Antimicrobials: access and sustainable effectiveness 4

Exploring the evidence base for national and regional policy interventions to combat resistance

Osman A Dar, Rumina Hasan, Jørgen Schlundt, Stephan Harbarth, Grazia Caleo, Fazal K Dar, Jasper Littmann, Mark Rweyemamu, Emmeline J Buckley, Mohammed Shahid, Richard Kock, Henry Lishi Li, Haydar Giha, Mishal Khan, Anthony D So, Khalid M Bindayna, Anthony Kessel, Hanne Bak Pedersen, Govin Permanand, Alimuddin Zumla, John-Arne Røttingen, David L Heymann

The effectiveness of existing policies to control antimicrobial resistance is not yet fully understood. A strengthened evidence base is needed to inform effective policy interventions across countries with different income levels and the human health and animal sectors. We examine three policy domains—responsible use, surveillance, and infection prevention and control—and consider which will be the most effective at national and regional levels. Many complexities exist in the implementation of such policies across sectors and in varying political and regulatory environments. Therefore, we make recommendations for policy action, calling for comprehensive policy assessments, using standardised frameworks, of cost-effectiveness and generalisability. Such assessments are especially important in low-income and middle-income countries, and in the animal and environmental sectors. We also advocate a One Health approach that will enable the development of sensitive policies, accommodating the needs of each sector involved, and addressing concerns of specific countries and regions.

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

Public Health England, London, UK (O A Dar FFPH, Prof D L Heymann MD); **Chatham House Centre on Global Health Security, London, UK** (O A Dar, Prof D L Heymann); **Aga Khan University, Karachi, Pakistan** (Prof R Hasan FRCPath); **School of Chemical & Biomedical**

Introduction

A range of policy initiatives have been launched to combat antimicrobial resistance. In this paper of the *Lancet* Series, we explore the evidence base for policy interventions in several contexts, from high-income countries (HICs) to low-income and middle-income countries (LMICs), and across the human health and animal sectors. By applying a One Health approach that bridges human, animal, and environmental health, and accounts for factors such as the demands of food production and commerce,[1] we examine policy interventions across three domains (figure): responsible use, through reducing public demand and supply by prescribers and dispensers; infection prevention and control to reduce the overall need for antimicrobials; and surveillance and monitoring systems, which can function as mechanisms to assess progress and hold relevant stakeholders accountable. Case studies (appendix pp 3–5, 8–9) show that many complexities exist in the implementation of these policies in diverse political and regulatory environments, and tailored solutions are therefore necessary.

Responsible use

The term "responsible use" implies that activities and capabilities of health systems are aligned to ensure that patients receive the right treatment at the right time, use these drugs appropriately, and benefit from them.[2]

Policies encouraging responsible use (ie, curbing excess use and reducing inappropriate demand) range from those focusing on health-care workers in outpatient settings, stewardship programmes in inpatient settings, national awareness campaigns, and structural reform policies to improve national health systems.[3,4] Although resistance of some indicator pathogens (appendix pp 1–2) has been reduced, these policies have been context specific and their assessments have generally failed to adequately explore issues such as their applicability across both public and private

Key messages

- The effect of antimicrobial resistance policies seems to be variable. The absence of progress is partly due to an insufficient evidence base to inform policy makers about the effectiveness, generalisability, and cost-effectiveness of initiatives.
- Policies encouraging responsible use of antimicrobials in primary care and outpatient settings have been proved effective but are not easily generalisable. Stewardship programmes in secondary care can be effective in encouraging responsible use of antibiotics and should be scaled up both in high-income countries and in low-income and middle-income countries (LMICs) where feasible.
- Sustained public awareness campaigns have shown some benefits, but these campaigns should be implemented with caution in LMICs, where cost and effects need improved assessment.
- Effective infection prevention and control interventions (IPCIs) can reduce the demand and need for antimicrobials, but evidence on appropriate IPCI strategies in LMICs is inadequate.
- Evidence of the most cost-effective systems for surveillance of antibiotic use and resistance remains weak worldwide. In the animal and environmental sectors, IPCIs and surveillance programmes are chronically underfunded.
- A global surveillance system should be created to secure accountability for control of antimicrobial resistance and improve between-country comparisons. For LMICs, an additional focus is needed to improve monitoring of drug quality and marketing to curb the production of counterfeit and substandard drugs.
- Standardised policy assessments should measure cost-effectiveness and acceptability to populations and stakeholders, and examine the political, regulatory, and technical environments in which the policies are implemented.
- A One Health approach will help to bridge gaps in levels of commitment of each sector and enable policy development that is inclusive, sensitive, and sufficiently flexible to accommodate the varying needs of different countries and regions.

Engineering, Nanyang Technological University, Singapore (Prof J Schlundt DVM); **University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland** (Prof S Harbarth MD); **Médecins Sans Frontières, London, UK** (G Caleo MD); **Arabian Gulf University, Manama, Bahrain** (Prof F K Dar FRCPath, Prof H Giha MD, Prof K M Bindayna PhD); **Christian Albrechts University, Kiel, Germany** (J Littmann PhD); **Southern African Centre for Infectious Disease Surveillance, Sokoine University of Agriculture, Morogoro, Tanzania** (Prof M Rweyemamu FRCVS); **London School of Hygiene & Tropical Medicine, London, UK** (E J Buckley MSc, H L Li MSc, M Khan PhD, Prof A Kessel MD, Prof D L Heymann); **Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, India** (Prof M Shahid MD); **Royal Veterinary College, London, UK** (Prof R Kock VMD); **Research Alliance for Advocacy and Development, Karachi, Pakistan** (M Khan); **Sanford School of Public Policy and Duke Global Health Institute, Duke University, Durham, NC, USA** (Prof A D So MD); **WHO Regional Office for Europe, Copenhagen, Denmark** (H B Pedersen MSc Pharm, G Permanand PhD); **University College London, London, UK** (Prof A Zumla FRCP); **National Institute for Health Research Biomedical Research Centre, University College Hospitals NHS Trust, London, UK** (Prof A Zumla); **Norwegian Institute of Public Health, Oslo, Norway** (Prof J-A Røttingen MD); **Department of Global Health and Population, Harvard T H Chan School of Public Health, Harvard University, Boston, MA, USA** (Prof J-A Røttingen); **and Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway** (Prof J-A Røttingen)

Correspondence to:
Dr Osman A Dar, Chatham House Centre on Global Health Security, London SW1Y 4LE, UK
osman.dar@phe.gov.uk

See Online for appendix

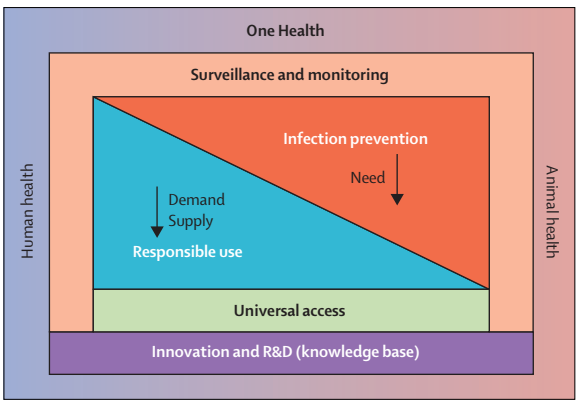

Figure: **Policy framework for sustainable access to effective antimicrobials**
A coherent framework of the different policy goals is necessary to tackle the complex public health and societal challenge of antimicrobial resistance. It needs to be rooted in a solid knowledge base and rely on investments and incentives for innovation and research and development (R&D). The premise should be to first secure universal access to antimicrobials so that they can be used appropriately when clinically warranted. The other sets of policy objectives are conservation strategies to preserve effectiveness. These strategies can rely on either reducing need through infection prevention or reducing unnecessary demand and supply, thereby fostering more responsible use. A robust surveillance and monitoring system is required to measure the state and progress of antimicrobial resistance control, serving as an important accountability mechanism. These sets of policies need to be framed from a One Health perspective that encompasses both human and animal health.

health-care sectors or the governance and regulatory requirements (eg, those of over-the-counter sales) necessary for effective implementation. Several countries, such as France, Iceland, and Belgium, have shown that responsible use policies in outpatient and primary care settings can reduce antimicrobial consumption, decrease resistance of specific pathogens, and save money (appendix).

Policies targeting health-care workers

The Antibiotic Smart Use programme in Thailand (appendix) has shown that alternative prescribing options—eg, oral rehydration and zinc for diarrhoeal diseases, and herbal drugs packaged in antibiotic-like capsules for viral infections of the upper respiratory tract—were important in restricting antibiotic prescription in outpatient and primary care settings. This policy might be attractive in environments where most patients attend private health care and prescriber remuneration depends on drug sales. In HICs, responsible use interventions in primary care have had mixed results.[5] For example, some educational programmes targeting prescribers have been effective in research settings but failed to show a decrease in antibiotic prescribing in real-world situations. Stewardship campaigns focusing on ambulatory and primary care prescribing behaviour have shown modest success on prescription rates.[6–9] Most campaigns show around 10% reductions in the number of prescriptions and seem to be effective only in the short term.[10] One of the most promising policy options in primary care is so-called back-up or delayed prescribing: the delay introduced between patients receiving their prescription and collecting the antimicrobials has been effective in reduction of antibiotic use, without increasing morbidity or affecting patient outcomes.[3,11,12]

Hospital-based stewardship policies seem to have been better studied than those at community or national levels. Antibiotic prescribing guidelines in secondary care provide the most compelling evidence of effectiveness, with studies showing an 80% reduction in the number of prescriptions issued for certain drug classes.[3] A systematic review of interventions to support such implementation[13] identified studies across 19 countries and compared persuasive and restrictive methods to improve antibiotic prescribing practice in hospitals. Persuasive methods advised physicians on how best to prescribe, whereas restrictive methods limited how they prescribed (eg, requiring approval from infection specialists). Both methods changed prescribing habits, and decreased numbers of hospital infections have also been reported in several countries. However, the authors graded much of the evidence on effectiveness as "poor" or "very poor", and noted a paucity of robust cost-effectiveness analyses. Advocating these methods in resource-constrained settings with little regulatory capacity is difficult and has the risk of compromising expenditure on other aspects of health-care delivery.[13]

Although some evidence of the effectiveness of responsible use policies has been reported in publicly funded health care, evidence from the private sector is notably lacking.[14] In areas such as south Asia, where 80% of patients seek care in the private health-care system, assessment of policies to regulate antimicrobial use is urgently needed. When control policies fail to adequately engage with the private health-care sector, readily available, substandard antimicrobials sold over the counter can drive resistance, posing challenges for both patients and physicians (appendix p 3).

Public awareness campaigns

A gap remains in the public's knowledge of appropriate antibiotic use and the causes of antimicrobial resistance, with levels of awareness and understanding varying substantially across countries. Many patients believe that antibiotics can cure viral infections, do not understand the basic mechanisms of resistance, and regularly self-medicate with leftover antibiotics and those sold over the counter.

An increase has been seen in the number of information campaigns[15] aimed to improve knowledge of appropriate use and reduce demand for antibiotics.[16] Campaign success depends on social, cultural, and geographical factors, and on existing barriers to prescribing. Since 2008, European public awareness campaigns have mainly centred on the introduction of a European Antibiotic Awareness Day (EAAD). Similar

campaigns have also been launched outside Europe—eg, Antibiotic Awareness Week in Australia. Since most antibiotics are prescribed in primary care, many campaigns focus on information about infections common in this context.

Campaigns such as the EAAD have received widespread support from participating countries; however, their effect on antibiotic resistance, consumption, and prescribing is difficult to assess.[3] Effects are dispersed and might be small, and few interventions have been examined for cost-effectiveness.[3] When awareness translates into reduced prescription rates is unclear. Improvements in adherence to antibiotic treatment regimens are difficult to measure, particularly for prescriptions in ambulatory care, which are not supervised. Moreover, comparative assessments of the effectiveness of public awareness campaigns are challenging because different countries use varying parameters to measure antibiotic use—eg, defined daily doses or number of packages prescribed per 1000 inhabitants per day.[17] For example, a study of EAAD effectiveness in the UK showed that the campaign had led to a minimal increase in public awareness, with no noticeable reduction in antibiotic use.[18] However, long-running campaigns, especially those in Australia and France, have been associated with modest but consistent improvement in consumer awareness and reduced number of prescriptions.[19,20]

Structural reform and strengthened health-care systems

The challenges of poor governance and inadequately resourced health systems affect all aspects of health-care delivery, including the ability to implement effective control policies at a national level. Weak regulation and misaligned financing models for health care can create perverse economic incentives for providers.

In Australia, the reduction in fluoroquinolone use in primary care has been attributed to strong government regulation, including a narrowed list of indications for quinolones through the national pharmaceutical subsidy scheme. Despite several years of educational initiatives following the publication of national antibiotic guidelines by the National Prescribing Service and Therapeutic Guidelines in 1978, no substantial progress in reducing use had been made; however, after the introduction of the narrowed list and removal of the subsidy, quinolone use dropped by 30% in 1994–95. The policy to withdraw public subsidies was effective, partly because of the high underlying price of quinolones in Australia, underlining the importance of understanding the national context of such policy successes.[21]

In China, antibiotics are substantially overprescribed because drug sales revenue constitutes a major proportion of health-care providers' income. In response to increasing antimicrobial resistance, China's first explicit attempt to steward antibiotic use was to formulate national hospital guidelines (2004) and a containment policy (2004), which sought to ban the sale of antibiotics to patients without a prescription. The effectiveness of these policies was not systematically assessed, and weak enforcement is likely to have restricted their success.[22] Further measures include a national task force to monitor and regulate clinical use (2011) and new clinical regulations (2012)[23] for hospitals defining best practice and imposing legal penalties for violations. Policy enforcement is key, and the experience in China (appendix) suggests that strengthening the health-care system is a prerequisite. In this case, it involves delinkage of monetary compensation for prescribers from antibiotic sales.

Strengthening of national drug regulatory authorities might also have a role in monitoring the marketing activities of pharmaceutical companies and ensuring drug quality by curbing the production of substandard and counterfeit antimicrobials. The pharmaceutical industry is known to, at times, pressurise both patients through intense marketing campaigns and doctors through bribery.[24] Well publicised criminal investigations of irresponsible practices of GlaxoSmithKline in China and Poland, for example, show a policy shift of national authorities.[25,26] In recognition of the threat posed by counterfeit and substandard drugs in particular, the Indian Government has adopted increasingly stringent sanctions on rogue producers and traders, including possible life imprisonment.[27] The effect of more robust regulatory policies remains to be assessed.

Policies in the animal sector

Antimicrobial resistance in animals represents a serious problem for human health,[28,29] and one of the greatest concerns is the emergence of multidrug-resistant bacterial strains and strains that are resistant to antimicrobials regarded as critically important for human medicine.[30] Bacteria in animal hosts can reach human beings through direct contact, food, or the environment. Non-therapeutic use of antimicrobials for growth promotion has been associated with resistance in animals. This situation has occurred in many countries and is well documented.[31,32] To remove the economic incentives for antimicrobial overuse, some governments have legislated to reduce veterinarian profit from antimicrobial sales. In Denmark, such interventions resulted in a 40% reduction in overall use and a reduction in tetracycline use from 37 tonnes in 1994 to 9 tonnes in 1995.[33] To compensate veterinarians for income loss, new advisory roles were created (eg, provision of technical support to farmers for animal health and biosecurity without antimicrobials). For large livestock holdings, monthly veterinary consultations were made mandatory. These actions seem to have resulted in more efficient and cost-effective management systems than previously unregulated ad-hoc arrangements (appendix).

Dutch initiatives have also resulted in a 56% reduction in animal antimicrobial use between 2007 and 2012.

Crucial factors of this plan were a memorandum of understanding between the animal sectors and the Dutch Association for Veterinarians (2008); a mandatory government policy demanding a reduction of 70% in antimicrobial use between 2009 and 2015; introduction of farm health and treatment plans with specified antibiotics; and prohibition of the use of new antibiotics.[34]

In many LMICs, a combination of large producers and smallholders often operate in parallel, and a loss of economies of scale has resulted in big drug suppliers moving to fewer regional centres, with ad-hoc traders filling the gap. At the same time, an increasing number of cheap generic drugs have become available.[35] Although these factors improved smallholders' access to drugs, they have compromised the quality and range of products available in environments with weak regulation, licensing delays, cash flow problems, and distribution difficulties. Surveys of antimicrobial use in animals in LMICs are inadequate but suggest a high level of farmer prescription, with around a third of countries allowing sales of over-the-counter antibiotics.[36,37] Furthermore, many livestock owners employ unskilled workers to treat animals, resulting in suboptimal dosing, incorrect administration, arbitrary drug combinations, and non-observance of withdrawal periods.[38–40] Stewardship interventions began in the 1990s and started with pilot projects in community-based animal health workers encouraging local control of drug use. However, these efforts were often undermined by inadequate supporting legislation and poorly paid veterinary officers supplementing salaries with drug sales.[41]

Although many veterinary authorities in LMICs have adopted international standards and regulations on drug use designed to facilitate control of antimicrobial resistance, the capacity to implement these guidelines is insufficient.[42] Some non-governmental organisations have provided a middle ground in capacity building, education, and facilitation of strengthened stewardship in LMICs, and improvements in both veterinary and paraveterinary sectors have been reported.[41–44] However, most of these programmes are restricted in scope and have not been subjected to robust assessment.

Awareness campaigns in the animal sector

Little evidence supports the effectiveness of policy initiatives that aim to raise awareness, change prescribing behaviour of veterinarians, or vary antimicrobial use by livestock farmers in the absence of strong central regulation. In the USA, where lobbyists exert substantial influence over law and policy makers, an increasingly coordinated awareness-raising drive among the public and health-care associations contributed to the introduction of the Preservation of Antibiotics for Medical Treatment Act (2013) bill to Congress.[45] However, the bill, which would mandate regulations to curb antibiotic use in animals, seems to have stalled in the Senate with fierce opposition from industry groups.[46] As a result, there is despondency over the bill's potential to strengthen the regulatory framework needed to reduce use, with some analysts estimating a minimal likelihood of it being enacted.[47] In March, 2015, a new bill was introduced that would require the US Food and Drug Administration to withdraw product approval for antimicrobial use in animals if a manufacturer cannot show that its drug poses no risk to human health.[48] The growing public awareness around the debate seems to have also affected food retailer and consumer demand, with McDonald's announcing that it will phase out the use of chicken raised with antibiotics, thus pressurising competitors to conform.[49]

In LMICs, awareness in farmers is low. A study showed that although most livestock keepers in Tanzania were using antibiotics to treat their animals, with some observing a withdrawal period before slaughter, around 40% were not aware of any related possible human health threats.[50] Well examined policy initiatives to raise awareness in the animal sector are absent, reinforcing a continuing theme of poor evidence from LMICs.

Infection prevention and control

Infection prevention and control interventions (IPCIs) can minimise the spread of pathogens, including those that are resistant, decrease the likelihood of infection in health-care settings, and reduce the overall need for antimicrobials.[51,52] Controlled clinical studies, and international benchmarking of infection control practices and rates of infection with resistant bacteria, have provided valuable information for advocacy and established a minimum set of evidence-based practices for control of epidemic or endemic drug-resistant pathogens in different health-care settings.[53] In particular, hand hygiene is now established as the most effective measure to prevent transmission of resistant bacteria during health-care delivery, as shown in the successful control of meticillin-resistant *Staphylococcus aureus* through national campaigns (eg, in Belgium and the UK) to improve hand hygiene compliance. The implementation of WHO's hand hygiene strategy is feasible and sustainable across a range of settings and leads to substantial compliance improvement.[54]

For IPCIs to be sustainable, they should target routine care practices and environmental reservoirs, and be adapted to local priorities. Accordingly, WHO proposed four core elements for health-care facilities—namely, hand hygiene, environmental cleaning, disinfection and sterilisation, and education of staff—and encourages national authorities to ensure application. Implementation remains challenging in LMICs, in which the frequent absence of access to even basic IPCI mechanisms results in a weak evidence base to support their introduction into such health-care settings.[55–57]

Therefore, a prime focus should be to reduce the burden of infections and the subsequent need for antimicrobials by promoting hand hygiene with soap,

improving access to clean water and sanitation, vaccination (eg, against pneumococcal infections, cholera, and typhoid fever), and more disease-specific measures such as reduction of sexually transmitted infections through condom use.[58–60] Several studies[61–63] have shown substantial reduction in resistant *Streptococcus pneumoniae* following the introduction of multivalent pneumococcal conjugate childhood vaccines, in both the vaccinated and the general population (through herd immunity). The integration of vaccination programmes into broader control strategies remains underassessed, with global initiatives operating mostly as separate entities. Encouragingly, financing for evidence-based IPCIs has increased, and collaborations are now operational worldwide through local, national, regional, and international networks (panel).

Effective IPCIs in the animal sector provide some notable examples. Policies encouraging the adoption of so-called all-in-all-out farming systems (ie, production systems whereby animals are prevented from commingling and with facilities cleaned between animal groupings) and reformulation of animal diets have been effective in reducing antibiotic consumption while maintaining livestock growth rates. Successes in LMICs include the widespread adoption of the infection-treatment immunisation method for East Coast fever control in east African cattle. The technique, based on injection of cattle with partially attenuated sporozoites of *Theileria parva* concurrently with longacting oxytetracycline, has proved effective in preventing infections, with no known contribution to the resistance burden.[69]

In aquaculture, the remarkable success in countries such as Norway in reducing antibiotic use through vaccination programmes is well described. However, the development of policies to progress these national successes to other countries has been slow.[70] The tripartite agreement between WHO, World Organisation for Animal Health (OIE), and the Food and Agriculture Organization (FAO) has piloted several One Health projects to do this.[71] Despite some successes, chronic underinvestment in IPCIs remains in the animal sector. The World Bank estimates that the funding needed for 60 low-income countries and 79 middle-income countries to bring their animal infection prevention and control systems up to OIE and WHO standards ranges from US$1·9 billion to US$3·4 billion per year.[72] Funding agencies have thus begun to allocate more spending to One Health initiatives, but the global effects of this policy shift in funding antimicrobial resistance control specifically remain to be examined.[73]

Surveillance and monitoring systems

Surveillance is fundamental to the control of antimicrobial resistance.[74] The 2001 WHO Global Strategy embedded surveillance of resistance, monitoring of antimicrobial use, and disease burden as its key components. Between-country comparisons can be a major political driver for change and an increased focus on antimicrobial resistance control, as shown in how the European Antimicrobial Resistance Surveillance System and European Surveillance of Antimicrobial Consumption Network (ESAC-Net) are functioning as accountability measures for European countries. The success of the two systems has seen the WHO Regional Office for Europe expand the ESAC-Net method to cover 14 additional countries in Europe.[75] Moreover, countries such as France, the UK, South Korea, and Turkey have now successfully implemented governmental targets that are based on public reporting of surveillance data.

Despite their importance, most international surveillance systems outside Europe have not been formally assessed in terms of validity, sustainability, and long-term effects on antibiotic resistance. The evidence base to determine the most cost-effective systems for surveillance of antibiotic use and resistance remains weak worldwide. Unsurprisingly, substantial differences exist between surveillance system needs because of varying cultures, seasonal practices, and population dynamics (appendix). Policy makers need help to decide on the most efficient surveillance systems to maximise scarce resources—should countries invest in continuous surveillance of all health-care settings, or can sufficient data be gathered with restricted sentinel surveillance or periodic prevalence studies?[76]

What are the best indicators to monitor antimicrobial use in different settings, and what is the value of aggregate-level versus individual patient-level information for guiding stewardship strategies? Aggregated

***Panel:* Selected examples of successful global infection prevention initiatives**

- The "Clean Care is Safer Care" campaign by WHO focuses on hand hygiene compliance in health-care workers. Since its inception in 2005, 134 WHO Member States and autonomous areas have participated in this initiative, reaching 9 million health-care workers, and more than 17 000 health-care facilities have committed to improve hand hygiene.[64]
- The GAVI Alliance finances vaccines and, to some extent, immunisation services in countries with a gross national income per person (according to the World Bank) of US$1570 or below (as of 2014). Its vaccine portfolio includes several vaccines for illnesses that would otherwise be treated with antibiotics—eg, pneumococcal, *Haemophilus influenzae*, and rotavirus infection (since diarrhoea is often inappropriately treated with antibiotics rather than oral rehydration salts and zinc).[65]
- The Global Fund Against AIDS, Tuberculosis and Malaria has financed the purchase of more than 310 million longlasting insecticidal mosquito nets to combat malaria and indirectly reduce the risk of emergence and spread of resistant malaria.[66]
- The World Bank, through its Water Partnership Program, has allocated US$24 million to improve the quality of drinking water and sanitation services in low-income countries, with additional funding (US$45·1 million) being allocated through the next phase of the programme.[67]
- UN Population Fund procures and distributes condoms (both male and female types) in low-income countries and actively promotes practices such as male circumcision to restrict sexually transmitted diseases of bacterial origin, particularly drug-resistant gonorrhoea.[68]

consumption data do not allow assessment of the quality and adequacy of individual prescribing decisions, although they provide measurable estimates of trends for benchmarking.[77] Several experts and policy makers suggest point-prevalence surveys of antibiotic use as a straightforward method to solve these issues.[78]

In LMICs with weak health systems and competing public health problems, constraints of infrastructure, trained personnel, data collection, and coordination result in diverging approaches and indicators to the monitoring of antibiotic use and resistance.[79] The absence of a global surveillance system to provide reliable and validated resistance data from all continents results in substantial knowledge gaps. Although several regional and national surveillance networks have been successfully established during the past two decades, most of them relate to HICs or specific pathogens (eg, Global Foodborne Infections Network for foodborne pathogens). Most networks have insufficient resources to standardise and assure the quality of diagnostic methods for detection of resistance, and data are often not systematically obtained or geographically representative. To achieve timely coordinated containment globally, the WHO's International Health Regulations could provide the legal framework for early detection and outbreak control of emerging pan-resistant bacteria.

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It has been suggested that laboratory and epidemiological surveillance should become part of a straightforward roadmap in which an agreed minimum dataset could be shared internationally.[80] This is challenging. Several international, publicly funded, voluntary surveillance systems of resistant pathogens have been set up, and each has its strengths and weaknesses (appendix). Many health-care facilities (especially those in the private sector) are reluctant to share resistance data because they are wary of reputational damage. Similarly, at the national level, widespread information about resistance is thought to negatively affect exports and medical tourism. Therefore, data contribution to both national and international surveillance might need to be mandated to be effective. Additionally, LMICs have few laboratories with the capacity for quality-assured microbiology and drug sensitivity testings.[81,82] Vertical programmes have been able to generate resources to overcome some of these obstacles and to provide infrastructural support for drug resistance surveys in several countries, but these are restricted to a few diseases, such as malaria, HIV, and tuberculosis affecting human health. Broadened efforts to improve quality are linked to quality assurance and accreditation programmes, and some notable successes have been achieved in Africa.[83–85]

To optimise use of surveillance data, comparative information is needed.[86] According to the OIE, 111 (62%) of its 178 member countries have no official system to obtain data for antimicrobial use in animals. This percentage rises to 94% (51 of 54 countries) in Africa and 95% (52 of 55 countries) in the Americas. Notably, in policy terms, 39% (43 of 111) of these countries still have no official plans to establish quantitative national surveillance and monitoring systems on antimicrobial use in animals.[87]

One of the first integrated animal–human national surveillance programmes was initiated in Denmark (the Danish Integrated Antimicrobial Resistance Monitoring and Research Program [DANMAP]) as a collaboration of stakeholders in the human health, food, and animal health sectors. Through DANMAP, the VetStat database was launched to monitor antimicrobial use of individual farms and was instrumental in the creation of the Danish Yellow Card system—a national antimicrobial monitoring and reduction scheme introduced in 2010. Individual farmers and veterinarians with exceptionally high antimicrobial use receive a yellow card, followed by a series of injunctions if use is not reduced. The initiative has resulted in year-on-year reduction in total use of up to 20%.[88] Several other European Union countries (Czech Republic, Norway, Sweden, Switzerland, Finland, France, the Netherlands, and the UK) have similar datasets, thus enabling between-country comparisons of antimicrobial use.[89] In 2009, the European Medicines Agency (EMA) launched European Surveillance of Veterinary Antimicrobial Consumption, which now monitors animal use of antimicrobials in 25 countries through sales data.[90]

In LMICs, few studies, most of which are cross-sectional, have been done on antimicrobial resistance in isolates from animals or animal products in the food chain. For example, *Salmonella* spp resistance was detected in more than 79% of isolates from an abattoir study in Kenya, but studies of antimicrobial resistance of *Salmonella* spp in patients did not confirm a link.[91] Almost no longitudinal studies have been done, surveillance systems are barely functioning, few countries have adopted WHONET (WHO's database software for the management and analysis of microbiology laboratory data),[92] and the OIE Standard and Codex Alimentarius Guidelines have not yet been applied. The need for improved surveillance in animals is clear, but policy initiatives to achieve this have made little progress beyond emphasising the scale of the problem.[82,93]

Since the 1970s, studies have highlighted the presence of antimicrobial resistance in environmental bacterial samples, suggesting a risk of resistance spreading from hospital and pharmaceutical effluent, sewage systems, and water treatment plants. Slurry from livestock farms has also been implicated.[94,95] Development of sentinel surveillance and sampling systems for high-risk environmental settings would thus seem an appropriate strategy for HICs and should be considered where technically feasible and affordable in LMICs. However, no countries have established such systems systematically outside research settings.

	Examples of effective interventions and policies	Weakness in evidence base	Challenges for generalisability of policy
Responsible use	• Alternative prescribing options at the national level for antibiotics • Back-up or delayed prescribing in publically funded high-income settings • Development and implementation of clinical antibiotic guidelines in secondary care • Persuasive and restrictive interventions in secondary care • National restrictions on antibiotic subsidies • Alternative reimbursement options for prescribers (in both human health and animal settings) • Bans on antibiotic use for animal growth promotion • Reorientation of veterinarians' role from prescribers to provision of technical support to farmers	• Long-term effects on prescribing behaviour have not been assessed • Insufficient robust cost-effectiveness analyses of all interventions • Little research into interventions targeted at the (unregulated) private sector in LMICs • Effect of regulatory policies on marketing and sale of antimicrobials remains to be assessed	• Widely varying governance structures and accountability mechanisms of health systems • Different methods of prescriber remuneration • Behaviour change interventions restricted by cultural settings where they have been trialled • Financial challenges in the animal and livestock sector, such as capital costs for changing practice, meat prices, and farm profitability • Wide national variations in health budget availability for antimicrobial resistance policies • Unregulated production of substandard and counterfeit drugs
Infection prevention and control	• Promote hand hygiene in health-care and community settings • Improve access to clean water and sanitation • Increase effective vaccine coverage in both human beings and animals	• Little evidence on effectiveness and appropriate implementation on IPCIs in LMICs • Poor cost-effectiveness assessment of IPCIs in health-care settings	• Insufficient integration of IPCI programmes in the community and antimicrobial resistance control policy • Chronic underfunding of IPCIs in the animal and livestock sector
Surveillance	• Integrate data for surveillance and antimicrobial use on a regional basis to enable between-country comparisons • Link resistance surveillance in the animal sector with regulatory sanctions against bad practice	• The evidence base to determine the most cost-effective systems for surveillance of antibiotic use and resistance remains weak worldwide • Little analysis of infrastructure and resource requirements for effective surveillance • Substantial differences across countries of indicators of and guidelines for surveillance in different settings; comparative data in human and animal health are therefore absent	• Transferability of surveillance systems that have been successful in HICs to LMICs is questionable because of infrastructure and resource differences • Surveillance of counterfeit and substandard antimicrobials is a priority in LMICs • Chronic underfunding of surveillance in the animal sector in LMICs

LMICs=low-income and middle-income countries. IPCIs=infection prevention and control interventions. HICs=high-income countries.

Table: **Potentially effective control interventions and challenges in the development of generalisable policies**

Discussion

Our analysis shows that the absence of progress in combating antimicrobial resistance is partly due to an insufficient or poor evidence base for the effectiveness of the myriad policies across the human health and animal sectors in both HICs and LMICs. Even in countries where policies have shown benefits in reduction of antimicrobial use or resistance, robust and complete policy assessments have been insufficient, with little information on cost-effectiveness and inadequate descriptions of the technical, political, and regulatory environment necessary for implementation (table). For example, development of a strategy to translate the success of Scandinavian countries in restricting antibiotic use in livestock rearing while maintaining meat production and profits remains difficult. Without substantial subsidies from the European Union, many livestock farmers in the region would be unable to operate profitably. Worldwide, the generalisability of demonstrably effective policies therefore remains a challenge.

The recent WHO action plan on antimicrobial resistance highlights areas in which research priorities should be aimed to fill gaps in the evidence base, emphasising the need for evidence-based policy development, especially in LMICs. Our findings concur with these priority areas, but also suggest that countries and regions should be mindful of their approach when adopting new policies, even the ones proven effective in another context.[5] Before rolling out policies nationally, pilot programmes should be done to ensure that policies are effective in their unique setting. This is particularly true of structural and regulatory reform policies or behavioural interventions, which are more context specific than policies targeting other areas of antimicrobial resistance control (eg, hospital stewardship or resistance monitoring). Stewardship programmes in both outpatient and hospital settings can effectively encourage responsible use of antibiotics, and their implementation should be scaled up in both HICs and LMICs. The evidence base is stronger for secondary care interventions, including the implementation of clinical guidelines and those targeting prescribing behaviour, than for interventions at the community level. However, the potential total effect will be larger in community settings, thereby suggesting the need for more rigorous studies. In community settings, back-up or delayed prescribing has proved effective, as have policies providing alternative prescribing options. Public awareness campaigns can also be effective when sustained, but their effect seems to wane and they should be implemented with caution, particularly in LMICs, where the cost-effectiveness of such programmes needs detailed assessment. In the animal sector, evidence from HICs suggests that curbing antibiotic use as growth promoters can reduce resistance. However, bans or other policy measures to achieve this outcome should be coupled with adequate investment in improved IPCIs for livestock and effective mechanisms to remunerate veterinarians and to reorient their roles.

Arguably, the approach with the greatest potential to reduce the need for antimicrobials is IPCIs, including vaccinations, handwashing, and improved access to water and sanitation. Effective promotion of IPCIs in LMICs has been slow, and strategies should therefore look for opportunities to integrate their activities and goals into these closely related development sectors.[96]

For **PreventionWeb** see http://www.preventionweb.net

Increasing implementation of effective responsible use interventions and IPCIs globally should be linked to a simultaneous push for improved resistance surveillance and antimicrobial use monitoring data, thereby ensuring accountability. Countries reporting drug resistance or high antimicrobial use should be offered financial and technical support to implement interventions that will reverse such trends and be incentivised to invest domestically.

With a range of surveillance systems operating in parallel worldwide, policy makers need to adopt those that best suit their needs. A broad cross-sectoral, multistakeholder programme of harmonisation and integration of global systems should be fostered to enable between-country comparisons of antibiotic use and resistance. This would enable an ordered integration of regions into a globalised surveillance system. As seen with DANMAP, integrated surveillance across human beings and animals has proved effective. Rapidly developing technologies, such as the use of whole-genome sequencing to identify resistant strains, will enable fully integrated national and global surveillance of both communicable diseases and antimicrobial resistance in human beings and animals.[97] Supporting efforts to make technologies cheaper and more accessible, and policies more widely applicable, should be prioritised.

For LMICs, improved monitoring of drug quality to curb the production of counterfeit and substandard antimicrobials is also necessary. Finally, IPCIs and surveillance in animals and the environment are chronically underfunded, and political appetite for investment is needed to increase capacity in many LMICs.

To address evidence gaps, comprehensive assessments and systematic reviews of interventions used in existing control policies are needed. The UK has taken an important stride in the human health sector with the publication of the National Institute of Health and Care Excellence (NICE) guidance on antimicrobial stewardship.[98,99] The guidance informs health workers, policy makers, commissioners of local health services, and patients of the steps needed to ensure appropriate use, showing that comprehensive approaches are feasible.[98,99]

However, enhanced support is needed to assess policies in LMICs and in the animal and environmental sectors. Standardised assessment frameworks should be developed and implemented; at present, even in well resourced settings where such frameworks exist, they are seldom applied appropriately.[76] In view of the complexity of designing assessments and the risks of misleading conclusions around generalisability, a multisectoral task force should be convened for this purpose.[100,101] Standardised analyses of contextual factors (eg, political structures, governance and regulation, and resource availability) should be included. Detailed case study approaches might be helpful, and an open-access central repository should be established for policy examples to enable comparisons of best practices.[101] This could be similar to PreventionWeb, the UN's website for Disaster Risk Reduction case studies.

Although the evidence base for policies to control antimicrobial resistance is scattered, countries have many options to choose from. However, these options need to be adapted before adoption to become context specific. Proper surveillance and monitoring are required to assess progress, contribute to an expanding knowledge base, and help to improve accountability within and between countries.

Our analysis focused on the human health and animal sectors, with little discussion of the environment or food and trade policy. However, these too are integral components of antimicrobial resistance control, and the One Health approach to policy development (figure) can bridge gaps between sectors. Powerful vested interests can derail a coordinated strategy both intentionally and unintentionally. These range from industry battles between competing lobbyists over antibiotic use in animals, to the continuing tussles of donor-funded vertical health-care programmes in LMICs that could potentially compete with control programmes for scarce resources.

As a result, an understanding of the political and economic context is as important as the scientific evidence base in the development of coordinated and effective policies. The wide-ranging sensitivities at play mean that a unified, inclusive process to policy development should be adopted—one that is rooted in a sound evidence base, sufficiently flexible to accommodate different settings, and fully funded.

Contributors

OAD, EJB, and DLH collated contributions from all authors and wrote the first draft. All authors contributed to the literature search, writing, and revision, and approved the final version.

Declaration of interests

We declare no competing interests.

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