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# A return to the pre-antimicrobial era?

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## Perspective

After many years out of the limelight, antimicrobial resistance (AMR) in bacteria is firmly back on the international political and scientific agenda (1, 2). The potential impact of AMR on hospital acquired bacterial infections such as Staphylococcus aureus and Acinetobacter baumannii in higher income countries has created both fear and a surge of motivation aimed at providing new solutions for the problem (3, 4). The political will and momentum to tackle AMR lies in higher income countries, but the medical, social and economic effects of AMR are likely to be felt the hardest in lower-income countries, particularly those in South and Southeast Asia and in sub-Saharan Africa. The identification and development of new drugs is a potential solution but is challenging and costly; any novel therapies introduced into low-income settings without a suitable infrastructure to understand and prevent the rapid development of resistance will likely be expensive and futile.

In many countries at the lower end of the global economic ladder, infections caused by multi-drug resistant (MDR) and extended drug resistant (XDR) bacteria are a common reality. Variants of bacterial pathogens carrying novel AMR mechanisms disproportionately originate in lower-income countries, with downstream consequences both within and outside the region in which they appear. This phenomenon was highlighted in 2008 by the emergence of the carbapenem-resistance-inducing New Delhi Metallo-beta-lactamase-1 (NDM-1) (5). This gene induces broad resistance against carbapenems and other β-lactams and was first identified in a Klebsiella pneumoniae strain isolated from a Swedish national on returning from India. The plasmids carrying this gene have since become common, and are having dramatic impact on the efficacy of carbapenems and other β-lactams in hospitals. A recent report described hospital outbreaks of Klebsiella pneumoniae in children on high-dependency wards in South Asia (6). These outbreaks were caused by particularly virulent variants, which induced a rapid-onset bacteraemia resulting in a 75% mortality rate in the infected children. The presence of NDM-1 within an already broadly antimicrobial resistant and highly virulent strain severely restricted the treatment options, with a direct impact on patient mortality. This and many other studies have shown that AMR gene thrive in low-income settings and can combine effortlessly with other resistance mechanisms. Further, these wide ranging combinations of drug resistance mechanisms can be maintained and then transferred within and between numerous bacterial species.


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The reasons behind the apparent amplification of the current risk in AMR infections in lower income countries are intricate and occasionally geographically driven, but there are common themes that highlight the key issues. First, the bacterial pathogens found in lower income settings (such as typhoid fever and tuberculosis meningitis) typically cause more severe infections than those in higher-income countries. Second, antimicrobials are widely available for purchase in the community without medical consultation and without government policies restricting their use; community overuse and under dosing are common. Third, the medical treatment, range of available antimicrobials, and healthcare facilities are generally better in higher income countries; the risk associated with having a poor outcome after infection with a resistant pathogen is therefore greater in lower income countries. Fourth, very few patients receive any form of conclusive diagnostic testing before, or indeed after, they are treated with an empiric antimicrobial regime. For example, febrile infections across Asia are commonly treated with a fluoroquinolone or a third-generation cephalosporin without diagnostic testing. Finally, the same classes of compounds used to treat human infections are routinely supplemented into animal feed to increase livestock production and, ultimately, agricultural profitability. In contrast, higher-income countries have guidelines for antimicrobial usage in animals, diagnostic laboratories, antimicrobial stewardship schemes and better healthcare structures on which to create sustainable AMR programmes. Such infrastructures and awareness mean that AMR infections are less common in high-income countries than in low-income countries and are mainly limited to healthcare settings. Additionally, when an issue with a particular AMR pathogen is identified in healthcare settings it can be tackled, as exemplified by the dramatic reduction through healthcare interventions of methicillin resistant Staphylococcus aureus (MRSA) associated infections throughout the healthcare structure in England and Wales (7). Advances in genome sequencing technologies and analysis techniques have laid bare the extent of the AMR problem and begun to explain the evolutionary mechanisms behind the maintenance and spread of AMR genes and AMR-inducing mutations. Phylogenetic reconstructions prove that the recent evolutionary histories of numerous bacterial pathogens from lower income settings have been shaped almost exclusively by recent and sustained antimicrobial exposure. The ability to time-stamp the emergence of specific linages and reconstruct pivotal evolutionary events enables identification the key drivers of new founder populations (8) For example, genomic data have shown that Vibrio cholerae, the major cause of epidemic diarrhoea disease in low-income settings, has radiated from the Bay of Bengal in several pandemic waves (see the map) (9). These waves have been shaped by the acquisition of an SXT (a chromosomal gene island) element that encodes a whole host of AMR determinants, including those active against sulfamethoxazole, trimethoprimsulphate, chloramphenicol, streptomycin and β-lactams. The clinical impact of AMR in cholera is poorly defined; however, many cholera patients are treated with empirical rehydration therapy and antimicrobials. Therefore, AMR in Vibrio cholera is likely to play a role in the duration of the infection and the asymptomatic transmission of the pathogen into the community after cessation of symptoms.

Typhoid fever serves as another good example. It is a common bloodstream infection caused by the bacterium Salmonella Typhi (see the image). Before the antimicrobial era the disease had a ~20% mortality rate, which was dramatically reduced when effective therapies were

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introduced. Following the emergence of multi-drug resistance, fluoroquinolones became the recommended therapy in the 1990s, but reduced susceptibility to this group of compounds emerged almost immediately. Genome sequencing has shown that the mutations that catalyse resistance to fluoroquinolones emerged in numerous lineages and on several occasions; today, one lineage with reduced susceptibility to fluoroquinolones has all but replaced all other variants (10, 11). The spread of this lineage is clinically relevant, because increasing resistance to fluoroquinolones correlates precisely with likelihood of treatment failure during fluoroquinolone therapy (12). We are on the verge of widespread resistance to fluoroquinolones in typhoid fever (13); there are few alternatives, and thus a very real possibility of a return to conditions like those in the pre-antimicrobial era. AMR in dangerous bacterial pathogens such as Salmonella Typhi, Vibrio cholerae and Klebsiella pneumoniae in low-income countries can only be tackled through a multifaceted approach that includes drug discovery programmes, sustainable antimicrobial usage policies, and disease prevention strategies including immunisation, improved sanitation, hospital infection control, and improved diagnostics. New generation vaccines and diagnostics for many common developing country bacterial infections are under exploration, but there are presently no programmes aimed at developing novel therapeutic agents specifically to treat dangerous bloodstream infections caused by pathogenic organisms like Salmonella Typhi and Klebsiella pneumoniae. There is an urgent need for those studying infections caused by AMR bacteria in low-income settings to establish connections with drug discovery groups and pharmaceutical companies in high-income countries (14). Examples such as the Tuberculosis Drug Accelerator (TBDA) programme (15) and the Medicines for Malaria Venture (MMV) (16) show how such platforms can be successful. These pioneering initiatives are beginning to link pharmaceutical companies, academia and disease experts across the “gene to bedside” spectrum in the locations where these diseases have the greatest impact. The MMV provides free, open access to a range of compounds with activity against a range of pathogens for independent researchers to screen, with users requested to publish their data in the public domain, thus continuing the drug development research cycle (17). The impact of bacterial AMR in lowincome countries is severe and likely to worsen. New antimicrobial agents may provide some respite against AMR and infections caused by such drug resistant pathogens. However, introducing novel broad range antimicrobials into the current melee of antimicrobial use and misuse in lower income countries would only have a short-term limited impact on infections caused by potentially life-threatening pathogens. Restricting the use of the same classes of antimicrobial compounds in animals and humans has to be an immediate priority, including a direct ban of any new antimicrobials developed for treating infections in humans. Lastly, new antimicrobial agents should only be administered to those who really need them. This means that the current capacity to perform microbial diagnostics and downstream antimicrobial susceptibility testing needs to be greatly improved, alongside the development of rational prescribing practice.

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