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Original Article

Why local antibiotic resistance data matters – Informing empiric prescribing through local data collation, app design and engagement in Zambia

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ABSTRACT

Background: Control of antimicrobial resistance (AMR) relies on local knowledge and local intervention implementation. Effective antibiotic stewardship requires locally-suitable prescribing guidelines. We aimed to use a novel digital tool (the ZARIApp) and a participatory approach to help develop locally-relevant empiric antibiotic prescribing guidelines for two hospitals in Lusaka, Zambia.

Methods: We produced an AMR report using samples collected locally and routinely from adults within the prior two years (April 2020 – April 2022). We developed the ZARIApp, which provides prescribing recommendations based on local resistance data and antibiotic prescribing practices. We used qualitative evaluation of focus group discussions among healthcare professionals to assess the feasibility and acceptability of using the ZARIApp and identify the barriers to and enablers of this stewardship approach.

Results: Resistance prevalence was high for many key pathogens: for example, 73% of 41 *Escherichia coli* isolates were resistant to ceftriaxone. We identified that high resistance rates were likely due to low levels of requesting and processing of microbiology samples from patients leading to insufficient and unrepresentative microbiology data. This emerged as the major barrier to generating locally-relevant guidelines. Through active stakeholder engagement, we modified the ZARIApp to better support users to generate empirical antibiotic guidelines within this context of unrepresentative microbiology data. Qualitative evaluation of focus group discussions suggested that the resulting ZARIApp was useful and easy to use. New antibiotic guidelines for key syndromes are now in place in the two study hospitals, but these have substantial residual uncertainty.

Conclusions: Tools such as the free online ZARIApp can empower local settings to better understand and optimise how sampling and prescribing can help to improve patient care and reduce future AMR. However, the usability of the ZARIApp is severely limited by unrepresentative microbiology data; improved routine microbiology surveillance is vitally needed.

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Abbreviations: AMR, Antimicrobial Resistance; AMS, Antimicrobial Stewardship; AST, Antimicrobial Susceptibility Testing; CLSI, Clinical and Laboratory Standards Institute; FGD, Focus group discussion; LMIC, Low- and middle-income country; SRL, Syndrome resistance level; WISCA, Weighted-incidence syndromic combination antibiogram

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Definitions

AMR report: a table showing how susceptible a series of organisms are to different antimicrobials.

Introduction

Antimicrobial resistance (AMR) is recognised as a threat to health worldwide [1,2]. The emphasis on the global nature of AMR has resulted in an increased focus on national-level burden estimates and high-level policy interventions. However, the accuracy of national-level estimates of the burden of AMR and the impact that interventions can have on this burden will rely on local factors, including clinical care pathways, knowledge of AMR burden and antibiotic use which vary substantially sub-nationally [3,4].

Local interventions such as directing empiric antibiotic prescribing should be linked to local resistance prevalence, but in practice this is rarely the case [5]. For low- and middle-income countries (LMICs) such as Zambia, there are often limited local data on resistance prevalence in important infection syndromes: for example a recent prescribing survey among hospitals throughout the 10 provinces of Zambia found that only 3% of all in-patients prescribed an antibiotic had a sample requested for culture and sensitivity testing [6]. Prior similar surveys in Ghana [7] and Nigeria [8] found equally low levels of microbiology-based prescribing. Correspondingly, there are few locally-tailored empiric prescribing guidelines [6,9]. Improving locally-tailored antibiotic stewardship (AMS) in LMICs could improve patient outcomes [10–12], prevent unnecessary escalation or misuse of antibiotics[13] and reduce AMR. Misuse and overuse of antimicrobials are key drivers of AMR [14]. Overuse of available antibiotics has been described in studies throughout sub-Sahara including Zambia [15–19]: a study in Zambia found that 67% of antimicrobials prescribed to non-critically ill hospitalised adults were inappropriately prescribed [15].

Zambia is a Lower-Middle income nation in southern sub-Saharan Africa, with a multi-sectoral AMR National Action Plan in place since 2017 [20], and has been contributing data to the Global Antimicrobial Resistance and Use Surveillance System [21] since 2016. Submitted data is generated from routinely collected samples processed through the central Ministry of Health microbiology laboratories but does not include samples from peripheral microbiology laboratories. Zambia has a set of national Standard Treatment Guidelines that covers the management of many medical and surgical conditions including infections, but only the tertiary referral hospital in Lusaka has hospital-specific antibiotic prescribing guidelines [15]. Neither were devised using local microbiology data.

Designing local empiric prescribing guidelines is challenging as it requires synthesising evidence from multiple data sources. We have previously attempted to overcome some of these difficulties by designing an online application decision making tool for empiric prescribing at the local or national level [22]. This combines syndrome aetiologies with resistance within individual bacteria to produce a syndrome-based metric of resistance. This type of syndrome metric, a weighted-incidence syndromic combination antibiogram (WISCA), was initially developed for abdominal-biliary and urinary tract infections [23]. Piloting this application to support hospital-level decision-making rather than using it solely as a theoretical exercise requires an understanding of the decision-making process, as well as how to deal with uncertainty in resistance due to sampling practices.

In this project, we collated local microbiology and antibiotic data in order to describe the current local AMR burden and availability of antibiotics. We then worked with key stakeholders to pilot use of our online application (ZARIApp), aiming to create a flexible open-access tool for generating hospital-level tailored empiric prescribing guidelines in LMIC settings. We aimed to use formal qualitative feedback from users to guide modifications to the ZARIApp, to result in a tool that best serves users to create locally-relevant guidelines despite the limitations of the data.

Methods

Setting

We undertook this mixed-methods study in two hospitals in Lusaka, Zambia from April - August 2022. We chose two of the largest hospitals in Lusaka in order to maximise the number of microbiology samples available to collate. We excluded the largest hospital in Lusaka as this hospital had existing empiric antibiotic guidelines in use. Hospital 1 is a primary level community hospital which has both in-patient and out-patient facilities including 8 in-patient wards. It has no intensive care facility. It serves a large urban low-income area of Lusaka with a population of more than 145,000 and has the highest patient density in Zambia with over 800 out-patients seen every day. Hospital 2 is a provincial hospital with tertiary level services and has both in-patient and out-patient facilities. It has an in-patient capacity of 800 beds, including 12 intensive care unit beds. It has a catchment area of 8 districts serving a population of more than 3 million people.

Data collation

We collated existing local microbiology data with information on local availability and cost of antibiotics. We followed the World Health Organisation's Global Antimicrobial Resistance and Use Surveillance System guidelines [21] to produce a routine AMR report for samples collected from adults (≥18 years) within the prior 2 years (April 2020 – April 2022) in each hospital. Due to low sample numbers we additionally collated results from the central Ministry of Health microbiology laboratory in Lusaka, which receives samples from both study hospitals as well as from other hospitals in Lusaka. Hospitals 1 and 2 from 2020 to 2021 had results on paper records which required manual collation. Hospital 2 for 2021–2022 and the central microbiology laboratory had results on electronic systems. Extraction, formatting, error checking and deduplication was performed manually. For deduplication, only one isolate was reported for each patient per surveyed specimen type and pathogen. All laboratories followed the Clinical and Laboratory Standards Institute (CLSI) system for Antimicrobial Susceptibility Testing (AST) (https://clsi.org/standards/). Data to inform guidelines for each infection syndrome was based on sample type rather than clinician diagnosis, as laboratory results were not linked to hospital records: blood culture results were used to inform sepsis guidelines, urine cultures for urinary tract infections, respiratory sample results for pneumonia guidelines, skin/wound swabs for cellulitis/soft tissue infections.

Guideline formation

We hosted a series of workshops using purposive sampling to invite 35 healthcare professionals alongside key stakeholders including Ministry of Health staff, hospital directors, infectious diseases physicians, microbiologists, and pharmacists. All professionals were either working in or governing one or both of the study hospitals. Of those invited, 26 attended and contributed to three initial stakeholder workshops followed by four subsequent meetings in each of the two study hospitals. During the workshops we orientated participants to the background of the project including collation of local microbiology and antibiotic data, introduced the ZARIApp, and gave a tutorial on how to use it. We then individually used the ZARIApp, to experiment with inputting the existing local data and exploring the output, and finally used the ZARIApp together as a

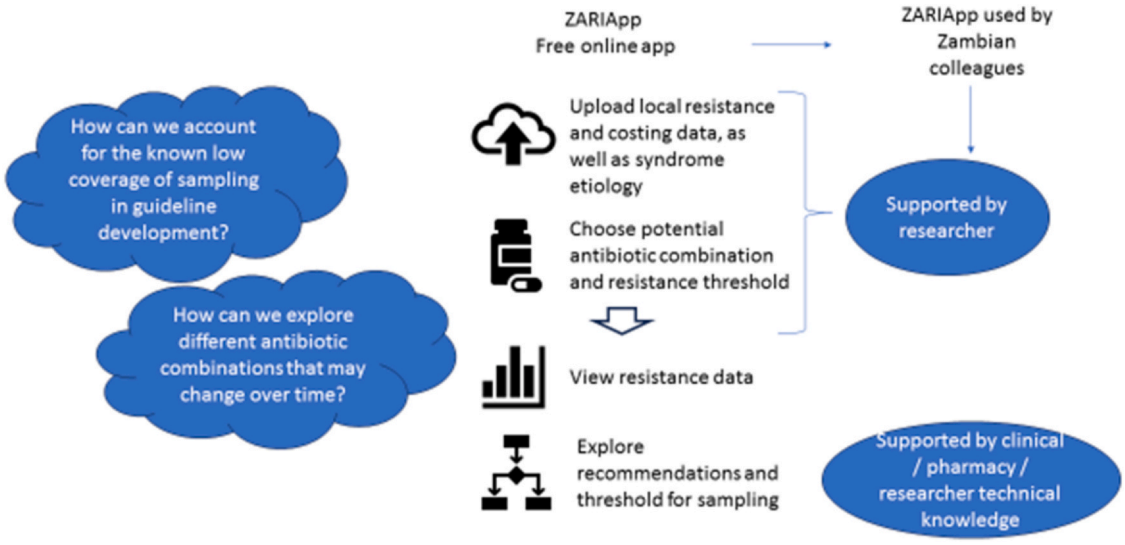


Fig. 1. A simple figure to summarise the workflow of the process we used to generate guidelines using the ZARIApp.

team to begin the discussions on guideline generation. During subsequent meetings we used the output from the ZARIApp to help generate and agree for each hospital a set of locally-relevant empirical antibiotic guidelines for important clinical syndromes. Fig. 1 summarises this process graphically.

We used focus group discussions (FGDs) to qualitatively evaluate the workshop participants' experience of using the ZARIApp to create the guidelines, including the ease or difficulties found using the app, and the usefulness of the app to help with antibiotic choices for the guidelines. We also solicited suggestions on improving the process. All participants of the workshops were invited to join the FGDs. Groups of 6 or 7 participants were formed. We obtained written informed consent from each participant. A Professor of Psychology from the University of Zambia (AM) gave training to experienced Zambian health care professionals to enable them to skillfully facilitate the FGDs. Discussions continued until no new themes emerged. We used handheld audio recorders to record and later transcribe the discussions. We used an inductive approach to thematic analysis to allow the data to determine emerging themes: we formulated the theories after the FGDs to identify the themes that emerged from the discussions. We adopted a semantic approach to analyse the explicit content of the data: we examined the meaning of words and phrases used during the FGDs to comprehend the intended purpose of the statements or discussions. We were therefore able to extract the key ideas discussed.

Once guidelines were complete, we obtained Ministry of Health approval to introduce the guidelines to each hospital.

App design

Alongside the stakeholder workshops and in response to participants' experience, the existing online tool [22] was iteratively updated to allow for (a) choice of antibiotic prescribing regimen, (b) inclusion of local syndrome aetiology and upload of local data on (c) resistance prevalence and (d) antibiotic costs. The output was tailored to include (e) a visualisation of resistance data and (f) a more detailed table of recommendations. The application was constructed using the R package *shiny* [24] and is available at https://gwenknight.shinyapps.io/zaria/. Fig. 2 gives a visualisation of how to use the ZARIApp.

The choice of therapy (a) allowed for up to 4 regimen choices (therapy line 1–4) with a dropdown choice of up to 3 antibiotics per regimen. For now, the ZARIApp includes no guidance on what antibiotics to combine in a regimen.

Data on resistance prevalence can be uploaded as an Excel file (template in Supplementary 1) by any user of the app or the preloaded Zambian data can be used. Syndrome aetiology can use that generated from the collected Zambia data or alternatively use a literature-based aetiology distribution if local data had insufficient samples to give reliable distribution estimates for a given aetiology. There is a check box on the ZARIApp which allows the user to choose this option. Costs can be uploaded as an Excel file (Supplementary 2). Users could choose to upload the cost per dose or the cost per standard treatment course of each antibiotic. The resistance threshold could, and should depending on the syndrome, be changed by the user but was set initially at 15% (an arbitrary threshold used in our previous work [22]).

The output shows a ranking of resistance within each bacterial species. The final output provides a table with a row for each proposed regimen (Fig. 3). Total cost of the regimen (per dose or per total treatment depending on cost parameters) is presented alongside a syndrome resistance level (SRL) which gives the weighted combination of resistance and aetiology, and is used to make the recommendation by comparing this projected resistance level to the threshold on the input tab. For each antibiotic in the regimen, if at least one has a SRL above the threshold, then the regimen is not recommended.

Also reported is the percentage of the bacteria causing this syndrome for which there is no resistance data ("Miss"; Fig. 3). In the main SRL, the assumption is that resistance in these missing bacteria is 0%, with a range shown in the medium and high SRL that assumed 50% (Med) or 100% (High) of the missing bacteria are resistant respectively.

Based on an awareness of the low levels of microbiological sampling coverage in Zambia (and other LMICs), we adapted the ZARIApp to explore the question "what percentage of patients with this syndrome are sampled in my setting?" and provide a "threshold for sampling" (Box 1). If a sample is not taken from a patient then their bacteria will not contribute to the denominator used to calculate the prevalence of resistance. Hence, this analysis aims to account for the bias in routine surveillance – often only patients for whom empiric therapy is failing are sampled. The threshold for sampling is "NA" in the ZARIApp if the resistance prevalence is already below the threshold.

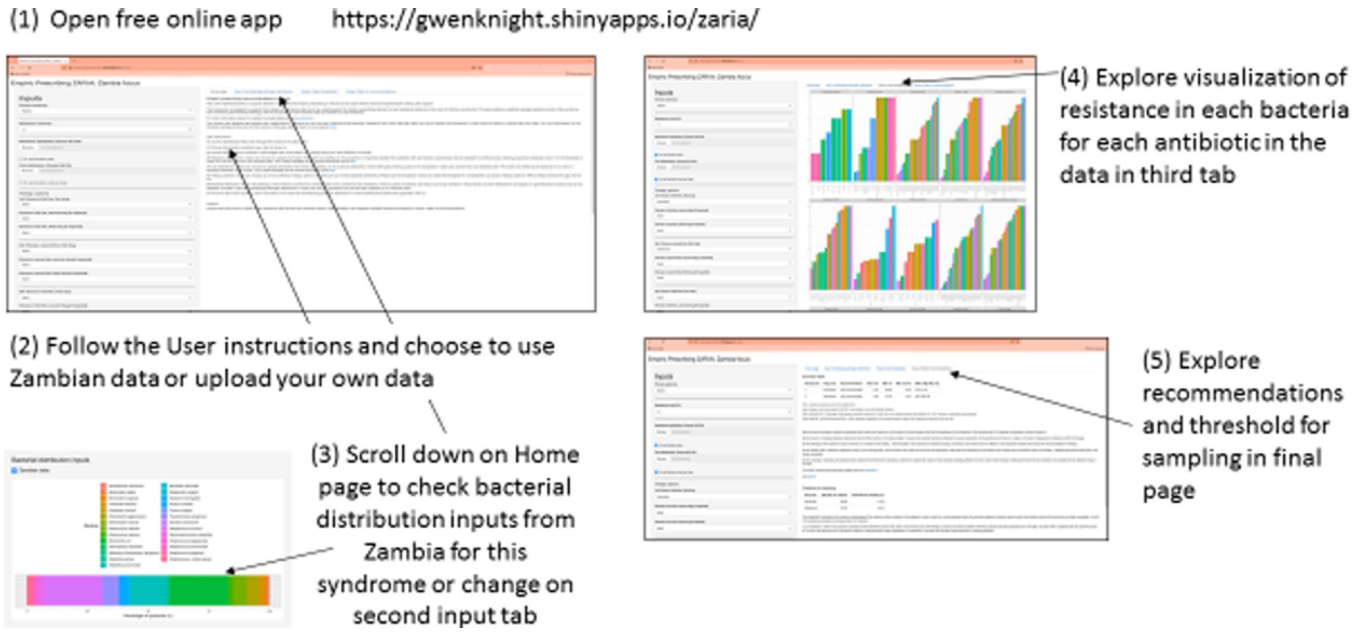


Fig. 2. ZARIApp usage.

Ethics approval

Ethics approval to undertake all aspects of this work was granted from the University of Zambia Biomedical Research Ethics Committee (Ref No: 1838–2021), the National Health Research Authority of Zambia (Ref No: NHRA00013/24/09/2021) and the London School of Hygiene and Tropical Medicine Ethics Committee (Ref No: 26593).

Results

Microbiology data

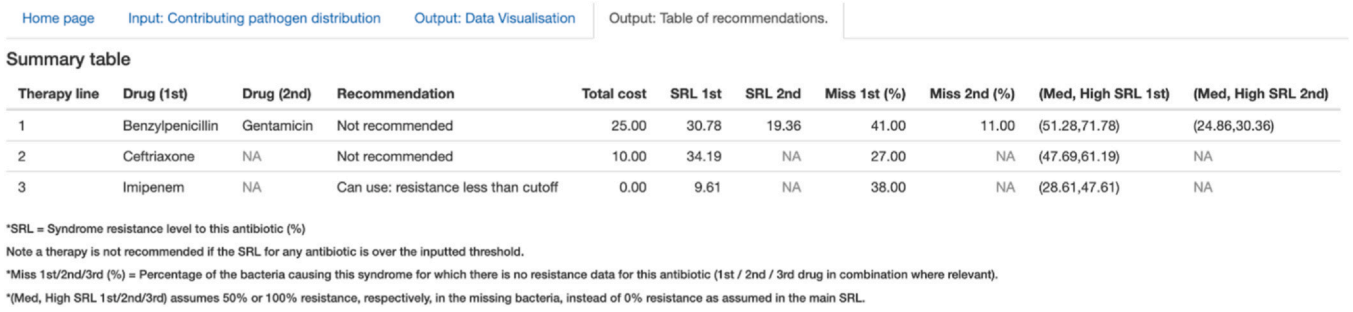
We collated samples that had been collected from patients between April 2020 – April 2022. This accumulated to 58 microbiology sample results that had identified growth of an organism from Hospital 1 and 1300 from Hospital 2, giving 52 and 941 respectively after error checking and deduplication as per the Global Antimicrobial Resistance and Use Surveillance System guidelines. The central laboratory gave an extra 17,204 sample results with organism growth before and 2632 results after error checking and deduplication. This amounted to a total of 3625 microbiology sample results that had identified growth of an organism. Electronic extraction of the results from Hospital 2 and the central laboratory caused additional erroneous duplication due to manual error which accounted for the large number removed on deduplication.

Half (51.9%) of all samples were from male patients. All samples were from adults, age 18 years or above. Urine samples, skin/wound swabs and blood cultures accounted for 1153 (31.8%), 867 (23.9%) and 804 (22.2%) samples respectively of all sample types collated (Table 1). Of all sample results collated *Escherichia coli* and *Staphylococcus aureus* were isolated from 630 (17.4%) and 442 (12.2%) samples respectively (Table 2). There were 655 (18.1%) isolates that were only identified to the genus-level or above. We did not use these to inform resistance rates.

We found frequent high rates of resistance, though there was a low number of samples for many antibiotic-organism combinations (Table 3). Of 210 *Staphylococcus aureus* isolates that were tested for susceptibility to cefoxitin, 47% were resistant (cefoxitin resistance is used as a surrogate marker for methicillin resistance). Of 41 and 157 *Escherichia coli* isolates that were tested for susceptibility respectively, 73% were resistant to ceftriaxone and 44% were resistant to gentamicin. There were 25 *E. coli* isolates tested for susceptibility to both ceftriaxone and gentamicin. Among these, 52% were resistant to both antibiotics.

Qualitative evaluation

Workshop participants comprised of 13 doctors, 10 pharmacists, 2 microbiology laboratory scientists - all of varying seniority (2 years to 22 years in role) - and 1 nurse. Thirteen participants of the initial


Home page | Input: Contributing pathogen distribution | Output: Data Visualisation | Output: Table of recommendations.

Summary table

Therapy line	Drug (1st)	Drug (2nd)	Recommendation	Total cost	SRL 1st	SRL 2nd	Miss 1st (%)	Miss 2nd (%)	(Med, High SRL 1st)	(Med, High SRL 2nd)
1	Benzylpenicillin	Gentamicin	Not recommended	25.00	30.78	19.36	41.00	11.00	(51.28,71.78)	(24.86,30.36)
2	Ceftriaxone	NA	Not recommended	10.00	34.19	NA	27.00	NA	(47.69,61.19)	NA
3	Imipenem	NA	Can use: resistance less than cutoff	0.00	9.61	NA	38.00	NA	(28.61,47.61)	NA

*SRL = Syndrome resistance level to this antibiotic (%)

Note a therapy is not recommended if the SRL for any antibiotic is over the inputted threshold.

*Miss 1st/2nd/3rd (%) = Percentage of the bacteria causing this syndrome for which there is no resistance data for this antibiotic (1st / 2nd / 3rd drug in combination where relevant).

*(Med, High SRL 1st/2nd/3rd) assumes 50% or 100% resistance, respectively, in the missing bacteria, instead of 0% resistance as assumed in the main SRL.

Fig. 3. Screenshot of online web tool ZARIApp showing example final output.

Box 1
Walk through of calculation steps to determine threshold for sampling with example.

What we know: Resistance prevalence in sample

Should we change antibiotic guidance based on this?

Need to know:

1) At what population-level resistance prevalence would we change antibiotic guidance?
Resistance cutoff value

2) What proportion of those not sampled are infected with susceptible bacteria?
Bias towards sampling infections failing empiric therapy so more likely to sample patients with resistant infections

3) What proportion of the total population were sampled?
Difficult to know from existing data, but often clinicians have an idea of this. Change the focus to:

What **maximum coverage** of the total population would the sample have to be for the estimated *population resistance prevalence* to be below the resistant cutoff value?

= Threshold for sampling

Example

10 patients with infection sampled,
5 patients with resistant isolates
= 50% resistance prevalence in sample

Use a 1) 15% resistance cutoff and
2) assume all those patients not sampled are infected with susceptible bacteria.

What is the threshold for sampling?

Sample coverage	Total population size (nearest individual)	Population resistance prevalence (resistance / total number)
100% (all patients with infection syndrome)	10	50%
50%	20	(5 / 20 =) 25%
30%	33	(5 / 33 =) 15% ← Resistance cutoff
10%	100	(5 / 100 =) 5%

Threshold for sampling = 30%

Implications:
- If the sample (n=10) represents more than 30% of the total population infected, then the population resistance prevalence is greater than the resistance cutoff and antibiotic use guidance should be changed*.
- If fewer than 30% of the total population with infection are sampled then antibiotic use guidance should not be changed*.

**Assuming that all those not sampled have infections with susceptible bacteria*

Table 1
Sample types of the collated microbiology results, with total numbers (n) and percentage of all samples (%).

Sample type	n	%
Urine	1153	31.8
Skin/wound swabs	867	23.9
Blood cultures	804	22.2
Respiratory	313	8.6
Stool	89	2.5
Cerebral spinal fluid	38	1.0
Ear / nose / throat	16	0.4
Tissue	6	0.2
Other	176	4.9
Missing data for sample type	163*	4.5
Total	3625	100

Other includes: vaginal/penile/urethral swabs, semen, eye swabs/discharge, pleural fluid, ascitic fluid, peritoneal fluid, joint aspirates and catheter tips; *Feedback re. missing data was given to the laboratory team and found to be due to a problem with the IT download system. This has subsequently been addressed.

Table 2
Organisms isolated among the collated microbiology sample results.

Organisms isolated	n	%
Escherichia coli	630	17.4
Staphylococcus aureus	442	12.2
Klebsiella pneumoniae	343	9.5
Pseudomonas aeruginosa	173	4.8
Enterococcus faecalis	70	1.9
Enterococcus faecium	41	1.1
Klebsiella aerogenes	39	1.1
Enterobacter cloacae	31	0.9
Acinetobacter baumannii	15	0.4
Streptococcus pneumoniae	12	0.3
Other	1829	50.5
Total	3625	100

stakeholder workshops participated in two FGDs. Each FGD lasted for roughly 120 min.

We coded the FGD data into 15 identified codes and grouped these into 7 themes (Table 4). Suggestions for improvement of the ZARIApp emerged as one of the themes. We identified 10 specific suggestions from the data on how the ZARIApp could be modified to improve its usefulness, clarity and ease of use. These suggestions were used to inform the app design section, described above in Section 2.4.

A universal strong level of support for using the ZARIApp to generate locally-relevant empirical guidelines was noted. The ZARIApp was found to be useful and easy to use by all participants. However, low levels of microbiology samples from patients leading to unrepresentative microbiology data emerged as the major barrier to generating locally-relevant guidelines. The high rates of resistance were thought to reflect over-representation of samples processed in the microbiology laboratories from patients with severe or complicated disease or those not responding to initial antibiotics, and the underrepresentation of samples from patients with uncomplicated disease and/or those who improve readily on initial empiric therapy. A multidisciplinary approach, infection/microbiology expert knowledge, AMR/AMS education and adequate internet access were all identified as important factors for the ZARIApp to function. Over time, it was thought that use of the ZARIApp and resulting guidelines could help influence improvements in routine surveillance and drug procurement.

We did not formally explore the reasons for few patients having microbiology samples requested and processed, though potential reasons were discussed among the teams contributing to guideline development. The foremost explanations given were irregular stock of consumables, and lengthy time from sample request to receiving the result, which was also thought to be due to irregular stock of consumables and therefore often the result was clinically unhelpful. Both factors were thought to contribute to a consequent 'culture of not taking cultures'.

ZARIApp improvements

A key addition to the ZARIAapp was the development of the threshold for sampling. Users of ZARIAapp are strongly encouraged to estimate the coverage of sampling in their setting (i.e. the proportion of patients with the relevant syndrome who have a sample collected), consider the level of resistance in those not sampled and

Table 3
Percentages of isolates tested that were susceptible for the common antibiotics used in our study setting and for the significant organisms isolated from routinely processed samples, expressed as "percentage of isolates susceptible (number of samples tested)".

Organism	Percent of isolates susceptible (number of samples tested)									
	Amox/ Clav	Ampicillin	Cefotaxime	Cefoxitin*	Ceftriaxone	Ciprofloxacin	Erythromycin	Gentamicin	Imipenem	Penicillin
Escherichia coli	68 (82)	10 (291)	35 (93)		27 (41)	37 (183)		56 (157)	98 (200)	
Staphylococcus aureus	100 (3)	50 (16)	50 (4)	53 (210)	100 (2)	60 (239)	53 (220)	83 (174)	67 (3)	
Klebsiella pneumoniae	54 (69)		26 (68)		12 (40)	39 (124)		42 (135)	93 (168)	
Pseudomonas aeruginosa		20 (5)**	0 (1)**		0 (1)**	83 (114)		77 (120)	94 (96)	
Enterococcus faecalis		65 (23)				55 (42)		100 (1)		
Enterococcus faecium						37 (32)				
Klebsiella aerogenes	25 (4)		14 (7)		50 (2)	18 (11)		40 (10)	87 (8)	
Enterobacter cloacae	33 (3)		0 (5)		67 (3)	56 (9)		67 (6)	100 (13)	
Acinetobacter baumannii		100 (1)	100 (1)		100 (2)	25 (12)		42 (12)	100 (10)	
Streptococcus pneumoniae			0 (1)		50 (2)		60 (5)			100 (2)

Amox/ Clav = Amoxicillin and Clavulanate combination; *Used as an alternative method of testing for methicillin resistant Staphylococcus aureus; **Testing Pseudomonas aeruginosa for these antibiotics is outside of the laboratory standard operating procedures and so was likely erroneous; All figures are presented for relevant bacteria-antibiotic combinations even for combinations with a very low sample number. These combinations with low sample numbers do not provide reliable estimates of susceptibility but show the extent and reality of low sample numbers; Of note, we have not included results for antibiotics that are not routinely available or used as a treatment option in our study setting. This includes clindamycin, nitrofurantoin and vancomycin. Trimethoprim sulfamethoxazole is widely available but is used extensively as prophylaxis and so rarely considered for use as treatment; The laboratories follow CLSI standards for susceptibility testing, but shortages of consumables can cause some samples to have incomplete susceptibility results.

combine this with the resistance prevalence in the sample to explore how close population resistance prevalence could be to the resistance threshold. If their estimated sampling proportion was close to the threshold for sampling then it may not be appropriate to use the antibiotic as an empirical choice, given the assumption that all those unsampled have an infection due to a susceptible bacteria. If the estimated sampling proportion was far lower the threshold for sampling then it may be reassuring that this could be an appropriate empirical treatment option despite the improbability that every unsampled case is infected with sensitive bacteria.

The complexity of the interplay between the percentage of the samples that are resistant, the prevalence of resistance in those unsampled and the percentage of patients not sampled that are resistant (Fig. 4) demonstrates the importance of understanding bias in settings to correctly interpret data. In highlighting the need to know both the (i) risk of resistance in those unsampled and (ii) how many are sampled, we demonstrate the importance of local knowledge in developing empiric antibiotic usage guidelines.

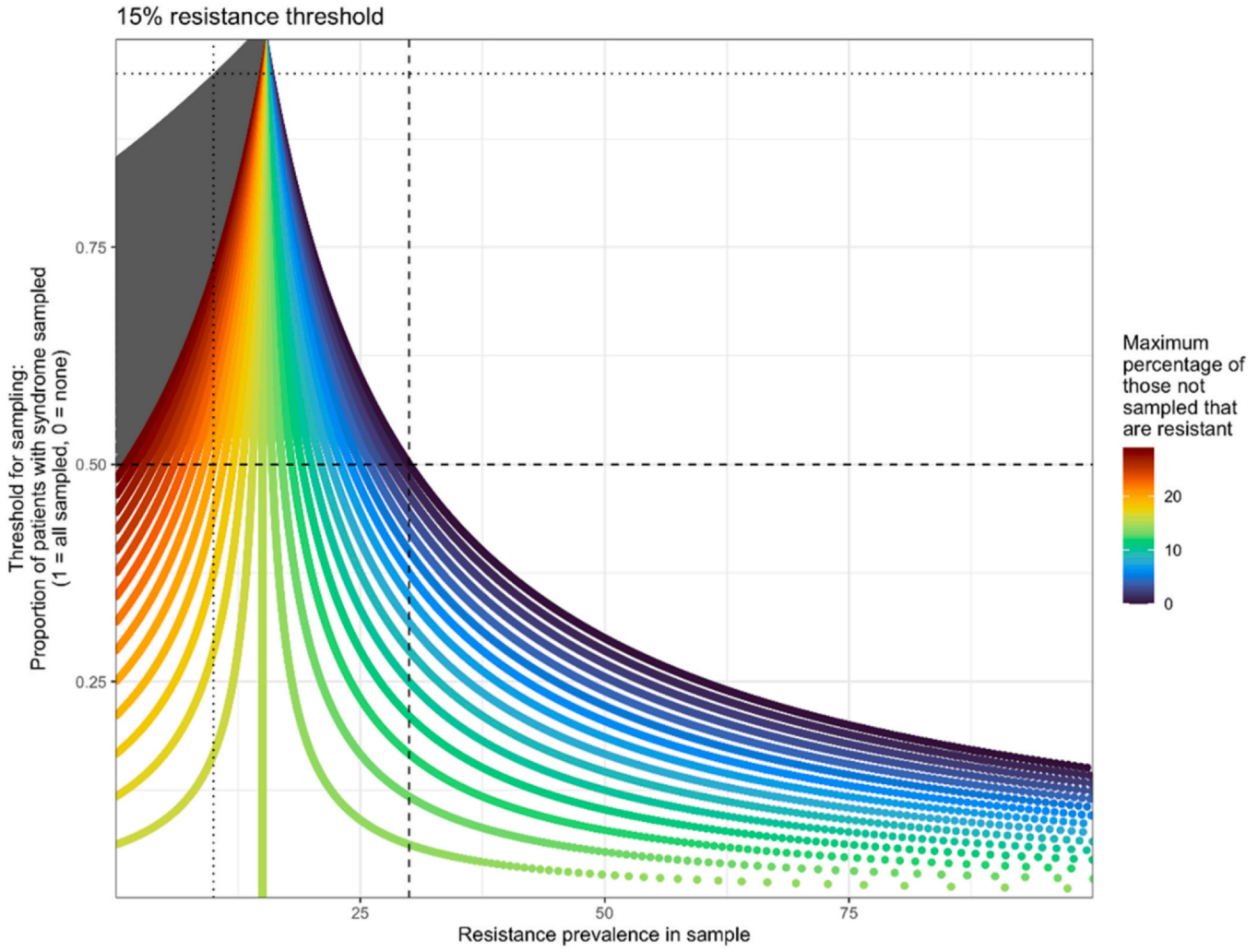
Discussion

We describe the first attempt to use a novel digital tool to support local clinicians and decision makers in a LMIC setting to use routine hospital data to inform local antibiotic empiric prescribing guidelines. Through a collaborative process with key stakeholders, we used and adapted the tool in response to user experience and feedback. The guidelines generated using the adapted tool are now in use in both study hospitals.

There was consensus among participants on the usefulness of the tool to inform locally-relevant empirical guidelines but the process highlighted challenges. Production of the local summary AMR report required time-intensive collation from paper records and manipulation

Table 4
Themes identified from the focus group discussions.

Theme	Number of times identified	Quotes
The ZARIApp is useful and easy to use	35	*"this app can really, really help, because we're using real data, we're not using data which is not from this region with microbes which are not particular to our region. So for me, I think it's something that can help us to even make more informed decisions as to what is best suited for our environment"* *"it was user friendly because I think I was encountering it for the first time and it didn't take me much time, not more than 5 min to understand what was going on"*
Current data is insufficient - better routine AMR surveillance is needed	31	*"we just need to improve the culture of actually doing cultures"* *"the data that we have is only representative of critical patients"* *"the only way we'll make good guidelines, is if we know what we are fighting"*
Suggestions for improvement	10	*"So the major thing being us having to change those values for each and every bacteria for each and every syndrome that we have the percentages, trying to work around them, putting the antibiotics according to the syndrome that you have. And then if it logs you out, you have to start all over again and start playing around with those things. Basically that was our biggest challenge. Yeah, so it'll be much easier if it could be another input file. You have the distribution percentages in a file and you just import it and then it populates it automatically"*
A multidisciplinary team with expert knowledge is required	7	*"I don't think AMS/AMR can be done by physicians. It can't be done by pharmacists and micro alone. You need to put your heads together"*
Education is important	5	*"We need to educate each other… on what are the best practises to reduce the emergence of resistant bugs"* *"if the grassroot is educated and it moves level by level, even such implementation will not require so much extra input, because the match has been lit, and you know, as it were, the proverbial grass is already burning"*
Adequate internet access is required	3	*"It's an easy app to use as long as the internet is good enough"*
The ZARIApp could help to influence improvements in routine surveillance and drug procurement	3	*"it's something that will help us do more cultures"* *"that can as well influence the policymakers in what kind of antibiotics they need to be procuring"*



Threshold for sampling

Drug (1st)	Drug (2nd)	Max SRL for regimen	Threshold for sampling (%)
Benzylpenicillin (IV)	Gentamicin (IV)	30.78	48.74
Ceftriaxone (IV)	NA	34.19	43.87
Imipenem	NA	9.61	NA

Fig. 4. Top: The threshold for sampling (y axis) at a 15% resistance cutoff when relaxing the assumption that those not sampled are totally susceptible (colours) has a non-linear relationship with the resistance prevalence in the sample (x axis). Values where more than 30% of those not sampled are resistant are shown in dark grey. The lines illustrate two examples: if 30% (dashed vertical line) of samples are resistant to an antibiotic then resistance within the non-sampled population must remain below ~15% (light green) and the proportion of sampling below ~50% (dashed horizontal line) for the resistance threshold to not be crossed. Alternatively, if 10% (dotted vertical line) of samples are resistant to an antibiotic, then the maximum percentage of those not sampled that have resistanceto an antibiotic can be above 30% if the sample goes up ~95% (dotted horizontal line) of all patients. Bottom: the threshold for sampling output as shown in the ZARIApp: a value of 48.74% means that, under the assumption that all those unsampled are infected with susceptible bacteria, this sample must be at most 48.74% of the population for the population resistance prevalence to be below the 15% threshold.

of electronic microbiology data to produce an analysable form. This is unrealistic to perform outside of a research setting and therefore limits the use of the ZARIApp to settings that have existing capacity to routinely produce an AMR report. Manual manipulation of the data also gives rise to the possibility of human error, such as we saw with data duplication during extraction from the laboratory system. A future option for reducing human error and increasing accessibility for hospitals that do not already have capacity to automate the production of AMR reports, is to link the ZARIApp to existing technology to automate the process, such as through the use of the Automated tool for Antimicrobial resistance Surveillance System [25], which is already linked to the widely available WHONET software [26]. Exploration of the possibility of this is currently underway.

Resistance rates for key pathogens found in our routinely-collated microbiology data were high, although sampling bias was thought to be a contributing factor to this. This led to a key output from our discussions: the formation of the threshold for sampling. If users believe the patients sampled in their setting do not include all patients with a particular syndrome and are biased towards those with more resistant infections then they can use the threshold for sampling to help with decision making. We also explored varying the assumption of total susceptibility in the non-sampled patients and found a complex relationship that can be helpful if the level of bias in sampling is known or can at least be estimated.

This work emphasises the substantial sampling bias that exists in routinely-collected microbiology sample data in LMIC. Our qualitative

analysis highlights that local clinicians are acutely aware of this, and yet this insight does not seem to be accounted for in most global estimates of burden trends [27]. The resulting concern is that without local sampling knowledge, resistance prevalence can be inferred to be higher than its true prevalence, which can then infer the need for usage of broad-spectrum antibiotics and consequently hinder efforts to reduce AMR selection. We hope that with the above threshold for sampling local clinicians and AMS teams can use this insight to better understand the importance of the patient group that they sample.

Formal exploration of factors that determine sampling practices would be helpful to better understand how to increase the proportion of patients who have samples requested and processed. Future work also needs to explore the importance of local empiric prescribing and the antibiotic prescribing pathway – what antibiotics *are* working informs who is sampled – to better understand the drivers of both antibiotic use and microbiological sampling.

We were unable to link microbiology samples to patient clinical data and so we were unable to distinguish community- from hospital-acquired infections. The sampling bias described is likely to be more pronounced in community-acquired than hospital-acquired infections and so the resulting guidelines will be especially biased towards increasing the spectrum of empiric antimicrobials in community-acquired infections. In this setting, the guidelines generated are therefore most useful for hospital-aquired infections.

An indirect but important issue that this work highlights is the lack of routine access to some key antibiotics in our study setting, including nitrofurantoin, clindamycin and vancomycin. As discussed during the FGDs, we hope that tools such as the ZARIApp can help to influence improvements in drug procurement as well as in all aspects of routine surveillance.

Our free online, open-access application can be utilised by any setting that has local resistance data, information on antibiotic costs and wishes to explore a range of regimen options. However, it produces recommendations that still need clinical support to interpret and use for empiric guideline formation. We provide no guidance on reasonable or effective regimen combinations and would advise that any output is assessed by trained clinicians, pharmacists, and local antibiotic guidance experts. The simple data manipulations provided by the WISCA (i.e. weighted averages) provide a syndrome resistance level which is more informative for clinical decision making than resistance prevalence at the level of individual bacteria, and so use of the tool provides the stewardship team with quick and easy access to this information to help support guideline development. With no trend data available on resistance, the ZARIApp could make no uncertainty estimates as to the likely resistance prevalence or uncertainty. A next step would be to include complexity such as uncertainty and long-term trends (e.g. [28]) but this would require data that is currently unavailable in these Zambian hospitals and many other LMICs. Further work needs also to consider access and antibiotic availability - the ZARIApp could then be used in real time as issues in supply of antibiotics arise to guide any recommendation adaptation.

Conclusions

We have piloted a novel digital tool resulting in the generation of empiric antibiotic prescribing guidelines for two hospitals in Lusaka, Zambia. We have presented a way for clinicians and policymakers to take their local data and produce recommendations relevant to their own local resistance patterns and available antibiotics. However, the usability of the ZARIApp is severely limited by a lack of sampling data; improved routine microbiology surveillance is vitally needed. Tackling the reasons for this lack of sampling by demonstrating the importance of such data to local clinical decision making is vital to optimise antibiotic use and hence slow AMR selection, as well as to improve patient outcomes. By designing tools such as the ZARIApp, we hope to facilitate the first steps to empower local settings to understand and optimise their own clinical decision making both in terms of how sampling can help improve patient care but also reduce mortality and future AMR.

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Authorship contributions

SF, AMA, SLB and GMK contributed to initial study concept. SF, ASCJ, JI, JAM, AMA, SLB and GMK contributed to study design. SF and SLB oversaw all study activities.UC, RN, TT, TM, MK, TM, IM, EC, AM, WM and LM contributed to data collation and guideline formation. GMK undertook all app adaptations. SLB performed the quantitative and qualitative data analysis. JAM advised on all qualitative aspects of the study. SLB and GMK wrote initial drafts and all authors contributed to final editing of the paper. All authors have approved the final article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.11.007.

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