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

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Keywords: Antimicrobial Resistance, effective antibiotics, access, policy interventions

Word count: Text (5360 words); Abstract/Summary (244 words)

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Summary/abstract
An array of local, national and global policy initiatives to control antimicrobial resistance (AMR) have been launched, but the effectiveness of these policies is not yet fully understood. A stronger evidence base to inform effective policy interventions in high and low/middle income country (HIC and LMIC) settings, and across both the human and animal sectors, is needed. We examine existing policies covering three domains: 1) responsible use, 2) surveillance and 3) infection prevention and control, and consider which policies are likely to be most effective at national and regional levels. Specific case studies highlight the complexities of applying AMR prevention and control policies across sectors and in widely varying political and regulatory environments, and demonstrate gaps that have emerged in the evidence base. We make recommendations for policy action given the current state of evidence

and demonstrate that there is a need for more comprehensive AMR control policy evaluations including of their cost-effectiveness and generalisibility; by providing a contextual analysis of the political, regulatory and technical environments in which they are implemented. This is especially important across LMICs, and in the animal and environmental sectors. We conclude that standardised frameworks for evaluating AMR control policies should be developed and a cross-sectoral open-access central repository established to capture national and regional experience. A 'One Health' approach would enable an inclusive, sensitive and flexible process for AMR policy development that accommodates the needs and circumstances of each sector involved, and addresses specific country and regional concerns.

Key messages panel

- An array of local, national and global policy initiatives on antimicrobial resistance (AMR) have been launched worldwide. The effectiveness of these policies appears to be variable, with many gaps in knowledge.
- Policies encouraging responsible use of antimicrobials in primary care/outpatient settings such as providing alternative prescribing options and back-up/delayed prescribing have been demonstrated to be effective. However, these and other interventions are context specific and not easily generalisable. Stewardship programmes in secondary care can be effective in encouraging responsible use of antibiotics and should be scaled up in both HICs and LMICs where feasible. Public awareness campaigns when sustained have shown some impact but should be implemented with caution particularly in LMICs, where the cost and impact of such campaigns needs better evaluation.
- In the animal sector, curbing antibiotic use as growth promoter can be effective in reducing AMR. However, policy measures to achieve this must be coupled with adequate investment in improved infection prevention and control strategies for livestock, and effective mechanisms for remunerating veterinarians/prescribers and re-orienting their roles.
- Reducing the demand and need for antimicrobials can be achieved through the implementation of effective Infection Prevention and Control interventions (IPCI) including vaccinations, hand washing, improved access to water and sanitation, and behaviour change. IPCI and surveillance in the animal and environmental sectors suffers from chronic underfunding and a significant investment of several billion dollars per annum is necessary to upgrade capacity in the vast majority of LMICs.
- A global surveillance system should be created to enable improved between-country comparisons of AMR and antibiotic use through a programme of harmonising and integrating existing surveillance systems. To do this requires the establishment of an adequately funded, cross-sectoral working group, with a mandate to negotiate with countries on a regional basis. For LMICs, additional focus is needed to improve monitoring of antimicrobial drug promotion and quality to curb the proliferation of counterfeits and substandard drugs. The sentinel surveillance of environmental settings likely to contribute to AMR should be initiated and piloted in HICs and its feasibility explored in lower income settings.

- 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 securing accountability. Countries reporting emerging drug resistance levels or high antimicrobial usage should be offered financial and technical support for implementing interventions to help reverse such trends, but should also be incentivized to invest systematically domestically.

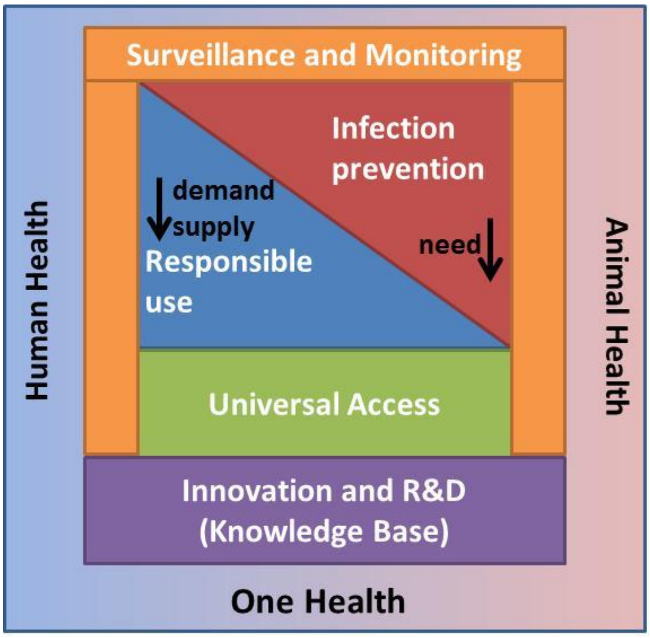
- Knowledge gaps indicate that there is a need for comprehensive policy evaluations that include measures of cost-effectiveness, acceptability to populations and stakeholders; and assessment of the political, regulatory and technical environments in which they are implemented. Systematic reviews of existing policies are required across human, animal and environmental health as related to AMR control. Standardised frameworks for policy evaluation should be applied and an open-access central repository established where national and regional AMR policy case studies can be captured.

- A 'One Health' approach to AMR may help bridge gaps in the levels of commitment being shown to each sector and enable policy development that is inclusive, sensitive and sufficiently flexible to accommodate the varying needs of different sectors, countries and regions.

Introduction

A range of policy initiatives have been launched to combat Antimicrobial Resistance (AMR). This paper explores the evidence base for policy interventions in a variety of contexts, from high and low/middle income countries (HICs and LMICs) and across the human and animal sectors. By applying a 'One Health' approach that bridges the interface between 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 broad AMR domains (Figure 1): 1) responsible use, through reducing public demand and supply by prescribers/ dispensers, 2) infection prevention and control to reduce the overall need for antimicrobials and 3) surveillance and monitoring systems, which can function as mechanisms for assessing progress and making relevant stakeholders accountable for their part of the overall AMR control strategy. Specific country and regional case studies highlight the need for tailored solutions and the complexities of applying AMR control policies in widely varying political and regulatory environments. While the focus of this paper is largely antibiotic resistance, lessons can be learned from other areas of global health policy and are reflected in this analysis.

Figure 1. Policy framework for sustainable access to effective microbials



Responsible use

The term 'responsible use' implies that health-system activities and capabilities are aligned to ensure that patients receive the right medicines at the right time, use them appropriately, and benefit from them.[2]

Policies encouraging responsible use, (i.e. curbing excess usage and reducing inappropriate demand), range from those focusing on healthcare workers in outpatient settings, stewardship programmes in inpatient settings, awareness raising national campaigns aimed at the public and structural reform policies designed to improve health systems at a national level.[3,4] Unfortunately, while some success has been demonstrated in reducing resistance rates of indicator pathogens, policies have been context-specific and their evaluations have generally failed to adequately explore issues such as their applicability across both the public and private healthcare sectors or the governance and regulatory requirements (e.g. of over-the-counter sales) necessary to implement them effectively. **Table 1** summarises several national examples demonstrating that responsible use policies in outpatient and primary care settings can reduce antimicrobial consumption, decrease resistance rates of specific pathogens and result in cost savings. It also illustrates the plurality of interventions that have been utilised.

Table 1: Selected examples of effective National Policies for Responsible Use in outpatient settings

Example	Action (best practice)	Result	Reference
France	National Plan to Control AMR • Surveillance for antimicrobial consumption • Surveillance for AMR • Infection control measures • Public Health Awareness • Education of Health Professionals • Rapid testing for *Streptococcus pyogenes* • Introduction of pneumococcal vaccine	• Antibiotic consumption reduced by 23% (2002-2007) but stabilized thereafter. In the over 60 years age group though consumption subsequently increased reaching pre-intervention levels. • MRSA from blood culture reduced from 33% (2001) to 26% (2007) • Penicillin non-susceptible S*treptococcus pneumoniae* from respiratory, otitis media and other specimens decreased from 53% (2002) to 38% (2006). In nasopharangeal samples from children 3-40 months at day care centres in South Eastern France, penicillin non-susceptible *S. pneumoniae* decreased from 34% (1999) to 19% (2008)	5, 6, 7 ,8
Iceland	Public media campaign on prudent use of antibiotics in children	• Reduction in antimicrobial usage • Decrease in incidence of Penicillin non-susceptible *S. pneumoniae*	9
Belgium	Campaigns and activities by the Belgian Antibiotic Policy Coordination Committee (BAPCOC) • Public awareness to promote prudent use of antibiotics in the community • National Hand Hygiene Campaign • Establishment of antibiotic teams in all hospitals • Surveillance for antimicrobial consumption and resistance • Infection control measures • Introduction of pneumococcal vaccine	Between 2000 and 2007 • A 32% reduction in antibiotic usage • Macrolide resistance in *S. pneumoniae* decreased from 36.5% to 26%; *a*nd in *S. Pyogenes* (among patients presenting with pharyngitis) from 17% to 2% • Penicillin non-susceptible S*treptococcus pneumoniae* from invasive isolates decreased from 17.7% to 10.0%	10
Australia	Antimicrobial restriction to reduce fluoroquinolone usage	• Fluoroquinolone resistance amongst Gram negative bacilli reduced to under 5%	6, 11, 12
Thailand	Antibiotics Smart Use (ASU) Programme: • Phase 1: Treatment guidelines and patient education • Phase 2:Expansion of network and integration of ASU into national policies • Phase 3: Sustainability through creation of social norms on rational use of antibiotics	• Phase 1 successful in reducing antibiotic prescriptions.	13
South Korea	Introduction of policy prohibiting physicians from dispensing drugs	Antibiotic prescribing for patients with presumed viral illness decreased from 80.8% in 2000 to 72.8% in 2001	14
Taiwan	• Policy prohibiting physicians from dispensing drugs • National Health Insurance stopped reimbursement for acute upper respiratory tract infections without proof of bacterial aetiology	More than 50% reduction in antibiotic usage for upper respiratory tract infection in the first year (1999-2001)	15, 16
Pakistan	Implementation of standardised approach to rationalise use of drugs in Acute Respiratory Infections at a Children's Hospital in 1990	Outpatient antibiotic usage decreased from 54.6% to 22.9% (1989- 1992)	17

Responsible use by healthcare workers

In outpatient primary care in LMIC settings, the ASU programme in Thailand[13] demonstrated that alternative prescribing options were important factors in increasing physicians' confidence to limit antibiotic prescription. The availability of appropriate alternative therapies such as oral rehydration and zinc for diarrhoeal diseases, and herbal medicines packaged in antibiotic-like capsules for viral upper respiratory tract infections helped achieve this. This may be an attractive policy option in many environments where private healthcare plays a large role in treating patients and prescriber remuneration is more heavily dependent on drug sales. In HICs, a recent review describes a range of highly heterogeneous findings for responsible use interventions in primary care.[18] For example, some educational programmes targeting prescribers have been demonstrably effective in research settings but have failed to show a decrease in antibiotic prescribing when applied at scale in real-world situations. Stewardship campaigns focusing on ambulatory and primary care prescribing behaviour have shown modest success on prescription rates.[19-22] Most campaigns show around 10% reductions in prescriptions and appear effective only in the short-run.[23,24] Multi-faceted campaigns that target both prescribers and consumers appear to yield better results than more narrowly designed interventions.[25] Amongst the most promising policy options in primary care is "backup/ delayed prescribing" which describes interventions that create a delay for patients between prescription and the collection of antimicrobials for infections. These have been shown to be effective in reducing antibiotic use, without increasing morbidity or affecting patient outcomes.[18,22,26, 27]

Hospital-based stewardship policies appear to have been better evaluated than those at community or national levels. The development and implementation of clinical antibiotic prescribing guidelines in secondary care provides the most compelling evidence of effectiveness with studies showing drops in prescribing of up to 80% for certain drug classes.[18] A recent systematic review of interventions to support such implementation identified 89 studies across 19 countries and compared both persuasive and restrictive methods designed to improve hospital antibiotic prescribing practice. Persuasive methods advised physicians on how to best prescribe or gave them feedback. Restrictive methods limited how they prescribed (e.g. requiring approval from infection specialists in order to prescribe antibiotics). The studies showed that both methods changed prescribing habits and several also demonstrated a decreased number of hospital infections. The restrictive methods appeared to have a longer effect than persuasive methods up to 6 months post-intervention. However, the authors graded much of the evidence on effectiveness as 'poor' or 'very poor' and noted a paucity of robust cost-effectiveness analyses across the identified studies. Advocating these methods in resource-constrained settings with limited regulatory capacity is problematic and not without the significant risk of compromising expenditure on other critical aspects of healthcare delivery. [28]

While there is some evidence of the effectiveness of responsible use policies aimed at curbing excess use in publicly funded healthcare systems, evidence from private sector is notably lacking.[29] In areas of the world such as South Asia, where 80% of patients seek care in the private healthcare system, evaluating policies to regulate or modulate antimicrobial use is urgently needed. **Case study 1** illustrates the challenges that patients and their physicians routinely face when AMR control policies fail to adequately engage with the private healthcare sector.

Responsible use and public awareness

There remains a considerable gap in the public's knowledge of both appropriate antibiotic use and the causes of AMR, with levels of awareness and understanding varying significantly across countries.[30] Many patients believe antibiotics cure viral infections, do not understand the basic mechanisms of AMR[30-32] and regularly self-medicate with left-over antibiotics.[33, 34]

There has been a noticeable increase in information campaigns.[3,35] aimed at improving knowledge on appropriate usage and at reducing antibiotic consumption by influencing demand.[36,37,23] A campaign's success also depends on social, cultural and geographical factors, as well as existing barriers to prescribing.[38,39] Since 2008, European public AMR awareness-raising activities have largely centred around the introduction of a European Antibiotic Awareness Day (EAAD).[40] Similar campaigns have also been conducted outside of Europe.[41,42] Most campaigns aim to provide patient information (leaflets, posters), or through mass media communication such as billboards or adverts.[23] Since the majority of antibiotics are prescribed in primary care, many campaigns focus on information about infections common in this context, such as respiratory tract infections.[43]

Campaigns such as the EAAD have received widespread and continued support from participating countries; however, their effect on AMR, antibiotic consumption and prescribing is difficult to evaluate.[3, 34] Effects will be dispersed and may be very small, and few interventions have been examined in terms of cost-effectiveness.[3, 23] It is not clear when awareness translates into lower rates of antibiotic prescriptions. Improvements in adherence to antibiotic treatment regimens are hard to measure, particularly for prescriptions in ambulatory care where intake is not supervised.[44] Moreover, comparative assessments of the effectiveness of public awareness campaigns are problematic as different countries use varying parameters for evaluations and for measuring antibiotic use e.g. Defined Daily Doses (DDD) or number of packages prescribed per 1,000 inhabitants/day.[45] An evaluation of EAAD effectiveness in the UK for instance concluded that the campaign had only led to a minimal increase in public awareness, with no observable reduction in antibiotic use.[46] However, long-running campaigns, especially in Australia and France, have been associated with modest but consistent improvements in consumer awareness, as well as a reduction in antibiotic prescribing..[47, 24] What has proved to be particularly challenging is communicating the differences between bacterial and viral infections.[30, 48]

Case study 1: The physican and patient perspective – how failure to engage the private sector in AMR control can impact health

A 43-year old male patient with a past history of tuberculosis infection presented at a tertiary care centre in Karachi, Pakistan, with a one-month history of hemoptysis, fever and weight loss. Though microscopy of broncho-alveolar lavage (BAL) for acid-fast bacilli (AFB) and Line Probe Assay (Hain Genotype MTBDRplus) were both negative, the patientwas started on a treatment regimen on the basis of radiological abnormalities. The BAL culture was later identified as multidrug resistant *M. tuberculosis* (MDR-TB) including resistance to quinolones. No source for the patient's MDR-TB could be identified. However, two years earlier he had been treated for a tuberculous pleural effusion. He had been compliant with his treatment but had procured medicines from the market privately.

The patient was commenced on second line therapy with Kanamycin, Moxifloxacin, Ethionamide, Cycloserine and Pyrazinamide.. Whilst initial improvement was noted in his clinical condition over the ensuing three months, he subsequently began to deteriorate. A chest x-ray revealed increased infiltrates in the left upper lobe. Sputum culture and sensitivity testing showed the pathogen was now resistant to all first and second line agents; the patient had Extensively Drug Resistant Tuberculosis (XDR-TB) sensitive only to Linezolid. Treatment was changed to a XDR-TB regimen including; Capreomycin, Linezolid, Moxifloxacin, Amoxicillin-clavulanate, Clarithromycin, Ethionamide, Pyrazinamide, Cycloserine and PAS. The patient improved and his chest x-ray showed disease localization to the left upper lobe. *M.tuberculosis* culture and smear after six months' of treatment were negative. In view of emerging evidence supporting surgical resection as complementing chemotherapy for localized MDR-/XDR disease[49, 50] the patient was referred for surgery. Unfortunately, surgery could not be performed due to limited operating room capacity for handling such infectious cases. The patient was continued on the XDR-TB regimen and at has remained smear and culture negative.

Policy efforts to respond

The private TB drug market in Pakistan, as in several high burden countries, is considerable – and mostly unregulated. Antimicrobials (including both first and second line anti TB agents) are easily available over the counter. Lack of controls and checks on the quality of medicines being sold results in the supply of substandard agents.[51-53] A recent multi-country study found that in neighbouring India, 10.1% of first-line Isoniazid and Rifampicin samples tested were substandard.[54]

While a number of factors are likely to contribute to the reported increase in number of XDR-TB cases from Pakistan[55] poor quality of TB drugs and inappropriate prescription have a significant role in driving resistance. For example, both Pakistan and India have reported increasing quinolone resistance.[56, 57] Frequent use of quinolones for suspected infections (including respiratory infections) significantly contributes to such increase.[58] Despite quality-assured drugs being supplied to the public sector through initiatives such as the Green Light Committee (GLC) for MDR-TB at concessionary prices for second line drugs for MDR-TB treatment[59] , the considerable private sector is simply not engaged with. [60, 61] The National Tuberculosis Control Programme of Pakistan has made significant strides towards disease control and is now expanding its engagement with the private healthcare sector. Drugs-for-performance agreements have been successfully applied in several public-private partnerships, as well as incentive based schemes to improve early case detection and encourage the reporting of suspected cases and improve surveillance coverage.[29] These efforts require further support and would be enhanced by legislation making tuberculosis a notifiable disease in Pakistan. The Chennai Declaration, a five-year plan to tackle antibiotic resistance in India[62] may provide a blueprint for other countries in the region including Pakistan to adapt and adopt if demonstrated to be effective.

Responsible use through structural reform and strengthened healthcare systems

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

In Australia, the commendable success of reducing primary care use of fluoroquinolones, has been attributed to a policy of strong government regulation including a narrowed list of indications for quinolones through its national pharmaceutical subsidy scheme. Despite several years of preceding educational initiatives, no significant impact had been made on reducing usage but following introduction of the narrowed list and removal of the subsidy, quinolone usage dropped by 30% in the 1994-1995 period. Researchers, recognize that the policy to withdraw public subsidies was effective, in part, because of the high underlying price of quinolones in Australia – underlining the importance of understanding the national context of such policy successes.[12]

In China, antibiotics are substantially overprescribed as drug sales revenue constitutes a major proportion of healthcare providers' incomes.[63] In response to increasing AMR, China's first explicit attempt to rationalize antibiotic use came in the shape of national hospital guidelines (2004)[64] and a concurrently launched containment policy, which sought to ban the sale of antibiotics to patients without prescription.[65] The effectiveness of these policy measures was not systematically evaluated, and weak enforcement is likely to have limited their impact. [66] Further measures introduced in recent years include the establishment of a national taskforce to rationalise clinical use (2011), and new clinical regulations (2012) [67] for hospitals that define best practice and impose legal penalties for violations.[68] Policy enforcement is key and the experience in China (**case study 2)** suggests that strengthening the healthcare system is a pre-requisite: in this case, it involves the realignment of economic incentives by de-linking monetary compensation for prescribers from antibiotic sales.

Strengthening national drug regulatory authorities may also have a role to play in monitoring the promotional activities of antimicrobial drug companies as well as ensuring their quality by limiting the proliferation of substandard and counterfeit antimicrobials. The pharmaceutical industry is known in some settings to pressurize both patients and doctors: patients through intense marketing campaigns[76] and doctors through bribery.[69] Well-publicised criminal investigations of irresponsible sales practices of GlaxoSmithKline in China and Poland, for example, demonstrate a policy shift towards the pharmaceutical industry more generally, by national authorities.[70, 71] In recognition of the threat posed by counterfeits and substandard drugs in particular, the Indian government has adopted increasingly stringent sanctions on pharmaceutical producers and traders including possible life imprisonment.[72] The impact of these more robust regulatory policies on marketing and sale of all drugs, including antimicrobials, remains to be assessed.

Case study 2: Antibiotic Prescription in China: Systemic and Contextual Drivers

In China, the prevalence of antibiotic use is very high.[63] In 2007, an estimated 90,000 tons of antibiotics were used in humans.[73] The Ministry of Health (MoH) set up the National Healthcare Associated Infection Surveillance System (NHAISS) in 2001 to monitor antibiotic usage in hospitals,[74] and the MoH National Antibacterial Resistance Investigation Net (Mohnarin) in 2004 to detect and monitor antibiotic resistance.[75] Even though NHAISS's data suggest that the prevalence of antimicrobial use in hospitals in China has decreased from 54.79% in 2001 to 46.64% in 2010,[74] Mohnarin's data show that the prevalence of resistant bacteria (over 40%), particularly hospital-associated pathogens (over 60% for MRSA and ESBL (+) *E.* coli) remained high during the period between 2000 and 2011.[75]

Perverse financial incentives that stem from the fee-for-service payment model adopted by state-owned healthcare providers are a primary driver for overprescribing of drugs.[76] As such, the national rural social insurance scheme has inadvertently led to the overprescribing of antibiotics in those who are covered, by lowering financial barriers to accessing healthcare.[77] Subsequent trial modifications within the scheme have demonstrated that changing the payment model from fee-for-service to a capitated budget with pay-for-performance was effective in reducing inappropriate and overprescribing of antibiotics.[78]

Without altering the overall financing model of healthcare, overprescribing is likely to persist. Financing of state-owned healthcare providers in China relies very heavily on the revenue of pharmaceutical sales (a government-granted 15% mark-up is applied to the procurement price of a pharmaceutical product);[79] as a result, a doctor's salary is typically linked with the volume and financial value of the drugs and services they provide. Recognising the need to delink doctors' salaries and hospital incomes from prescribing practices, the MoH launched the National Essential Medicines Policy (NEMP) in 2009 (its full implementation is limited to primary care). A key element of the NEMP is a zero mark-up policy whereby essential medicines are sold at procurement price plus a fixed distribution cost, leaving no profit margin for healthcare providers.[80] Instead, financial subsidy is provided by government to healthcare providers to encourage greater and more rational use of essential medicines.[81] Apart from eliminating financial incentives, the NEMP aims to rationalise prescription from other angles, including improving drug quality and accessibility to patients, and responding to regional requirements for specific drugs. However, currently available studies find mixed evidence for the impact of NEMP on antibiotic prescription in primary care: despite some potential improvements, overuse and irrational use of antibiotics remains a prevalent problem.[82-85]

Responsible use in the animal sector

AMR in animals represents a significant problem for human health[86-88] and the emergence of multidrug resistant bacterial strains and strains resistant to antimicrobials considered critically important in human medicine is of concern.[89-91] Bacteria hosted by animals can reach humans through direct contact, food and/or the environment.[92] Non-therapeutic use of antimicrobials in animals for growth promotion has been associated with high levels of AMR in the animal reservoir. This situation has occurred in many countries and is well-documented. [84,93,94] In many countries different stakeholders argued against banning antimicrobial grown promoter (AGP) use, often referring to a suggested negative economic and animal health effect. [95] However, other economic incentives still continue to affect the over-use of antimicrobials in most countries. To remove the economic incentives for antimicrobial overuse by veterinarians, some governments have legislated to reduce veterinarian profit from direct antimicrobial sales. In Denmark (1994), such interventions resulted in a 40% reduction in total use of antimicrobials, and a reduction in tetracycline use from 37 to 9 tons between 1994-5.[96] To compensate veterinarians for income loss from reduced antimicrobial sales, new advisory roles were created, e.g. providing technical support to farmers on improving animal health and biosecurity without antimicrobials. For big livestock holdings, monthly veterinary consultations were made mandatory. These actions seem to have resulted in more efficient and cost-effective management systems (**case study 3**).

Dutch initiatives have also resulted in reductions in animal antimicrobial use (56% between 2007 and 2012). Critical to the Dutch plan were: a Memorandum of Understanding between the animal sectors and the Dutch Association for Veterinarians (2008); a mandatory antimicrobial reduction regime implemented by government demanding a reduction of 70% by 2015 (compared to 2009 levels); introduction of farm health and treatment plans with specified antibiotics; and prohibition of use of new antibiotics.[97]

In many LMICs, the post-colonial era has brought changes in livestock/meat production industries, with significant shifts in land holdings and usage. A mix of large producers and smallholders often operate in parallel, with poorer communities moving from subsistence to cash-based economies. Loss of economies of scale have resulted in big drug suppliers moving to fewer regional centres, with ad hoc traders filling the vacuum; at the same time increasing numbers of cheap generic drugs have become available.[98] While improving smallholders' access to drugs, these factors have compromised the quality and range of products available in environments with weak regulation, licensing delays, cash flow problems and distribution difficulties. Surveys on antimicrobial usage in the animal sector in LMICs are patchy but indicate a proliferation of abuse and a high level of farmer-prescription, with around a third of countries allowing antibiotics over the counter.[99, 100] Furthermore, many livestock owners engage unskilled people to treat animals, resulting in sub-optimal dosing, incorrect administration, arbitrary drug combinations and non-observance of withdrawal periods.[101-104] Novel stewardship interventions began in the 1990s, with experiments 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.[105, 106]

Case study 3: Limiting antibiotic use in the animal sector- the policy evidence from Denmark

AGPs for animals were introduced and promoted by the drug industry, and generally accepted in animal husbandry for many years. Although some scientists at an early stage postulated that AGP use could lead to antimicrobial resistance in microorganisms which could then spread to humans,[107] the issue has remained contentious, with limited evidence available to quantify the increased risk of AMR spreading to humans from use in animals. One of the main reasons for this uncertainty is the complexity of evaluating the relative importance of different transmission routes from animals to humans, especially through food.

Despite accumulating evidence showing that AMR bacteria from farms resulted in human health problems, the level to which this was due to AGP and agricultural antimicrobial use in general remained debatable.[108] As early as 1969, the Swann Commission in the U.K. recommended that antimicrobials should not be used as AGP when they were used as therapeutic agents in human or animal medicine, or when associated with the development of cross-resistance to antimicrobials used in people.[107] This led to a ban of all use of AGP in food-animals if these antimicrobials were also important for therapeutic use in humans - first in the UK, and subsequently in the EU. The action was enforced on individual antimicrobials, but did not consider the chemical analogues of these drugs. Therefore, the use of antimicrobial analogues as AGP in Europe essentially allowed for the continued selection of cross-resistance to human therapeutic drugs.

It was several decades after the publication of the Swann Report before serious concerns around AGPs arose again. In Sweden, AGP use was banned in 1985, however, no scientific documentation, including baseline studies related to this ban have been published. In Denmark, concern was heightened by new findings regarding Avoparcin use as an AGP. Avoparcin is a chemical analogue to Vancomycin, an important human antimicrobial. A survey in 1995 revealed the first evidence that Avoparcin leads to the emergence of AMR; researchers found Vancomycin-resistant *Enterococcus* bacteria (VRE) in 80% of the chickens from conventional (Avoparcin using) farms, whereas none were found in chickens from organic farms.[109,110] In humans, a similar increase in VRE bacteria was seen, which could either be due to Vancomycin use in humans, or to human consumption of contaminated meat.[110, 111] Based on the relatively limited data presented, Danish farmer organizations agreed to a voluntary withdrawal of Avoparcin use in chickens (leading to a drop in VRE in chickens to <5% by 1998). In addition, the new Ministry of Food, Agriculture and Fisheries became responsible for managing the farm-to-fork chain, alongside the Ministry of Health, and initiated the integrated surveillance program, DANMAP. Based on the data from this surveillance program, further decisions were taken to reduce and eventually ban the use of AGP in Danish agriculture in 1998. In 2003, the EU decided to phase out all use of AGPs by 2006.[112] Neither the Danish nor the EU bans seem to have affected agricultural productivity negatively and Danish data for national pork production, documents a significant increase in the number of pigs produced from 1998 to 2011 (23 to 30 million pigs annually).[95]

Although many LMIC veterinary authorities have adopted international standards and regulations on drug use designed to facilitate control of AMR, the capacity to implement these guidelines is lacking.[113] Some NGOs have provided a middle ground in capacity building, education and facilitation of improved stewardship in LMICs and report improvements in both veterinary and para-veterinary sectors.[105,106,113,114] The majority of these programmes are limited in scope, however, and have not been robustly evaluated.

Raising awareness in the animal sector

In the animal sector there is limited evidence of the effectiveness of awareness-raising policy initiatives changing prescribing behaviour by veterinarians or varying antimicrobial use by livestock farmers in the absence of strong central regulation. In America, where lobby groups can exert significant influence over law and policymakers, an increasingly coordinated awareness raising drive both amongst the public and healthcare associations contributed to the introduction of the Preservation of Antibiotics for Medical Treatment Act (2013) bill to Congress. [115] The bill which would mandate introducing regulations to curb antibiotic use in animals, appears to have stalled in the Senate with fierce opposition from industry groups.[116, 117] Consequently, there is despondency over the bill's potential to strengthen the regulatory framework needed to curb excess use, with some analysts estimating a minimal likelihood of it being enacted.[118]In the latest salvo in this ongoing debate, a new bill has been introduced that would require the Federal Drug Administration to withdraw product approval for antimicrobial use in animals, if a drug maker cannot demonstrate that its antibiotic poses no risk to human health.[119] The growing public awareness around the debate appears to have influenced food retailer and consumer demand too, with McDonald's recently announcing it will phase out the use of chicken raised with antibiotics important to human health – thus pressurising competitors to follow suit.[120]

In LMICs, a lack of awareness amongst farmers is high, with one study conducted in Tanzania showing that while most livestock keepers were using antibiotics to treat their animals with some observing a withdrawal period prior to slaughter, approximately 40% were not aware of any related possible human health threats.[121] Well-evaluated policy initiatives aimed at raising awareness in the animal sector are conspicuous by their absence, reinforcing a continuing theme of poor evidence from LMICs.

Infection prevention and control

In human healthcare settings

Infection prevention and control interventions (IPCI) can minimize the spread of pathogens, including those that are resistant, decrease the likelihood of infection in healthcare settings and reduce the overall need for antimicrobial use.[122,123] Controlled clinical studies as well as international benchmarking of infection control practices and AMR infection rates have provided valuable information for advocacy and established a minimum set of evidence-based practices for control of epidemic or endemic AMR pathogens in different healthcare settings.[124] In particular, it is now established that hand hygiene is the most effective measure to prevent transmission of resistant bacteria during healthcare delivery, as shown in the successful control of MRSA through national campaigns to improve hand hygiene compliance.[125,126] The implementation of WHO's hand-hygiene strategy is feasible and sustainable across a range of settings in different countries and leads to significant compliance improvement.[127]

To be sustainable, IPCIs must target routine care practices, environmental reservoirs and be adapted to local priorities.[128] Accordingly, the WHO proposed a core concept of IPCI elements (hand hygiene, environmental cleaning, disinfection and sterilization, education of staff) for healthcare facilities, and encourages national authorities to ensure application. Implementation remains challenging in LMICs, with frequent lack of access to even basic IPCI mechanisms resulting in a weak evidence base to support their introduction into LMIC healthcare settings.[129-131]

IPCI in the community

Reducing the burden of infections (both incidence and transmission) and subsequent need for antibiotics must therefore be a prime focus, by promoting hand hygiene with soap, improving access to clean water and sanitation, vaccines (e.g. pneumococcal, cholera, typhoid fever) and more disease-specific measures such as reducing sexually transmitted infections through condom use.[132-135] Conversely, other interventions may exacerbate resistance, such as the large-scale use of azithromycin for yaws eradication potentially affecting resistance in other treponemes.[136] Several studies have shown significant reduction in resistant *S. pneumoniae* following the introduction of multivalent pneumococcal conjugate childhood vaccines, both in the vaccinated and the general population (through herd immunity).[137-139] The integration of vaccination programmes into broader AMR control strategies remains an under-evaluated policy intervention, with global initiatives operating mostly separately. Encouragingly, financing for evidence-based IPCI has increased and collaborations are now operational worldwide through local, national, regional and international networks (see **table 3**).

Table 3: Selected examples of successful global infection prevention initiatives

Infection prevention initiative	Reference
The 'Clean Care Is Safer Care' campaign by WHO focuses on hand hygiene compliance among health care workers. Since its inception in 2005, 134 WHO Member States and autonomous areas have participated in this initiative, reaching 9 million healthcare workers and more than 17 000 health-care facilities have committed to improve hand hygiene.	140
The GAVI Alliance finances vaccines and, to some extent, immunization services in developing countries, those with a gross national income per capita (according to the World Bank) below or equal to USD 1,570 (as of 2014). GAVI's vaccine portfolio includes several vaccines for illnesses that would otherwise be treated with antibiotics (pneumococci, *Haemophilus influenzae* and rotavirus (since diarrhoea is often inappropriately treated with antibiotics rather than oral rehydration salts and zinc).	141
The Global Fund Against AIDS, Tuberculosis and Malaria has financed the purchase of more than 310 million long-lasting insecticidal mosquito nets, to combat malaria and indirectly reduce the risk of emergence and spread of resistant malaria.	142
The World Bank through its Water Partnership Program has allocated USD 24 million to improve the quality of drinking water and sanitation services in low-income countries with additional funding being allocated through the next phase of the program.	143
UNFPA procures and distributes condoms (both male and female types) in developing countries as well as actively promotes other practices (e.g. male circumcision) to limit sexually transmitted diseases of bacterial origin, particularly drug-resistant gonorrhoea.	144

IPCI in animals

Effective IPCIs in the animal sector provide some notable examples. Policies encouraging the adoption of 'All-in-All-Out' farming systems (i.e. production systems whereby animals are moved into and out of facilities in distinct groups, preventing co-mingling and with facilities normally being cleaned between animal groupings) and reformulation of animal diets have been effective in reducing antibiotic consumption while maintaining livestock growth rates.[145-147]

Successes in LMIC settings include the widespread adoption of the infection-treatment immunization method for East Coast Fever control in East African cattle. The technique, based on injecting cattle with partially attenuated sporozoites of *Theileria parva* concurrently with long-acting oxytetracycline, has proved effective over several decades in preventing infections, with no known contribution to the AMR burden.[148]

In aquaculture too, the remarkable success demonstrated by countries such as Norway in reducing antibiotic use through vaccination programmes are well-described. However, developing policies to progress these limited national successes to other countries has been slow.[149] The tripartite agreement between WHO-OIE-FAO (World Organization for Animal Health and UN's Food and Agriculture Organization, respectively) has piloted several One Health projects to do this[150] Despite some successes, it is clear that there is chronic under-investment in IPCIs in the animal sector. The

World Bank estimates the funding needed for 60 low-income and 79 middle-income countries to bring their animal infection prevention and control systems up to OIE/WHO standards ranges from US$1.9 billion to US$3.4 billion per annum.[151] Funding agencies have thus recently begun to apportion more spending to 'One Health' initiatives, but the global effects of this policy shift in funding AMR control specifically remains to be evaluated.[152, 153]

Surveillance

Surveillance of antibiotic use and resistance in humans

Surveillance of antibiotic use and resistance is a cornerstone of efforts to control AMR.[154] The 2001 WHO Global Strategy[88] embedded surveillance of resistance, monitoring of antimicrobial usage and disease burden as key components. Between-country comparisons can be a major political driver for change and increased focus as shown in the European experience with the EARSS and ESAC networks thereby functioning also as accountability measures for countries.[155, 156] The success of the two systems has seen the WHO Regional Office for Europe expand use of the ESAC-Net method to cover 14 additional countries in Europe.[157] Moreover, several countries within Europe (e.g. France, Scotland, UK) and outside Europe (e.g. South Korea, Turkey) have now successfully implemented governmental targets based on public reporting of surveillance data. [158 ,159]

Despite their obvious importance, most international surveillance systems outside of Europe have not been formally evaluated in terms of validity, sustainability and long-term impact on antibiotic resistance. The evidence base to determine the most cost-effective systems for surveillance of antibiotic use and resistance remain weak worldwide. Policymakers in all settings need help deciding on the most efficient surveillance systems to maximise limited resources; should countries invest in systems of continuous ongoing surveillance of all healthcare settings or can sufficient data be gathered with more limited sentinel surveillance or periodic prevalence studies? [160]

For monitoring antibiotic use, there is debate about the best indicators in different settings, and the value of aggregate-level versus individual patient-level information for guiding stewardship strategies; aggregated consumption data do not allow evaluation of the quality and adequacy of individual prescribing decisions, although they provide measurable estimates of trends for benchmarking.[161] Several experts and policy makers suggest point-prevalence surveys of antibiotic use as a simple method to solve these issues.[162]

Unsurprisingly, there are significant differences between surveillance system needs due to varying cultures, seasonal practices and population dynamics (**case study 4**). 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 monitoring antibiotic use and resistance.[163,164]

Case study 4: New regions of collaboration; Developing a policy framework for AMR control in a region of exceptional Human, Animal and Microbiome mix and flux

The Gulf Cooperation Council (GCC) is a regional grouping of six high-income Arab states; Saudi Arabia, Oman, UAE, Kuwait, Qatar, and Bahrain. As populations have grown, so too have health budget allocations, and vast sums are expended on public and private sector health facilities. However, health and information systems directly affecting surveillance are lagging behind. A recent WHO report has indicated that, despite legislation, monitoring and evaluation of data remains weak; the EMRO region's AMR surveillance systems, including WHONET, and the GFN (Global Foodborne infections Network), have functioned poorly since they began in 2005.[165 ,166]

SURVEILLANCE CHALLENGES

Published reviews have highlighted the growing threat posed by AMR in the GCC; frequently linked to lax regulation and inappropriate usage of antimicrobials.[167, 168] To better understand the extent of the threat, surveillance is essential. However, there are several challenges to improving surveillance in the region. First, a lack of standardised data collection on health indicators is compounded by the presence of over 21 million foreign migrant workers, who constitute 45% of the resident GCC population but mostly remain outside the health indicator data for the region. Second, the region has significant transitory population flux (tourists, transit passengers and migrant workers) with its associated microbiome. Also, unique to the region is the annual Hajj gathering in Saudi Arabia, of up to 3 million pilgrims from every country of the world, over a 3-4 week period.[169] The size and variety of the microbial biomass that gets transported, mixed and re-distributed on such a massive scale is beyond the capacity of any available system to assay and track the AMR organisms. Mass movement of microbes in the GCC is also linked to the industrialization of food production. Together the GCC countries import $25.8 billion worth of the estimated total estimated $1 trillion global *Halal* meat market annually. While the microbial carriage rate in imported livestock or frozen poultry and meat remains undocumented, reports on fresh chicken and meat in local markets show a significant rate of microbial contamination with multi-drug resistant bacterial isolates.[170,171]

There is also a significant live animal trade in the region. Livestock are imported to feed growing populations and for sacrificial purposes at events such as the Hajj. The GCC accounts for 70% of Australia's live sheep exports. While the application of laws generally remains weak, enforcement is gradually improving with the GCC livestock quarantine Law no 8 (2003) first applied notably in 2012 to prevent a shipload of sick and dead Australian sheep arriving at any GCC ports. An example of an effective policy designed to maintain import standards while not adversely impacting exporting countries, is the public-private partnership of Saudi investors with Somalia. The partnership established quarantine facilities in Somalia, a major exporter of livestock to the region. Consequently, Somalia's ports now operate under international standards and enable disease-free exports of animals to a wider market, while adding value to the trade by providing ancillary services and increased employment in Somalia.[172] New regulatory measures in this sector are now emerging that will improve disease detection in animal and food products; Dubai has set up the International Center for Halal Food and Product accreditation. Surveillance testing of drug-resistant microbial contamination could easily be incorporated within these existing regulatory measures.

To tackle AMR more broadly, a series of collaborative solutions were proposed following the 2013 World Innovation Summit for Health (WISH), supported by the Qatar Foundation, including strengthening the role of the GCC Center for Infection Control in the development and implementation of policy and procedures for regional AMR control and prevention.[173] These efforts are expanding and gathering pace in more GCC settings through the WISH forum. A pan-GCC approach to AMR surveillance is thus feasible; to date, regional collaboration on health regulations has encouraged GCC countries to adopt several unified policies, including a 'group purchasing tenders' system to meet their pharmaceutical needs. Designed primarily to reduce costs, the system can also be used to ensure quality standards for antimicrobials, monitor usage and demonstrates that successful between-country collaboration is possible.

The absence of a global AMR surveillance system to provide reliable and validated AMR data from all continents results in significant knowledge gaps. Although several regional /national surveillance networks have been successfully established during the last two decades, most relate to HICs or specific pathogens (e.g. Global Foodborne Infections Network for foodborne pathogens, *Salmonella* spp and *Campylobacter* spp; WHO's Gonococcal Antimicrobial Surveillance Programme). Most AMR networks do not have sufficient resources to standardise and quality-assure diagnostic methods for detection of resistance, and data are often not systematically collected or geographically representative. Hence, they have limited effectiveness as early/rapid warning systems or in monitoring emerging AMR trends. To facilitate timely coordinated containment action at the global level, the WHO's International Health Regulations could provide the legal framework for early detection and outbreak control of emerging pan-resistant bacteria.[174]

It has been suggested that laboratory and epidemiological surveillance should become part of a simple road-map where an agreed minimum dataset could be shared internationally.[175] This goal is challenging. Many healthcare facilities (particularly in the private sector) are reluctant to share AMR data, wary of reputational damage. Similarly, at a national level, widespread information about AMR is thought to negatively impact on exports and medical tourism.[176] This indicates that contributing data to both national and international surveillance may need to be mandated to be effective. Additionally, in LMICs there is a paucity of laboratories with the capacity to perform quality-assured microbiology and drug sensitivity testing.[177-180] Vertical programs have been able to generate resources to overcome some of these obstacles and to provide infrastructural support for drug resistance surveys in a number of countries, but these are restricted to a few diseases.[181-183] Wider efforts to improve quality are linked to quality assurance and accreditation programs and some notable successes have been achieved in Africa.[182-184]

Table 2 summarizes important international, publicly-funded, voluntary surveillance systems of AMR pathogens, highlighting specific strengths and weaknesses. Notable is the widely distributed WHONET software for local laboratory support and standardized AMR reporting. Despite its 25-year history, this tool has not been fully exploited nor upgraded for collaborative, international surveillance of AMR, despite early promises and a few significant exceptions.[185, 186] (361)

Table 2: Strengths and weaknesses of large-scale, international public AMR reporting and surveillance systems of AMR in humans

Name / Organisation	**Coverage**	**Strengths**	**Weaknesses**
WHONET (WHO)	Worldwide (110 countries)	Standardized laboratory software support and AMR reporting tool, helping to monitor and manage AMR locally and regionally	Underused for global AMR surveillance and policy making Lacking commitment to upgrade software tool to gather AMR data
EARS-net (E-CDC)	Europe (29 countries)	Surveillance of invasive infections caused by AMR pathogens Large-scale implementation throughout Europe	Not real-time, not used as early warning system of emerging and novel AMR trends and pathogens Geographic variation in validity and representativeness of data
CAESAR (WHO/Europe)	Eastern Europe and Central Asia (13 non-EARS-net countries of the WHO European Region)	Setup of national AMR surveillance compatible to EARS-Net so that an overview can be obtained for the entire European region	Many non-EU countries lack routine surveillance capacities on which AMR surveillance has to be built
ReLAVRA (PAHO)	Americas (21 countries)	Analyses susceptibility data from all isolates at country level and collates the data from participating countries. Provides support for local interventions to contain AMR Ensures continuous quality improvement	Lack of resources and local commitment in some countries. Missing clinical information.

Integrated Disease Surveillance and Response (CDC)	Africa (43 countries)	Strengthens the capacity of African countries to conduct effective surveillance activities Uses data thresholds to trigger epidemiological investigations	Includes few pathogens only, not focused on AMR
Global Emerging Infections Surveillance and Response System (GEIS)	Worldwide (>30 countries)	Develops, implements, supports and evaluates an integrated open access system for timely, actionable and comprehensive health surveillance information for antimicrobial resistance, gastrointestinal infections, febrile and vector-borne infections, respiratory infections and sexually transmitted infections	Coverage limited to host nations supported by the US military
Worldwide Antimalarial Resistance Network (WWARN)	Worldwide	Provides high-quality data resources, customised research tools and services, and a global platform for exchanging scientific and public health information on malaria drug resistance	African regional networks to monitor emerging resistance failed to attract sustainable funding.
Gonorrhoea Antimicrobial Surveillance Programme (GASP) in the Western Pacific, South-East Asia, Europe, South America and the Caribbean	Worldwide	Advocates and collate data on gonococcal resistance in different regions of the world	Lacks financial and political commitment from countries, WHO and donors. No real time, geographically representative data to inform treatment strategies in all regions.
The Global Antibiotic Resistance Partnership (GARP)	India Kenya South Africa Vietnam Mozambique Nepal Tanzania Uganda	Network of institutes working on antibiotic resistance in low-income and middle-income countries.	Data manly collected from large academic centres.
Alliance for the Prudent Use of Antibiotics (APUA)	66 countries in Africa, Asia, and Latin America	Conducts large-scale national and international research and educational projects to control and monitor antibiotic resistance	Scattered activities in multiple countries.

Surveillance in animals and the environment

To optimize the use of surveillance data for public health action, comparative data are needed from national, regional and global levels.[187] The OIE has determined that 111 (73%) of 178 member countries have no official system for collecting data on antimicrobial use in animals. In Africa and the Americas this percentage rises to 95% and 96% of countries respectively. Significantly, in policy terms, 35% of these countries still have no official plans to establish national surveillance and monitoring systems on antimicrobial use in animals.[188]

One of the first national integrated animal (and human) surveillance programs was initiated in Denmark in 1996 (the Danish Integrated Antimicrobial Resistance Monitoring and Research Program, DANMAP) as a collaboration between commercial and public stakeholders, and human, food and animal health sectors working in the farm-to-fork food chain.[189] Through DANMAP, the VetStat database was initiated to monitor antimicrobial use at the single farm level and was instrumental in creating the Danish 'Yellow Card' system – a national antimicrobial monitoring and reduction tool introduced in 2010. Individual farmers and veterinarians with exceptionally high antimicrobial use now receive a yellow card, followed by a series of injunctions if usage is not reduced within given time limits. The initiative has resulted in year-to-year reductions in total antimicrobial use in animals of up to 20%.[190] In the EU, several other countries collect similar datasets, thus enabling between-country comparisons of antimicrobial use.[191] The European Medicines Agency (EMA) in 2009 launched ESVAC (European Surveillance of Veterinary Antimicrobial Consumption), which now monitors animal use of antimicrobials in 25 countries through sales data.[192]

In LMICs there are a few, mostly cross-sectional studies on antimicrobial resistance in isolates from animals or animal products in the food chain. For example, *Salmonella* resistance was detected in over 79% of isolates from an abattoir study in Kenya, but studies done on AMR in human patients did not confirm a link.[193] Almost no longitudinal studies or surveillance systems are functioning, few countries have adopted WHONET[194] and the OIE Standard and Codex Alimentarius Guidelines are not yet 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.[180, 195]

In recent years, studies have highlighted the presence of AMR in environmental bacterial samples. These suggest a risk of AMR spreading from hospital and pharmaceutical effluent, as well as from sewage systems and water treatment plants. Slurry from livestock farms has also been implicated.[196, 197] Developing sentinel AMR surveillance and sampling systems for higher 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.

Insufficient evidence base

Our analysis demonstrates that lack of progress on combatting AMR is partly due to an insufficient or poor evidence base for the effectiveness of the myriad policies already existing across the human and animal sectors in both HICs and LMICs. Even where policies have demonstrated benefits in reducing antimicrobial use or impacting resistance, robust policy evaluations have been lacking, with little available information on cost-effectiveness, and inadequate descriptions of the technical, political and regulatory environment necessary for implementation (see table 3). For example, developing a strategy to translate the success of Scandinavian countries in limiting antibiotic use in livestock rearing - while maintaining meat production and profits in LMICs (or other HICs) remains problematic. Without significant European Union subsidies, many livestock farmers in the region would be unable to operate profitably. The generalisability of demonstrably effective policies therefore remains a significant challenge. However, this cannot be an excuse for a continued lack of coordination in policy development.

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 interventions applied in secondary care settings, including the implementation of clinical guidelines and those targeting prescribing behaviour, but the potential total impact will be higher in community settings thereby indicating the need for more rigorous studies. In community settings back up/delayed prescribing has been shown to be effective, as are policies providing alternative appropriate prescribing options to antibiotics. Awareness-raising campaigns can also be effective when sustained, but should be implemented with caution particularly in LMICs, where the cost and impact of such campaigns needs better evaluation. In the animal sector, evidence from HICs suggests that curbing antibiotic use as growth promoters can reduce AMR. However, bans or other policy measures to achieve this must be coupled with adequate investment in improved IPCI for livestock, and effective mechanisms for remunerating veterinarians/veterinary officers and re-orienting their roles.

Arguably, the greatest potential impact globally on reducing the demand and need for antimicrobials comes from IPCIs, including vaccinations, hand washing, and improved access to water and sanitation. Where possible, collaborations should continue, with a focus on promoting IPCI in LMICs, which often lag behind in this area.[198] AMR strategies must thus look for opportunities to integrate their activities and goals into these closely related development sectors.

A move to increase implementation of effective responsible use interventions and IPCIs globally could be linked to a simultaneous push for improved resistance surveillance and antimicrobial use monitoring data, thereby securing accountability. Countries reporting emerging drug resistance levels or high antimicrobial usage should be offered financial and technical support for implementing interventions to help reverse such trends, but should also be incentivized to invest systematically domestically.

With a host of surveillance systems operating in parallel worldwide, countries and regions need to adopt those which best suit their needs and a broad cross-sectoral and multi-stakeholder programme of harmonisation and integration of global systems should be fostered for more meaningful between-country comparisons of AMR and antibiotic use. This would allow for a sustainable and ordered integration of regions into a globalised surveillance system. For LMICs, improving monitoring of drug quality to curb the proliferation of counterfeits and substandard antimicrobials is also necessary. IPCI and surveillance in the animal and environmental sectors suffer from chronic underfunding and political appetite for investment is required to spend the several billion dollars per annum necessary to upgrade capacity in many LMICs.

Need for better evaluations

To address evidence gaps, comprehensive evaluations are needed and systematic reviews of interventions used in existing policies as related to AMR control are required. Support for evaluating policies is especially necessary in LMICs and, specifically, in the animal and environmental sectors. Standardised frameworks for policy evaluations should be developed and applied for each sector. Even where such frameworks exist (such as for surveillance) they are seldom applied fully or as recommended even in well-resourced settings like Europe.[26] Given the complexity of designing appropriate evaluation frameworks and the well-described risks of misleading conclusions around generalisibility if the wrong framework is applied, a technical expert-led taskforce should be convened with representation from all sectors for this purpose.[199,200] Particular care would need to be paid to including standardised analyses of contextual factors like political structures, governance and regulation, and resource availability (human/financial and infrastructural) to obtain meaningful evaluations. Detailed case study approaches may therefore be most suitable, and an open-access central repository should be established where AMR policy case studies could be captured to facilitate lesson-learning and best practice comparisons.[200] This could be operated in a manner similar to PreventionWeb – the United Nations' website capturing case studies on different aspects of Disaster Risk Reduction.[201]

Conclusion

Even though the evidence base for policy interventions to combat AMR is scattered, there is still a rich menu of options for countries to choose from. However, these options need to be adapted before adoption to adjust for the specific context. This then calls for proper surveillance and monitoring to be able to track and evaluate progress and contribute to an expanding knowledge base across countries.

The analysis presented here focused on the human and animal sectors with limited discussion of environment-related AMR control and of food and trade policy. However, these too are integral components of AMR control and the 'One Health' approach to policy development advocated here may help to bridge gaps in the levels of commitment being shown to each sector. Powerful vested interests are able to derail a coordinated strategy both intentionally and unintentionally. These range from industry battles between competing lobby groups over antibiotic use in animals, to the continuing tussles of donor-funded vertical healthcare programmes in LMICs that could potentially compete with AMR control programmes for limited resources. Consequently, in all regions, a sound understanding of the political and economic context is as important as the scientific evidence base in developing coordinated and effective policies to control AMR. The wide ranging sensitivities at play mean it is important that a unified, inclusive process to policy development is adopted; one that is sufficiently flexible to accommodate the varying needs and circumstances of countries and regions, and one that is fully funded and implemented.

Table 3: A summary of potentially effective AMR control interventions and challenges in developing generalisable policies

	Examples of effective interventions/policies	**Weakness in evidence base**	**Challenges for generalisability of policy**
Responsible Use	• Providing alternative prescribing options at a national level for antibiotics (e.g. zinc and oral rehydration for diarrhoeal illness) • Back-up/Delayed prescribing in publically	• Long-terms impacts on prescribing behaviour have not been assessed • A dearth of robust cost-effectiveness analyses of all interventions • Very little research done on interventions targeted at the	• Widely varying governance structures and accountability mechanisms of health systems • Different methods of prescriber remuneration • Behaviour change interventions limited by

	funded high income settings.. • Development and implementation of clinical antibiotic guidelines in secondary care • Persuasive/Restrictive interventions in secondary care • National restrictions on antibiotic subsidies • Providing alternative re-imbursement options for prescribers (in both human and animal settings) • Bans on antibiotic use as AGPs • Re-orienting prescriber roles in the animal sector	(unregulated) private sector in LMICs • The impact of regulatory policies on marketing and sale of antimicrobials remains to be assessed	cultural settings where they have bee n trialled • Financial challenges in the animal/livestock sector such as capital costs for changing practice, meat prices and farm profitability. • Wide national variations in health budget availability for AMR policies • The unregulated proliferation of substandard and counterfeit drugs
Infection Prevention and Control	• Hand hygiene promotion interventions in healthcare and community settings • Improving access to water and sanitation • Increasing effective vaccine coverage in both human and animal sectors	• Evidence on effectiveness and appropriate implementation on IPCIs in LMICs is lacking. • Poor cost-effectiveness evaluation of IPCIs in healthcare settings	• A lack of integration of IPCI programmes in the community and AMR control policy. • Chronic underfunding of IPCI in the animal/livestock sector
Surveillance	• Integrate AMR surveillance and antimicrobial use on a regional basis to enable between-country comparisons. • Link surveillance of AMR in the animal sector to regulatory sanctions against bad practice	• The evidence base to determine the most cost-effective systems for surveillance of antibiotic use and resistance remain weak worldwide • A lack of analysis of infrastructure and resource requirements for effective surveillance • Significant differences across countriesof surveillance system indicators and guidelines for surveillance of antibiotic use and resistance in different settings; comparative data in human and animal health is therefore lacking	• Transferability of surveillance systems that have been successful in HICs to LMICs is questionable due to infrastructure and resource differences • Surveillance of counterfeit/substandard antimicrobials also a priority in LMICs • Chronic underfunding of surveillance in the animal sector in LMICs

Acknowledgements

We would like to thank Dr. Muhammad Irfan Department of Medicine, Aga Khan University, Pakistan for his help with case study 1.

Author roles

OD, EJB and DLH collated contributions from all authors and wrote the first draft. All authors contributed to the reference search for the piece, writing, revisions and final approval.

Conflicts of interest

All authors declare no conflict of interest.

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