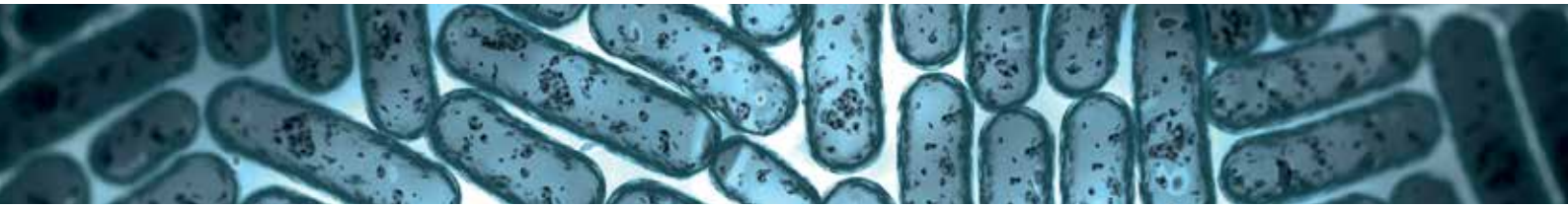
CHATHAM HOUSE

briefing paper



Tackling Antibiotic Resistance for Greater Global Health Security

Gemma L. Buckland Merrett

Centre on Global Health Security | October 2013 | GHS BP 2013/02

Summary points

- Antibiotic resistance is now recognized as a major global health security issue that threatens a return to the pre-antibiotic era, with potentially catastrophic economic, social and political ramifications. An extra burden is likely to hit resource-poor countries.
- Although bacteria naturally adapt to outsmart antibiotics, human actions accelerate the development and spread of resistance.
- Antibiotics need to be used judiciously, with effective stewardship and infection prevention and control, and a harmonized approach to their use in animal and human health should be fostered. There is also a need for practical economic models to develop new products that avoid rewarding researchers for what they do already.
- Choosing the right paradigms for sustainably stimulating R&D requires new measures to align the financial incentives for drug and diagnostic test development with public health needs. Incentives for infection control and appropriate stewardship are equally important.
- Integrated efforts involving academia, policy-makers, industry and interest groups will be required to produce a global political response with strong leadership, based on a coherent set of priorities and actions.

Introduction

Antibiotic drug resistance is an increasing threat to global health security, potentially compromising gains made in public health worldwide.[1] Resistance – when bacterial infections previously considered routine to treat survive exposure to antibiotics – is currently considered one of the greatest threats to health.[2] The discovery of antibiotics revolutionized medicine, transforming often fatal diseases into curable, or at least manageable, problems. They were viewed as a panacea. Although not a new phenomenon, resistance has become a more pressing issue over recent years as approximately 70 per cent of known bacteria have developed resistance to one or more antibiotics, threatening a return to the pre-antibiotic era. Resistance has been reported for entire classes of antibiotics, and untreatable multi-drug resistant bacteria are increasingly documented.[3]

The emergence and spread of drug resistance results from a myriad of ecological and evolutionary interacting factors, naturally occurring and human-made. As bacteria transfer genetically encoded resistance among themselves or acquire it from the environment, the evolutionary forces affecting resistance are ever-present, but there are controllable practices that can accelerate its spread. These include poor use and abuse of antibiotics (excessive and irrational use for treatment or prevention), availability of substandard products (particularly in low-income countries where antibiotics are easier to obtain without prescription and their quality can be questionable), increased global travel, medical tourism and trade, declines in research and development (R&D) for new medicines, poor application of infection control measures and use of antibiotics in the agricultural industry (particularly in the production of food).[4]

As some degree of resistance is inevitable, there will always be a need to continue producing new generations of antibiotics, even if the issues mentioned above were effectively addressed. The current urgent need for new antibiotics is not being met by the pharmaceutical industry. In 2004, only 1.6 per cent of drugs in development at the world's 15 largest drug companies (responsible for 93 per cent of antibiotics introduced between 1980 and 2003) were antibiotics. Most of the antibiotic classes were discovered before 1970 and over the past three decades only two new classes have become available.[5] However, in the absence of enlightened self-interest, this creates a classic example of the 'tragedy of the commons' where an individual's choice to use an antibiotic can affect the possibility of treating bacterial infections in other people, which cannot be solved alone by a costly race to keep one step ahead of resistance. A multi-faceted international effort is required to avert a 'global-scale failure'.[6]

The ramifications of resistance manifest themselves not just in the impact on human health, but also in potentially heavy economic costs, and difficulties in mobilizing political action to deal with it, nationally and globally. The immediate health consequences are increased sickness and death rates, prolonged illness and a greater risk of complications. In economic terms this leads to a loss of productivity and increased costs for diagnosis and treatment, which stretched health services have difficulty in affording.[7] It is difficult to quantify the geographical spread, health and economic burden imposed because the surveillance evidence currently available is very patchy. Estimates indicate that the excess deaths due to resistant hospital infections in Europe could exceed 25,000 annually while the overall costs are estimated to be €1.5 billion.[8]

1 Lee Howell (2013), *Global Risks 2013* (Geneva: World Economic Forum), http://www3.we forum.org/docs/WEFGlobalRisksReport2013.pdf.

2 Alfonso J. Alanis (2005), 'Resistance to Antibiotics: Are We in the Post-Antibiotic Era?', *Archives of Medical Research*, 36: 697–705.

3 Brad Spellberg et al. (2002), 'The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America', *Clinical Infectious Diseases*, 46(2): 155–64.

4 David L. Heymann (2006), 'Resistance to Anti-infective Drugs and the Threat to Public Health', *Cell*, 124: 671–75.

5 European Centre for Disease Prevention and Control/ European Medicines Agency (ECDC/EMEA) (2009), *The Bacterial Challenge: Time to React*, Joint Technical Report, http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.

6 Rachel Nugent et al. (2010), *The Race Against Drug Resistance*, Report of the Center for Development's Drug Resistance Working Group. http://www.cgdev.org/files/1424207_file_CGD_DRWG_FINAL.pdf.

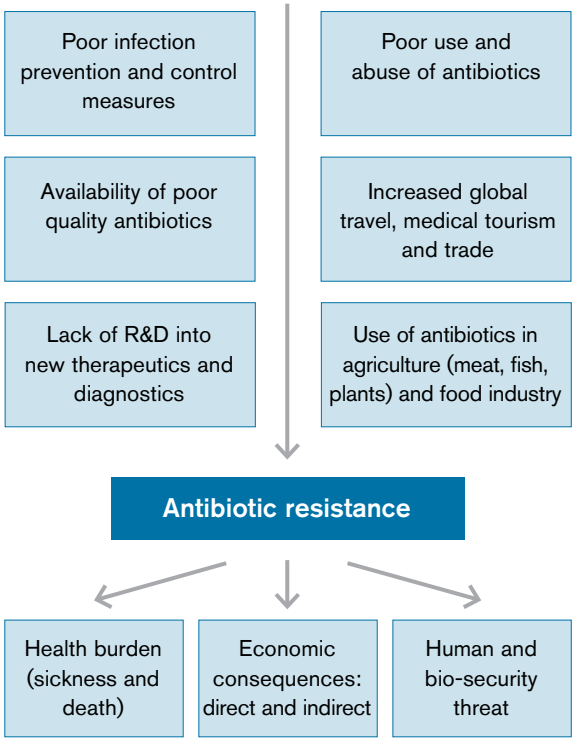
7 David Howard et al. (2003), 'The Global Impact of Drug Resistance' *Clinical Infectious Diseases*, 36: 4–10.

8 Heymann, 'Resistance to Anti-infective Drugs and the Threat to Public Health'.

Antibiotic resistance is estimated to cost the US health-care system $21–34 billion each year.[9] However, current estimates do not take into account externalities such as the wider effects on health systems and patients when there are no effective antibiotics.[10] Surveillance data are significantly poorer in low- and middle-income countries (LMICs); evidence suggests that 70 per cent of hospital-acquired neonatal infections in these countries are untreatable owing to resistance to first-line antibiotics, and that multi-drug resistance has forced clinicians to fall back on second- and third-line treatments, multiplying costs.[11] The main political ramification is that the paucity of accurate economic estimates means that antibiotic resistance does not 'cost enough' in evidence-based policy-making to be assigned the priority it deserves.[12] Even so, some argue the salient threat countries face if bacteria present themselves as multi-drug-resistant with no clinical solutions could result in 'catastrophic consequences, [which would be] potentially uncontrollable … resulting in civil and political unrest'.[13] These potential consequences are illustrated in Figure 1.

Resistance is not specific to bacteria. Antimicrobial resistance (AMR) has been developed by fungi, viruses (HIV, influenza) and parasites (malaria), but these are outside the scope of this paper. Two key factors involved in resistance are examined here: conservation (infection prevention and control, rational use in humans and rational use in agriculture); and innovation. The paper also identifies where efforts need to be focused, and suggests ways in which a global commitment could be fostered.

Figure 1: The drivers and consequences of antibacterial resistance



Current efforts

Several national, regional and global initiatives are engaged in tackling AMR, or more specifically antibiotic resistance. In 1998 the World Health Assembly of the World Health Organization (WHO) urged member states to develop suitable measures to tackle the former.[14] In 2000, WHO called the rise of AMR a global crisis, and in 2001 it released its first global strategy for its containment.[15] A Transatlantic Taskforce on AMR

9 ECDC/EMEA, *The Bacterial Challenge*.

10 Richard Smith and Joanna Coast (1995), 'Global Responses to the Growing Threat of Antimicrobial Resistance', CMH Working Paper Series, Paper No. WG2: 17, http://library.cph.chula.ac.th/Ebooks/HealthCareFinancing/WG2/Paperpercent20no.percent 20WG2_16.pdf.

11 Hajo Grundmann et al. (2011), 'A Framework for Global Surveillance of Antibiotic Resistance', *Drug Resistance Updates*, 14: 79–87.

12 Richard Smith and Joanna Coast (2013), 'The True Cost of Antimicrobial Resistance', *BMJ*, 347: 1493–98.

13 Infectious Diseases Society of America (IDSA) (2010), 'Antibiotic Resistance: Promoting Critically Needed Antibiotic Research and Development and Appropriate Use ("Stewardship") of these Precious Drugs', http://www.idsociety.org/uploadedFiles/IDSA Policy_ and_Advocacy/ Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Antimicrobials/Statements IDSATestimonypercent20Finalpercent20withpercent20referencespercent20060310.pdf.

14 World Health Organization (WHO) (1998), Fifty-first World Health Assembly Geneva, May 1998, WHA resolution 51.17, FIFTY Emerging and other communicable diseases: antimicrobial resistance http://apps.who.int/medicinedocs/index/assoc/s16334e/s16334e.pdf.

15 WHO (2001), *WHO Global Strategy for Containment of Antimicrobial Resistance*, http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf.

(TATFAR) was established in 2009 to increase EU and US collaboration, and it has focused primarily on improving the pipeline for new drugs. In the same year, the Swedish government promoted the issue during its EU presidency, particularly in relation to incentives for drug development.[16] The European Commission launched a Joint Programming initiative on AMR in 2010 to foster a more cohesive approach to research and integrate relevant scientific fields to create a shared vision. This was followed in 2011 by a 12-point EU Commission 'Action Plan against the Rising Threats from Antimicrobial Resistance'.[17] Similarly, 2011 saw a six-point policy package from WHO. The 2011 World Health Day was based on the premise of 'no action today, no cure tomorrow'.[18]

Independent efforts through networks and partnerships have served as important platforms for key players to advance the resistance agenda. These include the following.

- The Global Antibiotic Resistance Partnership, established by the Centre for Disease Dynamics, Economics and Policy, which explores incentives to slow the development and spread of resistance.[19]
- Re-Act (Action on Antibiotic Resistance), an independent global network, which aims to promote awareness and action and which helped organize a conference that was a precursor to the EU Commission action plan.[20]
- The Alliance for the Prudent Use of Antibiotics, which is engaged in research, surveillance, advocacy and education.[21]
- Over the past decade, the Infectious Diseases Society of America (IDSA) has championed the need for new antibiotic therapies ('Bad Bugs No Drugs – 10 by 20' initiative to support the development of ten new antibiotics by 2020).[22]
- The Center for Global Development funded a Working Group on Antibiotic Resistance that developed recommendations for global action.[23]

In 2012 the first ever meeting of medical societies in India on the issue resulted in a roadmap for efforts to tackle resistance in India.[24] The United Kingdom has also published a roadmap in 2013.[25] A number of other initiatives have been developed, such as the Innovative Medicines Initiative (IMI), Europe's largest public–private initiative, a joint undertaking between the EU and the European Federation of Pharmaceutical Industries and Associations which launched a €224 million programme in 2012 to develop new antibiotics.[26]

And yet, despite all of the global meetings and recommendations and the overall consensus that global coordination of efforts is paramount for tackling the problem, there is still no truly international action. Antibiotics are a potentially exhaustible resource, but the global incentive and coordination mechanisms that operate in other global common pool resources, such as fisheries, are lacking.

16 Elias Mossialos et al. (2010), 'Policies and Incentives for Promoting Innovation in Antibiotic Research', A report for the European Observatory on Health Systems and Policies, http://www.euro.who.int/data/assets/pdf file/0011/120143/E94241.pdf.

17 European Commission (2011), *Action Plan against the Rising Threats from Antimicrobial Resistance*, http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf.

18 WHO (2012), 'The Evolving Threat of Antimicrobial Resistance – Options for Action', http://whqlibdoc.who.int/ publications/2 012/9789241503181_eng.pdf.

19 Global Antibiotic Resistance Partnership, The Center for Disease Dynamics Economics & Policy, http://www.cddep.org/projects/global_antibiotic_resistance_partnership.

20 Website of ReAct, Action on Antibiotic Resistance, http://www.reactgroup.org/.

21 Website of the Alliance for the Prudent Use of Antibiotics, http://www.tufts.edu/med/apua/.

22 'Antibiotic Development: The10 X '20 Initiative', The Infectious Diseases Society of America, http://www.idsociety.org/uploadedfiles/idsa/policy_and_advocacy/current_topics_and_issues/.antimicrobial_resistance/10x20/images/bad%20bugs%20no%20drugs.pdf.

23 Nugent et al., *The Race Against Drug Resistance*.

24 A. Ghafur et al. (2013), '"The Chennai Declaration" Recommendations of "A roadmap to tackle the challenge of antimicrobial resistance" – A joint meeting of medical societies of India', *Indian Journal of Cancer*, http://www. indianjcancer.com/preprintarticle.asp?id=104065.

25 Department of Health (2013), *UK 5-Year Antimicrobial Resistance Strategy 2013 to 2018*. https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018.

26 Innovative Medicines Initiative, press release (2012), 'IMI launches €223.7 million programme for combatting antibiotic resistance', http://www.imi.europa.eu/sites/default/files/uploads/documents/Press%20Releases/IMIpressRelease6th Call FINAL.pdf.

From stewardship to infection prevention and control

An estimated 50 per cent of antibiotic use in hospitals is deemed inappropriate, and consumption of antibiotics correlates directly with the frequency of resistance at the country level.[27] Tackling resistance requires better use of antibiotics while preventing and controlling the transmission of resistance already present. WHO defines stewardship as 'the careful and responsible management of the well-being of the population', meaning it is the responsibility of everyone to use antibiotics wisely. But this requires clear and effective guidance for implementation.[28] The role of a stewardship programme is to balance the benefits of antibiotics for health against the need to minimize improper use, and to reduce use overall.

In most countries, primary care still accounts for the majority of antibiotic use, where poor prescribing is directly implicated in the development of resistant bacteria.[29] Poor prescribing can be attributed to a lack of knowledge, poor diagnosis, patient pressure and financial motivations on the part of the prescriber. Many countries have been successful in reducing primary-care prescribing, but such efforts require close attention to local economic incentives. For instance, France's 2002–07 National Action plan produced a 23 per cent reduction in antibiotic consumption through surveillance, public-awareness campaigns, education for health professionals and rapid testing for certain infections.[30] At the other end of the spectrum, China is one of the heaviest users of antibiotics and has a healthcare system with strong incentives for over-prescribing, as well as frequent self-administration of over-the-counter antibiotics. Evidence suggests the main driver of antibiotic abuse in China is not patients but physicians who prescribe more expensive antibiotics rather than cheaper versions because it is in their financial interest. To counter this, doctors' pay in China was recently delinked from sales of pharmaceuticals, while drugs were divided into three classes based on resistance rates, with only specialists allowed to prescribe drugs with high resistance.[31] Competition in outpatient healthcare markets can combat perverse incentives by raising the cost of prescribing antibiotics, thereby discouraging doctors from using certain ones.[32] This, however, is very context-specific.

> 'The main driver of antibiotic abuse in China is not patients but physicians who prescribe more expensive antibiotics rather than cheaper versions because it is in their financial interest'

Patients should also have a basic understanding of resistance and the judicious use of antibiotics. Their use varies widely owing to substantial national differences in cultural and socio-economic factors. Knowledge of appropriate use can dramatically reduce abuse, especially in the absence of contrary financial incentives.[33] In Thailand, a multifaceted response as part of an Antibiotic Smart Use programme used patient education measures, along with treatment

27 Marlies E. J. L. Hulscher, Richard P. T. M. Grol and Jos W. M. van der Meer (2010), 'Antibiotic Prescribing in Hospitals: A Social and Behavioural Scientific Approach', *The Lancet Infectious Diseases*, 10: 167–75; Nienke van de Sande-Bruinsma et al. (2008), 'Antimicrobial Drug Use and Resistance in Europe', *Emerging Infectious Diseases*, 14: 1722–30.

28 WHO (2000), *The World Health Report 2000: Health Systems: Improving Performance* (Geneva: WHO, 2000).

29 UK Department of Health (1998), *The Path of Least Resistance*, http://antibiotic-action.com/wp-content/uploads/2011/07/Standing-Medical-Advisory-Committee-The-path-of-least-resistance-1998.pdf.

30 Jean-Michel Azanowsky et al. (2008), 'Recent Trends in Antimicrobial Resistance among *Streptococcus pneumonia* and *Staphylococcus aureus* Isolates: The French Experience', *Eurosurveillance*, 13: 46.

31 Janet Currie, Wanchuan Lin and Wei Zhang (2011), 'Patient Knowledge and Antibiotic Abuse: Evidence from an Audit Study in China', *Journal of Health Economics*, 30: 933–49.

32 Daniel Bennett, Tsai-Ling Lauderdale and Che-Lun Hung (2008), 'Competing Doctors, Antibiotic Use, and Antibiotic Resistance in Taiwan', University of Chicago. http://chess.uchicago.edu/events/hew/fall08/bennett.pdf.

33 Currie et al., 'Patient Knowledge and Antibiotic Abuse'.

guidelines, to reduce antibiotic use by 18–46 per cent.[34] In US hospitals, antibiotics are often included within the global case-payment rate, which gives hospitals economic incentives to use cheaper generics first. They have been historically reimbursed for hospital-acquired infections, but not for efforts to control infection, so perversely rewarding hospitals with the highest infection rates.[35]

Thus economic incentives, among others, lead to inappropriate use of antibiotics and insufficient investment in infection control. Careful attention needs to be paid to how reimbursement occurs in each national healthcare sector.

Conserving current or future antibiotic resources is a key component of stewardship. Restricting use or pre-authorization of use, changing prescription requirements, carrying out hospital drug utilization reviews and using computer-based algorithms prompting professionals to prescribe appropriately are all viable conservation strategies.[36] However, robust studies evaluating such strategies are scarce. Barriers within organizations, such as the capacity for diagnostic tests, use of different guidelines within hospitals and the existing coordination, collaboration and communication channels, all represent significant determinants of effective antibiotic stewardship policy. A Cochrane Effective Practice and Organisation of Care Group[37] provided a classification of strategies, and deemed persuasive strategies more effective than restrictive ones.[38] Mandating that antibiotics be available only on prescription makes a difference, but this is context-specific and would be both unenforceable and counterproductive in many developing countries.[39] Curbing the use of second-line antibiotics and providing co-formulations of drugs that are less likely to lead to resistance, as is done with antimalarials, are potential approaches, but they need to be coupled with effective monitoring. Enabling the conservation of antibiotics by offering alternative therapies such as vaccines or improving diagnostics are also potential approaches (see below).[40]

In LMICs, quality control of medicines and security of the supply chain from manufacturer to end-user in terms of procurement, storage and sale are often poorly regulated or enforced. The sale and use of substandard drugs are common problems, as is the use of left-over drugs for self-medication. Therefore, regulating drug promotion, improving access to prescribers and prescribing the right antibiotics are key areas to tackle.

‘Regulating drug promotion, improving access to prescribers and prescribing the right antibiotics are key areas to tackle’

Infection prevention and control (IPC) also helps conserve antibiotics. Infections acquired in healthcare facilities that transfer to the community and vice versa result in a heavy death toll, as well as direct and indirect financial costs. Interventions involve establishing organizational structures and dedicated human resources; establishing guidelines, protocols and practices; and linking to public health services at the national and health-facility levels. Specific measures that have been studied as part of an IPC programme include hand hygiene, contact precautions, screening measures, readmission alert

34 WHO, ‘The Evolving Threat of Antimicrobial Resistance’.

35 Kevin Outterson and Olga Yevtukhova (2011), ‘Germ Shed Management in the United States’, Boston University School of Law Working Paper No. 11–19, http://ssrn.com/abstract=1838444.

36 Lucy Reynolds and Martin McKee (2009), ‘Factors Influencing Antibiotic Prescribing in China: An Exploratory Analysis’, *Health Policy*, 90: 32–36.

37 Cochrane Review Groups publish systematic reviews of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care. The Group is part of the Cochrane Collaboration, an international network of more than 31,000 people from more than 120 countries that has published more than 5,000 reviews in its online database.

38 Jeremy M. Grimshaw et al. (2012), ‘Knowledge Translation of Research Findings’, *Implementation Science*, 7: 50.

39 Ramanan Laxminarayan and David L. Heymann (2012), ‘Challenges of Drug Resistance in the Developing World’, *BMJ*, Vol. 344, e1567.

40 Nithima Sumpradit et al. (2012), ‘Antibiotics Smart Use: A Workable Model for Promoting the Rational Use of Medicines in Thailand’, *Bulletin of the World Health Organization*, 90: 905–13.

systems, patient placement, isolation of infected patients, education and environmental cleaning. The evidence as to their comparative effectiveness is limited, however.[41] As with most areas of stewardship, cost concerns hamper decisions to implement measures. However, economic analysis reveals programmes such as the 'cleanyourhands' promotional campaign in England can be beneficial.[42]

In 2005 WHO launched the First Global Patient Safety Challenge. A total of 125 member states pledged support for implementing IPC measures, but no mapping of progress in these countries has occurred.[43] In general, there are no international guidelines for appropriate use of antibiotics, regular assessments of their use and dissemination of results. The diversity of the determinants warrants an equally diverse range of strategies to improve use, yet system-wide perspectives involving healthcare facilities, regulatory agencies, dispensers and consumers are absent.[44] Often a genuine political commitment is lacking. However, where commitment exists, inadequate infrastructure, data on resistance and human resources are often impediments. In countries with restricted resources, choosing interventions and implementing sustainable changes are all context-dependent. This requires assessment of feasibility gaps and intervention efficacy, and intervention cost-effectiveness. Situation analyses at national and facility levels to help set goals and develop strategies are lacking.

Drug development and innovation not keeping pace

Any efforts to conserve existing antibiotics need to be complemented by the development of new ones. The lack of innovation in this field noted above is a result of scientific challenges and inadequate economic incentives, as well as the perception that the regulatory system imposes requirements that are disproportionate and overcostly.[45]

Despite the scientific challenge and criticisms of the current paradigm for drug discovery and development, there is still optimism within the scientific community.[46] Within academia, many new avenues are being explored, leading to the discovery of novel antibiotics or augmented old ones, along with a greater understanding of the science of drug resistance.[47] One of the main constraints on scientific discovery is the reduction in the number and diversity of drug development teams within industry and the ensuing depletion of skills within the field. Other barriers include the lack of shared resources in research to reduce development risks, and the depletion of academic funding.[48]

Antibiotics are used by most people, but relatively infrequently and for short periods only, and the majority are cheap and long out of patent protection. As an incentive for investing in R&D, this pattern of use is far less attractive to pharmaceutical companies than traditional blockbuster drugs taken by many people, every day, for long periods, and patent-protected for the first 10–15 years of their life. Measures taken to restrict antibiotic use in order to mitigate the development of resistance are a further disincentive to investing in R&D. At the extreme, a new antibiotic might be needed only in exceptional circumstances, which would necessitate some mechanism to finance R&D other than sales revenues.

41 Didier Pittet et al. (2000), 'Effectiveness of a Hospital-wide Programme to Improve Compliance with Hand Hygiene', *The Lancet*, Vol. 356, Issue 9238, pp. 1307–12.

42 National Patient Safety Agency (2004), 'The economic case: implementing near-patient alcohol handrub in your trust', http://www.npsa.nhs.uk/cleanyourhands/resource-area/evidence-base/?EntryId34=58433; Jonathan Cooke et al. (2007), 'Improving Practice – Working Together to Improve the Use of Antimicrobials', *Antimicrobial Chemotherapy*, 60, pp. 712–14.

43 WHO (2012), 'The Evolving Threat of Antimicrobial Resistance'.

44 Hulscher et al., 'Antibiotic Prescribing in Hospitals'.

45 Kevin Outterson et al. (2007), 'Will Longer Antimicrobial Patents Improve Global Public Health?', *The Lancet Infectious Diseases*, 7: 559–66.

46 David M. Livermore (2011), 'Discovery Research: The Scientific Challenge of Finding New Antibiotic', *Journal Antimicrobial Resistance*, 66: 1941–44; David Payne et al. (2007), 'Drugs for Bad Bugs: Confronting the Challenges of Antibacterial Discovery', *Nature Reviews Drug Discovery* 6: 29–40.

47 Gang Chen et al. (2011), 'A Strategy for Antagonizing Quorum Sensing', *Molecular Cell*, 42: 199–209; Lynne K. Garrity-Ryan et al. (2010), 'Small Molecule Inhibitors of LcrF, a *Yersinia pseudotuberculosis* Transcription Factor, Attenuate Virulence and Limit Infection in a Murine *Pneumonia* Model', *Infection and Immunity*, 78: 4683–90.

48 Laura J. V. Piddock (2012), 'The Crisis of No New Antibiotics – What is the Way Forward?', *Lancet Infectious Diseases*, 12: 249–53.

This is a type of market failure because the pricing mechanism fails to generate adequate returns to R&D in relation to the potential health benefits that would arise from it. Against that background, a new sustainable business model would be key to fuelling antibiotic development in the future.[49] Clear market signals to stimulate R&D, and delinking the cost of R&D from sales revenues, are prerequisites. In order to correct current misaligned incentives, the right institutions, incentives, cost- and risk-sharing, and funding mechanisms are needed.[50]

There are three main approaches to improving incentives for R&D and enhancing the resources devoted to it in both the private and public sectors:

- Private sector but publicly funded with push, pull or push/pull incentives,
- Primarily public sector, and
- Public–private collaboration.

A private-sector focus

Pull mechanisms aim to stimulate R&D by offering incentives such as guaranteed purchase of a final product, a prize or a special patent incentive. The success of a pull mechanism is largely dependent on the value of the reward on offer in relation to the perceived costs, risk and uncertainty involved in achieving that reward. Examples of pull mechanisms currently used include additional exclusivity periods to stimulate R&D relevant to children (paediatric exclusivity) or for rare diseases (orphan drugs). Various kinds of guaranteed purchase schemes have also been tried for vaccines, including an advance purchase commitment for pneumococcal vaccines.[51] The claimed advantage of pull funding (particularly purchase mechanisms) is that it is only paid out in the case of success. Examples include offering faster assessment processes and accelerated approval times, as used with the Generating Antibiotic Incentives Now (GAIN) Act in the United States (see below).[52] Yet difficulties surround the determination of the appropriate award size, the political acceptance of high-value reward and whether commitments by governments are credible in terms of being continued by their successors. Built on a competitive framework, such incentives offer little or no motivation for collaboration. This can be overcome, however, by other private-sector efforts to stimulate the pooling of knowledge.

Push mechanisms are research subsidies (or tax incentives) intended to encourage and finance R&D on particular topics or in particular areas. Examples include the many public-sector research grant schemes (such as from the US National Institutes of Health or the EU Research Directorate) and private-sector funding such as venture capital. They aim to fund directly relevant basic or later-stage R&D for novel products. The advantage of push funding is that it provides resources for entities that have no other access to working capital in the public or private sectors. The disadvantage is that resources are spent irrespective of results. In the private sector, venture capital is a major funding opportunity suitable for progressing compounds through Phase I and II trials, but it often looks for short-term returns and has become scarcer since the financial crisis. Neither the public nor the private sector is an easy source of funding for the most expensive part of the development process, Phase III trials, which test the efficacy and safety of the drug on a large number of patients. That is why Phase III trials are overwhelmingly dependent on the pharmaceutical industry, based on the potential returns provided through patent exclusivity.

Push mechanisms can only work if pull incentives are adequate. Combination push-pull mechanisms comprise elements of both incentives and include, for example, orphan drug incentives that combine grants, tax credits and market exclusivity.

49 Otto Cars, Anna Hedin and Andreas Heddini (2011), 'The Global Need for Effective Antibiotics – Moving towards Concerted Action', *Drug Resistance Updates*, 14: 68–9.

50 Richard Wise (2011), 'The Urgent Need for New Antibacterial Agents' *Journal of Antimicrobial Resistance*, 66: 1939–40.

51 Pneumococcal vaccine support page, GAVI Alliance, http://www.gavialliance.org/support/nvs/pneumococcal/.

52 Richard Bergström (2011), 'The Role of Pharmaceutical Industry in Meeting the Public Health Threat of Antibacterial Resistance', *Drug Resistance Updates*, 14: 77–78.

Table 1: Financing mechanism comparisons

	Example incentives	Advantages	Disadvantages
Push mechanisms	Grants and fellowships, funding for translational research, aimed at turning promising leads into new products	• Smaller financial disbursements • Removes barriers to entry • Attracts SMEs • Encourages manageable steps into R&D	• Risk of funding unsuccessful research • Risk borne almost entirely by funder • Principal-agent problem • Potential to reduce entrepreneurial drive
Pull mechanisms	Monetary prizes, patent buyout, advanced market commitments, global prize funds, health impact fund	• Rewards only successful research • More likely to encourage final product development • Minimizes inefficiencies of developers	• Risk borne entirely by developer • Attracts only developers with significant funding • Difficulty in predicting appropriate award size • Potential political and budgeting changes over duration of development may reduce credibility of reward
Legal and regulatory pull mechanisms	Pricing and reimbursement adjustments, intellectual property extensions, transferable intellectual property rights	• Rewards only successful research • More likely to encourage final product development • Maintains a link between product use and reward size • Minimizes developer inefficiencies	• Risk borne entirely by developer • May obstruct competition • Attracts only developers with significant funding

Source: Adapted from Table 7.1 in Elias Mossialos et al. (2010), 'Policies and Incentives for Promoting Innovation in Antibiotic Research', European Observatory on Health Systems and Policies.

Industry does not just consist of 'big pharma', and therefore reactions to incentives will be different depending on whether it is a small to medium-sized enterprise (SME), biotech start-up, generics firm etc. Table 1 summarizes the overall advantages and disadvantages of the basic mechanisms.[53]

There are a number of key criteria that ideally each mechanism should meet for antibiotic production, such as delinking revenue from sales, supporting conservation efforts, the ability to stimulate innovation, affordability and access in LMICs, sharing risk between beneficiary and funder, achieving political support and addressing the 'tragedy of the commons' effect. Each incentive comes with advantages and disadvantages, and only some have previously been applied to drug development. With little available evidence, the strengths and weaknesses of the individual mechanisms still need to be fully defined.

Primarily public-sector-focused approaches

Public-sector approaches involve increased funding for university and public-sector research based on pertinent scientific questions. Interdisciplinary research centres, a watchdog centre, a European research platform to support open access research, funding and facilitating collaborative efforts, offering grants and fellowships, and libraries of compounds and data are all potential mechanisms that can support R&D. Data and compound libraries can open the field for smaller firms and academia to pursue drug candidates, such as with the European Rare Disease Initiative. However, enabling mechanisms will need to be in place in order to translate research into actual therapeutics.[54]

Public–private collaborative approaches

Public–private approaches aid the sharing of experts, knowledge and chemical resources. One example is the

53 Mossialos et al., 'Policies and Incentives for Promoting Innovation in Antibiotic Research'.

54 Cars et al., 'The Global Need for Effective Antibiotics'.

Innovative Medicines Initiative (IMI), a joint undertaking between the European Union and the European pharmaceutical industry association, EFPIA. This is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. It supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. Public–private partnerships (PPPs) have also been created extensively in the last decade or so in order to stimulate R&D relevant to diseases that mainly affect developing countries (e.g. the Medicines for Malaria Venture or the Drugs for Neglected Diseases initiative). They are intended to stimulate R&D where the market provides inadequate incentives and have been credited with some success in strengthening the drug pipeline. A similar approach could be tried with antibiotics. One proposal is for a global foundation for antibiotic drug development and discovery, funded through philanthropy and PPPs, which could translate academic research and fully exploit drug candidates.[55]

There is much debate about how much additional incentive for industry would be necessary to spur R&D without providing disproportionate rewards.[56] The required balance of the different initiatives is up for discussion. Some argue private companies are the central actors for innovation, and that public initiatives such as IMI are already sufficient and simply need to be used more effectively. Others assert that a combination of push/pull approaches is most effective – tempered by a strategic use of public and philanthropic funding to leverage additional private-sector resources.[57] Still others claim that industry has limited capacity and that new approaches, decentralized networks or larger facilities are required. To date, truly innovative approaches have not been properly explored, nor has there been a full commitment from industry players to engage with the issue. There are potential roles for different actors depending on the stage in the drug development chain.[58] The difficulty in garnering full global support may prevent the urgent innovation needs from being met; hence recommendations that the EU, United States and Japan play a pivotal role in taking the first steps.[59]

Diagnostics

While effective antibiotics are the mainstay of addressing the problem, there is also an important complementary role for diagnostics. Better and faster diagnostics are needed to avoid the unnecessary use of antibiotics as a result of clinicians understandably playing safe in the absence of precise diagnosis. A spectrum of tools and technologies could have an impact, especially those suitable for LMIC settings. Diagnostics have a shorter development-to-point-of-use process, with typically lower R&D costs than drugs, but potentially a lower return. The best-case scenario is a diagnostic test that improves rational use and thereby delays resistance. Experiences with tuberculosis have been exemplary, expanding reference laboratory capacity and facilitating the rollout of new tools for remote locations, and the Tuberculosis Specimen and Strain Bank, which provides bio-specimens needed to evaluate tools.[60] New rapid diagnostics could also facilitate clinical trials of new antibiotics, permitting smaller, less expensive studies. Once such diagnostic tests are produced, doctors need to be incentivized to use them.[61]

Vaccines

More and better vaccines are the ultimate means to reduce the widespread use of antibiotics by preventing infection in the first place and conserving antibiotics. The pneumococcal vaccine has had a tremendous impact in preventing infection and unnecessary prescriptions.[62]

55 Piddock, 'The Crisis of No New Antibiotics'.
56 Ibid.
57 Anthony D. So et al. (2012), '3R's for Innovating Novel Antibiotics: Sharing Resources, Risks, and Rewards', *BMJ*, 344:e1782.
58 Brad Spellberg et al. (2011), 'Combating Antimicrobial Resistance: Policy Recommendations to Save Lives', *Clinical Infectious Diseases*, 52: S397–428.
59 IDSA, 'Antibiotic Resistance'.
60 Iruka Okeke et al. (2011), 'Diagnostics as Essential Tools for Containing Antibacterial Resistance' *Drug Resistance Updates*, 14: 95–106.
61 US Food and Drug Administration (FDA) (2008), 'Trials and Tribulations of Antibiotic Development', *The Lancet Infectious Diseases*, 8: 209.
62 Ron Dagan and Keith Klugman (2008), 'Impact of Conjugate Pneumococcal Vaccines on Antibiotic Resistance', *The Lancet Infectious Diseases*, 8: 785–95.

Enabling policies

Financing and incentives are only part of the problem. The regulatory environment is often cited as a major constraint to development because of the high cost of meeting requirements, relative to the expected rewards. In order to get new antibiotics to market, regulatory mechanisms governing this process may need re-engineering. The public health agenda and patient safety are supported by the regulation of drugs, but the process is regarded by some as too risk-averse in the case of antibiotics in spite of recent changes in regulatory policies. Despite antimicrobials having some of the fastest approval times of therapeutic classes, a number of factors need addressing in order to facilitate the situation. These include clearer guidance on the regulatory process, reducing the costs of clinical trials, shortening the time to conduct them and a review of sample size requirements (as proposed by IDSA with the Limited Population Antibacterial Drug approval mechanism), which would in turn help reduce costs and time, harmonize the process internationally and improve the dialogue between licensors, regulators and producers.[63]

Tuberculosis research has made efforts to rethink the paradigms of bringing drugs to market through the Open Source Drug Discovery Initiative. It has opened up a treatment for multi-drug-resistant tuberculosis to generic drug-makers to ensure continued availability. The use of prizes and the Critical Path to TB Drug Regimens initiative could speed the regulatory process. Open innovation can create opportunities for scientists to collaborate across organizations, disciplines and borders, but there is still a need for collaboration beyond virtual networks, and there are potentially complications with the patent situation. Other methods could include streamlining the clinical trials process for antibiotics, using a new regulatory framework of 'special designation for priority antibiotics', involving regulatory agencies to encourage co-development of drugs with diagnostics, and negotiating intellectual property rights to help relieve upstream bottlenecks in R&D. The GAIN Act, which came into effect in the United States in October 2012, aims to make antibiotic drug discovery more attractive to pharmaceutical companies by extending the term of exclusivity for the sale of selected antibiotics, allowing priority review and fast-track approval by the Food and Drug Administration and review of clinical trial guidelines for new antibiotics. However, a tangible impact remains to be seen and the act contributes nothing to incentives for better use.[64]

> 'The regulatory environment is often cited as a major constraint to development because of the high cost of meeting requirements, relative to the expected rewards'

Some in industry argue that the timeframe is crucial. The longer the situation remains as it is, the more likely companies will be to exit antibiotic research. Any new legislation will take time but the more an incentive can fit into an existing regulatory infrastructure, the faster it will reap rewards. This cannot all be carried out in isolation; collaboration and partnerships that support it should also be initiated.[65] It is claimed that the urgent response required by antibiotic resistance should be reflected in innovative measures to make these drugs available as soon possible. To facilitate that, it is argued that antibiotics should be given special status to avoid

63 Antoine Andremont et al. (2011), 'Fighting Bacterial Resistance at the Root: Need for Adapted EMEA Guidelines', *The Lancet Infectious Disease,* 11: 6–7; IDSA (2013), 'Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need', http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current _Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Statements/IDSA%20LPAD%20Statement%20to%20FDA.March%201%202013.pdf.

64 Roger Finch (2011), 'Regulatory Opportunities to Encourage Technology Solutions to Antibacterial Drug Resistance', *Journal of Antimicrobial Chemotherapy*, 66: 1945–47.

65 FDA, 'Trials and Tribulations of Antibiotic Development'.

possible complications arising from the read-across to other disease areas. This will require trust among developers and stakeholders that a 'safe harbour' to produce drugs with unique agreed parameters will be established.

Working towards a 'one-health' approach

Notwithstanding the impact of drivers for human use of antibiotics, their use within the agricultural sector (meat, fish and plants) is also a significant issue. Globally, more than 50 per cent of antibiotics are used in animal agriculture.[66] Evidence from the last 35 years has suggested a correlation between use in animal husbandry (livestock, poultry and aquaculture) and the spread of associated resistance genes in human pathogens, as well as direct transfer of resistant bacteria from animals to humans.[67] There is little extensive and effective monitoring of antibiotic resistance in animals; and the quantities and classes of antimicrobials used in animals are insufficiently documented or controlled. However, owing to the increasing global trade in food of animal origin, reports of resistance spreading from one country to another through this channel are increasing. Resistance can be spread by consumption and handling of raw or inadequately cooked food, by cross-contamination or through direct animal contact. The environmental dispersal of animal manure with high antibiotic content has potential regional and global implications. Some antibiotics are in simultaneous use in food animal and human medicine. Many so-called cost-effective technologies are now being applied to tackle food shortages in LMICs, such as spraying crops with antimicrobials and feeding fish farms with farm animal waste.[68] Antibiotic resistance is also a concern for animal health, but very little research covers this area, and only in a handful of countries are herds screened.[69] Therefore, the concept of expanding interdisciplinary collaborations and communication in all aspects of health care for humans, animals and the environment (the 'one-health' concept) is thought to have potential major gains in tackling resistance.

Controversial aspects are the use of antibiotics in animal husbandry for prevention of infection (prophylaxis), prevention of the spread of an infection detected in a small group of animals to the rest of the stock (metaphylaxis), and growth promotion, rather than for the treatment of infections themselves to maintain animal health. A number of international networks that coordinate resistance surveillance in human and animal populations, such as the Global Foodborne Infections Network and the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, have developed guidance documents for global standards for monitoring in animals. Alternatives to prophylactic antibiotic use are improvements in management practices and in measures such as hygiene and biosecurity, wider use of vaccines and introduction of probiotics into feed, robust monitoring programmes of local risk factors, and prudent-use guidelines and education. At first glance, it is more economical to prevent disease than to rely on treating it; however, this is not so when the wider societal costs of resistance are taken into account. In the case of animal husbandry, a focus on welfare and nutrition is therefore considered paramount. The use of fish vaccines in Norway, for example, reduced the use of antimicrobials by 98 per cent.[70] However, impact assessments and economic analyses of all interventions are lacking.

In countries where legal and regulatory systems govern the approval of veterinary medicines, implementation

66 WHO (2000), 'Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food', http://whqlibdoc.who.int/hq/2000/who_cds_csr_aph_2000.4.pdf.

67 Young-Guan Zhu et al. (2013), 'Diverse and Abundant Antibiotic Resistance Genes in Chinese Swine Farms', *PNAS Early Edition*, http://www.pnas.org/content/early/2013/02/05/1222743110.full.pdf+html.

68 Virginia Stockwell and Brion Duffy (2012), 'Use of Antibiotics in Plant Agriculture', *Scientific and Technical Review* (World Organisation for Animal Health), 31: 199–210.

69 Randall S. Singer, Richard Reid-Smith and William M. Sischo (2006), 'Stakeholder Position Paper: Epidemiological Perspectives on Antibiotic Use in Animals', *Preventive Veterinary Medicine*, 73: 153–61.

70 FAO/OIE/WHO (2012), 'Antimicrobial Use in Aquaculture and Antimicrobial Resistance', http://www.who.int/topics/foodborne_diseases/aquaculture_rep_13_16june 2006percent20.pdf.

varies. Indeed regulation is particularly complex when considering the cross-cutting nature of the authorities and industries involved, which could be considered a barrier to the effective formation and implementation of antibiotic policy.

Antibiotics are often used with little or no veterinarian consultation, especially given the availability of over-the-counter drugs and the fact that feeds containing antibiotics (the active ingredient) are not subjected to medicines regulation, which means disease diagnosis, treatment and welfare are not always adequately monitored. Pharmaceutical companies and veterinarians profit from antimicrobial use, but there are no conclusive data to demonstrate that this affects the prescribing practices of veterinarians.[71] Denmark placed restrictions on the degree to which veterinarians can profit from prescriptions, and several national veterinary organizations, such as the American Veterinary Medical Association, have developed prudent-use guidelines. It is thought such programmes would benefit both human and animal health if widely adopted, but their success has not yet been evaluated.[72] Since the announced ban on the use of antibiotics for growth promotion in the EU, surveillance in Denmark has shown that resistance declined with no effect on mortality.[73] However, the economic effects of this have not been properly documented.

In New Zealand all antibiotics must be registered and approved by the New Zealand Safety Authority, and cannot be used unless there is a veterinary prescription. Only approved traders are allowed to sell drugs, which may not be promoted or advertised to the public. Some recommend restricting the use in food production of antibiotics that are of critical importance to human health, as long as this is balanced with animal welfare, and WHO has produced a list of critical agents for human health.

In the United States, legislation has been introduced to eliminate the non-therapeutic use in animals of antibiotics deemed critical for treating human infections. Policy options for limiting these drugs include user fees and targeted bans. Members of agricultural and allied industries have concerns that restrictions on the use of antimicrobials in food and animal production would decrease incentives for new drug production and also decrease the efficiency of food production, which would in turn increase the requirement for prophylaxis and the incidence of infectious disease in animals. But restrictions might also result in no change to animal health or production efficiency.[74] An important leverage point in working with the agricultural sector is engaging the food industry on this issue. So far this has not been successful and appears to be a highly politicized issue.

‘An important leverage point in working with the agricultural sector is engaging the food industry on this issue. So far this has not been successful’

There are differing inter-country specificities regarding acceptable drug use and availability of drugs to food producers. The EU banned the use of antimicrobial rinses, which effectively shuts out US poultry imports. Russia has refused imports from the EU on the grounds that trace amounts of certain antibiotics are present.[75] This also complicates a straightforward comparison of policies. It is not clear whether restrictions on antibiotic use in food animals have affected trade, or could do so.

71 Institute of Medicine (2012), ‘Improving Food Safety Through a One Health Approach’, http://www.ncbi. nlm.nih.gov/books/NBK114485/.

72 Scott A. McEwen and Paula J. Fedorka-Cray (2002), ‘Antimicrobial Use and Resistance in Animals’, *Clinical Infectious Diseases*, 34: S93–S106.

73 Pal Johnsen et al. (2011), ‘Retrospective Evidence for a Biological Cost of Vancomycin Resistance Determinants in the Absence of Glycopeptide Selective Pressures’, *Journal of Antimicrobial Chemotherapy*, 66: 608–10.

74 Renée Johnson (2011), ‘Potential Trade Implications of Restrictions on Antimicrobial Use in Animal Production’, Congressional Research Service, http://www.fas.org/sgp/crs/misc/R41047.pdf.

75 Ibid.

However, restrictions need to be global in order to have a true impact.[76]

Many believe policies and management tools to facilitate the prudent use of antibiotics in the animal industry and in waste management are underdeveloped. They are certainly underfunded. The WHO global principles for the containment of antimicrobial resistance in animals intended for food formed the basis of recommendations stressed during the 2011 World Health Day. Proposals include creating monitoring systems at national and international levels, and introducing pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.[77] There is scope for international collaboration on the issue, especially through the tripartite mechanism of the World Organisation for Animal Health (OIE), Food and Agriculture Organization (FAO) and WHO, and promoting the 'one-health' initiative. The first OIE Global Conference on Responsible and Prudent Use of Antimicrobial Agents in Animals took place in March 2013 and recommended a number of strategies to help tackle resistance, such as supporting global implementation and harmonization of standards, improved surveillance and monitoring of antibiotic use, advocating the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products guidelines to ensure the quality of veterinary medicinal products, and supporting LMICs to strengthen their veterinary services.

Conclusion: fostering a global policy response

Antibiotic resistance is now being recognized as a global public health problem with worldwide medical and economic consequences. National and international efforts have had some success but they are limited in scope and coordination.[78] There is an urgent need for a globally coordinated multi-stakeholder approach. Experts agree recommendations made over a decade ago are still relevant today, but implementation of the WHO 2001 Global Strategy remains far from universal and the strategy was arguably 'strong on recommendations but not on implementation'.[79] TATFAR made a list of 17 recommendations, but with no discussion on incentives for reaching the stated objectives and no mandate to address the global problem. Implementation of recommendations like these requires political ownership, leadership and commitment, which has not, for the most part, been evident to date in the developed or developing world.[80] Without clear global leadership, nations will continue to behave as free riders and end up as victims of the 'prisoner's dilemma', where parties might not cooperate even though it is in their mutual interest to do so.

> 'Implementation of recommendations requires political ownership, leadership and commitment, which has not been evident to date in the developed or developing world'

A key facilitator for global action should be WHO and its 194 member states whose task should be to stimulate political commitment, shape collaborations, provide better guidance, strengthen surveillance and develop norms and standards.[81] However, despite achieving some success with vertical programmes for malaria and tuberculosis drug

76 US Government Accountability Office (2011), 'Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals', http://www.gao.gov/assets/330/323090.pdf.

77 WHO (2000), *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food*, report of a WHO consultation. http://whqlibdoc.who.int/hq/2000/who_cds_csr_aph_2000.4.pdf.

78 Smith and Coast, 'Global Responses to the Growing Threat of Antimicrobial Resistance'.

79 'The Endless Struggle', *The Lancet Infectious Diseases* (2011), 11: 253.

80 Jean Carlet et al. (2012), 'Ready for a World without Antibiotics? The Pensières Antibiotic Resistance Call to Action', *Antimicrobial Resistance and Infection Control*, 1, http://www.aricjournal.com/content/pdf/2047-2994-1-11.pdf.

81 Cars et al., 'The Global Need for Effective Antibiotics'.

resistance, the disease-specific focus at WHO makes the cross-cutting interventions required to tackle antibiotic drug resistance more difficult to achieve.[82] To bolster various national and international efforts, the organization has repeatedly called for action through a series of World Health Assembly resolutions urging tackling drug resistance at a global level.[83] However, to date these have had little impact.[84] Any further resolution, as may currently be under consideration, would need to be far more comprehensive and incorporate more concrete and binding commitments by governments in order to have the desired impact.

A global health architecture with laws, regulations, institutions, governance mechanisms, systems and tools to foster a sense of collective responsibility and open the space for action by relevant actors is a necessary way forward. Accurate surveillance data at the national and international level are paramount to informing effective strategies. Surveillance networks do exist but lack a formal framework for collaboration. More robust and reliable systems need to be implemented, perhaps leading to a worldwide network of resistance-surveillance laboratories that could assist in identifying, characterizing and containing new threats and could also aid the monitoring of implementation activities and their impact.[85] Systems of accountability, such as the International Health Regulations (IHR), offer a potential legal framework for international efforts and to help contain the inter-country risk of infection threats. They would also help to define the minimum standards for core capacity, responses and surveillance activities required.[85] But there are political, financial and technical obstacles to this and it is unlikely that WHO currently has the capacity and means to support countries in their compliance of an IHR mandate with regard to antibiotic resistance efforts. In addition, any international legal measures need to be incorporated into national laws, otherwise international efforts will be undermined.

There are complex trade-offs between activities when considering the required country-specific responses appropriate to counter resistance. Depending on the country, certain interventions will be easier and more effective than others. Those that leverage the best results should be used – in other words, they should be prioritized according to impact. Commitments require partnerships between policy-makers, academia, appropriate industry professionals and interest groups, starting at the highest political level to initiate momentum. The urgency of the issue should be matched with truly innovative thinking.

The main factors that policies need to address are the following.

- How to sustain and build on commitments that require investment in financial, infrastructure and human resources to ensure that global access and affordability are detached from future financial, political or economic forces.
- How to address the gaps in geographically representative data, laboratory capacity, diagnostic testing, data management and networking capabilities, methodological obstacles and a lack of coordination of surveillance networks.
- Choosing the right incentives to sustainably stimulate R&D and bring new accessible and affordable antibiotics and diagnostics to society while promoting conservation.
- Developing a harmonized global action plan that embodies the 'one-health' concept.
- How to instigate an immediate global political response, while ensuring a robust action plan is in place to meet urgent innovation needs.

82 Nugent et al., 'The Race Against Drug Resistance'.

83 WHO, Fifty-first World Health Assembly; WHO (2006), 'Improving the Containment of Antimicrobial Resistance, Resolution WHA58.27', http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_28-en.pdf.

84 Cars et al. (2011), 'The Global Need for Effective Antibiotics'.

85 Grundmann et al. (2011), 'A Framework for Global Surveillance of Antibiotic Resistance'.

86 Didier Wernli et al. (2011), 'A Call for Action: The Application of the International Health Regulations to the Global Threat of Antimicrobial Resistance', *PLos Medicine*, 8: e1001022.

Gemma Buckland Merrett wrote this paper while a consultant researcher at the Centre on Global Health Security at Chatham House.

The Centre on Global Health Security

The Centre on Global Health Security at Chatham House examines key global health challenges and how they manifest themselves as foreign policy and international affairs problems. It seeks to help leaders around the world – in government, private foundations, international organizations and business – reach well-informed decisions that improve global health security. It does so by conducting independent research and analysis and facilitating dialogue between the international affairs and public health communities.

Chatham House has been the home of the Royal Institute of International Affairs for ninety years. Our mission is to be a world-leading source of independent analysis, informed debate and influential ideas on how to build a prosperous and secure world for all.

Chatham House
10 St James's Square
London SW1Y 4LE
www.chathamhouse.org

Registered charity no: 208223

Cover image © istockphoto.com
Designed and typeset by Soapbox, www.soapbox.co.uk