BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030823
Article Type:	Protocol
Date Submitted by the Author:	04-Apr-2019
Complete List of Authors:	Gitaka, Jesse; Mount Kenya University, Research and Innovation Mureithi, Dominic; Maasai Mara University, Department of Animal Health and Production Ndegwa, Davies; Kenya Medical Training College Masika, Moses; University of Nairobi College of Health Sciences, Department of Medical Microbiology, Omuse, Geoffrey; Aga Khan University - Kenya Ngari, Moses; KEMRI/Wellcome Trust, Clinical Trial Facility Makokha, Francis; Mount Kenya University, Research and Innovation Mwaura, Peter; Mount Kenya University, Research and Innovation Kamita, Moses; Mount Kenya University, Research and Innovation Mathai, Ronald; Mount Kenya University, Research and Innovation Muregi, Francis; Mount Kenya University, Research and Innovation Mwau, Matilu; Kenya Medical Research Institute
Keywords:	Antimicrobial stewardship, Antimicrobial resistance, Implementation science

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Combating Antibiotic Resistance using Guidelines and Enhanced Stewardship in Kenya: An Implementation Science Approach

Jesse Gitaka[1], Dominic Mureithi[2], Davies Ndegwa[3], Moses Masika[4], Geoffrey Omuse[5], Moses Ngari[6], Francis Makokha[1], Peter Mwaura[1], Moses Kamita[1], Ronald Mathai[1], Francis Muregi[1], Matilu Mwau[7]

Affiliations

1. Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya
2. Department of Animal Health and Production, Maasai Mara University, P.O. Box 861-20500, Narok, Kenya.
3. Department of Medical Laboratory Sciences, Kenya Medical Training College P.O. Box 30195-00100, Nairobi, Kenya
4. Department of Medical Microbiology, College of Health Sciences, University of Nairobi, P.O. Box 30197-00100, Nairobi, Kenya.
5. Department of Pathology, Aga Khan University Hospital, P.O. Box 30270-00100, Nairobi, Kenya
6. KEMRI/Wellcome Trust Research Programme, Centre for Geographic Medicine Research - Coast, P.O. Box 230-80108, Kilifi, Kenya
7. Centre for Infectious and Parasitic Diseases Control Research, Kenya Medical Research Institute, P.O. Box 3-50400, Busia, Kenya

Correspondence: Jesse Gitaka
jgitaka@mku.ac.ke
Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya

Word count: 2708 words

Abstract

Introduction

Antibiotic resistance (AMR) is a growing problem globally especially in Sub-Saharan Africa including Kenya. Without any intervention, developing countries will be most affected due to the high burden of diseases. Studies have consistently shown that inappropriate use of antimicrobials is the major drivers of AMR. To address this challenge hospitals are now implementing antibiotic stewardship programs (ASPs), which have been observed to reduced antibiotic usage, decrease the prevalence of resistance and lead to significant economic benefits. However, the implementation of the guideline is highly dependent on settings in which they are rolled out. This study, employing an implementation science approach aims to address the knowledge and research gap in this area and provide critical data and experiences in using antibiotic guidelines and stewardship programs in the public health sector. This will provide evidence of ASP performance and potentially contribute to the county, national and regional policies on antibiotics use.

Methods

The study will be conducted in three geographically diverse regions each represented by two hospitals. A baseline study on antibiotic usage, resistance and de-escalation, duration of hospital stay, rates of readmission and costs will be carried out in the pre-implementation phase. The intervention, that is, the use of antibiotic guidelines and antibiotic stewardship programs will be instituted for 18 months using a stepwise implementation strategy that will facilitate learning and continuous improvement of stewardship activities and updating of guidelines to reflect the evolving antibiotic needs.

Ethics and dissemination

The proposal has been approved by the Mount Kenya University Ethics Review Committee and the National Commission for Science Technology and Innovation. Findings from this protocol will provide antibiotic guidelines informed by local bacteria susceptibility patterns, the establishment of Antibiotic Stewardship Committees (ASCs) in 6 County hospitals in Kenya, and data on antibiotics usage.

Key Words

Antimicrobial stewardship; Implementation science; Antimicrobial resistance

Article Summary

This protocol describes a proposed approach to be applied in order to develop antibiotic guidelines and antibiotic stewardship programs (ASPs) in different hospitals in Kenya. The guidelines as well as the ASPs will be developed based on local studies to understand the implementation challenges, derive lessons, understand the knowledge and research gap in this area.

Strengths and limitations of this study

- First study aimed at rolling out antimicrobial stewardship committees in multiple hospitals in Kenya concurrently.
- Use of implementation approach to support implement suggested guidelines for antimicrobial resistance surveillance.
- First hand evidence on the antimicrobial resistance in three diverse counties in Kenya.
- The study is limited to only three counties of the 47 counties in Kenya

Introduction

Antibiotic resistance is a serious public health concern globally and locally and fears of running out of antibiotics in the near future have been expressed.[1–3] In 2016, the World Health Organization (WHO), called for immediate and concerted efforts to mitigate this threat to global health that was estimated to contribute to 700,000 deaths in 2014 and projected to cause 10 million deaths in 2050 if inadequately mitigated.[4] The driving force for escalating rates of resistance is the injudicious use of antibiotics in patients and in livestock or release into the environment. These forces exert selective pressure for the rise and spread of resistant pathogens that may emerge by mutations or acquisition of plasmids carrying resistance genes.[5] In one study, prior antibiotic exposure was the key independent risk factor for the acquisition of multi-resistant.[6] Broad-spectrum antibiotics have the unintended consequence of selecting multidrug-resistant pathogens and increasing the likelihood of infection by fungi and *Clostridium difficile.*[7]

Nonetheless, the injudicious use of antibiotics is not unusual. In Africa, many patients do not receive treatment from the conventional health care system. Of those who receive antibiotics, 31.7 % of them do not consult a doctor for a prescription and a further 26.4% obtain the antibiotics from over-counter.[8] A study in South Africa found that 54.9% of antibiotics were inappropriately prescribed in intensive care unit settings while in the US, 20-50% of prescribed antibiotics are unnecessary or unwarranted.[9–11]

The rate of antimicrobial resistance in Kenya is worrying and rising. In one study, the prevalence of *Salmonella typhi* resistant to two or more antimicrobials was observed to have increased from 50% in 1998 to 78% in 2004 at Kenyatta National Hospital.[12] The Global Antibiotic Resistance Partnership – Kenya Working Group Report of 2011 identified antibiotic resistance as a key issue in Kenya and made bespoke recommendations to curtail the spread. These recommendations included the use of antibiotic guidelines that took into consideration local resistance surveillance data and enhanced antibiotic stewardship programs (ASPs).[13] Even so, these ASPs have not been instituted at county hospitals, and key implementation data and experiences are lacking in their roll out.

Antibiotic stewardship is defined as the optimum selection, dosage, and duration of antimicrobial treatment that yields the best clinical outcomes for the treatment or prevention of infection with the least toxicity to the patient and minimal impact on subsequent resistance.[14] It has the potential to lower treatment costs and realize economic benefits to the patient, health care system and the country at large.[15,16] Moreover, optimizing antibiotic use by minimizing exposure, fine-tuning dosage and reducing superfluous therapy and focusing treatment to the likely culprit pathogens is a strategy that boosts patient safety[17] and ultimately safeguards against antibiotic resistance.

Justification

Antibiotic resistance is a major health challenge globally and concerted efforts have been called for to limit the phenomena. Studies in Kenya have shown rising antibiotic resistance over the last 3 decades. Nonetheless, antibiotic guidelines and antibiotic stewardship programs which have been observed to lead to significant economic benefits, reduce antibiotic usage and lower the prevalence of resistance especially in Europe, North America, Japan, and South Africa have not been employed to tackle the challenge in the public health sector in Kenya. The GARP report of 2011, recognized use of guidelines and stewardship programs as a potential strategy in 'saving antibiotics' but noted the need for local studies to understand implementation

challenges, derive lessons and embed the strategy within the Kenyan health care system. This study, employing an implementation science approach aims to address the knowledge and research gap in this area and provide critical data and experiences in using antibiotic guidelines and stewardship programs in the public health sector.

Objectives of the Study

General Objectives

The overall aim of this project is to evaluate the impact of antibiotic guidelines for empirical treatment of urinary tract infections, community-acquired pneumonia, bacteremia and meningitis and antibiotic stewardship program on reducing usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays, rates of readmission and prevalence of antibiotic resistance in 6 county hospitals in Kenya.

Specific Objectives

1. To develop guidelines for antibiotic use for common infections.
2. To set up antibiotic steward committees (ASCs) in 6 county hospitals.
3. To train the ASCs to be able to perform their mandate.
4. To measure the usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays and rates of readmission in hospitals using the antibiotic stewardship strategy.
5. To ascertain antibiotic resistance patterns using culture, sensitivity, and genetic markers.
6. To establish the health care workers Knowledge, Attitudes and prescription Practices regarding antibiotics resistance, use of guidelines and ASPs.
7. To evaluate the economic benefits of using guidelines for antibiotics use and ASPs.

Expected Outputs of the research

1. Antibiotic guidelines informed by local bacteria susceptibility patterns.
2. Antibiotic Stewardship Committees (ASCs) in 6 County hospitals in Kenya.
3. Trained ASCs
4. Data on antibiotics usage, antibiotic de-escalation, duration of hospital stay and rates of readmission in hospitals using the antibiotic stewardship strategy
5. Map and data of antibiotic resistance pattern before and after implementation of the strategy.
6. Qualitative data on health care workers' knowledge, attitudes, and practices on the antibiotic usage and stewardship programs
7. Publication on cost-benefit analysis for using antibiotic guidelines and ASPs

Methodology

Setting

To be able to evaluate the antibiotic stewardship strategy across Kenya using an implementation science approach, the study will be conducted in 6 county hospitals (Kiambu County Referral Hospital, Bungoma County Hospital, Webuye Sub-County Hospital, Nakuru County Teaching and Referral Hospital, Thika Level 5 Hospital and Naivasha Sub-County Hospital).

Design

The study design will encompass a pre-implementation phase, a stepwise implementation phase, and an endline study to measure the changes in outcomes between the phases. A baseline study on antibiotic usage (Defined Daily Doses per 1000), antibiotic resistance (culture and genetic markers), antibiotic de-escalation, duration of hospital stays, rates of readmission, prescription patterns, and costs analysis will be carried out in the pre-implementation phase. The intervention, which is the use of antibiotic guidelines and antibiotic stewardship programs will be instituted in the 6 county hospitals for 18 months. The stepwise implementation strategy will facilitate learning cycles every 4-6 weeks and continuous improvement of stewardship activities and updating of guidelines to reflect evolving antibiotic needs in diverse settings. The end line study will be conducted and differences between the 2 phases evaluated as below (Statistical analysis).

In the baseline and endline studies, multidisciplinary strategies will be employed as follows

i. Health care workers knowledge, attitudes, and practices on antibiotic resistance, guidelines, and ASP will be studied qualitatively and quantitatively.
ii. Basic science approaches encompassing antibiotics culture sensitivity and molecular biology-genetic markers of resistance will be analyzed as detailed below.
iii. Clinical- patient outcomes will be studied to evaluate the guidelines.
iv. Health economics-cost savings on using guidelines and ASP will be evaluated as below.

Prevalence of inappropriate use of broad-spectrum antibiotics

The sample size is based on the prevalence of inappropriate use of broad-spectrum antibiotics of ~50%[9] in South Africa. To detect a reduction of the 50% inappropriate use of broad-spectrum antibiotics by 20% to 30% with a power of 90% and α of 0.05 in a two-sided test, a sample size of 410 in each county hospital would be adequate. In order to detect a reduction (20%) but with a power 80% the sample size would be 320 as shown in Figure 1 below.
With a 15% allowance for loss to follow up, a total of about 500 participants would be enough in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of inappropriate use of broad-spectrum antibiotics in 500 x 6= 3,000 patients for the 6 facilities.

Prevalence of antibiotic resistance

The sample size is based on the prevalence of antibiotic resistance of 78%[12] in 2004 at Kenyatta National Hospital, Kenya. To detect a reduction of the 78% antibiotic resistance by 10% to 68% with a power of 90% and α of 0.05 two-sided test, a sample size of 500 in each county hospital would be adequate. While to achieve a reduction (10%) but with power, 80% the sample size would be 220 as shown in Figure 2 below.

With 15% allowance for loss to follow up, a total of 600 participants would be enough in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of resistance in 600 x 6= 3,600 patients for the 6 facilities.

Antibiotic guidelines and ASPs: Development

Antibiotic guidelines will be formulated in consultation with senior clinicians in the study hospitals taking into account each hospital's antimicrobial resistance patterns. ASPs committee

will comprise the hospital physician, microbiologist, and pharmacist. Broad spectrum antibiotic prescriptions will be brought to the attention of the ASP committees who will also perform regular ward rounds 3 times a week in the initial stages and later once a week to optimize adherence to antibiotic guidelines. Furthermore, the guidelines will be promoted through teaching sessions, provision of pocket-size guideline cards to clinicians and pharmacists, large poster displays in the wards and through hospital and project websites.

Data collection

Laboratory assessment tools will be used to determine the preparedness of the laboratories to perform antibiotic sensitivity tests (see Additional file 1). In addition, knowledge, attitude and practices (KAP) about antibiotic prescribing and resistance among medical practitioners will be assessed using a KAP tool (See Additional file 2). A health system assessment tool will be used to gather baseline information on the antimicrobial stewardship activities in each hospital (see Additional file 3). Information on each hospital bed occupancy, antibiotic usage, and antibiotic resistance data will be collected from hospital information systems, pharmacy management systems and laboratory reporting systems respectively. Antibiotic usage will analyze the impact of the intervention on antibiotic usage comparing the intervention and control arms. Data on antibiotics issued to adult and children inpatients only will be factored excluding discharge and outpatient supplies.

To consistently compare antibiotic usage, the defined daily doses (DDD) will be used and expressed per 1000 occupied bed days (OBDs) to account for fluctuations in activity. The OBDs will be obtained from the hospital information systems.

Culture sensitivity and genetic analyses

Nasal swabs or tracheal aspirate, urine, wound swabs and blood samples will be taken from patients who have consented to the study for bacteriological analysis. Samples will be subjected to standard bacteriological analysis to isolate the culprit bacteria. Bacterial species will be confirmed by use biochemical test and analytical profiles index API strips (Bio Merieux France). Antimicrobial susceptibility test will be performed on isolated bacteria as per the Kirby-Bauer Method following manufacturer's instruction. Results will be interpreted using the Clinical and Laboratory Standards Institute (CLSI) tables.[18]

Any bacteria isolate found to be resistant to third generation cephalosporin's will be tested for production of extended spectrum Beta-lactamase (ESBLs) using the synergy disk diffusion test. Vancomycin Resistance Enterococci (VRE) will be identified using disc diffusion tests. Methicillin resistance in *S. aureus* (MRSA) will be detected by testing isolates resistant to cefoxitin by E test (AB Biodisk, Solna, Sweden) on Mueller–Hinton agar supplemented with 2% NaCl and incubated at 37°C for 24 h. The identified ESBLs, VRE and MRSA will be analyzed by PCR and sequencing to further identify the resistance genotype. *In vitro* conjugation tests will be performed to determine if resistance in bacteria is transferable.

Cost-benefit analysis for the use of antibiotic guidelines and Antibiotic Stewardship Program

A cost-benefit analysis (CBA) from a health facility and a national perspective will be performed. For health facilities, three cost drivers will be considered: pharmacy spending, length of stay, and antimicrobial stewardship interventions (training, infection control measures, etc.). For the country, we will consider, Disability-Adjusted Life years (DALYS),

work-days lost, and cost of treatment.[19–21] This will be done by collecting and analyzing data on patient income, length of hospital stay, death or disability occasioned by drug-resistant pathogens, hospital pharmacy expenditure and cost of training/rolling out antimicrobial stewardship guidelines. This data will be collected before and after antimicrobial stewardship interventions.

Data Management

Data will be recorded on a standardized Case Report Form (CRF) in use at every hospital by the trained study staff. The data will be held locally and uploaded to the secure central study server hosted at the Mount Kenya University main campus in Thika. This will be overseen by the Data Manager/statistician who will run regular reconciliation to derive the final study database. Access to the study database will be restricted and password protected.

Statistical analyses

The data will be analyzed using qualitative and quantitative methods. Qualitative data will be analyzed by subjecting the information to content analysis and presenting it in different emerging themes. The summaries of the data emanating from these themes will then be arranged on a case by case basis through the use of an Excel spreadsheet[22] and the analyses done by using NVIVO software. The quantitative data analyses will be done using Stata version 14 (Stata, Inc.). The differences between baseline and endline on all the study outcomes will be compared using appropriate statistical methods like McNemar's test, paired t-test and the Wilcoxon signed-rank test non-parametric test accounting for pairing and clusters (hospitals). Multivariable log-binomial regression analysis will be used to get risk factors for antibiotic resistance.

Ethical considerations

The proposal has been approved by the Mount Kenya University Ethics Review Committee (MKU/ERC/0764) and National Commission for Science Technology and Innovation (NACOSTI/P/18/33304/25986). The study will follow all provisions of the Declaration of Helsinki. Participants in the study will not incur any cost in the transport nor processing of the samples, neither will they receive any monetary inducements to participate in the study. Material transfer to laboratories outside of Kenya shall not be undertaken in this study. Informed written consent will be sought from the participants enrolled in the study.

Patient and Public Involvement

Patients and the public were not involved in designing this protocol.

Exit strategy and stakeholder involvement

In the process of developing this protocol, we have engaged physicians working in the proposed County hospitals and they have identified the challenge of antibiotic resistance as real and appreciate the opportunities that use of antibiotic guidelines and ASPs may provide in combating resistance, improving clinical care and saving costs. We plan to continue involving all the stakeholders in the process who include clinicians, laboratory personnel, pharmacists, public health officials, patients and scientists in the arena. We anticipate that the study findings will inform county and national policy on mitigating antibiotic resistance and raise public awareness on the need for judicious use of antibiotics. The project will use social media

platforms, websites of the collaborating institutions, and publications in peer-reviewed journals, local dailies and presentations in scientific meetings to further engage stakeholders and the public on this important issue and enhance the learning approach inherent in the strategy of implementation science for improved performance of the ASPs and the study in general.

Dissemination

Obtained results will be disseminated at different platforms which include research conferences and in peer-reviewed journals.

Discussion

The emergence of antimicrobial-resistant pathogens and a lack of new drugs to effectively treat these pathogens are the two main challenges in human health. There is thus the need to advocate for proper use of the currently available antimicrobial agents by safeguarding their effectiveness. Antibiotic stewardship has been shown to contribute to reducing antibiotic resistance [23,24] but this strategy has not been rolled out in most sub-Saharan countries in level 4 and 5 hospitals. The proposed work will employ an implementation research approach to evaluate the best strategies and derive lessons on mainstreaming antibiotic stewardship in these facilities. By leveraging on the health system approach, the implementation research will unmask real life impediments and opportunities and working with hospital teams co-design execution plans, monitoring and evaluation and sustainability of the stewardship programs.

Competing Interests

The authors declare no conflict of interest.

Grant Information

This protocol is supported by the Government of Kenya through the National Research Fund (NRF) grant to JG. The funder did not contribute to the design and decision to publish this protocol.

Availability of data and material

All data sets will be available to the public upon request.

Author Contributions

JG conceived the project, JG , DM, DN, MM, GO, MN, FM, PM, RM, FM, and MM developed the protocol, MK prepared the protocol for publication, all authors reviewed and approved the protocol.

Acknowledgment

Not applicable

Additional files

Additional file 1: Laboratory preparedness assessment tool

Additional file 2: Laboratory knowledge, attitude and practice (KAP) tool

Additional file 3: Health system tool

Figure Legend

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

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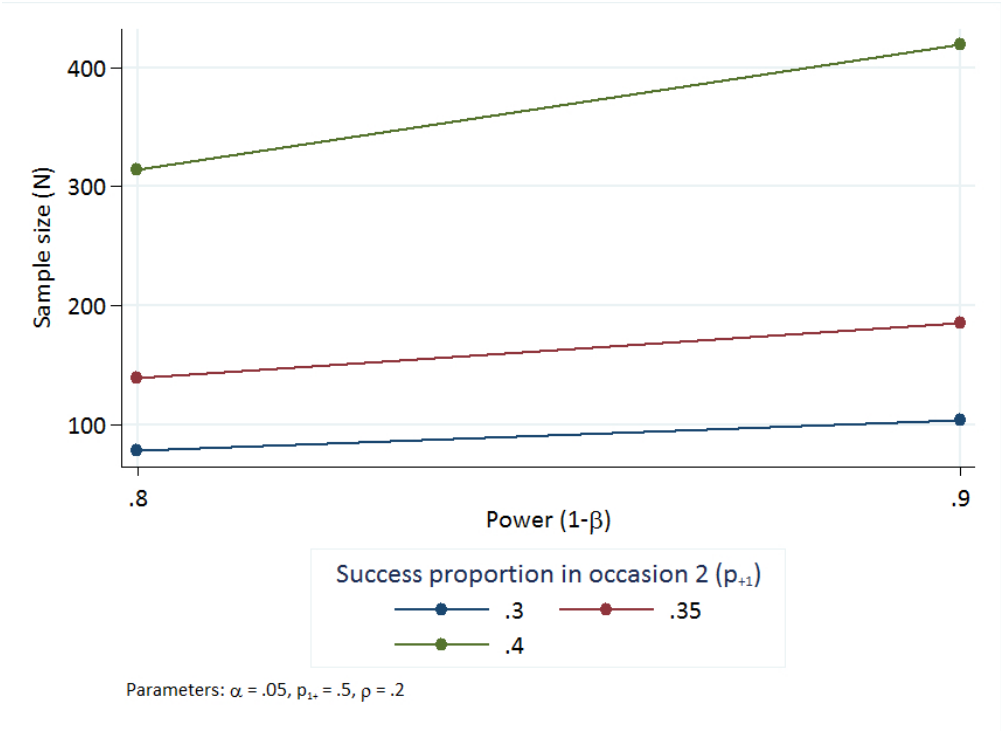

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

226x164mm (96 x 96 DPI)

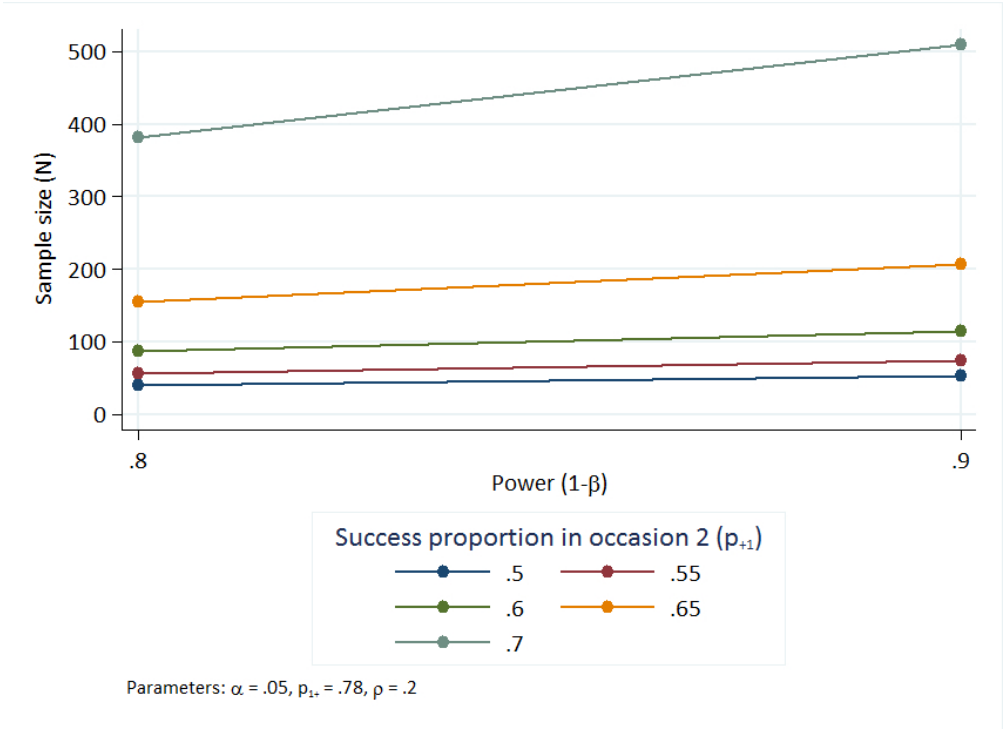

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

225x163mm (96 x 96 DPI)

A survey on Knowledge, Attitudes and Practice about antibiotic prescribing and resistance among medical practitioners in Kenyan local hospitals.

Thank you very much for accepting to participate in this study.

***You are kindly requested to answer the questionnaire honestly and completely independent of cross-consultations and/or verifications.**

Survey quality control

Date of interview: …… Start time..... End time.....

Interviewed by: .....Approved.....

Name of the Hospital…… Respondent's code……

QUESTIONS	ANSWERS
PART 1: GENERAL QUESTIONS	
1. *For how many years, since you graduated from medical school /medical training College, have you been working in a hospital (indicate cumulative years if worked in different hospitals)*	❖ *I am on attachment* ❖ *I am a trainee in medicine (internship)* ❖ *Less than one year* ❖ *1-3 years* ❖ *4 – 6 years* ❖ *7 years and more*
2. *In which department do you work?*	○ *Medicine /Emergency* ○ *Surgery* ○ *Paediatrics* ○ *Obstetrics and Gynaecology* ○ *Outpatient/A/E* ○ *Pharmacy* ○ *Other: ……*
3. *Designation (e.g. Consultant, Pharmacist, Nurse, etc.)*	……
PART 2: PRESCRIPTION PATTERN (PRACTICE)	
4. *How frequently do you prescribe antibiotics?*	❖ *More than once daily* ❖ *Once daily* ❖ *3 – 5 times a week* ❖ *1 – 2 times a week*

	❖ *less than once a week)*
5. To whom do you prescribe?	❖ *Patients at outpatient department* ❖ *Hospitalized patients* ❖ *Patients in out-patient department and hospitalised patients*
6. Do you follow any antibiotic prescription guidelines?	❖ *Yes* ❖ *No*
PART 3: AWARENESS AND ATTITUDE ON THE CURRENT SCOPE OF ANTIBIOTIC RESISTANCE	
7. Antibiotic resistance is a world-wide problem	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
8. Antibiotic resistance is a problem in my country	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
9. Antibiotic resistance is a problem in my hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
10. Antibiotics are overused in my hospital and in other hospitals of my country Kenya	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
11. Patients' demands for antibiotics contribute to the overuse of antibiotics in the hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
12. I think over-the-counter (OTC) medicines contribute to antibiotic misuse and subsequent antibiotic resistance	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
13. My awareness on local antibiotic resistance pattern is?	❖ *Excellent* ❖ *Good* ❖ *Average* ❖ *Very little* ❖ *None*
PART 4: CHOICE OF ANTIBIOTIC	
14. How confident are you about your knowledge of antibiotics?	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
15. What is your confidence level in prescribing antibiotics	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
16. How often do you check your decisions on antibiotic prescribing with a colleague?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
17. If you do consult a senior colleague, how frequent does he/she recommend prescription of a different antibiotic?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times*

	❖ *Mostly* ❖ *Always*
18. How often do you depend on antibiotic sensitivity data from the laboratory to vary your prescription	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
PART 5: SOURCE OF INFORMATION ON ANTIBIOTICS PRESCRIBING AND RESISTANCE	
19. During the past years, how many courses or trainings did you receive relating to antibiotics?	❖ *0* ❖ *1-3* ❖ *4-6* ❖ *6-10* ❖ *>10*
20. Among the sources of information about antibiotics listed below, which one did you consult in the last month?	
▪ *Information supplied by pharmaceutical companies*	❖ *Yes* ❖ *No*
▪ *Knowledge from training institutions*	❖ *Yes* ❖ *No*
▪ *Internet*	❖ *Yes* ❖ *No*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Yes* ❖ *No*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Yes* ❖ *No*
21. ***How do you appreciate the sources of information about antibiotics listed below?***	
▪ *Information supplied by pharmaceutical companies*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*

▪ *Information from University courses*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Internet*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Does your facility have a frequently released antibiogram?*	❖ *Yes* ❖ *No*
▪ *If yes, how useful is the antibiogram to you*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
PART 6: DECISION ABOUT ANTIBIOTIC PRESCRIBING	
22. When one prescribes an antibiotic, it is important to know the resistance pattern of the bacteria in the local setting	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
23. My choice of prescribing antibiotic is more influenced by the availability of antibiotics than by the cause of the infection	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
24. *My choice of prescribing antibiotic is more influenced by the cost of the drug to the patient*	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
25. *I'm always concerned about effectiveness and quality of an antibiotic when making my prescribing decisions*	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
26. *In regard to antibiotic guidelines, local guidelines are more useful than international guidelines*	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
27. *Antibiotic guidelines and antibiotic committees are rather obstacles than a help*	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
28. *I welcome the implementation of a training program about antibiotics*	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
PART 7: KNOWLEDGE ON USE OF ANTIBIOTICS	
29. *A 4-year-old child had diarrhoea in the last 4 days (3 stools daily). She had no fever during the past days nor at consultation. What is your treatment choice?*	❖ *Amoxicillin orally* ❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin/clavulanic acid orally*

	❖ *Oral rehydration salts with no antibiotic*
30. A 6-year-old child has fever (38°C), nasal discharge and a painful throat for two days. At visual inspection, the throat is reddish. What is your treatment choice?	❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin orally* ❖ *Amoxicillin/clavulanic acid orally* ❖ *No antibiotic*
31. During ward round, you have seen two patients with impaired renal function. - *Patient A is a 68-year-old male with cellulitis in the lower limb. He is administered clindamycin.* - *Patient B is a 64-year-old woman with diabetes who received treatment for sepsis with ceftriaxone empirically.* *In which case will you need to adjust the antibiotic dose?*	❖ *Patient A* ❖ *Patient B* ❖ *Patient A & B* ❖ *Neither patient A nor patient B*
32. Which one of the following antibiotics may be safely given during the first trimester of pregnancy?	❖ *Amoxicillin* ❖ *Ciprofloxacin* ❖ *Gentamicin*
33. Which of the following antibiotics has the best activity against anaerobes?	❖ *Ciprofloxacin* ❖ *Metronidazole* ❖ *Trimethoprim/sulphamethoxazole*
34. Methicillin resistant - Staphylococcus aureus is susceptible to:	❖ *Amoxicillin clavulanic acid* ❖ *Cefotaxime* ❖ *Ceftriaxone* ❖ *None of these antibiotics*
35. Which of the following antibiotics most effectively crosses the blood-brain barrier?	❖ *Clindamycin* ❖ *Ceftriaxone* ❖ *Vancomycin*
36. Aminoglycoside antibiotics such as gentamicin are most active when they are administered as follows:	❖ *Orally, three times daily* ❖ *Parenterally, once daily* ❖ *Parenterally, three times daily*

Thank you very much for your kind and honest participation

Questionnaire to assess laboratory capacity for AMR testing.

Objective: To assess capacity for Study sites laboratories to perform antimicrobial susceptibility testing and contribute to AMR surveillance				
Laboratory infrastructure and equipment				**Additional Information**
Q1	Does your lab have capacity to carry out basic bacteriology (process stool, urine, urethral/ cervical swabs, and blood)? (Perform bacterial culture, identification, and susceptibility testing)?		Yes	
			Partial	
			No	
Q2	Does your lab have resources for basic aerobic bacterial culture?		Yes	
			Partial	
			No	
Q3	Does your lab possess CO_2 incubators and CO_2 tank?		Yes	
			Partial	
			No	
Q4	Does your lab perform susceptibility testing by disc diffusion?		Yes	
			Partial	
			No	
Q5	Please indicate the presence and status of the following in your lab	Present (Tick)	Functional (Tick)	
	❖ Petri dishes			
	❖ Swabs for surface application of cultures			
	❖ Standardized susceptibility testing discs			
	❖ control strains of known susceptibility patterns			
	❖ Incubators			
	❖ Refrigerator			
	❖ Autostart backup for refrigerator/incubator			
	❖ Media preparation room			
	❖ Autoclave			
	❖ Compound microscope			
	❖ Weighing scale			
	❖ Biosafety cabinet Class 2			
	❖ Candle jar			
	❖ pH meter			
	❖ water distiller			
Q6	Does your lab have automated system (Vitek) to conduct Antimicrobial Susceptibility Testing?		Yes	
			Partial	
			No	

USE OF STANDARDIZED METHODS			
			Additional Information
Q7	Does your laboratory use Clinical Laboratory Standards Institute (CLSI) guidelines?	Yes	
		Partial	
		No	
Q8	Does your laboratory use CLSI interpretation breakpoints?	Yes	
		Partial	
		No	
Q9	Does your laboratory select individual antibiotics following CLSI guidelines?	Yes	
		Partial	
		No	
Q10	Are single isolates or pure cultures only used for final performance of antimicrobial susceptibility testing?	Yes	
		Partial	
		No	
Q11	Is the inoculum size standardized using a turbidity standard (0.5 McFarland) or other acceptable method?	Yes	
		Partial	
		No	
Q12	Does your lab have provision of standard microorganisms (ATCC) for internal quality control (useful in determining the potency of drugs or checking the quality of media)?	Yes	
		Partial	
		No	
Q13	For disk susceptibility tests, are zone sizes of controls measured and recorded?	Yes	
		Partial	
		No	
Q14	Are zone sizes of tests measured and used for recording sensitivity resistance?	Yes	
		Partial	
		No	
Q15	Does your lab use commercially prepared dehydrated AST media?	Yes	
		Partial	
		No	
Q16	Does your lab perform Susceptibility Testing directly from specimen based on clinical information?	Yes	
		Partial	
		No	
Q17	If direct susceptibility testing from specimen show mixed cultures, does your lab repeat susceptibility testing with isolated organisms?	Yes	
		Partial	
		No	
USE OF STANDARDIZED OPERATING PROCEDURES (SOPs)			
Q18	For antimicrobial susceptibility testing systems, are there do cumented criteria in	Yes	

	your institutions' SOPs for interpretation of the endpoint or zone size?	Partial	
		No	
Q19	Are guidelines established for the number and type of antibiotics reported for organisms isolated from different sites of infection?	Yes	
		Partial	
		No	
Q20	Do you report Antimicrobial Susceptibility Testing results based on Hospital policy (in consultation with Pharmacy, Infection control and Infectious diseases physicians.	Yes	
		Partial	
		No	
QUALITY ASSURANCE			
Q21	Is each new lot of susceptibility disks checked for activity before use?	Yes	
		Partial	
		No	
Q22	Does your lab use QC (quality control) strains to assess new lot of susceptibility discs?	Yes	
		Partial	
		No	
Q23	Are tolerance limits for potency of antimicrobials established (criteria for "out of control")?	Yes	
		Partial	
		No	
Q24	Does your laboratory procedure manual address unusual or inconsistent antimicrobial testing results?	Yes	
		Partial	
		No	
Q25	Does your lab participate in any Antimicrobial Susceptibility Testing related internal quality assurance program?	Yes	
		Partial	
		No	
Q26	Does your lab participate in any Antimicrobial Susceptibility Testing related external quality assurance program?	Yes	
		Partial	
		No	
Q27	Are out of control results reported to supervisory personnel?	Yes	
		Partial	
		No	

READINESS FOR AMR SURVEILLANCE			
Q28	Does your lab participate in antimicrobial resistance surveillance?	Yes	
		Partial	
		No	
Q29	Does your lab generate on routine basis antibiogram for purpose of monitoring the resistant and sensitivity patterns in your institution?	Yes	
		Partial	
		No	
Q30	Does your lab conduct all Antimicrobial Susceptibility Testing or forwards it to other labs?	Yes	
		Partial	
		No	
Q31	Does your lab receive samples for Antimicrobial Susceptibility Testing from other labs?	Yes	
		Partial	
		No	
Q32	Is Antimicrobial Susceptibility Testing cumulative data collected manually?	Yes	
		Partial	
		No	
Q33	Is Antimicrobial Susceptibility Testing cumulative data collected automatically using lab information system (LIS)?	Yes	
		Partial	
		No	
DETECTION OF SPECIFIC ORGANISMS			
Q34	Does your laboratory have the capacity of identifying resistance genotypes or resistant bacterial clones?	Yes	
		Partial	
		No	
EQUIPMENT MAINTENANCE			
Q35	Are Antimicrobial Susceptibility Testing equipment maintained appropriately and calibrated?	Yes	
		Partial	
		No	
Q36	Does your lab monitor incubator temperatures on a daily basis?	Yes	
		Partial	
		No	
CONTINUING MEDICAL EDUCATION			
Q37	**How often do you receive training in Bacteriology?**	Yes	
		Partial	
		No	
Q38	How often are you trained in conducting Antimicrobial Susceptibility Testing?		

STAFFING			
Q39	How many laboratory technologists are in the station?		
Q40	How many microbiologists are in the station?		
Q41	Does your laboratory have staff with Bachelor's degree qualification or higher?	Yes	
		Partial	
		No	
Q42	Do you engage a Consultant clinical microbiologist(s)?	Yes	
		Partial	
		No	
CONSUMABLES			
Q43	How often do you experience unavailability of consumables in Microbiology section? Eg Lack of biochemical reagents and media	Yes	
		Partial	
		No	
Q44	Does your lab experience delays in Antimicrobial Susceptibility Testing due to lack of reagents?	Yes	
		Partial	
		No	
Q45	Do frequent stock outs lead to low demand of cultures by clinicians?	Yes	
		Partial	
		No	
BIOSAFETY			
Q46	Does your lab autoclave/incinerate cultures prior to discard?	Yes	
		Partial	
		No	
Q47	Do you have handwashing facility in the laboratory?	Yes	
		Partial	
		No	
Q48	Does your lab get continuous supply of running water?	Yes	
		Partial	
		No	
Q49	Does your lab have soap supply in the handwash facility?	Yes	
		Partial	
		No	

	Core element 1: Senior hospital management leadership towards antimicrobial stewardship	Yes	No
1	Has your hospital management formally identified antimicrobial stewardship as a priority objective for the institution and included it in its key performance indicators?		
2	Is there dedicated, sustainable and sufficient budgeted financial support for antimicrobial stewardship activities (e.g., support for salary, training, or IT (information technology) support)?		
3	Does your hospital follow any (national or international) staffing standards for antimicrobial stewardship activities (e.g. number of full-time equivalent (FTE) per 100 beds for the different members of the antimicrobial stewardship team)?		
	Core element 2: Accountability and responsibilities		
4	Does your hospital have a formal/written antimicrobial stewardship programme/strategy accountable for ensuring appropriate antimicrobial use?		
5	Does your hospital have a formal organizational multidisciplinary structure responsible for antimicrobial stewardship (e.g., a committee focused on appropriate antimicrobial use, pharmacy committee, patient safety committee or other relevant structure)?		
6	Is there a healthcare professional identified as a leader for antimicrobial stewardship activities at your hospital and responsible for implementing the programme?		
7	Is there a document clearly defining roles, procedures of collaboration and responsibilities of the antimicrobial stewardship team members?		
8	Are clinicians, other than those part of the antimicrobial stewardship team (e.g. from the ICU, Internal Medicine and Surgery) involved in the antimicrobial stewardship committee?		
9	Does the antimicrobial stewardship committee produce regularly (indicate minimum time) a dedicated report which includes e.g. antimicrobial use data and/or prescription improvement initiatives, with time-committed short term and long term measurable goals/ targets for optimizing antimicrobial use?		
10	Is there a document clearly defining the procedures of collaboration of the antimicrobial stewardship team/committee with the infection prevention and control team/committee?		
	Core element 3: Available expertise on infection management		
11	Do you have access to laboratory/imaging services and to timely results to be able to support the diagnosis of the most common infections at your hospital?		
12	In your hospital are there, or do you have access to, trained and experienced healthcare professionals (medical doctor, pharmacist, nurse …) in infection management (diagnosis, prevention and treatment) and stewardship willing to constitute an antimicrobial stewardship team?		
	Core element 4: Education and practical training		
13	Does your hospital offer a range of educational resources to support staff training on how to optimize antimicrobial prescribing?		
14	Do the antimicrobial stewardship team members receive regular training in antimicrobial prescribing and stewardship?		
	Core element 5: Other actions aiming at responsible antimicrobial use		

15	Is a multidisciplinary antimicrobial stewardship team available at your hospital (e.g., greater than one trained staff member supporting clinical decisions to ensure appropriate antimicrobial use)?		
16	Does your hospital support the antimicrobial stewardship activities/ strategy with adequate information technology services?		
17	Does your hospital have an antimicrobial formulary (i.e. a list of antimicrobials that have been approved for use in a hospital, specifying whether the drugs are unrestricted, restricted (approval of an antimicrobial stewardship team member is required) or permitted for specific conditions)?		
18	Does your hospital have available and up-to-date recommendations for infection management (diagnosis, prevention and treatment), based on international/national evidence-based guidelines and local susceptibility (when possible), to assist with antimicrobial selection (indication, agent, dose, route, duration) for common clinical conditions?		
19	Does your hospital have a written policy that requires prescribers to document an antimicrobial plan (includes indication, name, dosage, duration, route and interval of administration) in the medical record or during order entry for all antimicrobial prescriptions?		
20	Does the antimicrobial stewardship team review/audit courses of therapy for specified antimicrobial agents or clinical conditions at your hospital?		
21	Is advice from antimicrobial stewardship team members easily available to prescribers?		
22	Is advice from antimicrobial stewardship team members easily available to prescribers?		
	Core element 6: Monitoring and surveillance (on a continuous basis)		
23	Does your hospital monitor the quality of antimicrobial use at the unit and/or hospital wide level?		
24	Does your stewardship programme monitor compliance with one or more of the specific interventions put in place by the stewardship team (e.g. indication captured in the medical record for all antimicrobial prescriptions)?		
25	Does your hospital monitor antibiotic susceptibility rates for a range of key bacteria?		
26	Does your hospital monitor the quantity of antimicrobials prescribed/ dispensed/purchased at the unit and/or hospital wide level?		
	Core element 7: Reporting and feedback (on a continuous basis)		
27	Does your stewardship programme share hospital-specific reports on the quantity of antimicrobials prescribed/dispensed/purchased with prescribers?		
28	Does your stewardship programme share facility-specific reports on antibiotic susceptibility rates with prescribers?		
29	Are results of audits/reviews of the quality/appropriateness of antimicrobial use communicated directly with prescribers?		

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030823.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Aug-2019
Complete List of Authors:	Gitaka, Jesse; Mount Kenya University, Research and Innovation Mureithi, Dominic; Maasai Mara University, Department of Animal Health and Production Ndegwa, Davies; Kenya Medical Training College Masika, Moses; University of Nairobi College of Health Sciences, Department of Medical Microbiology, Omuse, Geoffrey; Aga Khan University - Kenya Ngari, Moses; KEMRI/Wellcome Trust, Clinical Trial Facility Makokha, Francis; Mount Kenya University, Research and Innovation Mwaura, Peter; Mount Kenya University, Research and Innovation Kamita, Moses; Mount Kenya University, Research and Innovation Mathai, Ronald; Mount Kenya University, Research and Innovation Muregi, Francis; Mount Kenya University, Research and Innovation Mwau, Matilu; Kenya Medical Research Institute
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Evidence based practice, Medical management
Keywords:	Antimicrobial stewardship, Antimicrobial resistance, Implementation science

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Combating Antibiotic Resistance using Guidelines and Enhanced Stewardship in Kenya: a protocol for an Implementation Science Approach

Jesse Gitaka[1], Dominic Mureithi[2], Davies Ndegwa[3], Moses Masika[4], Geoffrey Omuse[5], Moses Ngari[6], Francis Makokha[1], Peter Mwaura[1], Moses Kamita[1], Ronald Mathai[1], Francis Muregi[1], Matilu Mwau[7]

Affiliations

1. Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya
2. Department of Animal Health and Production, Maasai Mara University, P.O. Box 861-20500, Narok, Kenya.
3. Department of Medical Laboratory Sciences, Kenya Medical Training College P.O. Box 30195-00100, Nairobi, Kenya
4. Department of Medical Microbiology, College of Health Sciences, University of Nairobi, P.O. Box 30197-00100, Nairobi, Kenya.
5. Department of Pathology, Aga Khan University Hospital, P.O. Box 30270-00100, Nairobi, Kenya
6. KEMRI/Wellcome Trust Research Programme, Centre for Geographic Medicine Research - Coast, P.O. Box 230-80108, Kilifi, Kenya
7. Centre for Infectious and Parasitic Diseases Control Research, Kenya Medical Research Institute, P.O. Box 3-50400, Busia, Kenya

Correspondence: Jesse Gitaka
jgitaka@mku.ac.ke
Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya

Word count: 3333 words

Abstract

Introduction

Antibiotic resistance (AMR) is a growing problem globally especially in Sub-Saharan Africa including Kenya. Without any intervention, developing countries will be most affected due to the high burden of diseases. Studies have consistently shown that inappropriate use of antimicrobials is the major drivers of AMR. To address this challenge hospital are now implementing antibiotic stewardship programs (ASPs), which have been observed to reduced antibiotic usage, decrease the prevalence of resistance and lead to significant economic benefits. However, the implementation of the guideline is highly dependent on settings in which they are rolled out. This study, employing an implementation science approach aims to address the knowledge and research gap in this area and provide critical data and experiences in using antibiotic guidelines and stewardship programs in the public health sector. This will provide evidence of ASP performance and potentially contribute to the county, national and regional policies on antibiotics use.

Methods

The study will be conducted in three geographically diverse regions each represented by two hospitals. A baseline study on antibiotic usage, resistance and de-escalation, duration of hospital stay, rates of readmission and costs will be carried out in the pre-implementation phase. The intervention, that is, the use of antibiotic guidelines and antibiotic stewardship programs will be instituted for 18 months using a stepwise implementation strategy that will facilitate learning and continuous improvement of stewardship activities and updating of guidelines to reflect the evolving antibiotic needs.

Ethics and dissemination

The proposal has been approved by the University of Nairobi-Kenyatta National Hospital Ethical and Research Committee (ERC), the Mount Kenya University Ethics Review Committee and Hospital-based Review Committees. Study findings will be presented to policy stakeholders and published in peer-reviewed scientific journals. It is anticipated the findings will inform local-based appropriate antibiotic use guidelines.

Key Words

Antimicrobial stewardship; Implementation science; Antimicrobial resistance

Strengths and limitations of this study

- First study aimed at rolling out antimicrobial stewardship committees in multiple hospitals in Kenya concurrently.
- Use of implementation approach to support implement suggested guidelines for antimicrobial resistance surveillance.
- First hand evidence on the antimicrobial resistance in three diverse counties in Kenya.
- The study is limited to only three counties of the 47 counties in Kenya

Introduction

Antibiotic resistance is a serious public health concern globally[1,2] and locally[3,4] and fears of running out of antibiotics options in the near future have been expressed. In 2016, the World Health Organization (WHO), called for immediate and concerted efforts to mitigate this threat to global health that was estimated to contribute to 700,000 deaths in 2014 and projected to cause 10 million deaths in 2050 if inadequately mitigated.[5] The driving force escalating rates of resistance is the injudicious use of antibiotics in patients and in livestock or release into the environment. These forces exert selective pressure which rise and increase spread of resistant pathogens that may emerge by mutations or acquisition of plasmids carrying resistance genes.[6] In one study, prior antibiotic exposure was the key independent risk factor for the acquisition of antibiotic multi-resistant.[7] Broad-spectrum antibiotics have the unintended consequence of selecting multidrug-resistant pathogens and increasing the likelihood of infection by fungi and *Clostridium difficile.*[8]

Nonetheless, the injudicious use of antibiotics is not unusual. In Africa, many patients do not receive treatment from the conventional health care system. Of those who receive antibiotics, 31.7 % do not consult a doctor for a prescription and a further 26.4% obtain the antibiotics over-counter.[9] A study in South Africa found that 54.9% of antibiotics were inappropriately prescribed in intensive care unit settings while in the US, 20-50% of prescribed antibiotics were unnecessary or unwarranted.[10–12]

The rate of antimicrobial resistance in Kenya is worrying and rising. In one study, the prevalence of *Salmonella typhi* resistant to two or more antimicrobials was observed to have increased from 50% in 1998 to 78% in 2004 at Kenyatta National Hospital.[13] The Global Antibiotic Resistance Partnership – Kenya Working Group Report of 2011 identified antibiotic resistance as a key issue in Kenya and made recommendations to curtail the spread. These recommendations included the use of antibiotic guidelines that took into consideration local resistance surveillance data and enhanced antibiotic stewardship programs (ASPs).[14] Even so, these ASPs have not been instituted at county hospitals, and key implementation data and experiences are lacking in their roll out.

Antibiotic stewardship is defined as the optimum selection, dosage, and duration of antimicrobial treatment that yields the best clinical outcomes for the treatment or prevention of infection with the least toxicity to the patient and minimal impact on subsequent resistance.[15] It has the potential to lower treatment costs and realize economic benefits to the patient, health care system and the country at large.[16,17] Moreover, optimizing antibiotic use by minimizing exposure, fine-tuning dosage and reducing superfluous therapy and focusing treatment to the likely culprit pathogens is a strategy that boosts patient safety[18] and ultimately safeguards against antibiotic resistance.

Justification

Antibiotic resistance is a major health challenge globally. Studies in Kenya have shown rising antibiotic resistance over the last 3 decades. Nonetheless, antibiotic guidelines and antibiotic stewardship programs which have been observed to lead to significant economic benefits, reduce antibiotic usage and lower the prevalence of resistance especially in Europe, North America, Japan, and South Africa have not been employed to tackle the challenge in the public health sector in Kenya. The GARP report of 2011, recognized use of guidelines and stewardship programs as a potential strategy in 'saving antibiotics' but noted the need for local studies to understand implementation challenges, derive lessons and embed the strategy

within the Kenyan health care system. This study, employing an implementation science approach aims to address the knowledge and research gap in this area and provide critical data and experiences in using antibiotic guidelines and stewardship programs in the public health sector.

Objectives of the Study

General Objectives

The overall aim is to evaluate the impact of antibiotic guidelines for empirical treatment of urinary tract infections, community-acquired pneumonia, bacteremia and meningitis and antibiotic stewardship program on reducing usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays, rates of readmission and prevalence of antibiotic resistance in 6 county hospitals in Kenya.

Specific Objectives

1. To develop guidelines for antibiotic use for common infections.
2. To set up antibiotic steward committees (ASCs) in 6 county hospitals.
3. To train the ASCs to be able to perform their mandate.
4. To measure the usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays and rates of readmission in hospitals using the antibiotic stewardship strategy.
5. To ascertain antibiotic resistance patterns using culture, sensitivity, and genetic markers.
6. To establish the health care workers knowledge, attitudes and prescription practices regarding antibiotics resistance, use of guidelines and ASPs.
7. To evaluate the economic benefits of using guidelines for antibiotics use and ASPs.

Expected Outputs of the research

1. Antibiotic guidelines informed by local bacteria susceptibility patterns.
2. Antibiotic Stewardship Committees (ASCs) in 6 County hospitals in Kenya.
3. Trained ASCs
4. Data on antibiotics usage, antibiotic de-escalation, duration of hospital stay and rates of readmission in hospitals using the antibiotic stewardship strategy
5. Map and data of antibiotic resistance pattern before and after implementation of the strategy.
6. Qualitative data on health care workers' knowledge, attitudes, and practices on the antibiotic usage and stewardship programs
7. Publication on cost-benefit analysis for using antibiotic guidelines and ASPs

Methodology

Setting

To be able to evaluate the antibiotic stewardship strategy across Kenya using an implementation science approach, the study will be conducted in 6 county hospitals (Kiambu County Referral Hospital, Bungoma County Hospital, Webuye Sub-County Hospital, Nakuru County Teaching and Referral Hospital, Thika Level 5 Hospital and Naivasha Sub-County Hospital).

Design

The study will utilize the reach, effectiveness, adoption, implementation and maintenance (RE-AIM) conceptual framework. RE-AIM involves the interaction of all the five factors and fits well with approaches that are system based[19]. The study design will encompass a pre-implementation phase, a stepwise implementation phase, and an endline study to measure the changes in outcomes between the phases. A baseline study on antibiotic usage (Defined Daily Doses per 1000), antibiotic resistance (culture and genetic markers), antibiotic de-escalation, duration of hospital stays, rates of readmission, prescription patterns, and costs analysis will be carried out in the pre-implementation phase. The intervention, which is the use of antibiotic guidelines and antibiotic stewardship programs, will be instituted in the 6 county hospitals for 18 months. The stepwise implementation phase will involve introduction of interventions as well as monitoring and evaluation of their effectiveness and thereafter improving the interventions where necessary. The strategy will facilitate learning cycles every 4-6 weeks and continuous improvement of stewardship activities and updating of guidelines to reflect evolving antibiotic needs in diverse settings. The end line study will be conducted and differences between the 2 phases evaluated as below (Statistical analysis).

In the baseline and endline studies, multidisciplinary strategies will be employed as follows

i. Health care workers knowledge, attitudes, and practices on antibiotic resistance, guidelines, and ASP will be studied qualitatively and quantitatively.
ii. Basic science approaches encompassing antibiotics culture sensitivity and molecular biology-genetic markers of resistance will be analyzed as detailed below.
iii. Clinical- patient outcomes will be studied to evaluate the guidelines.
iv. Health economics-cost savings on using guidelines and ASP will be evaluated as below.

Antibiotic guidelines and ASPs: Development

Antibiotic guidelines will be formulated in consultation with senior clinicians in the study hospitals taking into account each hospital's antimicrobial resistance patterns. ASPs committee will comprise of the hospital physician, microbiologist, and pharmacist. Broad spectrum antibiotic prescriptions will be brought to the attention of the ASP committees who will also perform regular ward rounds three times a week in the initial stages and later once a week to optimize adherence to antibiotic guidelines. Furthermore, the guidelines will be promoted through teaching sessions, provision of pocket-size guideline cards to clinicians and pharmacists, large poster displays in the wards and through hospital and project websites.

Data collection

Laboratory assessment tools will be used to determine the preparedness of the laboratories to perform antibiotic sensitivity tests (see Additional file 1). The tool will assess whether the laboratories have the equipment that are necessary to perform bacterial culture, identification, and susceptibility testing such as the carbon dioxide incubators, safety cabinets, and refrigerators among others. The tool will also determine whether the laboratories have the internationally recommended guidelines to perform susceptibility and quality assurance tests. In addition, knowledge, attitude and practices (KAP) about antibiotic prescribing and resistance among medical practitioners will be assessed using a KAP tool (See Additional file 2). The tool will target those medical practitioners who usually prescribe antimicrobial drugs in the hospitals

and will include the consultants, medical officers and the interns, clinical officers and the interns, as well as the pharmacists. The KAP tool will also determine the guidelines that the prescribers use to decide on the appropriate antimicrobial drug. A health system assessment tool will be used to gather baseline information on the antimicrobial stewardship activities in each hospital (see Additional file 3). Information on each hospital bed occupancy, antibiotic usage, and antibiotic resistance data will be collected from hospital information systems, pharmacy management systems and laboratory reporting systems respectively. Antibiotic usage will be analyzed in order to determine the impact of the intervention on antibiotic usage comparing the intervention and the control arms. Data on antibiotics issued to adult and children inpatients only will be factored excluding discharge and outpatient supplies.

To consistently compare antibiotic usage, the defined daily doses (DDD) will be used and expressed per 1000 occupied bed days (OBDs) to account for fluctuations in activity. The OBDs will be obtained from the hospital information systems.

Culture sensitivity and genetic analyses

Nasal swabs or tracheal aspirate, urine, wound swabs and blood samples will be taken from patients who have consented to the study for bacteriological analysis. Samples will be subjected to standard bacteriological analysis to isolate the culprit bacteria. Bacterial species will be confirmed by use of biochemical test and analytical profiles index API strips (Bio Merieux France). Antimicrobial susceptibility test will be performed on isolated bacteria as per the Kirby-Bauer Method following manufacturer's instruction. Results will be interpreted using the Clinical and Laboratory Standards Institute (CLSI) tables.[20]

Any bacteria isolate found to be resistant to third generation cephalosporin's will be tested for production of extended spectrum Beta-lactamase (ESBLs) using the synergy disk diffusion test. Vancomycin Resistance Enterococci (VRE) will be identified using disc diffusion tests. Methicillin resistance in *S. aureus* (MRSA) will be detected by testing isolates resistant to cefoxitin by E test (AB Biodisk, Solna, Sweden) on Mueller–Hinton agar supplemented with 2% NaCl and incubated at 37˚C for 24 h. The identified ESBLs, VRE and MRSA will be analyzed by PCR and sequencing to identify the resistance genotype. *In vitro* conjugation tests will be performed to determine if resistance in bacteria is transferable.

Cost-benefit analysis for the use of antibiotic guidelines and Antibiotic Stewardship Program

A cost-benefit analysis (CBA) from a health facility and a national perspective will be performed. For health facilities, three cost drivers will be considered: pharmacy spending, length of stay, and antimicrobial stewardship interventions (training, infection control measures, etc.). For the country, we will consider, Disability-Adjusted Life years (DALYS), work-days lost, and cost of treatment.[21–23] This will be done by collecting and analyzing data on patient income, length of hospital stay, death or disability occasioned by drug-resistant pathogens, hospital pharmacy expenditure and cost of training/rolling out antimicrobial stewardship guidelines. This data will be collected before and after antimicrobial stewardship interventions.

Study size

Prevalence of inappropriate use of broad-spectrum antibiotics

The sample size is based on the prevalence of inappropriate use of broad-spectrum antibiotics of ~50%[10] in South Africa. To detect a reduction of the 50% inappropriate use of broad-spectrum antibiotics by 20% to 30% with a power of 90% and α of 0.05 in a two-sided test, a sample size of 410 in each county hospital would be adequate. In order to detect a reduction (20%) but with a power 80% the sample size would be 320 as shown in Figure 1 below. With a 15% allowance for loss to follow up, a total of about 500 participants would be enough in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of inappropriate use of broad-spectrum antibiotics in 500 x 6= 3,000 patients from the 6 facilities.

Prevalence of antibiotic resistance

The sample size is based on the prevalence of antibiotic resistance of 78%[13] in 2004 at Kenyatta National Hospital, Kenya. To detect a reduction of the 78% antibiotic resistance by 10% to 68% with a power of 90% and α of 0.05 two-sided test, a sample size of 500 in each county hospital would be adequate. While to achieve a reduction (10%) but with power, 80% the sample size would be 220 as shown in Figure 2 below. With 15% allowance for loss to follow up, a total of 600 participants would be enough in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of resistance in 600 x 6 = 3,600 patients for the 6 facilities.

Data Management

Data will be recorded on a standardized Case Report Form (CRF) at every hospital by the trained study staff. The data will be held locally and uploaded to the secure central study server hosted at the Mount Kenya University main campus in Thika. This will be overseen by the Data Manager/statistician who will run regular reconciliation to derive the final study database. Access to the study database will be restricted and password protected.

Statistical analyses

The data will be analyzed using qualitative and quantitative methods. Qualitative data will be analyzed by subjecting the information to content analysis and presenting it in different emerging themes. The summaries of the data emanating from these themes will then be arranged on a case by case basis through the use of an Excel spreadsheet[24] and the analyses done by using NVIVO software. The quantitative data analyses will be done using Stata version 14 (Stata, Inc.). The differences between baseline and endline on all the study outcomes will be compared using appropriate statistical methods like McNemar's test, paired t-test and the Wilcoxon signed-rank test non-parametric test accounting for pairing and clusters (hospitals). Multivariable log-binomial regression analysis will be used to get risk factors for antibiotic resistance.

Ethical considerations

Approvals to carry out the study will be sought from the University of Nairobi-Kenyatta National Hospital Ethical and Research Committee (ERC), the Mount Kenya University Ethics Review Committee and each Hospital-based Review Committees. The study will follow all provisions of the Declaration of Helsinki. Participants in the study will not incur any cost in the transport nor processing of the samples, neither will they receive any

monetary inducements to participate in the study. Material transfer to laboratories outside of Kenya shall not be undertaken in this study. Informed written consent will be sought from the participants enrolled in the study.

Exit strategy and stakeholder involvement

In the process of developing this protocol, we have engaged physicians working in the proposed County hospitals and they have identified the challenge of antibiotic resistance as real and appreciate the opportunities that use of antibiotic guidelines and ASPs may provide in combating resistance, improving clinical care and saving costs. We plan to continue involving all the stakeholders in the process who include clinicians, laboratory personnel, pharmacists, public health officials, patients and scientists in the arena. We anticipate that the study findings will inform county and national policy on mitigating antibiotic resistance and raise public awareness on the need for judicious use of antibiotics. The project will use social media platforms, websites of the collaborating institutions, and publications in peer-reviewed journals, local dailies and presentations in scientific meetings to further engage stakeholders and the public on this important issue and enhance the learning approach inherent in the strategy of implementation science for improved performance of the ASPs and the study in general.

Dissemination

Obtained results will be disseminated at different platforms which include research conferences and in peer-reviewed journals. In addition, the findings will be shared in a dissemination forum bring together members of the health management teams at both the country and county levels, clinicians who do prescription of antimicrobial drugs, researchers and other key stakeholders.

Discussion

The emergence of antimicrobial-resistant pathogens and a lack of new drugs to effectively treat these pathogens are the two main challenges in human health. There is thus the need to advocate for proper use of the currently available antimicrobial agents by safeguarding their effectiveness. Antibiotic stewardship has been shown to contribute to reducing antibiotic resistance[25,26] but this strategy has not been rolled out in most sub-Saharan countries in level 4 and 5 hospitals. The proposed work will employ an implementation research approach to evaluate the best strategies and derive lessons on mainstreaming antibiotic stewardship in these facilities. By leveraging on the health system approach, the implementation research will unmask real life impediments and opportunities and working with hospital teams co-design execution plans, monitoring and evaluation and sustainability of the stewardship programs.

Most hospitals in Kenya lack the capacity to do antimicrobial sensitivity tests due to the lack of enough resources and technical knowhow among other challenges. This study will first do an assessment to determine the challenges that the hospitals are facing through interviews with clinicians and assessment of the capacity of the laboratories to perform the sensitivity tests. These steps will make up the initial phase and will guide the nature of implementations to be used during the implementation phase. It is hoped that the project will capacitate the laboratories in the six hospitals to do the tests and sensitize the clinicians on the need to prescribe antimicrobial drugs based on results obtained from the laboratory tests. Once the implementation phase is done, the final phase will be the endline phase where surveys similar

to the ones that were conducted during the baseline phase will be done in order to determine the impact of the implementation strategies taken in reducing the cost of treatment, days of stay in the hospital and burden on the health system among others.

The hospital management plays a key role in determining the allocation of resources to the hospitals. In this project we have proposed to involve the hospital management by including its members in the stewardship committees that will be established. This will ensure that the management is well informed about the challenges that are in the sections that are involved in surveillance and the progress that is being made. Involvement of the hospital management will also ensure that there is a buy-in of the recommendations made by the stewardship committee.

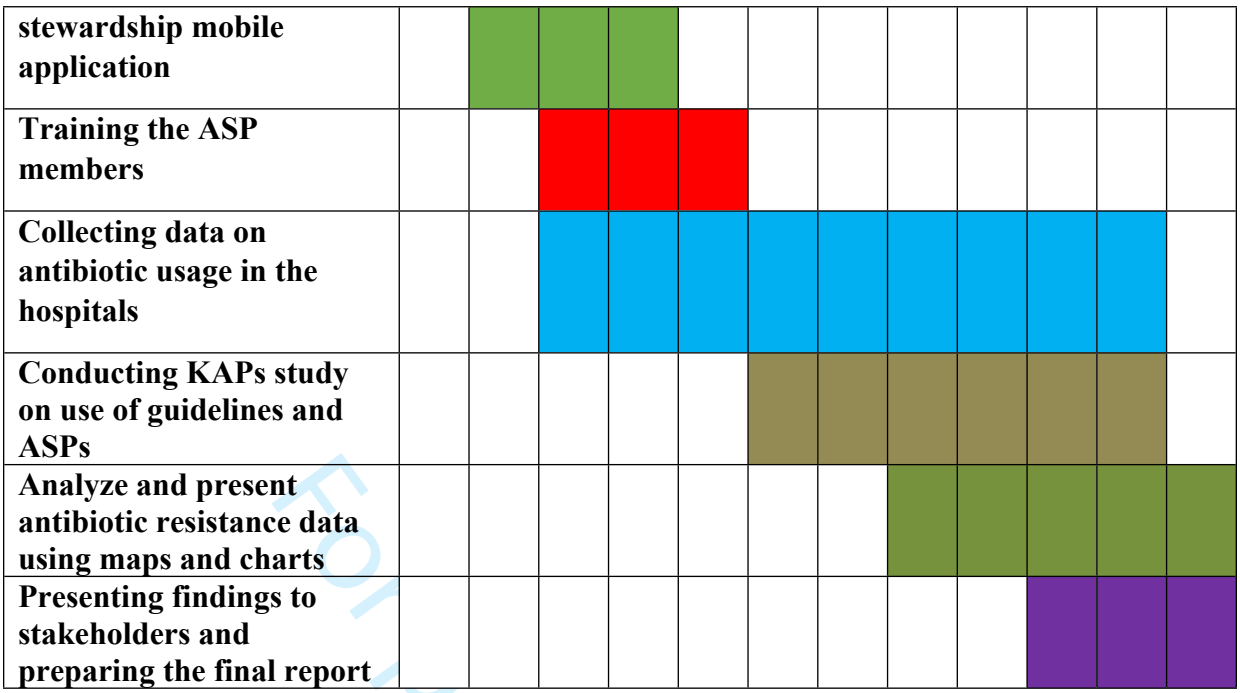
Although there is the need to establish antimicrobial stewardship committees in all the hospitals, the project proposes to start with the selected six hospitals with the hope that the same can be reproduced by other hospitals to establish similar committees in their hospitals.

Study timeline

The study is designed to take three years to complete. The study started enrolling on 2018 and participant recruitment will continue up to 2020 (Table 1). Currently, data collection on antibiotic usage in the hospitals is going on.

Table 1: Proposed study timelines.

Activity	2018				2019				2020			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Ethics clearance and authorization from study sites												
Baseline study on prevalence of antibiotic resistance and stewardship activities												
Identification of members for the antibiotic stewardship programs												
Development of antibiotic guidelines												
Adopting and preparing materials for ASP training												
Development of antibiotic guidelines and												



Competing Interests

The authors declare no conflict of interest.

Grant Information

This work was supported by The Kenya National Research Fund (grant number NRF/MKU/2017/007 to JG). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Patient and Public Involvement

No patient involved.

Availability of data and material

All data sets will be available to the public upon request.

Author Contributions

JG conceived the project, JG, DM, DN, MM, GO, MN, FM, PM, RM, FM, and MM developed the protocol, MK prepared the protocol for publication, all authors reviewed and approved the protocol.

Acknowledgment

Not applicable

Additional files

Additional file 1: Laboratory preparedness assessment tool

Additional file 2: Laboratory knowledge, attitude and practice (KAP) tool

Additional file 3: Health system tool

Figure Legends

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

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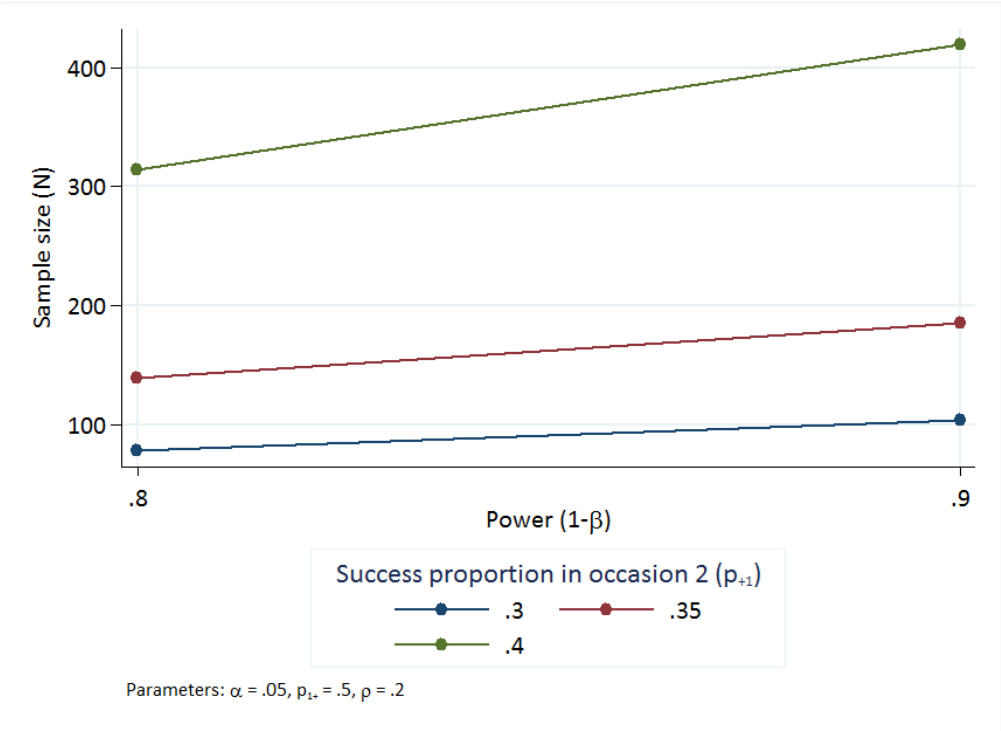

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

226x164mm (96 x 96 DPI)

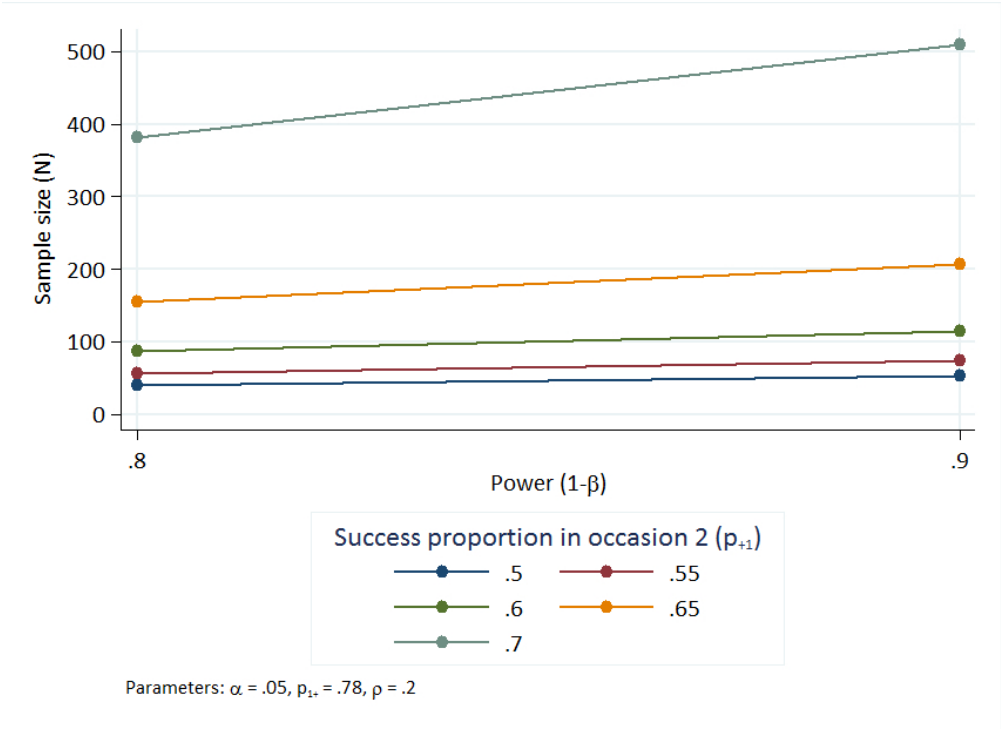

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

225x163mm (96 x 96 DPI)

A survey on Knowledge, Attitudes and Practice about antibiotic prescribing and resistance among medical practitioners in Kenyan local hospitals.

Thank you very much for accepting to participate in this study.

***You are kindly requested to answer the questionnaire honestly and completely independent of cross-consultations and/or verifications.**

Survey quality control

Date of interview: ..... Start time..... End time.....

Interviewed by: .....Approved.....

Name of the Hospital..... Respondent's code.....

QUESTIONS	ANSWERS
PART 1: GENERAL QUESTIONS	
1. *For how many years, since you graduated from medical school /medical training College, have you been working in a hospital (indicate cumulative years if worked in different hospitals)*	❖ *I am on attachment* ❖ *I am a trainee in medicine (internship)* ❖ *Less than one year* ❖ *1-3 years* ❖ *4 – 6 years* ❖ *7 years and more*
2. *In which department do you work?*	○ *Medicine /Emergency* ○ *Surgery* ○ *Paediatrics* ○ *Obstetrics and Gynaecology* ○ *Outpatient/A/E* ○ *Pharmacy* ○ *Other: .....*
3. *Designation (e.g. Consultant, Pharmacist, Nurse, etc.)*	.....
PART 2: PRESCRIPTION PATTERN (PRACTICE)	
4. *How frequently do you prescribe antibiotics?*	❖ *More than once daily* ❖ *Once daily* ❖ *3 – 5 times a week* ❖ *1 – 2 times a week*

	❖ *less than once a week)*
5. To whom do you prescribe?	❖ *Patients at outpatient department* ❖ *Hospitalized patients* ❖ *Patients in out-patient department and hospitalised patients*
6. Do you follow any antibiotic prescription guidelines?	❖ *Yes* ❖ *No*
PART 3: AWARENESS AND ATTITUDE ON THE CURRENT SCOPE OF ANTIBIOTIC RESISTANCE	
7. Antibiotic resistance is a world-wide problem	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
8. Antibiotic resistance is a problem in my country	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
9. Antibiotic resistance is a problem in my hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
10. Antibiotics are overused in my hospital and in other hospitals of my country Kenya	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
11. Patients' demands for antibiotics contribute to the overuse of antibiotics in the hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
12. I think over-the-counter (OTC) medicines contribute to antibiotic misuse and subsequent antibiotic resistance	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
13. My awareness on local antibiotic resistance pattern is?	❖ *Excellent* ❖ *Good* ❖ *Average* ❖ *Very little* ❖ *None*
PART 4: CHOICE OF ANTIBIOTIC	
14. How confident are you about your knowledge of antibiotics?	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
15. What is your confidence level in prescribing antibiotics	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
16. How often do you check your decisions on antibiotic prescribing with a colleague?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
17. If you do consult a senior colleague, how frequent does he/she recommend prescription of a different antibiotic?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times*

	❖ *Mostly* ❖ *Always*
18. How often do you depend on antibiotic sensitivity data from the laboratory to vary your prescription	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
PART 5: SOURCE OF INFORMATION ON ANTIBIOTICS PRESCRIBING AND RESISTANCE	
19. During the past years, how many courses or trainings did you receive relating to antibiotics?	❖ *0* ❖ *1-3* ❖ *4-6* ❖ *6-10* ❖ *>10*
20. Among the sources of information about antibiotics listed below, which one did you consult in the last month?	
▪ *Information supplied by pharmaceutical companies*	❖ *Yes* ❖ *No*
▪ *Knowledge from training institutions*	❖ *Yes* ❖ *No*
▪ *Internet*	❖ *Yes* ❖ *No*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Yes* ❖ *No*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Yes* ❖ *No*
21. ***How do you appreciate the sources of information about antibiotics listed below?***	
▪ *Information supplied by pharmaceutical companies*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*

▪ *Information from University courses*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Internet*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Does your facility have a frequently released antibiogram?*	❖ *Yes* ❖ *No*
▪ *If yes, how useful is the antibiogram to you*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
PART 6: DECISION ABOUT ANTIBIOTIC PRESCRIBING	
22. *When one prescribes an antibiotic, it is important to know the resistance pattern of the bacteria in the local setting*	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
23. *My choice of prescribing antibiotic is more influenced by the availability of antibiotics than by the cause of the infection*	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
24. My choice of prescribing antibiotic is more influenced by the cost of the drug to the patient	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
25. I'm always concerned about effectiveness and quality of an antibiotic when making my prescribing decisions	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
26. In regard to antibiotic guidelines, local guidelines are more useful than international guidelines	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
27. Antibiotic guidelines and antibiotic committees are rather obstacles than a help	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
28. I welcome the implementation of a training program about antibiotics	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
PART 7: KNOWLEDGE ON USE OF ANTIBIOTICS	
29. A 4-year-old child had diarrhoea in the last 4 days (3 stools daily). She had no fever during the past days nor at consultation. What is your treatment choice?	❖ *Amoxicillin orally* ❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin/clavulanic acid orally*

	❖ *Oral rehydration salts with no antibiotic*
30. A 6-year-old child has fever (38°C), nasal discharge and a painful throat for two days. At visual inspection, the throat is reddish. What is your treatment choice?	❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin orally* ❖ *Amoxicillin/clavulanic acid orally* ❖ *No antibiotic*
31. During ward round, you have seen two patients with impaired renal function. - *Patient A is a 68-year-old male with cellulitis in the lower limb. He is administered clindamycin.* - *Patient B is a 64-year-old woman with diabetes who received treatment for sepsis with ceftriaxone empirically.* *In which case will you need to adjust the antibiotic dose?*	❖ *Patient A* ❖ *Patient B* ❖ *Patient A & B* ❖ *Neither patient A nor patient B*
32. Which one of the following antibiotics may be safely given during the first trimester of pregnancy?	❖ *Amoxicillin* ❖ *Ciprofloxacin* ❖ *Gentamicin*
33. Which of the following antibiotics has the best activity against anaerobes?	❖ *Ciprofloxacin* ❖ *Metronidazole* ❖ *Trimethoprim/sulphamethoxazole*
34. Methicillin resistant - Staphylococcus aureus is susceptible to:	❖ *Amoxicillin clavulanic acid* ❖ *Cefotaxime* ❖ *Ceftriaxone* ❖ *None of these antibiotics*
35. Which of the following antibiotics most effectively crosses the blood-brain barrier?	❖ *Clindamycin* ❖ *Ceftriaxone* ❖ *Vancomycin*
36. Aminoglycoside antibiotics such as gentamicin are most active when they are administered as follows:	❖ *Orally, three times daily* ❖ *Parenterally, once daily* ❖ *Parenterally, three times daily*

Thank you very much for your kind and honest participation

Questionnaire to assess laboratory capacity for AMR testing.

Objective: To assess capacity for Study sites laboratories to perform antimicrobial susceptibility testing and contribute to AMR surveillance				
Laboratory infrastructure and equipment				**Additional Information**
Q1	Does your lab have capacity to carry out basic bacteriology (process stool, urine, urethral/ cervical swabs, and blood)? (Perform bacterial culture, identification, and susceptibility testing)?		Yes	
			Partial	
			No	
Q2	Does your lab have resources for basic aerobic bacterial culture?		Yes	
			Partial	
			No	
Q3	Does your lab possess CO_2 incubators and CO_2 tank?		Yes	
			Partial	
			No	
Q4	Does your lab perform susceptibility testing by disc diffusion?		Yes	
			Partial	
			No	
Q5	Please indicate the presence and status of the following in your lab	Present (Tick)	Functional (Tick)	
	❖ Petri dishes			
	❖ Swabs for surface application of cultures			
	❖ Standardized susceptibility testing discs			
	❖ control strains of known susceptibility patterns			
	❖ Incubators			
	❖ Refrigerator			
	❖ Autostart backup for refrigerator/incubator			
	❖ Media preparation room			
	❖ Autoclave			
	❖ Compound microscope			
	❖ Weighing scale			
	❖ Biosafety cabinet Class 2			
	❖ Candle jar			
	❖ pH meter			
	❖ water distiller			
Q6	Does your lab have automated system (Vitek) to conduct Antimicrobial Susceptibility Testing?		Yes	
			Partial	
			No	

USE OF STANDARDIZED METHODS			
			Additional Information
Q7	Does your laboratory use Clinical Laboratory Standards Institute (CLSI) guidelines?	Yes	
		Partial	
		No	
Q8	Does your laboratory use CLSI interpretation breakpoints?	Yes	
		Partial	
		No	
Q9	Does your laboratory select individual antibiotics following CLSI guidelines?	Yes	
		Partial	
		No	
Q10	Are single isolates or pure cultures only used for final performance of antimicrobial susceptibility testing?	Yes	
		Partial	
		No	
Q11	Is the inoculum size standardized using a turbidity standard (0.5 McFarland) or other acceptable method?	Yes	
		Partial	
		No	
Q12	Does your lab have provision of standard microorganisms (ATCC) for internal quality control (useful in determining the potency of drugs or checking the quality of media)?	Yes	
		Partial	
		No	
Q13	For disk susceptibility tests, are zone sizes of controls measured and recorded?	Yes	
		Partial	
		No	
Q14	Are zone sizes of tests measured and used for recording sensitivity resistance?	Yes	
		Partial	
		No	
Q15	Does your lab use commercially prepared dehydrated AST media?	Yes	
		Partial	
		No	
Q16	Does your lab perform Susceptibility Testing directly from specimen based on clinical information?	Yes	
		Partial	
		No	
Q17	If direct susceptibility testing from specimen show mixed cultures, does your lab repeat susceptibility testing with isolated organisms?	Yes	
		Partial	
		No	
USE OF STANDARDIZED OPERATING PROCEDURES (SOPs)			
Q18	For antimicrobial susceptibility testing systems, are there do cumented criteria in	Yes	

	your institutions' SOPs for interpretation of the endpoint or zone size?	Partial	
		No	
Q19	Are guidelines established for the number and type of antibiotics reported for organisms isolated from different sites of infection?	Yes	
		Partial	
		No	
Q20	Do you report Antimicrobial Susceptibility Testing results based on Hospital policy (in consultation with Pharmacy, Infection control and Infectious diseases physicians.	Yes	
		Partial	
		No	
QUALITY ASSURANCE			
Q21	Is each new lot of susceptibility disks checked for activity before use?	Yes	
		Partial	
		No	
Q22	Does your lab use QC (quality control) strains to assess new lot of susceptibility discs?	Yes	
		Partial	
		No	
Q23	Are tolerance limits for potency of antimicrobials established (criteria for "out of control")?	Yes	
		Partial	
		No	
Q24	Does your laboratory procedure manual address unusual or inconsistent antimicrobial testing results?	Yes	
		Partial	
		No	
Q25	Does your lab participate in any Antimicrobial Susceptibility Testing related internal quality assurance program?	Yes	
		Partial	
		No	
Q26	Does your lab participate in any Antimicrobial Susceptibility Testing related external quality assurance program?	Yes	
		Partial	
		No	
Q27	Are out of control results reported to supervisory personnel?	Yes	
		Partial	
		No	

READINESS FOR AMR SURVEILLANCE			
Q28	Does your lab participate in antimicrobial resistance surveillance?	Yes	
		Partial	
		No	
Q29	Does your lab generate on routine basis antibiogram for purpose of monitoring the resistant and sensitivity patterns in your institution?	Yes	
		Partial	
		No	
Q30	Does your lab conduct all Antimicrobial Susceptibility Testing or forwards it to other labs?	Yes	
		Partial	
		No	
Q31	Does your lab receive samples for Antimicrobial Susceptibility Testing from other labs?	Yes	
		Partial	
		No	
Q32	Is Antimicrobial Susceptibility Testing cumulative data collected manually?	Yes	
		Partial	
		No	
Q33	Is Antimicrobial Susceptibility Testing cumulative data collected automatically using lab information system (LIS)?	Yes	
		Partial	
		No	
DETECTION OF SPECIFIC ORGANISMS			
Q34	Does your laboratory have the capacity of identifying resistance genotypes or resistant bacterial clones?	Yes	
		Partial	
		No	
EQUIPMENT MAINTENANCE			
Q35	Are Antimicrobial Susceptibility Testing equipment maintained appropriately and calibrated?	Yes	
		Partial	
		No	
Q36	Does your lab monitor incubator temperatures on a daily basis?	Yes	
		Partial	
		No	
CONTINUING MEDICAL EDUCATION			
Q37	**How often do you receive training in Bacteriology?**	Yes	
		Partial	
		No	
Q38	How often are you trained in conducting Antimicrobial Susceptibility Testing?		

STAFFING			
Q39	How many laboratory technologists are in the station?		
Q40	How many microbiologists are in the station?		
Q41	Does your laboratory have staff with Bachelor's degree qualification or higher?	Yes	
		Partial	
		No	
Q42	Do you engage a Consultant clinical microbiologist(s)?	Yes	
		Partial	
		No	
CONSUMABLES			
Q43	How often do you experience unavailability of consumables in Microbiology section? Eg Lack of biochemical reagents and media	Yes	
		Partial	
		No	
Q44	Does your lab experience delays in Antimicrobial Susceptibility Testing due to lack of reagents?	Yes	
		Partial	
		No	
Q45	Do frequent stock outs lead to low demand of cultures by clinicians?	Yes	
		Partial	
		No	
BIOSAFETY			
Q46	Does your lab autoclave/incinerate cultures prior to discard?	Yes	
		Partial	
		No	
Q47	Do you have handwashing facility in the laboratory?	Yes	
		Partial	
		No	
Q48	Does your lab get continuous supply of running water?	Yes	
		Partial	
		No	
Q49	Does your lab have soap supply in the handwash facility?	Yes	
		Partial	
		No	

	Core element 1: Senior hospital management leadership towards antimicrobial stewardship	Yes	No
1	Has your hospital management formally identified antimicrobial stewardship as a priority objective for the institution and included it in its key performance indicators?		
2	Is there dedicated, sustainable and sufficient budgeted financial support for antimicrobial stewardship activities (e.g., support for salary, training, or IT (information technology) support)?		
3	Does your hospital follow any (national or international) staffing standards for antimicrobial stewardship activities (e.g. number of full-time equivalent (FTE) per 100 beds for the different members of the antimicrobial stewardship team)?		
	Core element 2: Accountability and responsibilities		
4	Does your hospital have a formal/written antimicrobial stewardship programme/strategy accountable for ensuring appropriate antimicrobial use?		
5	Does your hospital have a formal organizational multidisciplinary structure responsible for antimicrobial stewardship (e.g., a committee focused on appropriate antimicrobial use, pharmacy committee, patient safety committee or other relevant structure)?		
6	Is there a healthcare professional identified as a leader for antimicrobial stewardship activities at your hospital and responsible for implementing the programme?		
7	Is there a document clearly defining roles, procedures of collaboration and responsibilities of the antimicrobial stewardship team members?		
8	Are clinicians, other than those part of the antimicrobial stewardship team (e.g. from the ICU, Internal Medicine and Surgery) involved in the antimicrobial stewardship committee?		
9	Does the antimicrobial stewardship committee produce regularly (indicate minimum time) a dedicated report which includes e.g. antimicrobial use data and/or prescription improvement initiatives, with time-committed short term and long term measurable goals/ targets for optimizing antimicrobial use?		
10	Is there a document clearly defining the procedures of collaboration of the antimicrobial stewardship team/committee with the infection prevention and control team/committee?		
	Core element 3: Available expertise on infection management		
11	Do you have access to laboratory/imaging services and to timely results to be able to support the diagnosis of the most common infections at your hospital?		
12	In your hospital are there, or do you have access to, trained and experienced healthcare professionals (medical doctor, pharmacist, nurse …) in infection management (diagnosis, prevention and treatment) and stewardship willing to constitute an antimicrobial stewardship team?		
	Core element 4: Education and practical training		
13	Does your hospital offer a range of educational resources to support staff training on how to optimize antimicrobial prescribing?		
14	Do the antimicrobial stewardship team members receive regular training in antimicrobial prescribing and stewardship?		
	Core element 5: Other actions aiming at responsible antimicrobial use		

15	Is a multidisciplinary antimicrobial stewardship team available at your hospital (e.g., greater than one trained staff member supporting clinical decisions to ensure appropriate antimicrobial use)?		
16	Does your hospital support the antimicrobial stewardship activities/ strategy with adequate information technology services?		
17	Does your hospital have an antimicrobial formulary (i.e. a list of antimicrobials that have been approved for use in a hospital, specifying whether the drugs are unrestricted, restricted (approval of an antimicrobial stewardship team member is required) or permitted for specific conditions)?		
18	Does your hospital have available and up-to-date recommendations for infection management (diagnosis, prevention and treatment), based on international/national evidence-based guidelines and local susceptibility (when possible), to assist with antimicrobial selection (indication, agent, dose, route, duration) for common clinical conditions?		
19	Does your hospital have a written policy that requires prescribers to document an antimicrobial plan (includes indication, name, dosage, duration, route and interval of administration) in the medical record or during order entry for all antimicrobial prescriptions?		
20	Does the antimicrobial stewardship team review/audit courses of therapy for specified antimicrobial agents or clinical conditions at your hospital?		
21	Is advice from antimicrobial stewardship team members easily available to prescribers?		
22	Is advice from antimicrobial stewardship team members easily available to prescribers?		
	Core element 6: Monitoring and surveillance (on a continuous basis)		
23	Does your hospital monitor the quality of antimicrobial use at the unit and/or hospital wide level?		
24	Does your stewardship programme monitor compliance with one or more of the specific interventions put in place by the stewardship team (e.g. indication captured in the medical record for all antimicrobial prescriptions)?		
25	Does your hospital monitor antibiotic susceptibility rates for a range of key bacteria?		
26	Does your hospital monitor the quantity of antimicrobials prescribed/ dispensed/purchased at the unit and/or hospital wide level?		
	Core element 7: Reporting and feedback (on a continuous basis)		
27	Does your stewardship programme share hospital-specific reports on the quantity of antimicrobials prescribed/dispensed/purchased with prescribers?		
28	Does your stewardship programme share facility-specific reports on antibiotic susceptibility rates with prescribers?		
29	Are results of audits/reviews of the quality/appropriateness of antimicrobial use communicated directly with prescribers?		

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030823.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Sep-2019
Complete List of Authors:	Gitaka, Jesse; Mount Kenya University, Research and Innovation Kamita, Moses; Mount Kenya University, Research and Innovation Mureithi, Dominic; Maasai Mara University, Department of Animal Health and Production Ndegwa, Davies; Kenya Medical Training College Masika, Moses; University of Nairobi College of Health Sciences, Department of Medical Microbiology, Omuse, Geoffrey; Aga Khan University - Kenya Ngari, Moses; KEMRI/Wellcome Trust, Clinical Trial Facility Makokha, Francis; Mount Kenya University, Research and Innovation Mwaura, Peter; Mount Kenya University, Research and Innovation Mathai, Ronald; Mount Kenya University, Research and Innovation Muregi, Francis; Mount Kenya University, Research and Innovation Mwau, Matilu; Kenya Medical Research Institute
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Evidence based practice, Medical management
Keywords:	Antimicrobial stewardship, Antimicrobial resistance, Implementation science

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Combating Antibiotic Resistance using Guidelines and Enhanced Stewardship in Kenya: a protocol for an Implementation Science Approach

Jesse Gitaka[1], Moses Kamita[1], Dominic Mureithi[2], Davies Ndegwa[3], Moses Masika[4], Geoffrey Omuse[5], Moses Ngari[6], Francis Makokha[1], Peter Mwaura[1], Ronald Mathai[1], Francis Muregi[1], Matilu Mwau[7]

Affiliations

1. Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya
2. Department of Animal Health and Production, Maasai Mara University, P.O. Box 861-20500, Narok, Kenya.
3. Department of Medical Laboratory Sciences, Kenya Medical Training College P.O. Box 30195-00100, Nairobi, Kenya
4. Department of Medical Microbiology, College of Health Sciences, University of Nairobi, P.O. Box 30197-00100, Nairobi, Kenya.
5. Department of Pathology, Aga Khan University Hospital, P.O. Box 30270-00100, Nairobi, Kenya
6. KEMRI/Wellcome Trust Research Programme, Centre for Geographic Medicine Research - Coast, P.O. Box 230-80108, Kilifi, Kenya
7. Centre for Infectious and Parasitic Diseases Control Research, Kenya Medical Research Institute, P.O. Box 3-50400, Busia, Kenya

Correspondence: Jesse Gitaka
jgitaka@mku.ac.ke
Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya

Abstract

Introduction

Antibiotic resistance (AMR) is a growing problem globally especially in Sub-Saharan Africa including Kenya. Without any intervention, developing countries will be most affected due to the high burden of diseases. Studies have consistently shown that inappropriate use of antimicrobials is the major drivers of AMR. To address this challenge hospital are now implementing antibiotic stewardship programs (ASPs), which have been observed to reduced antibiotic usage, decrease the prevalence of resistance and lead to significant economic benefits. However, the implementation of the guideline is highly dependent on settings in which they are rolled out. This study, employing an implementation science approach aims to address the knowledge and research gap in this area and provide critical data and experiences in using antibiotic guidelines and stewardship programs in the public health sector. This will provide evidence of ASP performance and potentially contribute to the county, national and regional policies on antibiotics use.

Methods and analysis

The study will be conducted in three geographically diverse regions each represented by two hospitals. A baseline study on antibiotic usage, resistance and de-escalation, duration of hospital stay, rates of readmission and costs will be carried out in the pre-implementation phase. The intervention, that is, the use of antibiotic guidelines and antibiotic stewardship programs will be instituted for 18 months using a stepwise implementation strategy that will facilitate learning and continuous improvement of stewardship activities and updating of guidelines to reflect the evolving antibiotic needs.

Ethics and dissemination

Approvals to carry out the study have been sought from the National Commission for Science, Technology and Innovation and the Mount Kenya University Ethics Review Committee. In addition, approvals will be sort from each Hospital-based Review Committees where such committees are in place. Study findings will be presented to policy stakeholders and published in peer-reviewed scientific journals. It is anticipated the findings will inform local-based appropriate antibiotic use guidelines.

Key Words

Antimicrobial stewardship; Implementation science; Antimicrobial resistance

Strengths and limitations of this study

- First study aimed at rolling out antimicrobial stewardship committees in multiple hospitals in Kenya concurrently.
- Use of implementation approach to support implement suggested guidelines for antimicrobial resistance surveillance.
- First hand evidence on the antimicrobial resistance in three diverse counties in Kenya.
- The study is limited to only three counties of the 47 counties in Kenya

Introduction

Antibiotic resistance is a serious public health concern globally[1,2] and locally[3,4] and fears of running out of antibiotics options in the near future have been expressed. In 2016, the World Health Organization (WHO), called for immediate and concerted efforts to mitigate this threat to global health that was estimated to contribute to 700,000 deaths in 2014 and projected to cause 10 million deaths in 2050 if inadequately mitigated.[5] The driving force escalating rates of resistance is the injudicious use of antibiotics in patients and in livestock or release into the environment.[6] These forces exert selective pressure which rise and increase the spread of resistant pathogens that may emerge by mutations or acquisition of plasmids carrying resistance genes.[7] In one study, prior antibiotic exposure was the key independent risk factor for the acquisition of antibiotic multi-resistant.[8] Broad-spectrum antibiotics have the unintended consequence of selecting multidrug-resistant pathogens and increasing the likelihood of infection by fungi and *Clostridium difficile.*[9]

Nonetheless, the injudicious use of antibiotics is not unusual. In Africa, many patients do not receive treatment from the conventional health care system. Of those who receive antibiotics, 31.7 % do not consult a doctor for a prescription and a further 26.4% obtain the antibiotics over-counter.[10] A study in South Africa found that 54.9% of antibiotics were inappropriately prescribed in intensive care unit settings while in the US, 20-50% of prescribed antibiotics were unnecessary or unwarranted.[11–13]

The rate of antimicrobial resistance in developing countries Kenya included is worrying and rising.[14] In one study, the prevalence of *Salmonella typhi* resistant to two or more antimicrobials was observed to have increased from 50% in 1998 to 78% in 2004 at Kenyatta National Hospital.[15] The Global Antibiotic Resistance Partnership – Kenya Working Group Report of 2011 identified antibiotic resistance as a key issue in Kenya and made recommendations to curtail the spread.[16] These recommendations included the use of antibiotic guidelines that took into consideration local resistance surveillance data and enhanced antibiotic stewardship programs (ASPs).[16] Even so, these ASPs have not been instituted at county hospitals, and key implementation data and experiences are lacking in their roll out.

Antibiotic stewardship is defined as the optimum selection, dosage, and duration of antimicrobial treatment that yields the best clinical outcomes for the treatment or prevention of infection with the least toxicity to the patient and minimal impact on subsequent resistance.[17] It has the potential to lower treatment costs and realize economic benefits to the patient, health care system and the country at large.[18,19] Moreover, optimizing antibiotic use by minimizing exposure, fine-tuning dosage and reducing superfluous therapy and focusing treatment to the likely culprit pathogens is a strategy that boosts patient safety[20] and ultimately safeguards against antibiotic resistance.[21]

Justification

Antibiotic resistance is a major health challenge globally. Studies in Kenya have shown rising antibiotic resistance over the last 3 decades. Nonetheless, antibiotic guidelines and antibiotic stewardship programs which have been observed to lead to significant economic benefits, reduce antibiotic usage and lower the prevalence of resistance especially in Europe, North America, Japan, and South Africa have not been employed to tackle the challenge in the public health sector in Kenya. The GARP report of 2011, recognized use of guidelines and stewardship programs as a potential strategy in 'saving antibiotics' but noted the need for

local studies to understand implementation challenges, derive lessons and embed the strategy within the Kenyan health care system. This study, employing an implementation science approach aims to address the knowledge and research gap in this area and provide critical data and experiences in using antibiotic guidelines and stewardship programs in the public health sector.

Objectives of the Study

General Objectives

The overall aim is to evaluate the impact of antibiotic guidelines for empirical treatment of urinary tract infections, community-acquired pneumonia, bacteremia and meningitis and antibiotic stewardship program on reducing usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays, rates of readmission and prevalence of antibiotic resistance in 6 county hospitals in Kenya.

Specific Objectives

1. To develop guidelines for antibiotic use for common infections.
2. To set up antibiotic steward committees (ASCs) in 6 county hospitals.
3. To train the ASCs to be able to perform their mandate.
4. To measure the usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays and rates of readmission in hospitals using the antibiotic stewardship strategy.
5. To ascertain antibiotic resistance patterns using culture, sensitivity, and genetic markers.
6. To establish the health care workers knowledge, attitudes and prescription practices regarding antibiotics resistance, use of guidelines and ASPs.
7. To evaluate the economic benefits of using guidelines for antibiotics use and ASPs.

Expected Outputs of the research

1. Antibiotic guidelines informed by local bacteria susceptibility patterns.
2. Antibiotic Stewardship Committees (ASCs) in 6 County hospitals in Kenya.
3. Trained ASCs
4. Data on antibiotics usage, antibiotic de-escalation, duration of hospital stay and rates of readmission in hospitals using the antibiotic stewardship strategy
5. Map and data of antibiotic resistance pattern before and after implementation of the strategy.
6. Qualitative data on health care workers' knowledge, attitudes, and practices on the antibiotic usage and stewardship programs
7. Publication on cost-benefit analysis for using antibiotic guidelines and ASPs

Methods and analysis

Setting

To be able to evaluate the antibiotic stewardship strategy across Kenya using an implementation science approach, the study will be conducted in 6 county hospitals (Kiambu County Referral Hospital, Bungoma County Hospital, Webuye Sub-County Hospital, Nakuru

County Teaching and Referral Hospital, Thika Level 5 Hospital and Naivasha Sub-County Hospital).

Design

The study will utilize the reach, effectiveness, adoption, implementation and maintenance (RE-AIM) conceptual framework. RE-AIM involves the interaction of all the five factors and fits well with approaches that are system based[22]. The study design will encompass a pre-implementation phase, a stepwise implementation phase, and an endline study to measure the changes in outcomes between the phases. A baseline study on antibiotic usage (Defined Daily Doses per 1000), antibiotic resistance (culture and genetic markers), antibiotic de-escalation, duration of hospital stays, rates of readmission, prescription patterns, and costs analysis will be carried out in the pre-implementation phase. The intervention, which is the use of antibiotic guidelines and antibiotic stewardship programs, will be instituted in the 6 county hospitals for 18 months. The stepwise implementation phase will involve introduction of interventions as well as monitoring and evaluation of their effectiveness and thereafter improving the interventions where necessary. The strategy will facilitate learning cycles every 4-6 weeks and continuous improvement of stewardship activities and updating of guidelines to reflect evolving antibiotic needs in diverse settings. During the intervention phase, challenges faced during the implementation of the guidelines will be documented and used to advice on the changes that need to be made during the review of the guidelines. The end line study will be conducted and differences between the 2 phases evaluated as below (Statistical analysis).

In the baseline and endline studies, multidisciplinary strategies will be employed as follows

i. Health care workers knowledge, attitudes, and practices on antibiotic resistance, guidelines, and ASP will be studied qualitatively and quantitatively.
ii. Basic science approaches encompassing antibiotics culture sensitivity and molecular biology-genetic markers of resistance will be analyzed as detailed below.
iii. Clinical- patient outcomes will be studied to evaluate the guidelines.
iv. Health economics-cost savings on using guidelines and ASP will be evaluated as below.

Antibiotic guidelines and ASPs: Development

Antibiotic guidelines will be formulated in consultation with senior clinicians in the study hospitals taking into account each hospital's antimicrobial resistance patterns. ASPs committee will comprise of the hospital physician, microbiologist, and pharmacist. Broad spectrum antibiotic prescriptions will be brought to the attention of the ASP committees who will also perform regular ward rounds three times a week in the initial stages and later once a week to optimize adherence to antibiotic guidelines. Furthermore, the guidelines will be promoted through teaching sessions, provision of pocket-size guideline cards to clinicians and pharmacists, large poster displays in the wards and through hospital and project websites.

Data collection

Laboratory assessment tools will be used to determine the preparedness of the laboratories to perform antibiotic sensitivity tests (see Additional file 1). The tool will assess whether the laboratories have the equipment that are necessary to perform bacterial culture, identification, and
susceptibility testing such as the carbon dioxide incubators, safety cabinets, and refrigerators

among others. The tool will also determine whether the laboratories have the internationally recommended guidelines to perform susceptibility and quality assurance tests. In addition, knowledge, attitude and practices (KAP) about antibiotic prescribing and resistance among medical practitioners will be assessed using a KAP tool (See Additional file 2). The tool will target those medical practitioners who usually prescribe antimicrobial drugs in the hospitals and will include the consultants, medical officers and the interns, clinical officers and the interns, as well as the pharmacists. The KAP tool will also determine the guidelines that the prescribers use to decide on the appropriate antimicrobial drug. A health system assessment tool will be used to gather baseline information on the antimicrobial stewardship activities in each hospital (see Additional file 3). Information on each hospital bed occupancy, antibiotic usage, and antibiotic resistance data will be collected from hospital information systems, pharmacy management systems and laboratory reporting systems respectively. Antibiotic usage will be analyzed in order to determine the impact of the intervention on antibiotic usage comparing the intervention and the control arms. Data on antibiotics issued to adult and children inpatients only will be factored excluding discharge and outpatient supplies.

To consistently compare antibiotic usage, the defined daily doses (DDD) will be used and expressed per 1000 occupied bed days (OBDs) to account for fluctuations in activity following WHO guidelines.[23] The OBDs will be obtained from the hospital information systems.

Culture sensitivity and genetic analyses

Nasal swabs or tracheal aspirate, urine, wound swabs and blood samples will be taken from patients who have consented to the study for bacteriological analysis. Samples will be subjected to standard bacteriological analysis to isolate the culprit bacteria. Bacterial species will be confirmed by use of biochemical test and analytical profiles index API strips (Bio Merieux France). Antimicrobial susceptibility test will be performed on isolated bacteria as per the Kirby-Bauer Method following manufacturer's instruction. Results will be interpreted using the Clinical and Laboratory Standards Institute (CLSI) tables.[24]

Any bacteria isolate found to be resistant to third generation cephalosporin's will be tested for production of extended spectrum Beta-lactamase (ESBLs) using the synergy disk diffusion test. Vancomycin Resistance Enterococci (VRE) will be identified using disc diffusion tests. Methicillin resistance in *S. aureus* (MRSA) will be detected by testing isolates resistant to cefoxitin by E test (AB Biodisk, Solna, Sweden) on Mueller–Hinton agar supplemented with 2% NaCl and incubated at 37˚C for 24 h. The identified ESBLs, VRE and MRSA will be analyzed by PCR and sequencing to identify the resistance genotype. *In vitro* conjugation tests will be performed to determine if resistance in bacteria is transferable.

Cost-benefit analysis for the use of antibiotic guidelines and Antibiotic Stewardship Program

A cost-benefit analysis (CBA) from a health facility and a national perspective will be performed. For health facilities, three cost drivers will be considered: pharmacy spending, length of stay, and antimicrobial stewardship interventions (training, infection control measures, etc.). For the country, we will consider, Disability-Adjusted Life years (DALYS), work-days lost, and cost of treatment.[25–27] This will be done by collecting and analyzing data on patient income, length of hospital stay, death or disability occasioned by drug-resistant pathogens, hospital pharmacy expenditure and cost of training/rolling out antimicrobial

stewardship guidelines. This data will be collected before and after antimicrobial stewardship interventions.

Study size

Prevalence of inappropriate use of broad-spectrum antibiotics

The sample size is based on the prevalence of inappropriate use of broad-spectrum antibiotics of ~50%[11] in South Africa. To detect a reduction of the 50% inappropriate use of broad-spectrum antibiotics by 20% to 30% with a power of 90% and α of 0.05 in a two-sided test, a sample size of 410 in each county hospital would be adequate. In order to detect a reduction (20%) but with a power 80% the sample size would be 320 as shown in Figure 1 below. With a 15% allowance for loss to follow up, a total of about 500 participants would be enough in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of inappropriate use of broad-spectrum antibiotics in 500 x 6= 3,000 patients from the 6 facilities.

Prevalence of antibiotic resistance

The sample size is based on the prevalence of antibiotic resistance of 78%[15] in 2004 at Kenyatta National Hospital, Kenya. To detect a reduction of the 78% antibiotic resistance by 10% to 68% with a power of 90% and α of 0.05 two-sided test, a sample size of 500 in each county hospital would be adequate. While to achieve a reduction (10%) but with power, 80% the sample size would be 220 as shown in Figure 2 below. With 15% allowance for loss to follow up, a total of 600 participants would be enough in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of resistance in 600 x 6 = 3,600 patients for the 6 facilities.

Data Management

Data will be recorded on a standardized Case Report Form (CRF) at every hospital by the trained study staff. The data will be held locally and uploaded to the secure central study server hosted at the Mount Kenya University main campus in Thika. This will be overseen by the Data Manager/statistician who will run regular reconciliation to derive the final study database. Access to the study database will be restricted and password protected.

Statistical analyses

The data will be analyzed using qualitative and quantitative methods. Qualitative data will be analyzed by subjecting the information to content analysis and presenting it in different emerging themes. The summaries of the data emanating from these themes will then be arranged on a case by case basis through the use of an Excel spreadsheet[28] and the analyses done by using NVIVO software. The quantitative data analyses will be done using Stata version 14 (Stata, Inc.). The differences between baseline and endline on all the study outcomes will be compared using appropriate statistical methods like McNemar's test, paired t-test and the Wilcoxon signed-rank test non-parametric test accounting for pairing and clusters (hospitals). Multivariable log-binomial regression analysis will be used to get risk factors for antibiotic resistance.

Ethical considerations

Approvals to carry out the study have been sought from the National Commission for Science, Technology and Innovation (NACOSTI) (NACOSTI/P/18/33304/25986) and the Mount Kenya University Ethics Review Committee (MKU/ERC/0764). In addition, approvals will be sort from each Hospital-based Review Committees where such committees are in place. The study will follow all provisions of the Declaration of Helsinki. Participants in the study will not incur any cost in the transport nor processing of the samples, neither will they receive any monetary inducements to participate in the study. Material transfer to laboratories outside of Kenya shall not be undertaken in this study. Informed written consent will be sought from the participants enrolled in the study.

Exit strategy and stakeholder involvement

In the process of developing this protocol, we have engaged physicians working in the proposed County hospitals and they have identified the challenge of antibiotic resistance as real and appreciate the opportunities that use of antibiotic guidelines and ASPs may provide in combating resistance, improving clinical care and saving costs. We plan to continue involving all the stakeholders in the process who include clinicians, laboratory personnel, pharmacists, public health officials, patients and scientists in the arena. We anticipate that the study findings will inform county and national policy on mitigating antibiotic resistance and raise public awareness on the need for judicious use of antibiotics. The project will use social media platforms, websites of the collaborating institutions, and publications in peer-reviewed journals, local dailies and presentations in scientific meetings to further engage stakeholders and the public on this important issue and enhance the learning approach inherent in the strategy of implementation science for improved performance of the ASPs and the study in general.

Dissemination

Obtained results will be disseminated at different platforms which include research conferences and in peer-reviewed journals. It is hoped that five publications will be generated by the end of the study. The publications will cover areas ranging from the study protocol itself to the different aspects that will be focused on in the course of the project. Contextualized guidelines on judicious use of antibiotics in the six hospitals in Kenya will also be published for easy access by other health facility in and outside Kenya. In addition, the findings will be shared in a dissemination forum bring together members of the health management teams at both the country and county levels, clinicians who do prescription of antimicrobial drugs, researchers and other key stakeholders.

Discussion

The emergence of antimicrobial-resistant pathogens and a lack of new drugs to effectively treat these pathogens are the two main challenges in human health. There is thus the need to advocate for proper use of the currently available antimicrobial agents by safeguarding their effectiveness. Antibiotic stewardship has been shown to contribute to reducing antibiotic resistance[29,30] but this strategy has not been rolled out in most sub-Saharan countries in level 4 and 5 hospitals. The proposed work will employ an implementation research approach to evaluate the best strategies and derive lessons on mainstreaming antibiotic stewardship in these facilities. By leveraging on the health system approach, the implementation research will unmask real life impediments and opportunities and working with hospital teams co-design execution plans, monitoring and evaluation and sustainability of the stewardship programs.

Most hospitals in Kenya lack the capacity to do antimicrobial sensitivity tests due to the lack of enough resources and technical knowhow among other challenges.[31] This study will first do an assessment to determine the challenges that the hospitals are facing through interviews with clinicians and assessment of the capacity of the laboratories to perform the sensitivity tests. These steps will make up the initial phase and will guide the nature of implementations to be used during the implementation phase. It is hoped that the project will capacitate the laboratories in the six hospitals to do the tests and sensitize the clinicians on the need to prescribe antimicrobial drugs based on results obtained from the laboratory tests. Once the implementation phase is done, the final phase will be the endline phase where surveys similar to the ones that were conducted during the baseline phase will be done in order to determine the impact of the implementation strategies taken in reducing the cost of treatment, days of stay in the hospital and burden on the health system among others.

The hospital management plays a key role in determining the allocation of resources to the hospitals.[32] In this project we have proposed to involve the hospital management by including its members in the stewardship committees that will be established. This will ensure that the management is well informed about the challenges that are in the sections that are involved in surveillance and the progress that is being made. Involvement of the hospital management will also ensure that there is a buy-in of the recommendations made by the stewardship committee.

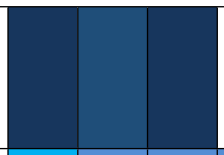
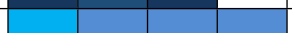
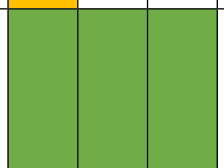
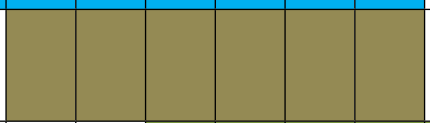
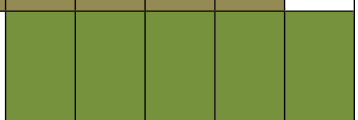
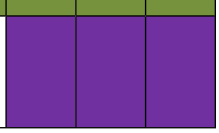
Although there is the need to establish antimicrobial stewardship committees in all the hospitals, the project proposes to start with the selected six hospitals with the hope that the same can be reproduced by other hospitals to establish similar committees in their hospitals.

Study timeline

The study is designed to take three years to complete. The study started enrolling on 2018 and participant recruitment will continue up to 2020 (Table 1). So far, stewardship committees have been established and workshops to sensitize the members conducted. Currently, data collection on knowledge attitude and practice by antibiotic prescribers in the hospitals is going on.

Table 1: Proposed study timelines.

Activity	2019				2020				2021			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Ethics clearance and authorization from study sites												
Baseline study on prevalence of antibiotic resistance and stewardship activities												

Identification of members for the antibiotic stewardship programs	
Development of antibiotic guidelines	
Adopting and preparing materials for ASP training	
Development of antibiotic guidelines and stewardship mobile application	
Training the ASP members	
Collecting data on antibiotic usage in the hospitals	
Conducting KAPs study on use of guidelines and ASPs	
Analyze and present antibiotic resistance data using maps and charts	
Presenting findings to stakeholders and preparing the final report	

Patient and Public Involvement

No patient involved.

Availability of data and material

All data sets will be available to the public upon request.

Acknowledgment

Not applicable

Additional files

Additional file 1: Laboratory preparedness assessment tool

Additional file 2: Laboratory knowledge, attitude and practice (KAP) tool

Additional file 3: Health system tool

Figure Legends

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

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Authors' Contributions

JG initiated the concepts of the study. JG, DM, DN, MMasika, GO, MN, FMakokha, PM, RM, FMuregi, and MMwau developed the protocol. JG, DM, DN, and MMasika will be involved in training the ASCs. DM, GO, MN, FMakokha, PM, RM, DN, and MK will help in data collection. MN and MK will be involved in data analysis. MK wrote the first draft of the manuscript. All authors reviewed and approved the protocol.

Funding Statement

This work was supported by The Kenya National Research Fund (grant number NRF/MKU/2017/007 to JG). The funders had no role in study design, decision to publish, or preparation of the manuscript.

Competing Interests

The authors declare no conflict of interest.

Word count: 3466 words

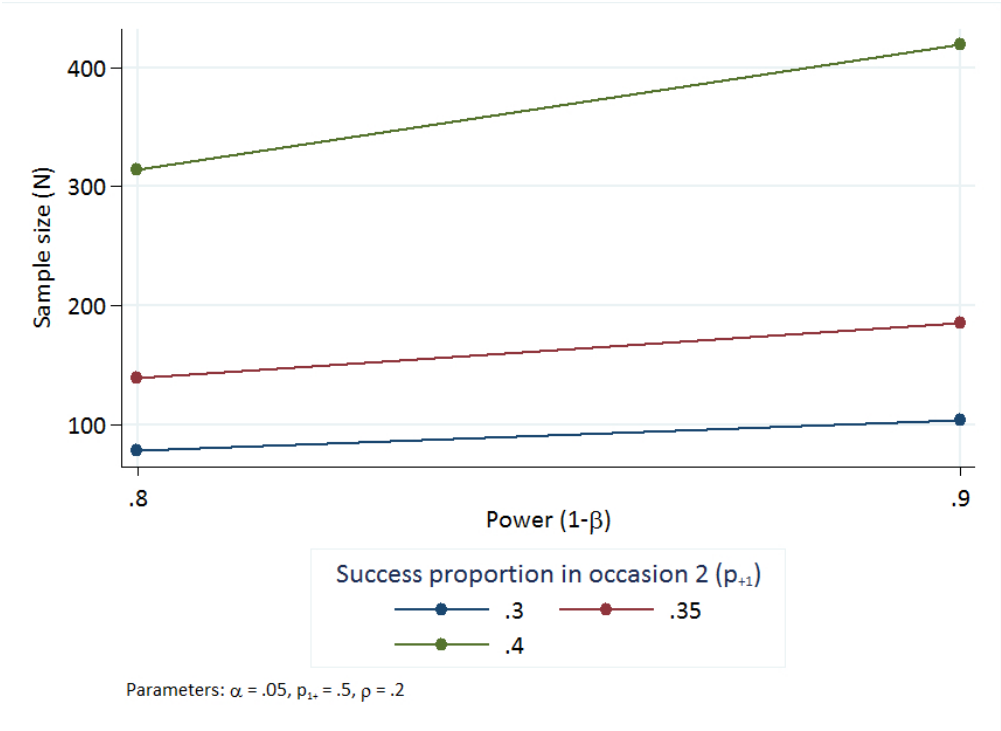

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

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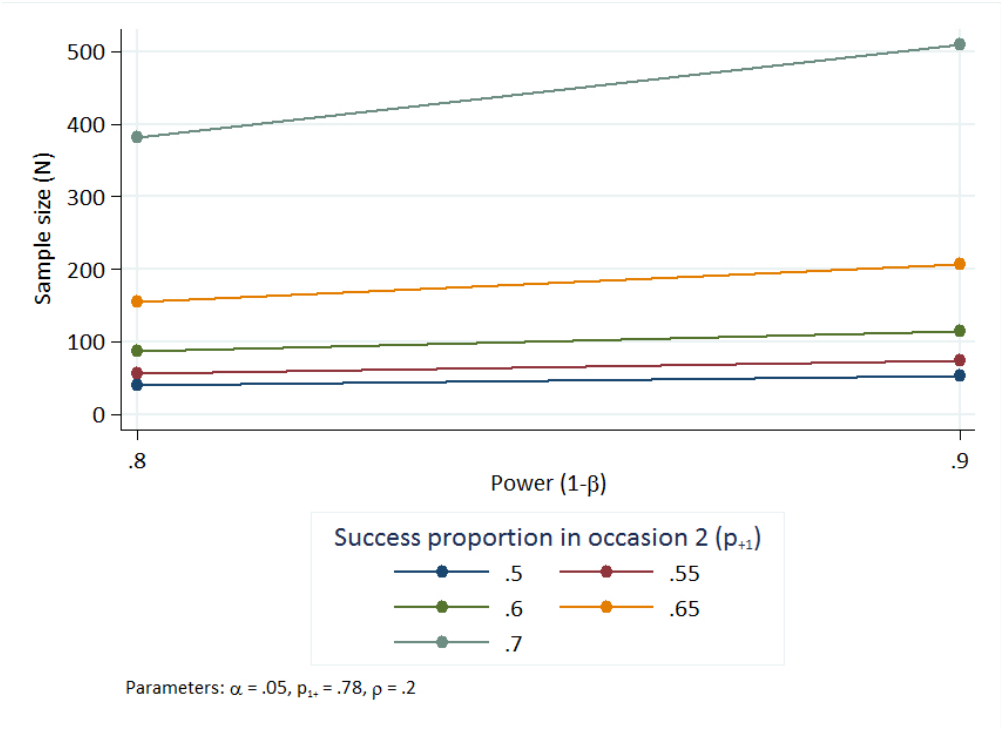

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

225x163mm (96 x 96 DPI)

A survey on Knowledge, Attitudes and Practice about antibiotic prescribing and resistance among medical practitioners in Kenyan local hospitals.

Thank you very much for accepting to participate in this study.

***You are kindly requested to answer the questionnaire honestly and completely independent of cross-consultations and/or verifications.**

Survey quality control

Date of interview: ..... Start time..... End time.....

Interviewed by: .....Approved.....

Name of the Hospital..... Respondent's code.....

QUESTIONS	ANSWERS
PART 1: GENERAL QUESTIONS	
1. *For how many years, since you graduated from medical school /medical training College, have you been working in a hospital (indicate cumulative years if worked in different hospitals)*	❖ *I am on attachment* ❖ *I am a trainee in medicine (internship)* ❖ *Less than one year* ❖ *1-3 years* ❖ *4 – 6 years* ❖ *7 years and more*
2. *In which department do you work?*	○ *Medicine /Emergency* ○ *Surgery* ○ *Paediatrics* ○ *Obstetrics and Gynaecology* ○ *Outpatient/A/E* ○ *Pharmacy* ○ *Other: .....*
3. *Designation (e.g. Consultant, Pharmacist, Nurse, etc.)*	.....
PART 2: PRESCRIPTION PATTERN (PRACTICE)	
4. *How frequently do you prescribe antibiotics?*	❖ *More than once daily* ❖ *Once daily* ❖ *3 – 5 times a week* ❖ *1 – 2 times a week*

	❖ *less than once a week)*
5. To whom do you prescribe?	❖ *Patients at outpatient department* ❖ *Hospitalized patients* ❖ *Patients in out-patient department and hospitalised patients*
6. Do you follow any antibiotic prescription guidelines?	❖ *Yes* ❖ *No*
PART 3: AWARENESS AND ATTITUDE ON THE CURRENT SCOPE OF ANTIBIOTIC RESISTANCE	
7. Antibiotic resistance is a world-wide problem	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
8. Antibiotic resistance is a problem in my country	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
9. Antibiotic resistance is a problem in my hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
10. Antibiotics are overused in my hospital and in other hospitals of my country Kenya	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
11. Patients' demands for antibiotics contribute to the overuse of antibiotics in the hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
12. I think over-the-counter (OTC) medicines contribute to antibiotic misuse and subsequent antibiotic resistance	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
13. My awareness on local antibiotic resistance pattern is?	❖ *Excellent* ❖ *Good* ❖ *Average* ❖ *Very little* ❖ *None*
PART 4: CHOICE OF ANTIBIOTIC	
14. How confident are you about your knowledge of antibiotics?	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
15. What is your confidence level in prescribing antibiotics	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
16. How often do you check your decisions on antibiotic prescribing with a colleague?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
17. If you do consult a senior colleague, how frequent does he/she recommend prescription of a different antibiotic?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times*

	❖ *Mostly* ❖ *Always*
18. How often do you depend on antibiotic sensitivity data from the laboratory to vary your prescription	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
PART 5: SOURCE OF INFORMATION ON ANTIBIOTICS PRESCRIBING AND RESISTANCE	
19. During the past years, how many courses or trainings did you receive relating to antibiotics?	❖ *0* ❖ *1-3* ❖ *4-6* ❖ *6-10* ❖ *>10*
20. Among the sources of information about antibiotics listed below, which one did you consult in the last month?	
▪ *Information supplied by pharmaceutical companies*	❖ *Yes* ❖ *No*
▪ *Knowledge from training institutions*	❖ *Yes* ❖ *No*
▪ *Internet*	❖ *Yes* ❖ *No*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Yes* ❖ *No*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Yes* ❖ *No*
21. ***How do you appreciate the sources of information about antibiotics listed below?***	
▪ *Information supplied by pharmaceutical companies*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*

▪ *Information from University courses*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Internet*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Does your facility have a frequently released antibiogram?*	❖ *Yes* ❖ *No*
▪ *If yes, how useful is the antibiogram to you*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
PART 6: DECISION ABOUT ANTIBIOTIC PRESCRIBING	
22. When one prescribes an antibiotic, it is important to know the resistance pattern of the bacteria in the local setting	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
23. My choice of prescribing antibiotic is more influenced by the availability of antibiotics than by the cause of the infection	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
24. My choice of prescribing antibiotic is more influenced by the cost of the drug to the patient	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
25. I'm always concerned about effectiveness and quality of an antibiotic when making my prescribing decisions	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
26. In regard to antibiotic guidelines, local guidelines are more useful than international guidelines	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
27. Antibiotic guidelines and antibiotic committees are rather obstacles than a help	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
28. I welcome the implementation of a training program about antibiotics	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
PART 7: KNOWLEDGE ON USE OF ANTIBIOTICS	
29. A 4-year-old child had diarrhoea in the last 4 days (3 stools daily). She had no fever during the past days nor at consultation. What is your treatment choice?	❖ *Amoxicillin orally* ❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin/clavulanic acid orally*

	❖ *Oral rehydration salts with no antibiotic*
30. A 6-year-old child has fever (38°C), nasal discharge and a painful throat for two days. At visual inspection, the throat is reddish. What is your treatment choice?	❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin orally* ❖ *Amoxicillin/clavulanic acid orally* ❖ *No antibiotic*
31. During ward round, you have seen two patients with impaired renal function. - *Patient A is a 68-year-old male with cellulitis in the lower limb. He is administered clindamycin.* - *Patient B is a 64-year-old woman with diabetes who received treatment for sepsis with ceftriaxone empirically.* *In which case will you need to adjust the antibiotic dose?*	❖ *Patient A* ❖ *Patient B* ❖ *Patient A & B* ❖ *Neither patient A nor patient B*
32. Which one of the following antibiotics may be safely given during the first trimester of pregnancy?	❖ *Amoxicillin* ❖ *Ciprofloxacin* ❖ *Gentamicin*
33. Which of the following antibiotics has the best activity against anaerobes?	❖ *Ciprofloxacin* ❖ *Metronidazole* ❖ *Trimethoprim/sulphamethoxazole*
34. Methicillin resistant - Staphylococcus aureus is susceptible to:	❖ *Amoxicillin clavulanic acid* ❖ *Cefotaxime* ❖ *Ceftriaxone* ❖ *None of these antibiotics*
35. Which of the following antibiotics most effectively crosses the blood-brain barrier?	❖ *Clindamycin* ❖ *Ceftriaxone* ❖ *Vancomycin*
36. Aminoglycoside antibiotics such as gentamicin are most active when they are administered as follows:	❖ *Orally, three times daily* ❖ *Parenterally, once daily* ❖ *Parenterally, three times daily*

Thank you very much for your kind and honest participation

Questionnaire to assess laboratory capacity for AMR testing.

Objective: To assess capacity for Study sites laboratories to perform antimicrobial susceptibility testing and contribute to AMR surveillance				
Laboratory infrastructure and equipment				**Additional Information**
Q1	Does your lab have capacity to carry out basic bacteriology (process stool, urine, urethral/ cervical swabs, and blood)? (Perform bacterial culture, identification, and susceptibility testing)?		Yes	
			Partial	
			No	
Q2	Does your lab have resources for basic aerobic bacterial culture?		Yes	
			Partial	
			No	
Q3	Does your lab possess CO_2 incubators and CO_2 tank?		Yes	
			Partial	
			No	
Q4	Does your lab perform susceptibility testing by disc diffusion?		Yes	
			Partial	
			No	
Q5	Please indicate the presence and status of the following in your lab	Present (Tick)	Functional (Tick)	
	❖ Petri dishes			
	❖ Swabs for surface application of cultures			
	❖ Standardized susceptibility testing discs			
	❖ control strains of known susceptibility patterns			
	❖ Incubators			
	❖ Refrigerator			
	❖ Autostart backup for refrigerator/incubator			
	❖ Media preparation room			
	❖ Autoclave			
	❖ Compound microscope			
	❖ Weighing scale			
	❖ Biosafety cabinet Class 2			
	❖ Candle jar			
	❖ pH meter			
	❖ water distiller			
Q6	Does your lab have automated system (Vitek) to conduct Antimicrobial Susceptibility Testing?		Yes	
			Partial	
			No	

USE OF STANDARDIZED METHODS			
			Additional Information
Q7	Does your laboratory use Clinical Laboratory Standards Institute (CLSI) guidelines?	Yes	
		Partial	
		No	
Q8	Does your laboratory use CLSI interpretation breakpoints?	Yes	
		Partial	
		No	
Q9	Does your laboratory select individual antibiotics following CLSI guidelines?	Yes	
		Partial	
		No	
Q10	Are single isolates or pure cultures only used for final performance of antimicrobial susceptibility testing?	Yes	
		Partial	
		No	
Q11	Is the inoculum size standardized using a turbidity standard (0.5 McFarland) or other acceptable method?	Yes	
		Partial	
		No	
Q12	Does your lab have provision of standard microorganisms (ATCC) for internal quality control (useful in determining the potency of drugs or checking the quality of media)?	Yes	
		Partial	
		No	
Q13	For disk susceptibility tests, are zone sizes of controls measured and recorded?	Yes	
		Partial	
		No	
Q14	Are zone sizes of tests measured and used for recording sensitivity resistance?	Yes	
		Partial	
		No	
Q15	Does your lab use commercially prepared dehydrated AST media?	Yes	
		Partial	
		No	
Q16	Does your lab perform Susceptibility Testing directly from specimen based on clinical information?	Yes	
		Partial	
		No	
Q17	If direct susceptibility testing from specimen show mixed cultures, does your lab repeat susceptibility testing with isolated organisms?	Yes	
		Partial	
		No	
USE OF STANDARDIZED OPERATING PROCEDURES (SOPs)			
Q18	For antimicrobial susceptibility testing systems, are there do cumented criteria in	Yes	

	your institutions' SOPs for interpretation of the endpoint or zone size?	Partial	
		No	
Q19	Are guidelines established for the number and type of antibiotics reported for organisms isolated from different sites of infection?	Yes	
		Partial	
		No	
Q20	Do you report Antimicrobial Susceptibility Testing results based on Hospital policy (in consultation with Pharmacy, Infection control and Infectious diseases physicians.	Yes	
		Partial	
		No	
QUALITY ASSURANCE			
Q21	Is each new lot of susceptibility disks checked for activity before use?	Yes	
		Partial	
		No	
Q22	Does your lab use QC (quality control) strains to assess new lot of susceptibility discs?	Yes	
		Partial	
		No	
Q23	Are tolerance limits for potency of antimicrobials established (criteria for "out of control")?	Yes	
		Partial	
		No	
Q24	Does your laboratory procedure manual address unusual or inconsistent antimicrobial testing results?	Yes	
		Partial	
		No	
Q25	Does your lab participate in any Antimicrobial Susceptibility Testing related internal quality assurance program?	Yes	
		Partial	
		No	
Q26	Does your lab participate in any Antimicrobial Susceptibility Testing related external quality assurance program?	Yes	
		Partial	
		No	
Q27	Are out of control results reported to supervisory personnel?	Yes	
		Partial	
		No	

READINESS FOR AMR SURVEILLANCE			
Q28	Does your lab participate in antimicrobial resistance surveillance?	Yes	
		Partial	
		No	
Q29	Does your lab generate on routine basis antibiogram for purpose of monitoring the resistant and sensitivity patterns in your institution?	Yes	
		Partial	
		No	
Q30	Does your lab conduct all Antimicrobial Susceptibility Testing or forwards it to other labs?	Yes	
		Partial	
		No	
Q31	Does your lab receive samples for Antimicrobial Susceptibility Testing from other labs?	Yes	
		Partial	
		No	
Q32	Is Antimicrobial Susceptibility Testing cumulative data collected manually?	Yes	
		Partial	
		No	
Q33	Is Antimicrobial Susceptibility Testing cumulative data collected automatically using lab information system (LIS)?	Yes	
		Partial	
		No	
DETECTION OF SPECIFIC ORGANISMS			
Q34	Does your laboratory have the capacity of identifying resistance genotypes or resistant bacterial clones?	Yes	
		Partial	
		No	
EQUIPMENT MAINTENANCE			
Q35	Are Antimicrobial Susceptibility Testing equipment maintained appropriately and calibrated?	Yes	
		Partial	
		No	
Q36	Does your lab monitor incubator temperatures on a daily basis?	Yes	
		Partial	
		No	
CONTINUING MEDICAL EDUCATION			
Q37	**How often do you receive training in Bacteriology?**	Yes	
		Partial	
		No	
Q38	How often are you trained in conducting Antimicrobial Susceptibility Testing?		

STAFFING			
Q39	How many laboratory technologists are in the station?		
Q40	How many microbiologists are in the station?		
Q41	Does your laboratory have staff with Bachelor's degree qualification or higher?	Yes	
		Partial	
		No	
Q42	Do you engage a Consultant clinical microbiologist(s)?	Yes	
		Partial	
		No	
CONSUMABLES			
Q43	How often do you experience unavailability of consumables in Microbiology section? Eg Lack of biochemical reagents and media	Yes	
		Partial	
		No	
Q44	Does your lab experience delays in Antimicrobial Susceptibility Testing due to lack of reagents?	Yes	
		Partial	
		No	
Q45	Do frequent stock outs lead to low demand of cultures by clinicians?	Yes	
		Partial	
		No	
BIOSAFETY			
Q46	Does your lab autoclave/incinerate cultures prior to discard?	Yes	
		Partial	
		No	
Q47	Do you have handwashing facility in the laboratory?	Yes	
		Partial	
		No	
Q48	Does your lab get continuous supply of running water?	Yes	
		Partial	
		No	
Q49	Does your lab have soap supply in the handwash facility?	Yes	
		Partial	
		No	

	Core element 1: Senior hospital management leadership towards antimicrobial stewardship	Yes	No
1	Has your hospital management formally identified antimicrobial stewardship as a priority objective for the institution and included it in its key performance indicators?		
2	Is there dedicated, sustainable and sufficient budgeted financial support for antimicrobial stewardship activities (e.g., support for salary, training, or IT (information technology) support)?		
3	Does your hospital follow any (national or international) staffing standards for antimicrobial stewardship activities (e.g. number of full-time equivalent (FTE) per 100 beds for the different members of the antimicrobial stewardship team)?		
	Core element 2: Accountability and responsibilities		
4	Does your hospital have a formal/written antimicrobial stewardship programme/strategy accountable for ensuring appropriate antimicrobial use?		
5	Does your hospital have a formal organizational multidisciplinary structure responsible for antimicrobial stewardship (e.g., a committee focused on appropriate antimicrobial use, pharmacy committee, patient safety committee or other relevant structure)?		
6	Is there a healthcare professional identified as a leader for antimicrobial stewardship activities at your hospital and responsible for implementing the programme?		
7	Is there a document clearly defining roles, procedures of collaboration and responsibilities of the antimicrobial stewardship team members?		
8	Are clinicians, other than those part of the antimicrobial stewardship team (e.g. from the ICU, Internal Medicine and Surgery) involved in the antimicrobial stewardship committee?		
9	Does the antimicrobial stewardship committee produce regularly (indicate minimum time) a dedicated report which includes e.g. antimicrobial use data and/or prescription improvement initiatives, with time-committed short term and long term measurable goals/ targets for optimizing antimicrobial use?		
10	Is there a document clearly defining the procedures of collaboration of the antimicrobial stewardship team/committee with the infection prevention and control team/committee?		
	Core element 3: Available expertise on infection management		
11	Do you have access to laboratory/imaging services and to timely results to be able to support the diagnosis of the most common infections at your hospital?		
12	In your hospital are there, or do you have access to, trained and experienced healthcare professionals (medical doctor, pharmacist, nurse …) in infection management (diagnosis, prevention and treatment) and stewardship willing to constitute an antimicrobial stewardship team?		
	Core element 4: Education and practical training		
13	Does your hospital offer a range of educational resources to support staff training on how to optimize antimicrobial prescribing?		
14	Do the antimicrobial stewardship team members receive regular training in antimicrobial prescribing and stewardship?		
	Core element 5: Other actions aiming at responsible antimicrobial use		

15	Is a multidisciplinary antimicrobial stewardship team available at your hospital (e.g., greater than one trained staff member supporting clinical decisions to ensure appropriate antimicrobial use)?		
16	Does your hospital support the antimicrobial stewardship activities/ strategy with adequate information technology services?		
17	Does your hospital have an antimicrobial formulary (i.e. a list of antimicrobials that have been approved for use in a hospital, specifying whether the drugs are unrestricted, restricted (approval of an antimicrobial stewardship team member is required) or permitted for specific conditions)?		
18	Does your hospital have available and up-to-date recommendations for infection management (diagnosis, prevention and treatment), based on international/national evidence-based guidelines and local susceptibility (when possible), to assist with antimicrobial selection (indication, agent, dose, route, duration) for common clinical conditions?		
19	Does your hospital have a written policy that requires prescribers to document an antimicrobial plan (includes indication, name, dosage, duration, route and interval of administration) in the medical record or during order entry for all antimicrobial prescriptions?		
20	Does the antimicrobial stewardship team review/audit courses of therapy for specified antimicrobial agents or clinical conditions at your hospital?		
21	Is advice from antimicrobial stewardship team members easily available to prescribers?		
22	Is advice from antimicrobial stewardship team members easily available to prescribers?		
	Core element 6: Monitoring and surveillance (on a continuous basis)		
23	Does your hospital monitor the quality of antimicrobial use at the unit and/or hospital wide level?		
24	Does your stewardship programme monitor compliance with one or more of the specific interventions put in place by the stewardship team (e.g. indication captured in the medical record for all antimicrobial prescriptions)?		
25	Does your hospital monitor antibiotic susceptibility rates for a range of key bacteria?		
26	Does your hospital monitor the quantity of antimicrobials prescribed/ dispensed/purchased at the unit and/or hospital wide level?		
	Core element 7: Reporting and feedback (on a continuous basis)		
27	Does your stewardship programme share hospital-specific reports on the quantity of antimicrobials prescribed/dispensed/purchased with prescribers?		
28	Does your stewardship programme share facility-specific reports on antibiotic susceptibility rates with prescribers?		
29	Are results of audits/reviews of the quality/appropriateness of antimicrobial use communicated directly with prescribers?		

BMJ Open

Combating Antibiotic Resistance using Guidelines and Enhanced Stewardship in Kenya: A protocol for an Implementation Science Approach

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030823.R3
Article Type:	Protocol
Date Submitted by the Author:	17-Dec-2019
Complete List of Authors:	Gitaka, Jesse; Mount Kenya University, Research and Innovation Kamita, Moses; Mount Kenya University, Research and Innovation Mureithi, Dominic; Maasai Mara University, Department of Animal Health and Production Ndegwa, Davies; Kenya Medical Training College Masika, Moses; University of Nairobi College of Health Sciences, Department of Medical Microbiology, Omuse, Geoffrey; Aga Khan University - Kenya Ngari, Moses; KEMRI/Wellcome Trust, Clinical Trial Facility Makokha, Francis; Mount Kenya University, Research and Innovation Mwaura, Peter; Mount Kenya University, Research and Innovation Mathai, Ronald; Mount Kenya University, Research and Innovation Muregi, Francis; Mount Kenya University, Research and Innovation Mwau, Matilu; Kenya Medical Research Institute
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Evidence based practice, Medical management
Keywords:	Antimicrobial stewardship, Antimicrobial resistance, Implementation science

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Combating Antibiotic Resistance using Guidelines and Enhanced Stewardship in Kenya: a protocol for an Implementation Science Approach

Jesse Gitaka[1], Moses Kamita[1], Dominic Mureithi[2], Davies Ndegwa[3], Moses Masika[4], Geoffrey Omuse[5], Moses Ngari[6], Francis Makokha[1], Peter Mwaura[1], Ronald Mathai[1], Francis Muregi[1], Matilu Mwau[7]

Affiliations

1. Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya
2. Department of Animal Health and Production, Maasai Mara University, P.O. Box 861-20500, Narok, Kenya.
3. Department of Medical Laboratory Sciences, Kenya Medical Training College P.O. Box 30195-00100, Nairobi, Kenya
4. Department of Medical Microbiology, College of Health Sciences, University of Nairobi, P.O. Box 30197-00100, Nairobi, Kenya.
5. Department of Pathology, Aga Khan University Hospital, P.O. Box 30270-00100, Nairobi, Kenya
6. KEMRI/Wellcome Trust Research Programme, Centre for Geographic Medicine Research - Coast, P.O. Box 230-80108, Kilifi, Kenya
7. Centre for Infectious and Parasitic Diseases Control Research, Kenya Medical Research Institute, P.O. Box 3-50400, Busia, Kenya

Correspondence: Jesse Gitaka
jgitaka@mku.ac.ke
Directorate of Research and Innovation, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya

Abstract

Introduction

Antibiotic resistance (AMR) is a growing problem globally especially in Sub-Saharan Africa including Kenya. Without any intervention, lower- and middle-income countries (LMIC) will be most affected due to already higher AMR levels compared to higher income countries and due to the far higher burden of diseases in the LMICs. Studies have consistently shown that inappropriate use of antimicrobials is the major driver of AMR. To address this challenge, hospital are now implementing antibiotic stewardship programs (ASPs), which have been shown to achieve reduced antibiotic usage, to decrease the prevalence of resistance and lead to significant economic benefits. However, the implementation of the guideline is highly dependent on the settings in which they are rolled out. This study, employing an implementation science approach, aims to address the knowledge gap in this area and provide critical data as well as practical experiences when using antibiotic guidelines and stewardship programs in the public health sector. This will provide evidence of ASP performance and potentially contribute to the county, national and regional policies on antibiotics use.

Methods and analysis

The study will be conducted in three geographically diverse regions, each represented by two hospitals. A baseline study on antibiotic usage, resistance and de-escalation, duration of hospital stay, rates of readmission and costs will be carried out in the pre-implementation phase. The intervention, that is, the use of antibiotic guidelines and antibiotic stewardship programs will be instituted for 18 months using a stepwise implementation strategy that will facilitate learning and continuous improvement of stewardship activities and updating of guidelines to reflect the evolving antibiotic needs.

Ethics and dissemination

Approvals to carry out the study have been obtained from the National Commission for Science, Technology and Innovation and the Mount Kenya University Ethics Review Committee. The approvals from the two institutions were used to obtain permission to conduct the study at each of the participating hospitals. Study findings will be presented to policy stakeholders and published in peer-reviewed scientific journals. It is anticipated the findings will inform local-based appropriate antibiotic use guidelines.

Key Words

Antimicrobial stewardship; Implementation science; Antimicrobial resistance

Strengths and limitations of this study

- First study aimed at concurrently rolling out antimicrobial stewardship committees in multiple hospitals in Kenya.
- Use of implementation approach to support implementation of suggested guidelines for antimicrobial resistance surveillance.
- Firsthand evidence on the antimicrobial resistance in three diverse counties in Kenya.
- The study is limited to only three of the 47 counties in Kenya.

Introduction

Antibiotic resistance is a serious public health concern globally[1,2] and locally[3,4] and fears of running out of antibiotic options in the near future have been expressed. In 2016, the World Health Organization (WHO) called for immediate and concerted efforts to mitigate this threat to global health, which was estimated to contribute to 700,000 deaths in 2014 and projected to cause 10 million deaths in 2050, if inadequately mitigated.[5] The driving force escalating rates of resistance is the injudicious use of antibiotics in patients, in livestock and in agriculture, and its unchecked release into the environment.[6] These forces raise and increase the spread of resistant pathogens that may emerge by mutations or acquisition of plasmids carrying resistance genes.[7] In one study, prior antibiotic exposure was the key independent risk factor for the acquisition of antibiotic multi-resistance.[8] Broad-spectrum antibiotics have the unintended consequence of selecting multidrug-resistant pathogens and increasing the likelihood of infection by fungi and *Clostridium difficile.*[9]

The injudicious use of antibiotics is widespread. In Africa, many patients do not receive treatment from the conventional health care system. Of those who receive antibiotics, 31.7 % do not consult a doctor for a prescription and a further 26.4% obtain the antibiotics over the counter.[10] A study in South Africa found that 54.9% of antibiotics were inappropriately prescribed in intensive care unit settings while in the US, 20-50% of prescribed antibiotics were unnecessary or unwarranted.[11–13]

The rate of antimicrobial resistance in developing countries like Kenya is worrying and rising.[14] For example, the prevalence of *Salmonella typhi* resistant to two or more antimicrobials was found to have increased from 50% in 1998 to 78% in 2004 at Kenyatta National Hospital.[15] The Global Antibiotic Resistance Partnership – Kenya Working Group Report of 2011 identified antibiotic resistance as a key issue in Kenya and made recommendations to curtail the spread.[16] These recommendations included the use of antibiotic guidelines that took into consideration local resistance surveillance data and enhanced antibiotic stewardship programs (ASPs).[16] However, these ASPs have not been instituted at county hospitals, and key implementation data and experiences are lacking in their roll out.

Antibiotic stewardship is defined as '*the optimum selection, dosage, and duration of antimicrobial treatment that yields the best clinical outcomes for the treatment or prevention of infection with the least toxicity to the patient and minimal impact on subsequent resistance'*.[17] It has the potential to lower treatment cost and realize economic benefits to the patient, health care system and the country at large.[18,19] Moreover, optimizing antibiotic use by minimizing exposure, fine-tuning dosage and reducing superfluous therapy and focusing treatment to the likely culprit pathogens is a strategy that boosts patient safety[20] and ultimately safeguards against antibiotic resistance.[21]

Justification

Antibiotic resistance is a major health challenge globally. Studies in Kenya have shown rising antibiotic resistance over the last 3 decades. Whilst antibiotic guidelines and antibiotic stewardship programs have been observed to lead to significant economic benefits, reduce antibiotic usage and lower the prevalence of resistance especially in Europe, North America, Japan, and South Africa, they have not been employed to tackle the challenge in the public health sector in Kenya. The GARP report of 2011, recognized the use of guidelines and stewardship programs as a potential strategy in 'saving antibiotics' but noted the need for local studies to understand implementation challenges, derive lessons and embed the strategy within

the Kenyan health care system. The here proposed study, employing an implementation science approach, aims to address the knowledge and research gap in this area and provide critical data and experiences in using antibiotic guidelines and stewardship programs in the public health sector.

Objectives of the Study

General Objectives

The overall aim is to evaluate the impact of antibiotic guidelines (antibiotic stewardship program) for empirical treatment of (i) urinary tract infections, (ii) community-acquired pneumonia, (iii) bacteremia and (iv) meningitis in terms of reducing usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays, rates of readmission and prevalence of antibiotic resistance in six county hospitals in Kenya.

Specific Objectives

1. To develop guidelines for antibiotic use for common infections.
2. To set up antibiotic steward committees (ASCs) in six county hospitals.
3. To train the ASC members such that they can fully perform their mandate.
4. To measure the usage of broad-spectrum antibiotics, antibiotic de-escalation, duration of hospital stays and rates of readmission in hospitals using the antibiotic stewardship strategy.
5. To ascertain antibiotic resistance patterns using culture, sensitivity, and genetic markers.
6. To establish the knowledge of health care workers, their attitudes and prescription practices regarding antibiotics resistance, use of guidelines and ASPs.
7. To evaluate the economic benefits of using guidelines for antibiotics use and ASPs.

Expected Outputs of the research

1. Antibiotic guidelines informed by local bacteria susceptibility patterns.
2. Antibiotic Stewardship Committees (ASCs) in six county hospitals in Kenya.
3. Trained ASC members.
4. Data on antibiotics usage, antibiotic de-escalation, duration of hospital stay and rates of readmission in hospitals using the antibiotic stewardship strategy.
5. Map and data of antibiotic resistance patterns before and after implementation of the strategy.
6. Qualitative data on the knowledge of health care workers, their attitudes, and practices regarding antibiotic usage and stewardship programs.
7. Publication on cost-benefit analysis for using antibiotic guidelines and ASPs.

Methods and analysis

Setting

To be able to evaluate the antibiotic stewardship strategy across Kenya using an implementation science approach, the study will be conducted in six county hospitals, namely (1) Kiambu County Referral Hospital, (2) Bungoma County Hospital, (3) Webuye Sub-County Hospital, (4) Nakuru County Teaching and Referral Hospital, (5) Thika Level 5 Hospital and (6) Naivasha Sub-County Hospital).

Design

The study will utilize the **R**each, **E**ffectiveness, **A**doption, **I**mplementation and **M**aintenance (RE-AIM) conceptual framework. RE-AIM involves the interaction of all the five factors and fits well with approaches that are system based[22]. The study design will encompass a pre-implementation phase, a stepwise implementation phase, and an endline study to measure the changes in outcomes between the phases. A baseline study on antibiotic usage (Defined Daily Doses per 1,000), antibiotic resistance (culture and genetic markers), antibiotic de-escalation, duration of hospital stays, rates of readmission, prescription patterns, and cost analysis will be carried out in the pre-implementation phase. The intervention, which is the use of antibiotic guidelines and antibiotic stewardship programs, will be instituted in the six county hospitals for 18 months. The stepwise implementation phase will involve introduction of interventions as well as monitoring and evaluation of their effectiveness, and thereafter improving the interventions where necessary. The strategy will facilitate learning cycles every 4-6 weeks and continuous improvement of stewardship activities and updating of guidelines to reflect evolving antibiotic needs in diverse settings. During the intervention phase, challenges faced during the implementation of the guidelines will be documented and used to advise on the changes required during the review of the guidelines. The end line study will be conducted and differences between the two phases evaluated as per statistical analysis laid out below.

In the baseline and endline studies, multidisciplinary strategies will be employed as follows

i. Knowledge of health care workers, attitudes, and practices on antibiotic resistance, guidelines, and ASP will be studied qualitatively and quantitatively.
ii. Basic science approaches, encompassing antibiotics culture sensitivity and molecular biology-genetic markers of resistance, will be analyzed as detailed below.
iii. Clinical patient outcomes will be studied to evaluate the guidelines.
iv. Health economics cost savings on using guidelines and ASP will be evaluated as below.

Antibiotic guidelines and ASPs: Development

Antibiotic guidelines will be formulated in consultation with senior clinicians in the study hospitals taking into account each hospital's antimicrobial resistance patterns. The ASP committee will comprise of a hospital physician, a microbiologist, and a pharmacist. Broad spectrum antibiotic prescriptions will be brought to the attention of the ASP committee members. The committee members will perform regular ward rounds, three times a week, in the initial stages. This will be reduced to once a week later in the project, to optimize adherence to antibiotic guidelines. Furthermore, the guidelines will be promoted through training sessions, provision of pocket-size guideline cards to clinicians and pharmacists, large poster displays in the wards and through hospital and project websites and social media (?).

Data collection

Laboratory assessment tools will be used to determine the preparedness of the laboratories to perform antibiotic sensitivity tests (see Additional file 1). The tool will assess whether the laboratories have the equipment necessary to perform bacterial culture, identification, and susceptibility testing, such as carbon dioxide incubators, safety cabinets, and refrigerators. The tool will also determine whether the laboratories have the internationally recommended guidelines to perform susceptibility and quality assurance tests. In addition, knowledge, attitude and practices (KAP) about antibiotic prescription and resistance among medical practitioners will be assessed using a KAP tool (See Additional file 2). The tool will target

those medical practitioners, who usually prescribe antimicrobial drugs in the hospitals and will include the consultants, medical officers as well as interns, clinical officers and pharmacists. The KAP tool will also determine the guidelines that the prescribers use to decide on the appropriate antimicrobial drug. A health system assessment tool will be employed to gather baseline information on the antimicrobial stewardship activities in each hospital (see Additional file 3). Information on bed occupancy, antibiotic usage, and antibiotic resistance data will be collected from each of the hospital information systems, pharmacy management systems and laboratory reporting systems, respectively. Antibiotic usage will be analyzed in order to determine the impact of the intervention on antibiotic usage comparing the intervention and the control arms. Data on antibiotics issued to adult and children inpatients only will be factored, excluding discharge and outpatient supplies.

To consistently compare antibiotic usage, the defined daily doses (DDD) will be used and expressed per 1,000 occupied bed days (OBDs) to account for fluctuations in activity following WHO guidelines.[23] The OBDs will be obtained from the hospital information systems.

Culture sensitivity and genetic analyses

Nasal swabs or tracheal aspirate, urine, wound swabs and blood samples will be taken from patients who have consented to the study for bacteriological analysis. Samples will be subjected to standard bacteriological analysis to isolate the culprit bacteria. Bacterial species will be confirmed by use of biochemical test and analytical profiles index API strips (bioMérieux France). Antimicrobial susceptibility tests will be performed on isolated bacteria as per the Kirby-Bauer Method following manufacturer's instruction. Results will be interpreted using the Clinical and Laboratory Standards Institute (CLSI) tables.[24]

Any bacteria isolate found to be resistant to third generation cephalosporins will be tested for production of extended spectrum beta-lactamase (ESBLs) using the synergy disk diffusion test. Vancomycin Resistant *Enterococci* (VRE) will be identified using disc diffusion tests. Methicillin resistant *S. aureus* (MRSA) will be detected by testing isolates resistant to cefoxitin using the E test (AB Biodisk, Solna, Sweden) on Mueller–Hinton agar supplemented with 2% NaCl and incubated at 37 ˚C for 24 h. The identified ESBLs, VRE and MRSA samples will be analyzed by PCR and sequencing to identify the resistance genotype. *In vitro* conjugation tests will be performed to determine if resistance in bacteria is transferable.

Cost-benefit analysis for the use of antibiotic guidelines and Antibiotic Stewardship Program

A cost-benefit analysis (CBA) from a health facility and a national perspective will be performed. For health facilities, three cost drivers will be considered: (a) pharmacy spending, (b) length of stay, and (c) antimicrobial stewardship interventions (training, infection control measures, etc.). At country level, we will consider Disability-Adjusted Life years (DALYS), work-days lost, and cost of treatment.[25–27] This will be done by collecting and analyzing data on patient income, length of hospital stay, death or disability occasioned by drug-resistant pathogens, hospital pharmacy expenditure and cost of training/rolling out antimicrobial stewardship guidelines. This data will be collected before and after antimicrobial stewardship interventions.

Study size

Prevalence of inappropriate use of broad-spectrum antibiotics

The sample size is based on the prevalence of inappropriate use of broad-spectrum antibiotics, documented as being about 50% in South Africa.[11] To detect a reduction of the 50% inappropriate use of broad-spectrum antibiotics by 20% to 30% with a power of 90% and α of 0.05 in a two-sided test, a sample size of 410 in each county hospital would be adequate. In order to detect a reduction (20%) but with a power 80%, the sample size would be 320 as shown in Figure 1. With a 15% allowance for loss to follow up, a total of about 500 participants would be sufficient in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of inappropriate use of broad-spectrum antibiotics in 500 x 6= 3,000 patients from the six facilities.

Prevalence of antibiotic resistance

The sample size is based on the prevalence of antibiotic resistance of 78%[15] in 2004 at Kenyatta National Hospital, Kenya. To detect a reduction of the 78% antibiotic resistance by 10% to 68% with a power of 90% and α of 0.05 two-sided test, a sample size of 500 in each county hospital would be adequate; while to achieve a reduction of 10% with power 80%, the sample size would need to be 220 (Figure 2). With 15% allowance for loss to follow up, a total of 600 participants would be sufficient in each of the selected county hospitals. Therefore, we shall evaluate the prevalence of resistance in 600 x 6 = 3,600 patients for the six facilities.

Data Management

Data will be recorded on a standardized Case Report Form (CRF) at every hospital by the trained study staff. The data will be held locally and uploaded to the secure central study server hosted at the Mount Kenya University main campus in Thika. This will be overseen by the Data Manager/statistician, who will run regular reconciliation to derive the final study database. Access to the study database will be restricted and password protected. The data will be stored in excel, jpeg and word files for the electronic cases. For archiving purposes, the Mount Kenya University electronic repository will be used to ensure the data is publicly available. Collected data will be retained accord to the policy governing the Mount Kenya University repository. The principal investigators involved in this study do not have any reasons that might prohibit the sharing of the data emanating from the study.

Statistical analysis

The data will be analyzed using qualitative and quantitative methods. Qualitative data will be analyzed by subjecting the information to content analysis and presenting it in different emerging themes. The summaries of the data emanating from these themes will then be arranged on a case by case basis through the use of an Excel spreadsheet[28] and the analyses performed using NVIVO software. Quantitative data analyses will be carried out using Stata version 14 (Stata, Inc.). The differences between baseline and endline on all the study outcomes will be compared using appropriate statistical methods, such as the McNemar's test, paired t-test and the Wilcoxon signed-rank test non-parametric test, accounting for pairing and clusters (hospitals). Multivariable log-binomial regression analysis will be used to elucidate risk factors for antibiotic resistance.

Ethics and Dissemination

Approvals to carry out the study have been obtained from the National Commission for Science, Technology and Innovation (NACOSTI) (NACOSTI/P/18/33304/25986) and the Mount Kenya University Ethics Review Committee (MKU/ERC/0764). In addition,

permission was obtained from each of the participating hospitals. This entailed submission of an introduction letter attaching the certificate of clearance from NACOSTI and the ethical review certificate from MKU. In Thika, Nakuru and Naivasha a research fee was paid as required by the hospital board. The study will follow all provisions of the Declaration of Helsinki. Participants in the study will not incur any cost associated with the transport or processing of the samples; neither will they receive any monetary inducements to participate in the study. Material transfer to laboratories outside of Kenya shall not be undertaken in this study. Informed written consent will be sought from the participants enrolled in the study.

Obtained results will be disseminated via different streams, including research conferences and in peer-reviewed journals. We are aiming for five publications to be generated by the end of the study. These will include the study protocol itself and the different aspects emerging during in the course of the project. Contextualized guidelines on judicious use of antibiotics in the six hospitals in Kenya will also be published in the Ministry of Health's website and that of the collaborating hospitals for easy access by other health facility in and outside Kenya. In addition, the findings will be shared in a dissemination forum bring together members of the health management teams at both the country and county levels, clinicians who do prescription of antimicrobial drugs, researchers, members of the public, and other key stakeholders. The dissemination forum will be held once at the end of the study.

Patient and Public Involvement

The study is mainly targeting clinicians who do antimicrobial proscription and, therefore, patients will not be directly involved in the study. Reports obtained from this study will, however, be made available to the patients in the participating hospitals through a dissemination forum and to the general public through publications.

Exit strategy and stakeholder involvement

In the process of developing this protocol, we have engaged physicians working in the proposed county hospitals, and they have identified the challenge of antibiotic resistance as real and appreciate the opportunities that use of antibiotic guidelines and ASPs may provide in combating resistance, improving clinical care and saving costs. We plan to continue involving all the stakeholders in the process, including clinicians, laboratory personnel, pharmacists, public health officials, patients and scientists. We anticipate that the study findings will inform county and national policy on mitigating antibiotic resistance and raise public awareness on the need for judicious use of antibiotics. The project will use social media platforms, websites of the collaborating institutions, and publications in peer-reviewed journals, local dailies and presentations in scientific meetings to further engage stakeholders and the public on this important issue and enhance the learning approach inherent in the strategy of implementation science for improved performance of the ASPs and the study in general. In case any of the hospitals drop out either during the baseline phase or early stages of the implementation phase, another hospital will be brought onboard. Replacements will not be considered during the late stages of the project.

Discussion

The emergence of antimicrobial-resistant pathogens and a lack of new drugs to effectively treat these pathogens are the two main challenges in human health. There is thus the need to advocate the proper use of the currently available antimicrobial agents by safeguarding their effectiveness. Antibiotic stewardship has been shown to contribute to reducing antibiotic

resistance,[29,30] but this strategy has not been rolled out in most sub-Saharan countries in level 4 and 5 hospitals. The proposed work will employ an implementation research approach to evaluate the best strategies and derive lessons on mainstreaming antibiotic stewardship in these facilities. By leveraging on a health system approach, the implementation research will unravel real life impediments and opportunities by working with hospital teams to co-design execution plans, monitor and evaluate and the sustainability of the stewardship programs.

Most hospitals in Kenya lack the capacity to carry out antimicrobial sensitivity tests, due to the lack of resources and technical knowhow, among other challenges.[31] This study will first provide an assessment to determine the challenges hospitals are facing; this will be done through interviews with clinicians and assessment of the capacity of the laboratories to perform the sensitivity tests. These steps will make up the initial phase and will guide the nature of implementations to be used during the implementation phase. It is hoped that the project will capacitate the laboratories in the six hospitals to do the tests and sensitize the clinicians on the need to prescribe antimicrobial drugs based on results obtained from the laboratory tests. After the implementation phase, the endline phase will involve surveys similar to those conducted during the baseline phase. This will allow determination of the impact of the implementation strategies taken in reducing the cost of treatment, length of hospital stay and burden on the health system, among others.

The hospital management teams play a key role in determining the allocation of resources to and within the hospitals.[32] In this project, we have proposed to involve hospital management by including its members in the stewardship committees that will be established. This will ensure that the management is well informed about the challenges in the sections involved in surveillance and the progress that is being made. Involvement of the hospital management will also ensure that there is a buy-in of the recommendations made by the stewardship committee.

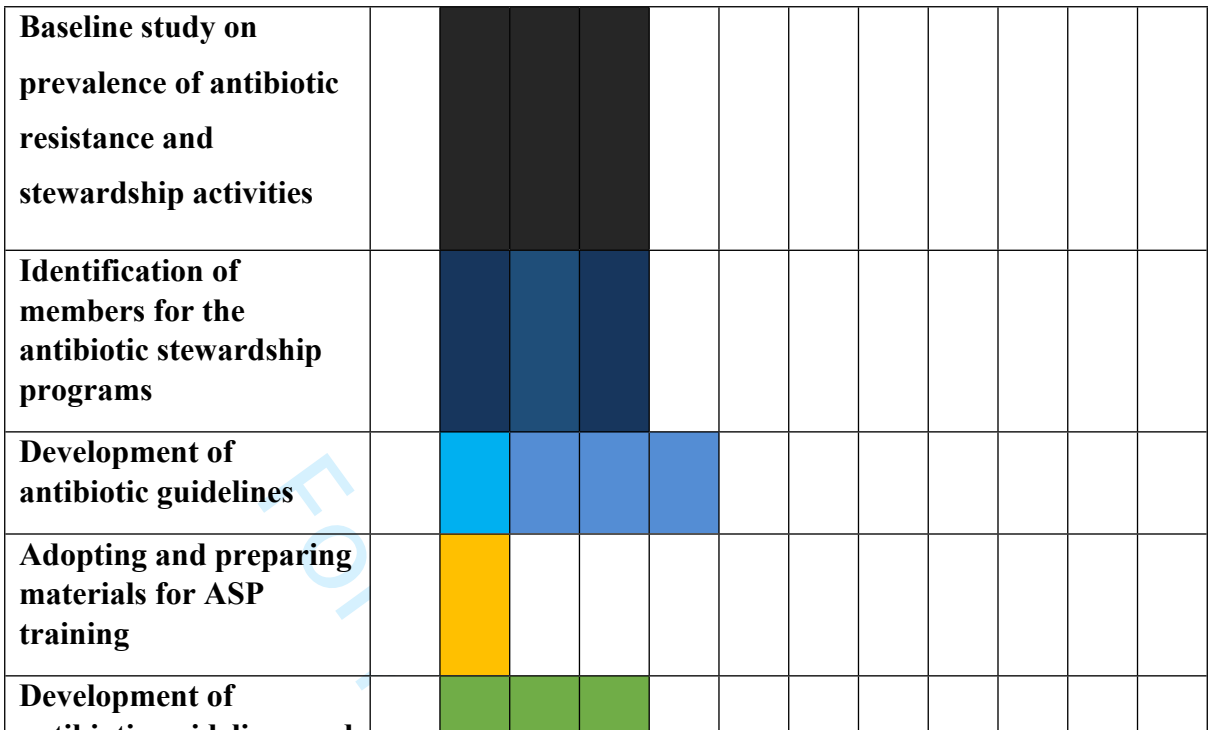
Although there is the need to establish antimicrobial stewardship committees in all the hospitals, the project proposes to start with the selected six hospitals with the hope that the same can be reproduced by other hospitals to establish similar committees in their hospitals.

Study timeline

The study is designed for a three-year period. Enrolment already started in 2018 and participant recruitment will continue up to 2020 (Table 1). So far, stewardship committees have been established and workshops to sensitize the members conducted. Data collection on knowledge, attitude and practice of antibiotic prescribers in the hospitals is already in progress.

Table 1: Proposed study timelines.

	2019				2020				2021			
Activity	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Ethics clearance and authorization from study sites												



Patient and Public Involvement

No patient involved.

Availability of data and material

All data sets will be available to the public upon request.

Acknowledgment

Authors acknowledge Professor Nicole Pamme, University of Hull, for proofreading the manuscript.

Additional files

Additional file 1: Laboratory preparedness assessment tool

Additional file 2: Laboratory knowledge, attitude and practice (KAP) tool

Additional file 3: Health system tool

Figure Legends

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

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Authors' Contributions

JG initiated the concepts of the study. JG, DM, DN, MMasika, GO, MN, FMakokha, PM, RM, FMuregi, and MMwau developed the protocol. JG, DM, DN, and MMasika will be involved in training the ASCs. DM, GO, MN, FMakokha, PM, RM, DN, and MK will help in data collection. MN and MK will be involved in data analysis. MK wrote the first draft of the manuscript. All authors reviewed and approved the protocol.

Funding Statement

This work was supported by The Kenya National Research Fund (grant number NRF/MKU/2017/007 to JG). The funders had no role in study design, decision to publish, or preparation of the manuscript.

Competing Interests

The authors declare no conflict of interest.

Word count: 3526 words

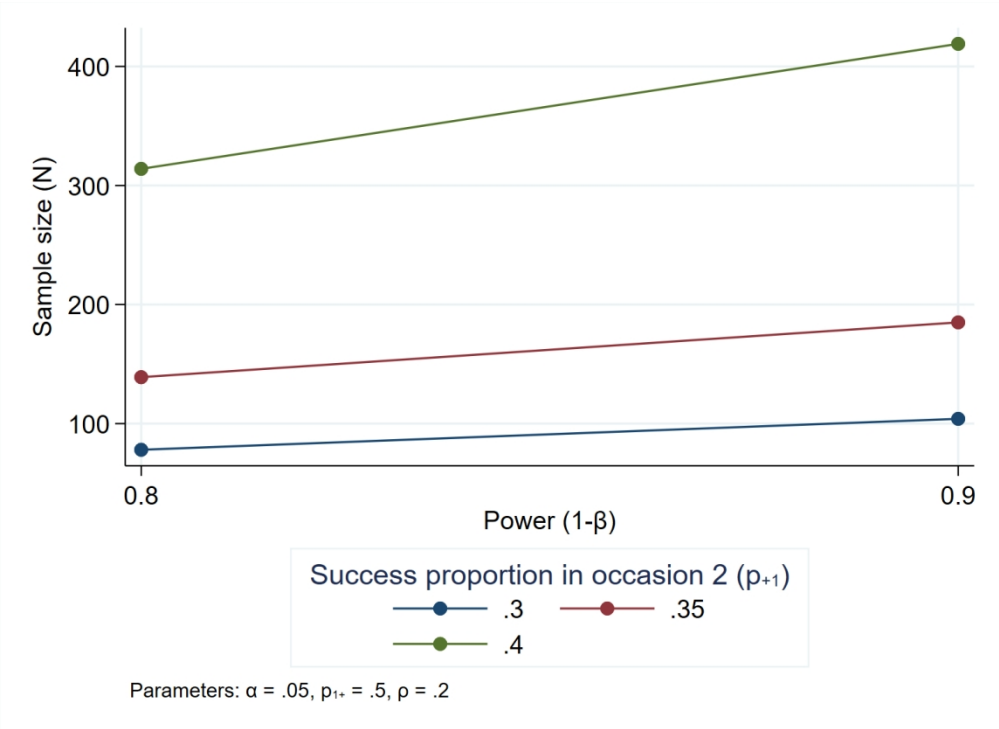

Figure 1: Statistical power analysis for sample size determination for the prevalence of inappropriate use of broad-spectrum antibiotics

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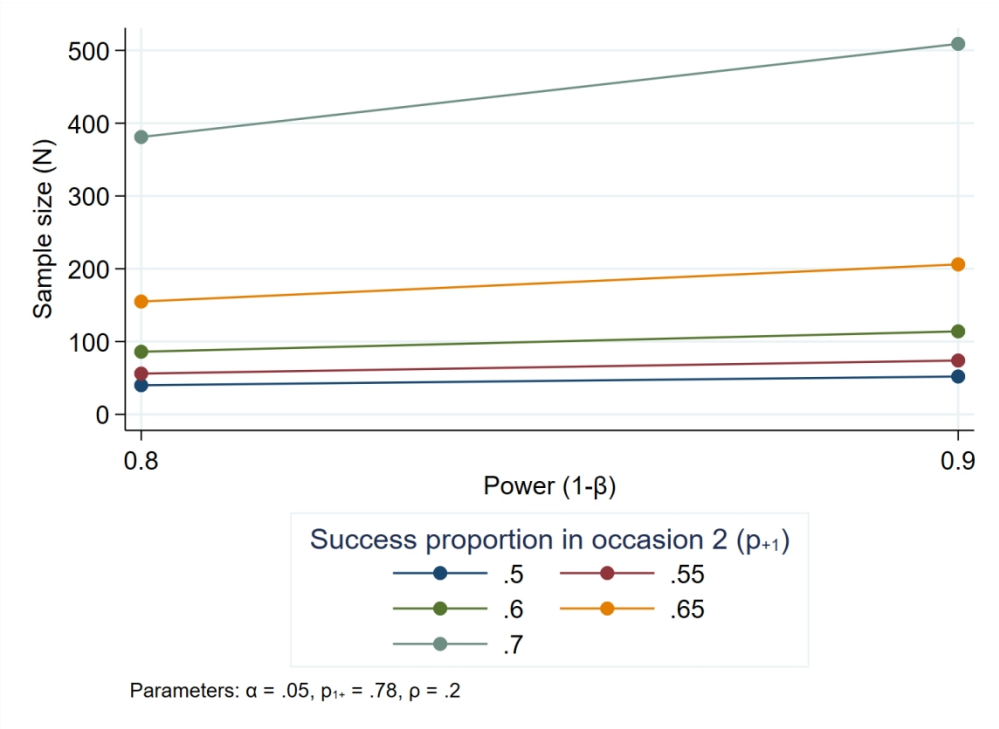

Figure 2: Statistical power analysis for sample size determination for the prevalence of antibiotics resistance

557x405mm (72 x 72 DPI)

A survey on Knowledge, Attitudes and Practice about antibiotic prescribing and resistance among medical practitioners in Kenyan local hospitals.

Thank you very much for accepting to participate in this study.

***You are kindly requested to answer the questionnaire honestly and completely independent of cross-consultations and/or verifications.**

Survey quality control

Date of interview: ..... Start time..... End time.....

Interviewed by: .....Approved.....

Name of the Hospital..... Respondent's code.....

QUESTIONS	ANSWERS
PART 1: GENERAL QUESTIONS	
1. *For how many years, since you graduated from medical school /medical training College, have you been working in a hospital (indicate cumulative years if worked in different hospitals)*	❖ *I am on attachment* ❖ *I am a trainee in medicine (internship)* ❖ *Less than one year* ❖ *1-3 years* ❖ *4 – 6 years* ❖ *7 years and more*
2. *In which department do you work?*	○ *Medicine /Emergency* ○ *Surgery* ○ *Paediatrics* ○ *Obstetrics and Gynaecology* ○ *Outpatient/A/E* ○ *Pharmacy* ○ *Other: .....*
3. *Designation (e.g. Consultant, Pharmacist, Nurse, etc.)*	.....
PART 2: PRESCRIPTION PATTERN (PRACTICE)	
4. *How frequently do you prescribe antibiotics?*	❖ *More than once daily* ❖ *Once daily* ❖ *3 – 5 times a week* ❖ *1 – 2 times a week*

	❖ *less than once a week)*
5. To whom do you prescribe?	❖ *Patients at outpatient department* ❖ *Hospitalized patients* ❖ *Patients in out-patient department and hospitalised patients*
6. Do you follow any antibiotic prescription guidelines?	❖ *Yes* ❖ *No*
PART 3: AWARENESS AND ATTITUDE ON THE CURRENT SCOPE OF ANTIBIOTIC RESISTANCE	
7. Antibiotic resistance is a world-wide problem	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
8. Antibiotic resistance is a problem in my country	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
9. Antibiotic resistance is a problem in my hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
10. Antibiotics are overused in my hospital and in other hospitals of my country Kenya	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
11. Patients' demands for antibiotics contribute to the overuse of antibiotics in the hospital	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
12. I think over-the-counter (OTC) medicines contribute to antibiotic misuse and subsequent antibiotic resistance	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
13. My awareness on local antibiotic resistance pattern is?	❖ *Excellent* ❖ *Good* ❖ *Average* ❖ *Very little* ❖ *None*
PART 4: CHOICE OF ANTIBIOTIC	
14. How confident are you about your knowledge of antibiotics?	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
15. What is your confidence level in prescribing antibiotics	❖ *Very confident* ❖ *Confident* ❖ *A bit confident* ❖ *Neutral/ I have no idea* ❖ *Not confident at all*
16. How often do you check your decisions on antibiotic prescribing with a colleague?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
17. If you do consult a senior colleague, how frequent does he/she recommend prescription of a different antibiotic?	❖ *Never* ❖ *Sometimes* ❖ *Half of the times*

	❖ *Mostly* ❖ *Always*
18. How often do you depend on antibiotic sensitivity data from the laboratory to vary your prescription	❖ *Never* ❖ *Sometimes* ❖ *Half of the times* ❖ *Mostly* ❖ *Always*
PART 5: SOURCE OF INFORMATION ON ANTIBIOTICS PRESCRIBING AND RESISTANCE	
19. During the past years, how many courses or trainings did you receive relating to antibiotics?	❖ *0* ❖ *1-3* ❖ *4-6* ❖ *6-10* ❖ *>10*
20. Among the sources of information about antibiotics listed below, which one did you consult in the last month?	
▪ *Information supplied by pharmaceutical companies*	❖ *Yes* ❖ *No*
▪ *Knowledge from training institutions*	❖ *Yes* ❖ *No*
▪ *Internet*	❖ *Yes* ❖ *No*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Yes* ❖ *No*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Yes* ❖ *No*
21. ***How do you appreciate the sources of information about antibiotics listed below?***	
▪ *Information supplied by pharmaceutical companies*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*

▪ *Information from University courses*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Internet*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *National guideline for empiric antimicrobial therapy*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *The World Health Organization's (WHO) guidelines for treatment of bacterial diseases*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
▪ *Does your facility have a frequently released antibiogram?*	❖ *Yes* ❖ *No*
▪ *If yes, how useful is the antibiogram to you*	❖ *Very useful* ❖ *Useful* ❖ *Not at all useful* ❖ *I do not know*
PART 6: DECISION ABOUT ANTIBIOTIC PRESCRIBING	
22. When one prescribes an antibiotic, it is important to know the resistance pattern of the bacteria in the local setting	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
23. My choice of prescribing antibiotic is more influenced by the availability of antibiotics than by the cause of the infection	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral*

	❖ *I disagree* ❖ *I strongly disagree*
24. My choice of prescribing antibiotic is more influenced by the cost of the drug to the patient	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
25. I'm always concerned about effectiveness and quality of an antibiotic when making my prescribing decisions	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
26. In regard to antibiotic guidelines, local guidelines are more useful than international guidelines	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
27. Antibiotic guidelines and antibiotic committees are rather obstacles than a help	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
28. I welcome the implementation of a training program about antibiotics	❖ *I strongly agree* ❖ *I agree* ❖ *Neutral* ❖ *I disagree* ❖ *I strongly disagree*
PART 7: KNOWLEDGE ON USE OF ANTIBIOTICS	
29. A 4-year-old child had diarrhoea in the last 4 days (3 stools daily). She had no fever during the past days nor at consultation. What is your treatment choice?	❖ *Amoxicillin orally* ❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin/clavulanic acid orally*

	❖ *Oral rehydration salts with no antibiotic*
30. A 6-year-old child has fever (38°C), nasal discharge and a painful throat for two days. At visual inspection, the throat is reddish. What is your treatment choice?	❖ *Trimethoprim/sulphamethoxazole orally* ❖ *Amoxicillin orally* ❖ *Amoxicillin/clavulanic acid orally* ❖ *No antibiotic*
31. During ward round, you have seen two patients with impaired renal function. - *Patient A is a 68-year-old male with cellulitis in the lower limb. He is administered clindamycin.* - *Patient B is a 64-year-old woman with diabetes who received treatment for sepsis with ceftriaxone empirically.* *In which case will you need to adjust the antibiotic dose?*	❖ *Patient A* ❖ *Patient B* ❖ *Patient A & B* ❖ *Neither patient A nor patient B*
32. Which one of the following antibiotics may be safely given during the first trimester of pregnancy?	❖ *Amoxicillin* ❖ *Ciprofloxacin* ❖ *Gentamicin*
33. Which of the following antibiotics has the best activity against anaerobes?	❖ *Ciprofloxacin* ❖ *Metronidazole* ❖ *Trimethoprim/sulphamethoxazole*
34. Methicillin resistant - Staphylococcus aureus is susceptible to:	❖ *Amoxicillin clavulanic acid* ❖ *Cefotaxime* ❖ *Ceftriaxone* ❖ *None of these antibiotics*
35. Which of the following antibiotics most effectively crosses the blood-brain barrier?	❖ *Clindamycin* ❖ *Ceftriaxone* ❖ *Vancomycin*
36. Aminoglycoside antibiotics such as gentamicin are most active when they are administered as follows:	❖ *Orally, three times daily* ❖ *Parenterally, once daily* ❖ *Parenterally, three times daily*

Thank you very much for your kind and honest participation

Questionnaire to assess laboratory capacity for AMR testing.

Objective: To assess capacity for Study sites laboratories to perform antimicrobial susceptibility testing and contribute to AMR surveillance				
Laboratory infrastructure and equipment				**Additional Information**
Q1	Does your lab have capacity to carry out basic bacteriology (process stool, urine, urethral/ cervical swabs, and blood)? (Perform bacterial culture, identification, and susceptibility testing)?		Yes	
			Partial	
			No	
Q2	Does your lab have resources for basic aerobic bacterial culture?		Yes	
			Partial	
			No	
Q3	Does your lab possess CO_2 incubators and CO_2 tank?		Yes	
			Partial	
			No	
Q4	Does your lab perform susceptibility testing by disc diffusion?		Yes	
			Partial	
			No	
Q5	Please indicate the presence and status of the following in your lab	Present (Tick)	Functional (Tick)	
	❖ Petri dishes			
	❖ Swabs for surface application of cultures			
	❖ Standardized susceptibility testing discs			
	❖ control strains of known susceptibility patterns			
	❖ Incubators			
	❖ Refrigerator			
	❖ Autostart backup for refrigerator/incubator			
	❖ Media preparation room			
	❖ Autoclave			
	❖ Compound microscope			
	❖ Weighing scale			
	❖ Biosafety cabinet Class 2			
	❖ Candle jar			
	❖ pH meter			
	❖ water distiller			
Q6	Does your lab have automated system (Vitek) to conduct Antimicrobial Susceptibility Testing?		Yes	
			Partial	
			No	

USE OF STANDARDIZED METHODS			
			Additional Information
Q7	Does your laboratory use Clinical Laboratory Standards Institute (CLSI) guidelines?	Yes	
		Partial	
		No	
Q8	Does your laboratory use CLSI interpretation breakpoints?	Yes	
		Partial	
		No	
Q9	Does your laboratory select individual antibiotics following CLSI guidelines?	Yes	
		Partial	
		No	
Q10	Are single isolates or pure cultures only used for final performance of antimicrobial susceptibility testing?	Yes	
		Partial	
		No	
Q11	Is the inoculum size standardized using a turbidity standard (0.5 McFarland) or other acceptable method?	Yes	
		Partial	
		No	
Q12	Does your lab have provision of standard microorganisms (ATCC) for internal quality control (useful in determining the potency of drugs or checking the quality of media)?	Yes	
		Partial	
		No	
Q13	For disk susceptibility tests, are zone sizes of controls measured and recorded?	Yes	
		Partial	
		No	
Q14	Are zone sizes of tests measured and used for recording sensitivity resistance?	Yes	
		Partial	
		No	
Q15	Does your lab use commercially prepared dehydrated AST media?	Yes	
		Partial	
		No	
Q16	Does your lab perform Susceptibility Testing directly from specimen based on clinical information?	Yes	
		Partial	
		No	
Q17	If direct susceptibility testing from specimen show mixed cultures, does your lab repeat susceptibility testing with isolated organisms?	Yes	
		Partial	
		No	
USE OF STANDARDIZED OPERATING PROCEDURES (SOPs)			
Q18	For antimicrobial susceptibility testing systems, are there do cumented criteria in	Yes	

	your institutions' SOPs for interpretation of the endpoint or zone size?	Partial	
		No	
Q19	Are guidelines established for the number and type of antibiotics reported for organisms isolated from different sites of infection?	Yes	
		Partial	
		No	
Q20	Do you report Antimicrobial Susceptibility Testing results based on Hospital policy (in consultation with Pharmacy, Infection control and Infectious diseases physicians.	Yes	
		Partial	
		No	
QUALITY ASSURANCE			
Q21	Is each new lot of susceptibility disks checked for activity before use?	Yes	
		Partial	
		No	
Q22	Does your lab use QC (quality control) strains to assess new lot of susceptibility discs?	Yes	
		Partial	
		No	
Q23	Are tolerance limits for potency of antimicrobials established (criteria for "out of control")?	Yes	
		Partial	
		No	
Q24	Does your laboratory procedure manual address unusual or inconsistent antimicrobial testing results?	Yes	
		Partial	
		No	
Q25	Does your lab participate in any Antimicrobial Susceptibility Testing related internal quality assurance program?	Yes	
		Partial	
		No	
Q26	Does your lab participate in any Antimicrobial Susceptibility Testing related external quality assurance program?	Yes	
		Partial	
		No	
Q27	Are out of control results reported to supervisory personnel?	Yes	
		Partial	
		No	

READINESS FOR AMR SURVEILLANCE			
Q28	Does your lab participate in antimicrobial resistance surveillance?	Yes	
		Partial	
		No	
Q29	Does your lab generate on routine basis antibiogram for purpose of monitoring the resistant and sensitivity patterns in your institution?	Yes	
		Partial	
		No	
Q30	Does your lab conduct all Antimicrobial Susceptibility Testing or forwards it to other labs?	Yes	
		Partial	
		No	
Q31	Does your lab receive samples for Antimicrobial Susceptibility Testing from other labs?	Yes	
		Partial	
		No	
Q32	Is Antimicrobial Susceptibility Testing cumulative data collected manually?	Yes	
		Partial	
		No	
Q33	Is Antimicrobial Susceptibility Testing cumulative data collected automatically using lab information system (LIS)?	Yes	
		Partial	
		No	
DETECTION OF SPECIFIC ORGANISMS			
Q34	Does your laboratory have the capacity of identifying resistance genotypes or resistant bacterial clones?	Yes	
		Partial	
		No	
EQUIPMENT MAINTENANCE			
Q35	Are Antimicrobial Susceptibility Testing equipment maintained appropriately and calibrated?	Yes	
		Partial	
		No	
Q36	Does your lab monitor incubator temperatures on a daily basis?	Yes	
		Partial	
		No	
CONTINUING MEDICAL EDUCATION			
Q37	**How often do you receive training in Bacteriology?**	Yes	
		Partial	
		No	
Q38	How often are you trained in conducting Antimicrobial Susceptibility Testing?		

STAFFING			
Q39	How many laboratory technologists are in the station?		
Q40	How many microbiologists are in the station?		
Q41	Does your laboratory have staff with Bachelor's degree qualification or higher?	Yes	
		Partial	
		No	
Q42	Do you engage a Consultant clinical microbiologist(s)?	Yes	
		Partial	
		No	
CONSUMABLES			
Q43	How often do you experience unavailability of consumables in Microbiology section? Eg Lack of biochemical reagents and media	Yes	
		Partial	
		No	
Q44	Does your lab experience delays in Antimicrobial Susceptibility Testing due to lack of reagents?	Yes	
		Partial	
		No	
Q45	Do frequent stock outs lead to low demand of cultures by clinicians?	Yes	
		Partial	
		No	
BIOSAFETY			
Q46	Does your lab autoclave/incinerate cultures prior to discard?	Yes	
		Partial	
		No	
Q47	Do you have handwashing facility in the laboratory?	Yes	
		Partial	
		No	
Q48	Does your lab get continuous supply of running water?	Yes	
		Partial	
		No	
Q49	Does your lab have soap supply in the handwash facility?	Yes	
		Partial	
		No	

	Core element 1: Senior hospital management leadership towards antimicrobial stewardship	Yes	No
1	Has your hospital management formally identified antimicrobial stewardship as a priority objective for the institution and included it in its key performance indicators?		
2	Is there dedicated, sustainable and sufficient budgeted financial support for antimicrobial stewardship activities (e.g., support for salary, training, or IT (information technology) support)?		
3	Does your hospital follow any (national or international) staffing standards for antimicrobial stewardship activities (e.g. number of full-time equivalent (FTE) per 100 beds for the different members of the antimicrobial stewardship team)?		
	Core element 2: Accountability and responsibilities		
4	Does your hospital have a formal/written antimicrobial stewardship programme/strategy accountable for ensuring appropriate antimicrobial use?		
5	Does your hospital have a formal organizational multidisciplinary structure responsible for antimicrobial stewardship (e.g., a committee focused on appropriate antimicrobial use, pharmacy committee, patient safety committee or other relevant structure)?		
6	Is there a healthcare professional identified as a leader for antimicrobial stewardship activities at your hospital and responsible for implementing the programme?		
7	Is there a document clearly defining roles, procedures of collaboration and responsibilities of the antimicrobial stewardship team members?		
8	Are clinicians, other than those part of the antimicrobial stewardship team (e.g. from the ICU, Internal Medicine and Surgery) involved in the antimicrobial stewardship committee?		
9	Does the antimicrobial stewardship committee produce regularly (indicate minimum time) a dedicated report which includes e.g. antimicrobial use data and/or prescription improvement initiatives, with time-committed short term and long term measurable goals/ targets for optimizing antimicrobial use?		
10	Is there a document clearly defining the procedures of collaboration of the antimicrobial stewardship team/committee with the infection prevention and control team/committee?		
	Core element 3: Available expertise on infection management		
11	Do you have access to laboratory/imaging services and to timely results to be able to support the diagnosis of the most common infections at your hospital?		
12	In your hospital are there, or do you have access to, trained and experienced healthcare professionals (medical doctor, pharmacist, nurse …) in infection management (diagnosis, prevention and treatment) and stewardship willing to constitute an antimicrobial stewardship team?		
	Core element 4: Education and practical training		
13	Does your hospital offer a range of educational resources to support staff training on how to optimize antimicrobial prescribing?		
14	Do the antimicrobial stewardship team members receive regular training in antimicrobial prescribing and stewardship?		
	Core element 5: Other actions aiming at responsible antimicrobial use		

15	Is a multidisciplinary antimicrobial stewardship team available at your hospital (e.g., greater than one trained staff member supporting clinical decisions to ensure appropriate antimicrobial use)?		
16	Does your hospital support the antimicrobial stewardship activities/ strategy with adequate information technology services?		
17	Does your hospital have an antimicrobial formulary (i.e. a list of antimicrobials that have been approved for use in a hospital, specifying whether the drugs are unrestricted, restricted (approval of an antimicrobial stewardship team member is required) or permitted for specific conditions)?		
18	Does your hospital have available and up-to-date recommendations for infection management (diagnosis, prevention and treatment), based on international/national evidence-based guidelines and local susceptibility (when possible), to assist with antimicrobial selection (indication, agent, dose, route, duration) for common clinical conditions?		
19	Does your hospital have a written policy that requires prescribers to document an antimicrobial plan (includes indication, name, dosage, duration, route and interval of administration) in the medical record or during order entry for all antimicrobial prescriptions?		
20	Does the antimicrobial stewardship team review/audit courses of therapy for specified antimicrobial agents or clinical conditions at your hospital?		
21	Is advice from antimicrobial stewardship team members easily available to prescribers?		
22	Is advice from antimicrobial stewardship team members easily available to prescribers?		
	Core element 6: Monitoring and surveillance (on a continuous basis)		
23	Does your hospital monitor the quality of antimicrobial use at the unit and/or hospital wide level?		
24	Does your stewardship programme monitor compliance with one or more of the specific interventions put in place by the stewardship team (e.g. indication captured in the medical record for all antimicrobial prescriptions)?		
25	Does your hospital monitor antibiotic susceptibility rates for a range of key bacteria?		
26	Does your hospital monitor the quantity of antimicrobials prescribed/ dispensed/purchased at the unit and/or hospital wide level?		
	Core element 7: Reporting and feedback (on a continuous basis)		
27	Does your stewardship programme share hospital-specific reports on the quantity of antimicrobials prescribed/dispensed/purchased with prescribers?		
28	Does your stewardship programme share facility-specific reports on antibiotic susceptibility rates with prescribers?		
29	Are results of audits/reviews of the quality/appropriateness of antimicrobial use communicated directly with prescribers?		