Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance

Nils Daulaire, Abhay Bang, Göran Tomson, Joan N. Kalyango, and Otto Cars

Introduction

The right to health is enshrined in the constitution of the World Health Organization[1] and numerous other international agreements. Yet today, an estimated 5.7 million people die each year (Table 1) from treatable infectious diseases, most of which are susceptible to existing antimicrobials if they were accessible. These deaths occur predominantly among populations living in poverty in low- and middle-income countries, and they greatly exceed the estimated 700,000 annual deaths worldwide currently attributed to antimicrobial resistance (AMR).[2] Ensuring universal appropriate access to antimicrobials is not only a critical part of realizing the right to health, it is necessary for mobilizing effective collective action against the development and spread of AMR.

A Strategy for Universal Access

The 1980s saw a dramatic global expansion of child health efforts, but they did not initially address pneumonia, which kills nearly a million children under five annually[3] and is the leading global cause of child deaths. Since bacterial pneumonia requires timely case management and treatment with antibiotics, this seemed like too much to ask of rudimentary primary health care systems and relatively unskilled health workers. However, a series of community-based intervention trials in the 1980s demonstrated that community health workers could reliably carry out presumptive diagnosis of pneumonia and treat cases with oral antibiotics, resulting in substantial mortality reduction among the population of children served.[4] Oral co-trimoxazole (trimethoprim/sulfamethoxazole) was used as the first line treatment of choice. More recent studies have utilized oral amoxicillin.[5]

These studies proved that it was feasible to provide wide-scale antibiotic access for effective treatment of childhood pneumonia, and their findings were adopted by WHO and UNICEF and incorporated into health facility-based Integrated Management of Childhood Illnesses and integrated Community Case Management programs.[6] However, proof of effectiveness and even policy adoption does not necessarily translate into general application. Although every region has shown progress in appropriate care-seeking for suspected childhood pneumonia, still only 30% of children with suspected pneumonia in sub-Saharan Africa receive antibiotics.[7] Much work remains to be done.[8]

Similarly, neonatal sepsis kills more than a third of a million newborn babies each year,[3] predominantly in low-income communities. Case fatality in the pre-antibiotic era was reported to be 90 percent.[9] Work carried out in India demonstrated that early community-level antibiotic treatment of newborns with presumed neonatal sepsis significantly reduced neonatal mortality.[10] Injectable gentamicin and oral co-trimoxazole were administered in the household by female

Nils Daulaire, M.D., M.P.H., *is Senior Visiting Scholar on Global Health Security at the Norwegian Institute of Public Health in Oslo, Norway.* **Abhay Bang, M.D., M.P.H.,** *is Director of SEARCH in Gadchiroli, India.* **Göran Tomson, M.D., Ph.D.,** *is Senior Professor of International Health Systems Research at the Departments of Learning, Informatics, Management and Ethics and Public Health Sciences at Karolinska Institutet in Stockholm, Sweden.* **Joan N. Kalyango, B.Pharm., M.S.C., Ph.D.,** *is Associate Professor of Pharmacy at Makerere University College of Health Sciences in Kampala, Uganda.* **Otto Cars, M.D., Ph.D.,** *is Senior Professor of Infectious Diseases at the Department of Medical Sciences at Uppsala University, Sweden and Founder of Re-Act: Action in Antibiotic Resistance.*

Table 1

Global Deaths (Thousands) Due to Selected Infections Amenable to Antimicrobial Treatment (2013)[3]

Lower respiratory infections/pneumonia*	2,466
Tuberculosis	1,290
Malaria	855
Neonatal sepsis and infections	366
Meningitis	304
Intestinal infections*	221
Sexually transmitted infections*	142
Maternal sepsis and infections	24
TOTAL	5,668

*All ages, excludes viral aetiologies

health workers. This field trial again provided clear evidence that assuring effective access to appropriate, low-cost antibiotics was feasible and could have a major impact on infant deaths in the world's poorest societies.

Similar findings have come from community-based programs aimed at malaria and tuberculosis.[11] Assessments carried out in a variety of settings have found that appropriately trained and supervised community workers are more likely to follow diagnosis and treatment protocols than either doctors or pharmacists,[12] minimizing the likelihood of development of resistance.

While it is clear that a large proportion of deaths caused by infections could be averted by full access to timely and appropriate antimicrobial treatment, this needs to be done under well-managed conditions, since inappropriate antimicrobial treatment is at best ineffective and at worst a contributor to the accelerated spread of resistance. A clear warning comes from the evidence of rapidly emerging artemisinin-resistant malaria in areas of Southeast Asia in which inappropriate and inadequate dosing, often driven by widespread and poorly managed commercial distribution of monotherapy, dubious quality drugs and weak application of global norms, appears to be the leading culprit.[13] This has obvious implications for the application of novel therapeutics discussed in other papers of this series.[14]

Even when well-managed, however, AMR will inevitably increase over time due to selective pressure. Warnings came early that the most common bacterial cause of childhood pneumonia, *Streptococcus pneumoniae*, was becoming increasingly resistant to co-trimoxazole.[15] However, the process towards a policy change was lengthy, and it was not until 2005 that the WHO changed its treatment recommendations and included amoxicillin as an alternative to co-trimoxazole[16] (the latest recommendations only include amoxicillin).[17] Similarly, in the treatment of neonatal sepsis, antibiotic resistance to the first line treatments (gentamicin and procaine benzylpenicillin) has long been evident in hospital settings among leading bacterial causes, such as *Staphylococcus aureus, Klebsiella and Escherichia coli*.[18] Although use of these antibiotics may still be retained in many settings, the changing resistance patterns need to be taken into consideration.

The prospect of diminishing effectiveness of first-line antimicrobials has serious implications for the affordability and accessibility of appropriate treatment. The potential need to shift to drugs that are costlier and more difficult to administer will have the greatest adverse impact on those living in low-income and underserved communities, reinforcing the need for mutual reinforcement of efforts aimed at improved access and those aimed at stewardship. Meaningful access is dependent on good stewardship and vice versa.[19]

Policy Implications

Implications for global efforts to reduce health inequity and assure the highest attainable standard of care for *all* the world's people are clear. New drug regimens and tailored programmatic approaches are on the table as we look to assure *appropriate* access to *effective* antimicrobials for all who need them to address the major infectious killers. However, the implications for the dissemination, use, and stewardship of innovative *new* antimicrobials consistent with a commitment to universal access make it clear that the world cannot afford to squander the next generation of therapeutics — or else, in a generation or less, we could once again be left with nothing.

Treatment Protocols

In order to assure that antimicrobials — both those currently in existence with clear therapeutic value, and novel future drugs — are accessible for all and effective for the longest possible time, the introduction of new treatment regimens should be carried out in light of what has been learned in programs focused on widespread and appropriate access, and that these efforts be directly tied to the development and introduction of new therapeutics. As a first step in this process, the global scientific community will need to strengthen its assessment of appropriate treatment

and usage, defining parameters for deciding which antimicrobials are effective in which areas of the world and useful at various levels of health care systems. This is an evidence-based normative process, and is reflected in the development of previous effective antimicrobial programs. Furthermore, this is not a static effort, but needs to be continuously reviewed and updated based on dynamics of use and evidence of emerging resistance.

International Framework and Regulations

Based on this assessment at the global level, national authorities, supported as necessary with external technical assistance and resources that could be guided and supported by an overarching international framework, must take responsibility for defining appropriate and evidence-based treatment regimens suited to both the local microbial ecology and delivery systems within their countries. We also must recognize the pluralistic nature of health systems, especially in low- and middle-income countries where the majority of drugs are often provided by a little-regulated private sector. This must, therefore, be a comprehensive health-systems approach[20] that assures universal access, and defines the key conditions and levels of care at which each important antimicrobial will be used. Crucially, this must be reinforced by international support for universalization of access, as well as agreements and strengthened regulatory regimes that reduce the likelihood of system-wide misuse, particularly of newly introduced drugs.

Community

For the right to health to be an important consideration of this process, and for universal access to be a central principle, the large majority of serious but common infections will need to be addressed within the communities in which they occur. As was demonstrated with the studies cited, large- scale impact can only be achieved with programs that are focused on and driven by community needs and realities.

The result of this process will be a rigorous clarification of who (what type of health provider) can use which antimicrobials (first, second, third line, novel), where (community, first level facility, hospital, tertiary hospital), and for what conditions (common but serious infections, rarer and more difficult to treat). This calls for a basic system of referral and care, and would be enormously undermined by a situation in which antimicrobials were permitted to simply flood the market with limited regulatory oversight. After all, access to antibiotic treatment is highly sought after by the rich and poor globally, and where governments have been unable to provide this access, markets have emerged to meet this demand. In the absence of supportive institutional arrangements, undesirable practices inevitably predominate.

Providers

The first line of such a system must be the presence of and effective access to knowledgeable and ubiquitous providers. The level of educational background of such providers will be highly context-specific to the countries involved, but in many of the poorest and most under-served areas, they will likely be community members with limited primary or secondary education who have been put through a highly selective and targeted training program that teaches them to do a few things extremely well. Health workers must also be continually prompted to carry out effective and routine follow-up of their patients under treatment, both as a basic standard of care, and to assure assiduous adherence to treatment regimens as a key tool of stewardship.

Program Management

Training and deployment of community-level workers are not in themselves sufficient to assure effective, good quality care. The ongoing effectiveness of such efforts is highly dependent on a reliable system of management, supply, financing, and support of these health care providers. While such programs do not need to be national in scope, national authorities must see to it that there is full coverage of their most at-risk communities and that obstacles to the effective management of their programs are dealt with as a top policy priority.

Cost

A key element in getting access to care to the community will be the affordability of the antimicrobials, and principles of both stewardship and global solidarity suggest that pricing and financing of novel antimicrobials at the national and subnational level must be undertaken with an eye towards innovative mechanisms, as described elsewhere in this series.[14] We cannot allow high cost to drive the poor out of the market. However, we must also assure that neither low cost nor excessive cost push novel antimicrobials into an unmanaged marketplace with high risk of counterfeiting and uncontrolled drug quality.

End Users

Low price is not in itself sufficient to assure low-income people the benefits of antimicrobial treatment. The implementation of a sustained effort to achieve system-wide changes in the use both of existing, still-effective antibiotics and future, new antibiotics requires informed and committed collaboration

at national and global levels. It will here be especially important to ensure the perspective of the end user, particularly the most under-served, within a system of controlled distribution and use of a new antibiotic.

appropriate and managed use, and the emergence of resistance would be significantly slowed.

Universal access to and rational use of antibiotics in public health programs has been proven feasible.

The world has a collective responsibility to preserve antibiotic effectiveness and access for all, and to see to it that the *right to health* is translated into meaningful action. Ensuring universal and appropriate access to essential medicines is a necessary precondition to any policy on restricting the use of antimicrobials in low-income settings; absent this, any restriction is likely to be ethically and politically challenged, or simply ignored.

Data

Surveillance data are essential for providing information on trends and magnitude of resistance, but there is as yet no global system to address this need. Absence of essential epidemiological data leads to delayed or suboptimal revisions of treatment guidelines, and strengthens the vicious circle of injudicious use of antibiotics by prescribers. This missing link has become critical, and if not addressed could well lead to recommendations to increase access to treatments that turn out to be ineffective. Additionally, good monitoring and data systems will allow early recognition of patterns of treatment failure that would allow far more rapid recognition of and response to emergence of resistance, allowing programs to make necessary adjustments before such resistance has had a chance to become widespread.

Conclusion

The world has a collective responsibility to preserve antibiotic effectiveness and access for all, and to see to it that the *right to health* is translated into meaningful action. Ensuring universal and appropriate access to essential medicines is a necessary precondition to any policy on restricting the use of antimicrobials in low-income settings; absent this, any restriction is likely to be ethically and politically challenged, or simply ignored.

The ideas put forward in this paper are not a promise of an end to the development of AMR, nor will they by themselves assure that all the world's people have effective access to antimicrobials at all times when they are critically needed. But by working towards universal access to appropriate treatment, coupled with meaningful efforts at regulation and stewardship, the balance of the world's depletable resource of antimicrobials would shift significantly towards

Unless the world's poorest populations, and the low- and middle-income countries in which they live, can be assured of universal access to effective antimicrobials, the current dynamic of misuse and accelerating resistance will not be reversed. This a clear example of a *global governance for health* issue,[21] where rich countries should set aside earmarked funds to assist in assuring universal effective access for the poor as part of a global grand bargain that in turn helps to protect the continued effectiveness of these drugs for all. Every country on earth stands to benefit from this effort.

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