; in total, 9/40 (23%) serious ADRs had at least one preventability factor present. The most common preventability factor was an inappropriate drug choice, which occurred in 6/40 (15%) serious ADRs. A wide variety of drugs were considered inappropriate in these cases, including benzathine benzylpenicillin, flucloxacillin, ceftriaxone, ferrous gluconate, clozapine, and amitriptyline. Inappropriate dose or route of administration occurred in 2/40 (5%) serious ADRs (drugs involved were vancomycin and metoclopramide), problems with patient adherence occurred in 2/40 (5%) serious ADRs (drugs involved were flucloxacillin and amitriptyline), insufficient laboratory monitoring occurred in 1/40 (2.5%) serious ADR attributed to tacrolimus, and a raised drug concentration occurred in 1/40 (2.5%) serious ADR attributed to tacrolimus. Alternative ways of reporting the proportion considered preventable are presented in Appendix Ixvii.

Among the 36 children with serious ADRs, one death occurred, and this was considered to be directly caused by an ADR which was the result of an error: benzathine benzylpenicillin (instead of benzylpenicillin sodium) was administered intravenously to a preterm neonate, resulting in fatal respiratory arrest. Six children with

serious ADRs remained in hospital at the end of our observation period, while 29 were discharged or transferred out. The median (IQR) length of stay observed among children with serious ADRs was 6 [3–12] days. Six serious ADRs present at the time of admission were managed entirely in the short-stay ward: two children with urticaria, two children with dystonia, and one child each with lower respiratory tract infection and convulsion. Five serious ADRs occurring during the hospitalisation prolonged the hospital stay, yet the affected children were still only managed in the short-stay ward, including three children with antibiotic-associated diarrhoea, and one child each with rash and raised transaminases.

No serious ADRs occurred among term neonates. For the multivariate logistic regression analysis, we therefore grouped term neonates together with infants. The logistic regression model (Table 6.5) confirmed the following independent associations with serious ADRs: preterm neonates, adjusted odds ratio (aOR) with 95% CI 5.97 (1.30 to 27.3) versus referent category of infants and term neonates; middle childhood, aOR 3.63 (1.24 to 10.6) versus infants and term neonates; HIV-infection, aOR 3.87 (1.14 to 13.2) versus HIV-negative; and increasing drug count, aOR 1.08 (1.04 to 1.12) per additional drug.

Table 6.5. Multivariate logistic regression model of factors associated with serious ADR (n=1001 first admissions with documented exposure to ≥ 1 drug(s))

		n	Bivariate analysis		Multivariate analysis	
			Unadjusted OR (95% CI)	P	Adjusted ^a OR (95% CI)	P
Age category ^b						
	Preterm neonate	31	5.14 (1.34 to 19.7)	0.017	5.97 (1.30 to 27.3)	0.021
Infant	Term neonate &	490	Referent			
	Toddler	137	1.07 (0.292 to 3.96)	0.914	1.13 (0.295 to 4.33)	0.858
	Early childhood	188	1.58 (0.567 to 4.42)	0.381	1.61 (0.521 to 4.97)	0.408
	Middle childhood	114	3.62 (1.40 to 9.40)	0.008	3.63 (1.24 to 10.6)	0.018
	Early adolescent	41	3.79 (1.00 to 14.4)	0.050	2.88 (0.667 to 12.5)	0.156
Sex						
	Male	564	Referent			
	Female	437	1.08 (0.537 to 2.16)	0.832	0.894 (0.428 to 1.87)	0.766
Hospital						
	RXWMCH	812	Referent			
	RMMCH	189	0.953 (0.388 to 2.34)	0.917	0.938 (0.324 to 2.71)	0.906
HIV category						

Negative	840	Referent			
Infected	29	5.44 (1.76 to 16.9)	0.003	3.87 (1.14 to 13.2)	0.031
Indeterminate	132	1.34 (0.502 to 3.57)	0.560	1.59 (0.502 to 5.05)	0.429
Total drug count					
Per additional drug	1001	1.09 (1.05 to 1.13)	<0.001	1.08 (1.04 to 1.12)	<0.001

^a Adjusted for other variables in the model

^b Preterm neonate, born before 37 completed weeks' gestation; term neonate, from birth to 27 days; infancy, 28 days to 12 months; toddler, 13 months to 24 months; early childhood, 25 months to 5 years; middle childhood, 6 years to 11 years; early adolescence, 12 years to 18 years.

ADR: adverse drug reaction; OR: odds ratio; RCWMCH: Red Cross War Memorial Children's Hospital; RMMCH: Rahima Moosa Mother and Child Hospital

In an exploratory logistic regression model (Appendix lxviii) weight-for-age z-score was not associated with serious ADR occurrence after adjustment for age, sex, hospital, HIV category, and drug count.

Four of 29 (13.8%) HIV-infected children in our survey experienced a serious ADR, including two who were admitted with serious ADRs present at the time of admission and another two who experienced serious ADRs during their admission. In three of the four cases, antiretroviral agents were implicated in the ADRs. None of the serious ADRs in HIV-infected children was considered preventable. The use of PMTCT was not implicated in any serious ADRs.

6.4.4 Non-serious ADRs

We found a further 120 non-serious ADRs, which we describe in appendices. These included 26 nonserious ADRs present at the time of admission (Appendix lxix) and 94 non-serious ADRs occurring during the admission (Appendix lxx). The most commonly implicated drug classes implicated in non-serious ADRs were systemic antibacterials (J01) in 48 ADRs, drugs for obstructive airway diseases (R03) in 23 ADRs, diuretics (C03) in 17 ADRs, mineral supplements (A12) in 11 ADRs, and systemic corticosteroids (H02) in 10 ADRs (Appendix lxxi).

6.5 Discussion

In two South African children's hospitals we found that 3.8 serious ADRs occurred per 100 drug-exposed admissions. Serious ADRs were associated with increasing drug exposure, HIV infection, and two age categories – premature neonates and middle childhood. A wide range of ADR manifestations occurred, and commonly implicated drug classes included antimicrobials, systemic corticosteroids, and antiviral agents. Considering that one in five serious ADRs was fatal or near-fatal, and about one in five serious ADRs was also preventable, these findings have significant public health importance.

It is difficult to compare the prevalence of ADRs across studies, due to differences in study settings and study designs. Nevertheless, a comprehensive 2012 systematic review⁷¹ estimated the proportion of paediatric admissions caused by ADRs to be 2.9% (95% CI 2.6 to 3.1%), using a denominator of all admissions and not only drug-exposed admissions. In our survey 1.8% of admissions were due to an ADR. However, our survey excluded admissions to the oncology ward, whereas the 2012 systematic review's figure is significantly influenced by two large surveys which found ADR-related admissions to oncology wards to be common^{198,199}. Published subsequent to the 2012 systematic review⁷¹, surveys from paediatric settings in sub-Saharan Africa suggested the proportion of admissions due to ADRs to be 5.7% (16/282) in Cape Town, South Africa¹⁰⁹, 4.7% (114/2433) in Eritrea¹⁰⁶, and 0.60% (12/2004) in Lagos, Nigeria⁹⁸. A study from Jimma, Ethiopia, with paediatric adverse drug events as outcome (i.e., a slightly different outcome than ADRs), determined the proportion of admissions to be adverse drug event-related as 0.63% (4/634)²⁰⁰. The prevalence of serious ADRs during paediatric admissions was not studied in the 2012 systematic review, although the prevalence of all in-hospital ADRs (i.e., of any seriousness) ranged from 0.6 to 16.8% among included studies⁷¹. An earlier systematic review found that 7 to 20% of in-hospital paediatric ADRs were serious⁷², with our study's proportion (20/114, 18%)

falling within this range. A previous study from Nigeria found that 0.29% (11/3821) of retrospectively reviewed paediatric admissions were prolonged due to serious ADRs⁹⁵. Our methodology, involving prospective review, probably explains why we found a much higher proportion of admissions (1.8%) being affected by serious ADRs occurring during the admission. Taking all these factors in consideration, our interpretation is that serious ADRs probably occurred at a similar frequency in our hospitals as in other paediatric settings in sub-Saharan Africa and elsewhere.

There is robust evidence from previous adult and paediatric systematic reviews^{71,72,201} confirming the association between ADR occurrence and increasing drug count. Although an association between serious ADR occurrence and sex was found in the majority of studies included in the 2012 paediatric systematic review⁷¹, we did not find any such association in this survey. Regarding associations with age, the association between ADR occurrence and prematurity which is attributable to reduced drug metabolism and clearance is also well established²⁰². Previous hospital-based surveys in the United Kingdom^{199,203}, United States¹⁹⁸, and in sub-Saharan Africa¹⁰⁶ have also, similar to our finding, described an association between ADR occurrence and later childhood. This association has been explained by older children's ability to communicate their ADRs better than younger children²⁰³. Another explanation could be that older children tend to be admitted for chronic disease processes requiring chronic medications with a greater exposure-time within which ADRs might occur, whereas younger children are mostly admitted for acute infectious disease processes requiring short-term treatment. HIV infection causes chronic immune stimulation, increased oxidative stress, and altered patterns of drug metabolism²⁰⁴, which may explain our finding that HIV infection was independently associated with the occurrence of serious ADRs. Our group has previously shown the same independent association between HIV infection and serious ADRs in South African adults^{104,105}, and an association between HIV infection and serious ADRs was also found in a recent paediatric survey from another Cape Town hospital¹⁰⁹. Lastly, despite our unadjusted analysis suggesting

an association between serious ADR occurrence and low weight-for-age, no such association was found after adjustment for other factors.

In the 2012 systematic review, between 7 and 98% of ADRs were reportedly preventable⁷¹. Our proportion of serious ADRs considered preventable, i.e. 23%, is considerably lower than the findings in our adult serious ADR surveys, where 43 to 45% of ADRs were considered preventable^{104,105}, but is in keeping with proportions from Nigeria (20%)⁹⁸ and Ethiopia (33%)²⁰⁰. The most common reason why serious ADRs were considered preventable in this survey was an inappropriate choice of drug (15%), which was also the most common reason in our adult surveys^{104,105} and one of the most common reasons (23%) cited in the 2012 systematic review⁷¹. Our survey did not yield a clear pattern of specific drugs considered inappropriate, with six different drugs involved in the six serious ADRs considered preventable for this reason.

In our survey, one child died due to an ADR, and this ADR was related to a medication error. Medication errors are common in sub-Saharan African hospitals: 75% of children admitted to general paediatric wards in a South African²⁰⁵ and an Ethiopian²⁰⁶ hospital were exposed to medication errors, as were 95% of children admitted to a South African paediatric intensive care unit²⁰⁷. High mortality and an association with medication error was also seen in the Ethiopian adverse drug event survey²⁰⁰, where 9% of adverse drug events resulted in permanent harm or death, with three of the four events that resulted in permanent harm in that survey being due to medication error. Higher mortality rates than ours occurred in Eritrea, where 19/114 (17%) children admitted for ADRs died due to their ADRs¹⁰⁶, and in Nigeria, where 2/12 (17%) of children admitted for ADRs died due to their ADRs⁹⁸. While our fatality rate may seem reassuringly low against these sub-Saharan African studies, it should be noted that an additional seven ADRs in our survey were considered near-fatal, meaning that 20% of serious ADRs may potentially have resulted in children's deaths.

The drug classes most commonly implicated in serious ADRs in our survey were systemic antibacterials, systemic corticosteroids, antivirals, psycholeptics, immunosuppressants, and analgesics. These mostly correspond with the findings of the 2012 systematic review⁷¹, bearing in mind we did not survey oncology wards and thus did not observe ADRs attributable to cytotoxics. Antibacterial agents were also commonly implicated in other sub-Saharan African surveys^{98,109,200}, particularly in association with rashes⁹⁸. Significantly, our list of commonly implicated drugs includes antivirals, which was not a common cause of ADRs in the 2012 systematic review⁷¹, and which, among three sub-Saharan African studies^{98,109,200} was only mentioned as a commonly implicated class of drugs in one¹⁰⁹.

Despite choosing sites with large paediatric ART clinics, where we expected to find admissions of HIV-infected children to be concentrated, our survey included a relatively low number of HIV-infected children among those admitted. We interpret this as evidence of the efficacy of PMTCT, which has resulted in decreasing paediatric HIV incidence and prevalence¹⁹⁰, and of the generally high efficacy and low toxicity associated with current paediatric antiretroviral regimens in use. Nevertheless, among the small number of HIV-infected children admitted during our survey, a high proportion (9/29, 31%) had ADRs, which is comparable to another South African survey in which 9/21 (43%) HIV-infected children admitted to hospital had ADRs¹⁰⁹. Our survey included 4/29 (14%) HIV-infected children with serious ADRs, of which three were attributed to the use of ART, illustrating the importance of continued vigilance when using these drugs.

One limitation of our study is that we have likely under-estimated ADR prevalence at the time of admission, as one in five folders were missing pre-admission drug exposure history, and we did not interview patients or caregivers to complement information not documented in clinical notes or verify the accuracy of recorded drug histories. Our choice of study wards (i.e., excluding surgical and oncology wards) also

resulted in under-ascertainment of ADRs associated with the use of anaesthetic and cytotoxic agents, which were major drivers of serious ADRs elsewhere^{198,199,203}. On the other hand, our study was strengthened by the inclusion of patients admitted to the short-stay ward, a setting that is often excluded^{109,198-200} from ADR surveys. We found that one quarter of all serious ADRs occurred in the short-stay ward and would have been missed had we not surveyed patients admitted there. Our study's representativeness was also strengthened by reviewing some, although admittedly not all, neonatal admissions, and by reviewing admissions to the intensive care unit.

A strength of our study was the development of a localised trigger tool to assist in identifying potential ADRs.

We did not determine the contribution of off-label use of drugs to the burden of ADRs. This was previously described as a risk factor for development of ADRs: in the 2012 systematic review⁷¹ three out of three studies which investigated it confirmed unlicensed or off-label use to be a risk factor for the occurrence of ADRs.

Our study was conducted in specific wards of two urban hospitals in the two best-resourced provinces of South Africa, and findings may therefore be considered context-specific, rather than generalisable to other settings. For this reason, replicating this survey in other wards, or in more resource-constrained or rurally located hospitals, and/or periodically repeating this survey or a scaled version thereof would provide a clearer picture of the burden of serious adverse drug reactions our children face.

6.6 Conclusions

Serious ADR prevalence at two paediatric hospitals in South Africa was, at 3.8 serious ADRs per 100 drug-exposed admissions, similar to the prevalence described in hospital settings elsewhere. Similar to other sub-Saharan African studies, a large proportion of serious ADRs were fatal or near-fatal, and around one-fifth of serious

ADRs were preventable. In keeping with South Africa's high burden of HIV, we found that the antiviral drug class was one of the most commonly implicated classes in serious ADRs. Serious ADRs were independently associated with increasing drug count, HIV infection, and two age categories: premature neonates and middle childhood.

Chapter 7 Overall discussion and conclusion

7.1. Addressing the thesis aims and objectives: summary of findings, strengths and weaknesses, and novel approaches

The first objective of this thesis was to compare the interrater agreement of two adverse drug reaction (ADR) causality assessment methodologies, using a sample of cases from our adult ADR admissions survey. There were two reasons for conducting this study. First, the outcome would decide the tool to be used for causality assessment of potential ADRs identified throughout the remainder of the thesis's research projects. While one would ideally have wanted to conduct a more comprehensive assessment of a variety of different tools before deciding on the "best" to use, this head-to-head comparison of two tools, each representative of a different methodology, was what was practically possible to conduct within the scope of this project. Second, however, this study would address a more general question on whether a method newly developed and apparently performing well in a specific setting elsewhere could be transferable and appropriate for local use. Our study resulted in the somewhat surprising and counterintuitive finding that the Liverpool ADR Causality Assessment Tool, a tool formatted as a seemingly easy to use flowchart, resulted in lower interrater agreement than an unstructured "global introspection" method. While our study was not designed to determine precise reasons for this, we postulated that a potential reason may be found in the design of the algorithm, allowing it to suffer loss of information. However, we also acknowledge that other reasons may explain our finding, such as factors inherent to the raters who applied the tool, to the nature of the potential ADRs we encountered, or to the way we collected, summarised, and presented information about the potential ADRs to the raters. Regardless of the precise reasons, we determined that the World Health Organization-Uppsala Monitoring Centre ADR causality assessment methodology would be used in our serious ADR surveys, because of its higher interrater agreement. In addition, we

demonstrated that tools developed in other settings may not necessarily be transferable to ours, and requires investigation before use.

The second objective of this thesis was to describe the burden of serious ADRs in adult and paediatric medical wards of selected hospitals in South Africa. A summary of the main findings of our three surveys, described in Chapters 4 to 6, is given in Table 7.1.

Table 7.1. Summary of serious ADR prevalence, preventability, presentation, and risk factors

	Serious ADR category and setting		
	ADRs contributing to death among adult inpatients	ADRs causing admission among adult inpatients	Serious ADRs among paediatric inpatients
Serious ADR prevalence	As proportion of all in-hospital deaths: 56/357 (16%)	As proportion of all admissions: 164/1951 (8.4%)	Per 100 drug-exposed admissions: 2.7 serious ADRs were present at admission and 1.9 serious ADRs occurred during the admission
Proportion of serious ADRs preventable	30/69 (43%)	73/164 (45%)	9/40 (23%)
Most common clinical presentations	Renal impairment, drug-induced liver injury, intracranial bleed, hypoglycaemia	Renal impairment, hypoglycaemia, drug-induced liver injury, haemorrhage, blood dyscrasias	Diarrhoea, respiratory depression, hyperkalaemia, dystonia, urticaria, bicytopenia
Drugs most commonly implicated	Tenofovir disoproxil fumarate, rifampicin, co-trimoxazole, furosemide, insulin	Rifampicin, tenofovir disoproxil fumarate, insulin, warfarin, enalapril	Prednisone, methylprednisolone, amoxicillin, mycophenolic acid, tacrolimus
Risk factors identified	Having higher drug exposure count, being HIV-positive and on ART, having higher non-HIV comorbidity score	Having female sex, having increasing drug exposure count, being HIV-positive and on ART, having increasing non-HIV comorbidity score	Being preterm neonate, being in middle childhood years, having increasing drug exposure count, being HIV-positive
Risk associated with HIV	HIV-positive persons on ART had four times the odds of ADR-related death compared with HIV-negative persons: aOR 4.4, 95% CI 1.6 to 12	HIV-positive persons on ART had twice the odds of ADR-related admission compared with HIV-negative persons: aOR 1.92, 95% CI 1.17 to 3.14	HIV-positive children had four times the odds of developing serious ADRs compared with HIV-negative children: aOR 3.87, 95% CI 1.14 to 13.2

ADR: adverse drug reaction; aOR: adjusted odds ratio; ART: antiretroviral therapy; CI: confidence interval

Our surveys found that the burden of serious ADRs in South Africa is different to that described in resource-rich settings, particularly among adults, and that it reflects South Africa's colliding epidemics of infectious and non-communicable disease. Similar to resource-rich settings, we encountered a number of serious ADRs associated with treatment for chronic lifestyle diseases, such as hypoglycaemia occurring with drugs

used in the management of diabetes mellitus. These serious ADRs were clustered in older adults and were often considered preventable. However, we encountered an additional burden of serious ADRs associated with the management of chronic infectious diseases, which clustered in younger adults, and were less often considered preventable.

We consistently found in all three surveys that HIV infection was associated with serious ADR outcomes: after adjustment for the total count of drugs used and for other factors, odds for serious ADRs were two- to four-fold higher in HIV-positive than in HIV-negative persons. At the time we conducted the surveys, the programmatically recommended first line ART for adults in South Africa was tenofovir disoproxil fumarate, lamivudine, and efavirenz¹⁷³. This combination has a much better safety profile than previously recommended first-line regimens which included drugs such as stavudine, zidovudine, and nevirapine. We strongly believe that, despite the apparent increased risk for serious ADRs, the prospect of benefit of antiretroviral therapy massively outweighs the risk of harm attributable to these drugs. Moreover, HIV treatment programmes are continually evolving and today dolutegravir has replaced efavirenz as recommended first-line treatment in South Africa, while tenofovir disoproxil fumarate has already been replaced by the less toxic prodrug tenofovir alafenamide in other sub-Saharan African countries' programmes. While our survey findings have lost some relevance over time, and current estimates of the size of the association between HIV infection and serious ADRs may be lower as a result of these programmatic changes, the fact these changes occur highlights the need for periodically repeating this type of surveillance activity and/or embedding ADR surveillance within treatment programmes.

A second "golden thread" seen in all the surveys was that inappropriate drug selection was the most common reason serious ADRs were considered preventable. In other words, patients received a drug for which no indication existed or against which a

contraindication existed. While we did not systematically seek the root causes of these errors in our surveys, we observed anecdotally that many of these errors did not occur at the time of the initial drug prescription, but rather that contra-indications developed later and were not picked up at the time repeat prescriptions were given. In this vein, we believe the first step towards prevention should be to provide decision support to prescribers, which is suited to limiting the occurrence of this type of errors.

A few points should be noted about our survey methodology. Sites were not randomly sampled, but were situated in four of South Africa's nine provinces, including some of the most resource-deprived provinces, and represented a mix of levels of care. Still, sites were all urban or peri-urban and not rural, and while we were deliberate in our choice to maximize representation of HIV-positive people in these surveys by including sites in areas of high HIV prevalence, we did not specifically target including other special populations such as pregnant women, people with cancer, people with renal impairment, etc. At the chosen sites, we were not always able to include all the subspeciality medical wards and intensive care units, particularly at the adult tertiary hospital in Cape Town. Nevertheless, we believe our surveys to be more representative than three previous ADR or adverse event hospital surveillance studies in South Africa which were summarised in Chapter 1⁵⁹⁻⁶¹.

Our surveys were not designed to be able to detect all serious ADRs. In our adult surveys, we only observed ADRs causing hospitalisation to the medical wards and ADRs contributing to the death of inpatients in the medical wards. However, we did not attempt to determine the burden of ADRs prolonging hospitalisation, or those that were near-fatal and occurred in hospital. While the latter two categories were included in the paediatric survey, none of our survey designs allowed for longitudinal follow-up of patients and so we could not detect disabling or incapacitating ADRs or those resulting in congenital abnormalities.

We were granted a waiver from obtaining participant consent for data collection by the ethics committees, as the data were collected by record review of routinely collected clinical information, without interaction with patients. This ensured that we were able to review the folder of every person admitted, minimising bias. In the adult admission survey, which was conducted prospectively, there was not one single missing folder, while only a few folders were missing at the stage of retrospective review in the paediatric survey. As illustrated in other studies included in the systematic review, such a low level of data missingness is unusual.

We implemented robust case-finding and case-confirmation methodology, using methods of hospital ADR surveillance which have been established since the 1960s. Potential ADRs were identified through intensive surveillance by a multidisciplinary team (involving a doctor and pharmacists). We used trigger lists to help identify potential ADRs, and these trigger tools were adapted for local use previously (adults) or alongside the survey (paediatrics). We collected drug utilisation data for all admitted patients regardless of the reason for admission, and we collected more extensive data in those with potential ADRs. One trade-off against the decision to collect data from record review only, rather than collecting information directly from patients after obtaining consent, was that we could not approach patients, caregivers, or other health care facilities for further information, for example in situations where a drug history was not documented in the folder. This situation affected approximately one in every five folders and may have resulted in under-ascertainment of the outcome.

Causal association, preventability, and seriousness were robustly assessed by a multidisciplinary panel including clinicians based at the research sites. Including these clinicians was particularly valuable in providing insights about local treatment guidelines and patterns, and local resource limitations, which may particularly influence decisions regarding preventability when using the Schumock and Thornton questionnaire³⁶. However, it is important to note that we required stricter evidence of

causal association in the adult admissions study than in the adult mortality study. In the latter, we considered “ADR-related” deaths to be any death where an ADR may have caused or contributed to the sequence of events that eventually resulted in death. In contrast, in the adult admissions study we required the ADR to be the main and sole cause of admission. This distinction was in part necessitated by the nature of the data available for review – cause of death was often difficult to precisely discern from the clinical notes whereas reasons for admission are routinely documented.

Our surveys required some novel approaches where limited evidence existed for how best to approach problematic situations. To describe the relationship between ADRs and death we decided to classify whether the ADR was considered “a contributing factor”, or “a major contributing factor” to the death, or did not contribute. Another such situation involved the question how to assess ADR causality when more than one drug could be implicated in the ADR. Going strictly by our chosen causality assessment methodology (or that of many other methods), ADR causality is assessed one drug at a time, and the presence of a second drug suspect reduces the likelihood that the index drug is considered causally related. We thought this unsatisfactory, for example in patients who presented with hypoglycaemia but who were on multiple hypoglycaemic agents where we felt convinced that it was the combination of medicines that resulted in the ADR, and that the effect of individual drugs could not be disentangled. Our solution was to assess ADR causality on the level of individual drugs only if the suspected ADR mechanism is a type B reaction (that is, an idiosyncratic, non-dose dependent ADR)^{33,193}. However, in dose-dependent, predictable type A reactions, we assessed causality on the basis of the combined effect of the drugs. Although this felt intuitively appropriate, we could not find any clear precedent in the literature.

The third objective of this thesis was to conduct a systematic review of the literature on the burden of serious ADRs in sub-Saharan Africa, including the results from our own surveys, in order to contextualise our findings.

We conducted a wide search, including grey literature such as theses and dissertations, non-peer-reviewed studies, and conference abstracts, and without language restriction. Despite this wide search we found only a handful of studies describing the ADR burden in sub-Saharan Africa. Assessing the study quality against the prespecified tool, these studies were generally of high quality. We also found that our own survey findings were quite representative of the situation in sub-Saharan Africa, with our serious ADR prevalence near the median of studies', and the types of ADRs and implicated drugs similar to those in other studies. In synthesis, we considered that the burden of ADRs in sub-Saharan Africa is underappreciated, and likely to be as high as that in high-income settings, that the quality of evidence coming out of the region is not low, and that HIV infection uniquely contributes to the ADR burden in this setting.

Considering all the above, the overall aim of this thesis, which was to provide high-quality descriptive data on the burden of serious ADRs in South Africa, was achieved.

7.2. Implications

7.2.1. Implications for clinical care, education, and health policy

Our work has implications for the clinical care of patients of which clinicians and policymakers should take note. First, as it has been shown by others that health care workers in South Africa may not have the knowledge or skills to identify and manage ADRs^{39,40,56-58}, our research reinforces that there is a need for health care worker education and training on drug safety, and for health care workers to have access to reliable sources of medicines information. The risk factors identified in our surveys may assist health care workers to identify ADRs earlier: the two risk factors consistently appearing in all three surveys were a higher drug count, and living with HIV.

Second, when it comes to prevention, clinicians and policymakers have an important role to play, and our surveys showed the most common reason for preventability to have been the inappropriate use of drugs. Most of the drugs causing preventable ADRs are only available on prescription, and anecdotally, in instances of inappropriate use we often saw that a contra-indication which had developed since the original drug prescription was issued, had not been detected or considered at the time a repeat prescription was issued. Prescribers of repeat prescriptions are often junior health care workers, and therefore the obvious starting point in limiting this harm is to provide better oversight over their prescriptions. This may be achieved by increased supervision from more senior clinicians, or more intense scrutiny of prescriptions by pharmacists for contraindications, or in the form of electronic prescribing with decision support, which does not currently exist in the South African public health sector. To take full advantage of such electronic prescribing and decision support systems they should however be linked to laboratory and/or clinical records to enhance checking against comorbid conditions forming contra-indications²⁰⁸. The gradual progression of chronic kidney disease provides a good example where a decision support system might flag inappropriate drug prescriptions or inappropriate dosages, based on linked laboratory kidney function results, and the system might suggest alternative regimens or dosages. It may well be pointed out here that, while acknowledging differences in methodology existed, there had been virtually no change in the proportion of serious ADRs in adults considered preventable in the surveys described in this thesis (43 to 45%), when compared to two earlier South African surveys in 2009 (46%) and 1985 (50%). This suggests the issue is not something that will improve over time by itself, but that it requires intervention to improve.

Third, clinicians and policymakers have a responsibility for providing patient education on the importance of early recognition of ADRs; improved health literacy and better access to health information, including patient information leaflets to be distributed together with medications, will be beneficial.

7.2.2. Implications for regulatory authorities

We have shared the results of our surveys with the South African Health Products Regulatory Authority's Pharmacovigilance Advisory Committee. We do not believe that our research has significant implications for medicines regulatory authorities: we did not detect any previously unknown ADRs, nor any unexpected signals regarding the frequency or seriousness of known ADRs. The Health Inspectorate, which is tasked with ensuring patient safety (in South Africa, the Office of Health Standards Compliance), should also take note of our findings, particularly regarding the high proportion of ADRs considered to have been preventable.

7.2.3. Implications for future research

Repeated studies are needed to monitor the burden of serious ADRs as disease patterns and treatment patterns change over time. Future studies may be scaled up to be even more representative, for example by including more primary care settings, and/or secondary and tertiary hospitals in a wider geographic distribution, or may be conducted at a smaller scale at representative sentinel sites. Our surveys did not specifically consider geriatric, psychiatric, oncology, or surgical settings, and the burden of ADRs in these settings in South Africa remains to be evaluated. While we consider our studies reasonably representative of the situation in South Africa, studies elsewhere in sub-Saharan Africa are lacking, as found in the systematic review we conducted.

We have demonstrated the importance of the localisation of study tools, and of testing their appropriateness prior to use, and whichever tools may be considered in future studies may require further evaluation, updating, and optimisation for the local setting. We have also introduced novel methods which require consideration and testing by others in the field: when multiple drugs were implicated in an ADR we either assessed causality for each individual implicated drug or for the combined effect of all the drugs,

based on ADR type; we also described the contribution of ADRs to patients' death as either "a contributor" or "a major contributor".

Our research has left several issues unexplored, and future studies should be conducted to describe the economic burden of ADRs, and the epidemiology of non-ADR related drug-related harm (such as harm from drug misuse or from therapeutic failure). Finally, research will be required to determine the efficacy of any preventive measures that may be implemented.

In all of these suggested future directions, it would be important to contextualise risks of harm caused by medicines against their prospects of benefit: the burden of harm caused by *untreated* medical conditions is undoubtedly larger.

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Appendices

Serious adverse drug reactions in sub-Saharan Africa in the era of antiretroviral treatment: A systematic review

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Abstract

We aimed to summarize and describe the burden of serious adverse drug reactions (ADRs) in sub-Saharan Africa (SSA) in the era of antiretroviral therapy. We searched Medline, CINAHL, Africa-Wide Information, Scopus, and Web of Science, without language restriction up to March 2021. We hand-searched reference lists, conference abstracts, and dissertation databases. We included studies reporting proportions of admissions attributed to ADRs, admissions prolonged by ADRs, or in-hospital deaths attributed to ADRs. Two reviewers independently screened the studies, reviewed the study quality using a previously published tool, and extracted the data. We tested for heterogeneity using I^2 -statistics and summarized the study results using medians and interquartile ranges. Subgroup analyses summarized the results by study quality, setting, methodology, and population. From 1005 unique references identified, we included 15 studies. Median study quality was 7/10; heterogeneity was very high. Median [IQR] proportion of admissions attributed to ADRs was 4.8% [1.5% to 7.0%] (14 studies) and 6.4% [4.0% to 8.4%] in nine active surveillance studies in adults. Two pediatric studies reported the proportion of admissions prolonged by ADRs (0.29% and 0.99%). Three studies reported the proportion of in-hospital deaths attributed to ADRs (2.5%, 13%, and 16%). Antiretroviral and antituberculosis drugs were often implicated in serious ADRs. Evidence of the burden of serious ADRs in SSA is patchy and heterogeneous. A few high-quality studies suggest that the burden is considerable, and that it reflects the regional impact of the HIV pandemic. Further characterization of this burden is required, ideally in studies of standardized methodology.

KEYWORDS

drug safety, medicine safety, pharmacoepidemiology, systematic review

1 | INTRODUCTION

The burden of adverse drug reactions (ADRs) in low- and middle-income countries (LMICs) may differ from that in high-income settings for a variety of reasons, including differences in disease burden, differences in drug utilization patterns, a potential lack of effective drug quality

control, and the high risk for prescribing and dispensing errors that occur in overburdened healthcare systems. Previous systematic reviews summarizing the global burden of ADRs¹⁻⁶ included only a few surveys from LMICs, which limits the generalizability of their results to LMIC settings.

In sub-Saharan Africa (SSA), an epidemiological transition is taking place, with high prevalence of both non-communicable

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disease and infectious disease, particularly HIV. The World Health Organization (WHO) first introduced guidelines for scaling up antiretroviral therapy (ART) in resource-limited settings in 2002.⁷ Large national ART programs in SSA could potentially contribute significantly to the burden of ADRs in this region.

Serious ADRs are those that result in death, are life-threatening, result in hospital admission or prolong an existing hospital admission, result in persistent or significant disability or incapacity, or result in a congenital anomaly or cancer.^{8,9} This systematic review aims to summarize and describe data on the burden of serious ADRs in SSA in the era of ART. We specifically focus on ADRs that cause hospital admission, prolong an existing hospital admission, or cause in-hospital death, as these three categories of serious ADRs are the ones most frequently measured by surveys, are reasonably easy to verify, are not subjectively judged, and do not require longitudinal data.

The specific objectives of this systematic review are:

1.1 | Primary objective

1. To summarize the proportions of hospital admissions attributable to ADRs, hospital admissions prolonged by ADRs, and in-hospital deaths attributable to ADRs in SSA in the ART era.

1.2 | Secondary objectives

1. To summarize the proportions of hospital admissions attributable to preventable ADRs, hospital admissions prolonged by preventable ADRs, and in-hospital deaths attributable to preventable ADRs in SSA in the ART era.
2. To describe common clinical presentations of serious ADRs, and drugs commonly implicated in serious ADRs, in SSA in the ART era.
3. To explore the contribution of HIV and ART to the burden of serious ADRs in SSA in the ART era.
4. To explore methodological and quality issues in ADR surveys conducted in SSA in the ART era.

2 | METHODS

2.1 | Criteria for considering studies for this review

We reviewed observational studies from SSA, published since 2002 (the year of the first WHO ART guideline for resource-constrained settings⁷), which reported any of the following proportions:

- the proportion of hospital admissions attributable to ADRs,
- the proportion of hospital admissions prolonged by ADRs, or
- the proportion of in-hospital deaths attributable to ADRs.

Prospective or retrospective cohort studies, cross-sectional studies, as well as data collected in the baseline survey / control arm

of trials were eligible for inclusion. Forty-eight countries, listed in the supplement, were defined as SSA countries in accordance with the World Bank's use of the term. We used original study authors' definitions of "ADR", "hospital", and "admission", but we specifically did not consider attendance at an emergency unit to be a hospital admission. We only included studies conducted in unselected hospital populations. No restrictions were applied in terms of publication language or type; we included studies available as abstracts only. No restrictions were applied in terms of study population age groups.

2.2 | Search methods for identification of studies

We searched five databases (Medline, CINAHL, Africa-Wide Information, Scopus, and Web of Science) for relevant journal articles.

The primary search strategy, developed with the help of a medical librarian, was based on a combination of free text and index term searches for searching Medline through EBSCOhost. Terms identifying SSA were derived from a recommendation by the University of North Carolina Libraries,¹⁰ and terms to identify ADRs were derived from a recommendation by the Cochrane Collaboration¹¹ and from terms used in a previous systematic review.¹² In addition to an "SSA concept" and an "ADR concept", we included two more search concepts, relating to the "seriousness" and the "prevalence" of ADRs. Search strategies for all databases are included in the supplement.

Database searches were most recently conducted on 02 March 2021. Results were uploaded to an electronic deduplication and screening tool.

Database searches for journal articles were supplemented by hand-searches conducted by one reviewer (JPM), including reference lists and lists of excluded studies of 30 previous review articles on various medicine safety topics,^{1-6,12-35} reference lists of articles included in the current review, abstract books of the 2002 to 2020 annual meetings of the International Society of Pharmacovigilance and the International Society of Pharmacoepidemiology, and theses and dissertations via five databases, detailed in the supplement. Potentially relevant reports were added to the electronic deduplication and screening tool.

2.3 | Screening of title/abstracts

After removing duplicates, two reviewers (JPM, and either NJ or GT) independently screened all reports on title and abstract. Reports were excluded if both reviewers agreed to exclude it; reasons for exclusion at this stage were not documented. Where no English-language abstract was available, we used an online translator (Google Translate) to assess the potential relevance of the report.

2.4 | Obtaining full-text articles

We were able to obtain full-texts of all the reports not excluded on title and abstract screening through the University of Cape Town

Libraries; we did not need to contact authors for full-texts. Where multiple reports were found to relate to one study, we combined the reports into one study at this point.

2.5 | Full-text screening

Full-text studies were reviewed for inclusion independently by two reviewers (JPM, and NJ, GT, or KC). Studies in languages other than English were translated through an online translator (Google Translate). Disagreement over inclusion was resolved through discussion between the two reviewers, and a third reviewer could arbitrate. A reason for exclusion of the study was documented.

2.6 | Quality assessment

Included studies were independently assessed for quality by two reviewers (JPM and GT) using a slightly modified version of a quality-assessment tool developed specifically for ADR surveys.¹² Our modification replaced the term 'severity' in the tool with the terms 'seriousness or severity'. We calculated a quality score for each study as the total number of 'yes' responses out of tool's ten questions.

2.7 | Data extraction

Two reviewers (JPM and GT) independently extracted data on study characteristics, the study setting, the study population, the study methodology, and study findings. (The data extraction form is included in the supplement). Disagreement was resolved through discussion between the two reviewers, and a third reviewer (KC) could arbitrate. We did not contact study authors with data extraction queries.

2.8 | Data synthesis

Studies were grouped according to the data they contained relevant to this systematic review's three co-primary objectives. Group 1 studies reported the proportion of hospital admissions attributed to ADRs, group 2 studies reported the proportion of hospital admissions prolonged by ADRs, and group 3 studies reported the proportion of in-hospital deaths attributable to ADRs; a study could be included in more than one group. Since findings could be reported on the level of the patient or on the level of the admission (i.e., allowing for re-admissions), we decided to use admission-level data if reported, and patient-level data if no admission-level data were reported.

In the primary analysis, we pooled data from all studies in each group, regardless of study quality, study setting, methodological considerations, or study populations. We tested for heterogeneity using I^2 statistics to decide whether to conduct meta-analysis: in the presence of heterogeneity, we would summarize the proportions mentioned above as medians and interquartile ranges; in the

absence of heterogeneity, we would conduct random-effects meta-analysis, calculating the pooled estimate proportion after Freeman-Tukey double arcsine transformation to stabilize the variances.

We explored the proportions mentioned above by subgroups relating to study quality, study setting, methodological considerations, and study populations. Depending on heterogeneity within each subgroup (using I^2 statistics) we would proceed to synthesize the data as above.

A similar approach was followed for the secondary objectives, where we summarized serious preventable ADRs. For the remainder of the secondary and explorative objectives, we narratively summarized clinical presentations commonly reported, drugs commonly implicated, and the contribution of HIV, ART, and methodological and quality issues.

3 | RESULTS

Our electronic search yielded 1183 references and our hand search yielded three more; after deduplication 1005 references remained. We excluded 964 references as irrelevant on title/abstract screening and assessed 41 studies for eligibility on full text. We excluded 26, listed in the supplement with reasons. The most common reason for excluding studies on full text was that no disaggregated numerator was reported. These included studies that did not distinguish between serious and non-serious ADRs, as well as studies of "umbrella topics", such as drug-related harm, which did not report ADRs separately. Fifteen studies³⁶⁻⁵³ were included in this systematic review (Figure 1).

Quality scores ranged from 1/10 (in one study) to 10/10 (in four studies). Median [IQR] quality score was 7 [3 to 10]. All studies clearly reported the study design (Table 1), and most also clearly described data collection methods. In general, studies reported using standard methods for assessing causality, preventability, and seriousness/severity; however, details of the processes applying these methods (for example, the people performing the assessments, solving disagreements, etc.) were less well reported. The study characteristic reported least often was the process of establishing seriousness.

Table 2 summarizes the characteristics of studies included in this review.

3.1 | Group 1 studies

Fourteen studies^{36-45,47-53} reported as outcome the proportion of admissions attributed to ADRs. To estimate the summary proportion of admissions attributed to ADRs, we first pooled all group 1 studies and tested for heterogeneity. Since very high heterogeneity was found ($I^2 = 98.2\%$), no meta-analysis was performed. The median [IQR] proportion of admissions attributed to ADRs among the 14 studies was 4.8% [1.5% to 7.0%] (Figure 2).

We investigated heterogeneity among subgroups based on study quality, study setting, study methodology, and study population. Since there was very high heterogeneity in each subgroup, no

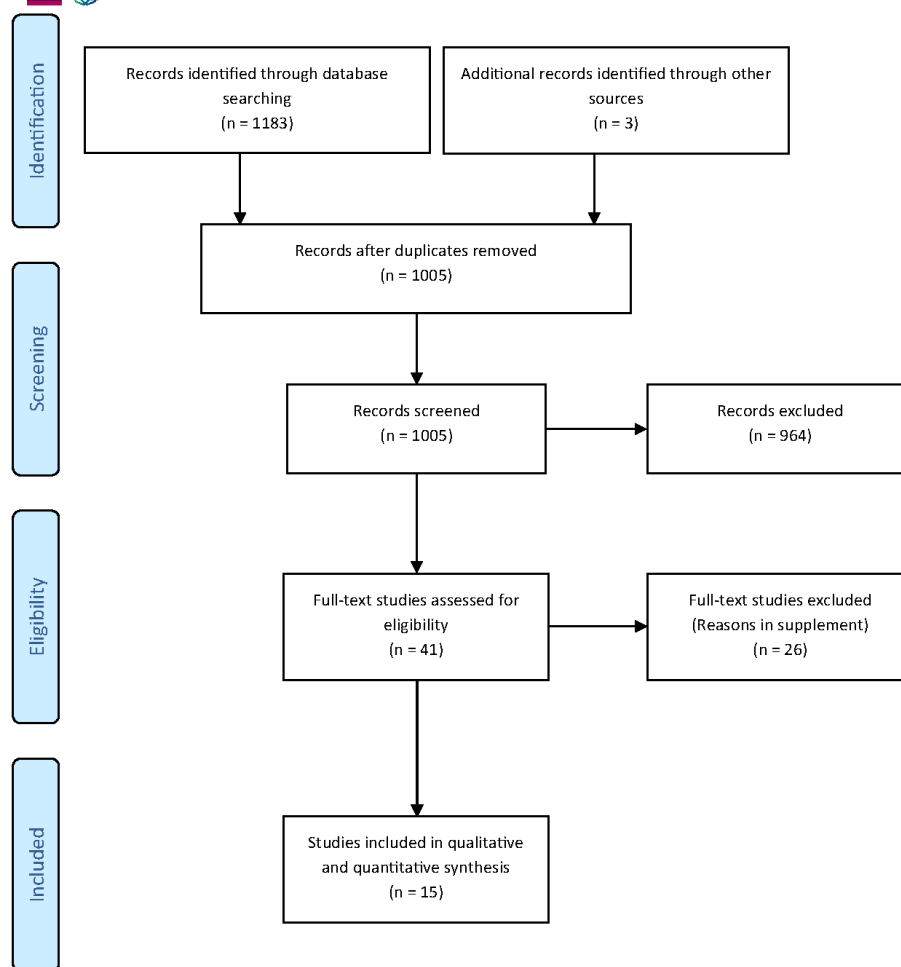


FIGURE 1 PRISMA diagram

meta-analysis by subgroup was performed. Heterogeneity and summary proportions, by subgroup, are presented in the supplement.

One study, reported only in two conference abstracts,^{44,45} was a low-quality report of a spontaneous ADR reporting system in the medical wards of a Nigerian hospital, where 30/2012 (1.5%) patients were reported to have had an ADR-related admission.

The remaining 13 studies were all conducted as active surveillance studies, eight of which were in adults,^{37-39,41-43,47,49,50,52} four in children,^{36,40,51,53} and one in a mixed adult and pediatric population.⁴⁸ As this latter study presented data for adults and children separately, we could extract separate adult and pediatric datasets from it. Key results from Group 1 studies, grouped by the ADR detection method (spontaneous reporting vs. active surveillance) and study population (adults vs. children) are presented in Table 3.

3.1.1 | Adult active surveillance studies

Nine active surveillance studies contributed adult data (Table 3). All were available as English full-text reports, except one Malian study reported in both French-language article³⁹ and French-language thesis³⁸ with English abstracts. An Ethiopian study was reported in two complementary articles.^{49,50} Median quality score was 7/10, ranging from 2/10 to 10/10. Studies were conducted in South Africa (two studies,^{37,47} both high quality), Nigeria (two studies^{43,52}), and in Eritrea,⁴⁸ Ethiopia,^{49,50} Malawi,⁴² Mali,^{38,39} and Uganda.⁴¹ Study duration ranged from 1 month to 16 months, for a median of 6 months. Six studies were single-center studies at secondary- / tertiary-level hospitals,^{37-39,42,43,49,50,52} while three were conducted in multiple hospitals,^{41,47,48} including primary-level hospitals in

TABLE 1 Quality assessment of 15 studies included in the systematic review (adapted from Smyth et al¹²)

Quality question	Number (proportion) 'yes'
01 Was study design clear?	15 (100%)
02 Were methods used to identify ADRs described in detail?	7 (47%)
03 Were data collection methods clearly described?	12 (80%)
04 Were the individuals who identified ADRs clearly described?	10 (67%)
05 Was the process of establishing the causal relationship described in detail?	8 (53%)
06 Were standard methods used in causality assessment?	13 (87%)
07 Was the process of establishing avoidability described in detail?	7 (47%)
08 Were standard methods used in avoidability assessment?	7 (47%)
09 Was the process of establishing seriousness or severity described in detail?	5 (33%)
10 Were standard methods used in seriousness or severity assessment?	8 (53%)

two.^{41,48} Where reported, all studies were conducted in medical wards,^{37-39,41,43,47,49,50,52} additionally including intensive care units in one.⁴⁷ Only one study reported universal sampling of all patients admitted to the study wards⁴⁷; non-random sampling of admitted patients was described in the remainder. In these studies, large numbers of potential participants were often excluded (35%⁴¹ 57%,⁵² 69%,^{49,50} 84%,⁴² and 96%⁴³ in five studies, but only 1%³⁷ and 4%^{38,39} in two others). Reasons for excluding potential participants included no consent,^{41,48-50,52} missing records,^{37,42,49,50} being too ill to cooperate,^{41,49,50,52} admissions for cancer chemotherapy^{38,39} or delivery,⁴⁸ readmissions,⁵² no drug exposure,^{49,50} or unclear reasons.⁴³

Most studies^{37-39,41,47-50,52} used prospective folder review as surveillance methodology, but only four^{37,41,47,48} reported this to have been conducted by multidisciplinary team. ADRs were mostly defined according to the WHO definition.^{37-39,41,43,48-50,52} Five studies^{37,41,42,47,49,50} reported a clear two-step method, with causality assessment conducted by a multidisciplinary team other than the surveillance team. Naranjo's causality assessment method (in 4 studies^{41,42,48-50}) and the WHO-UMC method (in three studies^{37,47,52}) were mostly used. Six studies reported assessing the preventability of ADRs, using Schumock and Thornton criteria in three studies^{37,41,47} and unreported or other methods in three studies.^{48-50,52}

Apart from summary demographic statistics, the population included in studies' denominator was generally poorly described. Mean or median age ranged from 36 to 50 years (reported in six studies^{37-39,41,47,49,50,52}), and the proportion of females from 42% to 56% (reported in seven studies^{37-39,41,43,47,49,50,52}). Only two studies reported the proportion of patients included in the denominator that were exposed to drugs before their admission.^{47,49,50} Only two studies described the most common reason for admission, being malaria⁴¹ and cardiovascular disease⁴⁷ respectively. HIV prevalence among patients included in the denominator was only reported in the South African studies, being 32% in the earlier³⁷ and 29% in the later⁴⁷ study. The proportion of patients in the denominator who were taking ART increased in the interval between these two studies from 5.2%³⁷ to 14%,⁴⁷ and was 11% in the Ethiopian study.^{49,50}

Among the nine active surveillance studies in adult populations, the median [IQR] proportion of admissions attributed to ADRs was 6.4% [4.0% to 8.4%]. Although more studies assessed the preventability of ADRs, only one study, from South Africa, reported the proportion of admissions attributed to preventable ADRs, which was 3.7%.⁴⁷

Four studies reported the drugs or drug classes implicated in ADRs causing admission to hospital,^{37,42,47,49,50} with striking similarities: antiretroviral agents, antituberculosis therapy, cardiovascular drugs, and hypoglycemic drugs predominated. Common clinical presentations of these ADRs, as reported in five studies,^{37-39,42,47,49,50} mostly related to their hepatotoxic and nephrotoxic effects, and hypoglycemia. Bleeds from non-steroidal anti-inflammatories and antithrombotic agents were less frequently reported.^{47,49,50}

Four studies reported HIV prevalence among patients who were admitted to hospital for ADRs. This was 38% in both South African studies,^{37,47} 28% in the Ethiopian study,^{49,50} and 3/3 in the Malawian study.⁴²

3.1.2 | Pediatric active surveillance studies

Five active surveillance studies contributed pediatric data (Table 3), including two from Nigeria,^{36,40} two from South Africa,^{51,53} and one from Eritrea.⁴⁸ All were available as English full-text articles, with median quality score 5/10, although two studies^{40,53} scored 10/10. Study duration ranged from 1 month to 36 months. Three studies were single-center studies at secondary- / tertiary-level hospitals^{36,40,51} while two were conducted in multiple hospitals,^{48,53} including primary-level hospitals in one.⁴⁸ One study⁵³ surveyed patients admitted to intensive care units in addition to those admitted to pediatric wards. Only one study reported universal sampling of all patients admitted to the study wards³⁶, non-random sampling of admitted patients was described in the remainder. In these studies, unknown numbers of potential participants were excluded for reasons including no consent,^{48,51} missing records,⁴⁰ short duration

TABLE 2 Characteristics of included studies

Study ID	Group*	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
Oshikoya (2007) ³⁶	1,2	36 months ending 2006, pediatric wards of single secondary/tertiary hospital in Nigeria	All pediatric patients admitted	Prospective and retrospective augmented folder review by multidisciplinary team	WHO definition, ⁵⁴ with specific inclusion: herbal / traditional medicines	Done according to Jones method, ⁵⁵ Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done. Criteria not reported
Mehta (2008) ³⁷	1,3	3 months in 2005, medical wards of single secondary/tertiary hospital in South Africa	Non-random sample of adult patients (>16 years) admitted: 1% excluded for missing records. All deaths of adult patients admitted.	Prospective folder review by multidisciplinary team	WHO definition, ⁵⁴ with specific exclusions: intentional overdose and poor adherence; specific inclusion: accidental overdose	Done by multidisciplinary team (different from ADE surveillance team), according to WHO-UMC method, ⁵⁶ Numerator includes cases rated definite, probable, and possible	Done by multidisciplinary team (different from ADE surveillance team), according to Temple criteria ⁵⁷	Done by multidisciplinary team (different from ADE surveillance team), according to Schumock criteria ⁵⁸
Soukho-Kaya (2010) ^{38,39}	1	12 months ending 2006, medical wards of single secondary/tertiary hospital in Mali	Non-random sample of adult patients admitted: 4% excluded for receiving cancer chemotherapy	Prospective folder review	WHO definition ⁵⁴	Done according to French method, ⁵⁹ Numerator includes cases rated definite and probable.	Implied (study reported serious outcomes)	Not done
Oshikoya (2011) ⁴⁰	1	18 months ending 2007, pediatric wards of single secondary/tertiary hospital in Nigeria	Non-random sample of pediatric patients admitted: unknown number excluded for admission <24 hours or repeat admission or missing records	Prospective augmented folder review by multidisciplinary team	Edwards and Aronson ⁸	Done by same investigators who conducted ADE surveillance, according to Jones method. ⁵⁵ Not reported which categories were included in numerator.	Implied (study reported serious outcomes)	Done by same investigators who conducted ADE surveillance, according to Schumock criteria ⁵⁸
Tunwikirize (2011) ⁴¹	1	6 months in 2005, medical wards of multiple hospitals (primary and secondary/tertiary) in Uganda	Non-random sample of adult patients (>13 years) admitted: 35% excluded for no consent or too ill to cooperate	Prospective folder review by multidisciplinary team	WHO definition, ⁵⁴ with specific exclusion: herbal / traditional medicines	Done by multidisciplinary team (different from ADE surveillance team), according to Narajo method. ⁶⁰ Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done according to Schumock criteria ⁵⁸

(Continues)

TABLE 2 (Continued)

Study ID	Group*	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
Kauffman (2014) ⁴²	1	6 months in 2012, single secondary/tertiary hospital in Malawi (wards not reported)	Non-random sample of adult patients (>18 years) admitted; 84% excluded for missing records	Retrospective folder review	Not defined	Done by multidisciplinary team (different from ADE surveillance team), according to Naranjo method; ⁶⁴ Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Not done
Aderemi-Williams (2015) ⁴³	1	12 months ending 2009, medical wards of single secondary/tertiary hospital in Nigeria	Non-random sample of adult patients admitted; 96% excluded for unclear reasons	Retrospective folder review	WHO definition, ⁵⁴ with specific exclusions: intentional overdose, accidental overdose, and poor adherence	Not done	Implied (study reported serious outcomes)	Not done
Ayetoro (2015) ^{44,45}	1	12 months ending 2014, medical wards of single secondary/tertiary hospital in Nigeria	Not applicable	Spontaneous reporting	Not defined	Not reported or unclear	Implied (study reported serious outcomes)	Not reported or unclear
Mouton (2015) ⁴⁶	3	1 month in 2013, medical wards and intensive care units of multiple secondary/tertiary hospitals in South Africa	All deaths of adult patients admitted	Retrospective folder review by single investigator	Aranson and Ferner, ⁶¹ with specific exclusion: intentional overdose	Done by multidisciplinary team (different from ADE surveillance team), according to WHO-UMC method; ⁵⁶ Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done by multidisciplinary team (different from ADE surveillance team), according to Schumock criteria ⁵⁸
Mouton (2016) ⁴⁷	1	1 month in 2013, medical wards and intensive care units of multiple secondary/tertiary hospitals in South Africa	All admissions of adult patients	Prospective folder review by multidisciplinary team	Aranson and Ferner, ⁶¹ with specific exclusions: intentional overdose and therapeutic failure	Done by multidisciplinary team (different from ADE surveillance team), according to WHO-UMC method; ⁵⁶ Numerator includes cases rated definite, probable, and possible	Done by multidisciplinary team (different from ADE surveillance team), according to Temple criteria ⁵⁷	Done by multidisciplinary team (different from ADE surveillance team), according to Schumock criteria ⁵⁸

(Continues)

TABLE 2 (Continued)

Study ID	Group*	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
Russom (2017) ⁴⁸	1	5 months in 2014, all hospitals (primary and secondary/tertiary) in Eritrea (wards not reported)	Non-random sample of adult and pediatric patients admitted; unknown number excluded for age <30 days or no consent or admitted for delivery	Prospective surveillance by multidisciplinary team.	WHO definition ⁵⁴	Done by investigators different from ADE surveillance team, according to Naranjo method. ⁶⁰ Numerator includes cases rated definite, probable, and possible	Done according to ICH/CiOMS criteria ⁹	Done according to P-method ⁶²
Angamo (2018) ^{49,50}	1,3	16 months ending 2016, medical wards of single secondary/tertiary hospital in Ethiopia	Non-random sample of adult patients (>18 years) admitted; 69% excluded for no consent or missing records or no drug exposure or not interviewed due to health or other reasons. All deaths of adult patients admitted.	Prospective augmented folder review by single investigator	WHO definition, ⁵⁴ with specific exclusions: intentional overdose, accidental overdose, drug abuse, and therapeutic failure	Done by multidisciplinary team (different from ADE surveillance team), according to Naranjo method. ⁶⁰ Numerator includes cases rated definite and probable	Done by same investigators who conducted ADE surveillance. Criteria not reported	Done. Criteria not reported
Makiwane (2019) ⁵¹	1	3 months in 2016, pediatric wards of single secondary/tertiary hospital in South Africa	Non-random sample of pediatric patients (<16 years) admitted; unknown number excluded for admission <24 hours or no consent	Prospective folder review by single investigator	WHO definition, ⁵⁴ with specific inclusion: herbal / traditional medicines	Done according to Naranjo method. ⁶⁰ Numerator includes cases rated definite, probable, and possible	Done according to ICH/CiOMS criteria ⁹	Not done
Adedapo (2020) ⁵²	1	12 months ending 2013, medical wards of single secondary/tertiary hospital in Nigeria	Non-random sample of adult patients admitted; 57% excluded for no consent or existing admissions or repeat admissions or very ill	Prospective augmented folder review	WHO definition, ⁵⁴ with specific inclusions: herbal / traditional medicines, medication errors	Done according to WHO-UMC method. ⁵⁶ Numerator includes cases rated definite, probable, and possible	Implied (study reported serious outcomes)	Done according to Wolfe criteria ³⁵

(Continues)

TABLE 2 (Continued)

Study ID	Group*	Surveillance period and setting	Denominator	Surveillance methodology (identifying candidate ADRs)	ADR definition	Causality assessment	Seriousness assessment	Preventability assessment
Mouton (2020) ⁵³	1,2	1 month in 2015, pediatric wards and intensive care units of multiple secondary/tertiary hospitals in South Africa	Non-random sample of admissions of pediatric patients; unknown number excluded for elective admissions, rehydration therapy, postnatal stays	Prospective and retrospective folder review by multidisciplinary team	Aronson and Ferner, ⁶¹ with specific exclusions: herbal / traditional medicines, intentional overdose, poor adherence, medication errors without harm, therapeutic failure	Done by multidisciplinary team (different from ADE surveillance team), according to WHO-UMC method. ³⁶ Numerator includes cases rated definite, probable, and possible	Done by multidisciplinary team (different from ADE surveillance team), according to Temple criteria ⁵⁷	Done by multidisciplinary team (different from ADE surveillance team), according to Schumock criteria ⁵⁸

*Group 1 studies report proportion of admissions attributed to ADRs. Group 2 studies report the proportion of admissions prolonged by ADRs. Group 3 studies report the proportion of in-hospital deaths attributed to ADRs.

admissions,^{40,51} admissions for rehydration,⁵³ repeat admissions,⁴⁰ elective admissions,⁵³ or neonatal admissions.^{48,53}

Four studies reported that multidisciplinary teams conducted the surveillance.^{36,40,48,53} Three studies^{36,40,48} defined ADRs according to the WHO definition. All studies included an assessment of causality, and four^{36,40,48,53} included an assessment of preventability, although precise methods varied.

Only one study reported the proportion of patients included in the denominator that were exposed to drugs before their admission.⁵³ Infectious diseases were frequently reported as the reason for admission.^{36,40,51,53} The proportion of children in the denominator population who had HIV infection was only reported in the two South African studies.^{51,53}

The proportion of admissions attributed to ADRs ranged from 0.4% to 5.7%, median [IQR] 1.8% [0.6% to 4.7%]. At the low end of the range were the two large Nigerian studies which seemingly included older children, with one study reporting the mean age among all admissions being 6.4 years.⁴⁰ In contrast, the South African studies' populations were younger (median age 1.4 years⁵¹ and 0.9 years⁵³). Hypersensitivity reactions, including erythema multiforme, Stevens Johnson syndrome, urticaria, and rashes were reported as the most common presentations, and antimicrobial medicines were most commonly implicated. Two studies reported the proportion of admissions attributed to preventable ADRs, which were 0.1%⁴⁰ and 0.5%⁵³ respectively. Only one study, conducted in South Africa, reported HIV prevalence among children admitted for ADRs, being 15%.⁵³

3.2 | Group 2 studies

We found no study conducted in adult populations reporting the proportion of hospital admissions prolonged by ADRs. Two pediatric studies, one from Nigeria³⁶ and one from South Africa⁵³ reported this proportion (Table 4). In the Nigerian study,³⁶ 0.29% children experienced ADR-related prolongation of their hospital admission. ADR preventability, presentations, implicated drugs, and HIV exposure were not reported. In the South African study⁵³ 0.99% admissions were prolonged by ADRs. Most prolongations were for antibiotic-associated diarrhea, although a variety of other admission-prolonging ADRs occurred, including ADRs attributed to corticosteroids and immunosuppressants. Only one study reported the proportion of admissions prolonged by preventable ADRs, being 2/1106 (0.19%).⁵³ Only one study, conducted in South Africa, reported HIV prevalence among children whose hospital stays were prolonged by ADRs, being 18%.⁵³

3.3 | Group 3 studies

Three high-quality adult studies, two from South Africa^{37,46} and one from Ethiopia,^{49,50} reported the proportion of in-hospital deaths to which ADRs contributed (Table 5). All three studies were conducted

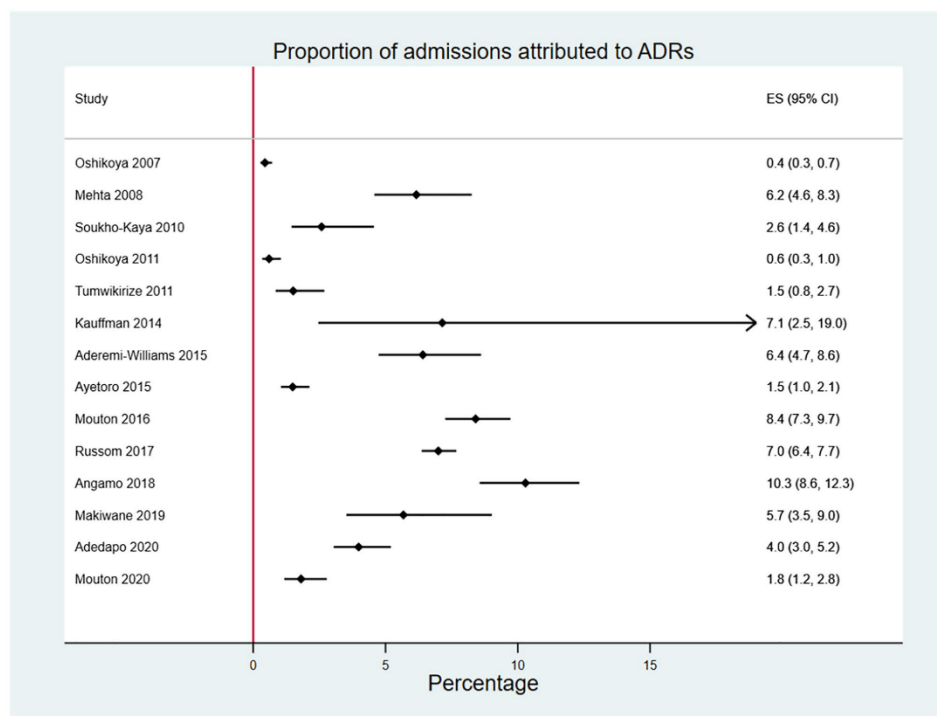


FIGURE 2 Forest plot of studies reporting proportion of admissions attributed to ADRs

among adults in secondary / tertiary hospitals, with one⁴⁶ also including patients in the intensive care unit. In two studies^{46,49,50} the proportion of deaths attributed to ADRs was the primary outcome measure, while the third³⁷ mentioned the proportion of deaths attributed to ADRs as an additional outcome. The Ethiopian survey^{49,50} only considered deaths from ADRs already present at time of admission, and not deaths from ADRs that developed during the hospital stay, and thus may have underestimated the deaths attributable to ADRs.

The three studies respectively found 2/80 (2.5%),³⁷ 56/357 (16%),⁴⁶ and 15/116 (13%)^{49,50} deaths were ADR-related.

The proportion of deaths attributed to preventable ADRs was reported in two studies: 28/357 (7.8%) in South Africa⁴⁶ and 14/116 (12%) in Ethiopia^{49,50} respectively.

These two studies also reported the proportion of ADR-related deaths in which decedents were people living with HIV (PLWH): 31/56 (55%)⁴⁶ and 7/15 (47%)^{49,50} respectively. In both studies, renal failure and drug-induced liver injury were the most common ADRs resulting in death, and both studies listed antiretrovirals and anti-tuberculosis drugs as the drugs most commonly implicated in ADR-related deaths.

Multivariable logistic regression in one study⁴⁶ identified HIV-infection with antiretroviral treatment, higher drug count, and

higher comorbidity score as independent risk factors for ADR-related death. Unadjusted bivariate analyses in the other^{49,50} also showed associations between ADR-related death and exposure to antiretroviral treatment, higher drug count, and higher comorbidity score, as well as pre-existing liver disease, a history of prior ADR, low body-mass index, and exposure to antituberculosis drugs.

In addition to the three studies included in this group, fatal ADR outcomes were reported by nine other studies included in this review.^{36,38-40,42,44,45,48,51-53} However, these nine studies did not report the proportion of ADR-related deaths against a denominator of all in-hospital deaths.

A Nigerian study⁵² reported seven deaths attributed to ADRs among 67 adults with serious and non-serious ADRs. These included three cases of Stevens Johnson Syndrome or toxic epidermal necrolysis with co-trimoxazole and phenytoin, two cases of hemorrhage with heparin and diclofenac, and two cases of hepatotoxicity with anti-tuberculosis therapy and herbal medicine. Two of the deaths occurred in PLWH. Among other adult studies, the Malawian study⁴² reported one fatal outcome (hyperlactatemia with stavudine) among their three patients with serious ADRs; the Malian study^{38,39} reported three fatal outcomes (hypoglycemia,

TABLE 3 Key results from studies reporting the proportion of admissions attributed to ADRs (Group 1 studies). Studies grouped by ADR detection method and population studied

Study	Proportion of admissions attributed to ADRs / Proportion of patients with admissions attributed to ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of patients with admissions attributed to ADRs who are PLWH
Spontaneous Reporting				
Ayetoro (2015) ^{44,45}	30/2012 (1.5%) patients.	NR	NR	NR
Active Surveillance, Adults				
Mehta (2008) ³⁷	41/665 (6.2%) patients.	Metabolic (16), endocrine (10), hepatic (8), and neuropsychiatric (8)	Cardiovascular (22), antiretrovirals (17), oral hypoglycemic agents (7), non-steroidal anti-inflammatories (7)	38% PLWH
Soukho-Kaya (2010) ^{38,39}	11/426 (2.6%) patients.	Hypoglycemia (5)	NR	NR
Tumwikirize (2011) ⁴¹	11/728 (1.5%) patients.	NR	NR	NR
Kauffman (2014) ⁴²	3/42 (7.1%) patients.	Anemia (1), hyperlactatemia (1), GIT distress (1)	Stavudine (2), metronidazole (1)	3/3 PLWH
Aderemi-Williams (2015) ⁴³	40/624 (6.4%) patients.	Not clear	Not clear	NR
Mouton (2016) ⁴⁷	164/1951 (8.4%) admissions.	Renal impairment (24), hypoglycemia (22), DILI (20), hemorrhage (19), blood dyscrasias (14)	Rifampicin (17), enalapril (13), insulin (14), tenofovir (14), warfarin (13)	64/164 (38%) in PLWH
Russom (2017) ⁴⁸ (adults)	295/3415 (8.6%) patients.	NR	NR	NR
Angamo (2018) ^{49,50}	103/1001 (10%) patients.	Hepatotoxicity (35), acute kidney injury (27), skin reactions (8), hypokalemia (7), gastrointestinal bleed/gastritis (7)	Isoniazid (23), furosemide (19), pyrazinamide (18) tenofovir (9), acetylsalicylic acid (9)	29/103 (28%) PLWH and on ART
Adedapo (2020) ⁵²	51/1280 (4.0%) patients.	NR	NR	NR
Active surveillance, children				
Oshikoya (2007) ³⁶	17/3821 (0.44%) patients.	Erythema multiforme (12)	Ampicillin (7), sulfadoxine / pyrimethamine (5), co-trimoxazole (5), phenobarbitone (3), herbs (2)	NR
Oshikoya (2011) ⁴⁰	12/2004 (0.60%) patients.	Erythema multiforme (5), Stevens-Johnson syndrome (2), macular and morbidiform rash (2)	Cotrimoxazole (6), ampicillin (4), sulfadoxine / pyrimethamine (3)	NR
Russom (2017) ⁴⁸ (children)	114/2433 (4.7%) patients.	NR	NR	NR
Makiwane (2019) ⁵¹	16/282 (5.7%) patients.	NR	NR	NR
Mouton (2020) ⁵³	20/1106 (1.8%) admissions.	Urticaria (2), dystonia (2)	Prednisone (2), metoclopramide (2)	3/20 (15%) PLWH

Abbreviations: NR, not reported; PLWH, people living with HIV.

and "colchicine-induced vomiting") among 39 patients with 47 serious and non-serious ADRs; and the spontaneous reporting study^{44,45} reported no fatal outcomes among 30 patients with serious ADRs.

Pediatric studies generally reported low absolute numbers of fatalities. However, fatal outcomes were reported to occur in a relatively high proportion of serious ADRs: 2/17 serious ADRs were fatal (Stevens-Johnson syndrome and hepatotoxicity) in one Nigerian study,³⁶ 2/12

TABLE 4 Key results from studies reporting the proportion of admissions prolonged by ADRs (Group 2 studies)

Study	Proportion of admissions prolonged by ADRs / Proportion of patients with admissions prolonged by ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of patients with admissions prolonged by ADRs who are PLWH
Oshikoya (2007) ³⁶	11/3821 (0.29%) patients.	NR	NR	NR
Mouton (2020) ⁵³	11/1106 (0.99%) admissions.	Diarrhea (4), bicytopenia (2)	Prednisone (3), methylprednisolone (3), tacrolimus (2), mycophenolic acid (2), amoxicillin (2)	2/11 (18%) PLWH

Abbreviations: NR, not reported; PLWH, people living with HIV.

TABLE 5 Key results from studies reporting the proportion of in-hospital deaths attributed to ADRs (Group 3 studies)

Study	Proportion of in-hospital deaths attributed to ADRs	Most common clinical presentations of ADRs (n)	Most commonly implicated drugs / classes (n)	Proportion of people whose in-hospital deaths were attributed to ADRs who were PLWH
Mehta (2008) ³⁷	2/80 (2.5%) deaths.	Acute renal failure (1), intracranial bleed (1)	Gentamycin (1), warfarin (1)	NR
Mouton (2015) ⁴⁶	56/357 (16%) deaths.	Renal failure (23), drug-induced liver injury (10)	Tenofovir (14), rifampicin (9), cotrimoxazole (7), furosemide (5), insulin (4)	31/56 (55%) PLWH
Angamo (2018) ^{49,50}	15/116 (13%) deaths.	Hepatotoxicity (7), kidney injury (4)	Isoniazid (6), pyrazinamide (3), tenofovir (2), efavirenz (2), enalapril (2), furosemide (2)	6/15 (40%) PLWH

Abbreviations: NR, not reported; PLWH, people living with HIV.

(Stevens-Johnson syndrome) in the other,⁴⁰ and 1/40 in a South African study.⁵³ No fatal outcomes were reported among 61 serious and non-serious ADRs in the other South African pediatric study.⁵¹

In the country-wide Eritrean survey 48 fatal ADRs were reported among 5,848 patients admitted.⁴⁸ The two most common ADRs resulting in death were anemia (attributed to various drugs, including zidovudine) and hepatotoxicity (mostly attributed to antituberculosis therapy). Drugs used in the management of HIV, TB, and opportunistic infections appear to have been implicated in 17 deaths.

4 | DISCUSSION

A small number of relatively high-quality studies report that serious ADRs contribute significantly to the burden of morbidity and mortality in SSA hospitals. Fourteen studies included in this review reported that a median 4.8% (IQR 1.5% to 7.0%) of admissions were attributed to ADRs; three studies reported that between 2.5% and 16% of in-hospital deaths were attributed to ADRs.

This systematic review demonstrated the paucity of drug safety data from hospital settings in sub-Saharan Africa, and echoes the paucity of drug safety data contributed from Africa to the global spontaneous reporting database described by others.⁶³ Only 15 studies fulfilled the inclusion criteria, despite the fact that we searched databases focused on Africa as well as grey literature, and despite searching without language restrictions. Even given the

overall low number of studies included, there were regional and population differences: two-thirds of the included studies came from just two countries, South Africa and Nigeria, and none from a Central African country; few studies were conducted in pediatric settings, and none specifically in older adults. These are populations to be covered in future ADR surveillance activities.

Study quality, as measured by the tool we applied, was generally high. Nevertheless, to fully comprehend the context within which ADRs occur, and the risk for their occurrence, it is essential to understand the denominator study population, including their diseases and their drug exposures.⁶⁴ Many studies included in this review did not clearly describe the denominator study population, and had this been included as a factor in the quality assessment, we may have reported lower quality overall. A further quality concern among nearly all studies included in this review is the high proportion of potential participants excluded from the surveillance activity. Non-participation was often over 50% and as high as 96% in one study, which may have resulted in a biased sample. Again, although this is a serious quality concern, it is not reflected in the quality assessment tool we used in this review.

We found very high heterogeneity among the study results, which can be attributed to high variability in study designs as described in Table 2, and also to high variability in the study settings and populations, potentially including some unreported differences. It is well-established that the reported prevalence of medication-related hospital admissions depends on the setting,

studied population, specific outcome investigated, and surveillance method.³⁹ Unfortunately, calls for greater standardization in the methodology of medicine safety studies^{8,61,64} have largely gone unheeded.

Because of this high heterogeneity we did not conduct meta-analysis of studies, but reported a median 4.8% (IQR 1.5% to 7.0%) as the proportion of admissions attributed to ADRs. This estimate agrees with the results of six earlier systematic reviews of ADR-related admissions,^{1–6} which estimated the proportion of admissions attributable to ADRs to range between 3.1% and 6.3% (some in subgroup analyses).

A 2018 systematic review of African studies of adverse drug events or medication errors in hospitals³³ differed from the current review as it included only peer-reviewed publications, included studies from North Africa and studies predating the ART era, and only distinguished between serious and non-serious events in some ADE cases. Moreover, despite defining ADRs as a subset of ADEs, the authors of that systematic review reported "overlooking" this factor,³³ in the end pooling studies reporting an outcome of ADRs together with those reporting an outcome of ADEs. In view of the methodological differences between the two systematic reviews, it is not surprising that there is little overlap in the studies included, and a very different result. For the comparable outcome we described in our Group 1 studies (proportion of admissions attributable to ADRs, $n = 14$ studies, median proportion 4.8%) and the earlier review's outcome of proportion of admissions as a direct result of ADEs ($n = 11$ studies, median proportion 2.8%),³³ only six studies were included in both reviews.

Another previous systematic review, published in 2016, aimed to compare adult ADR burdens in high-income countries and LMICs.¹⁶ The authors found the median proportion of admissions attributed to ADRs to be lower in LMICs (5.5%) than in high-income countries (6.3%).¹⁶ However, this review included only three studies from SSA among the 13 LMIC studies.¹⁶ Our comparable estimate (median 6.4% among nine adult active surveillance studies) is probably more representative, and read together with the results from other systematic reviews mentioned above^{1–6} probably dispels the idea that the burden of ADR-related admissions in SSA is lower than in high-income countries.

The proportion of in-hospital deaths attributed to ADRs in Europe was the topic of a 2021 systematic review. Six studies contributed 657 drug-related deaths out of 7578 in-hospital deaths, with the meta-analytic estimated proportion being 7.3% (95% CI 4.1% to 12.5%).⁶⁵ This estimate appears to agree with an earlier population-based study using linked databases in Sweden, in which 6.4% of in-hospital deaths were attributed to ADRs.⁶⁶ We identified only three studies conducted in SSA to report this particular outcome, and these reported 2.5%, 13%, and 16% of deaths in adult medical wards were attributed to ADRs. The low number of SSA studies reporting this proportion as outcome precludes any meaningful interpretation of this proportion. However, it is notable that in two of the studies a large proportion of the deaths were associated with preventable ADRs. In addition, it is notable that most deaths were due to renal

and liver injuries, with ART and antituberculosis therapy most often implicated. This stands in contrast with studies from Europe, which found hemorrhages to be most common fatal ADRs.^{65,66}

For several of our study objectives, we found limited data. Only two studies reported on admissions prolonged by ADRs, and there were minimal reports on admissions caused by or prolonged by preventable ADRs. These are knowledge gaps to be filled by future research.

Another exploratory objective yielding little data was describing the role played by HIV and ART in the serious ADR burden in SSA. Although rarely reported, it was consistently reported that HIV prevalence among patients with serious ADRs was higher than HIV prevalence among the denominator population.^{37,46,47,49,50,53} This imbalance was most pronounced for the outcome of ADR-related deaths. However, this finding should be interpreted with care. Where antiretroviral therapy was implicated in causing ADRs, these were often older antiretrovirals, including stavudine and efavirenz, and the ADRs were often unpredictable and unavoidable events. ART programs in SSA are continuously improving and introducing newer drugs with fewer toxicities: stavudine has been phased out as first-line ART option in the period 2006 to 2011,⁶⁷ and efavirenz is currently being phased out in favor of dolutegravir. Tenofovir alafenamide has better renal safety than tenofovir disoproxil fumarate⁶⁸ and may in future replace it in ART programs.

5 | CONCLUSION

We have shown that evidence of the burden of serious ADRs in SSA is patchy and highly heterogeneous. Nevertheless, a few high-quality studies suggest that the burden is considerable. A unique feature of the ADR burden in this region is the frequency at which people living with HIV appear affected, and the frequency with which ART and medicines used in the management of opportunistic infections are implicated in this burden. However, the risk of ADRs should be considered against the risks associated with non-treatment,⁶⁴ and there is no doubt that the benefit of these medicines massively outweigh their risk of harm. Further characterization of the serious ADR burden in SSA is required, particularly in pediatric and elderly populations, and in countries other than South Africa and Nigeria. This should ideally be performed by conducting studies of standardized methodology. As a first step toward limiting the risk of harm caused by medicines, the focus should be on avoiding preventable ADRs, which are often caused by errors. Investing in support systems that catch errors before harm occurs is required, particularly in under-resourced and overburdened health care settings such as those in SSA.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

JPM and KC conceived and designed the study. JPM conducted the searches. JPM, NJ, GT, and KC screened studies for inclusion. JPM, GT, and KC extracted the data and assessed the study quality. JPM

synthesized the data, conducted the analyses, and wrote the initial draft of the manuscript, under the supervision of KC. All authors critically reviewed and revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Mouton JP, Jobanputra N, Tatz G, Cohen K. Serious adverse drug reactions in sub-Saharan Africa in the era of antiretroviral treatment: A systematic review. *Pharmacol Res Perspect*. 2021;9:e00875. <https://doi.org/10.1002/prp2.875>

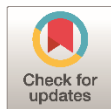
RESEARCH ARTICLE

Interrater agreement of two adverse drug reaction causality assessment methods: A randomised comparison of the Liverpool Adverse Drug Reaction Causality Assessment Tool and the World Health Organization-Uppsala Monitoring Centre system

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OPEN ACCESS

Citation: Mouton JP, Mehta U, Rossiter DP, Maartens G, Cohen K (2017) Interrater agreement of two adverse drug reaction causality assessment methods: A randomised comparison of the Liverpool Adverse Drug Reaction Causality Assessment Tool and the World Health Organization-Uppsala Monitoring Centre system. *PLoS ONE* 12(2): e0172830. doi:10.1371/journal.pone.0172830

Editor: Fabio Rapallo, Università degli Studi del Piemonte Orientale Amedeo Avogadro, ITALY

Received: April 19, 2016

Accepted: February 10, 2017

Published: February 24, 2017

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This research has been supported by the US President's Emergency Plan for AIDS Relief (PEPFAR, www.pepfar.gov) through the US Centers for Disease Control and Prevention (CDC, www.cdc.gov) under the terms of Cooperative

Abstract

Introduction

A new method to assess causality of suspected adverse drug reactions, the Liverpool Adverse Drug Reaction Causality Assessment Tool (LCAT), showed high interrater agreement when used by its developers. Our aim was to compare the interrater agreement achieved by LCAT to that achieved by another causality assessment method, the World Health Organization-Uppsala Monitoring Centre system for standardised case causality assessment (WHO-UMC system), in our setting.

Methods

Four raters independently assessed adverse drug reaction causality of 48 drug-event pairs, identified during a hospital-based survey. A randomised design ensured that no washout period was required between assessments with the two methods. We compared the methods' interrater agreement by calculating agreement proportions, kappa statistics, and the intraclass correlation coefficient. We identified potentially problematic questions in the LCAT by comparing raters' responses to individual questions.

Results

Overall unweighted kappa was 0.61 (95% CI 0.43 to 0.80) on the WHO-UMC system and 0.27 (95% CI 0.074 to 0.46) on the LCAT. Pairwise unweighted Cohen kappa ranged from 0.33 to 1.0 on the WHO-UMC system and from 0.094 to 0.71 on the LCAT. The intraclass correlation coefficient was 0.86 (95% CI 0.74 to 0.92) on the WHO-UMC system and 0.61 (95% CI 0.39 to 0.77) on the LCAT. Two LCAT questions were identified as significant points of disagreement.

Agreement Number GGH000371. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Discussion

We were unable to replicate the high interrater agreement achieved by the LCAT developers and instead found its interrater agreement to be lower than that achieved when using the WHO-UMC system. We identified potential reasons for this and recommend priority areas for improving the LCAT.

Introduction

Causality assessment of suspected adverse drug reactions (ADRs) is routinely performed in regulatory pharmacovigilance and in epidemiological ADR surveys. Nevertheless, there is no agreement on the best method for assessing causality of suspected ADRs. A 2008 systematic review identified 34 methods to assess ADR causality and grouped these as reaching a decision by global introspection, by following an algorithm, or by methods based on Bayesian probabilities [1]. Two methods in frequent use are the WHO-UMC system [2], which is an example of a global introspection method, and the algorithm published by Naranjo in 1981 [3].

The WHO-UMC system asks the rater to judge the likelihood of ADR causality into one of six outcome categories, being 'certain', 'probable / likely', 'possible', 'unlikely', 'conditional / unclassified' (a temporary outcome category, while further information is sought), or 'unassessable / unclassifiable'. Guidelines have been published to assist the rater, but these are intentionally non-explicit [2]. The Naranjo algorithm consists of ten questions to which a rater responds 'yes', 'no', or 'unknown'. Each response is allocated a score, and the sum of scores to the ten questions is usually converted into one of four outcome categories, namely 'definite', 'probable', 'possible', or 'doubtful'.

The Naranjo algorithm was adapted into a new assessment algorithm, the Liverpool ADR Causality Assessment Tool (LCAT) [4] by researchers involved in the Adverse Drug Reactions in Children project [5]. The LCAT arranges ten modified questions with their dichotomous responses into a flowchart to arrive at one of four outcome categories: 'definite', 'probable', 'possible', or 'unlikely' (Fig 1). The developers of the LCAT found it to result in a more even distribution of outcomes than the Naranjo algorithm, which yielded few 'definite' ADRs, and found that the LCAT had higher interrater agreement (IRA) than the Naranjo algorithm, as measured by the kappa statistic [4].

As the LCAT showed early promise of ease of use and high IRA, we considered its use in a prospective survey of ADRs resulting in admission to the medical wards of four hospitals in South Africa, which we have since published [6]. In order to make an informed choice of causality assessment methodology to use in the survey [6], we compared the IRA obtained with the LCAT with that obtained with the WHO-UMC system in a sample of cases from our survey [6]. Secondary aims were to describe the distribution of outcomes achieved with each method, and to investigate whether disagreements on the LCAT outcome could be traced back to specific decision points in the algorithm.

Methods

Design

This study was a two-arm IRA study, using a sample of cases identified as suspected ADR-related admissions during our hospital-based survey. In one arm of the study, we measured the IRA achieved when raters used the WHO-UMC, and we measured the IRA achieved when

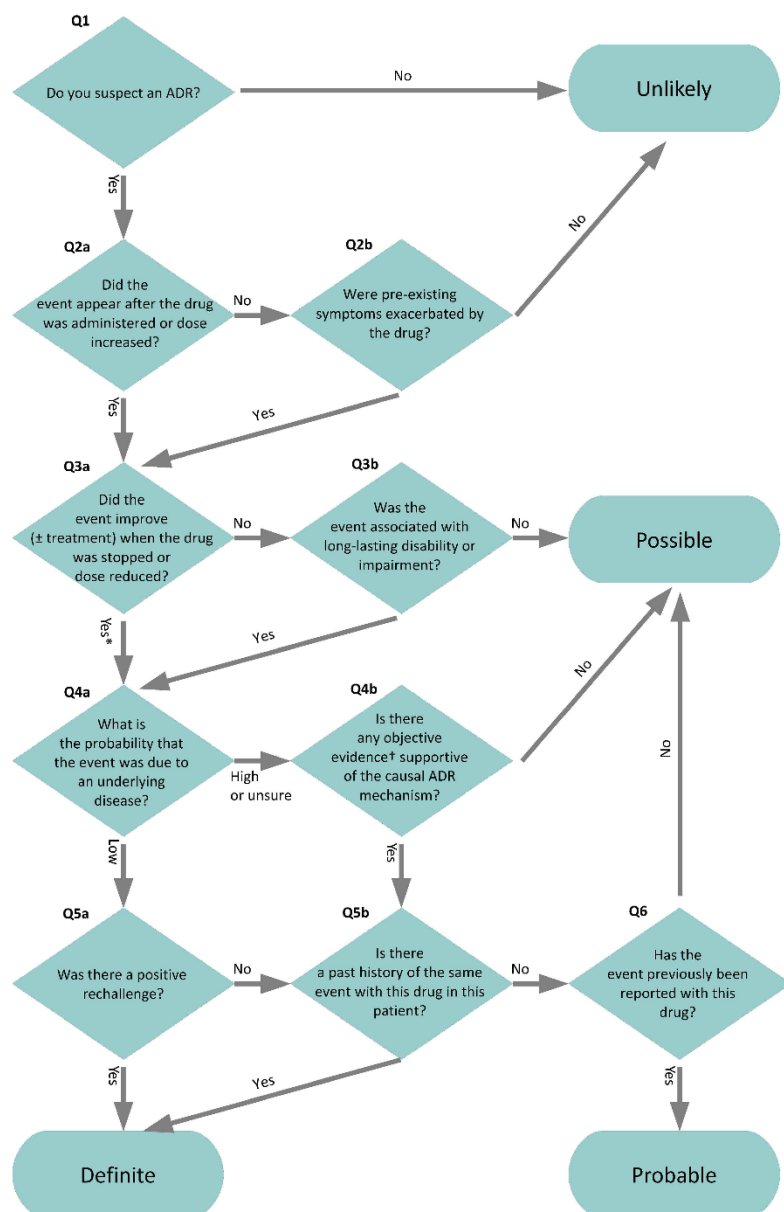


Fig 1. The Liverpool ADR Causality Assessment Tool (LCAT), with numbering of questions as used in this manuscript. * Yes or unassessable. Unassessable refers to situations where the medicine is administered on one occasion (e.g. vaccine), the patient receives intermittent therapy (e.g. chemotherapy), or is on medication which cannot be stopped (e.g. immunosuppressants). † Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient. LCAT reproduced under a Creative Commons Attribution License. Source: Gallagher [4].

doi:10.1371/journal.pone.0172830.g001

raters used the LCAT on the same cases in the second arm of the study. A novel aspect of our study design was to eliminate the need for a washout period between the two arms by using an incomplete, randomised design. Instead of having each rater assess each case by each method, our design used block randomisation to randomly allocate causality assessment methods to cases and raters, such that each case was assessed by a new random half of raters using one method and by the remaining raters using the second method.

In our survey, we reviewed the folders of all adults admitted to the medical wards of four South African hospitals over a 30-day period [6]. We identified suspected ADR-related admissions with the aid of a screening tool adapted from Rozich [7]. We defined an ADR according to the definition by Aronson and Ferner [8]. We did not regard cases of intentional drug overdose as ADRs. We recorded data from patients' clinical hospital records; we did not augment missing data from primary care sources. We received ethical approval from the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (reference numbers 576/2011 and 828/2015.) The research constituted non-interventional, anonymised chart review of information documented during routine clinical practice, and did not elicit any information directly from patients. We did not seek individual patient consent. This was approved by the Human Research Ethics Committee.

Four raters were purposefully chosen from our Department to perform the causality assessments. They were a physician/internist ('Rater 1'), two clinical pharmacists ('Rater 2' and 'Rater 3'), and a clinical pharmacologist ('Rater 4'), all with extensive experience in various pharmacovigilance roles.

We drew a random sample of ten cases from the 289 admissions flagged as suspected ADR-related admissions in our survey (total 1,951 admissions). We used these ten cases in a self-guided training session on the use of the LCAT and the WHO-UMC system. None of the raters had experience in using the LCAT prior to the training session, but all were familiar with ADR causality assessment by global introspection, although not necessarily with the WHO-UMC system.

We drew a second random sample of 48 cases after excluding the ten cases used in training. We allowed only one randomly selected admission per patient into the sample to avoid clustering of patients re-admitted. Similarly, when more than one drug was suspected to have caused an ADR, one of the suspect drugs was selected at random. Thus, we ended up with 48 unclustered drug-event pairs as samples for this analysis.

Each of the four raters performed causality assessment on the case from a standardised case printout of summary demographic, clinical, laboratory and drug history information in our database. The order of assessment was randomised for each rater to minimise the effect of learning. Communication between raters about the cases was not allowed, but raters were not blinded as to the purpose of their assessments and were allowed unrestricted access to reference sources. All assessments were recorded on a paper case assessment sheet. Raters were requested to trace the path of their assessment process when using the LCAT and to note any problems encountered in order to identify potentially problematic decision points on the LCAT flowchart.

In case no outcome category was achieved on the LCAT (e.g. the rater 'got stuck' in the flowchart due to a lack of information to answer a question), or a rater indicated they were unable to choose between two outcome categories, the outcome was coded as 'unassessable'. We requested raters not to use the 'conditional' outcome category on the WHO-UMC system. As a result of these factors, both methods yielded outcomes over five categories: 'definite' (the term 'certain' was considered equivalent), 'probable', 'possible', 'unlikely', and 'unassessable'.

Analysis

We generated a visual representation of each rater's distribution of outcomes against the mean distribution of outcomes, for each method, as a crude indicator whether our raters exhibited cognitive bias in selecting outcome categories.

To compare the methods' IRA, we calculated agreement proportions, kappa statistics, and the intraclass correlation coefficient as follows:

1. We defined exact agreement to exist between two raters using the same method if they assessed the case to the same outcome category (including both raters considering the case to be 'unassessable'), while extreme disagreement was defined to exist if they assessed the case to non-adjacent outcome categories (i.e. one 'probable' and the other 'unlikely', or one 'definite' and the other 'possible', or one 'definite' and the other 'unlikely'). Extreme disagreement was also defined to exist where one rater considered the case to be unassessable while the other did not. We calculated the proportion of exact agreement and extreme disagreement between each rater-pair, and we calculated the proportion of specific agreement on each outcome category [9,10].
2. We calculated pairwise Cohen's kappas among each of the six pairs of raters in an unweighted and a linearly weighted version, for each method. We tested for marginal homogeneity among each rater-pair's assessments by performing the Stuart-Maxwell chi-square statistic on a cross-tabulation of the two raters' assessments. We also calculated an overall ('global') kappa, for each method, in an unweighted and a linearly weighted version, with 95% confidence intervals constructed by a jackknife technique, using methodology proposed by Abaira [11] suitable for incomplete study designs such as ours. For the weighted kappa calculations, we excluded all cases where one or both raters considered the case to be 'unassessable'; the weight matrix was thus a 4x4 matrix.
3. We also calculated an intraclass correlation coefficient on each method, using a one-way absolute-agreement single-measures random-effects model (ICC1,1 in the classification of Shrout and Fleiss [12]). We again excluded cases where one or both raters considered the case to be 'unassessable' from this calculation.
4. In a sensitivity analysis, we investigated for variability in agreement outcomes when considering 'unassessable' ratings as missing data.

To identify potentially problematic decision-making nodes on the LCAT flowchart, we cross-tabulated raters' total number of positive and negative responses to each question. We also grouped raters into two groups (pharmacists versus clinicians) and cross-tabulated the groups' total number of positive and negative responses to each question. To interpret these cross-tabulations, we calculated chi-square statistics or performed Fisher's exact test, as appropriate. Lastly, for each of the LCAT questions we calculated the proportion of specific agreement achieved case-wise between the two raters [9].

Data analysis was performed in Stata version 13.1 (Stata Corporation, College Station, Texas, USA), including the macro 'kappa2' [13] to calculate the Abiraira kappa and its confidence intervals. We considered p-values <0.05 as significant.

Results

Subject characteristics

The 48 sampled patients had a median age of 51.5 years (interquartile range 33.5 to 62.5 years) and 30/48 (63%) were female. 24/48 (50%) were known HIV-infected, and 5/48 (10%) were on treatment for tuberculosis. The sampled drug suspects included antiretrovirals (lamivudine, tenofovir, zidovudine, efavirenz, emtricitabine, and stavudine, totalling 18 cases), cardiac agents (furosemide, hydrochlorothiazide, spironolactone, enalapril, perindopril, and nifedipine, totalling 8 cases), hypoglycaemic agents (5 cases), antituberculosis agents (4 cases), and warfarin (4 cases).

Distribution of outcomes and investigation for cognitive bias

The 48 cases sampled yielded 96 outcomes on each method (S1 Data). The WHO-UMC system resulted in 8 'definite', 11 'probable', 30 'possible', 34 'unlikely', and 13 'unassessable' outcomes. The LCAT resulted in 3 'definite', 29 'probable', 25 'possible', 32 'unlikely', and 7 'unassessable' outcomes. Individual raters' distribution of outcomes is given in S1 Table. S1 Fig plots the difference between each rater's individual distribution of outcomes and the four raters' mean distribution of outcomes when using the WHO-UMC system; S2 Fig shows identical plots when raters used the LCAT. These plots suggest that, regardless of the causality assessment method used, Rater 2 preferentially assessed cases as 'probable', Rater 3 preferentially assessed cases as 'possible' and Rater 4 preferentially assessed cases as 'unlikely'.

Interrater agreement

Table 1 shows rater-pairs' cross-tabulated outcomes when using the WHO-UMC system and Table 2 shows their outcomes when using the LCAT.

Using the WHO-UMC system, exact agreement between the two raters occurred in 34 of 48 cases (0.71, range 0.50 to 1.0 among the six rater-pairs). Two rater-pairs (the pair of clinicians and one of the internist-clinical pharmacist pairs) obtained exact agreement on all cases. Using the LCAT, exact agreement occurred in 22 of 48 cases (0.46, range 0.25 to 0.80 among the six rater-pairs, highest for the pair of clinicians). The difference in exact agreement was 0.25 (95% CI 0.025 to 0.47, McNemar's chi-square $p = 0.023$). Extreme disagreement occurred with the WHO-UMC system in 3 of 48 cases (0.063) and with the LCAT in 7 of 48 cases (0.15) (Table 3).

The proportion of specific agreement for each outcome category when using the WHO-UMC system was: for 'definite' 1.0, for 'probable' 0.55, for 'possible' 0.60, for 'unlikely'

Table 1. Pairwise distribution of outcomes, when using the WHO-UMC system.

	Definite	Probable	Possible	Unlikely	Unassessable
Unassessable	0	1	1	1	5
Unlikely	0	0	7	13	
Possible	0	4	9		
Probable	0	3			
Definite	4				

doi:10.1371/journal.pone.0172830.t001

Table 2. Pairwise distribution of outcomes, when using the LCAT.

	Definite	Probable	Possible	Unlikely	Unassessable
Unassessable	0	1	1	3	1
Unlikely	0	2	9	9	
Possible	0	9	3		
Probable	1	8			
Definite	1				

doi:10.1371/journal.pone.0172830.t002

0.76, and for 'unassessable' 0.77. The proportion of specific agreement for each outcome category when using the LCAT was: for 'definite' 0.67, for 'probable' 0.55, for 'possible' 0.24, for 'unlikely' 0.56, and for 'unassessable' 0.29.

Unweighted pairwise Cohen kappas (Table 3) on the WHO-UMC system ranged from 0.33 to 1.0 (mean 0.63, 95% CI 0.31 to 0.95) and on the LCAT from 0.094 to 0.71 (mean 0.28, 95% CI 0.037 to 0.52). The difference in means was 0.35 (95% CI 0.047 to 0.65) and non-zero at $p = 0.031$. Linearly weighted pairwise Cohen kappas (Table 3) ranged from 0.52 to 1.0 on the WHO-UMC system (mean 0.74, 95% CI 0.51 to 0.98), and from 0.077 to 0.88 on the LCAT (mean 0.44, 95% CI 0.14 to 0.74). The difference in means was 0.31 (95% CI 0.011 to 0.60) and non-zero at $p = 0.045$.

The overall unweighted Abiraira kappa on the WHO-UMC system was 0.61 (95% CI 0.43 to 0.80) and the linearly weighted Abiraira kappa 0.73 (95% CI 0.57 to 0.91). On the LCAT, overall unweighted Abiraira kappa was 0.27 (95% CI 0.074 to 0.46) and linearly weighted Abiraira kappa 0.45 (95% CI 0.25 to 0.67).

The ICC1,1 was 0.86 (95% CI 0.74 to 0.92) on the WHO-UMC system and 0.61 (95% CI 0.39 to 0.77) on the LCAT.

The results of the sensitivity analysis (S2 Table) were similar to those of the main analysis.

Investigation for potentially problematic questions on the LCAT

We observed only 13 out of the 36 'paths' theoretically possible on the LCAT flowchart among our results. The top three traces occurred 31 times, 21 times, and 20 times, respectively (S3 Table and S2 Data). On two cases raters disagreed on responses to the LCAT questions yet still arrived at the same outcome. Of 59 traces which proceeded beyond Q1 (see Fig 1 for our numbering of the LCAT questions), 35/59 (59%) did not reach Q5a, 29/59 (49%) did not reach Q6, and 27/59 (46%) did not reach Q5b.

Table 3. Exact agreement (EA), extreme disagreement (ED), unweighted pairwise Cohen kappa (κ) and linearly-weighted pairwise Cohen kappa (κ_w) for each of six rater-pairs, using two different causality assessment methods.

Rater-pair	WHO-UMC					LCAT				
	<i>n</i>	EA	ED	κ	κ_w	<i>n</i>	EA	ED	κ	κ_w
Raters 1 and 2	7	1.0	0	1.0	1.0	8	0.25	0.13	0.094	0.22
Raters 1 and 3	8	0.50	0	0.35	0.53	9	0.33	0	0.13	0.077
Raters 1 and 4	6	1.0	0	1.0	1.0	10	0.80	0.10	0.71	0.88
Raters 2 and 3	10	0.60	0.10	0.49	0.67	6	0.33	0.17	0.14	0.35
Raters 2 and 4	9	0.56	0.11	0.33	0.52	8	0.50	0.13	0.27	0.55
Raters 3 and 4	8	0.75	0.13	0.60	0.77	7	0.43	0.43	0.32	0.55

All cross-tabulations were marginally homogeneous, measured by Stuart-Maxwell chi-square statistic. EA: exact agreement. ED: extreme disagreement. κ : unweighted pairwise Cohen kappa. κ_w : linearly-weighted pairwise Cohen kappa.

doi:10.1371/journal.pone.0172830.t003

Cross-tabulating raters' positive and negative responses to each question on the LCAT (Table 4), we found disproportionate responses to two questions, Q4a and Q4b. The odds ratio for a positive response on Q4a from a clinician, compared to a pharmacist, was 5.1 (95% CI 1.6 to 16, $p = 0.006$). Q4b had 22 negative responses and 9 positive responses. Seven of the positive responses came from one pharmacist rater, and there were no positive responses from either clinician rater.

The proportions of specific agreement for each of the LCAT questions are given in S4 Table. Q4a showed the worst agreement (among questions with more than 10 paired responses), with the proportion of both positive and negative agreement on this question lower than 0.70.

Subjectively, our raters commented that they were unclear how to proceed on the LCAT flowchart in situations where (a) the drug was not withdrawn (as opposed to 'cannot be withdrawn'), (b) the patient died, (c) the patient's outcome (improved / deteriorated) was different than that of the event being considered, (d) there was a second potential drug cause (the LCAT gives no instruction on dealing with situations when combinations of drugs are implicated in one ADR, and only refers to drugs in the singular), and (e) laboratory results were not available. All four raters also independently reported being 'channelled' by the LCAT towards a 'probable' outcome when they intuitively considered a case to be 'definite'. There were three cases (a case of warfarin-associated haematuria, a case of isoniazid-associated liver injury, and a case of insulin-associated hypoglycaemia) where both raters using the WHO-UMC system assessed the case as 'definite', while both raters using the LCAT assessed the case as 'probable'.

Discussion

We were unable to replicate the high IRA, or the high proportion of 'definite' outcomes, reported by the developers of the LCAT. Instead, we found the LCAT's IRA, and its proportion of 'definite' outcomes, to be lower than those achieved by a method of global introspection. We identified potential explanations for the finding of lower IRA by tracing raters' decisional process on the LCAT flowchart.

Table 4. Distribution of raters' responses to LCAT questions.

Question ^a	Negative response ^b				Positive response ^c				p-value ^d
	Rater 1	Rater 2	Rater 3	Rater 4	Rater 1	Rater 2	Rater 3	Rater 4	
1	9	8	4	10	16	14	14	15	0.66
2a	0	0	0	1	16	14	14	14	0.73
2b	0	0	0	1	0	0	0	0	
3a	2	3	1	2	14	11	13	11	0.79
3b	1	0	0	1	1	3	1	1	0.57
4a	6	8	13	4	9	6	1	8	0.008
4b	6	1	11	4	0	7	2	0	<0.001
5a	9	6	1	7	0	0	0	1	0.63
5b	8	13	2	7	1	0	1	0	0.15
6	0	1	0	0	8	12	2	7	1.00

^a See Fig 1 for our numbering of questions on the LCAT flowchart.

^b Negative responses: 'High / Unsure' on question 4a, 'No' on all other questions.

^c Positive responses: 'Yes / Unassessable' on question 3a, 'Low' on question 4a, 'Yes' on all other questions.

^d Chi-square or Fisher's exact test, as appropriate.

doi:10.1371/journal.pone.0172830.t004

To our knowledge, this is the first study which measured the IRA of the LCAT since its development. Previous studies have reported the LCAT's sensitivity and specificity (against a 'gold standard' of consensual expert judgement) as identical to that of the Naranjo algorithm [14]; its distribution of outcomes (in a paediatric hospital-based survey) as similar to that of the Naranjo algorithm [15]; and the exact agreement obtained on the LCAT (between trainee specialists and a predefined 'correct' assessment by multidisciplinary panel) as ranging from 20% to 65% [16].

Expert clinical pharmacologists independently assessing ADR case reports by global introspection have been shown to disagree on ADR causality assessment, as well as the presence of drug-drug interactions, the contribution of the ADR to patients' admission and duration of hospitalisation, the presence of severe morbidity and ADR-related sequelae, and the contribution of the ADR to death [17]. As a result, global introspection has been criticised as 'neither reproducible, valid, nor accountable' [18], and it seems intuitive that an explicit, algorithmic method should result in higher IRA than an implicit, subjective method such as global introspection. This, in fact, had been shown by Naranjo et al. in the original publication on the development of their method, which used published case reports to determine IRA: on only an implicit ADR causality assessment comparable to the WHO-UMC system, pairwise unweighted kappa ranged from 0.21 to 0.37, but by applying the Naranjo algorithm, pairwise unweighted kappa improved to range from 0.69 to 0.86 [3].

Since the development of the Naranjo algorithm, however, two studies have compared its IRA to the IRA achieved on a method of global introspection and failed to replicate the higher IRA the Naranjo developers showed. First, in a routine hospital-based ADR surveillance programme, three paediatric clinical pharmacologists achieved similar IRA whether using implicit causality categories or the Naranjo algorithm [19]. A more recent study from the Liverpool group also found similar IRA whether using the WHO-UMC system or the Naranjo algorithm [20]. These studies raised the question whether the Naranjo algorithm is transferable to settings where users are unfamiliar with it or information is less complete than in published case reports.

Similar to the above two studies, which failed to replicate IRA reported by the Naranjo algorithm's developers, we were unable to replicate the IRA reported by the LCAT developers [4]. Whereas its developers found the LCAT's linearly weighted pairwise kappas to range from 0.50 to 0.85 and its 'global' unweighted kappa to be 0.60 (95% CI 0.54 to 0.67) [4], we found its linearly weighted pairwise kappas to range from 0.077 to 0.88 and its 'global' unweighted kappa to be 0.27 (95% CI 0.074 to 0.46).

We found the LCAT's IRA to be lower than that of the WHO-UMC system using a range of measures. The LCAT's calculated kappa statistics could be considered 'fair' to 'moderate' in terms of the frequently-used Landis and Koch interpretation [21], a category lower than WHO-UMC system's kappa statistics, which were 'moderate' to 'substantial'. Similarly, the LCAT's ICC (0.61) was a category lower than that of the WHO-UMC system (0.86) in the interpretation of Cicchetti [22] ('good' versus 'excellent'). Moreover, proportions of exact agreement and extreme disagreement among individual rater-pairs, and proportions of specific agreement on each category were consistently higher for the WHO-UMC system than the LCAT.

A possible explanation for the WHO-UMC system's higher IRA could be the LCAT's potential for disregarding information that may have otherwise contributed to the decision-making process. Loss of information can firstly occur in any algorithm designed with the potential to bypass some decision-making nodes. As pointed out previously, the LCAT flow-chart is structured in such a way that some questions cannot be reached under certain circumstances [14]. We found that potential information on rechallenge and on previous ADRs to the

drug was only taken into account in about half of assessments on the LCAT, as those specific questions were simply not reached by raters. Secondly, loss of information can occur in an algorithm when the rater makes a pragmatic choice when 'the true answer may be somewhere in-between' the options offered by the algorithm [23]. Our study was not designed to measure how often this may have happened, although our raters anecdotally reported some such instances.

In our study, both causality assessment methods resulted in assessments across all outcome categories. However, the WHO-UMC system resulted in proportionally more 'definite' and 'unassessable' outcomes, while the LCAT resulted in relatively more 'probable' outcomes. This contrasts with the LCAT developers' finding that 'definite' outcomes were most common [4].

The LCAT's 'channelling' towards 'probable' outcomes has previously been discussed [14]. It was pointed out that when a rater is unsure about the likelihood that an underlying disease caused the event, she is forced to disregard information about a positive rechallenge (which is generally considered to be a strong indicator of drug causation), as she is steered away from that question in the LCAT flowchart [14]. It was also pointed out that the design of the LCAT requires either a positive rechallenge or a past history of the same event with the same drug in the same patient in order to arrive at a 'definite' outcome, and that those conditions are seldom met in routine clinical practice [14].

It would appear that the LCAT, though designed to yield more 'definite' outcomes than the Naranjo algorithm, is unlikely to achieve this when using available routine clinical data as was the case in our study design. Nevertheless, in the absence of a gold standard, it remains unclear whether a method with a predilection for 'probable' outcomes or one with a predilection for 'definite' outcomes should be regarded as preferable.

We postulate some reasons for the differences between our findings and those of the LCAT developers [4]. First, although both studies' data came from prospective hospital-based ADR surveys, our study population were adults while theirs were children. A number of their patients presented with repeated episodes of febrile neutropenia attributed to cancer chemotherapy; our survey excluded oncology wards but included a large proportion of patients infected by HIV, and antiretroviral therapy was frequently suspected of causing ADRs. Second, there were differences between the raters in the two studies: we used only four raters versus the LCAT developers' seven, and our raters had a smaller spectrum of expertise. Our raters were not involved in the development of the LCAT, nor were they, before a training session, familiar with its use, and the LCAT developers had shown that IRA on the LCAT increased as their raters' familiarity with the method grew. Third, our assessments were based on available clinical case data summarised and captured onto a database, and not on raw case data in patient folders or data specifically collected for study purposes. Together with our use of a sensitive but non-specific trigger tool for case identification, this resulted in a high frequency of suspected ADRs ultimately assessed 'unlikely' and 'unassessable', unlike the LCAT developers' distribution of outcomes.

In addition to the methodological differences between the studies, we identified two questions in the LCAT flowchart as points of significant divergence. These were Q4a ("What is the probability that the event was due to an underlying disease?") and Q4b ("Is there any objective evidence supportive of the causal ADR mechanism?"). Answering these two questions requires some clinical judgement, and our pharmacist-raters answered these questions differently from our clinician-raters. This is not a novel finding: Naranjo et al. reported in their original paper that a question on alternative causes of the purported ADR resulted in most disagreement between their raters, with pharmacists answering the question differently to physicians [3]. Another early study tracing two raters' decision-making process on the Kramer algorithm [24] also found that decision nodes requiring raters to express some form of subjective judgement resulted in disagreement more frequently than decision nodes with 'factual' questions [25].

A modification of the LCAT was recently published, in which the modified tool was used in a pharmacogenetic study to phenotypically link one ADR (pancreatitis) to one class of drugs (thiopurines) [26]. This modification *inter alia* discarded four questions, including Q4b, rephrased four questions, including Q4a, and swapped the order of Q5a and Q4a. While the authors of the modification provided neither a justification for the modification, nor evidence of the modified tool's validity, and while it is debatable whether the modified tool would be useful outside such a restricted setting, it is tempting to speculate that they may have been faced with some of the same problems on Q4a and Q4b we have found.

We would suggest that improvements to the LCAT may be warranted. Such improvements should aim to reduce the tool's potential for loss of information, should focus on maximising agreement on the two 'subjective' questions identified as sources of disagreement, and should provide guidance on how to answer questions in ambiguous situations.

Limitations of our study include that case summaries may have lacked detailed information, that raters had prior familiarity with global introspection as a methodology but not with the LCAT, and that raters were aware of the purpose of their assessments. We conducted self-guided training in the use of the LCAT, which was not standardised; a training module [16] is still under development by the authors of the LCAT. We used a small convenience sample of raters, limiting the generalizability of our results. It appears that bias existed in raters' preference for certain outcome categories, which may have influenced our overall kappa estimates and ICC. However, bias was not present when calculating pairwise Cohen kappas (cross-tabulations were marginally homogeneous in all instances). For these reasons further interrater (and intra-rater) agreement studies would be essential to investigate the LCAT's usefulness, as well as that of any modifications to it.

Conclusion

Causality assessment of ADRs is an expression of the rater's uncertainty in assessing the strength of evidence in favour of drug causation, rather than an expression of any inherent quality of the ADR itself. Maximising IRA has therefore been criticised for 'suppressing' disagreement, when disagreement *per se* is valuable information [27]. Nevertheless, IRA remains a widely used way to quantify a method's repeatability. Our study suggests that causality assessment using the LCAT is less repeatable than a method of global introspection, when it is used outside of the setting in which it was developed.

Supporting information

S1 Data. Interrater agreement comma-separated data (.txt file). Key: tool 1 = WHO-UMC system; tool 2 = LCAT; outcome 1 = definite; outcome 2 = probable; outcome 3 = possible; outcome 4 = unlikely; outcome 5 = unassessable.
(TXT)

S2 Data. LCAT paths comma-separated data (.txt file).
(TXT)

S1 Fig. Difference between raters' individual distribution of outcomes and the four raters' mean distribution of outcomes, when using WHO-UMC method.
(PDF)

S2 Fig. Difference between raters' individual distribution of outcomes and the four raters' mean distribution of outcomes, when using LCAT.
(PDF)

S1 Table. Raters' distribution of outcomes when using two different causality assessment methods.

(PDF)

S2 Table. Results of sensitivity analysis.

(PDF)

S3 Table. Frequency of paths (traces) on the LCAT.

(PDF)

S4 Table. Case-wise response pairs to LCAT questions, and proportions of specific agreement on LCAT questions.

(PDF)

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Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Adverse drug reactions (ADRs) are implicated in 2.5–18% of deaths of hospitalized patients.
- Fatal ADRs are frequently preventable.
- There is a lack of evidence regarding the burden of ADR-related deaths in low- and middle-income countries, and in settings of high human immunodeficiency virus (HIV) and tuberculosis prevalence.

WHAT THIS STUDY ADDS

- In South African medical wards, a larger proportion of in-hospital deaths are ADR-related than previously described.
- Unlike the pattern in high income countries, the drugs implicated in ADR-related deaths were mostly drugs used in the treatment of HIV and tuberculosis, reflecting the high burden of these diseases in our setting.

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Keywords

adverse drug reaction, antiretroviral therapy, anti-tuberculosis therapy, in-hospital death, preventability, South Africa

Received

4 August 2014

Accepted

25 November 2014

Accepted Article

Published Online

5 December 2014

AIMS

Fatal adverse drug reactions (ADRs) are important causes of death, but data from resource-limited settings are scarce. We determined the proportion of deaths in South African medical inpatients attributable to ADRs, and their preventability, stratified by human immunodeficiency virus (HIV) status.

METHODS

We reviewed the folders of all patients who died over a 30 day period in the medical wards of four hospitals. We identified ADR-related deaths (deaths where an ADR was 'possible', 'probable' or 'certain' using WHO-UMC criteria and where the ADR contributed to death). We determined preventability according to previously published criteria.

RESULTS

ADRs contributed to the death of 2.9% of medical admissions and 56 of 357 deaths (16%) were ADR-related. Tenofovir, rifampicin and co-trimoxazole were the most commonly implicated drugs. 43% of ADRs were considered preventable. The following factors were independently associated with ADR-related death: HIV-infected patients on antiretroviral therapy (adjusted odds ratio (aOR) 4.4, 95% confidence interval (CI) 1.6, 12), exposure to more than seven drugs (aOR 2.5, 95% CI 1.3, 4.8) and increasing comorbidity score (aOR 1.3, 95% CI 1.1, 1.7).

CONCLUSIONS

In our setting, where HIV and tuberculosis are highly prevalent, fatal in-hospital ADRs were more common than reported in high income settings. Most deaths were attributed to drugs used in managing HIV and tuberculosis. A large proportion of the ADRs were preventable, highlighting the need to strengthen systems for health care worker training and support.

Introduction

Adverse drug reactions (ADRs) that result in death, particularly those considered to have been preventable, are of major public health interest. A population-based study in three Swedish counties found that 3% of all deaths were suspected to be due to ADRs, making ADRs the seventh most common cause of death [1]. This figure agrees with a systematic review [2] which ranked ADRs among the top six causes of death in the USA.

Most epidemiological data on ADR-related deaths come from hospital-based studies. Depending on the definitions and methods used, ADRs have been implicated in 2.5–18% of in-hospital deaths [3–7]. However, there are limited data on mortality associated with ADRs from resource-limited settings, in particular from settings with high human immunodeficiency virus (HIV) and tuberculosis prevalence. South Africa has implemented the world's largest roll-out of antiretroviral therapy (ART), with just over 2 million people on ART in 2012 [8], and has among the highest tuberculosis incidence globally, estimated to be 1000 new cases per 100 000 persons per year in 2012 [9].

A previous survey performed by our group at a secondary level hospital in South Africa in 2005 [7], showed that HIV-infected persons were twice as likely to be admitted with an ADR compared with persons who were HIV negative or whose HIV status was unknown. In that survey, antiretroviral drugs (ARVs) and drugs used to treat opportunistic infections were frequently implicated as causing ADRs, albeit that the survey was performed early in the ART era, when more toxic ARVs were in use. Thus, there is a need for larger studies to determine the current impact of ADRs on morbidity and mortality in our setting.

We performed a cross-sectional survey in the medical wards of four hospitals in South Africa to determine the mortality attributable to ADRs, to identify the drugs implicated in these ADR-related deaths, to determine the proportion of fatal ADRs that were preventable and to explore the effect of patients' HIV status on mortality attributed to ADRs.

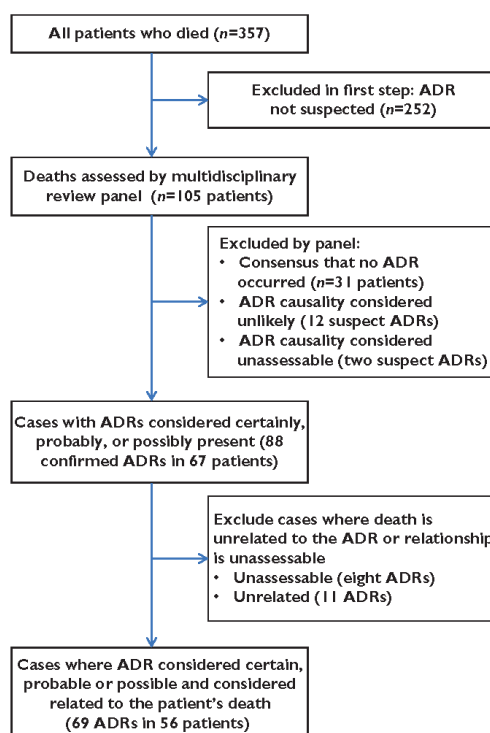
Methods

Study design and setting

Between April and September 2013, we identified all patients who died in the medical wards of Groote Schuur Hospital, Edendale Hospital, Cecilia Makiwane Hospital and Frere Hospital, over a 30 day period at each site, by daily scrutiny of ward and/or mortuary administrative records. A description of the sites is included in Table S1. We included all patients where a decision to admit had been made by the medical team, including those who died in the emergency unit while awaiting transfer to the ward.

Identification of suspected ADRs and causality assessment

We defined an ADR according to the definition of Aronson & Ferner [10], but we did not regard intentional overdoses or cases of immune reconstitution syndrome as ADRs. The assessment process flow is shown in Figure 1. Between October 2013 and April 2014, one author (JPM) reviewed each patient's medical notes, medication exposure over the 30 days prior to admission, prescription charts related to the admission, as well as the patient's laboratory data, using a trigger tool [11] to flag the deaths suspected to be related to ADRs, and additionally flagging all cases where the cause of death was unclear. We did not attempt to augment incomplete data from other sources. For each flagged case, JPM prepared a narrative summary of events, as well as a detailed summary of drug use (codified to five level ATC codes), investigative results and clinical problems (codified to ICD-10 codes).



ADR: adverse drug reaction

Figure 1

Flowchart describing the assessment process

A multidisciplinary review panel consisting of a clinical pharmacologist, a clinical pharmacist, and at least one but up to three physicians/internists met to assess each of the flagged cases for the presence of an ADR and its preventability. Each panellist was provided with the prepared case summaries and an electronic, anonymized copy of the hospital records. For each suspected ADR that was identified by one or more members of the review panel, the panel discussed its causality using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment [12], until consensus was reached. For ADRs categorized as 'possible', 'probable' or 'certain', the panel assessed the relationship between the ADR and the death of the patient. We categorized the relationship between ADR and death into one of four categories: (i) the ADR was a major contributor to the death of the patient, (ii) the ADR contributed to the patient's death, but was not the major contributor, (iii) the ADR was unrelated to the patient's death or (iv) the relationship between ADR and death could not be determined. The panel also decided on the preventability of the ADR using the criteria of Schumock & Thornton [13]. Where the panel could not reach consensus on the causality or preventability of an ADR, or on its relationship to the patient's death, the majority decision was recorded. In one case, where the panel consisted of four members who were evenly split in opinion over the presence/absence of an ADR, the third physician's opinion was sought following the panel meeting, to obtain a majority decision.

We defined an ADR-related death as a death where the panel held (either in consensus, or in majority) that, firstly, an ADR was 'possible', 'probable' or 'certain', according to the WHO-UMC methodology and that, secondly, the ADR was a major contributor or a contributor to the patient's death. An ADR was considered preventable if any one or more of the Schumock & Thornton criteria was answered in the affirmative.

For every patient who died, we calculated a comorbidity score modified from the Charlson comorbidity score [14]. As the original Charlson comorbidity score assigns a score for HIV infection that is probably inappropriately high in the era of ART [15] and as we wanted to explore the independent effect of HIV-infected status with and without antiretroviral therapy, we excluded a diagnosis of HIV/AIDS from the calculation of the modified Charlson comorbidity score. We also calculated a drug count for every patient by counting each drug to which the patient was documented to have been exposed in the period starting 3 weeks prior to the date of admission and ending on the day of death, excluding vitamin and mineral supplements. For fixed drug combinations, we counted each component drug individually.

Data entry and analysis

Data were entered into a Microsoft Access 2010 database and analyzed using Stata 13.1 (Stata Corporation, College

Station, Texas, USA). Continuous variables were summarized using medians and interquartile ranges, as they were non-normally distributed. We explored univariate associations for binary and categorical variables by cross-tabulation, and calculated chi-square statistics or performed Fisher's exact test as appropriate. As data were non-normally distributed, we used the Wilcoxon rank-sum test for between group comparisons of continuous and ordinal variables.

We constructed a multivariate logistic regression model exploring independent associations with ADR-related death. Variables were included in the model based on an *a priori* decision. We included the following variables in the model: age, sex, comorbidity score, drug count (using a binary variable by cutting the data at the median), HIV infection and antiretroviral treatment status (using a three category variable: HIV-negative or unknown status, HIV-infected and not on ART, HIV-infected on ART), and whether or not patients were being treated for tuberculosis. Assumptions of linearity were checked in the final model. We constructed a similar model, with the addition of the most recent CD4 count, in an analysis restricted to patients known to be HIV-infected. We used a significance level of 0.05.

Ethics

This study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (Reference no. 576/2011). Permission to conduct the research was granted by the respective hospitals' management and/or provincial Departments of Health.

Results

There were 1951 admissions and 357 deaths during the survey period, for a crude mortality rate of 18 deaths per 100 admissions. At the first level of review, 252 cases were assessed as having no suspected ADRs (Figure 1). The multidisciplinary panel reviewed the remaining 105 cases, and concluded that ADR-related causes contributed to the deaths of 56 of the 357 (16%) patients, which represents 2.9% of the 1951 patients admitted over the study period.

Sixty-nine different ADRs (four 'certain', 10 'probable' and 55 'possible', according to the WHO-UMC method) were identified to have contributed to the death of these 56 patients. Of the 56 patients, four had at least one 'certain' ADR, eight at least one 'probable' ADR and the remaining 44 had 'possible' ADRs contributing to death. In 51 cases, the panel reached consensus over the ADRs¹ and contribution to death, while in the remaining five cases the majority of the panel agreed on the ADR, with some dissent. Patient characteristics are summarized in Table 1. Table S2 lists individual patients' characteristics and details of the ADRs.

Table 1

Characteristics of patients whose deaths were considered ADR-related, vs. patients whose deaths were not considered ADR-related

	All deaths	ADR-related deaths	Other deaths	P value
All patients: <i>n</i>	357	56	301	
Females: <i>n</i> (%)	184 (52%)	30 (54%)	154 (51%)	<i>P</i> = 0.741
Age (years): median [IQR]	53 [38, 70]	52.5 [33, 65.5]	53 [39, 72]	<i>P</i> = 0.2209
Known HIV infected (%)	135 (38%)	31 (55%)	104 (35%)	<i>P</i> = 0.003
On treatment for TB (%)	55 (15%)	14 (25%)	41 (14%)	<i>P</i> = 0.030
Number of drugs exposed to: median [IQR]	7 [5, 11]	9 [7, 11]	7 [4, 11]	<i>P</i> = 0.0008
Modified Charlson co-morbidity score: median [IQR]	2 [0, 3]	2 [1, 3]	2 [0, 3]	<i>P</i> = 0.0246
Time from admission to death (days): median [IQR]	5 [3, 10]	6.5 [3, 11.5]	5 [3, 10]	<i>P</i> = 0.3478
HIV-infected patients only: <i>n</i>	135	31	104	
Females: <i>n</i> (%)	61 (45%)	15 (48%)	46 (44%)	<i>P</i> = 0.683
Age (years): median [IQR]	37 [30, 44]	37 [31, 52]	37 [30, 43]	<i>P</i> = 0.3393
CD4-count (cells mm ⁻³): median [IQR]*	52 [19, 167]	126 [32, 299]	41 [19, 109]	<i>P</i> = 0.0509
On ART (%)	66 (49%)	20 (65%)	46 (44%)	<i>P</i> = 0.047
On treatment for TB (%)	45 (33%)	12 (39%)	33 (32%)	<i>P</i> = 0.469
Number of drugs exposed to: median [IQR]	9 [6, 12]	9 [7, 10]	9 [6, 12]	<i>P</i> = 0.8053
Modified Charlson co-morbidity score: median [IQR]	0 [0, 2]	2 [0, 2]	0 [0, 2]	<i>P</i> = 0.0579
Time from admission to death (days): median [IQR]	5 [3, 8]	4 [2, 7]	5.5 [3, 8.5]	<i>P</i> = 0.2082

*20 patients missing data. ADR, adverse drug reaction; ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; TB, tuberculosis.

Table 2

Frequency at which various preventability factors were observed amongst 69 ADRs considered to have contributed to the death of 56 patients

Schumock & Thornton criteria	Number of occurrences
Was the drug involved in the ADR not considered appropriate for the patient's clinical condition based on published guidelines, clinical studies, abstracts, case reports, case series?	16
Was the dose, route and frequency of administration not appropriate for the patient's age, weight, or disease state (e.g. renal/hepatic function) based on published literature (e.g. South African Medicines Formulary, MIMS)	5
Was required therapeutic drug monitoring or other laboratory test not performed?	11
Was there a history of allergy or previous reaction to the drug?	0
Was a drug interaction involved in the reaction?	4
Was the serum drug concentration above the therapeutic range documented in adults?	0
Did compliance possibly contribute to the reaction?	2

ADR, adverse drug reaction.

Thirty of the 69 ADRs (43%) were considered preventable according to the Schumock & Thornton criteria [13]. Most often, this was because the drug was not considered appropriate for the patient, or because laboratory monitoring was inadequate (Table 2). In 28 of the 56 deaths (50%), at least one ADR was considered preventable.

Of the 357 deaths, 135 patients (38%) were known to be HIV-infected, 39 (11%) were known to be HIV-negative

and 183 (51%) had no HIV serology result. In the 135 HIV-infected patients, a higher proportion of patients who died from ADR-related causes were taking ARV therapy: 20/31 (65%) vs. 46/104 (44%). Of 55 patients on treatment for tuberculosis, 45 (82%) were co-infected with HIV.

Amongst the 56 patients with ADR-related deaths, 31 were HIV-infected, four were HIV-seronegative and the HIV status of 21 patients was unknown. When comparing the 31 HIV-infected patients to the 25 patients with negative or unknown HIV serology status, we found that ADR-related deaths in HIV-infected persons occurred at a significantly younger age (median [IQR] years 37 [31, 52] vs. 66 [55, 79], *P* < 0.00005), and in persons with a lower comorbidity score (median [IQR] score 2 [0, 2] vs. 3 [2, 4], *P* = 0.0010). There was no significant difference in the drug count (median [IQR] count 9 [7, 10] vs. 9 [7, 13], *P* = 0.5071), proportion female (48% vs. 60%, *P* = 0.386) or in the proportion of cases with at least one preventable ADR (48% vs. 52%, *P* = 0.788).

We constructed a multivariate logistic regression model to identify independent associations with ADR-related death (Table 3). HIV-infected patients on ART had increased odds of ADR-related death (adjusted odds ratio (aOR) 4.4, 95% confidence interval (CI) 1.6, 12). However, the odds of ADR-related death in HIV-infected patients not on ART was not significantly different from the reference group (adjusted OR 2.4, 95% CI 0.78, 7.1). Exposure to more than seven medicines prior to death was independently associated with increased odds of ADR-related death (aOR 2.5, 95% CI 1.3, 4.8). Increasing modified Charlson comorbidity score was associated with increased odds of ADR-related death (aOR 1.3, 95% CI 1.1, 1.7, for a one unit increase in score). Treatment for tuberculosis was

Table 3

Multivariate logistic regression model for the association between risk factors and ADR-related death ($n = 357$)

Variable	Patients, n (%)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)	Wald test P value
Sex	357			
Male	173 (48%)	1	1	
Female	184 (52%)	1.1 (0.62, 2.0)	1.2 (0.64, 2.2)	0.581
Age*	357	0.91 (0.78, 1.1)	1.1 (0.83, 1.3)	0.644
HIV group	357			
HIV serology negative or unknown	222 (62%)	1	1	
HIV-infected and not on ART	69 (19%)	1.5 (0.69, 3.2)	2.4 (0.78, 7.1)	0.127
HIV-infected and on ART	66 (18%)	3.4 (1.8, 6.7)	4.4 (1.6, 12)	0.003
TB infection status	357			
Not on treatment for TB	302 (85%)	1	1	
On treatment for TB	55 (15%)	2.1 (1.1, 4.2)	1.2 (0.53, 2.6)	0.689
Drug count	357			
≤ 7 drugs	181 (51%)	1	1	
> 7 drugs	176 (49%)	3.4 (1.8, 6.3)	2.5 (1.3, 4.8)	0.009
Modified Charlson comorbidity score†	357	1.2 (1.0, 1.5)	1.3 (1.1, 1.7)	0.009

*Included in the model as a continuous variable. The odds ratio is for a 10 year increase in age. †The odds ratio is for a one unit increase in the comorbidity score. ADR, adverse drug reaction; ART, antiretroviral therapy; TB, tuberculosis.

Table 4

Multivariate logistic regression model for the association between risk factors and ADR-related death in HIV-infected persons ($n = 115$)

Variable	Patients, n (%)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)	Wald test P value
Sex	115			
Male	61 (53%)	1	1	
Female	54 (47%)	1.4 (0.59, 3.4)	1.2 (0.47, 3.2)	0.664
Age*	115	1.3 (0.88, 2.0)	1.3 (0.80, 2.0)	0.305
CD4-count†	115	1.1 (1.0, 1.3)	1.1 (0.98, 1.3)	0.088
Antiretroviral therapy	115			
Not on ART	58 (50%)	1	1	
On ART	57 (50%)	2.9 (1.1, 7.3)	2.4 (0.86, 6.6)	0.096
TB infection status	115			
Not on treatment for TB	75 (65%)	1	1	
On treatment for TB	40 (35%)	1.5 (0.62, 3.7)	1.1 (0.42, 3.1)	0.802
Drug count	115			
≤ 7 drugs	41 (36%)	1	1	
> 7 drugs	74 (64%)	3.9 (1.2, 12)	3.6 (1.1, 12)	0.041
Modified Charlson comorbidity score‡	115	1.3 (0.95, 1.9)	1.2 (0.84, 1.8)	0.281

*Included in the model as a continuous variable. The odds ratio is for a 10 year increase in age. †Included in the model as a continuous variable. The odds ratio is for an increase of 50 cells mm^{-3} . ‡The odds ratio is for a one unit increase in the comorbidity score. ADR, adverse drug reaction; ART, antiretroviral therapy; TB, tuberculosis.

associated with ADR-related death on univariate, but not on multivariate analysis. Age and sex were not associated with ADR-related death.

To explore independent predictors of ADR-related death in HIV-infected patients, we constructed a second multivariate model restricted to the 115 patients known to be HIV-infected with complete data for all variables in the model (Table 4), including the variables above and CD4 count. After adjustment for age, sex, CD4 count, ART, tuberculosis treatment and modified Charlson score, only exposure to more than seven medicines prior to death

remained significantly associated with increased odds of ADR-related death (aOR 3.6, 95% CI 1.1, 12). ART and CD4 count were associated with ADR-related death on univariate, but not on multivariate analysis (which may be due to lack of power).

The drugs implicated in ADR-related deaths are listed in Table 5. The two most common ADRs contributing to death were renal failure and drug-induced liver injury. Drug-induced renal failure occurred in 23 patients, with tenofovir implicated as the cause in 14 (61%) of these. In all 14 of these cases, renal failure was considered 'possibly'

Table 5

Drugs implicated in ADR-related deaths, grouped according to ATC drug classes

Second-level ATC drug class*	Drugs*
A06 Drugs for constipation (1)	sodium sulfate/polyethylene glycol (1)
A10 Drugs used in diabetes (5)	insulin (4); metformin (1)
B01 Antithrombotic agents (7)	warfarin (2); heparin (1); enoxaparin (1); aspirin (3)
B05 Blood substitutes and perfusion solutions (1)	sodium chloride (1)
C02 Antihypertensives (2)	prazosin (1); hydralazine (1)
C03 Diuretics (9)	hydrochlorothiazide (2); furosemide (5); spironolactone (2)
C07 Beta blocking agents (2)	atenolol (2)
C08 Calcium channel blockers (2)	amlodipine (2)
C09 Agents acting on the renin-angiotensin system (3)	enalapril (2); perindopril (1)
H02 Corticosteroids for systemic use (3)	prednisone (3)
J01 Antibacterials for systemic use (11)	co-amoxiclavulanic acid (2); co-trimoxazole (7) ; erythromycin (1); ciprofloxacin (1)
J02 Antimycotics for systemic use (1)	fluconazole (1)
J04 Antimycobacterials (15)	rifampicin (9) ; isoniazid (3); pyrazinamide (3)
J05 Antivirals for systemic use (19)	aciclovir (1); lopinavir/ritonavir (1); stavudine (3); tenofovir (14)
L01 Antineoplastic agents (1)	chlorambucil (1)
L04 Immunosuppressants (1)	tacrolimus (1)
M01 Anti-inflammatory and antirheumatic products (3)	indomethacin (1); ibuprofen (2)
M04 Antigout preparations (2)	allopurinol (1); colchicine (1)
N02 Analgesics (3)	codeine (2); tramadol (1)
N03 Anti-epileptics (2)	clonazepam (1); valproate (1)
N05 Psycholeptics (1)	haloperidol (1)
N06 Psychoanaleptics (1)	amitriptyline (1)
R03 Drugs for obstructive airway diseases (1)	theophylline (1)
V03 Other therapeutic products (1)	polystyrene sulfonate (1)

*The number of times each drug and drug class was implicated in an ADR-related death appears in brackets. The three most commonly implicated drugs appear in bold. ADR, adverse drug reaction; ATC, anatomical therapeutic chemical.

related to tenofovir, mostly because of concomitant drug-related causes (four cases) or concomitant disease-related causes (eight cases). Other causal drugs identified (alone or in combination) were co-trimoxazole (three cases), rifampicin (two cases), furosemide (two cases), co-amoxiclavulanic acid (two cases) and ibuprofen, enalapril, spironolactone, ciprofloxacin, aciclovir and indomethacin (one case each). In 12 of these 23 cases (52%), the ADR was considered preventable, because of inadequate laboratory monitoring (seven cases), inappropriate use of the drug (five cases) and/or inappropriate dosing (two cases). Drug-induced liver injury occurred in 10 patients. In seven cases the causal drug was assessed to be an antituberculosis agent (rifampicin, isoniazid and/or pyrazinamide), and in three cases co-trimoxazole was implicated (alone or in combination with other drugs).

Table 6

Causes of death in cases where an ADR did not contribute to death

Cause of death	Frequency
Tuberculosis (confirmed or suspected)	56 (19%)
Cerebrovascular disease	44 (15%)
Respiratory infections	43 (14%)
Malignancies	25 (8%)
Infections (other*)	19 (6%)
Chronic obstructive airways disease	17 (6%)
Renal failure	13 (4%)
Cardiac failure and cardiomyopathy	11 (4%)
Meningo-encephalitis	11 (4%)
Liver failure	5 (2%)
Myocardial infarction	2 (1%)
Other† and unclear	55 (18%)
Total	301 (100%)

*Infections other than tuberculosis, respiratory infections and meningo-encephalitis. †Causes of death identified in one patient each: diabetic ketoacidosis, pulmonary embolism, asbestosis, obstructive hydrocephalus, myelitis, aplastic anaemia and pulmonary interstitial fibrosis.

Fluconazole, erythromycin and sodium valproate were each implicated once. In two of these 10 cases the ADR was considered to have been preventable. On both occasions use of the drug was not considered appropriate.

Stavudine was assessed as causing lactic acidosis contributing to the death of two patients and as causing neutropaenia contributing to the death of another. Lopinavir-ritonavir and rifampicin caused diarrhoea in two patients, thereby contributing to their death, and co-trimoxazole contributed to the death of two patients through bone marrow suppression.

Seven cases of drug-associated haemorrhage resulting in death occurred, five intracranial bleeds and two gastrointestinal bleeds. Drugs implicated in the intracranial haemorrhages were warfarin (two cases), aspirin (two cases) and heparin (one case), whereas one gastrointestinal bleed was attributed to a combination of colchicine, enoxaparin and aspirin, and the other to prednisone. Cardiovascular agents were implicated in 11 deaths, with diuretics the most common subclass of agents amongst these, implicated in eight deaths.

Table 6 lists the causes of death and the frequency of each cause among the 301 deaths where an ADR was not considered to contribute to the death. Mortality in this group of patients was mostly attributed to tuberculosis, respiratory infections and cerebrovascular disease.

Discussion

We found that ADRs contributed to the death of 2.9% of patients admitted to the adult medical wards of four geographically diverse hospitals in South Africa. The overall mortality rate in our study wards was 18 per 100

admissions and 16% of these deaths were ADR-related. Factors independently associated with ADR-related deaths were exposure to more than seven drugs, HIV-infected patients on ART and higher non-HIV co-morbidity score. ARVs, antituberculosis drugs and co-trimoxazole (which is virtually exclusively prescribed for the prevention and treatment of opportunistic infections in HIV-infected patients) were the most commonly implicated drugs in ADR-related deaths.

Our ADR-related inpatient mortality rate is considerably higher than has been reported in studies from high income countries. Norwegian researchers who used a broad definition of adverse drug events (including intoxications and medication errors) and conducted extensive pre- and post-mortem serum drug concentration measurements and autopsies, reported mortality attributable to drugs at 0.95% of all admissions in medical patients (18.2% of in-hospital deaths) [3, 4]. In a Finnish university hospital, deaths in 0.05% of admissions (5% of in-hospital deaths) were attributed to ADRs [5]. In a large study from the UK, 0.15% of patients admitted to two hospitals died from an ADR present on admission [16]. In another UK study, an ADR that developed in hospital was considered to have contributed to the deaths of 0.4% of the patients admitted (8.2% of in-hospital deaths) [6]. A study in three Swiss teaching hospitals reported an ADR-related mortality rate of 0.05% of admissions [17].

There are scanty data on the mortality rate of ADRs in low- to middle-income countries. A recent study at a tertiary hospital in China reported no deaths amongst 2739 patients who experienced an ADR during their admission [18], while two studies from hospitals in Brazil [19, 20] report zero and one death, respectively, amongst 81 and 212 patients with identified ADRs. Zargarzadeh *et al.* [21] found the mortality rate attributable to drug-related problems (including ADRs and therapeutic failures) to be 0.9% of all the admissions to three Iranian teaching hospitals. An Indian study reported an ADR-related mortality rate of 0.24% of all admissions [22], while another Indian study reported no ADR-related deaths amongst 1221 medical admissions [23]. In the previous ADR survey by our group, we found two ADR-related deaths out of 80 deaths occurring over a 3 month period in 2005 (i.e. 2.5%) in the medical wards of a secondary hospital in Cape Town [7]. There were 665 admissions included in the analysis, giving a mortality rate of 0.3% of admissions.

As already alluded to, the ADR definition used, and specifically the question whether ADRs considered 'possible' should be counted as ADRs or not, will influence the reported rate of ADRs. We decided *a priori* to include 'possible' ADRs in our analysis, but if we had limited our analyses only to those cases where an ADR was considered 'certain' or 'probable', we would have shown a mortality rate of 12/1951 admissions (0.61%), which is still in the upper range of rates previously reported (0.05% to 0.95%) or 12/357 deaths (3.4%).

Studies conducted in high income countries [1, 3–5, 16, 17] report that the most frequent fatal ADRs are gastrointestinal and intracranial haemorrhages attributed to warfarin, non-steroidal anti-inflammatory drugs, heparins, antiplatelet agents, corticosteroids and/or selective serotonin re-uptake inhibitors. We found that antiretrovirals, antituberculosis agents and/or co-trimoxazole were implicated in 27 ADR-related deaths, nearly half of all the ADR-related deaths identified, reflecting the very high burden of HIV and tuberculosis in our region.

Our multivariate regression analysis identified HIV-infection and treatment with ART as an independent risk factor for ADR-related death. While stavudine is no longer recommended as a first line drug due to its toxicity [24], it was still associated with the death of three patients in our series. In our survey, tenofovir, which has replaced stavudine due to its lower toxicity, was the single drug most commonly implicated in ADR-related deaths. Tenofovir can cause acute or chronic renal failure, but both are uncommon [25]. An additional insult, e.g. dehydration due to acute gastroenteritis, was present in many of the fatal cases of tenofovir-associated renal failure we identified. Dialysis facilities are limited in our region, even for acute renal failure, and many cases of severe renal failure have a fatal outcome.

Co-trimoxazole and/or anti-tuberculosis therapy was implicated in most cases of drug-induced liver injury (DILI) in our survey. In keeping with the idiosyncratic nature of most DILIs, we only identified a preventable ADR in 20% of the DILI cases, lower than the overall figure of 50% among all the deaths.

Known risk factors for the development of ADRs include multi-morbidity and polypharmacy [3, 4, 6, 19], and, in some but not all studies, advancing age [2, 6, 16, 21]. In our survey, more severe co-morbidity as measured by the modified Charlson comorbidity score, and exposure to a higher number of drugs before and during hospitalization, but not age, were associated with ADR-related death. This did not, however, hold true for the subgroup of HIV-infected persons, in whom the only independent predictor of ADR-related death was exposure to a higher number of drugs.

Forty-three per cent of the ADRs contributing to death in our survey were considered preventable. While methodological differences make it difficult to compare this figure with other studies, our proportion is in a similar range to figures previously described in South Africa (53% of community acquired ADRs and 33% of hospital acquired ADRs) [7] and in the UK (72% of community acquired [16] and 53% of hospital acquired [6] ADRs) and did not differ in the HIV-infected subgroup. Considering the preventability factors identified, training of health care workers should focus on avoiding inappropriate drug prescribing and on the importance of routine laboratory monitoring, particularly monitoring renal function.

Our study was limited by its design as a retrospective chart review of hospital data. Moreover, assessing ADR causation is always subjective, as is ascertaining the cause of death by means of folder review. However, the two-step assessment process, including the use of a trigger tool followed by the discussion of each case by a multi-disciplinary panel of experts offset the inherent subjectivity of the process to some extent. A strength of our study, increasing its generalizability, is that we included hospitals from three of South Africa's nine provinces, providing a mixture of secondary and tertiary level care, thereby increasing the survey's representativeness.

In conclusion, a larger proportion of in-hospital deaths were ADR-related in our survey than has previously been described in high income settings. Moreover, unlike the pattern in high-income countries, the drugs implicated in ADR-related deaths in our survey were mostly drugs used in the treatment of HIV and tuberculosis. The major contribution of antiretrovirals to ADR-related mortality in our setting reflects our high HIV disease burden rather than a high incidence of toxicity due to the ARV drugs used. It is concerning to note that more than half of the HIV-infected patients who died during our survey were not on antiretroviral therapy, despite having advanced HIV disease. There is a need for more studies in low- to middle-income countries characterizing ADR-related deaths and exploring appropriate systems to improve healthcare worker prescribing in order to minimize preventable drug-related harm.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare JPM, AS, CWN, NK, GM and KC had support for the submitted work from the Centers for Disease Control and Prevention (CDC), no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

This research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under terms of Cooperative Agreement Number GGH000371. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.

The authors gratefully acknowledge the clinical, nursing, administrative and managerial staff at the four hospitals for their assistance and support in this study.

Contributors

The study was conceptualized and designed by KC, GM, MB, UM, AGP, DPKW and AS. Data were collected by JPM, CWN and NK, while AS managed data. KC, GM, UM, AGP and DPKW constituted the panel of experts who performed causality assessments. JPM and KC analyzed the data. JPM, KC and GM wrote the first draft of this article. All authors contributed to the final paper.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1

Description of sites

Table S2

Characteristics of the 56 patients considered to have died from an ADR-related cause and details of their ADRs

Adverse Drug Reactions Causing Admission to Medical Wards

A Cross-Sectional Survey at 4 Hospitals in South Africa

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Abstract: Limited data exist on the burden of serious adverse drug reactions (ADRs) in sub-Saharan Africa, which has high HIV and tuberculosis prevalence. We determined the proportion of adult admissions attributable to ADRs at 4 hospitals in South Africa. We characterized drugs implicated in, risk factors for, and the preventability of ADR-related admissions.

We prospectively followed patients admitted to 4 hospitals' medical wards over sequential 30-day periods in 2013 and identified suspected ADRs with the aid of a trigger tool. A multidisciplinary team performed causality, preventability, and severity assessment using published criteria. We categorized an admission as ADR-related if the ADR was the primary reason for admission.

There were 1951 admissions involving 1904 patients: median age was 50 years (interquartile range 34–65), 1057 of 1904 (56%) were female, 559 of 1904 (29%) were HIV-infected, and 183 of 1904 (10%) were on antituberculosis therapy (ATT). There were 164 of 1951 (8.4%) ADR-related admissions. After adjustment for age and ATT, ADR-

related admission was independently associated ($P \leq 0.02$) with female sex (adjusted odds ratio [aOR] 1.51, 95% confidence interval [95% CI] 1.06–2.14), increasing drug count (aOR 1.14 per additional drug, 95% CI 1.09–1.20), increasing comorbidity score (aOR 1.23 per additional point, 95% CI 1.07–1.41), and use of antiretroviral therapy (ART) if HIV-infected (aOR 1.92 compared with HIV-negative/unknown, 95% CI 1.17–3.14). The most common ADRs were renal impairment, hypoglycemia, liver injury, and hemorrhage. Tenofovir disoproxil fumarate, insulin, rifampicin, and warfarin were most commonly implicated, respectively, in these 4 ADRs. ART, ATT, and/or co-trimoxazole were implicated in 56 of 164 (34%) ADR-related admissions. Seventy-three of 164 (45%) ADRs were assessed as preventable.

In our survey, approximately 1 in 12 admissions was because of an ADR. The range of ADRs and implicated drugs reflect South Africa's high HIV and tuberculosis burden. Identification and management of these ADRs should be considered in HIV and tuberculosis care and treatment programs and should be emphasized in health care worker training programmes.

(*Medicine* 95(19):e3437)

Editor: Akhilanand Chaurasia.

Received: February 26, 2016; revised: March 24, 2016; accepted: March 28, 2016.

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This research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under terms of Cooperative Agreement Number GGH000371. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.

MedDRA, the Medical Dictionary for Regulatory Activities terminology, is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA trademark is owned by IFPMA on behalf of ICH.

The authors have no funding and conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000347

Abbreviations: ACE = angiotensin converting enzyme, ADR(s) = adverse drug reaction(s), AIDS = acquired immunodeficiency syndrome, aOR = adjusted odds ratio, ART = antiretroviral therapy, ATC = anatomic therapeutic chemical, ATT = antituberculosis therapy, CI = confidence interval, DILI = drug-induced liver injury, DRESS = drug reaction with eosinophilia and systemic symptoms, HIV = human immunodeficiency virus, ICD-10 = International Statistical Classification of Disease and Related Health Problems, 10th Revision, IQR = interquartile range, LMIC(s) = low- and middle-income country (countries), MedDRA = Medical Dictionary for Regulatory Activities, NRTI(s) = nucleoside/nucleotide reverse transcriptase inhibitor(s), TDF = tenofovir disoproxil fumarate, WHO-UMC = World Health Organization-Uppsala Monitoring Centre.

INTRODUCTION

Data on the burden of serious adverse drug reactions (ADRs) in sub-Saharan Africa are limited. In this region, colliding epidemics of infectious and noncommunicable diseases,^{1–5} prevalent pharmacogenetic variants associated with increased risk of ADRs,^{6–9} widespread concomitant use of traditional remedies,^{8,10,11} and overburdened health care systems^{4,8,12–14} potentially contribute to the burden of drug-related harm.

In South Africa, an estimated 6.8 million people were HIV-infected by 2014, with approximately 2.9 million receiving

antiretroviral therapy (ART).¹⁵ Moreover, in 2013, the country's tuberculosis incidence was estimated at 860 new cases per 100,000 population, and 62% of tuberculosis patients were HIV-co-infected.¹⁶ A 2005 South African hospital survey found that HIV infection was a risk factor for serious ADRs, especially in patients receiving ART.¹⁷ Subsequently, as with other sub-Saharan African countries, there has been massive scale-up of the ART programme with earlier initiation and use of less-toxic first-line ART regimens.^{18,19}

We prospectively assessed medical admissions at 4 South African hospitals to determine the burden of ADRs resulting in hospital admission, to identify common serious ADRs, to identify the drugs implicated in these ADRs, to evaluate whether these ADRs were preventable, and to determine the influence of HIV infection on ADR burden and pattern.

METHODS

Setting and Study Design

We conducted a cross-sectional survey during 2013 in the adult medical wards of 4 hospitals. We prospectively reviewed all admissions over sequential 30-day periods at the sites. The survey sites represent 3 different provinces of South Africa and are a mixture of tertiary and regional hospitals. (See Supplementary Methods, Supplemental Digital Content 1, <http://links.lww.com/MD/A922>, for a detailed description of the 4 hospitals).

We conducted this survey in parallel with a survey of ADR-related deaths, which has previously been published.²⁰ The sample size was calculated to ensure adequate power for the mortality survey²⁰; we calculated that a sample size of 2000 would be needed to detect a mortality rate because of ADR of 0.3%, with a 95% confidence interval of 0.1% to 0.7% (using exact confidence interval method of Clopper-Pearson). (See figure, Supplemental Digital Content 2, <http://links.lww.com/MD/A922>, which demonstrates the extent of overlap between the 2 surveys' participants).

Processes and Study Team

One medical doctor and 2 pharmacists collected the data. For every admission, we recorded demographic information, drug exposure history, and diagnoses. From the admission records and investigation results, we identified the reason for the admission and flagged this where it was potentially related to an ADR, with the aid of a trigger tool (see Table, Supplemental Digital Content 3, <http://links.lww.com/MD/A922>, for the trigger tool used), adapted from Rozich.²¹ For flagged cases, we collected more detailed data, including laboratory results, and a more detailed drug history, which included start and stop dates, dosage regimens, and indications. We performed an exit clinical record review at patients' discharge, death, or approximately 1 week after the end of the survey period for those still in hospital at survey end, to verify and augment data and to add information on the management and outcome of potential ADRs. Clinicians and nursing staff were aware of the survey, but did not actively report potential ADRs to the study team. When the data collection team identified information of direct potential benefit to the patient, this was communicated to the hospital clinical team.

Admissions identified as potentially ADR-related were assessed by a multidisciplinary case review panel for ADR causality, preventability, and severity. The panel reached its assessment through consensus discussion. (See Supplementary

Methods, Supplemental Digital Content 1, <http://links.lww.com/MD/A922>, which describes details of the panel composition, case identification, and case assessment procedures).

Record Linkage to Identify All-Cause Mortality

We identified in-hospital deaths from hospital administrative records. We performed linkage to the national population register, using South African personal identity numbers, to identify deaths occurring within 30 days of discharge from hospital.

Definitions and Taxonomies Used

We recorded drug exposure for 30 days before admission. We identified patients documented to have zero drug exposure, and distinguished those from patients for whom no drug history was documented in the medical records. We coded drugs according to the Anatomic Therapeutic Chemical (ATC) Classification System of the World Health Organization Collaborating Center for Drug Statistics Methodology,²² with a few exceptions and assumptions (see Supplementary Methods, Supplemental Digital Content 1, <http://links.lww.com/MD/A922>, for an exposition of the exceptions and assumptions used in drug coding). We defined the drug count as the number of drugs with unique ATC codes over 28 days before admission, excluding topical preparations, vitamins, and mineral supplements. We defined first-line ART as 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a non-nucleoside reverse transcriptase inhibitor, and second-line ART as 2 NRTIs in combination with a ritonavir-boosted protease inhibitor, as per South African adult ART guidelines.²³

We recorded patients' diagnoses or clinical problems according to the International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10) codes. We calculated a comorbidity score for each admission, modified from the Charlson comorbidity score.²⁴ Our modification did not allocate points for a diagnosis of HIV/AIDS, as the HIV score assigned by the original Charlson method is probably inappropriately high in the era of ART,²⁵ and as we wanted to explore the independent effect of HIV infection on ADR-related admissions.

We performed causality assessment of suspected ADRs using the World Health Organization-Uppsala Monitoring Center (WHO-UMC) system for standardized case causality assessment.²⁶ We defined an ADR according to the definition of Aronson and Ferner.²⁷ We did not include intentional drug overdose, therapeutic failure, or cases of ART-associated immune reconstitution syndrome as ADRs. We coded ADRs to "preferred terms" contained in version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA, MedDRA Maintenance and Support Services Organization, McLean, VA, USA).

We considered a case to be an ADR-related admission if the multidisciplinary case review panel assessed the ADR as "possible," "probable," or "certain" according to WHO-UMC criteria, and the ADR was the main reason for the admission.

We considered ADRs to be preventable if the case review panel held that one or more of the Schumock and Thornton criteria²⁸ was present. We assessed ADR severity according to guidance from Temple et al²⁹ as causing temporary harm, permanent harm, near-death (including anaphylaxis and cardiorespiratory arrest), or death. We classified ADRs as type A (predictable from the pharmacological action of the drug) or type B (idiosyncratic) according to the Rawlins and

TABLE 1. Characteristics of Patients at Their First Admission to the Medical Wards of 4 Hospitals in South Africa, 2013 (n = 1904)

	All Patients (n = 1904)	Patients With an ADR-Related Admission (n = 162)	Patients Without an ADR-Related Admission (n = 1742)
Age			
Median (IQR), y	50 (34–65)	53 (36–65)	50 (33–65)
Sex			
Female	1057 (56%)*	108 (67%)	949 (55%)
HIV status			
Infected	559 (29%)	63 (39%)	496 (28%)
Negative	350 (18%)	19 (12%)	331 (19%)
Unknown	995 (52%)	80 (49%)	915 (53%)
ATT status at time of admission			
On ATT	182 (9.6%)	29 (18%)	153 (8.8%)
On isoniazid prophylaxis	9 (0.47%)	3 (1.9%)	6 (0.34%)
Neither on ATT nor on isoniazid prophylaxis	1713 (90%)	130 (80%)	1583 (91%)
Modified Charlson comorbidity score			
Median (IQR)	0 (0–1)	1 (0–2)	0 (0–1)
Range	0–7	0–5	0–7
Comorbidity score = 0	1045 (55%)	63 (39%)	982 (56%)
Comorbidity score = 1 or 2	664 (35%)	71 (44%)	593 (34%)
Comorbidity score ≥ 3	195 (10%)	28 (17%)	167 (9.6%)
Drug count, n = 1663†		n = 162	n = 1501
Median (IQR)	3 (1–5)	5 (4–7)	3 (1–5)
Range	0–20	1–17	0–20
Drug count = 0	239 (14%)	0 (0%)	239 (16%)
Drug count ≥ 5	571 (34%)	94 (58%)	477 (32%)

ADR = adverse drug reaction, ATT = antituberculosis therapy, IQR = interquartile range.

*Of whom 15/1057 (1.4%) were known to be pregnant. None of the pregnant females were admitted for ADR-related reasons.

†No drug history recorded in clinical records of 241/1904 (13%) patients.

Thompson classification³⁰ and used this classification to inform our assessment of causality and preventability in the event of >1 drug suspected in the ADR. For type B reactions with >1 drug suspect, we assessed causality and preventability for each drug suspect separately. However, for type A reactions, we assessed causality and preventability attributable to the combined action of all drug suspects. When a combination of type A and type B mechanisms was considered to have caused the ADR, we classified the ADR as type B.

Data Entry and Statistical Analysis

We entered data into an Access 2010 database (Microsoft Corporation, Redmond, WA), and analyzed data using Stata 13.1 (Stata Corporation, College Station, TX). We used cross-tabulation and χ^2 statistics to explore associations between binary and categorical variables. We summarized continuous variables using medians and interquartile ranges, owing to their non-normal distribution, and used the Wilcoxon rank-sum test for between-group comparisons of continuous variables. A *P* value of <0.05 was taken to indicate significant difference.

We constructed a generalized estimation equation model, with admissions clustered on the patient level for those with readmissions, to explore independent associations between ADR-related admission and age, sex, HIV infection, ART, ATT, drug count, and modified comorbidity score. Variables were selected for inclusion in the model a priori, at the time of study design. To categorize HIV infection and ART exposure, we constructed a 3-category variable: HIV-negative/unknown; HIV-infected and not

on ART; or HIV-infected and on ART. In the main model, we excluded admissions wherein patients were documented as not exposed to any drug before the admission, but included those in whom no drug history was recorded. In sensitivity analyses, we constructed 2 additional models, the first including all admissions, and the second excluding patients with missing drug histories as well as patients with documented zero drug exposure.

Ethics

The Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town approved this study (reference no 576/2011). We received permission to conduct the research by the respective hospitals' management and/or provincial Departments of Health.

RESULTS

Description of the Cohort: All Admissions

During the survey period, 1904 patients were admitted on 1951 occasions (1858 patients were each admitted once, 45 patients were each admitted twice, and 1 patient was admitted 3 times). In 242 of 1951 (12%) admissions, drug histories were not recorded in the medical records. Linkage with the population register was possible for only 866 of 1904 (45%) patients, because of missing personal identity numbers.

Patient characteristics at the time of their first admission are given in Table 1. HIV-infected patients were younger than HIV-negative/unknown patients (median age 36 years

TABLE 2. Summary of Characteristics of the 5 Most Common Adverse Drug Reactions That Caused Admission to the Medical Wards of 4 Hospitals in South Africa, 2013

	Renal Impairment	Hypoglycemia	Drug-Induced Liver Injury	Hemorrhage	Blood Dyscrasias
Number of ADR-related admissions	24 ^a	22	20	19	14
Clinical presentation	4/24 Had overlapping DILI.	18/22 Had renal impairment.	12 Cholestatic, 6 hepatocellular; 2 mixed, 4/20 had overlapping renal impairment.	7 GI bleed, 3 CNS bleed, 3 hemoptysis, 2 menorrhagia, 1 epistaxis, 1 hematuria, 1 hemarthrosis, 1 retroperitoneal bleed	5 Anemia, 5 thrombocytopenia, 3 leukopenia, 1 pancytopenia
Females, n (%)	11/24 (46%)	15/22 (68%)	12/20 (60%)	18/19 (95%)	6/14 (43%)
Median age in years (IQR)	40.5 (32.5–48.5)	60.5 (56–74)	35 (29.5–41.5)	67 (53–79)	40.5 (31–60)
HIV-infected, n (%)	17/24 (71%)	1/22 (4.5%)	18/20 (90%)	3/19 (16%)	11/14 (79%)
Median drug count (IQR)	5 (4–7)	3.5 (3–8)	4.5 (4–7)	5 (4–9)	5.5 (3–7)
Median comorbidity score (IQR)	1 (0–2)	3 (1–5)	0 (0–1)	1 (0–2)	0.5 (0–2)
Drugs associated with the ADR	11 Cases: TDF (alone, or in combinations with co-trimoxazole, aciclovir, indomethacin, co-amoxiclav); 9 cases: ACE-inhibitor (alone or in combinations with aspirin, furosemide, spironolactone, HCTZ, amlodipine, atenolol, hydrochlorothiazide, valproic acid); 2 cases: co-trimoxazole, 1 case: rifampicin, 1 case: co-amoxiclav and ibuprofen.	9 Cases: insulin only; 1 case: insulin and metformin; 3 cases: co-trimoxazole and insulin; 1 case: metformin; 1 case: insulin and unspecified oral hypoglycemic agents; 2 cases: sulfonylurea only; 6 cases: sulfonylurea and metformin.	8 Cases: rifampicin only; 3 cases: efavirenz only; 2 cases: co-trimoxazole only; 1 case: enalapril; 6 cases: various combinations of ART, NNRTIs, co-trimoxazole, erythromycin.	13 Cases: warfarin; 3 cases: acetylsalicylic acid; 2 cases: unspecified NSAIDs; 1 case: diclofenac.	4 Cases: co-trimoxazole; 3 cases: zidovudine only; 1 case: zidovudine & lamivudine; 1 case: stavudine, 1 case: methotrexate and chloroquine, 1 case: allopurinol and colchicine; 1 case: rifampicin and isoniazid; 1 case: rifampicin and amoxicillin; 1 case: valproic acid.
ADR classification	Type A Type B	22/22 (100%) 0/22 (0%)	0/20 (0%) 20/20 (100%), with 30 drug-ADR associations	19/19 (100%) 0/19 (0%)	10/14 (71%) 4/14 (29%), with 7 drug-ADR associations
Proportion preventable	Type A Type B	17/22 (77%) --	4/30 (13%) 2/30 (10%)	11/19 (58%) --	3/10 (30%) 0/7 (0%)
Reasons for preventability (case-wise, at least 1 implicated drug-ADR association was preventable for this reason)	Inappropriate dose Inadequate monitoring History of ADR Interaction Drug concentration Compliance	1/24 (4.2%) 4/24 (17%) 0/24 (0%) 0/24 (0%) 0/24 (0%) 12/24 (50%)	0/20 (0%) 0/20 (0%) 1/20 (5.0%) 0/20 (0%) 0/20 (0%) 7/20 (35%)	0/19 (0%) 4/19 (21%) 5/19 (26%) 4/19 (21%) 5/19 (26%) 3/19 (16%)	2/14 (0%) 1/14 (7.1%) 0/14 (0%) 0/14 (0%) 0/14 (0%) 3/14 (21%)
Combined all-cause mortality [†]	9 (8–13.5)	6 (3–10)	10 (7–25)	6 (4–8.5)	6 (5–15)
Median length of hospital stay if known to have left hospital alive: days (IQR)					

ACE = angiotensin converting enzyme, ADR = adverse drug reaction, ART = antiretroviral therapy, ATT = antituberculous therapy, CNS = central nervous system, DILI = drug-induced liver injury, GI = gastrointestinal, HCTZ = hydrochlorothiazide, IQR = interquartile range, NNRTI = non-nucleoside reverse transcriptase inhibitor, TDF = tenofovir disoproxil fumarate.

^aCount excludes 2 cases of proximal tubular dysfunction without renal impairment.

[†]All-cause mortality in-hospital and within 30 days of discharge.

[interquartile range, IQR: 30–44 years] vs median age 58 years [IQR: 43–70 years], $P < 0.001$). Of the HIV-infected patients, 251 of 559 (45%) were not on ART, 253 of 559 (45%) were on first-line ART, 18 of 559 (3.2%) on second-line ART, 3 of 559 (0.54%) on other ART combinations, 33 of 559 (5.9%) on unspecified ART, and 1 of 559 (0.18%) on zidovudine monotherapy for prevention of mother-to-child-transmission. The drugs most commonly included in ART regimens were efavirenz (240), lamivudine (213), and TDF (207). The median CD4 count was 142.5 cells/mm³ (IQR: 42–328) in the 494 HIV-infected patients with CD4 cell counts available. A total of 128 of 559 (23%) HIV-infected patients were on treatment for tuberculosis at the time of first admission, versus 54 of 1345 (4.0%) HIV-negative/unknown patients ($P < 0.001$).

Other common comorbidities included cardiovascular disease in 44% of patients, endocrine/metabolic disease in 31%, renal failure in 17%, and chronic lower respiratory disease in 8.8%. Forty percent of patients were exposed to cardiac agents before their first admission (including 29% to diuretics, 20% to angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers, 13% to calcium channel blockers, 12% to “statins”), 16% to antithrombotic agents (including 13% to aspirin), and 17% to blood glucose-lowering agents (including 6.8% to insulin). A total of 239 of 1904 (13%) patients were documented to have had zero drug exposure before their first admission.

The most common reasons for admission were cardiovascular disease (496/1951 [25%] admissions), respiratory disease (313/1951 [16%]), and infectious/parasitic disease (285/1951 [15%]) (See tables, Supplemental Digital Content 4, <http://links.lww.com/MD/A922>, Supplemental Digital Content 5, <http://links.lww.com/MD/A922>, and Supplemental Digital Content 6, <http://links.lww.com/MD/A922>, which describe the prevalence of comorbidities, patients' exposure to drugs before admission, and the cause of admission, respectively).

ADR-Related Admissions: Presentations and Implicated Drugs

We identified 164 ADR-related admissions, which represented 8.4% of all admissions (95% confidence interval [CI] 7.2%–9.7%). These 164 ADRs occurred in 162 patients, 2 of whom were each admitted twice for ADR-related reasons during the survey period.

Drugs used in the management of HIV and tuberculosis (ART, ATT, and co-trimoxazole) were implicated in 56 of 164 (34%) ADR-related admissions, and 63 of 164 (38%) ADR-related admissions occurred in HIV-infected patients.

The 5 most common ADRs resulting in admission were renal impairment (24 cases), hypoglycemia (22 cases), drug-induced liver injury (DILI) (20 cases), hemorrhage (19 cases), and blood dyscrasias (14 cases). These cases are summarized in Table 2 (Also see tables, Supplemental Digital Content 7, <http://links.lww.com/MD/A922>, Supplemental Digital Content 8, <http://links.lww.com/MD/A922>, Supplemental Digital Content 9, <http://links.lww.com/MD/A922>, Supplemental Digital Content 10, <http://links.lww.com/MD/A922>, and Supplemental Digital Content 11, <http://links.lww.com/MD/A922>, for patient-level detail regarding each of the five most common presentations). Renal impairment, DILI, and blood dyscrasias predominantly occurred in HIV-infected and younger patients, whereas hypoglycemia and hemorrhage predominantly occurred in HIV-negative/unknown and older patients.

Other common ADRs resulting in admission included cardiac failure (9 cases), confusion (8 cases), electrolyte

disturbances (7 cases), antineoplastic-, corticosteroid-, and immunosuppressant-associated pneumonia (4 cases), hypotension (4 cases), drug reaction with eosinophilia and systemic symptoms (DRESS) (4 cases), and ataxia (3 cases) (See tables, Supplemental Digital Content 12, <http://links.lww.com/MD/A922> and Supplemental Digital Content 13, <http://links.lww.com/MD/A922>, for patient-level details of these ADR-related admissions. Also see table, Supplemental Digital Content 14, <http://links.lww.com/MD/A922>, which maps the 164 ADRs to the multi-level MedDRA taxonomy).

Drugs and drug classes most commonly implicated in ADRs were NRTIs (23 times in 21 cases, with TDF implicated in 14, zidovudine in 4, stavudine in 3, and lamivudine in 2), rifampicin in 17, ACE-inhibitors in 15, insulin in 14, and warfarin in 13 cases (See table, Supplemental Digital Content 15, <http://links.lww.com/MD/A922>, for a full list of drugs implicated in ADR-related admissions). Figure 1 plots the proportion of ADRs in which the drug was implicated against the drug's frequency of use, for the 19 drugs implicated in ≥ 4 ADR-related admissions. Warfarin, phenytoin, and co-trimoxazole were the 3 drugs most frequently implicated in ADR-related admissions, relative to their frequency of use.

ADR-Related Admissions: Associations

Results of the generalized equation estimation model (excluding patients who were not exposed to drugs over the 30 days before admission) are presented in Table 3. ADR-related admission was independently associated with female sex, higher drug count, higher comorbidity score, and HIV-infection with ART. We did not find an association between ADR-related admission and age. Associations were similar in the sensitivity analyses (See table, Supplemental Digital Content 16, <http://links.lww.com/MD/A922>, for an alternative model including patients documented to have had zero drug exposure, and table, Supplemental Digital Content 17, <http://links.lww.com/MD/A922>, for an alternative model excluding patients in whom no drug history was recorded in the medical records).

ADR-Related Admissions: ADR Classification, Causality, Preventability, and Severity

A total of 126 of 164 (77%) ADRs were classified as type A, and 38 of 164 (23%) as type B. Thirty-six of 63 (57%) ADRs in HIV-infected patients were type A and 27 of 63 (43%) type B. This differed significantly from HIV negative/unknown patients in whom 90 of 101 (89%) ADRs were type A and 11 of 101 (11%) type B ($P < 0.001$). The causality assessment of ADRs, stratified by ADR type and HIV status, is described in Table 4.

Seventy-three of 164 (45%) ADRs resulting in admission were assessed as preventable. The drugs most commonly implicated in preventable ADRs were warfarin (11), insulin (10), phenytoin (9), furosemide (8) and metformin (8). Sixty-nine of 126 (55%) type A ADRs were assessed as preventable versus 4 of 38 (11%) type B ADRs ($P < 0.001$). In 24 of 126 (19%) type A ADRs, the drug was inappropriate; in 14 of 126 (11%), the dose, route, or frequency was inappropriate; in 25 of 126 (20%), monitoring was insufficient; in 11 of 126 (8.7%), the patient previously had an ADR to the drug; in 13 of 126 (10%), a drug interaction played a role; in 9 of 126 (7.1%), a supratherapeutic drug concentration was found; and in 4 of 126 (3.2%), adherence played a role. In 3 of 38 (7.9%) type B ADRs, at least 1 implicated drug was inappropriate for the patient, and in 1 of 38 (2.6%), the patient had a previous ADR to an implicated drug.

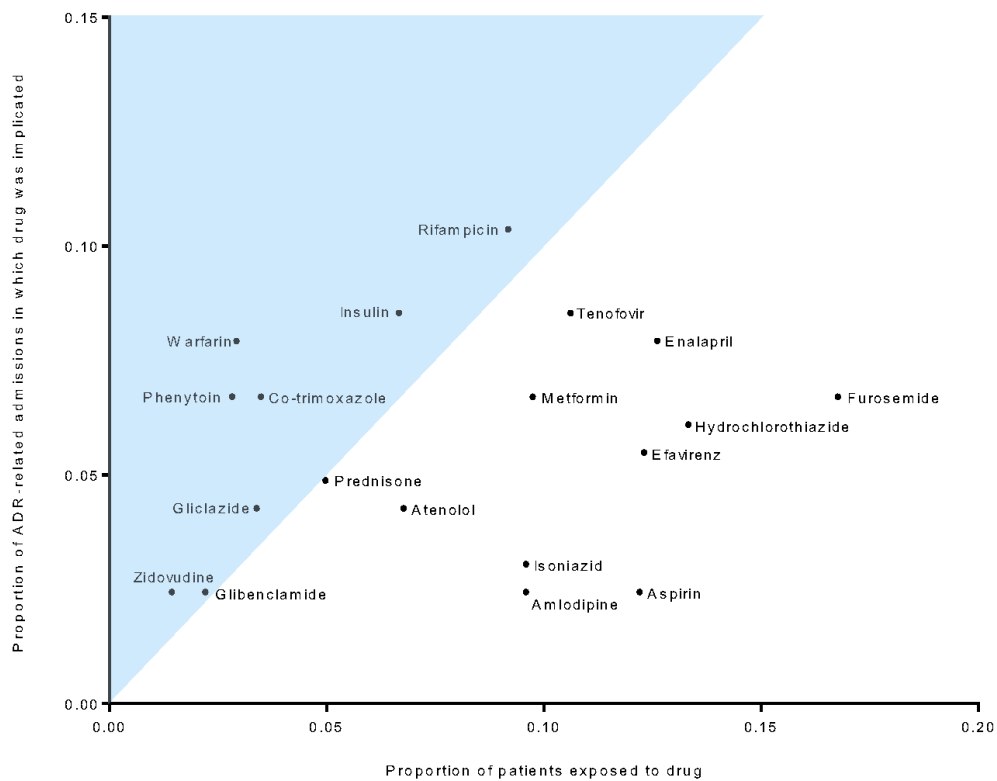


FIGURE 1. Scatterplot of 19 drugs implicated in at least 4 adverse drug reaction (ADR)-related admissions, showing proportion of patients exposed to the drug before their first admission versus the proportion of ADR-related admissions in which the drug was implicated. The shaded area represents those cases where the proportion of ADRs in which the drug was implicated was higher than the proportion of patients exposed to the drug.

Only 20 of 63 (32%) ADRs in HIV-infected patients were preventable versus 53 of 101 (52%) in patients who were HIV-negative/unknown ($P=0.009$). In 10 of these 20 cases, the ADR was assessed as preventable because the implicated drug was considered inappropriate.

We assessed 126 of 164 (77%) ADRs to have resulted in temporary harm, 6 of 126 (3.7%) to have resulted in permanent harm, 3 of 126 (1.8%) to have resulted in near-death, and 29 of 164 (18%) to have resulted in death. Table 5 shows that there was no association between the severity of ADRs and their preventability ($P=0.71$).

ADR-Related Admissions: Patient Outcomes

The median length of stay was 7 days (IQR: 4–11 days) in the 1528 admissions wherein the patient exited the hospital alive, and did not differ between admissions for ADRs (median 7 days, IQR: 4–10 days) and admissions for other reasons (median 7 days, IQR: 4–11 days, $P=.87$).

Combined all-cause mortality (in-hospital death or death within 30 days of discharge) among patients with an ADR-related admission was in 38 of 162 (23%) patients. This was no

different from combined all-cause mortality in patients admitted for other reasons (362/1742 [21%], $P=0.42$). However, combined all-cause mortality was significantly worse in HIV-infected patients with an ADR-related admission (24/63 [38%]) versus HIV-infected patients admitted for other reasons (117/496 [24%], $P=0.01$).

DISCUSSION

We found that 8.4% of admissions to adult medical wards of 4 hospitals in 3 provinces of South Africa were directly attributable to ADRs, with drugs used in the management of tuberculosis and HIV implicated in one-third of these admissions. ADRs in HIV-infected patients were more likely to be severe type B ADRs, were less likely to be preventable, and were associated with higher all-cause mortality. Nearly half of ADRs resulting in admission were preventable.

Six systematic reviews, of studies with a design comparable to ours, have estimated the proportion of adult medical admissions attributable to ADRs to range between 3.1% and 6.3%^{31–36} (See table, Supplemental Digital Content 18, <http://links.lww.com/MD/A922>, for a summary of these six reviews).

TABLE 3. Generalized Estimation Equation Model of Associations With Adverse Drug Reaction-Related Admission (n = 1711 Admissions in 1669 Patients), Excluding Patients Documented to Have Had Zero Drug Exposure Before Admission

	n	Crude		Adjusted*	
		OR (95% CI)	Wald P	OR (95% CI)	Wald P
Sex					
Male (referent)	724	1.00		1.00	
Female	987	1.54 (1.09–2.17)	0.01	1.51 (1.06–2.14)	0.02
Age†	1711	1.04 (0.95–1.13)	0.39	1.02 (0.91–1.14)	0.73
HIV and ART					
HIV-negative/unknown (referent)	1211	1.00		1.00	
HIV-infected, not on ART	186	0.85 (0.46–1.55)	0.59	1.15 (0.59–2.22)	0.68
HIV-infected, on ART	314	2.11 (1.46–3.04)	<0.001	1.92 (1.17–3.14)	0.009
Antituberculosis therapy					
Not on ATT (referent)	1524	1.00		1.00	
On ATT	187	2.05 (1.33–3.17)	0.001	1.22 (0.73–2.06)	0.45
Drug count‡	1711	1.20 (1.15–1.25)	<0.001	1.14 (1.09–1.20)	<0.001
Comorbidity score§	1711	1.29 (1.15–1.45)	<0.001	1.23 (1.07–1.41)	0.004

ART = antiretroviral therapy, ATT = antituberculosis therapy, CI = confidence interval, OR = odds ratio.

*Adjusted for other factors in the model.

†Included in the model as a continuous variable. The reported odds ratio is for each 10-year increment.

‡Included in the model as a continuous variable. The reported odds ratio is for each additional drug.

§Included in the model as a continuous variable. The reported odds ratio is for each additional point on the modified Charlson comorbidity score.

Studies from low- and middle-income countries (LMICs) are notably underrepresented in these reviews. Previous LMIC hospital-based surveys found the proportion of adult medical admissions attributable to ADRs to be 19% in Argentina,³⁷ 7.0% in Lebanon,³⁸ and 6.8% in India.³⁹ ADR burden data from sub-Saharan Africa, a setting of high HIV and tuberculosis prevalence, are scarce. In a previous South African survey, 6.3% of adult medical admissions were found to have been ADR-related.¹⁷ Although these differences may be because of variations in study design, they may also, when combined with our figure of 8.4%, suggest that ADRs may result in proportionally more medical admissions in LMICs than is the case in high-income countries.

The different burden and pattern of ADR-related admissions we observed may be explained as an effect of the colliding epidemics of infectious and noncommunicable diseases in

South Africa. In our study, a group of mostly elderly patients with multimorbidity presented with type A ADRs such as hypoglycemia, hemorrhages, and hypotension, which is not unlike typical ADR presentations seen in studies from high-income settings. A second group of patients in our survey were younger, with a burden of chronic infectious diseases (which is not allocated a score on the original or modified Charlson comorbidity score), and presented with more type B ADRs including DILI and blood dyscrasias. HIV-infected patients are known to be at increased risk for drug hypersensitivity reactions, particularly to co-trimoxazole^{40,41} and ATT,^{40–42} but the pathophysiology is not fully understood and likely to be multifactorial.^{40,41}

A meta-analysis of 6 observational studies found a decline in creatinine clearance attributable to TDF⁴³ that was approximately 10 times the rate of normal age-related decline⁴⁴, which

TABLE 4. Causality Assessment of Adverse Drug Reactions, Stratified by Type of Adverse Drug Reaction and by Human Immunodeficiency Virus Infection Status

ADR Type	Causality Rating	All Patients	HIV-Infected	HIV-Negative/Unknown
Type A	Certain	41/126 (33%)	6/36 (17%)	35/90 (39%)
	Probable	26/126 (21%)	7/36 (19%)	19/90 (21%)
	Possible	59/126 (47%)	23/36 (64%)	36/90 (40%)
Type B*	Certain	4/61 (6.6%) [†]	1/44 (2.3%) [‡]	3/17 (18%) [§]
	Probable	6/61 (9.8%) [†]	5/44 (11%) [‡]	1/17 (5.9%) [§]
	Possible	51/61 (84%) [†]	38/44 (86%) [‡]	13/17 (76%) [§]

ADR = adverse drug reaction.

*For type B ADRs with more than one drug suspect, causality assessment was performed on the level of the individual drug.

†There were 38 type B ADRs, with 61 drugs implicated.

‡Among HIV-infected patients, there were 27 type B ADRs, with 44 drugs implicated.

§Among HIV-negative/unknown patients, there were 11 type B ADRs, with 17 drugs implicated.

TABLE 5. Severity and Preventability of Adverse Drug Reactions Resulting in Admission

Severity Category	n	Preventable	Not Preventable
Temporary harm	126	56 (44%)	70 (56%)
Permanent harm	6	4 (67%)	2 (33%)
Near-death	3	1 (33%)	2 (67%)
Death	29	12 (41%)	17 (59%)
Total	164	73 (45%)	91 (55%)

was significantly greater than that seen in randomized controlled trials^{43,44} and probably reflects the “real-life” situation.^{43–45} TDF-associated renal impairment is not uncommon in sub-Saharan Africa,^{46,47} and our survey identified 11 cases with high mortality. In all of our cases of TDF-associated renal impairment, causality was assessed as “possible,” because of the presence of concomitant diseases and/or nephrotoxic drugs. TDF use in acutely ill patients with renal dysfunction in this region is of concern, particularly when TDF is co-prescribed with other potentially nephrotoxic drugs, as there is limited facilities for renal replacement therapy in sub-Saharan Africa.

All of the patients admitted because of DILI in our survey were HIV-infected and/or taking tuberculosis treatment. A very high incidence (15%) of DILI was reported in Ethiopians on ART, ATT, and cotrimoxazole.⁴⁸ Most of our patients with DILI showed a cholestatic liver enzyme pattern, which is similar to the Ethiopian study, and which often implicated rifampicin rather than isoniazid or pyrazinamide as the causative agent. Combined all-cause mortality among our DILI patients was 35%, which is considerably worse than the mortality rates of 5.2% to 11.5% reported in 4 observational studies from high-income settings.⁴⁹

We identified a large number of ADR admissions for hypoglycemia. In the majority of our cases, insulin was implicated and many patients had concomitant renal impairment. Most of the admissions for hypoglycemia were assessed as preventable, mostly because of insufficient blood glucose monitoring. Insufficient blood glucose monitoring was identified as a major problem in a rural setting in South Africa, where 48% of patients with diabetes mellitus had no blood glucose value recorded in their clinic records during the previous year.⁵⁰

Our finding that 45% of ADRs resulting in admission were preventable is in keeping with a 2012 meta-analysis, which estimated that 52% (95% CI: 42%–62%) of ADR-related admissions are because of preventable ADRs.⁵¹

Our study has a number of limitations. First, we relied on clinical data recorded in hospital clinical records and we did not have access to patients’ primary care medical records. Despite educating clinicians about our study, 1 in 8 folders had no drug history recorded, and the documented drug exposure before admission suggests there may have been poor documentation of contraceptives, over-the-counter agents, topical agents, and herbal remedies, which may have resulted in under-ascertainment of ADR-related admissions. Second, linkage with the South African population register was not possible for the majority of the patients included in our survey, as accurate personal identity numbers were not routinely documented at all sites, and thus we have under-ascertained post-discharge death. Third, assessment of ADR causality, severity, and preventability is subjective and assessment by expert judgment has

previously been criticized.^{52–54} We used a 2-step process, applying a sensitive screening instrument followed by a multi-disciplinary panel discussion of screened cases, to help mitigate the subjectivity associated with expert assessments.

Our study findings have limited generalizability outside secondary and tertiary settings in South Africa. Rather, it emphasizes how the local disease burden and drug use pattern influences the ADRs occurring in our setting. Public health programmes should factor in anticipated risks, including ADRs, and should incorporate risk-reduction measures. Our study demonstrates the feasibility of generating locally relevant pharmacoepidemiological data in a resource-limited setting, and the methodology we used is suited to be periodically repeated, scaled up, and/or transferred elsewhere. The key risk drivers that an approach such as this identifies can be turned into opportunities to improve quality of care.

ACKNOWLEDGEMENTS

We thank Andrew Boule and Nicky Maxwell from the Centre for Infectious Disease Epidemiology and Research (CIDER) at the University of Cape Town for data linkage with the South African population registry. We also thank the clinical, nursing, administrative, and managerial staff at the four hospitals for their assistance and support in this study.

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RESEARCH ARTICLE

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Serious adverse drug reactions at two children's hospitals in South Africa



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Abstract

Background: The high HIV prevalence in South Africa may potentially be shaping the local adverse drug reaction (ADR) burden. We aimed to describe the prevalence and characteristics of serious ADRs at admission, and during admission, to two South African children's hospitals.

Methods: We reviewed the folders of children admitted over sequential 30-day periods in 2015 to the medical wards and intensive care units of each hospital. We identified potential ADRs using a trigger tool developed for this study. A multidisciplinary team assessed ADR causality, type, seriousness, and preventability through consensus discussion. We used multivariate logistic regression to explore associations with serious ADRs.

Results: Among 1050 patients (median age 11 months, 56% male, 2.8% HIV-infected) with 1106 admissions we found 40 serious ADRs (3.8 per 100 drug-exposed admissions), including 9/40 (23%) preventable serious ADRs, and 8/40 (20%) fatal or near-fatal serious ADRs. Antibacterials, corticosteroids, psycholeptics, immunosuppressants, and antivirals were the most commonly implicated drug classes. Preterm neonates and children in middle childhood (6 to 11 years) were at increased risk of serious ADRs compared to infants (under 1 year) and term neonates: adjusted odds ratio (aOR) 5.97 (95% confidence interval 1.30 to 27.3) and aOR 3.63 (1.24 to 10.6) respectively. Other risk factors for serious ADRs were HIV infection (aOR 3.87 (1.14 to 13.2) versus HIV-negative) and increasing drug count (aOR 1.08 (1.04 to 1.12) per additional drug).

Conclusions: Serious ADR prevalence in our survey was similar to the prevalence found elsewhere. In our setting, serious ADRs were associated with HIV-infection and the antiviral drug class was one of the most commonly implicated. Similar to other sub-Saharan African studies, a large proportion of serious ADRs were fatal or near-fatal. Many serious ADRs were preventable.

Keywords: Adverse drug reaction, Pharmacoepidemiology, Prevalence, Trigger tool, HIV

Background

Patient safety is of central importance to all fields of medicine. However, in paediatric medicine, clinicians are faced with the reality that pre-registration drug safety data are often very limited, and that extrapolation from adult drug safety data may be inappropriate in view of children's physiological development. As such, post-marketing surveillance is critical in the ongoing safety appraisal of drugs given to children [1].

South Africa was home to an estimated 280,000 children living with HIV in 2017, of which an estimated 58% were on antiretroviral treatment (ART) [2]. Despite this high prevalence of HIV, and despite ART's notorious potential to cause adverse drug reactions (ADRs) and drug-drug interactions, drug safety is a relatively understudied field in South Africa. Local paediatric drug safety data could potentially contribute to clinical decision-making and health programme policy-making.

Our main aim with this survey was to describe the prevalence of serious ADRs in two paediatric hospitals in South Africa, including the prevalence of serious ADRs at the time of admission and the prevalence of serious ADRs occurring during the admission. Further

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aims were to describe serious ADR manifestations and the drugs implicated in serious ADRs, to describe the preventability of serious ADRs, to describe the prevalence and manifestations of non-serious ADRs in this setting, and to explore the influence of HIV on ADRs occurring in this patient population.

Methods

Design and setting

We conducted this observational study through folder review of data documented during routine clinical care of patients at two hospitals in South Africa: Red Cross War Memorial Children's Hospital (RCWMCH), situated in Cape Town, Western Cape province, and Rahima Moosa Mother and Child Hospital (RMMCH), situated in Johannesburg, Gauteng province. We selected these sites based on existing research collaborations. Both sites have paediatric ART clinics.

At RCWMCH, we surveyed all patients admitted electively and non-electively over a 30-day period in April and May 2015 to the general and specialist medical wards, to high-care beds in the medical wards, to the combined paediatric intensive care unit, and to the general section (but not the rehydration section) of the short-stay ward. We excluded admissions to surgical or oncology wards if the entire stay was spent in the surgical and oncology wards, but included those portions of surgical and oncology patients' admissions spent in the paediatric intensive care unit. The hospital provides limited neonatal services. Admission trends to RCWMCH have previously been described [3]. At RMMCH, we surveyed all patients admitted non-electively over a 30-day period in June and July 2015 to the medical wards and to the combined intensive care / high-care unit. Although RMMCH provides neonatology services, we only surveyed those neonates admitted to the intensive care / high-care unit, and not those admitted to the postnatal wards. Elective admissions to RMMCH, which were excluded from our survey, consisted mostly of children admitted as day patients for minor surgical procedures.

Sample size considerations

We calculated that a sample of 514 patients would detect a prevalence of serious ADRs present at admission of 2.9% (based on a previous systematic review [4]) with a 95% confidence interval (CI) of 1.6 to 4.8%, using the exact CI method of Clopper-Pearson [5]. Based on historic admission trends at the sites and specific wards included in the survey, we were confident that we would survey at least 514 admissions during the planned study duration.

Study processes

We consulted hospital administrative records every weekday during the 30-day survey period to identify all

new admissions. The survey team (a general practitioner and a pharmacist) reviewed each patient's clinical notes, medication prescription charts, and laboratory results as soon as possible after admission and approximately every second day thereafter until the patient's discharge or death, or until study closure, seven days after the end of the 30-day survey entry period. At the time of the patient's discharge, the survey team specifically reviewed the discharge summary prepared by the clinical team to verify and augment data already collected. For patients admitted to the RCWMCH short-stay ward, we conducted folder reviews retrospectively approximately five months following the admission, and not prospectively as described above, as piloting showed it to be too resource-intensive to survey admissions prospectively in this ward.

We abstracted demographic and clinical data (including medication histories) from all patients using electronic case report forms. The survey team identified *potential* ADRs during the folder review with the help of a trigger tool (Table 1, development described below). For cases flagged by the trigger tool, we abstracted a more detailed dataset, including relevant laboratory results, and details on the management and outcome of the potential ADR. In a second stage of ADR identification and assessment, a multidisciplinary team (the survey team, together with a paediatrician, a paediatrician highly experienced in neonatology, a clinical pharmacologist, and a clinical pharmacist) discussed flagged cases' abstracted data to reach consensus on causality (thereby determining whether the potential ADR was actually an ADR), ADR type, seriousness, and preventability, using definitions described below.

Definitions, classifications, and taxonomies

We defined ADRs according to the 2005 Aronson and Ferner definition [6]. We performed causality assessment according to the World Health Organization (WHO)-Uppsala Monitoring Centre system for standardised case causality assessment [7]. Those potential ADRs where drug causation was assessed as certain, probable, or possible were counted as ADRs. We specifically did not consider the following scenarios to be ADRs: intentional drug overdose, poisoning by or ingestion of non-medicinal products, poisoning by herbal or traditional remedies, therapeutic failures, complications associated with poor adherence, and medication errors which were not associated with any harm. We codified ADRs to 'preferred terms' in version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA®, MedDRA Maintenance and Support Services Organization, McLean, VA, USA). We classified ADRs as preventable if at least one of the Schumock and Thornton preventability questions [8] were answered affirmatively by the

Table 1 Trigger list used to assist in identifying potential adverse drug reactions

Category	Trigger
Use of these drugs (antidotes) suggests a potential ADR occurred	Naloxone
	Methadone
	Flumazenil
	Digoxin immune fab ("Digibind")
	Protamine sulphate
	Activated charcoal
	Biperiden / promethazine / diazepam
	Sodium polystyrene ("Kayexalate")
	Insulin with glucose
	Calcium gluconate
	Dextrose 10%
	Adrenaline (epinephrine)
	Systemic corticosteroid
	Diphenhydramine, prochlorperazine, promethazine, or any new antihistamine
	Antiemetics
	Oral vancomycin
	Granulocyte colony-stimulating factor
Supratherapeutic drug concentration suggests a potential ADR occurred	Digoxin > 1.5 nmol/L
	Theophylline > 110 µmol/L
	Lidocaine > 5 µg/L
	Phenytoin > 80 µmol/L
	Carbamazepine > 51 µmol/L
	Phenobarbital > 172 µmol/L
	Valproic acid > 700 µmol/L
	Gentamicin or tobramycin peak > 10 mg/L or 24 h trough > 2 mg/L
	Amikacin peak > 30 mg/L or 24 h trough > 2 mg/L
	Vancomycin trough > 25 mg/L or > 30 mg/L during continuous infusion
	Any other drug concentration reported as supratherapeutic
	Paracetamol concentration done (regardless of result)
Laboratory result (other than TDM) suggests a potential ADR occurred	Partial thromboplastin time (PTT) > 100 s
	International normalised ratio (INR) > 5
	Anti-factor Xa ≥ 1.5 IU/mL
	Platelet count < 50 × 10 ⁹ /L
	White cell count < 3 × 10 ⁹ /L
	Haemoglobin < 8 g/dL
	Pancytopenia
	<i>Clostridium difficile</i> positive stool after exposure to antibiotics
	Creatinine rising to above-normal range
	Hyponatraemia or Hypernatraemia
	Potassium < 3.5 mmol/L, in the absence of diarrhoea
	Potassium > 5.5 mmol/L
	Alanine transaminase (ALT) > three times upper limit of normal (ULN = 40 IU/L) in the presence of negative viral hepatitis screening test results
	Bilirubin > two times upper limit of normal (ULN = 21 µmol/L); if in a neonate, the neonate should also be on drugs

Table 1 Trigger list used to assist in identifying potential adverse drug reactions (*Continued*)

Category	Trigger
Clinical event suggests a potential ADR occurred	Serum glucose < 3 mmol/L, outside the perinatal period
	Hyperlactataemia on antiretroviral therapy
	Angioedema or lip swelling
	Rash or ulceration
	Mucositis or mucosal ulceration
	Pruritus
	Sudden onset wheezing
	Jaundice, new onset
	Dystonia, ataxia, torticollis, dyskinesia
	Retinopathy in premature infant on oxygen
	Hearing disturbance or hearing loss
	Seizure(s)
	Oversedation, lethargy, falls
	Decreased level of consciousness or pressure sores
	Delirium
	Fracture or osteoporosis
	Upper gastrointestinal bleed
	Arrhythmia, new
	Hypertension
	Nausea reported by parents / documented in file
	Constipation
	Biopsy of bone marrow, kidney, or liver
	Withdrawal symptoms
	Any other event suspected to be drug-related by doctor or nurse
	Unexplained medication stop
	Readmission to acute care unit within 14 days of discharge
	Readmission to intensive care unit within 48 h of transfer or discharge
	Require resuscitation in ward
	Death

multidisciplinary team. We classified ADRs in accordance with the Rawlins and Thompson classification as type A or type B [9]. We used this classification to decide the level at which we conducted causality and preventability assessment in the event that multiple drugs were implicated in the ADR, as described in a previous paper by our group [10]. If multiple drug suspects were implicated in a type A ADR, we assessed causality and preventability based on the combined action of all the drug suspects. If multiple drug suspects were implicated in a type B ADR, we assessed causality and preventability for each drug suspect-ADR pair separately. We categorised the seriousness of ADRs as per Temple [11], as causing: (i) increased monitoring but no harm; (ii) temporary harm, requiring treatment intervention; (iii) initial / prolonged hospitalization; (iv) permanent harm; (v) near-death; or (vi) death. We defined serious ADRs as

those ADRs resulting in hospital admission, or prolonging hospital admission, or causing permanent harm, near-death, or death.

We recorded drugs by generic names only and codified these according to the World Health Organization's Anatomical Therapeutic Chemical Classification System (ATC) [12]. We defined the total drug count as the number of unique ATC codes to which the patient was exposed over the 30-day period before the admission and during their observed hospital stay. We similarly calculated a background drug count (over the 30-day period before the admission) and an in-hospital drug count for each admission. When determining drug counts, we excluded drugs applied topically to the skin, eyes, ears, nose, throat, or mouth.

We categorised age according to National Institute of Child Health and Human Development Pediatric

Terminology as follows: preterm neonate, born before 37 completed weeks' gestation; term neonate, from birth to 27 days; infancy, 28 days to 12 months; toddler, 13 months to 24 months; early childhood, 25 months to 5 years; middle childhood, 6 years to 11 years; early adolescence, 12 years to 18 years [13]. We used the admission weight to calculate a weight-for-age z-score using standards developed in the WHO Multicentre Growth Reference Study [14] for infants, toddlers, and children in early childhood years. We abstracted HIV status as infected, negative, or unknown, and perinatal HIV exposure status in children <18 months old as exposed, unexposed, or unknown. We combined HIV status and perinatal HIV exposure into a single stratified variable as follows: [1] HIV-infected; [2] HIV-negative, consisting of children <18 months who were not perinatally exposed, children ≥18 months who were serologically negative, and children ≥18 months in whom HIV testing was not clinically indicated; and [3] an indeterminate group of children <18 months, who were or may have been perinatally exposed to HIV but whose HIV infection status was not yet confirmed.

Trigger tool development

We conducted a literature review to identify previous studies that used triggers to detect potential ADRs or harm in children, or potential ADRs in adults. We combined all the drug-related triggers from these various tools. A multidisciplinary panel of seven experts (a clinical pharmacist, a clinical pharmacologist, two paediatricians, a paediatric HIV clinician, and two research medical officers) then decided on the inclusion of each trigger in a two-round modified Delphi method. In round 1, each expert independently rated the inclusion of the trigger on a 5-point Likert scale (5 = strongly agree that the trigger should be included on the trigger tool; 1 = strongly disagree that the trigger should be included on the trigger tool). We calculated the median score, first (Q1), and third (Q3) quartiles for each trigger. We defined agreement to include each potential trigger as a median score ≥ 4 and Q1 ≥ 4, and agreement to exclude each potential trigger as a median score ≤ 2 and Q3 ≤ 2. Additionally, experts were asked to add potential triggers to the list during round 1. In round 2, experts met to discuss triggers without agreement to include or exclude, as well as all the potential triggers added during round 1. Experts then re-scored, or in the case of newly added triggers scored, these triggers independently on the same scale. We again defined agreement to include each potential trigger as a median score ≥ 4 and Q1 ≥ 4. Triggers with agreement to include in the first or second round were included in the final trigger list.

Data management and statistical analysis

We entered data into a purpose-built Access 2013 database (Microsoft Corporation, Redmond, WA). We analysed data using Stata 13.1 (Stata Corporation, College Station, TX), including the macro `igrowup_restrictado` (version 3.2.2, January 2011) [15] to calculate weight-for-age z-scores.

We summarised continuous variables by means and standard deviations, or by medians and interquartile ranges (IQR), depending on their distribution. We explored associations between binary and categorical variables through cross-tabulation and chi-square statistics, and we conducted between-group comparisons of continuous variables using the Wilcoxon rank-sum test or Student's *t* test, depending on the distribution. A *P* value of < 0.05 was taken to indicate statistically significant difference.

We conducted multivariate analysis of associations with serious ADR by constructing a logistic regression model. We limited this model to children documented to have been exposed to at least one drug before and / or during their admission, and to first admissions only in the event of multiple admissions per patient. Variables which were selected a priori for inclusion in the model as predictor variables were age category, sex, hospital site, the summary HIV infection / exposure category described above, and total drug count. In the subgroup of patients for whom weight-for-age z-scores could be calculated, we conducted an explorative analysis adding this variable to the model.

Ethical issues

Our study received ethical approval from the Human Research Ethics Committees of the University of Cape Town (approval number 576/2011) and the University of the Witwatersrand (clearance certificate number M140707). We received permission to conduct the research from both hospitals. We did not request individual patients' or caregivers' consent, as this study was a non-interventional review of medical records, and this was approved by the ethics committees. We shared anonymised study findings with the South African National Adverse Drug Event Monitoring Centre, which collects spontaneous reports on behalf of the national medicines regulator. Partial, provisional results were shared at the 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management and were published as an abstract [16].

Results

Trigger tool development

Our literature search yielded 31 articles. We compiled a list of 110 triggers from 16 included studies (see Additional file 1: Table S1). In round 1 of the modified Delphi method, we agreed to include 37 triggers and agreed to exclude one. In round 2, 74 triggers (72 from round 1

and two newly proposed triggers) were discussed. We agreed to include a further 35; the final trigger list consisted of 72 triggers (Table 1). Seventeen triggers refer to drugs used as antidotes (e.g. naloxone) or in the management of adverse events, 12 describe laboratory evidence of high drug concentrations, 16 refer to other abnormal laboratory values, and 27 relate to clinical events suggesting adverse drug events (e.g. unexplained medication stop.)

Sample description

There were 1050 patients and 1106 admissions (range one to four admissions per patient). Patient characteristics are described in Table 2, and admission characteristics in Table 3.

Respiratory infections were the most common reason for admission, forming one-third of admission diagnoses (see Additional file 1: Table S2). Beta-adrenergic inhalants, antipyretics, and penicillins and other beta-lactam antibiotics were the most common drugs to which children were exposed prior to their admission (see Additional file 1: Table S3), although one in five folders did not contain a pre-admission drug exposure history. The same drug classes, together with vitamin and mineral supplements, were also the most commonly used drugs during admissions (see Additional file 1: Table S4).

There were 29/1050 (2.8%) HIV-infected children: 24 were on ART before the admission, while five were newly diagnosed during the index admission and referred to start ART after discharge. Most (19/24, 79%) were on a regimen of ritonavir-boosted lopinavir and two nucleoside reverse transcriptase inhibitors (NRTIs), while 4/24 (17%) were on a regimen of a non-nucleoside reverse transcriptase inhibitor and two NRTIs, and 1/24 (4.2%) on an unknown regimen. The NRTIs in use were lamivudine in all 23 children, abacavir in 18, zidovudine in 4, and stavudine in 1. Fifty-one children were exposed to nevirapine for the prevention of mother-to-child HIV transmission (PMTCT) before and/or during their admissions, with additional zidovudine in 12 children.

Serious ADRs

The multidisciplinary panel confirmed the diagnosis of 160 ADRs, 40 of which were serious (18 caused admission, 14 prolonged admission, 7 were near-fatal, and one resulted in death). Twenty serious ADRs were present at the time of admission (see Additional file 1: Table S5), and 20 occurred during admission (see Additional file 1: Table S6). The crude prevalence of serious ADRs was 3.8 per 100 drug-exposed admissions, consisting of 2.7 serious ADRs present at admission per 100 drug-exposed admissions and 1.9 serious ADRs occurring during the admission per 100 drug-exposed admissions.

Alternative ways of expressing the ADR prevalence are given in the supplement (see Additional file 1: Table S7).

Thirty of 40 serious ADRs were classified as type A reactions; causality assessment rated seven type A ADRs as certain, six as probable, and 17 as possible. Ten of 40 serious ADRs were classified as type B reactions or were classified as a mixture of type A and B mechanisms. There were 17 drug-ADR pairs implicated in these ten ADRs, and causality assessment rated 2 pairs as certain, 5 as probable, and 10 as possible.

Serious ADR manifestations encountered more than once were: four cases of diarrhoea prolonging the admission, two cases of near-fatal respiratory depression, two cases of near-fatal hyperkalaemia, two cases of dystonia causing admission, two cases of urticaria causing admission, and two cases of bicytopenia prolonging the admission.

Individual drugs most commonly implicated in serious ADRs were: prednisone (H02AB07, 5 times), methylprednisolone (H02AB04, 3 times), amoxicillin (J01CA04, 3 times), mycophenolic acid (L04AA06, 3 times), and tacrolimus (L04AD02, 3 times). Drug classes most commonly implicated in serious ADRs were (by second-level ATC code): systemic antibacterials (J01) in 12 serious ADRs, systemic corticosteroids (H02) in 6 serious ADRs, psycholeptics (N05) in 4 serious ADRs, immunosuppressants (L04) in 4 serious ADRs, direct-acting antivirals (J05) in 4 serious ADRs, and analgesics (N02) in 3 serious ADRs (Table 4). Relative to the frequency of exposure to these drug classes, immunosuppressants (L04) were disproportionately frequently implicated (see Additional file 1: Figure S1).

Five of 30 (17%) type A serious ADRs and 4/17 (24%) type B serious ADR drug-event pairs were preventable; in total, 9/40 (23%) serious ADRs had at least one preventability factor present. The most common preventability factor was an inappropriate drug choice, which occurred in 6/40 (15%) serious ADRs. A wide variety of drugs were considered inappropriate in these cases, including benzathine benzylpenicillin, flucloxacillin, ceftriaxone, ferrous gluconate, clozapine, and amitriptyline. Inappropriate dose or route of administration occurred in 2/40 (5%) serious ADRs (drugs involved were vancomycin and metoclopramide), problems with patient adherence occurred in 2/40 (5%) serious ADRs (drugs involved were flucloxacillin and amitriptyline), insufficient laboratory monitoring occurred in 1/40 (2.5%) serious ADR attributed to tacrolimus, and a raised drug concentration occurred in 1/40 (2.5%) serious ADR attributed to tacrolimus. Alternative ways of reporting the proportion considered preventable are presented in the supplement (see Additional file 1: Table S8).

Among the 36 children with serious ADRs, one death occurred, and this was considered to be directly caused by an ADR which was the result of an error: benzathine

Table 2 Patient characteristics (n = 1050) at first admission to two children's hospitals, South Africa, 2015

	All patients (n = 1050)	Patients with ADR(s) (any seriousness) (n = 119)	Patients without ADR(s) (n = 931)	P-value
Age				
Median (IQR) months	11 (2 to 41)	20 (5 to 68)	10 (2 to 37)	P = 0.0010 ^e
Age categories^a				
Preterm neonates	32 (3.1%) ^{b, c}	6 (5.0%)	26 (2.8%)	P = 0.002 ^f
Term neonates	96 (9.1%) ^c	2 (1.7%)	94 (10%)	
Infants	421 (40%)	42 (35%)	379 (41%)	
Toddlers	139 (13%)	13 (11%)	126 (14%)	
Early childhood	198 (19%)	30 (25%)	168 (18%)	
Middle childhood	123 (12%)	18 (15%)	105 (11%)	
Early adolescence	41 (3.9%)	8 (6.7%)	33 (3.5%)	
Weight-for-age z-score mean (SD)				
Infants	-1.3 (2.0) (n = 418)	-2.4 (2.2) (n = 42)	-1.2 (2.0) (n = 376)	P = 0.0002 ^g
Toddlers	-0.45 (1.5) (n = 137)	-0.78 (1.2) (n = 13)	-0.41 (1.5) (n = 124)	P = 0.3870 ^g
Early childhood	-0.54 (1.6) (n = 165)	-0.54 (1.7) (n = 24)	-0.54 (1.5) (n = 141)	P = 0.9969 ^g
Sex				
Male	590 (56%)	69 (58%)	521 (56%)	P = 0.676 ^h
Female	460 (44%)	50 (42%)	410 (44%)	
HIV infection / exposure status				
HIV negative	887 (84%)	91 (76%)	796 (86%)	P = 0.003 ^f
HIV indeterminate	134 (13%)	19 (16%)	115 (12%)	
HIV infected	29 (2.8%) ^d	9 (7.6%)	20 (2.1%)	
Number of admissions				
One	1001 (95%)	109 (92%)	892 (96%)	P = 0.134 ^f
Two	43 (4.1%)	9 (7.6%)	34 (3.7%)	
Three	5 (0.48%)	1 (0.84%)	4 (0.43%)	
Four	1 (0.10%)	0 (0%)	1 (0.11%)	

^aPreterm neonate, born before 37 completed weeks' gestation; term neonate, from birth to 27 days; infancy, 28 days to 12 months; toddler, 13 months to 24 months; early childhood, 25 months to 5 years; middle childhood, 6 years to 11 years; early adolescence, 12 years to 18 years

^bPreterm neonates included 16/32 (50%) moderate to late preterm (32 to < 37 weeks' gestation), 12/32 (38%) very preterm (28 to < 32 weeks' gestation), and 4/32 (13%) extremely preterm (< 28 weeks' gestation) neonates

^cAmong all neonates (n = 128): 93/128 (73%) normal or high birth weight (≥ 2500 g), 18/128 (14%) low birth weight (1500 to 2499 g), 11/128 (8.6%) very low birth weight (1000 to 1499 g), and 6/128 (4.7%) extremely low birth weight (≤ 999 g)

^dOf whom 5/29 (17%) not yet on ART, and 24/29 (83%) on ART before and during admission. ART regimens were: 15/24 (63%) on abacavir (ABC) + lamivudine (3TC) + zidovudine (ZDV) + efavirenz (EFV), 3/24 (13%) on ABC + 3TC + efavirenz (EFV), 2/24 (8.3%) on zidovudine (ZDV) + 3TC + LPV/r, 1/24 (4.2%) on stavudine (D4T) + 3TC + LPV/r, 1/24 (4.2%) on AZT + 3TC + nevirapine (NVP), 1/24 (4.2%) on AZT + 3TC + EFV, and 1/24 (4.2%) on an unknown ART regimen

^eWilcoxon rank-sum test

^fFisher's exact test

^gStudent's t test

^hChi-square test

ADR adverse drug reaction; IQR interquartile range; SD standard deviation

benzylpenicillin (instead of benzylpenicillin sodium) was administered intravenously to a preterm neonate, resulting in fatal respiratory arrest. Six children with serious ADRs remained in hospital at the end of our observation period, while 29 were discharged or transferred out. The median (IQR) length of stay observed among children with serious ADRs was 6 [3–12] days. Six serious ADRs present at the time of admission were managed entirely in the short-stay ward: two children with urticaria, two children with dystonia, and one child each with lower

respiratory tract infection and convulsion. Five serious ADRs occurring during the hospitalisation prolonged the hospital stay, yet the affected children were still only managed in the short-stay ward, including three children with antibiotic-associated diarrhoea, and one child each with rash and raised transaminases.

No serious ADRs occurred among term neonates. For the multivariate logistic regression analysis, we therefore grouped term neonates together with infants. The logistic regression model (Table 5) confirmed the following

Table 3 Admission characteristics ($n = 1106$) at two children's hospitals in South Africa, 2015

	All admissions ($n = 1106$)	Admissions with ADR(s) (any seriousness) ($n = 120$)	Admissions without ADR(s) ($n = 986$)	P-value
Hospital				
RCWMCH	886 (80%)	100 (83%)	786 (80%)	$P = 0.349^c$
RMMCH	220 (20%)	20 (17%)	200 (20%)	
Type of admission				
Acute admission	998 (90%)	113 (94%)	885 (90%)	$P = 0.124^c$
Elective admission	108 (9.8%)	7 (5.8%)	101 (10%)	
Admission ward				
Short-stay ward only	514 (46%)	28 (23%)	486 (49%)	$P < 0.001^c$
Medical wards, not ICU ^a	459 (42%)	60 (50%)	399 (40%)	
Any time spent in ICU	133 (12%)	32 (27%)	101 (10%)	
Duration of stay observed (censored at study end) ($n = 1105$) ^b				
1 day	72 (6.5%)	2 (1.7%)	70 (7.1%)	$P < 0.001^c$
2 to 3 days	541 (49%)	27 (23%)	514 (52%)	
4 to 6 days	229 (21%)	20 (17%)	209 (21%)	
≥ 7 days	263 (24%)	71 (59%)	192 (19%)	
Median (days)	3	8	3	$P < 0.0001^e$
Interquartile range (days)	2 to 6	4 to 13	2 to 5	
Range (days)	1 to 34	1 to 34	1 to 34	
Total stay observed (patient-days)	5744	1198	4546	
Type of exit ($n = 1105$) ^b				
Discharged / transferred out	1038 (94%)	100 (83%)	938 (95%)	$P < 0.001^d$
Died	13 (1.2%)	2 (1.7%)	11 (1.1%)	
Censored (remained in-hospital by end of observation period)	54 (4.9%)	18 (15%)	36 (3.7%)	
Drug exposure over 30-day period before admission				
No drug history documented in folder	226 (20%)	12 (10%)	214 (22%)	$P < 0.001^c$
No drugs	130 (12%)	7 (5.8%)	123 (12%)	
Had ≥ 1 drug(s)	750 (68%)	101 (84%)	649 (66%)	$P < 0.0001^e$
Median background drug count	2 ($n = 880$)	4 ($n = 108$)	2 ($n = 772$)	
Interquartile range	1 to 4	2 to 7	1 to 4	
Range	0 to 47	0 to 42	0 to 47	
Drug exposure during admission ($n = 1105$) ^b				
No drugs	69 (6.2%)	2 (1.7%)	67 (6.8%)	$P = 0.028^c$
Had ≥ 1 drug(s)	1036 (94%)	118 (98%)	918 (93%)	
Median in-hospital drug count	4 ($n = 1105$)	11 ($n = 120$)	4 ($n = 985$)	$P < 0.0001^e$
Interquartile range	3 to 9	7 to 19	2 to 7	
Range	0 to 46	0 to 46	0 to 36	$P < 0.0001^e$
Median daily drug count	5 ($n = 5744$ patient-days)	9 ($n = 1198$ patient-days)	4 ($n = 4546$ patient-days)	
Interquartile range	3 to 8	5 to 13	2 to 7	
Range	0 to 29	0 to 29	0 to 23	
Total drug exposure (before and during admission)				
No drugs	49 (4.4%)	0 (0%)	49 (5.0%)	$P = 0.012^c$
Had ≥ 1 drug(s)	1057 (96%)	120 (100%)	937 (95%)	

Table 3 Admission characteristics ($n = 1106$) at two children's hospitals in South Africa, 2015 (Continued)

	All admissions ($n = 1106$)	Admissions with ADR(s) (any seriousness) ($n = 120$)	Admissions without ADR(s) ($n = 986$)	P-value
Median total drug count	6	12	5	$P < 0.0001^e$
Interquartile range	3 to 10	8 to 21	3 to 9	
Range	0 to 52	2 to 47	0 to 52	

^aMay have moved from short-stay to medical ward; may have included a high-care stay during the admission

^bDuration of stay, drug exposure during admission, and type of exit missing for one admission (an admission without an ADR)

^cChi-square test

^dFisher's exact test

^eWilcoxon rank-sum test

ADR adverse drug reaction; ICU intensive care unit; RCWMMH Red Cross War Memorial Children's Hospital; RMMCH Rahima Moosa Mother and Child Hospital

independent associations with serious ADRs: preterm neonates, adjusted odds ratio (aOR) with 95% CI 5.97 (1.30 to 27.3) versus referent category of infants and term neonates; middle childhood, aOR 3.63 (1.24 to 10.6) versus infants and term neonates; HIV-infection, aOR 3.87 (1.14 to 13.2) versus HIV-negative; and increasing drug count, aOR 1.08 (1.04 to 1.12) per additional drug.

In an exploratory logistic regression model (see Additional file 1: Table S9) weight-for-age z-score was not associated with serious ADR occurrence after adjustment for age, sex, hospital, HIV category, and drug count.

Four of 29 (13.8%) HIV-infected children in our survey experienced a serious ADR, including two who were admitted with serious ADRs present at the time of admission and another two who experienced serious ADRs

Table 4 Drug classes commonly implicated in serious ADRs and the associated ADR manifestations

Drug class	Serious ADRs
Systemic antibacterials (J01), implicated in 12 serious ADRs	• Diarrhoea with amoxicillin (2 cases) and with clarithromycin (1 case), prolonging the admissions • Urticaria with phenoxymethylpenicillin (1 case) and with ceftriaxone (1 case), causing the admissions • Maculo-papular rash with flucloxacillin, prolonging the admission • Respiratory arrest with intravenous benzathine benzylpenicillin (medication error), fatal • Red-man syndrome with vancomycin, near-fatal • Thrombocytopenia with amoxicillin, causing the admission • Agranulocytosis with co-trimoxazole (and zidovudine), causing the admission • Bicytopenia with ceftriaxone, co-trimoxazole (and ganciclovir), prolonging the admission • Metabolic acidosis with amikacin (and paracetamol), causing the admission
Systemic corticosteroids (H02), implicated in 6 serious ADRs	• Lower respiratory tract infection with prednisone, causing the admission • Upper respiratory tract infection with prednisone, causing the admission • <i>Pneumocystis jirovecii</i> pneumonia with prednisone and methylprednisolone, prolonging the admission • Salmonellosis with prednisone (and mycophenolic acid), prolonging the admission • Pancreatitis with prednisone and methylprednisolone, prolonging the admission • Sepsis with methylprednisolone (and mycophenolic acid and tacrolimus), prolonging the admission
Psycholeptics (N05), implicated in 4 serious ADRs	• Respiratory depression with chlorpromazine, lorazepam and diazepam (and phenobarbital), near-fatal • Respiratory depression with diazepam (and morphine and phenobarbital), near-fatal • Apnoea with midazolam, near-fatal • Delirium with clozapine, causing the admission
Immunosuppressants (L04), implicated in 4 serious ADRs	• Macrocytic anaemia with mycophenolic acid and tacrolimus, causing the admission • Neutropaenic sepsis with tacrolimus, prolonging the admission • Sepsis with mycophenolic acid and tacrolimus (and methylprednisolone), prolonging the admission • Salmonellosis with mycophenolic acid (and prednisone), prolonging the admission
Direct-acting antivirals (J05), implicated in 4 serious ADRs	• Agranulocytosis with zidovudine (and co-trimoxazole), causing the admission • Diarrhoea with lopinavir-ritonavir, prolonging the admission • Increased transaminases with efavirenz, prolonging the admission • Bicytopenia with ganciclovir (and ceftriaxone and co-trimoxazole), prolonging the admission
Analgesics (N02), implicated in 3 serious ADRs	• Respiratory depression with morphine (and diazepam and phenobarbital), near-fatal • Metabolic acidosis with paracetamol (and amikacin), causing the admission • Increased paracetamol plasma concentration, prolonging the admission

ADR adverse drug reaction

Table 5 Multivariate logistic regression model of factors associated with serious ADR ($n = 1001$ first admissions with documented exposure to ≥ 1 drug(s))

	<i>n</i>	Bivariate analysis		Multivariate analysis	
		Unadjusted OR (95% CI)	<i>P</i>	Adjusted ^a OR (95% CI)	<i>P</i>
Age category ^b					
Preterm neonate	31	5.14 (1.34 to 19.7)	0.017	5.97 (1.30 to 27.3)	0.021
Term neonate & Infant	490	Referent			
Toddler	137	1.07 (0.292 to 3.96)	0.914	1.13 (0.295 to 4.33)	0.858
Early childhood	188	1.58 (0.567 to 4.42)	0.381	1.61 (0.521 to 4.97)	0.408
Middle childhood	114	3.62 (1.40 to 9.40)	0.008	3.63 (1.24 to 10.6)	0.018
Early adolescent	41	3.79 (1.00 to 14.4)	0.050	2.88 (0.667 to 12.5)	0.156
Sex					
Male	564	Referent			
Female	437	1.08 (0.537 to 2.16)	0.832	0.894 (0.428 to 1.87)	0.766
Hospital					
RXWMCH	812	Referent			
RMMCH	189	0.953 (0.388 to 2.34)	0.917	0.938 (0.324 to 2.71)	0.906
HIV category					
Negative	840	Referent			
Infected	29	5.44 (1.76 to 16.9)	0.003	3.87 (1.14 to 13.2)	0.031
Indeterminate	132	1.34 (0.502 to 3.57)	0.560	1.59 (0.502 to 5.05)	0.429
Total drug count					
Per additional drug	1001	1.09 (1.05 to 1.13)	< 0.001	1.08 (1.04 to 1.12)	< 0.001

^aAdjusted for other variables in the model^bPreterm neonate, born before 37 completed weeks' gestation; term neonate, from birth to 27 days; infancy, 28 days to 12 months; toddler, 13 months to 24 months; early childhood, 25 months to 5 years; middle childhood, 6 years to 11 years; early adolescence, 12 years to 18 years

ADR adverse drug reaction; OR odds ratio; RXWMCH Red Cross War Memorial Children's Hospital; RMMCH Rahima Moosa Mother and Child Hospital

during their admission. In three of the four cases, anti-retroviral agents were implicated in the ADRs. None of the serious ADRs in HIV-infected children was considered preventable. The use of PMTCT was not implicated in any serious ADRs.

Non-serious ADRs

We found a further 120 non-serious ADRs, which we describe in the supplement. These included 26 non-serious ADRs present at the time of admission (see Additional file 1: Table S10) and 94 non-serious ADRs occurring during the admission (see Additional file 1: Table S11). The most commonly implicated drug classes implicated in non-serious ADRs were systemic antibacterials (J01) in 48 ADRs, drugs for obstructive airway diseases (R03) in 23 ADRs, diuretics (C03) in 17 ADRs, mineral supplements (A12) in 11 ADRs, and systemic corticosteroids (H02) in 10 ADRs (see Additional file 1: Table S12).

Discussion

In two South African children's hospitals we found that 3.8 serious ADRs occurred per 100 drug-exposed admissions. Serious ADRs were associated with increasing

drug exposure, HIV infection, and two age categories – premature neonates and middle childhood. A wide range of ADR manifestations occurred, and commonly implicated drug classes included antimicrobials, systemic corticosteroids, and antiviral agents. Considering that one in five serious ADRs was fatal or near-fatal, and about one in five serious ADRs was also preventable, these findings have significant public health importance.

It is difficult to compare the prevalence of ADRs across studies, due to differences in study settings and study designs. Nevertheless, a comprehensive 2012 systematic review [4] estimated the proportion of paediatric admissions caused by ADRs to be 2.9% (95% CI 2.6 to 3.1%), using a denominator of all admissions and not only drug-exposed admissions. In our survey 1.8% of admissions were due to an ADR. However, our survey excluded admissions to the oncology ward, whereas the 2012 systematic review's figure is significantly influenced by two large surveys which found ADR-related admissions to oncology wards to be common [17, 18]. Published subsequent to the 2012 systematic review [4], surveys from paediatric settings in sub-Saharan Africa suggested the proportion of admissions due to ADRs to be 5.7% (16/282) in Cape Town, South Africa [19], 4.7%

(114/2433) in Eritrea [20], and 0.60% (12/2004) in Lagos, Nigeria [21]. A study from Jimma, Ethiopia, with paediatric adverse drug events as outcome (i.e., a slightly different outcome than ADRs), determined the proportion of admissions to be adverse drug event-related as 0.63% (4/634) [22]. The prevalence of serious ADRs during paediatric admissions was not studied in the 2012 systematic review, although the prevalence of all in-hospital ADRs (i.e., of any seriousness) ranged from 0.6 to 16.8% among included studies [4]. An earlier systematic review found that 7 to 20% of in-hospital paediatric ADRs were serious [23], with our study's proportion (20/114, 18%) falling within this range. A previous study from Nigeria found that 0.29% (11/3821) of retrospectively reviewed paediatric admissions were prolonged due to serious ADRs [24]. Our methodology, involving prospective review, probably explains why we found a much higher proportion of admissions (1.8%) being affected by serious ADRs occurring during the admission. Taking all these factors in consideration, our interpretation is that serious ADRs probably occurred at a similar frequency in our hospitals as in other paediatric settings in sub-Saharan Africa and elsewhere.

There is robust evidence from previous adult and paediatric systematic reviews [4, 23, 25] confirming the association between ADR occurrence and increasing drug count. Although an association between serious ADR occurrence and sex was found in the majority of studies included in the 2012 paediatric systematic review [4], we did not find any such association in this survey. Regarding associations with age, the association between ADR occurrence and prematurity which is attributable to reduced drug metabolism and clearance is also well established [26]. Previous hospital-based surveys in the United Kingdom [18, 27], United States [17], and in sub-Saharan Africa [20] have also, similar to our finding, described an association between ADR occurrence and later childhood. This association has been explained by older children's ability to communicate their ADRs better than younger children [27]. Another explanation could be that older children tend to be admitted for chronic disease processes requiring chronic medications with a greater exposure-time within which ADRs might occur, whereas younger children are mostly admitted for acute infectious disease processes requiring short-term treatment. HIV infection causes chronic immune stimulation, increased oxidative stress, and altered patterns of drug metabolism [28], which may explain our finding that HIV infection was independently associated with the occurrence of serious ADRs. Our group has previously shown the same independent association between HIV infection and serious ADRs in South African adults [10, 29], and an association between HIV infection and serious ADRs was also found in a recent paediatric

survey from another Cape Town hospital [19]. Lastly, despite our unadjusted analysis suggesting an association between serious ADR occurrence and low weight-for-age, no such association was found after adjustment for other factors.

In the 2012 systematic review, between 7 and 98% of ADRs were reportedly preventable [4]. Our proportion of serious ADRs considered preventable, i.e. 23%, is considerably lower than the findings in our adult serious ADR surveys, where 43 to 45% of ADRs were considered preventable [10, 29], but is in keeping with proportions from Nigeria (20%) [21] and Ethiopia (33%) [22]. The most common reason why serious ADRs were considered preventable in this survey was an inappropriate choice of drug (15%), which was also the most common reason in our adult surveys [10, 29] and one of the most common reasons (23%) cited in the 2012 systematic review [4]. Our survey did not yield a clear pattern of specific drugs considered inappropriate, with six different drugs involved in the six serious ADRs considered preventable for this reason.

In our survey, one child died due to an ADR, and this ADR was related to a medication error. Medication errors are common in sub-Saharan African hospitals: 75% of children admitted to general paediatric wards in a South African [30] and an Ethiopian [31] hospital were exposed to medication errors, as were 95% of children admitted to a South African paediatric intensive care unit [32]. High mortality and an association with medication error was also seen in the Ethiopian adverse drug event survey [22], where 9% of adverse drug events resulted in permanent harm or death, with three of the four events that resulted in permanent harm in that survey being due to medication error. Higher mortality rates than ours occurred in Eritrea, where 19/114 (17%) children admitted for ADRs died due to their ADRs [20], and in Nigeria, where 2/12 (17%) of children admitted for ADRs died due to their ADRs [21]. While our fatality rate may seem reassuringly low against these sub-Saharan African studies, it should be noted that an additional seven ADRs in our survey were considered near-fatal, meaning that 20% of serious ADRs may potentially have resulted in children's deaths.

The drug classes most commonly implicated in serious ADRs in our survey were systemic antibacterials, systemic corticosteroids, antivirals, psycholeptics, immunosuppressants, and analgesics. These mostly correspond with the findings of the 2012 systematic review [4], bearing in mind we did not survey oncology wards and thus did not observe ADRs attributable to cytotoxics. Antibacterial agents were also commonly implicated in other sub-Saharan African surveys [19, 21, 22], particularly in association with rashes [21]. Significantly, our list of commonly implicated drugs includes antivirals, which

was not a common cause of ADRs in the 2012 systematic review [4], and which, among three sub-Saharan African studies [19, 21, 22] was only mentioned as a commonly implicated class of drugs in one [19].

Despite choosing sites with large paediatric ART clinics, where we expected to find admissions of HIV-infected children to be concentrated, our survey included a relatively low number of HIV-infected children among those admitted. We interpret this as evidence of the efficacy of PMTCT, which has resulted in decreasing paediatric HIV incidence and prevalence [2], and of the generally high efficacy and low toxicity associated with current paediatric antiretroviral regimens in use. Nevertheless, among the small number of HIV-infected children admitted during our survey, a high proportion (9/29, 31%) had ADRs, which is comparable to another South African survey in which 9/21 (43%) HIV-infected children admitted to hospital had ADRs [19]. Our survey included 4/29 (14%) HIV-infected children with serious ADRs, of which three were attributed to the use of ART, illustrating the importance of continued vigilance when using these drugs.

One limitation of our study is that we have likely under-estimated ADR prevalence at the time of admission, as one in five folders were missing pre-admission drug exposure history, and we did not interview patients or caregivers to complement information not documented in clinical notes or verify the accuracy of recorded drug histories. Our choice of study wards (i.e., excluding surgical and oncology wards) also resulted in under-ascertainment of ADRs associated with the use of anaesthetic and cytotoxic agents, which were major drivers of serious ADRs elsewhere [17, 18, 27]. On the other hand, our study was strengthened by the inclusion of patients admitted to the short-stay ward, a setting that is often excluded [17–19, 22] from ADR surveys. We found that one quarter of all serious ADRs occurred in the short-stay ward and would have been missed had we not surveyed patients admitted there. Our study's representativeness was also strengthened by reviewing some, although admittedly not all, neonatal admissions, and by reviewing admissions to the intensive care unit.

A strength of our study was the development of a localised trigger tool to assist in identifying potential ADRs.

We did not determine the contribution of off-label use of drugs to the burden of ADRs. This was previously described as a risk factor for development of ADRs: in the 2012 systematic review [4] three out of three studies which investigated it confirmed unlicensed or off-label use to be a risk factor for the occurrence of ADRs.

Our study was conducted in specific wards of two urban hospitals in the two best-resourced provinces of South Africa, and findings may therefore be considered

context-specific, rather than generalisable to other settings. For this reason, replicating this survey in other wards, or in more resource-constrained or rurally located hospitals, and/or periodically repeating this survey or a scaled version thereof would provide a clearer picture of the burden of serious adverse drug reactions our children face.

Conclusions

Serious ADR prevalence at two paediatric hospitals in South Africa was, at 3.8 serious ADRs per 100 drug-exposed admissions, similar to the prevalence described in hospital settings elsewhere. Similar to other sub-Saharan African studies, a large proportion of serious ADRs were fatal or near-fatal, and around one-fifth of serious ADRs were preventable. In keeping with South Africa's high burden of HIV, we found that the antiviral drug class was one of the most commonly implicated classes in serious ADRs. Serious ADRs were independently associated with increasing drug count, HIV-infection, and two age categories: premature neonates and middle childhood.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12887-019-1892-x>.

Additional file 1: Table S1. Trigger tool development: summary of included studies. **Table S2.** Reasons for admission at two children's hospitals, South Africa, 2015. **Table S3.** Background drugs most commonly in use among 1106 admissions at two children's hospitals in South Africa, 2015. **Table S4.** Drugs most commonly in use during 1105 admissions at two children's hospitals in South Africa, 2015. **Table S5.** Serious adverse drug reactions present at the time of admission at two children's hospitals, South Africa, 2015. **Table S6.** Serious adverse drug reactions occurring during hospital admission at two children's hospitals, South Africa, 2015. **Table S7.** Alternative ways of expressing ADR prevalence rates at two children's hospitals, South Africa, 2015. **Table S8.** Reasons adverse drug reactions were considered preventable at two children's hospitals, South Africa, 2015. **Table S9.** Exploratory analysis: Multivariate logistic regression model of factors associated with serious ADR incorporating weight-for-age z-scores, at two children's hospitals in South Africa, 2015. **Table S10.** Non-serious adverse drug reactions present at the time of admission at two children's hospitals, South Africa, 2015. **Table S11.** Non-serious adverse drug reactions occurring during admission at two children's hospitals, South Africa, 2015. **Table S12.** Drug classes implicated in non-serious adverse drug reactions at two children's hospitals, South Africa, 2015. **Figure S1.** Scatterplot of drug classes implicated in serious ADRs versus frequency of their use at two children's hospitals, South Africa, 2015.

Abbreviations

ADR(s): Adverse drug reaction(s); aOR: Adjusted odds ratio; ART: Antiretroviral treatment; ATC: Anatomical therapeutic chemical classification system; CI: Confidence interval; HIV: Human immunodeficiency virus; IQR: Interquartile range; NRTI: Nucleoside reverse transcriptase inhibitor; PMTCT: Prevention of mother-to-child transmission; Q1: First quartile; Q3: Third quartile; RCWMCH: Red Cross War Memorial Children's Hospital; RMMCH: Rahima Moosa Mother and Child Hospital; WHO: World Health Organization

Acknowledgements

We thank the patients who contributed data and their caregivers, as well as the clinical, nursing, administrative and managerial staff at both hospitals for their assistance and support in this study. In particular, we thank Dr. Gary Reubenson from RMMCH for his valuable feedback.

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Authors' contributions

MCFdS, JPM, RdW, UM, AS, and KC conceived and designed this study. MCFdS led the development of the trigger tool, while UM, KC, CS, AA, K-GT, RdW, and JPM served as experts in its development. AS developed the database and was responsible for data management. JPM and NJ collected the survey data and conducted initial case review, with assistance and oversight at the sites provided by CS and K-GT. JPM, NJ, UM, MK, CS, and KC constituted the multidisciplinary case assessment panel. JPM analysed the data and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Funding

This research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under terms of Cooperative Agreement Number GGH000371. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC. The funder had no role in the design of the study, in the collection, analysis, or interpretation of data, or in writing the manuscript.

Availability of data and materials

The anonymised datasets used in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Our study received ethical approval from the Human Research Ethics Committees of the University of Cape Town (approval number 576/2011) and the University of the Witwatersrand (clearance certificate number M140707). We did not request individual patients' or caregivers' consent, as this study was a non-interventional review of medical records, and this was approved by the ethics committees.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 6 August 2019 Accepted: 16 December 2019

Published online: 04 January 2020

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Appendix vi. List of SSA countries

- Angola
- Benin
- Botswana
- Burkina Faso
- Burundi
- Cabo Verde
- Cameroon
- Central African Republic
- Chad
- Comoros
- Democratic Republic of Congo
- Republic of Congo
- Côte d'Ivoire
- Equatorial Guinea
- Eritrea
- Eswatini (Swaziland)
- Ethiopia
- Gabon
- The Gambia
- Ghana
- Guinea
- Guinea-Bissau
- Kenya
- Lesotho
- Liberia
- Madagascar
- Malawi
- Mali
- Mauritania
- Mauritius
- Mozambique
- Namibia
- Niger
- Nigeria
- Rwanda
- Sao Tome and Principe
- Senegal
- Seychelles
- Sierra Leone
- Somalia
- South Africa
- South Sudan
- Sudan
- Tanzania
- Togo
- Uganda
- Zambia
- Zimbabwe

Appendix vii. Search strategy for Medline via EBSCOhost

#	Search string
S22	LIMIT S21 to published 20020101 or later
S21	S19 NOT S20
S20	PT Case Reports
S19	S8 AND S11 AND S15 AND S18
S18	S16 OR S17
S17	TX (Africa OR African OR Angola OR Benin OR Botswana OR Burkina OR Volta OR Burundi OR Urundi OR Cameroon OR Cameroons OR Cameroun OR Verde OR Chad OR Comoros OR Comoro OR Comores OR Mayotte OR Congo OR Zaire OR Ivoire OR Ivory OR Eritrea OR Ethiopia OR Gabon OR Gabonese OR Gambia OR Ghana OR Guinea OR Kenya OR Lesotho OR Basutoland OR Liberia OR Madagascar OR Malagasy OR Malawi OR Nyasaland OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Ruanda OR Principe OR Senegal OR Seychelles OR Sierra OR Somalia OR Sudan OR eSwatini OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe OR Rhodesia)
S16	MW ("Africa" OR "Africa South of the Sahara" OR "Africa, Central" OR "Africa, Eastern" OR "Africa, Southern" OR "Africa, Western" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Cabo Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Congo" OR "Cote d'Ivoire" OR "Ivory Coast" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "eSwatini" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe")
S15	S12 OR S13 OR S14
S14	TX (incidence OR prevalence OR occur* OR proportion OR rate OR number OR percent OR frequency OR epidemiology OR pharmacoepidemiology OR observational OR cohort OR prospective OR retrospective OR cross sectional OR monitor* OR surveillance)
S13	MW epidemiology
S12	MH ("morbidity+" OR "epidemiology+" OR "health care surveys+" OR "cohort studies+" OR "cross sectional studies+" OR "epidemiological monitoring+" OR "population surveillance+" OR "epidemiologic studies+")
S11	S9 OR S10
S10	TX (serious OR seriousness OR severe OR severity OR admission OR admitt* OR hospitaliz* OR hospitalis*)
S9	MH ("patient acuity+" OR "hospitalization+" OR "severity of illness index+")
S8	S5 OR S6 OR S7
S7	MH ("product surveillance, postmarketing+" OR "drug-related side effects and adverse reactions+" OR "pharmacoepidemiology+" OR "iatrogenic disease")
S6	TI ("ADR" OR "ADRs")
S5	S1 AND S4
S4	S2 OR S3
S3	TI (adverse N3 (reaction* OR event* OR effect* OR outcome*))
S2	TI (harm* OR safety OR toxicit* OR tolerability OR problem* OR "side effect" OR iatrogenic)
S1	TI (drug* OR medicine* OR medication* OR pharmaceutical* OR pharmacotherapy OR pharmacologic*)

TI: title. TX: full-text (title, abstract, keywords, and other fields). MH: MeSH subject heading (exact). MW: MeSH subject heading (contains word). PT: publication type. N3: proximity operator (terms occur within three words of one another, direction irrelevant). *: truncation symbol. +: explodes the subject heading (i.e., includes all MeSH headings nested under it.)

Appendix viii. Search strategy for CINAHL via EBSCOhost

#	Search string
S20	LIMIT S19 to Human and published since 20020101; EXCLUDE Medline records
S19	S8 AND S11 AND S15 AND S18
S18	S16 OR S17
S17	TX (Africa OR African OR Angola OR Benin OR Botswana OR Burkina OR Volta OR Burundi OR Urundi OR Cameroon OR Cameroons OR Cameroun OR Verde OR Chad OR Comoros OR Comoro OR Comores OR Mayotte OR Congo OR Zaire OR Ivoire OR Ivory OR Eritrea OR Ethiopia OR Gabon OR Gabonese OR Gambia OR Ghana OR Guinea OR Kenya OR Lesotho OR Basutoland OR Liberia OR Madagascar OR Malagasy OR Malawi OR Nyasaland OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Ruanda OR Principe OR Senegal OR Seychelles OR Sierra OR Somalia OR Sudan OR eSwatini OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe OR Rhodesia)
S16	MW ("Africa" OR "Africa South of the Sahara" OR "Africa, Central" OR "Africa, Eastern" OR "Africa, Southern" OR "Africa, Western" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Cabo Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Congo" OR "Cote d'Ivoire" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe")
S15	S12 OR S13 OR S14
S14	TX (incidence OR prevalence OR occur* OR proportion OR rate OR number OR percent OR frequency OR epidemiology OR pharmacoepidemiology OR observational OR cohort OR prospective OR retrospective OR cross sectional OR monitor* OR surveillance)
S13	MW (morbidity OR mortality)
S12	MH (Epidemiology+ OR "Nonexperimental Studies+")
S11	S9 OR S10
S10	TX (serious OR seriousness OR severe OR severity OR admission OR admitt* OR hospitaliz* OR hospitalis* OR death OR dying OR died OR fatal* OR mortal*)
S9	MH ("patient classification" OR "institutionalization+" OR "mortality+" OR "severity of illness indices+")
S8	S5 OR S6 OR S7
S7	MH ("drug evaluation+" OR "adverse drug events+" OR "drug toxicity+" OR "pharmacovigilance+" OR "iatrogenic disease+" OR "drug therapy+/ae/mo")
S6	TI ("ADR" OR "ADRs")
S5	S1 AND S4
S4	S2 OR S3
S3	TI (adverse N3 (reaction* OR event* OR effect* OR outcome*))
S2	TI (harm* OR safety OR toxicit* OR tolerability OR problem* OR "side effect" OR iatrogenic)
S1	TI (drug* OR medicine* OR medication* OR pharmaceutical* OR pharmacotherapy OR pharmacologic*)

TI: title. TX: full-text (title, abstract, keywords, and other fields). MH: CINAHL subject heading (exact). MW: CINAHL subject heading (contains word). N3: proximity operator (terms occur within three words of one another, direction irrelevant). *: truncation symbol. +: explodes the subject heading (i.e., includes all CINAHL headings nested under it). /ae: topical subheading "adverse effects". /mo: topical subheading "mortality"

Appendix ix. Search strategy for Africa-Wide Information via EBSCOhost

#	Search string
S17	LIMIT S16 to Publication year 2002 -
S16	S8 AND S11 AND S14 AND S15
S15	TX (Africa OR African OR Angola OR Benin OR Botswana OR Burkina OR Volta OR Burundi OR Urundi OR Cameroon OR Cameroons OR Cameroun OR Verde OR Chad OR Comoros OR Comoro OR Comores OR Mayotte OR Congo OR Zaire OR Ivoire OR Ivory OR Eritrea OR Ethiopia OR Gabon OR Gabonese OR Gambia OR Ghana OR Guinea OR Kenya OR Lesotho OR Basutoland OR Liberia OR Madagascar OR Malagasy OR Malawi OR Nyasaland OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Ruanda OR Principe OR Senegal OR Seychelles OR Sierra OR Somalia OR Sudan OR eSwatini OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe OR Rhodesia)
S14	S12 OR S13
S13	TX (incidence OR prevalence OR occur* OR proportion OR rate OR number OR percent OR frequency OR epidemiology OR pharmacoepidemiology OR observational OR cohort OR prospective OR retrospective OR cross sectional OR monitor* OR surveillance)
S12	SU (morbidity* OR mortal* OR epidemiol* OR incidence OR prevalence OR proportion OR rates OR observational OR prospective OR retrospective OR pharmacoepidemiology OR "health care surveys" OR "cohort study" OR "cross sectional" OR "population surv*")
S11	S9 OR S10
S10	TX (serious OR seriousness OR severe OR severity OR admission OR admitt* OR hospitaliz* OR hospitalis* OR death OR dying OR died OR fatal* OR mortal*)
S9	SU (hospitalization OR hospital admission OR hospital readmission OR admission OR readmission OR hospitalisation OR hospitalized OR hospitalised OR admit* OR patient acuity OR severe OR severity OR serious OR seriousness OR death OR died OR dying OR mortal* OR fatal*)
S8	S5 OR S6 OR S7
S7	SU ("adverse drug" OR "side effects" OR pharmacovigilance OR pharmacoepidemiology OR "drug related" OR iatrogenic)
S6	TI ("ADR" OR "ADRs")
S5	S1 AND S4
S4	S2 OR S3
S3	TI (adverse N3 (reaction* OR event* OR effect* OR outcome*))
S2	TI (harm* OR safety OR toxicit* OR tolerability OR problem* OR "side effect" OR iatrogenic)
S1	TI (drug* OR medicine* OR medication* OR pharmaceutical* OR pharmacotherapy OR pharmacologic*)

TI: title. TX: full-text (title, abstract, keywords, and other fields). SU: subject. N3: proximity operator (terms occur within three words of one another, direction irrelevant). *: truncation symbol.

Appendix x. Search strategy for Scopus

```
(( ( ( TITLE ( drug* OR medicine* OR medication* OR pharmaceutical* OR pharmacotherapy OR pharmacologic* ) )
AND ( ( TITLE ( harm* OR safety OR toxicit* OR tolerability OR problem* OR "side effect" OR iatrogenic ) ) OR ( TITLE (
adverse W/3 ( reaction* OR event* OR effect* OR outcome* ) ) ) ) OR ( TITLE ( "ADR" OR "ADRs" ) ) OR (
INDEXTERMS ( "adverse drug reaction" OR "drug induced disease" OR "pharmacovigilance" OR "drug fatality" OR
"drug safety" OR "drug surveillance program" OR "pharmacoepidemiology" OR "unspecified side effect" ) ) ) AND ( (
INDEXTERMS ( "hospital admission" OR "hospitalization" OR "hospital patient" OR "mortality" ) ) OR ( TITLE-ABS-KEY
( serious OR seriousness OR severe OR severity OR admission OR admitt* OR hospitaliz* OR hospitalis* OR death OR
dying OR died OR fatal* OR mortal* ) ) ) AND ( ( INDEXTERMS ( "morbidity" OR "mortality" OR "cross-sectional study"
OR "health survey" OR "medical record review" OR "population research" OR "incidence" OR "prevalence" OR
"retrospective study" OR "prospective study" OR "cohort analysis" OR "longitudinal study" OR "controlled study" ) )
OR ( TITLE-ABS-KEY ( incidence OR prevalence OR occur* OR proportion OR rate OR number OR percent OR
frequency OR epidemiology OR pharmacoepidemiology OR observational OR cohort OR prospective OR
retrospective OR cross AND sectional OR monitor* OR surveillance ) ) ) AND ( ( ( INDEXTERMS ( "Africa" OR "Africa
South of the Sahara" OR "Africa, Central" OR "Africa, Eastern" OR "Africa, Southern" OR "Africa, Western" OR "Angola"
OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Central African
Republic" OR "Chad" OR "Comoros" OR "Congo" OR "Cote d'Ivoire" OR "Ivory Coast" OR "Democratic Republic of the
Congo" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR
"Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania"
OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe"
OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR
"Swaziland" OR "eSwatini" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe" ) ) ) OR ( TITLE-
ABS-KEY ( africa OR angola OR benin OR botswana OR burkina OR volta OR burundi OR urundi OR cameroon OR
cameroons OR cameroun OR verde OR chad OR comoros OR comoro OR comores OR mayotte OR congo OR zaire
OR ivoire OR ivory OR eritrea OR ethiopia OR gabon OR gabonese OR gambia OR ghana OR guinea OR kenya OR
lesotho OR basutoland OR liberia OR madagascar OR malagasy OR malawi OR nyasaland OR mali OR mauritania
OR mauritius OR mozambique OR namibia OR niger OR nigeria OR rwanda OR ruanda OR principe OR senegal OR
seychelles OR sierra OR somalia OR sudan OR eswatini OR swaziland OR tanzania OR togo OR uganda OR zambia
OR zimbabwe OR rhodesia ) ) ) AND ( LIMIT-TO ( PUBYEAR , 2021 ) OR LIMIT-TO ( PUBYEAR , 2020 ) OR LIMIT-TO (
PUBYEAR , 2019 ) OR LIMIT-TO ( PUBYEAR , 2018 ) OR LIMIT-TO ( PUBYEAR , 2017 ) OR LIMIT-TO ( PUBYEAR , 2016 )
OR LIMIT-TO ( PUBYEAR , 2015 ) OR LIMIT-TO ( PUBYEAR , 2014 ) OR LIMIT-TO ( PUBYEAR , 2013 ) OR LIMIT-TO (
PUBYEAR , 2012 ) OR LIMIT-TO ( PUBYEAR , 2011 ) OR LIMIT-TO ( PUBYEAR , 2010 ) OR LIMIT-TO ( PUBYEAR , 2009 )
OR LIMIT-TO ( PUBYEAR , 2008 ) OR LIMIT-TO ( PUBYEAR , 2007 ) OR LIMIT-TO ( PUBYEAR , 2006 ) OR LIMIT-TO (
PUBYEAR , 2005 ) OR LIMIT-TO ( PUBYEAR , 2004 ) OR LIMIT-TO ( PUBYEAR , 2003 ) OR LIMIT-TO ( PUBYEAR , 2002 )
) ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) OR LIMIT-TO ( DOCTYPE , "no" ) OR LIMIT-TO ( DOCTYPE , "le" ) OR LIMIT-TO (
DOCTYPE , "cp" ) OR LIMIT-TO ( DOCTYPE , "sh" ) OR LIMIT-TO ( DOCTYPE , "ch" ) OR LIMIT-TO ( DOCTYPE , "cr" ) )
AND ( EXCLUDE ( EXACTKEYWORD , "Nonhuman" ) OR EXCLUDE ( EXACTKEYWORD , "Animal Experiment" ) OR
EXCLUDE ( EXACTKEYWORD , "Animal Model" ) ) ) AND NOT INDEX(medline)
```

TITLE-ABS-KEY: title, abstract, keywords. W/3: proximity operator (terms occur within three words of one another, direction irrelevant). *: truncation symbol.

Appendix xi. Search strategy for Web of Science

#	Search string
#14	Refine #13 by excluding MEDLINE
#13	LIMIT #12 to Publication years 2002-
#12	#11 AND #10 AND #9 AND #8
#11	TS=(Africa OR Angola OR Benin OR Botswana OR Burkina OR Volta OR Burundi OR Urundi OR Cameroon OR Cameroons OR Cameroun OR Verde OR Chad OR Comoros OR Comoro OR Comores OR Mayotte OR Congo OR Zaire OR Ivoire OR Ivory OR Eritrea OR Ethiopia OR Gabon OR Gabonese OR Gambia OR Ghana OR Guinea OR Kenya OR Lesotho OR Basutoland OR Liberia OR Madagascar OR Malagasy OR Malawi OR Nyasaland OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Ruanda OR Principe OR Senegal OR Seychelles OR Sierra OR Somalia OR Sudan OR eSwatini OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe OR Rhodesia)
#10	TS=(morbidity OR mortality OR epidemiology OR survey OR cohort OR "cross sectional" OR incidence OR prevalence OR proportion OR pharmacoepidemiology OR observational OR prospective OR retrospective OR monitoring)
#9	TS=(hospitalization OR admission OR mortality OR death OR fatal OR severe OR serious)
#8	#5 OR #6 OR #7
#7	TS=("postmarketing product surveillance" OR "adverse drug reaction*" OR "adverse drug event*" OR pharmacoepidemiology OR "iatrogenic disease")
#6	TI=("ADR" OR "ADRs")
#5	#1 AND #4
#4	#2 OR #3
#3	TI=(adverse NEAR/3 (reaction OR event OR effect OR outcome))
#2	TI=(harm OR safety OR toxicity OR tolerability OR problem OR "side effect*" OR iatrogenic)
#1	TI=(drug OR medicine OR medication OR pharmaceutical OR pharmacotherapy OR pharmacologic*)

TI: title search. TS: topic search *: truncation symbol.

Appendix xii. Search strategy for databases of theses and dissertations

Database	Interface	Search string
Networked Digital Library of Theses and Dissertations (NDLTD)	search.ndltd.org	(subject:"pharmacovigilance" OR subject:"pharmacoepidemiology" OR title:"adverse drug") AND (subject:"Africa" OR subject:"Sub-Saharan Africa" OR subject:"Angola" OR subject:"Benin" OR subject:"Botswana" OR subject:"Burkina Faso" OR subject:"Burundi" OR subject:"Cabo Verde" OR subject:"Cameroon" OR subject:"Central African Republic" OR subject:"Chad" OR subject:"Comoros" OR subject:"Democratic Republic of Congo" OR subject:"Republic of Congo" OR subject:"Cote d'Ivoire" OR subject:"Equatorial Guinea" OR subject:"Eritrea" OR subject:"Ethiopia" OR subject:"Gabon" OR subject:"Gambia" OR subject:"Ghana" OR subject:"Guinea" OR subject:"Guinea-Bissau" OR subject:"Kenya" OR subject:"Lesotho" OR subject:"Liberia" OR subject:"Madagascar" OR subject:"Malawi" OR subject:"Mali" OR subject:"Mauritania" OR subject:"Mauritius" OR subject:"Mozambique" OR subject:"Namibia" OR subject:"Niger" OR subject:"Nigeria" OR subject:"Rwanda" OR subject:"Sao Tome and Principe" OR subject:"Senegal" OR subject:"Seychelles" OR subject:"Sierra Leone" OR subject:"Somalia" OR subject:"South Africa" OR subject:"South Sudan" OR subject:"Sudan" OR subject:"Swaziland" OR subject:"Tanzania" OR subject:"Togo" OR subject:"Uganda" OR subject:"Zambia" OR subject:"Zimbabwe") Restrict to publication years 2002 to 2021
WorldCatDissertations	OCLC firstsearch via UCT libraries	((ti: adverse n3 drug) OR (kw: adverse n3 drug) OR kw: pharmacoepidemiology OR kw: pharmacovigilance) AND (kw: Africa OR kw: Sub-Saharan Africa OR kw: Angola OR kw: Benin OR kw: Botswana OR kw: Burkina Faso OR kw: Burundi OR kw: Cabo Verde OR kw: Cameroon OR kw: Central African Republic OR kw: Chad OR kw: Comoros OR kw: Democratic Republic of Congo OR kw: Republic of Congo OR kw: Cote d'Ivoire OR kw: Equatorial Guinea OR kw: Eritrea OR kw: Ethiopia OR kw: Gabon OR kw: Gambia OR kw: Ghana OR kw: Guinea OR kw: Guinea-Bissau OR kw: Kenya OR kw: Lesotho OR kw: Liberia OR kw: Madagascar OR kw: Malawi OR kw: Mali OR kw: Mauritania OR kw: Mauritius OR kw: Mozambique OR kw: Namibia OR kw: Niger OR kw: Nigeria OR kw: Rwanda OR kw: Sao Tome and Principe OR kw: Senegal OR kw: Seychelles OR kw: Sierra Leone OR kw: Somalia OR kw: South Africa OR kw: South Sudan OR kw: Sudan OR kw: Swaziland OR kw: Tanzania OR kw: Togo OR kw: Uganda OR kw: Zambia OR kw: Zimbabwe) AND yr: 2002-2021
ProQuest Dissertations & Theses A&I	UCT libraries	(diskw.Exact("Adverse drug event" OR "adverse side reactions" OR "Adverse side-effects" OR "Side effect" OR "Iatrogenic effects" OR "Adverse events in patients" OR "Hospital-acquired adverse events" OR "Adverse outcome" OR "Adverse drug events" OR "Adverse drug reaction(adr)" OR "Adverse drug safety" OR "Drug Safety" OR "Side effects (treatment)" OR "Metabolic adverse events" OR "Iatrogenic" OR "Iatrogenic harm" OR "Drug side effect" OR "Adverse outcomes" OR "Iatrogenic disease" OR "Drug related problems" OR "Adverse drug reactions" OR "Side-effect" OR "Rare adverse drug effects" OR "Adverse drug event detection" OR "Drug-related deaths" OR "Drug-related death" OR "Preventable adverse events" OR "Adverse Effects" OR "Adverse event reaction" OR "ADR" OR "Adverse side effects" OR "Severe adverse event" OR "Adverse effect" OR "Adr reporting systems" OR "Adverse event" OR "Adverse Drug Reaction" OR "Drugs side effect" OR "Adverse Event Reporting System" OR "Side-effect effect" OR "Adverse events" OR "Side effects") OR ALL(pharmacoepidemiology OR pharmacovigilance OR "adverse drug")) AND LOC("Africa" OR "Sub-Saharan Africa" OR "Angola" OR

		"Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cabo Verde" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Democratic Republic of Congo" OR "Republic of Congo" OR "Cote d'Ivoire" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe") AND (PD(2002) OR PD(2003) OR PD(2004) OR PD(2005) OR PD(2006) OR PD(2007) OR PD(2008) OR PD(2009) PD(2010) OR PD(2011) OR PD(2012) OR PD(2013) OR PD(2014) OR PD(2015) OR PD(2016) OR PD(2017) OR PD(2018) OR PD(2019) OR PD(2020) OR PD(2021))
Openthesis	www.openthesis.org	((TI("adverse") AND TI("drug")) OR (IF("adverse") AND IF("drug")) OR IF("pharmacoepidemiology") OR IF("pharmacovigilance")) AND (IF("Africa") OR IF("Sub-Saharan Africa") OR IF("Angola") OR IF("Benin") OR IF("Botswana") OR IF("Burkina Faso") OR IF("Burundi") OR IF("Cabo Verde") OR IF("Cameroon") OR IF("Central African Republic") OR IF("Chad") OR IF("Comoros") OR IF("Democratic Republic of Congo") OR IF("Republic of Congo") OR IF("Cote d'Ivoire") OR IF("Equatorial Guinea") OR IF("Eritrea") OR IF("Ethiopia") OR IF("Gabon") OR IF("Gambia") OR IF("Ghana") OR IF("Guinea") OR IF("Guinea-Bissau") OR IF("Kenya") OR IF("Lesotho") OR IF("Liberia") OR IF("Madagascar") OR IF("Malawi") OR IF("Mali") OR IF("Mauritania") OR IF("Mauritius") OR IF("Mozambique") OR IF("Namibia") OR IF("Niger") OR IF("Nigeria") OR IF("Rwanda") OR IF("Sao Tome and Principe") OR IF("Senegal") OR IF("Seychelles") OR IF("Sierra Leone") OR IF("Somalia") OR IF("South Africa") OR IF("South Sudan") OR IF("Sudan") OR IF("Swaziland") OR IF("Tanzania") OR IF("Togo") OR IF("Uganda") OR IF("Zambia") OR IF("Zimbabwe"))
Open Access Theses and Dissertations	oatd.org	title:((adverse AND drug) OR subject:(adverse AND drug) OR subject:(pharmacoepidemiology OR pharmacovigilance)) AND (subject: (Africa OR "Sub-Saharan Africa" OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR "Central African Republic" OR Chad OR Comoros OR "Democratic Republic of Congo" OR "Republic of Congo" OR "Cote d'Ivoire" OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR "Sao Tome and Principe" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR "South Sudan" OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe))

Appendix xiii. Data extraction form

1. **Study ID and inclusion criteria:**
 - a. First author surname: _____
 - b. Year of publication: _____
 - c. Completeness: Abstract only | Full-text
 - d. Does this study contain:
 - i. Data on admissions due to ADRs: Yes | No – if yes, complete sections 2, 3, and 4.
 - ii. Data on prolongation of hospitalisation due to ADRs: Yes | No – if yes, complete sections 2, 3, and 5.
 - iii. Data on in-hospital deaths due to ADRs: Yes | No – if yes, complete section 2, 3, and 6.
2. **Survey setting and population (complete in all cases):**
 - a. Country (if not stated, then corresponding author address determines): _____
 - b. Year of data collection: _____ | not stated
 - c. Number of hospitals: Single-centre | multicentre
 - d. Hospital(s) surveyed: Primary only (= "community") | Secondary / tertiary (= "teaching" / "university" / "specialist" / "referral" / "regional") / mixture | not stated
 - e. Wards surveyed:
 - i. Medical wards n.o.s.: Yes | No | not stated
 - ii. Medical speciality wards: No | not stated | Yes, specify: _____ (e.g. cardiology / nephrology / neurology)
 - iii. ICU: Yes | No | not stated
 - iv. Oncology: Yes | No | not stated
 - v. Surgical wards: Yes | No | not stated
 - vi. Paediatric wards: Yes | No | not stated
 - vii. Geriatric wards: Yes | No | not stated
 - f. Patients surveyed:
 - i. All pts | Random sample of pts | Non-randomised sample (describe) _____
 - ii. Did original authors have any specific exclusions in their survey? If yes, describe: _____
 - iii. Proportion of potentially identified patients excluded from the survey: _____
 - g. Duration of survey: _____ | not stated
3. **Study methodology (complete in all cases):**
 - a. ADE identification: Spontaneous reporting | Stimulated spontaneous reporting | Automated (computerised) EMR / labs surveillance | Active (human) surveillance | not stated or unclear
 - b. If Active surveillance:
 - i. Surveillance team: single investigator | unidisciplinary team | multidisciplinary team | not stated or unclear
 - ii. Surveillance source material: folder review only (including review of lab results) | folder review and additional methods (e.g. spontaneous reports / pt interview etc.) | not stated or unclear
 - iii. Surveillance orientation: Prospective | Retrospective | not stated or unclear
 - c. ADR determination:
 - i. Was an ADR determination (= causality assessment) done? Yes | No | not stated or unclear
 - ii. ADR definition used: WHO | Aronson | not stated | other: _____
 - iii. Regardless of claimed definition, do the authors include any of the following as an ADR?
 1. Adverse reactions to herbal / traditional medicines: Yes | No | unclear or not stated
 2. accidental overdose: Yes | No | unclear or not stated
 3. intentional overdose: Yes | No | unclear or not stated
 4. non-compliance: Yes | No | unclear or not stated
 5. drug abuse: Yes | No | unclear or not stated
 6. medication error: Yes | No | unclear or not stated
 7. therapeutic failure: Yes | No | unclear or not stated
 - iv. What evidence available to make ADR determination on? Spontaneous report ("Yellow card") | Summary of case notes (incl lab results) | Full case notes (= that which was available to clinical team) | Full case notes and additionally sourced evidence not available to clinical team, such as primary care records | not stated or unclear
 - v. Causality assessment:

1. Causality assessment by whom? single investigator unidisciplinary team multidisciplinary team not stated or unclear 2. Causality assessment done by same team as ADE identification team? Yes No not stated or unclear 3. Which tool? WHO-UMC Naranjo not stated or unclear other _____ 4. Which causality levels were included as ADRs? Only definite and probable Definite, probable, and possible Other _____ d. Seriousness determination: i. Done? Yes, formal seriousness determination done No, seriousness implied as study only reports on ADE/ADR <i>causing</i> admission/prolongation/death ii. Seriousness assessment by whom? single investigator unidisciplinary team multidisciplinary team not stated or unclear iii. Seriousness assessment done by same team as ADE identification team? Yes No not stated or unclear iv. Which tool? Hartwig not stated or unclear other _____ e. Preventability determination: i. Done? Yes No ii. Preventability assessment by whom? single investigator unidisciplinary team multidisciplinary team not stated or unclear iii. Preventability assessment done by same team as ADE identification team? Yes No not stated or unclear iv. Which tool? Schumock Hallas not stated or unclear other _____ 4. ADR-RELATED ADMISSIONS – Survey findings: a. Denominator: i. No. of patients ____ and/or No. of admissions ____ and/or No. of patients on drugs ____ and/or No. of admissions on drugs ____ ii. Age of patients in the denominator: mean ____ and/or median ____ and/or IQR ____ and/or range ____ iii. Proportion of denominator female: ____ iv. Proportion of denominator HIV-infected: ____ v. Other characteristics of the patients in the denominator (notable morbidity, specific exclusions, etc.): _____ b. Numerator: i. No of patients with ADR-related admission ____ and/or No. of admissions that are ADR-related ____ (note this is not ADRs present on admission, but ADRs implied as reason for admission) ii. No of patients with preventable ADR-related admission: ____ and/or No. of admissions that are related to preventable ADRs: ____ not stated iii. Does the study mention the most common clinical presentations of ADRs resulting in admission? Yes No. If yes, list up to top-5, with frequencies: _____ iv. Does the study mention the most common drugs implicated in ADR-related admission? Yes No. If yes, list up to top-5, with frequencies: _____ v. Does the study mention the most common drug classes implicated in ADR-related admissions? Yes No. If yes, list up to top-5, with frequencies: _____ vi. Other notable characteristics of the patients in the numerator, if mentioned (for example, HIV status): _____ 5. ADR-RELATED PROLONGATION OF HOSPITAL STAY – Survey findings: a. Denominator: i. No. of patients ____ and/or No. of admissions ____ and/or No. of patients on drugs ____ and/or No. of admissions on drugs ____ ii. Age of patients in the denominator: mean ____ and/or median ____ and/or IQR ____ and/or range ____ iii. Proportion of denominator female: ____ iv. Other characteristics of patients in the denominator (notable morbidity, specific exclusions, etc.): _____ b. Numerator: i. No of patients with ADR-related prolongation of hospital stay ____ and/or No. of admissions prolonged by ADR ____

- ii. No of **patients with preventable ADR-related prolongation of stay**: ____ and/or **No. of admissions prolonged by ADRs that were preventable**: ____ | not stated
- iii. Does the study mention the **most common clinical presentations** of ADRs resulting in prolongation of stay? Yes | No. If yes, list up to top-5, with frequencies: _____
- iv. Does the study mention the **most common drugs** implicated in ADR-related prolongation of stay? Yes | No. If yes, list up to top-5, with frequencies: _____
- v. Does the study mention the **most common drug classes** implicated in ADR-related admissions? Yes | No. If yes, list up to top-5, with frequencies: _____
- vi. **Other notable characteristics** of the patients in the numerator, if mentioned (for example, HIV status): _____

6. ADR-RELATED DEATHS – Survey findings:

- a. **Denominator**: No of in-hospital deaths: _____
- b. **Numerator**: No of in-hospital deaths that were ADR-related: _____
- c. **Numerator**: No of in-hospital deaths that were attributed to **preventable** ADRs: _____
- d. Does the study mention the **most common clinical presentations** of ADRs resulting in in-hospital death? Yes | No. If yes, list up to top-5, with frequencies: _____
- e. Does the study mention the **most common drugs** implicated in ADR-related in-hospital death? Yes | No. If yes, list up to top-5, with frequencies: _____
- f. Does the study mention the **most common drug classes** implicated in ADR-related admissions? Yes | No. If yes, list up to top-5, with frequencies: _____
- g. **Other notable characteristics** of the patients in the numerator, if mentioned (for example, HIV status): _____

Appendix xiv. Studies excluded on full-text review, with reason for exclusion

Not in sub-Saharan Africa

1. Iyer, K., et al., *Comparison of Drug Related Problems Associated with Use of Narrow Therapeutic Index Drugs and Other Drugs in Hospitalized Patients*. Journal of Young Pharmacists, 2018. **10**(3):318-321.
2. McClead, R.E., Jr., et al., *An internal quality improvement collaborative significantly reduces hospital-wide medication error related adverse drug events*. J Pediatr, 2014. **165**(6):1222-1229.

Not primary research

3. Blockman, M., *Adverse drug reactions - an update*. CME, 2009. **27**(2):80-83.
4. Mekonnen, A.B., et al., *Adverse Drug Events and Medication Errors in African Hospitals: A Systematic Review*. Drugs Real World Outcomes, 2018. **5**(1):1-24.

Not in a hospital

5. Elhadji, B.A.K., et al., *A surveillance system to measure childhood mortality and drug related adverse events in three districts in Senegal*, in *American Society of Tropical Medicine and Hygiene 59th Annual Meeting*. 2010, American Journal of Tropical Medicine and Hygiene: Atlanta. p. 361.

Not in unselected patients

6. Abrogoua, D.P., et al., *Pharmaceutical interventions in the management of tuberculosis in a pneumophthisiology department, Ivory Coast*. Ther Clin Risk Manag, 2016. **12**:1749-1756.
7. Bekele, F., et al., *Drug-related problems among patients with infectious disease admitted to medical wards of Wollega University Referral Hospital: Prospective observational study*. SAGE Open Med, 2021. **9**:2050312121989625.

Emergency unit presentations

8. Kamagaté M., Die-Kacou H., Yavo J.-C., et al. *Impact pharmacoeconomic of avoidable adverse drug reactions in emergencies*. Abstract presented at Congrès de Physiologie, de Pharmacologie, et de Thérapeutique, 23 to 25 March 2010, Bordeaux. Fundam Clin Pharmacol, 2010. **24**:92.
9. Mouton, J.P., et al., *Adult medical emergency unit presentations due to adverse drug reactions in a setting of high HIV prevalence*. Afr J Emerg Med, 2021. **11**(1):46-52.
10. Tipping, B., et al., *The burden and risk factors for adverse drug events in older patients - a prospective cross-sectional study*. South African Medical Journal, 2006. **96**(12): 1255-1259.

No disaggregated numerator

11. Ahmed, S.M., et al., *Medication-related problems among hospitalized pregnant women in a tertiary teaching hospital in Ethiopia: a prospective observational study*. BMC Pregnancy Childbirth, 2020. **20**(1):737.
12. Belayneh, Y.M., G. Amberbir, and A. Agalu, *A prospective observational study of drug therapy problems in medical ward of a referral hospital in northeast Ethiopia*. BMC Health Serv Res, 2018. **18**(1):808.
13. Birarra, M.K., T.B. Heye, and W. Shibeshi, *Assessment of drug-related problems in pediatric ward of Zewditu Memorial Referral Hospital, Addis Ababa, Ethiopia*. Int J Clin Pharm, 2017. **39**(5):1039-1046.
14. Bizuneh, G.K., et al., *A Prospective Observational Study of Drug Therapy Problems in Pediatric Ward of a Referral Hospital, Northeastern Ethiopia*. Int J Pediatr, 2020. **2020**:4323189.
15. Dedefo, M.G., A.H. Mitike, and M.T. Angamo, *Incidence and determinants of medication errors and adverse drug events among hospitalized children in West Ethiopia*. BMC Pediatr, 2016. **16**:81.
16. Eshetie, T.C., et al., *Adverse drug events in hospitalized children at Ethiopian University Hospital: a prospective observational study*. BMC Pediatr, 2015. **15**:83.
17. Eze, U.I.H., C.A. Oparah, and F.A. Lawal, *Identification of Drug Therapy Problems among Elderly in-patients of a Nigerian Teaching Hospital*. Nigerian Journal of Pharmaceutical Research, 2011. **9**(1):49-56.
18. Hailu, B.Y., et al., *Drug related problems in admitted geriatric patients: the impact of clinical pharmacist interventions*. BMC Geriatr, 2020. **20**(1):13.
19. Gokhul, A., P.M. Jeena, and A. Gray, *Iatrogenic medication errors in a paediatric intensive care unit in Durban, South Africa*. S Afr Med J, 2016. **106**(12):1222-1229.
20. Kiguba, R., C. Karamagi, and S.M. Bird, *Incidence, risk factors and risk prediction of hospital-acquired suspected adverse drug reactions: a prospective cohort of Ugandan inpatients*. BMJ Open, 2017. **7**(1):e010568.
21. Matsaseng, T. and J. Moodley, *Adverse events in gynaecology at King Edward VIII Hospital, Durban, South Africa*. J Obstet Gynaecol, 2005. **25**(7):676-80.

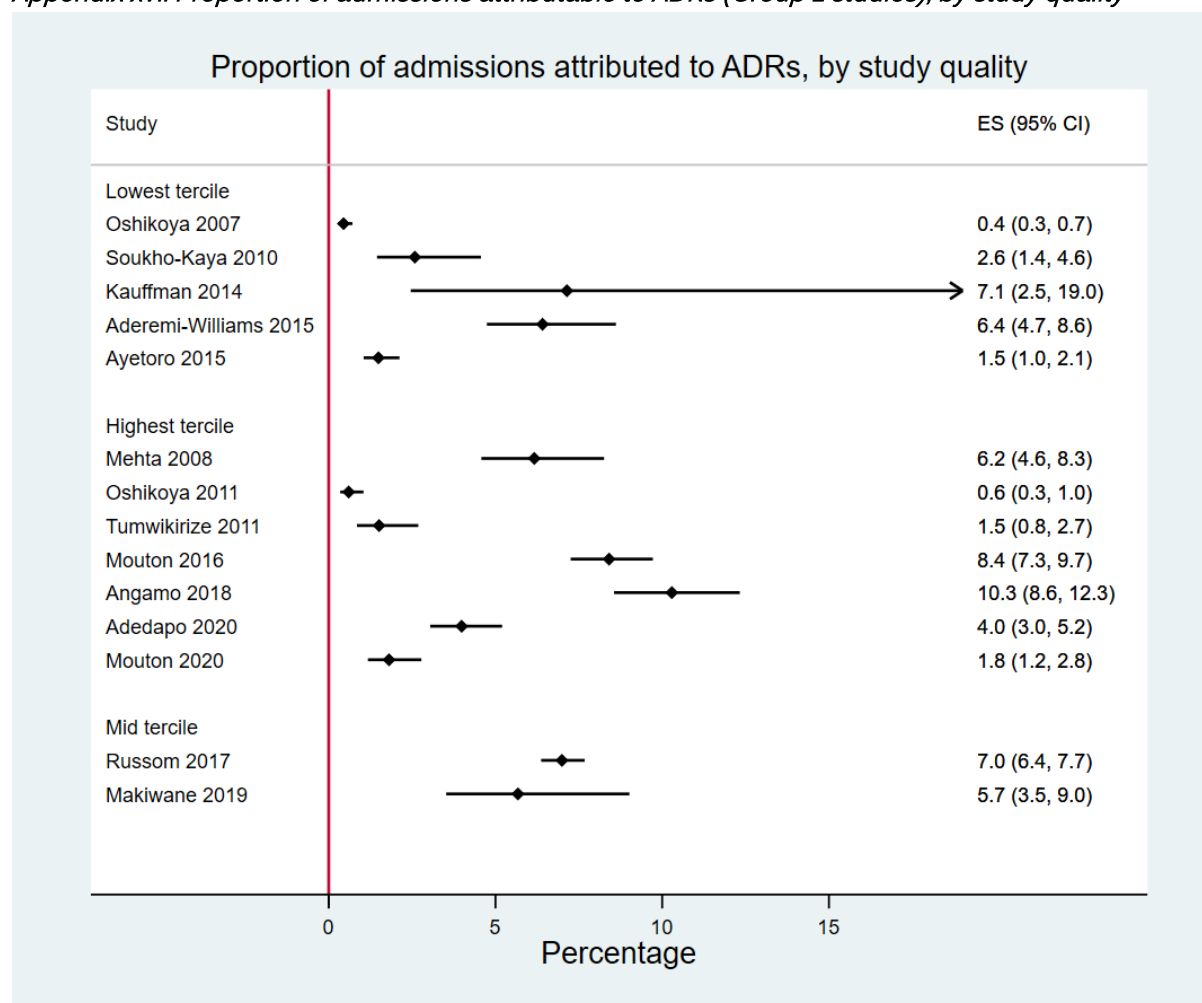
22. Müller, M., A. Gous, and N. Schellack, *Measuring adverse events using a trigger tool in a paper based patient information system at a teaching hospital in South Africa*. European Journal of Clinical Pharmacy, 2016. **18**(2):103-110.
23. Sahilu, T., et al., *Adverse Drug Events and Contributing Factors Among Hospitalized Adult Patients at Jimma Medical Center, Southwest Ethiopia: A Prospective Observational Study*. Curr Ther Res Clin Exp, 2020. **93**:100611.
24. Saka, S.A., M. Nlooto, and F. Oosthuizen, *American Geriatrics Society-Beers Criteria and adverse drug reactions: a comparative cross-sectional study of Nigerian and South African older inpatients*. Clin Interv Aging, 2018. **13**:2375-2387.
25. Tigabu, B.M., D. Daba, and B. Habte, *Drug-related problems among medical ward patients in Jimma university specialized hospital, Southwest Ethiopia*. J Res Pharm Pract, 2014. **3**(1):1-5.
26. Zeleke, A., T. Chanie, and M. Woldie, *Medication prescribing errors and associated factors at the pediatric wards of Dessie Referral Hospital, Northeast Ethiopia*. Int Arch Med, 2014. **7**:18.

Appendix xv. Studies reporting the proportion of admissions attributed to ADRs (Group 1 studies): heterogeneity and summary proportion, by subgroups

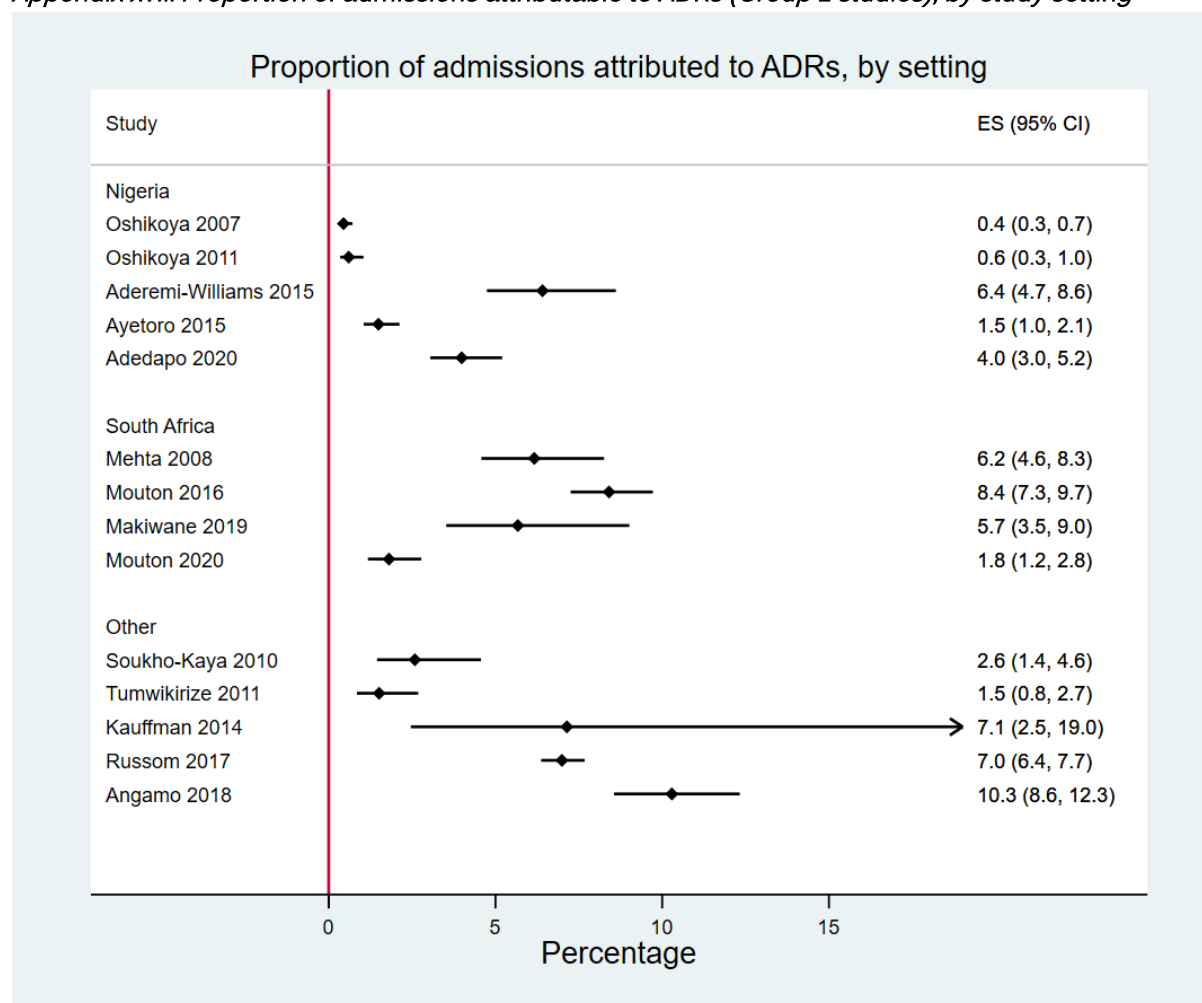
	Number of studies	I ²	Proportion of admissions attributed to ADRs (median [IQR])
Overall	14	98.2%	4.8% [1.5% to 7.0%]
Study quality			
Lowest tercile	5	95.7%	2.6% [1.5% to 6.4%]
Mid tercile	2	-	6.3% [5.7% to 7.0%]
Highest tercile	7	97.9%	4.0% [1.5% to 8.4%]
Setting			
Nigeria	5	97.0%	1.5% [0.6% to 4.0%]
South Africa	4	95.5%	5.9% [3.7% to 7.3%]
Other	5	95.4%	7.0% [2.6% to 7.1%]
Year of data collection			
2006 or earlier	4	96.5%	2.0% [1.0% to 4.4%]
2007 to 2012	3	-	6.4% [0.6% to 7.1%]
2013 or later	7	97.4%	5.7% [1.8% to 8.4%]
Single centre vs multicentre studies			
Single centre	10	97.5%	4.8% [1.5% to 6.4%]
Multicentre	4	97.5%	4.4% [1.7% to 7.7%]
Inclusion of ICU			
Included	2	-	5.1% [1.8% to 8.4%]
Excluded or not reported	12	98.2%	4.8% [1.5% to 6.7%]
Age groups (as reported)			
Children	4	93.4%	1.2% [0.5% to 3.7%]
Adults	9	96.1%	6.2% [2.6% to 7.1%]
Adults and children	1	-	7.0% [7.0% to 7.0%]
Age groups (splitting the dataset of Russom 2017)			
Children	5	97.6%	1.8% [0.6% to 4.7%]
Adults	10	96.6%	6.3% [2.6% to 8.4%]
Study duration			
≤1 month	2	-	5.1% [1.8% to 8.4%]
>1 month to ≤6 months	5	92.4%	6.2% [5.7% to 7.0%]
>6 months	7	98.0%	2.6% [0.6% to 6.4%]
ADR definition used			
WHO	9	98.3%	5.7% [2.6% to 6.4%]
Aronson & Ferner / Edwards & Aronson	3	-	1.8% [0.6% to 8.4%]
Not reported	2	-	4.3% [1.5% to 7.1%]
Detection method			
Active surveillance	13	98.2%	5.7% [1.8% to 7.0%]
Spontaneous reporting	1	-	1.5% [1.5% to 1.5%]
Surveillance orientation (if active surveillance, n = 13)			
Prospective	9	97.6%	5.7% [2.6% to 7.0%]
Retrospective	2	-	6.8% [6.4% to 7.1%]
Pro- and retrospective	2	-	1.1% [0.4% to 1.8%]
Surveillance team (if active surveillance, n = 13)			
Single investigator	2	-	8.0% [5.7% to 10.3%]
Multidisciplinary team	7	99.0%	1.8% [0.6% to 7.0%]
Not reported	4	71.3%	5.2% [3.3% to 6.8%]
Review methods (if active surveillance, n = 13)			
Folder review alone	9	93.9%	6.2% [2.6% to 7.0%]
Folder review augmented by other methods	4	98.9%	2.3% [0.5% to 7.1%]
Causality assessment method			
Naranjo	5	94.5%	7.0% [5.7% to 7.1%]

WHO-UMC	4	95.9%	5.1% [2.9% to 7.3%]
Other methods	3	-	0.6% [0.4% to 2.6%]
Not reported or not done	2	-	4.0% [1.5% to 6.4%]
Causal categories included in numerator			
Definite, probable, and possible	9	98.4%	5.7% [1.8% to 7.0%]
Definite and probable	2	-	6.4% [2.6% to 10.3%]
Not reported	1	-	0.6% [0.6% to 0.6%]

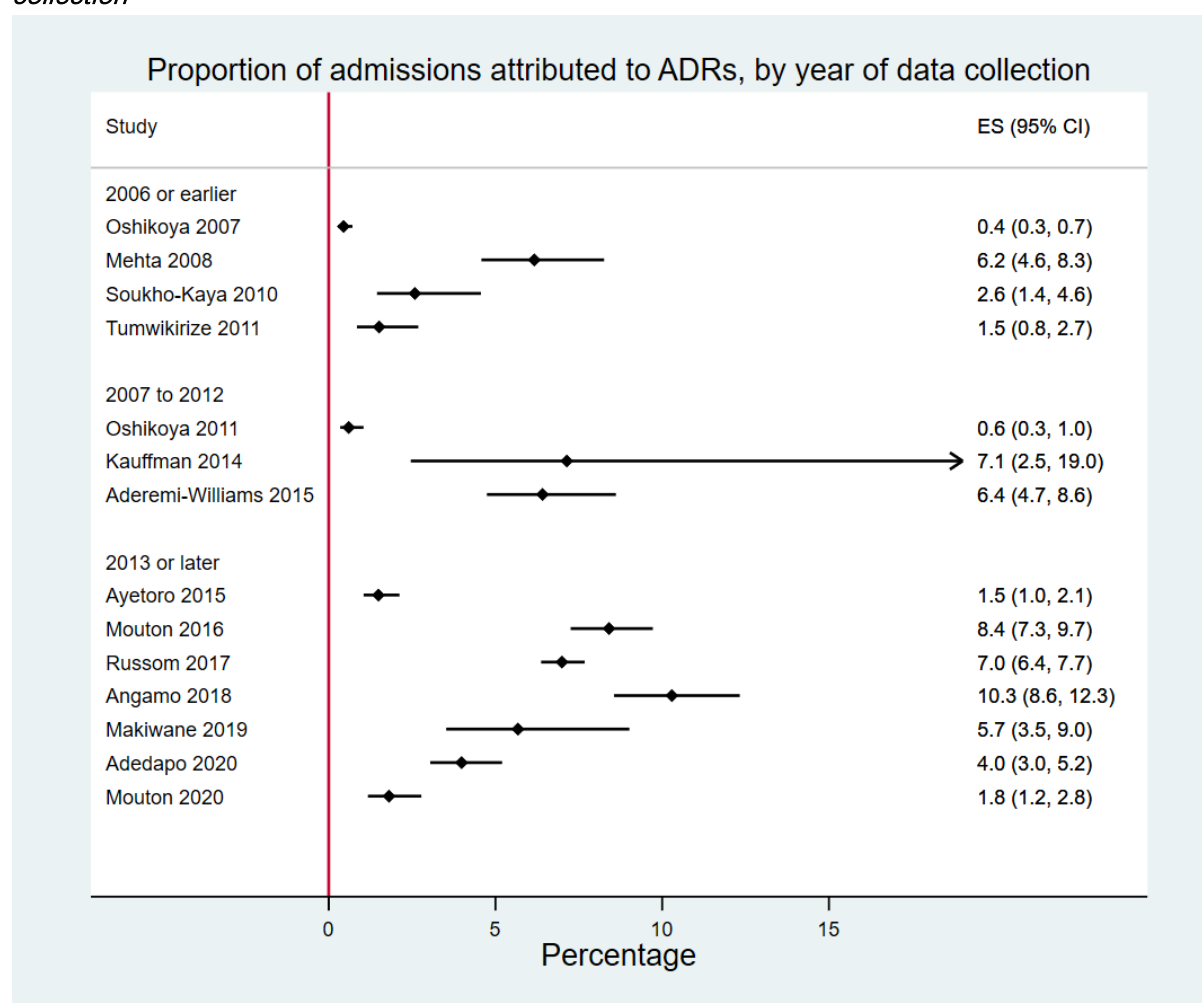
Appendix xvi. Proportion of admissions attributable to ADRs (Group 1 studies), by study quality



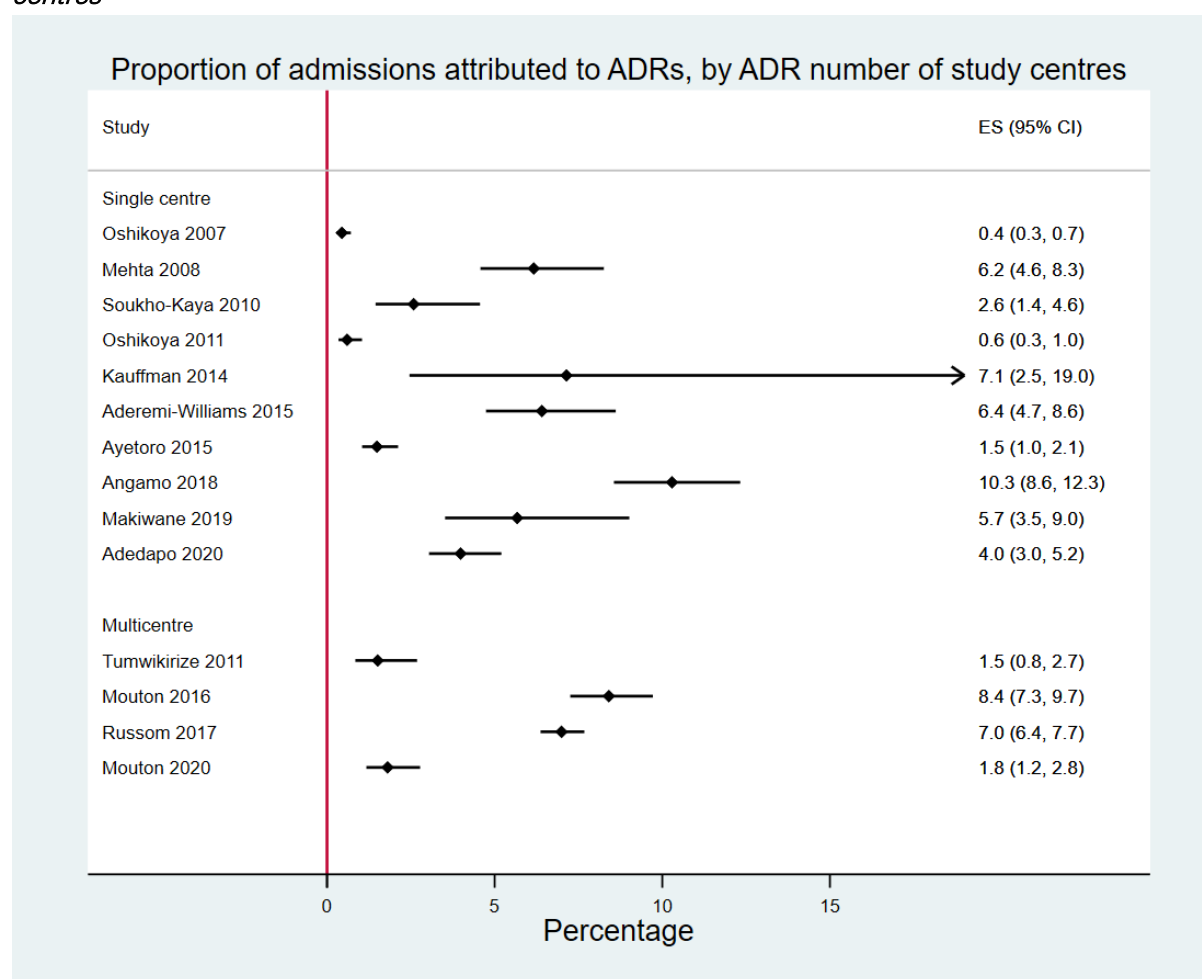
Appendix xvii. Proportion of admissions attributable to ADRs (Group 1 studies), by study setting



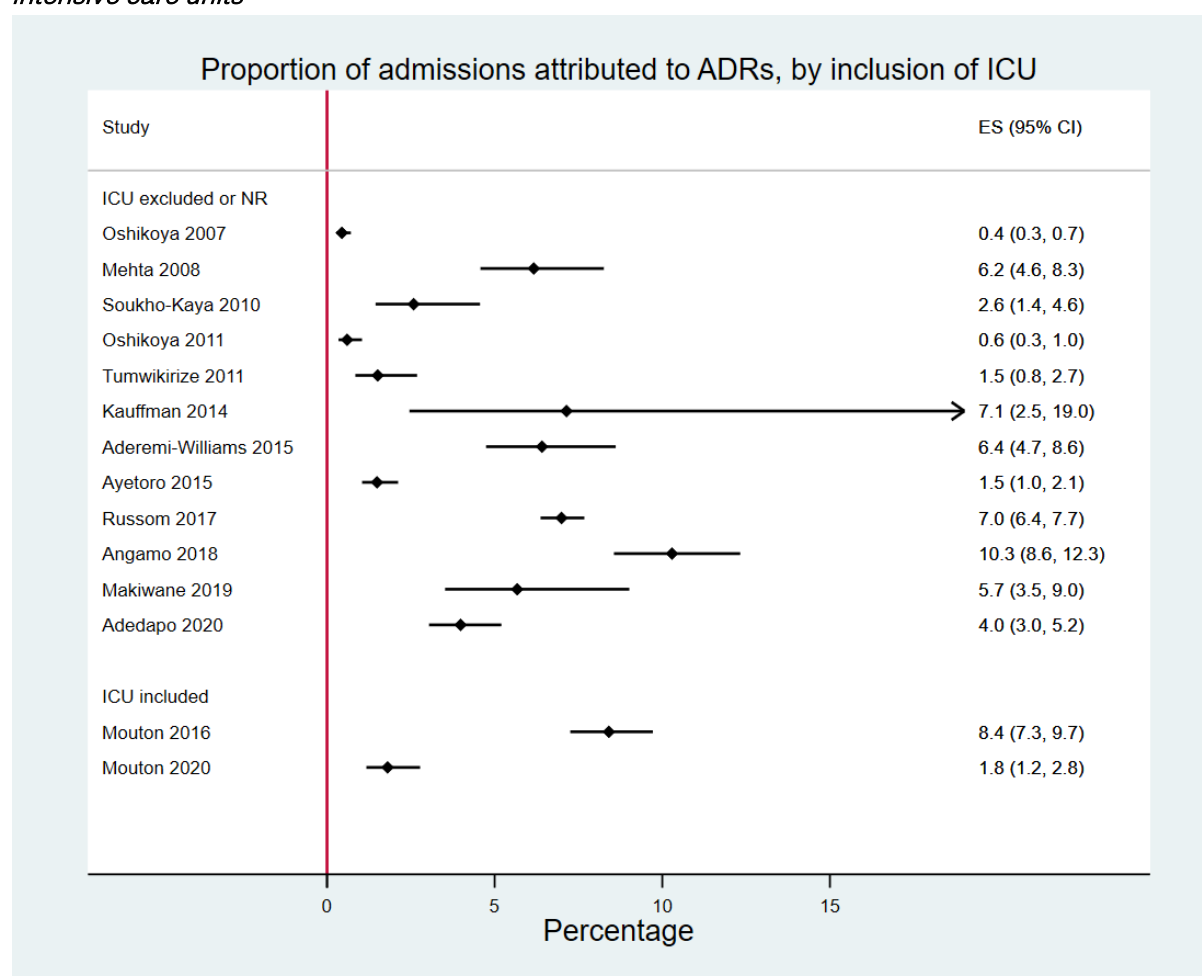
Appendix xviii. Proportion of admissions attributable to ADRs (Group 1 studies), by year of data collection



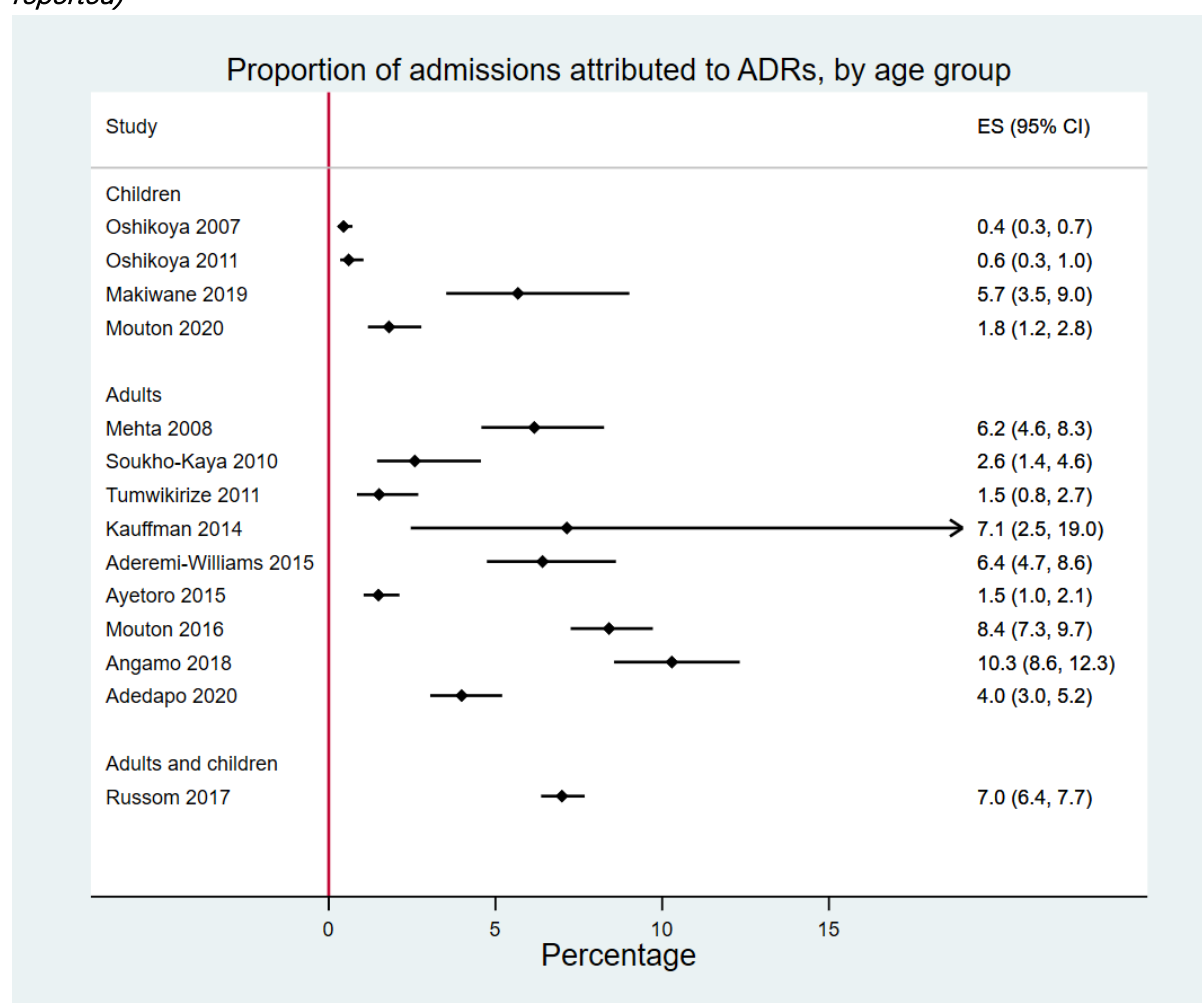
Appendix xix. Proportion of admissions attributable to ADRs (Group 1 studies), by number of study centres



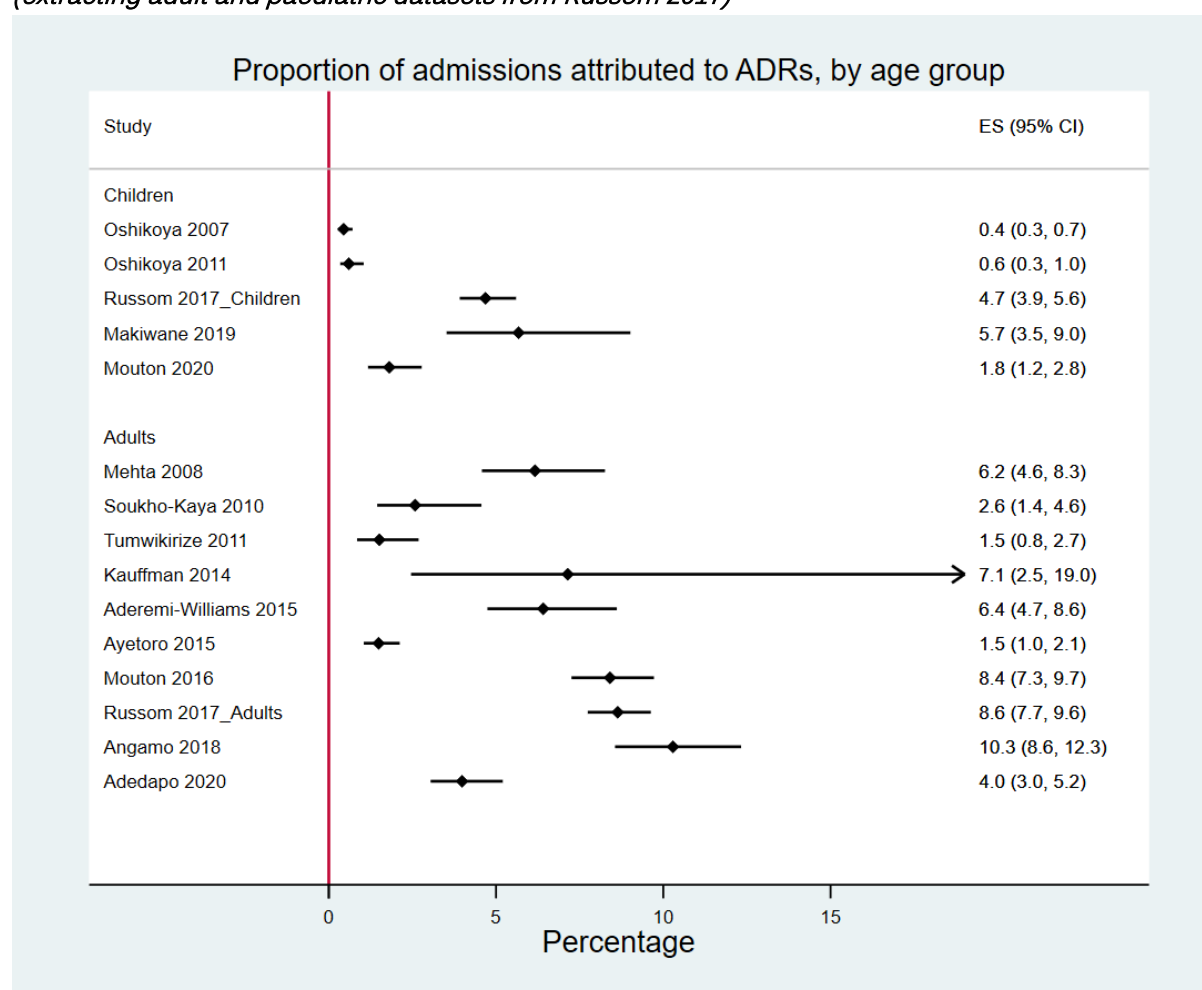
Appendix xx. Proportion of admissions attributable to ADRs (Group 1 studies), by inclusion of intensive care units



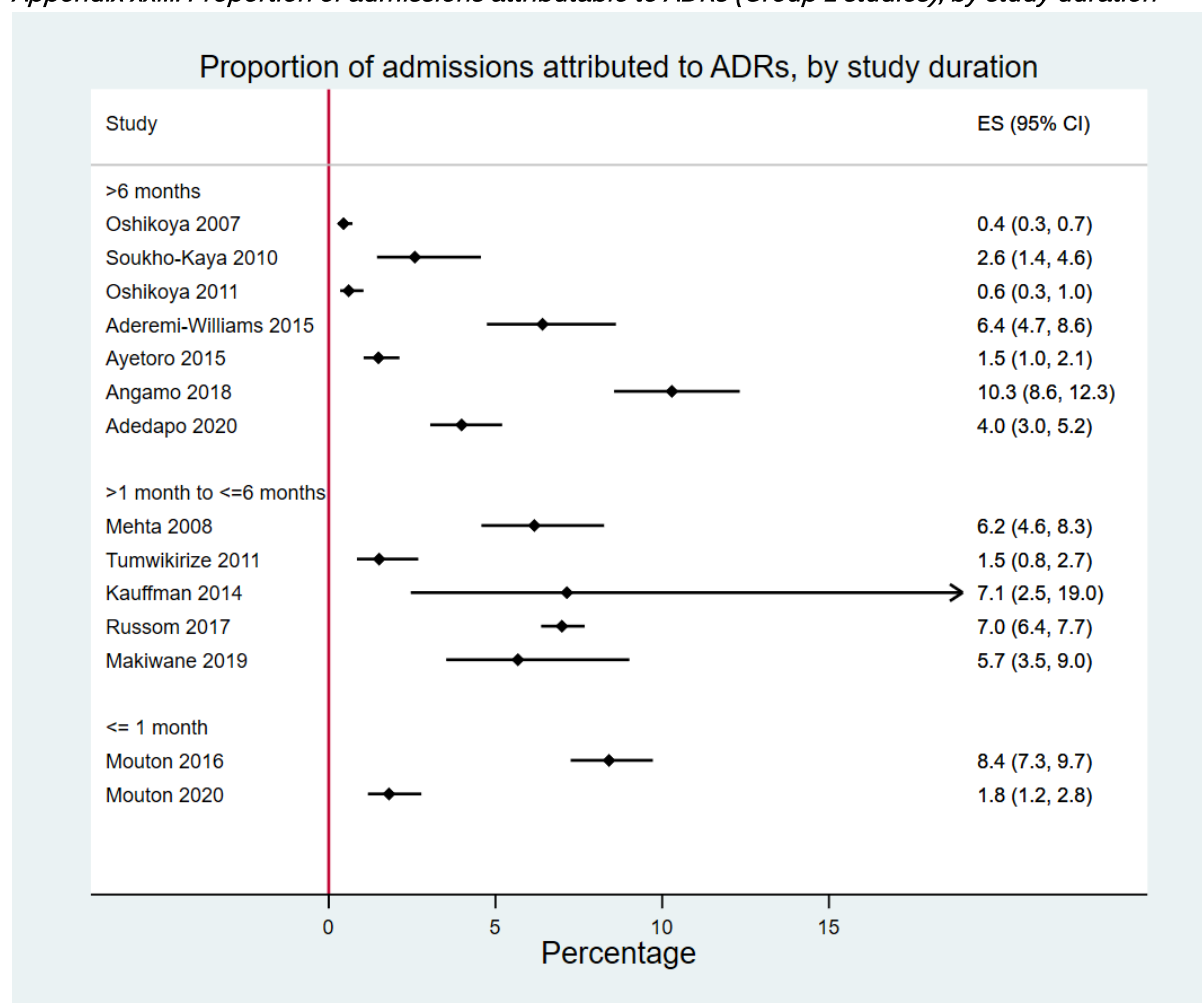
Appendix xxi. Proportion of admissions attributable to ADRs (Group 1 studies), by age groups (as reported)

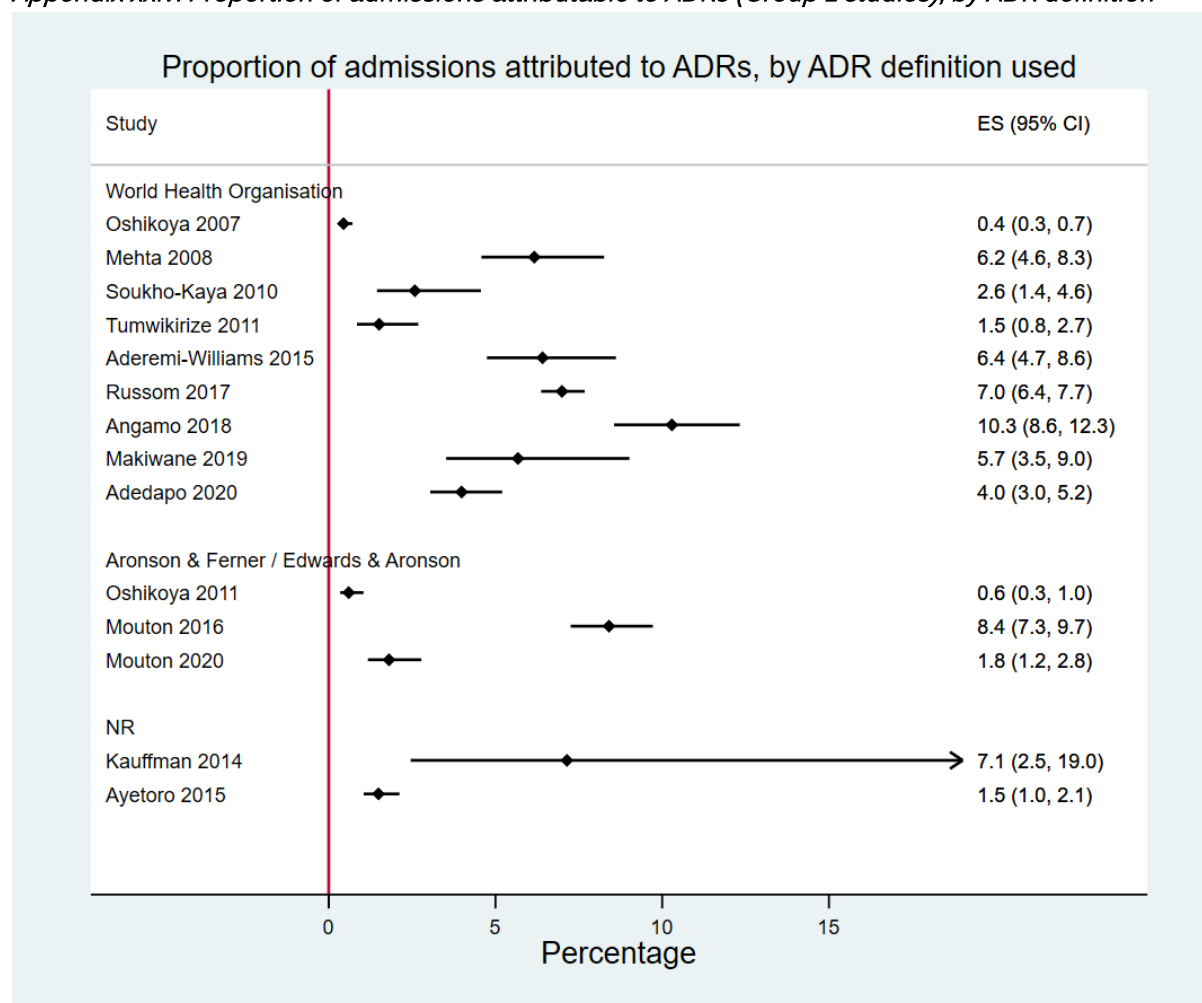


Appendix xxii. Proportion of admissions attributable to ADRs (Group 1 studies), by age groups (extracting adult and paediatric datasets from Russom 2017)

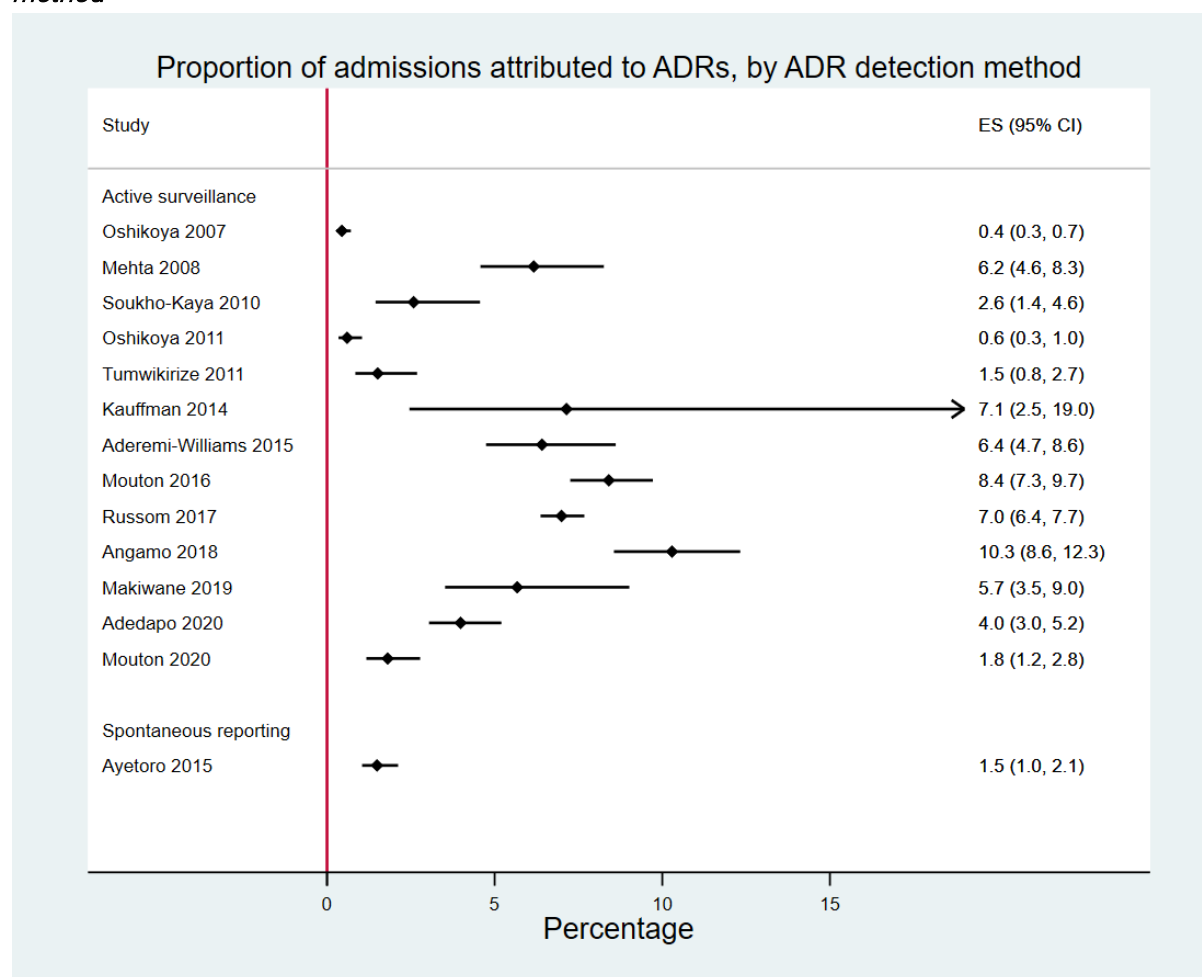


Appendix xxiii. Proportion of admissions attributable to ADRs (Group 1 studies), by study duration

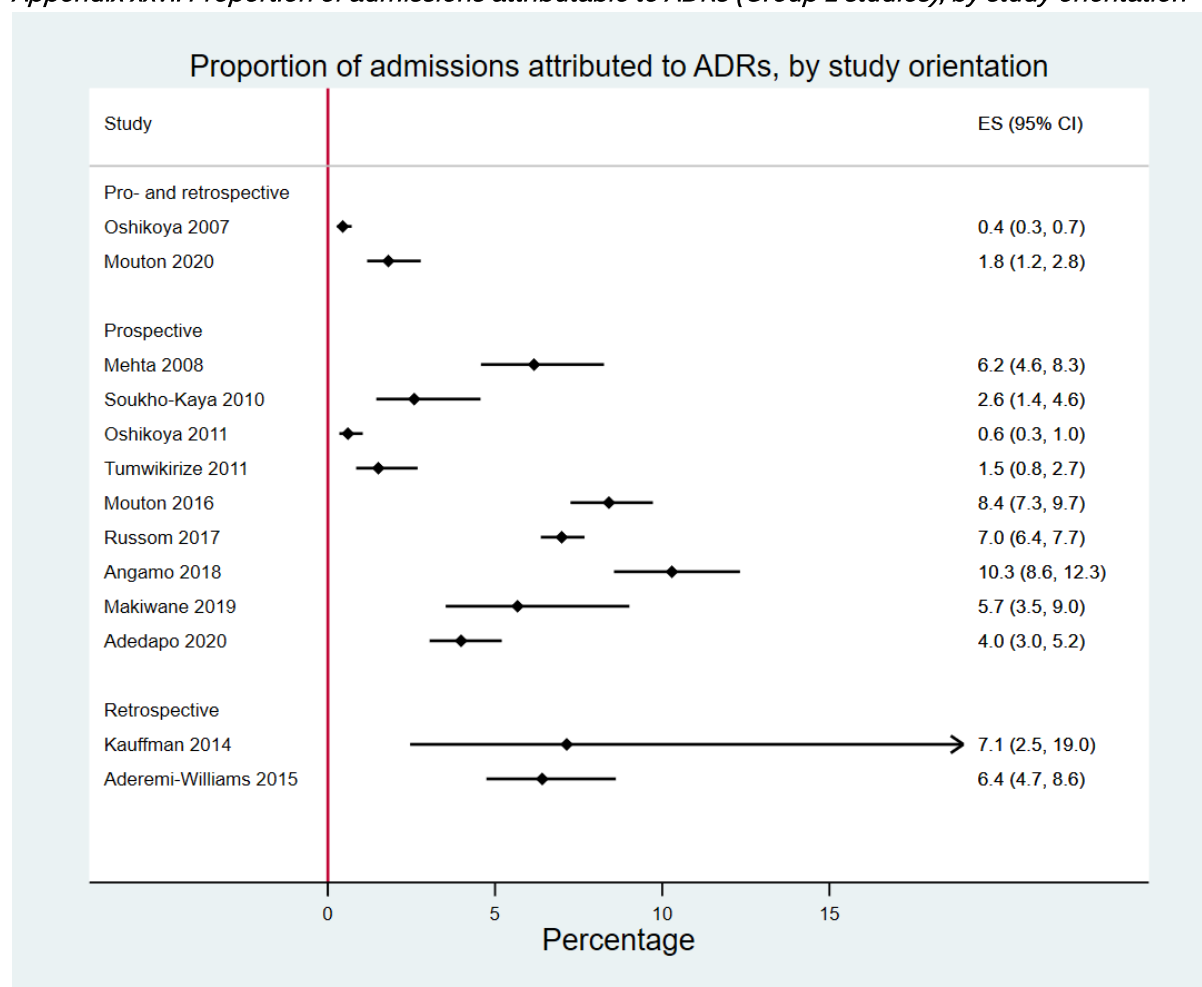




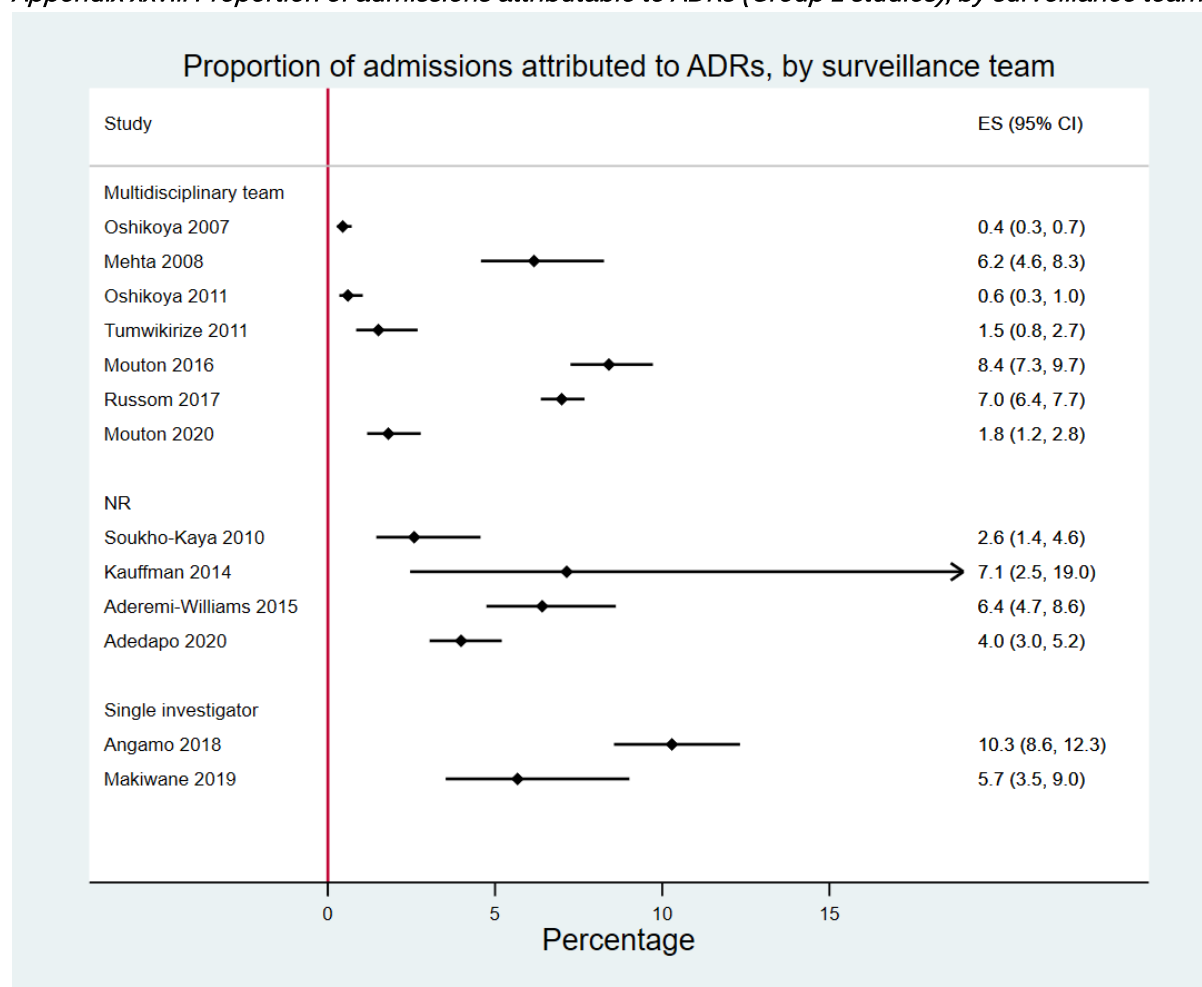
Appendix xxv. Proportion of admissions attributable to ADRs (Group 1 studies), by ADR detection method



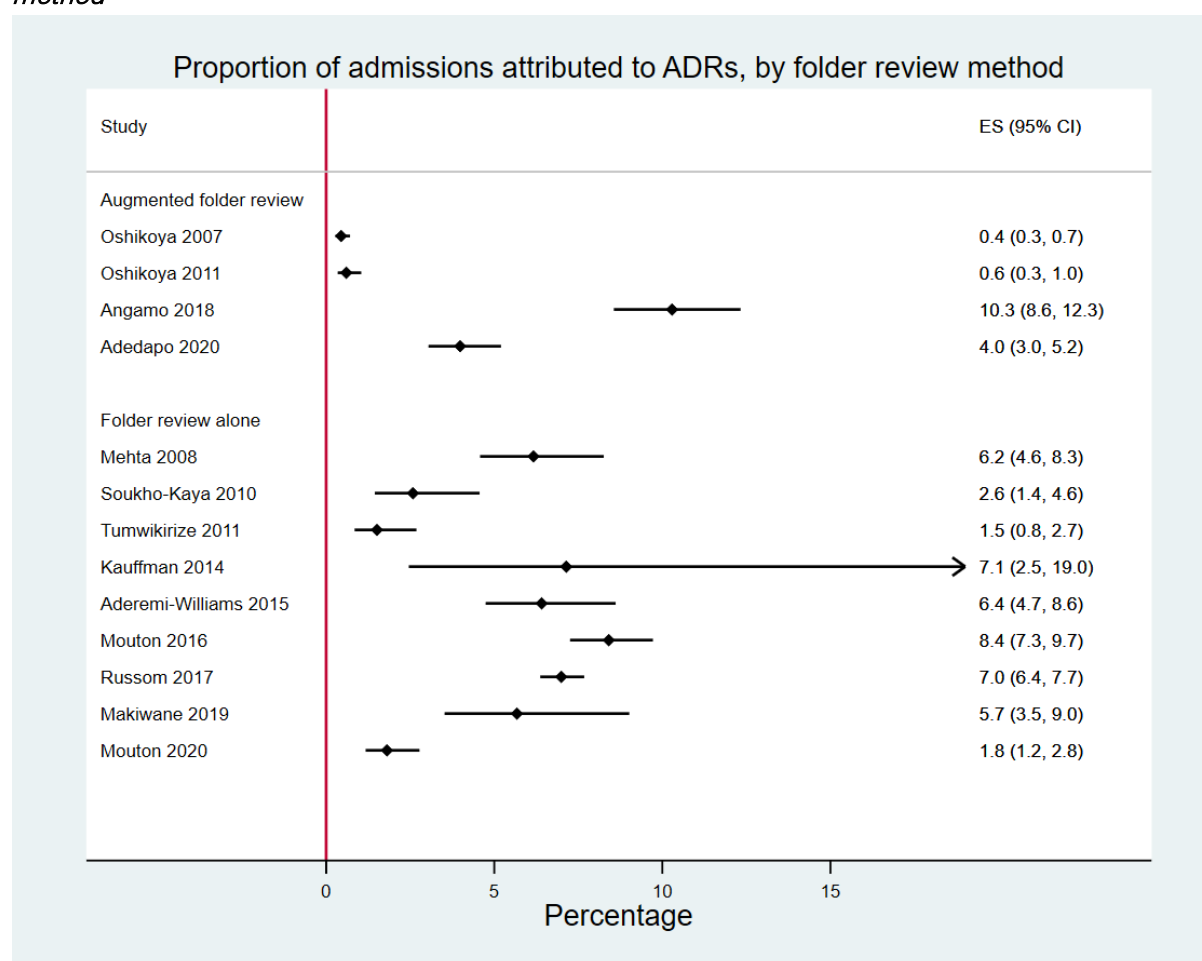
Appendix xxvi. Proportion of admissions attributable to ADRs (Group 1 studies), by study orientation



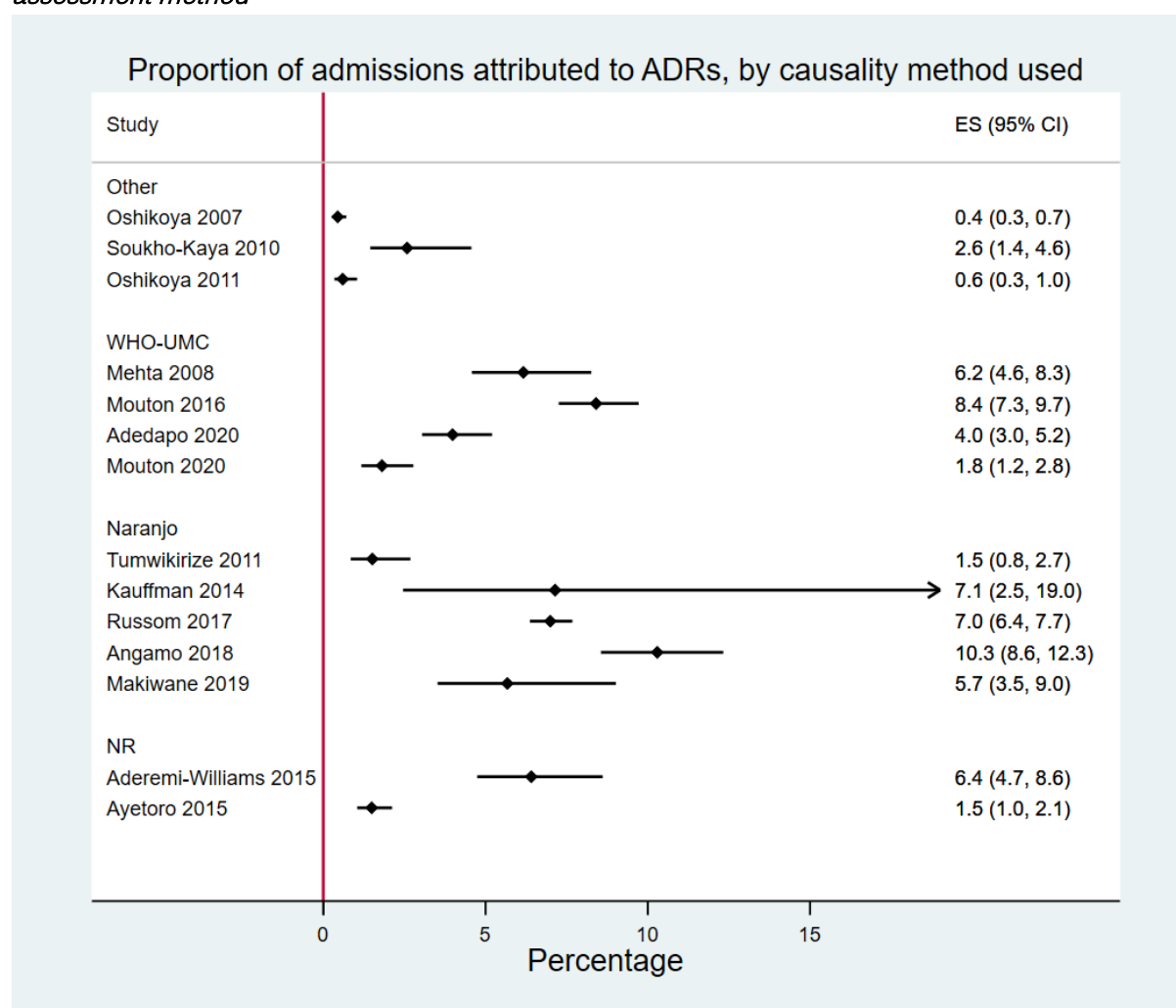
Appendix xxvii. Proportion of admissions attributable to ADRs (Group 1 studies), by surveillance team



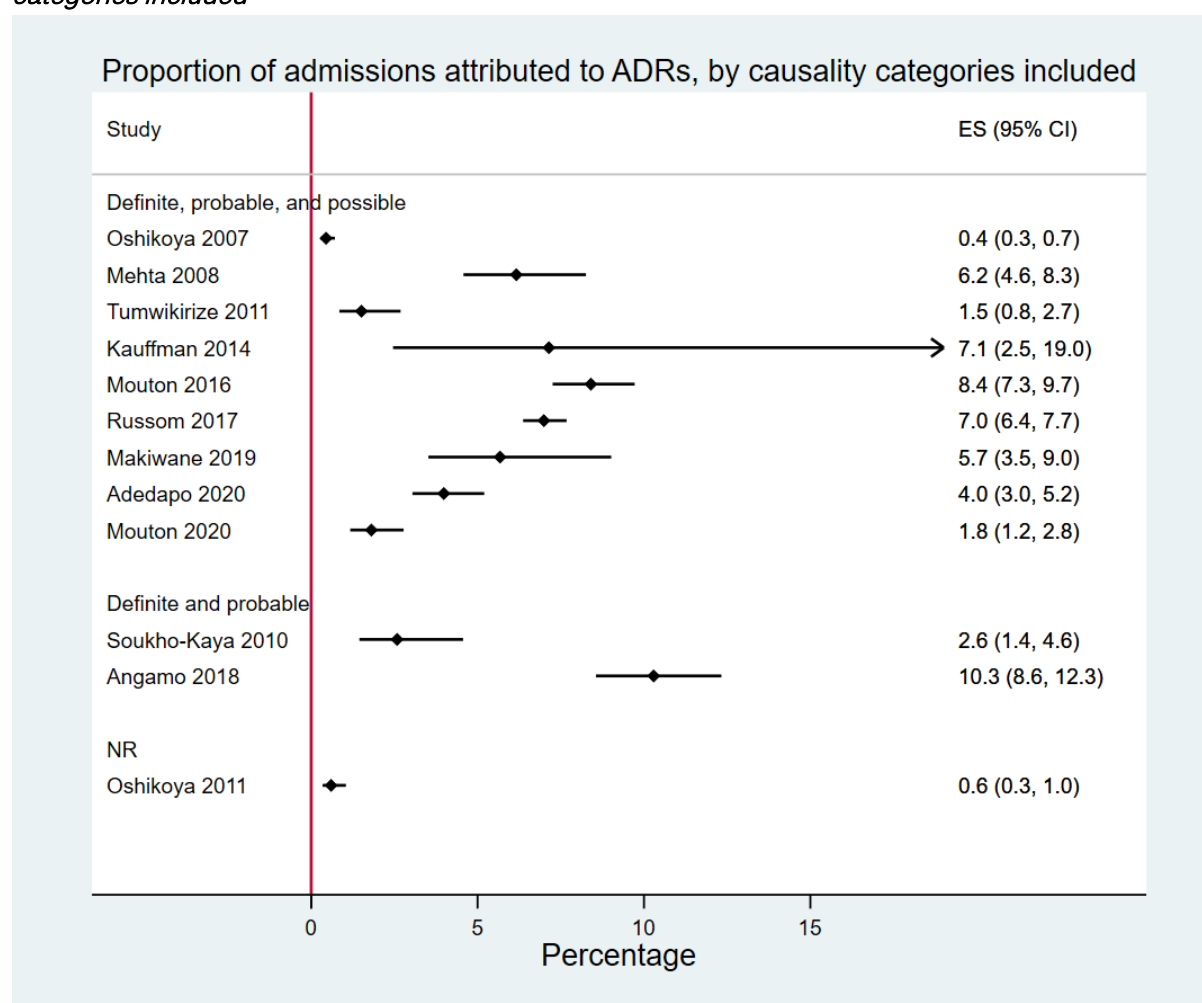
Appendix xxviii. Proportion of admissions attributable to ADRs (Group 1 studies), by folder review method



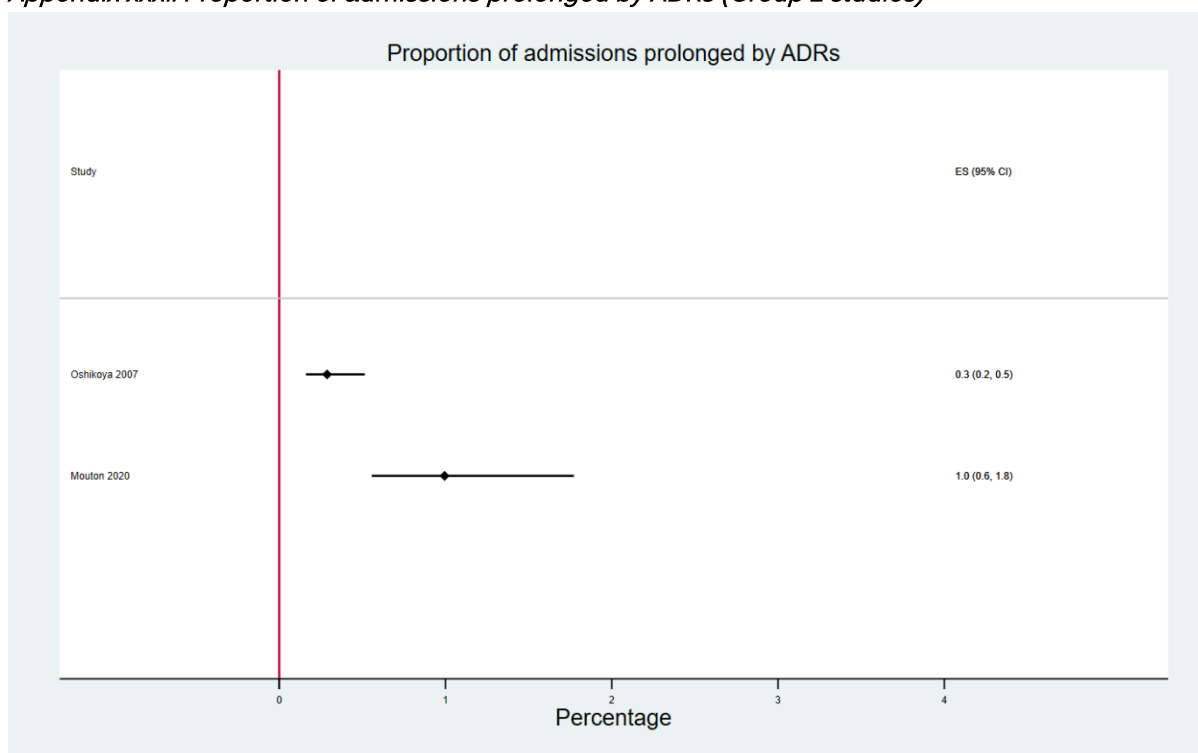
Appendix xxix. Proportion of admissions attributable to ADRs (Group 1 studies), by causality assessment method



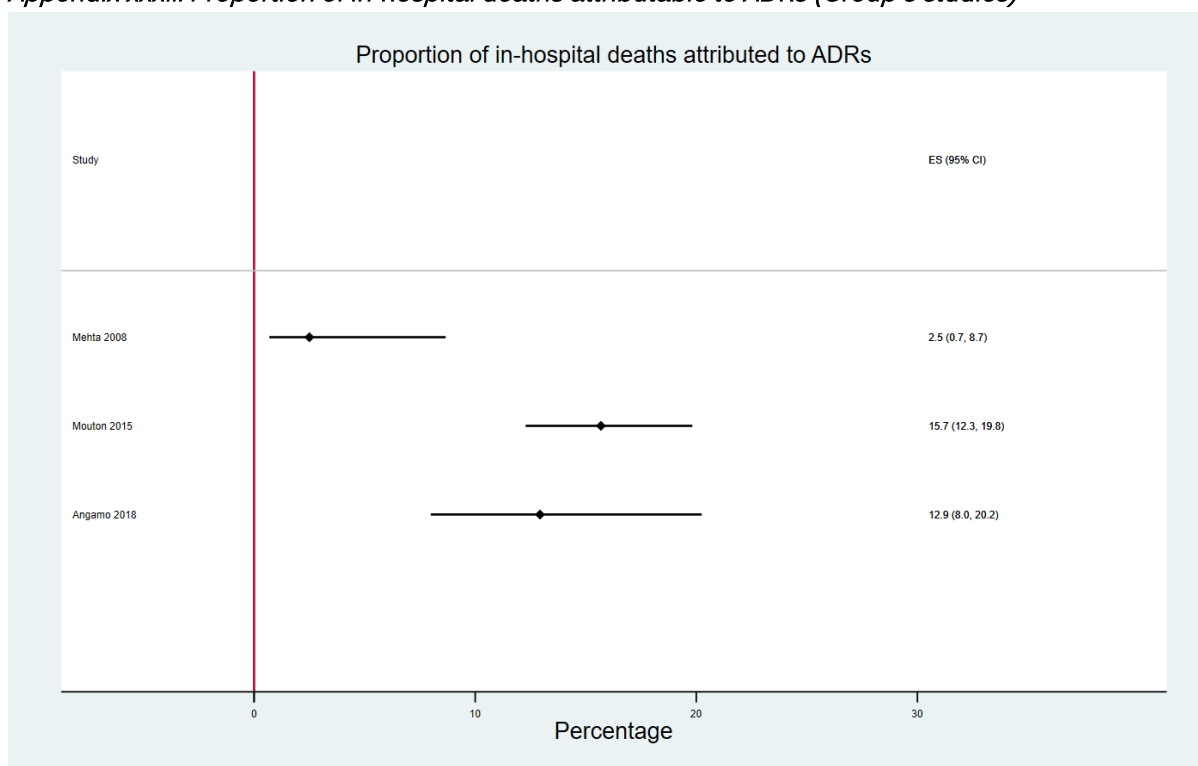
Appendix xxx. Proportion of admissions attributable to ADRs (Group 1 studies), by causality categories included



Appendix xxxi. Proportion of admissions prolonged by ADRs (Group 2 studies)



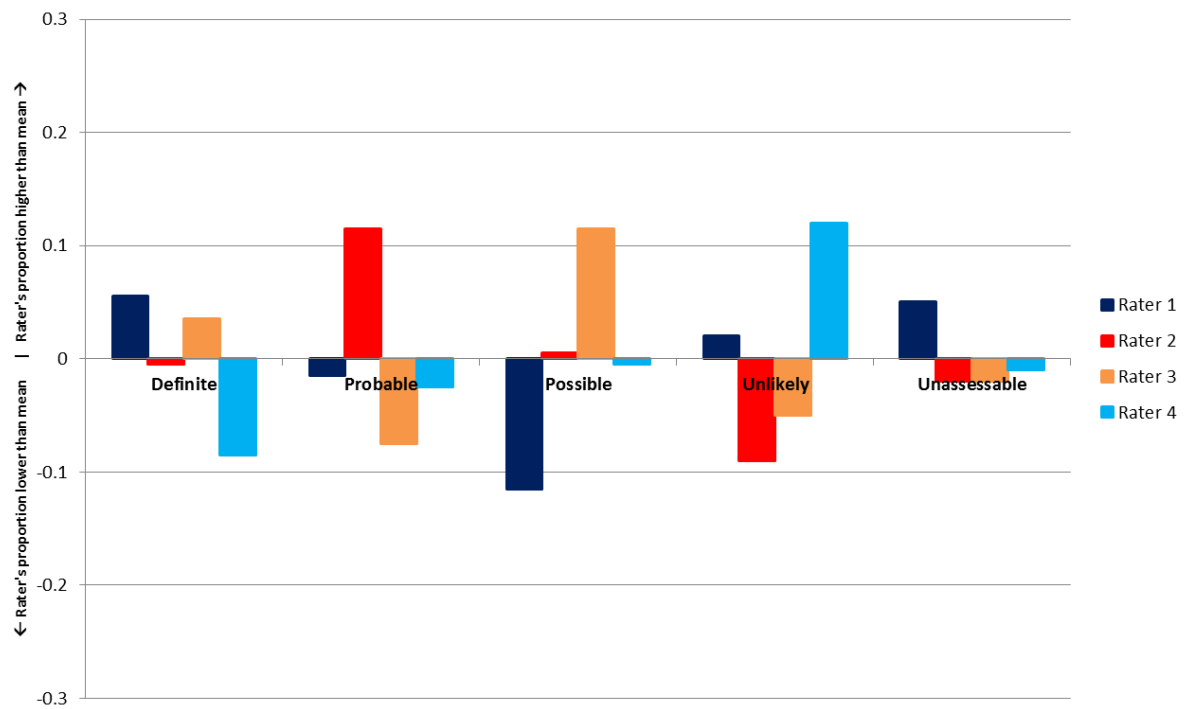
Appendix xxxii. Proportion of in-hospital deaths attributable to ADRs (Group 3 studies)



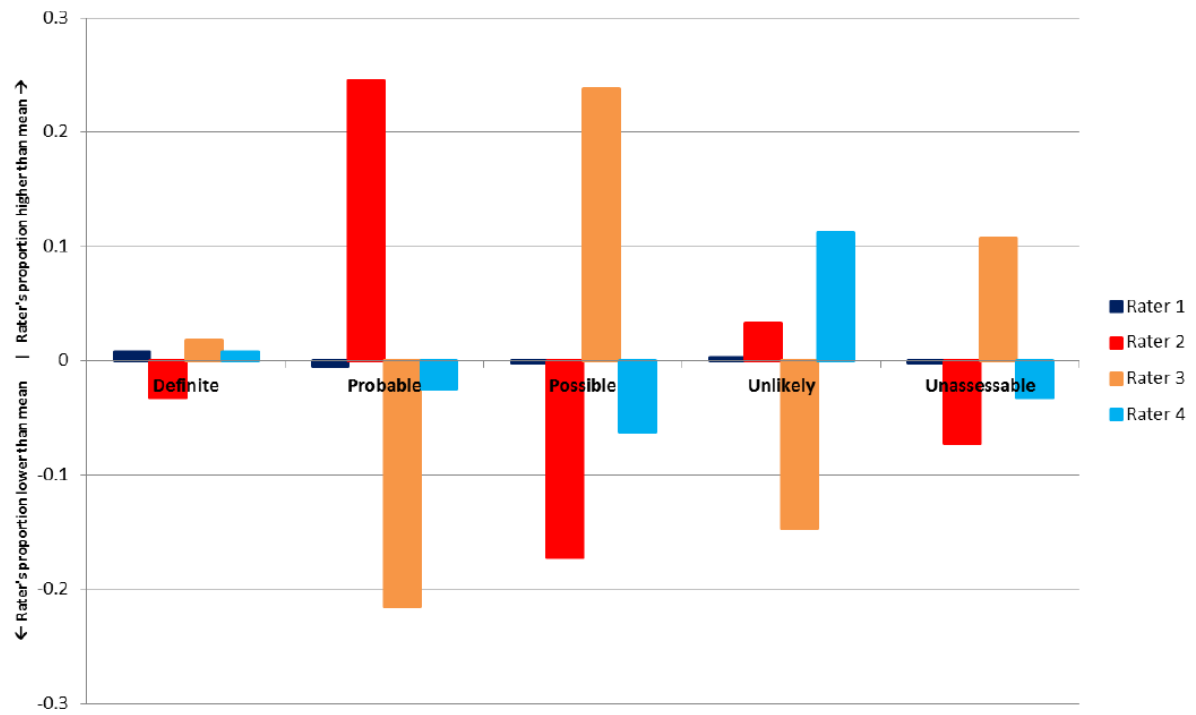
Appendix xxxiii. Raters' distribution of outcomes when using two different causality assessment methods

	Definite	Probable	Possible	Unlikely	Unassessable	Total
Rater 1 – WHO-UMC	3 (14%)	2 (10%)	4 (19%)	8 (38%)	4 (19%)	21
Rater 2 – WHO-UMC	2 (7.7%)	6 (23%)	8 (31%)	7 (27%)	3 (12%)	26
Rater 3 – WHO-UMC	3 (12%)	1 (3.9%)	11 (42%)	8 (31%)	3 (12%)	26
Rater 4 – WHO-UMC	0	2 (8.7%)	7 (30%)	11 (48%)	3 (13%)	23
<i>Subtotal: WHO-UMC</i>	<i>8 (8.3%)</i>	<i>11 (11%)</i>	<i>30 (31%)</i>	<i>34 (35%)</i>	<i>13 (14%)</i>	<i>96</i>
Rater 1 – LCAT	1 (3.7%)	8 (30%)	7 (26%)	9 (33%)	2 (7.4%)	27
Rater 2 – LCAT	0	12 (55%)	2 (9.1%)	8 (36%)	0	22
Rater 3 – LCAT	1 (4.6%)	2 (9.1%)	11 (50%)	4 (18%)	4 (18%)	22
Rater 4 – LCAT	1 (4.0%)	7 (28%)	5 (20%)	11 (44%)	1 (4.0%)	25
<i>Subtotal: LCAT</i>	<i>3 (3.1%)</i>	<i>29 (30%)</i>	<i>25 (26%)</i>	<i>32 (33%)</i>	<i>7 (7.3%)</i>	<i>96</i>
Combined total: WHO-UMC and LCAT methods	11 (5.7%)	40 (21%)	55 (29%)	66 (34%)	20 (10%)	192

Appendix xxxiv. Difference between raters' individual distribution of outcomes and the four raters' mean distribution of outcomes, when using WHO-UMC method.



Appendix xxxv. Difference between raters' individual distribution of outcomes and the four raters' mean distribution of outcomes, when using LCAT.



Appendix xxxvi. Results of sensitivity analysis.

Agreement measure	WHO-UMC system		LCAT	
	Result: main analysis	Result: sensitivity analysis*	Result: main analysis	Result: sensitivity analysis*
Exact agreement	34/48 (0.71)	29/40 (0.73)	22/48 (0.46)	21/42 (0.50)
Pairwise exact agreement (range)	0.50 to 1.0	0.43 to 1.0	0.25 to 0.80	0.25 to 0.89
Extreme disagreement	3/48 (0.063)	0/40	7/48 (0.15)	2/42 (0.048)
Pairwise unweighted kappa (range)	0.33 to 1.0	0.20 to 1.0	0.094 to 0.71	-0.04 to 0.82
Overall unweighted Abaira kappa	0.61 (95% CI 0.43 to 0.80)	0.60 (95% CI 0.38 to 0.82)	0.27 (95% CI 0.074 to 0.46)	0.29 (95% CI 0.066 to 0.52)
Proportions of specific agreement	'definite'=1.0 'probable'=0.55 'possible'=0.60 'unlikely'=0.76 'unassessable'=0.77	'definite'=1.0 'probable'=0.60 'possible'=0.62 'unlikely'=0.79	'definite'=0.67 'probable'=0.55 'possible'=0.24 'unlikely'=0.56 'unassessable'=0.29	'definite'=0.67 'probable'=0.57 'possible'=0.25 'unlikely'=0.62

* In the sensitivity analysis, all 'unassessable' ratings were considered missing data.

Appendix xxxvii. Frequency of paths (traces) on the LCAT.

Path*	Outcome	Frequency (%)
11.1.01.1.	Definite	1 (1.0%)
11.1.1.01.	Definite	1 (1.0%)
11.1.1.1..	Definite	1 (1.0%)
11.1.1.001	Probable	20 (21%)
11.1.01.01	Probable	4 (4.2%)
11.0101.01	Probable	3 (3.1%)
11.011.001	Probable	2 (2.1%)
11.1.00...	Possible	21 (22%)
11.00.....	Possible	2 (2.1%)
11.0100...	Possible	1 (1.0%)
11.1.01.00	Possible	1 (1.0%)
0.....	Unlikely	31 (32%)
100.....	Unlikely	1 (1.0%)
?.....	Unassessable	6 (6.3%)
11.?.....	Unassessable	1 (1.0%)

*Paths are represented as the sequence of responses to 10 questions, in the order Q1, Q2a, Q2b, Q3a, Q3b, Q4a, Q4b, Q5a, Q5b and Q6, labelled as per Figure 3.1. '1' indicates a positive response ('yes or unassessable' on Q3a, 'low' on Q4a, 'yes' on all other questions). '0' indicates a negative response ('high/unsure' on Q4a, 'no' on all other questions). '.' indicates that the decision point was not reached. '?' indicates that the rater was unsure how to proceed and terminated assessment at that point.

Appendix xxxviii. Case-wise response pairs to LCAT questions, and proportions of specific agreement on LCAT questions.

Question†	n (number of paired responses to the question)	Response pairs *			Specific agreement on positive response (proportion)	Specific agreement on negative response (proportion)
		pos/pos	pos/neg	neg/neg		
1	42	24	10	8	48/58 (0.83)	16/26 (0.62)
2a	24	23	1	0	46/47 (0.98)	0/1 (0.0)
3a	22	17	4	1	34/38 (0.89)	2/6 (0.33)
4a	20	7	9	4	14/23 (0.61)	8/17 (0.47)
5b	9	0	1	8	0/1 (0.0)	16/17 (0.94)
6	8	8	0	0	16/16 (1.0)	n/a
5a	7	0	0	7	n/a	14/14 (1.0)
4b	4	0	2	2	0/2 (0.0)	4/6 (0.67)
3b	1	1	0	0	2/2 (1.0)	n/a
2b	0	n/a	n/a	n/a	n/a	n/a

*'pos' = 'yes/unassessable' on Q3a, 'low probability' on Q4a, 'yes' on all other questions. 'neg' = 'high probability / unsure' on Q4a, 'no' on all other questions. 'pos/neg' includes 'pos/neg' and 'neg/pos' responses. 'n/a' = not applicable.

†Numbering of questions on the LCAT as per Figure 3.1.

Appendix xxxix Description of sites included in the mortality survey

	Location	Type of hospital	Wards included / excluded
Groote Schuur Hospital	Cape Town, Western Cape province	Tertiary teaching hospital	We included patients who died in the general medical wards and the short-stay medical ward, and excluded those who died in subspeciality wards and intensive care units.
Edendale Hospital	Edendale, KwaZulu-Natal province	Regional teaching hospital	We included patients who died in the general medical wards and excluded those who died in the intensive care unit. Edendale Hospital does not have subspeciality or short-stay medical wards.
Cecilia Makiwane Hospital and Frere Hospital (co-managed as East London Hospital Complex)	Mdantsane / East London, Eastern Cape province	Regional / tertiary teaching hospital complex	We included all patients who died in the general medical wards as well as medical patients who died in the high care and intensive care units. Cecilia Makiwane and Frere Hospitals do not have subspeciality or short-stay medical wards.

Appendix xl. Characteristics of the 56 patients considered to have died from an ADR-related cause and details of their ADRs

No	Age	Sex	HIV	Adverse drug reaction(s)	Implicated drug(s)	WHO causality category	Relation of ADR to death	Preventable
1	28	F	Pos	Renal failure with hyperkalaemia	Spironolactone	Certain	A contributor	Yes
2	25	M	Pos	Renal failure with hypocalcaemia	Tenofovir	Possible	A contributor	Yes
3	30	M	Pos	Renal failure	Tenofovir	Possible	A contributor	No
4	40	M	Pos	Renal failure*	Tenofovir	Possible	A contributor	Yes
5	29	M	Pos	Renal failure	Tenofovir	Possible	A contributor	Yes
6	45	M	Pos	Renal failure	Tenofovir	Possible	A contributor	Yes
7	54	F	Pos	Renal failure	Tenofovir	Possible	A contributor	Yes
8	33	M	Pos	Renal failure	Tenofovir	Possible	A contributor	Yes
9	32	M	Pos	Renal failure	Tenofovir	Possible	Major contributor	No
10	23	F	Pos	Renal failure	Co-trimoxazole	Possible	A contributor	No
11	31	F	Pos	Renal failure*	Co-amoxiclav, ibuprofen	Possible	A contributor	No
12	39	M	Pos	(1) Renal failure (2) Depressed consciousness	(1) Ciprofloxacin (2) Clonazepam, haloperidol	(1) Possible (2) Possible	(1) A contributor (2) A contributor	(1) No (2) No
13	52	F	Pos	Renal impairment	Tenofovir	Possible	A contributor	Yes
14	37	F	Pos	Acute kidney injury	Rifampicin, tenofovir	Possible	Major contributor	No
15	43	F	Pos	Acute kidney injury	Co-trimoxazole, tenofovir	Possible	Major contributor	No
16	34	M	Pos	(1) Acute kidney injury (2) Depressed consciousness	(1) Aciclovir, co-amoxiclav, indometacin, tenofovir (2) Codeine, tramadol	(1) Possible (2) Possible	(1) Major contributor (2) Major contributor	(1) No (2) Yes
17	58	F	Pos	(1) Acute kidney injury (2) Drug-induced liver injury	(1) Tenofovir (2) Co-trimoxazole, rifampicin	(1) Possible (2) Possible	(1) A contributor (2) Major contributor	(1) No (2) No
18	33	F	Pos	Drug-induced liver injury & renal failure†	Rifampicin	Probable	A contributor	No
19	44	M	Pos	Drug-induced liver injury & renal failure	Co-trimoxazole	Possible	A contributor	Yes
20	39	F	Pos	Drug-induced liver injury	Rifampicin	Possible	A contributor	Yes
21	34	M	Pos	Drug-induced liver injury	Rifampicin	Probable	A contributor	No
22	23	F	Pos	Drug-induced liver injury	Isoniazid, pyrazinamide, rifampicin	Probable	Major contributor	No
23	27	M	Pos	(1) Drug-induced liver injury (2) Bone marrow suppression	(1) Co-trimoxazole, fluconazole, isoniazid, pyrazinamide, rifampicin (2) Co-trimoxazole	(1) Possible (2) Possible	(1) A contributor (2) A contributor	(1) No (2) No
24	37	F	Pos	(1) Drug-induced liver injury (2) Hyperkalaemia	(1) Isoniazid, pyrazinamide, rifampicin (2) Spironolactone	(1) Possible (2) Probable	(1) Major contributor	(1) Yes (2) Yes

							(2) A contributor		
25	67	F	Pos	Intracranial bleed	Aspirin	Possible	Major contributor	No	
26	52	M	Pos	Lactic acidosis	Metformin	Possible	A contributor	Yes	
27	53	M	Pos	Lactic acidosis	Stavudine	Possible	A contributor	Yes	
28	61	F	Pos	(1) Lactic acidosis (2) Renal failure	(1) Stavudine (2) Tenofovir	(1) Probable (2) Possible	(1) Major contributor (2) A contributor	(1) No (2) No	
29	32	M	Pos	Bone marrow suppression	Co-trimoxazole	Possible	A contributor	No	
30	60	M	Pos	Neutropaenia	Stavudine	Possible	Major contributor	No	
31	65	F	Pos	(1) Diarrhoea (2) Sodium toxicity	(1) Lopinavir-ritonavir (2) 0.9% sodium chloride	(1) Possible (2) Possible	(1) A contributor (2) Major contributor	(1) No (2) Yes	
32	65	F	Unk	Renal failure with hyperkalaemia	Enalapril	Possible	A contributor	Yes	
33	62	F	Unk	(1) Renal failure (2) Anticholinergic effects	(1) Furosemide (2) Amitriptyline	(1) Possible (2) Possible	(1) A contributor (2) A contributor	(1) Yes (2) No	
34	51	M	Unk	Drug-induced liver injury*	Valproate	Possible	A contributor	No	
35	79	F	Unk	Intracranial bleed	Warfarin	Certain	Major contributor	Yes	
36	79	F	Unk	Intracranial bleed	Warfarin	Probable	Major contributor	No	
37	78	F	Unk	Intracranial bleed	Aspirin	Possible	Major contributor	No	
38	55	F	Unk	Intracranial bleed	Heparin	Possible	A contributor	Yes	
39	66	M	Unk	(1) Gastrointestinal bleed (2) Hypovolaemia	(1) Aspirin, colchicine, enoxaparin (2) Polyethylene glycol / sodium sulfate	(1) Possible (2) Possible	(1) Major contributor (2) Major contributor	(1) Yes (2) No	
40	70	F	Unk	Hyperkalaemia*	Perindopril	Possible	A contributor	No	
41	89	F	Unk	Hypokalaemia	Furosemide	Possible	A contributor	No	
42	80	M	Unk	Hypokalaemia	Sodium polystyrene sulfonate	Certain	Major contributor	Yes	
43	88	F	Unk	Hypokalaemia	Furosemide, hydrochlorothiazide, prednisone	Probable	Major contributor	Yes	
44	53	M	Unk	Hypoglycaemia	Insulin	Certain	A contributor	Yes	
45	22	M	Unk	Hypoglycaemia	Insulin	Possible	A contributor	Yes	
46	61	F	Unk	Hypoglycaemia, stroke	Insulin	Possible	A contributor	No	
47	74	F	Unk	(1) Hypoglycaemia (2) Masked awareness of hypoglycaemia (3) Hypotension, stroke	(1) Insulin (2) Atenolol (3) Amlodipine, atenolol, enalapril, hydralazine, hydrochlorothiazide	(1) Probable (2) Probable (3) Probable	(1) A contributor (2) A contributor (3) A contributor	(1) No (2) No (3) No	
48	58	M	Unk	Hypotension, stroke	Furosemide	Possible	A contributor	Yes	

49	67	M	Unk	Hypotension	Amlodipine, prazosin	Possible	A contributor	Yes
50	76	F	Unk	Bone marrow suppression, infection	Chlorambucil	Possible	A contributor	No
51	19	M	Unk	Pneumonia	Prednisone, tacrolimus	Possible	A contributor	No
52	87	F	Unk	Diarrhoea	Rifampicin	Possible	A contributor	No
53	79	M	Neg	(1) Renal failure	(1) Furosemide	(1) Possible	(1) A contributor	(1) Yes
				(2) Atrial fibrillation	(2) Theophylline	(2) Possible	(2) A contributor	(2) Yes
				(3) Gastrointestinal bleed	(3) Prednisone	(3) Possible	(3) A contributor	(3) No
54	62	F	Neg	Drug-induced liver injury	Erythromycin	Possible	A contributor	No
55	55	F	Neg	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Allopurinol	Certain	Major contributor	Yes
56	29	M	Neg	Angioedema	Codeine, ibuprofen	Possible	A contributor	No

Neg: HIV-seronegative; Pos: HIV-infected; Unk: HIV serology unknown

* The panel did not reach consensus: this ADR included as a majority decision

†The panel reached consensus on the assessment of this ADR attributable to rifampicin. Additionally, a majority of the panel considered it possible that the patient's DILI could be attributed to isoniazid and pyrazinamide, and her renal failure to ethambutol.

Appendix xli. Supplementary notes to Methods

Settings

Groote Schuur Hospital is a 975-bed urban academic hospital situated in Cape Town, in the Western Cape province, which provides secondary and tertiary level care, serves as a referral centre for approximately half of the province's population (2011 population: 5.8 million)²⁰⁹ and is associated with the University of Cape Town. At this hospital we surveyed the general medical wards during May and June 2013. We did not survey the sub-speciality wards (dermatology, neurology, cardiology, respiratory medicine and nephrology), the oncology wards, or the high care / intensive care units. Restricting the survey to general medical wards was done partly due to resource limitations but also to allow the patients at this site to be reasonably comparable to those at other sites, which did not have sub-specialist wards. In 2009, the crude inpatient mortality in the medical wards of Groote Schuur Hospital was shown to be 573/3465 patients (17%)²¹⁰ and the 12-month post-discharge mortality to be 145/415 (35%).²¹¹

Edendale Hospital is a 900-bed peri-urban regional teaching hospital situated near Pietermaritzburg, in the KwaZulu-Natal province (2011 population: 10.3 million).²⁰⁹ It provides care to the peri-urban community and serves as a referral centre for several district hospitals in the surrounding rural area. It is located at the epicentre of the HIV, tuberculosis and multidrug resistant tuberculosis epidemics in South Africa: a post-mortem study in 2008-2009 found that 94% of decedents in the medical wards of Edendale Hospital were HIV-seropositive, 50% had culture-positive tuberculosis at the time of death and 17% of these cultures were resistant to isoniazid and rifampicin.²¹² At Edendale Hospital, we surveyed the medical wards over 30 days during July and August of 2013. We did not survey the intensive care unit, and there were no high care unit or sub-speciality wards at the time of this survey.

Cecilia Makiwane Hospital, situated in the large peri-urban community of Mdantsane in the Eastern Cape province, and Frere Hospital, situated in the city of East London, are co-managed as the East London Hospital Complex and provide secondary and tertiary-level care. These hospitals also serve as referral centres for a significant part of the province (2011 population: 6.6 million).²⁰⁹ At these two teaching hospitals, we surveyed the general medical wards, as well as the high care and intensive care units, over 30 days during August and September 2013; there were no sub-speciality wards at the time of this survey. The burden of disease in the medical wards of these hospitals has not previously been published.

All four hospitals are public sector facilities. In the overburdened public health sector of South Africa, even at tertiary centres, elective medical admissions are rare and virtually all admissions to the medical wards occurred as emergencies via the emergency department or via primary care facilities.

Identification of new admissions

We identified all newly admitted patients using hospital administrative records. When possible, we cross-referenced administrative records with lists of admissions kept by the medical team on intake. We included in our survey all patients whom the medical team decided to admit, regardless of their actual admission status; thus, we included those patients who were discharged from or died in the emergency unit while still awaiting transfer to a ward. We collected data on weekdays; thus we identified newly admitted patients and collected the initial dataset within three days from the date of admission.

Multidisciplinary case review panels

We constituted two case review panels to review the causality, severity and preventability of cases identified as potential adverse drug reactions (ADRs). The first panel, consisting of a clinical pharmacist, a clinical pharmacologist,

and one to three physicians / internists, reviewed the cases of patients who died during the 30-day survey period. (For these patients, we had more detailed information in the form of a copy of their hospital folder, as well as a narrative case summary, prepared by the first author.) This panel's primary aim was to identify deaths in which ADRs played a causal or contributory role; results have been previously published.¹⁰⁴ For the purposes of our previous paper, the panel assessed the deaths of 105 patients: 28 of those were not included in the denominator of the current survey, as they were admitted prior to the current paper's 30-day survey period, and a further 48 patients' deaths were unrelated to ADRs, or related to ADRs that were not present on admission but developed in-hospital, or related to ADRs that were present on admission but did not form the main reason for admission. Those 48 cases are thus not included in the current study's numerator, but do form part of the current study's denominator. The remaining 29 patient folders which were assessed by the first case review panel fulfilled the inclusion criteria of the previous¹⁰⁴ and the current survey (i.e., were admitted due to an ADR and died during the 30-day survey period), and have thus been included in both studies' analyses.

The second panel, who assessed the suspected ADR-related admissions of patients alive at the end of the 30-day period, consisted of a research pharmacist, a clinical pharmacist, a general practitioner (GP), a second GP / medical epidemiologist, two clinical pharmacologists, and a physician. This panel performed their assessments in two rounds. In the first round, two GP-pharmacist pairs reviewed all 196 suspected ADR-related admissions, with the pairs reviewing the case independently from one another. Cases in which the two pairs disagreed on the WHO-UMC causality rating of any drug-event association were forwarded to the second round; cases where the two pairs agreed on the WHO-UMC causality rating of all drug-event associations were not forwarded to the second round. (In cases not forwarded to the second round, disagreements regarding preventability or severity were resolved through discussion by the panel members.) All seven panel members participated in the second round of assessment, during which the causality, preventability and severity of 132 cases were discussed until consensus was reached.

Three authors reconciled the data generated by the two assessment panels, as some methodological differences existed between their assessments: in the event of one ADR being attributed to multiple drug causes, the first panel (who assessed cases of patients who died) performed their causality assessment on each drug suspect individually. For the purposes of the current paper, however, we distinguish between Type A and Type B ADRs in our approach to causality assessment of these cases with multiple drug suspects, as described in the manuscript.

Presumptions and exceptions on Anatomic-Therapeutic-Chemical (ATC) coding

We presumed all aspirin to have been used for inhibition of platelet aggregation (and not for analgesia), and thus coded it to the ATC code B01AC06.

We presumed all bronchodilators and corticosteroids to have been inhaled, unless specifically documented to have been used systemically.

We coded antiretroviral and antituberculosis fixed drug combinations to the two, three, or four component drugs. We did not code other combinations to their components, but instead arbitrarily increased a patient's drug count with one unit for every combination drug recorded.

In the event that the precise drug was not known, but the class was, we coded the drug to the lowest level possible. For example, unspecified antihypertensive therapy was coded as C ('Cardiovascular system'). All insulins were recorded and reported as A10A ('Insulin and analogues'). Where the fourth-level drug code (class) exploded down to only one fifth-level code (drug), we reported the drug name. (For example, the fourth-level (class) code C03CA 'high-ceiling

diuretics: sulfonamides, plain' had only one member, the fifth-level (drug) code C03CA01 'furosemide'. For the purpose of this paper, we reported it as 'C03CA furosemide'.)

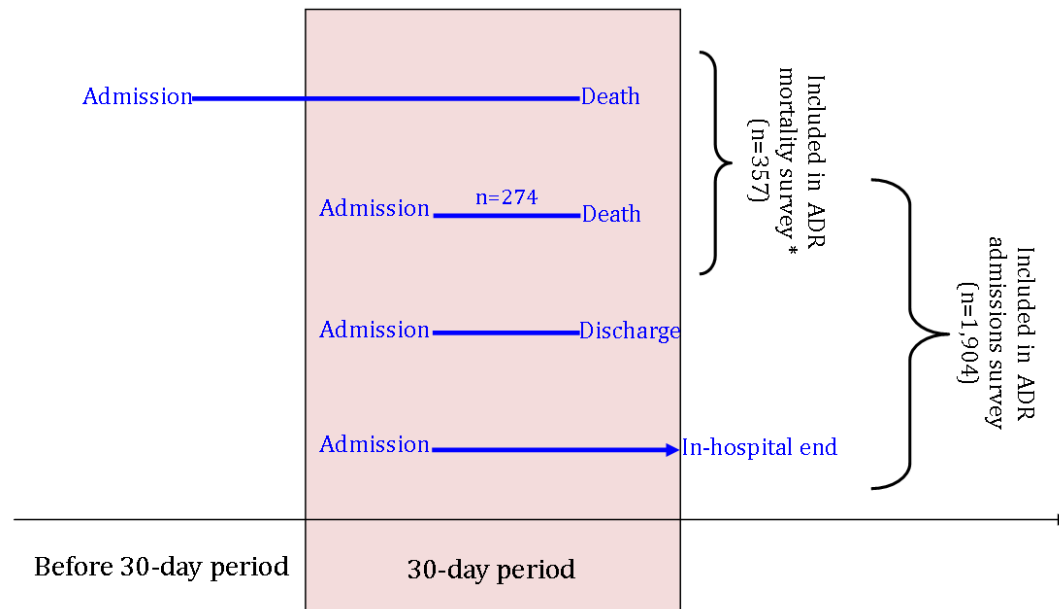
Reporting of ADRs

MedDRA® is a multiaxial classification system, with lower-level terms not mapping on a one-to-one basis to higher-level terms. For reporting purposes, we grouped MedDRA® 'preferred terms' as follows:

Reported ADR	MedDRA® 'preferred terms' included in the reported ADR
Blood dyscrasias	Anaemia, Anaemia macrocytic, Anaemia normochromic normocytic, Aplastic anaemia, Pancytopenia, Thrombocytopenia, Leukopenia, Neutropenia
Drug-induced liver injury (DILI)	Cholestatic liver injury, Hepatocellular liver injury, Mixed liver injury, Hepatorenal failure*
Renal impairment	Renal failure acute, Renal failure, Hepatorenal failure*
Haemorrhage	Gingival bleeding, Gastric haemorrhage, Gastrointestinal haemorrhage, Gastritis haemorrhagic, Lower gastrointestinal haemorrhage, Haemoptysis, Epistaxis, Haemarthrosis, Haematuria, Retroperitoneal haemorrhage, Menorrhagia, Cerebral haemorrhage, Haemorrhage intracranial, Subarachnoid haemorrhage

* Hepatorenal failure was reported under two grouped terms.

Appendix xlii. Schematic representation of overlap in the denominator of the current survey and a previously published survey () on ADR-related mortality. 274 patients were included in both surveys.*



Appendix xliii. List of triggers used to identify suspected adverse drug reactions

Event triggers	Drug order triggers	Laboratory result triggers	Suspected ADR
• Angioedema • Bronchospasm • Lip swelling • Rash or ulceration	• Adrenaline/epinephrine • Antihistamine • Corticosteroid • Promethazine for HSR		Hypersensitivity reaction
	• Flumazenil • Naloxone	• Amikacin peak > 30 or trough > 2 mg/L • Carbamazepine > 45 µmol/L • Digoxin > 1.5 nmol/L • Gentamicin peak > 8 or trough > 1 mg/L • Phenobarbital > 160 µmol/L • Phenytoin > 80 µmol/L • Theophylline >110 µmol/L • Tobramycin peak > 8 or trough > 1 mg/L • Valproic acid > 700 µmol/L • Vancomycin > 20 mg/L • Other toxic drug concentration • Paracetamol concentration done	Toxic drug effect
• Fracture • Osteonecrosis			Drug-induced bone disease
• Bone marrow biopsy	• GCSF/meropenem	• Haemoglobin <8 g/dL • Pancytopenia • Platelets < 50 x 10⁹/L • White blood cell count < 1.5 x 10⁹/L	Drug-induced bone marrow suppression
• New arrhythmia • New cardiac failure • New hypotension • Torsades de pointes	• Atropine • Magnesium sulphate		Drug-induced cardiovascular problem
• Ataxia • Decreased LOC • Delirium • Dizziness • Dyskinesia • Dystonia • Falls • Lethargy • Oversedation • Seizure(s) • Torticollis	• Biperidin • Diazepam for EPSE • Diazepam for seizure • Lorazepam stat for seizure • Phenytoin for seizure • Promethazine for EPSE		Drug-induced central nervous system problem
• Bleeding	• Fresh frozen plasma • Protamine sulphate • Vitamin K	• International normalised ratio (INR) >5 • Partial thromboplastin time (PTT) > 100 seconds	Drug-induced coagulation problem
	• Calcium gluconate • Insulin with glucose • Polystyrene sulfate	• Potassium <3.5 mmol/L • Potassium >5.5 mmol/L	Drug-induced electrolyte disturbance
• Gastroscopy • Nausea and vomiting	• Antidiarrhoeals • Antiemetic • Metoclopramide	• <i>Clostridium difficile</i> after antibiotics	Drug-induced gastrointestinal problem
	• Dextrose 50%	• Glucose < 3 mmol/L	Drug-induced hypoglycaemia
• New jaundice • Liver biopsy		• Alanine transaminase (ALT) > 3x ULN • Bilirubin > 2x ULN	Drug-induced liver injury

• Renal biopsy	• eGFR worsening / single new low • CrCl worsening / single new low • Creatinine rising / single new high	Drug-induced renal impairment
• Abrupt drug stop • HCW suspects ADR • Transfer to higher level of care		Event suggests ADR

ADR: adverse drug reaction, CrCl: creatinine clearance, eGFR: estimated glomerular filtration rate, EPSE: extrapyramidal side effects, GCSF: granulocyte colony stimulating factor, HCW: healthcare worker, HSR: hypersensitivity reaction, LOC: level of consciousness, ULN: upper limit of normal

Appendix xlv. Prevalence of comorbidities, according to ICD-10 classification, over the 4-week period prior to first admission (n=1904 admissions)

ICD-10 Chapter / Diagnostic Block	Count	Proportion
A00-B99 CERTAIN INFECTIOUS AND PARASITIC DISEASES	645	34%
A00-A09 Intestinal infectious diseases	41	2.1%
A15-A19 Tuberculosis *	200	11%
A30-A49 Other bacterial diseases	18	<1%
A50-A64 Infections with a predominantly sexual mode of transmission	6	<1%
A80-A89 Viral infections of the central nervous system	2	<1%
B00-B09 Viral infections characterized by skin and mucous membrane lesions	6	<1%
B15-B19 Viral hepatitis	5	<1%
B20-B24 Human immunodeficiency virus [HIV] disease †	559	29%
B25-B34 Other viral diseases	2	<1%
B35-B49 Mycoses	57	2.9%
B50-B64 Protozoal diseases	3	<1%
B85-B89 Pediculosis, acariasis and other infestations	1	<1%
B90-B94 Sequelae of infectious and parasitic diseases	2	<1%
C00-D48 NEOPLASMS	50	2.6%
C15-C26 Malignant neoplasms: Digestive organs	7	<1%
C30-C39 Malignant neoplasms: Respiratory and intrathoracic organs	3	<1%
C40-C41 Malignant neoplasms: Bone and articular cartilage	1	<1%
C45-C49 Malignant neoplasms: Mesothelial and soft tissue	7	<1%
C50-C50 Malignant neoplasms: Breast	5	<1%
C51-C58 Malignant neoplasms: Female genital organs	2	<1%
C60-C63 Malignant neoplasms: Male genital organs	4	<1%
C64-C68 Malignant neoplasms: Urinary tract	2	<1%
C69-C72 Malignant neoplasms: Eye, brain and other parts of central nervous system	3	<1%
C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites	3	<1%
C81-C96 Malignant neoplasms of lymphoid, haematopoietic and related tissue	7	<1%
D00-D09 In situ neoplasms	1	<1%
D10-D36 Benign neoplasms	4	<1%
D37-D48 Neoplasms of uncertain or unknown behaviour	5	<1%
D50-D89 DISEASES OF THE BLOOD AND HAEMOPOIESIS; CERTAIN DISORDERS OF THE IMMUNE SYSTEM	171	9.0%
D50-D53 Nutritional anaemias	30	1.6%
D55-D59 Haemolytic anaemias	1	<1%
D60-D64 Aplastic and other anaemias	114	6.0%
D65-D69 Coagulation defects, purpura and other haemorrhagic conditions	33	1.7%
D70-D77 Other diseases of blood and blood-forming organs	11	<1%
D80-D89 Certain disorders involving the immune mechanism	1	<1%
E00-E90 ENDOCRINE, NUTRITIONAL AND METABOLIC DISEASES	585	31%
E00-E07 Disorders of thyroid gland	35	1.8%
E10-E14 Diabetes mellitus	343	18%
E15-E16 Other disorders of glucose regulation and pancreatic internal secretion	15	<1%
E20-E35 Disorders of other endocrine glands	2	<1%
E40-E46 Malnutrition	2	<1%
E50-E64 Other nutritional deficiencies	7	<1%
E65-E68 Obesity and other hyperalimentation	59	3.1%
E70-E90 Metabolic disorders	257	13%
F00-F99 MENTAL AND BEHAVIOURAL DISORDERS	134	7.0%
F00-F09 Organic, including symptomatic, mental disorders	44	2.3%
F10-F19 Mental and behavioural disorders due to psychoactive substance use	30	1.6%

F20-F29 Schizophrenia, schizotypal and delusional disorders	18	<1%
F30-F39 Mood [affective] disorders	21	1.1%
F40-F48 Neurotic, stress-related and somatoform disorders	5	<1%
F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors	1	<1%
F70-F79 Mental retardation	14	<1%
F99-F99 Unspecified mental disorder	8	<1%
G00-G99 DISEASES OF THE NERVOUS SYSTEM	123	6.5%
G00-G09 Inflammatory diseases of the central nervous system	7	<1%
G10-G14 Systemic atrophies primarily affecting the central nervous system	3	<1%
G20-G26 Extrapyrarnidal and movement disorders	8	<1%
G30-G32 Other degenerative diseases of the nervous system	2	<1%
G35-G37 Demyelinating diseases of the central nervous system	2	<1%
G40-G47 Episodic and paroxysmal disorders	87	4.6%
G50-G59 Nerve, nerve root and plexus disorders	3	<1%
G60-G64 Polyneuropathies and other disorders of the peripheral nervous system	6	<1%
G70-G73 Diseases of myoneural junction and muscle	1	<1%
G80-G83 Cerebral palsy and other paralytic syndromes	7	<1%
G90-G99 Other disorders of the nervous system	4	<1%
H00-H59 DISEASES OF THE EYE AND ADNEXA	32	1.7%
H15-H22 Disorders of sclera, cornea, iris and ciliary body	2	<1%
H25-H28 Disorders of lens	4	<1%
H30-H36 Disorders of choroid and retina	6	<1%
H40-H42 Glaucoma	8	<1%
H46-H48 Disorders of optic nerve and visual pathways	2	<1%
H53-H54 Visual disturbances and blindness	12	<1%
H55-H59 Other disorders of eye and adnexa	1	<1%
H60-H95 DISEASES OF THE EAR AND MASTOID PROCESS	13	<1%
H65-H75 Diseases of middle ear and mastoid	1	<1%
H80-H83 Diseases of inner ear	1	<1%
H90-H95 Other disorders of ear	11	<1%
I00-I99 DISEASES OF THE CIRCULATORY SYSTEM	845	44%
I00-I02 Acute rheumatic fever	2	<1%
I05-I09 Chronic rheumatic heart diseases	22	1.2%
I10-I15 Hypertensive diseases	691	36%
I20-I25 Ischaemic heart diseases	123	6.5%
I26-I28 Pulmonary heart disease and diseases of pulmonary circulation	39	2.0%
I30-I52 Other forms of heart disease	194	10%
I60-I69 Cerebrovascular diseases	112	5.9%
I70-I79 Diseases of arteries, arterioles and capillaries	21	1.1%
I80-I89 Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	18	<1%
I95-I99 Other and unspecified disorders of the circulatory system	5	<1%
J00-J99 DISEASES OF THE RESPIRATORY SYSTEM	283	15%
J00-J06 Acute upper respiratory infections	3	<1%
J09-J18 Influenza and pneumonia	38	2.0%
J20-J22 Other acute lower respiratory infections	43	2.3%
J30-J39 Other diseases of upper respiratory tract	5	<1%
J40-J47 Chronic lower respiratory diseases	167	8.8%
J60-J70 Lung diseases due to external agents	7	<1%
J80-J84 Other respiratory diseases principally affecting the interstitium	12	<1%
J85-J86 Suppurative and necrotic conditions of lower respiratory tract	2	<1%
J90-J94 Other diseases of pleura	16	<1%
J95-J99 Other diseases of the respiratory system	17	<1%

K00-K93 DISEASES OF THE DIGESTIVE SYSTEM	133	7.0%
K00-K14 Diseases of oral cavity, salivary glands and jaws	3	<1%
K20-K31 Diseases of oesophagus, stomach and duodenum	54	2.8%
K35-K38 Diseases of appendix	1	<1%
K40-K46 Hernia	2	<1%
K50-K52 Noninfective enteritis and colitis	4	<1%
K55-K64 Other diseases of intestines	40	2.1%
K65-K67 Diseases of peritoneum	3	<1%
K70-K77 Diseases of liver	19	<1%
K80-K87 Disorders of gallbladder, biliary tract and pancreas	7	<1%
K90-K93 Other diseases of the digestive system	13	<1%
L00-L99 DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUE	44	2.3%
L00-L08 Infections of the skin and subcutaneous tissue	12	<1%
L10-L14 Bullous disorders	1	<1%
L20-L30 Dermatitis and eczema	5	<1%
L40-L45 Papulosquamous disorders	7	<1%
L60-L75 Disorders of skin appendages	2	<1%
L80-L99 Other disorders of the skin and subcutaneous tissue	18	<1%
M00-M99 DISEASES OF THE MUSCULOSKELETAL SYSTEM AND CONNECTIVE TISSUE	101	5.3%
M00-M03 Arthropathies: Infectious arthropathies	1	<1%
M05-M14 Arthropathies: Inflammatory polyarthropathies	51	2.7%
M15-M19 Arthropathies: Arthrosis	17	<1%
M20-M25 Arthropathies: Other joint disorders	6	<1%
M30-M36 Systemic connective tissue disorders	8	<1%
M40-M43 Dorsopathies: Deforming dorsopathies	2	<1%
M45-M49 Dorsopathies: Spondylopathies	2	<1%
M50-M54 Dorsopathies: Other dorsopathies	8	<1%
M60-M63 Soft tissue disorders: Disorders of muscles	3	<1%
M70-M79 Soft tissue disorders: Other soft tissue disorders	7	<1%
M80-M85 Osteopathies and chondropathies: Disorders of bone density and structure	2	<1%
N00-N99 DISEASES OF THE GENITOURINARY SYSTEM	373	20%
N00-N08 Glomerular diseases	6	<1%
N10-N16 Renal tubulo-interstitial diseases	4	<1%
N17-N19 Renal failure	323	17%
N20-N23 Urolithiasis	1	<1%
N25-N29 Other disorders of kidney and ureter	2	<1%
N30-N39 Other diseases of urinary system	33	1.7%
N40-N51 Diseases of male genital organs	14	<1%
N60-N64 Disorders of breast	1	<1%
N70-N77 Inflammatory diseases of female pelvic organs	5	<1%
N80-N98 Noninflammatory disorders of female genital tract	7	<1%
O00-O99 PREGNANCY, CHILDBIRTH AND THE PUERPERIUM	6	<1%
O10-O16 Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth, puerperium	3	<1%
O30-O48 Maternal care related to the fetus and amniotic cavity and possible delivery problems	1	<1%
O80-O84 Delivery	3	<1%
Q00-Q99 CONGENITAL MALFORMATIONS, DEFORMATIONS AND CHROMOSOMAL ABNORMALITIES	7	<1%
Q00-Q07 Congenital malformations of the nervous system	1	<1%
Q30-Q34 Congenital malformations of the respiratory system	1	<1%
Q38-Q45 Other congenital malformations of the digestive system	1	<1%
Q60-Q64 Congenital malformations of the urinary system	1	<1%

Q80-Q89 Other congenital malformations	3	<1%
S00-T98 INJURY, POISONING AND CERTAIN OTHER CONSEQUENCES OF EXTERNAL CAUSES	20	1.1%
S00-S09 Injuries to the head	2	<1%
S20-S29 Injuries to the thorax	1	<1%
S40-S49 Injuries to the shoulder and upper arm	1	<1%
S50-S59 Injuries to the elbow and forearm	1	<1%
S70-S79 Injuries to the hip and thigh	4	<1%
S80-S89 Injuries to the knee and lower leg	1	<1%
S90-S99 Injuries to the ankle and foot	1	<1%
T08-T14 Injuries to unspecified parts of trunk, limb or body region	1	<1%
T20-T32 Burns and corrosions	1	<1%
T36-T50 Poisoning by drugs, medicaments and biological substances	1	<1%
T51-T65 Toxic effects of substances chiefly nonmedicinal as to source	1	<1%
T66-T78 Other and unspecified effects of external causes	1	<1%
T80-T88 Complications of surgical and medical care, not elsewhere classified	3	<1%
T90-T98 Sequelae of injuries, of poisoning and of other consequences of external causes	1	<1%
V01-Y98 EXTERNAL CAUSES OF MORBIDITY AND MORTALITY	11	<1%
V80-V89 Accidents: Transport accidents: Other land transport accidents	1	<1%
W00-W19 Accidents: Other external causes of accidental injury: Falls	1	<1%
X60-X84 Intentional self-harm	3	<1%
X85-Y09 Assault	2	<1%
Y60-Y69 Complications of care: Misadventures	1	<1%
Y83-Y84 Complications of care: Without mention of misadventure	1	<1%
Y90-Y98 Supplementary factors related to causes of morbidity and mortality	2	<1%
Z00-Z99 FACTORS INFLUENCING HEALTH STATUS AND CONTACT WITH HEALTH SERVICES	318	17%
Z00-Z13 Persons encountering health services for examination and investigation	1	<1%
Z20-Z29 Persons with potential health hazards related to communicable diseases	4	<1%
Z30-Z39 Persons encountering health services in circumstances related to reproduction	1	<1%
Z40-Z54 Persons encountering health services for specific procedures and health care	1	<1%
Z55-Z65 Potential health hazards related to socioeconomic and psychosocial circumstances	6	<1%
Z70-Z76 Persons encountering health services in other circumstances	65	3.4%
Z80-Z99 Persons with potential health hazards related to family and personal history	275	14%

* This TB count differs from the main text (where it is 182/1904 = 9.6%): in the main text, we considered being on TBT as a proxy for TB infection. In the count in this table, in contrast, any indication of TB in the past four weeks is counted, including for example those patients who recently stopped TBT or those diagnosed but not compliant to treatment. This list may also include ones where a past history of TB was erroneously coded as TB in the past four weeks.

† This count is the same as main text: HIV infection diagnosed during hospital admission was uniformly considered to have been present in the four weeks prior to the admission and to therefore be a background condition.

Appendix xlv. Prevalence of drug use, according to ATC-classification, over the 4-week period prior to patients' first admission (n=1904)

Drug class / Drug	Count ^a	Proportion ^b
A ALIMENTARY TRACT AND METABOLISM	448	24%
A02 Drugs for acid-related disorders	97	5.1%
A02A Antacids	9	<1%
A02AA Magnesium compounds	1	<1%
A02AA05 Magnesium silicate	1	<1%
A02AB Aluminium compounds	1	<1%
A02AB01 Aluminium hydroxide	1	<1%
A02AH Antacids with sodium bicarbonate	2	<1%
Unspecified antacids	6	<1%
A02B Drugs for peptic ulcer and gastro-oesophageal reflux disease	93	4.9%
A02BA H2-receptor antagonists	10	<1%
A02BA01 Cimetidine	3	<1%
A02BA02 Ranitidine	5	<1%
Unspecified H2-receptor antagonists	2	<1%
A02BC Proton pump inhibitors	81	4.3%
A02BC01 Omeprazole	74	3.9%
A02BC02 Pantoprazole	5	<1%
A02BC03 Lansoprazole	2	<1%
A02BC05 Esomeprazole	1	<1%
A02BX Other drugs for peptic ulcer and gastro-oesophageal reflux disease	2	<1%
Unspecified drugs for peptic ulcer and gastro-oesophageal reflux disease	1	<1%
A03 Drugs for functional gastrointestinal disorders	43	2.3%
A03B Belladonna and derivatives, plain	12	<1%
A03BA Belladonna alkaloids, tertiary amines	1	<1%
A03BA01 Atropine	1	<1%
A03BB Belladonna alkaloids, semisynthetic, quaternary ammonium compounds	11	<1%
A03BB01 Butylscopolamine	11	<1%
A03F Propulsives	37	1.9%
A03FA Propulsives	37	1.9%
A03FA01 Metoclopramide	36	1.9%
A03FA03 Domperidone	1	<1%
A04 Antiemetics and antinauseants	1	<1%
A04A Antiemetics and antinauseants	1	<1%
A04AA Serotonin (5HT ₃) antagonists	1	<1%
A04AA01 Ondansetron	1	<1%
A04AA02 Granisetron	1	<1%
A05 Bile and liver therapy	1	<1%
A05A Bile therapy	1	<1%
A05AA Bile acid preparations	1	<1%
A05AA02 Ursodeoxycholic acid	1	<1%
A06 Laxatives	29	1.5%
A06A Laxatives	29	1.5%
A06AA Softeners, emollients	1	<1%
A06AA01 Liquid paraffin	1	<1%
A06AB Contact laxatives	8	<1%
A06AB02 Bisacodyl	2	<1%
A06AB06 Senna glycosides	7	<1%
A06AD Osmotically acting laxatives	18	<1%

A06AD11 Lactulose	15	<1%
A06AD18 Sorbitol	2	<1%
Unspecified osmotically acting laxatives	1	<1%
Unspecified laxatives	3	<1%
A07 Antidiarrhoeals, intestinal anti-inflammatory / anti-infective agents	28	1.5%
A07A Intestinal anti-infectives	7	<1%
A07AA Antibiotics	7	<1%
A07AA02 Nystatin	7	<1%
A07B Intestinal adsorbents	3	<1%
A07BA Charcoal preparations	3	<1%
A07BA01 Medicinal charcoal	3	<1%
A07C Electrolytes with carbohydrates	2	<1%
A07CA Oral rehydration salt formulations	2	<1%
A07D Antipropulsives	12	<1%
A07DA Antipropulsives	12	<1%
A07DA03 Loperamide	12	<1%
A07E Intestinal anti-inflammatory agents	5	<1%
A07EC Aminosalicilic acid and similar agents	5	<1%
A07EC01 Sulfasalazine	3	<1%
A07EC02 Mesalazine	2	<1%
Unspecified antidiarrhoeals	2	<1%
A09 Digestives, incl. enzymes	1	<1%
A09A Digestives, incl. enzymes	1	<1%
A09AA Enzyme preparations	1	<1%
A09AA02 Multienzymes (lipase, protease etc.)	1	<1%
A10 Drugs used in diabetes	321	17%
A10A Insulins and analogues	130	6.8%
A10AB Insulins and analogues, fast-acting	16	<1%
A10AC Insulins and analogues, intermediate-acting	18	<1%
A10AD Insulins and analogues, intermediate-acting combined with fast-acting	78	4.1%
A10AE Insulins and analogues, long-acting	1	<1%
Insulin, type unspecified	30	1.6%
A10B Oral blood glucose lowering drugs	225	12%
A10BA Biguanides	190	10%
A10BA02 Metformin	190	10%
A10BB Sulfonamides, urea derivatives	109	5.7%
A10BB01 Glibenclamide	43	2.3%
A10BB09 Gliclazide	66	3.5%
Unspecified oral blood glucose lowering drugs	11	<1%
Unspecified treatment for diabetes	18	<1%
A11 – A12 Vitamin and mineral supplements	212	11%
B BLOOD AND BLOOD FORMING ORGANS	370	19%
B01 Antithrombotic agents	305	16%
B01A Antithrombotic agents	305	16%
B01AA Vitamin K antagonists	57	3.0%
B01AA03 Warfarin	57	3.0%
B01AB Heparin group	36	1.9%
B01AB01 Heparin	13	<1%
B01AB05 Enoxaparin	23	1.2%
B01AC Platelet aggregation inhibitors, excl. heparins	238	13%
B01AC04 Clopidogrel	10	<1%
B01AC06 Acetylsalicylic acid	238	13%
B01AD Enzymes	7	<1%
B01AD01 Streptokinase	7	<1%

B02 Antihaemorrhagics	9	<1%
B02A Antifibrinolytics	4	<1%
B02AA Amino acids	4	<1%
B02AA02 Tranexamic acid	4	<1%
B02B Vitamin K and other haemostatics	5	<1%
B02BA Vitamin K	5	<1%
B02BA01 Phytomenadione	5	<1%
B03 Anti-anaemic preparations	77	4.0%
B03A Iron preparations	55	2.9%
B03AA Iron bivalent, oral preparations	54	2.8%
B03AA07 Ferrous sulfate	54	2.8%
B03AD Iron in combination with folic acid	2	<1%
B03AD02 Ferrous fumarate	2	<1%
B03B Vitamin B12 and folic acid	51	2.7%
B03BA Vitamin B12 (cyanocobalamin and analogues)	3	<1%
B03BA01 Cyanocobalamin	3	<1%
B03BB Folic acid and derivatives	48	2.5%
B03BB01 Folic acid	48	2.5%
B03X Other anti-anaemic preparations	2	<1%
B03XA Other anti-anaemic preparations	2	<1%
B03XA01 Erythropoietin	2	<1%
B05 Blood substitutes and perfusion solutions	12	<1%
B05B IV solutions	5	<1%
B05BA Solutions for parenteral nutrition	5	<1%
B05BA03 Carbohydrate solutions for parenteral nutrition	5	<1%
B05C Irrigating solutions	4	<1%
B05CX Other irrigating solutions	4	<1%
B05CX01 Glucose	4	<1%
B05X IV Solution additives	4	<1%
B05XA Electrolyte solutions	4	<1%
B05XA01 Potassium chloride	2	<1%
B05XA02 Sodium bicarbonate	2	<1%
C CARDIOVASCULAR SYSTEM	765	40%
C01 Cardiac therapy	133	7.0%
C01A Cardiac glycosides	40	2.1%
C01AA Digitalis glycosides	40	2.1%
C01AA05 Digoxin	40	2.1%
C01B Anti-arrhythmics, class I and III	7	<1%
C01BA Anti-arrhythmics, class Ia	1	<1%
C01BA03 Disopyramide	1	<1%
C01BD Anti-arrhythmics, class III	6	<1%
C01BD01 Amiodarone	6	<1%
C01C Cardiac stimulants, excl. cardiac glycosides	2	<1%
C01CA Adrenergic and dopaminergic agents	2	<1%
C01CA24 Epinephrine	2	<1%
C01D Vasodilators used in cardiac diseases	85	4.5%
C01DA Organic nitrates	85	4.5%
C01DA02 Glyceryl trinitrate	5	<1%
C01DA08 Isosorbide dinitrate	67	3.5%
C01DA14 Isosorbide mononitrate	26	1.4%
Unspecified nitrates	2	<1%
C01E Other cardiac preparations	2	<1%
C01EB Other cardiac preparations	2	<1%
C01EB10 Adenosine	1	<1%
C01EB17 Ivabradine	1	<1%

C02 Antihypertensives	35	1.8%
C02A Antiadrenergic agents, centrally acting	2	<1%
C02AB Methyldopa	2	<1%
C02AB01 Methyldopa (levorotatory)	2	<1%
C02C Antiadrenergic agents, peripherally acting	17	<1%
C02CA Alpha-adrenoreceptor antagonists	17	<1%
C02CA01 Prazosin	3	<1%
C02CA04 Doxazosin	14	<1%
C02D Arteriolar smooth muscle, agents acting on	22	1.2%
C02DB Hydrazinophthalazine derivatives	21	1.1%
C02DB02 Hydralazine	21	1.1%
C02DC Pyrimidine derivatives	1	<1%
C02DC01 Minoxidil	1	<1%
C03 Diuretics	559	29%
C03A Low-ceiling diuretics, thiazides	262	14%
C03AA Thiazides, plain	260	14%
C03AA03 Hydrochlorothiazide	260	14%
C03AB Thiazides and potassium in combination	2	<1%
C03AB03 Hydrochlorothiazide and potassium	2	<1%
C03B Low-ceiling diuretics, excl. thiazides	1	<1%
C03BA Sulfonamides, plain	1	<1%
C03BA11 Indapamide	1	<1%
C03C High-ceiling diuretics	327	17%
C03CA Sulfonamides, plain	327	17%
C03CA01 Furosemide	327	17%
C03D Potassium-sparing agents	80	4.2%
C03DA Aldosterone antagonists	79	4.1%
C03DA01 Spironolactone	79	4.1%
C03DB Other potassium-sparing agents	1	<1%
C03DB01 Amiloride	1	<1%
Unspecified diuretics	2	<1%
C05 Vasoprotectives	1	<1%
C05A Anti-haemorrhoidals for topical use	1	<1%
C05AX Other anti-haemorrhoidals for topical use	1	<1%
C05AX02 Bismuth preparations, combinations	1	<1%
C07 Beta-blocking agents	186	9.8%
C07A Beta-blocking agents	186	9.8%
C07AA Beta-blocking agents, non-selective	6	<1%
C07AA05 Propranolol	6	<1%
C07AB Beta-blocking agents, selective	134	7.0%
C07AB03 Atenolol	132	6.9%
C07AB07 Bisoprolol	2	<1%
C07AG Alpha- and beta-blocking agents	48	2.5%
C07AG02 Carvedilol	48	2.5%
C08 Calcium channel blockers	240	13%
C08C Selective calcium channel blockers with mainly vascular effects	230	12%
C08CA Dihydropyridine derivatives	230	12%
C08CA01 Amlodipine	187	9.8%
C08CA05 Nifedipine	44	2.3%
C08D Selective calcium channel blockers with direct cardiac effects	10	<1%
C08DA Phenylalkylamine derivatives	9	<1%
C08DA01 Verapamil	9	<1%
C08DB Benzothiazepine derivatives	1	<1%
C08DB01 Diltiazem	1	<1%
C09 Agents acting on the renin-angiotensin system	386	20%

C09A ACE-inhibitors, plain	369	19%
C09AA ACE-inhibitors, plain	369	19%
C09AA01 Captopril	6	<1%
C09AA02 Enalapril	246	13%
C09AA04 Perindopril	117	6.1%
C09B ACE-inhibitors, combinations	4	<1%
C09BA ACE-inhibitors and diuretics	4	<1%
C09BA03 Lisinopril and diuretics	1	<1%
C09BA04 Perindopril and diuretics	3	<1%
C09C Angiotensin II antagonists, plain	14	<1%
C09CA Angiotensin II antagonists, plain	14	<1%
C09CA01 Losartan	13	<1%
C09CA03 Valsartan	1	<1%
C09D Angiotensin II antagonists, combinations	1	<1%
C09DA Angiotensin II antagonists and diuretics	1	<1%
C09DA07 Telmisartan and diuretics	1	<1%
C10 Serum lipid reducing agents	223	12%
C10A Cholesterol and triglyceride reducers	220	12%
C10AA HMG-coA reductase inhibitors	217	11%
C10AA01 Simvastatin	208	11%
C10AA05 Atorvastatin	6	<1%
Unspecified statins	3	<1%
C10AB Fibrates	1	<1%
C10AB02 Bezafibrate	1	<1%
C10AC Bile acid sequestrants	2	<1%
C10AC01 Cholestyramine	2	<1%
Unspecified lipid reducing agents	3	<1%
Unspecified cardiovascular agents (*)	71	3.7%
D DERMATOLOGICALS	14	<1%
D01 Antifungals for dermatological use	5	<1%
D01A Antifungals for topical use	3	<1%
D01AC Imidazole and triazole derivatives	2	<1%
D01AC01 Clotrimazole	2	<1%
D01AE Other antifungals for topical use	1	<1%
D01AE02 Methylrosaniline (Gentian violet)	1	<1%
D01B Antifungals for systemic use	2	<1%
D01BA Antifungals for systemic use	2	<1%
D01BA01 Griseofulvin	2	<1%
D02 Emollients and protectives	3	<1%
D02A Emollients and protectives	3	<1%
D02AB Zinc products	1	<1%
D02AX Other emollients and protectives	2	<1%
D07 Corticosteroids, dermatological preparations	4	<1%
D07A Corticosteroids, plain	4	<1%
D07AA Corticosteroids, weak (Group I)	1	<1%
D07AA02 Hydrocortisone	1	<1%
D07AC Corticosteroids, potent (Group III)	3	<1%
D07AC01 Betamethasone	3	<1%
D07AD Corticosteroids, very potent (Group IV)	1	<1%
D07AD01 Clobetasol	1	<1%
D08 Antiseptics and disinfectants	2	<1%
D08A Antiseptics and disinfectants	2	<1%
D08AG Iodine products	1	<1%
D08AG02 Povidone-iodine	1	<1%
D08AX Other antiseptics and disinfectants	1	<1%

D08AX06 Potassium permanganate	1	<1%
G GENITO-URINARY SYSTEM AND SEX HORMONES	21	1.1%
G02 Other gynaecologicals	2	<1%
G02A Oxytocics	1	<1%
G02AB Ergot alkaloids	1	<1%
G02AB03 Ergometrine	1	<1%
G02C Other gynaecologicals	1	<1%
G02CB Prolactine inhibitors	1	<1%
G02CB01 Bromocriptine	1	<1%
G03 Sex hormones and modulators of the genital system	10	<1%
G03A Hormonal contraceptives for systemic use	9	<1%
G03AA Progestogens and oestrogens, fixed combinations	2	<1%
G03AA07 Levonorgestrel and oestrogen	2	<1%
G03AC Progestogens	5	<1%
G03AC01 Norethisterone	1	<1%
G03AC06 Medroxyprogesterone	4	<1%
Unspecified hormonal contraceptives	2	<1%
Unspecified sex hormones	1	<1%
G04 Urologicals	9	<1%
G04B Other urologicals, incl. antispasmodics	3	<1%
G04BD Urinary antispasmodics	3	<1%
G04BD04 Oxybutynin	3	<1%
G04C Drugs used in benign prostatic hypertrophy	8	<1%
G04CA Alpha-adrenoreceptor antagonists	8	<1%
G04CA02 Tamsulosin	8	<1%
H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	142	7.5%
H01 Pituitary and hypothalamic hormones and analogues	1	<1%
H01C Hypothalamic hormones	1	<1%
H01CB Antigrowth hormone	1	<1%
H01CB01 Somatostatin	1	<1%
H02 Corticosteroids for systemic use	118	6.2%
H02A Corticosteroids for systemic use, plain	118	6.2%
H02AB Glucocorticoids	118	6.2%
H02AB01 Betamethasone	1	<1%
H02AB02 Dexamethasone	4	<1%
H02AB04 Methylprednisolone	3	<1%
H02AB06 Prednisolone	4	<1%
H02AB07 Prednisone	97	5.1%
H02AB09 Hydrocortisone	23	1.2%
H03 Thyroid therapy	27	1.4%
H03A Thyroid preparations	23	1.2%
H03AA Thyroid hormones	23	1.2%
H03AA01 Levothyroxine sodium	23	1.2%
H03AA03 Combinations of levothyroxine and liothyronine	1	<1%
H03B Antithyroid preparations	4	<1%
H03BB Sulfur-containing imidazole derivatives	4	<1%
H03BB01 Carbimazole	4	<1%
J ANTI-INFECTIVES FOR SYSTEMIC USE	559	29%
J01 Antibacterials for systemic use	240	13%
J01A Tetracyclines	11	<1%
J01AA Tetracyclines	11	<1%
J01AA02 Doxycycline	11	<1%
J01C Beta-lactam antibacterials, penicillins	101	5.3%
J01CA Penicillins with extended spectrum	59	3.1%
J01CA01 Ampicillin	6	<1%

J01CA04 Amoxicillin	52	2.7%
J01CA12 Piperacillin	1	<1%
J01CE Beta-lactamase sensitive penicillins	6	<1%
J01CE01 Benzylpenicillin	4	<1%
J01CE02 Phenoxymethylpenicillin	2	<1%
J01CF Beta-lactamase resistant penicillins	8	<1%
J01CF02 Cloxacillin	4	<1%
J01CF05 Flucloxacillin	4	<1%
J01CG Beta-lactamase inhibitors	1	<1%
J01CG02 Tazobactam	1	<1%
J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	39	2.0%
J01CR02 Amoxicillin and enzyme inhibitor	39	2.0%
J01CR05 Piperacillin and enzyme inhibitor	1	<1%
Unspecified penicillins	1	<1%
J01D Other beta-lactam antibacterials	57	3.0%
J01DC Second-generation cephalosporins	5	<1%
J01DC02 Cefuroxime	5	<1%
J01DD Third-generation cephalosporins	52	2.7%
J01DD01 Cefotaxime	1	<1%
J01DD04 Ceftriaxone	50	2.6%
J01DD08 Cefixime	1	<1%
J01DH Carbapenems	1	<1%
J01DH03 Ertapenem	1	<1%
J01E Sulfonamides and trimethoprim	68	3.6%
J01EE Combinations of sulfonamides and trimethoprim, incl. derivatives	68	3.6%
J01EE01 Sulfamethoxazole and trimethoprim	68	3.6%
J01F Macrolides, lincosamides and streptogramins	15	<1%
J01FA Macrolides	13	<1%
J01FA01 Erythromycin	6	<1%
J01FA09 Clarithromycin	4	<1%
J01FA10 Azithromycin	3	<1%
J01FA15 Telithromycin	1	<1%
J01FF Lincosamides	2	<1%
J01FF01 Clindamycin	2	<1%
J01G Aminoglycoside antibacterials	8	<1%
J01GB Other aminoglycosides	8	<1%
J01GB03 Gentamicin	4	<1%
J01GB04 Kanamycin	4	<1%
J01M Quinolone antibacterials	23	1.2%
J01MA Fluoroquinolones	23	1.2%
J01MA01 Ofloxacin	1	<1%
J01MA02 Ciprofloxacin	17	<1%
J01MA14 Moxifloxacin	5	<1%
J01X Other antibacterials	1	<1%
J01XB Polymyxins	1	<1%
J01XB01 Colistin	1	<1%
Unspecified antibacterials	13	<1%
J02 Antimycotics for systemic use	26	1.4%
J02A Antimycotics for systemic use	26	1.4%
J02AC Triazole derivatives	26	1.4%
J02AC01 Fluconazole	25	1.3%
J02AC02 Itraconazole	1	<1%
J04 Antimycobacterials	198	10%
J04A Drugs for treatment of tuberculosis	197	10%

J04AB Antibiotics	179	9.4%
J04AB02 Rifampicin	179	9.4%
J04AC Hydrazides	187	9.8%
J04AC01 Isoniazid	187	9.8%
J04AD Thiocarbamide derivatives	4	<1%
J04AD03 Ethionamide	4	<1%
J04AK Other drugs for treatment of tuberculosis	138	7.2%
J04AK01 Pyrazinamide	134	7.0%
J04AK02 Ethambutol	134	7.0%
J04AK03 Terizidone	4	<1%
Unspecified treatment for tuberculosis	4	<1%
J04B Drugs for treatment of lepra	1	<1%
J04BA Drugs for treatment of lepra	1	<1%
J04BA02 Dapsone	1	<1%
J05 Antivirals for systemic use	320	17%
J05A Direct-acting antivirals	320	17%
J05AB Nucleosides and nucleotides, excl. reverse transcriptase inhibitors	6	<1%
J05AB01 Aciclovir	6	<1%
J05AE Protease inhibitors	20	1.1%
J05AE08 Atazanavir	1	<1%
J05AE30 Lopinavir-ritonavir	19	<1%
J05AF Nucleoside and nucleotide reverse transcriptase inhibitors	278	15%
J05AF01 Zidovudine	28	1.5%
J05AF02 Didanosine	1	<1%
J05AF04 Stavudine	37	1.9%
J05AF05 Lamivudine	213	11%
J05AF06 Abacavir	9	<1%
J05AF07 Tenofovir disoproxil	207	11%
J05AF09 Emtricitabine	62	3.3%
J05AG Non-nucleoside reverse transcriptase inhibitors	255	13%
J05AG01 Nevirapine	15	<1%
J05AG03 Efavirenz	240	13%
J05AX Other antivirals	1	<1%
J05AX08 Raltegravir	1	<1%
Unspecified antiretroviral therapy	41	2.2%
J07 Vaccines	1	<1%
J07B Viral vaccines	1	<1%
J07BB Influenza vaccines	1	<1%
L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	27	1.4%
L01 Antineoplastic agents	6	<1%
L01A Alkylating agents	1	<1%
L01AA Nitrogen mustard analogues	1	<1%
L01AA02 Chlorambucil	1	<1%
L01X Other antineoplastic agents	2	<1%
L01XE Protein kinase inhibitors	2	<1%
L01XE01 Imatinib	2	<1%
Unspecified antineoplastic agents	3	<1%
L02 Endocrine therapy	2	<1%
L02B Hormone antagonists and related agents	2	<1%
L02BA Anti-oestrogens	2	<1%
L02BA01 Tamoxifen	2	<1%
L04 Immunosuppressive agents	19	<1%
L04A Immunosuppressive agents	19	<1%
L04AA Selective immunosuppressive agents	1	<1%

L04AA06 Mycophenolic acid	1	<1%
L04AD Calcineurin inhibitors	3	<1%
L04AD01 Ciclosporin	1	<1%
L04AD02 Tacrolimus	2	<1%
L04AX Other immunosuppressive agents	16	<1%
L04AX01 Azathioprine	5	<1%
L04AX03 Methotrexate	11	<1%
M MUSCULO-SKELETAL SYSTEM	79	4.1%
M01 Anti-inflammatory and antirheumatic products	49	2.6%
M01A Anti-inflammatory and antirheumatic products, non-steroids	49	2.6%
M01AB Acetic acid derivatives and related substances	21	1.1%
M01AB01 Indometacin	6	<1%
M01AB05 Diclofenac	16	<1%
M01AE Propionic acid derivatives	22	1.2%
M01AE01 Ibuprofen	20	1.1%
M01AE02 Naproxen	1	<1%
M01AE51 Ibuprofen, combinations	2	<1%
M01AG Fenamates	1	<1%
M01AG01 Mefenamic acid	1	<1%
M01AH Coxibs	2	<1%
M01AH01 Celecoxib	1	<1%
M01AH04 Parecoxib	1	<1%
Unspecified non-steroidal anti-inflammatories	6	<1%
M02 Topical products for joint and muscular pain	7	<1%
M02A Topical products for joint and muscular pain	7	<1%
M02AA Anti-inflammatory preparations, non-steroids for topical use	1	<1%
M02AA13 Ibuprofen	1	<1%
M02AC Preparations with salicylic acid derivatives	5	<1%
Unspecified topical products for joint and muscular pain	1	<1%
M03 Muscle relaxants	4	<1%
M03A Muscle relaxants, peripherally acting agents	1	<1%
M03AB Choline derivatives	1	<1%
M03AB01 Suxamethonium	1	<1%
M03B Muscle relaxants, centrally acting agents	3	<1%
M03BX Other centrally acting agents	3	<1%
M03BX01 Baclofen	3	<1%
M04 Antigout preparations	22	1.2%
M04A Antigout preparations	22	1.2%
M04AA Preparations inhibiting uric acid production	18	<1%
M04AA01 Allopurinol	18	<1%
M04AC Preparations with no effect on uric acid metabolism	7	<1%
M04AC01 Colchicine	7	<1%
Unspecified antigout preparations	1	<1%
M05 Drugs for treatment of bone diseases	2	<1%
M05B Drugs affecting bone structure and mineralization	2	<1%
M05BA Bisphosphonates	2	<1%
M05BA04 Alendronic acid	2	<1%
N NERVOUS SYSTEM	427	22%
N02 Analgesics	228	12%
N02A Opioids	90	4.7%
N02AA Natural opium alkaloids	32	1.7%
N02AA01 Morphine	30	1.6%
N02AA08 Dihydrocodeine	2	<1%
N02AB Phenylpiperidine derivatives	2	<1%
N02AB02 Pethidine	2	<1%

N02AX Other opioids	65	3.4%
N02AX02 Tramadol	63	3.3%
N02AX52 Tramadol, combinations	2	<1%
N02B Other analgesics and antipyretics	185	9.7%
N02BE Anilides	185	9.7%
N02BE01 Paracetamol	160	8.4%
N02BE51 Paracetamol, combinations excl. psycholeptics	31	1.6%
N02BE71 Paracetamol, combinations with psycholeptics	2	<1%
Unspecified analgesics	6	<1%
N03 Anti-epileptics	139	7.3%
N03A Anti-epileptics	139	7.3%
N03AA Barbiturates and derivatives	3	<1%
N03AA02 Phenobarbital	3	<1%
N03AB Hydantoin derivatives	55	2.9%
N03AB02 Phenytoin	55	2.9%
N03AE Benzodiazepine derivatives	19	<1%
N03AE01 Clonazepam	19	<1%
N03AF Carboxamide derivatives	26	1.4%
N03AF01 Carbamazepine	26	1.4%
N03AG Fatty acid derivatives	60	3.2%
N03AG01 Valproic acid	60	3.2%
N03AX Other anti-epileptics	5	<1%
N03AX09 Lamotrigine	5	<1%
Unspecified anti-epileptics	7	<1%
N04 Anti-Parkinson drugs	23	1.2%
N04A Anticholinergic agents	18	<1%
N04AB Ethers chemically close to antihistamines	18	<1%
N04AB02 Orphenadrine	18	<1%
N04B Dopaminergic agents	5	<1%
N04BA Dopa and dopa derivatives	5	<1%
N04BA02 Levodopa and decarboxylase inhibitor	5	<1%
N05 Psycholeptics	100	5.3%
N05A Antipsychotics	67	3.5%
N05AA Phenothiazines with aliphatic side-chain	6	<1%
N05AA01 Chlorpromazine	6	<1%
N05AB Phenothiazines with piperazine structure	7	<1%
N05AB02 Fluphenazine	3	<1%
N05AB04 Prochlorperazine	4	<1%
N05AD Butyrophenone derivatives	33	1.7%
N05AD01 Haloperidol	33	1.7%
N05AF Thioxanthene derivatives	6	<1%
N05AF01 Flupentixol	2	<1%
N05AF05 Zuclopenthixol	4	<1%
N05AH Diazepines, oxazepines and thiazepines	6	<1%
N05AH02 Clozapine	2	<1%
N05AH04 Quetiapine	4	<1%
N05AN Lithium	1	<1%
N05AN01 Lithium	1	<1%
N05AX Other antipsychotics	11	<1%
N05AX08 Risperidone	11	<1%
Unspecified antipsychotics	4	<1%
N05B Anxiolytics	40	2.1%
N05BA Benzodiazepine derivatives	40	2.1%
N05BA01 Diazepam	24	1.3%
N05BA04 Oxazepam	4	<1%

N05BA06 Lorazepam	13	<1%
N05C Hypnotics and sedatives	9	<1%
N05CD Benzodiazepine derivatives	4	<1%
N05CD08 Midazolam	4	<1%
N05CF Benzodiazepine-related drugs	5	<1%
N05CF01 Zopiclone	4	<1%
N05CF02 Zolpidem	1	<1%
N06 Psychoanaleptics	63	3.3%
N06A Antidepressants	63	3.3%
N06AA Non-selective monoamine reuptake inhibitors	45	2.4%
N06AA09 Amitriptyline	42	2.2%
Unspecified non-selective monoamine reuptake inhibitors	3	<1%
N06AB Selective serotonin reuptake inhibitors	13	<1%
N06AB03 Fluoxetine	9	<1%
N06AB04 Citalopram	5	<1%
N06AX Other antidepressants	3	<1%
N06AX03 Mianserin	2	<1%
N06AX16 Venlafaxine	1	<1%
Unspecified antidepressants	2	<1%
N07 Other nervous system drugs	1	<1%
N07A Parasympathomimetics	1	<1%
N07AA Anticholinesterases	1	<1%
N07AA02 Pyridostigmine	1	<1%
Unspecified drugs acting on the nervous system	3	<1%
P ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	36	1.9%
P01 Antiprotozoals	35	1.8%
P01A Agents against amoebiasis and other protozoal diseases	26	1.4%
P01AB Nitroimidazole derivatives	26	1.4%
P01AB01 Metronidazole	26	1.4%
P01B Antimalarials	9	<1%
P01BA Aminoquinolines	9	<1%
P01BA01 Chloroquine	9	<1%
P03 Ectoparasiticides, incl. scabicides, insecticides and repellents	1	<1%
P03A Ectoparasiticides, incl. scabicides	1	<1%
P03AA Sulfur-containing products	1	<1%
Monosulfiram	1	<1%
R RESPIRATORY SYSTEM	219	12%
R01 Nasal preparations	7	<1%
R01A Decongestants and other nasal preparations for topical use	7	<1%
R01AA Sympathomimetics, plain	1	<1%
R01AA05 Oxymetazoline	1	<1%
R01AD Corticosteroids	6	<1%
R01AD01 Beclometasone	6	<1%
R02 Throat preparations	2	<1%
R02A Throat preparations	2	<1%
R02AA Antiseptics	2	<1%
R02AA20 Various throat antiseptics	2	<1%
R03 Drugs for obstructive airway	194	10%
R03A Adrenergics, inhalants	149	7.8%
R03AA Alpha- and beta-adrenoreceptor agonists	1	<1%
R03AA01 Epinephrine	1	<1%
R03AC Selective beta-2-adrenoreceptor agonists	148	7.8%
R03AC02 Salbutamol	144	7.6%
R03AC04 Fenoterol	5	<1%
R03AC12 Salmeterol	3	<1%

R03AC13 Formoterol	8	<1%
Unspecified beta-adrenergic inhalant	1	<1%
R03AK Adrenergics and other drugs for obstructive airway diseases	1	<1%
R03AK06 Salmeterol and other drugs for obstructive airway diseases	1	<1%
R03B Other drugs for obstructive airway diseases, inhalants	103	5.4%
R03BA Glucocorticoids	88	4.6%
R03BA01 Beclometasone	16	<1%
R03BA02 Budesonide	74	3.9%
Unspecified inhaled corticosteroid	1	<1%
R03BB Anticholinergics	36	1.9%
R03BB01 Ipratropium bromide	35	1.8%
R03BB04 Tiotropium bromide	1	<1%
R03C Adrenergics for systemic use	3	<1%
R03CC Selective beta-2-adrenoreceptor agonists	3	<1%
R03CC02 Salbutamol	3	<1%
R03D Other systemic drugs for obstructive airway diseases	67	3.5%
R03DA Xanthines	67	3.5%
R03DA04 Theophylline	64	3.4%
R03DA05 Aminophylline	2	<1%
R03DA54 Theophylline, combinations excl. psycholeptics	2	<1%
Unspecified treatment for obstructive airway diseases	28	1.5%
R05 Cough and cold preparations	5	<1%
Unspecified cough and cold preparations	5	<1%
R06 Antihistamines for systemic use	29	1.5%
R06A Antihistamines for systemic use	29	1.5%
R06AA Aminoalkyl ethers	3	<1%
R06AA02 Diphenhydramine	3	<1%
R06AB Substituted alkylamines	14	<1%
R06AB04 Chlorphenamine	14	<1%
R06AD Phenothiazine derivatives	6	<1%
R06AD02 Promethazine	6	<1%
R06AE Piperazine derivatives	8	<1%
R06AE03 Cyclizine	2	<1%
R06AE07 Cetirizine	6	<1%
R06AX Other antihistamines for systemic use	1	<1%
R06AX13 Loratadine	1	<1%
Unspecified systemic antihistamines	1	<1%
S SENSORY ORGANS	8	<1%
S01 Ophthalmologicals	8	<1%
S01C Anti-inflammatory agents and anti-infectives in combination	1	<1%
S01CA Corticosteroids and anti-infectives in combination	1	<1%
S01CA01 Dexamethasone and anti-infectives	1	<1%
S01E Antiglaucoma preparations and miotics	3	<1%
S01EA Sympathomimetics in glaucoma therapy	1	<1%
S01EA05 Brimonidine	1	<1%
S01ED Beta-blocking agents	2	<1%
S01ED02 Betaxolol	1	<1%
S01ED51 Timolol, combinations	1	<1%
S01K Surgical aids	1	<1%
S01KA Viscoelastic substances	1	<1%
S01KA02 Hypromellose	1	<1%
S01X Other ophthalmologicals	1	<1%
S01XA Other ophthalmological	1	<1%
S01XA20 Artificial tears and other indifferent preparations	1	<1%

Unspecified ophthalmologicals	4	<1%
V VARIOUS	4	<1%
V03 All Other therapeutic products	4	<1%
V03A All Other therapeutic products	4	<1%
V03AE Drugs for treatment of hyperkalaemia and hyperphosphataemia	4	<1%
V03AE01 Polystyrene sulfonate	4	<1%
ANY HERBAL PREPARATION	10	<1%

(a) Number of patients who took the drug during the 30 days before admission.

(b) As a proportion of 1904 patients.

Appendix xlv. Reason for admission, according to ICD-10 classification (n=1951 admissions)

ICD-10 Chapter / Code block	Count	Proportion
ADVERSE DRUG REACTIONS	164	8.4%
(various codes) Adverse drug reactions	164	8.4%
CERTAIN INFECTIOUS AND PARASITIC DISEASES	285	15%
A00-A09 Intestinal infectious diseases	49	2.5%
A15-A19 Tuberculosis	155	7.9%
A30-A49 Other bacterial diseases	16	<1%
A50-A64 Infections with a predominantly sexual mode of transmission	2	<1%
A80-A89 Viral infections of the central nervous system	6	<1%
B00-B09 Viral infections characterized by skin and mucous membrane lesions	1	<1%
B15-B19 Viral hepatitis	5	<1%
B20-B24 Human immunodeficiency virus [HIV] disease	12	<1%
B35-B49 Mycoses	30	1.5%
B50-B64 Protozoal diseases	8	<1%
B65-B83 Helminthiasis	1	<1%
NEOPLASMS	53	2.7%
C15-C26 Malignant neoplasms of digestive organs	8	<1%
C30-C39 Malignant neoplasms of respiratory and intrathoracic organs	19	<1%
C45-C49 Malignant neoplasms of mesothelial and soft tissue	2	<1%
C50-C50 Malignant neoplasm of breast	1	<1%
C69-C72 Malignant neoplasms of eye, brain and other parts of the central nervous system	2	<1%
C73-C75 Malignant neoplasms of thyroid and other endocrine glands	1	<1%
C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites	14	<1%
C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	4	<1%
D00-D09 In situ neoplasms	1	<1%
D10-D36 Benign neoplasms	1	<1%
DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS; CERTAIN DISORDERS INVOLVING THE IMMUNE MECHANISM	35	1.8%
D50-D53 Nutritional anaemias	6	<1%
D55-D59 Haemolytic anaemias	2	<1%
D60-D64 Aplastic and other anaemias	18	<1%
D65-D69 Coagulation defects, purpura and other haemorrhagic conditions	7	<1%
D70-D77 Other diseases of blood and blood-forming organs	1	<1%
D80-D89 Certain disorders involving the immune mechanism	1	<1%
ENDOCRINE, NUTRITIONAL AND METABOLIC DISEASES	87	4.5%
E00-E07 Disorders of thyroid gland	1	<1%
E10-E14 Diabetes mellitus	62	3.2%
E15-E16 Other disorders of glucose regulation	4	<1%
E70-E90 Metabolic disorders	20	1.0%
MENTAL AND BEHAVIOURAL DISORDERS	106	5.4%
F00-F09 Organic, including symptomatic, mental disorders	26	1.3%
F10-F19 Mental and behavioural disorders due to psychoactive substance use	25	1.3%
F20-F29 Schizophrenia, schizotypal and delusional disorders	41	2.1%
F30-F39 Mood [affective] disorders	5	<1%
F40-F48 Neurotic, stress-related and somatoform disorders	9	<1%
DISEASES OF THE NERVOUS SYSTEM	115	5.9%
G00-G09 Inflammatory diseases of the central nervous system	19	<1%
G10-G14 Systemic atrophies primarily affecting the central nervous system	1	<1%
G20-G26 Extrapyrarnidal and movement disorders	1	<1%
G35-G37 Demyelinating diseases of the central nervous system	2	<1%
G40-G47 Episodic and paroxysmal disorders	68	3.5%
G50-G59 Nerve, nerve root and plexus disorders	1	<1%

G60-G64 Polyneuropathies and other disorders of the peripheral nervous system	3	<1%
G80-G83 Cerebral palsy and other paralytic syndromes	14	<1%
G90-G99 Other disorders of the nervous system	6	<1%
DISEASES OF THE EYE AND ADNEXA	3	<1%
H40-H42 Glaucoma	1	<1%
H46-H48 Disorders of optic nerve and visual pathways	1	<1%
H53-H54 Visual disturbances and blindness	1	<1%
DISEASES OF THE EAR AND MASTOID PROCESS	1	<1%
H65-H75 Diseases of middle ear and mastoid	1	<1%
DISEASES OF THE CIRCULATORY SYSTEM	496	25%
I05-I09 Chronic rheumatic heart diseases	2	<1%
I10-I15 Hypertensive diseases	30	1.5%
I20-I25 Ischaemic heart diseases	91	4.7%
I26-I28 Pulmonary heart disease and diseases of the pulmonary circulation	31	1.6%
I30-I52 Other forms of heart disease	151	7.7%
I60-I69 Cerebrovascular diseases	152	7.8%
I70-I79 Diseases of arteries, arterioles and capillaries	2	<1%
I80-H89 Diseases of veins, lymphatic vessels and lymph nodes	36	1.9%
I95-I99 Other and unspecified disorders of the cardiovascular system	1	<1%
DISEASES OF THE RESPIRATORY SYSTEM	313	16%
J00-J06 Acute upper respiratory infections	3	<1%
J09-J18 Influenza and pneumonia	117	6.0%
J20-J22 Other acute lower respiratory infections	40	2.1%
J40-J47 Chronic lower respiratory diseases	98	5.0%
J60-J70 Lung diseases due to external agents	2	<1%
J80-J84 Other respiratory diseases principally affecting the interstitium	23	1.2%
J85-J86 Suppurative and necrotic conditions of the lower respiratory tract	6	<1%
J90-J94 Other diseases of pleura	18	<1%
J95-J99 Other diseases of the respiratory system	6	<1%
DISEASES OF THE DIGESTIVE SYSTEM	39	2.0%
K00-K14 Diseases of oral cavity, salivary glands and jaws	1	<1%
K20-K31 Diseases of oesophagus, stomach and duodenum	6	<1%
K55-K64 Other diseases of intestines	9	<1%
K65-K67 Diseases of peritoneum	4	<1%
K70-K77 Diseases of liver	13	<1%
K80-K87 Disorders of gallbladder, biliary tract and pancreas	2	<1%
K90-K93 Other diseases of the digestive	4	<1%
DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUE	7	<1%
L00-L08 Infections of the skin and subcutaneous tissue	5	<1%
L10-L14 Bullous disorders	1	<1%
L80-L99 Other disorders of the skin and subcutaneous tissue	1	<1%
DISEASES OF THE MUSCULOSKELETAL SYSTEM AND CONNECTIVE TISSUE	10	<1%
M15-M19 Arthropathies: Arthrosis	1	<1%
M20-M25 Arthropathies: Other joint disorders	1	<1%
M30-M36 Systemic connective tissue disorders	3	<1%
M50-M54 Dorsopathies: Other dorsopathy	2	<1%
M70-M79 Soft tissue disorders: Other soft tissue disorders	2	<1%
M91-M94 Osteopathies and chondropathies: chondropathies	1	<1%
DISEASES OF THE GENITOURINARY SYSTEM	61	3.1%
N00-N08 Glomerular diseases	7	<1%
N10-N16 Renal tubulo-interstitial diseases	4	<1%
N17-N19 Renal failure	30	1.5%
N20-N23 Urolithiasis	1	<1%
N30-N39 Other diseases of urinary system	19	<1%

PREGNANCY, CHILDBIRTH AND THE PUERPERIUM	2	<1%
O00-O08 Pregnancy with abortive outcome	1	<1%
O10-O16 Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and puerperium	1	<1%
CONGENITAL MALFORMATIONS, DEFORMATIONS AND CHROMOSOMAL ABNORMALITIES	3	<1%
Q20-Q28 Congenital malformations of the circulatory system	2	<1%
Q60-Q64 Congenital malformations of the urinary system	1	<1%
SYMPTOMS, SIGNS AND ABNORMAL CLINICAL AND LABORATORY FINDINGS	94	4.8%
R00-R09 Symptoms and signs involving the circulatory and respiratory systems	18	<1%
R10-R19 Symptoms and signs involving the digestive system and abdomen	13	<1%
R40-R46 Symptoms and signs involving cognition, perception, emotional state and behaviour	16	<1%
R50-R69 General symptoms and signs	39	2.0%
R70-R79 Abnormal findings on examination of blood, without diagnosis	2	<1%
R90-R94 Abnormal findings on diagnostic imaging and on function studies, without diagnosis	6	<1%
INJURY, POISONING AND CERTAIN OTHER CONSEQUENCES OF EXTERNAL CAUSES	5	<1%
S00-S09 Injuries to the head	1	<1%
S70-S79 Injuries to the hip and thigh	2	<1%
T80-T88 Complications of surgical and medical care	2	<1%
EXTERNAL CAUSES OF MORBIDITY AND MORTALITY	65	3.3%
X40-X49 Accidents: Other external causes	1	<1%
X60-X84 Intentional self-harm	64	3.3%
FACTORS INFLUENCING HEALTH STATUS AND CONTACT WITH HEALTH SERVICES	7	<1%
Z00-Z13 Persons encountering health services for examination and investigation	1	<1%
Z40-Z54 Persons encountering health services for specific procedures and health care	4	<1%
Z70-Z76 Persons encountering health services in other circumstances	2	<1%
TOTAL	1951	100%

Appendix xlvii. Summary of presentation of patients admitted for drug-induced renal impairment

Cas e	Age, sex	HIV, CD4	Presentation	Implicated Drugs (duration)	Causality	Preventable
1†	40 M	Pos (70)	Creat = 1026, K = 6.8; baseline creat = 145 (3m ago). Hypertension and previous CVA.	Tenofovir (unk)	Possible	Yes
2	56 F	Neg	Creat = 360, K = 4.0; no baseline available. Urinary tract infection.	Spiroonolactone (>3w), enalapril (>3w), and furosemide (>3w)	Possible	Yes
3†	25 M	Pos (297)	Creat = 139, K = 5.5 and hypocalcaemia; baseline creat = 65 (2m ago). Kaposi sarcoma, pulmonary TB and chronic gastroenteritis.	Tenofovir (3m)	Possible	Yes
4	41 F	Pos (416)	Creat = 268, K = 3.2 and proteinuria; baseline creat = 67 (4m ago). Biopsy: mild HIVAN, central sclerosing variant. Pulmonary TB.	Tenofovir (4m)	Possible	Yes
5†	49 M	Unk	Creat = 1038, K = 6.7; baseline not recorded, but known with chronic kidney disease, hypertension and diabetes.	Acetylsalicylic acid (unk), furosemide (unk), perindopril and HCTZ (unk), and valsartan (unk)	Possible	Yes
6†	30 M	Pos (unk)	Creat = 647, K = 5.0; no baseline available. Gastroenteritis, dehydration, lower respiratory tract infection	Tenofovir (2m or more)	Possible	No
7	42 M	Neg	Creat = 614, K = 4.5 and proteinuria. Biopsy: diabetic nodular glomerulosclerosis.	Enalapril (3d)	Probable	No
8	22 F	Pos (140)	Creat = 1337, K = 7.3 and proteinuria; baseline creat = 39 (3w ago). Suspected sepsis (raised inflammatory markers).	Tenofovir (3w)	Possible	No
9†	36 M	Pos (84)	Creat = 2300, K = 8.9 and proteinuria; baseline creat = 818 (5w ago). Chronic kidney disease previously attributed to HIVAN.	Captopril (4w), furosemide (2.5w), and HCTZ (2w)	Probable	Yes
10	32 M	Pos (31)	Creat = 303, K = 4.1 and proteinuria; baseline creat = 63 (3m ago). Pulmonary TB and chronic gastroenteritis.	Tenofovir (2m)	Possible	No
11†	65 F	Unk	Creat = 1541, K = 4.5; baseline creat = 350 (14m ago). Hypertension, diabetes, previous CVA, cardiac failure, gastroenteritis.	Enalapril (>1y)	Possible	Yes
12	56 F	Unk	Creat = 360, K = 4.0; no baseline available. Gastroenteritis and dehydration.	Amlodipine (>5y), atenolol (>5y), enalapril (>5y), furosemide (>2y), HCTZ (>5y), and hydralazine (>2y)	Possible	No
13	34 F	Pos (137)	Creat = 171, K = 2.2, phosphate low, chloride high, normal anion gap, acidosis; baseline creat = 68 (4m ago). TB meningitis.	Tenofovir (unk)	Possible	Yes
14†	43 F	Pos (103)	Creat = 1356, K = 5.2; no baseline available. Chronic gastroenteritis, dehydration.	Tenofovir (3m)	Possible	No
15	48 M	Unk	Creat = 807, K = 6.7 and proteinuria; baseline creat = 179 (18m ago). Type 2 diabetes, chronic kidney disease, gastroenteritis.	Spiroonolactone (unk), enalapril (unk), and furosemide (unk)	Possible	Yes
16		Neg		Rifampicin (4w)	Possible	No

Cas e	Age, sex	HIV, CD4	Presentation	Implicated Drugs (duration)	Causality	Preventable
	69 M		Creat = 1249, K = 5.7 and proteinuria; baseline creat = 72 (1m ago). Biopsy: acute tubular necrosis on background mild diabetic changes. Pulmonary TB.	Enalapril (unk)	Possible	No
17†	31 F	Pos (700)	Creat = 822, K = 4.6; no baseline available. Epilepsy, schizophrenia, urinary tract infection.	Co-amoxiclav (5d)	Possible	No
				Ibuprofen (5d)	Possible	No
18	28 F	Pos (218)	Creat = 605, K = 2.8; baseline creat = 112 (10d ago). Pulmonary TB.	Co-trimoxazole (unk)	Possible	No
				Tenofovir (for 2w, stopped 1m ago)	Possible	Yes
19†	34 M	Pos (167)	Creat = 712, K = 6.7; baseline creat = 69 (11m ago). Kaposi sarcoma, vomiting.	Aciclovir (for 1w, 3w ago)	Possible	No
				Co-amoxiclav (for 1w, 3w ago)	Possible	No
				Indometacin (for 1w, 3w ago)	Possible	No
				Tenofovir (unk)	Possible	No
20†	43 F	Pos (46)	Creat = 1552, K = 8.3; baseline creat = 52 (10w ago). Recurrent <i>H. influenzae</i> pneumonia, diarrhoea and vomiting.	Co-trimoxazole (unk)	Possible	No
				Tenofovir (unk)	Possible	No
21†*	33 F	Pos (37)	Hepatorenal failure (mixed LI and AKI). Creat = 608, K = 5.6; baseline creat = 51 (1m ago). Pulmonary TB. Severe hypertension, CVA.	Rifampicin (5d)	Probable	No
22*	50 M	Pos (165)	Hepatorenal failure (cholestatic LI and AKI). Creat = 1133, K = 6.1; baseline creat = 75 (6m ago).	Enalapril (unk) (Could not exclude a potential role played by traditional remedies)	Possible	No
23†*	44 M	Pos (unk)	Hepatorenal failure (hepatocellular LI and AKI). Creat = 259, K = 6.5; baseline creat = 112 (10d ago). Depressed level of consciousness.	Co-trimoxazole (unk)	Possible	Yes
24*	34 M	Pos (208)	Hepatorenal failure (cholestatic LI and AKI). Creat = 907, K = 4.0; baseline creat = 81 (5m ago).	Co-trimoxazole (unk)	Probable	No

* Case also included in appendix on patients presenting with DILI

† Patient died (from any cause) during admission or 30-day follow-up period

AKI: acute kidney injury; CD4: CD4-cell count (cells / μ L); Creat: serum- creatinine concentration (μ mol/L); CVA: cerebrovascular accident; d/w/m/y: duration in days / weeks / months / years; F: female; HCTZ: hydrochlorothiazide; HIVAN: HIV-associated nephropathy; K: serum potassium concentration (mmol/L); LI: liver injury; M: male; neg: HIV-seronegative; pos: HIV-seropositive; TB: tuberculosis; unk: unknown

Appendix xlviii. Summary of presentation of patients admitted for drug-induced hypoglycaemia

Case	Age, sex	HIV status	BG	Renal impairment	Relevant co-morbidities	Implicated drugs (duration)	Causality	Preventable
25	54 F	Neg	1.4	Yes: Creat=400		Gliclazide (unk) & metformin (unk)	Certain	Yes
26	74 F	Unk	2	Yes: eGFR=32	?Nosocomial sepsis (WCC=10)	Insulin (>10y)	Certain	Yes
27	79 F	Unk	2.1	No		Gliclazide (3d) & metformin (>6m)	Certain	Yes
28	77 F	Unk	1.2	Yes: eGFR=40	Dementia	Gliclazide (unk)	Certain	Yes
29	56 F	Unk	2.2	Yes: Creat=200		Insulin (unk), gliclazide (unk) & metformin (unk)	Certain	Yes
30	52 F	Neg	1.2	Yes: Creat=190	WCC=23	Insulin (unk)	Certain	Yes
31	68 F	Unk	1.9	Yes: Creat=233		Glibenclamide (unk) & metformin (unk)	Certain	Yes
32	60 F	Unk	2.2	No		Glibenclamide (unk) & metformin (unk)	Certain	Yes
33	77 M	Unk	2.8	Yes: Creat=103	?UTI (CRP=37) Dementia	Insulin (unk), gliclazide (unk) & metformin (unk)	Certain	Yes
34†	74 F	Unk	1.7	Yes: Creat=131	Old CVA, repeat CVA, WCC=10, CRP=24	Insulin (unk) & metformin (unk)	Certain	No
35	56 F	Unk	NR	Yes: Creat=88	Gastroenteritis, pneumonia	Gliclazide (unk) & metformin (unk)	Certain	Yes
36	70 F	Unk	NR	Yes: Creat=97		Insulin (>6m)	Certain	Yes
37	55 M	Unk	NR	No	Pneumonia (WCC=13, CRP<5) Skipped a meal but used insulin	Insulin (unk), glibenclamide (unk) & metformin (unk)	Certain	Yes
38†	53 M	Unk	0.7	Yes: eGFR=25		Insulin (1w)	Certain	Yes
39	56 M	Unk	1.8	Yes: eGFR=6	WCC=17	Glibenclamide (1m)	Probable	Yes
40†	73 F	Unk	0.5	Yes: eGFR=31	Sepsis (fever, WCC=14, neutrophilia)	Insulin (>2y)	Probable	No
41	56 F	Unk	0.7	No		Insulin (unk)	Certain	No
42†	61 F	Unk	1.1	Yes: Creat=700	New CVA	Insulin (unk) & unspecified oral hypoglycaemic agents	Certain	No
43	60 M	Unk	2.1	Yes: eGFR=18		Insulin (unk)	Certain	Yes
44	60 F	Unk	2	Yes: eGFR=45	WCC=9, CRP=36	Insulin (>2y)	Certain	Yes

Case	Age, sex	HIV status	BG	Renal impairment	Relevant co-morbidities	Implicated drugs (duration)	Causality	Preventable
45	78 M	Neg	1.8	Yes: eGFR=53	Bedsore (WCC=10, CRP=63)	Gliclazide (2m) & metformin (2m)	Probable	No
46	63 M	Pos	1.3	Yes: eGFR=48		Insulin (unk)	Certain	Yes

†Patient died (from any cause) during admission or 30-day follow-up period

BG: blood glucose nadir as recorded in file (mmol/L); Creat: creatinine (μmol/L); CRP: C-reactive protein (mg/L); CVA: cerebrovascular accident; d/w/m/y: duration in days/ weeks/ months/ years; eGFR: estimated glomerular filtration rate (as per laboratory report) (mL/min/1.73 m²); F: female; M: male; neg: HIV-seronegative; NR: not recorded; pos: HIV-seropositive; unk: unknown; UTI: urinary tract infection; WCC: white blood cell count (x10⁹/L)

Appendix xlix. Summary of presentation of patients admitted for drug-induced liver injury

Case	Age, sex	HIV	DILI classification at first presentation (t-bili:ALT:ALP)	Hepatic co-morbidity	Implicated drugs (duration)	Causality	Preventable
47	36 M	Pos	Cholestatic liver injury (71:30:305)		Rifampicin (>4m)	Possible	No
48	57 F	Unk	Cholestatic liver injury (74:13:146)	Alcohol liver disease, portal hypertension and oesophageal varices. Hepatitis C.	Rifampicin (<3w)	Possible	No
49†	58 F	Pos	Cholestatic liver injury (309:71:359)		Rifampicin (4m)	Possible	No
50†	36 F	Pos	Cholestatic liver injury (146:205:468)		Efavirenz (unk)	Possible	No
51†	34 M	Pos	Cholestatic liver injury (118:93:134)	Abdominal MDR-TB but no bile duct obstruction	Rifampicin (2m)	Probable	No
52	34 M	Pos	Cholestatic liver injury (53:47:169)		Rifampicin (2d)	Possible	No
53	19 F	Pos	Cholestatic liver injury (114:63:153)	Suspected IRIS	Rifampicin (3w) Co-trimoxazole (3w)	Possible Possible	No No
54†	29 F	Pos	Cholestatic liver injury (157:63:223)		Rifampicin (2w)	Possible	No
55	38 F	Pos	Cholestatic liver injury (16:355:973)		Efavirenz (unk)	Probable	No
56	20 F	Pos	Cholestatic liver injury (87:76:438)		Rifampicin (6w)	Possible	No
57	19 M	Neg	Hepatocellular injury (35:968:88)		Rifampicin (6w) Isoniazid (6w) Pyrazinamide (6w)	Possible Possible Possible	No No No
58	47 F	Pos	Hepatocellular injury (16:2237:356)		Erythromycin (course commenced 2w ago) Nevirapine (unk)	Possible Possible	No No
59†	37 F	Pos	Hepatocellular injury (164:1512:140)	Chronic Hepatitis B	Rifampicin (4m) Isoniazid (4m) Pyrazinamide (4m)	Possible Possible Possible	No No Yes
60	30 M	Pos	Hepatocellular injury (92:960:448)		Rifampicin (?5m) Efavirenz (?1y) Isoniazid (?5m)	Possible Possible Possible	No No No

Case	Age, sex	HIV	DILI classification at first presentation (t-bili:ALT:ALP)	Hepatic co-morbidity	Implicated drugs (duration)	Causality	Preventable
61	39 F	Pos	Hepatocellular injury (unk:825:218)	Previous DILI. This admission for repeat DILI during rechallenge.	Pyrazinamide (?5m)	Possible	No
					Rifampicin (2w)	Possible	Yes
					Isoniazid (2w)	Possible	Yes
62	22 F	Pos	Mixed liver injury (94:143:146)	Liver biopsy supports DILI	Efavirenz (6m)	Possible	No
21†*	33 F	Pos	Hepatorenal failure (mixed LI and AKI) (58:225:204)		Rifampicin (5d)	Probable	No
22*	50 M	Pos	Hepatorenal failure (cholestatic LI and AKI) (191:13:153)		Enalapril (unk) (Could not exclude a potential role played by traditional remedies)	Possible	No
23†*	44 M	Pos	Hepatorenal failure (hepatocellular LI and AKI) (73:558:124)	Chronic Hepatitis B	Co-trimoxazole (unk)	Possible	Yes
24*	34 M	Pos	Hepatorenal failure (cholestatic LI and AKI) (174:25:110)		Co-trimoxazole (unk)	Probable	No

* Case also included in appendix on patients presenting with renal failure

† Patient died (from any cause) during admission or 30-day follow-up period

AKI: acute kidney injury; ALP: alkaline phosphatase (IU/L); ALT: alanine transaminase (IU/L); d/w/m/y: duration in days/ weeks/ months/ years; DILI: drug-induced liver injury; F: female; IRIS: immune reconstitution inflammatory syndrome; LI: liver injury; M: male; MDR-TB: multidrug-resistant tuberculosis; neg: HIV-seronegative; pos: HIV-seropositive; t-bili: total serum-bilirubin (μmol/L); unk: unknown.

Appendix I. Summary of presentation of patients admitted for drug-related haemorrhage.

Case	Age, sex	HIV	Haemorrhage	Implicated Drugs	Indication for warfarin	Causality	Preventable
63	70 F	Unk	Gingival bleeding	Warfarin (INR > 10)	DVT	Certain	Yes
64	56 F	Unk	Gastric haemorrhage	Warfarin (INR = 4.8)	Valve replacement	Certain	Yes
65	61 F	Unk	Gastric haemorrhage	Diclofenac		Probable	No
66	90 F	Unk	Gastrointestinal haemorrhage	Acetylsalicylic acid		Possible	No
67	79 F	Unk	Gastrointestinal haemorrhage	NSAIDs, unspecified		Possible	No
68	83 M	Unk	Gastritis haemorrhagic	Acetylsalicylic acid		Possible	No
69	62 F	Unk	Lower gastrointestinal haemorrhage	Warfarin (INR = 4.7)	Valvular disease	Probable	No
70	58 F	Unk	Haemoptysis	Warfarin (INR = 4.9)	Valve replacement	Probable	Yes
71	18 F	Pos	Haemoptysis	Warfarin (INR > 10)	Right ventricular thrombosis secondary to DCMO	Certain	Yes
72	72 F	Unk	Haemoptysis	Warfarin (INR = 2.0)	Valvular disease	Possible	No
73	53 F	Neg	Epistaxis	NSAIDs, unspecified		Possible	No
74	77 F	Unk	Haemarthrosis	Warfarin (INR = 4.3)	DVT	Certain	Yes
75	87 F	Unk	Haematuria	Warfarin (INR > 10)	Atrial fibrillation	Certain	Yes
76	48 F	Unk	Retroperitoneal haemorrhage	Warfarin (INR = 1.5)	Valve replacement	Probable	Yes
77	40 F	Unk	Menorrhagia	Warfarin (INR > 10)	DVT	Certain	Yes
78	30 F	Pos	Menorrhagia	Warfarin (INR = 6.9)	DVT	Certain	Yes
79†	79 F	Unk	Cerebral haemorrhage	Warfarin (INR = 4.6)	DVT	Certain	Yes
80†	79 F	Unk	Haemorrhage intracranial	Warfarin (INR = 9.2)	Atrial fibrillation	Probable	Yes
81†	67 F	Pos	Subarachnoid haemorrhage	Acetylsalicylic acid		Possible	No

† Patient died (from any cause) during admission or 30-day follow-up period

F: female; M: male; neg: HIV-seronegative; pos: HIV-seropositive; unk: unknown; INR: international normalised ratio; NSAIDs: non-steroidal antiinflammatories; DVT: deep venous thrombosis; DCMO: dilated cardiomyopathy

Appendix li. Summary of presentation of patients admitted for drug-induced blood dyscrasias

Case	Age, sex	HIV	Adverse Drug Reaction	Implicated Drugs	Causality	Preventable
82	48 M	Pos	Anaemia	Zidovudine	Probable	Yes
83	58 F	Pos	Anaemia	Zidovudine	Possible	No
84	55 M	Pos	Anaemia macrocytic	Zidovudine and lamivudine	Probable	Yes
85	33 F	Pos	Anaemia normochromic normocytic	Zidovudine	Possible	No
86†	29 F	Pos	Aplastic anaemia	Co-trimoxazole	Certain	Yes
87†	32 M	Pos	Pancytopenia	Co-trimoxazole	Possible	No
88	33 F	Pos	Thrombocytopenia	Co-trimoxazole	Possible	No
89	65 M	Pos	Thrombocytopenia	Co-trimoxazole	Possible	No
90	23 M	Neg	Thrombocytopenia	Rifampicin	Probable	No
				Amoxicillin	Possible	No
91	31 M	Pos	Thrombocytopenia	Rifampicin	Possible	No
				Isoniazid	Possible	No
92	26 M	Pos	Thrombocytopenia	Valproic acid	Possible	No
93†	60 M	Pos	Neutropenia	Stavudine	Possible	No
94	63 F	Unk	Neutropenia	Allopurinol	Possible	No
				Colchicine	Possible	No
95	70 F	Unk	Leukopenia	Methotrexate and chloroquine	Certain	No

† Patient died (from any cause) during admission or 30-day follow-up period

F: female; M: male; neg: HIV-seronegative; pos: HIV-seropositive; unk: unknown;

Appendix lii. Summary of presentation of patients admitted for other* Type A adverse drug reactions

Case	Age, sex	HIV	Adverse Drug Reaction	Implicated Drugs	Causality	Preventable
96	22 F	Neg	Cardiac failure	Carvedilol	Possible	No
97	67 F	Unk	Cardiac failure	Carvedilol	Possible	Yes
98	79 M	Unk	Cardiac failure	Atenolol	Probable	Yes
99	52 F	Neg	Cardiac failure	Propranolol	Probable	No
100	72 F	Unk	Cardiac failure	Amlodipine and atenolol	Possible	Yes
101	55 F	Unk	Cardiac failure	Nifedipine	Possible	No
102	84 F	Unk	Cardiac failure	Atenolol	Possible	No
103	51 F	Neg	Cardiac failure	Atenolol and diltiazem	Possible	Yes
104	75 F	Unk	Cardiac failure	Atenolol	Possible	No
105	83 F	Unk	Hypotension	Enalapril and furosemide	Possible	No
106	55 M	Unk	Hypotension	Carvedilol, enalapril, and furosemide	Probable	Yes
107	53 M	Unk	Hypotension	Enalapril and furosemide	Possible	No
108	88 F	Unk	Orthostatic hypotension	Amlodipine, enalapril, and hydrochlorothiazide	Possible	Yes
109	75 F	Unk	Syncope	Tramadol, clonazepam, furosemide, propranolol, phenytoin, and levodopa with decarboxylase inhibitor	Possible	Yes
110	75 F	Unk	Cerebrovascular accident	Amlodipine, atenolol, enalapril, and hydrochlorothiazide	Possible	Yes
111	55 F	Unk	Acute myocardial infarction	Tranexamic acid	Possible	No
112	36 F	Pos	Gastritis	Acetylsalicylic acid and paracetamol (combination formulation)	Probable	Yes
113	52 F	Pos	Vomiting	Tenofovir-lamivudine-efavirenz (fixed drug combination)	Possible	No
114	45 F	Neg	Vomiting	Metformin	Certain	No
115†	65 F	Pos	Diarrhoea	Lopinavir-ritonavir	Possible	No
116	65 F	Unk	Pneumonia	Prednisone	Possible	No
117†	19 M	Unk	Pneumonia	Tacrolimus and prednisone	Possible	No
118	56 F	Unk	Pneumonia	Imatinib	Possible	No
119	57 F	Neg	Pneumonia	Azathioprine and prednisone	Possible	No
120	18 M	Unk	Gastroenteritis	Ciclosporin	Probable	No
121†	76 F	Unk	Pyelonephritis acute	Chlorambucil and prednisone	Possible	No
122†	27 F	Pos	<i>Pneumocystis jirovecii</i> pneumonia	Prednisone	Possible	No
123	50 M	Unk	Diabetes mellitus	Prednisone	Possible	No
124	64 F	Unk	Diabetes mellitus	Hydrochlorothiazide and prednisone	Probable	Yes
125	69 F	Unk	Hypokalaemia	Furosemide	Certain	Yes

Case	Age, sex	HIV	Adverse Drug Reaction	Implicated Drugs	Causality	Preventable
126†	56 F	Neg	Hypokalaemia	Hydrochlorothiazide	Possible	Yes
127	69 F	Unk	Hypokalaemia	Furosemide and prednisone	Certain	Yes
128	58 F	Unk	Hyperkalaemia	Enalapril	Probable	Yes
129	69 F	Pos	Hyponatraemia	Co-trimoxazole and hydrochlorothiazide	Probable	No
130	66 F	Unk	Hyponatraemia	Hydrochlorothiazide	Possible	No
131	47 F	Unk	Hyponatraemia	Hydrochlorothiazide	Possible	No
132†	53 M	Pos	Lactic acidosis	Stavudine	Possible	Yes
133†	61 F	Pos	Lactic acidosis	Stavudine	Probable	Yes
134	82 M	Unk	Asthenia	Digoxin	Certain	Yes
135	23 M	Unk	Confusional state	Phenytoin	Certain	Yes
136†	82 F	Unk	Confusional state	Tramadol	Possible	No
137†	89 F	Unk	Confusional state	Digoxin	Certain	Yes
138	43 F	Pos	Confusional state	Efavirenz	Possible	No
139	34 M	Pos	Confusional state	Efavirenz	Probable	No
140	62 F	Unk	Confusional state	Phenytoin	Certain	Yes
141	91 F	Unk	Confusional state	Tramadol, risperidone, and zopiclone	Probable	Yes
142	40 M	Unk	Confusional state	Phenobarbital and phenytoin	Probable	Yes
143†	39 F	Pos	Ataxia	Efavirenz	Possible	No
144	33 M	Unk	Ataxia	Phenytoin	Certain	Yes
145	36 M	Unk	Ataxia	Phenytoin	Certain	Yes
146	53 M	Unk	Loss of consciousness	Phenytoin	Probable	Yes
147	58 F	Unk	Generalised tonic-clonic seizure	Theophylline, chlorpromazine, and zuclopenthixol	Possible	No
148	65 M	Neg	Generalised tonic-clonic seizure	Theophylline	Possible	No
149	34 F	Pos	Optic neuritis	Ethambutol	Certain	Yes
150	34 F	Neg	Headache	Levonorgestrel and estrogen (combined oral contraceptive)	Possible	No
151	21 M	Unk	Hallucination	Phenytoin	Probable	Yes
152	29 M	Neg	Aggression	Phenytoin	Certain	Yes
153	40 F	Pos	Acute psychosis	Efavirenz	Possible	No
154†	44 F	Pos	Renal tubular disorder	Tenofovir	Possible	No
155	35 F	Pos	Renal tubular disorder	Kanamycin and tenofovir	Certain	Yes

* Excludes patients admitted for drug-induced hypoglycaemia, drug-induced blood dyscrasias, drug-related haemorrhage, and drug-induced renal failure / impairment. † Patient died (from any cause) during admission or 30-day follow-up period. F: female; M: male; neg: HIV-seronegative; pos: HIV-seropositive; unk: unknown

Appendix liii. Summary of presentation of patients admitted for all other* Type B adverse reactions

Case	Age, sex	HIV	Adverse Drug Reaction	Implicated Drugs	Causality	Preventable
156	69 F	Unk	Pancreatitis acute	Simvastatin	Possible	No
157	51 M	Pos	DRESS	Hydrochlorothiazide	Probable	No
158	22 F	Neg	DRESS	Phenytoin	Certain	No
159	72 M	Unk	DRESS	Phenytoin	Certain	No
160	38 F	Pos	DRESS	Rifampicin	Certain	No
161	58 M	Neg	Dermatitis exfoliative	Allopurinol	Possible	No
				Imatinib	Possible	No
162	36 F	Pos	Stevens-Johnson syndrome	Co-trimoxazole	Possible	No
				Unspecified ART	Possible	No
				Unspecified TBT	Possible	No
163	57 F	Unk	Angioedema	Perindopril	Certain	No
164	50 F	Unk	Interstitial lung disease	Methotrexate	Possible	No

* Excludes admissions for drug-induced liver injury, drug-induced renal impairment, and drug-induced blood dyscrasias

† No known deaths (from any cause) during admission or 30-day follow-up period

ART: antiretroviral treatment; DRESS: drug reaction with eosinophilia and systemic symptoms; F: female; neg: HIV-seronegative; pos: HIV-seropositive; M: male; TBT: tuberculosis treatment; unk: unknown

Appendix liv. All ADR-related admissions (n=164), mapped to higher-level terms, higher-level groups, and system-organ classes, according to the MedDRA® taxonomy. Asterisks indicate lower-level terms mapping to more than one heading

Adverse Drug Reaction	Frequency	Proportion ^a
Blood and lymphatic system disorders	14	8.5%
Anaemias, nonhaemolytic and marrow depression	6	3.6%
Anaemias	4	2.4%
Anaemia	2	1.2%
Anaemia, macrocytic (*)	1	<1%
Anaemia, normochromic normocytic	1	<1%
Marrow depression and hypoplastic anaemias	2	1.2%
Aplastic anaemia	1	<1%
Pancytopenia	1	<1%
Platelet disorders	5	3.1%
Thrombocytopaenias	5	3.1%
Thrombocytopaenia	5	3.1%
White blood cell disorders	3	1.8%
Leukopaenias	1	<1%
Leukopaenia	1	<1%
Neutropaenias	2	1.2%
Neutropaenia	2	1.2%
Cardiac disorders	14	8.5%
Heart failures	9	5.5%
Heart failures	9	5.5%
Cardiac failure	9	5.5%
Cardiac disorder signs and symptoms	4	2.4%
Cardiac signs and symptoms	4	2.4%
Haemoptysis (*)	3	1.8%
Syncope (*)	1	<1%
Coronary artery disorders	1	<1%
Ischaemic coronary artery disorders	1	<1%
Acute myocardial infarction (*)	1	<1%
Endocrine disorders	24	15%
Glucose metabolism disorders	24	15%
Hypoglycaemic conditions	22	13%
Hypoglycaemia (*)	22	13%
Diabetes mellitus	2	1.2%
Diabetes mellitus (*)	2	1.2%
Eye disorders	1	<1%
Ocular infections, irritations and inflammations	1	<1%
Optic nerve infections and inflammation	1	<1%
Optic neuritis (*)	1	<1%
Gastrointestinal disorders	14	8.5%
Gastrointestinal haemorrhages	5	3.1%
Non-site specific GI haemorrhage	3	1.8%
Gastrointestinal haemorrhage (*)	2	1.2%
Lower gastrointestinal haemorrhage (*)	1	<1%
Gastric and oesophageal haemorrhages	2	1.2%
Gastric haemorrhage (*)	2	1.2%
Gastrointestinal inflammatory conditions	2	1.2%
Gastritis (excl infective)	2	1.2%
Gastritis	1	<1%
Gastritis haemorrhagic (*)	1	<1%
Gastrointestinal signs and symptoms	2	1.2%
Nausea and vomiting symptoms	2	1.2%

Adverse Drug Reaction	Frequency	Proportion ^a
Vomiting	2	1.2%
Dental and gingival conditions	1	<1%
Gingival haemorrhages	1	<1%
Gingival bleeding (*)	1	<1%
Exocrine pancreas conditions	1	<1%
Acute and chronic pancreatitis	1	<1%
Acute pancreatitis	1	<1%
Gastrointestinal infections	1	<1%
Gastric and gastroenteric infections	1	<1%
Gastroenteritis (*)	1	<1%
Gastrointestinal motility and defaecation disorders	1	<1%
Diarrhoea (excl infective)	1	<1%
Diarrhoea	1	<1%
Peritoneal and retroperitoneal conditions	1	<1%
Peritoneal and retroperitoneal haemorrhage	1	<1%
Retroperitoneal haemorrhage (*)	1	<1%
General disorders and administration site conditions	4	2.4%
General system disorders	4	2.4%
Gait disorders	3	1.8%
Ataxia (*)	3	1.8%
Asthenic conditions	1	<1%
Asthenia	1	<1%
Hepatobiliary disorders	20	12%
Hepatic and hepatobiliary disorders	20	12%
Hepatocellular damage and hepatitis	16	9.8%
Cholestatic liver injury	10	6.1%
Hepatocellular injury	5	3.1%
Mixed liver injury	1	<1%
Hepatic failure and associated disorders	4	2.4%
Hepatorenal failure (*)	4	2.4%
Immune system disorders	8	4.9%
Allergic conditions	7	4.3%
Allergies to foods, food additives, drugs and other chemicals	5	3.0%
Drug reaction with eosinophilia and systemic symptoms (*)	4	2.4%
Dermatitis exfoliative (*)	1	<1%
Allergic conditions	1	<1%
Stevens-Johnson syndrome (*)	1	<1%
Angioedemas	1	<1%
Angioedema (*)	1	<1%
Autoimmune disorders	1	<1%
Nervous system autoimmune disorders	1	<1%
Optic neuritis (*)	1	<1%
Infections and infestations	8	4.9%
Infections - pathogen unspecified	6	3.7%
Lower respiratory tract and lung infections	4	2.4%
Pneumonia (*)	4	2.4%
Abdominal and gastrointestinal infections	1	<1%
Gastroenteritis (*)	1	<1%
Urinary tract infections	1	<1%
Pyelonephritis acute	1	<1%
Ancillary infectious topics	1	<1%
Inflammatory disorders following infection	1	<1%
Stevens-Johnson syndrome (*)	1	<1%

Adverse Drug Reaction	Frequency	Proportion ^a
Fungal infectious disorders	1	<1%
<i>Pneumocystis</i> infections	1	<1%
<i>Pneumocystis jirovecii</i> pneumonia (*)	1	<1%
Injury, poisoning and procedural complications	3	1.8%
Bone and joint injuries	1	<1%
Bone and joint injuries	1	<1%
Haemarthrosis (*)	1	<1%
Exposures, chemical injuries and poisoning	1	<1%
Poisoning and toxicity	1	<1%
Stevens-Johnson syndrome (*)	1	<1%
Injuries	1	<1%
Cerebral injuries	1	<1%
Subarachnoid haemorrhage (*)	1	<1%
Metabolism and nutrition disorders	34	21%
Glucose metabolism disorders	24	15%
Hypoglycaemic conditions	22	13%
Hypoglycaemia (*)	22	13%
Diabetes mellitus	2	1.2%
Diabetes mellitus (*)	2	1.2%
Electrolyte and fluid balance conditions	7	4.3%
Potassium imbalance	4	2.4%
Hypokalaemia	3	1.8%
Hyperkalaemia	1	<1%
Sodium imbalance	3	1.8%
Hyponatraemia	3	1.8%
Acid-base disorders	2	1.2%
Metabolic acidosis	2	1.2%
Lactic acidosis	2	1.2%
Vitamin-related disorders	1	<1%
Vitamin deficiencies	1	<1%
Anaemia macrocytic (*)	1	<1%
Musculoskeletal and connective tissue disorders	1	<1%
Joint disorders	1	<1%
Arthropathies	1	<1%
Haemarthrosis (*)	1	<1%
Nervous system disorders	22	13%
Neurological disorder	13	7.9%
Cortical dysfunction	8	4.9%
Confusional state (*)	8	4.9%
Coordination and balance disturbance	3	1.8%
Ataxia (*)	3	1.8%
Disturbances in consciousness	2	1.2%
Loss of consciousness	1	<1%
Syncope (*)	1	<1%
CNS vascular disorder	4	2.4%
CNS haemorrhages and cerebrovascular accidents	4	2.4%
Cerebral haemorrhage (*)	1	<1%
Cerebrovascular accident (*)	1	<1%
Haemorrhage intracranial (*)	1	<1%
Subarachnoid haemorrhage (*)	1	<1%
Seizures	2	1.2%
Generalised tonic-clonic seizures	2	1.2%
Generalised tonic-clonic seizure	2	1.2%
Cranial nerve disorders	1	<1%

Adverse Drug Reaction	Frequency	Proportion ^a
Optic nerve disorders	1	<1%
Optic neuritis (*)	1	<1%
Headaches	1	<1%
Headaches	1	<1%
Headache	1	<1%
Neuromuscular disorders	1	<1%
Autonomic nervous system disorders	1	<1%
Orthostatic hypotension (*)	1	<1%
Psychiatric disorders	11	6.7%
Deliria	8	4.9%
Confusion and disorientation	8	4.9%
Confusional state (*)	8	4.9%
Disturbances in thinking and perception	1	<1%
Perception disturbances	1	<1%
Hallucination	1	<1%
Personality disorders and disturbances	1	<1%
Behaviour and socialisation disturbances	1	<1%
Aggression	1	<1%
Schizophrenia and other psychotic disorders	1	<1%
Psychotic disorder	1	<1%
Acute psychosis	1	<1%
Renal and urinary disorders	28	17%
Renal disorders (excl nephropathies)	25	15%
Renal failure and impairments	24	15%
Renal failure acute	13	7.9%
Renal failure	7	4.3%
Hepatorenal failure (*)	4	2.4%
Renal infections and inflammations	1	<1%
Acute pyelonephritis	1	<1%
Nephropathies	2	1.2%
Nephropathies and tubular disorders	2	1.2%
Renal tubular disorder	2	1.2%
Urinary tract symptoms and signs	1	<1%
Urinary abnormalities	1	<1%
Haematuria (*)	1	<1%
Reproductive system and breast disorders	2	1.2%
Menstrual cycle and uterine bleeding disorders	2	1.2%
Menstruation with increased bleeding	2	1.2%
Menorrhagia	2	1.2%
Respiratory, thoracic and mediastinal disorders	10	6.1%
Respiratory tract infections	5	3.0%
Lower respiratory tract infections	4	2.4%
Pneumonia (*)	4	2.4%
Fungal lower respiratory tract infections	1	<1%
<i>Pneumocystis jirovecii</i> pneumonia (*)	1	<1%
Respiratory disorders	3	1.8%
Coughing and associated symptoms	3	1.8%
Haemoptysis (*)	3	1.8%
Lower respiratory tract disorders (excl obstruction and infection)	1	<1%
Parenchymal lung disorders	1	<1%
Interstitial lung disease	1	<1%
Upper respiratory tract disorders (excl infections)	1	<1%
Nasal disorders	1	<1%
Epistaxis (*)	1	<1%

Adverse Drug Reaction	Frequency	Proportion ^a
Skin and subcutaneous tissue disorders	7	4.3%
Epidermal and dermal conditions	6	3.7%
Dermatitis ascribed to specific agent	4	2.4%
Drug reaction with eosinophilia and systemic symptoms (*)	4	2.4%
Bullous conditions	1	<1%
Stevens-Johnson syndrome (*)	1	<1%
Exfoliative conditions	1	<1%
Dermatitis exfoliative (*)	1	<1%
Angioedema and urticaria	1	<1%
Angioedemas	1	<1%
Angioedema (*)	1	<1%
Vascular disorders	24	15%
Vascular haemorrhagic disorders	17	10%
Gastrointestinal haemorrhages	7	4.3%
Gastric haemorrhage (*)	2	1.2%
Gastrointestinal haemorrhage (*)	2	1.2%
Gastritis haemorrhagic (*)	1	<1%
Gingival bleeding (*)	1	<1%
Lower gastrointestinal haemorrhage (*)	1	<1%
Haemorrhages	7	4.3%
Haemoptysis (*)	3	1.8%
Epistaxis (*)	1	<1%
Haemarthrosis (*)	1	<1%
Haematuria (*)	1	<1%
Retroperitoneal haemorrhage (*)	1	<1%
Nervous system haemorrhagic disorders	3	1.8%
Cerebral haemorrhage (*)	1	<1%
Haemorrhage intracranial (*)	1	<1%
Subarachnoid haemorrhage (*)	1	<1%
Decreased and nonspecific blood pressure disorders and shock	5	3.0%
Vascular hypotensive disorders	4	2.4%
Hypotension	3	1.8%
Orthostatic hypotension (*)	1	<1%
Circulatory collapse and shock	1	<1%
Syncope (*)	1	<1%
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	1	<1%
Coronary necrosis and vascular insufficiency	1	<1%
Acute myocardial infarction (*)	1	<1%
Vascular disorders	1	<1%
Cerebrovascular and spinal vascular disorders	1	<1%
Cerebrovascular accident (*)	1	<1%

(a) Proportion of 164 ADR-related admissions

Appendix Iv. Drugs implicated in ADR-related admissions, by ATC-classification

Drug class / Drug	Number of ADR-related admissions in which the drug / drug class was implicated				Total ^e
	Type A ADRs (alone) ^a	Type A ADRs (comb) ^b	Type B ADRs (alone) ^c	Type B ADRs (comb) ^d	
A ALIMENTARY TRACT AND METABOLISM	12	11			23
A10 Drugs used in diabetes	12	11			23
A10A Insulins and analogues	9	5			14
A10B Oral blood glucose lowering drugs	3	11			14
A10BA Biguanides	1	10			11
A10BA02 Metformin	1	10			11
A10BB Sulfonamides, urea derivatives	1	9			11
A10BB01 Glibenclamide	1	3			4
A10BB09 Gliclazide	1	6			7
Unspecified oral blood glucose lowering drugs		1			1
B BLOOD AND BLOOD FORMING ORGANS	17	1			18
B01 Antithrombotic agents	16	1			17
B01A Antithrombotic agents	16	1			17
B01AA Vitamin K antagonists	13				13
B01AA03 Warfarin	13				13
B01AC Platelet aggregation inhibitors, excl. heparins	3	1			4
B01AC06 Acetylsalicylic acid	3	1			4
B02 Antihaemorrhagics	1				1
B02A Antifibrinolytics	1				1
B02AA Amino acids	1				1
B02AA02 Tranexamic acid	1				1
C CARDIOVASCULAR SYSTEM	16	16	4	1	37
C01 Cardiac therapy	2				2
C01A Cardiac glycosides	2				2
C01AA Digitalis glycosides	2				2
C01AA05 Digoxin	2				2
C02 Antihypertensives		1			1
C02D Arteriole smooth muscle, agents acting on		1			1
C02DB Hydrazinophthalazine derivatives		1			1
C02DB02 Hydralazine		1			1
C03 Diuretics	4	14	1		19
C03A Low-ceiling diuretics, thiazides	3	6	1		10
C03AA Thiazides, plain	3	6	1		10
C03AA03 Hydrochlorothiazide	3	6	1		10
C03C High-ceiling diuretics	1	10			11
C03CA Sulfonamides, plain	1	10			11
C03CA01 Furosemide	1	10			11
C03D Potassium-sparing agents		2			2
C03DA Aldosterone antagonists		2			2
C03DA01 Spironolactone		2			2
C07 Beta-blocking agents	6	6			12
C07A Beta-blocking agents	6	6			12
C07AA Beta-blocking agents, non-selective	1	1			2
C07AA05 Propranolol	1	1			2
C07AB Beta-blocking agents, selective	3	4			7
C07AB03 Atenolol	3	4			7
C07AG Alpha- and beta-blocking agents	2	1			3

Drug class / Drug	Number of ADR-related admissions in which the drug / drug class was implicated				Total ^e
	Type A ADRs (alone) ^a	Type A ADRs (comb) ^b	Type B ADRs (alone) ^c	Type B ADRs (comb) ^d	
C07AG02 Carvedilol	2	1			3
C08 Calcium channel blockers	1	5			6
C08C Selective calcium channel blockers with mainly vascular effects	1	4			5
C08CA Dihydropyridine derivatives	1	4			5
C08CA01 Amlodipine		4			4
C08CA05 Nifedipine	1				1
C08D Selective calcium channel blockers with direct cardiac effects		1			1
C08DB Benzothiazepine derivatives		1			1
C08DB01 Diltiazem		1			1
C09 Agents acting on the renin-angiotensin system	3	10	2	1	16
C09A ACE-inhibitors, plain	3	9	2	1	15
C09AA ACE-inhibitors, plain	3	9	2	1	15
C09AA01 Captopril		1			1
C09AA02 Enalapril	3	8	1	1	13
C09AA04 Perindopril			1		1
C09B ACE-inhibitors, combinations		1			1
C09BA ACE-inhibitors and diuretics		1			1
C09BA04 Perindopril and diuretics		1			1
C09C Angiotensin II antagonists, plain		1			1
C09CA Angiotensin II antagonists, plain		1			1
C09CA03 Valsartan		1			1
C10 Serum lipid reducing agents			1		1
C10A Cholesterol and triglyceride reducers			1		1
C10AA HMG-coA reductase inhibitors			1		1
C10AA01 Simvastatin			1		1
G GENITO-URINARY SYSTEM AND SEX HORMONES	1				1
G03 Sex hormones and modulators of the genital system	1				1
G03A Hormonal contraceptives for systemic use	1				1
G03AA Progestogens and oestrogens, fixed combinations	1				1
G03AA07 Levonorgestrel and oestrogen	1				1
H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	3	5			8
H02 Corticosteroids for systemic use	3	5			8
H02A Corticosteroids for systemic use, plain	3	5			8
H02AB Glucocorticoids	3	5			8
H02AB07 Prednisone	3	5			8
J ANTI-INFECTIVES FOR SYSTEMIC USE	25	4	14	14	57
J01 Antibacterials for systemic use	4	2	2	8	16
J01C Beta-lactam antibacterials, penicillins				3	3
J01CA Penicillins with extended spectrum				1	1
J01CA04 Amoxicillin				1	1
J01CR Combinations of penicillins, incl. beta-lactamase inhibitors				2	2
J01CR02 Co-amoxiclav				2	2
J01E Sulfonamides and trimethoprim	4	1	2	4	11

Drug class / Drug	Number of ADR-related admissions in which the drug / drug class was implicated				Total ^e
	Type A ADRs (alone) ^a	Type A ADRs (comb) ^b	Type B ADRs (alone) ^c	Type B ADRs (comb) ^d	
J01EE Combinations of sulfonamides and trimethoprim, incl. derivatives	4	1	2	4	11
J01EE01 Sulfamethoxazole and trimethoprim	4	1	2	4	11
J01F Macrolides, lincosamides and streptogramins				1	1
J01FA Macrolides				1	1
J01FA01 Erythromycin				1	1
J01G Aminoglycoside antibacterials		1			1
J01GB Other aminoglycosides		1			1
J01GB04 Kanamycin		1			1
J04 Antimycobacterials	1		9	9	19
J04A Drugs for treatment of tuberculosis	1		9	9	19
J04AB Antibiotics			9	8	17
J04AB02 Rifampicin			9	8	17
J04AC Hydrazides				5	5
J04AC01 Isoniazid				5	5
J04AK Other drugs for treatment of tuberculosis	1			3	4
J04AK01 Pyrazinamide				3	3
J04AK02 Ethambutol	1				1
Unspecified treatment for tuberculosis				1	1
J05 Antivirals for systemic use	20	3	3	6	32
J05A Direct-acting antivirals	20	3	3	6	32
J05AB Nucleosides and nucleotides, excl. reverse transcriptase inhibitors				1	1
J05AB01 Aciclovir				1	1
J05AE Protease inhibitors	1				1
J05AE30 Lopinavir-ritonavir	1				1
J05AF Nucleoside and nucleotide reverse transcriptase inhibitors	15	3		3	21
J05AF01 Zidovudine	3	1			4
J05AF04 Stavudine	3				3
J05AF05 Lamivudine		1			1
J05AF07 Tenofovir disoproxil	9	2		3	14
J05AF09 Emtricitabine		1			1
J05AG Non-nucleoside reverse transcriptase inhibitors	4	1	3	2	10
J05AG01 Nevirapine				1	1
J05AG03 Efavirenz	4	1	3	1	9
Unspecified antiretroviral therapy				1	1
L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	2	4	1	1	8
L01 Antineoplastic agents	1	1		1	3
L01A Alkylating agents		1			1
L01AA Nitrogen mustard analogues		1			1
L01AA02 Chlorambucil		1			1
L01X Other antineoplastic agents	1			1	2
L01XE Protein kinase inhibitors	1			1	2
L01XE01 Imatinib	1			1	2
L04 Immunosuppressive agents	1	3	1		5
L04A Immunosuppressive agents	1	3			5
L04AD Calcineurin inhibitors	1	1			2

Drug class / Drug	Number of ADR-related admissions in which the drug / drug class was implicated				Total ^e
	Type A ADRs (alone) ^a	Type A ADRs (comb) ^b	Type B ADRs (alone) ^c	Type B ADRs (comb) ^d	
L04AD01 Ciclosporin	1				1
L04AD02 Tacrolimus		1			1
L04AX Other immunosuppressive agents		2	1		3
L04AX01 Azathioprine		1			1
L04AX03 Methotrexate		1	1		2
M MUSCULO-SKELETAL SYSTEM	3			4	7
M01 Anti-inflammatory and antirheumatic products	3			2	5
M01A Anti-inflammatory and antirheumatic products, non-steroids	3			2	5
M01AB Acetic acid derivatives and related substances	1			1	2
M01AB01 Indometacin				1	1
M01AB05 Diclofenac	1				1
M01AE Propionic acid derivatives				1	1
M01AE01 Ibuprofen				1	1
Unspecified non-steroidal anti-inflammatories	2				2
M04 Antigout preparations				2	2
M04A Antigout preparations				2	2
M04AA Preparations inhibiting uric acid production				2	2
M04AA01 Allopurinol				2	2
M04AC Preparations with no effect on uric acid metabolism				1	1
M04AC01 Colchicine				1	1
N NERVOUS SYSTEM	9	4	3		16
N02 Analgesics	2	2			4
N02A Opioids	1	2			3
N02AX Other opioids	1	2			3
N02AX02 Tramadol	1	2			3
N02B Other analgesics and antipyretics	1				1
N02BE Anilides	1				1
N02BE51 Paracetamol, combinations excl. psycholeptics	1				1
N03 Anti-epileptics	7	2	3		12
N03A Anti-epileptics	7	2	3		12
N03AA Barbiturates and derivatives		1			1
N03AA02 Phenobarbital		1			1
N03AB Hydantoin derivatives	7	2	2		11
N03AB02 Phenytoin	7	2	2		11
N03AE Benzodiazepine derivatives		1			1
N03AE01 Clonazepam		1			1
N03AG Fatty acid derivatives			1		1
N03AG01 Valproic acid			1		1
N04 Anti-Parkinson drugs		1			1
N04B Dopaminergic agents		1			1
N04BA Dopa and dopa derivatives		1			1
N04BA02 Levodopa and decarboxylase inhibitor		1			1
N05 Psycholeptics		2			2
N05A Antipsychotics		2			2
N05AA Phenothiazines with aliphatic side-chain		1			1
N05AA01 Chlorpromazine		1			1
N05AF Thioxanthene derivatives		1			1

Drug class / Drug	Number of ADR-related admissions in which the drug / drug class was implicated				Total ^e
	Type A ADRs (alone) ^a	Type A ADRs (comb) ^b	Type B ADRs (alone) ^c	Type B ADRs (comb) ^d	
N05AF05 Zuclopenthixol		1			1
N05AX Other antipsychotics		1			1
N05AX08 Risperidone		1			1
N05C Hypnotics and sedatives		1			1
N05CF Benzodiazepine-related drugs		1			1
N05CF01 Zopiclone		1			1
P ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS		1			1
P01 Antiprotozoals		1			1
P01B Antimalarials		1			1
P01BA Aminoquinolines		1			1
P01BA01 Chloroquine		1			1
R RESPIRATORY SYSTEM	1	1			2
R03 Drugs for obstructive airway	1	1			2
R03D Other systemic drugs for obstructive airway diseases	1	1			2
R03DA Xanthines	1	1			2
R03DA04 Theophylline	1	1			2

(a) Number of type A ADR-related admissions in which the drug / drug class was the sole implicated drug.

(b) Number of type A ADR-related admissions in which the drug / drug class was an implicated drug in combination with other drugs.

(c) Number of type B ADR-related admissions in which the drug / drug class was the sole implicated drug.

(d) Number of type B ADR-related admissions in which the drug / drug class was an implicated drug together with other implicated drugs.

(e) Total number of ADR-related admissions in which the drug / drug class was implicated.

Appendix Ivi. Alternative multivariable logistic regression model of associations with adverse drug reaction-related admission, including all admissions (n=1951 admissions in 1904 patients)

Reaction-related admission, including all admissions (n=1951 admissions in 1964 patients)						
		Unadjusted		Adjusted		Wald <i>P</i> value
	n	OR	(95% CI)	OR	(95% CI)	
Sex						
Male (referent)	864	1.00		1.00		
Female	1087	1.69	(1.20 to 2.37)	1.57	(1.10 to 2.23)	.01
Age^a	1951	1.06	(0.98 to 1.15)	1.03	(0.92 to 1.15)	.64
HIV and ART						
HIV-negative/unknown (referent)	1378	1.00		1.00		
HIV-infected, not on ART	259	0.67	(0.37 to 1.21)	1.03	(0.53 to 1.98)	.94
HIV-infected, on ART	314	2.39	(1.66 to 3.45)	2.00	(1.21 to 3.31)	.007
Anti-tuberculosis therapy						
Not on ATT (referent)	1764	1.00		1.00		
On ATT	187	2.32	(1.51 to 3.58)	1.23	(0.72 to 2.11)	.45
Drug count^b	1951	1.23	(1.18 to 1.28)	1.17	(1.11 to 1.42)	<.001
Comorbidity score^c	1951	1.34	(1.20 to 1.51)	1.24	(1.07 to 1.42)	.003

(a) Included in the model as a continuous variable. The reported odds ratio is for each 10-year increment.

(b) Included in the model as a continuous variable. The reported odds ratio is for each additional drug.

(c) Included in the model as a continuous variable. The reported odds ratio is for each additional point on the modified Charlson comorbidity score.

ART: antiretroviral therapy, ATT: antituberculosis therapy, CI: confidence interval, OR: odds ratio.

Appendix Ivii. Alternative multivariable logistic regression model of associations with adverse drug reaction-related admission, excluding patients in whom no drug history was recorded in the medical records, as well as patients documented to have had zero drug exposure (n=1469 admissions in 1432 patients)

		Unadjusted		Adjusted		Wald <i>P</i> value
	n	OR	(95% CI)	OR	(95% CI)	
Sex						
Male (referent)	603	1.00		1.00		
Female	866	1.48	(1.05 to 2.09)	1.48	(1.04 to 2.10)	.03
Age^a	1 469	1.01	(0.92 to 1.09)	1.00	(0.90 to 1.13)	.94
HIV and ART						
HIV-negative/unknown (referent)	1 029	1.00		1.00		
HIV-infected, not on ART	126	1.06	(0.57 to 1.95)	1.26	(0.64 to 2.48)	.51
HIV-infected, on ART	314	1.74	(1.20 to 2.51)	1.75	(1.08 to 2.83)	.02
Anti-tuberculosis therapy						
Not on ATT (referent)	1 282	1.00		1.00		
On ATT	187	1.64	(1.06 to 2.52)	1.20	(0.73 to 1.98)	.48
Drug count^b	1 469	1.15	(1.10 to 1.20)	1.11	(1.05 to 1.17)	<.001
Comorbidity score^c	1 469	1.23	(1.09 to 1.39)	1.22	(1.06 to 1.40)	.004

(a) Included in the model as a continuous variable. The reported odds ratio is for each 10-year increment.

(b) Included in the model as a continuous variable. The reported odds ratio is for each additional drug.

(c) Included in the model as a continuous variable. The reported odds ratio is for each additional point on the modified Charlson comorbidity score.

ART: antiretroviral therapy, ATT: antituberculosis therapy, CI: confidence interval, OR: odds ratio.

Appendix Iviii. Summary of systematic reviews of studies determining the proportion of adult hospital admissions attributable to ADRs

Review	Restrictions applied at search stage						No of studies identified	No of patients/ admissions	Heterogeneity	Subgroup analyses?	Main outcome	Selected other outcomes
	Databases	Publication Date	Language	Settings	ADR definition	Design						
Einarson, 1993 ⁶²	Medline, Index Medicus, IPA	1966 to 1989	English only	No restriction	Cluff definition ¹⁵ and non-compliance. Excluded overdose, intentional poisoning, abuse, intoxication.	No restriction reported.	37	69 187 admissions	Not measured, but discussed range of study size and study duration.	Yes, for paediatric studies; and for non-compliance studies.	Median ADRad proportion of 37 studies is 4.9%, IQR 2.9% to 6.7%	Proportion of patients who die subsequent to ADRad (11 studies): 5.0% of ADRad patients; 0.3% of all admissions.
Muehlberger, 1997 ⁶³	Medline, EMBASE, Toxline, SoMed, Geriatrics, Deutsche Bibliographie, Chemical Abstracts	1970 to 1996	English or German	No restriction	Authors' definition had to be largely consistent with WHO definition ²¹³ .	No restriction.	25	160 354 admissions / consultations/ patients	Not measured, but implied in design of the analysis.	Yes, by setting, and by study design.	Median ADRad proportion of 25 studies is 4.1%, IQR 2.5% to 4.9%	Selective study setting, and comprehensive detection design, resulted in higher ADRad proportions. For studies of medical inpatients, with comprehensive monitoring (n=12 studies, n=20 037 admissions) median ADRad proportion is 5.8%, IQR 4.2% to 6.0%

Review	Restrictions applied at search stage						No of studies identified	No of patients/ admissions	Heterogeneity	Subgroup analyses?	Main outcome	Selected other outcomes
	Databases	Publication Date	Language	Settings	ADR definition	Design						
Lazarou, 1998 ⁶⁴	Medline, EMBASE, IPA, SCI, hand search	1966 to 1996	English (or English translation available)	Only US studies	WHO definition ²¹³ only; excluded 'possible' ADRs.	Only prospective studies included.	21 (in ADRad analysis)	28 017 patients (in ADRad analysis)	Not measured, but discussed.	Yes, for fatal ADRs.	Meta-analytic estimate 4.7% (95% CI 3.1% to 6.2%) admissions are ADRad.	Proportion of fatal ADRs (ADRad and ADR during inpatient stay): 0.32% of 46 625 patients studied.
Wiffen, 2001 ⁶⁵	Medline, EMBASE, IPA	1966 to 1999	No restriction	No restriction	No restriction, but excluded administration errors, non-compliance, overdose, abuse or therapeutic failure.	No restriction.	37 (in ADRad analysis)	133 741 patients (in ADRad analysis)	Not measured, but implied.	Yes, by study design, geographical setting, clinical setting, and date.	Weighted mean ADRad proportion is 3.1% (CI not reported).	Subgroup analyses combine ADRad and ADRs in inpatients.
Beijer, 2002 ⁶⁶	Medline, Cochrane Library, hand search	1966 to 2000	Not reported	No restriction	WHO definition ²¹³ . Excluded illicit drug use, abuse, therapeutic failure, overdose.	No restriction reported.	68	123 794 admissions	Confirmed heterogeneity: smaller studies show higher proportions.	Yes, by age group, date of publication, geographical region, and by clinical setting.	Weighted mean ADRad proportion is 4.9% (95% CI 4.8% to 5.0%).	For studies of non-elderly (n=51 studies, n=116 241 admissions): weighted mean ADRad proportion is 4.1% (95% CI 4.0% to 4.2%).

Review	Restrictions applied at search stage						No of studies identified	No of patients/ admissions	Heterogeneity	Subgroup analyses?	Main outcome	Selected other outcomes
	Databases	Publication Date	Language	Settings	ADR definition	Design						
Kongkaew, 2008 ⁶⁷	CINAHL, EMBASE, Medline	To Aug 2007	No restriction	No restriction	WHO definition ²¹³ or another ADR definition that mapped to it.	Only prospective studies included.	25	106 586 admissions	Confirmed heterogeneity: I ² = 98.5%.	Yes, by age group, and by ADR detection method.	Median ADRad proportion is 5.3%, IQR 2.7% to 9.0%.	For studies of adults (n=10 studies, n=11 477 patients): median ADRad proportion is 6.3%, IQR 3.9% to 9.0%.

ADR: adverse drug reaction; ADRad: admissions due to an adverse drug reaction; CI: confidence interval; CINAHL: Cumulative Index to Nursing and Allied Health Literature; EMBASE: Excerpta Medica Database; IPA: International Pharmaceutical Abstracts; IQR: interquartile range; SCI: Science Citation Index; WHO: World Health Organization

Appendix lix. Trigger tool development: summary of included studies

Author, year	Country	Main outcome	Adults / Children	Study setting	Development of tool	Intended for use by	No. of triggers
Jha, 1998 ²¹⁴	USA	ADE	Adults	Surgical, medical and ICU wards	ADE detection rules, based on combinations of simple medical conditions. Modified rules with low positive predictive value.	Computer	52
Rozich, 2003 ¹²²	USA	ADE	Adults & children	86 hospitals	Expert panel, pilot testing and refining of tool.	Human	24
Mehta, 2008 ⁶¹	SA	ADR	Adults	Medical wards	Additional triggers were added to increase sensitivity of the TT but method not defined.	Human	50
Hwang, 2008 ²¹⁵	South Korea	ADE	Adults	Surgical, medical and ICU wards	Expert panel selected and modified triggers to local clinical practices.	Computer	46
Franklin, 2010 ²¹⁶	UK	ADE	Adults & ?children	Surgical wards	Expert panel commented and approved triggers.	Human	23
Carnevali, 2013 ²¹⁷	Belgium	ADE	Adults	All admissions	Adapted to Belgian setting but method not mentioned.	Human	19
Sharek, 2006 ²¹⁸	USA, Canada	Harm / AE	Children*	15 NICUs	Expert panel developed list of AEs relevant to NICU, Delphi method, pilot, refined based on positive predictive value.	Human	17
Larsen, 2007 ²¹⁹	USA	AE	Children	1 PICU	NR	Human	25
Takata, 2008 ²²⁰	USA	ADE	Children	12 paediatric hospitals	Used Rozich ² in children, modified triggers based on positive predictive value, triggers added <i>a priori</i> .	Human	15
Sikdar, 2010 ²²¹	Canada	ADE	Children	1 emergency department	NR	Human	37
Agarwal, 2010 ²²²	USA	AE and ADE	Children	15 PICUs	Expert panel (10) compiled TT from references and personal experience. Modified TT based on Delphi method and low positive predictive value.	Human	22
Matlow, 2011 ²²³	Canada	AE	Children	3 acute care paediatric units (surgical and medical)	Literature review found 5 TT, compiled list. Expert panel used Delphi method to modify list.	Human	35
Lemon, 2012 ²²⁴	USA	AE	Children	1 paediatric hospital	Trigger must be electronically identifiable, frequency of trigger manageable, favourable positive predictive value, significant level of harm, not investigated by other teams.	Computer	14
Chapman, 2014 ²²⁵	UK	AE	Children	25 hospitals, 9 paediatric hospitals	Expert panel discussion compiled TT based on reference TT, local AEs, personal experience.	Computer	40

Call, 2014 ²²⁶	USA	ADE	Children	1 hospital - oncology, hematology and catastrophic diseases	Selected triggers based on the wide use in paediatric population.	Computer	6
Mouton, 2016 ¹⁰⁵	SA	ADR	Adults	4 hospitals, medical wards	NR	Human	59

* neonates

ADE: adverse drug event; ADR: adverse drug reaction; AE: adverse event; ICU: intensive care unit; NICU: neonatal intensive care unit; NR: not reported; PICU: paediatric intensive care unit; SA: South Africa; TT: trigger tool; UK: United Kingdom; USA: United States of America

Appendix ix. Reasons for admission at two children's hospitals, South Africa, 2015

ICD-10 Chapter / Code block	Count	Proportion
CERTAIN INFECTIOUS AND PARASITIC DISEASES	140	8.7%
A00-A09 Intestinal infectious diseases	56	3.5%
A15-A19 Tuberculosis	19	1.2%
A30-A49 Other bacterial diseases	30	1.9%
A50-A64 Infections with a predominantly sexual mode of transmission	1	0.06%
B00-B09 Viral infections characterized by skin and mucous membrane lesions	9	0.56%
B15-B19 Viral hepatitis	3	0.19%
B20-B24 Human immunodeficiency virus [HIV] disease	4	0.25%
B25-B34 Other viral diseases	4	0.25%
B35-B49 Mycoses	10	0.62%
B50-B64 Protozoal diseases	1	0.06%
B65-B83 Helminthiasis	1	0.06%
B85-B89 Pediculosis, ascariasis and other infestations	2	0.12%
NEOPLASMS	10	0.62%
C64-C68 Malignant neoplasms of urinary tract	1	0.06%
C69-C72 Malignant neoplasms of eye, brain and other parts of the central nervous system	2	0.12%
D10-D36 Benign neoplasms	5	0.31%
D37-D48 Neoplasms of uncertain or unknown behaviour	2	0.12%
DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS; CERTAIN DISORDERS INVOLVING THE IMMUNE MECHANISM	81	5.1%
D50-D53 Nutritional anaemias	25	1.6%
D55-D59 Haemolytic anaemias	3	0.19%
D60-D64 Aplastic and other anaemias	33	2.1%
D65-D69 Coagulation defects, purpura and other haemorrhagic conditions	5	0.31%
D70-D77 Other diseases of blood and blood-forming organs	14	0.87%
D80-D89 Certain disorders involving the immune mechanism	1	0.06%
ENDOCRINE, NUTRITIONAL AND METABOLIC DISEASES	97	6.1%
E00-E07 Disorders of thyroid gland	2	0.12%
E10-E14 Diabetes mellitus	2	0.12%
E15-E16 Other disorders of glucose regulation and pancreatic internal secretion	3	0.19%
E20-E35 Disorders of other endocrine glands	4	0.25%
E40-E46 Malnutrition	31	1.9%
E50-E64 Other nutritional deficiencies	2	0.12%
E70-E90 Metabolic disorders	53	3.3%
MENTAL AND BEHAVIOURAL DISORDERS	4	0.25%
F00-F09 Organic, including symptomatic, mental disorders	1	0.06%
F70-F79 Mental retardation	1	0.06%
F80-F89 Disorders of psychological development	2	0.12%
DISEASES OF THE NERVOUS SYSTEM	60	3.7%
G00-G09 Inflammatory diseases of the central nervous system	22	1.4%
G10-G14 Systemic atrophies primarily affecting the central nervous system	2	0.12%
G20-G26 Extrapyrmidal and movement disorders	5	0.31%
G35-G37 Demyelinating diseases of the central nervous system	1	0.06%
G40-G47 Episodic and paroxysmal disorders	21	1.3%
G50-G59 Nerve, nerve root and plexus disorders	1	0.06%
G60-G64 Polyneuropathies and other disorders of the peripheral nervous system	1	0.06%
G80-G83 Cerebral palsy and other paralytic syndromes	4	0.25%
G90-G99 Other disorders of the nervous system	3	0.19%
DISEASES OF THE EYE AND ADNEXA	13	0.81%
H10-H13 Disorders of conjunctiva	12	0.75%

H49-H52 Disorders of ocular muscles, binocular movement, accommodation and refraction	1	0.06%
DISEASES OF THE EAR AND MASTOID PROCESS	23	1.4%
H65-H75 Diseases of middle ear and mastoid	23	1.4%
DISEASES OF THE CIRCULATORY SYSTEM	33	2.1%
I10-I15 Hypertensive diseases	4	0.25%
I26-I28 Pulmonary heart disease and diseases of the pulmonary circulation	6	0.37%
I30-I52 Other forms of heart disease	20	1.2%
I70-I79 Diseases of arteries, arterioles and capillaries	1	0.06%
I80-I89 Diseases of veins, lymphatic vessels and lymph nodes	1	0.06%
I95-I99 Other and unspecified disorders of the cardiovascular system	1	0.06%
DISEASES OF THE RESPIRATORY SYSTEM	598	37%
J00-J06 Acute upper respiratory infections	56	3.5%
J09-J18 Influenza and pneumonia	202	13%
J20-J22 Other acute lower respiratory infections	270	17%
J30-J39 Other diseases of upper respiratory tract	5	0.31%
J40-J47 Chronic lower respiratory diseases	37	2.3%
J80-J84 Other respiratory diseases principally affecting the interstitium	1	0.06%
J90-J94 Other diseases of pleura	2	0.12%
J95-J99 Other diseases of the respiratory system	25	1.6%
DISEASES OF THE DIGESTIVE SYSTEM	40	2.5%
K00-K14 Diseases of oral cavity, salivary glands and jaws	6	0.37%
K20-K31 Diseases of oesophagus, stomach and duodenum	1	0.06%
K40-K46 Diseases of appendix	1	0.06%
K50-K52 Noninfective enteritis and colitis	11	0.69%
K55-K64 Other diseases of intestines	9	0.56%
K65-K67 Diseases of peritoneum	1	0.06%
K70-K77 Diseases of liver	6	0.37%
K80-K87 Disorders of gallbladder, biliary tract and pancreas	2	0.12%
K90-K93 Other diseases of the digestive system	3	0.19%
DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUE	31	1.9%
L00-L08 Infections of the skin and subcutaneous tissue	12	0.75%
L20-L30 Dermatitis and eczema	12	0.75%
L40-L45 Papulosquamous disorders	1	0.06%
L50-L54 Urticaria and erythema	4	0.25%
L80-L99 Other disorders of the skin and subcutaneous tissue	2	0.12%
DISEASES OF THE MUSCULOSKELETAL SYSTEM AND CONNECTIVE TISSUE	9	0.56%
M00-M03 Infectious arthropathies	1	0.06%
M30-M36 Systemic connective tissue disorders	4	0.25%
M60-M63 Disorders of muscles	1	0.06%
M86-M90 Other osteopathies	2	0.12%
M91-M94 Chondropathies	1	0.06%
DISEASES OF THE GENITOURINARY SYSTEM	54	3.4%
N00-N08 Glomerular diseases	6	0.37%
N10-N16 Renal tubulo-interstitial diseases	1	0.06%
N17-N19 Renal failure	20	1.2%
N30-N39 Other diseases of urinary system	26	1.6%
N40-N51 Disorders of male genital organs	1	0.06%
CERTAIN CONDITIONS ORIGINATING IN THE PERINATAL PERIOD	85	5.3%
P05-P08 Disorders related to length of gestation and foetal growth	5	0.31%
P20-P29 Respiratory and cardiovascular disorders specific to the perinatal period	10	0.62%
P35-P39 Infections specific to the perinatal period	31	1.9%
P50-P61 Haemorrhagic and haematological disorders of foetus and newborn	34	2.1%
P75-P78 Digestive system disorders of foetus and newborn	2	0.12%

P80-P83 Conditions involving the integument and temperature regulation of fetus and newborn	1	0.06%
P90-P96 Other disorders originating in the perinatal period	2	0.12%
CONGENITAL MALFORMATIONS, DEFORMATIONS AND CHROMOSOMAL ABNORMALITIES	52	3.2%
Q00-Q07 Congenital malformations of the nervous system	1	0.06%
Q20-Q28 Congenital malformations of the circulatory system	46	2.9%
Q38-Q45 Other congenital malformations of the digestive system	2	0.12%
Q60-Q64 Congenital malformations of the urinary system	1	0.06%
Q65-Q79 Congenital malformations and deformations of the musculoskeletal system	1	0.06%
Q80-Q89 Other congenital malformations	1	0.06%
SYMPTOMS, SIGNS AND ABNORMAL CLINICAL AND LABORATORY FINDINGS	218	14%
R00-R09 Symptoms and signs involving the circulatory and respiratory systems	59	3.7%
R10-R19 Symptoms and signs involving the digestive system and abdomen	17	1.1%
R20-R23 Symptoms and signs involving the skin and subcutaneous tissue	9	0.56%
R30-R39 Symptoms and signs involving the urinary system	1	0.06%
R40-R46 Symptoms and signs involving cognition, perception, emotional state and behaviour	1	0.06%
R50-R69 General symptoms and signs	122*	7.6%
R70-R79 Abnormal findings on examination of blood, without diagnosis	7	0.44%
R80-R82 Abnormal findings on examination of urine, without diagnosis	2	0.12%
INJURY, POISONING AND CERTAIN OTHER CONSEQUENCES OF EXTERNAL CAUSES	28	1.7%
S00-S09 Injuries to the head	7	0.44%
T08-T14 Injuries to unspecified part of trunk, limb or body region	1	0.06%
T15-T19 Effects of foreign body entering through natural orifice	1	0.06%
T20-T32 Burns and corrosions	3	0.19%
T36-T50 Poisoning by drugs, medicaments and biological substances	7	0.44%
T66-T78 Other and unspecified effects of external causes	5	0.31%
T80-T88 Complications of surgical and medical care	4	0.25%
EXTERNAL CAUSES OF MORBIDITY AND MORTALITY	16	1.0%
W65-W74 Accidental drowning and submersion	1	0.06%
X40-X49 Accidental poisoning by and exposure to noxious substances	12	0.75%
X85-Y09 Assault	2	0.12%
Y83-Y84 Surgery and other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of procedure	1	0.06%
FACTORS INFLUENCING HEALTH STATUS AND CONTACT WITH HEALTH SERVICES	10	0.62%
Z00-Z13 Persons encountering health services for examination and investigation	2	0.12%
Z20-Z29 Persons with potential health hazards related to communicable diseases	1	0.06%
Z40-Z54 Persons encountering health services for specific procedures and health care	4	0.25%
Z70-Z76 Persons encountering health services in other circumstances	2	0.12%
Z80-Z99 Persons with potential health hazards related to family and personal history and certain conditions influencing health status	1	0.06%
TOTAL	1602	100%

Reasons for admission are presented according to ICD-10 classification. More than one reason possible per admission.

* Including 93 admissions for convulsions

Appendix Ixi. Background drugs most commonly in use among 1106 admissions at two children's hospitals in South Africa, 2015

Drug class	ATC	Prior to <i>n</i> admissions	Frequency of use (N=1106)
Adrenergics, inhalants	R03A	281	25.41%
Other analgesics and antipyretics	N02B	277	25.05%
Beta-lactam antibacterials, penicillins	J01C	211	19.08%
Other beta-lactam antibacterials	J01D	152	13.74%
Other drugs for obstructive airway disease	R03B	125	11.30%
Corticosteroids for systemic use, plain	H02A	104	9.40%
Antiepileptics	N03A	88	7.96%
Multivitamins, combinations	A11A	80	7.23%
Direct acting antivirals	J05A	73	6.60%
Sulfonamides and trimethoprim	J01E	61	5.52%
Other mineral supplements	A12C	59	5.33%
Drugs for peptic ulcer and gastroesophageal reflux	A02B	58	5.24%
High-ceiling diuretics	C03C	58	5.24%
Vitamin B12 and folic acid	B03B	53	4.79%
Antihistamines for systemic use	R06A	47	4.25%
Vitamin A and D, incl. combinations	A11C	46	4.16%
Anxiolytics	N05B	45	4.07%
Potassium-sparing agents	C03D	44	3.98%
Aminoglycoside antibacterials	J01G	35	3.16%
Iron preparations	B03A	35	3.16%
Drugs for treatment of tuberculosis	J04A	31	2.80%
Laxatives	A06A	30	2.71%
ACE inhibitors, plain	C09A	28	2.53%
Macrolides, lincosamides and streptogramins	J01F	27	2.44%
I.V. solution additives	B05X	26	2.35%
Adrenergics for systemic use	R03C	25	2.26%
Calcium	A12A	24	2.17%
Anaesthetics, general	N01A	21	1.90%
Antibacterials (unspecified)	J01	20	1.81%
Opioids	N02A	20	1.81%

Background drug use was defined as drug use over a 30-day period before the admission. Drugs grouped by third-level ATC group

Appendix Ixii. Drugs most commonly in use during 1105 admissions at two children's hospitals in South Africa, 2015

Drug class	ATC	During <i>n</i> admissions	Frequency of use (N=1105)
Other analgesics and antipyretics	N02B	667	60.36%
Beta-lactam antibacterials, penicillins	J01C	658	59.55%
Adrenergics, inhalants	R03A	416	37.65%
Other mineral supplements	A12C	314	28.42%
Other beta-lactam antibacterials	J01D	297	26.88%
Multivitamins, combinations	A11A	292	26.43%
Aminoglycoside antibacterials	J01G	214	19.37%
Corticosteroids for systemic use, plain	H02A	178	16.11%
Vitamin B12 and folic acid	B03B	156	14.12%
Potassium	A12B	149	13.48%
Vitamin A and D, incl. combinations	A11C	147	13.30%
Direct acting antivirals	J05A	136	12.31%
Antiepileptics	N03A	130	11.76%
High-ceiling diuretics	C03C	129	11.67%
Opioids	N02A	121	10.95%
Anesthetics, general	N01A	118	10.68%
I.V. solution additives	B05X	116	10.50%
Other drugs for obstructive airway disease	R03B	113	10.23%
Antiadrenergic agents, centrally acting	C02A	99	8.96%
Intestinal anti-infectives	A07A	94	8.51%
Drugs for peptic ulcer and gastroesophageal reflux	A02B	89	8.05%
Antiinflammatory and antirheumatic preparations	M01A	86	7.78%
Hypnotics and sedatives	N05C	84	7.60%
Potassium-sparing agents	C03D	79	7.15%
Macrolides, lincosamides and streptogramins	J01F	77	6.97%
Viral vaccines	J07B	69	6.24%
Sulfonamides and trimethoprim	J01E	66	5.97%
Anxiolytics	N05B	61	5.52%
Drugs for treatment of tuberculosis	J04A	58	5.25%
Calcium	A12A	56	5.07%
Laxatives	A06A	54	4.89%
Other antibacterials	J01X	53	4.80%
Cardiac stimulants excl. cardiac glycosides	C01C	51	4.62%
Vitamin K and other haemostatics	B02B	49	4.43%
Antihistamines for systemic use	R06A	48	4.34%
Antinematodal agents	P02C	45	4.07%
Iron preparations	B03A	43	3.89%
Bacterial vaccines	J07A	40	3.62%
Other plain vitamin preparations	A11H	39	3.53%
Bacterial and viral vaccines, combined	J07C	34	3.08%
Muscle relaxants, peripherally acting	M03A	34	3.08%
Blood and related products	B05A	33	2.99%
Psychostimulants	N06B	33	2.99%
Ace inhibitors, plain	C09A	32	2.90%
Antimycotics for systemic use	J02A	27	2.44%
Other systemic drugs for obstructive airways disease	R03D	25	2.26%
Quinolone antibacterials	J01M	20	1.81%

Drugs grouped by third-level ATC group.

Appendix Ixiii. Serious adverse drug reactions present at the time of admission at two children's hospitals, South Africa, 2015

Patient	Sex	Age category	Weight (kg)	WFA-z	HIV category	ADR no.	ADR manifestation (MedDRA® PT)	Type	Implicated drug(s)	Seriousness	Causality	Preventable
1	F	PN	0.7		Neg	1	Neonatal respiratory depression	A	Remifentanyl	Caused admission	Possible	No
2	F	PN	1.9		Neg	2	Cardio-respiratory arrest	A	Fentanyl	Caused admission	Possible	No
3	M	PN	1.5		Neg	3	Respiratory arrest	B	Benzathine benzylpenicillin	Death	Definite	Yes
4	M	I		-5.5	Indet	4	Cardiogenic shock	A	Furosemide + spironolactone	Caused admission	Possible	No
5	M	T		-0.8	Neg	5	Urticaria	B	Phenoxyethylpenicillin	Caused admission	Definite	No
6	F	T		-1.3	Neg	6	Cardiac failure congestive	A	Carvedilol	Caused admission	Possible	No
7	M	T		-1.6	Pos	7	Lower respiratory tract infection	A	Prednisone	Caused admission	Possible	No
8	M	T		-2.6	Neg	8	Dystonia	A	Metoclopramide	Caused admission	Definite	No
9	F	EC		0.9	Neg	9	Urticaria	B	Ceftriaxone	Caused admission	Probable	Yes
10	M	EC		-3.1	Pos	10	Agranulocytosis	Mixed	Zidovudine Co-trimoxazole	Caused admission	Probable Possible	No No
11	F	EC	18		Neg	11	Convulsion	A	Isoniazid	Caused admission	Possible	No
12	M	MC	31		Neg	12	Thrombocytopenia	B	Amoxicillin	Caused admission	Possible	No
13	F	MC	Missing		Neg	13	Constipation	A	Ferrous gluconate	Caused admission	Possible	Yes
14	F	MC	25		Neg	14	Metabolic acidosis	A	Amikacin + paracetamol	Caused admission	Possible	No
15	F	MC	51		Neg	15	Delirium	A	Clozapine	Caused admission	Probable	Yes
16	F	MC	74		Neg	16	Upper respiratory tract infection	A	Prednisone	Caused admission	Possible	No
17	F	MC	28		Neg	17	Dystonia	A	Metoclopramide	Caused admission	Definite	Yes
18	M	EA	40		Neg	18	Somnolence	A	Amitriptyline	Caused admission	Definite	Yes
19	F	EA	42		Neg	19	Hyperkalaemia	A	Enalapril	Near-death	Definite	No
20	F	EA	37		Neg	20	Anaemia macrocytic	Mixed	Tacrolimus Mycophenolic acid Erythropoietin	Caused admission	Possible Possible Possible	No No No

F: female; M: male; Age categories: PN: preterm neonate, I: infancy, T: toddler, EC: early childhood, MC: middle childhood, EA: early adolescence; MedDRA® PT: Medical Dictionary for Regulatory Activities preferred term; WFA-z: weight-for-age z-score

Appendix Ixiv. Serious adverse drug reactions occurring during hospital admission at two children's hospitals, South Africa, 2015

Patient	Sex	Age category	Weight (kg)	WFA-z	HIV category	ADR no.	ADR manifestation (MedDRA® PT)	Type	Implicated drug(s)	Seriousness	Causality	Preventable
21	F	I		0.5	Indet	21	Respiratory depression	A	Lorazepam + chlorpromazine + diazepam + phenobarbital	Near-death	Probable	No
22	F	I		-6.8	Neg	22	Red man syndrome	B	Vancomycin	Near-death	Probable	Yes
23	M	I		-0.3	Indet	23	Respiratory depression	A	Morphine + diazepam + phenobarbital	Near-death	Possible	No
24	M	I		-1.5	Indet	24	Apnoea	A	Midazolam	Near-death	Possible	No
25	M	I		-1.6	Neg	25	Diarrhoea	A	Amoxicillin	Prolonged admission	Possible	No
26	M	I		-5.7	Pos	26	Diarrhoea	A	Lopinavir / ritonavir	Prolonged admission	Probable	No
27	M	I		-2.7	Neg	27	Diarrhoea	A	Clarithromycin	Prolonged admission	Possible	No
28	M	I		-0.5	Neg	28	Diarrhoea	A	Amoxicillin	Prolonged admission	Possible	No
29	M	I		-0.5	Indet	29	Analgesic drug level increased	A	Paracetamol	Prolonged admission	Definite	No
						30	Bicytopenia	A	Ceftriaxone + ganciclovir + co-trimoxazole	Prolonged admission	Possible	No
30	F	EC		0.8	Neg	31	Rash maculo-papular	B	Flucloxacillin	Prolonged admission	Possible	Yes
31	F	EC		-1.3	Neg	32	Neutropenic sepsis	A	Tacrolimus	Prolonged admission	Probable	Yes
32	F	EC	23		Neg	33	Sepsis	A	Methylprednisolone + tacrolimus + mycophenolic acid	Prolonged admission	Possible	No
33	M	MC	21		Neg	34	Hyperkalaemia	A	Enalapril	Near-death	Definite	No
						35	Renal failure acute	A	Furosemide	Near-death	Probable	No
34	M	MC	26		Pos	36	Transaminases increased	B	Rifampicin	Prolonged admission	Possible	No
									Pyrazinamide		Possible	No
									Isoniazid		Possible	No
									Efavirenz		Possible	No

35	F	MC	38	Neg	37	Bicytopenia	A	Cyclophosphamide	Prolonged admission	Definite	No
					38	Pancreatitis	B	Methylprednisolone Prednisone	Prolonged admission	Probable Probable	No No
					39	<i>Pneumocystis jirovecii</i> pneumonia	A	Prednisone + methylprednisolone	Prolonged admission	Possible	No
36	M	EA	41	Neg	40	Salmonellosis	A	Mycophenolic acid + prednisone	Prolonged admission	Probable	No

F: female; M: male; Age categories: I: infancy, EC: early childhood, MC: middle childhood, EA: early adolescence; MedDRA® PT: Medical Dictionary for Regulatory Activities preferred term; WFA-z: weight-for-age z-score

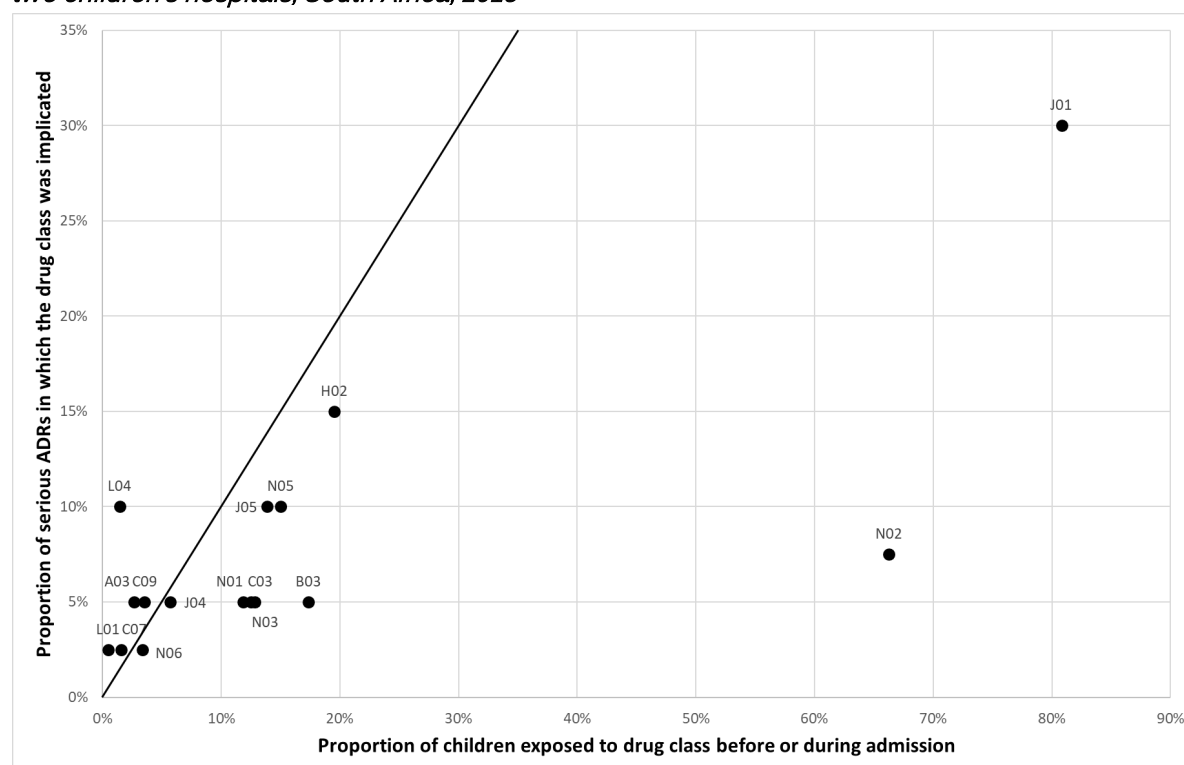
Appendix Ixv. Alternative ways of expressing ADR prevalence rates at two children's hospitals, South Africa, 2015

Outcome event	(n) events	Prevalence per 100 admissions	
		Denominator: all admissions ^a	Denominator: drug-exposed admissions only ^b
ADRs	160	14.5	15.1
Serious ADRs	40	3.62	3.78
Serious ADRs present at admission	20	1.81	2.67
Serious ADR occurring during admission	20	1.81	1.93
Non-serious ADRs	120	10.8	11.4
Non-serious ADRs present at admission	26	2.35	3.47
Non-serious ADR occurring during admission	94	8.51	9.07
ADRs present at admission	46	4.16	6.13
ADRs occurring during admission	114	10.3	11.0
Admissions with ≥ 1 ADR	120	10.8	11.4
Admissions with ≥ 1 serious ADR	36	3.26	3.41
Admissions with ≥ 1 serious ADR present at admission	20	1.81	2.67
Admissions with ≥ 1 serious ADR during admission	16	1.45	1.54
Admissions with ≥ 1 non-serious ADR	94	8.50	8.89
Admissions with ≥ 1 non-serious ADR present at admission	25	2.26	3.33
Admissions with ≥ 1 non-serious ADR during admission	72	6.52	6.95
Admissions with ≥ 1 ADR present at admission	41	3.71	5.47
Admissions with ≥ 1 ADR during admission	85	7.69	8.20

^a Denominator (N) = 1106 admissions for "present at admission" outcomes; N=1105 admissions for "during admission" outcomes; N=1106 admissions for "present at admission or during admission" outcomes

^b Denominator (N) = 750 drug-exposed admissions for "present at admission" outcomes; N=1036 drug-exposed admissions for "during admission" outcomes; N=1057 drug-exposed admissions for "present at admission or during admission" outcomes

Appendix lxvi. Scatterplot of drug classes implicated in serious ADRs versus frequency of their use at two children's hospitals, South Africa, 2015



Scatterplot of 15 drug classes (coded to second-level ATC codes) implicated in 40 serious ADRs. For points above the diagonal line, drug classes were disproportionately often implicated in ADRs, compared to their frequency of exposure. A03 = drugs for functional gastrointestinal disorders; B03 = antianaemic preparations; C03 = diuretics; C07 = beta blocking agents; C09 = agents acting on renin-angiotensin system; H02 = corticosteroids for systemic use; J01 = antibacterials for systemic use; J04 = antimycobacterials; J05 = antivirals for systemic use; L01 = antineoplastic agents; L04 = immunosuppressive agents; N01 = anaesthetics; N02 = analgesics; N03 = antiepileptics; N05 = psycholeptics; N06 = psychoanaleptics

Appendix Ixvii. Reasons adverse drug reactions were considered preventable at two children's hospitals, South Africa, 2015

	Proportion considered preventable							
	Drug-ADR-pair-level		ADR-level		Admission-level		Patient-level	
Schumock and Thornton preventability factor	Drug-ADR pairs with preventability factor present (N=264 pairs)	Drug-serious-ADR pairs with preventability factor present (N=60 pairs)	ADRs with preventability factor present (N=160 ADRs)	Serious ADRs with preventability factor present (N=40 ADRs)	Admissions with ≥1 ADR with preventability factor present (N=120 admissions)	Admissions with ≥1 serious ADR with preventability factor present (N=36 admissions)	Patients with ≥1 ADR with preventability factor present (N=119 patients)	Patients with ≥1 serious ADR with preventability factor present (N=36 patients)
Drug inappropriate	15 (5.7%)	6 (10%)	14 (8.8%)	6 (15%)	14 (12%)	6 (17%)	14 (12%)	6 (17%)
Dose/route inappropriate	5 (1.9%)	2 (3.3%)	5 (3.1%)	2 (5.0%)	5 (4.2%)	2 (5.6%)	5 (4.2%)	2 (5.6%)
Monitoring insufficient	8 (3.0%)	1 (1.7%)	8 (5.0%)	1 (2.5%)	8 (6.7%)	1 (2.8%)	7 (5.9%)	1 (2.8%)
History of ADR	1 (0.38%)	0	1 (0.63%)	0	1 (0.83%)	0	1 (0.84%)	0
Interaction	0	0	0	0	0	0	0	0
Raised drug concentration	2 (0.76%)	1 (1.7%)	2 (1.3%)	1 (2.5%)	2 (1.7%)	1 (2.8%)	2 (1.7%)	1 (2.8%)
Compliance	2 (0.76%)	2 (3.3%)	2 (1.3%)	2 (5.0%)	2 (1.7%)	2 (5.6%)	2 (1.7%)	2 (5.6%)
Any factor	26 (9.8%)	9 (15%)	25 (16%)	9 (23%)	24 (20%)	9 (25%)	23 (19%)	9 (25%)

Appendix Ixviii. Exploratory analysis: Multivariate logistic regression model of factors associated with serious ADR incorporating weight-for-age z-scores, at two children's hospitals in South Africa, 2015

Gender-AER incorporating weight-for-age z-score, at two children's hospitals in South Africa, 2010					
	n	Bivariate analysis		Multivariate analysis	
		Unadjusted OR (95% CI)	P	Adjusted ^a OR (95% CI)	P
Age category					
Infant	415	Referent			
Toddler	135	0.920 (0.250 to 3.39)	0.901	1.21 (0.295 to 4.94)	0.794
Early childhood	159	1.05 (0.323 to 3.38)	0.941	1.53 (0.391 to 5.93)	0.544
Sex					
Male	419	Referent			
Female	290	0.595 (0.207 to 1.71)	0.334	0.585 (0.196 to 1.74)	0.335
Weight-for-age z-score					
Per 1-unit increase	709	0.785 (0.623 to 0.989)	0.040	0.908 (0.687 to 1.20)	0.498
Hospital					
RXWMCH	589	Referent			
RMMCH	120	1.05 (0.298 to 3.72)	0.936	0.851 (0.221 to 3.28)	0.815
HIV category					
Negative	576	Referent			
Infected	22	9.95 (2.49 to 39.7)	0.001	6.21 (1.40 to 27.5)	0.016
Indeterminate	111	2.97 (0.977 to 9.04)	0.055	2.60 (0.737 to 9.19)	0.137
Total drug count					
Per additional drug	709	1.10 (1.04 to 1.15)	<0.001	1.07 (1.01 to 1.14)	0.022

n = 709 first admissions of infants, toddlers, and under-6-year-olds

^a Adjusted for other variables in the model

Appendix Ixix. Non-serious adverse drug reactions present at the time of admission at two children's hospitals, South Africa, 2015

Patient	Sex	Age category	Weight (kg)	WFA-z	HIV category	ADR no.	ADR manifestation (MedDRA® PT)	Type	Implicated drug(s)	Seriousness	Causality	Preventable
37	F	TN	3.6		Indet	41	Tachycardia	A	Salbutamol	Increased monitoring, no harm	Possible	No
38	F	I		-5.6	Indet	42	Normochromic normocytic anaemia	A	Zidovudine	Requires treatment, temporary harm	Possible	No
39	M	I		-0.8	Indet	43	Diarrhoea	A	Erythromycin	Increased monitoring, no harm	Possible	Yes
25	M	I		-1.6	Neg	44	Tachycardia	A	Epinephrine	Increased monitoring, no harm	Probable	No
40	M	T		-0.8	Neg	45	Hypokalaemia	A	Epinephrine + salbutamol	Requires treatment, temporary harm	Probable	No
41	M	EC		0.0	Neg	46	Transaminases increased	B	Co-amoxiclav	Requires treatment, temporary harm	Possible	No
42	M	EC		-1.2	Neg	47	Hypokalaemia	A	Furosemide	Increased monitoring, no harm	Possible	No
43	M	EC		-1.4	Neg	48	Bicytopenia	B	Furosemide	Increased monitoring, no harm	Possible	No
44	F	EC		0.8	Neg	49	Respiratory depression	A	Diazepam	Requires treatment, temporary harm	Possible	No
45	M	EC		0.0	Neg	50	Rash erythematous	B	Clarithromycin Amoxicillin	Requires treatment, temporary harm	Possible Possible	No Yes
46	F	EC		-0.6	Neg	51	Hallucination	A	Diphenhydramine	Increased monitoring, no harm	Possible	Yes
47	M	EC		-0.6	Neg	52	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Probable	No
10	M	EC		-3.1	Pos	53	Hyponatraemia	A	Co-trimoxazole	Requires treatment, temporary harm	Possible	No
48	M	EC	19		Neg	54	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Probable	No
49	F	EC	16		Neg	55	Tachycardia	A	Fenoterol	Increased monitoring, no harm	Possible	No
32	F	EC	23		Neg	56	Cushingoid	A	Methylprednisolone	Increased monitoring, no harm	Definite	No
12	M	MC	31		Neg	57	Cushingoid	A	Prednisone	Increased monitoring, no harm	Definite	No
50	M	MC	23		Neg	58	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Possible	No
34	M	MC	26		Pos	59	Hyponatraemia	A	Co-trimoxazole	Increased monitoring, no harm	Possible	No
16	F	MC	74		Neg	60	Cushingoid	A	Prednisone	Increased monitoring, no harm	Definite	No
51	M	MC	33		Neg	61	Hypokalaemia	A	Salbutamol + fenoterol	Requires treatment, temporary harm	Probable	No

					62	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Probable	No
52	M	EA	33	Neg	63	Somnolence	A	Phenobarbital	Increased monitoring, no harm	Definite	Yes
53	F	EA	22	Neg	64	Constipation	A	Atropine	Requires treatment, temporary harm	Possible	No
19	F	EA	42	Neg	65	Pruritus	B	Heparin	Increased monitoring, no harm	Definite	No
					66	Hypokalaemia	A	Polystyrene sulfonate	Increased monitoring, no harm	Definite	Yes

F: female; M: male; Age categories: TN: term neonate, I: infancy, T: toddler, EC: early childhood, MC: middle childhood, EA: early adolescence; MedDRA® PT: Medical Dictionary for Regulatory Activities preferred term; WFA-z: weight-for-age z-score

Appendix lxx. Non-serious adverse drug reactions occurring during admission at two children's hospitals, South Africa, 2015

Patient	Sex	Age category	Weight (kg)	WFA-z	HIV category	ADR no.	ADR manifestation (MedDRA® PT)	Type	Implicated drug(s)	Seriousness	Causality	Preventable
54	M	PN	0.9		Indet	67	Renal impairment	A	Amphotericin + vancomycin	Increased monitoring, no harm	Probable	No
55	M	PN	0.8		Neg	68	Convulsion	A	Imipenem-cilastatin	Requires treatment, temporary harm	Probable	No
56	F	TN	3.1		Neg	69	Hypernatraemia	A	Sodium chloride	Increased monitoring, no harm	Definite	No
57	F	PN	1.9		Indet	70	Convulsion	A	Morphine	Increased monitoring, no harm	Possible	No
						71	Hyponatraemia	A	Spironolactone + furosemide	Requires treatment, temporary harm	Possible	No
						72	Normochromic normocytic anaemia	A	Zidovudine	Requires treatment, temporary harm	Possible	Yes
58	M	I		-2.4	Indet	73	Diarrhoea	A	Gentamicin + ampicillin	Increased monitoring, no harm	Possible	No
59	F	I		-4.4	Indet	74	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Definite	Yes
60	M	I		-2.0	Neg	75	Dermatitis diaper	A	Amoxicillin	Requires treatment, temporary harm	Possible	No
61	F	I		-5.2	Neg	76	Diarrhoea	A	Ampicillin	Requires treatment, temporary harm	Possible	No
						77	Renal failure acute	A	Furosemide + gentamicin + spironolactone	Requires treatment, temporary harm	Probable	Yes
62	M	I		-1.9	Neg	78	Hypokalaemia	A	Furosemide	Requires treatment, temporary harm	Possible	No
						79	Renal impairment	A	Gentamicin	Requires treatment, temporary harm	Probable	Yes
21	F	I		0.5	Indet	80	Normochromic normocytic anaemia	B	Co-trimoxazole	Increased monitoring, no harm	Possible	No
63	F	I		-0.5	Neg	81	Diarrhoea	A	Ampicillin + clarithromycin + gentamicin	Increased monitoring, no harm	Possible	No
64	M	I		0.0	Neg	82	Diarrhoea	A	Amoxicillin + gentamicin + ampicillin	Requires treatment, temporary harm	Possible	No
65	F	I		-1.8	Pos	83	Hypokalaemia	A	Fenoterol	Increased monitoring, no harm	Possible	No
						84	Hyponatraemia	A	Co-trimoxazole	Increased monitoring, no harm	Possible	No

					85	Injection site phlebitis	A	Ganciclovir	Requires treatment, temporary harm	Possible	No
					86	Microcytic anaemia	A	Ganciclovir + co-trimoxazole	Requires treatment, temporary harm	Possible	No
					87	Oral candidiasis	A	Gentamicin + prednisone + ertapenem + ampicillin + azithromycin	Requires treatment, temporary harm	Possible	No
66	M	I	-1.9	Neg	88	Rash erythematous	B	Midazolam	Requires treatment, temporary harm	Possible	No
								Fluconazole		Possible	No
								Ganciclovir		Possible	No
								Co-trimoxazole		Possible	No
								Diazepam		Possible	No
								Clonidine		Possible	No
								Gentamicin		Possible	No
								Ampicillin		Possible	No
								Morphine		Possible	No
67	M	I	-2.0	Neg	89	Diarrhoea	A	Gentamicin + ampicillin	Increased monitoring, no harm	Possible	No
68	M	I	-5.4	Indet	90	Diarrhoea	A	Ampicillin + gentamicin + amoxicillin	Increased monitoring, no harm	Possible	No
69	M	I	-0.5	Neg	91	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Definite	No
70	F	I	-2.7	Neg	92	Coagulopathy	A	Heparin	Requires treatment, temporary harm	Probable	Yes
					93	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Probable	No
71	M	I	-6.4	Indet	94	Thrombocytopenia	B	Heparin	Increased monitoring, no harm	Probable	No
72	F	I	-4.4	Pos	95	Hyponatraemia	A	Co-trimoxazole	Increased monitoring, no harm	Possible	No
73	F	I	-4.6	Neg	96	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Probable	No
74	M	I	2.0	Neg	97	Diarrhoea	A	Gentamicin + ampicillin	Increased monitoring, no harm	Possible	No
75	M	I	2.0	Neg	98	Rash maculo-papular	B	Amoxicillin	Increased monitoring, no harm	Possible	No
76	F	I	-2.6	Neg	99	Hypokalaemia	A	Furosemide	Requires treatment, temporary harm	Possible	No
77	F	I	-1.8	Neg	100	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Probable	No
78	M	I	-0.5	Neg	101	Diarrhoea	A	Gentamicin + ampicillin + oseltamivir	Increased monitoring, no harm	Possible	No
79	F	I	-4.3	Indet	102	Gastroenteritis clostridial	A	Meropenem + ertapenem + cloxacillin	Increased monitoring, no harm	Probable	No

80	M	I	-2.8	Neg	103	Hypokalaemia	A	Furosemide	Requires treatment, temporary harm	Possible	No
81	M	I	-3.9	Neg	104	Diarrhoea	A	Co-amoxiclav	Increased monitoring, no harm	Possible	No
82	M	I	-2.1	Neg	105	Diarrhoea	A	Ceftriaxone	Increased monitoring, no harm	Possible	No
83	M	I	-6.0	Indet	106*	Hypokalaemia	A	Furosemide	Increased monitoring, no harm	Possible	No
					107*	Hypokalaemia	A	Furosemide	Requires treatment, temporary harm	Possible	No
					108	Hyponatraemia	A	Furosemide + spironolactone	Requires treatment, temporary harm	Possible	No
84	M	I	-0.1	Neg	109	Hypokalaemia	A	Salbutamol + aminophylline	Requires treatment, temporary harm	Possible	No
					110	Tachycardia	A	Salbutamol + aminophylline	Increased monitoring, no harm	Probable	No
85	M	I	-2.0	Neg	111	Diarrhoea	A	Co-amoxiclav	Increased monitoring, no harm	Possible	No
86	M	I	-2.4	Pos	112	Hyperkalaemia	A	Potassium chloride	Requires treatment, temporary harm	Definite	No
4	M	I	-5.5	Indet	113	Hyperkalaemia	A	Potassium chloride	Requires treatment, temporary harm	Definite	Yes
87	F	I	-1.1	Indet	114	Diarrhoea	A	Gentamicin + amoxicillin + ampicillin	Increased monitoring, no harm	Possible	No
88	M	T	1.0	Indet	115	Diarrhoea	A	Ceftriaxone + ampicillin	Increased monitoring, no harm	Possible	Yes
89	M	T	0.5	Neg	116	Diarrhoea	A	Clarithromycin + ceftriaxone	Increased monitoring, no harm	Possible	No
90	M	T	-2.2	Neg	117	Diarrhoea	A	Ampicillin + amoxicillin	Increased monitoring, no harm	Possible	No
91	M	T	-1.6	Neg	118	Diarrhoea	A	Co-amoxiclav	Increased monitoring, no harm	Probable	Yes
					119	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Probable	Yes
92	F	T	1.6	Indet	120	Diarrhoea	A	Amoxicillin + ampicillin + albendazole	Increased monitoring, no harm	Possible	No
93	M	T	-0.8	Neg	121	Hyponatraemia	A	Furosemide	Requires treatment, temporary harm	Possible	No
94	F	T	-1.2	Neg	122	Diarrhoea	A	Phenoxymethylpenicillin + amoxicillin	Increased monitoring, no harm	Possible	No
95	M	T	-0.1	Neg	123	Diarrhoea	A	Amoxicillin	Increased monitoring, no harm	Possible	No
96	F	EC	-3.4	Neg	124	Diarrhoea	A	Mebendazole + rifampicin + amoxicillin + ceftriaxone	Requires treatment, temporary harm	Possible	No
41	M	EC	0.0	Neg	125	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Probable	Yes
97	F	EC	-1.0	Neg	126	Oral candidiasis	A	Co-amoxiclav + prednisone	Requires treatment, temporary harm	Probable	No

98	M	EC	1.7	Neg	127	Hypokalaemia	A	Hydrochlorothiazide	Requires treatment, temporary harm	Possible	No
99	M	EC	-3.9	Pos	128	Vomiting	A	Co-trimoxazole	Increased monitoring, no harm	Possible	No
100	M	EC	-0.6	Neg	129	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Possible	No
101	M	EC	1.7	Neg	130	Diarrhoea	A	Gentamicin + amikacin + mineral salts in combination + lactulose + ampicillin + co-amoxiclav	Increased monitoring, no harm	Probable	No
102	M	EC	2.7	Neg	131	Vomiting	A	Nitrous oxide + sevoflurane + ketamine	Increased monitoring, no harm	Possible	No
103	F	EC	0.3	Neg	132	Hypokalaemia	A	Fenoterol	Requires treatment, temporary harm	Possible	No
					133	Tachycardia	A	Fenoterol	Increased monitoring, no harm	Possible	No
104	F	EC	-3.0	Neg	134	Hypokalaemia	A	Furosemide + salbutamol + prednisone	Increased monitoring, no harm	Probable	No
105	F	EC	-1.5	Neg	135	Hypokalaemia	A	Prednisolone + prednisone + methylprednisolone	Requires treatment, temporary harm	Probable	No
					136	Hypophosphataemia	A	Sucralfate + prednisolone + methylprednisolone + dexamethasone + prednisone	Requires treatment, temporary harm	Probable	No
					137	Renal impairment	A	Ibuprofen + gentamicin	Increased monitoring, no harm	Possible	No
					138*	Upper gastrointestinal haemorrhage	A	Ibuprofen	Requires treatment, temporary harm	Definite	No
					139*	Upper gastrointestinal haemorrhage	A	Ibuprofen + prednisone + prednisolone + methylprednisolone	Requires treatment, temporary harm	Definite	No
106	F	EC	1.2	Neg	140	Rash erythematous	B	Phenoxymethylpenicillin		Possible	No
								Omeprazole	Increased monitoring, no harm	Possible	No
								Furosemide		Possible	No
107	M	EC	-0.8	Neg	141	Convulsion	A	Ertapenem	Requires treatment, temporary harm	Possible	No
108	M	EC	-0.7	Neg	142	Tachycardia	A	Fenoterol	Increased monitoring, no harm	Possible	No
109	M	EC	22	Neg	143	Hypokalaemia	A	Salbutamol + fenoterol	Requires treatment, temporary harm	Probable	No

110	F	EC	28	Neg	144	Hypokalaemia	A	Salbutamol	Requires treatment, temporary harm	Probable	No
					145	Tachycardia	A	Salbutamol	Increased monitoring, no harm	Probable	No
32	F	EC	23	Neg	146	Diarrhoea	A	Ertapenem + meropenem	Increased monitoring, no harm	Possible	No
111	M	MC	18	Neg	147	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Possible	No
112	F	MC	23	Neg	148	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Probable	No
113	F	MC	17	Neg	149	Hyponatraemia	A	Furosemide	Requires treatment, temporary harm	Probable	No
114	M	MC	24	Neg	150	Tachycardia	A	Salbutamol + fenoterol	Increased monitoring, no harm	Definite	No
115	M	MC	17	Neg	151	Hallucination	A	Methylphenidate	Increased monitoring, no harm	Probable	No
					152	Peritonitis	A	Peritoneal dialytics	Requires treatment, temporary harm	Definite	No
116	F	MC	22	Neg	153	Renal impairment	Mixed	Furosemide	Requires treatment, temporary harm	Possible	No
								Captopril		Possible	No
								Ibuprofen		Possible	No
								Amikacin		Possible	No
35	F	MC	38	Neg	154	Hyperkalaemia	A	Potassium chloride	Increased monitoring, no harm	Definite	No
117	M	MC	23	Pos	155	Hyponatraemia	A	Co-trimoxazole	Increased monitoring, no harm	Possible	No
118	M	EA	Missin g	Neg	156	Constipation	A	Morphine	Requires treatment, temporary harm	Definite	No
119	F	EA	28	Neg	157	Gastroenteritis clostridial	A	Ertapenem + cefotaxime	Requires treatment, temporary harm	Probable	No
					158	Hypertension	A	Prednisone + tacrolimus	Requires treatment, temporary harm	Possible	No
					159	Hypokalaemia	A	Furosemide	Requires treatment, temporary harm	Possible	No
19	F	EA	42	Neg	160	Hypokalaemia	A	Polystyrene sulfonate	Requires treatment, temporary harm	Definite	Yes

F: female; M: male; Age categories: PN: preterm neonate, TN: term neonate, I: infancy, T: toddler, EC: early childhood, MC: middle childhood, EA: early adolescence; MedDRA® PT:

Medical Dictionary for Regulatory Activities preferred term; WFA-z: weight-for-age z-score

* Two distinct episodes of the same ADR occurred during the patient's admission

Appendix lxxi. Drug classes implicated in non-serious adverse drug reactions at two children's hospitals, South Africa, 2015

ATC code	Description	Implicated in <i>n</i> non-serious ADRs
J01	Systemic antibacterials	48
R03	Drugs for obstructive airway diseases	23
C03	Diuretics	17
A12	Mineral supplements	11
H02	Systemic corticosteroids	10
J05	Direct-acting antivirals	6
M01	Anti-inflammatories and antirheumatics	4
B01	Antithrombotics	3
N02	Analgesics	3
A02	Drugs for acid-related disorders	2
J02	Systemic antimycotics	2
N05	Psycholeptics	2
P02	Anthelmintics	2
V03	Other therapeutic products	2
A03	Drugs for functional gastrointestinal disorders	1
A06	Drugs for constipation	1
B05	Blood substitutes and perfusion solutions	1
C02	Antihypertensives	1
C09	Agents acting on renin-angiotensin system	1
J04	Antimycobacterials	1
L04	Immunosuppressants	1
N01	Anaesthetics	1
N03	Antiepileptics	1
N06	Psychoanaleptics	1
R06	Systemic antihistamines	1