

Potential Ways to Improve the Supply and Use of Quality-Assured Antibiotics Across Sectors in Developing Countries to Reduce Antimicrobial Resistance



Antimicrobial resistance (AMR) is growing across countries, especially among low- and middle-income countries (LMICs), increasing morbidity, mortality and costs.^[1-5] Consequently, a range of measures and initiatives are required to address this urgent public health problem to prevent AMR becoming the next pandemic, especially amongst critical African and Asian countries.^[5-9] We have already published Editorials in *Advances in Human Biology* regarding the potential measures that Governments and Health Authorities could instigate to improve the quality and efficiency of their medicine use, including antibiotics.^[10] In addition, potential programmes to reduce the high levels of inappropriate dispensing of antibiotics amongst community pharmacies, especially in LMICs, to reduce AMR.^[11] This includes the potential ways to effectively address the challenges with patients in LMICs often requesting antibiotics from prescribers or community pharmacy personnel for typically self-limiting conditions, exacerbated by their limited knowledge of antibiotics and AMR.^[12]

Other key areas to address to reduce AMR amongst LMICs include ensuring that key providers, including hospitals, are not faced with the shortages of critical antibiotics.^[13] Such a situation can lead to the prescribing of inappropriate or less effective antibiotics, which can result in treatment failures, potentially higher costs with using more expensive antibiotics, over use of broad-spectrum antibiotics, the transfer of patients to other facilities and/or patients being discharged early without full treatment, all potentially adding to AMR.^[13-19] The shortages of antibiotics amongst public hospitals in LMICs are exacerbated by concerns with payment, lack of proactivity including a lack of antimicrobial stewardship programmes (ASPs) incorporating therapeutic substitution policies, as well as limited forecasting ability and suboptimal information technology infrastructures.^[16,20-22] In addition, sudden changes in prescribing brought about by the changes in pharmaceutical company promotion and against current guidelines including the recent World Health Organization (WHO) AWARe guidance.^[23-28] We are aware that most regional studies assessing the extent of shortages of medicines in hospitals, including antibiotics, as well as potential ways forward, have typically taken place in Europe.^[18,29-31]

There is currently a paucity of studies across Africa, as well as amongst Asian countries, assessing the extent of shortages of antibiotics in hospitals, ongoing challenges as well as potential ways forward.^[19,32] This needs to be urgently addressed given the additional challenges in LMICs. These include challenges with introducing ASPs as well as available resources and personnel to track and improve antibiotic use in hospitals, in line with the goals in their AMR national action plans.^[33-36] In the meantime, there are activities that key hospital personnel can undertake to ensure and improve antibiotic availability and use in their hospitals whilst waiting for the findings from cross-national studies.

Activities include the instigation or updating of hospital antibiotic guidelines. However, any guideline should be based on robust international guidance, including the recent WHO AWARe book guidance, alongside knowledge of current antibiotic resistance patterns.^[5,26,37] Potential guideline targets include initiatives to reduce excessive prescribing of Watch and Reserve antibiotics in hospitals across LMICs to meet the United Nations' goals.^[38-43] In addition, reducing current overuse of antibiotics to prevent surgical site infections in hospitals, which is still prevalent across LMICs including African and Asian countries.^[40,43] These activities should reduce the need for hospitals to stock and track multiple antibiotics. In addition, focus procurement on a limited number of critical antibiotics to reduce the overall costs. Other activities include improving the monitoring of antibiotic use through improving electronic prescribing systems, instigating therapeutic interchange policies and quickly contacting prescribers to review possible therapeutic interchange and substitution when there are antibiotic shortages.^[16,18]

Concerns with antibiotic shortages are principally confined to the hospital sector amongst a number of LMICs.^[44] There are shortages of antibiotics in ambulatory care across LMICs; however, this appears mainly amongst primary healthcare centres (PHCs) that may not have sufficient funds to purchase all prescribed antibiotics for their patients; alternatively issues with forecasting leading to shortages.^[44]

Concerns with funding the purchasing of antibiotics for PHCs are exacerbated if there are sudden increasing in prices as recently seen in Nigeria.^[45,46] As a result, patients typically have to purchase prescribed antibiotics from community pharmacies and other drug sellers. Overall, critical issues generally regarding antibiotics in primary care appear to be more about their overuse and misuse rather than about shortages.^[25] The key concerns include current appreciable dispensing of antibiotics without a prescription across LMICs, including those from the WHO Watch list.^[44,47-50] The excessive dispensing of antibiotics is exacerbated by their considerable availability, especially where branded generics are available.^[44] This is illustrated in Pakistan where there are currently 2186 different brands of cephalosporins available in 6447 presentations and 1333 different brands of quinolones in 2586 presentations, which includes 393 brands of ciprofloxacin with 1158 presentations.^[51] The concern is that all these manufacturers are primarily focused on generating a profit, including pushing the government for higher prices.^[51,52] Increasing International Nonproprietary Name (INN) prescribing, along with ensuring quality generics, are key steps forward towards to reduce medicine prices and alleviate concerns amongst patients regarding generics.^[9,51-53]

Another key area to address to reduce AMR amongst key LMICs is ensuring that patients have access to affordable critical antibiotics in primary care and are not reliant on the informal sector with their worrying levels of cheaper substandard and counterfeit antibiotics.^[44-46,54] Increasing INN prescribing, along with enhancing the availability of quality-assured generics, are again crucial steps to reduce the prices of antibiotics, thereby reducing the attractiveness of the market for cheaper substandard antibiotics.^[51-54] Possible confusion amongst patients when multiple branded generics of the same molecule are being regularly dispensed will also be reduced by INN prescribing and packaging.^[51-53] Making antibiotics affordable will also reduce current practices among LMICs whereby antibiotics are stopped when patients feel better and are subsequently shared amongst families and friends, which should reduce AMR.^[44,45] These critical issues all need to be addressed moving forward among LMICs to reduce AMR, with primary care accounting for up to 95% of total antibiotic consumption amongst humans in developing countries.^[55]

The high reliance on the informal sector across LMICs is the result of several factors. These include readily available antibiotics in this sector as well as their affordability when the costs of visiting prescribers in healthcare clinics, alongside any dispensing costs, are factored in.^[56,57] This is a concern with, as mentioned, the greater dispensing of substandard and counterfeit medicines in informal versus formal sectors, contributing to AMR, with antibiotics accounting for the majority of counterfeit medicines currently seen.^[44,54,58-63] The informal sector is typically defined as containing unlicensed outlets, which may exist in shops, charge fees for their services typically in cash and staffed by people with minimal training.^[64-67] The lack of training of staff in the informal

sector, coupled with a higher prevalence of substandard and counterfeit antibiotics, adds to the growth of AMR in LMICs.^[59,61]

The first steps with reducing reliance on the informal sector for antibiotics across LMICs includes assessing the extent of the problem and the rationale behind the use of antibiotics. These are planned activities for the future, building on previous studies and reviews.^[44,64,66-68] In the meantime, we are seeing multiple activities across countries and continents to improve the quality of antibiotics being dispensed as well as to reduce the extent of counterfeit antibiotics being sold.^[44] Activities to improve the quality of antibiotics being dispensed include the WHO's 'Lomé Initiative' combined with for instance the establishment of the African Medicines Agency to help upgrade and harmonise regulatory activities across the continent as well as reduce duplication of effort.^[69-72] Reducing duplication will release more officers to track the presence of substandard and counterfeit antibiotics in the country.^[73] Alongside this, improved co-ordination with Interpol across Africa and Asia to track down suppliers of counterfeit antibiotics, which is already happening.^[74-77]

Other potential activities to improve the quality of available antibiotics in LMICs include compulsory re-registration and/or the removal of licenses where substandard antibiotics are detected.^[60,78] Combined with this, aggressive sanctions for manufacturers and suppliers, including informal suppliers, when counterfeit medicines are found. Activities could include removal of licences to operate/import antibiotics, extensive fines, disruption of informal sites and prison sentences.^[54,75,79] Other activities include improved packaging and the traceability of available antibiotics.^[54,62,80] We have already seen the Indian government forming a task force to tackle issues with falsified medicines through a number of activities including placing unique identification numbers and a bar code on medicine packs-containing antibiotics,^[77,81,82] with similar activities in other LMICs.^[62,83] Additional measures include streamlining the supply chains to improve traceability and reduce costs, especially since these are currently complex.^[84] Furthermore, focusing prescribing and dispensing of antibiotics for infectious diseases on the small number recommended in the WHO AWaRe guidance.^[26,27] Limiting the number of antibiotics used and their dosage should also help streamline production, including local production of antibiotics, thereby reducing costs and the attractiveness of this market for the informal sector.^[44]

In conclusion, there are multiple activities that key stakeholders can undertake across LMICs to improve future antibiotic use and reduce rising AMR rates. This includes proactively tackling antibiotic shortages in hospitals as well as implementing multiple inter-related measures to reduce the availability of counterfeit antibiotics in ambulatory care alongside the attractiveness of the informal sector. By doing so, help reduce affordability as a barrier to accessing and completing full

courses of antibiotics in ambulatory care. We will continue to explore these issues in upcoming planned research projects to provide future targeted direction.

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