Sustained reduction in third-generation cephalosporin usage in adult inpatients following introduction of an antimicrobial stewardship program in a large urban hospital in Malawi.

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Summary: An antimicrobial stewardship program, consisting of a prescribing guideline and point-prevalence surveys with prescriber feedback, was introduced at Queen Elizabeth Central Hospital in Malawi. The program was effective in reducing third-generation cephalosporin usage and was potentially cost-saving for the hospital.

ABSTRACT

Background: Third-generation cephalosporins (3GC) remain the first-choice empiric antibiotic for severe infection in many sub-Saharan African hospitals. In Malawi, limited availability of alternatives, mean that strategies to prevent spread of 3GC-resistance

(3GC-R) are imperative, however suitable approaches to antimicrobial stewardship (AMS) in low-income settings are not well studied.

Methods: We introduced an AMS intervention to Queen Elizabeth Central Hospital (QECH) in Blantyre. The intervention consisted of a smartphone prescribing application and regular point-prevalence surveys (PPS) with prescriber feedback. We evaluate the effects of the intervention on 3GC usage and on cost of providing antibiotics. Using thematic analysis of semi-structured interviews and participant observations, we additionally evaluate the acceptability of the stewardship program.

Results: The proportion of antibiotic prescriptions for a 3GC reduced from 193/241 (80.1%) to 177/330 (53.6%) (percentage decrease 26.5% [95%CI; 18.7 to 34.1]) with no change in case-fatality rate. Cost analysis estimated annual savings of US$15,000. Qualitative research revealed trust in the guideline and found its accessibility through smartphones helpful to guide clinical decisions. Operational health-system barriers and hierarchal clinical relationships lead to continued reliance on 3GC.

Conclusions: We report the successful introduction of an antimicrobial stewardship approach in Malawi. By focusing on pragmatic interventions and simple aims, we

demonstrate the feasibility, acceptability and cost-saving of a stewardship program where resources

are limited. In doing so, we provide a suitable starting point for expansion of AMS interventions in this and other low-income settings.

Keywords: antimicrobial resistance, antimicrobial stewardship, Africa south of the Sahara,

INTRODUCTION

Infection with antimicrobial resistant (AMR) pathogens is associated with high morbidity and mortality for patients and a significant economic burden on health systems [1, 2]. In sub-Saharan Africa (sSA), the prevalence of AMR in key pathogens, is amongst the highest in the world [3] and the mortality burden from drug-resistant infections is predicted to be huge [4]. Interventions which reduce excessive antimicrobial usage (AMU) have been shown to reduce AMR [5] and optimization of AMU is a key WHO target. However, antimicrobial stewardship (AMS) programs are typically tailored to high-income settings, frequently incorporating specialist infection liaison services, advanced microbiological diagnostics and a restrictive antibiotic formulary [5, 6]. Few hospitals in sSA have AMS programs in

place [7] and a better understanding of the ideal components of an effective and acceptable AMS intervention in a resource-limited setting is needed.

Ceftriaxone, a parenteral third-generation cephalosporin (3GC), has long been the antibiotic of choice in many sub-Saharan African hospitals, its once daily dosing regimen and broad-spectrum of activity, making it a useful and convenient choice in settings where diagnostics and nursing capacity are limited [8, 9]. In sSA the prevalence of 3GC resistance amongst key bloodstream pathogens is high [10] and widespread reliance on ceftriaxone has likely been a major driver of this class-level resistance [11-13].

In Malawi, sentinel surveillance from patients presenting to Queen Elizabeth Central Hospital (QECH) in Blantyre has demonstrated a rapid rise in 3GC-R amongst bloodstream Enterobacterales, occurring contemporaneously with the widespread roll-out of

ceftriaxone [14]. Limited availability of alternatives antibiotics, means that reducing class-level resistance to cephalosporins and preventing further AMR transmission, is of critical importance. AMS is a key strategy for achieving this [15], yet little is known about antibiotic prescribing practices at QECH, or what constitute deliverable, acceptable and sustainable interventions and targets for an AMS program in a resource-poor hospital.

The aim of this work was to establish and evaluate a formal AMS program on the adult medical wards at QECH. We conceived and introduced a locally appropriate antibiotic guideline and evaluated its impact on ceftriaxone usage and cost of antibiotic provision. Incorporating qualitative methodology, we additionally aimed to understand the barriers to and enablers of our stewardship approach.

METHODS

Setting

Malawi is a low-income country with low healthcare expenditure (~3% GDP) [16]. QECH is a 1300 bed unit and the only hospital providing free inpatient care in Blantyre. There are 200 adult medical beds, and ~70% of adult inpatients are HIV-

infected [17]. Quality assured blood culture and cerebrospinal fluid analysis are provided by the Malawi-Liverpool Wellcome Trust Clinical Research Programme (MLW), but there is no formal microbiology liaison service. Prior to this study, there were no formal AMS activities and no specific antibiotic guideline.

Study design

Overview

The stewardship program had three phases: a pre-implementation prescribing survey, designed to identify stewardship targets (January 2016); implementation of an antibiotic guideline (June 2016) and two post-implementation prescribing surveys (January 2017, January 2018). Point-prevalence surveys (PPS) with feedback to prescribers began at the start of the implementation phase and continued for 28-months. The study methods are described below and in more detail in the Supplementary Material.

Antibiotic prescribing surveys

Inpatient records were reviewed to collect data on key stewardship quality indicators. The pre-implementation survey was carried out by RL, DK and AK. RL then then drafted the antibiotic guideline. Post-implementation surveys were carried out by a doctor who was not involved in the implementation phase (KH). We adapted standardized stewardship quality indicators to suit local practice [18], focusing on

measurable targets such as 48-hour antibiotic review and duration of antibiotic prescription (Supplementary Methods, Table 1).

Stewardship intervention

A series of multidisciplinary team meetings were held to establish the AMS program, convening clinicians, nursing managers, hospital directorship, pharmacists and microbiologists. All key decisions involved senior clinicians active at QECH. Local antimicrobial susceptibility trends, antibiotic availability and national guidelines were reviewed and used to design a consensus based antibiotic guideline which was reviewed by all senior clinicians in the departments. In Malawi, the burden of severe bacterial infection is high and it is critical that AMS does not restrict access to potentially lifesaving therapy [19]. Our guideline therefore focused on the importance of recognizing and treating sepsis and on 48-hour antibiotic step down.

The guideline was distributed using booklets, posters and as a smartphone antibiotic application, Microguide (http://www.microguide.eu/). Microguide allows prescribers to access hospital-specific guidelines on their mobile devices or hospital intranet. The QECH version can be viewed at https://viewer.microguide.global/QECH/ADULT4.

Point-prevalence surveys

An average of two to three PPS were carried out/month. Two numerators were defined in each survey: number of patients on ceftriaxone and number of patients on at least one antibiotic. All adult medical inpatients whose notes were available at the time of the survey were included and results from each PPS were presented to Department of Medicine meetings the following day. These meetings are compulsory for all cadres of clinicians and medical students working within the department. Results were presented verbally by a study doctor who was clinically active on the medical wards. Attendees were informed what proportion of their patients were on ceftriaxone and what proportion were on at least one antibiotic and given a reminder to review their prescriptions.

Qualitative methods

Semi-structured interviews and observations with clinicians were carried out throughout the study (Supplementary Methods). Interviewees were purposively sampled based on their role in prescribing antibiotics and observations were conducted on medical ward rounds and in morning meetings. Transcripts and field notes were imported into Nvivo software package (QSR International Pty Ltd., version 11, 2015) and a thematic analysis was conducted.

Cost analysis

We explored the impact of the stewardship intervention on the direct health-provider costs of supplying antibiotics at QECH. First, we used data captured in the three prescribing surveys to estimate the total cost of all antibiotics given to participants in each survey. We divided this total cost by the total number of participants in each of the three surveys to estimate the average cost/participant. Secondly, we modelled how the stewardship intervention would impact on the mean cost/patient and the total annual cost of providing antibiotics to those admitted to the three medical wards (male medical; female medical; TB ward). We also estimated the annual cost of implementing the intervention (Supplementary Table 2).

Statistical analysis

Stewardship indicators from antibiotic surveys were described as proportions, and comparisons between pre -and post-implementation groups done using the χ^2 test. Confidence intervals were calculated using the Wilson method. Assuming that errors would be approximately normally distributed, a linear regression model was used to detect linear trends in the prevalence of ceftriaxone and all-antibiotic prescriptions over time. Seasonality was adjusted for using harmonic terms with a one-year period. For the PPS, data were recorded as missing if a patient file was not available at the time the survey was carried out. We assumed that missing records were missing at

random and therefore not likely to bias the prevalence estimates. Data were analyzed using the R statistical package version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

The study was approved by the Research Ethics Committees of the University of Malawi, the College of Medicine (P.10/15/1811) and the Liverpool School of Tropical Medicine

(15-052RS).

RESULTS

The records of 203 patients were reviewed in the pre-implementation survey (Survey 1). One hundred records were reviewed in the first post-implementation survey (Survey 2) and 200 in the second (Survey 3).

Table 1 shows characteristics for all included patients. HIV prevalence was consistent across all three surveys (61.2-61.6%), as was recorded ART coverage (79.6-81.4%). Median length of hospital stay and in-hospital mortality did not change pre- and post-intervention (Table 1). Rates of confirmed bloodstream infection ranged between 8.4 and 13.1%. The most frequently isolated pathogens were as previously reported from

QECH [19] and included *Salmonella* Typhi, *Salmonella* Typhimurium and *Klebsiella pneumoniae* (Supplementary Results, Table 3).

Clinically suspected focus of infection, as recorded in the medical notes, was similar across all surveys (Supplementary Results, Figure 1). Respiratory or central nervous system (CNS) infections were the most common syndromes recorded by admitting teams, whilst non-focal infection accounted for over 10% of recorded diagnoses. Across the three surveys, proportion of records in which a suspected focus of infection was not recorded prior to antibiotic administration fell, from 15.3% (Survey 1) to 6% (Surveys 2 and 3).

A reduction in 3GC usage was seen after implementation of the stewardship program, as measured by pre and post-implementation antibiotic surveys (Figure 1, Table 2), antibiotic PPS (Figure 2) and median duration of antibiotic prescription (Figure 1, Table 2).

The proportion of all antibiotic prescriptions for an intravenous 3GC fell from 193/241 (80.1%) to 177/330 (53.6%) (percentage decrease 26.5% [95%CI; 18.7 to 34.1])

between the first and last surveys and the median length of ceftriaxone course reduced from five to four days (Table 2). This paralleled an increase in clinician 48-hour review of antibiotic prescriptions, as documented in the medical notes. Prior to the stewardship intervention, only 54/241 (22.4%) of prescriptions showed evidence of a 48-hour review, which increased to 242/330 (73.3%) by the final antibiotic survey (percentage increase 50.9 [95%CI 43.4 to 58.4]). This and additional key

stewardship indicators from the pre- and post-implementation surveys are shown in Supplementary Results, Table 4.

The median number of charts included in each PPS was 100 (IQR 94-101). A median of 2 files (IQR 2-4) were recorded as missing in each survey. In the first PPS, 78% of patients on the ward were receiving ceftriaxone and 86% were receiving at least one antibiotic of any class. Figure 2 shows the results of 71 PPS carried out over a period of 28-months and a decline in ceftriaxone prescriptions over the study period ($p<0.01$). Although Table 2 shows an increase in ciprofloxacin and metronidazole prescriptions across the three prescribing surveys, there was no evidence of a linear trend in all-antibiotic prevalence over time

($p = 0.15$) (Figure 2). The coefficients of the harmonic terms in the regression model, suggested little evidence of seasonal variation in ceftriaxone usage ($p= 0.19$ and $p=0.65$ for sin and cosine terms respectively) or in overall antibiotic usage ($p=0.62$ and $p=0.30$ for sine and cosine terms respectively).

The total cost of antibiotics prescribed to patients in Survey 1, Survey 2 and Survey 3 was US$1907.04, US$584.78 and US$1404.34, respectively. The average cost per patient was US$9.39 (Survey 1), US$5.85 (Survey 2) and US$7.02 (Survey 3) (Supplementary Results, Table 5). Table 3 shows the mean cost/patient and total cost estimated from modelling the impact of the stewardship program across the three adult medical wards at QECH. The mean cost per patient and total costs were lower on the TB ward as many patients are admitted to this ward to receive the initial phase of TB treatment and the cost of anti-TB drugs were not included here. At patient level, the mean cost across the three adult medical wards is projected to fall from US$6.79 per patient, to US$5.23 per patient. The total annual cost of providing

antibiotics to these three wards is projected to fall from US$67,058.14 to US$51,566.60. The total annual cost of delivering the intervention was US$4,358.78 (Supplementary Methods).

Two rounds of semi-structured interviews were conducted: 20 in the pre-implementation period and 21 in the post-implementation period. Due to high turnover of junior level doctors on the medical wards, only one participant was interviewed before and after the guideline introduction. Characteristics of interviewees are summarized in Supplementary Results, Table 6. Analysis of qualitative data identified six key themes relating to the stewardship intervention: facilitators (accessibility of information, trust in guideline content, awareness) and barriers (operational barriers, hierarchical relationships and rationalized overprescribing). Themes are summarized below and key quotes are presented in Table 4.

Facilitators

Theme 1: Accessibility of information

The majority of participants in the post-implementation period reported use of the guideline (quotes 1.1 – 1.2) and regular consultation of Microguide was observed during ward rounds. This was in marked contrast to the pre-implementation interviews, in which participants cited a range of resources to guide prescribing and difficulty in finding locally relevant information (quotes 1.3 – 1.4). Junior level doctors in particular, perceived that they now had a new resource which would guide

them towards narrow-spectrum antibiotics, and valued the ability to access the guideline on their smartphones (quote 1.5).

Theme 2: Trust in the guideline content

Most participants felt invested in the guideline, noting the department's involvement in its inception and development (quotes 2.1-2.2). The locally appropriate nature of the guidance was cited as crucial in almost all post-implementation interviews, in particular with regard to antibiotic availability and pathogen (quotes 2.2-2.4).

Theme 3: Awareness and promotion of stewardship and AMR

The process surrounding introduction of the stewardship intervention was perceived to raise awareness of AMR and of overprescribing within the department. Physicians of all cadres reported thinking more about their antibiotic prescribing practices than before the intervention (quotes 3.1-3.2).

Barriers

Multiple routes to ceftriaxone overprescribing were identified in the thematic analysis in the pre- and post-implementation phase.

Theme 4: Operational barriers

An overarching theme across interviews and observations was the influence of resources on prescribing practices. Limited access to alternative antibiotics (quotes 4.1-4.3) and comprehensive diagnostics (quotes 4.4), and inadequate nursing capacity favoring antibiotics with once-daily dosing regimens (quote 4.5) were frequently cited as reasons for ceftriaxone use and overuse as perceived by participants.

Theme 5. Hierarchical relationships and prescribing practice

Hierarchical relationships between the different cadres of clinical staff shaped prescribing practices. Junior team members invariably took direction from senior colleagues on prescribing and a rigid hierarchy frequently prohibited junior team members from challenging the prescribing of peers or senior colleagues (quotes 5.1-5.3).

Theme 6: Rationalized overprescribing

Participants frequently described ceftriaxone as the rational choice in the clinical situations they faced, with the risk of undertreating individual patients taking priority over population level consequences of antibiotic overuse. Junior doctors considered intravenous antibiotics to be inherently superior to oral, particularly amongst inpatients where the burden of HIV and infection is high (quotes 6.1-6.3).

DISCUSSION

We demonstrate that antimicrobial stewardship is feasible and effective in a low-income country, in a hospital which has no specialist clinical microbiology or ward-level pharmacy service, a limited antibiotic formulary and no previous ethos of stewardship. A locally appropriate, pragmatic antibiotic guideline using smartphone technology, supported by a simple educational strategy of weekly 'reminders' led to a significant reduction in 3GC usage, an increase in the proportion of 48-hour antibiotic reviews and a cost-saving of over US$15,000 for the medical wards. Critically, case fatality rate did not change in the pre- and post- implementation surveys, nor on the medical wards in general during the study period.

Unlike in high-income settings, evidence for successful stewardship in LMICs is limited. AMS programs from Cambodia and South Africa have demonstrated substantial impact from AMS. However, whilst resource constrained, these settings are very different from Malawi, and their stewardship successes relied upon established pharmacy infrastructure [20, 21], specialist microbiology liaison [22] and a comprehensive formulary [23].

Whilst QECH benefits from sustained access to a quality assured blood culture service, we highlight multiple operational barriers to implementing stewardship that are distinct to

LMICs [24-27], especially reliance on ceftriaxone due to the clinical context: critically unwell patients, high burden of infectious disease and limited diagnostics. Clinical decision making is not only influenced by guidelines and operational constraints; social determinants of prescribing must be understood in order to effect a change in practice [28]. Hierarchy and peer pressures shaped antibiotic prescribing decisions in our study, as in other settings [26], but these influences have not previously been explored in Africa, where qualitative studies of stewardship have focused on nursing behaviors [24, 25] and general perceptions of AMR [29]. More in-depth social research should be undertaken to provide a deeper understanding of the mechanisms for changing behavior, if large scale programs are to be successful.

This study has several limitations. Although the PPS show a significant decline in prevalence of ceftriaxone usage over the study period, we have limited data from the pre-implementation phase. However, previous studies at QECH prior to the intervention, have shown ceftriaxone prescribing prevalence of 70-84% [19, 30], consistent with our pre-implementation findings. Further, we did not engage with an implementation science framework to guide the design of this first-stage qualitative study, which would be a necessary component of a scale up. We have implemented an AMS program on adult wards, but pediatric and community level antibiotic usage are likely to be major drivers of antibiotic consumption and thus AMR [31]. Large-scale stewardship must target these settings next.

We have demonstrated the sustainability of the AMS program over a 28-month period, but measuring its long-term impact, whilst essential, is outside the scope of this study. The potential cost-saving achieved by the reduction in antibiotic usage is key to the sustainability of our program and an antibiotic pharmacist could continue

the regular PPS. Involving clinical departments and hospital management in guideline development is fundamental to its sustainability. Our guideline is integrated into departmental teaching and the Microguide app. provides a function for real-time feedback from prescribers, allowing regular updates to be incorporated as often as required.

AMS programs in low-income countries are challenged by the dual burden of high prevalence of severe and often drug resistant infection, alongside insecure, variable access to a range of effective antimicrobials. We demonstrate, that stewardship can be adapted to this setting and by focusing on pragmatic interventions and simple targets, we show the feasibility, acceptability and cost-saving of a stewardship program in Malawi, which was successful in reducing third-generation cephalosporin usage. In doing so, we provide a suitable starting point for expanded, large-scale stewardship interventions in this and other resource-limited settings.

NOTES

ACKNOWLEDGEMENTS

The authors thank the clinical staff at Queen Elizabeth Central Hospital and the laboratory Staff at MLW.

FUNDING

This work was supported by the Malawi-Liverpool Wellcome Trust Major Overseas Programme Core Grant [grant number 206545/Z/17/Z]. RL is supported by a Wellcome Trust Clinical PhD Fellowship [University of Liverpool block award grant number 203919/Z/16/Z].

Potential conflicts of interest: DGL received grants from the Wellcome Trust, during the conduct of the study. All other authors report no potential conflicts.

REFERENCES

1 Cosgrove SE, Kaye KS, Eliopoulous GM, Carmeli Y. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in Enterobacter species. Arch Intern Med **2002**; 162(2): 185-90.

2 Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clin Infect Dis **2003**; 36(11): 1433-7.

3 Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal Colonization With Extended-spectrum Beta-lactamase-Producing Enterobacteriaceae and Risk Factors Among Healthy Individuals: A Systematic Review and Metaanalysis. Clin Infect Dis **2016**; 63(3): 310-8.

4 O'Neill J. Review on Antimicrobial Resistance Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. London: Review on Antimicrobial Resistance; 2014. Available from: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

5 Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev **2017**; 2: CD003543.

6 Schuts EC, Hulscher ME, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis **2016**; 16(7): 847-56.

7 Cox JA, Vlieghe E, Mendelson M, et al. Antibiotic stewardship in low- and middle-income countries: the same but different? Clin Microbiol Infect **2017**; 23(11): 812-8.

8 WHO. IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of illnesses with limited-resources. World Health Organization, 2011. https://apps.who.int/iris/bitstream/handle/10665/77751/9789241548281_Vol1_eng.pdf?sequence=1.

9 MoH, 2015. Malawi Standard Treatment Guidelines, Fifth Edition. http://apps.who.int/medicinedocs/documents/s23103en/s23103en.pdf.

10 Lester R, Musicha P, van Ginneken N, et al. Prevalence and outcome of bloodstream infections due to third-generation cephalosporin-resistant Enterobacteriaceae in sub-Saharan Africa: a systematic review. J Antimicrob Chemother **2019**.

11 Bamberger DM, Dahl SL. Impact of voluntary vs enforced compliance of third-generation cephalosporin use in a teaching hospital. Arch Intern Med **1992**; 152(3): 554-7.

12 Pallares R, Dick R, Wenzel RP, Adams JR, Nettleman MD. Trends in antimicrobial utilization at a tertiary teaching hospital during a 15-year period (1978-1992). Infect Control Hosp Epidemiol **1993**; 14(7): 376-82.

13 Dancer SJ. The problem with cephalosporins. J Antimicrob Chemother **2001**; 48(4): 463-78.

14 Musicha P, Cornick JE, Bar-Zeev N, et al. Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998-2016): a surveillance study. Lancet Infect Dis **2017**; 17(10): 1042-52.

15 Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis **2017**; 17(9): 990-1001.

16 UNICEF. 2018/19 Health Budget Brief. Towards Universal Health Coverage (UHC): Acheiving SDG 3 in Malawi. 2018. Available at https://www.unicef.org/esa/sites/unicef.org.esa/files/2019-04/UNICEF-Malawi-2018-Health-Budget-Brief.pdf. Accessed Jan 4th 2020.

17 Maheswaran H, Petrou S, Cohen D, et al. Economic costs and health-related quality of life outcomes of hospitalised patients with high HIV prevalence: A prospective hospital cohort study in Malawi. PLoS One **2018**; 13(3): e0192991.

18 Antimicrobial Stewardship Toolkit for Secondary Care: Start Smart – then Focus Available at: https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus.

19 Feasey NA, Houston A, Mukaka M, et al. A reduction in adult blood stream infection and case fatality at a large African hospital following antiretroviral therapy roll-out. PLoS One **2014**; 9(3): e92226.

20 Boyles TH, Naicker V, Rawoot N, Raubenheimer PJ, Eick B, Mendelson M. Sustained reduction in antibiotic consumption in a South African public sector hospital; Four year outcomes from the Groote Schuur Hospital antibiotic stewardship program. S Afr Med J **2017**; 107(2): 115-8.

21 Brink AJ, Messina AP, Feldman C, et al. Antimicrobial stewardship across 47 South African hospitals: an implementation study. Lancet Infect Dis **2016**; 16(9): 1017-25.

22 Fox-Lewis A, Hopkins J, Sar P, et al. Seroprevalence of Dengue Virus and Rickettsial Infections in Cambodian Children. Am J Trop Med Hyg **2019**; 100(3): 635-8.

23 Bassetti M, Poulakou G, Ruppe E, Bouza E, Van Hal SJ, Brink A. Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. Intensive Care Med **2017**; 43(10): 1464-75.

24 Mula CT, Middleton L, Human N, Varga C. Assessment of factors that influence timely administration of initial antibiotic dose using collaborative process mapping at a referral hospital in Malawi: a case study of pneumonia patients. BMC Infect Dis **2018**; 18(1): 697.

25 Mula CT, Human N, Middleton L. An exploration of workarounds and their perceived impact on antibiotic stewardship in the adult medical wards of a referral hospital in Malawi: a qualitative study. BMC Health Serv Res **2019**; 19(1): 64.

26 Fox-Lewis S, Pol S, Miliya T, Day NPJ, Turner P, Turner C. Utilization of a clinical microbiology service at a Cambodian paediatric hospital and its impact on appropriate antimicrobial prescribing. J Antimicrob Chemother **2018**; 73(2): 509-16.

27 Ahmed NH, Baba K, Clay C, Lekalakala R, Hoosen AA. In vitro activity of tigecycline against clinical isolates of carbapenem resistant Acinetobacter baumannii complex in Pretoria, South Africa. BMC Research Notes **2012**; 5.

28 Chandler CI, Jones C, Boniface G, Juma K, Reyburn H, Whitty CJ. Guidelines and mindlines: why do clinical staff over-diagnose malaria in Tanzania? A qualitative study. Malar J **2008**; 7: 53.

29 Gebretekle GB, Haile Mariam D, Abebe W, et al. Opportunities and barriers to implementing antibiotic stewardship in low and middle-income countries: Lessons from a mixed-methods study in a tertiary care hospital in Ethiopia. PLoS One **2018**; 13(12): e0208447.

30 Maheswaran H, Petrou S, MacPherson P, et al. Cost and quality of life analysis of HIV self-testing and facility-based HIV testing and counselling in Blantyre, Malawi. BMC Med **2016**; 14: 34.

31 Pereko DD, Lubbe MS, Essack SY. Surveillance of antibiotic use in the private sector in Namibia using sales and claims data. J Infect Dev Ctries **2016**; 10(11): 1243-9.

Table 1. Demographic and outcome data for patients included in the antibiotic surveys

	Survey 1 (n=203)	**Survey 2 (n=100)[a]**	**Survey 3 (n=200)**
Age, median (IQR), years	39 (30-53)	33 (25-45)	40 (30-50)
Male n/N (%)	102/203 (50.2)	447/100 (47.0)	103/200 (51.5)
HIV infected n/N (%)	122/198 (61.6) 5 unknown	49/85(57.6) 15 unknown	118/193(61.1) 7 unknown
On ART if HIV infected n/N (%)	98/122 (80.3)	39/49 (79.6)	96/118 (81.4)
LOS, median (IQR), days	7 (4-10)	7 (4-9)	7 (5-12)
In-hospital case-fatality n/N % (95% CI)	30/193 15.5 (10.9, 21.6) unknown outcome=10	17/100 17.0 (10.5, 26.1)	22/172 12.8 (8.4, 18.9) unknown outcome=8

Abbreviations: ART, antiretroviral therapy; LOS, length of stay

[a]Note that survey 2 was smaller than surveys 1 and 3 because of limited personnel available at the time or the survey.

Table 2. Antibiotic prescriptions on the medical wards

	Survey 1			Survey 2			Survey 3		
Antibiotic	**Proportion of prescriptions**		**Duration, days**	**Proportion of prescriptions**		**Duration, days**	**Proportion of prescriptions**		**Duration, days**
	Number[a]	**%**	**Median (IQR)**	**Number[a]**	**%**	**Median (IQR)**	**Number[a]**	**%**	**Median (IQR)**
3GC[b]	193/241	80.1	5.0 (3.0-8.0)	80/121	66.1	4.0 (2.0-7.0)	177/330	53.6	4.0 (2.0-7.0)
Ciprofloxacin	18/241	7.5	4.0 (3.0-4.0)	20/121	16.5	6.0 (5.0-7.0)	44/330	13.3	3 (1.75-7.25)
Amoxicillin	14/241	5.8	3.0 (2.0-5.0)	12/121	9.9	5.0 (2.5-7.0)	42/330	12.7	3.5 (1.0-6.0)
Metronidazole	9/241	3.7	7.0 (5.0-8.0)	4/121	3.3	3.0 (2.5-3.5)	33/330	10.0	3.0 (2.0-6.0)
Flucloxacillin	3/241	0.9	5.0 (3.0-11.5)	0	0	-	5/330	1.5	6.0 (1.0-15.0)
Erythromycin	2/241	0.8	4.0 (3.0-4.0)	0	0	-	1/330	0.3	1
Benzylpenicillin	1/241	0.4	6.0	1/121	0.8	1	1/330	0.3	12
Co-amoxiclav	1/241	0.4	6.0	1/120	0.8	3	9/330	2.7	2.0 (2.0-3.0)
Doxycycline	0	0	-	2/121	1.7	4.4 (4.25-4.75)	2/330	0.6	5
Gentamicin	0	0	-	1/121	0.8	1	4/330	1.2	1.5 (0-3.5)
Co-trimoxazole	0	0	-	0	0	-	12/330	3.6	4 (2.75-5.25)
All	**241**	**100**	**4.5 (3.0-7.0)**	**120**	**100**	**5.0 (2.0-7.0)**	**330**	**100**	**4 (2-6)**
*Total cost (US$)	**US$1907.04**			**US$584.78**			**US$1404.34**		
*Cost per patient (US$)	**US$9.39**			**US$5.85**			**US$7.02**		

Abbreviations: 3CG, third-generation cephalosporin; IQR, inter-quartile range

[a] Denominator is number of individual antibiotic prescriptions in each survey, not number of patients. An individual antibiotic prescription was defined as each prescription written on the patient's chart. If the antibiotic was switched, this was counted as a second prescription.

[b] Cefotaxime was used in place of ceftriaxone during a period of ceftriaxone shortage in 2017

*2017 US Dollars

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Table 3. Estimated health-provider cost of providing antibiotics to medical inpatients in QECH

	Pre-Stewardship program (2017 US$)	Post-Stewardship program (2017 US$)
Mean cost per patient (95% CrI):		
TB ward	5.14 (3.68, 6.59)	4.16 (3.00, 5.31)
Male medical ward	7.31 (6.34, 8.28)	5.90 (5.08, 6.72)
Female medical ward	6.53 (5.54, 7.52)	5.23 (4.45, 6.02)
All medical inpatients	**6.79 (6.15, 7.44)**	**5.23 (4.45, 6.01)**
Total cost per annum*:		
TB ward	4,313.74	3,491.69
Male medical ward	33,783.43	27,268.02
Female medical ward	25,960.97	20,806.89
All medical inpatients**	**67,058.14**	**51,566.60**

*based on admissions/year: 840 for TB ward; 4620 for Male medical ward; 3975 for Female medical ward

** total annual cost for all medical inpatients estimated from summing total annual costs for each ward

95% CrI: Credible interval based on

Table 4. Quotes from participant interviews and observations, shown by theme

Theme	Participant		Quote
1. Accessibility of information	Registrar, Post-implementation	1.1	….due to limited knowledge of antibiotics, I would just give a broad spectrum antibiotic, because to me that makes me well covered. The patient is going to improve….so whatever this patient has he is going to
	Registrar, Post-implementation	1.2	improve. But now at least I am able to sit down and think, what does, what do the guidelines say
	Intern, Pre-implementation	1.3	….for UTI, we used to using ciprofloxacin and now they are saying use nitrofurantoin and I keep forgetting the dosing because I've never used it my whole life, this is the first time.. Yeah so they do (help).
	Consultant, Pre-implementation	1.4	I remember the time we were switching from Cefotaxime to Ceftriaxone nobody knew what doses – you may find a meningitis patient given Cefotaxime 1g bd, another meningitis patient getting 1g Cefotaxime TDS, another bacterial meningitis got 1g od for about 3 days – which is when I saw the patient and changed the dose to the dosage I thought was nice. I feel we sometimes lack the guidance
	Consultant, Post-implementation	1.5	… there is so called Malawi standard treatment guidelines. There are some antibiotic guidelines but no proper antibiotic guidelines in queens that we can use as a facility as such. We do have a medical handbook in our department that we use, and it does help us, it does guide us on what antibiotics we should give, but it's not very detailed. I feel, it's not very specific, it's general, at the end of the day it's up to the clinician, should I give this antibiotic or not, I feel, because of a lack of a proper guideline, at times patients are started on the strongest antibiotic we have available, that's ceftriaxone, I find maybe they don't even meet the criteria to have that antibiotic, but everyone's on ceftriaxone. I think we don't have proper guidelines, in short.
			I think the fact that they've been made available in electronic forms and also there's

			a small booklet which you can carry to the wards. I think that it's a step in the right direction, I think we should have less excuses for not following the guidelines.
2. Trust in the content	Consultant, Post-implementation	2.1	I think we were part of the discussions and we were all consulted and told to make suggestions of the guidelines
	Consultant, Post-implementation	2.2	So I mean essentially the guidelines are based on the data that has been generated over the years in terms of the likely the commonest organisms that are affecting patients in our setting and… we were all consulted and told to make suggestions
	Consultant, Post-implementation	2.3	They are realistic guidelines… and what they've done, is they've made sure that most of the drugs that are usually in stock are there, so they are not some fancy drugs that you can hardly find here.
	Registrar, Post-implementation	2.4	In terms of coverage, it covers most of the important infections we see in our setting. And in terms of management I think it also gives us alternative in case one drug is out of stock there are always alternatives.
3. Awareness and promotion	Consultant, Post-implementation	3.1	I think the only notable change that I can comment is on the usage of ceftriaxone, because normally we get a report is it on every Thursday before the ward round on the percentage of ceftriaxone usage in the department, so I think from the figures, from the initial figures and the current figures it seems there has been a significant drop in terms of …usage of ceftriaxone. I think now not many people they are using ceftriaxone so meaning now they are following the guidelines so not giving ceftriaxone to each and every patient
	Registrar, Post-implementation	3.2	Yeah so since I think as a department there was quite a lot of awareness and raising awareness that we would have the antibiotic guidelines

4. Operational barriers	Registrar, Post-implementation	4.1	Let's say there's amoxicillin, but I'd want to give something slightly more broad spectrum, like augmentin. But there isn't. And probably the next best thing is ceftriaxone. So sometimes you use an antibiotic which you
	Registrar, Pre-implementation	4.2	didn't necesSArily want to use One of them is because the oral drug is out of stock, so the only choice I had was to give a broad spectrum that was IV, but if I had a
	Registrar, Post-implementation	4.3	chance I would have given an oral antibiotic. It has happened so many times, not once. For example there should be commitment from management to ensure that even simpler antibiotics should be made readily available
	Observation, Post-implementation	4.4	because even if broad spectrum antibiotics only are available and patient has come in with simple community acquired pneumonia, people may be tempted to use broad spectrum antibiotic, because they are only what is
	Consultant, Post-implementation	4.5	available. So, I think there should be a commitment from the management team to ensure that more antibiotics are available All the (non-infective) neurological cases viewed this morning had an infective differential. All of these patients had HIV so this is not just speculation, it's a real risk. Insufficiency of neuro-imaging means that the infective cause cannot be ruled out until we get an MRI or the LP or blood culture results get back – all of which will be 5 days When I arrived in 2009, the numbers of patients on our wards was really horrendous…so there will be one on the bed, one on the floor, all the way into the corridors. So if you had two trained nurses per shift it meant that they would be sitting at their desk drawing the antibiotics the whole day. …….if they were to do that four times a day they did nothing else. So ..patients stared getting maybe one dose, or 2 doses…..but never 4 doses. So we sort of like just slowly drifted towards ..once daily antibiotics, ceftriaxone.

5. Hierarchical relationships and prescribing practice	Observation, Post-implementation	5.1	There is a palpable power dynamic on this ward round. … Consultant says out loud we should stop ceftriaxone and wrote 'CSF normal, stop ceftriaxone'. He did not look at the drug chart and did not cross ceftriaxone off. No-on else on ward round crossed off …and we moved on to the next patient.
	Medical student, Pre-implementation	5.2	Certainly, ward round participants don't seem keen to speak unless directly addressed, maybe they don't want to cause disruption to the ward round by stopping to cross off antibiotic.
	Registrar, Pre-implementation	5.3	But as students when you see the files and you see people prescribe amoxicillin, ceftriaxone, you think that's the way to go because we see people practicing it, but then sometimes when you're on ward round you see a consultant prescribing an antibiotic which you never know is here… I think the interns who come to the department, they see most of the time people are on ceftriaxone, so when they are stuck, they will think that maybe by giving that, they will be off the hook.
6. Rationalized overprescribing	Registrar, Pre-implementation	6.1	That could be one possibility, because if I am certain you can just give an antibiotic which you feel is safe…
	Consultant, Post-Intervention	6.2	And when the patients are perceived to be quite unwell, that's where the problem of sticking to the guidelines seems to be an issue….
	Consultant, Post-intervention	6.3	It basically makes people not to think because they have a knee jerk reaction to everyone who has a fever, to give them ceftriaxone without thinking as to where the focus of infection is, so that you can choose an appropriate antibiotic for the focus of infection. So everyone just gives ceftriaxone as a fall-back position. So it stops people thinking about what is their ideal treatment in this setting.

FIGURE LEGENDS

Figure 1. Antibiotic usage pre- and post-implementation, shown as proportions of overall antibiotic prescriptions in the pre- and post-implementation antibiotic surveys. Survey 1 was pre-implementation and Surveys 2 and 3 were post implementation.

Figure 2. Point prevalence surveys of ceftriaxone and all antibiotics shown pre- and post-implementation. The antibiotic guideline was launched on 30th June 2016 (shown by dotted line) and the study period was from 30th January 2016 to 8th June 2018.

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Figure 1

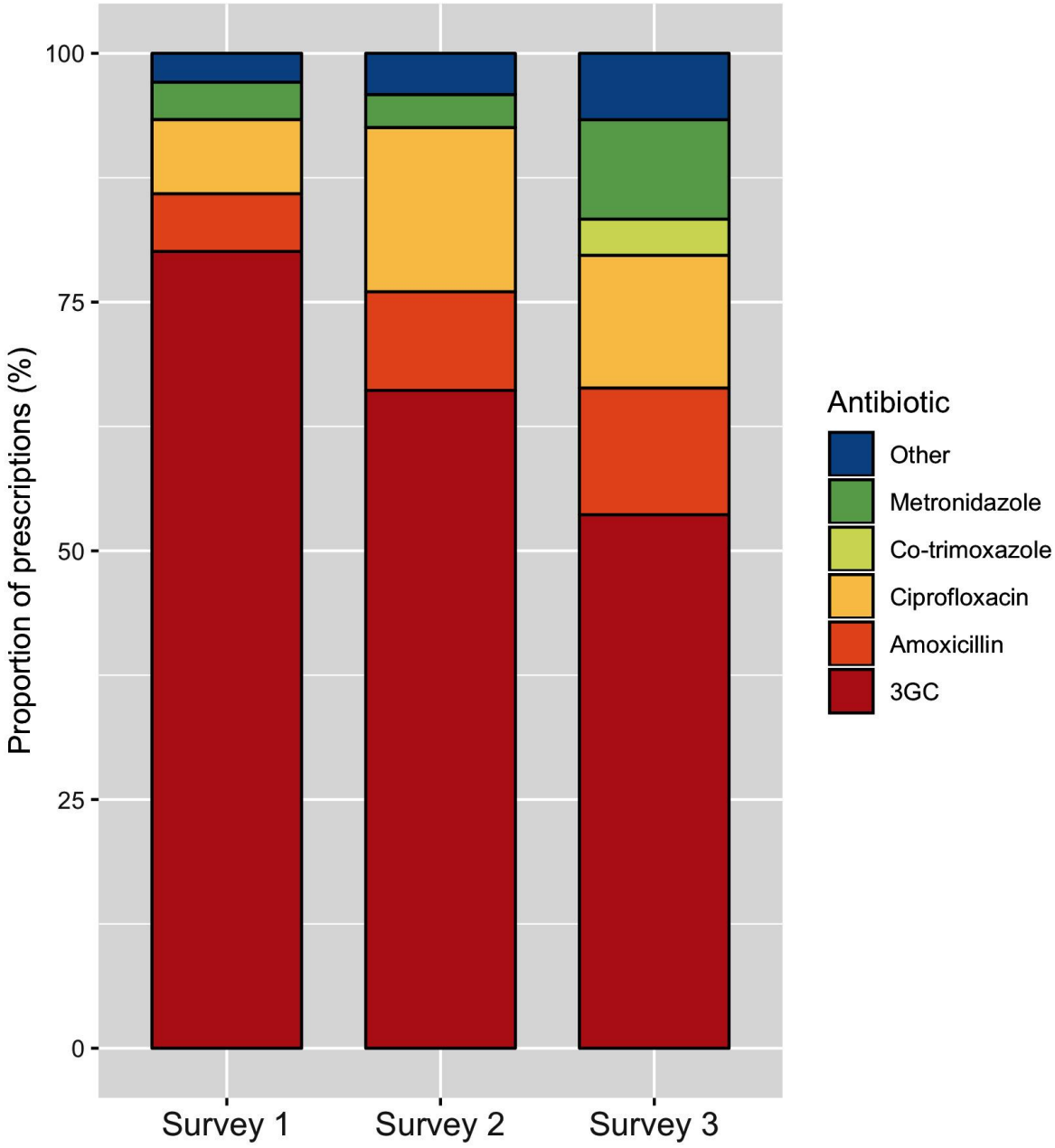

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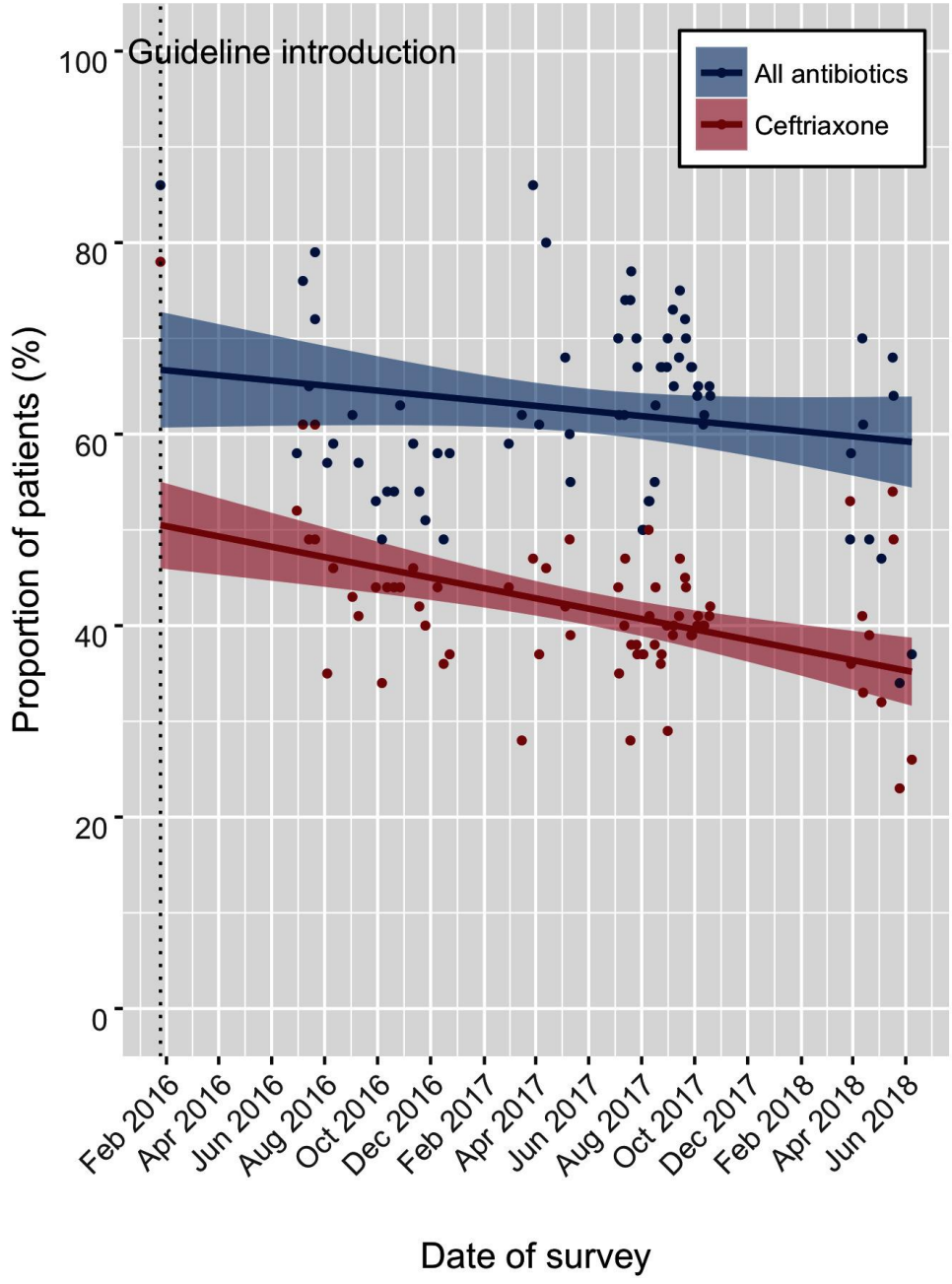
Figure 2



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