Antimicrobials: access and sustainable effectiveness 5

International cooperation to improve access to and sustain effectiveness of antimicrobials

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Securing access to effective antimicrobials is one of the greatest challenges today. Until now, efforts to address this issue have been isolated and uncoordinated, with little focus on sustainable and international solutions. Global collective action is necessary to improve access to life-saving antimicrobials, conserving them, and ensuring continued innovation. Access, conservation, and innovation are beneficial when achieved independently, but much more effective and sustainable if implemented in concert within and across countries. WHO alone will not be able to drive these actions. It will require a multisector response (including the health, agriculture, and veterinary sectors), global coordination, and financing mechanisms with sufficient mandates, authority, resources, and power. Fortunately, securing access to effective antimicrobials has finally gained a place on the global political agenda, and we call on policy makers to develop, endorse, and finance new global institutional arrangements that can ensure robust implementation and bold collective action.

Introduction

This Lancet Series has argued that both inadequate access to antimicrobials and antimicrobial resistance are daunting threats to both human and animal health—ie, a One Health approach is necessary to address these issues.1 The most cost-effective and time-efficient method is to protect the usefulness and longevity of existing antimicrobials, while continuing research into new vaccines, drugs, and related technologies, for much is still to be learnt about the mechanisms of infection and resistance.2 The starting point for any concerted policy action should be to expand access to life-saving antimicrobials worldwide, recognising that some parts of the world still face issues of poor sanitation and inadequate access to antimicrobials.3 However, expansion of access needs to be linked to improved approaches for combating resistance. Evidence shows that many interventions can be effective at national levels,4 but their implementation also requires global vigilance and action.

Coordination across sectors is necessary to preserve antimicrobial effectiveness. Gains in combating resistance through health-care interventions might be undercut by prolific use in agricultural settings. Strong conservation efforts, although medically appropriate, might hamper the business case for innovation that leads to new therapies. Boosting access without stewardship measures could drive resistance. Thus, although many actions can be taken independently at the national and sectoral levels, they will be more effective if coordinated globally across all relevant sectors and stakeholders.5

The complex policy challenges of improving access to and sustaining effectiveness of antimicrobials warrant interventions in several areas. This Lancet Series has used a framework spanning the breadth of policy goals needed.6 Improved surveillance and monitoring are crucial to obtain information on the present situation and progress.7 Universal access to antimicrobials needs to be a primary goal in all countries progressing towards universal health coverage.4 However, the need for antimicrobials can be lessened through improved infection control, and their use can become more appropriate by reducing misuse and overuse through

Key messages

• Global collaboration is necessary to improve access to antimicrobials and sustain their effectiveness. Although this is well known and accepted, present collaborative efforts remain far too modest and poorly funded.
• Interlinked global collaboration is needed in the policy areas of universal access, responsible use, and innovation. Increasing innovation and global access without responsible use provisions might increase the emergence of resistance. Strengthened efforts towards responsible use could lead to smaller and less lucrative markets, thus dampening innovation and possibly impeding access. To avoid improper incentives to waste antimicrobials, payments for antimicrobials should be delinked from the volumes sold.
• WHO cannot successfully tackle this problem on its own. Because of the multisectoral nature of the problem—requiring action across the health, agriculture, and veterinary sectors—and the need to build new business models for antimicrobial innovation and use, multisector coordination under a One Health model is necessary to bring about action and real change.
• Global actions to address this challenge need to be a combination of quick wins and long-term efforts. For example, a few large markets could agree to restrict certain classes of antimicrobials only to human use while a formal global mechanism is being negotiated and adopted. This combination of short-term and long-term strategies needs to be taken for each policy area—namely, surveillance, universal access, infection prevention, responsible use, and innovation.
• Global coordination and financing mechanisms need to be improved. Two leading institutional options are a new UN-level coordinating body and an international treaty with strong implementation mechanisms.
collaboration, and discuss how the resulting policies, international cooperation, recommend actions to improve
struggle to finance the implementation
progress towards these goals will rely on raised awareness
and financial assistance will be key to global success.
interventions that decrease both supply and demand.4
Progress towards these goals will rely on raised awareness
among the public and all relevant stakeholders (eg, policy
makers and health-care personnel).8 Advances also need
to build on an expanded knowledge base, through
innovation and research and development (R&D), to
achieve an increased understanding of mechanisms and
drivers of resistance,2 develop new technologies,1 and
design, implement, and assess interventions.1 The control
and reduction of resistance are public goods—ie,
achievements in which all stand to benefit. However, with
increasing antimicrobial resistance in low-income and
middle-income countries (LMICs),1 these nations will
struggle to finance the implementation of these policies,
and financial assistance will be key to global success.
In this last paper of the Series, we analyse how countries
and other stakeholders need to work together to achieve
these key policy goals. We identify existing gaps in
international cooperation, recommend actions to improve
collaboration, and discuss how the resulting policies
could be packaged for adoption and implementation.

Panel: Gaps in international collaboration

• Surveillance—no global database exists for antimicrobial
resistance or use, meaning that identification of
surveillance gaps is difficult or impossible. No publicly
available registry of laboratory capacity by country exists.
Surveillance data are rarely recorded in real time or
globally compatible in format.

• Infection control—a common repository for evidence of
infection prevention measures is absent. Substantial
financing and technical assistance is needed to help
low-income and middle-income countries (LMICs) to
implement evidence-based national infection
prevention programmes.

• Universal access—no internationally agreed mechanisms
exist to ensure affordability in LMICs. Financing to
support improved access to antibiotics is restricted.

• Responsible use in human beings—the framework to
restrict marketing of antimicrobials has not been agreed.
Capabilities to enforce existing regulations are insufficient,
and no internationally agreed quality measures for
optimum prescribing exist.

• Responsible use in animals—no global mechanisms exist
to reduce inappropriate use in animal husbandry or
restrict specific classes to human use only. Europe is the
only region that have banned the use of antibiotics in
livestock and agriculture as growth promoters or for
disease prevention.

• Innovation—existing incentives are not well aligned
to responsible use policies. The bulk of these initiatives were
not developed with the needs of LMICs in mind. The scale
of these initiatives is insufficient to ensure the
development of new antimicrobials, diagnostics, vaccines,
and related technologies that target unmet medical needs.

Strengthening international collaboration

We reviewed all World Health Assembly resolutions and
documentation related to antimicrobial resistance, in
addition to related scientific literature published in
2012–15, to identify core high-level policy areas—namely,
surveillance, universal access, responsible use, infection
control, and innovation. Improved implementation
across these policy areas is needed to ensure sustainable
access to effective antimicrobials. Together with the
other papers in this Series,1,4 we identified important
gaps in international collaboration in each of the five
policy areas (panel). However, the level of collaboration
necessary to ensure success will differ from policy to
policy. On the basis of the 5C Framework (figure),
previously used to analyse human resources for health,6
we assessed the minimum level of collaboration needed
for a policy to achieve its goal and the relevant
international policies (table 1).

Some global policy objectives can be met by
collaborative mechanisms that help to set common
norms, principles, and goals. This is the lowest level of
collaboration in the 5C Framework, one that is often
effectively fulfilled by UN entities and exemplified by
WHO’s resolutions on antimicrobial resistance.1
However, higher levels of collaboration are necessary for
other objectives. For example, another function of WHO is
to facilitate communication, which includes sharing
of information and data between countries—eg,
dissemination of guidance and educational material on
appropriate disease management and treatment
regimens.3 Coordination is essential for effective global
surveillance systems and for the uptake of adequate
infection control procedures.1,4 Other objectives—eg,
promotion of universal access, responsible use, and
innovation—will need even higher levels of collaboration,
including collaborative decisions and, at the highest
level, collective action (figure). Such international
 collaboration is necessary to ensure the success of many
policies that improve access to and sustain effectiveness
of antimicrobials (table 1).

Surveillance

Two related issues of surveillance are collection and
reporting of data, and strengthening of laboratory
capacity. WHO first passed a resolution in 1998 urging
Member States to develop surveillance systems for
antimicrobial agents.7 Despite the WHO global strategy
for containment of antimicrobial resistance (2001) and
recurrent calls to improve these global surveillance
efforts, little progress has been made in the past
15 years.8 Worryingly, the first antimicrobial resistance
global report on surveillance (2014) of existing national
systems9 showed that only 22 countries were able to report
on all nine bacterial species of international
concern. However, 114 of the 129 countries who
reported their status obtained data for at least
one species.
To comply with the International Health Regulations (IHR; 2005), each government is required to have access to laboratory services and obliged to report to WHO. At the WHO Executive Board Meeting in January, 2014, only 23 Member States were reported to be fully compliant with the IHR’s laboratory requirements. This self-reporting shows that many Member States, across all income categories, are struggling with the laboratory capacities stipulated by the IHR. Since these capacities are more comprehensive than those necessary for antimicrobial resistance surveillance, the actual magnitude of inadequate laboratory capacity directly related to antimicrobial resistance is unknown at present. In 2011, three UN agencies—WHO, World Organisation for Animal Health (OIE), and the Food and Agriculture Organization (FAO)—jointly initiated several collaborative projects that aimed to strengthen laboratory capacity. These projects included capacity building for compliance with laboratory quality standards, the development of international networks, and laboratory twinning initiatives.

A global surveillance system is essential to improve access to and sustain the effectiveness of antimicrobials. The communication of surveillance data can help to identify patterns of resistance and focus on necessary support. This is not a call for a new global super system but rather a coordinated effort to obtain data from present functioning systems, implement appropriate systems in countries without existing ones, report these data, and highlight the gaps annually. These data include the use of antimicrobials (in human beings and livestock, and for other agricultural purposes), the prevalence of antimicrobial resistance, and laboratory capacity, all by country, in a standard way so that valid comparisons can be made. This coordination will require cross-sectoral focus bridging the FAO, OIE, and WHO. To accurately report prevalence data, national and regional laboratory capacity has to be strengthened. Capacity-building plans, including technical and financial support, should be created for countries that are unable to report these data. As this function matures and as countries improve their reporting, interoperability and minimum data standards can be implemented.

**Infection control**

Many infection control collaborations are at work across the globe through local, national, regional, and international networks, as detailed by Dar and colleagues in this *Lancet* Series. However, many of these collaborations are underfunded. LMICs are lagging behind high-income countries, predominantly because of inadequate financial resources necessary for good infection control.

National infection prevention programmes are the mandate of governments, but external supportive financing of these efforts in LMICs should continue. These efforts should be linked to surveillance data so that those countries reporting increasing resistance levels or inappropriate use can receive technical and financial assistance to reverse these trends. On a global basis, it might be more efficient to speed the adoption of basic

**Figure: The 5C Framework—assessment of minimum collaboration needed for a successful policy**

This framework can be used to assess the minimum level of collaboration needed for a policy to deliver its stated goal. It is hierarchical—ie, level V (collective action) requires greater collaboration than level IV (collaborative decisions) and so on.
infection prevention measures than to create new drugs that are short-lived. Evidence of effective infection control interventions is a global public good and should be made readily available, including summaries appropriate for policy makers.3

### Universal access

Securing access to quality-assured antimicrobials is a core national responsibility, and policies that countries can use to improve access are discussed by Mendelson and colleagues in this *Lancet* Series.4 The coordinated
efforts of organisations such as The Global Fund to Fight AIDS, Tuberculosis and Malaria, Unitaid, and the US President’s Emergency Plan for AIDS Relief (PEPFAR) have greatly contributed to improved access to specific antimicrobials. However, antibiotics, diagnostics, and related prevention measures mostly fall outside the mandate of these organisations. Most first-line antibiotics are inexpensive, costing only pennies per treatment regimen. However, with the emergence of resistance, the cost ramps up substantially as second-line and third-line drugs are needed.\textsuperscript{19} Donors and governments need to prioritise universal access to affordable and effective antimicrobials as a key part of a comprehensive global solution, thereby contributing to progress towards universal health coverage.

Many untested alternatives to tackle the issue of antimicrobial access will need to be carefully balanced against economic incentives for innovation. One option is for manufacturers to sell their products globally at cost price while receiving rewards (eg, so-called benchmark payments) from high-income countries. These payments would not be tied to unit sales but to compliance with stipulations such as no promotional marketing of the product, sales levels in compliance with responsible use estimates in both human and animal populations, and equitable access. Another option could be that manufacturers offer nominal-royalty-bearing licences to other manufacturers in LMICs, with similar conditions on the licensees. A third option is to establish internationally agreed principles related to securing affordability in low-income countries, where price levels should be based on what can be achieved by competitive manufacturing. All of these options will need decisions that are made in collaboration across countries, with substantial financial support to promote universal access.

**Responsible use in agriculture**

Antibiotics are important in treatment of disease in both human beings and animals, but they are also being used in healthy animals as growth promoters and a substitute for good animal husbandry.\textsuperscript{1,4} In view of the devastating potential of antimicrobial resistance, all unnecessary use needs to be curbed. FAO, OIE, and WHO have the responsibility to raise awareness in their respective fields regarding maintenance of effective antimicrobials, with WHO having the primary mandate to articulate the public health need for urgent and sustained action. A need exists for a global agreement on responsible animal use by elimination of antibiotics used as growth promoters or as a routine prevention tool through herd treatment. Global collaboration and enforcement are necessary to ensure a level playing field, since reductions in access to antimicrobials might have implications on the running costs of a farm—eg, more oversight of livestock might be needed.\textsuperscript{1} Europe banned the use of antibiotics for growth promotion in 2006.\textsuperscript{17} The USA introduced non-compulsory measures in 2013, which have now resulted in binding withdrawals and label changes.\textsuperscript{8} The Chennai declaration aims to achieve an 80% compliance with the rule that antibiotics used for human treatment will not be used for growth promotion in food animals.\textsuperscript{8} In exchange for these prohibitions, R&D related to animal-specific solutions, such as vaccines and alternatives to antibiotics as growth
promoters, should be encouraged. While these agreements are being negotiated and implemented, a medium-term solution could be labelling suggestions to producers that are already adhering to the best practices. These foods could command higher prices, similar to those of organic or local foods. Several major US restaurant chains are already transitioning to use chicken and other meats produced without antibiotics used in human beings.

International trade law can be an obstacle to reduce or eliminate the use of antibiotics as growth promoters or for routine preventive herd treatment, since a formal national requirement to regulate or ban such use of antibiotics might be interpreted as a trade barrier through the World Trade Organization (WTO) rather than a public health measure. Therefore, WTO and regional trade agreements need to be engaged to ensure that necessary public health regulations related to antimicrobial resistance are respected.

Another option is to restrict medically important antimicrobials to human use only, leaving other classes, such as ionophores, exclusive to agricultural use. For example, to begin the process towards reaching a global consensus, the G20 countries could develop an agreement in which certain classes of new antimicrobials and other related health technologies are restricted for use in either human beings or animals, and incorporate this agreement into future trade agreements. This agreement could be coordinated through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a collaboration between the pharmaceutical industry and the regulatory authorities of Europe, Japan, and the USA. A potential result is that pharmaceutical manufacturers and animal feed providers would be less interested to produce an animal variety for the non-participating countries not only for reputational reasons but also for the limited profitability of the remaining markets. Additionally, innovation incentives for companies could be conditioned on compliance with these rules in every country. Once compliance exists in ICH, it could be transitioned to the more comprehensive International Conference of Drug Regulatory Agencies organised by WHO.

**Innovation**

Sustainable access to effective antimicrobials requires constant innovation, if only to prevent us from slipping back into a pre-antibiotic era. The largest multinational financing initiative so far for antimicrobial R&D is the Innovative Medicines Initiative (IMI), a public–private partnership between the European Union and the European pharmaceutical industry that aims to develop better and safer drugs. Its New Drugs for Bad Bugs (ND4BB) programme has invested more than €600 million in European antimicrobial R&D over 7 years, much of which has been targeted at Gram-negative bacteria. The European Union’s Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) aims to find routes for novel antibiotics and new anti-infectious disease strategies. Their first call, ‘InnovaResistance’, with a total budget of around €14 million, was launched in January, 2014, and included funding opportunities for optimisation of existing antimicrobials and identification of new bacterial targets and antibiotic compounds.

Several national initiatives are of a magnitude to have a global effect, even though their geographical scope is restricted. An announcement in June, 2014, stated that the £10 million Longitude Prize would focus on point-of-care diagnostics, with the creation of a ‘cost-effective, accurate, rapid and easy-to-use test for bacterial infections’. A similar diagnostic prize proposal was announced by the US Government in September, 2014. Some countries have also created partnerships with individual pharmaceutical companies; one such example is the 3–5-year collaboration between AstraZeneca and Singapore’s Agency for Science, Technology and Research to develop new drugs against Gram-negative bacterial infections. The Biomedical Advanced Research and Development Authority (BARDA) in the USA has partnered with GlaxoSmithKline (GSK) to develop new antibiotics with a potential of US$200 million for GSK if milestones are met. Total funding from the US National Institutes of Health for antibacterial resistance averaged US$90 million per year in 2013 and 2014.

Although an increasing investment is seen in relevant R&D, present initiatives are still insufficient to ensure the continued development of new antimicrobials, diagnostics, or related technologies. Most distressingly, these initiatives are not tied to responsible use policies. In particular, the existing R&D system closely links incentives for R&D to the potential price and volume of sales of the eventual product. This system leads to underinvestment in antibiotic research, high eventual prices for new products, and lacklustre company support of antibiotic stewardship. There is little assurance that the new drugs will not be wasted through inappropriate use. This market failure could be addressed by efforts to delink company profits from the sales volume for antimicrobials. Since it is a problem that affects all countries, including those with the financial means to fix it, it should be solvable. Complete global action is not necessarily required because the actions of a few high-income countries can have a disproportionately large global effect, and additional countries will join the effort in due course.

Therefore, a pledge from a group such as the G20 to increase their investment in R&D tied to responsible use and global access stipulations could have a substantial effect on the antimicrobial R&D landscape. The new products should be tied to responsible use provisions to minimise the development of resistance.
which would probably include agreement by manufacturers to not promote the products in exchange for payments that are not based on unit sales. Moreover, the innovators would need to ensure that their new products are globally available, as discussed in the section on universal access. These stipulations would be negotiated and enforced contractually between innovators and high-income countries.

Table 2: Overall recommendations for policy interventions

<table>
<thead>
<tr>
<th>Subobjective</th>
<th>National level</th>
<th>Global level</th>
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<tbody>
<tr>
<td><strong>Access</strong></td>
<td>Increase availability, affordability, and diagnostic targeting of effective antimicrobials</td>
<td>To achieve appropriate antimicrobial prescribing, LMICs should expand access to appropriate antimicrobials, especially in rural areas, including provision of laboratory support and increased access to diagnostics</td>
</tr>
<tr>
<td><strong>Responsible use</strong></td>
<td>Change professional behaviour</td>
<td>Stewardship programmes can be effective in encouraging appropriate use of antibiotics and should be scaled up in both HICs and LMICs where feasible</td>
</tr>
<tr>
<td><strong>Integration across the policy areas</strong></td>
<td>Strengthen infection control</td>
<td>Implementation of effective IPCIs needs to be supported, including vaccinations, hand hygiene, improved access to water and sanitation, food safety, and behaviour change</td>
</tr>
<tr>
<td><strong>Innovation</strong></td>
<td>New antibiotics, diagnostics, vaccines, and other relevant technologies</td>
<td>National policies should work in concert with global framework efforts, as antibiotic R&amp;D is a global endeavour</td>
</tr>
<tr>
<td><strong>Surveillance</strong></td>
<td>Increased innovation to meet the needs of LMICs</td>
<td>National-level research is needed to understand the particular needs of LMICs with regards to bacterial resistance, such as a rapid point-of-care diagnostic test that can improve clinical practice in low-resource settings</td>
</tr>
<tr>
<td><strong>Evidence base</strong></td>
<td>National research programmes need to address unanswered questions and research gaps, including how to minimise selection of resistance, secure quality of existing drugs, effectively reduce the prevalence and transmission of resistant pathogens, and better understand the basic mechanisms of resistance</td>
<td>Systematic reviews of existing policies are needed across human, animal, and environmental health and the key areas of resistance control, a standardised framework for policy examination should be applied and an open-access central repository of national, regional, and global policy case studies and assessment developed</td>
</tr>
</tbody>
</table>

LMICs=low-income and middle-income countries. HICs=high-income countries. WTO=World Trade Organization. SPS=sanitary and phytosanitary. IPCIs=Infection prevention and control interventions. R&D=research and development.
The global action plan to combat antimicrobial resistance

In this *Lancet* Series, we have identified a set of recommendations across the five policy areas both for individual countries and globally (table 2). Each one of these policy recommendations could be implemented individually but might work at cross purposes to each other as we have described. To create an effective and sustainable path forward, these recommendations should be implemented in concert.

At the 68th World Health Assembly in May, 2015, a global action plan to combat antimicrobial resistance was approved by Member States.34 This global action plan provides the framework for national plans to combat antimicrobial resistance, in which Member States need to define timelines, targets, and activities, and identify particular areas that need technical support from WHO and other partners. Successful implementation depends on Member States playing their crucial part to fulfil commitments, mobilise funding, implement appropriate surveillance programmes, build and support the necessary infrastructure (eg, laboratories), and introduce and enforce appropriate legislation.

The global action plan also gives WHO a clear mandate, leadership, and coordinating role, since WHO represents a natural platform for global health solutions that require improved communication and coordination among countries, including those of surveillance, infection control, and guidance on stewardship (table 1).13 Although many of the needed global actions have long been recognised, implementation by Member States, WHO, or other actors has been insufficient. A report from the WHO Secretariat concluded that past World Health Assembly resolutions, reports, and calls for mobilisation have not resulted in widely accepted global actions.35 Even though we suggest only six indicators, we believe that few countries can report on all six of them individually but might work at cross purposes to each other as we have described. To create an effective and sustainable path forward, these recommendations should be implemented in concert.

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National accountability and indicators

The great differentiator between the global action plan and past WHO resolutions has to be strong national accountability mechanisms to ensure that Member States create and implement their own plans to combat antimicrobial resistance. These mechanisms are likely to be a mixture of incentives and enforcement measures based on measurable indicators. For LMICs, external financing might be predicated upon development of a national plan to combat antimicrobial resistance and eventually report against a set of agreed indicators. Compliance to national plans can be reinforced by widely reporting results in plain language so that local media is engaged in national progress (see table 3 for examples of national indicators).

WHO’s South-East Asia Region is to be commended for developing its own indicators in 2010.13 Whereas this policy-oriented approach uses process indicators, we suggest data-driven targets, such as annual per-person antibiotic consumption, so that the indicators do not need to change when new national goals are proposed. Almost all of our suggested indicators (table 3) report against several policy areas. For example, annual per-person antibiotic consumption can report progress both in a country with insufficient access to antibiotics and in a country with overuse of antibiotics, showing that interlinkages exist between the policy areas.

Even though we suggest only six indicators, we believe that few countries can report on all six of them at present. Improved surveillance systems will need to be implemented; although such systems are costly and time-consuming, they are a precondition to establish accountability. For low-income countries, such systems

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Surveillance</td>
<td>IHR’s existing laboratory indicator (ie, Laboratory services) is available to test for priority health threats</td>
</tr>
<tr>
<td>Surveillance and access</td>
<td>Annual antibiotic consumption by drug and age</td>
</tr>
<tr>
<td>Surveillance and infection control</td>
<td>Annual incidence of antimicrobial resistance by pathogen and age (ie, a national threat assessment)</td>
</tr>
<tr>
<td>Surveillance and responsible use</td>
<td>Annual percentage of total antibiotic consumption in human use and agriculture, by drug, by animal species, drug, and purpose</td>
</tr>
<tr>
<td>Surveillance, responsible use, and access</td>
<td>Annual consumption of restricted-use antibiotics</td>
</tr>
<tr>
<td>Innovation and access</td>
<td>New molecular entities submitted to and approved by regulatory authorities, by therapeutic area per year, with a focus on drugs targeting priority pathogens identified through threat assessments</td>
</tr>
</tbody>
</table>

IHR=International Health Regulations. LMICs=low-income and middle-income countries.

Table 3: Potential national indicators in the WHO global action plan, by policy area
Among the five policy areas considered in this Series, we recognize that actors are insufficient to warrant unilateral action. In other cases, benefits for individual groups of actors are insufficient to warrant unilateral action. Among the five policy areas considered in this Series, we have shown that three—namely, access, responsible use, and innovation—will need collaborative global decisions or collective global action (table 1). We believe that the best way forward towards an international agreement on these three policy areas is not to tackle them independently but as one coherent package. These policy areas should be linked to deliver a sustainable and cost-effective solution—e.g., by substantially increased coordination of public sector R&D funding and incentives for innovation, both tied to stipulations of minimal marketing and to licensing intellectual property to manufacturers in LMICs who are also bound by responsible use provisions.

If the coherent package is constructed carefully, most of the diverse range of stakeholders will benefit from a long-term solution securing effective antimicrobials (table 4). High-income countries will need to pay most of the innovation bill but will, in return, protect their populations from infections that cross borders. More equitable access will be achieved for all countries in return for better infection control and stewardship. Low-income countries will get support for capacity building and be assured affordable and appropriate antimicrobials. R&D-based pharmaceutical companies will receive higher and more predictable rewards for antimicrobial innovations than they do at present, and generic-drug manufacturers will have opportunities to produce quality-assured drugs under licence. Restrictions in antibiotic use in agriculture will promote global fair competition, since all producers have to abide by the same public health measures, supported by research for alternatives to agricultural antibiotics.

### Achieving collective action

The responsibility to implement this coherent package needs to rest on sufficiently funded and empowered authorities. An institutional base and a forum for negotiation are necessary to ensure progress. WHO alone will be unable to facilitate the implementation of this package, and a multisectoral response—e.g., from a UN-appointed entity or one structured through a coalition of like-minded, proactive countries and actors—will be essential. Such a response can be rooted in international law or be an institutional solution originating from a top-level political declaration. An internationally binding agreement could be the end result after substantial momentum is achieved in national implementation.

An international legal mechanism can be negotiated at WHO or the UN General Assembly. One weakness of a treaty is the need to cover most or all nations through an incremental and scalable implementation, potentially starting first with public hospitals and clinics and expanding from there.

### Table 4: Benefits and costs accrued by a coherent package

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Costs</th>
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<tbody>
<tr>
<td>All countries</td>
<td>Increased investments to protect and sustain effectiveness of antimicrobials</td>
</tr>
<tr>
<td>Greatly improved global health; avoidance of the costs of a post-antimicrobial era (e.g., inability to perform routine surgeries and treat common infections); avoidance of the inevitable closure of borders and restraints on travel and trade that would follow from rampant epidemics</td>
<td></td>
</tr>
<tr>
<td>LMICs</td>
<td>Increased investments in health system capacities for surveillance, responsible use, and infection control</td>
</tr>
<tr>
<td>Enhanced access to affordable antimicrobials, including subsidised prices when necessary, financial and technical support for capacity strengthening in surveillance, responsible use, and infection control</td>
<td></td>
</tr>
<tr>
<td>Emerging economies</td>
<td>Increased investments in and enforcement of regulatory capacities, and investments in health system capacities for surveillance, responsible use, and infection control</td>
</tr>
<tr>
<td>Increased markets for producers of antimicrobials</td>
<td>Adherence to additional marketing regulations and cooperation on global public health goals</td>
</tr>
<tr>
<td>Sustainability of existing antimicrobials and the medical care system that depends on them</td>
<td></td>
</tr>
<tr>
<td>Innovative pharmaceutical companies</td>
<td>Increased investments in innovation through R&amp;D and aggregate reimbursement or delinked payments to producers; support to LMICs for capacity building</td>
</tr>
<tr>
<td>Increased rewards and incentives for innovation; decreased marketing expenses; reduced risk and structured rewards through delinked payments</td>
<td></td>
</tr>
<tr>
<td>Generic pharmaceutical companies</td>
<td>Adherence to additional marketing regulations, quality assurance, and other stipulations</td>
</tr>
<tr>
<td>Opportunity to manufacture antimicrobials on licence for LMICs</td>
<td></td>
</tr>
<tr>
<td>Agriculture</td>
<td>Increased investments in animal health and welfare, including alternatives to antibiotics</td>
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<td>A level playing field with global regulations regarding antibiotic use in agriculture, especially for meat production</td>
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<td>R&amp;D-research and development. LMICs=low-income and middle-income countries.</td>
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A coherent package of solutions

These interlinkages between policy areas complicate implementation, since each of the areas requires real effort for some actors, thereby blocking unanimous support. In other cases, benefits for individual groups of actors are insufficient to warrant unilateral action. Among the five policy areas considered in this Series, we have shown that three—namely, access, responsible use, and innovation—will need collaborative global decisions or collective global action (table 1). We believe that the best way forward towards an international agreement on these three policy areas is not to tackle them independently but as one coherent package. These policy areas should be linked to deliver a sustainable and cost-effective solution—e.g., by substantially increased coordination of public sector R&D funding and incentives for innovation, both tied to stipulations of minimal marketing and to licensing intellectual property to manufacturers in LMICs who are also bound by responsible use provisions.

If the coherent package is constructed carefully, most of the diverse range of stakeholders will benefit from a long-term solution securing effective antimicrobials (table 4). High-income countries will need to pay most of the innovation bill but will, in return, protect their populations from infections that cross borders. More equitable access will be achieved for all countries in return for better infection control and stewardship. Low-income countries will get support for capacity building and be assured affordable and appropriate antimicrobials. R&D-based pharmaceutical companies will receive higher and more predictable rewards for antimicrobial innovations than they do at present, and generic-drug manufacturers will have opportunities to produce quality-assured drugs under licence. Restrictions in antibiotic use in agriculture will promote global fair competition, since all producers have to abide by the same public health measures, supported by research for alternatives to agricultural antibiotics.
interconnected problems need integrated solutions. Concurrent expansion of access and reduction of inappropriate use are necessary, and innovation rewards have to be delinked from unit-based sales revenues so that payments are not generally based on the number and price of drugs sold. Securing effective antimicrobials calls for systemic and interdependent solutions.6,20–22

Global public goods, such as new antimicrobials, diagnostics, and treatment guidelines, should be secured through joint contributions and collaboration. Mobilisation of global solidarity will be necessary to secure resources and financing for universal access and for national capacities for surveillance, responsible use, and infection control. Coordination of these functions will require not only leadership and political will, but also strong implementation and potentially enforcement mechanisms.61

Fortunately, securing effective antimicrobials has finally gained a place on the global agenda. Member States have endorsed WHO’s global action plan to combat antimicrobial resistance.62 The USA has launched a national strategy and an action plan to address antibiotic resistance, which awaits Congressional action.63 The Transatlantic Task Force on Antimicrobial Resistance between the USA and the European Union has put forward a series of recommendations for joint action.64 South Africa has agreed to an antimicrobial resistance national strategy framework.65 The UK has initiated an independent review on antimicrobial resistance, which stated that development of ten new highly effective drugs in the next decade would cost less than US$25 billion (or 0.03% of global gross domestic product [GDP]).66 A recent report to the Nordic Council of Ministers67 recommended a global investment of 0.005% of annual global GDP over a 5-year period. There has also been a call for an intergovernmental antimicrobial panel, like the UN Intergovernmental Panel on Climate Change, which can synthesise and organise the available evidence to inform adoption and implementation of national policies.68 However, such a panel might be unnecessary, since a scientific consensus has already been reached regarding actions needed to secure effective antimicrobials.

Global actions need to integrate access to effective antimicrobials with infection prevention, responsible use of existing antimicrobials, surveillance, and innovation. These actions need to bridge the realms of public health, agriculture, animal husbandry, and trade. We have proposed a set of national and global recommendations (table 2) rooted in the analyses of this *Lancet* Series.69,70 Recommendations should be supported by strong implementation mechanisms that incorporate incentives for leaders to act on them, institutions that bring edicts into effect, and interests advocating their prioritisation.69–71 This implementation should lead to a new global institutional arrangement, either an international legal mechanism or a UN agency.

Deadly bacterial pathogens are present in every country of the world, and new resistant pathogens are evolving every day. We need to secure and expand our arsenal of antimicrobials. Therefore, we urge world leaders to consider, commit to, and champion implementation of these recommendations.


