Knowledge, attitudes and perceptions of antibiotic use and antibiotic resistance among private sector patients' and prescribers' in South Africa

By

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Declaration

I, *Elise Farley*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signature:

Date: 18 May 2017

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Dissertation Abstract

Antibiotic resistance (ABR), alternately referred to as antimicrobial resistance, has been labelled as the next big global health crisis. If current levels of ABR continue along the same trajectories, by 2050 ABR will cost the lives of 10 million people a year, ABR cannot be stopped but it can be slowed down. ABR occurs because the bacteria evolve to protect themselves from antibiotics. One of the main causes of ABR is the misuse and over prescription of antibiotics. The primary objective of the study is to ascertain the level of knowledge, attitudes and perceptions of appropriate antibiotic use and ABR, among prescribers and patients in private health care in South Africa. The secondary objective of the study is to explore associations between knowledge, attitudes and perceptions of prescribers and patients regarding antibiotic use and resistance.

This project consists of three main sections, a proposal, literature review and a journal ready article. All sections focus on ABR. The proposal lays a foundation for the need for the research, and explains how the research will be conducted. The literature review explores the existing evidence on the topic, and the final section is a secondary analysis of cross sectional study data, in which private practice patients and prescribers in South Africa completed a once-off anonymous survey. Data was analysed using Stata, T-tests, chi-squared tests, logistic regression models were used to assess associations between knowledge, attitudes and perceptions of both patients and prescribers.

We found that mean knowledge scores among patients (n=403, mean 9 out of 14, standard deviation [SD] 3) and providers (n=175, median 5 maximum 7, IQR 4, 6), were suboptimal and that poor knowledge was associated with perceptions and behaviours as well as prescribing practices that could lead to ABR. Associations between knowledge, attitudes and perceptions of patients and prescribers were explored in multivariate logistic regression models. After adjusting for education and sex, a 1-unit increase in patient knowledge score was associated with the belief that antibiotics will work less well in future if we over-use them now (aOR 1.3; 95% CI: 1.18, 1.43; pvalue <0.001). Prescribers with higher knowledge scores were less likely to report that they prescribe antibiotics when not necessary as antibiotics cannot harm the patient (aOR 0.55; 95% CI: 0.33, 0.91; pvalue 0.02). We also identified a large proportion (58%) of patients who were interested in alternatives to antibiotics and a large proportion (91%) of prescribers wanting educational material to facilitate conversations about resistance with patients.

Our study demonstrates gaps in patient and prescriber knowledge that are associated with potentially harmful perceptions and destructive behaviours regarding antibiotic use. These associations, together with our finding that patients and prescribers

would like more education on ABR, suggest that educational tools and patient-provider communication tools could promote rational antibiotic use.

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List of Abbreviations

ABR - Antibiotic Resistance
aOR - Adjusted Odds Ratio
CDC - Centers for Disease Control and Prevention
CI - Confidence Interval
GP - General Practitioner
HREC - Human Research Ethics Committee
IQR - Inter quartile range
KAP - Knowledge, attitudes and perceptions
MCR - Mobilised Colistin Resistance
MRSA - Methicillin-Resistant Staphylococcus Aureus
N - Sample size
OR - Odds Ratio
RTI - Respiratory tract infections
SD - Standard Deviation
STI - Sexually transmitted infections
UK - United Kingdom
URTI - Upper respiratory tract infections
USA - United States of America
USD - United States Dollars
WHO - World Health Organisation

Part A: Protocol

Title: Knowledge, attitudes and perceptions of antibiotic use and antibiotic resistance among private sector patients' and prescribers' in South Africa

Purpose of the Study

The primary objective of the study is to ascertain the level of knowledge, attitudes and perceptions of appropriate antibiotic use and antibiotic resistance (ABR), otherwise known as antimicrobial resistance, among prescribers and patients in South Africa. The secondary objective of the study is to explore associations between knowledge, attitudes and perceptions of patients and prescribers regarding antibiotic use and resistance. The hypothesis the study is that patients and prescribers have differing levels of knowledge, attitudes and perceptions about antibiotic use and resistance and that these factors influence decisions made, which ultimately impact upon ABR levels.

ABR is a global issue but is caused by prescribing and use at a local level, so needs to be understood locally. If resistance interventions are going to be successful, an understanding of current knowledge, attitudes and perceptions of a broad range of patients and prescribers need to be understood in a quantitative manner. These questions have been asked in other settings (as explored in the literature review section below), but this project will be able to offer answers from South African patients and prescribers. This project will yield unique insight into antibiotic prescribing, ideas about ABR, and insights into patients' and prescribers' understanding of the issue of resistance.

Background

The World Health Organisation (WHO) states that "antimicrobial resistance, within a wide range of infectious agents, is a growing public health threat of broad concern to countries and multiple sectors. … (It is a) problem so serious that it threatens the achievements of modern medicine. A post-antibiotic era- in which common infections and minor injuries can kill- far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century" (WHO 2014).

The word antibiotic was first used in 1941 by Selman Waksman and shortly after came the antibiotic age from 1945 – 1955 (Clardy et al. 2009). Penicillin was among the first antibiotic medications proved to effectively treat bacterial infections (Spencer 2003). Antibiotics have been used to treat conditions such as Whooping Cough, Streptococcal

Throat Infections, Urinary Tract Infections and Tuberculosis (CDC 2016). Antibiotics have prevented millions of deaths, and the years of biggest impact of these treatments are seen as the ‘golden age’. They are hailed as miracle drugs as they can effectively eliminate the bacteria without damaging the surrounding cells (Levy 1998).

ABR occurs because the bacteria evolve to protect themselves from antibiotics. Bacteria vary tremendously in their susceptibility to antibiotics. All bacteria are susceptible to sufficiently high doses of antibiotics, but the human body cannot tolerate some of these high doses, and this introduces the concept of resistance. ABR is either intrinsic (naturally occurring) or acquired (Hawkey 1998). Acquired resistance occurs in a ‘survival of the fittest’ effort by the bacteria to evolve to ensure protection against antibiotics.

ABR was first reported in the 1940’s and transferable resistance was first recognised in 1959 (Hawkey 1998). The USA reports that 2 million people become infected with resistant bacteria each year, and 23 000 people die as a result of these resistant bacterial infections (CDC 2016). Reported cases of ABR include diseases such as Tuberculosis, Staphylococcusaureus and Methicillin-Resistant Staphylococcus Aureus (MRSA) (WHO 2014). The emergence of the Mobilised Colistin Resistance (MCR) -1 gene which renders the last line antibiotic, colistin, futile has been the most recent discovery and has hailed calls for a united global approach to resistance (Liu 2015). The WHO (2016) has listed many concerns about ABR, these include poor surveillance, under reporting (especially of multi-drug resistant Tuberculosis), and the massive financial and human resource burden this will place on health care systems. A recent modelling review on the impact of ABR showed that by 2050, 10 million people will die each year as a direct result of resistance and there will be between a 2% to 3.5% loss of Global Gross Domestic Product. It will cost the world up to 100 trillion United States Dollars (USD) (O’Neill 2016).

One of the main causes of ABR is the misuse and over prescription of antibiotics. Antibiotics have been widely misused by humans which has increased the selection and spread of resistant bacteria (WHO 2016). The initially produced antibiotics in the 1940’s and 50’s are currently largely ineffective due to the evolution of antibiotic resistance (Clardy et al. 2009). The 1980’s were the last years of development of fully effective antibiotics (WHO 2014).

It is essential to preserve the efficacy of existing drugs through measures to minimize the development and spread of ABR to them, while efforts to develop new treatment options proceed (WHO 2014). Antibiotics should only be prescribed and used when absolutely

necessary (Levy 1998). Additions of antibiotics to animal feed should be minimised, as this has an unquantifiable impact on resistance levels (Hawkey 1998).

"Bacteria clearly have a wondrous array of biochemical and genetic systems for ensuring the evolution and dissemination of ABR" (Hawkey 1998). Antibiotics have become less effective, and ABR will rapidly outpace available treatment options (WHO 2014), and the result is a global health crisis. This study aims to understand the perceptions, attitudes and knowledge of patients and prescribers in South Africa about antibiotic use and resistance.

Summary of literature review

Patients' and prescribers' knowledge, attitudes and perceptions around antibiotic use and ABR will greatly vary from person to person, place to place, and continent to continent. There are however several commonalities, some of which this project may show as applicable to the South African context.

Clinicians' knowledge, attitudes and perceptions of ABR have been assessed in multiple studies. The systematic review (including 57 studies) conducted by McCullough *et al.* (2015) on clinicians' knowledge and beliefs about antibiotic resistance showed that the majority of clinicians had heard of ABR and believed it to be a serious issue. A smaller percentage believed it was a problem in their own practice. The majority of clinicians noted that ABR was mainly from patient non-adherence and excessive antibiotic use (McCullough, Rathbone, et al. 2015). An Australian study showed that there was confusion among General Practitioners (GPs) about the causes of resistance (Hardy-Holbrook et al. 2013). In another Australian based study, it was found that even if GPs are aware of ABR, they do at times feel pressure to prescribe antibiotics in order to pacify patients (Tonkin-Crine et al. 2011). Up to 40% of GP respondents in admitted to prescribing antibiotics to meet patients expectations (Hardy-Holbrook et al. 2013). Over prescription is a major issue, in a study conducted in India, over 60% of prescriptions were labelled as incorrect (Hadi et al. 2008). This could be a consequence of no standardised treatment protocols, or clinicians not keeping up to date on the latest treatment evidence. ABR is not only a concern for medical professionals. The economic and social impacts of this crisis will be massive (O'Neill 2014), and should be taken into consideration. Many medical professionals believe that the secondary impacts of ABR will have the biggest impact on society, but as few studies have attempted to narrow down actual estimates, there is limited reliable data on what secondary impacts can be expected (O'Neill, 2016). There are already international partnerships, particularly between Europe and the USA, working on standardised action to slow down

resistance (O'Neill, 2016), but this will need to move beyond these regions and into a global setting.

Studies around patients' knowledge, attitudes and perceptions have revealed that globally, there is a massive knowledge gap in regards to ABR, including within patient populations, and decision making and business circles (O'Neill, 2016). Individuals and communities show a great deal of uncertainty about resistance, and many people view it as a societal problem which will not affect them personally (Brooks et al. 2008). A systematic review (54 studies included) conducted by McCullough et al. (2015) on patients' beliefs and knowledge of ABR showed that the majority of patients believed resistance was a change in the human body, which made people themselves resistant. Many patients believed that not completing antibiotic courses, and excessive antibiotic use led to resistance and most patients believed that action to minimise ABR should be done by physicians (McCullough, Parekh, et al. 2015). The public also showed signs of confusion, and the majority of responses were not in line with prevailing biomedical research (Hawkings et al. 2007). Self-medication is also an issue, this occurs when patients receive antibiotics from pharmacists without having a prescription (Kotwani et al. 2012).This could be a rectifiable issue which could decrease overuse of antibiotics. Many patients state that it is not up to them to contribute to the control of resistance, but place that role in the hands of GPs (Brooks et al. 2008). This could be due to the low proportions of GPs who actually discuss ABR with patients (Hardy-Holbrook et al. 2013), or the incorrect reporting of ABR in the media. Many patients felt ABR was only a problem due to dirty hospitals, and hospital management was to blame. Less than a quarter of respondents stated that they could do anything about resistance (Hawkings et al. 2007).

The WHO has limited information on the extent of ABR in Africa as surveillance is only carried out in a handful of countries (WHO 2014). Little is known about patients' and prescribers' knowledge, attitudes and perceptions in the South African context. If the target of slowing down ABR is to become a reality, both patients and prescribers will need to be involved in the effort. Some instructions for physicians include not acceding to patients' demands for antibiotics, prescribing narrow targeting antibiotics and isolating hospital patients with multi-drug resistant infections. Patients should not demand antibiotics, and when they are necessary and prescribed, the full course should be taken (Levy 1998). Patients' and prescribers' knowledge, attitudes and beliefs can greatly alter the course of resistance.

Methodology

Study design

This project is a secondary analysis based on an original study titled *Knowledge, attitudes and perceptions of antibiotic use among patients' and prescribers' in Cape Town* which received approval from the University of Cape Town Human Research Ethics Committee (HREC REF: 610/2015). The original study was a cross-sectional survey evaluating prescribers' and patients' knowledge, attitudes and perceptions of antibiotic use and resistance. Data from the original study was not analysed, and so this current study will evaluate the data that was gathered during the original study. No new data will be collected.

Objectives

The main research question of this study is to assess the level of knowledge, attitudes and perceptions of ABR among prescribers and patients in South Africa.

There are four main objectives of the study.

1. *Assess the knowledge* that prescribers, General Practitioner Doctors (GPs) and patients have about appropriate antibiotic use and the problem of ABR.
2. *Describe the attitudes* of prescribers and patients towards antibiotic use and resistance.
3. *Describe the perceptions* of prescribers and patients regarding antibiotic use and resistance.
4. *Explore associations* between knowledge, attitudes and perceptions of prescribers and patients regarding antibiotic use and resistance.

Characteristics of the study population

Four hundred and three patients and 183 prescribers participated in the original study. Participants were included if they were General Practitioner (GPs) in private practice, as well as patients attending these practices. People under the age of 18 and not residing in South Africa were excluded.

Recruitment and enrolment

The original study employed a convenience and snowball-sampling approach. Patients were asked by reception staff at GP practices to complete the questionnaire when they arrived for consultations. Questionnaires and links to the website where the questionnaire could be completed were circulated to GPs who forwarded it on to their colleagues and it was presented at a number of academic meetings. Both patient (Appendix 3) and prescriber

(Appendix 4) questionnaires were available in soft and hard copies. There was no reimbursement for participation in the project.

Research Procedures and Data Collection Methods

Data collection for the original project has already been completed. The consent form and questionnaire were provided in the language that the participants were most comfortable with. Data was collected using online survey forms in multiple-choice style in SurveyMonkey (SurveyMonkey Inc., San Mateo, California, USA). Forms completed in hard copy were entered into SurveyMonkey by the research team. Data from the online survey was exported to Microsoft Excel format.

Data Safety and Monitoring

Extracted data will identify individuals only by code. All reports and publications will refer only to anonymous or pooled data. Hard copy forms are stored in a locked cupboard, which only the research team has access to. Soft copy data is stored in a password protected file, only accessible to the research team.

Data Analysis

The analysis will be divided into four main sections, to enable the objectives to be met. The first will be to evaluate the knowledge questions, the second the questions about perceptions, the third about attitudes and the fourth section will look for associations between the three previously mentioned sections. The data will be analysed using Stata version 14 (StataCorp LP, College Station, TX, USA). The survey questions had multiple-choice responses. We will therefore report proportions of respondents in each of the following: Age category, Professional Healthcare Group, proportions of correct responses to knowledge questions, proportions of participants exhibiting specific attitudes and perceptions.

In order to ascertain the level of knowledge of the respondents, a score will be assigned to each participant (out of 7 for prescribers and 14 for patients). Descriptive statistics and proportions will be used to show patterns about the attitudes and perceptions of respondents. Correct answers in the knowledge sections will be used to assess the proportion of knowledge each respondent has which is in line with current evidence based knowledge. Study population averages of the number of correct answers will be noted. The data will then be refined and examined for associations and connections, including assessing differences in the knowledge, attitudes and perceptions of providers and patients by sex and age group. Prescribing behaviour will be assessed by identifying differences in

the number of correct prescribing answers and looking for associations with the number of consultations per day. Patient expectations will be assessed through the prescriber answers, as well as the self-reported patients' answers. Associations will be examined between patient education level and answers to the knowledge questions, associations with patient behaviours will also be examined. Associations will be tested for significance using T-tests, Wilcoxon rank sum tests, Kruskal Wallis tests and multivariate logistic regression models. Testing methods will vary depending on normality of data. This analysis plan will enable the primary and secondary objectives of this study to be met.

Risks and Benefits

The original project has received approval from the Human Research Ethics Committee; the approval number is HREC REF: 610/2015. Individuals participating in the project were treated equitably and fairly. The major risks in the primary project were that patients and prescribers may feel uncomfortable with the questions asked in the survey. This could cause them to feel like they are not well educated in regards to antibiotic use and resistance. Prescribers could feel that their knowledge is being tested, and could feel frustrated by this. These risks were minimised by ensuring that respondents knew that participation in the survey was voluntary and anonymous; no identifying demographic data was collected. The principle of justice was upheld by ensuring those who shared in the risks of the project, shared in the post-study benefits.

The main benefits of the project to respondents, is that participants could through the survey, find out that they needed to learn more about correct antibiotic use and ABR. To ensure beneficence, benefits of the study for participants were maximised by making any interventions planned due to the study, available to respondents and information regarding the results will be sent out using the same networks as used during recruitment. Society will benefit from this research by being able to plan interventions based on evidence, to ensure that ABR can be slowed down. This project will further the knowledge base of this issue, and allow for a better understanding of antibiotic knowledge, attitudes and perceptions in the South African context.

Informed Consent Process

Informed Consent was obtained during the original project from each participant prior to participating in the survey and, in the case of the online version, was integrated into the survey form.

Privacy and Confidentiality

Participants in the study will be treated fairly and equitably. Privacy and Confidentiality are of utmost importance during the project and all completed surveys were anonymous and so a Patient Identification Number was allocated to each participant, names or other identifying data were never requested. All online surveys and collated data will be stored in a password protected file and paper surveys will be stored in a locked cabinet, both of which only the research staff can access. Paper and online data will be stored for 5 years and then destroyed, by shredding the paper surveys, and deleting all electronic files, as well as emptying the recycle bin. Although the results of this study may be published, no information that could identify any of the participants will be included. There was no reimbursement for participants for participating in the primary study.

Limitations

There are several limitations to this project, these include recruitment method. Convenience and snowball sampling have limitations in that it has the possibility of not being representative, generally the same types of respondents are included when using this method and so variation in answers is limited, and results are not always generalizable. The sampling in the primary study focussed on private practice GPs and patients who presented at those practices. In order to gain a better understanding of the South African context, investigation will need to be done which focuses on prescribers and patients in the public health sector. By gaining an understanding of both sectors, a broader more generalisable picture will be able to be ascertained. The urban only focus of the data collection is a further limitation of the study and further limits generalisability.

Another limitation is that the surveys are self-reported. This opens up opportunities for bias, in terms of reporting and social desirability bias, where prescribers could state that they know more about ABR than they actually do, or that they prescribe only when completely necessary, when in reality this is not the case. Patients could report they comply with proper antibiotic use standards, and that they never pressurise GPs to prescribe antibiotics, when actual behaviours could be different. This limitation will be taken into consideration when analysing the data and writing up the final report.

Write Up and Dissemination

The Knowledge, attitudes and perceptions of antibiotic use and ABR is a growing area of concern internationally. Similar projects have been completed in other research locations, but this project will allow region specific evidence to be in South Africa. The potential users of results generated from this study are other researchers, government and non-

governmental organizations and the communities who are researched themselves. We will aim to disseminate findings at internal and external meetings, and once the findings have been completed, compile the data into a paper which we will aim to publish.

References (Protocol)

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Hardy-Holbrook, R. et al., 2013. Antibiotic resistance and prescribing in Australia: Current attitudes and practice of GPs. *Healthcare Infection*, 18(4), pp.147–151.

Hawkey, P.M., 1998. The origins and molecular basis of antibiotic resistance. *BMJ (Clinical research ed.)*, 317(7159), pp.657–660.

Hawkings, N.J., Wood, F. & Butler, C.C., 2007. Public attitudes towards bacterial resistance: A qualitative study. *Journal of Antimicrobial Chemotherapy*, 59(6), pp.1155–1160.

Kotwani, A. et al., 2012. Irrational use of antibiotics and role of the pharmacist: An insight from a qualitative study in New Delhi, India. *Journal of Clinical Pharmacy and Therapeutics*, 37(3), pp.308–312.

Levy, S.B., 1998. The Challenge of Antibiotic Resistance. *Scientific American*, 278(3): pp 46-53.

McCullough, A.R., Parekh, S., et al., 2015. A systematic review of the public's knowledge and beliefs about antibiotic resistance. *Journal of Antimicrobial Chemotherapy*, 71(1), pp.27–33.

McCullough, A.R., Rathbone, J., et al., 2015. Not in my backyard: A systematic review of clinicians' knowledge and beliefs about antibiotic resistance. *Journal of Antimicrobial Chemotherapy*, 70(9), pp.2465–2473.

O'Neill, J., 2014. Antimicrobial Resistance : Tackling a crisis for the health and wealth of nations. *Review on Antimicrobial Resistance*, (December), pp.1–16.

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WHO, 2014. Antimicrobial resistance. *Bulletin of the World Health Organization*, 61(3), pp.383–94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22247201%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2536104&tool=pmcentrez&rendertype=abstract.

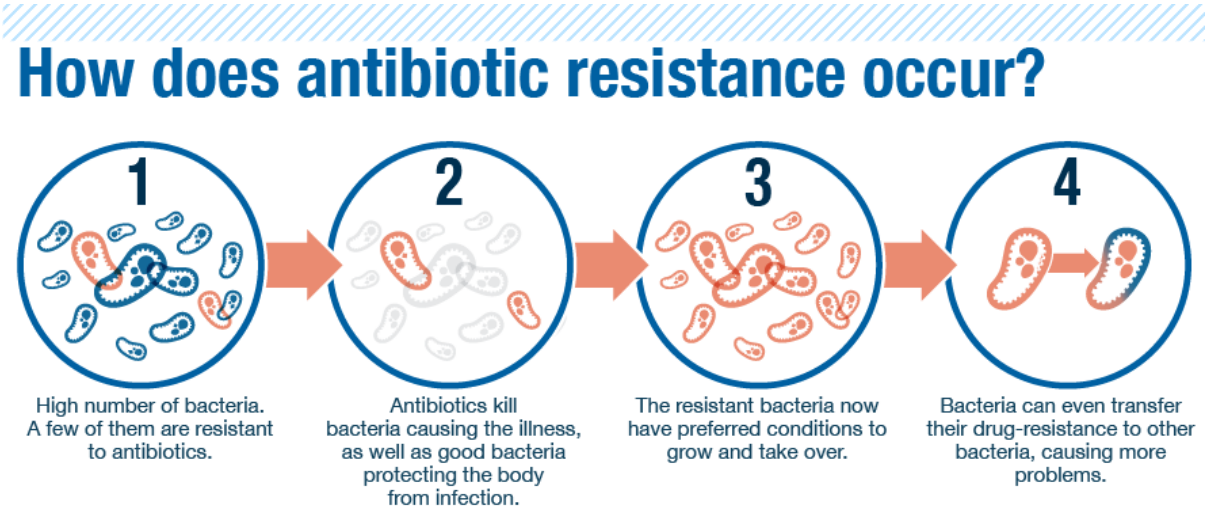
Part B: Structured literature review

Introduction

Antibiotic resistance (ABR), also known as antimicrobial resistance has been labelled as the next big global health threat. ABR is driven by over use, over prescription and non-adherence. ABR is not something that can be stopped, but it can be slowed down by understanding patients' and prescribers' knowledge, attitudes and perceptions of antibiotic use and resistance, and tailoring interventions around these. This literature review will explore findings from different studies on patients' and prescribers' knowledge, attitudes and perceptions of ABR as well as antibiotic use and prescription.

The projects discussed in this review fall within the context of a global health care web, where interlinkages are complicated and global standards and communication networks are not always highly functional. If ABR continues spreading at current rates, it will soon outweigh effective treatment options. This will mean thousands of deaths due to pathogens which are considered treatable today. ABR is a naturally occurring phenomenon, where bacteria develop and change to ensure their survival by becoming resistant to the antibiotics used to treat them. This means that the more antibiotics are used, the quicker resistance occurs. Figure B1 below illustrates how the use of antibiotics produces resistance.

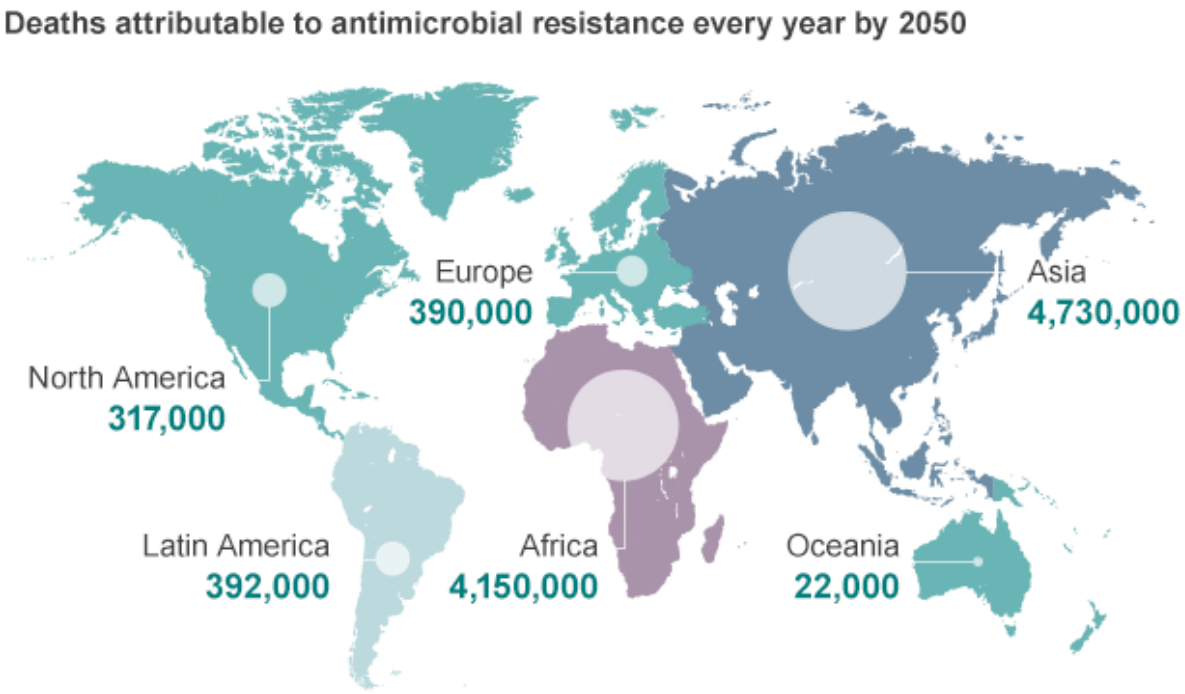
Figure B1 from (MeMed 2016)



The Centers of Disease Control and Prevention (CDC) reported that in the USA, 2 million people become infected with resistant bacteria each year, and 23 000 people die as a result of these resistant bacterial infections (CDC 2016). A recent modelling project on the impact of resistance revealed that by 2050 ABR will cost the world up to 100 trillion USD and 10 million people will die each year as a direct result of ABR if effective prevention programs

are not put in place (O'Neill, 2016) to slow resistance down. As can be seen in Figure B2 below, the majority of these deaths will be in Asia (4 730 000) and Africa (4 150 000). The WHO (2016) has listed many concerns about resistance; these include poor surveillance, under reporting and the massive financial and human resource burden that ABR will place on health care systems. ABR was the focus of a United Nations General Assembly meeting in September 2016, the 4th time in the history that a health topic has been the focus of such a meeting, showing the seriousness with which this issue is viewed (Mendelson et al. 2016). There is limited information on the extent of ABR in Africa as surveillance is only carried out in a handful of countries (WHO 2014).

Figure B2 from (O'Neill 2014)



Antibiotics have become less effective as a result of rising resistance levels and no new antibiotic classes have been developed since the 1980s.This means that resistance will rapidly outpace available treatment options (WHO 2014) and a global crisis will ensue. In order to slow down ABR, antibiotics should only be prescribed and used when absolutely necessary (Levy 1998). A further major use of antibiotics (which is not the primary focus of this literature review, but needs to be mentioned) is the use of antibiotics in animal husbandry. One use, which has been banned in some countries, is the addition of growth promotors to animal feed which has an unquantifiable impact on resistance levels (Hawkey

1998). The use of antibiotics in animal husbandry needs to be optimised and monitored in order to ensure best practices are followed which will minimise impacts on ABR.

Objectives

The objective of this literature review is to summarise and discuss the available evidence on knowledge, attitude and perceptions of antibiotic resistance and antibiotic use. This review will enable the author to assess what literature is available to assist in assessing the four main objectives of the study as follows:

Knowledge about antibiotic use and resistance will be assessed so that a clear understanding of local and global knowledge on correct antibiotic prescribing behaviour can be gained, as well as an understanding of what patients know about how and when to use antibiotics, and about both patients' and prescribers' knowledge around ABR. This will be helpful in assessing where there are gaps in knowledge in both groups, which could be beneficial for potential intervention planning.

Attitudes towards antibiotic use and resistance will be assessed to see what other studies have found in varying parts of the world. Attitudes regarding use and resistance are very important in terms of slowing down ABR. Literature on this facet could offer insight into potential global attitude patterns.

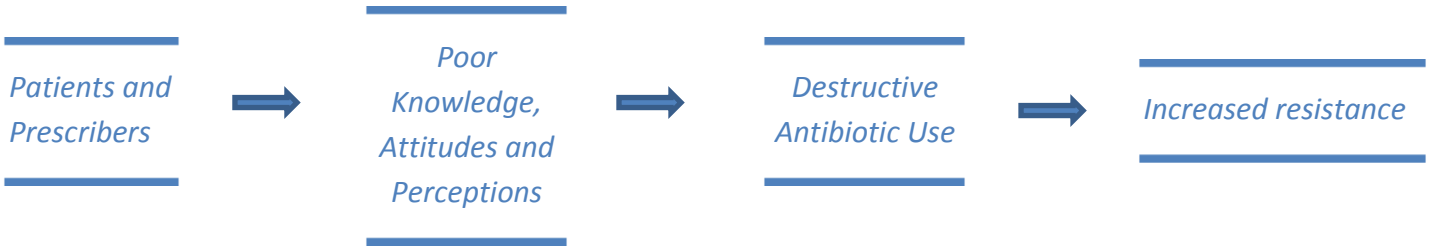
Perceptions of ABR and use will also be assessed to try and locate the reasons behind harmful behaviour, as negative attitudes which lead to negative behaviours are often based on incorrect perceptions. The review hopes to identify these incorrect perceptions, which could shed some light on the global situation and which will assist in placing the South African respondents in this study into a global context.

Associations between knowledge, attitudes and perceptions will then be assessed, to see what patterns emerge, and if any clear overlaps can be seen. If patterns emerge from the literature that illuminate these incorrect perceptions, there is the potential to intervene and change both perceptions and attitudes, by improving knowledge on these issues, and this will hopefully lead to behaviour change which will slow down resistance.

Conceptual Framework

It is hypothesised that poor antibiotic use and resistance knowledge, attitudes and perceptions leads to destructive antibiotic use which leads to increased resistance as illustrated in Figure B3 below. This project is assessing these facets in order to better understand the local context in regards to ABR.

Figure B3- Conceptual Framework



Methodology

Search Strategy

A search of primary studies and reviews was conducted on the PubMed, Medline and Cochrane databases. The search strategy used the terms detailed in Table B1 below. The titles and abstracts were screened and relevant studies identified.

Table B1- Electronic Search Strategy

#1	"Drug Resistance, Microbial"[Mesh]
#2 (PubMed)	("Anti-Bacterial Agents"[Mesh] AND "Drug Resistance, Microbial"[Mesh]) AND ("Knowledge"[Mesh] OR "Perception"[Mesh] OR "Attitude"[Mesh]) AND ("Patients"[Mesh] OR "General Practitioners"[Mesh])
#3	"antibiotic resistance" OR "perception" OR "attitudes" OR "knowledge"
#4	"ABR" OR "antimicrobial resistance" OR "AMR" AND "perception" OR "attitudes" OR "knowledge"
#5	"antimicrobial resistance" AND "perception" OR "attitudes" OR "knowledge"
#6	(All of the above searches) AND South Africa

Inclusion Criteria

Full text papers published in English, from 1990 – 2016 were included. Included studies focussed on the knowledge, attitudes and perceptions of patients and prescribers around antibiotic use, behaviours and resistance, as this was the focus of the planned study. Studies evaluating prescribing practices were excluded as this was not the focus of the study. Only papers showing research in humans were included. Systematic reviews and observational studies from high, middle and low income countries were included in order to get a global understanding of the topic. A quality assessment of included studies was made by reviewing the methods section of each paper. Outcomes of studies were extracted and data was placed in the table of results (below). These results are then discussed and general patterns that emerged are described.

Results

Patients' and prescribers' knowledge, attitudes and perceptions around antibiotic use and resistance vary but there are several commonalities. The majority of prescribers know ABR is a major issue but many feel pressure to prescribe antibiotics when not absolutely

necessary. Many patients believe the human body (rather than the microbial organism) becomes resistant to the antibiotics, and are not aware of the full scale of the issue, and think scientists can develop new antibiotics. These findings and others are detailed in Table B2 below.

Table B2- Details of Findings

Reference	Study Design	Location	Study Population	Knowledge, Attitude, Perceptions of Antibiotic Use and Resistance
Prescribers' Knowledge, Attitudes and Perceptions				
McCullough, Rathbone, Parekh, Hoffmann, & Del Mar, 2015	Systematic review including 57 studies of clinicians	North America and Europe	Prescribers	98% believe resistance is a serious problem, 67% believe it is a problem in their practice, and 89% believe it is a problem globally. 97% stated resistance was caused by excessive antibiotic use, and 90% stated non-adherence. Some individual studies listed in this review were also included in this systematic review.
Tonkin-Crine, Yardley, & Little, 2011	Systematic Review	Australia	General Practitioners prescribing for acute respiratory tract infections	GPs are aware of ABR, but feel pressure to prescribe antibiotics in order to pacify patients. In order to ensure acceptability of interventions, GPs should reflect on their own prescribing; management options must be clear, education is necessary, patient centred care is necessary.
Lopez-Vazquez, Vazquez-Lago, & Figueiras, 2012	Systematic review	High income settings	Prescribers (GPs and paediatricians)	Fourteen studies found a direct relationship between complacency and misprescription, two studies found no relationship. Seven studies found a direct relationship between fear and misprescription. Direct relationship between health care burden and misprescribing in seven studies, and no relationship in 6 studies. Two studies found a direct relationship between the pressure exerted by the pharmaceutical industry on prescribing, and two studies found no relationship.
Kenealy, Arroll, & Kenealy, 2013	Systematic review 11 studies	Not stated	Prescribers	Just under 1.2 million people are estimated to be prescribed antibiotics when first presenting with a common cold and acute purulent rhinitis. Participants receiving antibiotics did not get better more quickly, and symptoms were not less severe. If these antibiotics were not initially prescribed, a total average saving estimated to be £3.3 million.
Arnold 2009	Systematic Review	Not stated	Prescribers part of outpatient antibiotic resistance interventions	The effectiveness of an intervention on antibiotic prescribing depends to a large degree on the particular prescribing behaviour and the barriers to change in the particular community.
Goossen H, Ferech M, Vender SR, 2005	Cross sectional	26 countries in Europe	Outpatient care givers	Prescription of antibiotics in primary care in Europe varied greatly; the highest rate was in France (32.2 defined daily doses per 1000 inhabitants) and the lowest was in the Netherlands (10 defined daily doses per 1000 inhabitants).
Gulliford *et al*., 2014	Cross sectional	568 United Kingdom (UK) General Practices	Prescribers treating adults (18 – 59 year olds) with respiratory tract infections	Most UK general practices prescribe antibiotics to young and middle-aged adults with respiratory infections at rates that are considerably in excess of what is clinically justified. The median general practice prescribed antibiotics at 54% of respiratory tract infections (RTI) consultations (90 percentile- 69% of RTI consultations, 10th percentile-39% of RTI consultations).
Lee *et al*., 2014	Cross sectional	USA	Prescribers to outpatients	1.4 billion antibiotics dispensed from 2000 – 2010 to outpatients. Rates of broad spectrum antibiotic prescriptions doubled from 2000 to 2010.
Hardy-Holbrook, Aristidi, Chandnani, Dewindt, & Dinh, 2013	Cross sectional	Australia	730 General Practitioner (GPs)	40% of respondents stated they would prescribe antibiotics to meet patients' expectations. 50% of prescribers said they discussed antibiotic resistance with patients.
Abera, Kibret, & Mulu, 2014	Cross sectional	Ethiopia	Physicians and nurses	65% of physicians and 98% of nurses replied that they need training on antimicrobial stewardship. The two most important factors mentioned for ABR development were patients' poor adherence to prescribed antimicrobials (86%) and overuse of antibiotics (80.5%).

Dallas *et al*., 2015	Cross sectional	Australia	Early-career doctors in primary care prescribing for respiratory infection	Antibiotics were prescribed in 21.6% of encounters for upper respiratory tract infections (URTI) and 73.1% of encounters for acute bronchitis/ bronchiolitis. GP trainee antibiotic prescribing is higher than justified by guidelines.
Hadi *et al*., 2008	Cross sectional	Two governmental teaching hospitals in Indonesia	Prescribers treating patients for ≥5 days (departments of internal medicine, surgery, obstetrics and gynaecology; paediatrics.	Antibiotics were given to 84% of patients included in the study (834 of 999). Approximately 60% of prescriptions were classified as incorrect, either unjustified or inappropriate.
Mustafa, 2014	Qualitative	South Wales, UK	Family physicians	URTI consultations are sources of potential conflict, especially when patients expect antibiotics.
Brinsley, Sinkowitz-Cochran, & Cardo, 2005	Qualitative	USA	Prescribers treating hospitalised children	Prescribers thought ABR was more of a problem nationally (92%) than in their own institution (76%) or practice (60%).
Kotwani, Wattal, Joshi, & Holloway, 2012	Qualitative	India	Pharmacists	Understocked pharmacies- pharmacists can only dispense part of a prescription, and poor patients cannot afford to come back. Overstocked pharmacies- overprescribing occurs. Even though unqualified, most participants admitted to prescribing antibiotics for diarrhoea, common cold, mild fever, sore throat and cough.
Patients' Knowledge, Attitudes and Perceptions				
McCullough, Parekh, Rathbone, Del Mar, & Hoffmann, 2015	Systematic review including 54 studies of patients	Europe (43%), Asia (26%), North America (22%)	Patients	70% of participants had heard of the term antibiotic resistance, 88% believed the person becomes resistant to antibiotics, 53% believed resistance was a problem in their country. 70% believed ABR was due to excessive or unnecessary (74%) antibiotic use. Some individual studies listed in this review were also included in this systematic review.
Gebeyehu, Bantie, & Azage, 2015	Cross Sectional	Northwest Ethiopia	General population	30.9% of all antibiotic use was inappropriate. RTI symptoms (74.6%), diarrhoea (74.4%), and physical injury/wound (64.3%) were the three main reasons that the communities had used antibiotics inappropriately. 36% of all participants, 46.4% of urban and 30.6% of rural, had taken antibiotics in the past one year prior to the study period.
El Zowalaty *et al*., 2016	Cross sectional	Saudi Arabian	General population	63.6 % of participants reported to have purchased antibiotics without a prescription from pharmacies, 62% of respondents who used drugs without prescription agreed with the statement that antibiotics should be access-controlled. The overall level of awareness on antibiotics use among residents in Saudi Arabia is low.
Huttner, Goossens, Verheij, & Harbarth, 2010	Cross sectional	Europe (16), North America (3), Oceania (2), and Israel (1)	Outpatients in high-income countries	Surveys done after campaigns showed that those exposed to the campaigns were more likely to agree with standards of appropriate use of antibiotics and were less likely to expect antibiotics. After campaigns most doctors reported prescribing antibiotics less frequently than before (66% of doctors in France- 66%, Belgian- 63%). Educating the public about the differences between infections caused by viruses or bacteria seems difficult. In France, after successive campaigns over 5 years, 54% of the public still did not know that most upper RTIs are of viral origin and do not need treatment with antibiotics.
Sanya, Fakeye, Adisa, & Segun, 2013	Cross sectional	Nigeria	Non-medical undergraduate students	68% obtained their antibiotics through doctor's prescriptions, Financial constraints (73; 18.3%), long duration of treatment (70; 17.5%), side effects experienced (60;15.0%), polypharmacy (56;14.0%), tablet size (45;11.3%), and perceived low level of confidence in the prescriber (11; 2.8%) were major reasons for non-adherence.
Hounsa, Kouadio, & De Mol, 2010	Cross sectional	Côte d'Ivoire	Customers of pharmacies	Among 1,123 purchases of antibiotics 242 (21.5 %) were for self-medication. Out of the 1,765 people interviewed, 1,054 (59.7 %) had bought antibiotics for self-medication in the 12 months prior to our study.
Viberg, Kalala, Mujinja, Tomson, & Lundborg, 2010	Cross sectional	Tanzania	Customers of private pharmacies	79% stated that diseases caused by bacteria can be treated with antibiotics but 24% of these also said that antibiotics can be used for treating viral disease. Most (85%) said that sexually transmitted infections (STI) can be treated with antibiotics while 1% said the same about headache, 4% general weakness and 3% 'all diseases'. 72% had heard of antibiotic resistance.

McNulty, Nichols, French, Joshi, & Butler, 2013	Mixed methods (qualitative and cross sectional)	England	Participants with acute respiratory tract infections visiting pharmacies	53.1% of those contacting their GP about the infection expected an antibiotic prescription. Of the 452 (26%) responders who reported asking their GP or nurse for antibiotics in the past year, only 3.5% were refused them, 74% were prescribed antibiotics after some discussion and 23% without any discussion about their illness. 24% of respondents believed that antibiotics work on most coughs and colds, and 38% reported believing that antibiotics can kill viruses.
Brookes-Howell *et al*., 2014	Qualitative	Europe: Łódź, Cardiff, Tromsø and Barcelona	Parents of children with respiratory tract infections	79% (50 of 63) of parents accepted prescribing behaviour, regardless of antibiotic prescription. 20% (13/65) of parents disagreed with prescribers when they did prescribe antibiotics, whereas 4.6% (3/65) disagreed when antibiotics were not prescribed.
Hawkings, Wood, & Butler, 2007	Qualitative	Wales	46 patients aged 18 – 89 years old	87% of participants blamed GPs for over prescribing antibiotics. 24% stated poor hospital hygiene was thought to be the cause of resistance. 4 % stated resistance was cause by use of antibiotics in animals, and 3% stated it was because of antibiotic use in other countries.
Jin, Ely, Fang, & Liang, 2011	Qualitative	China (rural)	Patients	Patients can buy antibiotics freely from the pharmacies without prescription although this has formally been officially forbidden since 2004. The majority of participants believed the human body developed resistance to antibiotics.
Brooks, Shaw, Sharp, & Hay, 2008	Qualitative	Not stated	Primary care adult patients	Many primary care patients are unaware of what antibiotic resistance is and how it arises. Patients are uncertain of antibiotic resistance and methicillin resistant Staphylococcus aureus (MRSA) were. Patients believe that controlling resistance is out of their control.

Discussion

The table above outlines individual studies and some systematic reviews on the topic. As can be seen in the table, patients' and prescribers' knowledge, attitudes and perceptions differ over geographical areas, but there are certain commonalities. Stark contrasts can be seen between prescribers and patients understanding of ABR, the causes of resistance are often placed on the other party, and very little clear communication on the subject occurs between the two.

Prescribers' knowledge, attitudes and perceptions

Prescribers showed an understanding that ABR is a big issue. A systematic review reported that 98% of providers believed it was a serious problem, and approximately 90% of providers stated it was a global (McCullough *et al*., 2015) or national (Brinsley et al. 2005) issue. However considerably fewer providers considered it to be a local concern with 76% identifying it as an issue in their own institution (McCullough *et al*., 2015) and <70% in their own practice (Brinsley 2005; McCoullough *et al* 2015) . The title of the systematic review by McCoullagh *et al*. (2015) is therefore apt, *Not In My Backyard* (McCullough, Rathbone, et al. 2015).

Many prescribers attributed increasing ABR levels to patients not adhering to treatment (McCullough *et al*., 2015). Abera *et al*. (2014), reported that 86% of respondents stated that poor adherence was the cause of ABR (Abera et al. 2014). A further reason given by respondents for ABR was excessive antibiotic use, e.g. 97% in the review by McCullough *et al*. (2015) and 80% in a cross-sectional study in Ethiopia (Abera et al. 2014).

Nevertheless, few prescribers drew the link to themselves, in terms of prescribing behaviour which is an identified gap that would be a useful focus of interventions.

Poor prescribing behaviours can be seen in many of the papers including in the McCullough review (2015); antibiotics are often prescribed when unnecessary, unjustified, incorrect or inappropriate. Kenealy *et al*. showed that 1.2 million people are estimated to be prescribed antibiotics when first presenting with a common cold and acute purulent rhinitis, and that those who took antibiotics did not get better quicker, and their symptoms were not less severe (Kenealy et al. 2013). Guilliford *et al*. showed that most United Kingdom (UK) general practices prescribe antibiotics to young and middle-aged adults with respiratory infections at rates that are considerably in excess of what is clinically justified (Gulliford et al. 2014). Lee *et al* stated that rates of broad spectrum antibiotic prescriptions doubled from 2000 to 2010 (Lee et al. 2014), which could partially be explained by the expectations and pressure patients place on prescribers (Tonkin-Crine et al. 2011) (Mustafa 2014), as shown in one study where 40% of respondents stated they would prescribe antibiotics to meet a patients' expectations (Hardy-Holbrook et al. 2013). An Indonesian study showed that 60% of prescriptions were classified as incorrect, either unjustified or inappropriate (Hadi et al. 2008), and a UK study showed that GP trainees prescribe antibiotics at rates higher than justified by guidelines (Dallas et al. 2015). The Lopez *et al*. systematic review and Kotwani *et al* study (2012) reported relationships between misprescription of antibiotics and complacency, fear, health care burden and pressure exerted by the pharmaceutical industry (Lopez-Vazquez *et al*., 2012; Kotwani *et al*, 2012). These behaviours have negative consequences in terms of ABR, and also cost health care systems (and sometimes individual patients) a lot of money. For example, Kenealy *et al*, show that a total average saving estimated to be £3.3 million would occur if unnecessary antibiotics were not prescribed (Kenealy *et al*, 2013).

Little or no communication between prescribers and patients seemed to occur on the topic, and this was not seen as a priority by prescribers. For example, the McCoullough review shows that one of the main intervention strategies suggested by patients is to discuss ABR with their clinicians, however only 36% of respondents had ever discussed ABR with their doctor (McCullough *et al* 2016). A further study showed that only 50% of prescribers had discussed ABR with their patients (Hardy-Holbrook *et al*, 2013). This shows a niche opening for potentially effective interventions which should focus on self-efficacy.

All of these factors make the issue of ABR a complex one. Prescribers' knowledge, attitudes and perceptions cannot be looked at in isolation, as patients' roles in all of the above are crucial.

Patients' knowledge, attitudes and perceptions

The McCullough *et al.* review reported that 70% of patients had heard of antibiotic resistance but only half believed it was a problem in their own country (McCullough et al. 2016). The majority of respondents believed that antibiotic resistance occurs when the human body (Jin *et al*, 2011) rather than the microbial organism becomes resistant to the antibiotics; 88% of respondents reported this belief in the McCullough *et al* review (2016). 24% of respondents in the Viberg *et al* study stated that antibiotics could be used to treat viral infections (Viberg *et al*, 2010), as did 54% of respondents in the Huttner study (Huttner et al. 2010). There was a clear difficulty in the explanation of the difference in treatments for bacterial and viral infections, which led to some confusion about antibiotic use (Viberg *et al*, 2010).

Some patients had an accurate view of the causes of resistance,74% of respondents in one study stating that the reason for ABR was excessive and unnecessary antibiotic use (McCullough *et al*, 2016). Many of those who did know about resistance stated that they had no control over ABR levels (Brooks et al. 2008), and placed the blame for its occurrence on GPs and other prescribers, stating that they should not overprescribe (Hawkings et al. 2007). Patients did however acknowledge behaviours which are seen as harmful in terms of ABR. These behaviours include pressuring prescribers to prescribe antibiotics when not absolutely necessary (Brooks *et al* 2008 ; McNulty *et al*, 2013), self-medicating with antibiotics (Hounsa et al., 2010; El Zowalaty *et al*., 2016; Gebeyehu *et al*., 2015), purchasing antibiotics without prescriptions (El Zowalaty et al. 2016) and not following instructions for adherence to treatment with antibiotics (Sanya et al. 2013). Reasons for non-adherence were financial constraints, long duration of treatment, side effects experienced, tablet size and perceived low level of confidence in the prescriber (Sanya et al. 2013).

Antibiotic use rates were self-reported as high. A third of respondents in an Ethiopian study had taken antibiotics in the 12 months prior to the interview; 30% of this use was deemed inappropriate (Gebeyehu et al. 2015). 60% of respondents in the Hounsa *et al*. study had reported buying antibiotics for self-medication purposes in the last 12 months (Hounsa et al. 2010). These behaviours show possibilities for interventions.

Interventions

Interventions are needed in order to slow down ABR. Tonkin-Crine *et al* stated that prescribers should reflect on their own prescribing behaviours in order to ensure any ABR interventions were effective (Tonkin-Crine et al. 2011). Education programs and standardised treatment courses were suggested by many prescriber participants in these

studies, such as in the Abera *et al.* study where 65% of physicians and 98% of nurses stated they needed training (Abera et al. 2014). The effectiveness of educational programs was confirmed in the Huttner study which showed that education campaigns have a positive impact on patients' behaviours, and that patients were less likely to use unnecessary antibiotics if the ramifications had clearly been explained to them (Huttner et al. 2010). Due to education programs, patients became more accepting of the standard course of treatment (Huttner et al. 2010). This decreased the pressure placed on GPs to prescribe, and this could assist in decreasing the amount of unnecessary consumption of antibiotics. 66% of French GPs and 63% of Belgian GPs who were a part of the Huttner *et al*. study self-reported prescribing antibiotics less frequently after educational campaigns were run, but the same study found that educating the public about the differences between infections caused by viruses or bacteria was difficult (Huttner et al. 2010). These education programs need to be paired with other solutions and more rigorous research methods need to be implemented to test the effectiveness of these interventions as self-reporting can introduce bias.

A novel approach, and a major achievement in terms of finding solutions to this crisis, has been the formation of the New Drugs for Bad Bugs programme. This is a private public partnership with €650 million being invested across seven projects ranging from basic science to drug discovery, and the development of new business models all attempting to curb resistance (Matthiessen et al. 2016). Another collaborative effort is the formation of the Global Antimicrobial Conservation Fund which will provide capacity building financial and technical support. More surveillance funding is necessary in order to monitor the growing global spread of resistance. Along with this fund, a mass global education campaign is needed (Mendelson et al. 2016).

Limitations

There were several limitations of this review, one being the generalisability of studies found to the South African context, several biases in the studies, and the fact that very few associations were mentioned between knowledge, attitudes and perceptions.

The majority of the studies were from high income regions, and very few papers covered low and middle income settings. This makes a comparison to the South African context difficult, as the findings from the majority of the studies may not be generalizable to the South African context.

There was potential bias in some surveys. Recall bias is a possibility for those surveys that relied on self-reporting (Tonkin-Crine *et al*., 2011; Gulliford *et al*, 2014; Hardy-Holbrook *et al*., 2013; Dallas *et al*., 2015). Social desirability bias could also have been an issue as GPs may not have been honest about overprescribing to patients (McCullough *et*

al., 2015; Tonkin-Crine *et al*., 2011; Hardy-Holbrook *et al*., 2013), while patients may not have been honest about demanding antibiotics or other harmful behaviours (McCullough *et al*., 2016; El Zowalaty *et al*., 2016), and could be more likely to give positive answers on future behaviours (Huttner et al. 2010).

As not all the studies conducted used randomised sampling techniques, the people who ended up being respondents could be those who were more likely to have good prescribing habits, or who were more knowledgeable about ABR, all of which would introduce non-response bias and skew results. Fifty four percent of the 54 studies of patients' knowledge, attitudes and perceptions included in the McCoullagh review (2016) had high response rates and 34% had moderate response rates (McCullough et al. 2016). Among the 57 papers assessing clinicians' knowledge, attitudes and perceptions in a review by the same authors, a third had high, a third medium, and third low response rates (McCullough, Rathbone, et al. 2015).

Not many studies reviewed the associations between knowledge, attitudes and perceptions which is a further limitation of this review. The El Zowalaty study showed statistically significant associations between knowledge and gender, age and education (El Zowalaty et al. 2016), but associations between knowledge, attitudes and perceptions were not clear. The McCoullagh review did mention a knowledge gap whereby clinicians showed confusion about the duration of ABR which impacted upon prescribers' behaviours (McCullough, Rathbone, et al. 2015), but other associations did not seem to be explored.

The sample size in most of the studies was acceptable, the biggest were the McCoullough reviews, which included 11 593 clinicians (McCullough, Rathbone, et al. 2015) and 55 225 patients (McCullough et al. 2016).

Conclusion

The key findings of the review are that even though both patients and prescribers exhibit harmful behaviours that speed up ABR, they blame each other for the crisis. There is very little communication about the issue between the two parties, and the severity of the issue is not taken as seriously as it should be. Resistance is seen as a problem that occurs outside respondents' practices, or lives, or beyond their borders. The global nature of the issue seems to be lost.

Little is known about patients' and prescribers' knowledge, and attitudes and perceptions in the South African context. More information is needed in order to best plan interventions which can slow ABR down globally and in different local contexts. This need leaves a gap which this research project can fill, and it will add to the scant body of evidence

around patients' and prescribers' knowledge, attitudes and perceptions on ABR and prescribing behaviour in South Africa.

Understanding the local context is imperative in order to participate in the global fight against ABR, and the first step needs to be to ascertain how big the issue is in the local context, and what the current knowledge and plans are around trying to combat the issue. This project will not focus on ascertaining the breadth or depth of the resistance issue, but will focus on gaining an understanding of local prescribers' and patients' knowledge, attitudes and perceptions. This project will yield unique South African based insights into antibiotic prescribing, ideas about ABR, and insights into patients' and prescribers' understanding of the issue of resistance.

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Part C: Journal ready manuscript

*Structure requirements followed from PLOS One (requirements listed in Appendix 5)

Full Title: Knowledge, attitudes and perceptions of antibiotic use and antibiotic resistance among private sector patients' and prescribers' in South Africa a cross sectional study.

Short Title: Knowledge, attitudes and perceptions of antibiotic use among private sector patients' and prescribers' in South Africa.

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Abstract

Background: Antibiotic resistance (ABR) may be the next global health crisis. We aimed to describe South African patients' and prescribers' ABR knowledge, attitudes and perceptions (KAP).

Methods: We conducted a cross-sectional KAP survey among a convenience sample of prescribers and patients in South Africa. We used logistic regression to examine associations between knowledge and antibiotic use, beliefs, or behaviours.

Findings: Mean patient (n=403) knowledge scores (out of 14) were higher in females (p=0.0005) and those with more education (p=0.015);76% believed the human body becomes resistant. After adjusting for education and sex, a 1-unit increase in knowledge was associated with increased odds of the following beliefs: (i) important to finish the antibiotic course (aOR 1.34; 95% CI:1.16, 1.66); (ii) over use impacts ABR (aOR 1.3; 95% CI:1.18, 1.43) but reduced odds of (iii) demanding antibiotics should be given (aOR 0.84; 95% CI:0.74,0.94); (iv) feeling relieved (aOR 0.89; 95% CI:0.81, 0.97) or happy (aOR 0.905; 95% CI:0.82, 0.99) when prescribed antibiotics.

Prescribers (n=175) >55 years old had lower median knowledge scores (p=0.0005). Those who infrequently prescribe antibiotics when unnecessary had higher knowledge scores (p=0.01);70% feel pressure from patients to prescribe antibiotics.

Prescribers with higher knowledge scores were more likely to believe the following: (i) to decrease ABR, narrow spectrum antibiotics should be used (aOR 1.41; 95% CI:1.03, 1.92), (ii) explaining to patients disease features which should prompt follow up (aOR 1.76; 95% CI:1.01, 30.74). Prescribers with higher knowledge scores were less likely to report that antibiotics cannot harm the patient if they are not needed so they prescribe when not necessary (aOR 0.55; 95% CI: 0.33, 0.91).

Conclusion: The association between knowledge and behaviour/perceptions suggests that increasing patient and prescriber knowledge could influence antibiotic use behaviours.

Introduction

Antibiotic resistance (ABR) (alternately known as antimicrobial resistance) has been labelled a major health threat by the World Health Organisation (1). Currently 700 000 people die a year from ABR. By 2050, ABR will cost the lives of 10 million people a year if solutions are not followed to slow down its course (2). ABR occurs when bacteria become resistant to treatment by antibiotics (3) .This means that bacteria that cause common, currently easy to treat illnesses are becoming resistant to treatment options. Morbidity and mortality from these diseases could increase. The lifespan of all antibiotics is limited (1); the initially produced antibiotics which brought in the golden age of health care are now largely ineffective (4). Effective new antibiotics have not been produced since the 1980s (5).

ABR is accelerated by the over prescription and misuse of antibiotics (1). Rates of broad spectrum antibiotic prescriptions in the USA doubled from 2000 to 2010 (6) . An Indonesian study showed that antibiotics were given to 84% of patients included in the study and approximately 60% of the prescriptions were classified as incorrect, either unjustified or inappropriate (7). A systematic review of 57 studies found that 98% of prescribers think that ABR is a serious problem but only 67% believe it is a problem in their own practices (8) . Patients also believe ABR is a problem in their country, and 88% believe the human body, rather than the microbial organism, becomes resistant to the antibiotics (9) .

There is limited communication between patients and prescribers on the topic (10). This lack of understanding of the ramifications of overuse could be a potential cause of overprescribing as prescribers often feel pressurised to prescribe antibiotics due to patient requests and expectations (11), which leads to unnecessary use of antibiotics. Another systematic review found direct relationships between complacency, fear, health care burden and harmful prescribing behaviours (12). Seventy-four percent of respondents who asked for an antibiotic were prescribed one in a United Kingdom (UK) based study (13). Patients' lack of understanding of the true causes of ABR and not understanding their role in controlling ABR will decrease the effectiveness of intervention programs. One study showed that 87% of participants blamed ABR on general practitioners for over prescribing antibiotics (14); patients may feel that limiting ABR is out of their control (15).

There is a dearth of literature on ABR levels in Africa; there are limited surveillance programs (5), and not much monitoring of prescribing behaviours. Poor knowledge and understanding of ABR can lead to harmful antibiotic use and prescribing behaviours such as over using antibiotics, relying on broad spectrum treatments and taking antibiotics when not absolutely necessary, which then leads to increased ABR levels. The purpose of this study is to assess the knowledge, attitudes and perceptions of patients and prescribers in the private

health care setting in South Africa on antibiotic use and resistance in order to gain insight into possible interventions to effectively slow down ABR.

Methods

This study obtained ethical approval from the University of Cape Town Human Ethics Research Committee (HREC REF: 722/2016), and is an analysis of data collected during a cross sectional study (HREC REF: 610/2015) between October 2015 and December 2016. The survey was conducted among patients visiting General Practitioner (GP) practices and prescribers (GPs and Nurses) in health care facilities using a convenience sampling approach. Hard copies of the survey as well as a link to complete the survey online were distributed to private GP practices and presented at a number of academic meetings. Patients were asked by reception staff at GP practices to complete the survey when they arrived for consultations. The survey questionnaire and categories were developed in conjunction with similar tools found in the literature and through discussion with colleagues. The completion of the survey was preceded by respondents signing an informed consent form. Online surveys were completed on *SurveyMonkey* and hard copy surveys were entered onto *SurveyMonkey* by research staff. Inclusion criteria were: (i) over the age of 18, (ii) patient or prescriber at a private health care facility in South Africa, (iii) able to provide informed consent, (iii) willing to participate in the study. No identifying information was collected from participants.

Analysis was conducted using Stata 14. Descriptive statistics were used to show patterns about the attitudes and perceptions of respondents. Correct answers in the knowledge sections were used to assess the proportion of knowledge each respondent had which is in line with current evidence-based knowledge. Knowledge scores were calculated out of total number of questions answered by each participant and not the total number of questions in the survey. Knowledge scores for patients were normally distributed, and means and standard deviations are reported. Knowledge scores for prescribers were skewed, and medians and inter quartile ranges (IQR) are reported.

Associations between knowledge scores and demographic characteristics of patients were tested for significance using t-tests, and for prescribers using Wilcoxon rank sum tests. Prescribers' self-reported frequency of prescribing antibiotics was tested for association with knowledge scores using a Kruskal Wallis test. Associations between knowledge, attitudes and perceptions of patients and prescribers were explored in logistic regression models. Answers in the 'unsure' category of all behaviours/beliefs were grouped together with the

'disagree' category answers, to get a binary outcome. Logistic regression models for patient beliefs were adjusted *a priori* for sex and education, and models for prescriber beliefs were adjusted for age and type of practitioner (nurse or doctor).

Results

Demographic characteristics

Among 403 patients who completed the survey, the largest age groups were 25 – 34 years (n= 101, 27%) and 35 – 44 years (n= 92, 24%) and most (n=263, 72%) were female (Table 1). Fifty-four percent (n= 198) of patients' highest qualification was the completion of secondary school. Among 175 prescribers who completed the survey, 98% were doctors; 92% were solely from private practice. Many of prescribers (43%) were over the age of 55. Demographic characteristics are detailed in Table C1 below.

Table C1- Demographics

Patients (n=403)

	Category	*n (%)*
Age (years)	<25	32 (8%)
	25 - 34	101 (27%)
	35 - 44	92 (24%)
	45 - 54	72 (19%)
	55 - 64	55 (15%)
	>65	27 (7%)
Sex	Female	263 (72%)
	Male	102 (28%)
Highest Level of Education	Grade 1 - 8	5 (1%)
	Grade 9 - 11	25 (7%)
	Secondary School	198 (54%)
	University degree	93 (25%)
	Post graduate degree	45 (12%)

Prescribers (n = 175)

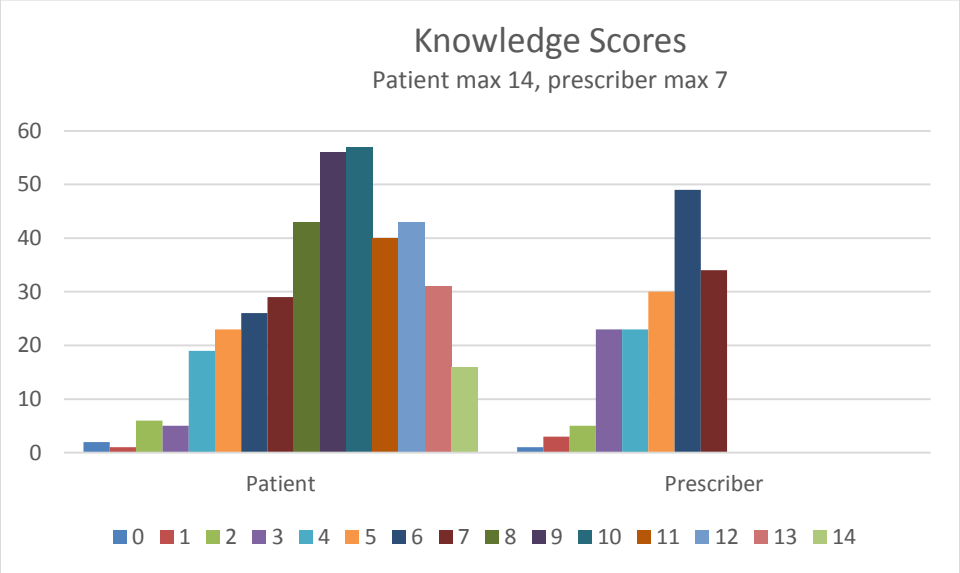
	Category	*n (%)*
Age (years)	25 - 34	13 (8%)
	35 - 44	51 (32%)
	45 - 54	29 (18%)
	>55	70 (43%)
Profession	Nurse	3 (2%)
	Doctor	164 (98%)
Practice Type	Public Sector	0 (0%)
	Private Sector	152 (92%)
	Both, mainly public	6 (4%)
	Both, mainly private	7 (4%)

Knowledge Scores

The knowledge scores of patients (n=403, 14 knowledge questions) and prescribers (n=175, 7 knowledge questions) are detailed in Figure C1 below. The mean knowledge score for patients was 9 (out of a maximum of 14, SD 3) and the prescribers' median score was 5 (out of a maximum of 7, IQR 4, 6). All of the questions were correctly answered by 16 (4%) patients and 34 (19%) prescribers; 2 (0.5%) patients and 1 (0.6%) prescribers

answered all of the questions incorrectly. The mean number of non-responsive participants per knowledge question was 11 patients (3%) and 37 prescribers (21%).

Figure C1 – Patient and Prescriber Knowledge Scores



Patient perceptions, attitudes and knowledge scores

Most patient respondents (76%) believed that ABR is when the human body becomes resistant to antibiotics and 76% believed antibiotics treat bacteria. Eighty percent of patients believe that you should not have access to antibiotics without a prescription and 43% believe new antibiotics will be discovered. Thirty-two percent have been to the doctor specifically for an antibiotic, 59% would be happy with advice on what to buy over the counter if the care provider told them they did not need an antibiotic and 58% felt worried when prescribed antibiotics, because they prefer not to take antibiotics unless absolutely necessary.

Associations between patient knowledge scores and demographic characteristics are explored in Table C2 below. Statistically significant associations, at the chosen level of 0.05, were found between the sex of patients and mean knowledge scores (female=9, SD 3; male=8, SD 3; p-value 0.0005). Patients whose highest qualification was below secondary school had a lower mean knowledge score (8, SD 3) compared to those who finished secondary school (9, SD 3, p-value 0.015).

Table C2- Association of patients' knowledge score and demographic characteristics

		n	Mean knowledge score (Max 14)	Std. Dev	*p value (t- tests)*
Sex	*Female*	263	9	3	0.0005
	Male	102	8	3	
Age	*Below 35*	133	9	3	0.39
	35 or Above	246	9	3	
Education					
	Below secondary school	30	8	3	0.015
	Above secondary school	330	9	3	

After adjusting for education and sex, a 1-unit increase in patient knowledge score is associated with an increase in odds of having the following beliefs: finishing prescribed courses of antibiotics is important (aOR 1.34; 95% CI: 1.16, 1.6); overuse of antibiotics leads to body becoming resistant to antibiotics (aOR 1.17; 95% CI: 1.069, 1.29); antibiotics will work less well in future if we over-use them now (aOR 1.3; 95% CI: 1.18, 1.43) (Table 3).

The following patient beliefs have a decrease in odds with every one unit of increase in knowledge score: If people demand an antibiotic, the doctor / nurse should give it to them (aOR 0.84; 95% CI: 0.74, 0.94); it is important to have antibiotics when one is very sick (aOR 0.89; 95% CI: 0.82, 0.97); feeling of relief when prescribed antibiotics because doctor/nurse realises patient is sick (aOR 0.89; 95% CI: 0.81, 0.97); feeling happy when prescribed antibiotics because health care visit was justified (aOR 0.905; 95% CI: 0.82, 0.99) (Table C3).

Table C3- Logistic regression model with patients' behaviours, attitudes and perceptions as outcome

Outcome (Behaviour/perception)	Adjusted OR* for effect of 1 unit increase in knowledge score	95% CI	p-value
It's important for me to finish the course of antibiotics I've been prescribed			
Agree	1.34	1.16, 1.60	<0.001
If people demand an antibiotic, the doctor / nurse should give it to them			
Agree	0.84	0.74, 0.94	0.004
When people take too many antibiotics their body becomes resistant to them			
Agree	1.17	1.069, 1.29	0.001
Antibiotics will work less well in future if we over-use them now			
Agree	1.30	1.18, 1.43	<0.001
Scientists will discover new antibiotics if the current ones stop working			
Agree	1.071	0.98, 1.16	0.103
When I am very sick, it is important to have antibiotics			
Agree	0.89	0.82, 0.97	0.013
When I tried simple remedies but they didn't work, it is important to have antibiotics			
Agree	0.94	0.86, 1.016	0.11
I have been to the clinic specifically because you wanted an antibiotic for you or your child			
Yes	1.06	0.96, 1.15	0.20
When prescribed antibiotics I feel relieved that the doctor/nurse realises I am sick			
Agree	0.89	0.81, 0.97	0.009
When prescribed antibiotics I feel happy because my visit was justified			
Agree	0.905	0.82, 0.99	0.035
When prescribed antibiotics I feel worried because I prefer not to take antibiotics unless absolutely necessary (Yes)			
Agree	1.069	0.97, 1.17	0.13

*Adjusted for sex and education

Prescriber perceptions, attitudes and knowledge scores

Ninety-eight percent of prescriber respondents stated that they believed antibiotics are overused in South Africa, 97% believe ABR is a big problem in South Africa and 70% feel pressure from patients to prescribe antibiotics. Thirty-two percent of prescribers will prescribe antibiotics half of the time if a patient expects an antibiotic but the prescriber does not think it is absolutely necessary, while 54% think other doctors prescribe antibiotics when they aren't absolutely necessary. When respondents had prescribed antibiotics that were not absolutely necessary, the main reasons they gave was pressure from patients (42%) and that the patients could not afford laboratory tests (22%). Prescribers >55 years old had a lower median knowledge score (4.6, IQR 3.5, 5.8) compared to younger prescribers (5.6, IQR 4.7, 6; p=0.0005) (Table C4).

Table C4- Association of prescribers' knowledge score and demographic characteristics (Wilcoxon Rank Sum Tests)

		N	Median knowledge score (Max 7)	IQR	*P value*
Age	*Below 55*	93	5.6	4.7, 6	0.0005
	55 or Above	70	4.6	3.5, 5.8	
Practitioner	*Doctor*	164	5.25	4.2, 6	0.78
	Nurse	3	4.75	3.5, 6	
Number of Consultations Per Day					
	Under 24	21	5	4, 6	0.503
	Above 24	23	5	4, 7	

Table C5 below shows the median knowledge scores for prescribers who self-reported prescribing antibiotics at differing frequencies when a patient expected them to but the prescriber felt they were not absolutely necessary. Knowledge scores were significantly associated with prescribing behaviours (p=0.01).

Table C5- Median knowledge scores for prescribers self-reported proportion of prescribing antibiotics when not absolutely necessary (Kruskal Wallis)

Proportion of times prescribed antibiotics when not necessary	n	*Median Knowledge Score*	*IQR*	*p-value*
Very often >90%	3	3	3, 5	0.01
Often >70%	10	4	3, 4	
About half the time 50%	54	4	3, 5	
Rarely <30%	65	4	3, 5	
Almost never <10%	38	5	4, 5	

After adjusting for age and type of practitioner (nurse or doctor), a 1-unit increase in knowledge score was associated with an increase in odds of having the following behaviours and beliefs: narrow spectrum antibiotics should be used instead of broad spectrum antibiotics where possible (aOR 1.41; 95% CI: 1.03, 1.92); when antibiotics are not necessary, I explain to patients features which, if they develop, should prompt them to seek further medical assistance (aOR 1.76; 95% CI: 1.01, 30.74) (Table 6). Those with higher knowledge scores were less likely to report that antibiotics cannot harm the patient if they are not needed so they prescribe when not necessary (aOR 0.55; 95% CI: 0.33, 0.908; pvalue 0.02) (Table C6).

Table C6- Logistic regression model with prescribers' behaviours, attitudes and perceptions as outcome

Outcome (Behaviour/perception)	Adjusted OR* for effect of 1 unit increase in knowledge score	95% CI	p-value
Antibiotics are overused in South Africa			
Agree	1.078	0.75, 1.54	0.68
Antibiotic resistance is a significant problem in South Africa			
Agree	1.63	0.95, 2.78	0.073
Lack of hand disinfection by healthcare workers causes the spread of antibiotic resistance			
Agree	1.064	0.84, 1.36	0.609
I would like more education on the appropriate use of antibiotics			
Agree	1.36	0.97, 1.87	0.067
I feel pressure from patients to prescribe antibiotics			
Agree	0.97	0.75, 1.25	0.82
The patient expects an antibiotic, so I prescribe even when unnecessary			
Agree	0.88	0.69, 1.1	0.27
I think other doctors often prescribe antibiotics when they are not necessary			
Agree	0.89	0.707, 1.13	0.33
Better use of antibiotics will reduce levels of antibiotic resistance			
Agree	1.21	0.57, 2.56	0.608
To decrease AMR, narrow spectrum antibiotics should be used instead of broad spectrum antibiotics where possible			
Agree	1.409	1.033, 1.92	0.03
I feel confident to prescribe antibiotics appropriately			
Agree	0.94	0.72, 1.24	0.67
Antibiotics don't need to be absolutely necessary, I just need to think they may help the patient so I prescribe when not necessary			
Agree	0.78	0.57, 1.073	0.12
Antibiotics can't harm the patient if they aren't needed so I prescribe when not necessary			
Agree	0.55	0.33, 0.908	0.02
I'm concerned about malpractice claims so I prescribe when not necessary			
Agree	0.95	0.73, 1.23	0.71
I only prescribe antibiotics when absolutely necessary			
Agree	1.069	0.84, 1.35	0.57
More resources to educate patients I would value more resources to educate patients to improve my antibiotic prescribing			
Agree	1.28	0.86, 1.93	0.21
More data on local antimicrobial resistance I would value the following resources to improve my antibiotic prescribing			
Agree	1.26	0.73, 2.2	0.408
When antibiotics are not necessary, I explain features which, if they develop, should prompt them to seek further medical assistance			
Often	1.76	1.01, 3.074	0.046
When antibiotics are not necessary, I prescribe symptomatic relief			
Often	1.34	0.96, 1.88	0.081

*Adjusted for age and type of practitioner

Discussion

We found that mean knowledge scores among patients and providers were suboptimal (patients 9/14; prescribers 5/7) and that poor knowledge was associated with perceptions and behaviours that could lead to ABR. We identified a large proportion of patients who were interested in alternatives to antibiotics. A large proportion of prescribers wanting educational material on ABR and for interactions with patients, findings suggest that there is substantial opportunity for intervention to reduce harmful practices.

Comparison with Other Studies

This project has yielded similar results to existing literature, in that prescribers feel that ABR is a big issue, but not in their specific practices (8,16). Prescribers feel a large amount of pressure from patients, and self-reported as giving in to this pressure which is similar to a study where 40% of respondents stated they would prescribe antibiotics to meet a patient's expectations (10). Many patients do not show a full understanding of ABR, which was also shown in the Jin *et al* study which showed that the majority of respondents believed that ABR occurs when the human body becomes resistant to the antibiotic (17). A novel finding of the study is that there are statistically significant associations between knowledge scores and certain destructive and protective use and prescribing behaviours. If knowledge levels are changed, it could be possible to influence these behaviours.

Strengths and Limitations

This study is important in that it offers insight in to South African private practice patients' and prescriber's knowledge, attitudes and perceptions and offers potential intervention points. However, the methods of this project place limitations on the generalisability of results; convenience sampling was used, and the project was conducted solely in the private health care sector. Selection bias could have occurred as only literate and/or computer literate participants would have opted in to complete the survey, and people with certain traits may have been more prone to accepting, such as those who felt confident about their knowledge of ABR or prescribers who were interested in continuing their professional development. A further selection bias factor is that only patients who were already at GP practices were requested to complete the survey and these participants could have more knowledge of available treatments such as antibiotics than those who are not integrated into this sector of the health care system. The sample size of nurse prescribers was very small and so results will only reflect doctor prescribers' knowledge, attitudes and perceptions. There was no mechanism in place to ensure that people did not complete the survey more than once, but given that the study took some time to complete and there was

no specific incentive to participate, double completions were unlikely. Social desirability bias could be introduced as the accuracy of answers could not be assessed as they are self-reported and anonymous, but this was minimised as the surveys were anonymous. Further research using alternate sampling methods is needed to remove the effects of these biases and confounders.

Potential Interventions

This study has yielded information which may assist in planning interventions to slow down ABR. Responses from patients included 59% (n= 238) stating that if antibiotics were not needed, they would be happy if the doctor explained to them the best over the counter treatment options, 36% (n= 144) stated they would be satisfied with a vitamin injection, and 44% (n= 177) stated they would want reassurances and information about the illness. This is useful information which could be passed on to prescribers so that they learn alternate strategies which have been shown to be successful by others in the field.

Many prescribers (n=156, 86%) stated they wished to have more education on the appropriate use of antibiotics. Prescribers stated that they would value clearer guidelines to improve their antibiotic prescribing in hard copy (78%), on smart phone apps (77%) or on interactive internet platforms (76%). These could be useful mediums to use when conducting intervention programs.

Interventions can include developing communication aids for prescriber/ patient interactions as 91% of prescribers requested education resource aids for discussions on ABR with patients. The majority (96%) of prescribers requested data on local ABR, which shows the need for further research into this crisis, and the importance of the dissemination of all research findings.

Educational programs for both patients and prescribers which have been shown to be successful in a range of settings (18), could be an effective intervention in South Africa. Education programs could utilise all forms of media, social, television and radio to run the education campaigns, further research on the most effective tools should be conducted, and proven methods should then be continued.

These suggestions show useful pathways that could be used to educate both patients and prescribers on the damage of over prescription, and about the ABR crisis. Interventions should focus on increasing knowledge about ABR, which could then have an impact on the attitudes, perceptions and behaviours of both patients and prescribers.

Conclusion

Our study demonstrates gaps in patient and prescriber knowledge that are associated with potentially harmful perceptions and behaviours regarding antibiotic use. These associations together with our finding that patients and prescribers would like more education on ABR, suggest that educational tools and patient-provider communication tools could promote rational antibiotic use.

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Part D: Appendices to the dissertation

Appendix 1- Ethics committee approval for primary study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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05 November 2015

HREC REF: 610/2015

Dr T Boyles
Infectious Diseases and HIV Medicine
G-16.68
NGSH

Dear Dr Boyles

PROJECT TITLE: KNOWLEDGE, ATTITUTES AND PERCEPTION OF ANTIBIOTIC USE AMONG PATIENTS AND PRESCRIBERS IN CAPE TOWN

Thank you for your response letter dated 15 October 2015, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

Hrec/ref: 610/2015

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Hrec/ref: 610/2015

Appendix 2- Ethics committee approval for this study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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13 October 2016

HREC REF: 722/2016

A/Prof M Davies
Public Health & Family Medicine
Room 5.42, level 5, entrance 5
Falmouth Building

Dear A/Prof Davies

PROJECT TITLE: KNOWLEDGE, ATTITUDES AND PERCEPTIONS OF ANTIBIOTIC USE AMONG PATIENTS AND PRESCRIBERS IN SOUTH AFRICA (LINKED TO SUB-STUDY 610/2015) MPH CANDIDATE - MS E FARLEY

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th October 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Elise Farley will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 3- Patient Questionnaire (with percentile answers)

Demographics

Gender

n	Female	Male
365	72.05%	27.95%

Your age

n	<25	25-34	35-44	45-54	55-64	>65
379	8.44%	26.65%	24.27%	19.00%	14.51%	7.12%

Highest level of education

n	Grade 1 -8	Grade 9 - 11	Matric	University degree	Post graduate degree
366	1.37%	6.83%	54.10%	25.41%	12.30%

Knowledge Questions (Correct answers in bold)

1. Which of the following is true? (True/False/Unsure)	n	True	False	Unsure
a) K01a Antibiotics are good for treating germs called viruses	393	52.93%	**39.19%**	7.89%
b) K01b Antibiotics are good for treating germs called bacteria	392	**76.53%**	15.05%	8.42%
c) K01c Colds, 'flu and runny nose are usually caused by germs called bacteria	389	61.70%	**28.02%**	10.28%
d) K01d Our body has 'good' bacteria which keeps us healthy	395	**81.52%**	9.37%	9.11%
e) K01e Antibiotics can be harmful by killing the 'good' bacteria	391	**62.15%**	20.97%	16.88%
f) K01f Antibiotics only kill the 'bad' bacteria that make you sick	391	34.94%	**53.92%**	11.14%
g) K01g People can be allergic to antibiotics	395	**86.33%**	6.08%	7.59%
h) K01h Antibiotics can cause diarrhoea	391	**73.66%**	10.74%	15.60%
i) K01i All people with a sore throat need antibiotics	388	14.69%	**74.74%**	10.57%
j) K01j Antibiotics are needed for most sexually transmitted infections (STI's)	392	**40.31%**	32.14%	27.55%
k) K01k People with pneumonia need antibiotics	390	**68.46%**	11.28%	20.26%
l) K01 l Antibiotics are needed for most urine infections	393	**58.02%**	24.68%	17.30%

2. Which of the following are true? (True/False/Unsure)	n	True	False	Unsure
a) K02a Antibiotics do not have side-effects	396	11.87%	**79.04%**	9.09%
b) K02b Antibiotics can upset your body's natural balance	393	**77.61%**	10.18%	12.21%

Beliefs	n	Agree	Disagree	Unsure
c) B02c It's important for me to finish the course of antibiotics I've been prescribed	394	89.85%	7.36%	2.79%
d) B02d If people demand an antibiotic, the doctor / nurse should give it to them	393	11.96%	81.17%	6.87%
e) B02e Antibiotics should be available without a prescription	392	11.99%	82.65%	5.36%
f) B02f Antibiotics are strong and you should only take themwhen you really need them	392	81.63%	13.52%	4.85%

3. With regard to antibiotic resistance, which of the following are true

	n	True	False	Unsure
a) B03a When people take too many antibiotics their body becomes resistant to them	390	75.64%	13.59%	10.77%
b) B03b When people take too many antibiotics the germs becomes resistant to them	389	68.89%	13.62%	17.48%
c) B03c Antibiotics will work less well in future if we over-use them now	387	64.34%	20.93%	14.73%
d) B03d Antibiotic resistance is likely to be very costly to the world	379	58.84%	15.57%	25.59%
e) B03e Scientists will discover new antibiotics if the current ones stop working	384	42.71%	18.23%	39.06%

4. When is it most important to have antibiotics? (True/False/Unsure)

	n	True	False	Unsure
a) B04a When the doctor or nurse thinks I have a bacterial infection	383	72.85%	16.45%	10.70%
b) B04b When I have been sick for a long time	382	54.97%	31.15%	13.87%
c) B04c When I am very sick	381	58.01%	27.82%	14.17%
d) B04d When I tried simple remedies but they didn't work	380	50.79%	36.58%	12.63%
e) B04e It's not about how sick I am, it depends what kind of illness I have	382	83.51%	8.90%	7.59%

5. B05 Have you ever been to the clinic specifically because you wanted an antibiotic for you or your child?

	n	%
Yes (Continue to question 6)	382	31.68%
No (Go to question 7)		68.32%

6. B06 If yes, what were your beliefs about antibiotics? (Tick all that apply)

	n	% of those who said yes to 5
a) I thought antibiotics would make me / my child better	95	24.87%
b) I think antibiotics work well because you can only get them from the doctor/nurse	56	14.66%
c) Antibiotics are harmless so it's better to be safe	31	8.12%
d) I believed they would help me get back to work sooner	64	16.75%
e) It's good to have a stock of antibiotics at home for when you need them	29	7.59%
f) I'm a woman of child bearing age and am confident I can self-diagnose cystitis	16	4.19%

7. B07 Have you ever been told that antibiotics are not needed for you or your child?

	n	%
Yes	371	52.56%
No		47.44%

If yes, what did the doctor / nurse do? (tick all that apply)	n	% of those who said yes to 7
a) Explained that I / my child had a virus and antibiotics will not help	128	34.50%
b) Explained that antibiotics have side-effects which could make me feel worse	58	15.63%
c) Explained what to expect in terms of symptom resolution	68	18.33%
d) I was given written information about why antibiotics would not help and may cause harm	31	8.36%
e) I was given written information about what to expect in terms of symptom resolution	35	9.43%
f) I was told I / my child needed follow-up if symptoms did not improve	115	31.00%
g) I was prescribed symptomatic relief	103	27.76%
h) I was given a delayed prescription for antibiotics (a prescription I could only collect after a few days if I wasn't better)	62	16.71%

Attitudes

8. A08 If you or your child had a cough or cold and the doctor or nurse said you didn't need antibiotics, which of the following is likely to leave you satisfied with the consultation? (tick all that apply)

	n	% of total respondents
a) Advice on what to buy over the counter	238	59.06%
b) A different medicine that is only available on prescription	134	33.25%
c) A homeopathic remedy	23	5.71%
d) An injection of vitamins	144	35.73%
e) Referral to a traditional healer	23	5.71%
f) Information and reassurance about the illness	177	43.92%
g) I would only be satisfied if I was given an antibiotic	52	12.90%

9. A09 Which of the following apply to you? (True/False/Unsure)	n	True	False	Unsure
a) I have taken antibiotics that were prescribed for a friend or family member	355	10.42%	87.32%	2.25%
b) I have saved unused antibiotics to use at a later time	362	17.68%	80.11%	2.21%
c) I have given my antibiotics to a friend or family member	358	12.85%	84.92%	2.23%
d) I've exaggerated my symptoms to get antibiotics	360	8.33%	87.22%	4.44%

10. A10 How do you feel when the doctor or nurse prescribes antibiotics (Yes/Unsure/No)	n	True	False	Unsure
a) Relieved that the doctor/nurse realises I am sick	347	43.23%	47.55%	9.22%
b) Happy because my visit was justified	335	34.03%	59.70%	6.27%
c) Annoyed because too many antibiotics are being prescribed	328	25.91%	61.89%	12.20%
d) Worried because I prefer not to take antibiotics unless absolutely necessary	340	57.65%	35.00%	7.35%

Appendix 4- Prescriber Questionnaire (with percentile answers)

Knowledge, attitudes and perceptions of antibiotic use among prescribers in South Africa

Demographics

	n	Private sector	Both mostly private	Both mostly public
Where do you practice?	165	92,12%	4,24%	3,64%

	n	Doctor	Nurse
Nurse or doctor	167	98,20%	1,80%

	n	25-34	35-44	45-54	>55
Your age	163	7,98%	31,29%	17,79%	42,94%

	n	<5	6-23	15-24	>24
Approximately how many patient consultations do you perform a day?	44	6,82%	0,00%	40,91%	52,27%

Beliefs and attitudes

1. How much do you agree with the following statements (agree/disagree/unsure):	n	Agree	Disagree	Unsure
a. B01a Antibiotics are overused in South Africa	157	98,09%	0,00%	1,91%
b. B01b Antibiotic resistance is a significant problem in South Africa	157	96,82%	1,27%	1,91%
c. B01c New antibiotics are available to deal with the problem of resistance	156	19,87%	69,23%	10,90%
d. B01d Inappropriate use of antibiotics drives antibiotic resistance	156	99,36%	0,64%	0,00%
e. B01e Better use of antibiotics will reduce levels of antibiotic resistance	156	98,08%	1,28%	0,64%
f. B01f Use of broad spectrum antibiotics when equally effective narrower spectrum antibiotics are available can increase antibiotic resistance	156	84,62%	5,13%	10,26%
g. B01g Patients not finishing their course of antibiotics drives resistance	157	85,99%	8,28%	5,73%
h. B01h Lack of hand disinfection by healthcare workers causes the spread of antibiotic resistance	156	58,33%	31,41%	10,26%
I. B01j A good knowledge of antibiotics is important to my work as a doctor	156	100,00%	0,00%	0,00%
j. B01j I would like more education on the appropriate use of antibiotics	156	85,90%	12,18%	1,92%
k. B01k I feel confident to prescribe antibiotics appropriately	154	73,38%	11,69%	14,94%

l. B01l I feel pressure from patients to prescribe antibiotics	154	70,13%	25,97%	3,90%

2. B02 How often do you use the following resources to guide you antibiotic prescribing? (often/sometimes/never)

	n	Never	Often	Sometimes
a. B02a. Textbooks	157	27,39%	19,75%	52,87%
b. B02b. Medical journals	156	14,10%	27,56%	58,33%
c. B02c. International/national/provincial/institutional guidelines	156	16,67%	38,46%	44,87%
d. B02d. Tablet or smartphone apps	153	47,06%	27,45%	25,49%
e. B02e. Consultation with colleagues	154	12,99%	21,43%	65,58%
f. B02f. Consultation with specialists in microbiology/infectious diseases	156	25,00%	27,56%	47,44%
g. B02g. Pharmaceutical representative	156	28,21%	21,79%	50,00%

3. B03 How much do you agree with the following statements? I would value the following resources to improve my antibiotic prescribing (agree/disagree/unsure)

	n	Agree	Disagree	Unsure
a. B03a.Interactive internet based courses	151	76,82%	9,93%	13,25%
b. B03b. Clearer guidelines for tablet or smartphone apps	149	77,18%	12,08%	10,74%
c. B03c.Clearer guidelines in written form	152	77,63%	13,16%	9,21%
d. B03d.Weekend courses by specialists	151	68,21%	20,53%	11,26%
e. B03e.Weekend courses by General Practitioners	48	29,17%	41,67%	29,17%
f. B03f.Better access to diagnostic tests such as point-of-care CRP	148	71,62%	11,49%	16,89%
g. B03g.More resources to educate patients	150	91,33%	5,33%	3,33%
h. B03h.More data on local antimicrobial resistance	153	96,08%	2,61%	1,31%

4. B04. If a patient expects an antibiotic but you don't think it's absolutely necessary, how often do you prescribe them?

	n	%
a. Very often >90%	170	1,76%
b. Often >70%		5,88%
c. About half the time 50%		31,76%
d. Rarely <30%		38,24%
e. Almost never <10%		22,35%

5. B05. If you prescribe antibiotics that are not absolutely necessary, what are some of the reasons? (multiple answers allowed)

	n	% of all respondents
a. B05a. The patient expects an antibiotic	73	41,71%

b. B05b. Antibiotics don't need to be absolutely necessary, I just need to think they may help the patient	21	12,00%
c. B05c.Antibiotics can't harm the patient if they aren't needed	6	3,43%
d. B05d.Patients can't afford laboratory tests	66	37,71%
e. B05e.I'm concerned about malpractice claims	38	21,71%
f. B05f.Not applicable – I only prescribe antibiotics when absolutely necessary	62	35,43%

6. B06.How often do you think other doctors prescribe antibiotics when they aren't absolutely necessary?

	n	
a. Very often >90%	166	13,86%
b. Often >70%		53,61%
c. About half the time 50%		25,90%
d. Rarely <30%		5,42%
e. Almost never <10%		1,20%

7. B07. When the patient has an infection but antibiotics are not indicated how often do you use the following strategies (often/sometimes/never)?

	n	Never	Often	Sometimes
a. B07a.Explain that the patient has a virus and antibiotics will not help	148	0,68%	86,49%	12,84%
b. B07b.Explain that antibiotics have side-effects which could make them feel worse	145	17,24%	45,52%	37,24%
c. B07c.Explain what to expect in terms of duration of symptoms	141	4,96%	75,18%	19,86%
d. B07d.Explain features which, if they develop, should prompt them to seek further medical assistance	51	3,92%	84,31%	11,76%
e. B07e.Given written information about why antibiotics would not help and may cause harm	142	77,46%	4,23%	18,31%
f. B07f.Given written information about what to expect in terms of symptom resolution	141	75,18%	5,67%	19,15%
g. B07g.Explain the need for follow-up if symptoms don't improve	144	0,00%	89,58%	10,42%
h. B07h.Prescribed symptomatic relief	144	4,86%	86,11%	9,03%
I. B07i.Give a delayed prescription for antibiotics (a prescription that can only be collected after a few days if the patient isn't better)	145	30,34%	28,97%	40,69%

j. B07j.Prescribe antibiotics anyway	140	54,29%	5,00%	40,71%

Knowledge Questions (Correct answers in bold)

8. K08. A 30-year-old female patient with no significant past medical history asks you to prescribe an antibiotic. She has had a cough productive of green sputum for 1 week following an upper respiratory tract infection. The vital signs and examination of the chest are normal. What is the correct course of action?

	n = 48
a. Prescribe an antibiotic for community acquired pneumonia	4,17%
b. Give symptomatic treatment, advice, and information about the condition	**77,08%**
c. Prescribe an antibiotic for bronchitis	16,67%
d. Refer the patient to hospital	2,08%
e. Investigate for tuberculosis	0,00%

9. K09. A 35-year-old man who has well controlled HIV (CD4 360 and viral load <50) has been coughing for 2 weeks. He was given 5 days of co-amoxiclav which have not helped. He has been feeling a little feverish and sweaty but examination is unremarkable. What is your preferred strategy?

	n = 164
a. Reassure him that he has a viral infection that will resolve spontaneously	17,68%
b. Prescribe a second course of co-amoxiclav	0,61%
c. Prescribe moxifloxacin to cover atypical / resistant respiratory pathogens	8,54%
d. Prescribe azithromycin to cover atypical / resistant respiratory pathogens	10,98%
e. Test sputum for TB	**62,20%**

10. K10. A 66-year-old man who is hypertension with mild chronic renal impairment has been feeling 'under the weather' for 2 weeks. He is coughing and producing green sputum. His respiratory rate is 32 and blood pressure 100/55. There is bronchial breathing with crepitations in the left lower zone. What is your preferred course of action?

	n = 108
a. Refer immediately to hospital with likely diagnosis of pneumonia	**65,74%**
b. Test with sputum for TB	1,85%
c. Prescribe co-amoxiclav orally and plan to review in a few days	22,22%
d. Prescribe moxifloxacin orally and plan to review in a few days	7,41%
e. Give bronchodilators in your clinic and see how he responds	2,78%

11. K11. A 20-year-old woman is complaining of mild suprapubic pain for 2 days. She is not pregnant. Urine dipstick shows protein 1+, Blood neg, leukocyte esterase neg, nitrites neg. What is your preferred course of action?

n = 159

a.	Send a urine sample for MC+S and prescribe an antibiotic for uncomplicated cystitis	16,98%
b.	Prescribe an antibiotic for uncomplicated cystitis	10,69%
c.	**Consider UTI unlikely and look for alternative causes of proteinuria and suprapubic pain**	**66,67%**
d.	Prescribe an antibiotic for uncomplicated cystitis and investigate reasons for protein and blood in the urine	5,66%
e.	Refer to hospital immediately for pyelonephritis	0,00%

12. K12. A 30-year-old man has had a sore throat and runny nose for 5 days but is otherwise well. His oropharynx is inflamed; there is no exudate on the tonsils and no tender cervical adenopathy. He asks for and antibiotic for 'Strep throat'. What is your preferred course of action?

n= 158

a.	**Give advice about symptomatic treatments and information about expected duration of illness**	**81,65%**
b.	Investigate for diphtheria	1,27%
c.	Prescribe penicillin VK	1,27%
d.	Investigate for acute EBV infection (glandular fever)	3,80%
e.	Prescribe amoxicillin	12,03%

13. K13. A 25-year-old woman presented with a UTI last week, your colleague prescribed ciprofloxacin as a single dose and sent a urine sample which shows *E.Coli* resistant to ciprofloxacin and sensitive to co-amoxiclav, gentamicin & ertapenem. She has returned as she still has dysuria but she is no worse. What would be your preferred course of action?

n = 162

a.	Refer to hospital for treatment of this resistant organism	4,32%
b.	Prescribe ciprofloxacin for 3 days	0,62%
c.	**Prescribe co-amoxiclav for 3-5 days**	**84,57%**
d.	Prescribe oral gentamycin for 3 days	1,85%
e.	Repeat the urine sample	8,64%

14. K14. A 40-year-old woman has had 3 days of profuse watery diarrhoea up to 8 times per day. There is no blood or mucus and no-one else in the family is unwell. She is not clinically dehydrated. What would be your preferred course of action?

n =163

a.	**Prescribe oral rehydration solution and anti-diarrheal medication**	**70,55%**
b.	Send stool for MC&S and await results	20,25%
c.	Prescribe metronidazole orally	1,23%
d.	Prescribe ciprofloxacin orally	4,29%
e.	Prescribe ciprofloxacin and metronidazole orally	3,68%

Appendix 5 - Authors instructions for chosen Journal

Source: (http://journals.plos.org/plosone/s/submission-guidelines#loc-style-and-format)

Style and Format

File format	Manuscript files can be in the following formats: DOC, DOCX, RTF, or PDF. Microsoft Word documents should not be locked or protected. LaTeX manuscripts must be submitted as PDFs. Read the LaTeX guidelines.
Length	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for Symbol font.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers	Include page numbers and line numbers in the manuscript file.
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
Reference style	PLOS uses “Vancouver” style, as outlined in the ICMJE sample references.

See reference formatting examples and additional instructions below.

Manuscript Organization

Manuscripts should be organized as follows. Instructions for each element appear below the list.

Beginning section	*The following elements are required, in order:*
	Title page: List title, authors, and affiliations as first page of manuscript
	Abstract
	Introduction
Middle section	*The following elements can be renamed as needed and presented in any order:*
	Materials and Methods
	Results
	Discussion
	Conclusions (optional)
Ending section	*The following elements are required, in order:*
	Acknowledgments
	References
	Supporting information captions (if applicable)
Other elements	Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately.
	Tables are inserted immediately after the first paragraph in which they are cited.
	Supporting information files are uploaded separately.

Parts of a Submission

Title

Include a full title and a short title for the manuscript.

Title	Length	Guidelines	Examples
Full title	250 characters	Specific, descriptive, concise, and comprehensible to readers outside the field	Impact of cigarette smoke exposure on innate immunity: A *Caenorhabditis elegans* model

			Solar drinking water disinfection (SODIS) to reduce childhood diarrhoea in rural Bolivia: A cluster-randomized, controlled trial
Short title	100 characters	State the topic of the study	Cigarette smoke exposure and innate immunity SODIS and childhood diarrhoea

Titles should be written in sentence case (only the first word of the text, proper nouns, and genus names are capitalized). Avoid specialist abbreviations if possible. For clinical trials, systematic reviews, or meta-analyses, the subtitle should include the study design.

Author List

Authorship requirements

All authors must meet the criteria for authorship as outlined in the authorship policy. Read the policy. Those who contributed to the work but do not meet the criteria for authorship can be mentioned in the Acknowledgments. Read more about Acknowledgments.

The corresponding author must provide an ORCID iD at the time of submission by entering it in the user profile in the submission system. Read more about ORCID.

Author names and affiliations

Enter author names on the title page of the manuscript and in the online submission system.

On the title page, write author names in the following order:

First name (or initials, if used)

Middle name (or initials, if used)

Last name (surname, family name)

Each author on the list must have an affiliation. The affiliation includes department, university, or organizational affiliation and its location, including city, state/province (if applicable), and country.

If an author has multiple affiliations, enter all affiliations on the title page only. In the submission system, enter only the preferred or primary affiliation.

Author names will be published exactly as they appear in the manuscript file. Please double-check the information carefully to make sure it is correct.

Corresponding author

The submitting author is automatically designated as the corresponding author in the submission system. The corresponding author is the primary contact for the journal office and the only author able to view or change the manuscript while it is under editorial consideration.

The corresponding author role may be transferred to another coauthor. However, note that transferring the corresponding author role also transfers access to the manuscript. (To designate a new corresponding author while the manuscript is still under consideration, watch the video tutorial below.)

Only one corresponding author can be designated in the submission system, but this does not restrict the number of corresponding authors that may be listed on the article in the event of publication. Whoever is designated as a corresponding author on the title page of the manuscript file will be listed as such upon publication. Include an email address for each corresponding author listed on the title page of the manuscript.

 How to select a new corresponding author in Editorial Manager

Consortia and group authorship

If a manuscript is submitted on behalf of a consortium or group, include the consortium or group name in the author list, and include the full list of members in the Acknowledgments or in a supporting information file. Read the group authorship policy.

Author Contributions

Enter all author contributions in the submission system during submission. The contributions of all authors must be described using the CRediT Taxonomy of author roles. Read the policy.

Contributions will be published with the final article, and they should accurately reflect contributions to the work. The submitting author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

PLOS ONE will contact all authors by email at submission to ensure that they are aware of the submission.

Cover letter

Upload a cover letter as a separate file in the online system. The length limit is 1 page.

The cover letter should include the following information:

Summarize the study's contribution to the scientific literature

Relate the study to previously published work

Specify the type of article (for example, research article, systematic review, meta-analysis, clinical trial)

Describe any prior interactions with PLOS regarding the submitted manuscript

Suggest appropriate Academic Editors to handle your manuscript (see the full list of Academic Editors)

List any opposed reviewers

IMPORTANT: Do not include requests to reduce or waive publication fees in the cover letter. This information will be entered separately in the online submission system.

Read about publication fee assistance.

Title page

The title, authors, and affiliations should all be included on a title page as the first page of the manuscript file.

Download sample title, author list, and affiliations page (PDF)

Abstract

The Abstract comes after the title page in the manuscript file. The abstract text is also entered in a separate field in the submission system.

The Abstract should:

Describe the main objective(s) of the study

Explain how the study was done, including any model organisms used, without methodological detail

Summarize the most important results and their significance

Not exceed 300 words

Abstracts should not include:

Citations

Abbreviations, if possible

Introduction

The introduction should:

Provide background that puts the manuscript into context and allows readers outside the field to understand the purpose and significance of the study

Define the problem addressed and why it is important

Include a brief review of the key literature

Note any relevant controversies or disagreements in the field

Conclude with a brief statement of the overall aim of the work and a comment about whether that aim was achieved

Materials and Methods

The Materials and Methods section should provide enough detail to allow suitably skilled investigators to fully replicate your study. Specific information and/or protocols for new methods should be included in detail. If materials, methods, and protocols are well established, authors may cite articles where those protocols are

described in detail, but the submission should include sufficient information to be understood independent of these references.

We encourage authors to submit detailed protocols for newer or less well-established methods as supporting information. Read the supporting information guidelines.

Human or animal subjects and/or tissue or field sampling

Methods sections describing research using human or animal subjects and/or tissue or field sampling must include required ethics statements. See the reporting guidelines for human research, clinical trials, animal research, and observational and field studies for more information.

Data

PLOS journals require authors to make all data underlying the findings described in their manuscript fully available without restriction, with rare exception.

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Acknowledgments

Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution.

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Source	Format
Published articles	Hou WR, Hou YL, Wu GF, Song Y, Su XL, Sun B, et al. cDNA, genomic sequence cloning and overexpression of ribosomal protein gene L9 (rpL9) of the giant panda (*Ailuropoda melanoleuca*). Genet Mol Res. 2011;10: 1576-1588. Devaraju P, Gulati R, Antony PT, Mithun CB, Negi VS. Susceptibility to SLE in South Indian Tamils may be influenced by genetic selection pressure on TLR2 and TLR9 genes. Mol Immunol. 2014 Nov 22. pii: S0161-5890(14)00313-7. doi: 10.1016/j.molimm.2014.11.005 *Note: A DOI number for the full-text article is acceptable as an alternative to or in addition to traditional volume and page numbers.*
Accepted, unpublished articles	Same as published articles, but substitute “Forthcoming” for page numbers or DOI.
Web sites or online articles	Huynen MMTE, Martens P, Hilderlink HBM. The health impacts of globalisation: a conceptual framework. Global Health. 2005;1: 14. Available from: http://www.globalizationandhealth.com/content/1/1/14.
Books	Bates B. Bargaining for life: A social history of tuberculosis. 1st ed. Philadelphia: University of Pennsylvania Press; 1992.
Book chapters	Hansen B. New York City epidemics and history for the public. In: Harden VA, Risse GB, editors. AIDS and the historian. Bethesda: National Institutes of Health; 1991. pp. 21-28.
Deposited articles (preprints, e-prints, or arXiv)	Krick T, Shub DA, Verstraete N, Ferreiro DU, Alonso LG, Shub M, et al. Amino acid metabolism conflicts with protein diversity; 1991. Preprint. Available from: arXiv:1403.3301v1. Cited 17 March 2014.
Published media (print or online newspapers and	Fountain H. For Already Vulnerable Penguins, Study Finds Climate Change Is Another Danger. The New York Times. 29 Jan 2014. Available from: http://www.nytimes.com/2014/01/30/science/earth/climate-change-taking-toll-on-penguins-

Source	Format
magazine articles)	study-finds.html. Cited 17 March 2014.
New media (blogs, web sites, or other written works)	Allen L. Announcing PLOS Blogs. 2010 Sep 1 [cited 17 March 2014]. In: PLOS Blogs [Internet]. San Francisco: PLOS 2006 - . [about 2 screens]. Available from: http://blogs.plos.org/plos/2010/09/announcing-plos-blogs/.
Masters' theses or doctoral dissertations	Wells A. Exploring the development of the independent, electronic, scholarly journal. M.Sc. Thesis, The University of Sheffield. 1999. Available from: http://cumincad.scix.net/cgi-bin/works/Show?2e09
Databases and repositories (Figshare, arXiv)	Roberts SB. QPX Genome Browser Feature Tracks; 2013 [cited 2013 Oct 5]. Database: figshare [Internet]. Available from: http://figshare.com/articles/QPX_Genome_Browser_Feature_Tracks/701214.
Multimedia (videos, movies, or TV shows)	Hitchcock A, producer and director. Rear Window [Film]; 1954. Los Angeles: MGM.

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