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Commentary

Universal access to key essential antibiotics—Recent amoxicillin global shortages mask a wider policy failure

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The United Nations General Assembly on AMR in 2024 is an opportunity to focus attention on the importance of universal access to safe, effective, and affordable essential antibiotics. Defining these key essential antibiotics and reducing the technical and economic barriers to their sustainable and equitable access should be a core component of the Universal Health Coverage Action Agenda.

Introduction

Improving sustainable access to essential medicines remains a major global concern. European Union recommendations to avoid future antibiotic shortages for respiratory tract infections (RTI) include enhanced monitoring, increased regional production of selected Access and Watch antibiotics, and development of an EU "critical medicines list" [1]. Amoxicillin (+/− clavulanate) is the key oral antibiotic on the EU critical medicine list, as the first line recommended treatment for RTI in most European guidelines, including France, Germany, UK, and Belgium (the critical list also includes penicillin V, azithromycin, and clarithromycin). Both the FDA and EMA have also reported amoxicillin as a drug shortage [2,3]. The immediate cause is increased demand following a resurgence of respiratory viral and streptococcal infections after COVID-19. But shortages of antibiotics, particularly narrow-spectrum Access penicillins (amoxicillin, penicillin) have been reported globally for many years. The supply problem of older generic drugs is not specific to antibiotics. The 2019 FDA Task Force on Drug Shortages report noted the lack of incentive to produce less profitable, low-price drugs, uncertain revenue streams, "race to the bottom" pricing and lack of rewards for high quality systems [4], with similar findings noted by the Organisation for Economic Cooperation and Development [5].

The 2022 WHO AWaRe Book [6] provides detailed guidance on the choice of drug, dose, and duration for 35 infections in children and adults in

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both the primary care and hospital setting, following a detailed review process, including all GLASS microbiology data [7]. The WHO now recommends amoxicillin (+/− clavulanate) as the first-choice antibiotic for adults and children in 10 of the 12 most common primary care infections for all WHO regions. The other oral antibiotics in the EU critical medicine list are penicillin V (Access- AWaRe Book recommended in only two RTI's), azithromycin (Watch—recommended mainly for enteric fever), and clarithromycin (Watch—recommended in adults with severe pneumonia), while other Access and Watch antibiotics are recommended for sexually transmitted infections. Amoxicillin (+/− clavulanate) is therefore globally the **critical** Access antibiotic, the WHO recommendation both for community acquired pneumonia in children/adults and *all* other RTIs. Amoxicillin remains very effective against the main pathogens causing RTIs in primary care globally. The median rate of penicillin resistance in *Streptococcus pneumoniae* (the leading causative pathogen in RTI's globally) was 2.7 % in the WHO GLASS 2021 report, which focusses on invasive isolates [8]. The AWaRe Book recommends higher doses of amoxicillin to achieve drug levels over current EUCAST/CLSI break points of the most prevalent pathogens [9]. The AWaRe system is the accepted method of monitoring antibiotic use in humans and setting future targets on optimal use, with the Global Leader's Group now recommending that 80 % of antibiotic use should be from the Access group [10]. Ensuring the sustainable supply of amoxicillin will be critical to ensure future targets of increasing Access antibiotic use can be met in both the high income (HIC) and low-and-middle income (LMIC) settings. Maintaining access to amoxicillin in an effective, quality, and affordable formulation in primary health care globally is a key component of achieving SDG 3.8 (universal health coverage) [11], but the drug shortages noted above are only part of a wider access failure.

Amoxicillin is generally a very low-price medicine, with a slim profit margin kept low by very high-volume sales, multiple suppliers, and a very price-sensitive market. UNICEF's procurement price for amoxicillin 250 mg dispersible tablets is USD 0.43 for 20 tablets [12]. The volumes sold globally are very high, with billions of courses of amoxicillin (+/− clavulanate) used in adults and children annually, making this likely the most common medicine prescribed for humans. Despite high volume of sales, its low price (in many but not all countries) and narrow profit margin risks disincentivising all components of the supply chain. There are many financial incentives for manufacturers, wholesalers, pharmacies, and physicians to supply higher priced products [13], encouraging the use of generally higher cost oral broad-spectrum Watch antibiotics, helping to explain why their use has doubled [14]. Setting ambitious and context-specific policy targets for total and relative levels of prescribing of Access antibiotics (principally amoxicillin) could be part of the solution, increasing the focus on physicians, healthcare systems and pharmacies with high prescribing and sales of oral Watch antibiotics. Within countries, the cost savings associated with moving from a *high Watch* to a *high Access* primary care oral antibiotic exposure model are potentially very significant but difficult to realise. As with many generic medicines, the public health value of amoxicillin is clearly much higher than its current apparent value. The WHO has provided guidance on potential pharmaceutical pricing policy interventions [13]. There is a critical need to maintain equitable, affordable access to the patient. Additional strategies including forecasting of use and early warning systems are required to mitigate shortages and their associated higher costs. Patient and prescriber lack of trust in generics also drives use of more expensive originator medicines, increasing patient costs [15]. Oral antibiotics are one of the most reported sub-standard and falsified medicines, contributing to major trust concerns but the WHO has established some mechanisms to help member states address this issue [16].

However, in some LMIC settings stockouts, shortages, lack of quality assurance, and markedly higher prices of older generic antibiotics are common. National antibiotic policy targets aimed at increasing the use of Access antibiotics are threatened by the lack of an assured delivery within the healthcare system while implementation of AMR National Action Plans is challenged by lack of funding. A higher mortality in children with pneumonia is more strongly associated with a lack of access to antibiotics rather than AMR [17]. Although many patients obtain treatment through the informal sector, there has been a lack of focus on the need to improve access to effective treatment for common infections in primary care.

This is a complex problem, but some practical steps could be taken. There needs to be a more detailed analysis to define the "access gap" for antibiotics and which drugs, countries and regions are most affected, including the underlying causes of the unmet need. WHO facility surveys have demonstrated a concerning lack of access to key antibiotics. In a recent review of 13,561 facilities, co-trimoxazole and metronidazole were in stock at 89.5 % and 87.1 % of facilities, but other Access and Watch antibiotics, including amoxicillin, were stocked in less than 50 % [18]. A more formal process led by the WHO could define a shorter list of "key access" antibiotics as part of the AWaRe system as there are 18 oral antibiotics on the 2023 Essential Medicines List (EML) [19]. A robust transparent methodology is required to assess the multiple criteria that need to be considered to define critical infections in the AWaRe Antibiotic Book and the antibiotics that should always be available at health centres to treat them using a public health approach, including clinical efficacy, safety, cost, impact on resistance. This would include not only the most appropriate medicine, but also the dose, duration, and formulation to simplify program delivery for adults and children.

A clearer assessment of the structural barriers in last mile medicine delivery is required, including what is "antibiotic specific" in the barriers to accessing weak primary health care services. Strategic public investment in the supply side is underway in the EU and could be expanded to other regions. Future regional investment in pharmaceutical manufacturing should focus on essential antibiotic provision based on population health needs.

There is no clear delivery program for "key access" antibiotics yet, and a pilot project to identify the feasibility, cost and barriers would likely need to be linked to an existing delivery mechanism. A clear monitoring and evaluation framework needs to be developed, although a limited adaptation of the WHO and Demographic and Health Surveys program facility surveys assessing medicines availability (Service availability and readiness assessment (SARA) and Service Provision Assessment (SPA) respectively) [20,21] aligned with the DHIS2 (District Health Information Software 2) [22] data collection platform could be a way forward to track availability and usage [18]. Treatment with amoxicillin is already collected in the DHS SPA sick child observation protocol [23]. Further integration of access to antibiotics and effective treatment of bacterial infections as part of universal health coverage could support the assessment and investment in countries (Box). Equally, the potential adverse consequences of this approach need to be considered. Deriving critical lists of antibiotics runs the risk of increasing prices overall and reducing affordability and access to the poorest families not included in any roll out program. Consolidating the market around a smaller number of "key access" antibiotics could potentially increase shortages if suppliers are not incentivised or engaged to meet new demands. Markedly increasing access to antibiotics with limited guidance on their optimal use runs the risk of increasing inappropriate use, driving further resistance.

Recent initiatives further highlight the focus on ensuring access to antibiotics as a key strategy for tackling AMR: The UK Government has recently announced up to £50 million funding to support countries and institutions in Africa in accessing essential antimicrobials [24]; the 77th World Health Assembly also notes universal access to affordable, quality and appropriate treatment of infections based on the AWaRe system is one of the three strategic priorities in AMR [25]; the 2024 Lancet AMR Series also focussed on the inequity of current patterns of global antibiotic use, with lower levels of use seen in poorer countries with higher infection burden and mortality [26]. The Series takes a novel benchmarking approach to assist countries to determine appropriate levels of national use based on population health need. The United Nations General Assembly on AMR in 2024 (UNGA-AMR) provides a major opportunity to focus on the antibiotic access gap and recommend clear steps towards equity of universal access to effective antibiotics and improve clinical outcomes.

Box.

Potential integration of access to antibiotics with Universal Health Coverage (SDG 3.8) assessments

- The inclusion of access to effective antibiotics could be considered as a UHC tracer indicator for SDG 3.8.1, coverage of essential health services.
- The current UHC Service Coverage Index [27] includes health seeking behaviour in families for a child with an acute respiratory infection, but could include whether the appropriate antibiotic was available and affordable at the facility the family visited (SDG indicators 3.8.1 (coverage of essential health services) and SDG 3.8.2 (catastrophic health spending)).
- The assessment of infectious diseases (SDG 3.3 (communicable diseases) and UHC SDG 3.8.1 sub-index) includes the treatment or prevention for TB, HIV, and malaria, but not for other common bacterial infections; these assessments could be updated to include key bacterial infections based on the AWaRe Book.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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