Antimicrobials: access and sustainable effectiveness 3

Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries

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Access to quality-assured antimicrobials is regarded as part of the human right to health, yet universal access is often undermined in low-income and middle-income countries. Lack of access to the instruments necessary to make the correct diagnosis and prescribe antimicrobials appropriately, in addition to weak health systems, heightens the challenge faced by prescribers. Evidence-based interventions in community and health-care settings can increase access to appropriately prescribed antimicrobials. The key global enablers of sustainable financing, governance, and leadership will be necessary to achieve access while preventing excess antimicrobial use.

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This is the third in a **Series** of five papers about access to and sustainable effectiveness of antimicrobials

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Introduction—balancing access and excess

Antimicrobials are life-saving drugs that, together with vaccination and improvements in the social determinants of disease, have a fundamental worldwide effect on individual and public health. Access to antimicrobials and prevention measures has been a crucial factor in the 50% reduction in maternal and child deaths since 1990.[1] However, in 2010, the number of deaths of children younger than 5 years still reached 7·6 million.[2] The importance of increasing access to antimicrobials, vaccination, and other prevention measures against infectious diseases in countries that have had challenges in implementation of maternal, neonatal, and child health interventions has been highlighted.[3] Furthermore, access lies at the heart of most of the UN Sustainable Development Goals (SDGs). Most importantly, SDG 3.3 aims, "by 2030, to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases".[4]

Therefore, unrestricted access to antimicrobials can potentially lead to substantial population health gains in the short term. Such gains might extend beyond reductions in morbidity and mortality for individual infections. Results from a 2009 study have shown reduction in overall mortality in Ethiopian children treated with azithromycin as part of a trachoma eradication programme,[5] and a systematic review[6] reported positive effects on childhood growth of a range of antibiotics given as part of studies focusing mainly on malnutrition.

Despite these beneficial effects, to avoid compounding the long-term ecological disaster of antimicrobial resistance that is unfolding now, unrestricted access should go hand-in-hand with appropriate use of antimicrobials. Some tough decisions will need to be made. Using the two examples outlined above, despite the reduction in overall mortality, mass azithromycin use for trachoma control increased the rate of pharyngeal carriage of macrolide-resistant *Streptococcus pneumoniae*.[7] Similarly, despite the potential positive effects of antibiotics in growth promotion in children, the intense selection pressure resulting from such a strategy needs to be carefully considered, just as it has been in animal feed, in which the use of antimicrobials for growth promotion has been banned in the European Union since 2006.[8]

While Dar and colleagues[9] in this *Lancet* Series highlight the evidence base for interventions that increase responsible use through appropriate prescribing, we will focus on the factors that drive and enable access to antimicrobials and related approaches that are necessary to ensure appropriate use.

Guiding principles and measures

The main drivers of excess are related to high infectious disease burden as a result of improper prevention, availability of substandard drugs because of deficient regulatory and enforcement capacity, insufficient health personnel or community health workers, or inadequate

Key messages

- Access to quality-assured antimicrobials is part of the human right to health, yet universal access is often undermined in low-income and middle-income countries (LMICs).
- No model exists that increases access while minimising excess; hence, access programmes need to be context-adjusted and applied across a range of health-care settings.
- To achieve appropriate antimicrobial prescribing, LMICs have to strengthen their health systems, including health insurance, provision of laboratory support, and increased access to diagnostics and primary prevention measures.
- Delinkage to uncouple sales from innovation in research and development (R&D) should be adopted, so that public health needs drive advances in antimicrobials and diagnostics.
- As a global challenge, universal access demands a long-term commitment, with sustained financing from all affected countries, to move away from present donor-driven models in resource-poor states.
- The key enablers of access to antimicrobials—ie, financing, R&D, equitable management of knowledge and intellectual property, so-called managed marketing, and procurement and distribution of antimicrobials—should be strengthened to support the World Health Assembly Global Action Plan to combat antimicrobial resistance.

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See Online for appendix

training and skills among them. Little access to diagnostics and laboratory services to guide treatment compounds the problem.

Important principles and measures to promote appropriate antimicrobial use are therefore necessary to improve access to quality-assured antimicrobials, health services, prevention measures, diagnostics (preferably at the point of care), prescribing guidelines, and education. Promotion of innovation for public health needs and strengthening of health systems underpin these important principles, which expand on the traditional so-called access to medicines strategies, in which generic competition has been a crucial driver.[10] An integrated approach is clearly needed to tackle antimicrobial resistance and ensure appropriate antimicrobial use, especially against bacterial infections.

Access for all in need

Access to essential medicines, of which antimicrobials are one example, is part of the right to health—ie, the enjoyment of the highest attainable standard of health, which is one of the state's obligations under human rights law.[11,12] The principle of access to essential antimicrobials for those in need is often undermined in low-income and middle-income countries (LMICs) by financial, infrastructural, and human resource limitations. Universal access to antimicrobials is not only about availability. Rather, an integrated approach to appropriate prescribing, enabled by availability of affordable antimicrobials, is needed.

Philippe Lissac/Godong/Corbis

Figure: **A medicine shop at Dantokpa market, Cotonou, Benin**

Novel organisational, financing, logistic, and procurement models have been developed in several vertical treatment programmes for malaria, HIV, and tuberculosis.[13] These models could be adapted to improve access to and lower the price of other antimicrobials. One example is the Affordable Medicines Facility—malaria (AMFm). Although its results could not be fully assessed, phase 1 of AMFm, a financing model operational in 2010–13, increased access to quality-assured artemesinin-based combination therapies (ACTs) in the private (ie, for-profit) sector, in which regulation was often weak. This reduced the use of artemesinin monotherapies and poor-quality combination therapies, which drive resistance.[14] Increased availability was achieved by negotiation of appropriate pricing with wholesalers and through a high-level subsidy from The Global Fund provided to all wholesalers.[15] In November, 2012, The Global Fund board decided to integrate the AMFm into core Global Fund grant management and financial processes. An important critique of the AMFm was that improved rational use of ACTs was not a specific strategic objective. As a result, according to WHO, "the co-payment of quality-assured ACTs was not coupled with that of rapid diagnostic tests (RDTs), and the initiative did not promote the expansion of malaria diagnostic testing".[16] Nonetheless, programmes that enable price reduction of quality-assured products through collective purchasing power and pooled procurement models can be highly successful[13] and could be a part of international strategies to promote appropriate antibiotic use.

Although these price reduction initiatives have mostly been successful in LMICs, they do not guarantee improved access, and substantial challenges remain, especially in remote regions or small pharmacies.[17] In some parts of the world, including sub-Saharan Africa, access to quality-assured antimicrobials is limited, whereas in others, especially in Asia, these antimicrobials might be sold alongside substandard, falsified, or counterfeit drugs (figure; appendix). In countries where antimicrobials are sold over the counter, inappropriate overuse usually involves an unsuitable choice of drug, dose, and treatment duration. However, no clear evidence suggests that antimicrobials obtained over the counter without prescription are used less appropriately than those prescribed.[18] Differences also exist between public and private pharmacies, with the latter often stocking a wider range of antimicrobials.[19] Internet antimicrobial sales also have the potential to drive inappropriate use; a third of 138 unique vendors identified as selling antibiotics did so without a prescription, whereas the rest required prescriptions to be provided online.[20]

Use of generic drugs has successfully driven down costs in high-income countries (HICs) and LMICs. Although savings of up to 73% for injectable generic cephalosporins have been reported in China,[21] distrust of generics driven by the brand companies and legitimate quality questions are often reasons of underuse in LMICs.[22,23] Revitalisation of the generic drug option through quality-assured products is needed to regain trust and promote use.[24] Generics produced locally to rigorous good manufacturing practice standards might enhance access. Capacity strengthening of medicine regulatory authorities is a prerequisite for a strong policy for generic drugs. Pharmaceutical companies operating in Africa report difficulties in complying with technical requirements of individual countries, and such difficulties could delay access and affect pricing.[25]

For LMICs, no single model exists that increases access while limiting excess. Access programmes need to be context-adjusted (eg, for rural or urban environments and level of economic development) and applied across a range of health-care settings (including private-sector development). Prescription-only regulation might not be practical for countries with inadequate health delivery systems with few qualified prescribers, and might restrict appropriate access to antimicrobials. In such settings, strengthening capacity of community pharmacists and other health workers to make good decisions on dispensing antimicrobials (ie, appropriate use) through education, feasible evidence-based algorithms, and guidelines is crucial, as are community involvement and education.

Increasing access to antimicrobials might have different effects on resistance, depending on the prescribing, health system, and economic environment. In many HICs where overuse is common, increasing access will further drive selection pressure and propagate resistance.[26–28] The situation in LMICs is more heterogeneous both between countries in the same region and within countries, where rural and urban areas might differ substantially. In many Asian countries, where most of the world's antimicrobials are produced[29,30] and overuse is common,[18,31] increasing access without other combined measures might not be desirable. However, in LMICs where people have little access to antimicrobials, are not able to afford a full course of treatment, and can obtain only substandard falsified drugs or cheaper and improper drugs to which the organism is already resistant, increasing access can reduce selection pressure.

Access to health services

In view of human resource shortages[32] and limited access to public health facilities in LMICs, several innovative community-based strategies have been developed and tested to improve antimicrobial access for millions who live at or beyond the periphery of the health system (panel 1). In many parts of the world, private practice physicians or pharmacists (including drug shops and private medicine vendors) are the primary access points for antimicrobials. A recent Ugandan household survey[47] identified poor access to drugs of assured quality, in addition to inappropriate antimicrobial sales and use.

Although the private sector has the potential to reduce inequities in access,[48] inadequate and inappropriate diagnosis, overuse of antimicrobials, and insufficient or incorrect advice being provided to patients or their caregivers are substantial risks. Concerns about the widespread inappropriate use of antibiotics in India led to the Chennai declaration and its first phase of implementation in 2014.[49,50] Involvement of private practice physicians and pharmacists in improving access and prudent drug use is key to success.

Panel 1: Community-based interventions

Integrated Community Case Management (iCCM)

Children in the lowest wealth quintile are least likely to receive early and appropriate treatment for malaria, pneumonia, and diarrhoea.[33] To improve access to treatment, many countries have been testing and scaling up iCCM. This equity-based approach has several potential benefits, including reduction in the overuse of expensive and inappropriate treatments by implementing rapid diagnostic tests (RDTs; eg, for malaria),[34,35] which improves access to appropriate antimicrobials,[32,36,37] thereby limiting resistance.[34,38]

Recognising the potential for diagnostics-guided, evidence-based paediatric treatment algorithms, WHO and UNICEF released a joint statement justifying the need for iCCM and making recommendations on its implementation in 2012.[39] These recommendations included needs assessment and situation analysis for community-based treatment services, training for community health workers, a communication and social mobilisation plan, attention to supply chain, and service delivery models.

Task sharing

Sharing the task of prescribing between doctors and other health workers can improve access.[40]

- In Zambia, a 45% reduction in neonatal mortality was achieved by training traditional birth attendants to do a modified neonatal resuscitation protocol for babies with respiratory distress, identify signs of possible neonatal infection and administer a dose of oral amoxicillin, and help with referral to the nearest rural health centre.[41]
- In 2013, Zaidi and colleagues[42] reported the use of four simplified regimens for the treatment of newborns with possible serious bacterial infection, the caregivers of whom refused referral to secondary care, in five sites in Africa. Three regimens that included different durations of oral amoxicillin and injectable gentamicin resulted in equivalent levels of treatment failure to injectable penicillin and gentamicin.
- In rural Maharashtra state, India, home-based newborn care by trained village health workers, including assessment for possible serious bacterial infection and pre-referral administration of injectable gentamicin, resulted in a 16% decrease in neonatal sepsis case fatality and a 62% reduction in all-cause neonatal mortality.[43]
- Appropriately trained community health workers can classify and treat malaria and pneumonia, thereby helping to avoid inappropriate antimicrobial use.[44] In South Africa, primary care nurses safely initiated and represcribed antiretroviral therapy without affecting mortality.[45] Mobile clinics have also been tested as a strategy to improve delivery of such therapy to patients in remote areas. Those attending mobile clinics were mostly men, and they had lower HIV infection rates and higher CD4 counts than did individuals who did not attend these clinics.[46]

Access to prevention measures

Access to interventions that reduce the overall burden of infections (both incidence and transmission), and thereby prevent the need for antimicrobials in the first place, could affect antimicrobial resistance (appendix).

Many of these interventions are simple health promotion strategies, such as improving access to clean water and sanitation. In Karachi, Pakistan, washing hands with soap reduced both diarrhoea and acute respiratory infections by half, and the incidence of impetigo that would have required antibiotics was reduced by a third.[51] Male medical circumcision, male and female condoms, vaginal microbiocides, and scaling-up of antiretroviral treatment for prevention have proved to be important prevention measures in HIV, as have increased active case finding, use of isoniazid prevention therapy, and integration of HIV-TB services in the control of tuberculosis.

Access to vaccination remains key, and closing the gap on under-reached populations for both new and existing vaccines should be a priority, as exemplified by the GAVI alliance (formerly the Global Alliance for Vaccines and Immunizations). Several studies have shown significant reduction in resistant *S pneumoniae* infections after the introduction of multivalent pneumococcal conjugate childhood vaccines, both in vaccinated children and in the general population (through herd immunity).[52–54] The integration of vaccination programmes into broader antimicrobial resistance control strategies remains underassessed, especially with regards to policies that combat resistance with global vaccine and control initiatives, which are not always coordinated.

Some prevention measures can themselves increase resistance—eg, mass azithromycin use for trachoma control in Ethiopia[5] was associated with increased carriage of macrolide-resistant *S pneumoniae*.[7] The proposed large-scale use of azithromycin to eradicate yaws[55] raises similar concerns and the potential to alter resistance patterns in other endemic treponemes, such as *Treponema pallidum*.[56] This could have serious implications in the management of syphilis, and careful monitoring and assessment will be necessary.

Access to diagnostics

Overprescription of antimicrobials is typically driven by diagnostic uncertainty around undifferentiated fever (one for which a definite cause is unapparent). The reasons for lack of access to diagnostics are multifactorial and include unavailability of point-of-care tests; underuse of diagnostic services because of long laboratory turnaround times, poor performance characteristics, or affordability issues; little access to laboratory services; and inadequate maintenance and assurance of quality of laboratory equipment. RDTs, many of them done at the point of care, allow confirmation of infection before treatment and can potentially help to ensure appropriate use of antimicrobials. For example, the automated real-time nucleic acid amplification system Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) confirms the presence of rifampicin-resistant *Mycobacterium tuberculosis* within 2 h. However, rollout of Xpert MTB/RIF has been restricted in many settings by its energy and temperature requirements and its high capital costs.[57]

Fear of missing a diagnosis of bacterial infection was a strong motivator to prescribe antimicrobials by primary care physicians in India.[58] By contrast, access to point-of-care RDTs for malaria led to a reduction by four times in inappropriate antimalarial prescribing in children younger than 5 years by community health workers in rural Zambia, and an increase by five times in early appropriate use of antibiotics for pneumonia,[34] with similar results in Zanzibar.[59] However, single-disease RDTs give only a part picture and have the potential to lead to overprescribing of antibiotics.

In d'Acremont and colleagues' two-centre study[60] of outpatient children in low-malaria-endemic setting in Tanzania, although lower respiratory tract infection was the most common diagnosis, fewer than 13% cases were caused by bacteria. An important area for study is the development of more point-of-care diagnostics for common infections and their integration into clinical algorithms to optimise diagnosis and appropriate antimicrobial prescribing. These diagnostics will include those for endemic infections such as enteric fever, a major cause of morbidity and mortality in Asia, which relies on old, insensitive tests with poor specificity.[61] Point-of-care tests for biomarkers such as C-reactive protein, which has been shown to reduce antibiotic prescribing for respiratory tract infection in HICs,[62] should be incorporated where appropriate.

Hence, what is needed in LMICs is a point-of-care test to differentiate fever caused by bacterial and viral infections and to predict the need for antibiotics. When used in parallel with guidelines and antimalarial RDTs, such a test can substantially enhance appropriate antibiotic prescribing. A multiplex laboratory device that can detect a range of important bacterial infections can help to guide more directed antibiotic use. An automated diagnostic system to test for resistance against antibiotics, which might not need to be at the point of care, will also help to guide antibiotic use and promote local surveillance. Despite the potential advantages of point-of-care tests, few studies of their cost-effectiveness have been done in LMICs.[63,64] However, a comprehensive framework—based on assessment of diagnostic accuracy, clinical effect, and costs—to optimise such studies has been proposed.[65] The ideal test would be rapid, allowing quick clinical decision making by care providers at the point of care, have acceptable test efficacy, and be cost-effective.

Access to evidence-based management protocols, service provision enhancement, and education

The provision of straightforward physician-directed educational material in isolation generally has little effect on physician behaviour.[66] However, basic algorithmic

guidelines can improve appropriate antimicrobial delivery, especially if they are integrated with more complex, system-wide interventions.[66–68] If coupled to an expanding RDT capability, programmes such as the WHO Integrated Management of Childhood Illness (IMCI),[67] which has been introduced in more than 75 countries, and the related Integrated Management of Adolescent and Adult Illness (IMAI) could be expanded and adapted for wider patient and disease groups. IMCI and IMAI aim to improve case management skills of health workers, overall health systems, and family and community health practices, and promote appropriate self-care and help seeking in LMICs. Furthermore, both programmes seek to train health workers to identify patients who can be safely managed at primary-level facilities and those that need to be referred to high levels of care. Assessments of IMCI have shown improvements in performance of health workers and quality of care, with more rapid initiation of antibiotic treatment, correct antibiotics administered, increased use of first-line recommended agents, and reductions in childhood mortality.[68,69] However, the choice of antimicrobials and the algorithms used in IMCI and similar programmes needs to be regularly reviewed to ensure continued effectiveness, and local antimicrobial resistance patterns and epidemiology also need to be taken into account. International collaboration to develop and support antimicrobial resistance surveillance and monitoring in LMICs is an essential part of the WHO's Global Action Plan in this regard.

Insufficient access or capacity to use clear and authoritative guidelines that are integrated with evidence-based protocols for prescribing antimicrobials other than antiretrovirals in adult populations compounds management uncertainty and fuels overuse by primary care physicians and pharmacists.[58,70] Successful education-based interventions to improve appropriate prescribing from economically developed settings could be adapted for use in LMICs (panel 2). However, we stress that the issue in HICs is more one of reducing prescribing of antibiotics that are unlikely to benefit patients in a context where serious bacterial infections are rare and complications uncommon,[82] and so these interventions need careful adaptation and assessment in LMICs.

Panel 2: **Persuasive and restrictive interventions from economically developed settings that could be adapted for possible use in low-income and middle-income countries**

Community practitioners

- Multifaceted interventions are most effective at achievement of overall reduction in antibiotic use, and interactive educational approaches outperform didactic education.[66]
- Blended learning programmes with a combination of online, seminar-based, and context-bound learning with practice using simulated patients might be beneficial in settings where relevant facilities (eg, reliable internet connection with sufficient bandwidth) are available. This approach safely reduced all-cause antibiotic prescribing at a general medical practice level over a year.[71]
- Group education meetings that included general practitioners and their collaborating pharmacists resulted in decreased antibiotic prescribing.[72]
- Training of clinicians in enhanced consultation skills and point-of-care tests of C-reactive protein have an additive effect on safe appropriate antibiotic use, and both are cost effective, an important factor in resource-poor settings.[73,74]

Hospital practitioners

- The UK Start Smart Then Focus campaign,[75] which aims to achieve optimum antimicrobial stewardship by ensuring rapid prescription of the right antibiotic at the right dose at the right time followed by active review at 48 h, Thailand's Antibiotics Smart Use programme,[76] and Vietnam's VINARES programme[77] could be adopted in low-income and middle-income countries that have adequate surveillance and stewardship programmes.

Public awareness campaigns

- National campaigns aimed at the public and prescribers have had mixed results.[78]
- Campaigns in England, Spain, Germany, and Greece have not been associated with important reductions in antibiotic use in the community or in increased knowledge about the appropriate use of antibiotics.
- By contrast, campaigns in France, Belgium, Norway, and Sweden achieved important reductions in antibiotic use. Multifaceted campaigns repeated over several years seemed to distinguish successful campaigns from unsuccessful ones.
- Long-term sustainability of clinician and community-wide interventions, and the effect of such interventions on resistance are hard to measure and often not assessed.
- An online pledge campaign has been initiated in Australia.[79]
- Clinicians who sign and display a poster-sized commitment letter in the USA prescribed fewer antibiotics.[80]
- Regional campaigns such as the European Union's annual Antibiotic Awareness Day allow focused issues to be highlighted, such as school-based interventions.[81]

Access to appropriate antimicrobials of assured quality

Weak health systems and lack of regulatory authorities, which often characterise LMICs, compound problems of access. Poor drug quality increases selection pressure, and substandard and falsified drugs remain a serious problem in resource-limited settings (appendix).[83,84] Although some such drugs contain no active ingredients and hence do not drive resistance, those with suboptimal concentrations of antimicrobials will do so.

As multidrug-resistant organisms become more prevalent, access to specific antimicrobials for these infections becomes an international issue. For some of these organisms, there is renewed reliance on old drugs that have been deregistered, such as colistin for carbapenemase-producing Gram-negative bacteria. Colistin became available in the 1960s but was replaced a decade later by less toxic antibiotics.[85] Studies of the optimum pharmacokinetic, pharmacodynamic, and therapeutic strategic approach for such drugs are crucial if we were to restrict the development of resistance.[86,87] Mechanisms to accelerate drug registration in LMICs are needed; access to parenteral artesunate, which is proven more effective than quinine for severe malaria,[88,89] is restricted in many endemic countries, predominantly because producers are not meeting good manufacturing practice standards, although parenteral artesunate has WHO prequalification as an essential drug.[90] Several countries have developed access programmes supplying

artesunate and incorporating expensive quality assurance checks.[91] Quality-assured, affordable artesunate produced under good manufacturing practice is urgently needed to help with registration of the drug in LMICs and thereby improve access.

In LMICs, drug quality is further impeded by insufficient laboratory capacity to assess bioavailability. Worldwide, the problem is being addressed by innovative tailored programmes—eg, Green Light Committee for multidrug-resistant tuberculosis treatment provides quality-assured drugs at concessionary prices.[92] In 2014, Unitaid, a global institution for financing of diagnostics and treatment, approved grants of US$160 million to ensure access to quality-assured drugs for hepatitis C, multidrug-resistant tuberculosis (bedaquiline and delamanid), and malaria in LMICs.[93]

New and often expensive antimicrobials are generally needed to optimise treatment of multidrug-resistant organisms—eg, linezolid for multidrug-resistant tuberculosis or meticillin-resistant *Staphylococcus aureus*, and echinocandins for drug-resistant *Candida* spp. Achieving price reductions for such drugs in LMICs would improve access and is discussed by Årdal and colleagues[94] in this *Lancet* Series.

Access to new innovations

Much of the world's innovation capability is located in HICs and predominantly within the private sector, with drug development driven mostly by profitable market opportunities.[95] The pharmaceutical industry is incentivised to bring new products to the market through a global system of intellectual property rights regulated in the agreement on Trade-Related Aspects of Intellectual Property Rights and its national equivalents.[96] The intellectual property rights system encourages industry to take risks to finance the development of new medical breakthroughs by promising a 20-year period of market exclusivity that is secured through a patent monopoly. The absence of competition means that companies can charge high prices, allowing them to recoup investment outlays and subsequently reinvest into future medical innovations. This can be seen as a system of so-called linkage, since the incentive for drug development is linked to the potential profitability and sales of new products. Public health needs have often had a secondary role in driving innovation in both LMICs and HICs. In the case of antibiotics, the risk-adjusted net present value (an adjusted return of investment index) scores unfavourably to other areas of public health—eg, 100 versus 1150 for a musculoskeletal drug.[97] Antibiotics clearly remain an unfavourable area of investment.[98,99]

The principle of delinkage can be an important alternative to enable innovation for public health needs. Delinkage involves separation of the financing and rewarding of research and development (R&D) from the price of the product and the volume of sales.[100] Therefore, substantial upfront funding is needed to reward successful needs-driven innovation. For example, public funding could be secured to buy out patents or through appropriate licensing agreements, thus allowing an alternative model of production and controlled appropriate use.[101] Alternative incentives will need to be put in place to orientate R&D efforts towards priority health needs rather than marketing and sales opportunities. Delinkage will have three important functions: it drives innovation in otherwise commercially unattractive areas; removes the perverse incentive to promote new drugs that do not meet clinical priorities or in clinically inappropriate situations, something especially important in the area of antibiotics, in which incentives related to prescribing or sales should not exist; and reconciles innovation with access, since R&D outlays do not have to be recouped through product sales.[102]

An important precept of delinkage is that rewards have to be sufficient to stimulate and reward R&D investment in a given area. Incentives can take the form of many different types of push and pull mechanisms in combination—eg, conditional grants, milestone and end-stage prizes, patent buyouts, advanced marketing commitments, and priority review vouchers.[103,104] R&D that goes into the production of the instruments needed to address antibiotic resistance needs to take into account the resources and conditions of LMICs, and examples of such efforts are vaccines that do not require cold chain and those that can be administered without injection. Novel antibiotics that target multidrug-resistant bacteria, including strains prevalent in LMICs, are urgently needed, and point-of-care RDTs requiring minimum instrumentation are important in settings with little laboratory infrastructure. Such technologies need to be scalable and accessible in all areas of need.

Importantly, delinkage as a concept would be useful for the development and conservation of as-yet-undeveloped antibiotics—eg, restriction of licensing terms on new therapies to generic companies. Alternative solutions will need to be implemented to control sales of existing generic antibiotics.

Health systems strengthening

Limited access to and overuse of antimicrobials often coexist within one health system and cannot be tackled by targeting any one of these challenges in isolation.[105] For interventions and policies aiming for universal access and appropriate use to be successful, measures to strengthen health systems are needed. These measures should be designed from a systems perspective[106] and take into account possible barriers and facilitators on individual, household and community, health facility, health sector, national, and global levels, and also the dynamics between these barriers and facilitators. Successful design and implementation depend on good multilevel governance (within the health system and beyond) and careful change management at all systems levels.

Global governance is needed in the redesign of financial arrangements for provision of and access to effective antimicrobials. Global public–private partnerships have already contributed towards financing and ensuring access to essential technologies, such as vaccines, that help to contain antimicrobial resistance.[107] Effective national and health system governance has a major role in ensuring, through policies and regulations, appropriate financing and commitment for strategies aimed at access and appropriate use. National taskforces dealing with access to antimicrobials and containment of resistance at the highest decision-making levels could oversee scale-up of evidence-informed interventions, collection of surveillance data, and assessment and review of interventions. In LMICs, in which government commitments are often low, funding is scarce, and health systems are weak, championship at the central level is essential to improve cash flow towards health information systems, laboratory infrastructure, and human resources training.[108] Similarly, information flow (surveillance and gathering of clinical, microbiological, and antimicrobial use data) from low levels of the health system towards high levels is needed for national medicine regulatory agencies to align resources, regulations, and incentives, creating feedback loops that promote access to, but curb overuse of, antimicrobials.

Good governance at the health facility level means that individual institutions commit to and invest in training of health workers and maintenance of appropriate information on antimicrobial use and resistance. Multidisciplinary teams that ensure good governance are instrumental in the creation and implementation of flexible and enforceable regulatory frameworks to balance access and excess of antimicrobials.[109] Substantial challenges are to develop electronic reporting systems and increase access to trained members of such multidisciplinary teams to ensure good governance in LMICs. The contextual imperatives of antimicrobials and their use demand that health systems research, behavioural science, and social marketing are used to address barriers to uptake of new technologies and models of care, and scale-up and implementation of recommended interventions.[109] Taking a less passive view on patients' roles and exploring the potential of interventions at the household and community levels can guide the design of innovative programmes for education, especially in community-care settings.[110,111]

Mechanisms to implement access and minimise excess

To implement core principles and measures driving access worldwide, sustainable financing, governance, and leadership are necessary. As a global challenge, long-term commitment, with sustained financing from all affected countries, is needed to improve universal access to and appropriate use of antimicrobials. Therefore, it will be important to move away from the present donor-driven model for LMICs, especially since coordination of resources might be necessary at international, regional, and local levels. Mobilisation of financial resources for antimicrobials should be linked to the overall global financing frameworks proposed for achieving universal health coverage.[100] Innovative financing models will need to be sought, and one such example is crowd-financing, as seen in Unitaid's use of small levies on airline tickets to fund global health initiatives.[93] Another proposal for sustainable financing is fixed country contributions to a global funding mechanism to allow delinkage of R&D for drugs and diagnostics, as recommended by the WHO Consultative Expert Working Group.[103] Finally, core funding by member states to UN agencies will be essential to ensure implementation of UN-driven strategies, specifically the global action plan on antimicrobial resistance developed by WHO.[112]

The global health architecture to ensure access to drugs—consisting of a range of initiatives such as The Global Fund, Unitaid, the Medicines Patent Pool, Clinton Health Access Initiative, and product development partnerships—is predominantly restricted to HIV/AIDS, tuberculosis, and malaria. In its present form, it is unlikely to meet the combined and complex needs to drive access to antimicrobials. Adaptation of the mandates of the existing initiatives might prove insufficient; therefore, a new separate mechanism might be necessary to promote the approaches needed to address antimicrobial resistance, particularly innovation of, access to, and responsible use of antibiotics. Such a mechanism could, at the global level, be mandated to mobilise pooled funding for R&D and antimicrobial conservation; enable procurement and managed distribution; work nationally and regionally with drug regulatory authorities to minimise availability of substandard, falsified, or counterfeit drugs; and together with countries ensure surveillance of access, use, and resistance. Transparency and governance that ensure country ownership, and an appropriate relation with WHO at the global level, will be decisive to ensure support from countries and effective functioning of any new agency. At the country level, working with national health systems and regulatory agencies will be crucial to ensure monitoring of access and surveillance of resistance to minimise excess.

To promote responsible access, political leadership at the local, regional, and international levels will need to deal with a range of issues, such as financing, R&D, equitable management of intellectual property, regulation, procurement, product quality assurance, and enhancement of laboratory functioning and surveillance systems. Many of these issues will be discussed in subsequent papers in this Series.[9,94] However, considerable work will be needed to elucidate how solutions can be implemented in a holistic way where required.

Conclusions and recommendations

The challenge for LMICs, and indeed many HICs, in accessing quality-assured antimicrobials, infection prevention measures, and the instruments needed to enable appropriate prescribing demands a context-adjusted approach that can be applied across a range of health-care settings. We recommend national-level research and assessments to understand the particular needs of LMICs, with respect to access to effective antimicrobials, and to have a heightened focus on access of populations to vaccines as a central antimicrobial resistance control strategy. In this Series, Dar and colleagues[9] propose a repository of such assessments of policies be established, and here we stress the importance also of doing so in resource-poor settings.

Efforts to improve global access for antimicrobials need to build in and enhance existing provisions for appropriate use, such as strengthening of health systems by provision of technical and financial support, and increasing access to diagnostics and primary prevention measures. Moreover, laboratory capacities and surveillance activities will need to be reinforced to allow countries to closely monitor their access to specific antimicrobials and adjust to alternative drugs when resistance emerges. We recommend that the use of surveillance data should become standard practice for countries to monitor appropriate use and implement any necessary corrective actions. Although present initiatives in infectious diseases focus predominantly on access to drugs for HIV, tuberculosis, and malaria, such is the global threat from bacterial resistance that we recommend a new separate mechanism to be specifically developed to address antibacterial access and combat resistance, as discussed by Årdal and colleagues[94] in this *Lancet* Series.

Delinkage of innovation from profit projections and sales will ensure that public health needs drive innovation and marketing practices. As a global challenge, universal access necessitates a long-term commitment, with sustained financing from all affected countries, to move away from existing donor-driven models in resource-poor states. The global health provision architecture should be strengthened to meet the combined and complex needs of driving access, while minimising emergence of resistance. If the global action plan adopted by the World Health Assembly is to succeed, it will need to incorporate the key enablers—ie, financing, R&D, equitable management of knowledge and intellectual property, so-called managed marketing (eg, organised and planned licensing, production, procurement, supply, and sales of a specific antibiotic, possibly between a manufacturer and a group of countries, or mandated by global health actors), and procurement and distribution of quality-assured antimicrobials.

Contributors

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Declaration of interests

We declare no competing interests.

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