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Keeping It Real: Antibiotic Use Problems and Stewardship Solutions in Low- and Middle-income Countries

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Abstract: Antimicrobial resistance is a global health threat and there is an urgent need to manage antibiotic use to slow its development. However, antimicrobial stewardship interventions in low- and middle-income countries (LMIC) have been limited in terms of their resourcing, feasibility and effectiveness in the face of greater challenges in child mortality. We sought to gather together examples of antibiotic use problems faced by clinicians in LMIC, many of which are unique to these settings, and real-world antimicrobial stewardship solutions identified, with the goal of learning broader lessons that might be applicable across LMIC.

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Antibiotics have been one of the miracles of modern medicine, both in terms of treating previously fatal bacterial infections, and preventing infections in patients needing complex management such as those with cancer or requiring surgery.[1,2] However, widespread use of antibiotics has accelerated the development of antimicrobial resistance (AMR) globally so that previously effective drugs have become ineffective.[3,4] Development of new drugs has not kept pace with the increase in AMR, resulting in infections becoming difficult, and sometimes impossible, to treat, raising the specter of a postantibiotic era.[5] It is estimated that in the absence of effective public health interventions, AMR will contribute to over 10 million deaths by 2050, with associated economic losses.[6] The World Health Organization (WHO) has declared AMR one of the most urgent health threats of our time and that safeguarding the effectiveness of antibiotics is a public health priority.[7]

Antimicrobial stewardship (AMS) aims to preserve antibiotic effectiveness through interventions that are persuasive (education and feedback), restrictive (guidelines and controls) and structural (governance and audits).[8] Successful implementation of AMS is expected to limit the negative impacts of antibiotic use such as drug toxicity and AMR, while not worsening, and indeed improving, patient outcomes.[9] AMS programs have been implemented and evaluated extensively in high-income countries, and have shown great success.[10] In resource-constrained settings of low- and middle-income countries (LMIC), however, there is growing recognition of the barriers and challenges that impede the implementation of AMS.[11] Compared with the developed world, developing countries experience vast infrastructural limitations which both drive the problem of AMR and undermine the feasibility of AMS. These include high patient load with poor infection control practices in healthcare facilities, paucity of diagnostic laboratories with delays in results, over-the-counter (OTC) availability of antibiotics, substandard drug quality and critical drug shortages.[12,13] In addition, the evidence for AMS for children in LMIC is limited in terms of the effectiveness and feasibility of interventions.[13–15]

Given the challenges and relative paucity of evidence for AMS programs in children in LMIC, we aimed (1) to identify real-world solutions to problems and (2) to determine whether there were broader lessons from such innovations.

METHODS

An open call was made for clinicians to describe their experiences in finding solutions to real-world antibiotic use problems in low- and middle-income settings. The definition of LMIC used was according to the World Bank group. The request was sent out via e-mail in September 2020 to individuals via the World Society of Paediatric Infectious Diseases, and also through the World Society of Paediatric Infectious Diseases regional member societies: African (AfSPID), Asian (ASPID), Australasian (ANZPID), European (ESPID), North American (PIDS) and South American (SLIPE). Clinicians in LMIC were requested to author a brief "real world problem, real world solution" for AMS and/or Infection Prevention and Control (see accompanying paper "Keeping It Real: Infection Prevention and Control Problems and Solutions in Low- and Middle-income Countries") describing their setting, the problem encountered and the solution(s) applied by them in their workplace that could "help colleagues in other parts of the world solve the same problem or understand the challenges of work in LMIC." Potential AMS areas for consideration were suggested, but not limited to: antibiotic overuse and misuse, access to antibiotics and microbiology, guidelines and education. Further follow-up queries for additional details were sometimes sought after the initial contribution. The experiences were collated, edited for length and style and are presented here.

REAL-WORLD SITUATIONS

Contributions were received from Africa, Asia and Latin America from primary care physicians, pediatricians, public health specialists, intensive care specialists, microbiologists and clinical pharmacists who described the AMS challenges and the solutions implemented by them in their local settings (Table 1).

Excessive Use of Broad-spectrum Antibiotics in Hospitalized Children

Studies about inappropriate antibiotic use have frequently focused on hospitals, because larger centers often have better resources to audit their use.

Setting: A tertiary hospital in Bolivia with the only pediatric intensive care unit (PICU) in the public sector, which receives 300 admissions per year.

Problem: In 2016, we had an alarming increase in infections with multidrug-resistant *Acinetobacter baumannii* in our PICU (carbapenem resistance over 90%), with a rate of 8 per 100 admissions.[16] This resulted in increased length of stay, increased cost for colistin (the only antibiotic to which the infection was susceptible) and higher mortality.

Solution: We took a combined epidemiologic and AMS approach. Environmental studies found no healthcare personnel carriage, but *A. baumannii* was found on a fan. The presence of colonizing bacteria *Staphylococcus aureus, Staphylococcus epidermidis* and *Enterobacter* spp. in patients had a strong negative association with *A. baumannii* infection. The empirical antibiotic regimen for sepsis had become very broad in the form of imipenem, clindamycin and amikacin, and we hypothesized that this was contributing to the bacterial ecologic imbalance. The empirical recommendation was changed to third generation cephalosporins and aminoglycosides, keeping imipenem and clindamycin in reserve. Thereafter, there was reduction in infection with *A. baumannii*.

Lessons: Using an epidemiologic approach to a local problem, we addressed the root cause and provided a tailored solution.

Setting: An inpatient unit of a public pediatric hospital in Sao Paulo, Brazil.

Problem: Intravenous (IV) antibiotics are frequently given for excessive durations in LMIC, partly through a lack of guidance. In our setting, the median IV antibiotic duration for hospitalized children with uncomplicated community-acquired pneumonia was 4 days (interquartile range, 3–6). Guidelines from high-income countries recommend IV to oral switch with clinical improvement, usually within 48–72 hours.[17,18] However, in our study, only 22% children switched at the appropriate time and the most common reason (61%) to switch was accidental loss of venous access.

Solution: We implemented a checklist with eligibility criteria for switch from IV to oral antibiotics after 48 and 72 hours, including tolerance of oral fluids, absence of vomiting, improvement of respiratory distress, absence of lethargy and reduction in fever. The results were that IV to oral switch happened appropriately in 97% patients, with resulting decreases in IV duration (4–3 days; $P < 0.01$), total duration of antibiotics (10–7 days; $P < 0.01$) and length of stay in hospital (5.5–4.5 days; $P = 0.04$).[19]

Lessons: Recommendations made in high-income countries can be appropriately targeted and result in successful outcomes in a low-income setting.

Setting: A tertiary teaching hospital in Bangkok, Thailand, with approximately 200 pediatric beds and 8000 admissions per year.

TABLE 1. Healthcare Specialty and Setting of Contributors Reporting Antimicrobial Stewardship Challenges

Region	Respondent Specialty (and No.)	Healthcare Setting	AMS Problem Described
Latin America			
Bolivia	Pediatric intensive care 1	PICU	High prevalence of multidrug-resistant bacterial infections
Brazil	Clinical pharmacy 1	Hospital PICU	Unwarranted prolonged IV antibiotic use without oral switch
			Errors in antibiotic monitoring
Asia			
Thailand	Pediatric ID 2	Hospital	Overuse of broad-spectrum antibiotics in hospital
Philippines	Pediatric ID 1	Hospital community	Overuse of broad-spectrum antibiotics in hospital
India	Public health and primary care 1	Primary care	Over-the-counter sale of antibiotics and self-medication
			Antibiotic self-medication in the community
Africa			
Kenya	Pediatrics 2	Hospital	Overuse of broad-spectrum antibiotics in hospital
	Nursing 1	NICU	Overuse of broad-spectrum antibiotics in ICU then shortages
Mauritius	Clinical microbiology 1	NICU	Antifungal shortages in ICU setting
Tanzania	Pediatrics 1	Hospital	Poor microbiology systems and communication of results
Nigeria	Pediatric pulmonology 1	Community	Over-the-counter sale of antibiotics and self-medication
Malawi	Pediatrics 2	Community	Over-the-counter sale of antibiotics and self-medication
Botswana	Pediatrics 1	Hospital	Poor antibiotic use quality assurance
Ethiopia	Pediatric ID 1	NICU	Intravenous antibiotic shortages
		Hospital	Oral antibiotic shortages and inappropriate substitution
		Outpatient	Failure of laboratory diagnostics for multiple reasons
		Hospital	Limited laboratory and human resources for AMS

AMS indicates antimicrobial stewardship; ID, infectious disease, IV, intravenous; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

Problem: In 2016, 31% of pediatric prescribing at our hospital was inappropriate.[20] Meropenem was the most commonly prescribed antimicrobial, overall (22%) and in PICU (29%). This coincided with sharp increases in carbapenem-resistant Enterobacteriaceae (CRE): rates among *Klebsiella pneumoniae* isolates were 22% and *Escherichia coli* 4%.[21] This CRE increase was reflected nationally.[22]

Solution: We implemented a bundle of AMS measures: (1) The AMS team developed and distributed local practice guidelines; (2) Prospective audit and feedback, including specifically on meropenem use, was implemented during twice-weekly AMS rounds; (3) Meropenem consumption by day of therapy per 1000 patient-days was reported publicly every 3 months. The greatest challenge we faced was the low acceptance of de-escalation recommendations because physicians were concerned about effectiveness of alternatives. There were significant decreases in day of therapy/1000 days pre- and post the intervention for vancomycin (31%) and colistin (62%).[23] Meropenem prescribing was more stubborn, and although there was 12% reduction, this was not significant. There was no change in length of stay or mortality.

Lessons: While we had some successes, it may not be sufficient to develop guidelines based on local microbiology. It is important to address clinician anxiety to effect behavioral change.

Setting: The pediatric department in a national referral hospital in Manila, The Philippines.

Problem: There was widespread excessive use by junior medical staff of broad-spectrum antibiotics. The empiric guidelines were being ignored, and it was common for patients to have antibiotics changed every 24 hours if they were perceived not to be improving. Examples included starting piperacillin-tazobactam if a patient still had fever, without assessing for a source or the need for antibiotics at all.

Solution: We started 1-day interactive educational workshops for junior staff. Topics include principles of antibiotic use, pharmacokinetics/pharmacodynamics, IV-oral switch and other de-escalation. Activities include small group discussions, case analysis, role-playing, team-building and contests. At the end, attendees are asked to pledge to use antibiotics responsibly. The workshops receive consistently positive feedback. Since they started, juniors adhere more to the guidelines, hold off changing antibiotics until 48–72 hours, and do not start antibiotics just for fever. Over the same period, resistance to -third generation cephalosporins in nosocomial infections has decreased at our hospital. While there have been other AMS interventions at our institution, we believe the workshops have facilitated behavioral change.

Lessons: There are ways of making learning about rational antibiotic use fun and interactive, through promoting engagement, interaction and participation.

Setting: A district hospital in rural Kenya with approximately 5000 pediatric admissions/year.

Problem: There was widespread empirical use of broad-spectrum antibiotics, particularly third generation cephalosporins, for children presenting with fever, lethargy (provisionally diagnosed as "malaria or meningitis") or upper/lower respiratory symptoms. With overcrowded wards and minimal infection control, multidrug-resistant organisms have subsequently been rife.[24] Sporadic outbreaks of extended spectrum β-lactamase (ESBL)–producing Enterobacteriaceae have therefore occurred, with high mortality.[25]

Solution: We established an education program by launching a local enrollment site in a Diploma of Child Health program: a graduate-entry, online program for doctors, clinical officers and nursing staff that builds knowledge, skills and confidence in diagnosing and treating children. The goal was that by encouraging broader differentials and greater diagnostic accuracy, antibiotic prescribing could be reduced. Funding was obtained from a non-Governmental organization to facilitate enrollment. While empirical antibiotic prescribing has not yet been formally audited, feedback indicates that clinicians now more frequently consider viral infections, and consider metabolic and endocrine causes of lethargy before broadening antibiotics in children not responding to first-line treatment. Three years later, local staff are now orchestrating the tutoring and course to the great benefit of their own staff.

Lessons: Clinicians are often eager to improve their diagnostic acumen, and education is an empowering tool to support rationalization of antibiotic use.

Setting: Public general hospital neonatal intensive care units (NICUs) in Mauritius.

Problem: In 2001, meropenem became available in Mauritius and empirical treatment in NICUs gradually changed from cefotaxime and amikacin to meropenem and amikacin. This combination worked well for 10 years, until CRE (most resistant to both meropenem and amikacin) started to be identified and these multiresistant bacteria have been a problem in ICUs (initially in adults) since 2015. Some NICUs have started to use meropenem and colistin empirically for hospital-acquired sepsis. Recently, there were small outbreaks in 3 different NICUs with *Klebsiella* spp. resistant to carbapenems and colistin.

Solution: The only available antibiotic to which isolates were susceptible was chloramphenicol, and this was used with variable results. In the first unit, 4 of 5 recovered but in the second 2 of 3 developed thrombocytopenia with bleeding and died. By the third NICU outbreak, the country had run out of IV chloramphenicol, so oral chloramphenicol was used with poor outcomes. The bacteria were susceptible to tigecycline, and 1 family obtained some from abroad but treatment of their infant was unsuccessful. Other newer agents not yet available in Mauritius either showed no susceptibility (eg, ceftazidime-avibactam—likely because many of our CRE are New Delhi metallo-beta lactamase producers) or we are unable to test susceptibilities (eg, cefiderocol).

Lessons: That there is no good solution shows the problem of increasing broad-spectrum use. It relies on concomitant development of ever-broader antibiotics which may not be available in LMIC or for children.

Overuse of Antibiotics in Children in the Community

Despite a large focus on hospitals, the vast majority of antibiotic prescribing and administration in children is in the community.

Setting: An urban primary healthcare outpatient clinic in a low-income area in Delhi, India. Healthcare services are provided by government doctors alongside private licensed and unlicensed practitioners.

Problem: An infant attending for routine immunization was noted to have scabies. The mother, who was illiterate with a low socioeconomic background, informed that the rash had been treated for the last 3 months by an unlicensed practitioner with multiple courses of antibiotics. The infant had developed persistent diarrhea and was failing to thrive. A clinic survey among mothers found that most infants were prescribed multiple antibiotic courses by local private practitioners. The government doctors were sometimes less favored since they were perceived as not prescribing adequate medication to their children, especially antibiotics.

Solution: The infant was effectively treated with 5% permethrin cream and cessation of antibiotics. His mother was counseled on the adverse effects of antibiotics. A broader community intervention was developed, with educational talks to mothers, focused on the long-term health risks of antibiotic overuse. The mothers were supported to adhere to medical advice through laboratory confirmation of infection where possible. Further surveys are planned to assess changes in parental attitudes and practices towards antibiotics. The broader problem remains of individuals dispensing antibiotics (illegally) without no formal medical training.

Lessons: That 1 child can act as a signal for what is happening in the broader community. Educating mothers is an important way of creating community understanding of the risks of antibiotics in children.

Setting: The community in northwestern Tanzania.

Problem: OTC sales of antibiotics are common, which encourages irrational prescribing by those who can prescribe, including use of antibiotics for common colds and diarrhea. Parents will frequently stop their child's antibiotics early so that there will be leftover medicine for next time, and if an antibiotic has cured a serious infection in hospital, parents frequently purchase the same antibiotics for subsequent febrile episodes. The local community are pastoralists where people also use leftover antibiotics to treat their chickens or cows if they think the animals are not well. It is common practice to open 1 or 2 capsules of any antibiotic on hand and mix it in the drinking water for the sick animal. As a consequence of this rampant antibiotic use, resistance to commonly available antibiotics has increased rapidly. In previously sensitive community bacteria, there is 100% resistance to ampicillin, cloxacillin and chloramphenicol, and nearly 90% resistance to cephalosporins.

Solution: There is an urgent need to revisit rules on antibiotic prescriptions and OTC sale of antibiotics. The government regulates antibiotic sales through the pharmacy body and it is against the law to sell antibiotics without prescription. However, this is not enforced, and no one is summoned or even investigated for dispensing antibiotics without prescription. Any antibiotic can be acquired without prescription, as long as you can pay for it. However, banning all OTC sales may have financial implications for the government and antibiotics can be life-saving in some situations, particularly for those who live far from a medical center. Restriction of second- and third-line drugs may be the answer, with guidelines on which antibiotics can be sold and for which clinical situations. National antibiotic guidelines are available, but they are outdated, and this could be a good opportunity to update them and incorporate this. A focus of effort should be put on educating parents about the dangers of indiscriminate and potentially out-of-date use.

Lessons: There is no quick and easy fix to systemic irrational antibiotic use.

Setting: The community in south-western Nigeria.

Problem: Antibiotics are frequently taken without prescription in Nigeria, through widespread OTC supply. This situation is sustained because of a weak healthcare system whereby patients do not have quick access to doctors who can diagnose and prescribe antibiotics if required. These antibiotics are purchased on the advice of pharmacists and patent proprietary medicine vendors who have no medical training.

Solution: There are huge challenges to solving this problem. Simply banning sales of antibiotics not prescribed by doctors would not work as it puts patients at risk, and there would be no political incentive for this. Ideally, to solve this problem properly would require an improved National Health Insurance System so patients have easy access to healthcare. Unfortunately, at present, the National Health Insurance System covers only a small fraction of the population. In the meantime, 1 possibility would be to train patent medicine sellers (who have the largest patronage) on use of simple clinical signs, for example, to diagnose pneumonia. This could be done through the minimal training given to Community Health Extension Workers. In this context, the use of dispersible amoxicillin for treating nonsevere pneumonia may be appropriate, with potential limitations on the number and breadth of available OTC antibiotics.

Lessons: This problem has yet to be solved, but there are potential interim approaches that could have an impact, even if not solving the problem entirely.

Setting: Urban communities in the Philippines.

Problem: Public awareness about AMR was very low. Antibiotics were used indiscriminately, often with an inflated sense of their effectiveness.[26] Surveys showed antibiotic self-medication was rampant (31%–66%), and sharing with family members occurred frequently (78%).[27] It was common to take a few doses "just in case" for viral symptoms, and patients could access antibiotics, including antituberculous drugs, without a prescription, with 1 or a few tablets available for purchase at a time.[28–30] Antibiotics were readily available in sari-sari stalls, small roadside stores without a pharmacist that sell grocery items. In 1 study, 60% sari-sari stalls sold antibiotics and 59% antibiotics were missing expiration dates.[27] Pharmacists were rarely seen even in drugstores, with only cashiers manning the dispensary.

Solution: As part of the Philippine Action Plan to Combat Antimicrobial Resistance, a nationwide television, radio and social media campaign was launched (2016–2018). This targeted the masses to educate them about AMR, its causes and effects, self-medication and buying antibiotics without prescription. Short infomercials with emotional storylines and famous Department of Health officials were showcased to convey the messages. Strict implementation of the law on prescription-only dispensing for antibiotics was enforced with higher fines for drugstores if caught, and pharmacists now consistently present. Antibiotics are rarely seen in sari-sari stalls, especially in urban areas, as the law which bans antibiotics from being sold outside drugstores and hospital pharmacies is implemented. Consumers are more aware of the existence of AMR. Such campaigns should be repeated regularly to sustain these gains.

Lessons: Government prioritization can be highly effective, both in enforcing laws, and in impacting on consumer health literacy and attitudes. In the Philippines, the Department of Health works closely with the WHO and professional societies.

Antibiotic Shortages

In resource-poor settings, lack of reliable access to antibiotics makes the ability to provide consistency around antibiotic prescribing and stewardship challenging.

Setting: The NICU of a large tertiary care referral hospital in Lilongwe, Malawi.

Problem: Infants are admitted regularly to the NICU with undifferentiated fever and the empirical antibiotic choice was ampicillin and gentamicin. Lacking easy access to bacterial cultures, infants were often continued on this combination. One day, supply chain difficulties led to the hospital running out of gentamicin with no anticipation of receiving more from the national stockpile in a timely fashion. As we are the referral center, no other local hospitals had surplus gentamicin.

Solution: The empirical regimen was changed to ampicillin and ceftriaxone, as the hospital did not have access to cefotaxime either. However, in a matter of days, those 2 antibiotics also ran out and the clinicians found themselves with very few options to treat septic infants—either oral antibiotics such as ciprofloxacin and trimethoprim-sulfamethoxazole or less appealing choices such as chloramphenicol. In an attempt to exhaust all options, staff went digging through the deep shelves of the hospital pharmacy. Several vials of piperacillin/tazobactam were discovered collecting dust, potentially not used because staff were unfamiliar with it. Some vials were a couple of months past their use-by date, so these were used first to avoid wastage in this dire situation. This antibiotic was repurposed for neonatal sepsis (and most other infections) for over a month, until stock of narrower spectrum antibiotics such as penicillin and gentamicin became available again.

Lessons: Shortages challenge staff to think critically about how to modify best practice and clinical guidelines.

Setting: A large public district hospital in Blantyre, Malawi, with 90,000 children attending the emergency department each year.

Problem: We noted a number of children managed in outpatients not responding to courses of oral antibiotics. For example, a child with a chest infection had been prescribed amoxicillin for 7 days, and on review when they were no better, the parent was asked whether their child had taken the antibiotics. They responded that they had been advised to give it twice a day for 5 days (instead of the expected 3 times a day), and when questioned further, instead of a white dispersible amoxicillin tablet, the pharmacy had given them dull red tablets. Discussion with the pharmacy staff revealed that amoxicillin was out of stock and they had substituted it with trimethoprim/sulfamethoxazole. This was not the first time this kind of substitution had happened, and cannot be assumed to be appropriate.[31]

Solution: Pharmacy were engaged to (a) keep clinicians up to date with which antibiotics were out of stock, so that we could avoid prescribing them; and (b) if the shortage was not apparent until the patient presented their prescription, to send the patient back to the clinic for the clinicians to determine a suitable alternative for the specific patient.

Lessons: Failure of antibiotics is not always due to antibiotic failure, but sometimes failure in other systems such as communication.

Setting: Public general hospital NICUs in Mauritius.

Problem: Before 2016, the only parenteral antifungal agent available in Mauritius was conventional amphotericin B. However, amphotericin B should be used with caution in renal impairment or if in combination with other potentially nephrotoxic drugs such as aminoglycosides, vancomycin or colistin, which were frequently used in the empirical treatment of neonatal sepsis. Despite local representatives of major pharmaceutical companies being made aware of this issue, there was reluctance to spend time and effort registering more expensive parenteral antifungals as the local market was considered too small, even in adults, with local stock likely to remain unused by the expiry date. The challenge has been in identifying alternative options for the treatment of candidemia in neonates.

Solution: Oral fluconazole is readily available in Mauritius and is well absorbed. An oral suspension of fluconazole was therefore prepared by hospital pharmacists by crushing the tablets and administering orally or via a nasogastric tube. Neonatologists acknowledged that the actual bioavailability of fluconazole prepared and administered in this way may not be exactly what is expected as pharmacokinetics in neonates can be highly variable. However, the resulting outcomes have been considered satisfactory with deaths from neonatal candidemia rare.

Lessons: Sometimes it is necessary to rethink practice in resource-limited settings, for example, that bloodstream infection always needs parenteral treatment. However, in the process of developing novel management, it is important to monitor use to provide an evidence base for new practice.

Setting: A large central referral hospital in Blantyre, Malawi, with 28,000 children admitted each year.

Problem: Children with sepsis due to Gram-negative organisms were treated with gentamicin and were not responding to treatment. This was not due to antibiotic resistance, as the initial blood culture growths were sensitive to gentamicin.

Solution: We investigated a number of possibilities including whether the gentamicin was being drawn up correctly, if the children were missing doses, if the gentamicin was of good quality and whether the laboratory had got the results muddled. During our investigations, we noted that the gentamicin vial, which was 80 mg/2 mL and required dilution, was kept post dilution and reused until empty. We cultured the contents of the gentamicin vial and it grew a resistant *Enterobacter* spp., which we determined to be the likely cause of the nonresponse. All opened vials now have to be discarded at the end of the day regardless of how much remained and the problem was solved.

Lessons: Failure of antibiotics is not always due to antibiotic failure, but sometimes failure in other systems such as quality assurance. Limited resources may necessitate pragmatic solutions such as multiple use of vials, but the safety and quality of this alternate use should be monitored.

Problems With Laboratory Results

AMS relies on diagnostic facilities for culture and susceptibility testing, but laboratory resources and logistics may be unreliable.

Setting: A tuberculosis (TB) clinic in Botswana.

Problem: A preschool-age boy was treated for clinical and imaging features of TB. There were adherence concerns, and after 6-month completion, he represented with the same symptoms. On this occasion, sputum was obtained that was positive for TB and fortunate access to GeneXpert MTB/RIF test showed rifampicin resistance. He was started on an empirical regimen for multidrug-resistant TB, including clofazimine and para-aminosalicylic acid, but with further weight loss the drug choice was questioned. It was discovered that the sputum was never received by the mycobacterial culture laboratory. Repeat samples were delayed in transit and by the time a culture was processed, it was negative, although remained smear positive. In the meantime, the whole country had run out of both clofazimine and para-aminosalicylic acid (for over a year), so his regimen was changed to linezolid, levofloxacin and cycloserine. The pharmacy only had adult tablets so it was a challenge to provide pediatric formulations and dosing, and unfamiliarity with the drugs resulted in cycloserine being accidentally replaced with cyclosporin for 1 month. A number of problems have therefore contributed to making this child difficult to manage.

Solution: For the individual, the solution was to maximize nutrition, while balancing the risk benefit of a toxic regimen without confirmation of drug resistance. The pharmacy found solutions to the lack of pediatric formulations through making syrups and crushing tablets, but lack of consistent pharmacokinetic data for these methods of administration remains problematic. The National Tuberculosis Reference Laboratory (set up with the support of the WHO) is the only laboratory in the country that can provide TB culture and susceptibility testing.[32] However, it is not enough just to have a laboratory—there need to be sufficient reagents and collecting tubes, diagnostic tools that are sensitive in children, a reliable transport process and a cold chain.

Lessons: Multiple barriers can impact on accurate diagnostics: lack of susceptibility testing, lack of understanding of the importance of critical samples, lack of integrity and transport of samples. This is further compounded by lack of drug availability and unfamiliarity. In the long term, addressing all of these through education, resourcing and logistical support, are required. In the short term, without accurate diagnostics, clinicians may have to make decisions based on “first do no harm” and sequentially working through clinical options.

Setting: A 700-bed referral hospital in Addis Ababa, Ethiopia, serving 20,000 inpatients and 330,000 outpatients per year.

Problem: Hospital-acquired infection had a high mortality of 18% at our hospital, and multidrug-resistant bugs were frequently isolated in clinical samples.[33] Enterobacteriaceae constituted half of all blood culture isolates with the large majority resistant to third generation cephalosporins and a quarter of *Klebsiella* spp. resistant to carbapenems. Clinical teams were historically reluctant to take preantibiotic blood cultures, not perceiving any value in the results. This was for various reasons including poor communication of clinical data for microbiologists, suboptimal sampling, poor laboratory techniques and difficulty in interpreting results.

Solution: We developed a 2-pronged approach with the hospital's partner, the McGill University Health Centre: (1) An automated blood culture system was donated by bioMerieux, for which we developed standard operating procedures, training of laboratory staff and subsequently antibiograms. (2) Twice-weekly pharmacist-led AMS sessions. The pharmacists (previously predominantly involved in dispensing) were trained in AMS and clinicians were educated on its importance and encouraged to participate in AMS sessions, where verbal and written feedback was given.[34] The improved bacteriology service increased confidence among clinicians, with blood culture requests increasing from 2 to 45 per day within 18 months after implementation. During the first 10 months of AMS sessions, 707 antibiotic recommendations were made, with 54% to discontinue. Unfortunately, AMS sessions later ceased, although the laboratory improvements remained. Within 5 months following discontinuation of AMS, antimicrobial use doubled and the mean duration on antibiotics increased significantly by 4.1 days, a 47% increase. Most concerningly, mortality increased from 7% to 15%.

Lessons: Prioritizing investing in bacteriology laboratory diagnostics, clinical microbiology training and AMS had an impact on antibiotic use and mortality from hospital-acquired infections. The investment needs to persist to maintain these outcomes.

Setting: Private clinics and public general hospitals in Mauritius.

Problem: In the late 1990s, neonatal mortality was increasing in private and public hospitals from septicemia caused by ESBL-producing *Klebsiella* spp. Empirical treatment was with ampicillin, cefotaxime and gentamicin but the bacteria were almost always resistant to all of these. Unfortunately, because blood cultures were processed manually, positive results usually only became available 3–4 days later, by which time the infant may have died. Even then, these results frequently did not reach clinicians, because there was little communication with the microbiology laboratory. When a patient was no longer on the ward, the results were filed in medical records and clinician would be unaware of the results of deceased patients.

Solution: (1) An audit showed that blood culture isolates within 24 hours of birth were predominantly group B streptococci susceptible to penicillin, and after 48 hours were most commonly Enterobacteriaceae resistant to cephalosporins and gentamicin, and susceptible to amikacin and carbapenems. (2) A microbiologist was employed who discussed cases with the clinicians even after the death of infants. Laboratory data were presented to pediatricians during medical education. (3) The empirical recommendations for neonatal sepsis arising after 48 hours changed to include amikacin. The importance of infection control was also emphasized. The number of deaths caused by ESBL-producing *Klebsiella* spp. subsequently dropped. Since 2015 with introduction of automated systems, culture and susceptibility results are available within 2–3 days.

Lessons: Investing in a microbiologist improved the availability, interpretation and communication of laboratory results, leading to a change in practice that directly impacted on neonatal mortality.

Setting: A PICU in a private referral hospital in Sao Paulo, Brazil.

Problem: Use of vancomycin was problematic in the PICU because of issues with vancomycin levels. Trough levels were measured daily and were frequently collected outside the time window (over 2 hours before administration) due to prescription or nursing error. These errors led to misinterpretation of results, with false reassurance from the excessive frequency of measurement. In addition, trough levels do not have a strong correlation with the therapeutic range in children, due to wide physiologic and pharmacokinetic variation.

Solution: We developed an institutional protocol for vancomycin monitoring using the ratio of the 24-hour area under the concentration–time curve to the minimum inhibitory concentration as the parameter that best characterizes the effectiveness of vancomycin. Before implementation, there was intense multidisciplinary education for prescribers and pharmacists on the rationale, timing, calculation and how to adjust dosing. Once the therapeutic target is reached, monitoring is performed once a week, unless there is major clinical change or worsening renal function. This intervention has reduced the total number of measures performed and increased the target attainment of vancomycin therapy.

Lessons: Doing something less frequently and well gave improved results, so there was value in taking the time to get it right.

OVERALL LESSONS LEARNED

The totality of these experiences shows that ingenious problem-solving and pragmatic solutions can be found, through necessity, in resource-limited settings. We report on the large number of problems facing LMIC in addressing AMR, from limited access to antibiotics and microbiology, to poor health literacy and unregulated antibiotic sales. We provide anecdotal evidence from LMIC of the power of small-scale AMS training programs of healthcare providers, locally developed guidelines and education of parents, translating into improved antibiotic prescribing. Several examples of novel, rapidly scalable AMS solutions were identified.

There are problems at every level in the goal of improving antibiotic use in LMIC, fueled by lack of resources and consequent competing priorities and skewed financial incentives. At the highest level, governments—particularly those with an election cycle—prioritize the greatest current problem (childhood infection–related mortality) over a problem that exists and is looming in the future (antibiotic resistance–related mortality) but whose impact does not currently appear to be as great. Pharmaceutical companies are incentivized toward expanding antibiotics sales, and governments may also be unwilling to penalize them if there are other financial benefits from collaborating with them.[35] At the level of pharmaceutical sales outlets, financial incentives toward legal or illegal OTC dispensing without prescription are often greater than penalties. In addition, leveling penalties in resource-constrained settings with limited access to licensed healthcare providers is morally challenging.[36–38] In these settings of high childhood mortality and where untrained or unlicensed clinicians compete with licensed medical providers, there are financial incentives for acquiescing to parental demand for antibiotics over trying to avoid antibiotic overuse.[39] In the United Kingdom, financial incentives for general practitioners reduced antibiotic prescriptions, but these kind of incentives are an untested strategy in LMIC.[40] At parent level, poor education and limited access to formal healthcare results in high self-medicating, and this extends to using antibiotics for subsequent episodes, other family members and even animals.[41] Educating caregivers is a viable and easily implementable real-world solution against antibiotic overuse.[42,43] Multiple weak logistical links can compound each problem, and issues may be different even in the same setting, for example, different levels of OTC prescribing in different areas of

India.[37,44] Consequently, a systems approach is needed that recognizes and addresses the interplay of different factors and integrates solutions at each level of the problem.[45]

Medication shortages and supply difficulties are not surprising in resource-deprived health systems. There is growing recognition that antibiotic shortages can drive antibiotic resistance through replacement with broader-spectrum antibiotics, and by opening the marketplace to substandard and false drugs.[46] We observed that the nonavailability of essential antibiotics for children in LMICs often compelled treating clinicians to settle for suboptimal alternatives with either lack of proven efficacy, safety, and with higher risk of driving resistance. Similarly, unreliable access to microbiologic diagnostics may undermine patient prognosis in absence of guidance on therapy, while increasing risk of resistance by encouraging empirical use of broad-spectrum antibiotics. The feedback loop that some authors described of increasing empiricism (broad-spectrum antibiotic use leading to increased AMR leading to the need for even broader antibiotic use) should provide a salutary lesson for trials showing very broad-spectrum empirical antibiotics to have improved outcomes.[47] This is an unsustainable situation, and the development of new ever-broader antibiotics is not keeping pace with the rate of increase of AMR. It is important to mitigate the risks posed by some of these solutions by auditing ongoing outcomes to ensure the solution does not create new problems.

The strengths of the study are that it provides insight into the real-world antibiotic problems faced by on-the-ground healthcare workers that a formal study cannot, and provides inspiration and hope for others trying to find pragmatic AMS solutions. This approach can enable the development of tailor-made interventions to enhance AMS which are adapted to the local environment instead of generalized actions that may lack feasibility for implementation and result in policy failure.

Limitations include that a formal sampling method was not used, which limits the representativeness of the respondents. Furthermore, the settings described have considerable variation in terms of access and availability of drugs and diagnostics, thereby limiting the generalizability of the findings. Veterinarians and others involved in the animal-human one health approach for managing AMR were not included and their expertise would inform broader solutions.

These problems and shortages encountered by the authors of these vignettes challenge staff to think critically about how to modify best-practices and clinical guidelines when faced with a situation where full resources are not available. They provide solidarity to others in LMIC healthcare settings that they are not alone in facing these real-world problems, and encouragement that often simple, inexpensive and potentially scalable solutions can be found.

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