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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

Challenges Facing PICUs in Low- and Middle-Income Countries in the Treatment of Emerging Multidrug-Resistant Organisms: a Review and Perspective from a South African PICU

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Abstract

Purpose of Review Antimicrobial resistance continues to increase throughout the world, with the impact on critically ill children in low- and middle-income paediatric intensive care units largely unknown.

Recent Findings There has been a global shift indicating a predominance of Gram-negative bacilli among multidrug-resistant isolates. A 4-year review (2019 to 2022) found a progressive and substantial increase in the incidence of carbapenem-resistant *Klebsiella pneumoniae* (29% to 51%) alongside high levels of carbapenem-resistant *Acinetobacter baumannii* (93%) within the paediatric intensive care unit at the Chris Hani Baragwanath Academic Hospital in South Africa. The pharmacological treatment of these infections relies heavily on the continued use of carbapenems, often in combination with colistin.

Summary The burden of antimicrobial resistance is disproportionately borne, particularly within sub-Saharan Africa and South Asia. The resource-constrained South African public healthcare system, already significantly burdened by both HIV and TB, continues to face several challenges in combating the growth in antimicrobial resistance. Limited access, largely driven by prohibitive costs, to sophisticated laboratory techniques and newer pharmacological agents, leaves the implementation of effective infection prevention and control and antimicrobial stewardship programmes as the most pragmatic options to address the problem.

Keywords Multidrug-resistant organisms · Antimicrobial resistance · Colistin · HIV · Infection prevention and control · Antimicrobial stewardship

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Clinical Vignette

A two-month-old well-nourished HIV-positive male infant was transferred to the paediatric intensive care unit (PICU) for respiratory failure secondary to a suspected bacterial nosocomial pneumonia. The infant, admitted six days prior to the general paediatric wards at the Chris Hani Baragwanath Academic Hospital (CHBAH), had been initially managed as a community acquired pneumonia with co-amoxiclav. Trimethoprim/sulfamethoxazole and prednisone had been initiated on day three in the wards following a diagnosis of pneumocystis pneumonia informed by a positive Pneumocystis PCR. Piperacillin-tazobactam and amikacin were initiated on admission to the PICU and were discontinued on PICU Day 6 (D6) upon clinical improvement. In the interim, on PICU D3, the child had developed refractory hypercarbia which prompted transition from conventional mechanical ventilation to high frequency oscillatory ventilation. Screening investigations for tuberculosis proved negative and thus antiretrovirals were added to the overall treatment regimen.

The second week in PICU was largely uneventful until evidence of a second nosocomial infection on PICU D14. As per local AMS guidelines, empiric piperacillin-tazobactam together with amikacin were initiated again. Microbiological samples taken at the time of deterioration revealed an extensively drug-resistant *Acinetobacter baumannii* (blood culture) and a carbapenem-resistant *Klebsiella pneumoniae* (tracheal aspirate) as the potentially causative organisms. Colistin and meropenem were chosen for targeted therapy against both organisms and discontinued after 12 days (PICU D30) following clinical improvement and progressive reduction in serial PCT measurements. Unfortunately, the infant deteriorated again with evidence of hypoperfusion requiring vasopressor support 72 hours later. Meropenem and amikacin were chosen as empiric antibiotics and the corresponding blood culture grew a carbapenem-resistant *Klebsiella pneumoniae* (now confirmed as OXA-48 producing). Despite the re-initiation of colistin once the culture result became available, the child demised on PICU D39.

The clinical case presented above is illustrative of typical challenges encountered when managing patients in a South African state sector PICU. South Africa, still hampered by its history of social and economic segregation despite almost 30 years after democracy, is nonetheless listed by the World Bank as an upper-middle-income country yet had the highest inequality in income distribution worldwide in 2014 [1, 2]. The historical fragmentation of healthcare services into state (public) and private sectors with vastly different resource availability continues to exert its influence on modern South Africa [3] A 2009 review of the South African healthcare system reported that less than 15% of the population accounted for 46% of all healthcare expenditure through private medical schemes [3]. A further 21% of the population was generally dependent on the public sector for hospital care, while the remaining two thirds of the population is entirely dependent on the public sector for services [3]. By 2019, the proportion of the population covered by private medical schemes had increased marginally to 17.2% [4]. In effect, the overburdened and underfunded SA public sector is subject to similar conditions found in other low- and middle-income countries (LMICs). Unsurprisingly, the South African state healthcare sector, crippled by these enormous healthcare resource inequalities, likely continues to produce healthcare outcomes often worse than those in many lower income countries [3]. As such, this review will be written from the perspective of the state sector.

Introduction

Critically ill children within PICU represent a particularly vulnerable patient population [5, 6]. The dysregulation and immaturity of the immune response, the regular occurrence of invasive procedures, the presence of indwelling devices which disrupt anatomical protective barriers, and the administration of medications such as sedatives, muscle relaxants, steroids, proton pump inhibitors, and broad-spectrum antibiotics collude to render the ICU as the epicentre of infections [5, 7]. Intensive care populations suffer one of the highest occurrence rates of nosocomial infections, with an ever-increasing proportion due to multidrug-resistant organisms, further characterising the ICU as the centre of antimicrobial resistance [7].

Antimicrobial resistance (AMR) continues to increase throughout the world and has been acknowledged as a global crisis [8]. Antimicrobial resistance is a leading cause of death globally. Unsurprisingly, the highest burden befalls LMICs particularly within sub-Saharan Africa and South Asia [9••]. The Antimicrobial Resistance Collaborators estimated close to 5 million deaths were associated with bacterial AMR in 2019, of which 1.27 million deaths were directly attributable to AMR [9••] The UK-commissioned Review on Antimicrobial Resistance predicts that, if unchecked, AMR could kill approximately 10 million people per year by 2050 [10, 11].

A major challenge impeding efforts to address this problem is the dynamic nature of the development of AMR. The rapid evolution in the incidence of AMR in both established and emerging pathogens has led to an organisation as prominent as the Infectious Diseases Society of America (IDSA) adopting an alternate approach to the preparation of guidance documents to assist practitioners at the bedside. Traditional methodologies employing systematic reviews and GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) were determined to be poorly suited to AMR and have thus been superseded by guidance prepared by smaller groups of experts, without a formal grading of evidence, available online and subject to frequent review [12]. The rise of multidrug resistance in Gram-negative bacteria (MDR-GNB), both proportionally and mechanistically, is of particular concern [8]. Understanding the burden of AMR and the leading antimicrobial susceptibility patterns is important in making informed location-specific decisions, particularly regarding infection prevention and control (IPC) programmes, access to essential antimicrobials, and research and development of new antimicrobials [9••].

Low- and middle-income countries house more than 75% of the world's population [13]. In 2011, the World Health Organization (WHO) reported that the number of patients affected by healthcare-associated infections (HAIs) in LMICs is potentially up to threefold higher than high-income countries, suggesting a vast difference in the absolute number of patients [13, 14]. The increased impact of systems related risk factors (Fig. 1) within LMICs likely underlies the discrepant prevalence [15]. This report and others acknowledged difficulties in obtaining accurate epidemiological data from LMICs stemming from under-reporting and a paucity of functioning national surveillance systems [13, 15–17]. What little data is available has generally come from studies in Eastern Mediterranean, Latin American, and a few Asian countries. Sub-Saharan Africa remains conspicuously absent from most accounts [13].

Patient-related

- Length of healthcare facility stay
- Use of invasive devices
- Extremes of patient ages
- Patient comorbidities
- Mechanical ventilatory support
- ICU admission

System-related (more prevalent in LMICs)

- Lack of resources and surveillance systems
- Lack of personnel and understaffing
- Lack of education in IPC and HAIs
- Overcrowding
- Lack of supplies – including cleaning supplies & soaps

Fig. 1 Risk factors for the acquisition of healthcare-associated infections (including multidrug-resistant organisms) [15]

The increase in multidrug-resistant organism (MDRO) infections in LMICs is driven by a series of factors generally present across geographic regions including high prevalence of infectious diseases begetting high rates of antibiotic prescription, poor regulation of antibiotic usage including access to over-the-counter sales and absence of antibiotic stewardship programmes, shortages of trained staff which ensure rudimentary infection control, and weak surveillance programmes. Finally, laboratory services, particularly point-of-care diagnostics, remain unaffordable, limiting effective targeting of causative organisms, thereby perpetuating the persistence of broad-spectrum antibiotic prescribing patterns. These patterns of antibiotic prescribing inadvertently ensure both extensive collateral disruption of patients' microbiomes and increased selection pressure, thus increasing the risk of acquisition of HAIs, further fuelling the vicious cycle of increased AMR [13, 15, 16].

The Pattern of MDRO Infections in PICUs in LMICs

The Antimicrobial Resistance Collaborators have recently published their analysis of the Global Burden of Disease (GBD) database and other associated data sources, which provided the most comprehensive global estimates of AMR. Worldwide in 2019, six pathogens were responsible for three quarters of deaths associated with AMR, namely (by decreasing order of mortality impact), *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* [9••]. The share of AMR burden caused by each pathogen differed substantially across the globe. Collectively within countries comprising the high-income super-region, approximately half of deaths associated with AMR were linked to just two pathogens: *S. aureus* (25.4%) and *E. coli* (24.3%). In comparison, the distribution of leading pathogens in sub-Saharan Africa (the GBD super-region with the highest death rates associated with AMR) was different, each individually accounting for a smaller share of the AMR burden: *S. pneumoniae* 19.0% and *K. pneumoniae* 17.5%, followed by *E. coli* and *S. aureus* (both > 10%) [9••].

Unfortunately, a comparable overview of the burden of AMR specifically within LMIC PICUs does not exist, limited to isolated reports occasionally incorporating critically ill neonates and children [18–22]. When including similarly sparse reports from adult LMIC ICUs, the distribution of MDR-GNB organisms remained surprisingly consistent with

K. pneumoniae often the most commonly isolated, followed by either *P. aeruginosa* or *A. baumannii* [18, 20, 23–26].

There are no previously published data pertaining to the situation in South African PICUs; however, two reports from general paediatric departments in South African academic hospitals showed that GNB cause a majority, accounting for 57.7% and 60.2% of bloodstream infections (BSI). Similar to the ICU studies, *K. pneumoniae* was the most commonly isolated; however, *E. coli* proved the next most common, perhaps reflecting the difference in the studies' setting [27, 28].

National South African Surveillance Data

The National Institute for Communicable Diseases (NICD) in South Africa conducts surveillance to report trends in pathogen-specific data via GERMS-SA. Since July 2015, GERMS-SA has been monitoring trends in healthcare-associated BSI caused by carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant *A. baumannii* (CRAB) [30]. The period 2015–2019 saw a steady increase in the number of cases of CRE and CRAB BSIs. Among the 2490 collective cases of CRE and CRAB, 22.4% of those with known HIV statuses ($n = 1\ 393$) were also HIV-positive. Alarmingly, 20% and 44% of all CRE and CRAB BSIs, respectively, occurred in infants, consistent with the findings of the Burden of AMR Collaborative Group, who highlighted that the highest estimated burden of AMR in Europe was among infants, including the greatest increase in attributable mortality [29, 30].

Antimicrobial susceptibility testing (AST) was conducted on 430 CRE isolates, with *K. pneumoniae* as the predominant organism (80%, $n = 346$) once again. Ninety-two percent of isolates expressed carbapenemase genes, the highest being OXA-48 or variants (61%; 264/430) or NDM (29%; 127/430). Seventy-six percent of isolates (326/429) were susceptible to tigecycline. Testing of 1423 CRAB isolates confirmed retention of colistin susceptibility among all, but 4%, recording breakpoints of < 4 mg/L, with no plasmid mediated mcr1-5 genes detected [30]. This work begins to address the previously noted knowledge gap relating to mechanisms of colistin resistance in LMICs [31, 32].

Clinical Microbiology Laboratory Challenges in LMICs

Clinical microbiology laboratories currently use several bacterial identification and AST methods depending on their equipment and expertise. Classical culture-dependent methods (such as disk diffusion test and microdilution) are characterised by lengthy processing times relating to bacterial isolation and identification [33]. The significant rise in MDROs necessitates an urgent need for more rapid and reliable tests to improve infection diagnosis and support timely antimicrobial prescribing, especially for critically ill children [33, 34].

Automated blood culture systems with continuous growth monitoring, automated detection, identification with mass spectrometry (MALDI-TOF MS), and automated AST (MALDI Biotyper) have substantially decreased turnaround times and increased simplicity in high-income countries [33, 35]. Further sophistication incorporating molecular techniques (such as PCR and DNA microarray) potentially provides deeper insights into resistance mechanisms via the targeted detection of resistance genes, albeit limited by the number of currently available genetic probes [33, 34]. These genetic techniques are both highly sensitive and specific but are expensive to perform and difficult to interpret [34]. Microfluidics-based and isothermal diagnostics are promising tools employing real-time analysis to minimise culture dependency, thereby allowing for AST and minimum inhibitory concentration (MIC) determination within a few hours [33, 36]. The associated increase in costs and demand for technical expertise leave many of these options outside the reach of LMICs [37].

With the advances in technologies for bacterial identification and AST readily available in high-income countries, the gap between those settings and LMICs continues to widen [35]. Numerous challenges within clinical microbiology laboratories in LMICs continue to limit capacity. Inadequacies of infrastructure, equipment, human resources, and quality assurance programmes coupled with other logistical failings impede the adoption of state-of-the-art identification and testing in LMICs [9, 35, 38, 39]. Ironically, South Africa's current standard for the application of clinical microbiology remains conventional culture-based techniques which are labour-intensive and complex, requires skilled staff and sophisticated laboratory equipment, and remains relatively expensive [35, 38]. Against this reality, consideration should be given to the potential adoption of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) defined rapid AST (RAST) methodology, performed directly from positive blood culture bottles, thereby effectively reducing turnaround times, without significant cost increments [34, 40, 41].

The Management of MDROs Relevant to the South African State Sector

The overarching management approach to the MDRO dilemma entails a combination of pharmacologically treating established infections and more importantly, preventing the transmission of these organisms via effective infection

prevention and control (IPC) while simultaneously mitigating selection pressure driving the emergence of new resistant strains with effective antimicrobial stewardship (AMS) [42].

Recent treatment guidelines published by the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) have specifically sought to address the antimicrobial managements of multidrug-resistant Gram-negative bacterial (MDR-GNB) infections [12••, 43••]. The decision to focus exclusively on MDR-GNB was empirically driven, with 70% of European disease burden (cases and attributable deaths) caused by MDR-GNBs, which echoed similar contemporary findings from the USA [29, 44]. Unsurprisingly, both societies have adopted an organism-centric approach to the recommendations as the European data revealed that 86% of median attributable deaths were caused by just six organisms, of which five were GNBs (methicillin-resistant *S. aureus* accounted for 21%). The five GNBs listed in descending order of attributable mortality were third-generation cephalosporin-resistant *E. coli* (3GCephREC), carbapenem-resistant *P. aeruginosa* (CRPA), third-generation cephalosporin-resistant *K. pneumoniae* (3GCephRKP), carbapenem-resistant *A. baumannii* (CRAB), and carbapenem-resistant *K. pneumoniae* (CRKP) [29].

Both guidelines specified drug options for treatment of Enterobacterales, *P. aeruginosa*, and *A. baumannii* [12••, 43••]. The IDSA guidelines additionally addressed *Stenotrophomonas maltophilia* [12••]. Drug options incorporate both established or "old" drugs and newer agents (defined as being approved after 2010) including standalone drugs (cefiderocol, plazomicin, eravacycline) and ß-lactam/ß-lactamase inhibitor combinations (ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam) [43••].

Two of the four new ß-lactam/ß-lactamase inhibitor combinations are now approved by the South African Health Products Regulatory Authority. A best practice guideline has been published to promote appropriate use of ceftolozane-tazobactam and ceftazidime-avibactam [42]. Despite enthusiastic adoption within the private sector, the high costs of these agents have largely precluded their introduction within the state sector to date [42, 45].

Chris Hani Baragwanath Academic Hospital

The Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, Johannesburg, is the third-largest hospital in the world with approximately 3200 active beds of which 408 are for paediatric inpatients [46]. The PICU is a general nine-bedded unit catering for children from 1 month up to 16 years of age. Clinical samples (excluding screening) collected during the period 2019–2022 within the PICU returned a total of 2 018 positive de-duplicated microbiological isolates (unpublished data). The number of GNBs was 994 (49.3%) of which 487 (48.9% of tested isolates) were third-generation cephalosporin-resistant/extended-spectrum ß-lactamases (ESBLs). Collectively, 302 (31.3%) were carbapenem-resistant with 90 (9.1% of total GNBs) being CREs. OXA-48 was the most frequently detected carbapenemase consistent with the 2019 NICD national surveillance data [30]. Resistance patterns of individual organisms

Table 1 Antimicrobial resistance (AMR) of clinical isolates from the paediatric intensive care unit at Chris Hani Baragwanath Academic Hospital, 2019–2022

Organism	Isolates, *n* (%)	Isolates tested for AMR (*n*)	Resistance (%)
Klebsiella pneumoniae	247 (24.8)		
- Extended-spectrum ß-lactamase		247	70.7
- Carbapenem-resistant		243	31.7
- AmpC ß-lactamase		236	28.0
Acinetobacter baumannii	213 (21.4)		
- Third-generation cephalosporin-resistant		213	81.7
- Carbapenem-resistant		213	90.1
Pseudomonas aeruginosa	106 (10.7)		
- Third-generation cephalosporin-resistant		106	3.8
- Carbapenem-resistant		105	17.1
- Fourth-generation cephalosporin-resistant		100	5.0
Escherichia coli	84 (8.5%)		
- Third-generation cephalosporin-resistant		80	22.5
Staphylococcus aureus	160 (15.6)		
- Methicillin-resistant		160	20.0
Streptococcus pneumoniae	25 (2.4)		
- Penicillin-resistant		24	4.2

are presented in Table 1. Concerningly, during the 4-year period, there was a progressive and substantial increase in the incidence of CRKP (29 to 51%) together with a small increment in CRABs, but from an extremely high baseline (89 to 93%). The true proportional significance of the organisms presented in Table 1 would certainly have been even higher, considering that 290/1024 (28.3%) of Gram-positive isolates were coagulase-negative staphylococci, testimony to sub-optimal IPC practices.

The antibiogram in concert with a limited range of available antibiotics dictates the current approach to the pharmacological treatment of MDR-GNBs at the CHBAH PICU. Empiric piperacillin-tazobactam is combined with amikacin, followed by culture-targeted carbapenem monotherapy for ESBLs or a combination of colistin and a carbapenem (with the lowest MIC) for CREs and CRABs, in keeping with other South African centres [42]. This of course creates significant dependence on colistin, which is not straightforward to access, as it remains unregistered in South Africa. Of note, continuation of this practice is contrary to the recent recommendations provided by both the IDSA and ESCMID guidelines [12••, 43••]. A recent review of carbapenem and polymyxin resistance in Africa, incorporating WHO Global Antimicrobial Resistance Use and Surveillance System (GLASS) data, reported low levels of polymyxin resistance within South Africa but noted the presence of 10 different resistance determinants to carbapenems and polymyxin combined [32]. The relative cost, compounded by efficacy concerns in the treatment of pneumonia and BSIs, has precluded tigecycline usage to date. Lastly, IDSA recommends the routine involvement of infectious disease specialists in the management of patients with MDROs [12••, 43••]. Currently, there are just three board-certified paediatric infectious disease specialists employed at CHBAH (personal communication), which makes realisation of this recommendation extremely difficult.

Infection Prevention and Control and Antimicrobial Stewardship

The limited pharmacological options in LMICs intensify the need for effective IPC and AMS programmes, which are themselves dependent on resources. The fact remains that fundamental tenets of IPC, such as hand hygiene, routine use of gloves and facemasks, and contact precautions, remain unattainable due to ongoing shortages in basic provisions such as soap, water, antiseptic hand rubs, gloves, and masks. Shortages of sterile gowns and aprons when performing invasive procedures potentially skew the risk–benefit ratio toward iatrogenic harm. The shortage of essential equipment drives the re-usage of medical equipment designed for single use, further exposing patients to increased risk of acquiring HAIs [13, 15•]. Furthermore, widespread shortages of trained personnel and diagnostic tools together with inadequate organisational infrastructure undermine attempts to effectively introduce and maintain IPC and AMS programmes in these environments [13, 15•, 16]. Lastly, LMICs are also vulnerable to the impact of corruption, embezzlement, theft of antimicrobials, and other equipment and the intentional procurement of poor-quality generic drugs to maximise the misappropriation of precious funds [13].

Recognition by the WHO that implementation of the measures to address IPC and AMS is often the largest challenge in LMICs led to the development of an interim practical manual to support the national implementation of the WHO guidelines on core components of infection prevention and control programmes in 2017 and a WHO practical toolkit for AMS in LMICs in 2018 [47, 48]. Prioritisation of resources dictates that efforts should initially focus on inexpensive yet high-impact measures with specific consideration of suitability to local environments to ensure a balance between feasibility, effectiveness, and cost [15•]. A multimodal strategy approach such as the PROGRESS model is considered essential to the successful initiation of programmes in LMICs [15•]. A selection of relevant interventions is shown in Fig. 2.

Political will (at institutional and national level) is arguably the element most crucial to the success of IPC and AMS programmes. Despite widespread recognition of the importance of support from key decision makers, its impact is woefully underestimated in LMICs [15•]. In South Africa, where the adequacy of governance, at provincial and national levels, is often a source of disharmony between

- Political will, commitment and support of institutional policies and organizational structure from the hospital authorities
- Appropriate number of healthcare personnel trained in infection control
- Presence of an IPC programme including surveillance
- Appropriate health care infrastructure
- Continuous supply of antiseptics and disinfectants
- Promotion of hand hygiene
- Contact and isolation precaution implementation
- Patient cohorting
- Enhanced environmental cleaning
- Essential antimicrobials for treating infections
- Continuing education and research
- Establish reliable goals and feedback mechanisms
- Virtual infection prevention and control

Fig. 2 Possible interventions in LMICs to mitigate healthcare-associated infection and AMR (most are relatively inexpensive strategies) [13, 15•, 16, 50]

healthcare workers and administrators, it is difficult to draw attention to the evolving threat posed by MDROs, when it may not necessarily serve predetermined political agendas.

Surveillance is crucial to detect trends and specific problem areas to allow focusing of remedial efforts, and despite the challenges often faced by LMICs, it is imperative to overcome or circumnavigate these barriers to ensure the implementation of surveillance in these settings [15•]. Both prospective clinical and automated surveillance is often too resource intensive for low-resource settings. A study in South Africa evaluated the respective efficacies of antimicrobial prescription surveillance, laboratory surveillance, and repeated point prevalence surveys and found that a combination of antimicrobial prescription with laboratory surveillance maximised sensitivity while limiting the false-positive rate [49]. This combination could thus provide the most accurate, cost-effective estimates of HAI incidence and, by extension, MDRO incidence in these settings, despite resource constraint.

The unprecedented challenges of the COVID-19 pandemic saw the emergence of virtual IPC, which referred to the use of technologies and strategies separated geographically or temporally from the point of medical care to control the spread of contagious diseases. Virtual IPC can extend the impact of globally scarce resources such as infectious diseases specialists, public health practitioners, and epidemiologists, thereby increasing access and offering the potential for improved quality of healthcare in LMICs [50].

Impact of HIV and TB on MDROs

People living with HIV are at increased risk of infection with resistant organisms due to more frequent healthcare utilisation and the widespread use of co-trimoxazole prophylaxis [51–53]. This potentially immune-suppressed group was found to be twice as likely to be colonised with MDROs, thereby increasing their odds of MDRO infections [51]. Higher colonisation rates with MDR *E. coli* and *K. pneumoniae* was found in HIV-positive patients in Cameroon [54]. In Zimbabwe, despite relatively high antiretroviral coverage rates, community-acquired infection with MDR-GNB was common [55]. A study among HIV-positive patients at CHBAH, prior to the availability of antiretrovirals, found an increase in penicillin resistance in *S. pneumoniae* isolates [56]. Whether HIV infection similarly increases the rate of development and acquisition of resistance in GNBs is yet to be elucidated.

Another challenge in settings like South Africa is the high burden of tuberculosis which adds further complexity to the MDRO problem. Patients hospitalised with TB are at increased risk of MDRO infections due to prolonged hospital length of stays, the high risk of co-morbid HIV infection, and the potential presence of pulmonary complications such as bronchiectasis. Current treatment recommendations for drug-resistant TB include drugs such as linezolid, levofloxacin, moxifloxacin, bedaquiline, imipenem-cilastatin, meropenem, and amikacin [57]. It remains to be seen whether this practice places TB patients at increased risk of acquiring other MDRO infections, increases selection pressure promoting the development of even more extensively resistant mycobacteria, and encourages the development and transfer of resistance from mycobacteria, thereby adversely impacting the efficacy of these agents against other bacterial pathogens.

Healthcare workers in LMICs were found to have a fivefold increased rate of healthcare exposure associated with new TB infections compared to their counterparts in high-income countries [58]. While this is alarming from an occupational health point of view, it also highlights the difficulties in preventing nosocomial spread of pathogens such as TB and MDROs in LMICs given the limited access to purpose-specific isolation cubicles for infected patients.

Conclusion

Antimicrobial resistance continues to increase throughout the world, fast becoming a leading cause of death globally. The greater burden is disproportionately borne by LMICs, particularly within sub-Saharan Africa and South Asia. Critically ill populations, especially children and neonates, are at greatest risk for the acquisition of MDRO infections. The CHBAH has seen an emergence of MDR-GNBs (especially *K. pneumoniae* and *A. baumannii*), possibly reflecting other centres in LMICs, although data is lacking. Sophisticated laboratory techniques and newer pharmacological agents remain out of reach for many LMICs, thus limiting the adoption of optimal pharmacological treatment as per recent international guidelines. Effective IPC programmes, incorporating infection surveillance, coupled with pragmatic AMS interventions, represent relatively inexpensive solutions for LMICs, provided that there is sufficient support from policymakers and hospital authorities.

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Compliance with Ethical Standards

Ethics Approval Ethical approval was granted by the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg (clearance certificate: M230508).

Competing Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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