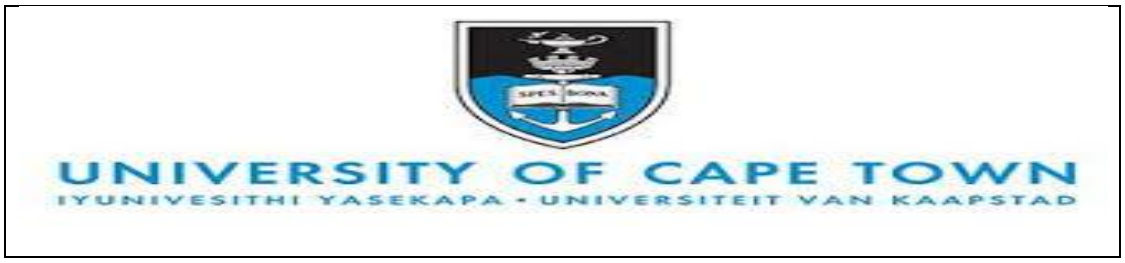

The use of m-Health active participant centred (MAPC) systems to improve surveillance of adverse events following Immunization (AEFIs) in Zimbabwe.

By

Priscilla Patricia Munyaradzi NYAMBAYO (Nee Makoni)

Thesis presented for the Degree of Doctor of Philosophy (PhD)

In the Department of Epidemiology and Biostatics, School of Public Health & Family Medicine,

Faculty of Health Sciences, University of Cape Town.

Date of submission: 28 March 2024

Primary Supervisor: Associate Professor Ushma C. Mehta

Co-Supervisor: Professor Michael Gold

Declaration of Authenticity

I declare that this thesis is my own work and that each source of information used has been acknowledged by means of a complete reference. This thesis has not been submitted before for any other research project, degree or examination at any university.

Plagiarism is the use of another person's work and pretending that it is yours.

I declare that the work reported in this thesis is original, apart from what has been properly referenced and cited. The Vancouver Referencing Style for citation and referencing is used.

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Date:28/03/2024

Priscilla Patricia Munyaradzi Nyambayo

Inclusion of Publications in a PhD Thesis

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy in the Division of Public Health Medicine, School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work included in this thesis is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or, in the case of multi-authored published papers, constitutes work for which the candidate was the lead author. This thesis includes a published manuscript, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy of the University of Cape Town.

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Nyambayo PPM, Gold MS, Mehta UC, Clarke S, Manyevere R, Chirinda L, Zifamba EN, Nyamandi T. Efficacy and feasibility of SMS m-Health for the detection of adverse events following Immunization (AEFIs) in resource-limited setting-The Zimbabwe stimulated telephone assisted rapid safety surveillance (Zm-STARSS) randomised control trial. Vaccine. 2023 Oct 26;41(45):6700-6709. doi: 10.1016/j.vaccine.2023.09.037

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to included chapter 3 titled 'Descriptive study of AEFI surveillance system in Zimbabwe" as a publication ready chapter and chapters 1,2, 5-6 as monograph chapters.

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Student name: Priscilla Patricia Munyaradzi Nyambayo Student Number: MKNPRI010

Thesis Abstract

Thesis Title: **The use of m-Health active participant centred (MAPC) systems to improve surveillance of adverse events following Immunization (AEFIs) in Zimbabwe.**

Introduction

A robust national AEFI surveillance system ensures timely AEFI detection, good quality AEFI reports, prompt case investigation and robust causality assessment for corrective AEFI case management, signal detection and appropriate feedback ultimately to improve public safety and trust in vaccines and the Immunization programme. Each AEFI surveillance method has advantages and disadvantages. This **thesis aimed** to develop an evidence-based and empirical foundation to guide recommendations for the use of mHealth for **a**ctive **v**accine **s**afety **s**urveillance (AVSS) in Zimbabwe to strengthen its passive (spontaneous) AEFI surveillance system.

The primary hypothesis of the **thesis** is that an mHealth application system that supports AEFI detection and reporting is a feasible approach to supporting active AEFI surveillance in Zimbabwe.

Method

I used mixed methods comprising a scoping and narrative literature review, a descriptive evaluation of Zimbabwe's AEFI system, a **r**andomised **c**ontrol **t**rial (RCT) to assess the impact of the **Zimbabwe s**timulated **t**elephone **a**ssisted **r**apid **s**afety **s**urveillance (Zm-STARSS) approach, and a consumer and healthcare professional (HCP) survey to assess their experience and the acceptability of Zm-STARSS.

Results

The scoping and narrative review revealed that most MAPC AEFI surveillance studies (92%, 24/26) were conducted in High Income Countries(HICs) and only two in Low Middle-Income Countries (LMICs). The mean response rate to (Short Message Services)SMS prompts was 71% among 23 studies. Out of 1440 assessed Zimbabwean AEFI reports 54.2% were non-serious, 29.7% non-serious but deemed medically important, 6.6% causing prolonged hospitalizations and 8.1% fatal. In the Zm-STARSS RCT, despite a relatively low (31%, n = 704) response rate, we demonstrated that the SMS group had a 2% AEFI detection rate compared to 0% in the passive control arm. Of the 31 HCPs and 96 consumers who responded, 96% and 71%, respectively, supported the use of Zm-STARSS for improving AEFI reporting. Respondents identified lack of feedback after reporting, fear of negative consequences, and mobile phone costs as major barriers to SMS reporting.

Conclusion and recommendations

The paucity of MAPC surveillance in LMICs highlights the need for more active surveillance of AEFIs in these regions. Zm-STARSS AEFI surveillance improved AEFI detection and reporting in an LMIC setting. Although the response rate was lower than what was seen in HICs, potential barriers to responding can be mitigated with simple reprogramming. Therefore, we recommend its use in LMIC settings. To support this improved reporting and ensure appropriate responses to these reports, it is imperative to strengthen the remaining elements of AEFI surveillance, including case investigation, causality assessment, case management and feedback. In addition, prioritising training and awareness initiatives aimed at mitigating factors contributing to underreporting, including addressing HCPs and consumers' fear of victimisation, is essential. The cost of MAPC for both consumers and HCPs should be minimised to improve AEFI reporting in Zimbabwe and similar LMICs. This may require engagement with mobile phone operators to lower rates (toll-free) for mHealth surveillance systems. Further studies should investigate the feasibility and effectiveness of the mHealth approach in other LMIC settings, particularly

consumer response rates, impact on AEFI reporting rates and the regulatory and Immunization programmes' responses to these reports.

Key words: Adverse **e**vents **f**ollowing **Immunization**s (AEFI), **a**dverse **e**vents of **s**pecial **i**nterest (AESI), mobile-health (mHealth), **mHealth** for **a**ctive **p**articipant **c**entred (MAPC) AEFI surveillance Short Message Services (SMS), **Zimbabwe** **s**timulated **t**elephone **a**ssisted **r**apid **s**afety **s**urveillance (Zm-STARSS) study, vaccine vigilance.

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I wish to acknowledge above all, my Savior the Lord Jesus Christ, God and the Holy Spirit for life, health, provision, amazing grace, and guidance that enabled me to write this thesis. Dominus Pastor. Special thanks to my former boss Mr Mafios Dauramanzi former Medicines Control Authority of Zimbabwe (MCAZ) Director General who inspired me to do a work-related PhD as part of capacity building of the national pharmacovigilance programme in a resource limited setting.

I'm grateful and indebted to my supervisors Associate Professor Ushma C. Mehta, CIDER (Centre for Infectious Disease Epidemiology and Research), Professor Maia Lesosky, Chairperson Department of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Professor Susan Cleary and Ms Gill Morgan for their mentorship, patience, assistance, and guidance.

Special thanks to Professor Michael S. Gold, Associate Professor, University of Adelaide Department Pediatrics, Women's and Children's Hospital, Adelaide 5005, Australia. He motivated and supported me during very challenging moments. Mr Stephen Clarke, Software Architect, Flexis Systems (formerly known as Chord Wizard Systems), Australia for technical support and providing Zm-STARSS software for the study. Special thanks to ECONET Wireless Ltd Zimbabwe for providing Zm-STARSS mobile app test code and assisting in testing ZM-STARSS, with the MCAZ ICT Manager Mr Tichaona Nyovhi. They made it possible for Zm-STARSS mHealth app to operate successfully throughout the project in detecting AEFIs for most vaccines including COVID-19 vaccines, in Zimbabwe.

Thanks a million, to the study sponsors World Health Organization (WHO), Zimbabwe Country Office, WHO Global Vaccine Safety Initiative (GSVI), University of Adelaide Australia, and my employer the Medicines Control Authority of Zimbabwe (MCAZ). Special thanks to all the Zm-STARSS study team I worked with at MCAZ:ICT, Finance, Administration Pharmacovigilance and Clinical Trials (PVCT) Division, National AEFI Committee, ICT, vaccination study sites at Citimed hospital Chitungwiza, and Chitungwiza Central hospital, study participants, and the Zimbabwe Expanded Programme on Immunization (ZEPI) Ministry of Health and Child Care (MoHCC). Thanks a million, to my family for their unwavering support especially my children, Emmanuel, John, Hephzibah and husband Andrew who believed in me and encouraged me always, my mother-in-law Violet, my brother David, sister Edith, and my late mum Christine and dad Mark who always encouraged me to do the very best.

I also thank those who helped in editing and proofreading the manuscripts.

May the Lord richly bless all of you.

List of Figures:

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List of Abbreviations and Acronyms

ADR	Adverse Drug Reaction
AEFI	Adverse Events Following Immunization
AESI	Adverse events of special interest
API	Application Programming Interface
ART	Anti-Retroviral Therapy
Au-STARSS	Australian Stimulated Telephone Assisted Rapid Safety Surveillance
AVSS	Active vaccine safety surveillance
CATI	Computer assisted telephone interview
CONSORT	Consolidated Standards Reporting Trials
COVID-19	Coronavirus 2 (SARs-CoV-2) disease
DHIS	District Health Information System
eHealth	Electronic health
EWZL	Econet Wireless Zimbabwe Ltd
EPI	Expanded Programme on Immunization
GACVS	Global Advisory Committee on Vaccine Safety
GAIA	Global Alignment on Immunization safety Assessment in pregnancy consortium
GCP	Good Clinical Practice
GMP	Good Manufacturing Processes
GVP	Good Vigilance Practice
GVSI	Global Vaccine Safety Initiative
HCP(s)	Healthcare professional(s)
HoD	Head of Division

HIC	High Income Country
HICs	High Income Countries
ICF(s)	Informed Consent Form(s)
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
ICT	Information and Communications Technology
IT	Information Technology
IMNCI	Integrated Management of Child Health Illnesses program
LMIC	Low-and-Middle Income Country
LMICs	Low-and- Middle Income Countries
MASCA	Medicines and Allied Substances Control Act (Chapter 15:03)
MCAZ	Medicines Control Authority of Zimbabwe
MeDRA	Medical Dictionary for Regulatory Activities
MEFI	Medical event following Immunization.
MAPC	mHealth for active participant centered (MAPC) AEFI surveillance.
MMR	Measles, mumps and rubella vaccine
mHealth	mobile health
MoHCC	Ministry of Health and Child Care
MR	Measles Rubella
MRCZ	Medical Research Council of Zimbabwe
MMR	Measles Mumps Rubella
NHMRC	National Health Medical Research Committee
NIDs	National Immunization Days
NPC	National Pharmacovigilance Center
NPP	National Pharmacovigilance Policy
NRA	National Regulatory Authority
OPV	Oral Polio Vaccine

PCV	Pneumococcal Conjugate Vaccine
PI	Principal Investigator
PIM	Pharmacist Initiated Medicines
POTRAZ	Postal and Telecommunications Regulatory Authority of Zimbabwe
PT(s)	Preferred term(s)
PV	Pharmacovigilance
PVCT	Pharmacovigilance and Clinical Trials
PNO	Provincial Nursing Officer
RCT	Randomised Controlled Trial
RHCP(s)	Research Health Care Professionals(s)
SMS	Short Message Service(s)
STARSS	Stimulated Telephone Assisted Rapid Safety Surveillance
SOC(s)	System organ classification (s)
tOPV	Trivalent Oral Polio Vaccine
UCT	University of Cape Town
UMC	Uppsala Monitoring Centre
UNDP	United Nations Development Program
UNICEF	United Nations Children's Emergency Fund
UZ	University Of Zimbabwe
VACFA	Vaccines for Africa
VPDs	Vaccines Preventable Disease(s)
VISP	Vaccine Induced Seropositivity
WCBA	Women of Child-Bearing Age
WBR	Web-Based Reporting

WHO-IST	World Health Organization-Inter-Support Team
WHO JRF	World Health Organization (WHO) Joint Reporting form (JRF)
ZEPI	Zimbabwe Expanded Programme on Immunization
Zm-STARSS	Zimbabwe-Stimulated Telephone Assisted Rapid Safety Surveillance

Glossary of Definitions

Adverse event following Immunization (AEFI) is defined as "any untoward medical occurrence, symptom or disease which follows Immunization that does not necessarily have a causal relationship with the usage of the vaccine" -The WHO and The Council for International Organizations of Medical Sciences (CIOMS) definition.

Adverse events of special interest (AESI) is defined as a "clinically important untoward medical occurrence that is either known to occur following administration of the type of vaccine under study (for example, hypotonic-hyporesponsive episodes or febrile convulsions) or is considered to be a possible risk on the basis of knowledge of the content of the vaccine and/or its interaction with the host immune system (for example, autoimmune disease or antibody-dependent enhanced clinical disease)" -WHO definition.

Active vaccine safety surveillance (AVSS) is defined as "a data collection system that seeks to ascertain as completely as possible the number of AEFIs and underlying causes in each population via a continuous organized process" -CIOMS definition.

"Stimulated ***T***elephone ***A***ssisted ***R***apid ***S***afety ***S***urveillance **(STARSS)** or **Australia *S***timulated ***T***elephone ***A***ssisted ***R***apid ***S***afety ***S***urveillance **(Au-STARSS)** randomised controlled trial' studies of SMS mHealth and active AEFI surveillance were successfully conducted in Australia. The Au-STARSS is one of two published randomised controlled trials (RCT) which has compared the AEFI detection rate in an active (SMS surveillance) and control (passive surveillance) groups. The study evaluated the feasibility and acceptability of SMS based surveillance using a two-step process with an initial SMS being the entry point for detection whilst a subsequent digital interaction elicited information to determine the nature of the

event . The outcome of the Au-STARSS study showed a 13-fold greater AEFI detection rate in the SMS group (Pearson' $\chi 2$ test = 76.0, $p < 0.0001$) compared to the control group (passive surveillance)".

Efficacy, effectiveness and efficiency. The Oxford and Cambridge dictionaries state that efficacy, effectiveness and efficiency are synonymous terms, with some scientific fields imposing artificial interpretations of these terms. Some authors have tried to provide clarity on the distinctions between efficacy, effectiveness, and efficiency within the healthcare context. They defined '**efficacy'**, as "the ability of a given intervention under excellent or controlled conditions in healthcare systems, '**effectiveness'** as the ability of an intervention to have a meaningful effect on patients in normal clinical conditions, and '**efficiency'** as doing things in the most economical way"

mHealth active participant centred (MAPC) AEFI surveillance system is part of participatory approach to AEFI surveillance that is increasingly being recognised as a complement to the widely used passive surveillance, particularly in LMICs and HICs. The participatory approach to AEFI surveillance entails the patients reporting health events to the authorities. Using this approach, AVSS or post-marketing AEFI surveillance or has been implemented using mobile devices mHealth active participant centred (MAPC) is part of 'mobile health' (mHealth). An mHealth application using SMS-based follow up of vaccinees as a form of MAPC AEFI surveillance could improve case detection and AEFI reporting such as Au-STARSS, STARSS or Zm-STARSS.

Mobile health (mHealth) is defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices".

Vaccine hesitancy was defined in 2015 by The SAGE Working Group defined vaccine as “a delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence”. The definition was recently updated in 2022 by other authors as “a state of indecision and uncertainty about vaccination before a decision is made to act (or not act)”

Vaccine pharmacovigilance is “the science and activities relating to the detection, assessment, understanding and communication of AEFIs and other vaccine- or Immunization-related issues, and to the prevention of untoward effects of the vaccine or Immunizations”

Contents

Chapter 1 Thesis Introduction

Thesis title: **The use of m-Health active participant centred (MAPC) systems to improve surveillance of adverse events following Immunization (AEFIs) in Zimbabwe.**

Overall thesis layout/presentation: *Overall thesis layout/presentation is based on the University of Cape Town, Health Sciences thesis requirements including Vancouver referencing style for references, table of contents, list of acronyms and abbreviations, including definitions stated in the main text. The thesis has 6 chapters, structure and rationale are briefly explained under chapter 1 and illustrated in* ***Figure 1*** *below with more detailed information under each chapter 2-6.*

Chapter 1 provides the thesis study title, overall introduction, conceptual framework, and structure leading to the formulation of the justification, problem statement, research question, hypothesis, purpose, aim, objectives, methodology, limitations, ethical approvals, and quality assurance*.*

1.1 Abstract:

Introduction: Globally, Immunization is a critical public health intervention credited with saving millions of lives by reducing the burden of vaccine preventable diseases (VPDs) including COVID-19 disease. Although people get protection through safe and effective vaccines, in rare instances, adverse events following Immunization (AEFI) may occur, reducing public trust in vaccination. This negatively affects vaccination uptake which could lead to an increased incidence in VPDs. A robust AEFI surveillance system is therefore considered a key component of the Zimbabwe National Immunization Programme (NIP). This surveillance system aims to respond timeously to AEFIs, support AEFI case management, assess causality of reported cases and perform signal detection. Innovative strategies to strengthen national

AEFI surveillance systems including for pandemic vaccines are therefore a public health priority.

Research Question and Aim: Recent developments in high income countries (HICs) have shown that vaccinee participatory AEFI surveillance using mHealth technology known as '**mHealth a**ctive **p**articipant **c**entred (MAPC) AEFI surveillance system' could be applied in Zimbabwe, given its high mobile phone penetration rate (93.4%). The overarching research question was: Can 'MAPC AEFI surveillance be feasibly applied in Zimbabwe to support better detection and response to AEFIs?' Broadly, the aim or purpose of the study was to establish the challenges of the Zimbabwe AEFIs surveillance system including for COVID-19 vaccines in a low middle income country (LMIC) setting and to test the feasibility of using the MAPC AEFI surveillance system in Zimbabwe.

Methods: Firstly, a scoping literature review study of MAPC AEFI surveillance systems was conducted to investigative baseline evidence on challenges related to SMS response rates, AEFI reporting rates, types of technology, implementation, cost, as well as the experiences of consumers and healthcare professionals (HCPs). The literature was assessed from a LMIC perspective. **Secondly**, we conducted a descriptive study of the Zimbabwe AEFIs surveillance system by assessing the AEFI cases reported using VigiBase, VigiLyze and causality assessment outcomes; we also evaluated how the Zimbabwean AEFI surveillance system performs using the World Health Organisation (WHO) Global Bench Marking Tool (GBMT) criteria. **Thirdly**, we conducted a randomised clinical trial (RCT) comparing reporting rates between a type of MAPC AEFI surveillance system known as "**Zimbabwe *S***timulated ***T***elephone ***A***ssisted ***R***apid ***S***afety ***S***urveillance (Zm-STARSS)" and routine AEFI surveillance in Chitungwiza a peri-urban district of Zimbabwe. **Fourthly**, nested within the RCT, we conducted a sub-study to explore the experiences of healthcare professionals (HCPs) and vaccinees, or parents or guardians of infant vaccinees, with mHealth for AEFI surveillance by administering surveys to these groups. **Finally,** we developed recommendations on the feasibility of using Zm-STARSS in Zimbabwe,

reflecting also on the potential applicability of this active AEFI surveillance tool in other similar settings and scenarios.

Dissemination of the results: Chapter 4 (Zm-STARSS) was published in Vaccines Journal. Chapters 2, 3 and 5 will also be published in peer reviewed journals. Study findings will also be disseminated through the Medicines Control Authority of Zimbabwe (MCAZ) Medicines Safety Bulletin and website. Additionally, the findings will be shared with diverse stakeholders such as the Zimbabwe National Immunization Advisory Group (NITAG), Ministry of Health and Childcare (MoHCC) NIP, healthcare staff at provincial district levels including vaccination clinics and study sites. Other fora where the results will be disseminated are the WHO African Vaccine Regulatory Forum (AVAREF) and the International Pharmacovigilance Regulatory AfriSummit. Finally, the thesis will be published on the University of Cape Town (UCT) portal.

Ethical Approvals: Ethical approval was obtained from the University of Cape Town (UCT) Health Research Ethics Committee (HREC) (HREC Ref 184/2020). Ethical permission was also obtained from the Medical Research Council of Zimbabwe (MRCZ)" (reference MRCZ/A/2286) and the Director of Health Services, Chitungwiza City Health Department, Zimbabwe.

Key words: "Adverse Events Following Immunizations (AEFI)", "adverse events of special interest (AESI), mobile-health (mHealth), "**mHealth** for **A**ctive **P**articipant **C**entred (MAPC) AEFI surveillance, Short Message Services (SMS), "**Zimbabwe** **S**timulated **T**elephone **A**ssisted **R**apid **S**afety **S**urveillance (Zm-STARSS)" study.

Publications arising from the thesis: The UCT Doctoral Degrees Board (DDB) approved that Chapter 4 be submitted as a published paper of Zm-STARSS with the following reference:

1) Nyambayo PPM, Gold MS, Mehta UC, Clarke S, Manyevere R, Chirinda L, Zifamba EN, Nyamandi T. Efficacy and feasibility of SMS m-Health for the detection of adverse events following Immunization (AEFIs) in resource-limited setting-The Zimbabwe stimulated telephone assisted rapid safety surveillance (Zm-STARSS) randomised control trial. Vaccine 41 (2023)6700-6709; S0264-410X(23)01107-6. Doi: 10.1016/j.vaccine.2023.09.037. ***(Chapter 4 research publication)*.**

Chapter 3 titled 'Descriptive study of AEFI surveillance system in Zimbabwe' was submitted as a "publication ready format" and Chapters 1, 2, 5 and 6 were submitted as thesis monograph chapters as approved by the UCT Doctoral Degrees Board (DDB).

1.2 Introduction and background

Vaccination, AEFI surveillance in the Zimbabwe context, the need for active AEFI surveillance

According to the Zimbabwe National Statistic Agency (ZIMSTAT) and the World Bank 2022 ratings, Zimbabwe is a low middle income country (LMIC) with a population of 16.3 million; the per capita Gross Domestic Product (GDP) stands at USD1267, the international poverty rate measured at USD2.15 is 39.8% and the country has low economic growth(1). The World Health Organization (WHO) 2023 report states that Zimbabwe has 0.14 physicians and 1.85 midwives/nurses per 1000 population. This is well below the Sustainable Development Goals (SDGs) index threshold of combined 4.45 midwives, nurses, and doctors per 1000 population(1). The Zimbabwe Inter-Census Demographic Survey 2017 and United Nations International Children's Emergency Fund (UNICEF) 2018 report disclosed that "infant and under-five mortality rates were 52 deaths per 1,000 live births and 72 deaths per 1,000 live births, respectively"(2). Every year about 600 000 Zimbabwean children under five years are vaccinated.

Globally, Immunization is a critical public health intervention that reduces vaccine preventable diseases (VPDs) including COVID-19 disease thereby saving millions of lives. Although vaccines usually have high safety and efficacy, sometimes in rare instances severe, or serious AEFIs occur, and these reduce public perception of safety and trust in vaccination(3-5). The WHO and 'The Council for International Organizations of Medical Sciences (CIOMS)' define an 'Adverse Event Following Immunization (AEFI)' as "any untoward medical occurrence, symptom or disease which follows Immunization that does not necessarily have a causal relationship with the usage of the vaccine"(6). There has been a notable increase in vaccine hesitancy, particularly after the introduction of COVID-19 vaccines. Vaccine hesitancy was initially defined as 'the reluctance or refusal to vaccinate despite the availability of vaccines' (7). In 2015 The SAGE Working Group defined vaccine hesitancy as 'a delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence'(8).The definition

was recently updated in 2022 by other authors as ‘a state of indecision and uncertainty about vaccination before a decision is made to act (or not act)’(9).

Vaccine hesitancy hampers progress made in effectively tackling VPDs in many countries including Zimbabwe, putting millions of people at risk of illness and even death. Just before the COVID-19 pandemic started, the WHO established that vaccine hesitancy is one of the top 10 global health threats and emphasised the need for innovative strategies to combat it (10). Several studies over the years have cited the limitations of most vaccine development clinical trials phases (I-III) due to relatively small sample sizes; these trials may fail to detect rare AEFIs that occur infrequently at rates of at least 1 in 10 000 or more vaccinees, including adverse events of special interest (AESI)(11). The WHO defined an AESI as a “clinically important untoward medical occurrence that is either known to occur following administration of the type of vaccine under study (for example, hypotonic-hyporesponsive episodes or febrile convulsions) or is considered to be a possible risk on the basis of knowledge of the content of the vaccine and/or its interaction with the host immune system (for example, autoimmune disease or antibody-dependent enhanced clinical disease)”(12). In clinical trials, AEFI documentation may often be shortened to adverse event (AE). In addition to developing effective robust national AEFI surveillance systems, each country is also required to have a system of measuring background rates of AEFIs so as to be able to make meaningful benefit risk assessments of vaccine related AEFIs(13).

Vaccines are complex biological products with limited pre-licensure studies that may not detect rare adverse reactions due to the small, controlled populations included in these clinical trials (14). The formulation of vaccines includes ingredients designed to elicit desired immune responses. These may use adjuvants or protein conjugation to polysaccharide (conjugate vaccines)(14). Some vaccines may also contain antibiotics, stabilisers or preservatives to reduce contamination during the manufacturing process or to maintain their sterility and effectiveness throughout the cold chain distribution process(14). What is therefore required for vaccine safety surveillance is AEFI notification/reporting, data collection and storage, case investigation, causality assessment, cause-specific response and

communication. Classification of an AEFI is only possible after causality assessment, which is evident from the WHO definition of AEFI and why all events following Immunization must be reported. Causality assessment is conducted to determine whether the event was caused by the vaccine or not. The WHO AEFI causality assessment algorithm 2019, classified AEFIs into 5 different groups/categories, namely " (a) vaccine product related; (b) vaccine quality defects; (c) Immunization error; (d) Immunization stress-related response; and (e) coincidental event"(15). Irrespective of the causality assessment category a NIP should have a robust surveillance system that identifies and responds timeously to all these types of AEFI scenarios. Failure to detect and manage serious AEFIs may result in serious illness or sudden death after vaccination, thereby triggering bad publicity. Consequently, prospective vaccinees may stop participating in vaccination programmes, potentially leading to outbreaks of VPDs in the country. Hence, the thesis was conducted with the aim of improving AEFI surveillance to minimise/eliminate VPD occurrence.

There are additional shortcomings to AEFI surveillance such as lack of timely feedback and inadequate data quality to support causality assessment. Throughout the research study, it is vital to note that mHealth only addresses one component of the AEFI surveillance system that is, case detection. Effective and timely case investigation, assessment, and feedback to reporters and vaccinees remain important components that require attention. The Zm-STARSS alone cannot address all the aspects of AEFI surveillance hence it is a limitation of the study. This thesis focused on improving the AEFI case detection component, a critical arm of managing AEFIs(16). Considering that vaccines are mainly given to people in good health to protect against possible occurrence of VPDs in the future, the NIP should ensure vaccines are safe and Immunization programmes are trusted(7, 17). Given the inherent shortcomings of passive (spontaneous/voluntary) AEFI surveillance systems currently used in Zimbabwe, such as under reporting, there is great need to develop and operate a reliable, cost-effective and capable active AEFI surveillance system that would increase AEFI detection, reduce VPDs and enhance public trust (6, 18).

In accordance with WHO recommendations, Zimbabwe's national AEFI surveillance system is co-ordinated by the national pharmacovigilance centre, which is run by the "Medicines Control Authority of Zimbabwe (MCAZ)" together with the "Zimbabwe Expanded Programme on Immunization (ZEPI) and Ministry of Health and Child Care (MoHCC)"(15). The AEFI surveillance process is outlined in the Guidelines 2017 and COVID-19 Vaccines AEFI surveillance Guide 2021 (19, 20). The process includes passive AEFI detection, case reporting, causality evaluation, benefit and risk assessment, management including mitigation strategies, feedback, and public health communication. Zimbabwe has a relatively low and variable AEFI reporting ratio ranging from 0 to 20 AEFIs "per 100 000 surviving infants" per year from 2000 to 2018(21). Zimbabwe does not always meet the annual minimum recommended goal of 10 AEFIs 'per 100 000 surviving infants' as stipulated by the WHO Joint Reporting Form (21). However, in 2021 the WHO Global Advisory Committee on Vaccine Safety (GACVS) recommended a new case-based vaccine safety indicator for monitoring progress in AEFI surveillance in all age groups i.e. 'one or more serious AEFI per 1 million total population per year'(22). In addition, they recommended the use of electronic reporting tools to overcome challenges of paper-based tools and facilitate the flow of information from district to provincial and national levels(22).

Based on AEFI reporting rates in other countries, underreporting is likely to be considerable since most African countries do not meet the WHO annual target of 10 AEFIs per 100 000 infants that survive (21, 23). Under-performing AEFI surveillance system has the potential to negatively affect the performance of ZEPI. The Zimbabwe national pharmacovigilance centre publications noted that the commonly reported passive surveillance AEFIs from 2005 to 2018 included pain/redness/swelling/injection site abscess, fever, convulsions, diarrhoea, nausea/vomiting, rash, excessive crying, breast milk aspiration, drowsiness/ irritability or encephalitis, anaphylaxis and/or sudden infant death (18, 24). This list of commonly reported AEFIs demonstrates the value of strengthening the Zimbabwe national AEFI surveillance system. Local injection site reaction reports could indicate preventable programmatic errors such as poor injection technique or problems with cold chain management. Serious AEFIs such as infant persistent crying caused by whole cell pertussis-based vaccines, that might cause

breast milk aspiration leading to death, require early detection, risk minimisation and communication(25).

Early and complete AEFI detection is a vital step towards investigating and appropriately responding to serious AEFIs. These could potentially derail the Immunization programme and reduce confidence in vaccination. Broadly, the AEFI surveillance aims to identify AEFIs, manage AEFI case investigation, implement corrective action(s) to facilitate patient recovery, prevent or minimise the occurrence of similar AEFIs in the future, and communicate effectively throughout the process. Therefore, timely and high-quality case detection is a key component of an AEFI surveillance system. This thesis was conducted to assess the Zimbabwean AEFI case detection system and test the effectiveness and feasibility of introducing an innovative MAPC AEFI surveillance approach as a means of encouraging early detection and management of AEFIs in Zimbabwe.

1.3 COVID-19 vaccines deployment in Zimbabwe and the need for active AEFI surveillance

Zimbabwe started procuring COVID-19 vaccines in February 2021 with the aim of reaching a target of 10 million vaccinated people (60% of country population) to ensure adequate coverage to reduce the transmission and hospitalisation associated with the deadly COVID-19 disease. According to the WHO website on 18 August 2023, Zimbabwe had 265 716 confirmed cases of COVID-19 disease with 5713 deaths reported to WHO; a total of 13 935 112 COVID-19 vaccines were administered in Zimbabwe from February 2021 to 7 July 2023. The COVID-19 vaccine rollout further motivated the need for a better AEFI surveillance system for early case detection and management. Since February 2021, in consideration of the COVID-19 pandemic, the Zimbabwe national AEFI surveillance system has been adapted to included monitoring of COVID-19 vaccines. This adaptation includes training of healthcare professionals countrywide on the deployment of COVID-19 vaccines and reporting procedures through the AEFI surveillance passive system. Given the rapid introduction of novel vaccines and relatively low AEFI reporting rates, there was a need to improve the

reporting infrastructure to detect any new safety signals while ensuring public confidence in the new vaccines. Several authors (19. 22, 23) have advocated for the implementation of active AEFI surveillance systems for the timely monitoring COVID-19 vaccines, highlighting the importance of this thesis study.

1.4 Mobile Health and active AEFI surveillance approaches.

The main aim of the research was to determine the feasibility, applicability and efficacy of MAPC AEFI surveillance system. mHealth active participant centred (MAPC) is part of 'mobile health' (mHealth). 'Mobile health is defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices"(26). Vaccine pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and communication of AEFIs and other vaccine- or Immunization-related issues, and to the prevention of untoward effects of the vaccine or Immunizations"(6). To safeguard patient health, there is need for "active vaccine safety surveillance". "The Council for International Organizations of Medical Sciences defines active vaccine safety surveillance (AVSS)" as "a data collection system that seeks to ascertain as completely as possible the number of AEFIs and underlying causes in each population via a continuous organized process" (6, 27). In AVSS, Immunization data are gathered with clearly defined goals to investigate one or more AEFIs including predetermined AESIs (6, 27). Mobile health utilises mobile phones and information communication technology in healthcare and treatment interventions (28). Globally, mHealth is a growing area of research because of its widespread adoption including the widespread use of "smart" mobile phones and the declining cost of mobile technology (28, 29).

One possible application of mHealth is AVSS. There are studies showing the feasibility of mHealth for AVSS to strengthen safety surveillance (30). Mobile phone-based applications and SMS have been successfully tested for enhancing a variety of aspects of Immunization programmes including Immunization reminders, measuring vaccine coverage and improving logistics and communication(31). These applications of mHealth have been tested

successfully in a variety of countries including China, Guatemala, Kenya, Pakistan and Zimbabwe (30, 31). At the time of initiating this study, there were few published studies from LMIC on MAPC AEFI surveillance(32, 33). Most published studies were from HICs, mainly Australia and Canada where SMS mHealth has been used for active adverse event surveillance following seasonal influenza vaccines(34-36).

Timely data collection and reporting is usually a challenge when AEFI surveillance is paper based. There are issues with completeness of the report, delayed submission, missing reports and under reporting. Rapid technological developments have created several opportunities to innovatively conduct AEFI surveillance. Among the technological developments that can be tapped for AEFI surveillance are the digital tools which can eliminate the paper-based method of data collection and reporting. In HICs, vaccine dose tracking as well as vaccine confidence monitoring have reliably been done with digital tools (28).

The participatory approach to AEFI surveillance is increasingly being recognised as a complement to the widely used passive surveillance, particularly in LMICs (37, 38) . The participatory approach to AEFI surveillance entails the patients reporting health events to the authorities. Using this approach, post-marketing AEFI surveillance has been implemented using mobile devices (39, 40).

'***S***timulated ***T***elephone ***A***ssisted ***R***apid ***S***afety ***S***urveillance (Au-STARSS) randomised controlled trial' studies of SMS mHealth and active AEFI surveillance were successfully conducted in Australia, a HIC (41, 42) hence this thesis aimed to investigate if a similar methodology could be used to improve AEFI detection in Zimbabwe, a LMIC.

The Global System for Mobile communication Association (GSMA) projected that "By the end of 2020, 495 million people would have subscribed to mobile services in Sub-Saharan Africa, representing 46% of the region's population and this is projected to rise to 615 million by 2025, or (50% of the region's population)"(43). According to the Abridged Postal &

Telecommunications Regulatory Authority of Zimbabwe (POTRAZ) Sector Performance Report Third Quarter 2022, the total number of mobile phone subscribers in Zimbabwe was 14.3million and the number of data including internet subscription was 9.64 million. This translates to mobile phone penetration and internet of 93.4% and 63% respectively.

The researcher took note that the application of mHealth for active AEFI surveillance in Zimbabwe may face challenges such as failure to detect AEFIs, low SMS response rates from vaccinees, and other barriers (26). Understanding the challenges of applying mHealth for active AEFI surveillance in Zimbabwe is critical prior to expansion of such a surveillance system in a resource-limited country like Zimbabwe.

1.5 Thesis Justification:

The study was critical for the following reasons:

a) Vaccine safety surveillance in a LMIC like Zimbabwe required strengthening for early detection of AEFIs. A preliminary background study of the Zimbabwe AEFIs surveillance system was conducted as part of the thesis to identify the gaps that the descriptive study aimed to address.

b) In HIC, MAPC AEFI surveillance has been shown to enhance AEFI detection hence the need to test for effectiveness in a LMIC like Zimbabwe. A scoping literature review study of MAPC AEFI surveillance was conducted as part of the thesis to generate exploratory evidence on acceptability, AEFI reporting rates, SMS response rates, cost, experience of consumers and healthcare workers, and challenges of SMS MAPC AEFI surveillance. The literature was assessed from a LMIC perspective.

c) An mHealth SMS based surveillance system to follow up vaccinees as a form of active AEFI surveillance was investigated for feasibility and efficacy.

d) There was very little information on efficacy and/or experience of mHealth for AEFI detection in Zimbabwe, so this study addressed important gaps in knowledge within the scientific community.

e) This study shed more light on the acceptability of MAPC AEFI surveillance by both consumers (participants) and healthcare professionals (HCPs).

Thesis Problem Statement:

Zimbabwe's National Immunization Programme (NIP) needs a robust AEFI surveillance system to ensure patient safety, promote vaccine acceptance and enhance public trust in the national Immunization programmes. Zimbabwe's passive AEFI surveillance system is ineffective in detecting AEFIs thereby posing serious challenges to the safety of vaccinees and undermining public confidence in the Immunization programme. **An mHealth application using SMS-based follow up of vaccinees as a form of MAPC AEFI surveillance could improve case detection and AEFI reporting.**

The **Thesis Research Aim** was to develop an evidence-based and empirical foundation to guide recommendations for the use of MAPC in Zimbabwe to improve vaccine surveillance and enhance the safety of consumers. The thesis aimed to investigate the performance of MAPC AEFI surveillance in various countries; assess the capabilities of Zimbabwe AEFI surveillance systems in detecting AEFIs and test the feasibility and iMAPCt of the STARSS m-health system as a tool to augment AEFI case detection in Zimbabwe.

The **Thesis Primary hypothesis** was that an mHealth application system that supports AEFI detection and reporting is a feasible approach to supporting active AEFI surveillance in Zimbabwe. The Zimbabwean AEFI surveillance system can benefit from the implementation of mHealth to support active patient-centred case detection and reporting.

Research question: Can the use of MAPC improve AEFI surveillance in Zimbabwe?

Null hypothesis: An SMS-based mHealth application has no effect on the active AEFI surveillance approach in Zimbabwe i.e., there is no difference between the intervention MAPC system (CATI arm) and the Control group.

Figure 1 below shows the research journey and justification of the study. The Thesis structure is illustrated in ***Figure 1*** in line with the research question and specific thesis study chapter objectives below:

The feasibility and value of the SMS-active follow-up approach was determined by i) exploring existing knowledge and research around the use of SMS-based AVSS for AEFI detection; ii) examining the existing passive surveillance AEFI system in Zimbabwe; iii) measuring the difference in reporting rates between the Zm-STARSS active and passive reporting systems; iv) assessing the user experience and acceptance of the Zm-STARSS mHealth SMS system, and v) making recommendations based on the thesis overall findings.

Most medical researchers and practitioners the world over prioritise the importance of efficient, and cost-effective use of resources, particularly when considering vaccine efficacy, effectiveness or efficiency relative to cost. The Oxford and Cambridge dictionaries state that efficacy, effectiveness and efficiency are synonymous terms, with some scientific fields imposing artificial interpretations of these terms. Some authors have tried to provide clarity on the distinctions between efficacy, effectiveness, and efficiency within the healthcare context. They defined '**efficacy'**, as "the ability of a given intervention under excellent or controlled conditions in healthcare systems, '**effectiveness'** as the ability of an intervention to have a meaningful effect on patients in normal clinical conditions, and '**efficiency'** as doing things in the most economical way"(44).

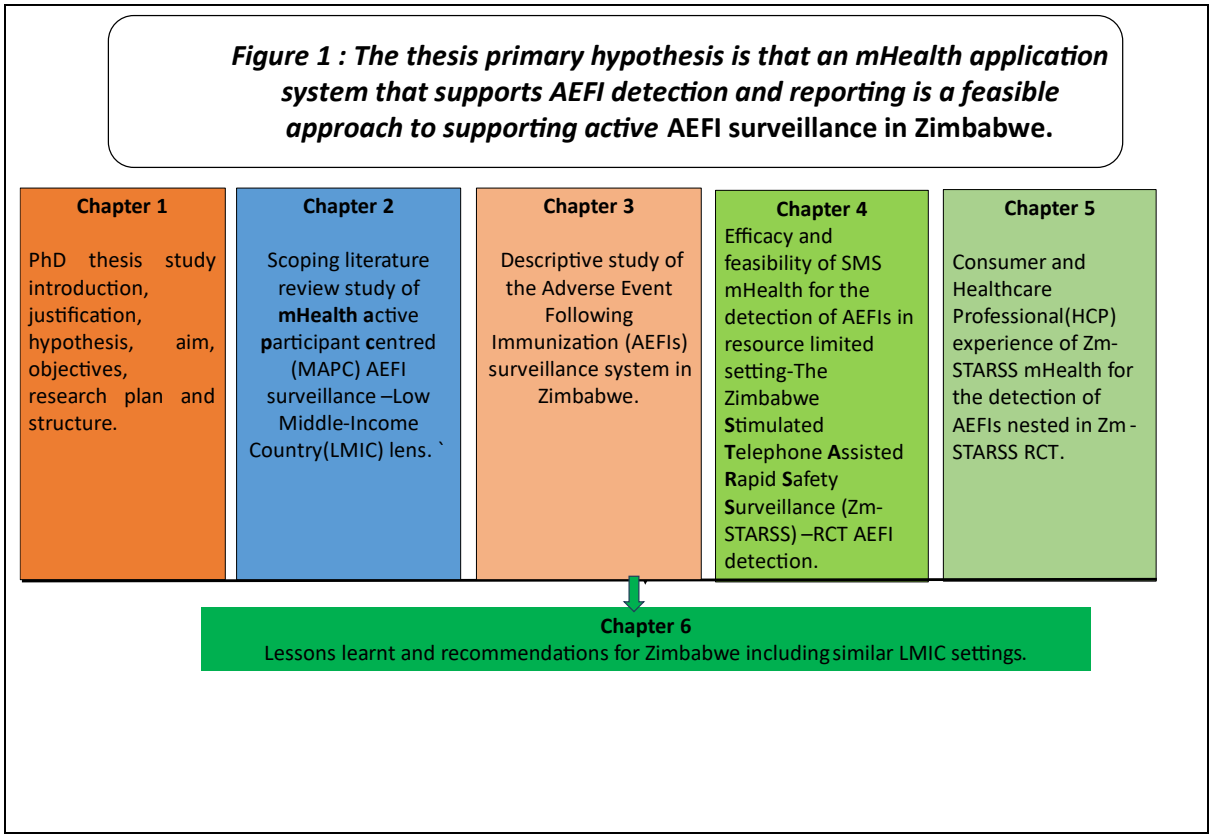


Figure 1: Summary of the PhD thesis research plan in line with the research question.

Having discussed the research problem statement , research aim, research question, primary hypothesis and research justification, the next section discusses research bias, confounding factors and limitations

1.6 Bias, confounding factors and limitations:

1.6.1 Declarations: Limitations, potential bias and confounding factors

Limitations, potential bias and confounding factors were individually addressed in each thesis chapter. The focus of this thesis is largely on AEFI case detection rather than case investigation, causality assessment, and the provision of feedback. Moreover, due to challenges encountered as a result of lockdown during COVID-19, the physical group discussions could not be conducted as approved by the UCT HREC Committee (see Appendix 1). As such we did not conduct interviews of HCPs from two selected control vaccination clinics that did not use Zm-STARSS.

Data was only collected from HCPs from the active sites that employed the mHealth tool. These HCPs were interviewed through online pre and post study online surveys (Appendix 6-7) as well as during study close-out virtual/hybrid meetings, (see **Appendix 1).** This was a chapter on case control study involving interviews of HCPs from two selected vaccination clinics that did not use Zm-STARSS, was affected and only study vaccination clinics HCPs were interviewed through online pre and post study online surveys **(Appendix 6-7)** including study close out virtual/hybrid meetings. This may have contributed to the limitations and bias observed in that chapter. Given that the Zm STARRS was only tested in Zimbabwe, during the COVID-19 pandemic, there may be limitations to the generalisation of the findings in other LMIC settings. Most possible biases and/or confounding factors were minimised and acknowledged for each chapter of the PhD study thesis in line with the “Strategic Advisory Group of Experts” (SAGE) guidelines for recommendations for vaccination programmes, ethical and biostatics requirements. Information gleaned from literature reviews conducted by other authors was acknowledged using the Vancouver referencing style. The use of Zm-STARSS randomised controlled trial (RCT) golden standard methodology minimised bias.

1.6.2 Ethical considerations and participant consent.

Ethical approval was granted by the University of Cape Town (HREC 184/2020) (***Appendix 1***) and by Medical Research Council of Zimbabwe (MRCZ) (MRCZ/A/2268) (***Appendix 2)***. Study sites approval was obtained from Ministry of Health and Director Health Services, Chitungwiza Municipality (***Appendix 3***). Study participants signed consent forms before taking part in the research. All research data is published in anonymised format to protect participants. The thesis protocol and amendments to include the COVID-19 vaccines were approved by the UCT Health Research Ethics Committee (HREC) committee, Medical Research Council of Zimbabwe (MRCZ) Ethics committee and Chitungwiza Hospital Ethics committee.

Chapter 2 Scoping Literature Review

Chapter 2 Title: A scoping literature review of the use of mHealth tools for active participant centered adverse events following Immunizations surveillance in low middle-income countries (LMICs).

Chapter 2 reviewed literature on mHealth tools for active surveillance of adverse events following immunizations. Gaps were identified that could be closed using SMS based applications in low middle income setting.

2.1 Abstract:

Introduction: The applications facilitated by mobile phone technology are rapidly expanding globally and this includes health-related interventions, and medical products vaccine pharmacovigilance. mHealth technology has been used to enhance adverse events following Immunization (AEFI) surveillance in high income countries (HICs). There is limited evidence on the feasibility of such mHealth technology in low middle-income countries (LMICs). This scoping and narrative literature review focused on assessing the value and the feasibility of mHealth Active Participant Centered (MAPC) AEFI surveillance systems and how this may apply in LMICs.

Methods: I carried out a scoping review using Joanna Briggs Institute (JBI) approach from 1970 to December 2022 studies. MEDLINE via PubMed was also used together with CINAHL, Scopus, Cochrane Library and Africa -wide via EBSCOs. Criteria for assessments of the studies were based on the mHealth platform, country experience, key findings of uptake, acceptability, response rates, cost and key challenges identified.

Results: Most studies 24/26 (92%) were conducted in HICs from 2010 to December 2022, with evidence of MAPC surveillance improving AEFI reporting rates for most vaccines. The consumer vaccinees SMS mean response rate was 71% for 23 studies using mixed digital technologies methods mostly conducted in HICs.

Conclusion: The evidence-based findings showed that MAPC AEFI surveillance occurred mostly in countries with well-resourced healthcare services including adequate AEFI surveillance programs and consumer participation. In LMICs there is the potential to take advantage of mobile phone technology penetration that is increasing for health surveillance. However, critical resource limitations and expertise may limit the feasibility of MAPC AEFI surveillance.

Key words: Short Message Services (SMS), mHealth Active **P**articipant **C**entered (MAPC) AEFI surveillance system, Scoping Literature Review.

2.2 Introduction:

Immunization is “globally one of the most cost-effective ways of preventing or reducing the severity of infectious diseases including, most recently, COVID-19 disease” (6, 45), however serious reaction(s) rarely occur post vaccination. An adverse event following Immunization(AEFI) is “any untoward medical occurrence after Immunization that does not necessarily have a causal relationship with the usage of the vaccine”(6, 27). No matter the cause, an AEFI can reduce public support and confidence as well as affect program reputation. Whilst most HICs have well developed vaccine pharmacovigilance systems to detect and respond to AEFIs these are less developed in LMICs. There are vaccines exclusively used in LMICs so safety information and decisions to manage AEFIs should come from these LMICs. In view of this there is need for LMICs to generate AEFIs data by implementing robust and effective surveillance systems. Unfortunately, most LMIC use passive paper based AEFI surveillance with most reports from health care professionals (HCPs) who underreport events. Sometimes not all the information availed is captured hence reports are incomplete (6). Inadequate AEFI monitoring and reporting systems lead to slow or lack of detection of AEFIs which compromise subsequent investigation and management of cases including assessment for causality. Vaccine preventable diseases (VPDs) can increase when potential vaccinees no longer participate in programs because of negative publicity that erodes trust caused by poor AEFI surveillance and/or case management. In most LMIC’s some people also don’t report AEFIs due to several limitations such as unaffordable communication services or mobile phones, lack of knowledge, fear to express their experiences and limited access to primary health care systems (46).

Active Vaccine Safety Surveillance (AVSS) is defined as “a data collection system that seeks to ascertain as completely as possible the number of AEFIs and underlying causes in each population via a continuous organized process”(6, 27). To implement AVSS it is critical to adopt new technologies and tools and to capitalize on emerging digital health tools (47, 48). Mobile Health (mHealth) is one digital tool which has been defined as “medical and public

health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices"(48).

The aim of the scoping review was to focus on assessing mHealth active participant centered (MAPC) for AEFI surveillance using SMS and/or mobile apps, while identifying gaps in knowledge and research including practical challenges to inform the application of this surveillance method in a LMIC.

2.3 Methods:

This scoping review was conducted in line with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) requirements and the latest Joana Briggs Institute (JBI) guidance for scoping reviews (49, 50). Due to the limited number of studies of MAPC surveillance in LMICs, from the scoping literature review, in addition to the overall data extraction summarized table, I undertook a more detailed review of these studies to understand what was going on including any relevant published commentaries and review articles. Given that the commentaries and reviews articles had at least four relevant common thematic areas the results were presented as such in relation to MAPC AEFI surveillance. The fundamental guiding principles of scoping literature review and search strategy with the searchers with assistance from a qualified UCT librarian in scoping literature review methodology was done, including review of the findings by the student and two supervisors.

2.3.1 Search strategy:

Searches in line with the research question and inclusion criteria were systematically performed on the following search engines: PubMed, Scopus, Embase, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, google scholar and grey literature. Online database searches were done in December 2022 by the first author with assistance from an experienced librarian.

The search criteria are listed in ***Appendix 1****.* All articles identified are listed in the data extraction table in **A*ppendix* 2** and *Prisma Flow* ***Figure 2***. The first author conducted the literature review and the second and third authors verified and resolved any disagreements, in line with the JBI Scoping Reviewers Manual (49, 50). Available full text articles were downloaded, and outstanding articles were sourced through the University of Cape Town library or via the corresponding authors.

2.3.2 Inclusion criteria:

The scoping Literature Review Search explored use of mHealth technology for AEFI detection and/or surveillance for licensed vaccines including routine Immunizations as well as vaccines used in national or regional campaigns or pandemics and emergency use authorisation of COVID-19 vaccines. All published studies, opinions, editorial, commentaries, reviews, and interviews focusing on MAPC AEFI surveillance of all licensed vaccines of all age groups were searched from January 1970 to December 2022 to ensure all studies were included since the discovery of mobile phones. All published studies in all languages were included if automatically translated by the search tools into English language.

2.3.3 Exclusion criteria

Papers reviewing the use of mHealth for reporting AEFI or the use of mHealth to support other elements of the Immunization programme such as Immunization reminders and/or increase in Immunization coverage were excluded. Studies on social media were excluded. Papers only written in other languages that could not be translated via Google translate and papers that could not be sourced were excluded. Studies using participant centred active AEFI surveillance without using mHealth were excluded such as web applications, emails, telephone calls, or Telewatch or digital diaries.

2.3.4 Target population and participants

Published literature which included the use of mHealth systems for vaccinees of any age or person of any age (neonates, infants, children, adolescents, young adults, adults including the elderly and pregnant women) in HICs and LMICs and receiving any licensed vaccine(s) including COVID-19 vaccines were studied.

2.3.5 Data extraction and collection

A data extraction form was used to systematically extract data from the included studies for assessment of study quality and evidence synthesis. In addition to basic details of the article (first author, journal name, year of publication etc.), details of the study were summarized in the data extraction table, ***Appendix 4***. This included the type of mHealth system assessed, aims and objectives, performance measures such as system effectiveness and feasibility, cost, key findings, and study limitations. Studies were grouped based on the mHealth systems used to conduct AEFI surveillance ***Table 1***. Published commentaries, editorials and other soft literature were also reviewed and incorporated into the discussion. Focus was to establish whether the MAPC system supported AEFI surveillance successfully in the settings in which it was used, whether there were any challenges encountered in implementation and whether there were any lessons learnt that would assist in ensuring the success of such a system in an African setting.

2.4 Results

2.4.1 PRISMA Flow diagram for MAPC AEFI surveillance studies

The PRISMA process identified 589 potential studies with 26 studies and 13 commentaries, editorials, opinions, and reviews meeting the inclusion criteria, ***Figure 2***.

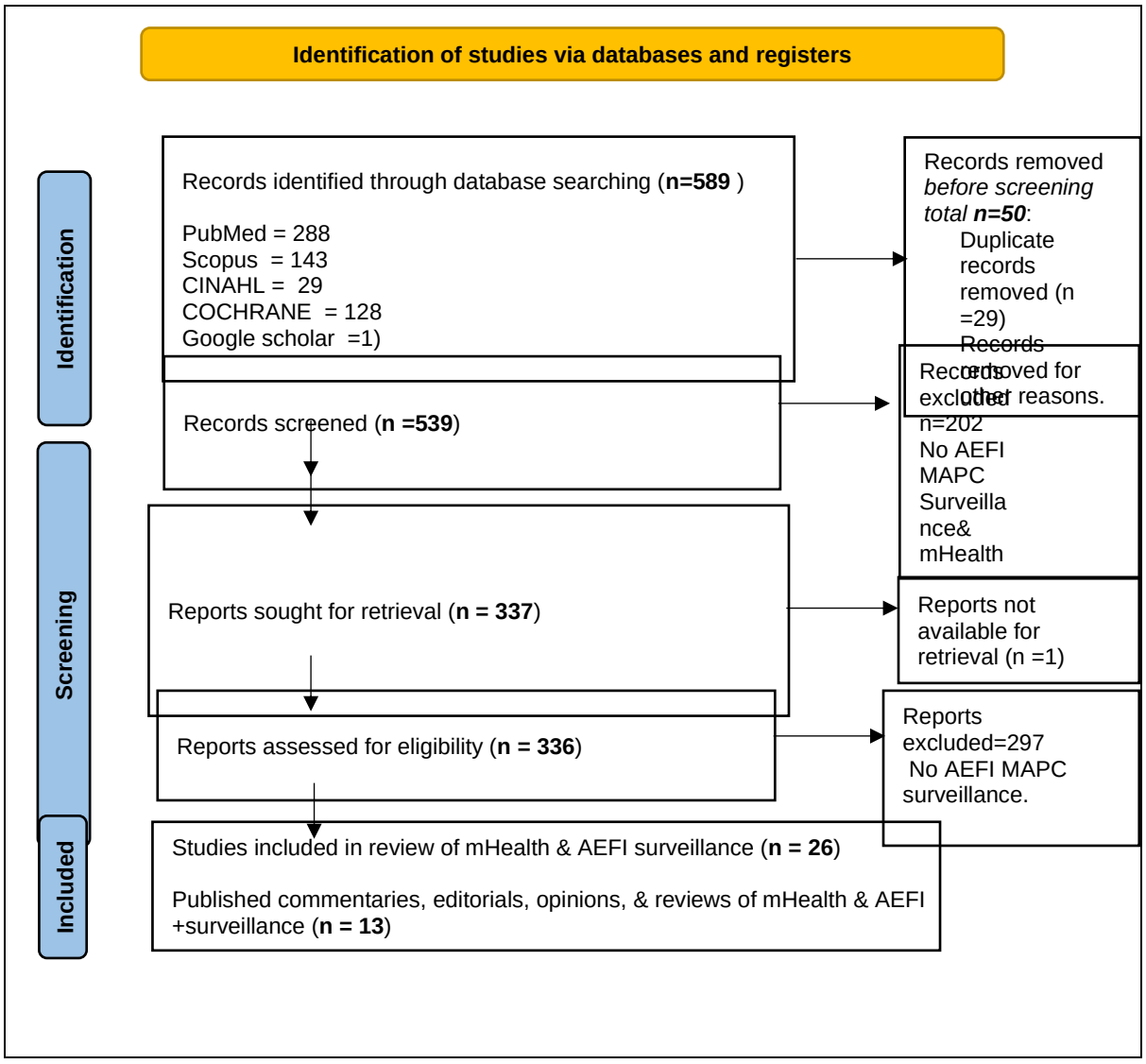


Figure 2: PRISMA Flow diagram for MAPC AEFI surveillance studies

2.4.2 MAPC AEFI surveillance studies

The essential findings from the 26 MAPC AEFI surveillance studies are included in ***Table 1*** below. The extracted summary data includes the jurisdiction [World Health Organization(WHO) region] of the study, the objective(s) of the surveillance study, the time points and events under surveillance, the study design and/or surveillance system, the population monitored, sample size and vaccines covered and a commentary on the study findings including strengths and limitations.

Table 1: Summary of scoping literature review of 26 studies' findings

Author (Ref) Country, WHO Region	**mHealth Active AEFI surveillance system and # of Time points of event AEFI surveillance**	**Objectives.**	**Study Design & Surveillance system(s).**	**Population monitored; sample size & vaccine covered.**	**Study findings, strengths and limitations.**
1. Roseblum et al 2022(51) HIC, WHO AMR.	V-Safe system. Voluntary system. # Daily from days 0-7 post vaccination.	Reviewed VAERS and V-safe data during first 6 months of USA COVID-19 vaccination programme.	Observational study for both VAERS and V-Safe system.	n=7 914 583 vaccinees received COVID-19 mRNA vaccines. Completed at least one V-Safe health survey. 298 792 852 mRNA vaccine doses administered.	Safety profile of COVID-19 vaccines. 340522 reports. 1049.2 non-serious reports per million doses and 90.4 serious reports per million doses via VAERS. Massive dataset included pregnancy exposures and outcomes. SMS combined with web based AEFI survey. Response rate not stated.
2. Stockwell MS et al 2017(52) USA, HIC, WHO AMR.	USA SMS system 2017 CATI Brand name not stated. # 0d, 2d,3d & 10d post vaccination.	Assessed fever frequency after paediatric live attenuated versus inactivated influenza vaccines.	Observational study.	(84.1% [n = 540]) eligible 24 to 59 months old children & guardians enrolled. Live attenuated influenza vaccine (LAIV) quadrivalent (LAIV4) or IIV (trivalent IIV3 or quadrivalent IIV4.	61 % SMS response rate timely & 39% paper diaries return delayed. AEFI reporting rates low & fever frequencies on d 0 to d2 similar for LAIV4 & any IIV3 or IIV4.

3. Gold MS et al 2022(41).(Australia) WHO WPR.	STARSS (Stimulated Telephone-Assisted Rapid Safety Surveillance). # 0-2d, 7d, 14d and 21-day post vaccination.	Evaluated AEFI detection efficacy of STARSS SMS tool for active AEFI surveillance.	Multi-center randomised controlled trial (RCT).	n=6338. Adults and children/ guardian vaccinees.	90.2% SMS response rate. AEFI reporting rate (4.3% vs. 0.3% controls). AEFI detection rate is 13-fold greater in SMS group c.f. controls. AEFI report completion rate higher in SMS CATI (58.2%) rather than web-based report (30.5%). Web-based AEFI report completed faster from AEFI event time. Opt-in consent system > reporting rate than opt-out AuxVaxSafety system.
4. Gold MS et al 2022(42). (Australia WHO WPR)	STARSS SMS system.	Evaluated consumer acceptability of STARSS SMS system.	Study nested within STARSS RCT, questionnaire-based survey.	1200 (20%) of RCT participants, of which 1139 completed the questionnaire.	96% indicated SMS-based surveillance "should be done". 62% should be done with consent. Consent and data privacy highlighted as key issues. Few participants non-compliance was largely demographic rather than attitudinal.
5. Choi YY et al 2021(53). South Korea, HIC, WHO WPR.	Telephonic interview & self-report questionnaire. # Monitored AEs 15-30 minutes and 7 days post vaccination dose cf. passive AEFI surveillance.	Examined safety of BNT162b2 COVID-19 vaccines in adults≥75years of age.	Observational study	2123 elderly (>75-years old) COVID-19 vaccinees. 807 (38%) CATI. Proxy responses accepted.	79.1% & 90.9% SMS response rates after 1st and 2nd doses. Overall response rate 82.3%. Proxy responses increased with age. AEFI reporting rate 50-45% local AEFIs & 16-26% systemic AEFIs 1st & 2nd doses respectively. Higher response rate after 2nd dose due to selection bias i.e., only included 1st dose respondents.
6. Bae S et al 2021(54). South Korea, HIC, WHO WPR.	South Korea, mHealth AEFI surveillance SMS system. # 3 days post vaccination.	AEFI surveillance of 1st doses ChAdOx1 nCoV-19 and BNT162b2 vaccines administered in HCPs.	Observational study.	n=7,625 South Korean HCPs.	76.9% overall SMS response rate & AEFI reporting rate higher in ChAdOx1 (93.3%) than BNT162b2 (80.1%; P < 0.001).
7. Menni C 2021(55).UK-HIC, WHO EUR.	UK- ZOE COVID-19 Symptom 2021 Study mHealth app and mobile self-report questionnaire. # 8-day post vaccination.	Phase 3 investigation of safety & effectiveness of BNT162b2 and ChAdOx1 nCoV-19 vaccines.	Observational study.	Adults n=3106 of 103622 vaccinated & n= 50340 of 464 356 unvaccinated controls.	13.5% SMS response rate & AEFI reporting rate 13·5% (38 155 of 282 103) vaccinees systemic AEFIs after 1st dose 1.4x for ChAdOx1 nCoV-19 & 1.2x for BNT162b2.
8. Nguyen M.T.H. et al 2020(56). Germany, HIC, WHO EUR.	SafeVac mHealth mobile app. # 0 to 3 months post vaccination questions asked at 15-time intervals.	Feasibility of a German SafeVac mHealth app for AEFI surveillance use by bank employees.	Observational study.	n= 462 consented to participate. Seasonal Influenza vaccines AEFI surveillance.	337 of 462 (72.9%) one entry used app. 207 (61.4%) used app in 3 months study period. Only 6 completed the usability survey. Participants cited reservations on confidentiality of SMS app. Correct app entry associated with increasing age and higher.

9. Nguyen M.T.H et al 2021(57). Germany, HIC, WHO EUR.	Germany mHealth mobile app-based prototype. #0-3 days post vaccination.	Feasibility of a German mHealth app, AEFI use by bank employees for seasonal influenza vaccination Nov 2017.	Observational study.	153 employees, n= 65 (42%) agreed to participate & completed the survey.	63% rated positive App use. 46 (71%) experienced difficulties using app and internet connection. Push notification tolerated. Lack of time and data protection concerns raised. 43% (28) Participants declined participation cited reservations of mobile app, data protection and demand for transparency.
10. Guedel D S et al 2021(58). Switzerland, HIC, WHO EUR.	Switzerland SmartVax 2021. # 3 days post vaccination.	Feasibility & acceptance study of SmartVax Smart phone based AEFI system.	Observational pilot feasibility and acceptance study.	Influenza & Zoster vaccinees adults n=276 (46.6%), 33.3% HCP, 20.1% patients) received 625 vaccinations.	90.3% SMS response rate and 29.8% AEFI reporting rate.
11. Singh G et al 2021(59). Australia, HIC, WHO WPR.	Australia SmartVax 2021.	Determined pharmacists' experiences with SmartVax:	A qualitative descriptive study	n=15 Pharmacists. COVID-19 vaccines.	Positive SmartVax perceptions. Small qualitative study.
12. Salter S M et al 2020(45). Western Australia (WA) HIC.	Australia SmartVax 2020. # 1-7 days post vaccination.	SMARTVax active AEFI surveillance system in 22 pharmacies cf. passive surveillance in 90 general practice (GP) and other clinics).	Observational study. March and October 2020	>10-year-olds. n=101,440 influenza vaccinees (6,992 from pharmacies; 94,448 from non-pharmacy sites.)	SMARTVax SMS response rate 96.1% within 1day and 76.4% day 7. AEFI reporting rate 4.8% pharmacists n=247 cf. 6.0% non- pharmacists n=4,356.
13. Westphal DW et al 2016(60). Australia, HIC, WHO WPR.	Australia SmartVax. # 3 days post vaccination.	SmartVax feasibility paediatric study on reactogenicity profiles and impact assessment of revised childhood Immunization schedule.	Observational study.	3992 vaccination visits. n= 1667 children<5. 3906 SMSs sent. Diphtheria–Tetanus–Pertussis–Poliomyelitis (DTPP) vaccine.	74.2% SMS response rate among 1216 of 1667 patients included. Response to first SMS within 2 hours for 81.3% of responders. AEFI reporting rate 8.2%.
14. Leeb A et al 2014 (61) Australia, HIC, WHO WPR.	Australia SmartVax. # 1-3 days post vaccination.	Effectiveness study of SmartVax to monitor AEFIs in GP.	Observational study	n=3281 children/guardian pairs taking Influenza vaccines and others.	80% SMS response rate 1st day and 72.6 % within day 3 post vaccination.
15. Cashman P et al 2020(62) Australia HIC, WHO WPR.	Australia Vaxtracker. # 0 to 28 days post vaccination.	Explored potential barriers to participation in Vaxtracker automated active AEFI surveillance by Aboriginal parents of children vaccinees.	Observational study.	Aboriginal children (47.2%) versus non-Aboriginal children (25.4%) in 105 non-Aboriginal families. (Aboriginal n=13/28, non-Aboriginal n=75/91). Influenza or DTPa vaccines.	SMS response rate & AEFI reporting rate lower in Aboriginal children guardians (25.4%). c.f. non-Aboriginal children (47.2%). Complex sampling matrix. Findings showed lower SMS mHealth MAPC AEFI surveillance uptake in some socioeconomically disadvantaged Aboriginals in a HIC.

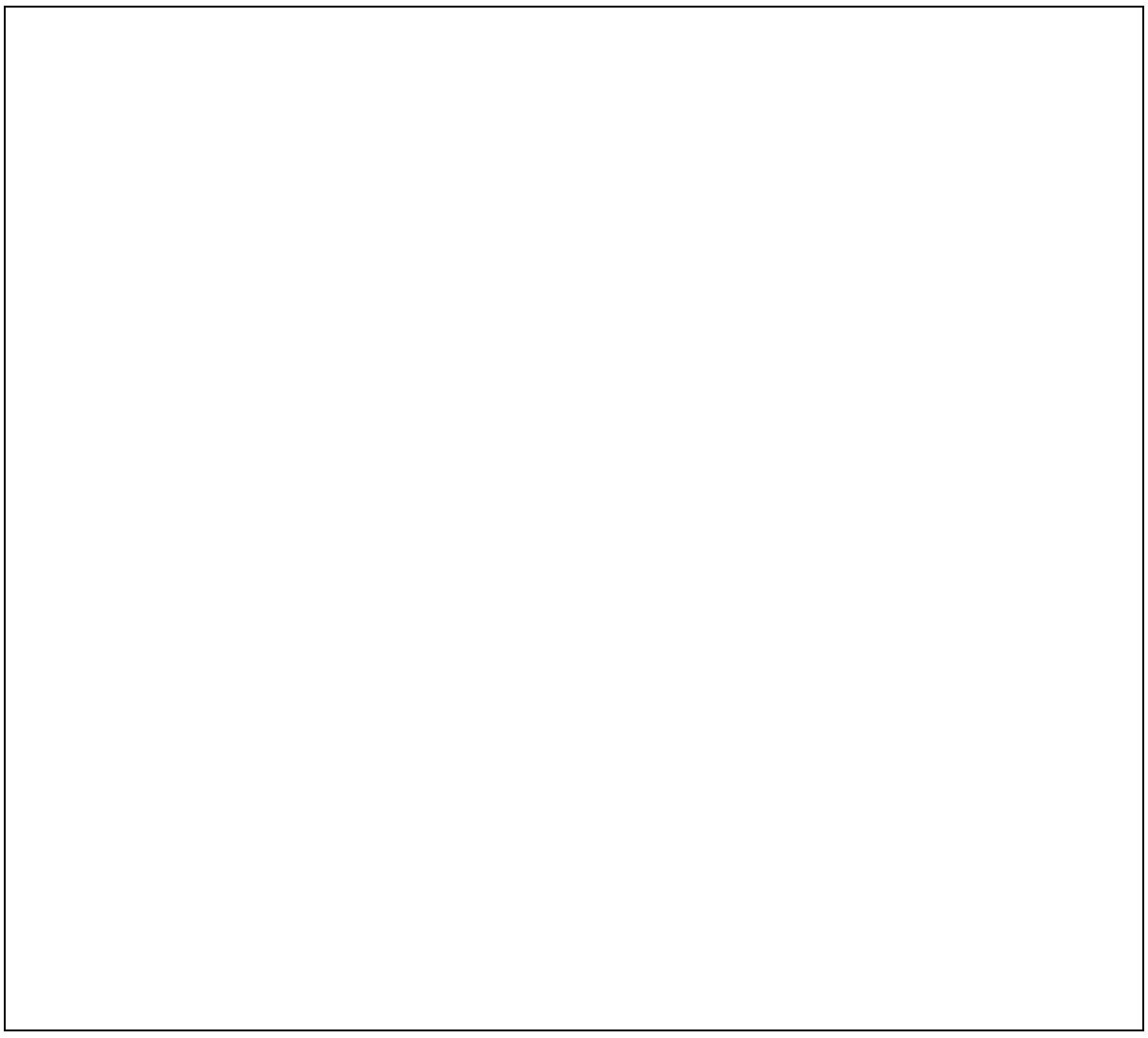
16.Cashman P et al 2014 (63) Australia, HIC, WHO WPR.	Australia Vaxtracker. # 3- & 42-days post vaccination.	Vaxtracker web-based survey for active Post Marketing Surveillance (PMS) of AEFIs.	Prospective study Vaxtracker.	n=477 children 6 months to <10 years administered Inactivated influenza vaccine.	57% & 61% SMS response rates in 2012 & 2013 respectively. AEFI reporting rates were not stated although acute & delayed AEFIs were detected.
17.Pillsbury A J et al 2020(64) Australia. HIC, WHO WPR	SmartVax (most used) and Vaxtracker deployed. #3 to 5 days post vaccination.	AusVaxSafety study. PMS safety profile of 2018 influenza vaccines, an adjuvanted trivalent inactivated influenza vaccine (aIIV3) and high-dose trivalent inactivated influenza vaccine (HD-IIV3).	Observational study	Adults ≥ 65 years. n=72013 administered Influenza vaccine aIIV3 and HD-IIV3.	69.6 % SMS response rate. HD-IIV3 (8.9%) higher AEFI reporting rate than aIIV3(6.4%) (P < .001). Denominator data but AEFI events not clinically verified by healthcare professionals including fatalities. Causality assessment is not necessarily done.
18.Pillsbury A J et al 2017 (65) Australia. HIC, WHO WPR.	AusVaxSafety. Day 3 post vaccination.	Feasibility study of AusVaxSafety AEFI surveillance of children seasonal influenza vaccines in children, in 2015.	Observational study.	n= 7402 children administered Influenza Meningococcal B vaccines.	75% SMS response rate. AEFI reporting rates lower fever for influenza vaccine 7.3% c.f. 30.3% (p < .001) higher rates for Meningococcal B vaccine. Concomitant vaccines caused more fever (7.5% versus 2.8%; p < .001).
19.Reagan AK et al 2015(66). Australia, HIC, WHO WPR.	Fast Mum SMS system. # Day 7 post vaccination.	Investigated FAST Mum mHealth active AEFI surveillance cf. post-vaccination AEFIs self-reported by pregnant women versus non-pregnant women receiving TIV.	Observational study comparing the reactogenicity of trivalent influenza vaccine (TIV) in pregnant and non-pregnant women.	Pregnant women= 3173 however response from 1086 pregnant & 314 non-pregnant women (Total 1400). Infuenza vaccines.	86% SMS response rate AEFI reporting rates similar for pregnant & non pregnant women (13.0% & 17.3%, respectively; OR=1.2 [95% CI: 0.8-1.8]). SMS active AEFI surveillance used successfully in maternal health. TIV is safe in pregnancy as well.
20. Regan AK et al 2014(67). Australia, HIC, WHO WPR.	FAST Mum SMS system. # Day 7 post vaccination.	FAST Mum AEFI surveillance for Trivalent Influenza Vaccine (TIV) for pregnant women.	Prospective study Using SMS to monitor AEFIs trivalent influenza vaccination in pregnant women.	n= 5155 pregnant women administered Trivalent Influenza Vaccine (TIV).	83.6 % SMS response rate higher than 63% telephone response P < 0.001. AEFI reporting rate not stated.
21. Stuurman AL et al 2017(68) Belgium, HIC WHO EUR.	Belgium 2017 MAPC AEFI Surveillance system. Brand name not stated. #0 to 7 days post vaccination.	Assessed feasibility of collecting reactogenicity data within one month of start of a vaccination campaign in Belgium.	Feasibility study.	n=100 adults aged 18 to 65 years. Post vaccination of inactivated seasonal influenza vaccine, in occupational setting.	68% SMS response rate & AEFI reporting rate: 68% local AEFIs & 65% general AEFIs & 51% reported both a local & a general AEFIs.
22. Baron S et al 2013(32). Cambodia. LMIC, WHO WPR.	Cambodia Frontline SMS - prompts AEFI Surveillance system. # 48hour post vaccination.	To field test Frontline SMS software to see whether it could provide effective and timely notification of AEFI.	observational study. Pilot proof of concept.	Cambodian adults >18 years old. n=184 (13.8%) of 1331 vaccinees, agreed to participant in study. Hepatitis B 41.8%, influenza 11.9%, tetanus	71.7% - 54.9% SMS response rate after 1st response & 16.8% after further prompts. AEFI reporting rate 17.4% (23) reported benign AEFIs and 82.6% no AEFIs.

				10.9%, & HPV (10.9%) vaccines administered.	
23. Wilson K et al 2016 (36) Canada, HIC, WHO AMR.	CANADA CANVAS (Canadian National Vaccine Safety Network) 2016. #Day 1- & 6-months post vaccination.	Evaluated the feasibility, usability and proof-of-concept mobile App to facilitate AEFI reporting for CANVAS network for seasonal influenza vaccine.	Observational study	n=76 adults consented, 48(63%) successfully downloaded App and 38 (50%) completed all surveillance surveys.	SMS response rate 63% (48) 50% (38) completed survey.86% preferred SMS App. Both acute & delayed AEFIs were detected. AEFI reporting rate not stated.
24. Bettinger JA et al 2014(69). Canada, HIC, WHO AMR.	CANADA 2014 SMS web system. #2 & 7days post vaccination.	Feasibility study of Rapid Online Identification of AEFIs After Influenza Immunization in Children by PCIRN's National Ambulatory Network.	Observational study.	n=1230 guardians & children. Trivalent influenza vaccine & live attenuated intranasal vaccine.	72% of online SMS survey response rate & 11% by phone responded. AEFI reporting rate not stated although AEFIs detected.
25. Zeng J et al 2019(70). China, MIC, WHO WPR. Zhonghua Yu Fang Yi Xue Za Zhi	Chinese SMS mobile system 2019. #30min, 3- & 30-days post vaccination after each dose of EV-A71 Immunization.	Evaluated PMS profiles of inactivated enterovirus type 71 (EV-A71) vaccine (Vero cell).	Observational study. Mixed methods by field observation, participants phone-calls or face-to-face interview.	11 cities Chinese n= 45 239 children who received 71 243 doses EV-A71 vaccine. Inactivated enterovirus A71 vaccine (Vero cell)	SMS response rate not stated. AEFI reporting rates higher in 30min 1.016%- & 3-day 0.698% 1st & 2nd doses post vaccination. Mobile phone calls mostly used for following up AEFI surveillance.
26. Sesay F. F et al 2014 (33). Sierra Leone, WHO African Region (AFR).	Sierra Leone mobile app EpiSurveyor 2014	Measured coverage of Vitamin A Supplementation (VAS) and measles vaccination plus AEFIs during Maternal and Child Health Week (MCHW).	Observational study	Children vaccinees and guardians' pairs in Vitamin Measles vaccines campaign.	90% SMS response rate. Higher AEFI reporting rate via SMS linked post event coverage survey (29.1%) than MCHW (0.01%) (p,0.0001). Mobile app EpiSurveyor done post vaccination. Time points of AEFI surveillance not stated.

2.4.3 WHO region and geographic location of studies

MAPC AEFI surveillance has grown steadily over the past 9 years, with almost half of the studies being published from 2020-2021. From 2013 to 2022, 26 studies were identified with 24 (92.3%) occurring in HICs (Australia, Belgium, China, Canada, Germany, Switzerland, UK and USA) and the remaining 2 (7.7%) were from LMICs, with only one study occurring in Africa (Sierra Leone). More than half of the included studies, 15/26 (57.7%), were from the WHO

Western Pacific Region of which the majority 12/26 (46.2%) were conducted in Australia. Please refer to ***Figure 3*** below.



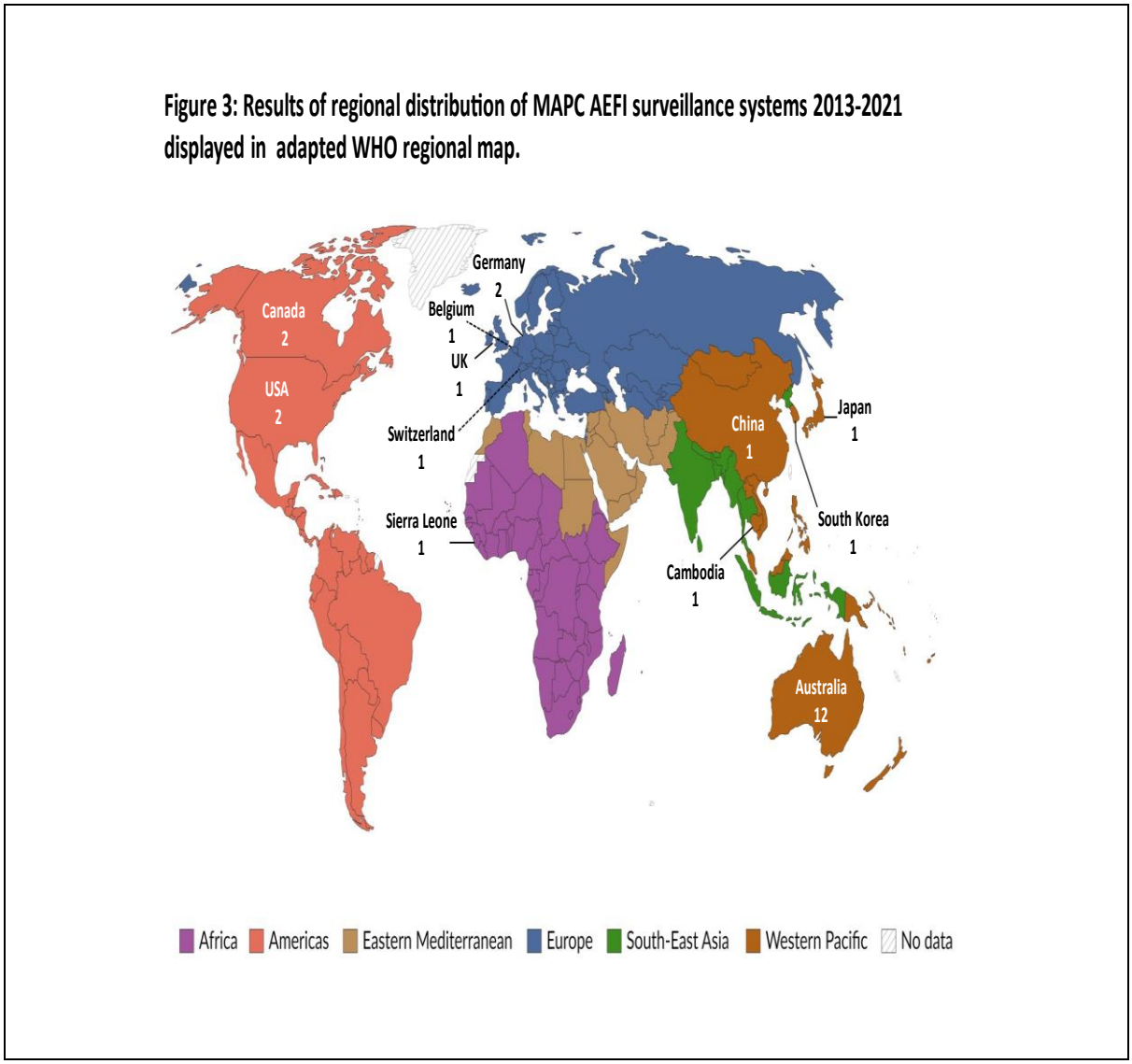


Figure 3: Results of regional distribution of MAPC AEFI surveillance systems 2013-2021

Having presented the MAPC AEFI surveillance studies and their geographic locations ,the next section discusses their study designs and vaccines under surveillance.

2.4.4 Study design and vaccines under surveillance

There was only one randomised control trial study design [24,25] with all remaining studies being observational. The usual setting for the studies was within the context of post-marketing surveillance and not pre-licensure clinical trials. The majority of MAPC studies targeted seasonal influenza vaccines for surveillance (n=13) [2, 8, 9, 10, 15, 16,17, 18, 19, 20, 21, 23,24] with more recent studies evaluating COVID-19 vaccines (n=6)[1, 5, 6, 7, 11, 12]. Other specific targeted vaccines included: Zoster, (10), Measles (26), Meningococcal (18) and an inactivated enterovirus vaccine (25). Several studies included multiple vaccines recommended as part of the Immunization programme (n=5)[3, 4, 13, 14,22]. All age groups were included for surveillance with two studies focusing on pregnant mothers (19,20) and one on an aboriginal population (15).

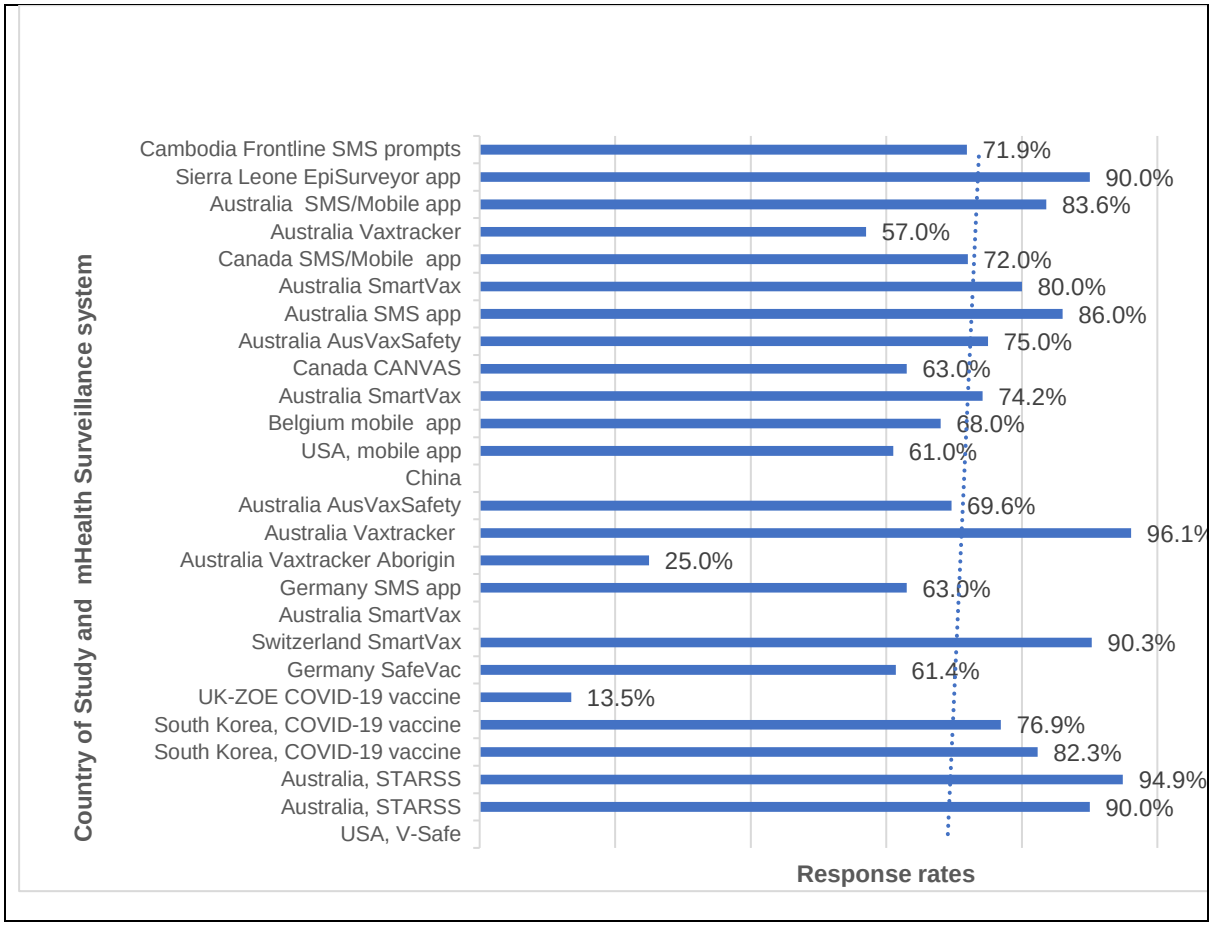
2.4.5 Time points for surveillance and events under surveillance

The day(s) that the SMS were sent post vaccination varied widely, from 0 to 180 days post-vaccination (0,2,3,4,7,14,21,28 & 180 days). Most studies (77%) solicited events within 7 days of vaccination with only 6 (23%) studies soliciting an adverse event after 7 days and one study after 180 days.

2.4.6 SMS response rates

For MAPC AEFI surveillance the SMS response rate was defined as the proportion of study participants who responded to the SMS prompt sent post-vaccination to solicit their AEFI experience. The SMS response rates for the studies have been summarised in ***Figure 4***. The mean was 71.2% (standard deviation +/- 0.2004). Three studies did not state the SMS and/or Mobile App AEFI response rates (32, 60, 69). The SMS response rates ranged from a low of 13.5% (UK-ZOE) to 96% (Aus-Vaxtracker). Australia had the highest number of studies totaling 12/26 (46%) and the highest response rates of 96.1% for SmartVax, 90.3% for a Swiss-SmartVax study and 90.2% for a **s**timulated **t**elephone **a**ssisted **r**apid **s**afety **s**urveillance (STARSS) system(41). A variety of approaches were used to solicit more detailed information once a positive response to the initial request for information via SMS was received. These

included the use of an embedded link to a website with a dedicated app questionnaire, or a dedicated app with questionnaires nested in these(45) or a computer-assisted telephonic interview (CATI) in which a health care worker contacts a respondent to obtain additional details of the event(41).



*For China study and USA, V-Safe study, no response rate was reported.

Figure 4: MAPC AEFI surveillance SMS response rate (n=23)

2.4.7 Detailed review of MAPC studies in LMICs from the scoping literature review.

Because of the limited number of studies from LMIC's we undertook a more detailed review of these LIMCs studies found from the scoping review results. Baron et al evaluated MAPC for AEFI surveillance in Cambodia which at that time (2012) did not have a passive surveillance system in place (32). This pilot project enrolled 184 adults over 18 years of age who owned a cell phone, lived in an urban setting and attended an International Vaccination Centre. Two days following vaccination 184 participants received an SMS asking if an unwanted event had

occurred. The final SMS response rate was 71.7% with 23.5% of this group requiring additional contact to solicit a reply to the lack of an initial SMS response or to get more detail of the AEFI. Of those who replied to the SMS 17.4% reported an adverse event which was mild and expected. The time from SMS dispatch to reply was within the same day in 75.8% of participants. The authors noted the high response rates and ascribed this to the nature of recruitment which involved a detailed explanation of the study. Limitations included bias towards recruitment of younger and more affluent participants, nevertheless, this pilot project was thought to provide evidence for potential feasibility of MAPC for AEFI surveillance in Cambodia.

A mass measles and Vitamin A supplementation campaign was conducted in Sierra Leone in 2012, with a post-event coverage survey conducted (PECS). The WHO EPI cluster sampling method was used to identify 30 clusters with 5,621 caregivers interviewed. Data was collected by a specific application with data collected, stored and transmitted using mHealth. AEFI data was obtained from 92% of the interviewed caregivers with 29% reporting one or more of the common AEFI. This compares with a reporting rate of AEFIs, for all the vaccinated cohort (n=1 179 605), to maternal and child health workers of 0.01%. This included common AEFIs although one death 3 days post-vaccination was reported(33). In summary, although the methodology differs in each of these two studies the response rates were high and common AEFIs were frequently reported. Some studies found that combining emails with an SMS or inclusion of web apps had a better response rate than SMS alone(34, 45).

2.4.8 Summary of themes and opinions, commentaries and editorials.

I included commentary papers in our scoping review to understand the global scope of mHealth in supporting AEFI surveillance in accordance with the four common themes published. This was a limitation in the study due to the limited information and few studies of MAPC AEFI surveillance in LMICs. Of the 13 published commentary papers that met the inclusion criteria all were from HIC and this included two (15%) from North America with the remaining 11 (85%) from Europe. These commentaries included important points on quality,

quantity, and timeliness of AEFI reporting, direct consumer vaccinees/guardian involvement, support for improved safety data analyses and feedback to reporters but excluded comments on feasibility, barriers, cost, and challenges. The commentaries were not evidence-based studies per se but made important advocacy for the use of mHealth to improve AEFI surveillance as part of a holistic improvement of Immunization in national programs. No specific methodology was used to derive these thematic areas discussed below. The results of the 13 commentaries were summarized into four thematic areas found after analysis:

2.4.9 mHealth and eHealth for information sharing and advocacy.

mHealth and eHealth technologies showed effectiveness as advocacy and knowledge sharing tools to support Immunization programmes. Digital health technologies with social media surveillance can be exploited to identify and respond to public information needs when delivering vaccination campaigns(47). Interactive and user-friendly chatbots, can provide vaccinees/guardians with information they need about vaccinations (e.g., VACC tool)(71). Mobile Apps allow dissemination of correct information to patients (72). There is need to use Artificial Intelligence (AI) to analyse large AEFI datasets to exclude inherent biases (73). VACC Tool^{TM} empowers parents to be well informed about vaccinations(74). A social ecological model-based framework for the use of technology to promote vaccination and AEFI surveillance is worth exploring in LMICs through evidence gathering was proposed (38). To express the highest impact of communication technology strategies communication should be closely intertwined with surveillance activities, to inform timely and effective public health actions (75, 76).

2.4.10 mHealth and eHealth and AEFIs surveillance.

MAPC has shown value in HIC settings to empower patients to provide direct information on their experience and have the potential to improve AEFI reporting, signal detection and central pooling of data into the hands of the regulators and Immunization programmes. In many AEFI surveillance systems, patients do not report most of their health events through HCPs unlike the USA that has the highest number of reports directly from consumers (47).

The USA V-Safe mobile App and the UK Yellow card mobile App can empower individuals to provide early AEFIs reports (73). Mobile Apps enable clinicians to identify and diagnose potential adverse events at point of care (74). Mobile Apps may reduce under reporting of rare AEFIs (77). Mobile technology could improve vaccine registries and potentially AEFI reporting (78).

2.4.11 mHealth, eHealth and vaccine uptake.

The ultimate goal of an expanded use of digital tools would be to increase Immunization coverage thereby reducing vaccine-preventable disease incidence and improve AEFI surveillance by timely communications with Immunization providers, HCPs, vaccinees and parents/guardians(47).The COVID-19 vaccine apps like USA V-Safe App improve consumers'(vaccinees/guardian) engagement with AEFI surveillance and advocacy to address vaccine hesitancy which could affect consumer behavior and increase vaccine uptake (72).

2.4.12 mHealth and eHealth including quality of AEFI reporting.

Mobile devices can improve the timeliness and accuracy of data collected (including AEFIs) on central Immunization information systems (78). SMS and mobile Apps could allow for the early assessment of patients experiencing AEFIs (79). VACC Tool app assists doctors to assess patients and compare their clinical presentation to a set of diagnostic algorithms for AEFIs and follow up (77, 80). Automated question and answer systems may help improve quality of information transmitted to pharmacovigilance agencies including AEFIs (80).

2.5 Discussion

The WHO Vaccine Safety Blueprint requires that all countries have a robust passive AEFI surveillance system (81, 82). Moreover, each country needs to contribute AEFI reports to the WHO global database (VigiBase) so that these collective AEFI datasets can be used to support signal detection, analysis and identification of risk minimisation opportunities. It has been recommended that passive surveillance of AEFI can be enhanced by MAPC surveillance (37)

since this has the potential advantage of obtaining information directly from vaccinees or their guardians. Our review has demonstrated a paucity of studies within LMICs with only two studies not conducted in a HIC (32, 33). Nevertheless, in these LMIC studies the SMS response rates were high and equivalent to those from HICs. MAPC AEFI surveillance remains largely untested in an LMIC setting and requires further evaluation.

MAPC has specific advantages, which could include the targeting of specific vaccines for enhanced AEFI surveillance. The initial growth of MAPC AEFI surveillance, in Australia, was following concerns about the safety of the annually reformulated seasonal influenza vaccines. Safety surveillance of seasonal influenza vaccines is less relevant in LMICs because these vaccines are not widely used in these jurisdictions. However, this surveillance method could be relevant in LMICs' for novel vaccines (such as, ebola, malaria and dengue) which are not used in a HIC. For pandemic vaccines there is great need to generate safety data as fast as possible for assessment after regulators' emergency use authorisation (EUA) and during large scale rollout. During the COVID 19 pandemic a sizable number of AEFI surveillance projects using MAPC were successfully implemented in HICs but not in LMICs (37, 83).

Whilst enhanced surveillance is an advantage there are inherent limitations to MAPC surveillance, which should be appreciated prior to implementation in LMIC's. Although surveillance can be implemented at different time points, post-vaccination, most systems did not send SMS prompts 2 weeks after vaccination. During the first 0 to 3 days most responses were received and response rates significantly declined to 14 days making it difficult to account for responses after 14 days of Immunization. Although common and expected AEFIs related to vaccine reactogenicity are usually reported via MAPC systems, the aim should be to enhance surveillance for serious events. Serious, adverse events of special interest (AESIs) and co-incidental events, such as those due to co-morbid conditions such as infection malnutrition, are likely to be more common in LMICs. Once reported as an AEFI these serious events will require further and immediate case investigation, management and communication at a sub-national or national level. This will have resource implications for

the health system and could be a challenge, if not addressed this could undermine public confidence in vaccine safety.

Further lessons should be learnt from implementing MAPC in HIC's. Integrating the MAPC system into already existing eHealth surveillance systems is important. Some HICs have built effective Immunization databases and systems that manage and keep confidential information that is connected to other national electronic record databases (45, 83). Unfortunately, majority of LMICs have weak electronic systems delivering health programs including Immunizations. Linkage between preventive and curative services, medicine and vaccine exposures and health events through a unique patient identifier are usually lacking. Digital integration is a major challenge for LMIC's but they are required to address Strategic Priority 1 of the Immunization Agenda 2030, specifically the key areas of focus being; Health Information System Integration *("data are also integrated into national health information systems")* and Vaccine Safety Monitoring *("Ensure that national Immunization programmes can detect and respond to any concern about vaccine safety by continuous monitoring")* (84).

During the design and implementation phases consumer engagement should occur. Our scoping review has identified the challenges end users face and what they would like to be addressed in health applications they would gladly use. (56). MAPC surveillance method provides a unique opportunity for consumers to be engaged in their experiences post-Immunization. In HIC's, users of healthcare facilities including consumers of vaccines/medicines monitor and track their health using modern technology that is digital, but this is likely to differ significantly from consumers in a LMIC. The scoping review did not identify any studies of LMIC consumer engagement in the design of this surveillance.

How MAPC surveillance data can be communicated to stakeholders, including consumers to promote vaccine confidence is critical. In 2019 the WHO identified vaccine hesitancy as one of the 10 important priorities for improving health because it reduces number of people

wanting to get vaccinated thereby increasing diseases that can be prevented by vaccines (85, 86). There is need for more studies in LMIC to investigate the role or impact of digital tools such as mHealth in improving vaccination coverage and uptake and reducing hesitancy by facilitating knowledge transfer, consumer engagement and communication of reminders to vaccinees. Informed consumers that are appropriately engaged are most likely to fully participate in vaccination programs, thereby improving Immunization coverage. Fundamentally, AEFI surveillance systems improve information flow and increase engagement with users, can enhance Immunization plans by helping the public to make meaningful decisions. By sharing MAPC AEFI surveillance information with all stakeholders, public confidence is re-affirmed in national Immunization programs (37, 83).

Finally, lessons can be learnt from adverse drug reactions (ADR) and AEFI mobile phone reporting applications, used by healthcare providers. There are several enhanced spontaneous smartphone mobile Apps for passive monitoring of ADRs that have been connected to the national databases as well as WHO VigiBase (87). Some passive ADR apps such as The UK Yellow card mobile App and WEBRADAR MedSafety App have been extended from HICs to LMICs namely Zambia, Botswana, Nigeria, Ethiopia, South Africa and Ghana (84). These active surveillance Apps for AEFI do not use SMS signals in time points (88). Studies in Peru and Cambodia on digital technologies to monitor unintended events in real-time after consumers had taken medicines/ vaccines (87) are limited. The ability to embed MAPC AEFI surveillance systems in the ADR and AEFI reporting Apps and apply them to clinical trials and routine administration and management of medicines and vaccines is worth investigating (37).

In summary, before MAPC AEFI surveillance systems can be scaled up in LMICs there is a great need to first evaluate their feasibility, applicability, efficacy and cost effectiveness. Digital tools can be useful to enhance Immunization information systems, surveillance of AEFIs and VPDs which are attributes at the heart of any Immunization program (37, 83). Considering that LMICs are challenged financially, thorough testing and evaluation of the capabilities of MAPC systems should be undertaken before adoption to ensure maximum benefit from the

investments. MAPC systems for AEFI surveillance should fit into Immunization programs without complex integrations or prohibitive costs. For successful adoption of MAPC, key decision makers and stakeholders like vaccine regulators, health facility staff, consumers, program managers, government health staff, communication service providers (e.g. mobile operators), health funders and sponsors should be consulted and effectively engaged. There is a paucity of information on the feasibility, practicality and cost of adopting and expanding MAPC systems. In rural areas, for example where most African citizens live, evidence should be gathered to determine how AEFI surveillance could be improved through accessibility of affordable SMS, internet and mobile based Apps as mobile phone coverage and data services improve.

2.6 Conclusion

In conclusion, the scoping review showed that MAPC AEFI surveillance is growing but primarily in HICs. Consumers could be empowered by MAPC AEFI surveillance to control their healthcare journeys. Consumers could be assisted to detect, inform, present and control AEFIs. More scientific evidence should be gathered on how feasible, applicable and cost effective MAPC systems are compared to other interventions. Moreover, suitable approaches to gather more detailed clinical data on AEFI that can support case investigations and causality assessments from mHealth respondents needs to be explored in these settings. Also, consumer and HCP interest, acceptance, adoption including utilization is key. A holistic approach to adopt MAPC surveillance systems could overcome limitations due to shortages of HCPs, improve AEFI surveillance, reporting, management of AEFI cases and causality assessment. This could boost public confidence, reduce vaccine hesitancy, improve performance of Immunization programs, improve vaccine coverage and help eliminate VPDs.

Chapter 3 Descriptive study of AEFI surveillance system in Zimbabwe

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Chapter 3 topic: **Descriptive study of AEFI surveillance system in Zimbabwe**

Chapter 3 reviewed the Zimbabwe national AEFI surveillance system highlighting strengths, weaknesses/challenges and opportunities for improvement. The end goal is finding cost effective ways to strengthen AEFI surveillance and save lives.

3.1 Abstract

Introduction: Functional national systems that monitor adverse events following immunization (AEFIs) are vital for implementing evidence-based vaccination policy while ensuring the safe access to these life-saving technologies. These systems can counteract vaccine hesitancy by increasing public trust and uptake in vaccination, minimising the burden of vaccine-preventable diseases (VPDs). Ensuring that these systems function optimally is a critical public health imperative. This is a novel study evaluating the AEFI surveillance system including causality assessment, in Zimbabwe.

Aim: This study aimed to provide a review of Zimbabwe's national AEFI surveillance system since its launch in 1998, highlighting strengths, weaknesses, and opportunities for improvement.

Method: We conducted an in-depth analysis of all AEFI reports received from 1998 to 2021, assessing reporting trends and overall performance of the AEFI system in terms of vaccinees' demographic characteristics, AEFI reporting ratio, causality assessment, programmatic errors/clusters, quality of reports using VigiGrade® completeness score, geographical distribution of reports and identification of opportunities to strengthen the national AEFI

system in Zimbabwe. The WHO Global Benchmarking Tool (GBT) was used to assess regulatory performance in terms of AEFI surveillance. Duplications were excluded and reports with evidence of AEFI(s) after vaccination were included.

Results: A total of 1440 AEFI reports were received from 1998-2021. There was a steady increase of AEFI reports per annum particularly from 2006 to 2021 with a more dramatic increase during the COVID-19 epidemic resulting in an AEFI reporting ratio of 43.46/million adults for COVID-19 vaccinations in 2021. The reporting ratio exceeded the WHO recommended minimum AEFI reporting ratio of 10 per 100000 surviving infants during eleven years (47.84%) out of the twenty-three years since inception of the surveillance. The GBT assessment demonstrated that the AEFI surveillance system evolved for all manufacturers or license holders.

Conclusion: Close partnership between the Immunization program and regulatory authority has enhanced AEFI surveillance in Zimbabwe. Incomplete AEFI case investigations and timely AEFI detection are challenges that need to be addressed. System strengthening should include consideration of digital innovations to improve detection, optimising case investigation of serious AEFIs including post-mortems, and utilising VigiPoint disproportionate analysis for signal detection.

Key words: AEFI surveillance system, AEFI causality assessment, mHealth active participant centred (MAPC) AEFI surveillance, VigiGrade Completeness score and WHO Global Bench Marking Tool Version VI(GBT).

3.2 Background

Globally, Immunization is one of the most cost-effective ways of preventing or reducing the severity of infectious diseases including, most recently severe acute respiratory syndrome coronavirus (SARS-CoV-2). Ensuring that vaccines are safe, effective, and of good quality is a responsibility shared by manufacturers, members of the distribution chain, national Immunization programs (NIPs) and the national medicines regulatory agency (89). Timely detection and investigation of adverse events following Immunization (AEFIs), causality assessment, identification of signals, response and appropriate communication are essential for promoting the safety of public health vaccines (90, 91). In rare instances, however, AEFIs might result in diminished public trust in vaccination and hence the Immunization program's ability to achieve high coverage (14, 27, 92). The African region contributes a cumulative total of only 0.9% of individual case safety reports (ICSRs) to the WHO global surveillance safety database known as VigiBase (93). Most of these reports relate to medicines such as antiretrovirals, anti-tubercular and antibiotic medications rather than vaccines (93). Scientific evidence on the local AEFIs is lacking in most Low Middle-Income Countries (LMICs), including Zimbabwe.

In Zimbabwe, AEFI surveillance is an activity that is overseen as a partnership between the national medicines regulatory agency (NMRA), which is the Medicines Control Authority of Zimbabwe (MCAZ), the NIP and the Zimbabwe Expanded Programme on Immunization (ZEPI), the latter being housed within the Ministry of Health and Child Care (MoHCC) (21, 88, 94, 95). The MCAZ National Pharmacovigilance Centre (NPC) has been delegated the responsibility of overseeing AEFI surveillance since 1998 and is a full member of the WHO International Drug Monitoring Program (93, 96, 97). Zimbabwe's AEFI process flow is detailed in ***Figure 5*** below. MCAZ processes all AEFIs received from ZEPI for causality assessment done monthly or may be expedited by the national AEFI committee if deemed necessary for fatal cases or cases causing community concern or reflected in the media. As a contributing member, Zimbabwe transmits all AEFI reports into the VigiBase® Database, aggregated AEFI data for the AEFI Joint Reporting Form (JRF) and electronic AEFI (eJRF) for COVID-19 vaccines that are global indicators for vaccine safety surveillance and trends in AEFI reporting (18, 21, 93, 97). The

AEFI signal detection may use the VigiBase database disproportionality analysis, including reporting to the WHO AEFI Joint Reporting Form (JRF) for vaccines and eJRF for COVID-19 vaccines (21).

The ***Figure 5*** below show the Zimbabwe AEFI surveillance process flow from vaccination sites to ZEPI and MCAZ National PV Centre that work closely together.

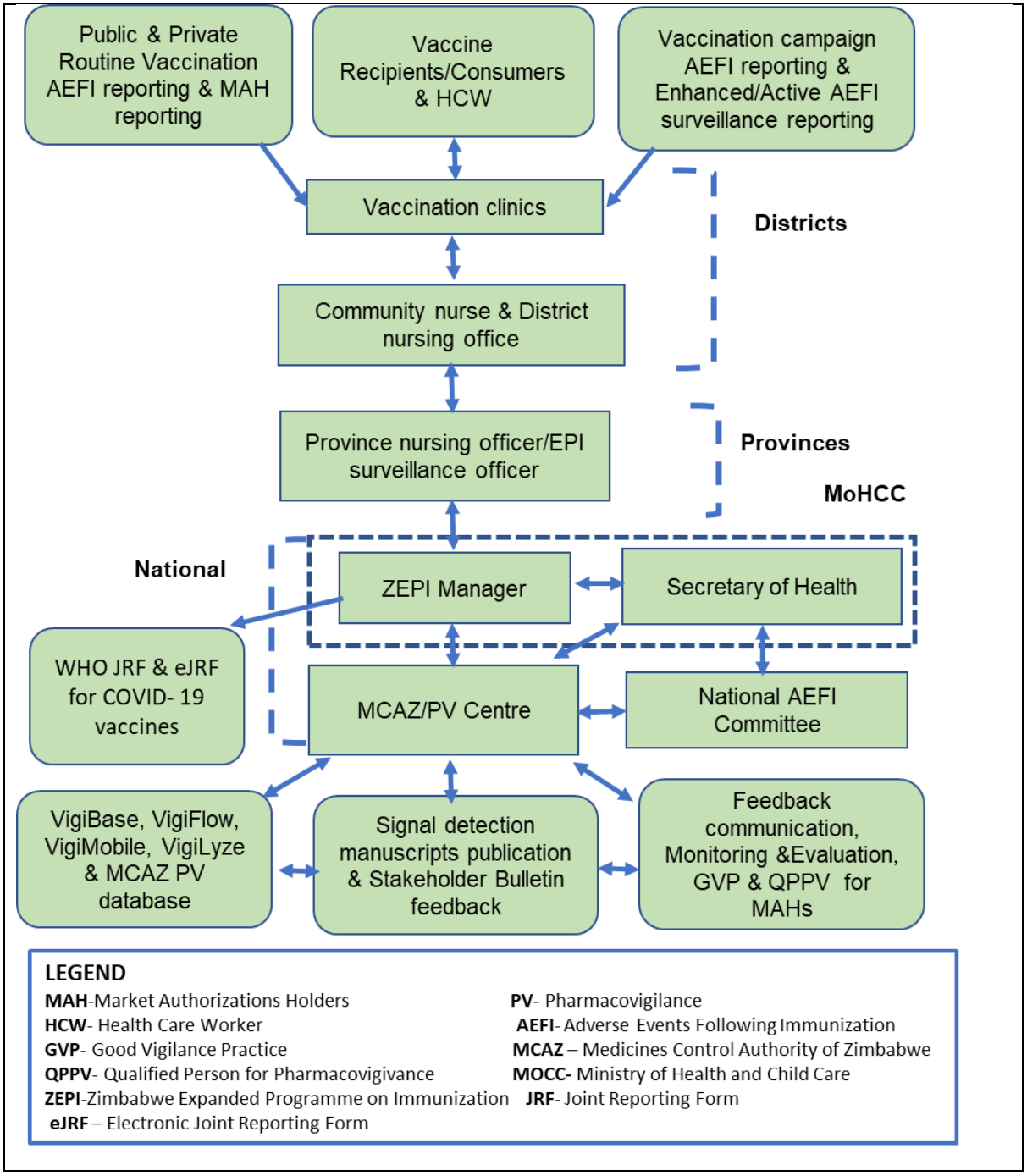


Figure 5: Zimbabwe AEFI surveillance process flow from vaccination sites to ZEPI and MCAZ National PV Centre.

The general aim of this study was to provide a descriptive review of the AEFI surveillance system and AEFI reporting trends in Zimbabwe since 1998, highlighting strengths, weakness, and opportunities for improvement. The specific aims were as follows:

a) To describe the AEFI reports received according to the vaccinees' demographic characteristics, suspected vaccine(s), and AEFIs reported in accordance with VigiBase medical dictionary for regulatory activities (MedDRA) system organ classification (SOC) and preferred terms (PTs).
b) To reflect on the trends in the national AEFI reporting rate per 100 000 surviving infants between 1998 and August 2022 for childhood vaccines and using vaccinated population statistics for adult COVID-19 vaccines.
c) To describe the causality assessment system of AEFIs and its performance in terms of AEFI cause specific classification.
d) To describe the AEFI Immunization programmatic errors/clusters identified through the spontaneous AEFIs causality assessment.
e) To assess the trend in the quality of the Zimbabwean AEFI reports as determined by the VigiGrade® completeness score in the VigiBase® database.
f) To report the geographical distribution of AEFI reporting sites.
g) To assess the performance of the AEFI system in and according to the independent GBT assessment AEFI surveillance indicators.
h) To identify opportunities to strengthen the national AEFI system in Zimbabwe based on the above analyses.

3.3 Methods

3.3.1 Vaccines administered

Approximately 300 000 to 550 000 Zimbabwean children less than 18 years are vaccinated annually with vaccine coverage rates of 80% to 95% per antigen, according to the Global Alliance for Vaccines and Immunization (GAVI) annual reports from 2012 to 2021. In addition, 6 429 117 adults received COVID-19 vaccines first doses and 4 785 620 received second doses from February 2021 to August 2022.

3.3.2 AEFI reports

AEFI reports received from these adult and paediatric vaccinee populations from 1998 to August 2022 are included in this report. I included all deduplicated AEFI reports received by the MCAZ NPC and ZEPI, verifiable by original AEFI hard copies or AEFI electronic copies reports processed and uploaded onto the inhouse ePV system database, VigiFlow®, VigiBase® and VigiLyze® databases. The AEFI reports were analysed based on their seriousness, type of antigen, type of AEFI reported, and demographic data of the vaccinees. MedDRA system organ class (SOC) and preferred terms (PTs) were used to summarise the types of AEFIs reported (28, 29). The annual AEFI reporting rates were calculated separately for childhood and COVID-19 vaccines. The AEFI reporting rate for childhood vaccines was calculated by dividing the total number of pediatric AEFI (serious and non-serious) reports received in a year by the total number of surviving infants per year and reported as per 100 000 surviving infants per year (annual United Nations Development Fund (UNDP) statistics for surviving infants per year for Zimbabwe 1998 to 2021). The denominator for the COVID-19 vaccine reporting rate was the total number of adults vaccinated with either 1 or 2 doses from February 2021 to August 2022 based on ZEPI data since each vaccination was seen as a separate opportunity for AEFI(s). Causality assessment was done by the national AEFI committee, who were trained in the WHO AEFI causality assessment method (2019) for non-serious AEFIs and serious AEFIs. The initial report and supporting case investigation forms, and postmortem results were reviewed in accordance with the WHO protocols (98-100).

3.3.3 AEFI completeness and quality

I assessed the system's ability to detect Immunization errors and clusters as identified by the AEFI national committee. The assessment of completeness and quality of the Zimbabwe AEFIs reports was determined by the VigiBase VigiGrade® completeness score (101). The maximum VigiGrade completeness score is 1 and the minimum is zero based on four AEFI completeness criteria that include patient information (sex, age, medical history, concurrent conditions); adverse event information (event description, outcome of reaction); medicine/vaccine information (vaccine generic/trade name, time to onset, indication for use); and availability of additional information (challenge, rechallenge, case narrative, AEFI case investigation, laboratory results, including postmortem reports) (101). The quality of the AEFI report determines the extent to which the report can be reliably assessed for causality, and can be incorporated into risk-benefit decision-making (101). The annual median score of the VigiGrade completeness was measured for three types of ICSRs, that is, VigiGrade vaccines AEFIs, combined vaccines and non-vaccine reports, and non-vaccine reports received by MCAZ mostly via hard copy reporting by healthcare professionals (HCPs). The geographical distribution of AEFI reports was based on the reporting site names that determined the province(s) from which these reports arose. The heat map reflected the relative frequency of AEFI reports by each province.

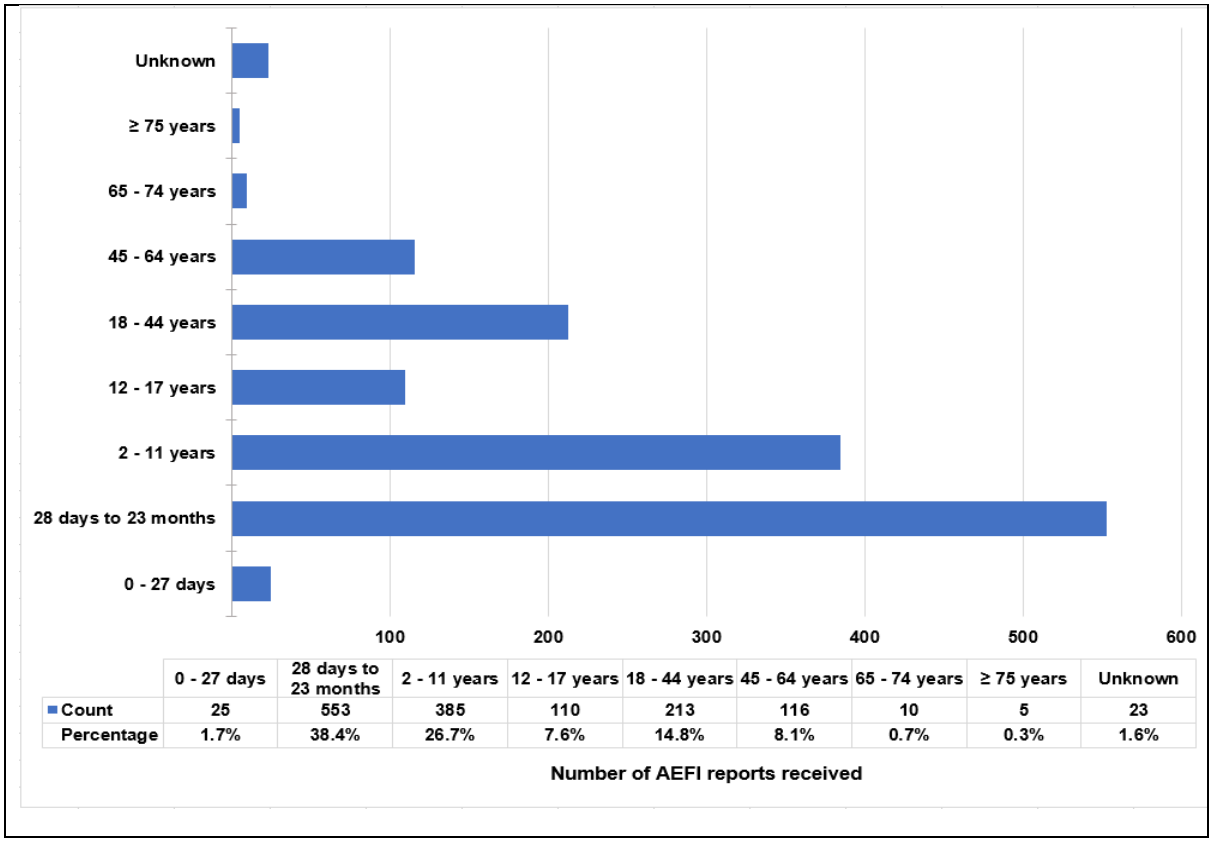
3.3.4 WHO Benchmarking tool

The WHO Global Benchmarking Tool (GBT) is an objective tool used for evaluating national regulatory systems, identifying strengths and opportunities, building regulatory capacity for medicines and vaccines, including AEFI surveillance, harmonisation, and reliance (102). I used the results of the independent WHO GBT assessment of MCAZ's National Pharmacovigilance Centre (NPC) in August 2021. Finally, we identified opportunities to strengthen the national AEFI system of Zimbabwe by examining gaps and weakness identified in the AEFI system including the WHO GBT vigilance indicators.

3.4 Results

From 1998 to August 2022, a total of 6 001 ICSRs were received by the MCAZ NPC of which 1 442 (24.0%) were AEFIs, 3 551 (59.2%) were ADRs, 546 (9.1%) Serious Adverse Events (SAEs) from clinical trials and 462 (7.7%) ADRs/SAEs from the pharmaceutical industry market authorisation holders (MAHs). No pregnancy associated AEFIs were reported. The majority of AEFI reports were submitted by health care providers primarily Immunization nurses but some reports were submitted by hospital medical and nursing practitioners.

The demographic characteristics of the vaccinees were as follows: 653 (45.4%) were males, 755 (52.4%) were females and 32 (2.2%) were of unknown sex. The majority of AEFI reports occurred after routine childhood vaccines and were reported in infants between 28 days and 23 months (38.4%) and those 2 to 11 years (26.7%) of age. Adult reports (18 to 44 years of age) accounted for 14.8% of all reports with most occurring after a COVID-19 vaccine. **Figure 6** below summarises the age groups of vaccinees who experienced AEFI.



	0 - 27 days	28 days to 23 months	2 - 11 years	12 - 17 years	18 - 44 years	45 - 64 years	65 - 74 years	≥ 75 years	Unknown
Count	25	553	385	110	213	116	10	5	23
Percentage	1.7%	38.4%	26.7%	7.6%	14.8%	8.1%	0.7%	0.3%	1.6%

Figure 6*:* Age Groups of Vaccinees Experiencing AEFIs from 1998 to 2021

As reflected in **Table 2** *below*, COVID-19 vaccines were the most frequently implicated vaccines (n = 338; 17.6% of all AEFI reports) with no concomitant or co-reported vaccines. Oral polio vaccine was the second most frequently suspected or co-reported vaccine (n = 319; 16.6% of all AEFI reports), followed by the measles vaccine (11.4%), Measles, Rubella vaccine (9.0%), Pentavalent vaccine (8.9%), pneumococcal vaccine (5.6%), Typhoid vaccine (5.3%), Rotavirus vaccine (3.2%), HPV vaccine (2.0%), and BCG vaccine (1.7%).

Table 2: AEFI reports by suspected vaccines and co-reported vaccines.

Co-reported active ingredients (WHODrug)	Suspected or Interacting vaccine	Co-reported active vaccines	Total	% Suspected/ Interacting vaccine	% Co-reported medicines or vaccines Percentage
Polio vaccine	299	20	319	16.6%	1.0%
Measles vaccine	218	1	219	11.4%	0.1%
Covid-19 vaccine	338	0	338	17.6%	0.0%
Measles: Rubella vaccine	172	1	173	9.0%	0.1%
Pentavalent vaccine	170	1	171	8.9%	0.1%
Pneumococcal vaccine	106	1	107	5.6%	0.1%
Typhoid vaccine	102	0	102	5.3%	0.0%
DTP vaccine	82	0	82	4.3%	0.0%
Rotavirus vaccine	61	1	62	3.2%	0.1%
HPV vaccine	39	0	39	2.0%	0.0%
BCG vaccine	32	1	33	1.7%	0.1%
Bacterial and viral vaccines, combined	21	1	22	1.1%	0.1%
Hepatitis B vaccine	18	0	18	0.9%	0.0%
Vaccines	17	1	18	0.9%	0.1%
Tetanus vaccine	16	0	16	0.8%	0.0%
Diphtheria vaccine	11	0	11	0.6%	0.0%
Cholera vaccine	10	0	10	0.5%	0.0%
DTP vaccine; HIB vaccine	5	0	5	0.3%	0.0%
Rabies vaccine	3	0	3	0.2%	0.0%
DTP vaccine, Hepatitis B vaccine	2	0	2	0.1%	0.0%
Rubella vaccine	1	0	1	0.1%	0.0%

Table 3 below shows that the majority of AEFIs, as classified by MedDRA SOC and PT, included general disorders and site administration conditions (26.0%) encompassing events such as local injection site reactions, pain, swelling, reduced mobility as well as persistent crying. Additionally, skin and subcutaneous tissue disorders (21.3%), gastrointestinal disorders (15.5%), and infections /infestations (13.3%) were prevalent.

Table 3: Suspected AEFIs classified as MedDRA (PTs).

AEFI Reaction (MedDRA) System Organ Classification (SOC)	Count	Percentage	AEFI reaction MEDRA Preferred Terms (PT)
SOC: General disorders and administration site conditions	289	26.0%	Injection site reactions 227(20.6%), crying 29(2.6%), Swelling 8(0.7%), Paralysis 6(0.5%), Hyperthermia 3(0.3%), Pain in extremity 2(0.2%), Mobility decreased 1(0.1%), Peripheral swelling 1(0.1%), Extensive swelling of vaccinated limb 1(0.1%)
SOC: Skin and subcutaneous tissue disorders	237	21.3%	Rash 204(18.4%), Pruritus 35(3.2%), Skin reaction 4(0.4%), Dermatitis bullous 3(0.3%), Skin discolouration 2(0.2%), Skin exfoliation 2(0.2%), Skin swelling 2(0.2%), Stevens-Johnson syndrome 1(0.1%)
SOC: Gastrointestinal disorders	172	15.5%	Vomiting 135(12.2%), Diarrhoea 110(9.9%), Abdominal pain 19(1.7%), Decreased appetite 9(0.8%), Poor feeding infant 4(0.4%), Nausea 3(0.3%), Abdominal discomfort 1(0.1%), Abdominal distension 1(0.1%), Diarrhoea haemorrhagic 1(0.1%), Gastroenteritis 1(0.1%), Intussusception 1(0.1%)
SOC: Infections and infestations	148	13.3%	Pyrexia 133(12.0%), Chills 3(0.3%), Pneumonia 2(0.2%), Measles 1(0.1%), Tonsillitis 1(0.1%), Sepsis 1(0.1%), Upper respiratory tract infection 1(0.1%), Cellulitis 1(0.1%), Toxic Shock Syndrome(TSS) 1(0.1%)
SOC: Nervous system disorders	69	6.2%	Seizure 28 (2.5%), Headache 22 (2.0%), Asthenia 14 (1.3%), Dizziness 11 (1.0%), Malaise 5 (0.5%), Fatigue 2 (0.2%), Febrile convulsion 2 (0.2%), Lethargy 2 (0.2%), Loss of consciousness 2 (0.2%), Syncope 1(0.1%)
SOC: Respiratory, thoracic and mediastinal disorders	37	3.3%	Cough 14(1.3%), Dyspnoea 10(0.9%), Respiratory distress 2(0.2%), Pulmonary embolism 1(0.1), Pulmonary oedema 1(0.1%), Breath sounds abnormal 1(0.1%), Chest discomfort 1(0.1%), Chest pain 1(0.1%), Hypoxia 1(0.1%), Aspiration 2(0.2%), Tachypnoea 1(0.1)
SOC: Eye disorders	18	1.6%	Ocular hyperaemia 5 (0.5%), Eye inflammation 4(0.4%), Conjunctivitis 3(0.3%), Eye irritation 3(0.3%), Eyelid oedema 3(0.3%), Eye discharge 1 (0.1%), Eye pain 1(0.1%), Eye swelling 1(0.1%), Vision blurred 1 (0.1%), Eyelids pruritus 1 (0.1%)
SOC: Metabolism and nutrition disorders	13	1.2%	Hyperhidrosis 1(0.1%)
SOC: Immune system disorders	11	1.0%	Anaphylactic reaction 6(0.5%), Hypersensitivity 5(0.5%), Lymphadenitis4(0.4%), Face oedema 3(0.3%), Lymphoedema 1(0.1%), Auricular swelling 1(0.1%), Oedema 1(1.0%), Periorbital oedema 1(0.1%), Swelling face 1(0.1%), Lip swelling 1(0.1%), Angioedema 1 (0.1%)
SOC: Vascular disorders	4	0.4%	Oedema peripheral 4(0.4%), Gangrene 1(0.1%), Shock 1(0.1%), Shock symptom 1(0.1%),
SOC: Blood and lymphatic system disorders	4	0.4%	Epistaxis 5(0.5%), Haemorrhage 1(0.1%)
SOC: Musculoskeletal and connective tissue disorders	3	0.3%	Dystonia 1(0.1%), Diplegia1(0.1%)
SOC: Investigations	2	0.2%	Medication error 1(0.1%)
SOC: Psychiatric disorders	1	0.1%	Sleep disorder 1(0.1%).
SOC: Injury, poisoning and procedural complications	1	0.1%	Tenderness 1(0.1%)
SOC: Hepatobiliary disorders	1	0.1%	Jaundice 1(0.1%)
SOC: Ear and labyrinth disorders	1	0.1%	Rhinitis 1(0.1%)
SOC: Cardiac disorders	1	0.1%	Cardio-respiratory arrest 1(0.1%)

Footnote: 'Injection site reactions' includes the following MedDRA PTs: injection site abscess, injection site abscess sterile, abscess, injection site reaction, injection site swelling, injection site inflammation, injection site pain, vaccination site swelling, injection site haemorrhage, injection site erythema, injection site necrosis, injection site urticaria, injection site cellulitis and application site cellulitis. 'Rash' includes the following MedDRA PTs: urticaria, rash pruritic, rash macular, rash erythematous and septic rash. 'Seizures' includes the following MedDRA PTs: febrile convulsion and seizures. 'Death' includes the following MedDRA PTs: sudden death, death neonatal, and sudden infant death syndrome.

Figure 7 below shows the reported frequency of suspected AEFI's grouped according to MedDRA PT with the most frequently reported symptoms being vomiting (12.2%), pyrexia (12%), injection site abscess (11%), diarrhoea (9.9%), rash (9.8%) and urticaria (6.3%).

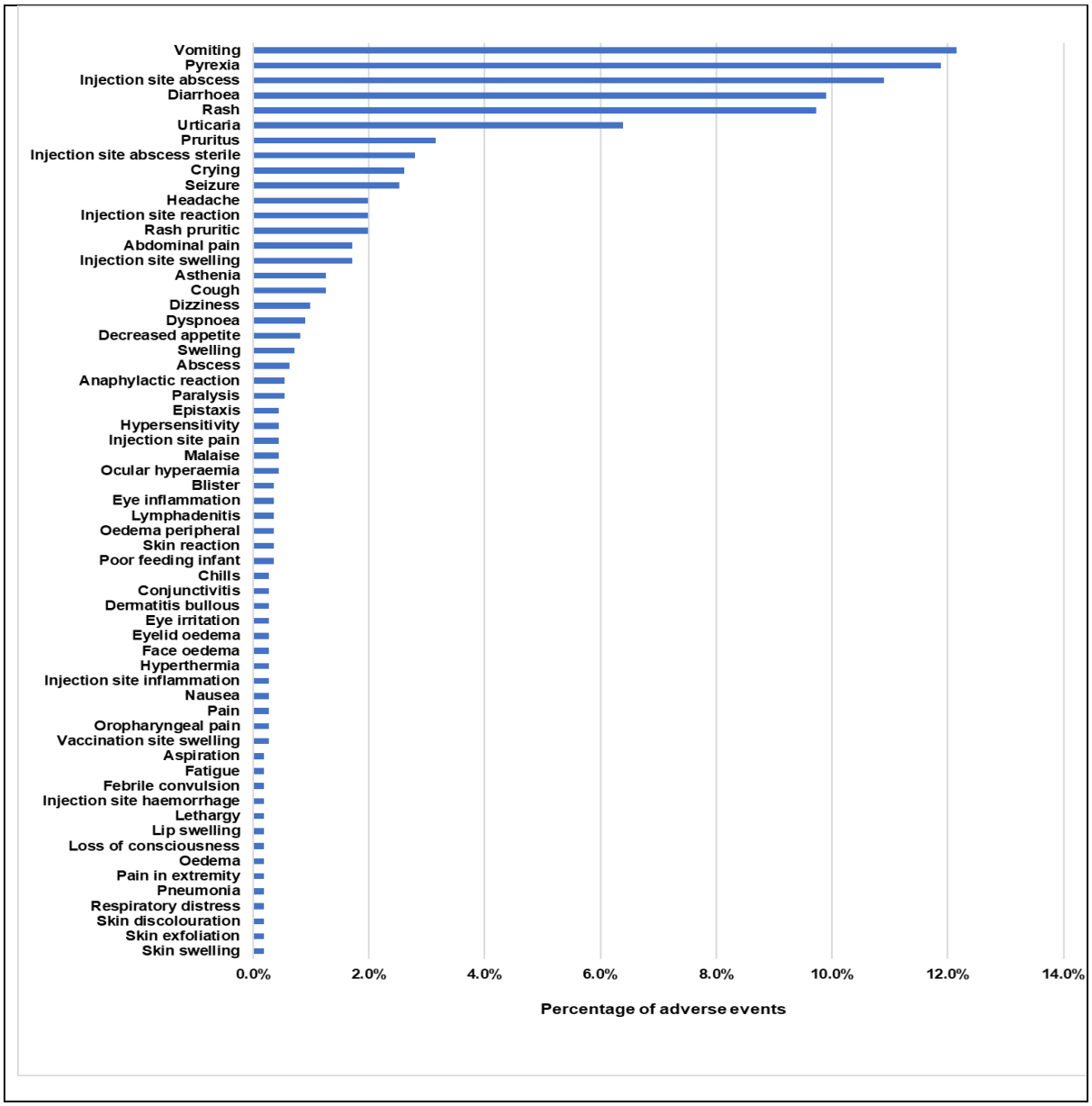


Figure 7 : Suspected AEFIs classified as MedDRA (PTs).

The annual AEFI reporting ratios for surviving infants and COVID-19 vaccines adult vaccinees as well as percentage of AEFIs that were non-serious, non-fatal serious and fatal are recorded in ***Figure 8*** below. The AEFI reporting ratios ranged from 0 to 38 per year per 100 000 surviving

infants with peak reporting rates noted in 2009 (28), 2010 (24), 2016 (24), and the highest in 2021 (37). The reporting ratio exceeded the WHO recommended minimum AEFI reporting ratio of 10 per 100 000 surviving infants for 11/23 years (47.8%) since inception of the surveillance system. The COVID-19 vaccination programme in adults yielded a total of 338 reports (23% of all AEFI reports) over a 7-month period from February 2021 to August 2022 with an AEFI reporting ratio of 44.36 per 1 million COVID-19 doses.

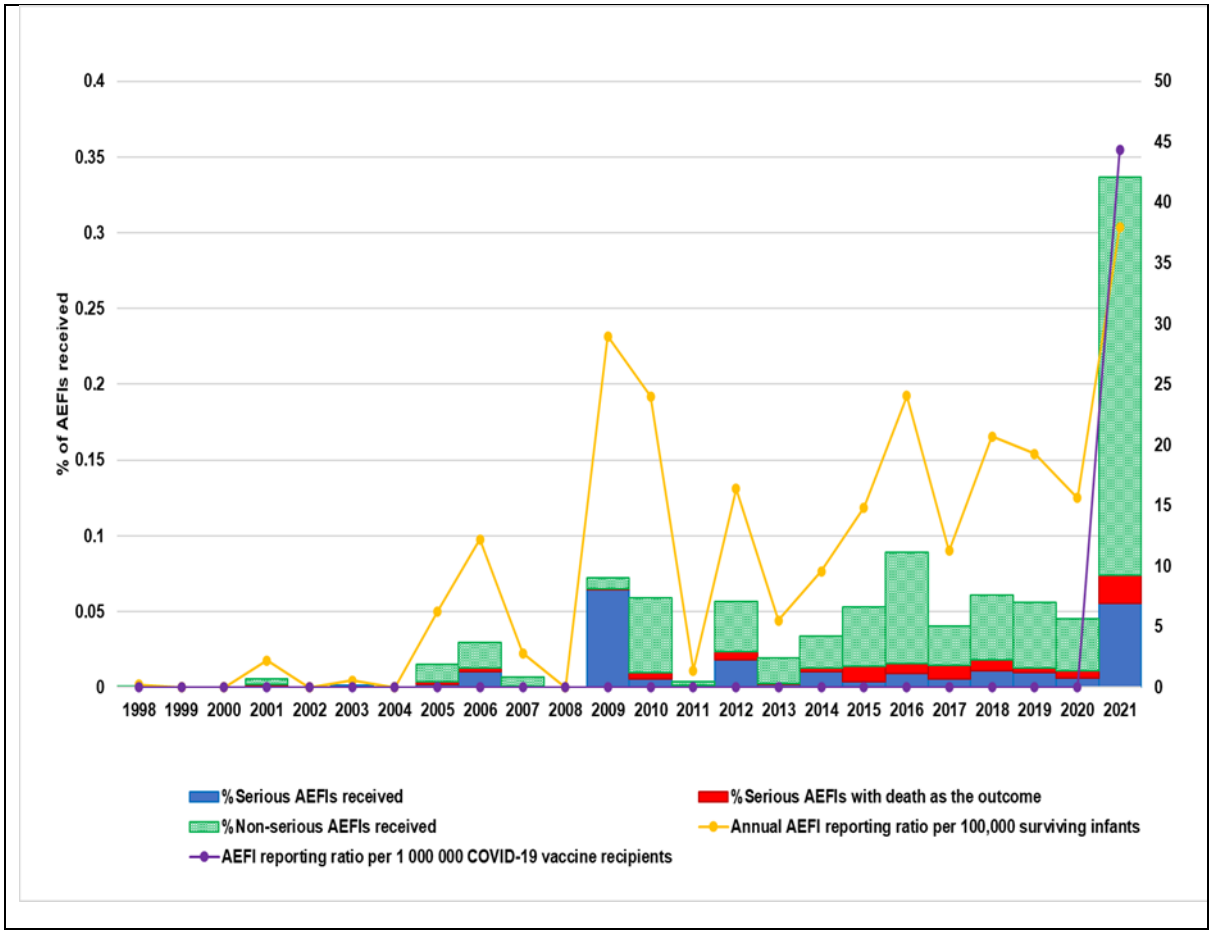


Figure 8: ***Annual AEFI reporting ratios, serious and non-serious AEFIs (1998-2021).***

In terms of seriousness, 780 (54.2%) AEFI reports were non-serious, 427 (29.7%) were non-serious medically important conditions of unknown severity, and 233 (16.1%) were classified as serious. Of the serious reports 116/233 (50%) were fatal and 95/233 (41%) caused/prolonged hospitalisation (refer to **Table 4** below).

Table 4*: Categories of seriousness of suspected AEFIs received from 1998 to August 2022 by MCAZ NPC*

Seriousness criteria	Number of AEFI reports	Percentage of total AEFI reports
Death	116	8.1%
Life threatening	19	1.3%
Caused/prolonged hospitalization	95	6.6%
Disabling/incapacitating	2	0.1%
Congenital anomaly/birth defect	1	0.1%
Other medically important condition	427	29.7%
Unknown	780	54.2%
TOTAL	1,440	100.0%

Of the 116 reports of death as an AEFI, 64/116 (55.2%) were classifiable in terms of causality assessment due to the availability of postmortem results (***Figure 9***). However, 54/116 (46.5%) were unclassifiable due to no postmortem in 6/116 (5.2%) or an inconclusive postmortem in 2/116 (1.7%) or for 44/116 (37.9%) cases, it was not known if postmortem was done or not, but no cause of death was evident. Of all the deaths reported 101/116 (87.1%) occurred after childhood vaccines and 15/116 (12.9 %) after an adult COVID-19 vaccine. All fatal AEFI cases were investigated, however, the limiting factor in establishing cause of death was the lack of postmortem results due to unavailability of postmortem facilities, and in some cases the next of kin refused to have postmortem done. For the 64 classifiable fatal AEFI cases, using the WHO AEFI Aide-Memoire of causality assessment, 7 cases were classified as A1, 2 cases were classified as A3; 5 were classified as B1; 17 cases were classified as coincidental; and using the WHO-UMC causality categories, 18 cases were classified as possible; 13 cases were classified as probable, and 2 cases were classified as unlikely.

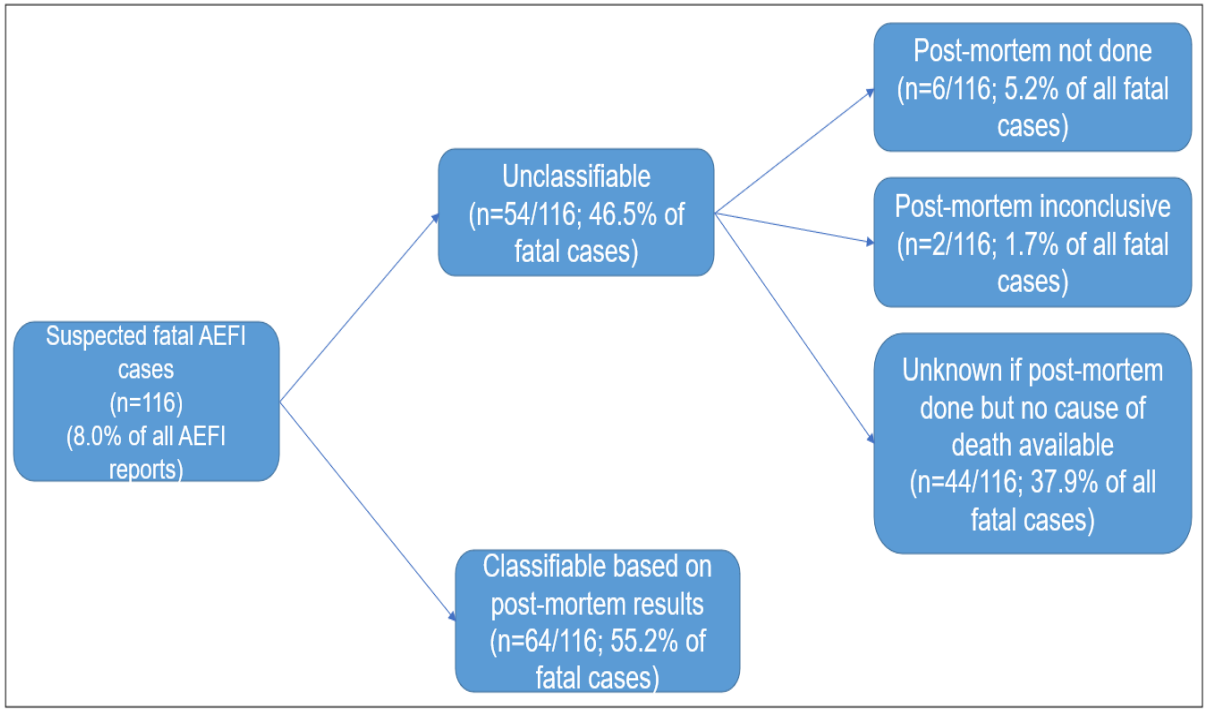
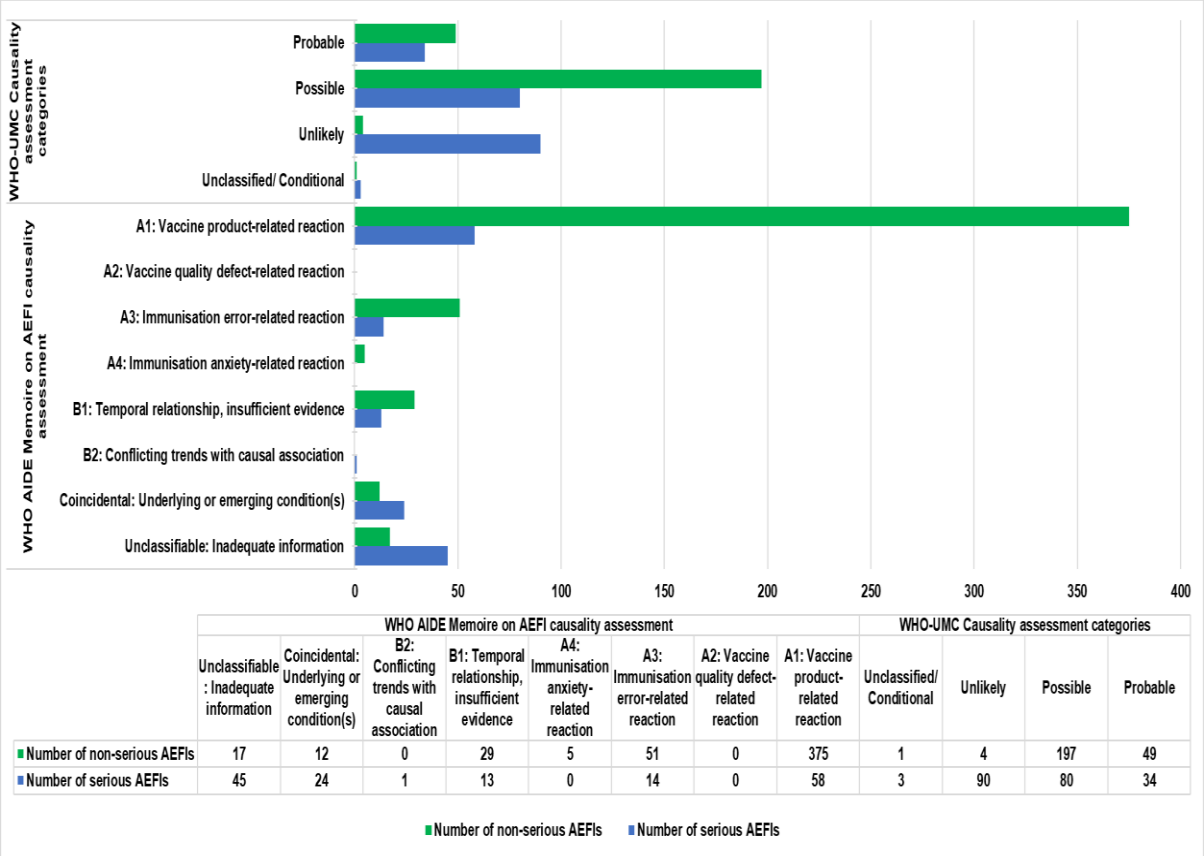


Figure 9: *Suspected fatal AEFIs, postmortems and causality* assessment.

The National causality committee assessed 1 104 AEFI reports initially using the Bradford Hill based criteria from 1998-2013, and then the WHO causality assessment methodology (with revisions) from 2014-2019 (103) (***Figure 10***). Three hundred and seventy five (34%) AEFI reports were classified as vaccine product-related reaction (A1), 51 (4.6%) as Immunization error-related reaction (A3), 29 (2.6%) as demonstrating a temporal relationship but with insufficient evidence to prove causal association (B1), 17 (1.5%) were unclassifiable due to inadequate information (D), 12 (1.1%) as coincidental underlying or emerging conditions (C), and 5 (0.5%) as Immunization anxiety-related reactions (A4). The serious AEFIs included 58 (5.3%) vaccine product-related reactions (A1), 14 (1.3%) Immunization error-related reactions (A3), 13 (1.2%) a temporal relationship insufficient evidence (B1), 45 (4.1%) unclassifiable due to inadequate information and 24 (2.2%) coincidental underlying or emerging conditions (C).

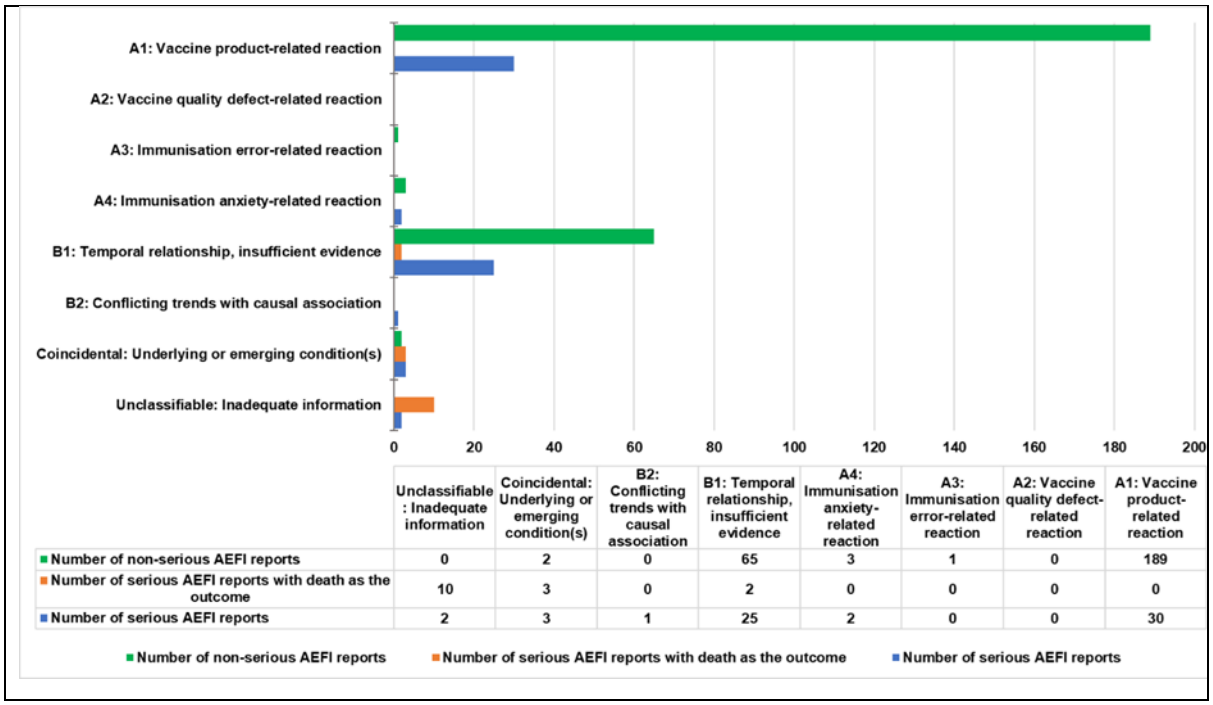


	WHO AIDE Memoire on AEFI causality assessment								WHO-UMC Causality assessment categories			
	Unclassifiable : Inadequate information	Coincidental: Underlying or emerging condition(s)	B2: Conflicting trends with causal association	B1: Temporal relationship, insufficient evidence	A4: Immunisation anxiety-related reaction	A3: Immunisation error-related reaction	A2: Vaccine quality defect-related reaction	A1: Vaccine product-related reaction	Unclassified/ Conditional	Unlikely	Possible	Probable
Number of non-serious AEFIs	17	12	0	29	5	51	0	375	1	4	197	49
Number of serious AEFIs	45	24	1	13	0	14	0	58	3	90	80	34

Figure 10: Children vaccinees AEFIs causality assessment outcomes.

A total of 338 COVID-19 AEFIs were reported to MCAZ NPC and ZEPI. Most adult COVID-19 vaccine AEFIs (260/338 - 77%) were non-serious, and many adverse events (87%) were resolved (***Figure 11*** below). Causality assessment outcomes for non-serious AEFIs were 189 (55.9%) vaccine product related reactions (A1), 65 (19.2%) temporal relationship insufficient evidence (B1), 3 (0.9%) Immunization anxiety related reactions (A4), 2 (0.6%) coincidental underlying or emerging conditions (C), and 1 (0.3%) Immunization error-related reaction (A3). Serious AEFIs causality assessment outcomes were 30 (8.9%) A1 vaccine product-related reaction, 25 (7.4%) B1 temporal relationship insufficient evidence, 3 (0.9%) coincidental underlying or emerging conditions, 2 (0.6%) A4 Immunization anxiety related reaction, and 2 (0.6%) unclassifiable due to inadequate information. Finally, outcomes for COVID-19 serious AEFIs deaths were 10 (3.0%) unclassifiable due to inadequate information, 3 (0.9%) were coincidental underlying or emerging conditions, and 2 (0.6%) were B1 temporal relationship

due to insufficient evidence. I differentiated between unclassifiable cases and cases ineligible for causality assessment.



	Unclassifiable: Inadequate information	Coincidental: Underlying or emerging condition(s)	B2: Conflicting trends with causal association	B1: Temporal relationship, insufficient evidence	A4: Immunisation anxiety-related reaction	A3: Immunisation error-related reaction	A2: Vaccine quality defect-related reaction	A1: Vaccine product-related reaction
Number of non-serious AEFI reports	0	2	0	65	3	1	0	189
Number of serious AEFI reports with death as the outcome	10	3	0	2	0	0	0	0
Number of serious AEFI reports	2	3	1	25	2	0	0	30

Figure 11: Adult COVID-19 vaccinee AEFIs causality assessment outcomes.

Immunization error-related reactions were analysed and the most common event was injection site abscess(n=38) (**Figure 12** below). Injection site abscesses were most frequently reported after the Pentavalent (DPT-HepB-Hib) vaccine (n =23) then the MR/ MMR vaccine (n = 11) and BCG vaccine (n = 9). The study focused mostly on those AEFIs where the reporter stated the antigen(s) suspected to have caused the injection site reaction. In most cases those injectable antigens were usually administered in combination, hence it was difficult to single out one antigen except of course for the pentavalent that is formulated and administered as a multi-antigen preparation.

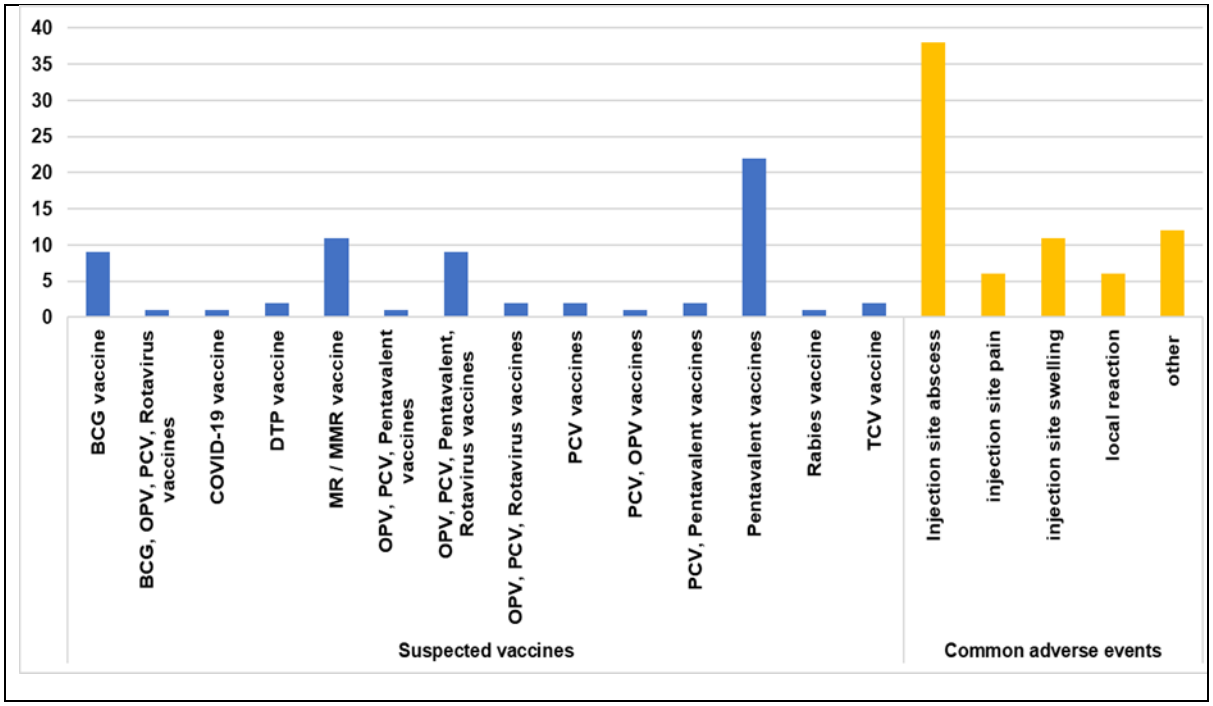


Figure 12: AEFIs Immunization error-related reactions.

AEFI reports from 1998 to August 2022 were received from all 11 provinces geographically distributed in Zimbabwe (***Figure 13*** below). Most reports (373, 25.8%) were from the capital, Harare. Only 21 (1%) of the AEFI reports were not identified by location.

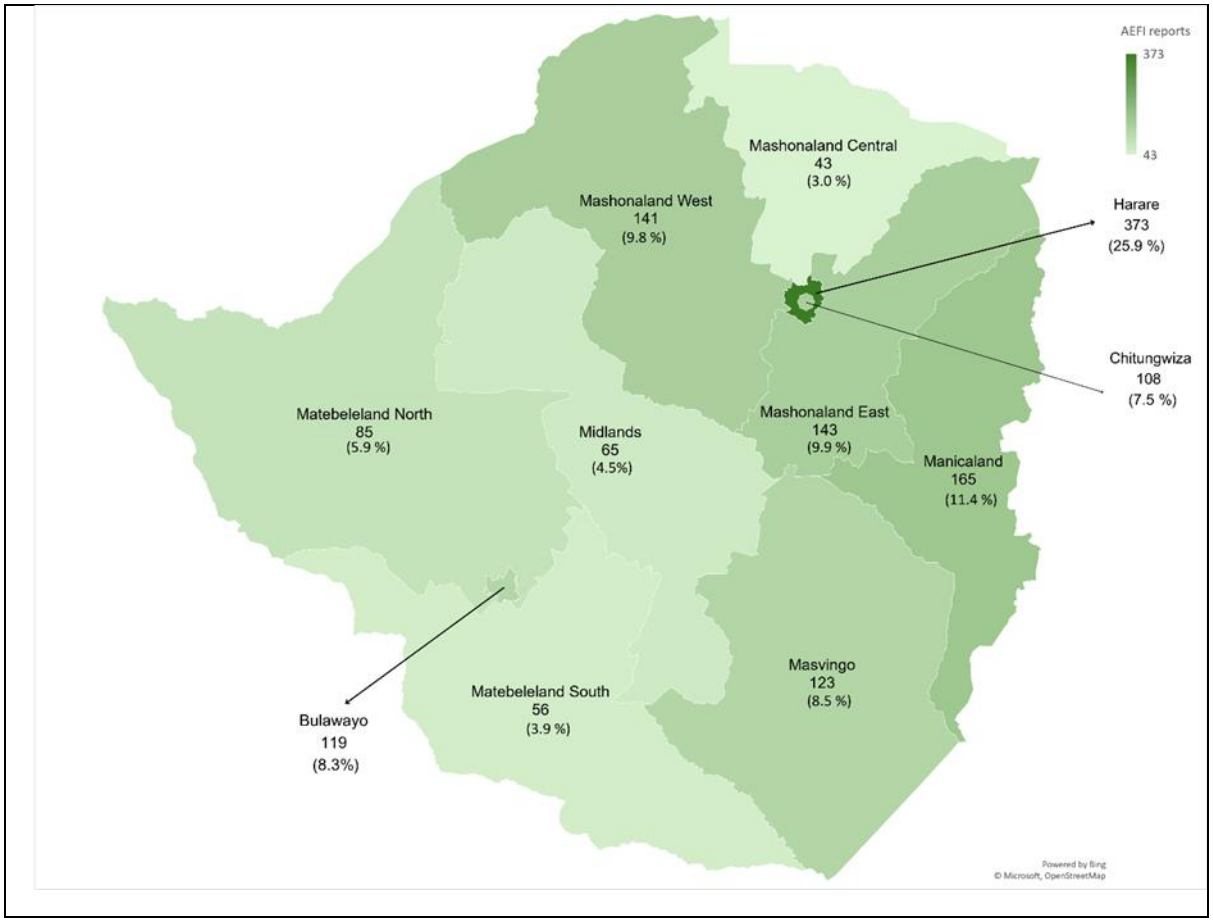


Figure 13: Geographical distribution of AEFI reports in Zimbabwe: 1998-2022.

The Zimbabwe AEFIs reports VigiGrade completeness scores ranged from 0.53 to 0.90 for combined vaccines and non-vaccines (concomitant medicines) (**Figure 14**). For vaccines alone the range was 0.22 to 0.90 (***Figure 15*** *below*) and non-vaccines medicines alone ADR/SAEs reports, 0.61 to 0.97 (**Figure 16** below). The results demonstrated that Zimbabwe AEFIs reports are of high quality, including ADR and SAEs reports. The quality for the AEFI reports, however, decreased after 2019 due to the COVID-19 pandemic. The likely cause would have been limited health staff and resources, and compounded by pressures such as infected staff, quarantines, lockdowns, and staff attrition during this time. Reports for 2022 data were limited at the time of data analysis, showing only reports for quarters 1 and 2.

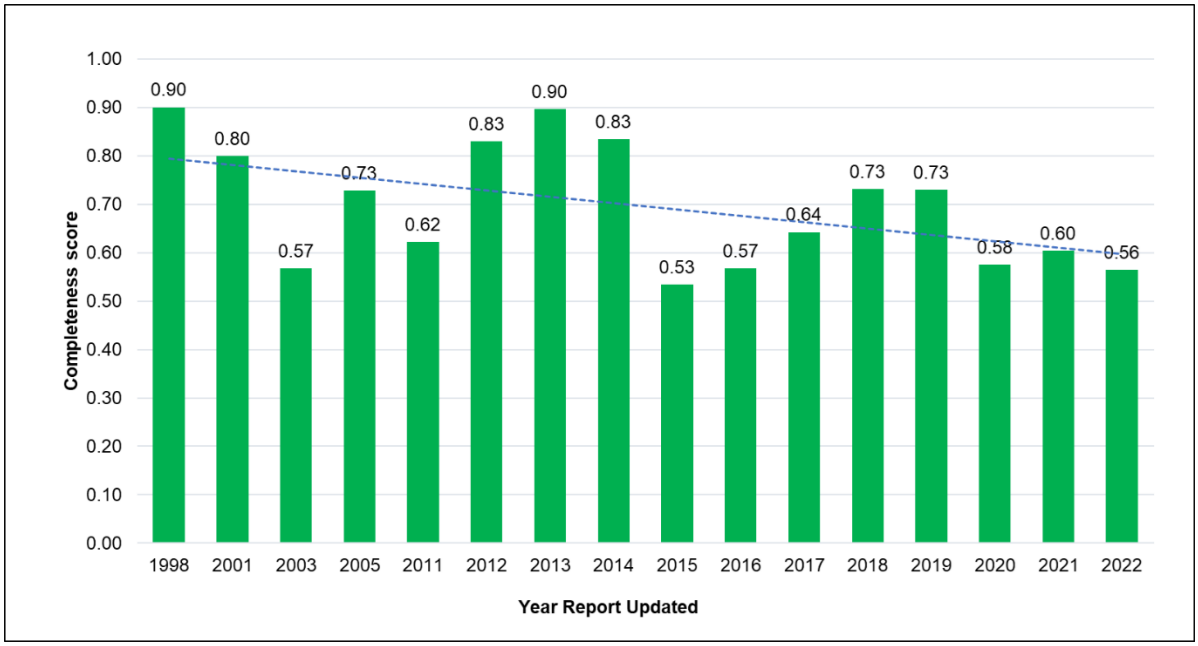


Figure 14: Zimbabwe VigiGrade combined vaccine and non-vaccine AEFIs completeness *score.*

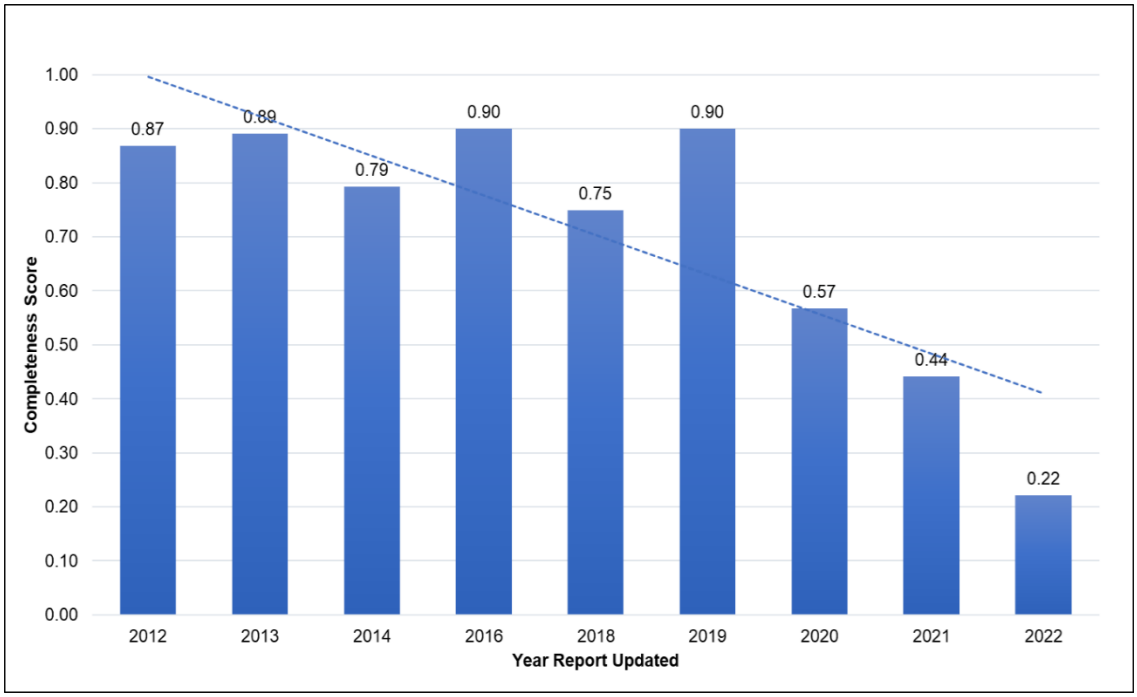


Figure 15: *Zimbabwe VigiGrade vaccines alone completeness score.*

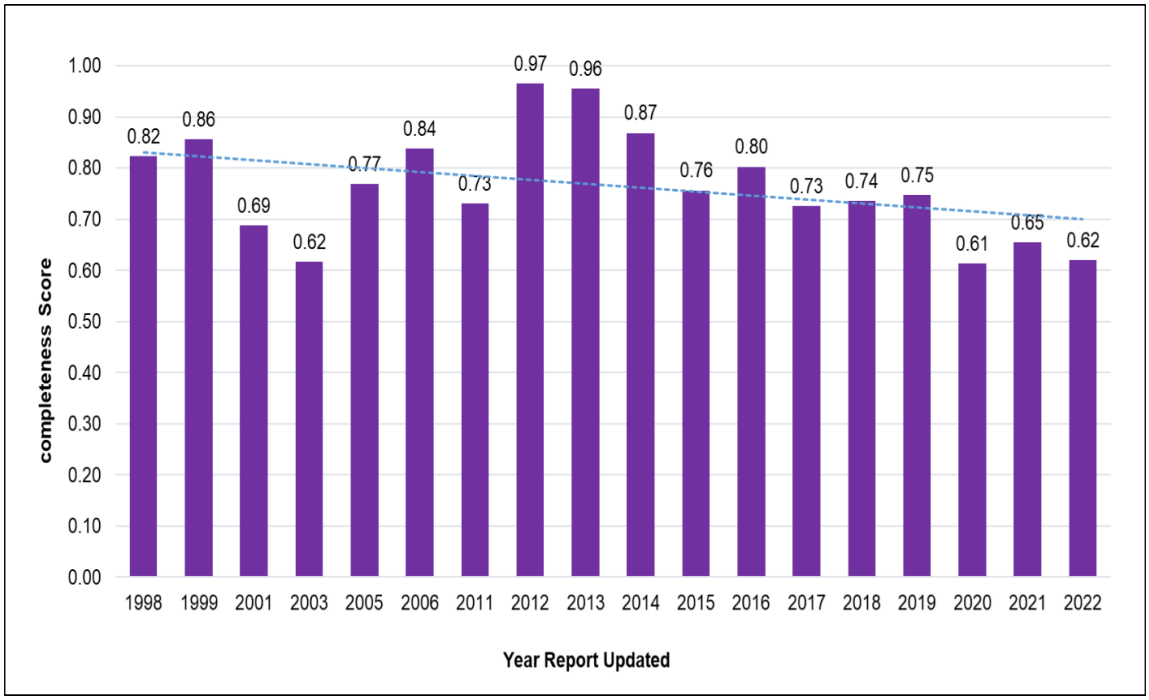


Figure 16: ***Zimbabwe VigiGrade non-vaccines ADRs/SAEs completeness score.***

The cutoff of high score is 0.5-1.0 (50-100%).MCAZ underwent an assessment by the WHO using the GBT in August 2021 which demonstrated that 85% of the vigilance indicators were complied with. These included AEFI reporting guidelines, AEFI reporting, AEFI case investigation and stakeholders' engagement through feedback letters, newsletters, trainings, circulars, and media communications. The report recommended strengthening legislation for the vigilance system, manufacturers' Good Vigilance Practice (GVP) and Qualified Persons for Pharmacovigilance (QPPV). These legal requirements were addressed by MCAZ circulars 3/2022 and 13/2022 and signed confirmation by most medicines/vaccines manufacturers having GVP/QPPV systems in 2022. The MCAZ NPC developed a system for conducting manufacturers GVP/QPPV training sessions and GVP inspections. Maturity level 3 was obtained for clinical trials regulation oversight that includes mandatory reporting of ICSRs (ADRs, AEFIs and SAEs) by clinical trials.

3.5 Discussion

In this study we have evaluated the Zimbabwean AEFI surveillance system over a 15-year period (1998-2022). The surveillance system has not always been functional but since 2009 AEFI reporting has improved markedly. Over the 10-year period from 1998 to 2008, the surveillance system met the WHO minimum AEFI reporting ratio of 10 per 100 000 surviving infants in only one of the years (2006). However, over the subsequent 12 years (from 2009 to 2021) due to joint MCAZ NPC and ZEPI enhanced AEFI surveillance training, the WHO benchmark was achieved in 9/13 (69%) of the years (18, 24, 46). More recently, the highest AEFI reporting ratio of 43.46 per million COVID-19 vaccine recipients occurred in 2021. The highest AEFI reporting ratios in 2021 were also contributed in part by the feasibility study of mHealth active participant centred (MAPC) AEFI surveillance study conducted in Zimbabwe, based on the Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) Australian study innovation (43). All 11 provinces contributed AEFI reports suggesting that the system functions throughout Zimbabwe. The VigiGrade completeness scores show a variability in range with a reduction in 2021 (based on partial data) but likely to be due to the challenging factors associated with the COVID-19 pandemic.

A limitation of the study is that we were unable to stratify rates of AEFIs for individual vaccines or vaccine combinations (other than for the COVID-19 vaccines), according to age or geographical location. The most frequently reported AEFIs were associated with those childhood vaccines administered as part of the ZEPI or as part of the COVID-19 vaccine roll-out. The characteristics of the reported AEFIs, as classified by MedDRA (SOC/PT), were those consistent with expected and common reactions (injection site reactions, fever, rash). Of all the AEFI reports 233 (16.1%) were classified as serious which is consistent with the WHO recommendations of reporting all events (serious or non-serious) that are a concern to the vaccinee, parent or healthcare provider. However, in 2009, the majority 100/111 (90%) of AEFI reports were serious and this is explained by a cluster of 100 serious AEFIs of nausea, vomiting and diarrhea which were reported during a measles vaccination campaign in the Hurungwe district, Mashonaland West province. Following an investigation by MCAZ NCP and ZEPI, the measles vaccine diluent batch samples which were evaluated did not meet sterility

specifications and the events were Immunization error-related reactions. The outcome was MCAZ engagement with the vaccine procurement agent to strengthen all vaccination clinics countrywide to prevent similar AEFI clusters.

There were 116 reports of death as an AEFI, of which 64 (55%) could be classified because the cause of death was determined after a postmortem. Although a higher postmortem rate would have been required to reduce the rate of reports that were unclassifiable, this postmortem rate is likely to be high for a LMIC. There were seven unfortune children suspected to have experienced anaphylaxis as an AEFI of which one recovered; six cases resulted in death of which one was documented as having anaphylaxis after postmortem. Five cases had no postmortem, hence cause of death was unknown and causal association to the vaccine was considered unclassifiable. There was only one reported case of suspected anaphylaxis AEFI for the COVID-19 vaccinee and the patient recovered.

Case investigation of AEFIs and causality assessment systems are well established in Zimbabwe. Of the 1 440 reported AEFIs 1 104 (77%) underwent a causality assessment review and 644 (45%) were evaluated using the WHO causality assessment tool, conducted by the experienced National AEFI Committee trained by WHO over the years. In accordance with the WHO requirements for terms of reference (TOR) of the National AEFI Committee, the Committee consists of ten specialists, such as pediatricians, neonatologists, physicians, cardiologists, immunologists, epidemiologists, toxicologists, clinical pharmacologists, and public health experts. In April 2017, WHO coordinated an India-Zimbabwe project titled, 'Inter-country study to assess the inter-rater reliability of the WHO AEFI causality assessment methodology and the usage of the new WHO AEFI causality assessment software'. It was conducted by the Zimbabwe National AEFI Committee and India New Delhi National AEFI Committee. The quantitative aspect of the study determined that there was realistic agreement between assessors in their findings using kappa coefficient analysis that measured agreement after swapping cases for causality assessment by the national committees of both countries (Personal communication). The qualitative aspect of the study results identified

areas of the causality assessment that were subsequently made more robust using more accurate and clearer language and these changes were incorporated into the revised WHO AEFI causality assessment manual.

The operation of the AEFI surveillance system is underpinned by a legislative framework as demonstrated by the GBT assessment; it met the desired international standard of a well-functioning national vigilance system at maturity level 3, in May 2023, according to the WHO GBT independent assessment report.

Although we have demonstrated that Zimbabwe currently has a robust surveillance system for the detection, reporting, analysis and causality assessment of AEFIs, there are challenges and limitations. This includes a lack of denominator data, no total number of exposed patients and no background reaction rates. Reporting biases may arise due to media attention following serious AEFIs during vaccination campaigns. In the context of a pandemic vaccine such as COVID-19, the challenge is in addressing widespread misinformation disseminated via social media that focuses on vaccine safety and perpetuates vaccine hesitancy (86, 92).

The main challenges of AEFI causality assessment were that 54/118 unfortunate death cases were unclassifiable due to lack of postmortems either by refusal by next of kin or unavailability of postmortem facilities. Some authors advocate that postmortem should be mandatory in all deaths temporarily related to vaccine administration (103). It is also recommended that such postmortems should be conducted in line with the Letulle technique for clinical and forensic assessment in case of suspected death related to vaccines (103). The Zimbabwe primary healthcare postmortem services have inadequate human resources for basic postmortem investigations.

Consideration of country background rates for rare fatal AEFIs is key to determining the benefit risk profiles. Therefore ZEPI, MCAZ NPC, Mutare hospital and Edith Opperman clinic

Harare, successfully participated in a WHO feasibility study of Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) project case definitions based on levels of diagnostic certainty for pregnancy and neonatal outcomes. The study results showed that modification of the GAIA stillbirth definition could help avoid potential misclassification in LMICs (104, 105). The study underscored the need for greater data literacy and inter-sectoral collaboration among healthcare providers, pharmacovigilance, and health program managers to promote harmonised approaches (case definitions and data elements) for capturing adverse outcomes of pregnancy (105, 106).

Access to timely and complete AEFI data is critical and this could be facilitated using eHealth and mHealth. In 2019 the MCAZ NPC launched an electronic AEFI report system with a mobile app and desktop offline system; however, the uptake was low because most public vaccination clinics did not have the capacity for online reporting except for the aggregate data sent via the District Health Information Services (DHIS2). We have investigated the use of mHealth active participant-centred surveillance using SMS as a potential AEFI surveillance tool in Zimbabwe. Given the increasing penetration of mobile technology in Zimbabwe, it is possible to conduct such feasibility studies if more resources were available (83).

Given that causality assessment was not always conclusive for suspected AEFI fatalities due to inadequate postmortem information, there is a need to strengthen AEFI case investigations and increase postmortem facilities countrywide. Postmortem rate in LMICs is low due to the inherent LMICs challenges(107). The MCAZ NPC, in line with the WHO GBMT indicators for vigilance, should also conduct signal detection of AEFIs using the global AEFI database (VigiBase) and disproportionate analysis. There should be a collaborative approach between government and academia which could include the determination of background rates of adverse events of special interest.

The limitation of this study is that it is based mostly on spontaneous retrospective AEFI case series from 1998 to 2022, not comprehensive clinical notes/case reviews. Hence, caution is required in interpretation of AEFI symptoms, signs and diagnoses temporarily associated with

vaccination but not necessarily causally associated with vaccine(s) (108). To reduce errors and duplication, only AEFI data uploaded on VigiBase, MCAZ NPC ePV system and Excel databases with verifiable hard copy AEFI reports from ZEPI and the national pharmacovigilance center were used. There is a possibility that, due to underreporting, a few AEFIs reports might be missed if they were not reported to ZEPI and/or MCAZ national pharmacovigilance centre. Timeliness of AEFI reporting, case investigation and causality assessment were not part of the study objectives since it required further monitoring and evaluation studies beyond the scope of this thesis. A small number of AEFI reports were unclassifiable because of insufficient information even after following up letters were sent requesting more information from the reporters. Although feedback is routinely provided to AEFI reporters, the nature, completeness and quality of such feedback was not included in this descriptive study.

3.6 Conclusion

This study has demonstrated a robust AEFI surveillance system in Zimbabwe with highest AEFI reporting ratio of 43.46 per million COVID-19 vaccine recipients in 2021 and meeting the WHO benchmark AEFI reporting ratio of 10 per 100 000 surviving infants in 9/13(69%) of the years. The Zimbabwe AEFI surveillance system however requires strengthening in the areas of timely AEFI detection and AEFI case investigation including completion of postmortems to enable 100% causality assessment of fatal cases, VigiPoint disproportionate analysis signal detection and risk minimisation. AEFI case investigation initiatives ought to prioritise postmortems of fatal AEFI cases as incomplete assessment of causation in 64/116 (55%) fatal cases might severely compromise public confidence in vaccines. This requires adequate postmortem facilities at vaccination clinics, and referral district and provincial hospitals. Effective AEFI detection, case management, risk minimisation and promotion of vaccinees safety require ZEPI and MCAZ to use dependable, efficient, and cost effective electronic AEFI systems and to explore the use of VigiMobile and MAPC surveillance systems. Strong collaboration between the national Immunization program and NRA national pharmacovigilance centre is critical for strengthening the national AEFI surveillance system in a resource-limited country.

Chapter 4 Efficacy and feasibility of SMS m Health for detection of AEFIs

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Chapter 4 Topic: Efficacy and feasibility of SMS m-Health for the detection of adverse events following Immunization (AEFIs) in resource-limited setting—The Zimbabwe stimulated telephone assisted rapid safety surveillance (Zm-STARSS) randomised control trial.

Chapter 4 is the monograph format of the approved publication by the DDB detailing the thesis research study on the "Efficacy and feasibility of SMS m-Health for the detection of adverse events following Immunization (AEFIs) in resource-limited setting-The Zimbabwe stimulated telephone assisted rapid safety surveillance (Zm-STARSS) randomised control trial" (109).

4.1 Abstract

Introduction: The **m**Health **a**ctive **p**articipant **c**entred (MAPC) adverse events following Immunization (AEFI) surveillance is a promising area for early AEFI detection resulting in risk minimisation. Passive (spontaneous) AEFI surveillance is the backbone for vaccine pharmacovigilance, but has inherent drawbacks such as underreporting, and requires strengthening with active surveillance methods.

Aim: The Zimbabwe **s**timulated **t**elephone **a**ssisted **r**apid **s**afety **s**urveillance (Zm-STARSS) randomised controlled trial (RCT) sought to evaluate the efficacy and feasibility of AEFI detection using a short message service (SMS) and **c**omputer **a**ssisted **t**elephone **i**nterview (CATI) approach.

Method: A multicentre Zm-STARSS RCT enrolled consented adult vaccinees or parents or guardians of children receiving vaccines, including COVID-19 vaccines, at study vaccination clinics. At enrolment study participants were randomised to either SMS-CATI group or control group. Short Message Service prompts were sent on Days 0–2 and 14 post-vaccination(s) to the SMS-CATI group to ascertain if an adverse event following Immunization (AEFI) had occurred. However, no SMSs were sent to the control group. Among the SMS-CATI group, those who responded "Yes" to SMS prompts were interviewed by research Healthcare professionals (RHCPs) who completed a CATI to determine if an AEFI/AEFI had occurred, whilst an AEFI in the control group was determined from passive AEFI reporting channels. The primary study outcome was the AEFI detection rate in the SMS-CATI group compared to the control group.

Results: A total of 4 560 participants were enrolled after signed informed consent. All were encouraged to report AEFIs and were randomised automatically on a 1:1 basis into two arms: the SMS CATI intervention group (n = 2 280) and a control passive AEFI surveillance group (n = 2 280) on Day 0. A total of 704 (31%) participants responded to the SMS prompts, with 75% (528/704) indicating "No" and 25% (176/704) reporting "Yes" to seeking medical attention or attendance post-Immunization. Sixty-nine percent (121/176) completed a CATI survey but in only 36% (44/121) was the AEFI confirmed. There were no AEFIs reported in control group participants. The detection rate of a AEFI associated with medically attendance or attention using the SMS-CATI methodology was 2% (44/2 280) on an intention to treat cohort.

Conclusion: Despite the low SMS response and CATI completion rate, I demonstrated that the Zm-STARSS SMS system improves AEFI detection by 2% (44/2280) on an intention to treat cohort, compared to passive AEFI surveillance 0% detection. I recommend that this and similar approaches are explored further using cost-effective multi-channel digital approaches for holistic pharmacovigilance to improve AEFI detection in Low Middle-Income Countries (LMICs) for all vaccines.

Key words: Zimbabwe **S**timulated **T**elephone **A**ssisted **R**apid **S**afety **S**urveillance (Zm-STARSS), **m**Health **a**ctive **p**articipant-**c**entred (MAPC) Adverse Events Following Immunization (AEFI) surveillance.

4.2 Introduction

A functional national Immunization programme is integral to enhancing public health and pandemic preparedness. A key priority for each Immunization programme should be vaccine pharmacovigilance and in particular, the surveillance of adverse events following Immunization (AEFI). Passive post-marketing AEFI surveillance is recommended globally. However, there are both inherent limitations and significant challenges in implementing this method such as underreporting and incomplete information(6, 27). In most LMICs, AEFI surveillance systems are limited due to paper-based underreporting, delayed incomplete or incorrect information and ultimately delayed AEFI case management(27, 110). Weak spontaneous AEFI surveillance systems result in low reporting, delayed AEFI detection, delayed case investigation/management, delayed causality assessment, and preventable serious AEFIs. This might result in lack of public trust in vaccines reducing vaccine uptake and ultimately, increased vaccine preventable diseases (VPDs)(85). In LMICs, the challenges that contribute to AEFI underreporting are further heightened by consumer illiteracy, poverty, inadequate overstretched primary healthcare systems and unavailability of digital technologies (85, 111).

Most LMICs in Africa have contributed the least number of adverse events to the WHO VigiBase database(93). In recent years, including the COVID-19 pandemic, some LMICs have introduced passive enhanced AEFI surveillance using mHealth reporting tools, such as the African Union Smart Safey Surveillance MedSafety App piloted in a few African countries (Bukina Faso, Ethiopia, Ghana, Nigeria, Zambia and South Africa)(112, 113). The VigiMobile app, which is linked to the WHO AEFI VigiFlow VigiBase database, was recently piloted in 2023 in Zimbabwe and few selected countries, after the conduct of the Zm-STARSS study. However, the uptake of the VigiMobile system is still under assessment.

Some studies, mostly in HICs have reported successful mHealth active AEFI surveillance systems linked to other digital tools such as web apps, eHealth and electronic (e) record linkage from 2009 to 2023. Initially focussed on influenza vaccines and other vaccines, these systems have expanded to include the monitoring of COVID19 vaccines as well(34, 83). In some LMICs, updated versions of the District Health Information Systems (DHIS) are used to collate various Ministry of Health programs performance monitoring indicators, including Immunization coverage and outcomes as well as AEFI surveillance. These systems typically involve completion of paper-based forms at the vaccinations clinics as aggregate data(114). The DHIS tools were found to have inadequate AEFI form report data of only 15 core values or less, short of the critical 25 core variables required for AEFI case investigations and causality assessment(114). Most DHIS tools are usually limited since they are not linked to any primary health system digital, eHealth and mHealth applications due to unavailability of these unaffordable advanced systems in most LMICs. Challenges were experienced with some African countries in conducting active AEFI surveillance using DHIS2 since most hospital sites did not meet the assessment criteria(115).

First, the e-Health technology, which mobile health (m-Health) is part of, is now applied globally to improve health surveillance and outcomes. A noteworthy area is the application of digital tools to improve Immunization programmes including AEFI surveillance. Secondly, the m-Health for active vaccine safety surveillance (AVSS) is eliciting growing interest because of its ability to engage consumers directly to elicit AEFI reports, which could overcome some of the limitations inherent in passive reporting by healthcare professionals (HCPs)(37, 41, 83). The **m-Health active participant-centred (MAPC) AEFI surveillance** could be defined as a data collection system that seeks to ascertain as completely as possible, the number of AEFIs in a defined population via a continuous organised process(6).

4.2.1 mHealth approaches

The m-Health approaches are showing promise as a tool to improve AEFI detection in many high-income countries (HICs). This approach directly prompts vaccinees or their caregivers to report an AEFI quickly and seek care(37, 41, 45, 83). A Canadian scoping review of MAPC AEFI surveillance suggests that mHealth could be the method for collecting self-reported subjective symptoms from vaccinees which could complement existing AEFI surveillance systems(83). The study recommends the evaluation of digital solutions to improve vaccine surveillance systems for contemporary and future public health needs(83). The performance of these m-Health approaches in LMIC settings is poorly described with only Cambodia(32) and Sierra Leone(116) reporting on their experiences for active m-Health adverse drug reactions (ADRs) but not on AEFIs. Moreover, the underperformance of the m-Health system in Aboriginal communities in Australia highlights the need to assess the feasibility and performance of such systems in culturally diverse populations with poor socioeconomic groups(62).

A comprehensive evaluation of SMS-based AEFI surveillance is required prior to diverting scarce public health resources towards widespread implementation(41). The Australian **s**timulated **t**elephone **a**ssisted **r**apid **s**afety **s**urveillance (Au-STARSS) is one of two published randomised controlled trials (RCT) which has compared the AEFI detection rate in active (SMS surveillance) and control (passive surveillance) groups. The study evaluated the feasibility and acceptability of SMS based surveillance using a two-step process with an initial SMS being the entry point for detection whilst a subsequent digital interaction elicited information to determine the nature of the event(41). The outcome of the Au-STARSS study showed a 13-fold greater AEFI detection rate in the SMS group (Pearson's χ^2test = 76.0, $p < 0.0001$) compared to the control group (passive surveillance)(41). The Zm-STARSS platform could also be explored in the future as an active pharmacovigilance tool for antiretrovirals and antituberculosis medicines, and other medicines used to manage the growing burden of non-communicable diseases among persons living with HIV in Zimbabwe(117).

4.2.2 Zm STARSS Proof of Concept

Established in 1997, the Zimbabwe national AEFI surveillance system has continued to grow, but the burden of reporting AEFIs by overwhelmed HCPs has remained a key barrier to the timely detection of serious or severe AEFIs(18, 24). Zm-STARSS RCT is a proof-of-concept study evaluating SMS based surveillance for AEFI detection in a LMIC using an adapted Au-STARSS mHealth platform. The objective was to ascertain if STARSS could be adapted, implemented, and evaluated in Zimbabwe for the detection of AEFI.

4.2.3 Aim and hypothesis.

The primary aim was to determine if Zm-STARSS was more effective in detecting an AEFI than routine passive reporting of AEFIs. The primary hypothesis was that the proportion of people in which an AEFI is detected is greater in the SMS intervention group compared to a comparison group (passive surveillance). The secondary aim was to provide a narrative description covering the challenges of establishing a Zm-STARSS platform.

4.3 Methods

Study population, sample size and inclusion criteria.

A total of 4 560 individuals presenting for vaccination at CITIMED and Chitungwiza hospitals in peri urban Chitungwiza near Harare, Zimbabwe, were eligible for enrolment from November 2020 to August 2021. Participants were eligible if they understood English (Zimbabwe's official language), were adult vaccinees, or were parents or guardians of vaccinated children under the age of 18 years, had access to a functional mobile phone and consented to being part of the study.

4.3.1 Exclusion criteria

Vaccinees who were unwell before vaccination, child vaccinees associated with multiple births (e.g., a twin child) and children with a parent/guardian ≤ 18 years were not eligible for enrolment. Multiple births e.g., twins were excluded since this inclusion was likely to confuse the parents/guardians if the individual children were randomised to different groups.

4.3.2 Consent process.

Opt-in, informed consent was sought. Participants were informed that the study was examining diverse ways of monitoring vaccine 'side-effects' and that they could receive a follow-up SMS to ascertain any adverse event requiring attention, together with an invitation to provide further details (by CATI) of their 'experience' during the post-vaccination period. Consent was obtained for receipt of SMSs, participation in a CATI interview and access to any passive AEFI reports submitted to the Zimbabwe Expanded Programme on Immunization (ZEPI) and Medicines Control Authority of Zimbabwe (MCAZ) through a database search for performance of a causality assessment by the national AEFI Committee.

4.3.3 Study design and randomisation.

All study staff received training in the Zm-STARSS protocol from qualified MCAZ national pharmacovigilance centre study researchers, which included informed consent process and compliance with good clinical practice (GCP). Training took place two to three days before conduct of the study with continuous monitoring and retraining taking place throughout the study period. All study site nurses were blinded to the randomisation. After enrolment all participants and guardians were informed on how to report an AEFI regardless of their allocated group. The study sites nurses were provided with AEFI paper-based reporting forms. Both study site nurses and national pharmacovigilance research staff verified records at both EPI, MCAZ and study sites for any SMS or paper-based reports from both CATI arm and control arm. The Zm-

STARSS software was customised to include all national ZEPI antigens including COVID-19 vaccines.

The Zm-STARSS study design included only two randomised groups (SMS and control) and excluded the web-based component which was in the Au-STARSS, because of the high cost and limited internet access to healthcare professionals (HCPs) and vaccinees. The Zm-STARSS trial was a multi-centre, single-blinded and active-controlled parallel two-grouped RCT with a repeated measures design to collect responses to SMSs sent on Days 0-2 and 14 post-Immunizations to ascertain whether the participant had experienced an AEFI, that was associated with medical admission or attention. Participants were enrolled at both CITIMED and Chitungwiza hospitals vaccination sites. Site selection was based on availability of reliable internet services to enable the platform to function. Randomisation was implemented using an algorithm residing in the study server which allowed automatic allocation in a 1:1 ratio in permuted sequence to the SMS intervention or the control group. The participant was the unit of allocation, which occurred on receipt of the vaccinee's Immunization and demographic data into the study portal. Research healthcare professionals (RHCPs) involved with the enrolment of participants and Immunization providers were blinded to the allocation.

4.3.4 SMS dispatch and response

Participant and vaccinee data extracted from a completed enrolment form were entered manually by RHCPs, via a secure web portal, and within 48 hours of vaccination. Upon receipt of the data, an information technology (IT) application located on the MCAZ server, automated the dispatch of SMSs without daily restriction (with a curfew between 8 PM and 8AM), and managed the flow of outgoing and incoming SMSs, including customised SMS replies to these responses. On receipt of the enrolment data participants were reminded via SMS that they should expect follow-up messages on Days 0-2 and 14 post-Immunizations. These time intervals were consistent with the expected temporal onset of reactions for the vaccines administered to the

participants in the study. A welcome message was sent immediately to each participant on enrolment Day 0. A survey message was sent to each participant 48 hours after their vaccination date and time. To ensure that survey messages were always sent at the correct time for each participant (48 hours after vaccination) the system prevented the enrolment of participants if their vaccination was already more than 48 hours old.

Each prompt SMS message aimed to determine if an AEFI had occurred by asking the question: "*Since vaccination has **the person who has been vaccinated** seen a medical doctor, nurse, pharmacist, healthcare worker or health traditional healer because the **child or adult vaccinated** has been unwell?" Please respond "Yes" or "No."* Those who responded "Yes" were contacted telephonically to complete an AEFI report which took the form of a CATI administered by a RHCP. The purpose of the CATI was to obtain details about the AEFI so it could be determined if this was consistent with the WHO, AEFI definition(118). The CATI interview questionnaire included most of the 25 AEFI core variables as recommended by WHO(118). The "No" SMS responders were sent an automated SMS acknowledgement. A final SMS prompt was sent on Day 14 post-vaccination. The specific wording of the SMSs is detailed in ***Table 5** below***.**

Table 5*: Details of the wording of the SMSs generated following enrolment and randomisation to the SMS-CATI intervention group.*

Vaccination day Reminder SMS **Day 0-2 (within 48 hours)**	'Welcome to the STARSS Study. Since vaccination has the person who has been vaccinated experienced an AEFI or seen a medical doctor, nurse, pharmacist healthcare worker or health traditional healer because the child or adult vaccinated has been unwell? Please respond Yes or No'.
Reminder SMS **Day 14**	'Welcome to the STARSS Study. Since vaccination has the person who has been vaccinated experienced an AEFI or seen a medical doctor, nurse, pharmacist healthcare worker or health traditional healer because the child or adult vaccinated has been unwell?' Please respond Yes or No'.
SMS response from portal to "YES" participants reply at Days 0-2 and 14	**Randomised to SMS mHealth Computer Assisted Telephone Interview (CATI) arm**
	STARSS Study: "Thank you for letting us know that you received health advice after the vaccination. We will call you in the next 24 hours to find out more".

The CATI sought to verify the following details on Days 0-2 and 14 post-vaccinations if participants responded "Yes" to the SMS prompts: 1) vaccine(s) administered and batch numbers already prefilled at enrolment on the online Zm-STARSS by the nurses and available on participant's hard

copy vaccination card; 2) type of medical attention sought; 3) adverse symptom(s); 4) other details including hospitalisation and recovery. An AEFI report was regarded as confirmed if the reported vaccination details were the same as those documented through the Zm-STARSS online recruitment portal, if medical attention/attendance following the Immunization was confirmed and one or more symptom(s) were reported. No follow-up occurred for the participants randomised to the control and the occurrence of an AEFI was determined from the ZEPI and MCAZ AEFI database/AEFI line listing.

4.3.5 Zm-STARSS-information technology (IT) platform

The Zm-STARSS IT platform was centralised, with encrypted data transmitted securely from the two study sites to a secure MCAZ server. The IT platform provided a single site for collating participant demographics, Immunization data, and SMS messages serving as a repository for all data collected from CATI reports. The platform automatically dispatched and received SMS messages. The vaccinee's Immunization details (vaccine antigen(s), brand, batch number, vaccine administration site(s), date, and time together with demographic information (vaccinee's name, date of birth (DOB), sex, address, and mobile number) were collected at enrolment. Participant reports of an AEFI automatically triggered an email alert to RHCPs. Access to the site was password protected and RHCPs had access to the global dashboard. All portals offered a real-time view of the AEFI and AEFI reports, and all data were added to a single structured query language (SQL) database stored in the study server, which allowed export of the data (CSV format) and circumvented the need for unsecure data transmission.

The Zm-STARSS surveillance system was developed with assistance from Econet Wireless Zimbabwe Ltd (Econet), (a company with 65% mobile phone market share) and in line with the Postal and Telecommunications Regulatory Authority of Zimbabwe (POTRAZ) requirements for SMS mobile phone test codes. A major challenge was that participants would have insufficient telephone credit to respond to the automatic SMS messages. This could introduce a significant bias in the perceived responsiveness of participants, and the reported/unreported symptoms.

To address this issue, Econet created a test channel pre-paid by MCAZ, where participants' SMSs were not charged, and hence successful transmission could be achieved despite insufficient telephone credit.

4.3.6 AEFI outcome measures and definitions

For the SMS-CATI group a AEFI notifier was defined as a participant who replied "Yes" to the SMS prompt on at least one of the time points (Days 0-2 or 14). A participant was deemed to not have had an AEFI if a "No" response was received at any of the time points. An AEFI was defined as completed when all four CATI verification steps had occurred. An event was classified as an AEFI if it met the WHO case definition. Zimbabwe's national AEFI expert committee trained by WHO performed the causality assessment on all reported cases according to the WHO AEFI causality assessment algorithm (2019) (13). Some participants however might experience more than one AEFI, e.g., abscess and convulsions.

The number of AEFI cases in each group (SMS vs control) formed the basis for the analysis of the primary outcome. Since multiple AEFI reports may have been completed for the same participant, the primary outcome was based on a single individual. For the control group all AEFI reports for the duration of the RCT, were matched to the vaccinee's details (name, date of birth (DOB), antigens, date of vaccination, vaccination clinic or study site and name of the reporter) to determine if a report had been received within 14 days of vaccination. Any submitted report was counted as an AEFI for the control group.

4.3.7 Secondary outcomes

Compliance with SMS was assessed by the number and percentage of participants who responded with a "Yes" or "No" response to the surveillance SMS. Fully compliant responders were defined as responders at the three points (Days 0-2 and 14), partial compliers were those responding at Days 0-2 or 14 time points and non-compliers never responded at all. AEFI completion was assessed by the number and percentage of participants, in the SMS-CATI group,

who notified an AEFI and whose report was completed and verified by the RHCPs. The time for detection of an AEFI was defined as the time (in hours) from medical attendance/attention to completion of the AEFI report for the SMS-CATI group or the time from healthcare attendance to receipt of an AEFI report by ZEPI or MCAZ for the control group.

4.3.8 Statistical analysis plan

The primary analyses were performed on the intention-to-treat (ITT) population, with participants analysed per their allocated pools. Given the low AEFI cases expected in the control group, two-tailed Fisher's exact tests (a = 0.025) were done to compare the events in the SMS group to those in the control group. Pearson's χ^2tests were carried out for the demographic characteristics, such as gender, age, sex, index of socio-economic advantage and disadvantage as well as the vaccine characteristics to determine any significant differences between the SMS and control groups, including those participants who responded "Yes" or "No" to the SMS or the non-responders to any SMS. Median and 95% confidence intervals based on the binomial distribution were used to describe the median time in hours of the various time lags from enrolment to AEFI detection.

4.4 Results

4.4.1 Eligibility, enrolment, randomisation, and intention to treat numbers.

Between November 2020 and August 2021, a total of 5 541 eligible adults and children attending the two Immunization sites were approached and screened for enrolment. A total of 4 560 who met inclusion criteria and signed the consent forms were enrolled and randomly assigned (1:1) equally to the SMS or the control groups, and 981 subjects were excluded with details documented in the consort diagram (refer to ***Figure 17*** *below*).

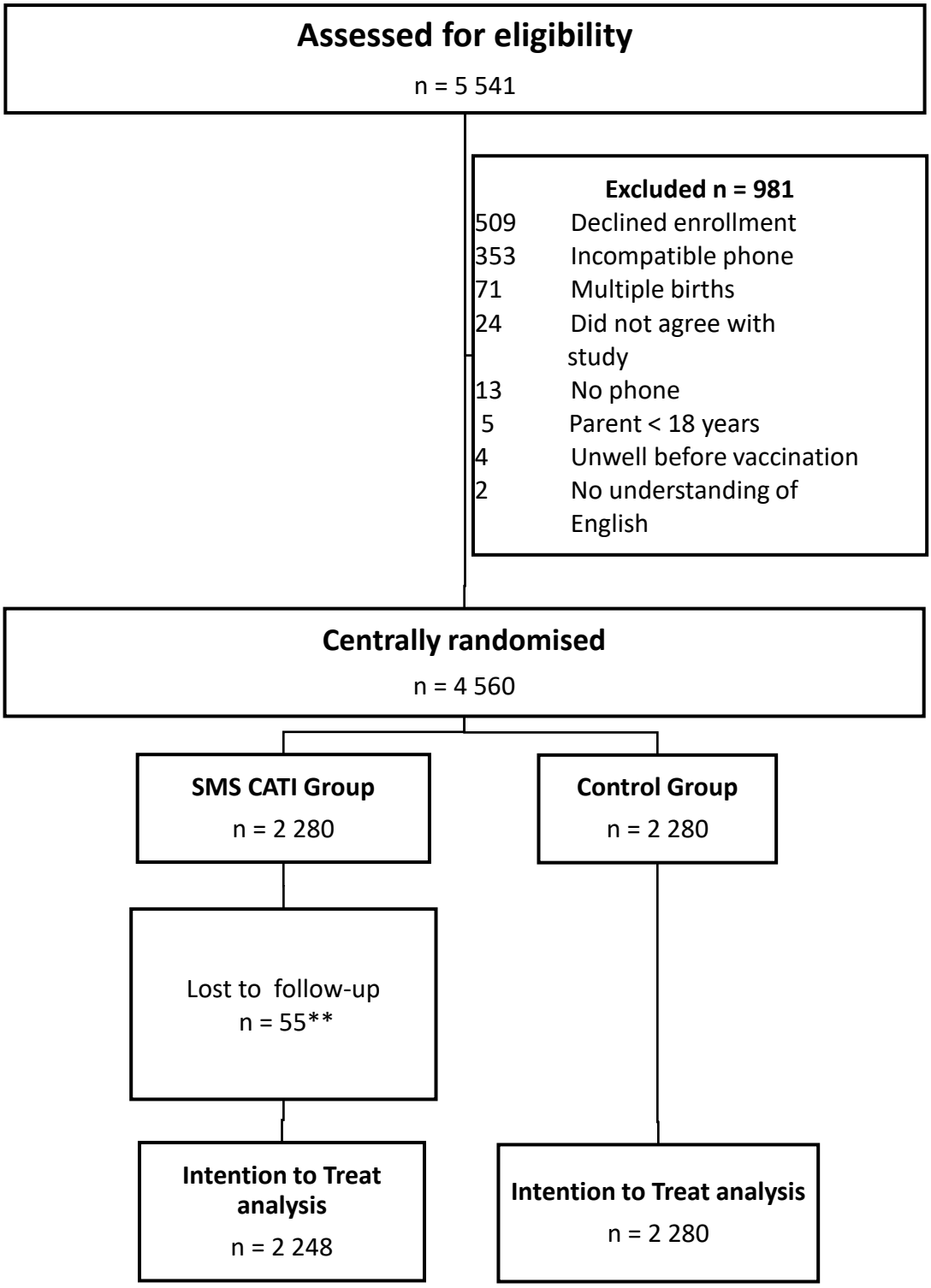

Figure 17: ***Zm-STARSS CONSORT diagram for Intention To Treat analysis.***

** **n** = 55 Participants who responded "Yes" to SMS Day 0-2 and/or 14 prompts post-vaccination were however considered lost to follow-up since they did not respond to the RHCPs phone calls (3 attempts at different times) to conduct a CATI survey to ascertain if the "Yes" meant if the person vaccinated had experienced an AEFI or not.

4.4.2 Participant demographic and vaccine characteristics.

The demographic and vaccine characteristics of enrolled participants are detailed in ***Table 5*** below**.** Whilst participants were distributed across a wide age range (birth to 65 and above years), 2 551 (55.9%) were aged *from birth* to six months (or with almost equal gender balance (females 2 157 or 47.3% and males 2 401 or 52.7%). A total of 11 different vaccines were administered to 4 560 participants, with the following combinations being administered: Bacille Calmette-Guerin BCG (37.5%) was the most frequently administered followed by Sinopharm COVID-19 vero cell vaccine (27.7%), Sinovac COVID-19 vero cell vaccine (18.2%), oral polio vaccine (OPV), Pneumococcal-Pentavalent (DTP-Hib-HepB)-Rotavirus (6.9%), Diphtheria Tetanus Pertussis (DTP), booster Measles Rubella (MR) (5.0%), Pneumococcal Rotavirus (4.3%) PCV and Sputnik V COVID-19 vaccine (0.1%). ***Table 6*** shows that the Pearson χ^2tests revealed no significant differences in any of the demographic or vaccine characteristics between the SMS intervention or control groups except for the education status p = 0.042 that is statistically significant, with marginally more individuals in the SMS-CATI group having a degree or A level or O level (Cambridge/ZIMSEC)**.**

Table 6*: *Gender, age, socio-economic status, and vaccine characteristics of participants in each trial arm.

	SMS-CATI group **n = 2280 (%)**	**Control group** **n = 2280 (%)**	**Total** **n = 4560 (%)**	**Pearson Chi-Square p value**	**Comment**
Site **Chitungwiza Central** **CITIMED**	1160 (50.9) 1120(49.1)	1161(50.9) 1119(49.1)	2321(50.9) 2239(49.1)	p = 0.976	NS
Gender of vacinees - Female - Male - Other	1053 (46.2) 1226 (53.8) 1 (0.0)	1104 (48.4) 1175 (51.6) 1 (0.0)	2157 (47.3) 2401 (52.7) 2 (0.0)	p = 0.318	NS
Age range of vacinees Median (IQR) 0 - 6 months 7 months - 5 years 6 - 14 years 15 - 39 years 40 - 64 years 65 years and above	 1280 (56.1) 212 (9.3) 1 (0.0) 301 (13.2) 374 (16.4) 112 (4.9)	 1273 (55.8) 212 (9.3) 0 (0.0) 297 (13.0) 393 (17.2) 105 (4.6)	 2551 (55.9) 424 (9.4) 1 (0.0) 580 (12.7) 758 (16.6) 246 (5.4)	p= 0.884	NS
Marital status of the vacinees or guardians				p= 0.877	NS

D - divorced	6 (0.3)	6 (0.3)	12 (0.3)		
F - de Facto	1 (0.0)	3 (0.1)	4 (0.1)		
M - married	2,009 (88.1)	2,001 (87.7)	4,010(87.9)		
S - single	201 (8.8)	202 (8.9)	403 (8.8)		
W - widowed	63 (2.8)	68 (3.0)	131 (2.9)		
Education of the vacinees or guardians				p= 0.042	SIG
D - degree	255 (11.2)	199 (8.7)	454 (10.1)		
I - diploma	201 (8.8)	218 (9.6)	419 (9.1)		
C - Certificate	7 (0.3)	8 (0.4)	15 (0.3)		
A - Cambridge/ZIMSEC A' level O level	224 (9.8)	202 (8.8)	426 (9.3)		
	1,593 (69.9)	1,653(72.5)	3,246(71.2)		
Work Status of the vacinees or guardians				p= 0.917	NS
Unemployed	715 (31.4)	715(31.4)	1,430(31.3)		
Employed	708 (31.1)	704(30.9)	1,412(31.0)		
Domestic duties	566 (24.8)	572(25.1)	1,138(25.0)		
Self employed	221 (9.7)	229(10.0)	450(10.0)		
Student	70 (3.1)	60 (2.6)	130 (2.7)		
Housing Status of vaccinees or guardians				p= 0.696	NS
Owned	1,334(58.5)	1,347(59.1)	2,681(58.8)		

Rented	946(41.5)	933(40.9)	1,879(41.2)		
Number of vaccines received.					
1	1,649 (72.3)	1,643 (72.1)	3,292 (72.2)	p > 0.05	NS
2	118 (5.2)	110 (4.8)	228 (5.0)		
3	98 (4.3)	97 (4.3)	195 (4.3)		
4	415 (18.2)	430 (18.8)	845 (18.5)		
Vaccines administered.				p > 0.05	NS
BCG	864 (37.9)	848 (37.2)	1712 (37.5)		
DTP booster-OPV-PCV-Rotavirus	1 (0.0)	1 (0.0)	2 (0.0)		
DTP booster-MR-OPV	98 (4.3)	97 (4.3)	195 (4.3)		
DTP booster-MR-OPV-Pentavalent	0 (0.0)	1 (0.0)	1 (0.0)		
MR	118 (5.2)	110 (4.9)	228 (5.0)		
Sinopharm COVID-19	151 (6.6)	164 (7.2)	315 (6.9)		
Sinovac COVID-19	1 (0.0)	3 (0.1)	4 (0.1)		
	633 (27.8)	628 (27.5)	1261 (27.7)		
	414 (18.2)	428 (18.8)	842 (18.2)		

NS – Not Significant. SIG – Significant.

4.4.3 Primary outcome determination of AEFI notification, verification, report completion and AEFI causality classification

The SMS responses, AEFI completion and final AEFI classification for the participants randomised to the SMS-CATI group are detailed in ***Figure 18*** *below*. A total of 6 840 SMSs were dispatched to the participants within Days 0-2 and 14 post-vaccinations. Overall, 69% (1 576/2 280) of participants, in the SMS intervention groups, were classified as non-compliant. Of the 704 SMS (31% of 2280) responses received, 75% (528/704) indicated that "No" AEFI had been experienced whilst 25% (176/704) responded "Yes" to experiencing an AEFI, (***Figure 18*** *below***)** at one or more of the time points (Day 0-2 and/or 14). In this group of 176 participants, 81 were partial compliers (responded to one SMS) and 95 were complete compliers (responded to all SMS). Of the 176 who were "Yes" respondents, 31% (55/176) could not be contacted for a CATI despite at least 3 separate attempts. The remaining 69% (121/176) were contacted successfully by RHCPs who completed their CATI and 36% (44/121) of these were assessed as they met the WHO AEFI criteria. The remainder, 64% (77/121) did not experience an AEFI. No passive AEFI reports were identified in the control group after verification of the ZEPI and MCAZ AEFI databases.

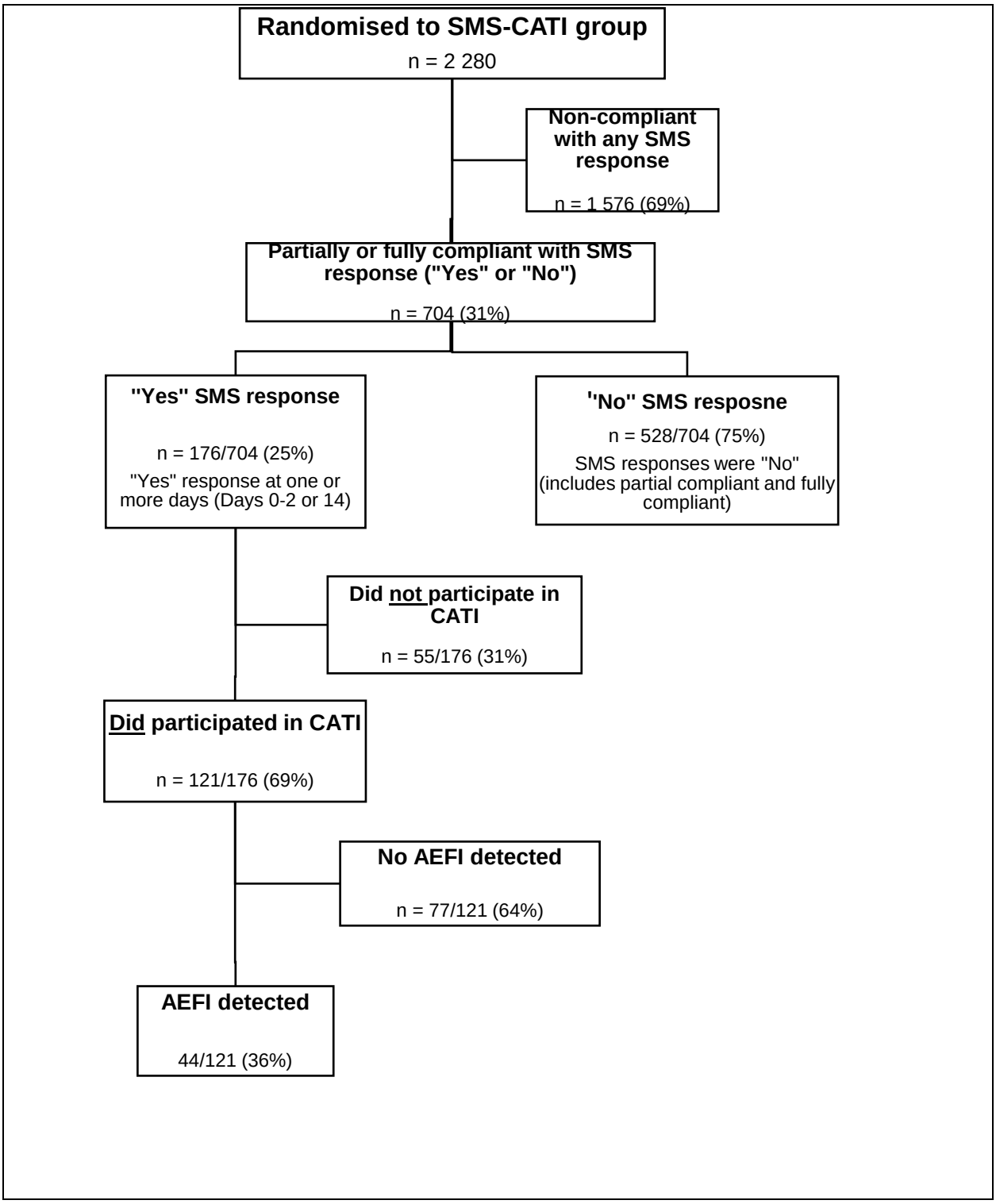

Figure 18: ***SMS-CATI group participants – SMS response, MEFI report notification, verification of AEFI report completion.***

The overall health care attended AEFI in the SMS intervention group was 2% (44/2 248) with no AEFI detection in the control group. The AEFI detection rate was 2% greater in the SMS group compared to the control group (0%); Fisher's exact test (2-sided), $p < 0.0001$) which is statistically significant. The non-response rates to SMS prompts did not differ significantly for the Day 0-2 and 14 post-vaccination SMS prompts. However, those participants who responded to the SMS ("Yes" or "No") compared with the non-responders demonstrated Pearson X^2 significant differences for education level, employment, and housing status but not for marital status, gender, and number of children, as shown in ***Table* 7** below.

Table 7: Participants randomised to SMS-CATI who responded ("Yes" or "No") compared with non-responders to day 0-2 and 14 SMS according to demographic and socioeconomic status, n=704

Participants who responded ("Yes" or "No") vs non-responders	**Pearson Chi square P Value**	**Comment**
Education Level	< 0.001	O Level and below disproportionately were non-responders.
Employment Status	< 0.001	The unemployed and those employed by organisations disproportionately were non-responders.
Housing Status	0.005	Homeowners disproportionately were non-responders.
Marital Status	0.217	Marital status did not affect response rates.
Gender	0.16	Gender did not affect response rates.
Number of Children	0.115	Number of children did not affect response rates.

4.4.4 Reported AEFIs and causality assessment classifications in the SMS group

The adverse symptom and causality assessment classifications of those in the SMS group are shown in ***Table 8*** below, including the Adverse Dictionary for Regulatory Activities (MedDRA) term reactions system organ classifications (SOCs) and preferred terms (PTs), suspected vaccines, and causality assessment outcomes done by the National AEFI Committee using the WHO AEFI causality assessment algorithm (2019) (13). Fever was the most frequently reported symptom with a rate of 3.0% (21/704), followed by rash (1.4% and diarrhoea (1.0%) and vomiting (1.0%), with all other symptoms reported with a frequency of less than 1.0%. In the ITT analysis 2% (44/2 248) of all SMS participants experienced an AEFI and reported seeking health advice from HCPs. Of these, 25% (11/44) were hospitalised including one fatality (***Table 7*** *below*). The reported rate of hospitalisation was 0.5% (11/2 280). Participants sought advice mostly from a community health advisor (57%) followed by a pharmacist (18%), GP (13.6%) or nurse (11.4%).

***Table 8*: Adverse symptoms in the individuals randomised to the SMS-CATI intervention group.**

AEFI Reaction (MedDRA) System Organ Classification (SOC)	**AEFI reaction MedDRA Preferred Terms (PT)**	**CATI group (n = 704) responded**	**Suspected Vaccine(s)**	**Causality assessment****
General disorders and administration site conditions	Abscess	2 (0.3)	BCG (1) OPV-PCV-Pentavalent-Rotavirus (1)	A1
	Injection site pain/ injected limb pain	5 (0.7)	BCG (2) OPV-PCV-Pentavalent-Rotavirus (3)	A1
	Crying	2 (0.3)	OPV-PCV-Pentavalent-Rotavirus (2)	A1
Skin and subcutaneous tissue disorders	Boils	2 (0.3)	Sinovac COVID-19 vaccine (2)	B1
	Rash	10 (1.4)	BCG (4) MR (1) OPV-PCV-Pentavalent-Rotavirus (4) Sinovac COVID-19 vaccine (1)	A1(9), C (1)

Respiratory, thoracic and mediastinal disorders	Chest pain	2 (0.3)	Sinovac COVID-19 vaccine (1) Sinopharm COVID-19 vaccine (1)	B1
	Cough	3 (0.4)	Sinovac COVID-19 vaccine (1) OPV-PCV-Pentavalent-Rotavirus (2)	B1(1) C (2)
	Difficulty breathing	3 (0.4)	OPV-PCV-Pentavalent-Rotavirus (3)	C
Gastrointestinal disorders	Diarrhea	8 (1.1)	BCG (1) MR (2) OPV-PCV-Pentavalent-Rotavirus (3) Sinovac COVID-19 vaccine (1) Sinopharm COVID-19 vaccine (1)	A1
	Loss of appetite	3 (0.4)	BCG (1) Sinovac COVID-19 vaccine (2)	A1(1), B1(2)
	Vomiting	8 (1.1)	BCG (3) MR (1) DTP booster-MR-OPV (1) OPV-PCV-Pentavalent-Rotavirus (2)	A1(6), B1(2)

			Sinopharm COVID-19 vaccine (1)	
Nervous system disorders	Fatigue	2 (0.3)	Sinovac COVID-19 vaccine (2)	A1
	Headache	3 (0.4)	Sinovac COVID-19 vaccine (3)	A1
Infections and infestations	Fever	21 (3.0)	BCG (5) DTP booster-MR-OPV (1) MR (2) OPV-PCV-Pentavalent-Rotavirus (12) Sinovac COVID-19 vaccine (1)	A1
	Other symptoms[++]	16 (2.3)		A1(3), B1(5), C(7), U(1)

[++]These AEFI reactions include chills, cramps, bloated stomach, jaundice, nasal congestion, nausea, oral thrush, pimples on head, redness, seizures, swelling and tonsils. There was one unfortunate case where a 1-day old baby girl died after BCG vaccination. She experienced fever on the same day post vaccination, she deteriorated and was subsequently hospitalised. She was treated with antibiotics and intravenous fluids, but unfortunately, she did not improve. Post-mortem was not conducted hence the cause of death could not be determined.

Causality assessment classification based on WHO AEFI Algorithm 2019 key is as follows: **A1. Vaccine product-related reaction, **B1.** Temporal relationship is consistent but there is insufficient

definitive evidence for vaccine causing event (may be new vaccine-linked event), **C.** Coincidental-Underlying or emerging conditions or conditions caused by exposure to something other than vaccine, and U. Unclassifiable fatal case due to lack of post-mortem.

4.4.5 Time to detection of an AEFI

For those SMS participants who had a confirmed AEFI the time to detection of an AEFI was determined (***Table 9*** *below*). For the time periods of vaccination to symptom onset and vaccination to AEFI notification there was a wide distribution as expected because participants received vaccines with a variable reactogenicity profile. However, the median time was 17.0 hours (95% CI: 9.0–23.0) from onset of symptoms to presenting for Adverse attention, regardless of when this occurred following Immunization. The median time from Adverse attendance to Zm-STARSS completion of an AEFI report was 525.6 hours (95% CI: 487.6–581.2).

Table 9*: *Time to AEFI detection; Surveillance time points (in hours) in participants with confirmed AEFIs for Zm-STARSS, RCT mHealth SMS CATI intervention group, n=44.

Time points	**SMS mHealth CATI Group in hours (95% CI)**	**Calculation**
Vaccination to onset of symptoms	17.0 (9.0 - 23.0)	Onset symptoms (React Time) - Vaccination Time (Enrolment Time)
Onset of symptoms to medical attendance/attention	93.1 (68.5 - 115.9)	Medical Attention (Medic time) - Onset symptoms (React Time)
Medical attendance/attention to completed AEFI report	525.6 (487.6 - 581.2)	AEFI report (Create Time)- AEFI notification (Medic Time) = Time to AEFI

		detection that is primary study end point.

4.5 Discussion

The STARSS platform was designed to address some of the deficiencies inherent in passive surveillance with low rates of AEFI detection. If an AEFI occurs and is not reported, this is due to barriers in the AEFI reporting cycle, confusion among HCPs as to what type of events constitute a reportable AEFI and unsatisfactory reporting processes(108, 119, 120). Targeting consumers is a strategy to improve AEFI reporting(37, 41, 83, 120). Our SMS surveillance prompts were designed to ascertain if a serious or severe event, which prompted medical attention or attendance, had occurred. I designed the first SMS questionnaire in collaboration with a broad range of medical and community health care advisors with the aim of capturing as many potential AEFIs as possible. Using the Zm-STARSS we demonstrated that the detection rate of medical attention and/or attended AEFI using SMS-based surveillance exceeded reporting by passive surveillance. This occurred despite high non-compliance rates to SMS responses. Contrasting the Au-STARSS with the Zm-STARSS provides some valuable insights into the implementation of SMS based surveillance in a LMIC. The SMS-based AEFI detection rates in Zm-STARSS were 2%, compared with a rate of 5.3% in the Au-STARSS-CATI group. For AEFI passive surveillance the rates were 0% and 0.3% (respectively, for Zm and Au-STARSS). Overall, hospitalisation rates, following Immunization, were 6-fold higher for Zm-STARSS (0.5%) compared with Au-STARSS rate (0.08%), which is likely to reflect co-incidental diseases, including SARS Cov-2 infection. This underlies the importance of performing causality assessment for serious AEFI reports, using the WHO methodology (13) to differentiate adverse vaccine reactions from co-incidental events, which are likely to have occurred with greater frequency in Zm-STARSS. Collectively these trials have demonstrated the utility of the STARSS platform in both HIC and LMIC settings.

The SMS non-compliance rate in Zm-STARSS was 69% compared with 9.7 % in the Au-STARSS, although the latter had an additional time point for a solicited response (Day 7). The rates of SMS

non-compliance (response) have varied between different SMS AEFI surveillance studies and a comparison has limitations because of the variability in the timing, number and content of the SMSs, different populations, cultures, mHealth services cost in LMICs, and study settings(41). In general, studies with opt-in consent show non-compliance rates which vary between 10% and 30% (41, 68, 121).

There are several likely reasons for the higher non-compliance rates in Zm-STARSS. First, it was noted that a low education level and unemployment were associated with a higher rate of non-response. Both factors need further interrogation. Second, the study was conducted during the peak of the COVID-19 pandemic presenting inherent challenges in its implementation. Some HCPs and community members succumbed to COVID-19 while some of the RHCPs tested COVID-19 positive, requiring quarantine and prolonged absence from work from time to time. Furthermore, access to phone credit in a LMIC setting is likely to be a significant barrier to SMS responses.

We conclude that SMS in LMICs could be ineffective where mobile phone plan pricing structures often encourage data-only plans (without an allocated phone number) and where phones are often used with Wi-Fi communications only. Future studies should investigate the use of online/digital messaging services such as WhatsApp, Viber, Meta messenger and Sasai. The preferred platforms would obviously depend on local popularity, and support for multiple pathways may be required for best coverage. The IT platform could connect to the API gateways of these services and send instant messages through their networks instead of the telephone network.

These options are likely to introduce their own issues around privacy and confidentiality in capturing and recording recipient health information and around adverse treatment of messages

by spam filters. However, digital services do not rely on a formal mobile number, they rather offer the promise of broader access to the local population than SMS and circumvent issues around transmission of replies being prevented due to lack of credit on the participant phone. In LMICs, SMS platforms on cheaper mobile phones are more accessible than online/digital messaging. If a user is offline, there is no communication. Furthermore, the user requires a smartphone/tablet/computer to go online/digital, which is more expensive than a flip phone. I may therefore conclude that using online/digital messaging, in addition to SMS could be more effective in LMICs if resources permitted.

In the Zm-STARSS, 69% of the "Yes" respondents completed a CATI survey compared with 83% in the Au-STARSS-CATI group. As noted above this is likely a reflection of the context of the Zm-STARSS during the COVID-19 pandemic and the limitations of availability of telephone credit and connectivity in a LMIC. Of the 64% (77/121) SMS "Yes" respondents who did not actually experience an AEFI, it might be due to cultural reasons as most Shona speaking people who made up most of the study participants usually interpret "Yes" to imply they are alright or in good health. Similarly, due to cultural factors, Shona people do not always reply to wedding/birthday invitations, funerals, etc., hence the high non-response rates to the post-vaccination SMS prompts.

The median time of about 17.0 hours (CI 95%: 9.0–23.0) from onset of symptoms to presenting for medical attention, regardless of when this occurred following Immunization, was similar for Zm-STARSS and Au-STARSS. However, the median time from medical attendance to completion of an AEFI report in Zm-STARSS [525.6 hours (CI 95%: (487.6–581.2)] was longer than in Au-STARSS [74.8 hours (CI 95%: (54.3–96.1)], for the CATI arm. This is likely to reflect the difficulties facing RHCPs in implementing the Zm-STARSS trial particularly during the COVID-19 pandemic. The MAPC web-based reporting (WBR) has the potential advantage of a shortened time to AEFI detection as demonstrated in the Au-STARSS. However, this is currently difficult in a LMIC

because of limited internet connectivity and expensive online/digital tools. Further studies are required to explore the use of appropriate and timely communication methods to ascertain the barriers to obtaining information about healthcare events following Immunization for vaccinees or their guardians.

The Zm-STARSS study has demonstrated the utility of an SMS-based surveillance platform to enhance AEFI reporting, like the findings observed in Au-STARSS (4). This has been demonstrated despite higher non-compliance and non-CATI completion rates in a LMIC setting. The researchers were so far not aware of any publications evaluating MAPC AEFI surveillance in Africa. The relative costs and benefits of implementing active SMS-based AEFI surveillance alongside passive surveillance remains to be determined. These should be assessed using evidence-based cost-effective holistic approaches and consider integration with other existing or future m-Health, e-Health and digital initiatives in resource limited settings. The Zm-STARSS system may also be considered for use by HCPs and any other HCPs digital AEFI reporting pathways such as VigiMobile when these system(s) become available in Zimbabwe. Modification of the Zm-STARSS SMS platform to enable HCPs to report AEFIs using SMS is possible in the future.

4.6 Conclusion

Short Message Service-based AEFI surveillance can improve AEFI detection in an LMIC setting by 2% (44/2280) on an intention to treat cohort, compared to passive AEFI surveillance 0% detection. Short Message Service-based AEFI surveillance should therefore be considered as an approach to augment passive surveillance in these settings for both COVID-19 vaccines and childhood vaccines although the challenges of using SMS mentioned in the discussion ought to be addressed. The findings of Zm-STARSS should inform the wider use of SMS-based AEFI surveillance which is particularly relevant at this time given the need to establish robust pharmacovigilance systems to monitor existing and novel pandemic vaccines. The utility of SMS-based surveillance in AEFI signal detection is another useful risk minimisation factor amongst

other considerations for evidence-based integration with other e-Health, digital health, and m-Health systems in resource-limited settings.

Limitations, confounding factors and/or bias.

The resource and technology constraints inherent in Zm-STARSS resulted in a modified study design featuring only three SMS prompts without a web-based review component, unlike Au-STARSS. The use of a Zm-STARSS test code meant that some participants could not be enrolled if they only subscribed to the other two mobile phone operators. I am uncertain if the participants who responded "Yes" to Days 0-2 and 14 SMS prompts but did not respond to CATI surveys by the RHCPs could have sought medical attention. Confounding factors and bias were minimised by the RCT study design. Additionally, further studies are required to investigate the reasons for the high SMS non-response rates and to identify other factors that may predict response rates in LMIC settings. The study sites included the largest vaccination clinics in a peri-urban setting in Chitungwiza, hence the results might not be representative of a rural population. An additional limitation is that those with cell-phone access are not representative of the whole vaccinated population. As explained in the discussion, all possible efforts were made to encourage reporting of AEFIs by all participants and guardians in both CATI arm and the control passive AEFI surveillance group, with verification conducted by EPI and MCAZ research staff. The absence of AEFI reporting in the control arm is likely to be a limitation of the passive AEFI surveillance system itself rather than limitation of the study design.

Declarations

Ethics approval and consent to participate: The Zm-STARSS (II) RCT (ACTRN12614001046695) obtained ethical approval from the Medical Research Council of Zimbabwe (MRCZ) under reference MRCZ/A/2268. Ethical approvals were also obtained from the Director of Health Services City of Chitungwiza Municipality Department and the University of Cape Town (UCT)

Human Research Ethics Committee (HREC 184/2020) for the Zm-STARSS study. The data were published in deidentified anonymised format.

Consent for publication. The authors obtained consent for publication of the manuscript from the MCAZ National Pharmacovigilance Centre, the custodian of the safety data since this is a work-related study.

Competing of interest: The authors declare no conflict of interest nor potential competing interest.

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Author Contributions: PPMN designed the study and wrote the main manuscript as the lead author. PPMN, LC, RM, TN, and ENZ conducted the study. MSG and SC provided Zm-STARSS Technical IT support, and copy rights based on AU-STARSS Australia, University of Adelaide innovation. MSG, SC, and UM supervised the study, data cleaning and reviewed the manuscript. PPMN analysed data and performed major analysis including tables and figures. All authors read and approved the final manuscript. All co-authors signed the letter of support that the research study design, implementation, data analysis and publication were mainly done by the PhD student PPMN and agreed to submission of the work for her PhD examination.

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Chapter 5 Consumer and Healthcare profession (HCP) Experience of Zm-STARSS MAPC AEFI surveillance

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Chapter.5 Topic: Consumer and Healthcare profession (HCP) Experience of 'Zm-STARSS mHealth Active Participant Centred (MAPC) Adverse Events Following Immunization (AEFI) Surveillance' Sub Study Nested in the Zimbabwe Stimulated Telephone Assisted Rapid Safety Surveillance (Zm-STARSS) Randomised Control Trial.

Chapter 5 of the thesis study investigated the experience, facilitators and barriers or challenges faced by consumers and HCPs in implementing the Zm-STARSS mHealth active participant-centred (MAPC) AEFI surveillance.

5.1 Abstract

Introduction: Active vaccine safety surveillance is critical for early adverse events following Immunization (AEFIs) detection, promotion of patient safety and vaccines acceptance. Although there is rapid penetration of mobile phones and mHealth technology in low middle-income countries (LMICs), few studies have explored the use of mHealth for active AEFI surveillance, including experiences of both vaccinees and healthcare professionals (HCPs). This study investigated the experience of mHealth in the 'detection of AEFIs nested in the 'Zimbabwe Stimulated Telephone Assisted Rapid Safety Surveillance (Zm-STARSS) randomised control trial (RCT)' at two peri-urban vaccination clinics in Chitungwiza from November 2020 to August 2021.

Aim: This study investigated the experience, facilitators, and barriers or challenges faced by consumers and HCPs during the implementation of the 'Zm-STARSS mHealth active participant-centred (MAPC) AEFI surveillance'.

Methods: I conducted pre- and post-vaccination surveys to gauge consumers' attitudes towards the Zm-STARSS AEFI surveillance system to investigate any challenges and assess its suitability for safety monitoring of vaccines, including both COVID-19 and routine paediatric vaccines. Additionally, I sought to determine whether written informed consent should be required to contact consumers via their mobile telephones to monitor vaccine safety. Pre- and post-nested surveys were conducted within the Zm-STARSS RCT to assess HCPs' knowledge, attitudes, and practices (KAP) related to AEFI surveillance. These surveys aimed to identify barriers and facilitators of Zm-STARSS AEFI surveillance.

Results: The majority (71%, n = 96) of the consumers who responded to the experience survey agreed to Zm-STARSS AEFI surveillance post-vaccination for 'COVID-19 vaccines including routine childhood vaccines. The majority (96%, n = 31) of the HCPs who responded recommended the use of Zm-STARSS AEFI surveillance. Over 50% of HCPs believed that lack of feedback after AEFI investigations, and concerns about negative consequences were barriers to AEFI reporting. Mobile phone data and internet costs were identified as barriers/deterrents by HCPs.

Conclusion: The study provided important evidence for the feasibility of implementing the Zm-STARSS MAPC AEFI surveillance. Consideration of cost-effective technologies incorporating social media platforms for monitoring safety of medicines and vaccines in a LMIC will be critical.

Key words: 'Zimbabwe **S**timulated **T**elephone **A**ssisted **R**apid **S**afety **S**urveillance (Zm-STARSS-RCT)', short message services (SMS), 'mHealth **a**ctive **p**articipant-**c**entred (MAPC) adverse events following Immunization (AEFI) surveillance'.

5.2 Introduction and background

Vaccines are usually administered to healthy people to prevent diseases, saving millions of lives globally (14, 122). Due to the inherent biopharmaceutical properties of the vaccines, interactions with comorbid conditions, vaccinee susceptibility to hypersensitivity reactions, adverse events following Immunizations (AEFIs) may occasionally occur (14, 122). Spontaneous (passive) AEFI surveillance, while it is the backbone of vaccine safety surveillance, is compromised by delayed/under reporting, reporting biases and incomplete or poor-quality reporting (27). Strengthening AEFI surveillance is recommended using other options of active AEFI surveillance such as digital or mHealth active participant centred (MAPC) AEFI surveillance (37, 83, 95). Studies on consumer or healthcare professionals (HCPs) experience of mHealth AEFI surveillance system have been conducted in high income countries (HICs) and are lacking in low middle income countries (LMICs) (56, 83, 121, 123).

5.2.1 MAPC AEFI surveillance scoping review

Globally, studies on mHealth approaches have primarily been conducted in HICs settings where technology availability, literacy, and access to stable internet connections are high, and the HCPs to patient ratios are higher than in LMICs. A scoping review of MAPC AEFI surveillance using digital approaches included 30 published studies with the majority from Australia (n = 17), [SmartVax (n = 8), Vaxtracker (AusVaxSafety (n = 7), Australia STARSS (n = 2)]; Canada (n = 6), [CANVAS Network], a few from the USA and European Union and Asia (83, 121, 123). Moreover, the actual cost of SMS for consumers (vaccinees and guardians) and HCPs, as well as the overall implementation expenses of the mHealth system on governmental agencies or mobile companies, in HICs compared to LIMCs are rarely published (47). The human, financial and technological resources required to implement an mHealth programme differ in each country depending on available resources, mobile communication regulations, the socioeconomic and cultural profile of consumers, and general feasibility of implementing such a system.

According to a WHO (2023) report, Zimbabwe is a LMIC with 0.14 physicians and 1.85 “midwives/nurses per 1000 capita”, i.e., well “below the Sustainable Development Goals (SDGs) index threshold of 4.45 midwives, nurses, and doctors per 1000” (124). Zimbabwe’s primary healthcare services are therefore mostly nurse-driven and this is reflected in the reporter profile in pharmacovigilance reports of the ‘individual case safety reports (ICSRs) submitted to the WHO global’ database (VigiBase); 72% are reported by nurses and 21% by physicians (124). The primary objectives of the Zm-STARSS RCT study were to compare AEFI detection rates between repeated SMS texts on Days 0-2 and 14 post-vaccination, and passive reporting. The findings of this RCT are published elsewhere (109). Understanding the experiences of consumers and HCPs as well as the facilitators and barriers to AEFI reporting, is essential if Zm-STARSS MAPC AEFI surveillance is to be widely implemented in a particular setting (42, 62, 121, 125).

5.2.2 Objectives

The primary objective of the study was to explore the experiences of both consumers and study sites vaccination clinics HCPs regarding the use of mHealth for the detection of AEFIs with the ‘study nested within the Zimbabwe Stimulated Telephone Assisted Rapid Safety Surveillance (Zm-STARSS) randomised control trial (RCT)’.

The s**econdary objectives** of the study were to:

i) identify facilitators and barriers to effective implementation of the mHealth system in a LMIC viz., Zimbabwe.

ii) describe the practical challenges encountered in the implementation of the mHealth system in Zimbabwe, including factors such as skills, attitudes and knowledge related to AEFI surveillance.

iii) describe participants’ sociodemographic predictors of SMS response rates.

5.3 Methods

This study was nested within the Zm-STARSS AEFI surveillance RCT. The Zm-STARSS was conducted in Zimbabwe during the peak of the COVID-19 pandemic. A description of the primary trial methodology and outcomes has been published (109). The screening and enrolment log of consumers that stated reasons for non-enrolment into the study was completed by site HCPs. The HCPs pre and post Zm-STARSS surveys were sent to nurses, doctors and IT staff at both vaccination clinics, sample size n=32.

5.3.1 Zm STARSS Pre and post vaccination surveys

Upon enrolment on Day 0, after signing informed consent forms, all participants (n = 4 560) and guardians of child vaccinees completed a pre-vaccination survey that included their demographic data, age, sex, education, marital status, work status, child count and housing status (i.e. if they rented or owned a house). Adult vaccinees and guardians of child vaccinees who answered "Yes" to at least one of the "SMS prompts sent on Days 0, 2 and 14" were included in a post-vaccination experience survey conducted by research staff during Computer Assisted Telephonic Interviews (CATIs). This survey was performed in the same telephonic interview that was conducted to ascertain if an AEFI had occurred or not. The survey also included additional questions to assess consumers' knowledge regarding which authorities should be responsible for monitoring vaccine safety, the suitability of the Zm-STARRS tools for vaccine safety monitoring in Zimbabwe, and whether written informed consent was required to use consumers' mobile numbers for monitoring vaccine safety. These post-vaccination experience surveys were conducted within one to three weeks post-vaccination by research staff. I also administered pre- and post-nested questionnaires for the study sites vaccination clinics HCPs **(Appendix 6 and 7 below)** within the Zm-STARSS RCT experience through online SurveyMonkey assessing HCPs' knowledge, attitudes, and practices (KAP) related to AEFI surveillance; barriers, and facilitators of Zm-STARSS AEFI surveillance, and its suitability for safety monitoring of COVID-19 including routine childhood vaccines were also explored.

5.3.2 Statistical analysis method

Statistical analyses were performed using IBM SPSS Statistics 26 software. The characteristics and survey responses of participants and HCPs were reported using frequencies and percentages for categorical variables. Continuous data were descriptively summarised using means, medians, modes and standard deviations. Two-tailed Fisher's exact test (FET), Chi Square test and contingency tables were used to compare the sociodemographic data of those vaccinees in the CATI group who responded "Yes" to at least one SMS, to the whole ZM-STARSS RCT cohort of participants (n = 4 560). A significant finding ($p < 0.05$) of a difference in a particular sociodemographic characteristic would suggest a problem in the representativeness of the surveyed vaccinee cohort compared to the overall cohort. A key limitation and bias of this consumer survey is that only those who replied "Yes" (i.e., and not those who replied "No") were surveyed - so only those who experienced an AEFI or at least thought they had would have been surveyed. This needs to be clearly stated as a limitation.

5.4 Results

5.4.1 Nested consumer investigative experience study in Zm-STARSS RCT

Between November 2020 and August 2021, a total of 5 541 eligible adults and children attending the two Immunization sites were approached and screened for enrolment. A total of 4 560 who met inclusion criteria and signed the consent forms were enrolled and randomly assigned (1:1) equally to the SMS or the control groups. A total of 981 subjects were excluded with reasons documented on the screening and enrolment logs summarized as follows: 509 declined enrolment, 353 had incompatible phones, 71 had multiple births, 24 did not agree with the study, 13 had no mobile phone, five were parents/guardian < 18 years, four were unwell before vaccination and two claimed no understanding of English (109). A total of 704/2 280 (31%) enrolled in the SMS group responded either with a "Yes" (n = 176 respondents) or a "No" (n = 528 respondents) to one or more SMS messages. Of those who responded "Yes", 136/176 (77%)

were included in the consumer experience study of Zm-STARSS survey (see Figure 1). The other consumers 40/704 (6%) who responded “Yes” to SMS messages were not reachable i.e., there was no response from their phones after at least three call attempts and some numbers were not available. The reasons for non-enrolment (n = 528) could not be included in the survey since they were “No” responses to the Day 0, 2 or 14 post-vaccinations with no AEFI and did not wish to be interviewed further. **Figure 19** below shows the Zm-STARSS RCT Consumer consort diagram.

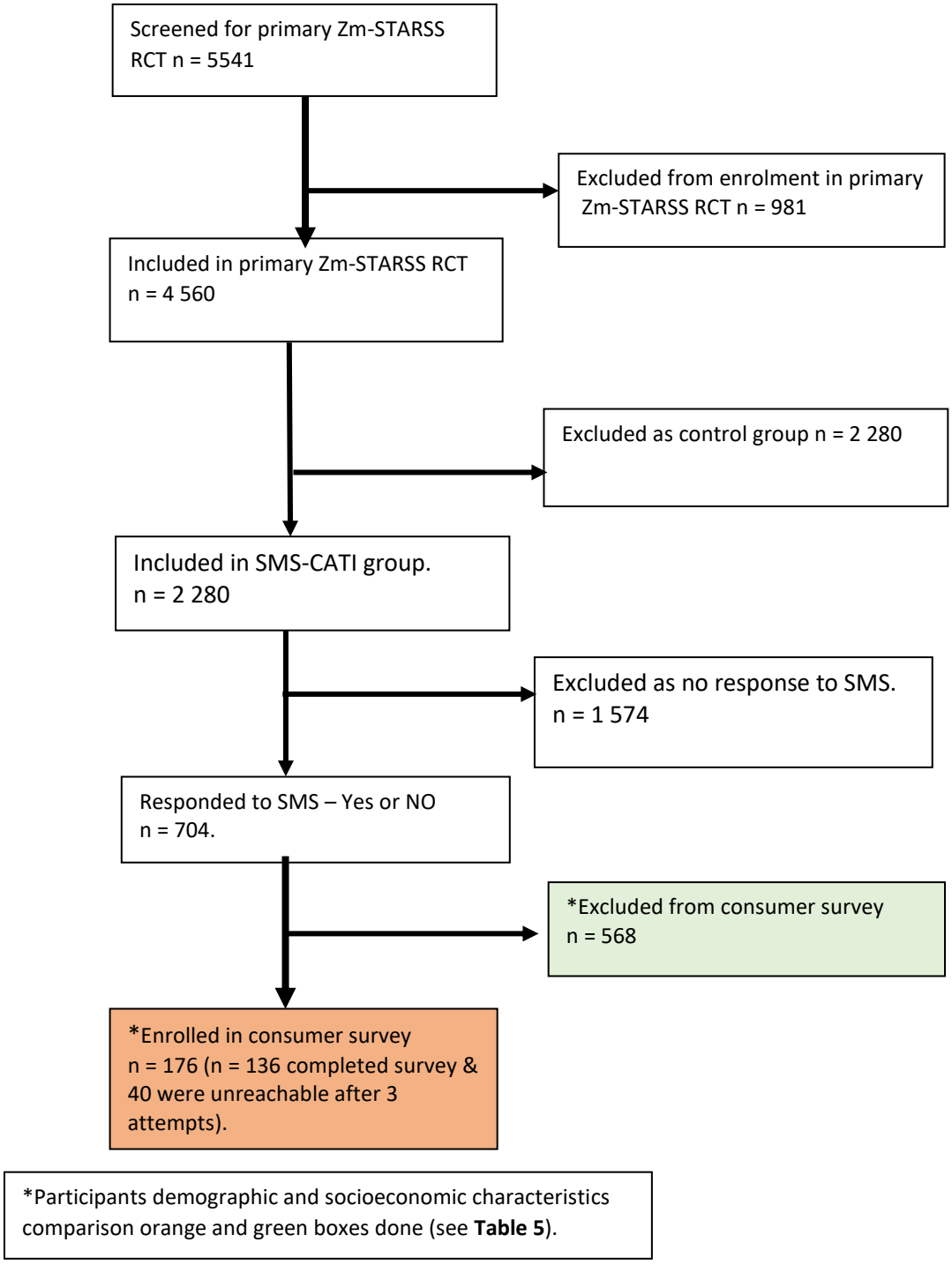


Figure 19: ***Zm-STARSS RCT consumer consort diagram.***

**All participants were born in Zimbabwe and spoke mainly English and Shona.

Table 10 below compares the sociodemographic characteristics of the total RCT cohort with those who completed the pre- and post-vaccination surveys after having responded "Yes" to the SMS. There were no significant differences in these characteristics between the total cohort enrolled in the RCT and this surveyed subgroup that would suggest any specific selection bias in terms of the sociodemographic characteristics.

Table 10*: *Comparison of sociodemographic characteristics of surveyed participants(n=136) and enrolled participants (n=4560) using two tailed Fisher Exact Test (FET).

Participant Characteristics	**Total Participants (n = 4560) (%)**	**CATI Survey "Yes" Respondents' (n = 136) (%)**	**P Value***	**Statistical significance.**
Study Site			0.082	Not significant
CITIMED Hospital	2 321 (50.9)	77 (57.0)		
Chitungwiza Central Hospital	2 239 (49.1)	59 (43.0)		
Age of children vaccinees guardians & adult vaccinees. <6 months	2 553 (56.0)	85 (3.3)	0.263	Not significant
6 months to < 5 years	424 (9.3)	11 (8.0)		
6years-14years	1	0 (0)		

15 years to 39 years	598 (13.1)	21 (15.4)		
39years < to 64 years	767 (16.8)	15 (11.0)		
> 64 years	217 (4.80	4 (2.9)		
Gender			0.683	Not significant
Female	2 159 (47.3)	67 (49.3)		
Male	2 401 (52.7)	69 (50.5)		
Housing status			0.217	Not significant
Owned	2 681 (58.8)	73 (53.7)		
Renting	1 879 (41.2)	63 (21.5)		
Education level			0.881	Not significant
A level	426 (9.3%)	15 (11.0)		
Certificate	15 (0.3%)	0 (0)		
Degree	454 (10.0%)	14 (10.3)		
Diploma	419 (9.2%)	10 (7.2)		
O level or below	3 246 (71.2%)	97 (71.3)		
Marital status			0.065	Not significant
Divorced	12 (0.3%)	0 (0)		
De facto	4 (0.1%)	0 (0)		

Married	4 010 (87.9%)	111 (81.6)		
Single	403 (8.8%)	22 (16.2)		
Widowed	131 (2.9%)	3 (2.2)		
Work Status			0.175	Not significant
Domestic duties	1 138 (25.0%)	26 (19.1)		
Employed by organisation	1 412 (31.0%)	37 (27.2)		
Self employed	450 (9.9%)	16 (11.8)		
Student	130 (2.9%)	6 (4.4)		
Unemployed	1 430 (31.4%)	51 (37.5)		
Child Count			0.313	Not significant
1 child	1 348 (29.6%)	39 (28.7)		
2 children	1 317 (28.9%)	44 (32.4)		
3 children	1 027 (22.5%)	31 (22.8)		
4 children	599 (13.1%)	12 (8.9)		

5 children	180 (3.9%)	9 (6.6)		
6 children	89 (2.0%)	1 (0.7)		

* p value < 0.05 denotes statistical significance.

Table 11 below shows a summary of post-vaccination survey responses from consumers or guardians (n = 136) on vaccine regulation and AEFI surveillance oversight in Zimbabwe. Most consumers 104/136 (76%) believed that checking of vaccine quality and safety in Zimbabwe was mainly done by HCPs although the government health department, vaccine companies and independent researchers have a role to play as well. The majority 96/136 (71%) of the surveyed participants agreed to be followed up by SMS post vaccination without their initial consent. Most of the surveyed participants 128/136 (94%) recommended using the Zm-STARSS mHealth system for monitoring the safety of both COVID-19 vaccines and routine childhood vaccines.

Table 11: ***Post-vaccination survey responses from consumers/guardians on vaccine regulation and AEFI surveillance oversight.***

Total responders	**Responders (%) n =136**
Who is checking on vaccine quality in Zimbabwe?	
Health professionals such as nurses and doctors	104 (76%)
Government Health Department	19 (14%)
Vaccine companies	10 (7%)
Independent health researchers	3 (2%)
Unsure	5 (4%)

Who do you think is checking the vaccines safety in Zimbabwe?	
Health professionals such as nurses and doctors	104 (76%)
Government Health Department	19 (14%)
Vaccine companies	10 (7%)
Independent health researchers	3 (2%)
Unsure	5 (4%)
How do you feel about being followed up with SMS post vaccination?	
Do it without my consent	96 (71%)
Do it with my consent	26 (19%)
Situational i.e., depending on the circumstances	11 (8%)
Unsure	2 (2%)
Do not follow me up	1 (1%)
Would you recommend using Zm-STARSS mHealth system for monitoring COVID-19 vaccines safety and routine children vaccines safety?	
Yes	128 (94%)
Do not know	5 (4%)
Unsure	3 (2%)

Table 12 below shows the key findings of the HCPs experience survey (n = 32) including demographic and work experience data at both study sites.

Table 12*: *Demographic and employment history of the HCPs in the pre- and post Zm-STARSS experience survey.

	Pre-HCPs experience study survey **n = 32 (%)**	**Post-HCPs experience study survey** **n = 32 (%)**
Gender of HCPs		
Female	24 (75)	24 (75)
Male	8 (25)	8 (25)
Age Group		
31 years to 40 years	15 (47)	15 (47)
41 years to 50 years	8 (25)	8 (25)
51yrs to 60 years	8 (25)	7 (22)
below 30 years	1 (3)	2 (6)
Profession/Job title		
Midwife	15 (47)	12 (38)
Nurse manager	5 (16)	4 (13)

Registered general nurse (RGN)	3 (9)	3 (9)
Doctor	2 (6)	2 (6)
Matron	2 (6)	3 (9)
Health promotion officer**	1 (3)	1 (3)
IT administrator**	1 (3)	2(6)
Surveillance officer EPI	1 (3)	1(3)
Paediatrician	1 (3)	1(3)
Pharmacist	1 (3)	3 (9)
Years of Experience		
1 year to 5 years	11 (34)	4 (13)
6 years to 10 years	5 (16)	4 (13)
11 years to 15 years	9 (28)	12 (38)
16 years to 20 years	4 (16)	3 (9)
Above 20 years	3 (12)	9 (28)
Hospital department		
Postnatal ward	8 (21)	8 (25)
Children vaccination clinic	2 (6)	2 (9)

COVID-19 vaccination clinic	4 (12)	2 (9)
Caesarean ward	7 (21)	7 (22)
Maternity	2 (6)	3 (9)
EPI City Health supervisor	1 (3)	1 (3)
Deputy Director National EPI Program	1(3)	1 (3)
Health promotion	1 (3)	1 (3)
Information technology (IT)	1 (3)	1 (3)
National EPI manager	1 (3)	1 (3)
Paediatric wards	2 (6)	2 (6)
Pharmacy	1 (3)	2 (3)
Medical officer	1 (3)	1 (3)

From *Table* 10 above:

*****An equal number per site of HCPs with similar roles and qualifications participated in the Zm-STARSS RCT study and completed the survey. A total of 34 pre-study and 32 post-study HCPs completed the experience survey, i.e., a response rate of 100%. One HCP succumbed to COVID-19 disease and the other HCP relocated during the study period and could not participate in the post-study survey, hence their pre-study survey inputs were excluded in the final analysis.

******The IT administrators were included as they were critical for the smooth running of the Zm-STARSS software. Health promotion officers, who are part of all hospitals and clinics in Zimbabwe, routinely engage consumers in health education including around Immunization in

order to improve coverage; this was especially so during the COVID-19 pandemic when COVID-19 vaccination hesitancy was high (86).

5.4.2 Factors that determine AEFI reporting

Table 13 below shows the HCPs' KAP of AEFIs reporting, information technology and mHealth technology factors that may assist use of Zm-STARSS mHealth AEFI surveillance. Most HCPs claimed to have been trained in AEFI reporting, were familiar with AEFI reporting forms and requirements for reporting, had encountered patients with AEFIs, and some claimed to have submitted AEFI(s) reports in practice. At least half of the HCPs surveyed identified lack of feedback and fear of negative consequences for reporting an AEFI as barriers to reporting AEFI. Lack of access to the paper-based forms and uncertainty about what to report were also identified as barriers. While most nurses had mobile phones, less than a third reported having reliable access to data for phone calls and SMSs. Most HCPs who participated in the study had access to subsidised resources and skills to implement Zm-STARSS RCT, such as mobile phones (30, 88%), tablets or iPads (19, 56%), computer skills (23, 68%), voice and SMS bundles (11, 32%), and data bundles (9, 27%). Most HCPs recommended affordable user-friendly mobile phones, accessible and reliable mobile networks, affordable voice, SMS, and data packages, toll-free numbers, and appropriate training for successful implementation of Zm-STARSS AEFI surveillance.

Table 13: Pre-Zm-STARSS study experience survey of HCPs AEFI reporting knowledge and mHealth technology barriers/facilitators.

Health care Professional Survey **Total n = 32 HCPs**	
How many AEFIs did each HCP see in their career?	
1-4	19 (59)
5-10	4 (13)
11-20	1 (3)
Greater than 20	2 (6)
Never seen an AEFI	6 (19)
Barriers, reasons for HCPs not reporting AEFI(s).	
Lack of feedback after investigations	18 (53)
Concerns about negative consequences	17 (50)
Unavailability of AEFI reporting form	15 (44)
Unavailability of AEFI case Investigation form	15 (44)
Uncertainty about what and when to report	14 (41)
Lack of support from supervisor	12 (35)
Not enough time to report	10 (29)
Hoping that minor reactions will ease away	1 (3)
HCPs indication of those who should monitor vaccine safety and programs.	

Health professionals	33 (97)
Expanded Programme on Immunization (EPI)-MoHCC	33 (97)
National Pharmacovigilance Centre (MCAZ)	32 (94)
Vaccine manufacturers	29 (85)
Health researchers	29 (85)
Parents/guardians of children who are vaccinated.	22 (65)
What are the trusted sources of vaccine information?	
Vaccine manufacturer	19 (56)
Immunization nurse	15 (44)
Doctor	13 (38)
Medical journal	7 (21)
Public media	3 (9)
Family and friends	2 (6)
Internet	2 (6)
Key technologies and skills each HCP were confident of operating	
Mobile phone (cell phone)	33 (97)
Tablet or iPad	27 (79)
Computer operating skills	25 (74)

Searching the internet	25 (74)
Laptop or desktop computer	24 (71)
Social media (e.g., WhatsApp, Facebook, Twitter, Instagram)	24 (71)
Key technologies and skills each one HCP had at work.	
Mobile phone (cell phone)	30 (88)
Computer operating skills	23 (68)
Wi-Fi connection	20 (59)
Laptop or desktop computer	19 (56)
Tablet or iPad	13 (38)
Voice and SMS bundles	11 (32)
Data bundles	9 (27)
What are the basics needed by HCPs for Zm-STARSS implementation?	
Voice and SMS bundles	12 (35)
Mobile phone (cell phone)	12 (35)
Data bundles	12 (35)
Computer operating skills	12 (35)
Tablet or iPad	12 (35
Wi-Fi connection	12 (35)

Laptop or desktop computer	12 (35)
What are the key things required to implement Zm-STARSS?	
Computer skills	20 (59)
Laptop or desktop	12 (35)
Tablet or iPad	12 (35)
Mobile phone	12 (35)
Data bundles	12 (35)
Voice and SMS bundles	12 (35)
Wi-Fi connection	12 (35)

Table 13 below presents results of the **post**-Zm-STARSS RCT study experience of the 32 HCPs included in the survey, highlighting inhibitors and promoters to implementing Zm-STARSS MAPC AEFI surveillance. Most of the HCP respondents agreed with statements 1-7 regarding inhibitory factors to the implementation of the Zm-STARSS RCT mHealth tool, as well as statements 1-5 concerning promoting factors for implementing Zm-STARSS mHealth, listed in **Table 14** below. **The responses were ranked using a Likert scale (strongly disagree 1, disagree 2, neutral 3, agree 4 and strongly agree 5), hence the median, mean and mode were calculated based on the Likert scale results.

Table 14: Post-Zm-STARSS RCT experience survey by HCPs identified inhibitors and

facilitators.

** Responses were ranked using a Likert scale (strongly disagree 1, disagree 2, neutral 3, agree 4 and strongly agree 5) with median, mean and mode.			
Question/survey statement of inhibitory factors to implementation of Zm-STARSS RCT mHealth tool.	**Responses**		
	Median	**Mean**	**Mode**
1. Lack of knowledge can inhibit (make it difficult) to use Zm-STARSS SMS mHealth tool for AEFI surveillance.	4.5	4.4	4
2. Decreased sensory perception can inhibit (make it difficult) the use Zm-STARSS SMS mHealth tool for AEFI surveillance.	4.0	4.4	4
3. Lack of desire to use technology can inhibit (make it difficult) the use Zm-STARSS SMS mHealth tool for AEFI surveillance.	4.0	4.4	4
4. Lack of training can inhibit (make it difficult) the use Zm-STARSS SMS mHealth tool for AEFI surveillance.	4.5	4.3	4
5. HCPs fear of negative consequences of reporting an AEFI can inhibit (make it difficult) to use Zm-STARSS SMS mHealth tool for AEFI surveillance.	4.0	4.3	4
6. Failure by patients/guardians to detect AEFI can inhibit (make it difficult) the use Zm-STARSS SMS mHealth tool for AEFI surveillance.	4.0	4.2	4
7. Poorly designed mobile phone interface between sender and receiver of messages may inhibit (make it	4.0	3.6	4

difficult) adoption of Zm-STARSS SMS mHealth tool for AEFI surveillance.			
Question survey statement of promoting factors to implement Zm-STARSS RCT mHealth tool.			
1. Reliable mobile phone network (e.g., prompt delivery of SMS) may facilitate (make it easy) adoption of Zm-STARSS SMS mHealth tool for AEFI surveillance.	5	4.7	5
2. Previous experience with mobile phone technology can facilitate (make it easy) to use Zm-STARSS SMS mHealth tool for AEFI surveillance.	5	4.6	5
3. Willingness to learn can facilitate (make it easy) the use Zm-STARSS SMS mHealth tool for AEFI surveillance.	5	4.7	5
4. Age maturity can facilitate (make it easy) to use Zm-STARSS SMS mHealth tool for AEFI surveillance.	4.0	3.5	4
5. Cost/Affordability of mobile phone airtime can facilitate (make it easy) adoption of Zm-STARSS SMS mHealth tool for AEFI surveillance.	3.5	4.0	4

Table 15below shows the recommendations by HCPs (n = 32) on the implementation of the Zm-STARSS SMS mHealth tool in Zimbabwe. Most of the HCPs involved in the project recommended the use of the Zm-STARSS as a tool to improve AEFI reporting both for novel vaccines such as COVID-19 and for routine childhood Immunizations. Some key suggestions that were supported by respondents to strengthen the performance of the system centred around reducing the personal cost, and accessibility of the system through inclusion of all mobile phone operators and providing toll-free lines as well as ensuring freely available internet services to access the websites for web/app-based reporting AEFI tools.

Table 15: Recommendations by HCPs on implementation of Zm-STARSS SMS mHealth tool in Zimbabwe.

What should be improved on Zm-STARSS SMS mHealth tool before implementation countrywide?	
No response to this question	11 (34
Include all mobile phone operators	7 (33)
Use toll-free numbers or free websites	6 (29)
Everyone should have access to mobile network	3 (14)
Use WhatsApp messages for AEFI surveillance	2 (10)
Train HCPs and practice Zm-STARSS system	2 (10)
Use mobile application to monitor AEFI surveillance	1 (5)
Would you recommend Zm-STARSS SMS mHealth tool for monitoring children's routine Immunization vaccines safety?	
YES	31 (97)
NO	1 (3)
Would you recommend Zm-STARSS SMS mHealth tool for monitoring COVID-19 vaccines safety?	
YES	31 (97)

NO	1 (3)

5.5 Discussion:

Most of the 128 (94%) consumers who participated in the experience survey recommended using the Zm-STARSS mHealth system for monitoring COVID-19 vaccines and routine childhood vaccination safety. Similar findings of consumers' willingness to report AEFIs initially via paper-based copies or electronically before the COVID-19 era were found in most studies in HICs and fewer in LMICs (37, 120, 126). Some countries in Africa, e.g., Ghana, Kenya, Nigeria, South Africa, and Zimbabwe, traditionally use spontaneous AEFI paper-based reporting forms; recently they have developed eHealth/mHealth AEFI reports for consumers and HCPs, with gradual uptake (113). Africa has the least number of AEFIs in the WHO VigiBase and VigiAccess global safety databases (124, 127). The USA has the highest number of ICSRs including AEFIs in VigiBase and VigiAccess; the country has contributed the highest consumer digital reporting globally via the VAERS, an open access system (83, 124, 127). Although the Zm-STARSS consumer experience sample size was relatively small, these favourable results are comparable to those obtained from a survey nested within a similar Australian trial (Au-STARSS RCT) where 1 139 (95%) participants sampled in the acceptability questionnaire indicated that "SMS-based surveillance should be done" (8).

The positive results of the Zm-STARSS RCT consumer mHealth experience survey were like those in other quantitative or qualitative studies in HICs where participants recommended use of MAPC AEFI surveillance (37, 83, 123, 128). The majority of participants surveyed in Germany expressed concerns over lack of privacy associated with mHealth for vaccine safety monitoring (56, 121). A Zimbabwe study that interviewed doctors about feasibility of use of eHealth records cited lack of privacy as a concern for eHealth technology (129). The same study also identified other factors inherent in resource limited settings such as lack of funding and bureaucratic hurdles as inhibitors of eHealth implementation in public hospitals in Zimbabwe.

Most of the participants 96 (71%) who responded to the experience survey postvaccination agreed to being contacted in the future for Zm-STARSS AEFI monitoring post-vaccination without the need for prior consent. This applies to responders/guardians who received COVID-19 vaccines or routine Immunization. Taking vaccinees' contact details on vaccination cards and medical records by vaccination clinics to be kept confidential is routine practice in Zimbabwe hence that might explain the willingness and cooperative attitude shown by the surveyed participants. This contrasts with the Au-STARSS study where only 38% indicated that surveillance should be done without consent being obtained (123). The Zm-STARSS cohort participants included in this survey were only those who responded with a "Yes" to the SMS, representing a selection bias. I do not know what those who responded "No" or non-responders would have recommended, hence it is an important limitation to the Zm-STARSS study.

The relatively lower responses to SMS and CATI interviews conducted in Zm-STARSS compared to Au-STARSS appeared to be consistent with similar studies among minority groups in HICs such as the Aboriginal gap study in Australia (62). The Aboriginal gap study cited lack of trust, limited airtime, or internet as some of the reasons for the low responses to the SMS, as well as email and web-based follow up messages postvaccination. The key challenges in resource limited populations might be prohibitive cost of airtime, internet services and IT technology equipment, limited technical skills and lack of trust in the surveillance system. Most MAPC AEFI surveillance systems conducted in high income populations indicate better experiences of mHealth when mixed with web based AEFI surveillance applications yielding relatively higher response rates averaging 72%; this results in higher AEFI detection rates in mHealth, or web applications mixed with other digital health technologies (37, 41, 83, 122, 123).

While the Zm-STARSS randomised control trial (RCT) study design helped reduce most biases in the quantitative RCT study, some bias may have been introduced in this acceptability/feasibility study. Firstly, the STARSS test code was unable to accommodate participants who did not use Econet phone services. This technical and regulatory limitation was not experienced in the Au-STARSS RCT (41, 123). Furthermore, Zm-STARSS was conducted during the peak of the COVID-19 pandemic with strict social distancing hence the ability to conduct consumer and HCP surveys face to face was compromised. As a result, I utilised the CATI interviews to solicit feedback on the Zm STARRS system from vaccinees or their guardians. Similarly, HCPs were asked to complete pre- and post- experience online SurveyMonkey® questionnaires online which may have compromised our ability to obtain more detailed feedback from them. Due to human resources and financial constraints, it was not possible to conduct telephonic experience studies of some of the participants who responded "No" to the SMS messages. The benefit risk minimisation approach to only follow up those who responded "Yes" to SMS prompts with CATI surveys was used in the Zm-STARSS RCT consumer experience study since for routine Immunizations, vaccinees and their guardians do not receive any follow up from vaccination clinics unless they report spontaneous AEFIs and require AEFIs case management at the vaccination clinics or hospitals.

From the pre- and post-experience study surveys results, most HCPs indicated that they were knowledgeable in AEFIs and had experienced some AEFIs in their careers. An online survey was conducted at baseline to assess site staff's knowledge, attitudes and perceptions of AEFI surveillance. An in-depth survey was beyond the scope of this thesis given the challenges of the COVID-19 lock down that physical interviews could not be done.

The HCPs cited basic barriers to reporting AEFIs consistent with other studies in both LMICs and HICs such as lack of feedback after investigations, concerns about negative consequences, unavailability of AEFI reporting forms, unavailability of AEFI case investigation forms, uncertainty about what and when to report, lack of support from supervisors, not enough time to report and

hoping that minor reactions would ease away (45, 130, 131). This study is unique, if not novel, in that it explored pre- and post-Zm-STARSS RCT MAPC AEFI surveillance experiences by exploring HCP proficiency in mHealth technology/IT skills, availability of IT equipment, and promoters of successful implementation of Zm-STARSS AEFI surveillance. Factors that inhibit AEFI surveillance were cited by the surveyed HCPs as lack of HCP training in AEFI surveillance, fear of victimisation after AEFI reporting, lack of phone network coverage, complexity, and cost of phone technology. These negative attitudes and experiences in AEFI reporting by some of the HCPs require addressing in future AEFI surveillance trainings. It is essential to promote a no victimisation (no shame no blame) policy and ensure timely feedback. In addition, availability of internet services, electricity, and relevant IT gadgets is vital to enable successful use of mHealth AEFI reporting(132).

It is important to note that MAPC AEFI surveillance alone is not likely to address all the barriers to AEFI reporting and that regulators including NIPs need to also improve provision of feedback, address concerns of staff around negative consequences by providing no-fault approaches to case investigations and other responses to AEFI. Other relatively new enhanced spontaneous reporting mHealth and digital health apps such as MedSafety apps recently introduced through the African Unity (AU) Smart Safety Surveillance (3S) initiative pilot study in Ethiopia, Ghana, Kenya, Nigeria and South Africa have shown positive results for COVID-19 AEFI surveillance [Poster number International Society of Pharmacovigilance (ISOP)23-P113]. One example is the acceptability study for the Ghana MedSafety app for reporting medicine Adverse Drug Reactions (133). Unfortunately, these well-resourced AU 3S digital apps initiatives were not yet available to most African countries including Zimbabwe at the time of the thesis study.

For successful implementation of Zm-STARSS, most HCPs recommended inclusion of all Zimbabwe mobile network operators, AEFI toll-free numbers or “subsidised websites”, use of WhatsApp messages for AEFI surveillance, use of mobile applications (Apps) for AEFI surveillance and training of HCPs to use the Zm-STARSS system and other AEFI systems. Under “subsidised

websites" the HCPs clarified that internet services and tools to access the internet were too expensive for most HCPs. The majority (31, 97%) of HCPs in the post-Zm-STARSS RCT study survey recommended use of the Zm-STARSS SMS mHealth system to monitor childhood and adult COVID-19 vaccine safety. The recommendations are important and consistent with an LMIC setting where basic IT and mobile phone systems are expensive. Also, commercial power (electricity) is unreliable, and citizens can hardly afford innovative technologies that may enhance lives. Incorporating SMS and low-cost social media platforms such as WhatsApp, Facebook, WeChat, and Instagram in AEFI surveillance systems may therefore improve detection and intervention in LMICs. Regulators and policy makers should reduce mHealth accessibility costs to the consumers and HCPs by availing toll-free numbers and affordable social media platforms, data, voice, and SMS services to improve AEFI reporting.

5.6 Conclusion:

The Zm-STARSS RCT experience study is a novel evidence-based MAPC AEFI surveillance study of consumers and HCPs. The study was conducted at the peak of the COVID-19 pandemic in a peri-urban setting of a LMIC. Most HCPs recommended appropriate AEFI training, affordable user-friendly mobile technology, accessible and reliable mobile phone networks, affordable airtime packages as well as toll-free numbers for successful implementation of mHealth MAPC AEFI surveillance in a LMIC. Most HCPs and consumers surveyed recommended use of the Zm-STARSS system for monitoring the safety for routine childhood vaccines and COVID-19 vaccines**.**

Declarations and Limitations.

Only 176 out of 704 (19%) participants who responded to "No" or "Yes" to SMS prompts post-vaccination were surveyed due to the limitation explained above. When I compared the demographics of those who completed the survey with the whole cohort including those who did not respond, I saw no significant differences in basic sociodemographic characteristics. While I

recognise that this does not eliminate the bias that was probably introduced by only including those who responded “Yes”, these are not significant characteristics that would predict response to these SMSs. There is a possibility that those who responded “Yes”, might exhibit bias toward being more supportive of such an intervention. However, more robust feasibility studies that canvass the inputs of those who response “Yes” or “No” as well as non-responders are needed for mHealth MAPC interventions in LMIC settings. Due to the COVID-19 pandemic lockdown period when the study was conducted, virtual post study sites HCPs discussions were done and most comments raised including faciliators and barriers of MAPC surveillnce were confirmatory to the HCPs online survey post study results presented above. It was impossible to conduct physical group discussions of study vaccinees due to the COVID-19 pandemic lockdown and virtual/hybridmeetings could not be done since most vaccinees participants did not have adequate internet access.

Chapter 6 MAPC Systems can improve AEFI Surveillance

Chapter 6 Title: The use of m-Health active participant centred (MAPC) systems to improve surveillance of adverse events following Immunization (AEFI): The case of Zimbabwe's Stimulated Telephone Assisted Rapid Safety Surveillance (Zm-STARSS pilot study nested in the national pharmacovigilance programme.

Chapter 6 summarises the key research findings, lessons learnt, evidence-based recommendations and conclusion of the study.

6.1 Background and introduction

Globally, vaccines administered routinely, within campaigns or pandemics save millions of lives (134, 135). In rare cases however, serious AEFIs including Adverse Events of Special Interest (AESI) and serious consequences of programmatic errors may adversely contribute to the risk-benefit profile of the vaccines (136). Many vaccines are used almost exclusively in LMICs, e.g. novel oral polio vaccine type 2(nOPV2), whole cell pertussis, malaria vaccines and various Covid-19 vaccine platforms, supporting the need for robust AEFI surveillance in these countries to better understand the vaccines' safety profiles (137-140).

In most LMICs including Zimbabwe, spontaneous AEFI surveillance systems are weak because of underreporting, inefficient manual slow reporting systems, missing or incorrect case reports, limited capacity for case investigation, delayed AEFI case management, inconclusive causality assessment and lack of feedback to reporters and affected vaccinees (109). These shortcomings can have a negative impact on public safety by promoting mistrust in vaccines and increasing

vaccine hesitancy, thereby increasing the likelihood of 'vaccine preventable diseases (VPDs)' (141). The AEFI underreporting in most LMICs is worsened by vaccinees' (public) ignorance, illiteracy, digital illiteracy, resource limitations at individual level and in primary healthcare systems and lack of digital technologies to support reporting (109). Public concerns about vaccine safety can devastate public confidence and must therefore be systematically and promptly identified (34, 83). Lack of record linkage between preventative and curative services and limited access to clinical care for most citizens make prompt identification, referral, causal association and clinical management of AEFIs or AESIs more challenging in most LMICs (83, 109).

Digital health services have the potential to be impactful where healthcare resources are scarce and the proportion of patients to trained HCPs is very high (109). Digital health can empower individual patients by granting them the ability to monitor their healthcare progress including AEFI reporting and case management of (109).

mHealth active **p**articipant **c**entred (MAPC) AEFI surveillance is a promising approach to detection of early AEFIs (usually within 2-4 weeks of vaccination) that has been applied in some HICs and is important for informing the benefit-risk assessment of vaccines/vaccinations (45, 83). mHealth active participant centred (MAPC) AEFI surveillance uses SMS and/or other mHealth systems to proactively solicit AEFI and AESIs reports from vaccinees and vaccinees' guardians. In most cases the MAPC AEFI surveillance software is designed to generate and disseminate SMS prompts to vaccinees on selected day(s) (0, 1, 2, 3, 7, 14, 21, or 28) post-vaccination to ask about their experience with AEFI/AESIs. For those who respond "Yes" to the SMS prompt, a variety of approaches are employed to obtain more specific information from the respondent. These include provision of a simple linked web-based survey, or a computer assisted telephone interviews (CATI) often by the HCPs who originally performed the vaccination. If the event is deemed to meet the criteria of an AEFI or AESI, the report is processed similarly to routine spontaneously reported AEFI. This involvescase investigation for AEF/AESI case management and causality assessment. The 'Zm-STARSS' randomised controlled trial (RCT) evaluated the efficacy and feasibility of AEFI detection using a short message service (SMS) to prompt vaccinees to report AEFIs followed by CATI to obtain more information about the AEFI (109). The study

initiatives are in accordance with the Sustainable Development Goals (SGDs) 3, 'Target 3.8' that states that "Achieve universal health coverage (UHC) including financial risk protection, access to quality essential healthcare services".

6.1.1 Thesis Problem Statement

Zimbabwe's passive AEFI surveillance system is plagued by severe underreporting of AEFIs thereby posing serious challenges to the safety of vaccinees and public confidence in the Immunization programme. Novel approaches need to be tested and assessed to support improved AEFI case detection and reporting in LMIC settings such as Zimbabwe.

Thesis hypothesis: An mHealth application using SMS-based follow up of vaccinees as a form of MAPC AEFI surveillance could help to improve case detection and AEFI reporting.

Thesis research question and aim: Recent developments in (HICs) have shown that AEFI surveillance using mHealth technology to support direct participation of vaccinees, known as MAPC AEFI surveillance could be applied in Zimbabwe given its high mobile phone penetration rate of 97.5%(142). The overarching research question for this thesis is: Can MAPC AEFI surveillance be feasibly and effectively applied in Zimbabwe to support better detection and response to AEFI? Broadly, the thesis aimed to describe the status and challenges of the current AEFI surveillance and to test the 'efficacy and feasibility of MAPC AEFI surveillance' as a tool 'to improve AEFI case detection' in Zimbabwe, a low middle income country' (LMIC).

6.1.2 Thesis overall research objectives and methods

Firstly, I conducted a scoping and narrative literature review study of the MAPC AEFI surveillance system to generate exploratory evidence on 'SMS response rates', 'AEFI reporting rates', cost, experience, and gaps in implementing the system. The literature was assessed from a LMIC perspective. **Secondly**, I conducted a descriptive study of Zimbabwe's AEFIs surveillance system by assessing the AEFI cases reported to VigiBase using the VigiLyze analytic tool, and reviewing

causality assessment outcomes, while also assessing the strengths and gaps of the Zimbabwean 'AEFI surveillance system' using the independent WHO Global Bench Marking Tool (GBMT) criteria for regulatory oversight of vaccines, particularly their safety. **Thirdly,** I conducted a Randomised Clinical Trial (RCT) comparing reporting rates between a type of MAPC AEFI surveillance system known as "**Zimbabwe *S*timulated *T*elephone *A*ssisted *R*apid *S*afety *S*urveillance (Zm-STARSS) RCT" with routine AEFI surveillance in Chitungwiza, a peri-urban district of Zimbabwe. **Fourthly**, nested within the RCT, a sub-study was conducted to explore consumers' and healthcare professionals' (HCPs) experience of mHealth for AEFI surveillance by administering surveys to these HCPs and vaccinees or parents/guardians of infant vaccinees. **Finally,** I developed recommendations and conclusions on strengthening the Zimbabwe AEFI surveillance system including the feasibility of using Zm-STARSS in Zimbabwe. Additionally, I reflected on the potential applicability of this active AEFI surveillance tool in other similar LMICs.

6.2 Overview of Research findings

6.2.1 Scoping and narrative literature review findings: Performance of mHealth in AEFI surveillance

Most of the studies reviewed, (92% (24/26) were conducted in HICs from January 2010 to December 2021 and showed clear evidence of MAPC AEFI surveillance improving consumer response rates and early detection, maingly for early responses to vaccination (within 14-28 days including non-serious, serious AEFIs and programmatic errors). Some studies made use of MAPC AEFI surveillance integrated with other digital applications, such as web based and electronic health records which supported the collection of more specific details of the adverse event. The USA V-Safe system linked to their Vaccines Adverse Event Reporting System (VAERS) and pregnancy registries (11, 34, 83). The mean response rate of vaccinees to the SMS prompts was 71% in the 23 studies included in the review. According to the World bank reports, "HICs have higher per capita income that is a measure of the amount of money earned per person in a nation or geographic region". This ultimately results in HIC consumers having high buying power to access digital health technologies, adequate Immunization AEFI surveillance programmes and

adequate primary healthcare services with electronic health records as well as the primary passive AEFI surveillance systems linked in most cases to digital and MAPC AEFI surveillance enhancing systems. There was limited "MAPC AEFI surveillance in LMICs" (only Cambodia and Sierra Leone) with no evidence of scale up. The two LMIC studies had limited evidence of efficacy of AEFI detection since one feasibility study in Sierra Leone was for SMS enhanced AEFI surveillance for vitamin A and meningococcal vaccine and the other feasibility study in Cambodia, used an SMS system for monitoring adverse drug reactions (ADRs) of medicines that improved responses and reporting rates (32, 33). MAPC AEFI surveillance in HICs was shown to be effective in monitoring seasonal novel vaccines such as influenza and pandemic COVID-19 vaccines in all ages, including special populations such as pregnant women, children and the elderly. An MAPC AEFI surveillance study in Australia that compared Aboriginal and non-Aboriginal populations showed less adherence in the Aboriginal population due to inherent resource limited challenges such as cost of internet for web-based surveys and airtime (62). Based on these findings, I opted for testing efficacy and feasibility of an SMS computer assisted telephone interview (CATI) MAPC AEFI surveillance system in Zimbabwe rather than web-based applications, due to high availability and affordability of SMS based services but limited access to data for web-based surveys. Broadband or internet service in Zimbabwe still has limited coverage and is expensive for ordinary citizens including HCPs and vaccinees.

Key message: In most MAPC AEFI studies conducted in HICs, response rates were high and attempts to obtain more information on the AEFI either through web-based or CATI appraches were reasonably successful. Diminished success among Aboriginal populations in Australia and the elderly in America-USA suggested the need to investigate MAPC feasibility particularly in LMIC settings, justifying the need for this thesis and in particular, the RCT. Most mHealth AEFI surveillance systems in HICs such as the **Australia (Au)**-**s**timulated **t**elephone **a**ssisted **r**apid **s**afety **s**urveillance (STARSS) [Au-STARSS] achieved notably high AEFI response rates, reaching up to 96% for SMS and web-based responses. Additionally, "Au-STARSS"" had the highest "AEFI detection rate" that was 13-fold greater in the SMS group when compared with controls (4.3 vs 0.3)" (41).

From the scoping and narrative literature review I therefore concluded that “MAPC AEFI surveillance“ is mostly implemented in HICs hence the requirement for efficacy and feasibility of “MAPC AEFI surveillance studies in LMICs” due to increasing availability of mobile phones. The lack of evidence of the use of mHealth AEFI surveillance in LMIC settings justifies the value of the study. The review found that data on the performance of LMIC MAPC AEFI surveillance systems are extremely limited hence evidence is required on its efficacy, feasibility, as well as the experiences of consumers and HCPs, alongside other digital technologies. Integration of MAPC surveillance into national AEFI surveillance systems has the potential to incorporate HCPs/consumer experience on vaccine safety, thereby improving AEFI reporting and possibly AEFI case management. ***From scoping and narrative literature review of MAPC AEFI surveillance systems, I concluded that more studies of MAPC AEFI surveillance utilising the ubiquitous mHealth technology are needed in LMICs.***

6.2.2 Status of AEFI surveillance system in Zimbabwe before Zm-STARSS, descriptive research study findings.

Passive spontaneous AEFI surveillance has been the mainstay of AEFI surveillance in Zimbabwe for over 23 years. Zimbabwe’s AEFI surveillance system encounters the same drawbacks of underreporting encountered globally with AEFI reporting ratios of 0 to 43 reports/100 000 surviving infants per annum over the last 23 years. In almost half those years (11/23 years - 47.8%), the country reached or exceeded the “WHO minimum AEFI reporting ratios of ≥ 10 AEFI reports per 100 000 surviving infants”. The highest Zimbabwe “AEFI reporting ratio of 43.46/million” adults was reached in 2021 because of the introduction of COVID-19 vaccinations, with reports also coming from the Zm-STARSS RCT.

Over the 23-year period, evaluation of the AEFIs found that half (58/116) of the fatal AEFIs had incomplete information such as missing autopsies making causality assessment outcomes inconclusive.

The WHO Global Bench Marking Tool (GBMT) assessment in May 2023 noted the feedback system for received AEFI reports, which includes signed letters sent by MCAZ to all bulletins and follow up letters for missing information. This independent assessment awarded the vigilance system the desired maturity level 3 (ML3) indicating a stable and well-functioning system that met most of the regulatory indicators. WHO noted close collaboration between the EPI and MCAZ national pharmacovigilance center. I concluded that strengthened collaboration between the national Immunization programme (ZEPI-MoHCC) with the national regulatory agency MCAZ, has improved the AEFI spontaneous surveillance system in Zimbabwe over the 23-year period from 1998 to 2022. Further improvements should explore innovative digital technologies to improve detection, case investigation of serious AEFI, capacity for postmortem and causality assessment and signal detection tools. A study of the cholera vaccination campaign in Chipinge District, Zimbabwe shed some important insight that consumer vaccinee guardians were afraid to report AEFIs due to fear of victimisation (46). More HCP and consumer education on reporting AEFIs and reassurance is required to minimise the barriers for AEFI reporting; there should also be provisions for vaccine injury compensation schemes as done in some HICs (143, 144).

Key Message: The AEFI system of Zimbabwe received a maturity level 3 using the Global Benchmarking Tool recognising it as a reasonably stabe and well-functioning system. Nevertheless, barriers to reporting, low reporting rates, incomplete case investigations, particularly autopsies of fatal cases, and inconclusive causality assessment are all recognised as areas for improvement. This thesis focuses on improving reporting rates through participant-centred AEFI reporting. Inadequate delayed AEFI reports and case investigations for effective case management and causality assessments are key gaps that require addressing. This includes holistic improvements of the national AEFI surveillance cycle including MAPC AEFI surveillance, as illustrated in **Figure 20** below **titled 'Elements for an enhanced AEFI surveillance in Zimbabwe.'**

6.3 Performance of MAPC AEFI surveillance: Efficacy and feasibility of Zm-STARSS

I assessed the efficacy and feasibility of Zm-STARSS RCT at two peri urban large vaccination clinics in Chitungwiza. On their vaccination day, 4 560 consented participants were enrolled [encouraged to report AEFIs and randomised automatically on a 1:1 basis into the active SMS CATI group (n = 2 280) or a control passive group (n = 2 280). A total of 704 (31%) participants responded to the SMS prompts, with 75% (528/704) indicating "No" and 25% (176/704) reporting "Yes" to seeking medical attention or attendance post-Immunization] (109). Of those reporting "Yes", a total of 69 % (121/176) completed a CATI survey but in only 36% (44/121) was the AEFI confirmed whilst no AEFIs were reported in control group(109). Therefore, out of the 2 280 SMS respondents 44 of them (2%) said they experienced AEFI whilst no one (0%) responded from the control group. This was statistically significant ($p < 0.0001$ for 2 sided Fishers Exact test).

The study showed that the use of MAPC in Zimbabwe could enhance AEFI reporting rates although response to the SMS was lower compared to HICs, and in many cases the response "Yes" was not necessarily a correct response to the presence of an AEFI. Statistical evidence shows that the Zm-STARSS CATI group detected AEFIs better than the passive AEFI surveillance control group **therefore I rejected the thesis null hypothesis.**

Key message: Zm STARSS improves AEFI detection in an LMIC setting albeit not to the extent in HICs (109). Factors influencing the low response need to be investigated further. Nevertheless, I recommend Zm-STARSS and similar approaches to support improved case detection of AEFIs and ADRs in LMICs settings.

6.4 Healthcare professionals and consumer experience and acceptability

Healthcare professionals (HCPs) and vaccinees were generally receptive to the MAPC AEFI surveillance approach.

When interviewed HCPs and vaccinees accepted Zm-STARSS as a tool to improve AEFI detection and reporting. Over 50% of HCPs interviewed at the study vaccination clinics stated that lack of feedback after AEFI investigations and concerns about negative consequences of reporting were key barriers to AEFI reporting. HCPs also identified mobile phone data and internet costs as barriers to the use of Zm-STARSS. Key suggestions that were supported by HCP respondents to strengthen SMS based MAPC include reducing the SMS cost and ensuring HCPs and consumer reporters use mobile phone networks of their choice without any restrictions. Use of toll-free numbers and easy access to affordable broadband could enhance AEFI reporting. The acceptability or experience survey of ZmSTARSS RCT was done by interviewing telephonically "136 vaccinees/guardians who responded "YES" to the SMS prompts post vaccinations". Most of the participants interviewed (96, 71%) agreed that surveillance through Zm-STARSS could be done in the future without their consent whereas in the Au-STARSS study only 38% indicated that surveillance should be done without consent being obtained (42). Nevertheless, if such a system is used as a national public health surveillance tool, careful consideration of consent procedures is crucial. Options such as waiving consent, an opt-out or opt-in system must align with national ethical and legal policies. The limitation however was the rather small sample size interviewed and this was noted as a potential bias of the result. Most consumers who responded "NO" to the SMS prompts could not be further contacted due to the unavailability of HCPs to continue phoning after 3 failed attempts. A key challenge/limitation noted in the CATI approach was that it was labour-intensive and contacting respondents was difficult - even those who said "Yes". This might have been an inherent COVID-19 pandemic challenge that could have resulted in a low CATI response rate and potentially introduced bias in that only those consumers who responded "Yes" to the SMS were surveyed using the CATI system.

Both HCP and consumer surveys recommended use of the Zm-STARSS SMS mHealth system to monitor childhood and adult COVID-19 vaccine safety. Affordability and availability of technology is a major concern in LMICs that may need to be addressed through innovative approaches such as toll-free numbers and affordable social media platforms, provision of data, voice, and SMS services to improve AEFI reporting. Incorporating SMS and low-cost social media platforms such as WhatsApp, Facebook, WeChat, and Instagram in AEFI surveillance systems may enhance detection and intervention in LMICs. The programmatic iMAPCt of implementing MAPC AEFI surveillance in an LMIC setting needs to take into consideration cost of the system itself and the iMAPCt of increased SMS AEFI responses/AEFI reporting on human resource requirements for both the EPI and national PV centres to process such reports promptly, timely provision of feedback including reassurance of reporters from fear of victimisation and completion of case investigations to prepare AEFI reports for causality assessment should also be prioritised. Given that Zm STARSS was conducted only in one urban/peri-urban setting excluding rural areas, the findings may not be representative of other LMIC settings. Despite the above shortcomings, evidence from the RCT shows that Zm-STARSS AEFI surveillance can improve the Zimbabwe AEFI surveillance system through early detection, and prompt and increased reporting of AEFIs.

Key Messages

While fully supported by both HCPs and consumers as a valuable component of Immunization safety surveillance, the survey identified other elements of the national AEFI system that need concurrent strengthening. These include completion of case investigations, providing feedback to reporters and offering reassurance to alleviate reporters' concerns about adverse consequences of reporting. Moreover, the logistical, human resource and financial resources that influence the success of MAPC AEFI surveillance would need to be considered.

6.5 Practical opportunities and challenges in incorporating MAPC AEFI surveillance in LMICs

Vaccines used exclusively in LMICs are increasing. These include malaria vaccine, RTS,S/AS01 and R21/Matrix-M; type 2 novel oral polio vaccine (nOPV2); polio vaccines; bacteria-based ghosts (BGS) cell derived vaccines;and dengue fever, Ebola, and meningococcal vaccines. There is also a growing repertoire of vaccines targeting pregnant women known as 'respiratory syncytial virus (RSV) and Group- B Streptococcus (GBS) vaccines'. Given that most LMICs have the highest per capita vaccinee populations, there is a need for rapid collection of safety data for these products through cost effective active AEFI surveillance methods that augment spontaneous reporting. There is also an opportunity to explore customised MAPC AFEI surveillance approaches for other medicines ADRs/SAEs in both private and public health programmes, including consumers with non-communicable diseases (NCDs), comorbid conditions, tuberculosis, HIV/AIDs and new prevention products such as Pre-exposure prophylaxis products (PrEP) for HIV. As illustrated in **Figure 20** below, while the research showed that MAPC AEFI surveillance significantly improves AEFI reporting rates, there is need for a holistic approach to consider other aspects of national AEFI surveillance systems (**steps 1-6**) and (**inputs 1-6**) to be strengthened to cope with reporting increased case investigation, causality assessment, signal detection, feedback including benefit/risk communication to reporters if reporting rates increase.

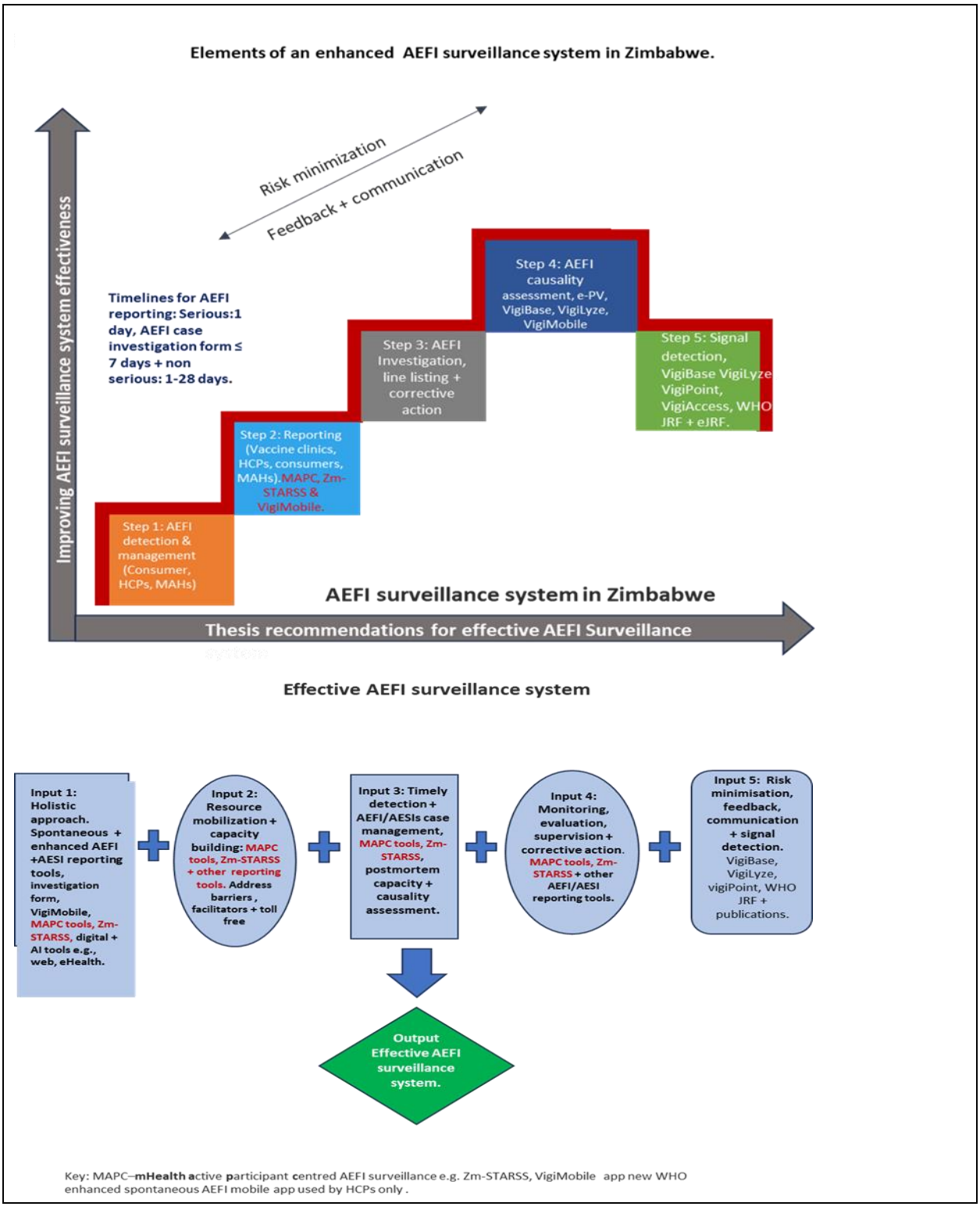


Figure 20: Elements of an enhanced AEFI surveillance system in Zimbabwe.

6.6 Strengths and limitations of the Thesis as a whole

This thesis employed a variety of methodologies to address the key objectives. These approaches included a scoping literature review study, a descriptive study, a randomised controlled trial and a survey conducted telephonically and in-person among consumers and HCPs respectively. The pre and post survey sought to establish their experiences and perceptions that fed into the acceptability of the 'MAPC AEFI surveillance system'. Due to the COVID-19 pandemic lockdown period when the study was conducted, post study virtual study sites HCPs discussions were done and most comments raised including faciliators and barriers of MAPC surveillnce were confirmatory to the HCPs online survey monkey post study results presented above. It was however impossible to conduct physical group discussions of study vaccinees due to the COVID-19 pandemic lockdown and virtual meetings could not be done since most vaccinees participants did not have adequate internet access. The study however identified key challenges encountered in piloting the sytem in an LMIC setting. The coincidental occurrence of the pandemic and the introduction of novel COVID-19 vaccines during the time of the RCT provided an excellent opportunity to understand how the system would perform in a scenario for which it was originally designed (i.e., to assess the safety of novel and seasonal vaccines). The pandemic also highlighted some of the limitations of the system while also contributing to changes in the conduct of the study that would introduce bias and confounding.

Limitations, potential bias and confounding

As mentioned above, possibly the key challenge and strength/uniqueness of this thesis research was its successful execution in the heart of the COVID-19 pandemic. I encountered challenges contacting study participants after enrollment. The quarantine of some key study personnel exposed to COVID-19 and the general increased pressure on HCPs and the healthcare system during this period posed logistic challenges in general, although all participants enrolled signed hard copy informed consent forms and most of the data were collected via the CATI and Zm-STARSS software, that included an AEFI case investigation platform. These experiences will

inform future programming of such systems as described above. The use of QR codes linked to a self-enrollment web page as an opt-in procedure is one example of an approach that could address enrollment if the consumers can afford web-based internet platforms (45). Enrollment for the Zm-STARSS study was confined to peri urban and urban settings with relatively good and reliable internet connectivity, better access to care, higher literacy levels and greater access to mobile technologies compared to rural and remote settings. This limits our ability to assess the feasibility and effectiveness of MAPC across the entire country or in other LMIC settings. Although every effort was made to reduce the risk of bias and confounding, the inclusion of only those who responded "Yes" to the SMS in the feasibility and experience/acceptability study represents a significant selection bias. It is possible that those who did not respond or those who responded "No" to the SMS may have had a different view of the acceptability of this approach as well as different perspectives on the need for consent. Additional research could be done to explore in more detail barriers to higher response rates as well as other barriers to reporting AEFIs among HCPs/vaccinees. This could be embedded in studies assessing the cost-effectiveness of MAPC as a tool to improve case detection and reporting of AEFIs. Wherever possible, the studies included in this thesis were designed or analysed to minimise the effects of bias, and/or confounding factors. Where bias /confounding could have influenced the results, these were acknowledged in each thesis chapter. A thorough review of the literature was performed to support the approach of this thesis including the analysis and interpretation of the findings. As illustrated in **Figure 20** above, the focus of this thesis is largely on the AEFI case detection part of the AEFI surveillance cycle rather than case investigation, causality assessment, signal detection and the provision of feedback. However, Chapter 3 evaluated the Zimbabwean AEFI surveillance cycle/system and its performance over a 23-year period, providing important insights into other areas that could be strengthened to support the introduction of MAPC AEFI monitoring.

6.7 Key thesis research recommendations

Figure 20 above provides an overview of the key findings and conclusions of the thesis in the context of an overarching enhanced national AEFI surveillance system in Zimbabwe and similar LMICs. It encapsulates the opportunities identified in this thesis for improved detection and reporting through mHealth MAPC, capacity building and resource mobilisation to support improved timeliness and quality of reports, case investigations, causality assessment, case management and feedback. It recognises the importance of leveraging the existing digital tools such as VigiLyze and VigiPoint to support signal detection including identifying opportunities to improve coverage and effectiveness of the AEFI system. It also demonstrates the role of the WHO Global benchmarking tool to incentivise countries into investing time and resources into AEFI surveillance as an overarching regulatory and health systems strengthening initiative. Lastly, the figure demonstrates the stepwise approach to building a robust AEFI system in Zimbabwe, with good quality and timely AEFI detection/reporting being recognised as the foundation for an effective Immunization safety surveillance programme.

From the thesis findings stated above, I **recommend** further investigation of Zm-STARSS and other similar approaches using holistic cost-effective multi-channel digital methodologies for AEFI pharmacovigilance to enhance AEFI detection in LMICs for all vaccines, perhaps initially focussing on novel vaccines being introduced into the country. The following were identified as important factors that need to be considered:

- The cost of MAPC for both consumers and HCPs should be minimised to improve AEFI reporting in Zimbabwe and other similar resource limited settings in Sub-Saharan Africa. Mobile phone operators for example, should charge lower rates (toll-free) for mHealth surveillance systems as a public service.

- Further research is needed to assess whether the MAPC can detect AESIs in addition to routine early non-serious adverse events.

- In resource-limited settings, where human resources within government are also limited, the importance of increasing reporting/processing of non-serious expected AEFIs versus

prioritising the detection of serious AEFI through other approaches such as hospital-based surveillance may need to be explored.

- Moreover, it would be useful to assess the additional value provided by digital AEFI reporting apps (e.g., the WHO new spontaneous HCPs VigiMobile AEFI mobile app and the MedSafety App developed by the UK Medical Health Products Regulatory Authority). The Vigimobile app was recently launched in Zimbabwe but **not** for use by consumers (109, 145, 146). A few other selected African countries recently piloted Med Safety ADR and AEFI App as a reporting system for HCPs as well as consumers although no publications were available at the time of writing this thesis. Two recent studies on the Med Safety App, both with small sample sizes, indicated that positive findings were mainly for medicines ADRs acceptability in small populations; 33 (27.3%) consumers responded in Ghana(133) and 49 (%) HCPs in Uganda (113).
- Further studies would be useful to investigate the impact of Artificial Intelligence(AI), machine learning and other upcoming digital technologies on AEFI surveillance, signal detection and benefit risk management communication.

6.8 Conclusion

MAPC AEFI surveillance has not been tested adequately in LMICs. This thesis provided much-needed data on the performance of such a system (Zm STARRS) in an urban/peri-urban centre in Zimbabwe. The study demonstrated the potential of such a system in improving reporting dates of AEFI in a country with a relatively low spontaneous reporting rate for AEFI. The study demonstrated the challenges and limitations but also the potenital value of such a system, particularly in situations like pandemics e.g., COVID-19 disease, which saw expedited introduction of new vaccines. This system provides a user-friendly inexpensive approach of obtaining consumer AEFI reports with CATI platform for AEFI case investigation as well. However,

the thesis also demonstrated that educating HCPs to report, dispelling their fears and misunderstandings about AEFI reporting, providing easier reporting platforms for HCPs, improving capacity to perform case investigations (including autopsies), conducting causality assessments and offering useful feedback should also be prioritised in order to ensure that the system as a whole meets its intended purpose.

Moreover, participant factors such as the cost and access to the internet and other digital services also need to be considered when programming the introduction of such a system in an LMIC setting. Future studies should further investigate the feasibility/acceptance of an 'MAPC AEFI surveillance' system used in more diverse settings including urban/rural settings, new/routine vaccines with different modes of follow-up to the SMS. Additionally, feedback approaches that are context-appropriate would also need to be developed and tested.

References

1. Chapungu L. The COVID-19- Health Systems Nexus

2021.

2. UNICEF.org. Zimbabwe Child mortality 2023 [Available from: https://data.unicef.org/.

3. Parrella A, Gold M, Marshall H, Braunack-Mayer A, Watson M, Baghurst P. Parental views on vaccine safety and future vaccinations of children who experienced an adverse event following routine or seasonal influenza vaccination in 2010. Hum Vaccin Immunother. 2012;8(5):662-7.

4. Gold MS, Balakrishnan MR, Amarasinghe A, MacDonald NE. An approach to death as an adverse event following immunization. Vaccine. 2016;34(2):212-7.

5. Jarrett C, Wilson R, O'Leary M, Eckersberger E, Larson HJ. Strategies for addressing vaccine hesitancy–A systematic review. Vaccine. 2015;33(34):4180-90.

6. Heininger U, Holm K, Caplanusi I, Bailey S, Abdoellah SA, Arellano F, et al. Guide to active vaccine safety surveillance: Report of CIOMS working group on vaccine safety–executive summary. Vaccine. 2017;35(32):3917-21.

7. Chen RT, Shimabukuro TT, Martin DB, Zuber PL, Weibel DM, Sturkenboom M. Enhancing vaccine safety capacity globally: A lifecycle perspective. Vaccine. 2015;33:D46-D54.

8. MacDonald NE. Vaccine hesitancy: Definition, scope and determinants. Vaccine. 2015;33(34):4161-4.

9. Larson HJ, Gakidou E, Murray CJ. The vaccine-hesitant moment. New England Journal of Medicine. 2022;387(1):58-65.

10. Wagner AL, Masters NB, Domek GJ, Mathew JL, Sun X, Asturias EJ, et al. Comparisons of vaccine hesitancy across five low-and middle-income countries. Vaccines. 2019;7(4):155.

11. Black SB, Chandler RE, Edwards KM, Sturkenboom MC. Assessing vaccine safety during a pandemic: Recent experience and lessons learned for the future. Vaccine. 2023;41(25):3790-5.

12. Phillips A, Jiang Y, Walsh D, Andrews N, Artama M, Clothier H, et al. Background rates of adverse events of special interest for COVID-19 vaccines: A multinational Global Vaccine Data Network (GVDN) analysis. Vaccine. 2023;41(42):6227-38.

13. Pillsbury A, Phillips A, Deng L, Quinn H, Macartney K, Gidding H. Background incidence rates of selected adverse events of special interest (AESI) to monitor the safety of COVID-19 vaccines. Vaccine. 2023;41(22):3422-8.

14. Akanmori BD, Traore T, Balakrishnan M, Maure C, Zuber P, Mihigo R. Vaccine Safety and Pharmacovigilance in the African Region. Afr health monit(Online). 2015.

15. Soltani S, Matin BK, Gouya MM, Zahraei SM, Moradi G, Chehri O, et al. A prospective cohort study protocol: monitoring and surveillance of adverse events following heterologous booster doses of Oxford AstraZeneca COVID-19 vaccine in previous recipients of two doses of Sinopharm or Sputnik V vaccines in Iran. BMC Public Health. 2023;23(1):1415.

16. Laryea EB, Frimpong JA, Noora CL, Tengey J, Bandoh D, Sabblah G, et al. Evaluation of the adverse events following immunization surveillance system, Ghana, 2019. PloS one. 2022;17(3):e0264697.

17. Arya H, Bhatt TK. Vaccine regulation and ethics. System Vaccinology: Elsevier; 2022. p. 389-400.

18. Shaum A, Mujuru HA, Takamiya M, Ticklay I, Nathoo K, Sreenivasan N, et al. Enhanced surveillance for adverse events following immunization during the 2019 typhoid conjugate vaccine campaign in Harare, Zimbabwe. Vaccine. 2022.
19. Zimbabwe Expanded Program on Immunisation MoHaC. Adverse Events Following Immunization Surveillance Guidelines 3rd Edition 2017 [cited 2023 9 October 2023]. Available from: https://www.mcaz.co.zw/?smd_process_download=1&download_id=2522
20. Zimbabwe MCAo. GL03-Rev-0_May-2021-Guideline for Pharmacovigilance of COVID-19 Vaccine AEFI Safety Surveillance 2021 [Available from: https://www.mcaz.co.zw/?smd_process_download=1&download_id=3053.
21. Lei J, Balakrishnan MR, Gidudu JF, Zuber PL. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015. Vaccine. 2018;36(12):1577-82.
22. Organization WH. Report of the meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS), 1–3 December 2020. Wkly Epidemiol Rec. 2021;96:13-20.
23. Salman O, Topf K, Chandler R, Conklin L. Progress in Immunization Safety Monitoring—Worldwide, 2010–2019. Morbidity and Mortality Weekly Report. 2021;70(15):547.
24. Masuka JT, Khoza S. Adverse events following immunisation (AEFI) reports from the Zimbabwe expanded programme on immunisation (ZEPI): an analysis of spontaneous reports in Vigibase® from 1997 to 2017. BMC Public Health. 2019;19(1):1166-.
25. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. New England Journal of Medicine. 1996;334(6):349-56.
26. Gurupur VP, Wan TT. Challenges in implementing mHealth interventions: a technical perspective. Mhealth. 2017;3.
27. Bahri P, Rägo L. CIOMS Guide To Vaccine Safety Communication–Executive summary. Vaccine. 2019;37(3):401-8.
28. Free C, Phillips G, Watson L, Galli L, Felix L, Edwards P, et al. The effectiveness of mobile-health technologies to improve health care service delivery processes: a systematic review and meta-analysis. 2013;10(1):e1001363.
29. Hurt K, Walker RJ, Campbell JA, Egede LEJGjohs. mHealth interventions in low and middle-income countries: a systematic review. 2016;8(9):183.
30. Oliver-Williams C, Brown E, Devereux S, Fairhead C, Holeman IJJm, uHealth. Using mobile phones to improve vaccination uptake in 21 low-and middle-income countries: systematic review. 2017;5(10).
31. Marcolino MS, Oliveira JAQ, D'Agostino M, Ribeiro AL, Alkmim MBM, Novillo-Ortiz D. The iMAPCt of mHealth interventions: systematic review of systematic reviews. JMIR mHealth and uHealth. 2018;6(1):e23.
32. Baron S, Goutard F, Nguon K, Tarantola A. Use of a text message-based pharmacovigilance tool in Cambodia: pilot study. Journal of medical Internet research. 2013;15(4):e68.
33. Sesay FF, Hodges MH, Kamara HI, Turay M, Wolfe A, Samba TT, et al. High coverage of vitamin A supplementation and measles vaccination during an integrated Maternal and Child Health Week in Sierra Leone. International health. 2015;7(1):26-31.
34. Cashman P, Macartney K, Khandaker G, King C, Gold M, Durrheim DN. Participant-centred active surveillance of adverse events following immunisation: a narrative review. International health. 2017;9(3):164-76.

35. Pillsbury AJ, Glover C, Jacoby P, Quinn HE, Fathima P, Cashman P, et al. Active surveillance of 2017 seasonal influenza vaccine safety: an observational cohort study of individuals aged 6 months and older in Australia. BMJ open. 2018;8(10):e023263.
36. Wilson K, Atkinson KM, Westeinde J, Bell C, Marty K, Fergusson D, et al. An evaluation of the feasibility and usability of a proof of concept mobile app for adverse event reporting post influenza vaccination. Hum Vaccin Immunother. 2016;12(7):1738-48.
37. Cashman P, Macartney K, Khandaker G, King C, Gold M, Durrheim DN. Participant-centred active surveillance of adverse events following immunisation: a narrative review. Int Health. 2017;9(3):164-76.
38. Kolff CA, Scott VP, Stockwell MS. The use of technology to promote vaccination: A social ecological model based framework. Hum Vaccin Immunother. 2018;14(7):1636-46.
39. Muehlhans S, Richard G, Ali M, Codarini G, Elemuwa C, Khamesipour A, et al. Safety reporting in developing country vaccine clinical trials—a systematic review. 2012;30(22):3255-65.
40. Ngabo F, Nguimfack J, Nwaigwe F, Mugeni C, Muhoza D, Wilson DR, et al. Designing and Implementing an Innovative SMS-based alert system (RapidSMS-MCH) to monitor pregnancy and reduce maternal and child deaths in Rwanda. 2012;13.
41. Gold M, Lincoln G, Cashman P, Braunack-Mayer A, Stocks N. Efficacy of m-Health for the detection of adverse events following immunization–The stimulated telephone assisted rapid safety surveillance (STARSS) randomised control trial. Vaccine. 2021;39(2):332-42.
42. Gold M, Lincoln G, Bednarz J, Braunack-Mayer A, Stocks N. Consumer acceptability and validity of m-Health for the detection of adverse events following immunization–The Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) randomised control trial. Vaccine. 2021;39(2):237-46.
43. GSMA. The Mobile Economy Sub Saharan Africa 2021 2021 [cited 2023 9 October 2023]. Available from: https://www.gsma.com/mobileeconomy/wp-content/uploads/2021/09/GSMA_ME_SSA_2021_English_Web_Singles.pdf.
44. Burches E, Burches M. Efficacy, effectiveness and efficiency in the health care: The need for an agreement to clarify its meaning. Int Arch Public Health Community Med. 2020;4(1):1-3.
45. Cashman P, Moberley S, Chee K, Stephenson J, Chaverot S, Martinelli J, et al. Participant centred safety surveillance of health care workers receiving influenza vaccination. Vaccine. 2019;37(18):2427-9.
46. Gadzayi MR, Mukuzunga M, Chadambuka A, Chiwanda S, Govha E, Gombe NT, et al. An Evaluation of the Adverse Events Following Immunization Surveillance System: A Case of the Oral Cholera Vaccine Mass Campaign, Chimanimani and Chipinge Districts, Zimbabwe, 2019. 2020.
47. Tozzi AE, Gesualdo F, D'Ambrosio A, Pandolfi E, Lopalco P. Can digital tools be used for improving immunization programs? Frontiers in public health. 2016;4:36.
48. Istepanian RS. Mobile Health (m-Health) in Retrospect: The Known Unknowns. International Journal of Environmental Research and Public Health. 2022;19(7):3747.
49. Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, et al. A scoping review on the conduct and reporting of scoping reviews. BMC medical research methodology. 2016;16(1):1-10.
50. Peters MD, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI evidence synthesis. 2020;18(10):2119-26.
51. Rosenblum HG, Gee J, Liu R, Marquez PL, Zhang B, Strid P, et al. Safety of mRNA vaccines administered during the initial 6 months of the US COVID-19 vaccination programme: an observational study of reports to the Vaccine Adverse Event Reporting System and v-safe. The Lancet Infectious Diseases. 2022;22(6):802-12.
52. Stockwell MS, Broder KR, Lewis P, Jakob K, Iqbal S, Fernandez N, et al. Assessing fever frequency after pediatric live attenuated versus inactivated influenza vaccination. Journal of the Pediatric Infectious Diseases Society. 2017;6(3):e7-e14.

53. Choi YY, Kim M-K, Kwon HC, Kim GH. Safety Monitoring after the BNT162b2 COVID-19 Vaccine among Adults Aged 75 Years or Older. Journal of Korean medical science. 2021;36(45).
54. Bae S, Lee YW, Lim SY, Lee J-H, Lim JS, Lee S, et al. Adverse reactions following the first dose of ChAdOx1 nCoV-19 vaccine and BNT162b2 vaccine for healthcare workers in South Korea. Journal of Korean medical science. 2021;36(17).
55. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. The Lancet Infectious Diseases. 2021.
56. Nguyen M, Ott J, Caputo M, Keller-Stanislawski B, Klett-Tammen C, Linnig S, et al. User preferences for a mobile application to report adverse events following vaccination. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2020;75(1):27-31.
57. Nguyen MTH, Krause G, Keller-Stanislawski B, Glöckner S, Mentzer D, Ott JJ. Postmarketing Safety Monitoring After Influenza Vaccination Using a Mobile Health App: Prospective Longitudinal Feasibility Study. JMIR Mhealth Uhealth. 2021;9(5):e26289.
58. Guedel DS, Peters IJ, Banderet F, Epple V, Egli S, Mehling M, et al. Smartphone-based active vaccine safety surveillance (SmartVax) at a Swiss adult vaccination clinic–a pilot study. Swiss medical weekly

2021(49).
59. Singh G, Nesaraj R, Bchara N, Kop B, Leeb A, Nissen L, et al. Immunisation provider experiences with an automated short message service-based active surveillance system for monitoring adverse events following immunisation: A qualitative descriptive study. Digital health. 2021;7:20552076211038165.
60. Westphal DW, Williams SA, Leeb A, Effler PV. Continuous active surveillance of adverse events following immunisation using SMS technology. Vaccine. 2016;34(29):3350-5.
61. Leeb A, Regan AK, Peters IJ, Leeb C, Leeb G, Effler PV. Using automated text messages to monitor adverse events following immunisation in general practice. Med J Aust. 2014;200(7):416-8.
62. Cashman P, Munnoch S-A, Clark K, Allan N, Clarke S, Macartney K, et al. The Aboriginal gap in online active vaccine safety surveillance. Australian Indigenous HealthBulletin. 2020;1(1):3.
63. Cashman P, Moberley S, Dalton C, Stephenson J, Elvidge E, Butler M, et al. Vaxtracker: active on-line surveillance for adverse events following inactivated influenza vaccine in children. Vaccine. 2014;32(42):5503-8.
64. Pillsbury AJ, Fathima P, Quinn HE, Cashman P, Blyth CC, Leeb A, et al. Comparative Postmarket safety profile of adjuvanted and high-dose influenza vaccines in individuals 65 years or older. JAMA network open. 2020;3(5):e204079-e.
65. Pillsbury A, Quinn H, Cashman P, Leeb A, Macartney K. Active SMS-based influenza vaccine safety surveillance in Australian children. Vaccine. 2017;35(51):7101-6.
66. Regan A, Blyth C, Tracey L, Mak D, Richmond P, Effler P. Comparison of text-messaging to voice telephone interviews for active surveillance of adverse events following immunisation. Vaccine. 2015;33(31):3689-94.
67. Regan AK, Blyth CC, Mak DB, Richmond PC, Effler PV. Using SMS to monitor adverse events following trivalent influenza vaccination in pregnant women. Aust N Z J Obstet Gynaecol. 2014;54(6):522-8.
68. Stuurman AL, Verstraeten T, De Schryver A. Rapid assessment of the reactogenicity of a 2016-2017 seasonal influenza vaccine: results from a feasibility study. Expert review of vaccines. 2017;16(2):187-91.

69. Bettinger JA, Vanderkooi OG, MacDonald J, Kellner JD. Rapid online identification of adverse events after influenza immunization in children by PCIRN's National Ambulatory Network. The Pediatric Infectious Disease Journal. 2014;33(10):1060-4.
70. Zeng J, Tang T, Wang Y, Lyu H, Huang J, Li X, et al. Post-marketing multi-center safety surveillance of inactivated enterovirus A71 vaccine (Vero cell). Zhonghua yu Fang yi xue za zhi [Chinese Journal of Preventive Medicine]. 2019;53(3):252-7.
71. Dasgupta N, Lazard A, Brownstein JS. Covid-19 vaccine apps should deliver more to patients. The Lancet Digital Health. 2021;3(5):e278-e9.
72. Simeoni R, Maccioni G, Giansanti D, editors. The Vaccination Process against the COVID-19: Opportunities, Problems and mHealth Support. Healthcare; 2021: Multidisciplinary Digital Publishing Institute.
73. Health TLD. Can technology increase COVID-19 vaccination rates? The Lancet Digital Health. 2021.
74. Rath B. Vienna Vaccine Safety Initiative. Hum Vaccin Immunother. 2018;14(5):1038-41.
75. Gesualdo F, Bucci LM, Rizzo C, Tozzi AE. Digital tools, multidisciplinarity and innovation for communicating vaccine safety in the COVID-19 era. Hum Vaccin Immunother. 2021:1-4.
76. Gesualdo F, Bucci LM, Rizzo C, Tozzi AE. Digital tools, multidisciplinarity and innovation for communicating vaccine safety in the COVID-19 era. Hum Vaccin Immunother. 2022;18(1):1865048.
77. Mammas IN, Spandidos DA. Advancing challenges in Paediatric Virology: An interview with Professor Barbara A. Rath, Co-founder and Chair of the Vienna Vaccine Safety Initiative. Experimental and therapeutic medicine. 2019;18(4):3231-7.
78. Wilson K, Atkinson KM, Deeks SL, Crowcroft NS. Improving vaccine registries through mobile technologies: a vision for mobile enhanced Immunization information systems. Journal of the American Medical Informatics Association. 2016;23(1):207-11.
79. Benis A, Tamburis O, Chronaki C, Moen A. One Digital Health: A unified framework for future health ecosystems. Journal of Medical Internet Research. 2021;23(2):e22189.
80. Hoppe C, Obermeier P, Muehlhans S, Alchikh M, Seeber L, Tief F, et al. Innovative digital tools and surveillance systems for the timely detection of adverse events at the point of care: a proof-of-concept study. Drug Saf. 2016;39(10):977-88.
81. Organization WH. Global vaccine safety blueprint: the landscape analysis. World Health Organization; 2012.
82. Organization WH. Global vaccine safety blueprint 2.0 (GVSB2. 0) 2021-2023. 2021.
83. Psihogios A, Bota AB, Mithani SS, Greyson D, Zhu DT, Fung SG, et al. A scoping review of active, participant-centred, digital adverse events following immunization (AEFI) surveillance: A Canadian immunization research network study. Vaccine. 2022.
84. WHO. IMPLEMENTING THE IMMUNIZATION AGENDA 2030:A Framework for Action through Coordinated Planning, Monitoring & Evaluation,Ownership & Accountability, and Communications & Advocacy. WHO website 2020.
85. Nyambayo P, Manyevere R, Chirinda L, Zifamba EN, Marekera SF. Descriptive Research Study of the Adverse Events Following Immunization (AEFIs) Surveillance System in Zimbabwe. Clinical Case Reports and Studies. BRS Publishers. 2023;2(2):2837-565.
86. Mundagowa PT, Tozivepi SN, Chiyaka ET, Mukora-Mutseyekwa F, Makurumidze R. Assessment of COVID-19 vaccine hesitancy among Zimbabweans: A rapid national survey. PloS one. 2022;17(4):e0266724.

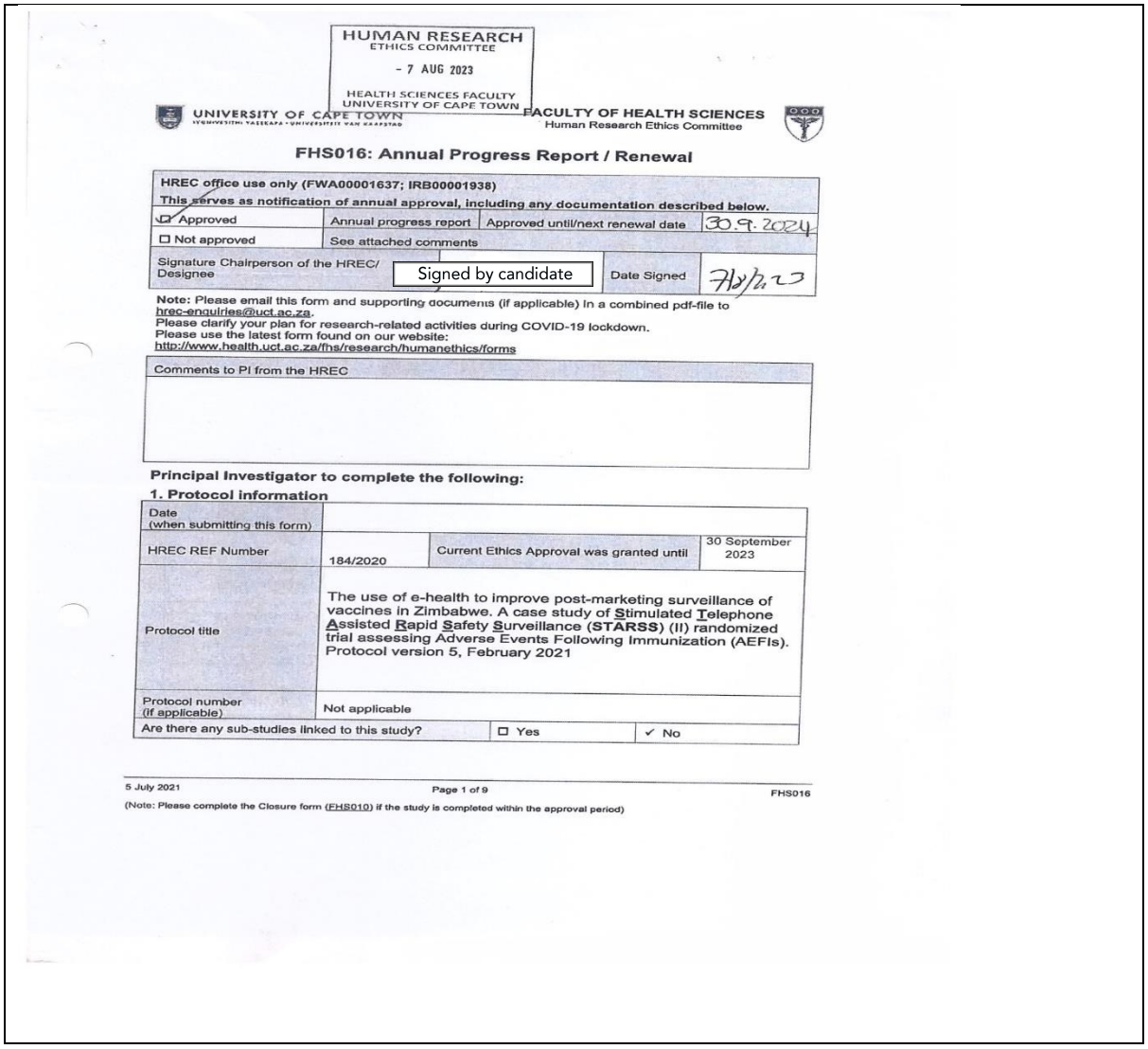
87. Fukushima A, Iessa N, Balakrishnan MR, Pal SN. Smartphone-based mobile applications for adverse drug reactions reporting: global status and country experience. BMC Medical Informatics and Decision Making. 2022;22(1):1-20.
88. Iessa N, Macolic Sarinic V, Ghazaryan L, Romanova N, Alemu A, Rungapiromnan W, et al. Smart Safety Surveillance (3S): Multi-Country Experience of Implementing the 3S Concepts and Principles. Drug Saf. 2021:1-14.
89. Sithole T, Mahlangu G, Salek S, Walker S. Evaluation of the Regulatory Review Process in Zimbabwe: Challenges and Opportunities. Therapeutic Innovation & Regulatory Science. 2021;55(3):474-89.
90. Clothier HJ, Hosking L, Crawford NW, Russell M, Easton ML, Quinn J-A, et al. Bacillus Calmette-Guerin (BCG) vaccine adverse events in Victoria, Australia: analysis of reports to an enhanced passive surveillance system. Drug Saf. 2015;38(1):79-86.
91. Clothier HJ, Lawrie J, Russell MA, Kelly H, Buttery JP. Early signal detection of adverse events following influenza vaccination using proportional reporting ratio, Victoria, Australia. Plos one. 2019;14(11):e0224702.
92. Sampath V, Rabinowitz G, Shah M, Jain S, Diamant Z, Jesenak M, et al. Vaccines and Allergic reactions: the past, the current COVID-19 pandemic, and future perspectives. Allergy. 2021.
93. Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Olsson S, Sartori D, et al. Adverse drug reaction reporting in Africa and a comparison of individual case safety report characteristics between Africa and the rest of the world: analyses of spontaneous reports in VigiBase®. Drug Saf. 2016;39(4):335-45.
94. Chandler RE. Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. BMJ. 2019;365.
95. Chandler RE. Optimizing safety surveillance for COVID-19 vaccines. Nature Reviews Immunology. 2020;20(8):451-2.
96. Zvanaka S, Tsitsi J, Chonzi P, Shambira G, Gombe NT, Tshimanga M. Evaluation of the adverse events following immunizations surveillance system in Harare City, Zimbabwe, 2016: a descriptive cross sectional study. Pan African Medical Journal. 2017;28(1).
97. Ampadu HH, Esseku Y, Dodoo AN. Evidence-Based Pharmacovigilance for Medicines Used in Public Health Programs in Africa. Evidence-Based Pharmacovigilance: Springer; 2018. p. 185-99.
98. Tozzi AE, Asturias EJ, Balakrishnan MR, Halsey NA, Law B, Zuber PL. Assessment of causality of individual adverse events following immunization (AEFI): a WHO tool for global use. Vaccine. 2013;31(44):5041-6.
99. Lee H, Kang H-Y, Cho S, Park S, Kim A-Y, Jung S-Y, et al. Causality assessment guidelines for adverse events following immunization with a focus on guillain–barré syndrome. Vaccines. 2020;8(1):101.
100. Butler M, Tamborska A, Wood GK, Ellul M, Thomas RH, Galea I, et al. Considerations for causality assessment of neurological and neuropsychiatric complications of SARS-CoV-2 vaccines: from cerebral venous sinus thrombosis to functional neurological disorder. Journal of Neurology, Neurosurgery & Psychiatry. 2021;92(11):1144-51.
101. Bergvall T, Norén GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Saf. 2014;37(1):65-77.
102. Guzman J, O'Connell E, Kikule K, Hafner T. The WHO Global Benchmarking Tool: a game changer for strengthening national regulatory capacity. BMJ Glob Health. 2020;5(8).
103. Pomara C, Sessa F, Ciaccio M, Dieli F, Esposito M, Giammanco GM, et al. COVID-19 vaccine and death: causality algorithm according to the WHO eligibility diagnosis. Diagnostics. 2021;11(6):955.

104. Stuurman AL, Sharan A, Jahagirdar S, Elango V, Riera-Montes M, Kashyap N, et al. WHO global vaccine safety multi-country collaboration project on safety in pregnancy: Assessing the level of diagnostic certainty using standardized case definitions for perinatal and neonatal outcomes and maternal immunization. Vaccine: X. 2021;9:100123.
105. Sharan A, Stuurman AL, Jahagirdar S, Elango V, Riera-Montes M, Kashyap NK, et al. Estimating baseline rates of adverse perinatal and neonatal outcomes using a facility-based surveillance approach: A prospective observational study from the WHO Global Vaccine Safety Multi-Country Collaboration on safety in pregnancy. EClinicalMedicine. 2022;50:101506.
106. Sharan A, Jahagirdar S, Stuurman AL, Elango V, Riera-Montes M, Kashyap NK, et al. Operational lessons learned in conducting an international study on pharmacovigilance in pregnancy in resource-constrained settings: The WHO Global Vaccine safety Multi-Country collaboration project. Vaccine: X. 2022;11:100160.
107. Maixenchs M, Anselmo R, Sanz A, Castillo P, Macete E, Carrilho C, et al. Healthcare providers' views and perceptions on post-mortem procedures for cause of death determination in southern Mozambique. PLoS One. 2018;13(7):e0200058.
108. Dey A, Wang H, Quinn H, Hiam R, Wood N, Beard F, et al. Surveillance of adverse events following immunisation in Australia annual report, 2017. Commun Dis Intell. 2019;43:1-28.
109. Nyambayo PP, Gold MS, Mehta UC, Clarke S, Manyevere R, Chirinda L, et al. Efficacy and feasibility of SMS m-Health for the detection of adverse events following immunisation (AEFIs) in resource-limited setting-The Zimbabwe stimulated telephone assisted rapid safety surveillance (Zm-STARSS) randomised control trial. Vaccine. 2023.
110. Meher BR. Vaccine pharmacovigilance in India: Current context and future perspective. Indian Journal of Pharmacology. 2019;51(4):243.
111. Aborigo RA, Welaga P, Oduro A, Shaum A, Opare J, Dodoo A, et al. Optimising reporting of adverse events following immunisation by healthcare workers in Ghana: A qualitative study in four regions. Plos one. 2022;17(12):e0277197.
112. Meyer J, Schonfeldt M, Bamford L, Dawood H, Dlamini S, Gray C, et al. COVID-19 Vaccine Safety Surveillance and Causality Assessment of Adverse Events Following Immunisation: Lessons from South Africa: An International Journal of Medical Toxicology and Drug Experience. Drug Saf. 2022:1171-2.
113. Kiguba R, Olsson S, Waitt C. Pharmacovigilance in low-and middle-income countries: A review with particular focus on Africa. British journal of clinical pharmacology. 2023;89(2):491-509.
114. Nsubuga F, Alfred D, Gyasi SO, Ampeire I, Kabwama SN. Low reporting of adverse events following immunization, during a Measles-Rubella catchup and Polio mass vaccination campaign in Uganda; 2019. 2022.
115. Zeleke ED, Yimer G, Lisanework L, Chen RT, Huang W-T, Wang S-H, et al. System and facility readiness assessment for conducting active surveillance of adverse events following immunization in Addis Ababa, Ethiopia. International Health. 2023:ihac085.
116. Tsafack M, Ateudjieu J. Improving community based AEFI (Adverse Events Following Immunization) reporting rate through telephone" beep" in a Cameroon health district: a randomized field trial. Pan African Medical Journal. 2015;22(1).
117. Smit M, Olney J, Ford NP, Vitoria M, Gregson S, Vassall A, et al. The growing burden of noncommunicable disease among persons living with HIV in Zimbabwe. AIDS (London, England). 2018;32(6):773.
118. Bohn-Goldbaum E, Cross T, Leeb A, Peters I, Booy R, Edwards KM. Adverse events following influenza immunization: understanding the role of age and sex interactions. Expert Review of Vaccines. 2022;21(3):415-22.

119. Gidudu JF, Shaum A, Dodoo A, Bosomprah S, Bonsu G, Amponsa-Achiano K, et al. Barriers to healthcare workers reporting adverse events following immunization in four regions of Ghana. Vaccine. 2020;38(5):1009-14.
120. Clothier HJ, Selvaraj G, Easton ML, Lewis G, Crawford NW, Buttery JP. Consumer reporting of adverse events following immunization. Hum Vaccin Immunother. 2014;10(12):3726-30.
121. Munnoch S-A, Cashman P, Peel R, Attia J, Hure A, Durrheim DN. Participant-Centered online active surveillance for adverse events following vaccination in a large clinical trial: feasibility and usability study. Journal of Medical Internet Research. 2019;21(10):e14791.
122. Bettinger JA, Sadarangani M, De Serres G, Valiquette L, Vanderkooi OG, Kellner JD, et al. The Canadian National Vaccine Safety Network: surveillance of adverse events following immunisation among individuals immunised with the COVID-19 vaccine, a cohort study in Canada. BMJ open. 2022;12(1):e051254.
123. Gold MS, Lincoln G, Bednarz J, Braunack-Mayer A, Stocks N. Consumer acceptability and validity of m-Health for the detection of adverse events following immunization - The Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) randomised control trial. Vaccine. 2021;39(2):237-46.
124. Nyambayo PP, Gold MS, Mehta UC. Data-Driven vigiPoint identification study of Zimbabwe ICSRs compared with RoW VigiBase data with and without USA reports. Fortune Journal of Health Sciences. 2023;6:237-45.
125. Cajita MI, Hodgson NA, Lam KW, Yoo S, Han H-R. Facilitators of and barriers to mHealth adoption in older adults with heart failure. Computers, informatics, nursing: CIN. 2018;36(8):376.
126. Parrella A, Gold M, Braunack-Mayer A, Baghurst P, Marshall H. Consumer reporting of adverse events following immunization (AEFI) Identifying predictors of reporting an AEFI. Hum Vaccin Immunother. 2014;10(3):747-54.
127. Yamoah P, Oosthuizen F. An Assessment of the Reporting Pattern of Adverse Events Following Immunizations in VigiAccess. Global Journal of Health Science. 2018;10(11):46.
128. Appiah B, Poudyal A, Burdine JN, Asamoah-Akuoko L, Anum DA, Kretchy IA, et al. Factors that influence the intention to use mobile phone caller tunes for patient reporting of adverse drug reactions: a qualitative study. Ther Adv Drug Saf. 2019;10:2042098619871190.
129. Furusa SS, Coleman A. Factors influencing e-health implementation by medical doctors in public hospitals in Zimbabwe. South African Journal of Information Management. 2018;20(1):1-9.
130. Crann SE, Barata PC, Mitchell R, Mawhinney L, Thistle P, Chirenje ZM, et al. Healthcare providers' perspectives on the acceptability and uptake of HPV vaccines in Zimbabwe. Journal of Psychosomatic Obstetrics & Gynecology. 2016;37(4):147-55.
131. Jeon M, Kim J, Oh CE, Lee J-Y. Adverse events following immunization associated with coronavirus disease 2019 vaccination reported in the mobile vaccine adverse events reporting system. Journal of Korean medical science. 2021;36(17).
132. Davey S, Davey A. Medical errors in practice which medical fraternity must not forget: A critical look. International Journal of Health System and Disaster Management. 2013;1(3):190.
133. Seaneke SK, Darko DM, Nkansah E, Asamoa-Amoakohene A, Ashie A, Sampson Ewudzie J, et al. First results from the lessons learnt from the deployment of the Med Safety App for reporting adverse drug reactions in Ghana. Digital health. 2023;9:20552076231211276.
134. Rodrigues CM, Plotkin SA. IMAPCt of vaccines; health, economic and social perspectives. Frontiers in microbiology. 2020;11:1526.
135. Gostin LO, Hodge JG, Bloom BR, El-Mohandes A, Fielding J, Hotez P, et al. The public health crisis of underimmunisation: a global plan of action. The Lancet Infectious Diseases. 2020;20(1):e11-e6.

136. Bhandari B, Rayamajhi G, Lamichhane P, Shenoy AK. Adverse events following immunization with COVID-19 vaccines: a narrative review. BioMed research international. 2022;2022.
137. Braun MM, Mootrey GT, Salive ME, Chen RT, Ellenberg SS, Group VW. Infant immunization with acellular pertussis vaccines in the United States: assessment of the first two years' data from the Vaccine Adverse Event Reporting System (VAERS). Pediatrics. 2000;106(4):e51-e.
138. Geier DA, Geier MR. An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines. Brain and Development. 2004;26(5):296-300.
139. Müller-Nordhorn J, Hettler-Chen C-M, Keil T, Muckelbauer R. Association between sudden infant death syndrome and diphtheria-tetanus-pertussis immunisation: an ecological study. BMC pediatrics. 2015;15(1):1-8.
140. Huang WT, Chen RT, Hsu YC, Glasser JW, Rhodes PH. Vaccination and unexplained sudden death risk in Taiwanese infants. pharmacoepidemiology and drug safety. 2017;26(1):17-25.
141. Kapuria B, Hamadeh RS, Mazloum F, Chaalan K, Aung K, Higgins E, et al. Immunization as an Entry Point (IaEP) for Primary Health Care (PHC) and Beyond Healthcare Interventions-Process and Insights from an integrated approach at Lebanon. Frontiers in Health Services. 2023;3:1251775.
142. (POTRAZ) PaTRAoZ. Abridged-Sector-Performance-Report-2023. 2023.
143. Mungwira RG, Guillard C, Saldaña A, Okabe N, Petousis-Harris H, Agbenu E, et al. Global landscape analysis of no-fault compensation programmes for vaccine injuries: A review and survey of implementing countries. PLoS One. 2020;15(5):e0233334.
144. Crum T, Mooney K, Tiwari BR. Current situation of vaccine injury compensation program and a future perspective in light of COVID-19 and emerging viral diseases. F1000Research. 2021;10.
145. mondiale de la Santé O, Organization WH. Report of the Meeting of the WHO Global Advisory Committee on Vaccine Safety, 15–16 May 2023–Rapport de la réunion du Comité consultatif mondial de l'OMS pour la sécurité des vaccins, 15-16 mai 2023. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 2023;98(32):345-54.
146. mondiale de la Santé O, Organization WH. Weekly Epidemiological Record, 2023, vol. 98, 32 [full issue]. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 2023;98(32):345-54.

Appendix 1_UCT Committee Ethical Approvals HREC 184/2020



HUMAN RESEARCH ETHICS COMMITTEE
- 7 AUG 2023
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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.9.2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signed by candidate	Date Signed	7/8/23

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)			
HREC REF Number	184/2020	Current Ethics Approval was granted until	30 September 2023
Protocol title	The use of e-health to improve post-marketing surveillance of vaccines in Zimbabwe. A case study of Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) randomized trial assessing Adverse Events Following Immunization (AEFIs). Protocol version 5, February 2021		
Protocol number (if applicable)	Not applicable		
Are there any sub-studies linked to this study?	☐ Yes	✓ No	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.	
Principal Investigator	Assoc. Prof Ushma Mehta
Department / Office Internal Mail Address	Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, UCT. Ushma Mehta ushma.mehta@uct.ac.za

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	✓ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)**appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	✓
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	
Contact person	
Telephone number	
Email Address	
2. Internal Journal Billing:	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

1. Completed FHS016 annual renewal application form 2023
2. STARSS (II) Protocol version 5, February 2021
3. Copy of protocol thesis chapter 3 published manuscript titled "Descriptive Research Study of the Adverse Events Following Immunization (AEFIs) Surveillance System in Zimbabwe" Surveillance system available under the following : https://bioresscientia.com/journals/clinical-case-reports-and-studies/articles-in-press
4. Copy of protocol thesis chapter 4 published manuscript tilted "Data driven vigiPoint identification study of adverse events reporting patterns for Zimbabwe reports in VigiBase WHO global database" available under the following: https://fortuneonline.org/articles/data-driven-vigipoint-identification-study-of-adverse-event-reporting-patterns-for-zimbabwe-reports-in-vigibase-who-global-databas.html
5. Copy of STARSS manuscript submitted to Vaccine journal for publication will be shared once published.

3. Protocol status (tick ✓)

☐	Open Enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

✓	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	4560
Number of participants enrolled, since last HREC Progress report (continuing review)	4560
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	24 (0.43%) of total screened i.e., <1%

6. Cumulative summary of participants

Total number of participants who provided consent	4560
Number of participants determined to be ineligible (i.e. after screening)	0
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	4560
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

HREC:

The Medicines Control Authority of Zimbabwe (MCAZ) as the national pharmacovigilance center led by the PhD student and in collaboration with national Zimbabwe Expanded Program on Immunization embarked on strengthening the national AEFI surveillance system by conducted the STARSS(II) protocol titled "The use of e-health to improve post-marketing surveillance of vaccines in Zimbabwe. A case study of Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) randomized trial assessing Adverse Events Following Immunization (AEFIs)". Protocol version 5 February 2021. A total of 4560 vaccinees were enrolled (including children/guardian pairs and adult COVID-19 vaccinees). All available data collected analysis and most manuscript submitted for publication. Thesis preparation is in progress for submission in accordance with UCT requirements.

1) Protocol chapter 1 Introduction completed
2) Protocol Chapter 2 Scoping literature review being completed.
3) Protocol Chapter 3: This chapter aimed to describe the existing AEFI surveillance system in Zimbabwe with a detailed analysis of the AEFI reports. Data analysis done and manuscript published copy available under the following hyperlink: titled "Descriptive Research Study of the Adverse Events Following Immunization (AEFIs) Surveillance System in Zimbabwe" Surveillance system available under the following :

   https://bioresscientia.com/journals/clinical-case-reports-and-studies/articles-in-press

4) Copy of protocol thesis chapter 4 published manuscript tilted "Data driven vigiPoint identification study of adverse events reporting patterns for Zimbabwe reports in VigiBase WHO global database" available under the following: https://fortuneonline.org/articles/data-driven-vigipoint-identification-study-of-adverse-event-reporting-patterns-for-zimbabwe-reports-in-vigibase-who-global-databas.html
5) Protocol Chapter 5: Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) randomized trial efficacy of AEFIs detection and consumer acceptability study. Data analysis completed, manuscript written and submitted to Vaccine Journal for publication.
6) Protocol Chapter 6: Nested in Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) randomized trial was consumer and Healthcare Workers (HCWs) experience study. Final data nalysis in progress and manuscript drafting.
7) Protocol Chapter 7: Thesis recommendations writing in progress.

8. Protocol violations and exceptions (tick ✓ all that apply)

☐	No prior violations or exceptions have occurred since the original approval

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

✓	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐	No Prior amendments have been made since the original approval
✓	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised*, or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
None since previous renewal submission in September 2022.

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g., in the case of abnormal or incidental clinical findings, distress or anxiety)?		
✓ Yes	☐ No	☐ Not applicable
If yes, please describe:		
The STARSS study is about testing mHealth efficacy in AEFI detection and acceptability by consumer vaccinees and HCWs. A total of 41 participants experienced 87 AEFIs including 4 serious AEFIs. All recovered except one unfortunate baby who died in hospital study site during treatment for pneumonia that started a few days prior to vaccination. All AEFI causality assessment was done by the National AEFI Committee and feedback sent to reporters. There were no AEFIs reported in the control passive surveillance arm. AEFI log was attached and approved in the HREC annual renewal application 2022 since study was conducted from November 2020 to August 2021.		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
✓ Yes MRCZ & MCAZ	☐ No	☐ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report? N/A		
☐ Yes	☐ No	✓ Not applicable

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓)	Shown no change
If there has been a change, please explain:	
All 4560 participants were enrolled by signed informed consent process and educated on monitoring AEFIs at both study sites by HCWs. In addition, survey questions were administered during screening, enrolment and follow up. The STARSS protocol intervention Computer-assisted telephonic interview (CATI) arm supported the early detection of AEFIs by SMS on Day 0, 2 and 14 post vaccination so that all AEFI were appropriately managed. 40 participants recovered fully except for the unfortunate one baby who was diagnosed, admitted, and treated for pneumonia. This case was unrelated to vaccination. Although there is likely to have been some individual benefit of earlier access to care, we are unable to prove statistically that the risk to participants decreased.	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

Studies have demonstrated that such mHealth participant centred (MPAC) AEFI surveillance reporting mechanisms can reduce under-reporting and increase early detection of potential signals of AEFI while providing an opportunity for vaccinees to report their experiences post-vaccination (refs 1-3). A recently published scoping review evaluating conducted by Canadian researchers concluded that: "Active, participant centered, digital AEFI surveillance is an area actively being researched as depicted by the literature landscape mapped by this scoping review. We hypothesize that the AEFI surveillance approach herein described could become a primary method of collecting self-reported subjective symptoms and reactogenicity from vaccinees, complementing existing systems. Future evaluation of identified digital solutions is necessary to bring about improvements to current vaccine surveillance systems to meet contemporary and future public health needs"(4). Since most studies were conducted in HICs we hypothesized that additional studies need to assess the feasibility aspects, whether such reporting improves care-seeking behaviour or access to care of those who experience AEFI, particularly serious AEFI, in LMICs.

References:

1. Gold M, Lincoln G, Cashman P, Braunack-Mayer A, Stocks N. Efficacy of m-Health for the detection of adverse events following immunization–The stimulated telephone assisted rapid safety surveillance (STARSS) randomised control trial. Vaccine. 2021;39(2):332-42.
2. Gold M, Lincoln G, Bednarz J, Braunack-Mayer A, Stocks N. Consumer acceptability and validity of m-Health for the detection of adverse events following immunization–The Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) randomised control trial. Vaccine. 2021;39(2):237-46.
3. Cashman P, Macartney K, Khandaker G, King C, Gold M, Durrheim DN. Participant-centred active surveillance of adverse events following immunisation: a narrative review. Int Health. 2017;9(3):164-76.
4. Psihogios A, Bota AB, Mithani SS, Greyson D, Zhu DT, Fung SG, et al. A scoping review of active, participant-centred, digital adverse events following immunization (AEFI) surveillance: A Canadian immunization research network study. Vaccine. 2022.

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**			
☐ Yes		✓No study enrolment. Study follow was up completed in August 2021. Data analysis completed. PhD thesis writing and manuscripts for publication in progress.	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI	Signed by candidate	Date	2 August 2023

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix 2 Ethical Approvals by Medical Research Council of Zimbabwe (MRCZ)

Telephone: 791792/791193
Telefax: (263) - 4 – 790715
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
No. 20 Cambridge Road
Avondale
Harare
Zimbabwe

CONTINUING APPROVAL

REF: MRCZ/A/2286 **01 September 2022**

Priscilla Nyambayo
Medicine Control Authority of Zimbabwe
106 Baines Avenue
Harare

RE:- The use of e-Health to improve post-marketing surveillance of vaccines in Zimbabwe, A case study of Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) randomized trial assessing Adverse Events Following Immunization (AEFIs)" Protocol version 5 February 2021.

Thank you for the application for review of Research Activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review:-

a) MRCZ Annual Renewal Form 102
b) Progress Report

- **APPROVAL NUMBER** : **MRCZ/A/2286**

This number should be used on all correspondence, consent forms and documents as appropriate.

- **TYPE OF MEETING** : **Expedited**
- **EFFECTIVE APPROVAL DATE** : **12 April, 2022**
- **EXPIRATION DATE:-** : **11 April, 2023**

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted three months before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING**: All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices or website.
- **MODIFICATIONS**: Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices or website.
- **QUESTIONS**: Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrcz.org.zw

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.
- In addition to this approval, all clinical trials involving drugs, devices and biologics (including other studies focusing on registered drugs) require approval of Medicines Control Authority of Zimbabwe (MCAZ) before commencement.

Yours Faithfully

Signed by candidate

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
SEP 2022
APPROVED
20 CAMBRIDGE ROAD, AVONDALE, HARARE

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Telephone: +2638644073772/791193
E-mail: mrcz@mrcz.org.zw
Website: www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazowe Street
P. O. Box CY 573
Causeway
Harare

REF: MRCZ/A/2286

18 March, 2021

Priscilla Nyambayo
Medicine Control Authority of Zimbabwe (MCAZ)
106 Baines Avenue
Harare

RE: - Amendment request for an approved study entitled: The use of e-health to improve post-marketing surveillance of vaccines in Zimbabwe. A Case Study of Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) - Randomized Controlled Trial Assessing Adverse Events Following Immunization (AEFIs). Version 5.0 February 2021

We refer to your correspondence dated 9 March, 2021 on the above-mentioned subject.

Please be advised that the MRCZ has **reviewed** and **approved** your request to:

- To monitor the safety of the Sinopharm vaccines and any other COVID-19 vaccines for Adverse Events Following Immunisation (AEFIs) deployed by the Zimbabwe Expanded Program on Immunisation.
- Include additional informed consent form for healthcare workers (HCWs) and/or any adult who receive the COVID 19 Sinopharm vaccines, and any other COVID-19 vaccines first or second dose.

Based on the above, the following study documents have been approved:

1. STARSS (II) protocol Version 5.0 dated February 2021
2. STARSS Vaccine healthcare worker adult and ICF Version 5.0 dated February 2021

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2021 -03- 18
APPROVED
P.O. BOX CY 573 CAUSEWAY HARARE

Yours Faithfully

Signed by candidate

.....

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

Telephone: +2638644073772/791193
E-mail: mrcz@mrcz.org.zw
Website: www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazowe Street
P. O. Box CY 573
Causeway
Harare

REF: MRCZ/A/2286

9 October 2020

Priscilla Nyambayo
Medicine Control Authority of Zimbabwe (MCAZ)
106 Baines Avenue
Harare

RE: - Amendment request for an approved study entitled: The use of e-health to improve post-marketing surveillance of vaccines in Zimbabwe. A Case Study of Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) - Randomized Controlled Trial Assessing Adverse Events Following Immunization (AEFIs). Version 3.0 February 2020

We refer to your correspondence dated February 3, 2020 on the above-mentioned subject.

Please be advised that the MRCZ has **reviewed** and **approved** your request to:

- Make minor changes to include COVID-19 infection prevention measures.

Based on the above, the following study documents have been approved:

1. STARSS (II) protocol Version 4.0 dated July 2020
2. STARSS Guardian/parental ICF Version 4.0 dated July 2020 (English, Shona, Ndebele, Back translation)

Yours Faithfully

Signed by candidate

.....
MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2020 -09- 19
APPROVED
FOR CHAIRPERSON, HARARE

Telephone: 791792/791193
Telefax: (263) - 4 – 790715
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

APPROVAL

REF: MRCZ/A/2286

12 April, 2018

Priscilla Nyambayo
Medicine Control Authority of Zimbabwe
106 Baines Avenue
Harare

RE:- The use of e-health to improve post-marketing surveillance of vaccines in Zimbabwe. A Case Study Of Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) (II) - Randomized Trial Assessing Adverse Events Following Immunisation (AEFIs). Version 2, March 2018

Thank you for the application for review of Research Activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review:-

a) STARSS Protocol Version 2, March 2018
b) STARSS Parental Informed Consent Form (ICF), Version 2, March 2018 (English, Shona and Ndebele)
c) STARSS Parental Informed Consent Form (ICF), Version 2, March 2018 (Shona and Ndebele Back-translation)
d) Data collection tools (English, Shona and Ndebele)

- **APPROVAL NUMBER : MRCZ/A/2286**

This number should be used on all correspondence, consent forms and documents as appropriate.

- **TYPE OF MEETING : Expedited review**
- **EFFECTIVE APPROVAL DATE : 12 April, 2018**
- **EXPIRATION DATE:- : 11 April, 2019**

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted three months before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING**: All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices or website.
- **MODIFICATIONS**: Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices or website.
- **QUESTIONS**: Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrcz.org.zw

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.

Yours Faithfully

Signed by candidate

.....

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2018 -04- 12
APPROVED
P.O. BOX CY 573 CAUSEWAY, HARARE

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Appendix 3: Study Sites Ethical Approvals

CHITUNGWIZA MUNICIPALITY

All Correspondence to be addressed to the Town Clerk

If Calling, Please
Ask for .Dr. T. I. Kasu

P. O. Box 70, ZENGEZA
CHITUNGWIZA.
Cell: 0772 375 284
0719 004 607
0712 832 801
E-mail dhschitungwiza@gmail.com
dr.tonykasu@hotmail.com

OUR REF :
YOUR REF :
DATE : 02 November 2020

Medicines Control Authority of Zimbabwe
106 Baines Avenue
HARARE

Attention: Priscilla Nyambayo

RE: REQUEST FOR PERMISSION TO CONDUCT STARSS STUDY TRAINING

The above matter refers

Thank you for your communication. I have gone through the project documents and have no objection of the implementation of the project in Chitungwiza.

For any further assistance of an operational nature from the Chitungwiza City Health Department for this project, please approach Matrons Zhakata and Munyuwki, as well as the EPI focal person for Chitungwiza City Health Department

Signed by candidate

CHITUNGWIZA MUNICIPALITY
DIRECTOR OF HEALTH SERVICES (T) 04
12 NOV 2020
P. O. BOX CZA 70, CHITUNGWIZA

Dr. T. I. KASU
DIRECTOR HEALTH SERVICES

PPN??

CITY OF HARARE

Director of Health Services

DR PROSPER CHONZI
MBChB, MPH,MBA

All correspondence to be addressed to the
DIRECTOR OF HEALTH SERVICES

Ref:----------

Your Ref:----------

DIRECTOR OF HEALTH SERVICES
Rowan Martin Building,
Civic Centre,
Pennefather Avenue,
off Rotten Row,
Harare, Zimbabwe.

P.O. Box 596
Telephone: 753326
753330/1/2
Fax: (263-4) 752093

01 February 2018

Mr R Rukwata
Acting Director General
Medicines Control Authority of Zimbabwe
106 Baines Avenue
HARARE

Dear Sir

RE: REQUEST FOR PERMISSION TO CARRYOUT A PROJECT

I acknowledge receipt of your letter in connection with the above

Permission has been granted for you to carry out a study entitled: ***"Proof of concept and demonstration project for e-health surveillance of adverse events following immunization (AEFI) for vaccines in Zimbabwe setting using a Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) Innovation method"*** from January 2018 to January 2019 at HARARE City Clinics.

For further assistance please liaise with the Nursing Manager at Rowan Martin Building and the Sisters In Charge at the clinics.

Yours faithfully

RECEIVED
05 FEB 2018
REGISTRY

Signed by candidate

DIRECTOR OF HEALTH SERVICES
IM/rm

Nursing Manager - Rowan Martin Building
EPI Officer
Sisters In Charge - Harare City Health clinics

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2018 -02- 07
RECEIVED
[illegible] HARARE

Telephone: +263-4-722187
Telegraphic Address:
"MEDICUS", Harare
Fax: +263-4-794734
(702293 FHP)
Telex: MEDICUS 22211ZW

ZIMBABWE

Reference:

Ministry of Health and Child
Welfare
P. O. Box CY1122
Causeway
HARARE

21 March 2018

The Director-General
Medicines Control Authority of Zimbabwe
106 Baines Avenue
Harare

Attention:- Ms G.N Mahlangu

RE: Permission to conduct the proposed project titled "Proof of concept and demonstration project for e-health surveillance of adverse events following immunization (AEFI) for vaccines in Zimbabwe setting using a Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) Innovation method" and request for WHO technical support.

We refer to your letter dated 13th March 2018 requesting for permission to select other two suitable vaccination clinic sites with internet access for the Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) pilot project.

Permission has been granted to work with CITIMED and Chitungwiza hospitals to conduct the STARSS pilot study as they have internet access suitable for the project software that was identified.

Signed by candidate

SECRETARY FOR HEALTH & CHILD CARE
(01) SECRETARY'S OFFICE
22 MAR 2018
P. BAG CY... CAUSEWAY
HARARE

Major General (Dr) G. Gwinji
SECRETARY FOR HEALTH & CHILD CARE

THE UNIVERSITY OF ADELAIDE
AUSTRALIA

DISCIPLINE OF PAEDIATRICS
SCHOOL OF PAEDIATRICS & REPRODUCTIVE HEALTH
FACULTY OF HEALTH SCIENCES
THE UNIVERSITY OF ADELAIDE
SA 5005 Australia

Postal address:
University Department of Paediatrics
WOMEN'S AND CHILDREN'S HOSPITAL
75 King William Road
NORTH ADELAIDE SA 5006

Telephone: +61 8 8161 7266
Facsimile: +61 8 8161 7031

CRICOS Provider Number 00123M

Mr Stephen Clarke
Software Architect
ChordWizard Systems
systems@chordwizard.com
http://www.chordwizard.org

Dear Stephen

Re STARSS II – application of STARSS I to the Zimbabwe context

This letter is to strongly support your involvement in the adaption of the STARSS I platform to the Zimbabwe context (STARSS II). The STARSS II is a research project in which I am providing technical support. The lead investigator is the head of Pharmacovigilance of the Medicines Control Authority of Zimbabwe, Priscilla Nyambayo. The STARSS II has received approval from the Medicines Research council of Zimbabwe (MRCZ/A/2286, on the 12 April 2018 and has received funding from the World health Organisation.

I am the principle investigator for STARSS I which is an NHMRC funded trial. The STARSS I platform was developed by yourself. The STARSS system, in part, was based on VAXTRAKER which was developed in conjunction with the Hunter New England Health Service.

It is certainly my intent that the platform or adaptations of this are made available for public health use and that agreements should be in place to prevent the IP of the system to be used for commercial use by any third parties. I will address any potential IP issues with the University of Adelaide and seek advice as to whether formal agreements are required.

With kind regards

Signed by candidate

Professor Michael Gold

Discipline of Paediatrics
School of Paediatrics & Reproductive Health
THE UNIVERSITY OF ADELAIDE

Cc Professor David Durrheim

Signed by candidate

Appendix 4: Record of Scoping Literature Review Search Strategy-Specific Search Queries for All Databases

Record of Scoping Literature Review Search Strategy Specific Search Queries for All Databases Used for SMS And/or Mobile App mHealth Active Participant Centred AEFI Surveillance. Abstracts of identified documents were read, and full text of relevant documents were retrieved for inclusion in the review. Reference lists of retrieved documents were also searched to identify additional publications			
Database searched	Search terms	Results	Sources used
Part 1 Scoping Literature Review Search explored use of mHealth technology for AEFI detection and/or surveillance for licensed and/or EUA COVID-19 vaccines 1970-December 2021.			
PubMed-Part 1 Scoping Literature Review Search Licensed and/or EUA COVID 19 vaccines, mHealth & AEFI surveillance.	**Set 1.** INDEX (Medline)	**28,027,655**	**13**
	Set 2. ((TITLE-ABS-KEY (covid-19 OR "coronavirus 2019" OR sars-cov-2 OR sars-2 OR "severe acute respiratory syndrome coronavirus 2")) AND (TITLE-ABS-KEY ("adverse effect*" OR "side effect*" OR "Adverse Events Following Immunization" OR "adverse events following Immunization" OR aefi OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug-Related Side Effect* and Adverse Reactions*" OR "Adverse Drug Reaction Reporting Systems*")) AND (TITLE-ABS-KEY (vaccine* OR vaccination* OR Immunization OR Immunization OR Astra-Zeneca OR Pfizer OR "Johnson & Johnson" OR "Johnson and Johnson" OR Sinovac OR	**13**	**13**

	SinoPharm OR Moderna OR sputnik OR Covax OR covaxin)) AND (TITLE-ABS-KEY ("mobile health" OR mhealth OR "mobile phone*" OR "mobile app*" OR "cell phone*" OR "smartphone app*" OR 3g OR 4g OR 5g OR ehealth OR telemedicine))) AND NOT (INDEX (medline))		
	Set 3. ((TITLE-ABS-KEY (covid-19 OR "coronavirus 2019" OR sars-cov-2 OR sars-2 OR "severe acute respiratory syndrome coronavirus 2")) AND (TITLE-ABS-KEY ("adverse effect*" OR "side effect*" OR "Adverse Events Following Immunization" OR "adverse events following Immunization" OR AEFI OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug-Related Side Effect* and Adverse Reactions*" OR "Adverse Drug Reaction Reporting Systems*")) AND (TITLE-ABS-KEY (vaccine* OR vaccination* OR Immunization OR Immunization OR astra-Zeneca OR pfizer OR "Johnson & Johnson" OR "Johnson and Johnson" OR Sinovac OR SinoPharm OR Moderna OR sputnik OR Covax OR Covaxin)) AND (TITLE-ABS-KEY ("mobile health" OR mhealth OR "mobile phone*" OR "mobile app*" OR "cell phone*" OR "smartphone app*" OR 3g OR 4g OR 5g OR ehealth OR telemedicine))) AND NOT (INDEX (medline)) AND (LIMIT-TO (LANGUAGE , "English"))	**13**	**13**
	1 AND 2 AND3 **Limits: ALL Languages** **Time frame:1970-2021**	**13**	**13**
CINAHL – Part 1 Scoping Literature	**Set 1.** (Covid-19 OR "coronavirus 2019" OR sars-cov-2 OR sars-2 OR "severe acute respiratory syndrome coronavirus 2"	**126,305**	**4**

Review Search.			
	Set 2. (“adverse effect*" OR "side effect*" OR "Adverse Events Following Immunization" OR "adverse events following Immunization" OR aefi OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug Related Side Effect* and Adverse Reactions*" OR "Adverse Drug Reaction Reporting System*")	**1,477,616**	**4**
	Set 3. (vaccine* OR vaccination* OR Immunization OR Immunization OR AstraZeneca OR pfizer OR "Johnson & Johnson" OR "Johnson and Johnson" OR Sinovac OR SinoPharm OR Moderna OR sputnik OR Covax OR Covaxin)	**234,043**	**4**
	Set 4. (“mobile health" OR mhealth OR "mobile phone*" OR "mobile app*" OR "cell phone*" OR "smartphone app*" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)	**99,448**	**4**
	1 AND 2 AND 3 AND 4 AND 5 **Limits: All languages** **Time frame:1970-2021**	**4**	**4**
COHCRANE Part 1 Scoping Literature Review Search Licensed and/or EUA COVID 19 vaccines, mHealth &	**Set 1.** (Covid-19 OR "coronavirus 2019" OR sars-cov-2 OR sars-2 OR "severe acute respiratory syndrome coronavirus 2" **and** **Set 2.** (“adverse effect*" OR "side effect*" OR "Adverse Events Following Immunization" OR "adverse events following Immunization" OR aefi OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug Related Side Effect* **and** **Set 3**. Adverse Reactions*" OR "Adverse Drug Reaction Reporting System*") **and** (vaccine* OR vaccination* OR Immunization OR Immunization OR AstraZeneca OR pfizer OR "Johnson & Johnson" OR "Johnson and		

AEFI surveillance.	Johnson" OR Sinovac OR SinoPharm OR Moderna OR sputnik OR Covax OR Covaxin) **and** **Set 4.** (“mobile health" OR mhealth OR "mobile phone*" OR "mobile app*" OR "cell phone*" OR "smartphone app*" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)		
	1 AND 2 AND 3 AND 4 **Limits: All languages** **Time frame:1970-2021**	**25**	**25**
SCOPUS. Part 1 Scoping Literature Review Search, Licensed and/or EUA COVID 19 vaccines. mHealth & AEFI surveillance	**Set 1** TITLE-ABS-KEY (covid-19 OR “coronavirus 2019” OR sars-cov-2 OR sars-2 OR “severe acute respiratory syndrome coronavirus 2”)	**189,524**	**49**
	Set 2 TITLE-ABS-KEY (“adverse effect*” OR “side effect*” OR “Adverse Events Following Immunization” OR “adverse events following Immunization” OR AEFI OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug-Related Side Effect* and Adverse Reactions*" OR "Adverse Drug Reaction Reporting Systems*")	**6,082,682**	**49**
	Set 3 TITLE-ABS-KEY (vaccine* OR vaccination* OR Immunization OR Immunization OR astra-Zeneca OR Pfizer OR “Johnson & Johnson” OR “Johnson and Johnson” OR Sinovac OR SinoPharm OR Moderna OR Sputnik OR COVAX OR covaxin)	**623,509**	**49**
	Set 4 TITLE-ABS-KEY (“mobile health” OR mhealth OR “mobile phone*” OR “mobile app*” OR “cell phone*” OR “smartphone app*” OR 3g OR 4g OR 5g OR ehealth OR telemedicine)	**278,995**	**49**
	Set 5	**49**	**49**

	(TITLE-ABS-KEY (covid-19 OR "coronavirus 2019" OR sars-cov-2 OR sars-2 OR "severe acute respiratory syndrome coronavirus 2")) AND (TITLE-ABS-KEY ("adverse effect*" OR "side effect*" OR "Adverse Events Following Immunization" OR "adverse events following Immunization" OR aefi OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug-Related Side Effect* and Adverse Reactions*" OR "Adverse Drug Reaction Reporting Systems*")) AND (TITLE-ABS-KEY (vaccine* OR vaccination* OR Immunization OR Immunization OR Astra-Zeneca OR pfizer OR "Johnson & Johnson" OR "Johnson and Johnson" OR Sinovac OR SinoPharm OR Moderna OR sputnik OR Covax OR Covaxin)) AND (TITLE-ABS-KEY ("mobile health" OR mhealth OR "mobile phone*" OR "mobile app*" OR "cell phone*" OR "smartphone app*" OR 3g OR 4g OR 5g OR ehealth OR telemedicine))		
	1 AND 2 AND 3 AND 4 AND 5 **Limit: All languages** **Time frame:1970-2021**	**49**	**49**
Part 2 Scoping Review Literature Search explored use of mHealth technology for AEFI detection and /or surveillance for licensed other, vaccine.			
Data base searched	**Search Terms**	**Results**	**Sourced used**
PubMed - Part 2a Scoping Literature Search- Other licensed vaccines.	**Set 1** Search: (“mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)	**166,857**	
	Set 2 Search: "Telemedicine"[Mesh] Sort by: Most Recent	36,281	

	Set 3 Search: ((“mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh])	**166,857**	
	Set 3 Search: (adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)	**4,452,053**	
	Set 4 Search: "Long Term Adverse Effects"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] Sort by: Most Recent	**127,890**	
	Set 5 Search: "Injection Site Reaction"[Mesh] Sort by: Most Recent	**276**	
	Set 6 Search: (((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Long Term Adverse Effects"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Injection Site Reaction"[Mesh])	**4,473,144**	
	Set 7 Search: (vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR smallpox OR chickenpox OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR flu OR influenza OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR "Whooping cough" OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR Ebola OR "Japanese encephalitis")	**4,421,052**	

	Set 8 Search: "Vaccines"[Mesh] Sort by: Most Recent	**243,595**	
	Set 9 Search: "Immunization"[Mesh] Sort by: Most Recent	**186,361**	
	Set 10 Search: "Measles-Mumps-Rubella Vaccine"[Mesh] OR "Herpes Zoster Vaccine"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Chickenpox Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Smallpox Vaccine"[Mesh] OR "Rubella Vaccine"[Mesh] OR "Poliovirus Vaccine, Oral"[Mesh] OR "Poliovirus Vaccine, Inactivated"[Mesh] OR "Mumps Vaccine"[Mesh] OR "Measles Vaccine"[Mesh] OR "Plague Vaccine"[Mesh] OR "BCG Vaccine"[Mesh] OR "Heptavalent Pneumococcal Conjugate Vaccine"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "Influenza Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "Papillomavirus Vaccines"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR "Ebola Vaccines"[Mesh] OR "Adenovirus Vaccines"[Mesh] OR "Haemophilus influenzae type b polysaccharide vaccine" [Supplementary Concept] OR "Haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate" [Supplementary Concept] OR "Malaria Vaccines"[Mesh] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR "Japanese Encephalitis Vaccines"[Mesh] OR "Rabies Vaccines"[Mesh] OR "Respiratory Syncytial Virus Vaccines"[Mesh] OR "Lyme Disease Vaccines"[Mesh] OR "diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae b conjugate-hepatitis B vaccine" [Supplementary Concept] OR "diphtheria-tetanus-five component acellular pertussis-inactivated poliomyelitis - Haemophilus influenzae type b conjugate vaccine" [Supplementary Concept] OR "13-valent pneumococcal vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, L1 type 16, 18" [Supplementary Concept] OR "Hib-MenCY-TT vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, TA" [Supplementary Concept] OR "Haemophilus influenza type b	**132,380**	

	polysaccharide vaccine-tetanus toxin conjugate" [Supplementary Concept] OR "Dengue Vaccines"[Mesh] OR "Poliovirus Vaccines"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Cholera Vaccines"[Mesh] OR "Anthrax Vaccines"[Mesh] OR "Haemophilus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Tetanus Toxoid"[Mesh] OR "Diphtheria Toxoid"[Mesh] OR "Hepatitis A Vaccines"[Mesh] Sort by: Most Recent		
	Set 11 Search: (vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR smallpox OR chickenpox OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR flu OR influenza OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR "Whooping cough" OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR Ebola OR "Japanese encephalitis" OR malaria OR Lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue)	**4,623,653**	
	Set 12 Search: ((vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR smallpox OR chickenpox OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR flu OR influenza OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR "Whooping cough" OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR ebola OR "Japanese encephalitis" OR malaria OR lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue)) OR ("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Herpes Zoster Vaccine"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Chickenpox Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Smallpox	**4,656,420**	

	Vaccine"[Mesh] OR "Rubella Vaccine"[Mesh] OR "Poliovirus Vaccine, Oral"[Mesh] OR "Poliovirus Vaccine, Inactivated"[Mesh] OR "Mumps Vaccine"[Mesh] OR "Measles Vaccine"[Mesh] OR "Plague Vaccine"[Mesh] OR "BCG Vaccine"[Mesh] OR "Heptavalent Pneumococcal Conjugate Vaccine"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "Influenza Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "Papillomavirus Vaccines"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR "Ebola Vaccines"[Mesh] OR "Adenovirus Vaccines"[Mesh] OR "Haemophilus influenzae type b polysaccharide vaccine" [Supplementary Concept] OR "Haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate" [Supplementary Concept] OR "Malaria Vaccines"[Mesh] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR "Japanese Encephalitis Vaccines"[Mesh] OR "Rabies Vaccines"[Mesh] OR "Respiratory Syncytial Virus Vaccines"[Mesh] OR "Lyme Disease Vaccines"[Mesh] OR "diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae b conjugate-hepatitis B vaccine" [Supplementary Concept] OR "diphtheria-tetanus-five component acellular pertussis-inactivated poliomyelitis - Haemophilus influenzae type b conjugate vaccine" [Supplementary Concept] OR "13-valent pneumococcal vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, L1 type 16, 18" [Supplementary Concept] OR "Hib-MenCY-TT vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, TA" [Supplementary Concept] OR "Haemophilus influenza type b polysaccharide vaccine-tetanus toxin conjugate" [Supplementary Concept] OR "Dengue Vaccines"[Mesh] OR "Poliovirus Vaccines"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Cholera Vaccines"[Mesh] OR "Anthrax Vaccines"[Mesh] OR "Haemophilus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Tetanus Toxoid"[Mesh] OR "Diphtheria Toxoid"[Mesh] OR "Hepatitis A Vaccines"[Mesh])		

		Set 13 Search: ((((vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR smallpox OR chickenpox OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR flu OR influenza OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR "Whooping cough" OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR ebola OR "Japanese encephalitis" OR malaria OR lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue)) OR ("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Herpes Zoster Vaccine"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Chickenpox Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Smallpox Vaccine"[Mesh] OR "Rubella Vaccine"[Mesh] OR "Poliovirus Vaccine, Oral"[Mesh] OR "Poliovirus Vaccine, Inactivated"[Mesh] OR "Mumps Vaccine"[Mesh] OR "Measles Vaccine"[Mesh] OR "Plague Vaccine"[Mesh] OR "BCG Vaccine"[Mesh] OR "Heptavalent Pneumococcal Conjugate Vaccine"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "Influenza Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "Papillomavirus Vaccines"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR "Ebola Vaccines"[Mesh] OR "Adenovirus Vaccines"[Mesh] OR "Haemophilus influenzae type b polysaccharide vaccine" [Supplementary Concept] OR "Haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate" [Supplementary Concept] OR "Malaria Vaccines"[Mesh] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR "Japanese Encephalitis Vaccines"[Mesh] OR "Rabies Vaccines"[Mesh] OR "Respiratory Syncytial Virus Vaccines"[Mesh] OR "Lyme Disease Vaccines"[Mesh] OR "diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae b conjugate-hepatitis B vaccine" [Supplementary Concept] OR "diphtheria-tetanus-five component	**4,798,169**	

	acellular pertussis-inactivated poliomyelitis -Haemophilus influenzae type b conjugate vaccine" [Supplementary Concept] OR "13-valent pneumococcal vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, L1 type 16, 18" [Supplementary Concept] OR "Hib-MenCY-TT vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, TA" [Supplementary Concept] OR "Haemophilus influenza type b polysaccharide vaccine-tetanus toxin conjugate" [Supplementary Concept] OR "Dengue Vaccines"[Mesh] OR "Poliovirus Vaccines"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Cholera Vaccines"[Mesh] OR "Anthrax Vaccines"[Mesh] OR "Haemophilus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Tetanus Toxoid"[Mesh] OR "Diphtheria Toxoid"[Mesh] OR "Hepatitis A Vaccines"[Mesh])) OR ("Immunization"[Mesh])) OR ("Vaccines"[Mesh])		
	Set 14 Search: (((("mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh])) AND (((((vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR smallpox OR chickenpox OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR flu OR influenza OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR "Whooping cough" OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR ebola OR "Japanese encephalitis" OR malaria OR lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue)) OR ("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Herpes Zoster Vaccine"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Chickenpox Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Smallpox Vaccine"[Mesh] OR "Rubella Vaccine"[Mesh] OR "Poliovirus Vaccine,	**8,975**	

	Oral"[Mesh] OR "Poliovirus Vaccine, Inactivated"[Mesh] OR "Mumps Vaccine"[Mesh] OR "Measles Vaccine"[Mesh] OR "Plague Vaccine"[Mesh] OR "BCG Vaccine"[Mesh] OR "Heptavalent Pneumococcal Conjugate Vaccine"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "Influenza Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "Papillomavirus Vaccines"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR "Ebola Vaccines"[Mesh] OR "Adenovirus Vaccines"[Mesh] OR "Haemophilus influenzae type b polysaccharide vaccine" [Supplementary Concept] OR "Haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate" [Supplementary Concept] OR "Malaria Vaccines"[Mesh] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR "Japanese Encephalitis Vaccines"[Mesh] OR "Rabies Vaccines"[Mesh] OR "Respiratory Syncytial Virus Vaccines"[Mesh] OR "Lyme Disease Vaccines"[Mesh] OR "diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae b conjugate-hepatitis B vaccine" [Supplementary Concept] OR "diphtheria-tetanus-five component acellular pertussis-inactivated poliomyelitis - Haemophilus influenzae type b conjugate vaccine" [Supplementary Concept] OR "13-valent pneumococcal vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, L1 type 16, 18" [Supplementary Concept] OR "Hib-MenCY-TT vaccine" [Supplementary Concept] OR "human papillomavirus vaccine, TA" [Supplementary Concept] OR "Haemophilus influenza type b polysaccharide vaccine-tetanus toxin conjugate" [Supplementary Concept] OR "Dengue Vaccines"[Mesh] OR "Poliovirus Vaccines"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Cholera Vaccines"[Mesh] OR "Anthrax Vaccines"[Mesh] OR "Haemophilus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Tetanus Toxoid"[Mesh] OR "Diphtheria Toxoid"[Mesh] OR "Hepatitis A Vaccines"[Mesh])) OR ("Immunization"[Mesh])) OR ("Vaccines"[Mesh]))) AND ((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following		

	Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Long Term Adverse Effects"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Injection Site Reaction"[Mesh]))		
	Set 15 Search: (vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR ebola OR "Japanese encephalitis" OR malaria OR lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue)	**4,530,707**	
	Set 16 Search: (vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR ebola OR "Japanese encephalitis" OR malaria OR lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue OR flu OR influenza)	**4,623,458**	
	Set 17 Search: "Measles-Mumps-Rubella Vaccine"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Rubella Vaccine"[Mesh] OR "Poliovirus Vaccine, Oral"[Mesh] OR "Poliovirus	**4,623,458**	

	Vaccine, Inactivated"[Mesh] OR "Mumps Vaccine"[Mesh] OR "Measles Vaccine"[Mesh] OR "Plague Vaccine"[Mesh] OR "BCG Vaccine"[Mesh] OR "Heptavalent Pneumococcal Conjugate Vaccine"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "Influenza Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "Papillomavirus Vaccines"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR "Ebola Vaccines"[Mesh] OR "Adenovirus Vaccines"[Mesh] OR "Malaria Vaccines"[Mesh] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR "Japanese Encephalitis Vaccines"[Mesh] OR "Rabies Vaccines"[Mesh] OR "Respiratory Syncytial Virus Vaccines"[Mesh] OR "Lyme Disease Vaccines"[Mesh] OR "Dengue Vaccines"[Mesh] OR "Poliovirus Vaccines"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Cholera Vaccines"[Mesh] OR "Anthrax Vaccines"[Mesh] OR "Haemophilus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Tetanus Toxoid"[Mesh] OR "Diphtheria Toxoid"[Mesh] OR "Hepatitis A Vaccines"[Mesh]		
	Set 18 Search: ("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Rubella Vaccine"[Mesh] OR "Poliovirus Vaccine, Oral"[Mesh] OR "Poliovirus Vaccine, Inactivated"[Mesh] OR "Mumps Vaccine"[Mesh] OR "Measles Vaccine"[Mesh] OR "Plague Vaccine"[Mesh] OR "BCG Vaccine"[Mesh] OR "Heptavalent Pneumococcal Conjugate Vaccine"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "Influenza Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "Papillomavirus Vaccines"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR "Ebola Vaccines"[Mesh] OR "Adenovirus Vaccines"[Mesh] OR "Malaria Vaccines"[Mesh] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR "Japanese Encephalitis Vaccines"[Mesh] OR "Rabies Vaccines"[Mesh] OR "Respiratory	**4,652,220**	

	Syncytial Virus Vaccines"[Mesh] OR "Lyme Disease Vaccines"[Mesh] OR "Dengue Vaccines"[Mesh] OR "Poliovirus Vaccines"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Cholera Vaccines"[Mesh] OR "Anthrax Vaccines"[Mesh] OR "Haemophilus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Tetanus Toxoid"[Mesh] OR "Diphtheria Toxoid"[Mesh] OR "Hepatitis A Vaccines"[Mesh]) OR ((vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR ebola OR "Japanese encephalitis" OR malaria OR lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue OR flu OR influenza))		
	Set 19 Search: (((("mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh])) AND ((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Long Term Adverse Effects"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Injection Site Reaction"[Mesh]))) AND (("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Rubella Vaccine"[Mesh] OR "Poliovirus Vaccine, Oral"[Mesh] OR "Poliovirus Vaccine, Inactivated"[Mesh] OR "Mumps Vaccine"[Mesh] OR "Measles Vaccine"[Mesh] OR "Plague Vaccine"[Mesh] OR "BCG Vaccine"[Mesh] OR "Heptavalent Pneumococcal Conjugate	**8,916**	

	Vaccine"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "Influenza Vaccines"[Mesh] OR "Meningococcal Vaccines"[Mesh] OR "Papillomavirus Vaccines"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR "Ebola Vaccines"[Mesh] OR "Adenovirus Vaccines"[Mesh] OR "Malaria Vaccines"[Mesh] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR "Japanese Encephalitis Vaccines"[Mesh] OR "Rabies Vaccines"[Mesh] OR "Respiratory Syncytial Virus Vaccines"[Mesh] OR "Lyme Disease Vaccines"[Mesh] OR "Dengue Vaccines"[Mesh] OR "Poliovirus Vaccines"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Cholera Vaccines"[Mesh] OR "Anthrax Vaccines"[Mesh] OR "Haemophilus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Tetanus Toxoid"[Mesh] OR "Diphtheria Toxoid"[Mesh] OR "Hepatitis A Vaccines"[Mesh]) OR ((vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR h1n1 OR polio OR "inactivated Polio vaccine" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Human papillomavirus" OR hpv OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR ebola OR "Japanese encephalitis" OR malaria OR lyme OR cholera OR typhoid OR adenovirus OR herpes zoster OR pertussis OR dengue OR flu OR influenza)))		
	Set 20 Search: (vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B")	**166,916**	
	Set 21 Search: ("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Hepatitis A Vaccines"[Mesh])	**17,054**	

	Set 22 Search: ((vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B")) OR (("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Hepatitis A Vaccines"[Mesh]))	**171,929**	
	Set 23 Search: ((((vaccine OR vaccination OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B")) OR (("Measles-Mumps-Rubella Vaccine"[Mesh] OR "Yellow Fever Vaccine"[Mesh] OR "Rotavirus Vaccines"[Mesh] OR "Hepatitis B Vaccines"[Mesh] OR "Hepatitis A Vaccines"[Mesh]))) AND ((("mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh]))) AND ((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Long Term Adverse Effects"[Mesh] OR "Adverse Drug Reaction Reporting Systems"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Injection Site Reaction"[Mesh]))	**150**	
	1 AND 2 AND 3 AND 4 AND 5 AND 6 AND 7 AND 8 AND 9 AND 10 AND 11 AND 12 AND 13 AND 14 AND 15 AND 16 AND 17 AND 18 AND 19 AND 20 AND 21 AND 22 AND 23 **Limit: All languages** **Time frame:1970-2021**	**150**	**150**
PubMed - Part 2b Scoping	**Set 1** Search: (vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)	**2,441,341**	

Literature Search-Other licensed vaccines.			
	Set 2 Search: (adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)	**4,455,877**	
	Set 3 Search: "Drug-Related Side Effects and Adverse Reactions"[Mesh] Sort by: Most Recent	**122,129**	
	Set 4 Search: "Long Term Adverse Effects"[Mesh] Sort by: Most Recent	**695**	
	Set 5 Search: "Adverse Drug Reaction Reporting Systems"[Mesh] Sort by: Most Recent	**8,070**	
	Set 6 Search: "Antigens"[Mesh] Sort by: Most Recent	**1,091,716**	
	Set 7 Search: ((vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)) OR ("Antigens"[Mesh])	**2,441,341**	
	Set 8 Search: ((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Long Term Adverse Effects"[Mesh])) OR ("Adverse Drug Reaction Reporting Systems"[Mesh])	**4,476,983**	

	Set 9 Search: (mhealth OR mobile health OR ehealth)	**84,697**	
	Set 10 Search: "Telemedicine"[Mesh] Sort by: Most Recent	**36,335**	
	Set 11 Search: ((mhealth OR mobile health OR ehealth)) OR ("Telemedicine"[Mesh])	**84,697**	
	Set 12 Search: (“mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)	**167,240**	
	Set 13 Search: ((((vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)) OR ("Antigens"[Mesh])) AND (((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Long Term Adverse Effects"[Mesh])) OR ("Adverse Drug Reaction Reporting Systems"[Mesh]))) AND ((("mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR 3g OR 4g OR 5g OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh]))	**1,614**	
	Set 14 Search: (“mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR ehealth OR telemedicine)	**73,100**	

	Set 15 Search: (((("mobile health" OR mhealth OR "mobile phone" OR "mobile app" OR "cell phone" OR "smartphone app" OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh])) AND (((vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)) OR ("Antigens"[Mesh]))) AND (((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Long Term Adverse Effects"[Mesh])) OR ("Adverse Drug Reaction Reporting Systems"[Mesh]))	**167**	
	Set 16 Search: (mobile health OR mhealth OR mobile phone OR mobile app OR cell phone OR smartphone app OR ehealth OR telemedicine)	**103,960**	
	Set 17 Search: ((((mobile health OR mhealth OR mobile phone OR mobile app OR cell phone OR smartphone app OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh])) AND (((vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)) OR ("Antigens"[Mesh]))) AND (((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Long Term Adverse Effects"[Mesh])) OR ("Adverse Drug Reaction Reporting Systems"[Mesh]))	**384**	
	Set 18 Search: ((“mobile health" OR mhealth OR mobile phone OR mobile app OR cell phone OR smartphone app OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh])	**88,161**	

	Set 19 Search: (((("mobile health" OR mhealth OR mobile phone OR mobile app OR cell phone OR smartphone app OR ehealth OR telemedicine)) OR ("Telemedicine"[Mesh])) AND (((vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)) OR ("Antigens"[Mesh]))) AND (((((adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)) OR ("Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR ("Long Term Adverse Effects"[Mesh])) OR ("Adverse Drug Reaction Reporting Systems"[Mesh]))	**255**	
	1 AND 2 AND 3 AND 4 AND 5 AND 6 AND 7 AND 8 AND 9 AND 10 AND 11 AND 12 AND 13 AND 14 AND 15 AND 16 AND 17 AND 18 AND 19 **Limit: All languages** **Time frame:1970-2021**	**255**	**255**
CINAHL Part 2 Other licensed vaccines, mHealth & AEFI surveillance. Interface – EBSCO host Research Databases	**Set 1.** ("mobile health" OR mhealth OR mobile phone OR mobile app OR cell phone OR smartphone app OR ehealth OR telemedicine)	82,932	
	Set 2. (Adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)	1,410,904	
	Set 3. (Vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)	373,893	

Search Screen - Basic Search Database - Africa-Wide Information.	**1 AND 2 AND 3** **Limit: All languages** **Time frame:1970-2021**	**29**	**29**
COCHRANE Part 2 Scoping Literature Review Search, Other licensed vaccines, mHealth & AEFI surveillance.	**Set 1.** (Vaccine OR vaccines OR vaccination OR vaccinations OR Immunization OR Immunization OR antigen OR antigens)	73681	
	Set 2. ("mobile health" OR mhealth OR mobile phone OR mobile app OR cell phone OR smartphone app OR ehealth OR telemedicine)	13443	
	Set 3. (Adverse effect OR adverse effects OR side effect OR side effects OR Adverse Events Following Immunization OR adverse events following Immunization OR AEFI OR reaction OR reactions)	378683	
	1 AND 2 AND 3 **Limit: All languages** **Time frame:1970-2021**	**103**	**103**
SCOPUS Part 2 Scoping Literature Review Search, Other licensed vaccines, mHealth & AEFI surveillance.	**Set 1.** TITLE-ABS-KEY ((“adverse effect*” OR “side effect*" OR "Adverse Events Following Immunization" OR "adverse events following Immunization" OR aefi OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug-Related Side Effect* and Adverse Reactions*" OR "Adverse Drug Reaction Reporting Systems*"))	**6,102,031**	
	Set 2.	**228,264**	

	TITLE-ABS-KEY ((vaccine* OR vaccination* OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR smallpox OR chickenpox OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR influenza OR h1n1 OR flu OR influenza OR polio OR "inactivated Polio vaccin*" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Hepatitis B" OR "Human papillomavirus" OR hpv OR "Whooping cough" OR pneumococcal OR meningococcal OR shingles OR polysaccharide OR toxoid OR dt OR dtp OR "rotavirus vaccine*" OR ebola OR "Japanese encephalitis"))		
	Set 3. TITLE-ABS-KEY (((“mobile health” OR mhealth OR “mobile phone*” OR “mobile app*” OR “cell phone*” OR “smartphone app*” OR 3g OR 4g OR 5g OR ehealth OR telemedicine)))	**281,356**	
	Set 4. 1 AND 2 AND 3 **Limit: All languages** **Time frame:1970-2021** (TITLE-ABS-KEY (("adverse effect*" OR "side effect*" OR "Adverse Events Following Immunization" OR "adverse events following Immunization" OR aefi OR reaction* OR "adverse reaction*" OR "adverse event*" OR "serious adverse event*" OR "Long Term Adverse Effect*" OR "Drug-Related Side Effect* and Adverse Reactions*" OR "Adverse Drug Reaction Reporting Systems*"))) AND (TITLE-ABS-KEY ((vaccine* OR vaccination* OR Immunization OR Immunization OR measles OR mumps OR rubella OR mmr OR rotavirus OR smallpox OR chickenpox OR yellow AND fever OR "Hepatitis A" OR "Hepatitis B" OR influenza OR h1n1 OR flu OR influenza OR polio OR "inactivated Polio vaccin*" OR ipv OR rabies OR tetanus OR tt OR td OR hepb OR pentavalent OR hib OR "Hemophilus influenza type b" OR "Hepatitis B" OR "Human papillomavirus" OR hpv OR "Whooping cough" OR pneumococcal OR meningococcal OR shingles OR	**71**	**71**

	polysaccharide OR toxoid OR dt OR dtp OR "rotavirus vaccine*" OR ebola OR "Japanese encephalitis"))) AND (TITLE-ABS-KEY ((("mobile health" OR mhealth OR "mobile phone*" OR "mobile app*" OR "cell phone*" OR "smartphone app*" OR 3g OR 4g OR 5g OR ehealth OR telemedicine))))		

APPENDIX 5: Efficacy and feasibility Zm-STARSS RCT publication

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Efficacy and feasibility of SMS m-Health for the detection of adverse events following immunisation (AEFIs) in resource-limited setting-The Zimbabwe stimulated telephone assisted rapid safety surveillance (Zm-STARSS) randomised control trial

Priscilla P.M. Nyambayo [a,*], Michael S. Gold [b], Ushma C. Mehta [c], Stephen Clarke [d], Rumbidzai Manyevere [a], Libert Chirinda [a], Edlyne N. Zifamba [a], Tatenda Nyamandi [a]

[a] Pharmacovigilance and Clinical Trials Division, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe
[b] University of Adelaide, Discipline of Paediatrics, Women's and Children's Health Network, Adelaide, Australia
[c] Centre for Infectious Disease Epidemiology and Research, School of Public Health, University of Cape Town, South Africa
[d] Flexis Systems Pty Ltd, PO Box 352, Mayfield, NSW 2304, Australia

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ABSTRACT

Introduction: The mHealth active participant centred (MAPC) adverse events following immunisation (AEFI) surveillance is a promising area for early AEFI detection resulting in risk minimisation. Passive (spontaneous) AEFI surveillance is the backbone for vaccine pharmacovigilance, but has inherent drawbacks of under reporting, and requires strengthening with active surveillance methods.

Aim: The Zimbabwe stimulated telephone assisted rapid safety surveillance (Zm-STARSS) randomised controlled trial (RCT) sought to evaluate the efficacy and feasibility of AEFI detection using a short message service (SMS) and computer assisted telephone interview (CATI) approach.

Method: A multicentre Zm-STARSS RCT enrolled consented adult vaccinees or parents or guardians of children receiving vaccines, including COVID-19 vaccines, at study vaccination clinics. At enrolment study participants were randomised to either SMS-CATI group or control group. SMS prompts were sent on days 0–2 and 14 post-vaccination to SMS-CATI group to ascertain if a medically attendance or attention due to an Adverse event following immunisation (AEFI) had occurred. However, no SMSs were sent to the control group. SMS-CATI group who responded "Yes" to SMS prompts were interviewed by research healthcare workers (RHCWs) who completed a CATI to determine if an AEFI had occurred whilst an AEFI in control group was determined from passive AEFI reporting channels. The primary study outcome was the AEFI detection rate in the SMS-CATI group compared to the control group.

Results: A total of 4560 participants were enrolled after signed informed consent, all were encouraged to report AEFIs and randomised automatically on 1:1 basis into two arms SMS CATI intervention group (n = 2280) and a control passive AEFI surveillance group (n = 2280) on day 0. A total of 704 (31 %) participants responded to the SMS prompts, with 75 % (528/704) indicating "No" and 25 % (176/704) reporting "Yes" to seeking medical attention or attendance post-immunisation. 69 % (121/176) completed a CATI survey but in only 36 % (44/121) was the AEFI confirmed. There were no AEFIs reported in control group participants. The detection rate of a AEFI associated with medically attendance or attention using the SMS-CATI methodology was 2 % (44/2280) on an intention to treat cohort.

Abbreviations: STARSS, Stimulated Telephone Assisted Rapid Safety Surveillance; Zm-STARSS, Zimbabwe Stimulated Telephone Assisted Rapid Safety Surveillance; Au-STARSS, Australian Stimulated Telephone Assisted Rapid Safety Surveillance; ADR, adverse drug reaction; AEFI, Adverse Events Following Immunisation; API, Application Programming Interface; AVSS, Active vaccine safety surveillance; CATI, Computer Assisted Telephone Interview; Econet, Econet Wireless Zimbabwe Ltd; eHealth, Electronic health; HCW/HCWs, Healthcare worker(s) or research healthcare workers; HICs, High-Income Countries; MAPC, mHealth active participant-centred; MCAZ, Medicines Control Authority of Zimbabwe; MedDRA, Medical Dictionary for Regulatory Activities; m-Health, Mobile health; POTRAZ, Postal and Telecommunications Regulatory Authority of Zimbabwe; PT(s), Preferred term(s); RHCW(s), Research Health Care Workers(s); SOC(s), System organ classification (s); WBR, Web-Based Reporting; ZEPI, Zimbabwe Expanded Programme on Immunisation.

* Corresponding author.
E-mail address: pnyambayo@mcaz.co.zw (P.P.M. Nyambayo).

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Conclusion: Despite the low SMS response and CATI completion rate, we demonstrated that Zm-STARSS SMS system improves AEFI detection compared to passive AEFI surveillance. We recommend that this and similar approaches are explored further using cost-effective multi-channel digital approaches for holistic pharmacovigilance to improve AEFI detection in Low Middle-Income Countries (LMICs) for all vaccines.

1. Introduction

A functional national immunisation programme is integral to enhance public health and pandemic preparedness. A key priority for each immunisation programme should be vaccine pharmacovigilance and in particular the surveillance of adverse events following immunisation (AEFI). Passive post-marketing AEFI surveillance is recommended globally. However, there are both inherent limitations and significant challenges in implementing this method such as under reporting and incomplete information [1,2]. In most LMICs, AEFI surveillance systems are limited due to paper-based under reporting, delayed incomplete or incorrect information and ultimately delayed AEFI case management [2,3]. Weak spontaneous AEFI surveillance systems result in low reporting delayed AEFI detection, delayed case investigation/management, causality assessment and preventable serious AEFIs. This might result in lack of public trust in vaccines reducing vaccine uptake and ultimately increased vaccine preventable diseases (VPDs) [4]. In LMICs, the challenges that contribute to AEFI underreporting are further heightened by consumer illiteracy, poverty, inadequate overstretched primary health care systems and unavailability of digital technologies [4,5]. Most LMICs in Africa contributed the least number of adverse events to the WHO Vigibase database [6]. In recent years including the COVID-19 pandemic some LMICs introduced passive enhanced AEFI surveillance using mHealth reporting tools such as the African Union Smart Safey Surveillance MedSafety App piloted in a few African countries (Bukina Faso, Ethiopia, Ghana, Nigeria, Zambia and South Africa) [7,8]. VigiMobile app linked to the WHO, AEFI VigiFlow VigiBase database was recently piloted in 2023 in Zimbabwe and few selected countries, after the conduct of the Zm-STARSS study however VigiMobile system uptake is still under assessment. Some studies mostly in HICs reported successful mHealth active AEFI surveillance systems linked to other digital tools such as web apps, eHealth and electronic (e) record linkage since 2009 to 2023 initially for influenza vaccines/ other vaccines and then expanded to monitoring COVID-19 vaccines as well [9,10]. Some LMICs use District Health Information Systems (DHIS) updated versions that are used to collate most Ministry of Health programs performance monitoring indicators with immunisation coverage and outcomes including AEFI surveillance usually originally completed on paper-based forms at the vaccinations clinics as aggregate data [11]. The DHIS tools were found to have inadequate AEFI form report data of only 15 core values or less, short of the critical 25 core variables required for AEFI case investigations and causality assessment [11]. Most DHIS tools are usually limited since they are not linked to any primary health system digital, eHealth and mHealth applications due to unavailability of these unaffordable advanced systems in most LMICs. Challenges were experienced with some African countries in conducting active AEFI surveillance using DHIS2 since most hospital sites did not met the assessment criteria [12].

First, the e-Health technology, which mobile health (m-Health) is part of, is now applied globally to improve health surveillance and outcomes. A noteworthy area is the application of digital tools to improve immunisation programmes including AEFI surveillance. Secondly, the m-Health for active vaccine safety surveillance (AVSS) is eliciting growing interest because of its ability to engage consumers directly to elicit AEFI reports, which could overcome some of the limitations inherent in passive reporting by health professionals [10,13,14]. The m-Health active participant-centred (MAPC) AEFI surveillance continuous organised process [1].

The m-Health approaches are showing promise as a tool to improve AEFI detection in many high-income countries (HICs). This approach directly prompts vaccinees or their caregivers to report an AEFI quickly and seek care [10,13–15]. A Canadian scoping review of MAPC AEFI surveillance suggests that mHealth could be the method for collecting self-reported subjective symptoms from vaccinees which could complement existing AEFI surveillance systems [10]. The study recommends the evaluation of digital solutions to improve vaccine surveillance systems for contemporary and future public health needs [10]. The performance of these m-Health approaches in LMIC settings is poorly described with only Cambodia [16] and Sierra Leone [17] reporting on their experiences for active m-Health adverse drug reaction (ADRs) but not on AEFIs. Moreover, the underperformance of the m-Health system in aboriginal communities in Australia highlights the need to assess the feasibility and performance of such systems in culturally diverse populations with poor socioeconomic groups [18].

A comprehensive evaluation of SMS-based AEFI surveillance is required prior to diverting scarce public health resources towards widespread implementation [14]. The Australian stimulated telephone assisted rapid safety surveillance (Au-STARSS) is one of two published randomised controlled trials (RCT) which has compared the AEFI detection rate in an active (SMS surveillance) and control (passive surveillance) groups. The study evaluated the feasibility and acceptability of SMS based surveillance using a two-step process with an initial SMS being the entry point for detection whilst a subsequent digital interaction elicited information to determine the nature of the event [14]. The outcome of the Au-STARSS study showed a 13-fold greater AEFI detection rate in the SMS group (Pearson' χ^2 test = 76.0, $p < 0.0001$) compared to the control group (passive surveillance) [14].

Established in 1997, the Zimbabwe national AEFI surveillance system has continued to grow, but the burden of reporting AEFIs by overwhelmed health workers (HCWs) has remained a key barrier to the timely detection of serious or severe AEFIs [19,20]. Zm-STARSS RCT is a proof-of-concept study evaluating SMS based surveillance for AEFI detection in a LMIC using an adapted Au-STARSS mHealth platform. The objective was to ascertain if STARSS could be adapted, implemented, and evaluated in Zimbabwe for the detection of AEFI.

1.1. Aim and hypothesis

The primary aim was to determine if Zm-STARSS was more effective in detecting an AEFI than routine passive reporting of AEFIs. The primary hypothesis was that the proportion of people in which an AEFI is detected is greater in the SMS intervention group compared to a comparison group (passive surveillance). The secondary aim was to provide a narrative description covering the challenges of establishing a Zm-STARSS platform.

2. Methods and materials

2.1. Study population, sample size and inclusion criteria

A total of 4560 individuals presenting for vaccination at CITIMED and Chitungwiza hospitals in peri urban Chitungwiza near Harare, Zimbabwe, were eligible for enrolment from November 2020 to August 2021. Participants were eligible if they understood English (Zimbabwe's

mobile phone and consented to being part of the study.

Exclusion criteria: Vaccinees who were unwell before vaccination, child vaccinees associated with multiple births (e.g., a twin child) and children with parents/guardians who are minors (< 18 years) were not eligible for enrolment. Multiple births e.g., twins were excluded since this inclusion was likely to confuse the parents/guardians if the individual children were randomized to different groups.

2.2. Consent process

Opt-in, informed consent was sought. Participants were informed that the study was examining diverse ways of monitoring vaccine 'side-effects' and that they could receive a follow-up SMS to ascertain any adverse event requiring attention, together with an invitation to provide further details (by CATI) of their 'experience' during the post-vaccination period. Consent was obtained for receipt of SMSs, participation in a CATI interview and access to any passive AEFI reports submitted to Zimbabwe Expanded Programme on Immunisation (ZEPI) and Medicines Control Authority of Zimbabwe (MCAZ) through a database search for performance of a causality assessment by the national AEFI Committee.

2.3. Study design and randomisation

All study staff were trained in the Zm-STARSS protocol by qualified MCAZ national pharmacovigilance centre study researchers including informed consent process and compliance with good clinical practice (GCP) 2–3 days before conduct of the study including continuous monitoring and retraining's throughout the study period. All study site nurses were blinded to the randomisation. After enrolment all participants and guardians were informed on how to report an AEFI regardless of their allocated group. The study sites nurses were provided with AEFI paper-based reporting forms. Both study site nurses and national pharmacovigilance research staff verified records at both EPI, MCAZ and study sites for any SMS or paper-based reports from both CATI arm and control arm. The Zm-STARSS software was customised to include all national ZEPI antigens including COVID-19 vaccines. Zm-STARSS study design included only two randomised groups (SMS and control) and excluded the web-based component which was in the Au-STARSS, because of the high cost and limited internet access to health care workers (HCWs) and vaccinees. The Zm-STARSS trial was a multi-centre, single-blinded and active-controlled parallel two-grouped RCT with a repeated measures design to collect responses to SMS's sent on days 0–2 and 14 post-immunisations to ascertain whether the participant had experienced an AEFI, that was associated with medical admission or attention. Participants were enrolled at both CITIMED and Chitungwiza hospitals vaccination sites. Site selection was based on availability of reliable internet services to enable the platform to function. Randomisation was implemented using an algorithm residing in the study server which allowed automatic allocation in a 1:1 ratio in permuted sequence to the SMS intervention or the control group. The participant was the unit of allocation, which occurred on receipt of the vaccinee's immunisation and demographic data into the study portal. Research healthcare workers (RHCWs) involved with the enrolment of participants and immunisation providers were blinded to the allocation.

2.4. SMS dispatch and response

Extraction of participant and vaccinee data from a completed enrolment form was entered manually by RHCWs, via a secure web portal, and within 48 h of vaccination. Upon receipt of this data an information technology (IT) application, located on the MCAZ server, automated SMSs to be dispatched without daily restriction (with a curfew between 8 PM and 8AM) and managed the flow of outgoing and incoming SMSs which included customised SMS replies to these responses. On receipt of the enrolment data participants were reminded via SMS that they should expect follow-up messages on days 0–2 and 14 post-immunisations. These time intervals were consistent with the expected temporal onset of reactions for the vaccines administered to the participants in the study. A welcome message was sent immediately to each participant on enrolment day 0. A survey message was sent to each participant 48 h after their vaccination date and time. To ensure that survey messages were always sent at the correct time for each participant (48 h after vaccination) the system prevented the enrolment of participants if their vaccination was already more than 48 h old.

Each prompt SMS message aimed to determine if an AEFI had occurred by asking the question: *"Since vaccination has **the person who has been vaccinated** seen a medical doctor, nurse, pharmacist, healthcare worker or health traditional healer because the **child or adult vaccinated** has been unwell?" Please respond "Yes" or "No."* Those who responded "Yes" were contacted telephonically to complete an AEFI report which took the form of a CATI administered by a RHCW. The purpose of the CATI was to obtain details about the AEFI so that it could be determined if this was consistent with the WHO, AEFI definition [21]. The CATI interview questionnaire included most of the 25 AEFI core variables as recommended by WHO [21]. The "No" SMS responders were sent an automated SMS acknowledgement. A final SMS prompt was sent on day14 post-vaccination. The specific wording of the SMSs is detailed in Table 1.

The CATI sought to verify the following details on day 0–2 and 14 post vaccination if participants responded Yes to the SMS prompts: 1) vaccine(s) administered and batch numbers already prefilled at enrolment on the online Zm-STARSS by the nurses and also available on participant's hard copy vaccination card; 2) type of medical attention sought; 3) adverse symptom(s); 4) other details including hospitalisation and recovery. An AEFI report was regarded as confirmed if the reported vaccination details were the same as those documented through the Zm-STARSS online recruitment portal, if medical attention/attendance following the immunisation was confirmed and one or more symptom(s) were reported. No follow-up occurred for the participants randomised to the control and the occurrence of an AEFI was determined from the ZEPI and MCAZ AEFI database/AEFI line listing.

2.5. Zm-STARSS-information technology (IT) platform

The Zm-STARSS IT platform was centralised, with encrypted data transmitted securely from the two study sites to a secure MCAZ server. The IT platform provided a single site for the collation of participant demographics, immunisation data, and SMS messages including repository for all data collected from CATI reports. The platform automatically dispatched and received SMS messages. The vaccinee's immunisation details (vaccine antigen(s), brand, batch number, vaccine administration site(s), date, and time together with demographic

Table 1
Details of the wording of the SMS's generated following enrolment and randomisation to the SMS-CATI intervention group.

Vaccination day Reminder SMS Day 0–2 (within 48 h)	Welcome to the STARSS Study. 'Since vaccination has the person who has been vaccinated experienced an AEFI or seen a medical doctor, nurse, pharmacist healthcare worker or health traditional healer because the child or adult vaccinated has been unwell?' Please respond Yes or No'.
Reminder SMSs Day 14	Welcome to the STARSS Study. 'Since vaccination has the person who has been vaccinated experienced an AEFI or seen a medical doctor, nurse, pharmacist healthcare worker or health traditional healer because the child or adult vaccinated has been unwell?' Please respond Yes or No'.
SMS response from portal to "YES" participants reply at days 0–2 and 14	**Randomised to SMS mHealth Computer Assisted Telephone Interview (CATI) arm** STARSS Study: "Thank you for letting us know that you received health advice after the vaccination. We will call you in the next 24 h to find out more".

information (vaccinee's name, date of birth (DOB), sex, address, and mobile number) were collected at enrolment. Participant reports of a AEFI automatically triggered an email alert to RHCWs. Access to the site was password protected and RHCWs had access to the global dashboard. All portals offered a real-time view of the AEFI and AEFI reports, and all data was added to a single structured query language (SQL) database stored in the study server, which allowed export of the data (CSV format) and circumvented the need for unsecure data transmission. The Zm-STARSS surveillance system was developed with assistance from Econet Wireless Zimbabwe Ltd (Econet), (a company with 65 % mobile phone market share) and in line with the Postal and Telecommunications Regulatory Authority of Zimbabwe (POTRAZ) requirements for SMS mobile phone test codes. A major challenge was that participants would have insufficient telephone credit, to respond to the automatic SMS messages. This could introduce a significant bias in the perceived responsiveness of participants, and the reported/unreported symptoms. To address this issue, Econet created a test channel pre-paid by MCAZ, where participants' SMSs were not charged, and hence successful transmission could be achieved despite insufficient telephone credit.

2.6. AEFI outcome measures and definitions

For the SMS-CATI group a AEFI notifier was defined as a participant who replied "Yes" to the SMS prompt on at least one of the time points (0–2 or 14 days). A participant was deemed to not have had a AEFI if a "No" response was received at any of the time points. A AEFI was defined as completed when all four CATI verification steps had occurred. An event was classified as an AEFI if it met the WHO case definition. Zimbabwe's national AEFI expert committee trained by WHO performed the causality assessment on all reported cases according to WHO AEFI causality assessment algorithm (2019) [13]. Some participants however might experience more than one AEFI, e.g., abscess and convulsions.

The number of AEFI cases in each group (SMS vs control) formed the basis for the analysis of the primary outcome. Since multiple AEFI reports may have been completed for the same participant, the primary outcome was based on a single individual. For the control group all AEFI reports for the duration of the RCT, were matched to the vaccinee's details (name, date of birth (DOB), antigens, date of vaccination, vaccination clinic or study site and name of the reporter) to determine if a report had been received within 14 days of vaccination. Any submitted report was counted as an AEFI for the control group.

2.7. Secondary outcomes

SMS compliance was assessed by the number and percentage of participants who responded with a "Yes" or "No" response to the surveillance SMS. Fully compliant responders were defined as responders at the three points (0–2 and 14 days), partial compliers were those responding at 0–2 or 14-days' time points and non-compliers never responded at all. AEFI completion was assessed by the number and percentage of participants, in the SMS-CATI group, who notified an AEFI and whose report was completed and verified by the RHCWs. The time for detection of an AEFI was defined as the time (in hours) from medical attendance/attention to completion of the AEFI report for the SMS-CATI group or the time from healthcare attendance to receipt of an AEFI report by ZEPI or MCAZ for the control group.

2.8. Statistical analysis plan

The primary analyses were performed on the intention-to-treat (ITT) population, with participants analysed per their allocated pools. Given the low AEFI cases expected in the control group, two-tailed Fisher's exact tests ($\alpha = 0.025$) were done to compare the events in the SMS group to those in the control group. Pearson' χ^2 tests were carried out for the different demographic characteristics, such as gender, age, sex, index of socio-economic advantage and disadvantage as well as the vaccine characteristics to determine any significant differences in the SMS group and control groups, including those participants who responded "Yes" or "No" to the SMS or the non-responders to any SMS. Median and 95 % confidence intervals based on the binomial distribution were used to describe the median time in hours of the various time lags from enrolment to AEFI detection.

3. Results

3.1. Eligibility, enrolment, randomisation, and intention to treat numbers

Between November 2020 and August 2021, a total of 5,541 eligible adults and children attending the two immunisation sites were approached and screened for enrolment. A total of 4,560 who met inclusion criteria and signed the consent forms were enrolled and randomly assigned (1:1) equally to the SMS or the control groups, and 981 subjects were excluded with details documented in the consort diagram (Fig. 1).

3.2. Participant demographic and vaccine characteristics

The demographic and vaccine characteristics of enrolled participants are detailed in Table 2. Whilst participants were distributed across a wide age range (birth to 65 and above years), 2,551 (55.9 %) were aged from birth to 6 months (or with almost equal gender balance (females 2,157 or 47.3 % and males 2,401 or 52.7 %). A total of 11 different

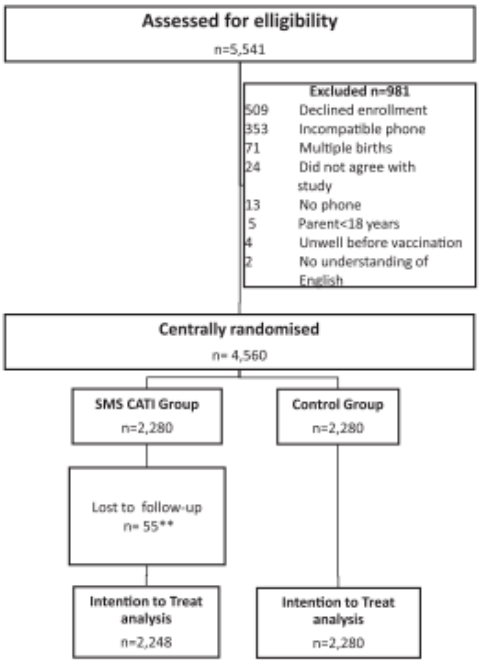

Fig. 1. Zm-STARSS CONSORT diagramme for Intention To Treat analysis. ** **n** = 55 Participants who responded "Yes" to SMS day 0–2 and/or 14 prompts post vaccination were however considered lost to follow since they did not respond to the RHCWs phone calls (3 attempts at different times) to conduct a CATI survey to ascertain if the "Yes" meant if the person vaccinated had experienced a MEFI/AEFI or not.

Table 2
Gender, age, socio-economic status, and vaccine characteristics of participants in each trial arm.

	SMS-CATI group n=2280 (%)	Control group n=2280 (%)	Total n=4560 (%)	Pearson Chi-Square 95% CI p value	Comment
Site					
Chitungwiza Central	1160 (50.9)	1161 (50.9)	2321 (50.9)	p = 0.976	NS
CITIMED	1120 (49.1)	1119 (49.1)	2239 (49.1)		
Gender					
Female	1053 (46.2)	1104 (48.4)	2157 (47.3)	p = 0.318	NS
Male	1226 (53.8)	1175 (51.6)	2401 (52.7)		
Other	1(0.0)	1 (0.0)	2 (0.0)		
Age range					
Median (IQR)					NS
0–6 months	1280 (56.1)	1273 (55.8)	2551 (55.9)	p = 0.884	
7 months–5 years	212 (9.3)	212 (9.3)	424 (9.4)		
6–14 years	1 (0.0)	0 (0.0)	1 (0.0)		
15–39 years	301 (13.2)	297 (13.0)	580 (12.7)		
40–64 years	374 (16.4)	393 (17.2)	758 (16.6)		
65 years and above	112 (4.9)	105 (4.6)	246 (5.4)		
Marital status					
D - divorced	6 (0.3)	6 (0.3)	12 (0.3)	p = 0.877	NS
F - de Facto	1 (0.0)	3 (0.1)	4 (0.1)		
M - married	2,009 (88.1)	2,001 (87.7)	4,010 (87.9)		
S - single	201 (8.8)	202 (8.9)	403 (8.8)		
W - widowed	63 (2.8)	68 (3.0)	131 (2.9)		
Education					
D - degree	255 (11.2)	199 (8.7)	454 (10.1)	p = 0.042	SIG
I - diploma	201 (8.8)	218 (9.6)	419 (9.1)		
C - Certificate	7 (0.3)	8 (0.4)	15 (0.3)		
A - Cambridge/ ZIMSEC A' level	224 (9.8)	202 (8.8)	426 (9.3)		
	1,593 (69.9)	1,653 (72.5)	3,246 (71.2)		
Work Status					
Unemployed	715 (31.4)	715 (31.4)	1,430 (31.3)	p = 0.917	NS
Employed	708 (31.1)	704 (30.9)	1,412 (31.0)		
Domestic duties	566 (24.8)	572 (25.1)	1,138 (25.0)		
Self employed	221 (9.7)	229 (10.0)	450 (10.0)		
Student	70 (3.1)	60 (2.6)	130 (2.7)		
Housing Status					
Owned	1,334 (58.5)	1,347 (59.1)	2,681 (58.8)	p = 0.606	NS
Rented	946 (41.5)	933 (40.9)	1,879 (41.2)		
Number of vaccines received.					
1	1,649 (72.3)	1,643 (72.1)	3,292 (72.2)	p > 0.05	NS
2	118 (5.2)	110 (4.8)	228 (5.0)		
3	98 (4.3)	97 (4.3)	195 (4.3)		
4	415 (18.2)	430 (18.8)	845 (18.5)		
Vaccines administered.					
BCG	864 (37.9)	848 (37.2)	1712 (37.5)	p > 0.05	NS
DTP booster-OPV-PCV-Rotavirus	1 (0.0)	1 (0.0)	2 (0.0)		
DTP booster-MR-OPV	98 (4.3)	97 (4.3)	195 (4.3)		
DTP booster-MR-OPV-Pentavalent	0 (0.0)	1 (0.0)	1 (0.0)		
MR	118 (5.2)	110 (4.9)	228 (5.0)		
Sinopharm COVID-19	151 (6.6)	164 (7.2)	315 (6.9)		
Sinovac COVID-19	1 (0.0)	3 (0.1)	4 (0.1)		
	633 (27.8)	628 (27.5)	1261 (27.7)		
	414 (18.2)	428 (18.8)	842 (18.2)		

NS – Not Significant SIG-Significant.

vaccines were administered to 4,560 participants, with the following combinations being administered; Bacille Calmette-Guerin BCG (37.5 %) was the most frequently administered followed by Sinopharm COVID-19 vero cell vaccine (27.7 %), Sinovac COVID-19 vero cell vaccine (18.2 %), oral polio vaccine (OPV) - Pneumococcal-Pentavalent (DTP-Hib-HepB)-Rotavirus (6.9 %), Diphtheria Tetanus Pertussis (DTP) booster Measles Rubella (MR) (5.0 %), Pneumococcal Rotavirus (4.3 %) PCV and Sputnik V COVID-19 vaccine (0.1 %). Table 2 shows that the Pearson χ^2 tests have no significant differences in any of the demographic or vaccine characteristics between the SMS intervention or control groups except for the education status p = 0.042 that is statistically significant, with marginally more individuals in the SMS-CATI group having a degree or A level (Cambridge/ZIMSEC).

3.3. Primary outcome determination of AEFI notification, verification, report completion and AEFI causality classification

The SMS responses, AEFI completion and final AEFI classification for the participants randomised to the SMS-CATI group are detailed in Fig. 2. A total of 6,840 SMSs were dispatched to the participants within 0–2 and 14-days post-vaccination. Overall, 69 % (1,576/2,280) of participants, in the SMS intervention groups, were classified as non-compliant. Of the 704 SMS (31 % of 2280) responses received, 75 % (528/704) indicated that "No" AEFI had been experienced whilst 25 % (176/704) responded "Yes" to experiencing an AEFI,(Fig. 2) at one or more of the time points (day 0–2 and/or 14). In this group of 176 participants, 81 were partial compliers (responded to one SMS) and 95 were complete compliers (responded to all SMS). Of the 176 who were "Yes" respondents 31 % (55/176) could not be contacted for a CATI despite at least 3 separate attempts. The remaining 69 % (121/176) were

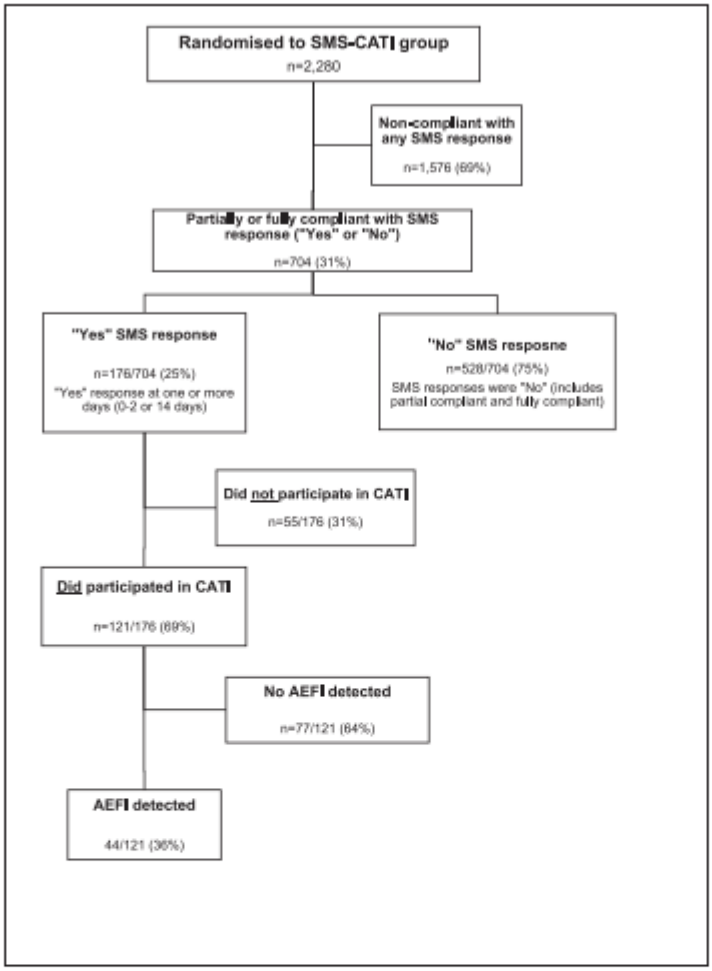

Fig. 2. SMS-CATI group participants – SMS response, MEFI report notification, verification of AEFI report completion.

contacted successfully by RHCWs who completed their CATI and 36 % (44/121) of these were assessed as they met the WHO AEFI criteria. The remainder 64 % (77/121) did not experience an AEFI. No passive AEFI reports were identified in the control group after verification of the ZEPI and MCAZ AEFI databases.

The overall health care attended AEFI in the SMS intervention group was 2 % (44/2,248) with no AEFI detection in the control group. The AEFI detection rate was 2 % greater in the SMS group compared to the control group (0 %); Fisher's exact test (2-sided), $p < 0.0001$) which is statistically significant. The non-response rates to SMS prompts did not differ significantly for the day 0–2 and 14 post vaccination SMS prompts. However, those participants who responded to the SMS ("Yes" or "No") compared with the non-responders demonstrated Pearson X^2 significant differences for education level, employment, and housing status but not for marital status, gender, and number of children, as shown in Table 4.

3.4. Reported AEFIs and causality assessment classifications in the SMS group

The adverse symptom and causality assessment classifications of those in the SMS group are shown in Table 3 including the Adverse Dictionary for Regulatory Activities (MedDRA) term reactions system organ classifications (SOCs) and preferred terms (PTs), suspected vaccines, and causality assessment outcomes done by the National AEFI Committee using the WHO AEFI causality assessment algorithm (2019) [13]. Fever was the most reported symptom with a rate of 3.0 % (21/704), followed by rash (1.4 % and diarrhoea (1.0 %) and vomiting (1.0 %) with all other symptoms reported with a frequency of <1.0 % (Table 3). In the ITT analysis 2% (44/2,248) of all SMS participants experienced an AEFI and reported seeking health advice from HCWs. Of these, 25% (11/44) were hospitalised including one fatality (Table 3). The reported rate of hospitalisation was 0.5% (11/2,280). Participants sought advice mostly from a community health advisor (57%) followed by a pharmacist (18%), GP (13.6%) or nurse (11.4%).

Table 3
Adverse symptoms in the individuals randomised to the SMS-CATI intervention group.

AEFI Reaction (MedDRA) System Organ Classification (SOC)	AEFI reaction MedDRA Preferred Terms (PT)	CATI group (n = 704) responded	Suspected Vaccine(s)	Causality assessment[++]
General disorders and administration site conditions	Abscess	2 (0.3)	BCG (1) OPV-PCV-Pentavalent-Rotavirus (1)	A1
	Injection site pain/ injected limb pain	5 (0.7)	BCG (2) OPV-PCV-Pentavalent-Rotavirus (3)	A1
	Crying	2 (0.3)	OPV-PCV-Pentavalent-Rotavirus (2)	A1
Skin and subcutaneous tissue disorders	Boils	2 (0.3)	Sinovac COVID-19 vaccine (2)	B1
	Rash	10 (1.4)	BCG (4) MR (1) OPV-PCV-Pentavalent-Rotavirus (4) Sinovac COVID-19 vaccine (1)	A1(9), C (1)
Respiratory, thoracic and mediastinal disorders	Chest pain	2 (0.3)	Sinovac COVID-19 vaccine (1) Sinopharm COVID-19 vaccine (1)	B1
	Cough	3 (0.4)	Sinovac COVID-19 vaccine (1) OPV-PCV-Pentavalent-Rotavirus (2)	B1(1) C (2)
	Difficulty breathing	3 (0.4)	OPV-PCV-Pentavalent-Rotavirus (3)	C
Gastrointestinal disorders	Diarrhea	8 (1.1)	BCG (1) MR (2) OPV-PCV-Pentavalent-Rotavirus (3) Sinovac COVID-19 vaccine (1) Sinopharm COVID-19 vaccine (1)	A1
	Loss of appetite	3 (0.4)	BCG (1) Sinovac COVID-19 vaccine (2)	A1(1), B1(2)
	Vomiting	8 (1.1)	BCG (3) MR (1) DTP booster-MR-OPV (1) OPV-PCV-Pentavalent-Rotavirus (2) Sinopharm COVID-19 vaccine (1)	A1(6), B1(2)
Nervous system disorders	Fatigue	2 (0.3)	Sinovac COVID-19 vaccine (2)	A1
	Headache	3 (0.4)	Sinovac COVID-19 vaccine (3)	A1
Infections and infestations	Fever	21 (3.0)	BCG (5) DTP booster-MR-OPV (1) MR (2) OPV-PCV-Pentavalent-Rotavirus (12) Sinovac COVID-19 vaccine (1)	A1
	Other symptoms[++]	16 (2.3)		A1(3), B1 (5), C(7), U (1)

[++] These AEFI reactions include chills, cramps, bloated stomach, jaundice, nasal congestion, nausea, oral thrush, pimples on head, redness, seizures, swelling and tonsils. There was one unfortunate case where a 1-day old baby girl died after BCG vaccination. She experienced fever on the same day post vaccination, she deteriorated and was subsequently hospitalized. She was treated with antibiotics and intravenous fluids, but she didn't improve. Post-mortem was not conducted hence the cause of death could not be determined.

[++] Causality assessment classification based on WHO AEFI Algorithm 2019 key is as follows: **A1.** Vaccine product-related reaction, **B1.** Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event), **C.** Coincidental-Underlying or emerging conditions or conditions caused by exposure to something other than vaccine, and **U.** Unclassifiable fatal case due to lack of post-mortem.

Table 4
Participants randomised to SMS-CATI who responded ("Yes" or "No") compared with non-responders to day 0–2 and 14 SMS according to demographic and socioeconomic status, n = 704.

Participants who responded (Yes or No) vs non-responders	Pearson Chi square P Value	Comment
Education Level	<0.001	O Level and below disproportionately were non-responders
Employment Status	<0.001	The unemployed and those employed by organizations disproportionately were non-responders
Housing Status	0.005	Homeowners disproportionately were non-responders
Marital Status	0.217	Marital status did not affect response rates
Gender	0.16	Gender did not affect response rates
Number of Children	0.115	Number of children did not affect response rates

3.5. Time to detection of an AEFI

For those SMS participants who had a confirmed AEFI the time to detection of an AEFI was determined (Table5). For the time periods of vaccination to symptom onset and vaccination to AEFI notification there

Table 5
Time to AEFI detection; Surveillance time points (in hours) in participants with confirmed AEFIs for Zm-STARSS, RCT mHealth SMS CATI intervention group, n = 44.

Time points	SMS mHealth CATI Group in hours (95 % CI)	Calculation
Vaccination to onset of symptoms	17.0 (9.0–23.0)	Onset symptoms (React Time) -Vaccination Time (Enrolment Time)
Onset of symptoms to medical attendance/ attention	93.1 (68.5–115.9)	Medical Attention (Medic time) - Onset symptoms (React Time)
Medical attendance/ attention to completed AEFI report	525.6 (487.6–581.2)	AEFI report (Create Time)- AEFI notification (Medic Time) = Time to AEFI detection that is primary study end point.

vaccines with a variable reactogenicity profile. However, the median time was 17.0 h (CI 95 %: 9.0–23.0) from onset of symptoms to presenting for Adverse attention, regardless of when this occurred following immunisation. The median time from Adverse attendance to Zm-STARSS completion of an AEFI report was 525.6 h (CI 95 %: 487.6–581.2).

4. Discussion

The STARSS platform was designed to address some of the deficiencies inherent in passive surveillance with low rates of AEFI detection. If an AEFI occurs and is not reported, this is due to barriers in the AEFI reporting cycle, confusion among HCWs as to what type of events constitute a reportable AEFI and an unsatisfactory reporting processes [22–24]. Targeting consumers is a strategy to improve AEFI reporting [10,13,14,23]. Our SMS surveillance prompts were designed to ascertain if a serious or severe event, which prompted medical attention or attendance, had occurred. We designed the first SMS questionnaire to include a broad range of medical and community health care advisors with the aim of capturing as many potential AEFI as possible. Using the Zm-STARSS we demonstrated that the detection rate of medical attention and/or attended AEFI using SMS-based surveillance exceeded reporting by passive surveillance. This occurred despite high non-compliance rates to SMS responses. Contrasting the Au-STARSS with the Zm-STARSS provides some valuable insights into the implementation of SMS based surveillance in a LMIC. The SMS-based AEFI detection rates in Zm-STARSS were 2 %, which compares with a rate of 5.3 % in the Au-STARSS-CATI group. For AEFI passive surveillance the rates were 0 % and 0.3 % (respectively, for Zm and Au-STARSS). Overall, hospitalisation rates, following immunisation, were 6-fold higher for Zm-STARSS (0.5 %) compared with Au-STARSS rate (0.08 %), which is likely to reflect co-incidental diseases, including SARS Cov-2 infection. This underlies the importance of performing causality assessment for serious AEFI reports, using the WHO methodology [13] to differentiate adverse vaccine reactions from co-incidental events, which are likely to have occurred with greater frequency in Zm-STARSS. Collectively these trials have demonstrated the utility of the STARSS platform in both HIC and LMIC settings.

The SMS non-compliance rate in Zm-STARSS was 69 % compared with 9.7 % in the Au-STARSS, although the latter had an additional time point for a solicited response (Day 7). SMS non-compliance (response) rates have varied between different SMS AEFI surveillance studies and a comparison has limitations because of the variability in the timing, number of and content of the SMSs, different populations, cultures, mHealth services cost in LMICs, and study settings [14]. In general, studies with opt-in consent show non-compliance rates which vary between 10 and 30 % [14,25,26]. There are several likely reasons for non-compliance rates in Zm-STARSS. First, it was noted that a low education level and unemployment was associated with a higher rate of non-response both factors which need further interrogation. Second, the study was conducted during the peak of the COVID-19 pandemic with inherent challenges in implementation of the study with some HCWs and community members succumbing to COVID-19 and some of the RHCWs testing COVID-19 positive requiring quarantine and prolonged absence from work from time to time. Furthermore, access to phone credit in a LMIC setting is likely to be a significant barrier to SMS responses. We conclude that SMS in LMICs could be ineffective where mobile phone plan pricing structures often encourage data-only plans (without an allocated phone number) and where phones are often used with Wi-Fi communications only. Future studies should investigate the use of online/digital messaging services such as WhatsApp, Viber, Meta messenger and Sasai. The preferred platforms would obviously depend on local popularity, and support for multiple pathways may be required for best coverage. The IT platform could connect to the API gateways of these services and send instant messages through their networks instead of the telephone network. These options are likely to introduce their own issues around privacy and confidentiality in capturing and recording recipient health information and around adverse treatment of messages by spam filters. However, digital services do not rely on a formal mobile number, they rather offer the promise of broader access to the local population than SMS and avoid the issue around transmission of replies being prevented due to lack of credit on the participant phone. In LMICs, SMS platforms on cheaper mobile phones are more accessible than online/digital messaging. If a user is offline, there is no communication. Furthermore, the user requires smartphone/tablet/computer to go online/digital, which is more expensive than a flip phone. We may therefore conclude that using online/digital messaging, in addition to SMS could be more effective in LMICs if resources permitted.

In the Zm-STARSS, 69 % of the "Yes" respondents completed a CATI survey compared with 83 % in the Au-STARSS-CATI group. As noted above this is likely a reflection of the context of the Zm-STARSS during the COVID-19 pandemic and the limitations of availability of telephone credit and connectivity in a LMIC. Of the 64 % (77/121) SMS "Yes" respondents who did not actually experience an AEFI it might be due to cultural reasons as most Shona speaking people who were most of the study participants usually regard "Yes" as to imply they are alright or in good health. Similarly, due to cultural factors, Shona people do not always RSVP to wedding/birthday invitations, funerals etc. and hence the high non-response rates to the post-vaccination SMS prompts.

The median time of about 17.0 h (CI 95 %:9.0–23.0) from onset of symptoms to presenting for medical attention, regardless of when this occurred following immunisation, were similar for Zm-STARSS and Au-STARSS. However, the median time from medical attendance to completion of an AEFI report in Zm-STARSS [525.6 h (CI 95 %: (487.6–581.2)] was longer than the Au-STARSS [74.8 h (CI 95 %: (54.3–96.1)], for the CATI arm. This is likely to reflect the difficulties for RHCWs in implementing the Zm-STARSS trial particularly during the COVID-19 pandemic. MAPC web-based reporting (WBR) has the potential advantage of a shortened time to AEFI detection as demonstrated in the Au-STARSS. However, this is currently difficult in a LMIC because of limited internet connectivity and expensive online/digital tools. Further studies are required to using appropriately and timely communication methods to ascertain the barriers to obtaining information about health care attended events following immunisation for vaccinees or their guardians.

The Zm-STARSS has demonstrated the utility of an SMS-based surveillance platform to enhance AEFI reporting as shown in Au-STARSS [4]. This has been demonstrated despite higher non-compliance and non-CATI completion rates in a LMIC setting. The researchers were so far not aware of any publications evaluating MAPC AEFI surveillance in Africa. The relative costs and benefits of implementing active SMS-based AEFI surveillance in addition to passive surveillance remains to be determined and should be considered using evidence-based cost-effective holistic approaches of integration with other existing or future m-

Health, e-Health including digital initiatives in resource limited settings. The Zm-STARSS system may also be considered for use by HCWs and any other HCW digital AEFI reporting pathways such as VigiMobile when these system(s) become available in Zimbabwe. Consideration for modifying this Zm-STARSS SMS platform to have HCW report AEFI using SMS is possible in the future.

4.1. Conclusion

SMS-based AEFI surveillance can improve AEFI detection in a LMIC setting and should be considered as an approach to augment passive surveillance in these settings for both COVID-19 vaccines and childhood vaccines. However, the challenges of using SMS mentioned in the discussion ought to be addressed. The findings of Zm-STARSS should inform the wider use of SMS-based AEFI surveillance which is particularly relevant at this time for establishing robust and novel pharmacovigilance systems to monitor existing and novel pandemic vaccines. The utility of SMS-based surveillance in AEFI signal detection is another useful risk minimisation factor amongst other considerations for evidence-based integration with other e-Health, digital health, and m-Health systems in resource-limited settings.

4.2. Limitations, confounding factors and/or bias

The limitations of the inherent resource and technology limited challenges of Zm-STARSS resulted in a different study design of only 3 SMS prompts with no web-based review component unlike Au-STARSS. The use of a Zm-STARSS test code meant that some participants could not be enrolled if they only subscribed only to the other two mobile phone operators. We are uncertain if the participants who had responded "Yes" to day 0–2 and 14 day SMS prompts but did not respond to CATI surveys by the RHCWs could have sought medical attention. Confounding factors and bias were minimised by the RCT study design. Additionally, further studies are required to investigate the reasons for the high SMS non-response rates and to identify other factors that may predict response rates in LMIC settings. The study sites included the largest vaccination clinics in a peri-urban setting in Chitungwiza hence the results might not be representative of a rural population. An additional limitation is that those with cell-phone access are not representative of the whole vaccinated population. As explained under the discussion section above, all possible efforts were made to encourage reporting of AEFIs by all participants and guardians in both CATI arm and control passive AEFI surveillance including verification by the EPI and MCAZ research staff. The study result of zero AEFI reporting in the control arm is likely to be a limitation of the passive AEFI surveillance system itself rather than limitation of the study design.

Ethics approval and consent to participate

The Zm-STARSS (II) RCT (ACTRN12614001046695) was approved by the Medical Research Council of Zimbabwe (MRCZ) ethical approval referenced MRCZ/A/2268 and MRCZ ethical exemption (reference E/148) from consenting participants for passive AEFI surveillance. Ethical approvals were also obtained from the Director of Health Services City of Chitungwiza Municipality Department and the University of Cape Town (UCT) Human Research Ethics Committee (HREC 184/2020) for the Zm-STARSS study. The data was published in deidentified anonymised format.

Consent for publication

The authors obtained consent for publication of the manuscript from the MCAZ National Pharmacovigilance Centre the custodian of the safety data since this is a work-related study.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Priscilla Patricia Munyaradzi Nyambayo reports a relationship with Medicines Control Authority of Zimbabwe that includes: employment. The corresponding author and all the co-authors have NO conflict of interests at all. No editorial capacity, no pharmaceutical funding nor any other funding received. The funding for the study was done by the Medicines Control Authority of Zimbabwe (MCAZ) in accordance with its mandate for the National Pharmacovigilance Centre. Additional funding for the project was obtained from World Health Organization and University of Adeliade, Australia and paid to the Medicines Control Authority of Zimbabwe NOT the corresponding author nor any co-authors. So corresponding and co-authors wrote declaration emails of NO conflict of interests and NO competing interests.

Data availability

The data that has been used is confidential.

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References

[1] Heininger U, Holm K, Caplanusi I, Bailey S, Abdoellah SA, Arellano F, et al. Guide to active vaccine safety surveillance: report of CIOMS working group on vaccine safety–executive summary. Vaccine 2017;35(32):3917–21.
[2] Bahri P, Rägo L. CIOMS guide to vaccine safety communication-executive summary. Vaccine 2019;37(3):401–8.
[3] Meher BR. Vaccine pharmacovigilance in India: current context and future perspective. Ind J Pharmacol 2019;51(4):243.
[4] Nyambayo P, Manyevere R, Chirinda L, Zifamba EN, Marekera SF. Descriptive Research Study of the Adverse Events Following Immunization (AEFIs) Surveillance System in Zimbabwe. Clinical Case Reports and Studies. BRS Publishers, vol. 2(2); 2023. 2837-565.
[5] Aborigo RA, Welaga P, Oduro A, Shaam A, Opare J, Dodoo A, et al. Optimising reporting of adverse events following immunisation by healthcare workers in Ghana: a qualitative study in four regions. PLoS One 2022;17(12):e0277197.
[6] Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Olsson S, Sartori D, et al. Adverse drug reaction reporting in Africa and a comparison of individual case safety report characteristics between Africa and the rest of the world: analyses of spontaneous reports in VigiBase®. Drug Saf 2016;39(4):335–45.
[7] Meyer J, Schonfeldt M, Bamford L, Dawood H, Diamini S, Gray C, et al. COVID-19 vaccine safety surveillance and causality assessment of adverse events following immunisation: lessons from South Africa: an International Journal of Medical Toxicology and Drug Experience. Drug Saf 2022;1171–2.
[8] Kiguba R, Olsson S, Waitt C. Pharmacovigilance in low-and middle-income countries: A review with particular focus on Africa. Br J Clin Pharmacol 2023;89 (2):491–509.
[9] Cashman P, Macartney K, Khandaker G, King C, Gold M, Durrheim DN. Participant-centred active surveillance of adverse events following immunisation: a narrative review. Int Health 2017;9(3):164–76.
[10] Psihogios A, Bota AB, Mithani SS, Greyson D, Zhu DT, Fung SG, et al. A scoping review of active, participant-centred, digital adverse events following immunization (AEFI) surveillance: a Canadian immunization research network study. Vaccine 2022.
[11] Nsubuga F, Alfred D, Gyasi SO, Ampeire I, Kabwama SN. Low reporting of adverse events following immunization, during a Measles-Rubella catchup and Polio mass vaccination campaign in Uganda, 2019; 2022.
[12] Zeleke ED, Yimer G, Lisanework L, Chen RT, Huang W-T, Wang S-H, et al. System and facility readiness assessment for conducting active surveillance of adverse events following immunization in Addis Ababa, Ethiopia. Int Health 2023:ihac085.
[13] Gold M, Lincoln G, Cashman P, Braunack-Mayer A, Stocks N. Efficacy of m-Health for the detection of adverse events following immunization–The stimulated telephone assisted rapid safety surveillance (STARSS) randomised control trial. Vaccine 2021;39(2):332–42.

[14] Cashman P, Moberley S, Chee K, Stephenson J, Chaverot S, Martinelli J, et al. Participant centred safety surveillance of health care workers receiving influenza vaccination. Vaccine 2019;37(18):2427–9.
[15] Baron S, Goutard F, Nguon K, Tarantola A. Use of a text message-based pharmacovigilance tool in Cambodia: pilot study. J Med Internet Res 2013;15(4):e68.
[16] Tsafack M, Ateudjieu J. Improving community based AEFI (Adverse Events Following Immunization) reporting rate through telephone" beep" in a Cameroon health district: a randomized field trial. Pan African Med J 2015;22(1).
[17] Cashman P, Munnoch S-A, Clark K, Allan N, Clarke S, Macartney K, et al. The Aboriginal gap in online active vaccine safety surveillance. Australian Indig HealthBull 2020;1(1):3.
[18] Masuka JT, Khoza S. Adverse events following immunisation (AEFI) reports from the Zimbabwe expanded programme on immunisation (ZEPI): an analysis of spontaneous reports in Vigibase® from 1997 to 2017. BMC Public Health 2019;19(1):1166.
[19] Shaum A, Mujuru HA, Takamiya M, Tickay I, Nathoo K, Sreenivasan N, et al. Enhanced surveillance for adverse events following immunization during the 2019 typhoid conjugate vaccine campaign in Harare, Zimbabwe. Vaccine 2022.
[20] Bohn-Goldbaum E, Cross T, Leeb A, Peters I, Booy R, Edwards KM. Adverse events following influenza immunization: understanding the role of age and sex interactions. Expert Rev Vaccines 2022;21(3):415–22.
[21] Gidudu JF, Shaum A, Dodoo A, Bosomprah S, Bonsu G, Amponsa-Achiano K, et al. Barriers to healthcare workers reporting adverse events following immunization in four regions of Ghana. Vaccine 2020;38(5):1009–14.
[22] Clothier HJ, Selvaraj G, Easton ML, Lewis G, Crawford NW, Buttery JP. Consumer reporting of adverse events following immunization. Hum Vaccin Immunother 2014;10(12):3726–30.
[23] Dey A, Wang H, Quinn H, Hiam R, Wood N, Beard F, et al. Surveillance of adverse events following immunisation in Australia annual report, 2017. Commun Dis Intell 2019;43:1–28.
[24] Munnoch S-A, Cashman P, Peel R, Attia J, Hure A, Durrheim DN. Participant-Centered online active surveillance for adverse events following vaccination in a large clinical trial: feasibility and usability study. J Med Internet Res 2019;21(10):e14791.
[25] Stuurman AL, Verstraeten T, De Schryver A. Rapid assessment of the reactogenicity of a 2016–2017 seasonal influenza vaccine: results from a feasibility study. Expert Rev Vaccines 2017;16(2):187–91.

APPENDIX 6: Pre- study HCPs Questionnaire online survey monkey

MCAZ Medicines Control Authority of Zimbabwe

STARSS ZIMBABWE AEFI SURVEILLANCE

STARSS II STUDY of AEFI SURVEILLANCE: QUESTIONNAIRE FOR HEALTH CARE WORKERS(HCW)

Thank you for your informed consent as a healthcare provider to voluntarily participate in the completion of pre-and post- study STARSS questionnaire. The aim of the descriptive questionnaire is to investigate health care acceptability of Stimulated Telephone Assisted Rapid Surveillance system (STARSS) of Adverse Events Following Immunization(AEFI) surveillance including knowledge perceptions and practice of health care providers. The information gathered will be treated as strictly confidential. The results of the STARSS AEFI surveillance study and acceptability study will be disseminated to the study sites and key stakeholders in an anonymous format. Should you require any further clarifications please email pnyambayo@mcaz.co.zw.

Thank you for your assistance.

Kind regards

Mrs Priscilla Nyambayo

* 1. Participant's Job Title:(Tick only one)

Paedriatrician Doctor Nurse Manager Matron Midwife Registered General Nurse(RGN)

Primary Care Nurse(PCN) Clinical pharmacologist Pharmacist

Other (please specify)

2. What is your gender?

Female

Male

3. Please state your age:

below 30 years 31 year to 40 years 41 year to 50 years 51yrs to 60 years Above 60 years

* 4. What are your years of Professional Experience?

1 year to 5 years 6 years to 10 years 11 years to 15 years 16 years to 20 years Above 20 years

1

* 5. Which hospital department do you work ?

- Caesarean Ward
- Vaccination Clinic (OPD)
- Postnatal Ward
- Neonatal ward
- Other (please specify)

* 6. Please note that this is a brief quiz on your knowledge around vaccinations and AEFI. Please answer the questions to the best of your ability. We are not testing your competence but rather assessing whether the national training in AEFI is effective and adequate.

Question: How do you respond to the following statements?

There are no contraindications to vaccinations used in immunization schedule.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 7. AEFI include medical events that may not be caused by vaccines.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 8. An AEFI can be caused by programme errors such as a reconstituted vaccine stored longer than the recommended period or an incorrect injection technique.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 9. AEFI investigation includes examination of operational aspects of immunization programme.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 10. If a parent complains about a mild illness in their child that is clearly not due to the vaccine but blames the vaccination, you would not report this as an AEFI.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 11. A system for monitoring and assessing the safety of vaccines exists in Zimbabwe.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 12. The timeline for reporting a serious AEFI is 24 hours in Zimbabwe.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 13. The vaccine batch number and expiry date should be recorded on the vaccination card and AEFI form.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 14. Treatment of a coincidental illness falsely attributed as a vaccine reaction should **not** be delayed until investigations are confirmed.

Strongly agree Agree Neutral Disagree Strongly disagree

* 15. All injection site abscesses after vaccination should be reported as AEFI.

Strongly agree Agree Neutral Disagree Strongly disagree

* 16. In the case of severe/serious/clusters of AEFI, both the *AEFI reporting form* and the *AEFI Case Investigation and Management forms* should be completed.

Strongly agree Agree Neutral Disagree Strongly disagree

* 17. Hydrocortisone injection should always be kept in the immunization clinic emergency trolley in case of hypersensitivity reactions after vaccination.

Strongly agree Agree Neutral Disagree Strongly disagree

* 18. Routine administration of paracetamol before vaccination can reduce the risk of fever after vaccination.

Strongly agree Agree Neutral Disagree Strongly disagree

* 19. Case investigation of serious AEFI is initiated at national level once AEFI form has been received.

Strongly agree Agree Neutral Disagree Strongly disagree

* 20. Have you ever seen an AEFI form at your medical facility or hospital?

Yes No Unsure

* 21. Have you ever seen a case investigation form at your medical facility?

Yes No Unsure

* 22. Do you have access to the national AEFI guidelines?

Yes No Unsure

* 23. Have you ever received training on AEFI reporting?

Yes No Unsure

* 24. Have you seen an AEFI in your career?

- Yes
- No
- Unsure

25. If Yes to question 24 above- Have you ever reported an AEFI in your career?

Yes No Unsure

26. If Yes to question 24 above- , approximately how many cases have you seen?

1 2 to 4 5 to 10 above 10

27. If Yes to question 24 above: ,What types of AEFI have you reported? **Tick all those that apply**

- [ ] None- I have never reported.
- [ ] Fever
- [ ] Convulsions
- [ ] Shock
- [ ] Other (please specify)
- [ ] Abscesses, redness or injection site swelling
- [ ] BCG lymphadenitis
- [ ] Death
- [ ] acute flaccid paralysis (AFP)

28. If you saw an AEFI but did not report AEFI, which of the following made you not do it? **Tick all that apply**

- [ ] Not enough time to report
- [ ] Could not find AEFI form
- [ ] Non Serious AEFI
- [ ] Other (please specify)
- [ ] Serious AEFI
- [ ] Don't know who to report to
- [ ] Uncertain whether the event was reportable
- [ ] Not sure about reporting procedures

* 29. Reporting an AEFI such as abscess will make me feel guilty or ashamed about having caused harm to a child I vaccinated?

Strongly agree Agree Neutral Disagree Strongly disagree

* 30. I am reluctant to report an AEFI when I am not confident about the diagnosis.

Strongly agree Agree Neutral Disagree Strongly Disagree

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* 31. Poor monitoring of AEFIs can result in a reduction in public confidence in immunization and hence negatively affect immunization coverage.

Strongly agree Agree Neutral Disagree Strongly disagree

32. The following questions ask how you feel about AEFI surveillance system. Your responses are confidentially treated.

Reporting an AEFI can lead to personal consequences.

Strongly agree Agree Neutral Disagree Strongly Disagree

33. Regardless of whether or not you have reported an AEFI in the past, which of the following factors do you believe stand in your way or serve as a barrier to your reporting an AEFI . **Tick all the options that apply**

- Uncertainty about what and when to report
- Not enough time to report
- Unavailability of AEFI reporting form
- Unavailability of Case Investigation form
- Lack of support from supervisor
- Concerns about negative consequences
- Lack of feedback after investigations
- Other (please specify)

* 34. I believe that reporting and investigating of AEFI is mostly the responsibility of health care providers.

Strongly agree Agree Neutral Disagree Strongly disagree

* 35. I believe that reporting and investigating of AEFI is both the responsibility of vaccinee's parent/guardian and health care providers

Strongly agree Agree Neutral Disagree Strongly disagree

* 36. Do you believe that enhancing AEFI surveillance could help build public trust in immunization programmes?

Strongly agree Agree Neutral Disagree Strongly disagree

* 37. Do you believe that nurses and doctors play a vital role in the diagnosis. reporting, investigation and management of AEFIs?

Strongly agree Agree Neutral Disagree Strongly disagree

* 38. Do you think you need additional training on how to diagnose, report, investigate and manage AEFIs?

Strongly agree Agree Neutral Disagree Strongly disagree

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* 39. Do you believe that immunization staff at the medical facility or hospital are usually too busy to report AEFI?

Strongly agree Agree Neutral Disagree Strongly disagree

* 40. Do you believe that all staff working at vaccination clinic/ health facility including nursing assistants should know about AEFIs?

Strongly agree Agree Neutral Disagree Strongly disagree

* 41. The following questions are about your ideas and opinions around vaccines, immunization programs and their safety.
In general, how safe would you say the vaccines given in Zimbabwe are?

Very Safe Safe Not sure Unsafe Very Unsafe

42. Who do you think should be involved in the process of monitoring vaccine, immunization programs and their safety? **Tick all that apply**

- Health professionals
- National Pharmacovigilance Centre (MCAZ)
- Vaccine manufacturers
- Health researchers
- Expanded Programme on Immunization(EPI)-MoHCC
- Parents/guardians of children who are vaccinated
- Other (please specify)

43. On a scale of 1 to 5 (1 = most trusted) rank the following in order of importance as trusted sources of information about vaccine safety?

	1st	2nd	3rd	4th	5th
family and friends					
Immunization nurse					
Doctor					
Vaccine manufacturer					
Internet					
Public media					
Medical journals					

* 44. Have you ever been trained on how to counsel parents/guardians about safety of the vaccine and potential vaccine side effects or reactions when their children are being vaccinated?

Yes No Can't remember

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* 45. I am concerned that a vaccine might cause a serious or disabling side effect.

Strongly agree Agree Neutral Disagree Strongly disagree

* 46. I think it is important for children to receive all the recommended vaccinations.

Strongly agree Agree Neutral Disagree Strongly Disagree

* 47. I am concerned that the vaccine might not work and the child might still get the disease?

Strongly agree Agree Neutral Disagree Strongly Disagree

* 48. Sending text messages to parents/guardians about how their children responded to vaccination may improve AEFI reporting and safety monitoring of children.

Strongly agree Agree Neutral Disagree Strongly Disagree

* 49. I think sending text messages to parents/guardians of vaccinated children asking them about any possible side effects could cause undue concern about the safety of vaccination.

Strongly agree Agree Neutral Disagree Strongly disagree

50. On a scale of 1 to 5(with 1 being the most important) could you rank in order of importance the top five things needed by a healthcare provider to implement SMS (mHealth) for AEFI surveillance.

	1st	2nd	3rd	4th	5th
Computer typing skills					
Laptop or desktop computer					
Tablet or ipad					
Mobile phone(cellphone)					
Data bundles					
Voice and SMS					
Internet connection					

51. What do you think are the minimum basic things required for a healthcare provider to successfully implement SMS(mHealth) system for AEFI safety surveillance.(**Tick all that apply)**

- computer typing skills
- Laptop or desktop computer
- Tablet or iPad
- Mobile phone (cellphone)
- Data bundles
- Voice and SMS bundles
- Wifi connection

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52. Which of the following information technologies and skills are you confident of operating or performing? **Tick all that apply.**

- [ ] Computer typing skills
- [ ] Laptop or desktop computer
- [ ] Tablet or iPad
- [ ] Mobile phone (cellphone)
- [ ] Searching the internet
- [ ] Social media (e.g. Whatsapp, Facebook, Twitter, Instagram)

Other (please specify)

53. Which of the following information technologies and skills do you readily have access to? **Tick all that apply**

- [ ] Computer typing skills
- [ ] Laptop or desktop computer
- [ ] Tablet or iPad
- [ ] Mobile phone (cellphone)
- [ ] Data bundles
- [ ] Voice and SMS bundles
- [ ] Wifi connection

* 54. Questions 54 to 57 are statements that help us to determine how you feel about receiving and following up a cellphone/mobile SMS text message from the child's parent/guardian after vaccination to check the safety of the vaccination using clinic cellphone/mobile phone.

How do you agree with the statement that SMS text messages promote vaccination safety monitoring?

Strongly agree Agree Neutral Disagree Strongly agree

* 55. As a health care worker I have time to respond to mobile phone(cellphone)vaccination SMS at our health facility or hospital.

Strongly agree Agree Neutral Disagree Strongly Disagree

* 56. Receiving and following up on mobile phone(cellphone) vaccination SMS helps me do my job as a vaccination official

Strongly agree Agree Neutral Disagree Strongly Disagree

* 57. Engagement of the child's guardian is important and necessary in AEFI surveillance.

Strongly agree Agree Neutral Disagree Strongly Disagree

* 58. Have you ever used STARSS (II) SMS Mobile system for AEFI surveillance in Zimbabwe?

- [ ] Yes
- [ ] No

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59. To use the STARSS study SMS text message system to monitor vaccine safety, someone must collate responses to the text messages and, if needed, contact the guardian of vaccinated child/children).

Who of the following should have access to this text message information? **Tick all boxes that apply**

- ☐ The Doctor/ GP at the medical facility
- ☐ Immunization nurse
- ☐ Department of Health
- ☐ Other (please specify)
- ☐ Vaccine Manufacturer
- ☐ Independent body

* 60. Which of the following attributes of a health care provider can *facilitate (make it easy)* **or** *Inhibit (make it difficult)* to use STARSS (II), SMS health for AEFI surveillance? Write **YES** in front of attributes that **facilitate** and **NO** in front of to those that **inhibit**.

Previous experience with mobile technology	
Willingness to learn	
Lack of knowledge	
Decreased sensory perception	
Lack of the need for Technology	
Age maturity	

* 61. Which of the following context-related attributes *facilitate (make it easy)* **or** *inhibit (make it difficult)* to use STARSS (II) or SMS health for AEFI surveillance? Write **YES** in front of attributes that facilitate and **NO** in front of those that inhibit.

lack of training	
Doctor's recommendation to use STARSS for AEFI surveillance	
Nurse's recommendation **NOT** to use STARSS for AEFI surveillance	
Management of EPI, MoHCC or MCAZ recommendation to use use STARSS for AEFI surveillance	
Participant's availability of mobile (cell) phone and having airtime	
Health care worker fear of consequences of AEFI reporting	
Parents not able to detect AEFI	
Parents understanding of AEFI reporting	

* 62. Which of the following attributes of technology *facilitate (make it easy)* **or** *inhibit(make it difficult)* to use STARSS (II) or SMS health for AEFI surveillance? Write **YES** in front of attributes that **facilitate** and **NO** in front of those that **inhibit**.

Overall ease of use of technology	
Presence of useful features e.g . prompt SMS delivery	
Poorly designed mobile phone interface between sender and receiver of messages	
Cost of mobile handsets, laptops and computers	
Cost of airtime and phone bill	

* 63. I feel that a Vaccination SMS system is an appropriate way of improving reporting of AEFIs

Strongly agree Agree Neutral Disagree Strongly disagree

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* 64. I feel that an SMS system will encourage and support me to follow up the SMS text message from the child's guardian using the clinic's mobile (cell) phone.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

* 65. What do you think are some of the challenges that are likely to be encountered when implementing STARSS (II) SMS AEFI Surveillance system in Zimbabwe?

* 66. Would you recommend STARSS SMS (mHealth) for AEFI surveillance if the study's results are positive?

- Yes
- No
- Not Sure
- Please explain your answer

* 67. Having experienced the STARSS mHealth SMS technology, do you feel that it is an appropriate way of improving reporting of AEFI?

- Yes
- No
- Not Sure
- Explain your answer

* 68. Please describe any challenges you experienced during the implementation of the STARRS system at the medical facility

69. During the study how did you feel about receiving and following up SMS text messages from the parent/guardian of a child after vaccination to check the safety of the vaccine using the clinic mobile (cell) phone? **Tick all that apply**

- In control or in charge of my work
- Happy to assist
- Uncertain or Confusing
- Being responsible
- Inconvenienced

* 70. Do you have any concerns about the STARSS (II) system for AEFI surveillance

Yes No Not Sure

Please explain your answer

* 71. Do you believe this STARSS (II) mHealth AEFI surveillance system will work in the long run in Zimbabwe?

Yes No Not Sure

Please explain your answer

* 72. In your own words, can you tell us what your overall impression of the STARSS system for AEFI surveillance is?

73. Would you recommend using STARRS (II) mHealth Surveillance System for monitoring safety of COVID -19 vaccines?

Yes No Neutral

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APPENDIX 7: Post study HCPs Questionnaire online survey monkey

MCAZ Medicines Control Authority of Zimbabwe

POST STUDY STARSS ZIMBABWE AEFI SURVEILLANCE

POST STUDY STARSS II STUDY of AEFI SURVEILLANCE: QUESTIONNAIRE FOR HEALTH CARE WORKERS(HCW)

Thank you for your informed consent as a healthcare provider to voluntarily participate in the completion of pre-and post- study STARSS questionnaire. The aim of the descriptive questionnaire is to investigate health care acceptability of Stimulated Telephone Assisted Rapid Surveillance system (STARSS) of Adverse Events Following Immunization(AEFI) including knowledge perceptions and practice of health care providers. The information gathered will be treated as strictly confidential. The results of the STARSS AEFI surveillance study and acceptability study will be disseminated to the study sites and key stakeholders in an anonymous format. Should you require any further clarifications please email pnyambayo@mcaz.co.zw.

Thank you for your assistance.

Kind regards

Mrs Priscilla Nyambayo

* 1. Participant's Job Title:(Tick only one)

- Paedriatrician
- Doctor
- Nurse Manager
- Matron
- Midwife
- Registered General Nurse(RGN)
- Primary Care Nurse(PCN)
- Clinical pharmacologist
- Pharmacist
- Other (please specify)

2. What is your gender?

- Female
- Male

3. Please state your age:

- below 30 years
- 31 year to 40 years
- 41 year to 50 years
- 51yrs to 60 years
- Above 60 years

1

* 4. What are your years of Professional Experience?

- ◯ 1 year to 5 years
- ◯ 6 years to 10 years
- ◯ 11 years to 15 years
- ◯ 16 years to 20 years
- ◯ Above 20 years

* 5. Which hospital department do you work ?

- ◯ Caesarean Ward
- ◯ Vaccination Clinic (OPD)
- ◯ Postnatal Ward
- ◯ Neonatal ward
- ◯ Other (please specify)

* 6. AEFI include medical events that may not be caused by vaccines.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly disagree

7. To use the mHealth SMS based text message system to monitor vaccine safety, someone must collate responses to the text messages and, if needed, contact the guardian of vaccinated child/children).

Who of the following should have access to this text message information? **Tick all boxes that apply**

- ☐ Immunization nurse clinic
- ☐ Immunization doctor clinic
- ☐ National Pharmacovigilance Center-MCAZ
- ☐ Other (please specify)
- ☐ Zimbabwe Expanded Program on Immunization Program
- ☐ Vaccine manufacturer

8. Previous experience with mobile phone technology can facilitate (make it easy) to use STARSS (II) SMS health tool for AEFI surveillance.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neutral
- ◯ Disagree
- ◯ Strongly disagree

9. Willingness to learn can facilitate (make it easy) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

10. Age maturity can facilitate (make it easy) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

11. Lack of knowledge can inhibit (make it difficult) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

12. Decreased sensory perception can inhibit (make it difficult) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

13. Lack of desire to use technology can inhibit (make it difficult) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

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14. Lack of training can inhibit (make it difficult) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

15. Doctor's recommendation to use SMS text message for AEFI surveillance can facilitate(make it easy) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

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POST STUDY STARSS ZIMBABWE AEFI SURVEILLANCE

16. Nurse's recommendation to use SMS text message for AEFI surveillance can facilitate(make it easy) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

17. Zimbabwe Expanded Program on Immunization(ZEPI) of MOHCC recommendation to use SMS text message for AEFI surveillance can facilitate(make it easy) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

18. Participant's mobile phone reachability or accessibility can facilitate(make it easy) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

19. Health Care Worker's fear of negative consequences of reporting an AEFI can inhibit(make it difficult) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

20. Failure by parents/guardians to detect AEFI can inhibit(make it difficult) to use STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

21. Parents/guardians understanding of AEFI can facilitate(make it easy) adoption of STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

22. User friendly technology may facilitate (make it easy) adoption of STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

23. Reliable mobile phone network (e.g. prompt delivery of SMS) may facilitate (make it easy) adoption of STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

24. Poorly designed mobile phone interface between sender and receiver of messages may inhibit (make it difficult) adoption of STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

25. Cost of mobile phones, computers and laptops facilitate(make it easy) adoption of STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

26. Reasonable cost of mobile phone airtime can facilitate (make it easy) adoption of STARSS (II) SMS health tool for AEFI surveillance.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

* 27. I feel that SMS text message based vaccination surveillance system is an appropriate way of improving reporting of AEFIs.

Strongly agree | Agree | Neutral | Disagree | Strongly disagree

* 28. I feel that SMS text message based vaccination surveillance system can help me follow up the SMS text message from the child's parent/guardian using the clinic's mobile phone(cellphone).

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

* 29. What do you think are some of the challenges that are likely to be encountered when implementing SMS text message -based AEFI Surveillance systems in Zimbabwe?

* 30. Would you recommend STARSS (II) SMS -based system for AEFI surveillance if the study's results are positive?

Yes | No | Not Sure

Please explain your answer

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* 31. Having experienced STARSS (II) SMS AEFI surveillance system in Chitungwiza study, do you feel that it is an appropriate way of improving AEFI reporting ?

Yes No Not Sure

Explain your answer

32. Please describe any challenges you might have experienced during the implementation of the STARSS (II) SMS -based AEFI surveillance system at your immunization clinic?

* 33. Do you have any concerns about STARSS (II) SMS based system for AEFI surveillance?

Yes No Not Sure

Please explain your answer

* 34. Do you believe this STARSS (II) SMS based AEFI surveillance system can work in the long run in Zimbabwe?

Yes No Not Sure

Please explain your answer

35. Could you tell us in your own words what is your overall impression of STARSS (II) SMS-based system for AEFI surveillance ?

* 36. Would you recommend STARSS (II) SMS-based AEFI surveillance system for monitoring safety of COVID -19 vaccines?

Yes No Neutral