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SHORT COMMUNICATION

Focus on Antimicrobial Resistance (AMR)
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Unmet needs for management of drug-resistant infections: low- and middle-income countries' viewpoint

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ABSTRACT

Drug-resistant infections are a serious threat globally which demands cost-effective solutions to meet the unmet needs in their diagnosis and treatment. Gram-negative pathogens, drug-resistant tuberculosis, and multidrug-resistant *Salmonella typhi* have been reported as cause of resistant infections in developing countries. Here, we discuss the priority pathogens and conditions for which feasible solutions adaptable to low-resource settings are required to address the antimicrobial resistance in pathogens. These solutions will be helpful in containing the spread of antimicrobial resistance and better patient outcomes.

Keywords: Antibiotic, Antimicrobial resistance, Diagnostics, India, Infection, Low- and middle-income countries

Introduction

Drug-resistant infections are major public health concerns that are associated with high morbidity and mortality in patients, and result in exorbitant health and economic burden (1,2). In 2019, 4.95 million deaths were estimated due to resistant bacterial infections (3). The burden of drug-resistant infections remains high in low-resource healthcare settings, especially in low- and middle-income countries (LMICs) including India (3,4,1,5). Rampant misuse of antimicrobials (in humans and animal husbandry), unregulated over-the-counter availability, poor healthcare facilities and infection control practices, and lack of accurate diagnostics to support treatment decisions are few of the major drivers of antimicrobial resistance (AMR) in communities and hospitals (5,6).

In the past few years, reports on multidrug-resistant infections due to gram-negative bacteria have increased globally (3,4), which represent a critical unmet medical need, for which interventions are required. Gram-negative pathogens *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter spp. have become public health concerns (3,7,8) that are difficult to control due to acquisition of different resistance markers. *Streptococcus pneumoniae* infections have been associated with high mortality in children aged below 5 years, and in 2015, 50% of all pneumococcal deaths were reported in four countries of Africa and Asia (3,9). In neonates, antimicrobial-resistant infections have been associated with approximately 23% of deaths, with over 55% of AMR prevalence among sepsis-causing pathogens (3,10).

Published data from India have reported concerning rates of AMR among pathogens including *Enterococcus faecium*, *Staphylococcus aureus*, *Enterobacter* spp., *Salmonella Typhi*, etc. (7,11,12). An increase in infections due to carbapenem-resistant *K. pneumoniae* and *A. baumannii* has been reported from India and other countries (7,11,13). Hospital-acquired infections (HAIs) are another major concern especially in resource-constrained low-income settings where higher infection rates due to gram-negative pathogens have been reported than in developed countries (11,14). A recent HAI surveillance study from India reported high rates of carbapenem resistance in *Klebsiella* spp., *Acinetobacter* spp., and *Pseudomonas* spp. (15) and observed reduced susceptibility to extended-spectrum cephalosporins. This study also highlights *Candida auris* as an emerging multidrug-resistant threat in bloodstream infection (BSI) and urinary tract infection (UTI). Therefore, fungal pathogens such as *Candida* spp. require close monitoring for trends of infections, outbreaks, and susceptibility.

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Enteric fever and especially typhoidal *Salmonella* endemic to South and Southeast Asia and sub-Saharan Africa require continuous monitoring where changing resistance trends have been reported due to fluoroquinolones and cephalosporins (16, 17). Drug-resistant bacteria such as third-generation cephalosporin-resistant *E. coli*, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant *E. coli*, carbapenem-resistant *K. pneumoniae*, and third-generation cephalosporin-resistant *K. pneumoniae* represent serious challenges in patient management, especially in critically ill patient with comorbidities (3,4,7,11,14).

Treating these drug-resistant infections exerts high economic burden on healthcare and patients. Therefore, pathogens exhibiting resistance to antimicrobials for which there are limited treatment options represent a critical unmet medical need for diagnostics and therapeutic interventions. However, the priority pathogens or conditions as well as healthcare settings need to be prioritized as per local healthcare systems and burden of resistant infections.

Managing and containing drug-resistant infections in low-resource healthcare settings requires a multipronged approach consisting of the following steps:

- Effective surveillance systems are required to provide correct estimates of drug-resistant infections at national and regional levels.
- Strengthening of existing healthcare facilities by improving availability of laboratory services, diagnostics, and trained health personnel and, in parallel, enabling new health facilities at peripheral settings.
- Supporting research and innovations to develop rapid diagnostics and new treatment options such as drug molecules, targeted therapies, vaccines, and repurposing old antibiotics.
- Effective socio-behavioral tools and systems to create awareness among prescribers and general public to enable judicious utilization of existing antimicrobials.

Addressing the diagnostic gap

Improving diagnosis helps in generating evidence-based prescriptions to reduce empirical use of antimicrobials. There is a need for quality diagnostics with fast turnaround time for pathogen identification and susceptibility testing to address the problem of AMR (18). In LMICs, accurate and affordable diagnostic tests to differentiate viral and bacterial infections are a priority where resources and capacities are limited, and antibiotics are routinely misused for viral infections. Diagnostics for diagnosis of sepsis and typhoid fever are urgently required to contain spread of resistant infections and reduce morbidity and mortality, especially in neonatal sepsis. Typhoid and enteric fever are major concerns for LMICs with poor sanitation practices. Rapid diagnostic tests for UTIs, fever, and respiratory infections (lower and upper tract) are another unmet need, where empirical treatments result in heavy misuse of antibiotics. Global burden study in 2019 has also reported the dominance of lower respiratory infections, BSIs, and intra-abdominal infections as major infections attributable to AMR (3).

Over the last decade, several molecular diagnostics have been developed for pathogen identification and detection of genes(s) or gene mutations for presence or absence of resistance to antimicrobials (19). Despite the expedited diagnosis, these tests are expensive and need infrastructure and trained resources to provide results, thus limiting their use in resource-limiting settings. In LMICs, indigenously developed low-cost diagnostics have potential to fill this diagnostic gap and help in containing AMR (18). However, indigenous efforts in developing new diagnostics for AMR need to be supported and guided by delineating the local priorities and facilitators as per country's disease burden and healthcare requirements.

Need of new and reformulated antimicrobials and alternatives

The reliance on new drugs or combinations to fight AMR will only provide momentary relief as pathogens will evolve mechanisms to acquire resistance to antimicrobials. Analyzing and reducing antibiotic consumptions across human and animal husbandry sectors, research on intervention strategies and resistance rates can help in tailoring strategies and infection-specific treatment guidelines. The existing antibiotics also need to be utilized for developing new formulations to improve patient outcomes. There is a need to determine top combinations of antibiotics for BSI and study the efficacy of these combinations, preferably with contemporary isolates to provide effective combinations for the treatment of resistant infections. Pharmacokinetic/pharmacodynamic (PK/PD) and safety data on antibiotics and their combinations in different age groups are essential to effectively treat resistant infections.

It is also imperative to understand that the need for new antibiotics for LMIC is different from those of high-income countries as in countries like India, for example, predominant carbapenemase present in gram-negative isolates are metallo-β-lactamases (NDM, VIM) and not KPC (7). This also holds true for *P. aeruginosa* as the newer drugs for gram-negatives (ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam) do not have activity against metallo-β-lactamases. This becomes an important aspect for drug developers for consideration with regard to LMICs. Low-cost solutions are therefore urgently needed to preserve the efficacy of available antibiotics/antibiotic alternatives such as virulence blockers, immune modulators, vaccines, etc. Research efforts need to be prioritized for new treatment strategies such as re-appropriation of old drugs, delivery strategies and for resistance mechanisms such as efflux pump inhibitors, and bacteriophage treatment.

Strengthening surveillance of drug-resistant infections

Tracking resistance trends is important to reduce the burden of infections in hospitals and community settings. Data generated through surveillance can be used in defining guidance for treatment in common syndromes and diagnosis of infections. It is important to implement infection prevention and control, antimicrobial stewardship practices, and

immunization program and reduce over- and misuse of antimicrobials. National estimates of resistant infections, etiology of infections, type of infections, and local resistance rates and patterns can be utilized to set research priorities regarding challenges and opportunities to tackle resistant pathogens in different healthcare and community settings.

In conclusion, evidence-based treatment strategies will be effective in preventing and managing resistant infections. Affordable and accessible quality diagnostics with fast turnaround time will help in enabling better patient care and survival outcomes, thus reducing economic burden on healthcare.

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