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Antibiotic resistance—the need for global solutions

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The causes of antibiotic resistance are complex and include human behaviour at many levels of society; the consequences affect everybody in the world. Similarities with climate change are evident. Many efforts have been made to describe the many different facets of antibiotic resistance and the interventions needed to meet the challenge. However, coordinated action is largely absent, especially at the political level, both nationally and internationally. Antibiotics paved the way for unprecedented medical and societal developments, and are today indispensible in all health systems. Achievements in modern medicine, such as major surgery, organ transplantation, treatment of preterm babies, and cancer chemotherapy, which we today take for granted, would not be possible without access to effective treatment for bacterial infections. Within just a few years, we might be faced with dire setbacks, medically, socially, and economically, unless real and unprecedented global coordinated actions are immediately taken. Here, we describe the global situation of antibiotic resistance, its major causes and consequences, and identify key areas in which action is urgently needed.

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Part 1: Global epidemiology of antibiotic resistance and use

The rise of resistance

The decreasing effectiveness of antibiotics in treating common infections has quickened in recent years, and with the arrival of untreatable strains of carbapenem-resistant Enterobacteriaceae, we are at the dawn of a postantibiotic era.[1] In high-income countries, continued high rates of antibiotic use in hospitals, the community, and agriculture have contributed to selection pressure that has sustained resistant strains,[2] forcing a shift to more expensive and more broad-spectrum antibiotics. In low-income and middle-income countries (LMICs), antibiotic use is increasing with rising incomes, high rates of hospitalisation, and high prevalence of hospital infections.

Resistance arises as a consequence of mutations in microbes and selection pressure from antibiotic use that provides a competitive advantage for mutated strains. Suboptimum antibiotic doses help stepwise selection of resistance. Resistance genes are borne on chromosomal, and increasingly, on transmissible extrachromosomal elements. The resulting resistant clones—eg, meticillin-resistant *Staphylococcus aureus* (MRSA) USA 300, *Escherichia coli* ST131, and *Klebsiella* ST258) are disseminated rapidly worldwide. This spread is facilitated by interspecies gene transmission, poor sanitation and hygiene in communities and hospitals, and the increasing frequency of global, travel, trade, and disease transmission.

Resistance is spreading worldwide

Even before penicillin was introduced, resistant strains of bacteria had been detected.[3] The selection pressure caused by the use of millions of tonnes of antibiotics over the past 75 years since antibiotics were introduced has made almost all disease-causing bacteria resistant to antibiotics commonly used to treat them. The rapid evolution of bacterial resistance is clear in the case of β-lactamases class of antibiotics. Nearly 1000 resistance-related β-lactamases that inactivate these antibiotics have been identified, a ten-times increase since before 1990.[4]

Resistance has spread worldwide. Antibiotic-resistant gonorrhoea emerged in Vietnam in 1967,[5] then spread to the Philippines, and finally the USA.[6] NDM enzymes, first reported in 2008, are now found worldwide.[7] The distribution of resistance genes, such as Enterobacteriaceae-

Panel: **Contributions to the Commission**

The Commission is a single document, each group of authors take responsibility for the text and views expressed in their individual parts.

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producing extended-spectrum β-lactamase (ESBL), NDM-1, and *Klebsiella pneumoniae* carbapenemase (KPC), indicates the ease with which resistance can spread. Findings of a study[8] done in New Delhi showed NDM-1-producing bacteria (including *Shigella boydii* and *Vibrio cholera*) in two (4%) of 50 drinking water samples and 51 (30%) of 171 seepage samples suggesting the possibility of acquiring resistance outside health-care facilities.

Quinolone antibiotics in particular are an example of misadventure. These drugs are synthetic and so do not arise in nature, yet 30 years after their widespread introduction resistance is epidemic.[9] More specifically, whole genome studies suggest that quinolone resistance was a crucial factor in the evolution of hospital MRSA.[10] Such examples of antibiotic-driven evolution go a long way to explaining present epidemics of resistant health-care-associated infections.[11]

In health-care settings, the spread of a resistant clone can be rapid and have severe consequences for vulnerable hosts. Carbapenem resistance among common Enterobacteriaceae has increased sharply over the past decade. In 2012, 4·6% of acute-care hospitals in the USA reported at least one health-care associated infection caused by carbapenem-resistant enterobacteria. The proportion of Enterobacteriaceae that were resistant to carbapenems increased from 0% in 2001 to 1·4% in 2010, with most of the increase recorded in *Klebsiella* spp.[1]

Health-care associated infections are also increasingly recognised in LMICs. Findings of a recent review[12] showed that pooled prevalence of health-care associated infections in resource-limited settings (15·5 per 100 patients) was twice the average prevalence in Europe (7·1 per 100 patients). Incidence of infections acquired in intensive care units in developing countries (pooled density 47·9 per 1000 patient-days) was three times the rate in the USA (13·6 per 1000 patient-days). Health-care associated infections in neonatal intensive care units in some countries (15·2–62·0 infections per 1000 patient-days) are up to nine times more common than in the USA (6·9 infections per 1000 patient-days). Both the need for antibiotics and the burden of resistance are likely to increase with the rate of health-care associated infections in LMICs.

These trends are globally consistent. Hospital data from developing countries suggest that resistance to the WHO-recommended regimen of ampicillin and gentamicin in pathogens causing neonatal infections (in the first 28 days of life) is common: 71% of isolates of *Klebsiella* spp and 50% of *E coli* are resistant to gentamicin.[13] Resistance is also a problem in early-onset, presumably maternally acquired, neonatal infections reported from hospital series in developing countries. 60–70% of *E coli* and nearly 100% of isolates of *Klebsiella* spp are ampicillin resistant, and 40–60% are resistant to gentamicin.[14] High rates of ESBL production in *E coli* have restricted the use of second-line treatment with extended-spectrum cephalosporins.[15] Many newborn babies in hospitals in south Asia are now treated with carbapenems as first-line treatment for sepsis or presumed sepsis. Most worrying is the emergence of pan-resistant untreatable carbapenem-resistant Enterobacteriaceae and *Acinetobacter* spp infections associated with high mortality in neonatal nurseries.[16]

In Pakistan, the emergence of pan-resistant bacterial isolates such as *Acinetobacter* spp and carbapenem-resistant enterobacteria as causes of health-care associated sepsis in hospitals is rendering these infections untreatable.[16–18] 50–60% of community-acquired Gram-negative pathogens such as *E coli* associated with urinary tract infections have become resistant to common oral antibiotics (eg, amoxicillin, cefixime, and ciprofloxacin), complicating outpatient management.

Between July 2010 and August 2011, 72% of 1294 viable *K pneumoniae* isolates from sentinel sites in South Africa had antibiograms suggestive of ESBL production.[19] Compounding this problem is the emergence of several carbapenemase-resistance mechanisms. NDM-1 was first detected in South Africa in September 2011,[20] and of 70 carbapenem resistant enterobacteria isolates from private and public hospitals received by the Antimicrobial Resistance Reference Laboratory between May and July 2013, 19 tested positive for NDM-1.[21]

In India, *E coli* isolated from urine cultures of pregnant women in their first trimesters in the community (n=1815) showed highest overall resistance to ampicillin, naladixic acid, and co-trimoxazole, as 75%, 73%, and 59%, respectively, between 2004 and 2007.[22] 30% showed resistance to injectable antibiotics, such as aminoglycosides (represented by gentamicin). In a study of bloodstream infections,[23] the proportion of *E coli* producing ESBLs increased from 40% in 2002 to 61% in 2009, and the proportion of *K pneumoniae* with carbapenem resistance increased from 2·4% to 52%.

Increasing rates of resistance to colistin and polymyxin B in Gram-negative organisms are being reported from countries around the world, including South Korea,[24] Italy,[25] Greece,[26,27] and Saudi Arabia.[28] Moreover, there is some evidence of cross-resistance to colistin and host antimicrobial peptides that are part of the body's immune response.[29]

Hospital-acquired MRSA arises worldwide. In high-income countries, it is being tackled with a combination of new antibiotics and better hospital infection control, but community strains of MRSA continue to proliferate.[30] In LMICs such as South Africa, 52% of 1147 *S aureus* viable isolates from hospitalised bacteraemic intensive care unit patients were MRSAs. Gram-positive infections are less common in India, but high rates of MRSA in clinical isolates in various studies in India have been documented as 54·8% (range 32–80%).[31] In Pakistan, rates of MRSA have been fairly consistent since the mid-2000s at roughly 50%.[32] However, community-acquired MRSA are increasingly reported, and rates range from 5–10%.[33]

The high burden of resistant infections

Although poorly quantified, the global burden of resistance is probably concentrated in three major categories: longer

duration of illness and higher rates of mortality in patients with resistant infections, increasing costs of treatment for resistant infections, and inability to do procedures that rely on effective antibiotics to prevent infection.

An estimated 25 000 people die every year in Europe from antibiotic-resistant bacteria.[34] In the USA in 2005, an estimated 94 000 invasive MRSA infections required hospitalisation and were associated with 19 000 deaths.[35] A recent report by the US Centers for Disease Control and Prevention conservatively estimated that at least 2 million illnesses and 23 000 deaths a year in the USA were caused by antibiotic resistance.[36] These estimates are useful for suggesting scale, but imprecise because resistant infections are more common in individuals on long courses of antibiotic treatment; it is difficult to ascertain whether resistance is the cause of death or a correlate of long antibiotic treatment, hospitalisation, and underlying sickness. Few reliable estimates are available for LMICs, but the higher burden of infectious disease and restricted access to new antibiotics suggest a higher burden than in high-income countries.

Findings of a study[37] of patients with bloodstream infections and pneumonia in 537 intensive care units in ten countries showed that the risk of death (hazard ratio) associated with antimicrobial resistance (additional to that of the infection) was 1·2 (1·1–1·4) for pneumonia and 1·2 (0·9–1·5) for bloodstream infections caused by bacteria resistant to ceftazidime (*A baumannii* or *Pseudomonas aeruginosa*), third-generation cephalosporins (*E coli*), and oxacillin (*S aureus*). Attributable mortality risk was highest for *S aureus* in both pneumonia and bloodstream infections. However, antimicrobial resistance did not significantly increase length of stay. *P aeruginosa* caused the highest burden of health-care-associated infections because of its high prevalence and the pathogenicity of both its drug-sensitive and drug-resistant strains.

Multistate models, used to address the temporal dynamics of admission, infection, discharge, and death, have found that, compared with patients without *S aureus* bacteraemia, the death hazard was 5·6 times greater with MRSA (95% CI 3·36–9·41) and 2·7 times greater with meticillin-sensitive *S aureus* (MSSA) bacteraemia (95% CI 1·33–5·39).[38] After adjustment for comorbidity, hospitalisation, age, and sex, the death hazard was 2·9 times greater with MRSA (95% CI 1·70–4·88) and 1·7 times greater with MSSA (95% CI 0·84-3·47). A long-term follow-up study[39] of 2000 patients with *S aureus* or *E coli* bloodstream infections found an 80–150% increase in mortality associated with resistance at 30 days after infection. At 90 days, MRSA had twice the attributable risk of death relative to MSSA.[38]

In LMICs, where the ability to pay for second-line drugs is limited, worse health outcomes, especially in neonates are more common. Even with effective antibiotics, infections are the major cause of neonatal deaths, which in turn account for more than a third of the global burden of child mortality.[13] More than half of neonates with ESBL sepsis can die (*vs* a quarter of neonates with non-ESBL infections), and a half of neonates with MRSA die (*vs* 21% of neonates with MSSA).[40] At these rates of mortality, roughly 106 514 neonatal deaths are attributable to Gram-negative organisms and *S aureus*, and 58 319 are attributable to ESBL resistance and MRSA in India alone.

In addition to the costs to human lives, high economic costs for health care exist,[41] and these resources could be deployed elsewhere.[42] Resistant infections are more expensive to treat and patients infected with resistant strains of bacteria are more likely to require longer hospitalisation and face higher treatment costs than are patients infected with drug-susceptible strains.[43,44] According to one estimate, between 1997 and 1998, increases in drug resistance raised the cost of treating ear infections by about 20% (US$216 million).[45] Reduced *Streptococcus pneumonia* sensitivity to penicillin in many parts of the world has resulted in the need for more expensive antibiotics including fluoroquinolones, oral cephalosporins, and macrolides, driving up the cost of treatment. In vitro resistance of *S pneumoniae* to β-lactams, macrolides, and other antibiotics has increased worldwide as a result of the global dissemination of a few pandemic clones. However, the most of roughly 826 000 pneumococcal disease deaths in children younger than 5 years likely result from poor access to antibiotics rather than drug resistance.[46] Although linezolid remains active against most *Staphylococcus* spp, resistance has emerged and is moving upwards.[47] Linezolid resistance has also been reported in *Enterococcus faecium*[48] and *Enterococcus faecalis*.[49]

A third consequence of resistance is related to the inability to do other interventions such as surgery, transplantation, and chemotherapy.[50] Investigators of a recent study estimated that, without effective antibiotics, 30–40% of patients having total hip replacements would have a postoperative infection, with a case-fatality rate of roughly 30%.[51] This burden, although poorly quantified, affects all countries and is likely to be the main way in which resistance drives up health-care costs.

Uses of human and agricultural antibiotics are increasing

Antibiotic use is a main driver of selection pressure that contributes to resistance, and because consumers do not understand this problem, the drugs are among the world's most commonly purchased. Most antibiotics are used unnecessarily, in commercially driven agriculture, and by physicians uncertain of a diagnosis or treating largely self-limiting bacterial or viral infections. In high-income countries, patients with resistant infections can turn to more expensive, newer-generation antibiotics, but in developing countries, where infectious diseases are common and the burden is high, patients might be unable to obtain or to afford second-line treatments.

Large differences in the frequency of resistant infections have been noted, both across European countries[52] and among regions of the USA.[53,54] Variations

in antibiotic consumption, both between and within countries,[52,55–59] might explain the differences. Consumption of antibiotics in countries reporting data to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) in 2010 varied from 11·1 (Estonia) to 39·4 (Greece) defined daily doses per 1000 inhabitants per day.[60] Consumption of carbapenems increased in 15 of 19 countries reporting data to ESAC-Net between 2007 and 2010. Data from ResistanceMap from the USA suggested that between 2007 and 2010, there was a downward national trend in outpatient antibiotic consumption. Prescriptions fell by 17% between 1999 and 2010. However, states in southeast USA continued to consume more than twice the amount of antibiotics per person than did those in the Pacific northwest and New England.

For more on **ResistanceMap** see http://www.cddep.org/ResistanceMap/key-findings#.UnJxKfk73To

Worldwide, antibiotic consumption is on the rise (figure 1). Although carbapenems are expensive, sales in Egypt, India, and Pakistan have increased with over-the-counter availability.

Non-prescription antibiotic use is common in many LMICs, where ensuring that people who truly need antibiotics have access while discouraging unnecessary use is a challenge. Non-prescription use accounts for 19–100% of antibiotic use outside northern Europe and North America.[61] Even when prescriptions are needed to obtain antibiotics, physicians might not adequately screen for appropriate use.

In Japan and the USA, patients drive expectations for antibiotic prescribing. In China, hospitals that rely on pharmaceutical sales for income have an incentive to overprescribe; one study[62] estimated that a quarter of revenue in two hospitals came from antibiotic sales. In India, doctors routinely receive compensation from drug sellers in exchange for directing patients to their pharmacies. Antibiotic sales increase with insurance status of patients because patients with insurance are likely to be less price sensitive.[63] Antibiotic prescribing might also be affected by competition between health-care providers; in Taiwan, a one standard deviation increase in competition raises antibiotic prescription by up to 2·4%.[64] Competition from unsanctioned providers also exacerbates competitive pressure on legitimate medical professionals. Little evidence exists that trained providers give more appropriate treatment than do untrained pharmacy attendants, perhaps because pharmacists often mimic prescription patterns of other local providers and unwittingly copy both desirable and undesirable practices. A study[65] from Thailand found that a pharmacy's proximity to a hospital improved the appropriateness of antibiotics sold.

Many drivers of antibiotic consumption are based in human medicine, but antibiotic use in veterinary medicine and for growth promotion and disease prevention in agriculture, aquaculture, and horticulture is also a major contributing factor. Although precise estimates are scarce,

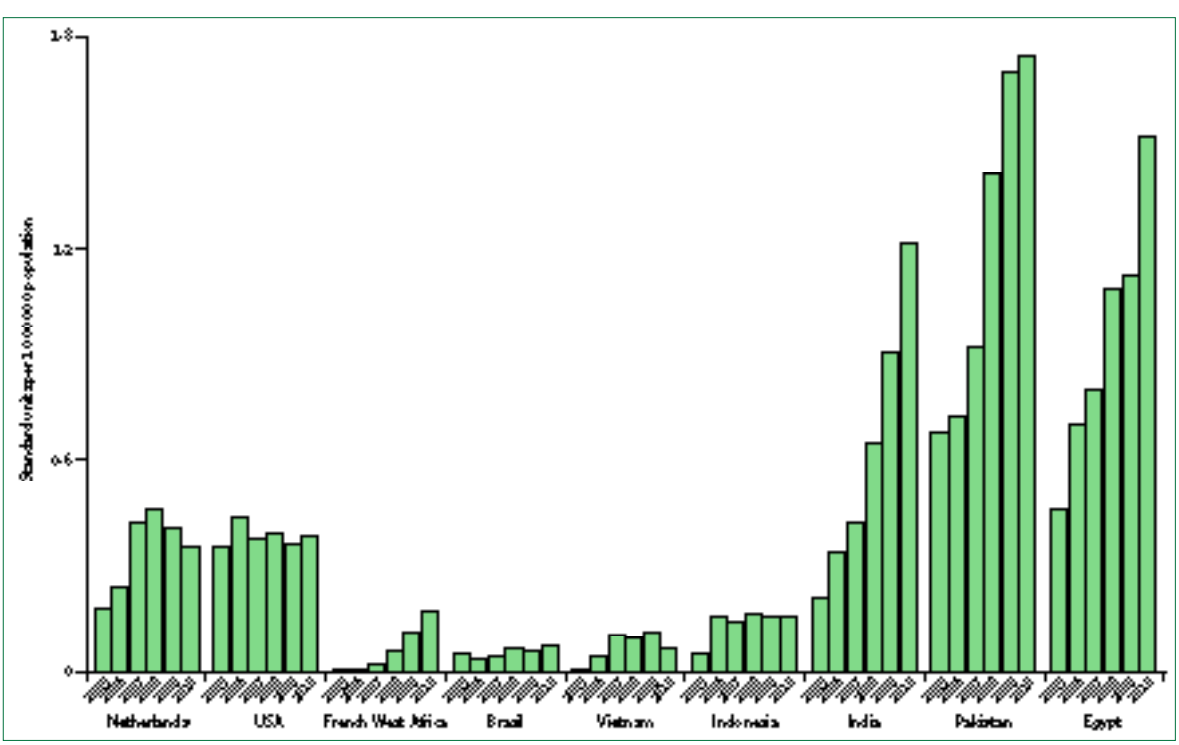

Figure 1: **Trends in retail sales of carbapenem antibiotics for Gram-negative bacteria**
Based on data obtained from IMS Health's MIDAS™ database. *An IMS grouping of Benin, Burkina Faso, Cameroon, Congo (Brazzaville), Gabon, Guinea, Ivory Coast, Mali, Senegal, and Togo.

of the crudely estimated 100 000–200 000 tonnes of antibiotics manufactured every year,[66] most goes to the agricultural, horticultural, and veterinary sectors. The finding of low levels of resistance in polar bears on the isolated Arctic archipelago of Svalbard supports the hypothesis that ecological resistance close to human settlements is anthropogenic in origin (figure 2).[67] Although the transfer of antibiotic resistance plasmids from treated animals to human beings has been long suspected,[68] findings from recent studies using whole-genome sequencing have confirmed animal-to-human transfers of resistance genes.[69]

A global system for surveillance of antibiotic use and resistance and its health and economic burden is urgently needed. Surveillance should include environmental sampling in addition to examination of clinical isolates.

Louise Murray/Science Photo Library

Figure 2: **Antibiotic resistance in nature, such as that identified in polar bears in Svalbard, is likely anthropogenic**

Part 2: Getting out of the impasse

How did we end up here?

The lack of understanding of the unique features and risk of resistance has paved the way for the present epidemic. Moreover, few studies have been done on the magnitude of the burden to convince policy makers of the urgent need to react. Since the penicillin era, antibiotics have been viewed as wonder drugs that could be prescribed without fear of harm, despite early warnings of consequences such as antibiotic resistance and side-effects.[70,71] Their use has spread into many non-medical areas, and has been unregulated, both legally and illegally. Antibiotic resistance is perceived as a complex medical problem. Antibiotics are different from all other drug groups in that the effects of their use extend far beyond individual patients. Even more worrying is the accumulating evidence that antibiotic use in seriously ill but uninfected patients can actually increase mortality.[72]

Traffic and selling of antibiotics at markets, shops, and pharmacies is largely unregulated, without prescription, and even without involvement of a person with pharmaceutical training.[61] This widespread access is made easier by the internet and marketing stunts for free or cheap antibiotics. Selective information and material incentives from pharmaceutical companies influence doctors in affluent countries, leading to some regulation of their activities; however, with new markets emerging, more influence is to be expected in low-resource settings, which often do not have other sources of information and training. For instance, prescribers in Kisangani, the Democratic Republic of Congo, mentioned pharmaceutical companies as the first source of information about antibiotics.[73] Production and use continues to increase generally in an uncontrolled way in developing countries.[74]

In the non-medical arenas of agriculture, aquaculture, and intensive farming, huge amounts of antibiotics are used in some countries—up to four-times the amount used in human medicine.[75] There is little separation of the types of antibiotic used in human beings and animals.

Moving on

National approaches and commitment

Countries that have implemented comprehensive national strategies have been the most successful in controlling resistance.[76–79] These strategies include, but are not restricted to, good health-care infrastructure and health insurance for all; limited drug advertising; surveillance of antibiotic use and to detect resistance in human beings and animals; policies for prudent antibiotic use in human beings and animals; standardised infection control policies and sufficient staffing; antibiotic stewardship programmes in hospitals and other health-care facilities; and isolation or decontamination of patients with resistant organisms.[76] In particular, several European countries have introduced these strategies. Additionally, countries with cases of antibiotic resistance have found a targeted national approach successful—eg, the UK for control of MRSA and *Clostridium difficile*.[77] Israel controlled KPC by a national approach,[78] and the USA has implemented various initiatives.[79] However, these programmes need time and patience to be set up and need to be backed by visionary governments with adequate funding. A stepwise approach to a national strategy according to a contextualised and prioritised road map might be the best way forward for most settings. In resource-poor countries, there has been much less progress, although China and India notably have made important steps recently. A meeting of professional societies in India issued its Chennai declaration[80] and the Chinese Government has enacted policies to restrict antibiotic use, including the initiation of a campaign on antibiotic resistance, stratification of antibiotic use, and enforced restriction on drug prescription.[81] Proposals for the stepwise development of activities of a national task force based on experiences from several LMICs are being developed by the Global Antibiotic Resistance Partnership (Ramanan Laxminarayan, Personal Communication).

For more on the **Global Antibiotic Resistance Partnership** see http://www.cddep.org/projects/global_antibiotic_resistance_partnership

Rational antibiotic use in hospitals

The set of activities and policies to improve the rational use of antibiotics is also known as antibiotic stewardship. Essential elements of an antibiotic policy include a stable and restrictive list of antibiotics in use, standard treatment guidelines, audit and feedback of prescriptions, surveillance of bacterial resistance and antibiotic use, and education at all levels.[82] Antibiotic stewardship has typically been developed in the hospital context in resource-rich countries, but stewardship activities should be expanded to primary care on a national level. Its combined goals are improved outcomes for patients, containment of antibiotic resistance, and increased cost-effectiveness of care. Antibiotic stewardship should be done by all health-care facilities and should be part of accreditation programmes.

Effective stewardship programmes can decrease antibiotic use by 20–40%, incidence of health-care-associated infections (*C difficile*, MRSA, and others), lengths of stay, and prevalence of bacterial resistance.[83,84] Ideally, stewardship teams should include an infectious diseases physician, a (clinical) pharmacist with infectious diseases training, a clinical microbiologist, information system specialist, infection control professional, and a hospital epidemiologist, but such specialists might not be available.[85]

Barriers to the implementation of effective and sustainable programmes exist in many regions of the world. The bottlenecks for implementing stewardship in both resource rich and poor countries are often strikingly similar, largely as a result of insufficient leadership, commitment, and funding. Standard treatment guidelines, which are essential to steer the use of antibiotics, can be counterproductive if not updated regularly and well implemented. National guidelines, particularly in LMICs, if present, are often outdated or not disseminated to the genuine prescribers, who in turn might use a combination of outdated textbooks, international but locally irrelevant guidelines, or just the habits of their teacher.[86] Concentrated efforts at national levels are needed to invest in the revision of standard treatment guidelines into clear, simple, updated, evidence-based, locally relevant, and accessible documents. A recent national project launched in Vietnam has, as one of its objectives, the development of updated guidelines for several important infectious disease syndromes.[87] Establishing the resistance threshold for particular infections warranting the switch to an alternative empirical antibiotic is a particular challenge.[88]

Rational antibiotic use in the community

A programme on rational antibiotic use or antibiotic stewardship in the community should cover a wide range of settings, such as ambulatory care facilities, pharmacies, drug vendor outlets, households, and agriculture. Overuse and irrational use of antibiotics, either driven by the supply or demand sides, have been documented in all these settings.[89] On the supply side, physicians are often role models for other health professionals and patients who learn how to use antibiotics from their prescriptions.[2] Apart from medical training, physicians are influenced by their peers, and perceived demands of patients. Therefore, physicians might find it difficult to comply with treatment guidelines.[90] These barriers to compliance should be removed or minimised, and options for alternative actions for guideline compliance should be simultaneously provided.[91] Examples of options for non-antibiotic treatment in viral or self-limiting infections are the prescription of herbal medicines, as opposed to antibiotics,[92] and use of a delayed prescription technique with explicit instructions for patients about when to use antibiotics.[93]

To encourage guideline compliance, consequences of irrational use of antibiotics should be reframed to be relevant to the self-interest of prescribers and institutions. Motivational measures include pay-for-performance policy,[92] the audit-feedback mechanism on antibiotic prescribing rates of individual prescribers,[94] and public disclosure on antibiotic prescribing rates of each health-care facility or area.[95] Major challenges arise when antibiotic prescriptions are a source of revenue for individuals or institutions, either by a fee-for-service remuneration scheme[96] or drug-promotion incentives.[97] In this case, a combination of the audit-feedback and the public disclosure measures seems to be useful. However, in many resource-poor countries, doctors own the pharmacies and, therefore, the financial incentives to prescribe expensive antibiotics are even greater than with a fee-for-service reimbursement. In these settings, separation of prescription and dispensing activities are needed.

On the demand side, self-medication by consumers with antibiotics purchased without a prescription is common, especially in eastern and southern Europe, Africa, South America, and Asia.[61] Consumers have positive attitudes towards antibiotics, but paradoxically they have poor knowledge about these drugs and diseases.[98] The availability of antibiotics without prescription—an important enabling factor—mainly results from absence of prescription-only regulation, ineffective law enforcement, poverty-driven practice, culture, and norms.[99,100] Suboptimum compliance on use, including taking leftover antibiotics from previous treatment courses and sharing unused drugs with other people, is common in both developed and developing countries.[101] Improvements in health-care financing might positively affect access to a full course of antibiotics.

Ideally, consumers should have access to accurate information on antibiotics and infectious diseases instead of access to antibiotics without prescription. A ban of over-the-counter sale of antibiotics has been implemented in many countries including Chile.[102] Some countries launch national campaigns (eg, the US Centers for Diseases Control and Prevention's Get Smart or Antibiotic Awareness Day in the European Union [EU]), with the aims of improving knowledge of

For more on the **Get Smart campaign** see http://www.cdc.gov/getsmart/

resistance and lowering of antibiotic use among consumers and prescribers.[103]

For countries with inadequate health delivery systems, prescription-only regulation might impede access to antibiotics. Although regulation is crucial to safeguard access to antibiotics, a transition towards such regulation needs governmental commitment and improvements in health systems that are not possible in many countries. Hence, antibiotic stewardship programmes need to be adjusted to local conditions—eg, use of telemedicine to help with treatment decisions and the referral process[104] and to help community pharmacists make good decisions about antibiotic dispensing. More research is needed on how to balance the effects of specific interventions on individual health versus increasing the resistant bacterial population. In low-resources countries, stewardship programmes to empower drug vendors on rational use of antibiotics seem promising, but further research is needed.[105]

Education and changing social norms

When irrational use of antibiotics repeatedly happens among the public and health professionals, it becomes the norm. To break this pattern, antibiotic stewardship programmes should focus not only on appropriate use, but also on ensuring sustainability of behavioural change and reorientation of social norms.[92,106] Such a stewardship programme in an LMIC is the Antibiotic Smart Use Program in Thailand.[92] Many bottlenecks remain in the promotion and sustainability of good prescription practices, especially with regards to social norms. Solutions need to focus on multifaceted and multilevel interventions that define local barriers and beliefs, which can vary widely between cultures, countries, and regions.

Education of all health-care workers, laboratory staff, veterinarians, and the public on appropriate antibiotic use and antibiotic resistance is essential, and educational strategies have recently been reviewed.[107] Although education alone might not be powerful enough as an intervention, it generates knowledge that is essential for health-care workers to understand and support the resistance control programmes; such education should be started very early in the medical curriculum.[107] The role of up-to-date undergraduate and postgraduate education is even more important in settings with restricted access to medical literature.

Clear information for policy makers about antibiotic resistance and its effect on public health has a crucial role in making this complex problem tangible; initiatives such as the Drug Resistance Index might help to achieve this.[108] Educational and awareness campaigns for the general public might help to generate an understanding that can support the prescriber to withhold antibiotics.[109] Although hard endpoints are difficult to define and to measure, these campaigns seem to contribute to more careful use of antibiotics. Education should be tailored and started early on to shape behaviour rather than having to change it.

Infection control

Better than treatment of infection is, of course, prevention. From a resistance perspective, prevention reduces antibiotic use and the spread of resistant bacteria; however, prevention is not the main strategy to control resistance because antibiotic use also needs to be controlled. Nevertheless, at the community level, improvement of sanitation, access to clean water, poverty reduction, and vaccination will have a huge effect on both infectious disease incidence and transfer of and colonisation with resistant genes and multidrug-resistant organisms.

At the hospital level, prevention of health-care-associated infections, which are often multidrug resistant, is essential, but challenging. Besides hand hygiene, the importance of which cannot be overemphasised, benchmarking (open comparison of between health-care facilities) of frequencies of health-care-associated infections is useful to decrease the number of these infections. Observation makes one more careful; most of the infection control policies in place have been developed around MRSA, vancomycin-resistant enterococci, *C difficile*, catheter-related bloodstream infections, catheter-associated urinary tract infections, and ventilator pneumonia. Infection control interventions need to be reassessed and improved in an era with multidrug-resistant Gram-negative bacilli and mobile antibiotic resistance genes. Additionally, cultural barriers for implementation of basic hygiene procedures are probably a widespread problem and need much more study.

Role of diagnostics

Efforts to improve microbiological laboratories are underway. Speed of testing and laboratory automation have been the focus of recent developments. In trying to reduce testing time, various methods have been developed (eg, PCR-based tests, various point-of-care tests, and MALDI-TOF mass spectrometry). These tests are supplementary to detect disease-causing pathogens next to traditional culture-based methods because they detect only the pathogens for which the test is designed.[110,111] Diagnostic methods that reduce antibiotic use or narrow the spectrum should be promoted. Even if these methods do not have a direct benefit on clinical outcome, reduction of antibiotic pressure can help to slow induction and spread of resistance.[112–114]

Besides direct care of patients, the results of diagnostic microbiology testing are used to inform local, regional, and national surveillance systems. A successful example is the significant reduction in MRSA bacteraemia in hospitals in the UK since implementation of mandatory MRSA surveillance in 2001.[115] Surveillance of bacterial resistance generates essential information, which promotes and directs stewardship activities. The scarcity of quality-assured microbiology laboratories in low-resource settings and lack of priority given in the past decades to sustained bacterial surveillance have led to large empty areas on the worldwide resistance maps, especially for sub-Saharan Africa and rural Asia.[116]

Peter Chadwick/Science Photo Library

Figure 3: **Waste-water treatment facilities can be hotspots for horizontal transfer of resistance**

Quality-assured basic microbiology services and routine bacterial resistance surveillance are urgently needed in most of these areas. Positive experiences in high-income settings, such as Europe,[117] with its easy-to-understand, interactive, and yearly updated data, could inspire policy makers in other regions. The addition of antibiotic resistance to death registers might help to raise awareness of antibiotic resistance on the priority agenda of policy makers.

Beyond use in human beings

Bolder interventions outside hospitals and a move to ecological antibiotic stewardship are needed. Strategies should be focused on control of non-human sources of antibiotics, resistant bacteria, and resistance genes, such as agriculture and waste water from the pharmaceutical industry. The issue of antibiotic resistance should be part of the one-health movement. Use of antibiotics as growth promoters should be banned worldwide as has happened in the EU. In Denmark, the banning of growth promoters in livestock resulted in a net reduction of animal antibiotic use with no or minor increases in production costs without increased incidence of zoonotic infections in human beings.[118] Worryingly, last resort drugs, such as colistin, are being used extensively in agriculture.[119] Recent initiatives, also in the EU, are trying to limit the use of this drug in agriculture.

The environment is key in the spread of resistance. For example, wastewater treatment facilities can be a hotspot for horizontal resistance gene transfer (figure 3).[120] Strategies to reduce this mode of transfer are warranted, including neutralisation of antibiotics in wastewater and in the environment generally. Findings from a recent study[121] showed that chlorination of drinking water can actually concentrate some antibiotic resistant genes. Research efforts need to focus on how to reduce and neutralise manmade antibiotic pressure and how to control the resistance gene pool in hotspot environments.

Research

Research efforts need to be focused on intervention strategies and solutions rather than doom-and-gloom reports. Until recently, MRSA and vancomycin-resistant enterococci governed the resistance agenda, but now, multidrug-resistant Gram-negative bacteria are the main cause for concern. However, findings (summarised in the recent Cochrane reports[122] and elsewhere) show that community and hospital antibiotic stewardship interventions can modulate prescription enough to reduce resistance in many organisms in some settings. Time-series analysis can be used by all hospitals with computerised databases of antibiotic consumption and resistance rates. This approach allows interventions to be tailored to individual scenarios and prediction of resistance rates, and this information can be used to develop local treatment guidelines.

Besides antibiotics, new treatment strategies under investigation include methods to stop plasmid replication[123] or resistance mechanisms such as efflux pump inhibitors.[124] Furthermore, bacteriophage treatment—used in the 1920s and later in the Soviet era—is being investigated as another potential strategy, but regulatory requirements for these types of drugs are challenging,[125] and their use might not extend to life-threatening infections.

Safeguarding the future

Will any set of interventions be effective enough, in view of the present wave of antibiotic resistance? Suggested interventions are not optional, they are basic requirements to ensure rational use of antibiotics and optimum outcomes for patients. Enlightened national and global leadership is needed along with sufficient technical capacity at all different policy levels. Comprehensive national and international plans, like those in the EU,[126] are needed, and should have similar visibility and effect to those for other important health problems such as HIV, tuberculosis, and malaria. Additionally, these national plans need to take into account their interfaces with health-care organisation, quality assurance and financing, and professional education. The scientific community should clarify the causes, scale, and fast pace of the evolution of resistance. Antibiotic resistance should be on the global political agenda, not just the agendas of infectious disease meetings.

Emphasis is placed on reinvigoration of the drug discovery industry, but there is a sense that all low-hanging fruit have already been picked and that new developments, even if successful, cannot sate demand and will be only a temporary fix. Many people believe that with billions of years of evolution, bacteria will always be better genetic engineers than people. Antibiotics are a natural product of bacteria and so resistance mechanisms are not new. Therefore, antibiotics are a precious public good and their intended and unintended environmental release needs to be monitored and controlled.

Stewardship efforts might win a battle, they will certainly not win the war. Antibiotic stewardship—an

integral part of standard care provision—should be part of hospital accreditation. Besides, a holistic, ecological, one-health approach is needed. There is an urgent need to stop enriching the resistance gene pool with unnecessary antibiotic pollution. The issues of antibiotic resistance are akin to those of global warming due to excess use of carbon-based fuels with the resultant pollution, and we need a worldwide agenda, perhaps like the Kyoto agreement, but with much more adherence.[127] Solutions will not be easy and, paradoxically, might include increasing the price of antibiotics to put a true value on their use, while maintaining the delicate balance between overuse versus lack of access. There is room for innovative ideas in quality assurance, health financing, and social marketing.

The future of antibiotics and survival of every human being that acquires a bacterial infection will depend on the serious commitment of many stakeholders, including government authorities, policy makers, health-care workers, university teachers, pharmaceutical companies, and consumers.

Part 3: Minimising the time to effective treatment—rapid diagnostic testing

Diagnostic uncertainty drives irrational use

Diagnostic (viral or bacterial cause) or prognostic (life-threatening or self-limiting infection) uncertainty makes it difficult for clinicians to know when to provide and when to withhold antibiotic treatment. Consequently, antibiotics are overused in hospitals and outpatient settings, resulting in increased antibiotic resistance[52] and the pandemic spread of highly resistant bacterial clones.[128] Findings of studies of patients with acute cough—one of the most common reasons for consultation in primary care and antibiotic prescription in high income countries—showed that antibiotics did not meaningfully change important outcomes.[129,130] Since the early days of discovery of bacteria, culture-based assays have remained the gold standard for identification of pathogens and susceptibility testing. However, these methods are slow, typically identifying causative pathogens in at best 24 h, and returning susceptibility results in 48 h. Minimisation of time to effective treatment decreases morbidity and mortality in severe infection.[131]

The effects of antibiotic resistance on human health are probably highest in countries with the lowest income because the spread of resistant bacteria is facilitated by poor hygiene, contaminated food, polluted water, overcrowding, and increased susceptibility to infection because of malnutrition or HIV. Personalised medicine based on novel and rapid diagnostic strategies should help identify patients who need antibiotics. In many such settings, the need for alternative technologies is also pressing, because routine culture and susceptibility testing are not provided, even to support diagnosis of life-threatening infections like pneumonia and meningitis (figure 4).[132] Immunoassays provided a faster option, but the potential for changing the landscape of diagnostic testing became clear with the development of the PCR in the 1980s.[133] Since then, we have seen a technological revolution with the development of many complex, highly specific molecular diagnostic assays. These systems can decrease the time needed for detection of biomolecules, like proteins and nucleic acids, from a few hours to a few minutes, and should greatly improve medical diagnostics. However, most of these technologies have not yet reached clinical diagnostic laboratories.

Defining the medical needs

Many available rapid diagnostic tests are designed on the basis of microbiological grounds and detect as many microbes as possible, rather than on clinical grounds to address the real medical need. Furthermore, no consensus exists on how quickly tests should produce results to identify patients who really need an antibiotic—should companies only invest in developing technologies that produce results in less than 30 min in primary care or less than 1 h in hospital care? If so, very few companies have technologies in their pipelines that can meet these requirements. So should a first dose of antibiotics be given and then treatment adjusted on the basis of diagnostic test results?

How do the needs (eg, speed, robustness of system, cost, and user friendliness) in industrialised countries compare with those in lower resource settings? And how will these needs fit with the different health-care models and reimbursement systems? Should companies develop tests that identify pathogens and detect resistance, or is the identification of which organisms caused the infection not important as long as doctors know which antibiotics are needed? Which antibiotic resistance genes are always expressed in vivo and could therefore be targeted in the system? Quantitative microbial cultures with cut-offs (expressed in colony forming units per mL) are used to distinguish between colonisation and infection, but should technologies be developed that also define molecular load thresholds (expressed in number of DNA copies per mL) to distinguish the colonisation and infection status of potential pathogens in different types of samples? How should diagnostics be used in clinical trials to identify patients infected with targeted pathogens or multidrug-resistant organisms? Many companies are struggling to align their business goals with the technology solutions because these fundamental questions have not been properly addressed by experts in the specialty. A technology road map on rapid diagnostic tests for infectious diseases is needed to help forecast, plan, and coordinate technology developments that meet real medical needs.

Huge technical challenges

Molecular tests can reduce the time to yield results but come with many drawbacks, including complex sample preparation, little integration of the different steps, inability to handle large volumes or multiplexing for

Biophoto Associates/Science Photo Library

Figure 4: Culture-based methods remain the cornerstone of diagnosis and resistance testing

detection of many different targets, and high cost. Ideally, so-called sample-in to results-out technologies are needed that integrate sample preparation, amplification, detection, and analysis. The system should be able to detect pathogens and host biomarkers (proteins and nucleic acids) simultaneously. Sample preparation remains the largest bottleneck in miniaturised diagnostics:[134] large volumes (several millilitres of blood) need to be reduced to small amounts (in the order of microlitres); the microbial load in the sample can vary a lot and be very low; the target should remain intact, but many complex specimens contain nucleases or inhibitors of nucleic acid amplifications. Therefore, most sample preparations of available miniaturised molecular systems rely on many operations, and need several liquid additions and washing steps.

Most microfluidics-based systems rely on conventional benchtop sample preparation, thus restricting their use in point-of-care tests with limited or no laboratory access. Conversion of these off-cartridge sample preparation steps to cartridge-based microfluidic systems will be challenging because the microscale physical conditions (eg, the surface/volume ratio) can alter the assay conditions. Additionally, the reliability and cost of lab-on-a-chip systems typically increase with a factor per added component, such as fluidic interfacing, valving, pumping, microscale mixing, and waste disposal. Although microfluidics offer great promise in the area of rapid diagnostics, a microscale assay needs to be carefully designed, in which novel solutions should provide integrated functionalities in a minimum amount of unit steps and in a minimum cartridge size. Finally, most rapid diagnostic tests are based on detection of nucleic acids, but several other technologies are being pursued (eg, impedance and magnetic resonance) and several national and global initiatives are supporting the development of these new technologies.

Lack of guidance for assessments

Few guidelines for the assessment of clinical diagnostic tests for infectious diseases exist. Companies often claim sensitivities and specificities close to 100% without oversight on the design and conduct of the diagnostic assessments. Moreover, these values are calculated with spiked or archived samples, and are not indicative of the real-world situations in which tests will be used. Other factors often not taken into account (eg, conditions of storage and shelf life) are also important, especially in LMICs.[135] If standards are available for the assessment of diagnostic tests, they are published in industrialised countries and are not necessarily applicable to diseases prevalent in other settings.[136] Finally, few studies investigated rapid diagnostic tests in terms of effect on antibiotic use or resistance, or patients' outcomes.

Poor performance of molecular tests

Despite excellent analytical sensitivity and specificity, the test might perform poorly in clinical trials or routine use, depending on study groups (screening *vs* diagnosis, symptomatic *vs* asymptomatic, active *vs* latent infection), setting (low *vs* high prevalence), complexity of test (done by trained *vs* unskilled staff), and comparator (more or less sensitive than the comparator test). Assessment of molecular tests has been mainly analytical and few were extensively assessed with clinical specimens from clearly defined populations of patients from a wide geographic area. Findings from multicentre studies showed significant variations of detection rates of molecular tests between laboratories, with different or even the same tests, even though some of the laboratory personnel were very experienced with the use of amplification assays.[137,138] Standardisation of methods and reference reagents is needed for complete quality assessment programmes, including proficiency panels to assess the performance of molecular tests. A network of designated diagnostic laboratories that can assess molecular tests, alongside routine diagnostic testing, would be a step forward.

No proven clinical benefit

Assessment of the quality of molecular tests should take clinical usefulness into account. However, diagnostic tests are sold and used without good evidence of effectiveness, especially in developing countries, and the endpoints that should be used in clinical trials have not been agreed upon. Very few well designed preclinical and clinical trials have been done to show that rapid diagnostic testing improves clinical outcome or reduces antibiotic resistance. Although more recently, clinical trials on the performance and effectiveness of diagnostic tests were funded by the public sector (eg, the European Commission's Framework Programmes), most trials are still sponsored by the

industry (many of these are small biotechnology companies, which have limited resources and expertise to do such trials).

No studies have assessed the best integration of tests into health-care practice. The danger is that novel and expensive technologies could become representative of high-quality care with little evidence to support their use. Technological innovations that allow more personalised medicine are likely to raise rather than lower health-care costs. A McKinsey report[139] estimated that four countries (Austria, Portugal, Spain, and the USA) would spend more than 20% of their gross domestic product on health care, and only five of 21 Organisation for Economic Cooperation and Development countries (Denmark, Italy, the Netherlands, Sweden, and the UK) would spend less than 15% by 2040. The USA would allocate nearly 30% of its economic output to health care by 2040. Therefore, if new technologies are to be successfully implemented, we will need to move away from the business-as-usual approach, to develop new and smarter pathways of care, and to show that they are cost-effective.

What samples should be used?

No consensus exists on the best sampling sites for detection of pathogens in many infectious diseases. Good studies comparing different specimens are scarce or results inconsistent. Most of these studies are based on conventional diagnostic microbiology and cannot be extrapolated to molecular diagnostics. For example, acute community-acquired respiratory tract infections are the commonest reason for the prescription of antibiotics. However, we do not know what the best specimens are to detect many of the pathogens causing respiratory tract infections, or how to distinguish between organisms infecting the lower respiratory tract and those colonising the rhinopharynx (eg, nasal aspirate, nasopharyngeal aspirate, nasal swab, nasopharyngeal swab, nasal wash, oropharyngeal swab, or sputum). Depending on the organism, distinct differences are seen when comparing different specimens by use of conventional diagnostic microbiology.[140] However, with more sensitive molecular methods, such as nucleic amplification systems, the differences in recovery rates between the respiratory specimens might be more subtle.

Role in antibiotic stewardship is controversial

Over the past decade, the prevalences of infections caused by ESBL-producing and carbapenemase-producing Gram-negative bacteria have increased significantly.[128] A rapid assay that can detect infection with such organisms should improve outcomes for patients because delay in initiation of effective antimicrobial treatment tends to be associated with increased mortality.[131] However, whether rapid diagnostics for detection of genetic resistance markers are useful to guide treatment remains controversial. First, the available molecular assays are not truly rapid diagnostic systems because many of them require bacterial DNA as a template and hence, are heavily reliant on conventional culture.[141] Second, whether susceptibility tests are enough or whether laboratories should still seek ESBLs and carbapenemases directly is unclear.[142] Third, limited data suggest an association between minimum inhibitory concentrations (MICs) and outcomes for patients with Gram-negative infections.[143] Hence phenotypic testing based on MIC values might guide antimicrobial treatment better than do genotypic tests that detect the resistance mechanism. If the susceptibility test results (susceptibility category or MIC, irrespective of resistance mechanism) should guide treatment, molecular assays for detection of ESBLs or carbapenemases might have little value for management of infected patients. For infection control purposes, these assays could still be very useful in the detection of carriers and prevention of transmission.

Many barriers for use

Research needs to move beyond comparison of point-of-care test performance with laboratory tests to an agenda of understanding barriers and opportunities regarding uptake into routine care. Despite findings from several studies showing that simple and user-friendly tests for detecting C-reactive protein[144] and procalcitonin[145] are effective in achieving important reductions in antibiotic prescribing, these tests are still not widely used. Many barriers, including physicians' attitudes towards diagnostic testing, approval by regulatory authorities, recommendation by guidelines, social, ethical, economical, and political factors, affect the uptake of new diagnostic technologies and delivery into health systems. Many countries, especially in low-resource settings, do not regulate in-vitro diagnostics or require submission of clinical trial data.[136] Input and help from behavioural sciences and social marketing are needed to address barriers to acceptance of rapid diagnostic tests and to help understand motivational factors that could help to overcome hurdles to effective use of these tests in management of patients.

Guidelines de-emphasise diagnostic microbiology

Many guidelines do not recommend conventional diagnostics to identify the pathogens or they recommend treatment initiation within a short timeframe (eg, treatment of community-acquired pneumonia), leading to excessive empirical treatment with broad-spectrum antibiotics.[146] Additionally, in developing countries, where access to diagnostic laboratories is limited, patients presenting with a particular syndrome are treated for all major causes. Although generally cheap, this approach results in inappropriate antibiotic treatment without syndromic diagnosis of disease. Rapid diagnostic tests for detection of causative agents or biomarkers at the point of care are needed to allow prompt and specific targeting with a narrow-spectrum antibiotic. Rapid diagnostics would boost development of narrow-spectrum antibiotics because companion diagnostics are a prerequisite to the prescription

of these drugs. Improved diagnostics would also reduce the cost of clinical trials by enabling focused enrolment of only those patients infected with target pathogens.

Part 4: The interface between people and animals

Antibiotic use in animals

Use of antibiotics in animals and its potential effect on human health has been a controversy for at least half a century, presently fuelled by the crisis of resistance. Predictably the debate is polarised. Results of scientific studies have sometimes been conflicting, which is confusing for readers unfamiliar with the context. Although the discussion here is restricted to terrestrial animals excluding honeybees, aquaculture is also important in the overall discussion.

Use for growth promotion

The growth-promoting effect of low doses of antimicrobials was discovered in the late 1940s.[147] Feeding subtherapeutic doses of antimicrobials became an integral part of intensive rearing of animals. Undoubtedly, these practices supported the intensification of modern food production by facilitating early weaning, increased animal densities, and cheap feed sources.[148] Furthermore, suboptimum growth caused by unsanitary conditions is sometimes compensated with addition of antibiotics to feed.[148] Worldwide, many substances have been or are used, some of which are not used in human medicine (eg, flavophospholipol) and some from classes that are (eg, the macrolide tylosin). How these substances lead to increased growth rate is unclear, but prevention of enteric diseases, such as weaning diarrhoea, probably has an important role.[148] Low doses of tetracycline also reduces morbidity and increases growth of premature children.[149]

Where authorised, antibiotics used for growth promotion can generally be purchased over the counter without veterinary involvement. In many countries, growth promoting use of several antimicrobials is authorised and widely practised. In the EU, restricted authorisation of antimicrobial types began several decades ago. On the basis of recommendations by a committee chaired by Professor Michael M Swann, the UK withdrew authorisation for growth promotion of several substances including tetracyclines and penicillin in 1971.[150] The EU and neighbouring countries followed suit in the 1970s. Sweden banned the all use of antimicrobials for growth promotion in 1986, and Denmark, Finland, and Norway abandoned all such use in the late 1990s.[151] Finally, all growth promoting use was abandoned in the EU in 2006. In the USA, the Food and Drug Administration (FDA) has released draft guidelines on judicious use of antimicrobials in the rearing of animals for food production. These recommendations aim to reduce the overall use of medically important antimicrobials and include veterinary oversight and consultation. If this guidance is adhered to, a gradual phasing out of growth promoting use is to be expected.

For more on **ESVAC** see http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp

The effect of low doses of antimicrobials for growth promotion on antimicrobial resistance has been documented for several substances.[152] For example, use of the glycopeptide avoparcin was associated with the selection of vancomycin-resistant enterococci;[153] after its withdrawal, the prevalence of resistance decreased.[154]

Veterinary use

Generally, the most common indications for antimicrobial treatment or preventive use in terrestrial animals reared for food production are enteric and respiratory disorders in young animals and mastitis in dairy cows.[155] Untreated, these disorders affect animal welfare and productivity and can sometimes lead to substantial mortality. Therapeutic use can include individual animals, but can also be treatment of a group of diseased animals by injection or orally. Preventive use can be anything from targeted interventions to control the spread of a diagnosed disease in a defined group of animals to routine treatment of all animals during specific periods of stress such as weaning, after transportation, or when combining new animals with a herd or mixing animals from different sources. Preventive use is mostly given via feed or water. With some exceptions, the antimicrobial classes used are the same as those used in human medicine. However, some newer types of antimicrobials, such as carbapenems, oxazolidinones, and glycylcyclines are not used for animals reared for food.

Regulations and practices vary widely around the globe and are probably affected by the economic and social context. In the EU, all antimicrobials for systemic use in animals reared for food production are on prescription only. In other parts of the world, antimicrobials for treatment might be on prescription, whereas some products indicated for prevention are not. In other areas, regulation and capacity to supervise can be very weak. The World Organisation for Animal Health (OIE) provides guidance and capacity building, especially in those areas.

Data for amounts of antimicrobials sold for or used in animals are still scarce in most regions of the world. The network for European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) was formed by the European Medicines Agency on request by the European Commission to collect comparable data for consumption of antimicrobials for animals in the EU. Only data aggregated for all animal species are collected. To correct for differences in animal populations over time and between countries, a population correction unit was developed, roughly equal to the estimated live weight of the animal population in each country. Data for 2011 suggest substantial differences in amounts sold in participating countries.[156] Many factors might explain this finding, including a blunt unit of measurement and differences in composition of the animal populations and systems for production and disease profiles between countries. Furthermore, many of the participating countries have only recently set up systems for data

collection and at least a couple of years are probably needed to establish a good baseline. However, other explanations must exist, such as differences in ways to prevent diseases and prescription behaviour. In most countries, products are mostly intended for medication of groups of animals via feed or water. Overall, tetracyclines, sulphonamides, and penicillins were the main classes sold. In the EU, monitoring of resistance in commensals from healthy animals are reported to the European Food Safety Authority; when figures on sales of antimicrobials are compared with figures on resistance—in *E coli* to tetracycline, for example—countries reporting lower sales also report lower prevalences of resistance.[156,157] However, because the use of antimicrobials varies between animal species and even between production systems, further associations between sales and resistance are hampered by the dearth of sales data by animal species. A process aiming to set up systems for harmonised collection of sales data by species and to develop more refined units of measurement is underway within ESVAC.

Complex pathways

The interface between human beings and animals is complex; numerous possible pathways exist for transmission of resistant bacteria. The fact that resistance genes can be transferred between different commensal bacterial species and from those to pathogens adds to the complexity. Exposure through food is the most commonly studied transmission route and the most important. The most likely source of resistant bacteria in food of animal origin is contamination from animals' intestines during slaughter, but there are numerous other stages in food production where contamination with microbes, or amplification or reduction of their numbers, can happen (figure 5). Furthermore, exchange of resistance genes between bacteria from different sources can happen at all stages, including in the kitchen.[158] Food is traded internationally, which means that local production does not equal local consumption. Epidemiological studies of food-borne transfer of antimicrobial resistance sometimes generate conflicting results. Less explored are potential environmental routes.[159] Manure and biological solids applied to land might contain both antimicrobials and resistant bacteria. Through run-off from fertilised land or directly from sewage, contamination of surface water can also occur. Spread to human beings and animals is possible through contact with soil, irrigation of crops, contact with water, or with wildlife.

Evidence of spread

Direct spread of MRSA from animals to people in close contact is well documented.[160] Transfer of community or hospital-associated MRSA from people to animals has also been reported.[160] Food-borne transmission of non-typhoid salmonella and of campylobacter from animals is well established and arises whether bacteria are resistant or not.[161,162] More recently, handling or consumption of contaminated poultry meat has been implicated as a source of *E coli* causing urinary tract infections in women.[163] Less understood is transfer indirectly via the environment. After land application of manure, salmonella and campylobacter will survive for some time in soil, depending on the environmental conditions.[164] Contamination of vegetables and other crops directly from soil or through irrigation with contaminated water is a possible but poorly documented route of spread.

Direct evidence of spread of resistance genes between the microbiotas of various animal species and people is difficult to obtain, and the precise routes of spread more difficult to discern. However, indirect evidence clearly suggests that such transmission does happen. Findings from an early experimental study[68] showed spread of an *E coli* multiresistance plasmid between chickens and from chickens to people in contact with the animals. On a population level, studies of dissemination of genes conveying resistance to antimicrobials used in animals but not in people or vice versa provide strong indications of the direction of spread. In former East Germany, a streptothricin antimicrobial was introduced for growth promotion in 1983. Shortly after the introduction, a streptothricin-resistance gene carried on a transposon was recorded in *E coli* from pigs. Subsequently, the resistance gene appeared in *E coli* from farmers, their family members, from urinary tract infections of urban citizens, and later also in salmonella and shigella isolated from cases of diarrhoea in people.[153] Another example of putative spread is the gene *aacC4*. This gene conveys resistance to apramycin, gentamicin, and tobramycin in Enterobacteriaceae. Apramycin is an aminoglycoside used only in animals, mostly mixed in feed. The gene *aacC4* gene has been identified in *E coli* and *Salmonella enterica* serotype Typhimurium (*S typhimurium*) from animals and their environment, but also to a limited extent in people.[165]

The detection of vancomycin-resistant enterococci with the *vanA*-gene cluster in animals in the EU triggered

Ria Novosti/Science Photo Library

Figure 5: **High standards of food processing can prevent contamination of food with bacteria**

several investigators to explore possible transfer from animal to human enterococci. Although some types of the gene cluster are found only in people, an overlap has been reported between types found in isolates from animals and from human beings.[153] In an experimental study, Lester and colleagues[166] showed transfer of the gene cluster from ingested animal to human enterococci in the intestine of three of six healthy volunteers not receiving antimicrobials. Thus, transient carriage of animal-derived commensals can result in transfer of resistance genes to bacteria likely to be better adapted to human hosts.

The most challenging question hitherto is to what extent animals contribute to the spread of genes conveying ESBL or plasmid-mediated AmpC-type enzymes. Because ESBL and AmpC production can be conveyed by many different genes, which can be carried on different plasmids, many possible permutations exist. Occurrence of *E coli* producing various ESBLs or AmpC in companion animals, horses, and animals reared for food production is increasingly reported.[167] In several studies, isolates from animals or food products have been compared with isolates from human beings in the community or in hospitals. In a study from the Netherlands,[168] 20% of the isolates from people carried any of the two most commonly occurring plasmid-gene combinations occurring on broiler meat on the domestic market, suggesting transmission via food. By contrast, in a study from Sweden,[169] the overlap between the plasmid-gene combination that dominates in broilers raised in that country was rare in clinical isolates from human beings. The reasons for the differing results are not known, but various context-specific factors along the farm-to-fork chain might be implicated—eg, differences in amounts and types of antimicrobials used in broiler production.

An investigation of the temporal patterns of occurrence of various genes conveying ESBL or AmpC-production suggests that in many cases, emergence in human medicine seems to pre-date emergence in various animals. For example, CTX-M-15 is one of the most commonly reported ESBLs in human beings worldwide, but is rarely reported in animals reared for food production.[167] By contrast, CTX-M-15 is commonly reported from wild birds.[159] At least some of the genes conveying ESBL or AmpC might originally have been introduced in various animal populations from human carriers, maybe through environmental routes. If so, they have subsequently been spread between animals, farms, and regions leading to the present situation. Recent occasional findings of carbapenemases in Enterobacteriaceae originating from animals reared for food production[170] might also be explained by introduction from other sources. Carbapenems are not authorised for use in animals, but through the use of any β-lactam or other antibiotic to which the carrying bacteria is resistant, these genes can now be amplified through co-selection and spread in animal populations.

The effect

A direct effect of emergence and spread of antimicrobial resistance in bacteria of animal origin is the loss of effectiveness of antimicrobials used for treatment of animals. This aspect is poorly documented, but without effective treatment of serious diseases, mortality and morbidity would increase with negative effects on animal welfare. In the rearing of animals for food production, there would also be consequences for productivity and economy. These effects are not limited to intensively reared animals. In LMICs, infectious diseases in animals can have a substantial effect on the economy of a local community dependent on small-scale rearing of animals.[155] Eventually, the spread of resistance could lead to a local food security problem with negative effects on public health.

More studied, and far more controversial, is the potential effect of spread of bacteria and resistance genes from animals on public health. Guidance for risk assessment of food-borne antimicrobial resistance has been agreed by the Codex Alimentarius Commission.[171] A full quantitative risk assessment in this area requires large amount of data including relevant endpoints, such as public health burden of resistance. Because of the many possible routes of transmission and the complexity of resistance epidemiology, different attempts to estimate the risk have yielded quite different results. Environmental aspects could be taken into account in risk assessments related to antimicrobial resistance.[152,172] Models made with such an approach could provide a more holistic understanding of the importance of different effects of use of antimicrobials and in the identification of the most crucial control points.

WHO has developed a list ranking antimicrobial classes according to their importance for public health. Two criteria were used: whether the drug is the sole treatment or one of few alternatives to treat serious human diseases, or used to treat diseases caused by organisms that might be transmitted via non-human sources or might acquire resistance genes from non-human sources. Antimicrobials that meet both these criteria are classified as critically important. The WHO list can be used to support decisions about data collection, risk assessment, and risk management. To further support allocation of resources, WHO has prioritised critically important antimicrobials: fluoroquinolones, third and fourth generation cephalosporins, and macrolides are viewed as the highest priority for risk analysis.[173]

Although the exact effect of transfer of resistance genes or bacteria in any given context remains diffuse, food borne pathogens and MRSA are spread from animals to people. Strong circumstantial evidence suggests that resistance genes circulate between people, animals, and the environment. Any further increase in prevalence among animals will increase the likelihood of spread to other realms. Additionally, even rare transfer events could have a substantial effect if secondary amplification takes place in hospitals and the community.[174] Veterinary

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medicine and agriculture need to apply antimicrobial stewardship to curb further emergence and spread of antimicrobial resistance in the sector.

Time to move on from blame and shame

The use of antimicrobials for animals reared for food production remains controversial. Knowledge gaps in the understanding of the broader resistance dynamics, conflicting results in various studies, and in particular the difficulty quantifying the potential effect on public health are important barriers for change. This situation has led to a polarised debate, in which some state that the effect is small, while others argue that there is major harm.

Policies vary between countries and regions, and are not restricted to antimicrobials for animals, animal health and welfare, and food safety. Food is traded globally and other factors such as economic, export, and trade policies can play a part, as can consumers' expectations of access to affordable quality food products. Interests in these areas might well be conflicting, and this is important to acknowledge in the debate and in decision making.

General guidance spanning regulatory needs and prudent use of antimicrobials is provided by all international organisations: the OIE, WHO, and the UN Food and Agriculture Organization (FAO). Implementation of prudent use relies on the daily work of farmers and veterinarians. Legitimate conflicting interests can surround this implementation—eg, production economy and the ethical obligation to care for diseased animals. In view of the polarised debate, veterinarians and farmers might feel that they are blamed for a problem they perceive is essentially generated by medical doctors.[175] This situation might lead to a defensive attitude and does not cater for productive solutions. A way forward would be to acknowledge that human health, animal health, and the environment are all interlinked, and that the responsibility for dealing with the problems of resistance is shared by all stakeholders. Strong local and global partnerships are needed in which policy makers, academia, and professionals from all sectors work together to improve present systems. The common goal should be to preserve the effect of antimicrobials for future generations of human beings, but also for animals. Antimicrobials should only be used when needed. In the case of animals, this means that growth promotion and routine prevention with antimicrobials also used for treatment should be phased out, as recommended by the Swann Committee.[150] When needed, antimicrobials should be used judiciously. Furthermore, long-term efforts are needed with a focus on reducing the need for treatments by improving infection control and management and by developing robust systems.

Part 5: The access and excess dilemma

A global balance

To tackle antibiotic resistance needs not only a renewal of the depleted pipeline of novel antibacterial drugs, but conservation of those now in use. A failure to do so might lead to rolling back major achievements in modern medicine.[176] Because resistance inevitably follows antibiotic use, the paradox is that populations—both in industrialised countries and LMICs—can face challenges of access and excess. Even in high-income countries, antibiotic use ranges widely, with three times greater outpatient consumption in Cyprus than in the Netherlands.[177] The evidence points to increasing use of antibiotics in hospitals over time, much of it not consistent with clinical guidelines.[122] Although some patients are prescribed unnecessary courses of antibiotics, others are not given appropriate treatment.

This challenge is one of access and rational use, as defined as "how to ensure that when [patients] need drug therapy the appropriate drug is prescribed for them, it is effective and of acceptable quality and safety, it is available at the right time at a price they can afford, it is dispensed correctly and it is taken in the right dose at the right intervals and for the right length of time".[178] With this definition in mind, challenges associated with access of antibiotics begin with a recognition of the right to health, but result from therapeutic, financial, and structural barriers. Therapeutic access refers to the bottlenecks—scientific and financial—in bringing new antibiotics to market. Financial access characterises the difficulty in affording a rational course of antibiotic treatment, and structural access addresses the obstacles to delivering antibiotics effectively in the system and using them rationally at the clinical level in-country. Each of these barriers to access need to be surmounted if an antibiotic is to progress from bench to bedside. These barriers are also shown in the so-called glocalisation of antibiotics (ie, how a global product integrates into local markets). Delays in the entry of novel antibiotics—and delays in the availability of complementary technologies like diagnostics or vaccines—can affect the access and use of antibiotics in a local market.

Importantly, excess or overuse also contributes to problems of antibiotic access. Antibiotics are overused for many reasons, including patients' expectations of prescribed treatment; information asymmetry at the user, prescriber, or provider levels; diagnostic uncertainty; and the many financial incentives for overprescription, all of which drive both presumptive and unnecessary use of antibiotics. The excessive use of antibiotics traces, in part, from the revenues their use generates for health systems and health-care providers. In China, the dispensation of drugs comprises a substantial part of provider incomes, and data from 28 cities reveal a prescription rate of antibiotics twice that recognised as appropriate by WHO.[179] Such financial incentives exist at all levels of the system, from pharmaceutical companies to procurement agencies, retailers, prescribers, and dispensers, and include the informal market.

Strategic points for intervention

From bench to bedside, strategic points for intervention exist to address access and excess in antibiotic use. The

For more on **FIND** see http://www.finddiagnostics.org/

For more on **PATH** see http://www.path.org/

interaction among prescribers, dispensers, and patients is central in this value chain. However, surrounding this chain is a health-care delivery system with many points at which policy leverage might positively or negatively affect access to antibiotics.[180]

To balance access and excess requires reconceptualisation of the delivery of antibiotics as a complex adaptive system. The interaction between the components of such a complex system is non-linear. Product, information, and financing flow through the value chain of pharmaceutical delivery of antibiotics. Adequate regulation of these flows through the value chain can balance access and excess use of antibiotics in the delivery system. The value chain includes multifaceted innovation, dissemination and introduction of new techniques, technology, and rules, scaling up and implementation of these approaches, and then assessment and monitoring of their effect on access and excess of antibiotics.

Innovation in tackling antibiotic resistance

With the dearth of novel antibiotics, scientific bottlenecks in the research and development pipeline need to be overcome, from identification of promising leads and crossing from basic and translational research to improvement of clinical trials without sacrificing safety and targeting reimbursement.[181] To ensure access, but not excess, investment in research and development should be unlinked from returns. Measures such as extended data exclusivity and premium pricing are not the answer. Such approaches tie revenues to volume-based sales, and worse yet, higher prices place access to those in need at risk. Alternatively, public funding could be conditioned to buy out patents. Manufacturers could then be licensed to produce antibiotics on a scale appropriate for rational use.[182]

Innovation is needed, not only for the development of new antibiotics, but also for combination therapy. Of course, there is the synergistic action of using drugs in combination, such as trimethoprim and sulfamethoxazole in co-trimoxazole, amoxicillin, and clavulanic acid, or even perhaps someday silver with some antibiotics.[183] However, there is also the reality that if the probabilities of resistance to drugs A and B are independent, then the chances of developing resistance to both drugs used together will be much less likely—the product of those probabilities.[184] By targeting many mechanisms of resistance simultaneously, combination therapy might help slow the emergence of resistance.[185]

Innovation is also needed for technologies complementary to novel antibiotics. Preventive vaccines can reduce the need for antibiotic treatment,[186] but better diagnostics can both accelerate the recruitment of patients with multidrug-resistant infections into clinical trials and narrow the use of new antibiotics once on the market. As a method to hold resistance in check, the potential of diagnostics might be underused. Diagnostics in the USA guide 60–70% of health decisions, but might account for only 2% of health expenditures.[187] The health-care expenditure on diagnostics in LMICs is similarly low.[188] Product development partnerships like the Foundation for Innovative New Diagnostics (FIND) and Partners Advancing Transitions in Healthcare (PATH) have made important contributions to bringing diagnostics suited to low-resource settings to market. Notably, FIND supported the development of the GeneXpert MTB/RIF system, which not only identifies patients with smear-positive tuberculosis, but also establishes resistance to rifampicin from untreated sputum samples in less than 2 h.[189] Product profiles for point-of-care testing that returns susceptibility results in hours, not days, can provide a road map for targeted grand challenges in diagnostics research for bacterial pathogens.

The assessment of syndromic management and the clinical algorithms based on existing diagnostic methods have to complement the development of new diagnostics. A clinical algorithm now allows community health workers to make a presumptive diagnosis of acute lower respiratory infection, but had a better diagnostic been available, unnecessary treatments might have been avoided.[190] Even where access to such technologies exists, distrust in the quality of diagnostics, the paucity of timely results from diagnostic tests, and the fear of poor outcomes, can prompt clinicians to set aside diagnostic test findings. Improved diagnosis—part technology, part syndromic management—can reduce uncertainty about whether to treat with antibiotics or not. Taken to scale, the advent of simple diagnostic tests for yaws and trachoma could help reduce the need for mass administration of antibiotics, such as azithromycin.[191–193] Improved diagnostics can help convert a vicious cycle into a more virtuous one.

Dissemination and introduction of antibiotic treatment

Antibiotics, costing as little as \$0·13 to \$2·03 per patient, could save an estimated 509 000 lives from newborn sepsis and pneumonia every year.[194] In fact, fewer than a third of children with suspected pneumonia in LMICs receive potentially life-saving antibiotics (such as amoxicillin provided twice daily for 3–5 days) for treatment. The gap between children younger than 5 years who receive treatment and those who do not can be quite pronounced when a comparison is made between the top and bottom quintile of households on the basis of wealth.[195] By contrast, antibiotics are too often prescribed for diarrhoea when oral rehydration salts and zinc would better serve patients.[196] Access to such treatment contributes to growing community-wide drug resistance. In higher income countries like the USA, overuse of antibiotics for upper respiratory infections not only persists,[197] but is also implicated in the widespread use of broad-spectrum antibiotics, for patients treated in ambulatory care.[198] The increased risk of drug-resistant infection further decreases the clinician's threshold to prescribe antibiotics more often and with broader spectrum, thereby feeding a vicious cycle. In some places and over the internet, antibiotics can be obtained without prescription.[199] Worse yet, substandard

antibiotics may be ineffective but still contribute to drug resistance. For those living on less than $1 per day, upfront purchase of a complete course of antibiotics might be beyond financial reach, and adherence to a full course of prescribed antibiotics is unlikely.

Access to antibiotics is not just a matter of innovation in product development; even for existing drugs delivery may be wanting, especially in resource-limited settings. For example, data from a study in Tanzania[200] suggested that Gram-negative sepsis in children was associated with a mortality rate double that of malarial infection. Nearly half the neonates with Gram-negative sepsis at a tertiary hospital in the Mwanza region had infections resistant to third-generation cephalosporins. However, almost all of the Gram-negative enteric bacteria were sensitive to meropenem, a drug too expensive and often unavailable in many LMICs.[201]

Narrowly framed interventions aimed at dissemination and introduction of antibiotics and their rational use might focus exclusively on health-care providers in hospitals and clinics (figure 6). This narrow view has focused past efforts on prescription audits and provider training. Stewardship implies both effective treatment of patients with antibiotics and minimisation of collateral damage from the use of these drugs. A meta-analysis of studies[122] of antibiotic stewardship programmes suggested approaches that restrict prescription of antibiotics had larger effect than did persuasive approaches, but that over time, the differences were not statistically significant. Even if some multifactorial interventions under study seem more promising than others, one approach is unlikely to suit all settings. Meta-analyses can incorporate publication bias that comes from not reporting negative findings and thus fail to capture the underlying heterogeneity of study settings.[94]

Effective antibiotic stewardship efforts, however, need broader control over product, information, and financing. The flow of antibiotic product is in the system might be controlled by restriction of formularies, requirement of preauthorisation of antibiotic use, and de-escalation of broad-spectrum coverage when a pathogen is identified. Prospective audits with intervention and feedback, education of patients, guidelines for providers, and computer-assisted strategies affect the flow of information in the system. Approaches such as offering a safety-net antibiotic prescription for otitis media and instructing parents not to fill the prescription unless symptoms worsen or do not improve after 48 h, might help set the default option in favour of rational use.[201] Such an approach involves re-engineering the process by which health care is delivered. Additionally, checklists—perhaps through antibiotic order forms, computer order entry, or infectious disease consultant approval—can ensure more rational use of antibiotics.[202] The appropriateness of these approaches is context-dependent and might differ between LMICs and higher income settings.

From bench to bedside, there are both financial and non-financial incentives and affects on decision-making. Incentives do not consistently align in a way that promotes antibiotic stewardship or rational use. Even low levels of resistance can amplify into greater societal costs as clinicians minimise risks to patients by prescribing broader spectrum, presumptive treatment. Mothers who bring children to health centres might seek antibiotics not just for that episode of illness, but stockpile the extra antibiotic for that future occasion when reaching the clinic might not be so easy—a survival strategy where access is limited. Realignment of incentives to providers, prescribers, dispensers, and users is important to encourage correct use of antimicrobial treatment, including proper diagnosis, correct choice of treatment, generic prescription, and generic substitution.

Another strategic point of intervention might be in procurement of antibiotics, in which innovative approaches can provide access and prevent excess. For example, the facilitation of the supply of second-line treatment for multidrug-resistant tuberculosis. Such treatment can be 50–200 times more expensive than first-line treatment. The Green Light Committee reviews applications and provides technical assistance to countries seeking drugs to treat multidrug-resistant tuberculosis. Companies provide these drugs at concessionary prices through the Green Light Committee process, with the assurance that the drugs will be used appropriately and in a way that minimises resistance.[203]

Scale-up and implementation

Breakthrough approaches to solve the access and excess dilemma will need the integration of antibiotic stewardship programmes into health-care delivery systems. Without such vision, stewardship programmes might remain experimental or pilot interventions without substantial effect on antimicrobial resistance or access to life-saving treatment.

An effective new diagnostic test for bacterial acute lower respiratory infections could save at least 405 000 children's

Mauro Fermariello/Science Photo Library

Figure 6: **Dispensary staff are key in providing access to antibiotics, but also have a role in preventing excess**

lives per year.[190] For example, the value of a rapid diagnostic test for malaria in the setting of fever will vary by local prevalence of the disease, by seasonal changes, and by how often another cause of fever, like pneumonia, might coincide with a positive malaria diagnostic test finding. Local context matters. However, when such testing protocols are applied, do health-care providers adjust to the context? Evidence from the scientific record on the effect of diagnostic testing on prescription behaviour is mixed.[204,205] The increased prescription of antibiotics in the setting of a negative rapid diagnostic test finding for malaria might lead to improved rational use, or it could just result in overprescription of antibiotics as compensatory behaviour to mollify patients' expectations of treatment.[206]

In the health-care delivery system, antibiotic stewardship might be through integrated community case management. Applied to malaria, diarrhoea, and pneumonia, this strategy includes community health workers in the management of uncomplicated childhood illness and the referral of more complicated cases. Factors, ranging from how compatible programmes are with local sociocultural beliefs to how secure supply inventories of drugs and diagnostics are, can affect the introduction of integrated community case management.[207] In a study in Burkina Faso, Ghana, and Uganda,[208] community health workers were taught to use rapid diagnostic tests for malaria and to count the respiratory rate to diagnose pneumonia. Although compliance with the test results was high and unnecessary use of artemisinin combination treatments curbed, varying degrees of both antibiotic overuse and underuse were noted. After a simple clinical algorithm, community health workers in rural Zambia used rapid diagnostic tests with few adverse events, reliably dispensed artemether–lumefantrine for malaria and amoxicillin for pneumonia, and effectively managed their supply of medicines.[209] The dispensing of antipyretics to children with negative results of rapid diagnostic tests also seemed to help meet caregiver expectations.

Bridging the divide between individual and collective action will also be key. The misuse of antibiotics confers risks upon the individual, not just the wider community. These risks include the selection of resistant and more virulent infections, opening the door to opportunistic fungal infections, and leading to subsequent, more drug-resistant rounds of bacterial infections. Similar trends can be seen at the organisational level. Is there a failure of collective action when no individual insurer will invest in infection control at a local hospital, in case other insurers free-ride off that investment? Nor will any individual drug company show self-restraint in marketing an antibiotic when its therapeutic competitors do not. Collective action will need new forms of partnerships, such as pooling of the insured risks for infection control at a hospital.

Antibiotics are not just part of routine episodic care in the prophylaxis and treatment of bacterial infections. As the experience of population-wide campaigns such as ivermectin treatment for onchocerciasis has shown, removal of the barrier of drug costs alone is not sufficient to ensure delivery.[210] In scaling-up this programme to reach 25 million people every year in Africa, Merck acknowledged that this donation needed complementary investment to train health-care workers to integrate such efforts into the delivery system.[211] Most notably, the campaign to eradicate trachoma has come to rely on one dose of azithromycin, although this is part of a larger SAFE strategy, including surgery for trichiasis and advanced disease, facial cleanliness to reduce transmission, and environmental improvements. In addition to ready-to-use therapeutic food, findings from a recent study[212] support the routine use of antibiotics as a part of the management of severe acute malnutrition, which claims 1 million children's lives every year.

A policy tension might arise between saving lives with short-term mass campaigns that advocate antibiotics, and increased mortality as a result of increased antibiotic resistance. However, investigators piloting such interventions are already making such calculations. A trial investigating the effect of mass administration of azithromycin on the reduction of childhood mortality in Tanzania, Niger, and Malawi is underway. The study's lead investigator, Thomas Lietman acknowledged this trade-off: "We think we will select for antibiotic resistance. However, many of us believe that might be a price worth paying if there is truly a reduction in childhood mortality."[213] The investigators will carefully monitor the development of antibiotic-resistant diseases in the target communities. Lietman notes that in communities treated for trachoma, azithromycin resistance dissipated within 2 years of mass administration ending. Moreover, azithromycin is seldom used in sub-Saharan Africa, and resistant infections remain susceptible to many classes of other antibiotics. The unanswered question is whether this picture of infection will remain true in Africa?

The lessons learnt from a mass campaign differ from those gained from the treatment of episodic illness. However, the episodic treatment of bacterial infections also needs infrastructure for effective delivery. Treatment of acute rheumatic fever to prevent carditis and the sequelae of valvular lesions includes secondary prophylaxis with antibiotics. Adherence to the regimen of monthly, intramuscular injections might best be delivered with a control programme, equipped with a central register, a supply of benzathine penicillin G, and appropriate outreach. Additionally, the plans underway for eradication of yaws might include a diagnostic test for *Treponema pallidum* and allow for targeting an oral dose of azithromycin to those individuals infected.[214] The challenge in all these efforts will be to scale-up antibiotic use but to minimise drug resistance from unnecessary or inappropriate use.

Monitoring and assessment of access and excess

Successful antibiotic stewardship programmes need effective feedback loops to be established in health-care

systems and mobilisation of data as triggers for follow-on action. Taking stock of these programmes, quality measures, such as time to first antibiotic for a patient with community-acquired pneumonia, are useful. Some have argued such programmes should be assessed on outcomes, not just process measures. Although relating specific measures causally to antibiotic stewardship programmes can be challenging, infection-related mortality, hospital length of stay, readmission rates, *C difficile* infection rates, and antibiotic resistance levels can be useful outcome dimensions to track.[215] Just as vital signs like blood pressure, heart and respiratory rate, and body temperature give a snapshot of a patient's illness, select quality measures can give a similar picture of how effectively an intervention is tackling antibiotic resistance in the health-care delivery system. Data from such surveillance can provide useful feedback to antibiotic stewardship programmes, which can be redesigned to take stock of positive, negative, intended, and unintended effects highlighted in thorough monitoring and assessment.

Trends of antibiotic use can be mapped,[216] and perhaps the discovery of regional or local differences might encourage responsible parties to act. However, linking surveillance to action can be challenging. The Institute for Healthcare Improvement applies a continuous quality improvement approach, consisting of plan–do–study–act in its work.[217] To tackle antibiotic resistance, collaborations involving like-minded groups can encourage the sharing of such continuous quality improvement lessons among local innovators. A process of collaborative improvement among institutions facing similar difficulties was the hallmark of the Institute for Healthcare Improvement's breakthrough collaborative.[218] As part of its state-wide Antibiotic Stewardship Program Initiative, the California Department of Public Health has also set about developing collaborations among hospitals that share common challenges.[219]

Achieving access without excess

For the 1 billion people who live on less than $1·25 a day, a full course of antibiotics paid for upfront might not be affordable. The balance of access and excess poses an important ethical question as to who should access antibiotics, under what circumstances, and who should make these decisions if they should not be left to the discretion of users, or even prescribers and providers. If antibiotics are treated as a non-renewable resource, access to both new and existing products needs to be thought about carefully.

Taking a systems approach, tackling antibiotic resistance involves intervention at the level of innovation, dissemination and introduction, scale-up and implementation, and monitoring and assessment. Every stage offers the opportunity to re-engineer the system. To develop new antibiotics, financing models that delink research and development investment from revenue returns are needed. The productive focus for a grand challenge competition could also be the effective development and deployment of technologies complementary to antibiotics, notably diagnostics. To disseminate and introduce these technologies, antibiotic stewardship might have to go beyond audit and feedback to realignment of incentives. This might also require strategic points for intervention beyond providers, prescribers, and patients, such as at the level of procurement of antibiotics, to be found.

The scale-up and implementation of these interventions needs infrastructure, not unlike that of mass administration campaigns, but as exemplified in efforts to treat acute rheumatic fever, these might need longer term commitments to tracking and follow-up of patients such as in a central registry. Scaling up is also associated with rethinking how incentives work when moving from individual to collective action. New institutional arrangements might be needed to pool and share the costs and benefits of these interventions across providers, insurers, or drug companies. Finally, monitoring and assessment requires effective feedback loops that transform surveillance into follow-on action. Learning collaborations of like-minded individuals or institutions are one promising approach to motivate change and to share lessons from such efforts.

Access to new antibiotics will need to be controlled through strong regulatory, procurement, and distribution oversight while existing products will need to be protected and their shelf-life extended through coherent and inclusive approaches to antibiotic resistance. Suggested solutions to this major issue lie in interventions aimed at re-engineering the delivery system. Public health services can partner with and actively promote accredited drug-dispensing outlets, where rational use might be strictly audited; rational use might be enabled through vouchers delivered through mobile-phone-based money transfers. Various approaches to ensure that the full course of antibiotics is taken, not just dispensed, need to be piloted. These scenarios are only examples of system-wide approaches that aim at finding the right balance between access and excess.

For more on the **Antibiotic Stewardship Program Initiative** see http://www.cdph.ca.gov/programs/hai/Pages/AntimicrobialStewardshipProgramInitiative.aspx

Part 6: Challenges of antibiotic resistance in weak health systems

An underestimated burden

Over the past decade, antibiotic resistance has risen alarmingly worldwide.[220] Among the key players, including global health donors, pharmaceutical companies, technical agencies, and governments,[221] patients and physicians have the strongest effect on resistance rates, because selection and spread of resistant organisms is mainly a local process based on practices in individual hospitals and communities.[222]

In LMICs with weak health systems, the effect of antimicrobial resistance on health and economics is largely underestimated and incompletely understood. At least two-thirds of childhood mortality is related to

infections, and children are therefore probably more vulnerable than are adolescents and adults.[223] The increase in resistant strains among bacteria causing some of the commonest childhood infections (eg, newborn sepsis, meningitis, pneumonia, diarrhoea, and typhoid) can make clinical outcomes worse and render first-line empirical antibiotic regimens ineffective.

Therefore, the challenge lies not only in the use of existing knowledge to make antimicrobial resistance a national health priority, but also in the implementation of customised containment strategies.[90] These strategies must, however, successfully integrate scale-up of proven interventions at the service delivery level with a sustainable self-evaluation process whereby action plans are reviewed and revised on the basis of collected evidence.[224]

Antibiotic resistance in priority pathogens

Neonatal sepsis

Studies of newborn sepsis from Bangladesh, Ethiopia, Nepal, Tanzania, Cameroon, Ghana, India, Nigeria, Pakistan, Yemen, Vietnam, Philippines, and Egypt,[40,225–235] support trends in pathogens and resistance highlighted by Waters and co-workers[14] and Zaidi and colleagues.[236] The high proportion of resistance among Enterobacteriaciae (*Klebsiella* spp and *E coli*), the leading cause of newborn sepsis in developing countries, to ampicillin, gentamicin, ceftriaxone, and ciprofloxacin, is concerning. Neonatal nurseries in some LMICs report meticillin resistance rates of 17–28% in *S aureus* isolates.[40,216,237] Similarly, Lubell and colleagues[238] recorded poor susceptibility to almost all commonly used antibiotics in pathogens such as *S aureus* and *Klebsiella* spp. Without rigorous evidence, most clinicians agree that 90% susceptibility or higher of potential pathogens to antibiotics in critical care settings like neonatal intensive care units, and 80% or higher in non-critical health-care settings, is acceptable.

Pneumonia and meningitis

Streptococcus pneumoniae, a leading cause of community-acquired pneumonia and bacterial meningitis in children is increasingly resistant to macrolides, third generation cephalosporins, and fluoroquinolones. Although penicillin non-susceptibility of *S pneumoniae* (PNSP) does not seem to affect outcome of antibiotic treatment in patients with pneumococcal pneumonia,[239] PNSP might be of great clinical significance in deciding treatment options for life-threatening infections such as meningitis. Prevalence of PNSP ranges from 0% in Pakistan[240] to 44% in Algeria,[241] amoxicillin resistance from 20% in Algeria, Morocco, and Tunisia,[242] to 46% in Malta,[241] and cefotaxime resistance from 8% to 17% in North Africa.[242,243] Macrolide resistance is as common as 33% of isolates in Venezuela and 38% in Mexico.[244] Fluoroquinolone resistance is found in 3% of isolates in Pakistan[240] and up to 24% in Bangladesh.[245] Dual non-susceptibility to both amoxicillin and erythromycin was reported in 30% of isolates in one North African cohort.[242]

Diarrhoeal pathogens

Vibrio cholerae, salmonella, shigella, *E coli*, and campylobacter accounted for 500 000 diarrhoeal deaths in 2010.[246] Cholera is still a public health priority in most LMICs; however, resistance to the recommended antibiotics (co-trimoxazole, chloramphenicol, sulphonamides and nalidixic acid) has been reported from countries in South Asia and Africa.[247–251] In most of sub-Saharan Africa and Bangladesh, resistance to co-trimoxazole and furazolidone is increasing, whereas resistance to tetracycline fluctuates from year to year.[252–254] Resistance and reduced susceptibility against tetracycline, ciprofloxacin, and azithromycin have also been reported,[248,255,256] suggesting the importance of epidemiology to guide treatment.

In LMICs, *Shigella flexneri* is the commonest cause of bacillary dysentery in children younger than 5 years. Resistance to ampicillin, tetracycline, co-trimoxazole, and chloramphenicol is common in developing countries.[257] In Africa and Asia, resistance against ciprofloxacin—the WHO recommended antibiotic for bacillary dysentery in children—rose from 0·6% to 30% over 10 years.[258] Further, reports of emerging resistance to second-line antibiotics such as third-generation cephalosporins and azithromycin are of great concern.[259]

Increased resistance to flouroquinolones and macrolides is also being reported for campylobacter. Ciprofloxacin resistance rates range from 65% to 88% in Bangladesh,[260] whereas rates of resistance from African countries range from 5% to 38%.[257,261] Antibiotic use in veterinary medicine can cause fluoroquinolone resistance in campylobacter.[262] Multidrug resistance (to ampicillin, chloramphenicol, and co-trimoxazole) in *S enterica* serotype Typhi (*S typhi*) is associated with increased severity and high case fatality rates of typhoid fever.[261] Fluoroquinolones, macrolides, and cephalosporins are the second-line, albeit costlier, regimens for treating typhoid fever. However, fluoroquinolone resistance is increasing in India (44%) and Pakistan (58%), and susceptibility is decreasing in Congo (15%) and Cambodia (80%).[263–266] In Kenya,[267] more than 77% of the *S typhi* were multidrug resistant, much higher than the reported 52% in Ghana[268] and 29% in Egypt.[263] Additionally, the proportion of *S typhi* in Kenya that are multidrug resistant and resistant to nalidixic acid with decreased susceptibility to fluoroquinolones had risen from 1% in 2000 to nearly 25% in 2008.

Surveillance for resistance trends, monitoring rational use of antibiotics, and development of clinical management guidelines to standardise treatment can curtail development of resistance against the remaining mainstay of treatment, third-generation cephalosporins.

In sub-Saharan Africa, non-typhoidal salmonella are the dominant contributors to invasive bacterial disease. These bacteria are the second commonest cause of neonatal meningitis and the third commonest cause of bacterial meningitis in children older than 2 months in Malawi and Kenya.[269,270] However, data from some reports suggest

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S typhi is the main serotype in Africa.[267,271] Multidrug resistance and decreased susceptibility to fluoroquinolones are now widespread among non-typhoidal salmonella, causing invasive bacterial disease in Kenya and Malawi,[272–274] and other parts of sub-Saharan Africa.[275–277] This situation poses a major challenge to treatment and management of disease. In a study from the Democratic Republic of the Congo,[278] rates of multidrug resistance varied from 37% to 80% between different provinces. 10% of the *S typhimurium* strains isolated from Kinshasa were also resistant to azithromycin. Recently, a very high rate (48%) of cephalosporin resistance has been reported from India, especially in *S enterica* serotype Agona.[279]

Risk factors for resistance in childhood disease pathogens

Antibiotic misuse

User-related factors such as self-medication, non-compliance, misinformation, and advertising pressures in combination with other factors such as ignorance, lack of education, and inaccessibility to health care and diagnostic facilities, are the major drivers of resistance. Poverty compounds the problems, because patients do not have access to clean water and hygiene and are at an increased risk of acquiring infections. Individuals living in poverty also have poor baseline nutritional status to fight off infections and are at risk of treatment termination due to affordability issues.[280] Other factors relating to health-care providers that may lead to inappropriate prescribing include insufficient training, unprofessional conduct, and paucity of diagnostic facilities, leading to incorrect selection of antibiotics.[280]

Inappropriate prescriptions resulting from economic incentives offered by pharmaceutical companies and inaffordability of appropriate dose and duration of antibiotic regimens perpetuate a vicious circle of suboptimum treatment leading to antimicrobial resistance. Another cause of antibiotic misuse among prescribers and patients is lack of awareness of the health priority status of antimicrobial resistance among every tier of health-care personnel in developing countries.[280]

The highest burden of deaths caused by infectious diseases is in south Asia and sub-Saharan Africa.[232] Countries in these regions also report a high prevalence of multidrug-resistant pathogens with poverty of resources contributing to poor containment of resistant organisms in hospital and community settings,[13] and inadequate training of prescribers and laboratory personnel,[280] contributing to rising resistance through inappropriate empirical antibiotic choices, and laboratory diagnostics.[224]

Quality of antibiotics

Poor countries suffer from lack of regulations for pharmaceutical products, leading to availability of counterfeit and low-quality antibiotics. Use of these ineffective antibiotics amplifies resistance and leads to purchase of more potent and expensive antimicrobials to treat resistant strains.[100] Policies for appropriate supervision by regulatory agencies are needed to control the sale and supply of expired and counterfeit drugs.

Lack of antibiotic stewardship and poor infection control

Absence of antibiotic stewardship is associated not only with emergence of resistance, but also with poor outcomes for patients.[281,282] Apart from appropriate laboratory infrastructure, both stewardship and infection control require teams of a clinical infectious disease physician, clinical pharmacist, and committed hospital administration, which are scarce in LMICs.

Furthermore, insufficient infection control surveillance systems within hospitals in LMICs[12] with inherent problems (eg, overcrowding and insufficient equipment and trained personnel) leads to spread of nosocomial infections and even outbreaks caused by resistant pathogens.[13] This scenario has huge financial implications for developing countries and can lead to exponential increase in treatment costs besides increase in morbidity and mortality.[12,283,284] These resistant pathogens become a commensal reservoir of resistant genes and are spread to the community through unsafe water and poor sanitation. A history of hospitalisation is an important risk factor for acquisition of resistant infection in family members.[284] Infection control and antibiotic use are inter-related and the individual contribution by each of these factors is difficult to seperate.[285]

Paucity of surveillance information

Surveillance data are essential for providing information on trends and magnitude of resistance. Unfortunately, timely availability of such data from developing countries is scarce.[286,287] Causes of this data lag and lack include technical constraints such as non-existence of data collection and analysis infrastructure, poor laboratory infrastructure, and weak leadership and governance to recognise resistance and its public health (clinical, financial, and pharmacological) implications. Absence of essential epidemiological data leads to delayed or suboptimum revisions in guidelines, and strengthens the vicious circle of injudicious use of antibiotics by prescribers on the basis of anecdotal or non-evidence-based experience.[287] Local antibiograms with pathogen-specific susceptibility data are crucial in choosing the best empirical antibiotic in resource-constrained settings[287] and are heavily rely on quality-assured laboratory support and an intact information system.

Paucity of leadership and governance

Without appropriate oversight, policy makers are unable to assimilate known information about global and regional drivers of resistance and its public health implications or to recognise the problem as a national health priority. As a result, policy makers will struggle to propose and implement sustainable, multidisciplinary, and multitier (pharmaceuticals, food and agriculture, human resources, financing, and information systems) strategies that link

science to practicality.[288–290] Corruption within health systems is of particular importance in LMICs where it can lead to siphoning off of smaller and therefore more precious health budgets. Poor record keeping and general human-resource mismanagement further add to inaccurate burden estimation. Furthermore, because of the lack of transparency and accountability, countries with the most need might miss out on opportunities to attract donors and strengthen their health systems.[291]

Combating antimicrobial resistance

An effective strategy to combat resistance needs action and involvement of individual institutions that commit to implementation of antibiotic stewardship programmes, invest in their development and operation, train existing or employ essential staff, and maintain relevant records.[220,221] In countries with weak health systems, hurdles such as insufficient funds, inadequate infrastructure and management, shortage of trained personnel, non-existent or poorly implemented infection control policies, and poor surveillance records[292] need to be addressed and overcome.

Although control and containment strategies should mainly target individual hospitals and communities, vision and direction should come from the platform of national health ministries. In 2012, medical societies in India put together an implementable road map for resistance containment in the country that pushed for central coordination and implementation support from the government.[293] Therefore, physicians can play an important part in advocacy for containment of resistance and give relevant technical input to a national taskforce. In addition to setting national objectives and goals, functions of the taskforce can include seeking and maintaining global partnerships with potential funding agencies, engaging relevant ministries (agriculture, pharmaceutical industry, information, and education) for support functions, regular customisation of the national antibiotic policy by review and feedback of surveillance data, and pushing for legislation through advocacy.[87] Taskforces can customise available guidelines prepared by local and global experts to fit individual country contexts.[220,294,295]

For more on **GAVI** see http://www.gavialliance.org/

Some success stories from LMICs are encouraging. For example, Burkina Faso and Ghana have created confidence in global donors, inviting external investment in strengthening systems through committed steps that ensure transparency and accountability in management of public finances.[296] Honduras and Chad have used public expenditure tracking surveys to understand how resource flows in health systems can be abused.[297,298] In Mexico, a transparency and access to public information law was successfully implemented in 2002,[299] which paved the way for a citizens' audit into funds redirected from an HIV programme.[300] For other countries such as Pakistan, with the most deterioration reported between 1996–2004,[301] deeper systematic reform could be the answer.[295] Championship at the central level is essential to improve cash flow into resources like information systems, laboratory infrastructure, and personnel training.

Systems-support guidelines provide information on appropriate indicators (ie, scientific, population, and systems data) for development of antibiotic resistance information databases.[302] The central taskforce must standardise laboratory reporting of resistant pathogens in an electronic programme through liaison between local microbiologists, infectious disease specialists or general clinicians, and information technology experts. Fraser and colleagues[303] reported successful implementation of electronic medical systems as pilot projects in, Haiti, Malawi, and Peru. This capacity building can be taken up as a systems-strengthening project with partial commitment from both individual governments and competitive bidding for external funding. The task force needs to provide software programs to hospitals across the country so that nosocomial and community pathogens can be identified and resistant clones tracked at district, provincial, and national levels.[87]

Taskforce finances need to match annual agendas. Global experts, local legislators, financial experts, epidemiologists, public health experts, and private–public sector representatives can be stakeholders in the finance and ensure the best use of resources for evidence-driven strategies. Optimum coverage of BCG, diphtheria, pertussis, *Haemophilus influenzae* b, pneumococcal and measles vaccines, now available in most developing countries with Global Alliance for Vaccines and Immunisation (GAVI) support, can contribute to reduction in antibiotic resistance by reducing disease occurrence and thus the use of millions of doses of antibiotics.[304,305] Public–private partnerships have been suggested as a possible way for non-GAVI eligible countries to bridge the vaccination gap.[306] Imperfect vaccines targeting drug-resistant pathogens have also been suggested as a method to improve the population-wide proportion of drug-resistant versus drug-sensitive strains.[307]

Overall use of antibiotics can decrease with diagnostic information.[52] Validation of point-of-care tests for respiratory tract infections, the leading cause of overprescription of antibiotics in children, might be an important step towards improved antibiotic use.[135]

Education and training incentives to health-care providers such as prescribers and dispensers in the community and members of infection control and therapeutic committees within hospitals have been recommended.[224] Direct education of patients also improved antibiotic compliance and decreased use of unindicated drugs in Peru.[224] Training at all levels of a multilevel health system should be in conjunction with systems-strengthening steps such as provision of necessary resources (eg, printed guidelines, data systems, and reporting protocols).

Important steps to contain resistance at the primary health-care level include country-wide scale-up of integrated management of treatment protocols for neonates and children,[308] optimum vaccination coverage,[305]

development and dissemination of education material for practitioners and patients on rational use of antibiotics,[92] marketing and provision of access to rapid diagnostics,[309] and making outpatient treatment guidelines for standardisation of antibiotic use readily available.

At the secondary or tertiary level, infection control committees should be implemented with WHO recommendations. Institution champions and teams need to be chosen. Data collection, analysis, and dissemination should be done at primary, secondary, and tertiary levels through pre-prepared software made available by the national taskforce. For example, in Vietnam despite legislation supporting antimicrobial resistance containment, implementation of antimicrobial stewardship at service delivery level became better with technical support from the Vietnam resistance project (VINARES), a private–public partnership.[87]

Part 7: Improving the interface between academia and the pharmaceutical industry

The need for new antibiotics

Antibiotic discovery has stalled, but we do not know how to restart the engine. The golden age of antibiotic discovery between 1929 and the 1970s saw more than 20 new classes of antibiotic reach the market.[310,311] Since then, only two new classes have reached the market.[312,313] Analogue development seems to be drying up because the number of analogues that can be derived within one class is finite.[1] The attitudes of regulators and payers have also discouraged development of so-called "me too" products. The net result is that the worldwide antibiotic pipeline for new antibiotic classes active against highly resistant Gram-negative bacteria is almost dry;[314–316] the only novel class in early clinical development has recently been withdrawn.[315,317] However, the situation for Gram-positives is better because compounds from two new classes have been marketed in the past 15 years (linezolid in 2000 and daptomycin in 2006),[312,313] and one more is in the pipeline.[315] Meanwhile, new analogue development and combinations of old antibiotics with, for example β-lactamase inhibitors, are struggling to keep pace with the relentless emergence of antibiotic resistant bacteria with new resistance profiles. In our view, if the world is to return to the golden age, it needs to make new classes of antibiotics and will need up to 20 new classes to reach the market within the next 20–60 years.[310] Because resistance arises to all antibiotics, whether they are a new class or an analogue of an old class, it could be argued that new classes are not needed, only compounds that target highly resistant pathogens, including those resistant to other drugs in its class.

We believe that, eventually, chemists will run out of options if no new classes are marketed because the chemical options for variations within one class structure are finite. Some Gram-negative bacteria such as NDM-1 producing *K pneumoniae* are already resistant to almost all antibiotics, including carbapenems; chemists struggle to find treatments for some highly resistant bacteria with the range of available classes. Ideally, new classes should be rolled out gradually and evenly over an extended period, and the new discovery and development should be paired with a better and more effective stewardship approach to protect existing drugs and those that are newly developed. However, if new classes of antibiotics are rolled out too slowly, millions of people are likely to die because resistance will arise to all new antibiotics over time. Gaps in coverage against highly resistant bacteria have already appeared and there will be larger gaps in the future if more antibiotics are not produced quickly enough. Furthermore, the discovery of new classes of antibiotics is unlikely to be steady and even. After all, it might be impossible to discover and market enough new analogues or classes to keep up with the continuous emergence of antibiotic resistance, especially in Gram-negative bacteria.

The need for new antibiotics is obvious, but the urgency varies. In hospitals, especially in intensive care units in some parts of some countries, there are dangerous levels of highly resistant bacteria.[318] In other countries, highly resistant bacteria are less common, especially in the community.[319,320] So the global response to antibiotic resistance, in terms of efforts in antibiotic discovery, is likely to vary with percieved threat.

Why has antibiotic discovery stalled?

After the end of the golden age, academic bacteriology moved away from antibiotic discovery. There was a view that infectious diseases had almost been eliminated and that industry would market an endless stream of antibiotics. Initially, in the 1970s and 1980s, the pharmaceutical industry did produce a stream of antibiotics. These were analogues but not new classes. In retrospect, we believe that this was a fundamental mistake, because, although analogue development is low risk compared with novel class discovery and development, analogues eventually become more difficult to come by. The ingenuity of the medicinal chemists is overcome by nature, in the form of relentless emergence of new forms of bacterial antibiotic resistance. Although resistance arises to first-in-class antibiotics after marketing, a new class of compounds widens the opportunities for chemists to create new analogues that target highly resistant bacteria. Unfortunately, industry, encouraged by academia, made a second fundamental mistake, namely to enter genomics on the grounds that this would lead to many new classes of antibiotics—an endeavour that failed.[310] Industry closed many antibiotic research laboratories. As a result, the world is left with a decreasing stock of effective antibiotics, an inadequate pipeline of new classes and analogues, a broken antibiotic market, a paucity of antibiotic discovery infrastructure in academia, and insufficient infrastructure in industry.

A report[321] commissioned by the Swedish Government concluded that the antibiotics market should have rational intervention, the effective life of existing and new antibiotics should be preserved, push–pull incentive

models should exist, and legal regulatory changes should be made. A high-level conference hosted by the Swedish Government (figure 7)[322,323] concluded that three reasons explain the empty pipeline: scientific challenges; regulatory requirements, such as needing superiority or non-inferiority trials; and market failure (ie, absence of appropriate incentives to develop medicines for which use will be restricted). The political conclusions made by the EU health ministers, who met after the conference, resulted in an action plan from the European Commission,[324] which is being implemented. This meeting was followed by a global conference in 2010.[325]

The Pharmaceutical Research and Manufacturers of America recently asked the FDA for a more flexible approach to regulation of new antibiotics.[326] The European Medicines Agency has relaxed its guidelines for clinical antibiotic trials in four ways: first, patients can be enrolled in trials after receipt of a dose of previous antibiotic treatment, making enrolment possible; second, organism-specific rather than disease-specific studies can be done; third, small studies can be used to support approval of antibiotics that treat resistant, critical infections; and fourth, clinical response endpoints can be assessed at test-of-cure visits.[327]

The Infectious Diseases Society of America (IDSA) has proposed the 10 x '20 Initiative, which calls for the development of ten new, safe, and efficacious systemically given antibiotics by 2020, but progress remains elusive.[328] Despite this encouraging attention by policy makers and regulators, some are now questioning whether modern medicine can continue in the future without more effective antibiotics.[176,329]

The need to improve antibiotic stewardship

Under the existing business model, major pharmaceutical companies presumably market products to maximise volume. This is not a desirable situation for new antibiotics. For example, some countries use antibiotics less well than others, thereby increasing antibiotic resistance, which is then carried around the world to other countries. On the contrary, delinkage is needed, in which most revenues should be generated not through sales but through a mixed model of income from push funding (such as through the Innovative Medicines Initiative), pull incentives (such as advance purchase commitments or new market exclusivities), and in-market sales.[325] Furthermore, models for global access at affordable prices should be agreed upfront—a fact that emphasises the need for new financing and incentives. The advantage of this approach is that new antibiotics could be put on the shelf until they are needed, and their use could be restricted, thereby prolonging their shelf-life. The disadvantage of this approach is that the pharmaceutical industry might continue to be wary of investment in antibiotic development, although advance purchase commitments or new market exclusivities could offset this. The reason for industry's reluctance to invest is because such restrictions lead to a large reduction in the value of the antibiotic at discovery. The Office of Health Economics[330] has estimated that, with restrictions, the net present value of antibiotic to a drug company is minus $50 million, whereas a new musculoskeletal drug, without restrictions, is worth $1 billion.[327] The Generating Antibiotic Incentives Now (GAIN) Act has recently been introduced in the USA and allows prolonged exclusivity[327] and other provisions. This act could increase the value of antibiotics to companies, thereby encouraging companies to enter the field; however, it does not address the issue of stewardship. If a drug is to be used as a last resort, what good are market exclusivity rights?

The IDSA has suggested[331] an alternative way forward that could provide an increased unit price for new antibiotics and reduce the cost of clinical trials, thus providing economic incentives for investment while restricting use. This proposal calls for a new regulatory approach, the limited population antibiotic drug provision, through which antibiotics could be approved after small, low-cost clinical superiority trials that target highly resistant bacteria that potentially cause lethal disease. The antibiotic would receive a very narrow label that would help to protect it from overuse. Although if introduced, this new regulation could both encourage investment and restrict use, the high unit price would need to be addressed for global access, especially in developing countries.

Reuters/Pontus Lundahl/Scanpix (Sweden Health)

Figure 7: **The Swedish Government, particularly Minister of Health Goran Hagglund, have helped define the problem of antibiotic resistance thus far**

The academia–industry interface

The infrastructure of antibiotic discovery in academia and the pharmaceutical industry has fallen to a dangerously low level. A prolonged loss of skills in both sectors means few people have experience of antibiotic discovery, especially of new classes. If a university or a company has no people engaged in antibiotic discovery, it is unlikely to produce new ideas in this area.

In academia, emphasis is placed on new ideas. In our experience, there is no shortage of new ideas in universities, although there needs to be a critical mass of people in an institution who think about antibiotic discovery. However, translation of these ideas into a marketed antibiotic is difficult, time-consuming, and expensive. Universities and other institutions try hard to address the translation of basic research ideas into real products. This issue is sometimes addressed by encouragement of academics to patent their ideas. Most ideas do not progress much beyond this stage because there are not enough entrepreneurs or companies willing to take on high-risk projects. This gap needs to be filled.

Equally relevant is an opportunity to repurpose existing compounds and those that were discontinued from development with new scientific knowledge. Without patents and other market exclusivities, few incentives exist to invest in projects to bring back old antibiotics, or to test new combinations or regimens.

New ideas for antibiotic discovery also come from small and medium sized enterprises (SMEs) in the area. Ideas originate from academia, other companies, or from the SME itself. Translation of ideas into preclinical antibiotic development is something that such enterprises often do well, and some progress into early stage clinical trials. In our view, there is a need for many more SMEs in antibiotic discovery. A new grant-giving system is needed, and a new system of loans for SMEs in this area is also necessary. Infrastructure to bring these companies and academia together is needed at the level of those who are actually associated with research and development of antibiotics. This organisation should be at national and international levels.

In the golden era of antibiotic discovery, major pharmaceutical companies were the home of new ideas, development, and marketing. The huge success of antibiotics in shaping modern medicine is mainly a result of the efforts of these companies. Unfortunately, those days are over. Ideas for new drugs, not just new antibiotics, are too few to support major companies. However, phase 3 clinical trials are so expensive (the average cost is $70 million per trial)[332] that major companies will usually need to be involved in antibiotic drug development. These companies become included in antibiotic development by in-house efforts, collaborations with academia, buying or investing in SMEs, or mergers with other large pharmaceutical companies. Expansion of collaboration between major pharmaceutical companies and academia is needed.

New business models

Antibiotic recovery plan

The existing resource of antibiotic discovery in academia and industry is too restricted to be effective. An interface between two organisations, each of which has inadequate antibiotic discovery, is not going to succeed. The infrastructure of academia and industry needs urgently to be rebuilt, which would be expensive and the responsibility of industry and governments. Because antibiotic resistance is believed to be as serious as climate change, governments should take appropriate action to address the issue. Coates[333] suggested that the European Commission sets up an antibiotic recovery plan, of a similar type to the Marshall Plan in 1948. Other major governments (eg, Japan and the USA) should also fund their own plans. Indeed, the USA has the elements of such an antibiotic recovery plan, already reasonably well funded, a public–private partnership mechanism akin to the Marshall Plan, which is called the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). This consists of many agencies of the US Federal Government, including National Institute of Allergy and Infectious Diseases, Biomedical Advanced Research and Development Agency, and several Department of Defense agencies. This model is in action, as evidenced by various recently announced multimillion dollar investments. This initiative should be welcomed; however, it has not yet produced the marketed antibiotics that are needed, especially against Gram-negatives, perhaps because of insufficient time. Additionally, this initiative is probably insufficient to bring enough antibiotics to market for the entire world. A high proportion of loans and grants from governments, say 60%, would be invested as loans in the antibiotic discovery industry, most of which would be SMEs because novel ideas increasingly come from smaller companies. The loans would be administered by a bank with the revolving-door model.[333] Collateral would be provided by government and interest rates should be very low. However, recipient companies would need to repay the loans to the government. The money could then be lent to another company in the antibiotic discovery business. This would leave 40%, which would be used to fund grants to universities, SMEs, and major pharmaceutical industries, and pay down debt.

Pharmaceutical industry collaboration

The Innovative Medicines Initiative, funded by the European Federation of Pharmaceutical Industries and Associations, is the biggest public–private initiative in Europe. It is distinct from the EU Framework Programmes and aims to accelerate the development of better medicines for patients. The initiative seeks to improve collaboration between industry and academia, which has been identified as a potential way forward for some years.[334] 40 projects are in motion that cover many areas of medicine including antibiotic resistance (eg, COMBACTE and PreDICT-TB). Further Innovative Medicines Initiative funds will be targeted at antibiotic drug discovery in the New Drugs for Bad Bugs programme, if these funds were to be available at early stages of antibiotic discovery that could have a substantial effect.

For more on the **Innovative Medicines Initiative** see http://www.imi.europa.eu/#&panel1-8

The Innovative Medicines Initiative is dominated by major pharmaceutical partners and is run along the lines of grants from the European Commission, which means

that deliverables are set at the beginning by the partners. The strength of the Innovative Medicines Initiative is its connection with major pharmaceutical companies, which means that drug development is emphasised; its weakness is that it can only fund projects that are already underway, and might create intellectual property challenges arising from collaborations between public–private partnerships, academia, and industry. The initiative does not solve the root of the antibiotic discovery problem—too few novel class and analogue candidates in early stage clinical development. Other collaborative translational research models include a new NIH centre in the USA[335] and Cancer Research UK,[336] but these are not focused on antibiotic discovery.

Charitable organisations

The Bill & Melinda Gates Foundation has led the way in antibiotic development, especially for tuberculosis. Bedaquiline, which has been supported by the foundation was marketed in December 2012 for highly resistant tuberculosis,[337] is the first new drug to be launched for the disease in 40 years. This is a model that could also be used in development of drugs for Gram-negative and Gram-positive bacteria.

For more on **MMV** see http://www.mmv.org/about-us

Academia–industry collaboration

The Innovative Medicines Initiative is just one example of academia–industry collaboration. Although optimised for development, the predetermined delivery of grants is, in our view, too rigid to stimulate research ideas. Other models include embedding an SME in academia. This can work well at the research idea end of the scale, but needs a robust legal agreement between the SME and the academic institution, and an understanding of industry, which is not always present in academia.

For more on the **DNDi** see http://www.dndi.org/about-us/overview-dndi.html

Not-for-profit organisations can also play a part in the promotion of collaboration. For example, Antibiotic Discovery-UK[338] was set up in 2012 to bring together universities and SMEs interested in antibiotic discovery. This is simple to set up, by organising meetings of academics and industrial workers who have experience in antibiotic discovery, development, and market authorisation. It is a low cost way of starting collaborations that can be advantageous when applying for funding from grant-giving bodies. If other countries were to use this model, representatives of each country could then form—eg, Antibiotic Discovery-Europe or America. Antibiotic discovery with world coverage would also be a low cost model. Inevitably conflicts of interest will occur, and legal contracts may be required to prevent industry sponsorship from slowing publication of results, restricting the sharing of findings, or suppressing reporting of adverse drug reactions.

Only now is the awareness and urgency of the problem of antibiotic resistance reached a level that a new sustainable global system can be built. For tuberculosis, malaria, and leishmaniasis, Open Source Drug Discovery is a good example. The organisation was founded in 2008 and seeks to provide affordable health care to developing countries. It is led by the Council of Scientific and Industrial Research India team with more than 7500 registered users from more than 130 countries around the world who engage in open access drug discovery—making it the largest collaborative group in drug discovery in the world. The idea is to discover and develop drugs with public funding. An example of its activities is GlaxoSmithKline making 177 potent non-cytotoxic antituberculosis hits publicly available.[339] If successful, this consortium could help to discover cheap antibiotics, presumably via the generic market route. Under present regulatory constraints in developed countries, it would be difficult to raise sufficient money from governments for late-stage clinical trials in, for example, Gram-negative bacterial ventilator-associated pneumonia, but the regulatory landscape might change to accommodate much cheaper routes for antibiotics to reach the market.

For more on **Open Source Drug Discovery** see http://www.osdd.net/about-us

Another global model is Medicines for Malaria Venture (MMV), a not-for-profit public–private partnership, set up in Switzerland in 1999 with the objective of affordable antimalarial drug discovery and development. For example, MMV in partnership with Sigma-Tau has developed dihydroartemisinin–piperaquine (Eurartesim), which has been granted regulatory approval by the European Medicines Agency for the treatment of uncomplicated *Plasmodium falciparum* malaria. This is a potential model for the development of new anti-Gram-negatives in collaboration with industry. Although the expense of discovery and development of new antibiotics might challenge such a model.

The Drugs for Neglected Diseases Initiative (DNDi) was founded in 2003 as a not-for-profit drug research and development body. It is a collaboration between seven global institutions from the public sector: the Oswaldo Cruz Foundation in Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, the Pasteur Institute in France, Médecins sans Frontières, and an international research organisation, the UNDP–World Bank–WHO Special Programme for Research and Training in Tropical Diseases, which acts as a permanent observer. DNDi works on leishmaniasis, sleeping sickness, Chagas' disease, malaria, paediatric HIV, and filarial disease in partnership with private industry, public institutions, academia, and non-governmental organisations. The initiative has delivered an impressive five new treatments, seven in clinical, and seven in preclinical development. The advantage of this system is the collaboration of the public sector with humanitarian and international research organisations. The disadvantage is the constraints of operating in a low-cost environment, without obvious financial incentives for large-scale investment from pharmaceutical companies.

A new funding model has been developed by the Global Fund to Fight AIDS, Tuberculosis, and Malaria. The fund operates as a financial instrument, not an implementing entity, and supports programmes from national plans. Proposals are assessed by an independent review process. The advantage of such a fund is that the money raised is spent on programmes relevant to partner countries. The fund is not focused on antibiotic resistance, but this could change because some developing countries have a big problem already with highly resistant bacterial infections, including tuberculosis.

Could the World Bank have a role? The World Bank provides loans to developing countries for capital programmes; its goal is to reduce poverty and can provide loans for research and development, which could include antibiotic resistance.

Construct an antibiotic discovery programme?

On the grounds that one model is unlikely to be enough, could we combine many different models and create an effective global antibiotic discovery programme?

Countries could set up not-for-profit overarching networks of people involved in antibiotic discovery. These networks would then form the basis of a global network and could give rise to an open source for antibiotic discovery. Collaborations with major partners such as countries and institutions could be modelled on the DNDi. Funding could come from inclusion of antibiotic discovery by charitable organisations such as the Gates Foundation and by the Global Fund and World Bank. Changes to the regulation of antibiotic development for highly resistant bacterial pathogens using the IDSA suggestion of the limited population antibiotic drugs could be used. Alternatively, regulations could be changed towards those that already exist for annual influenza vaccines, in which postmarketing safety surveillance would be mandatory. Cofunding through the Innovative Medicines Initiative is an attractive solution, but will only work when a financier has been found for the 50% required by the private sector. In addition, a loan system, of the type used in the Marshall Plan, would enable a large number of phase 3 clinical trials, the most expensive part of antibiotic development, to be done. Loans are preferable to grants in the long-term, because once paid back money can be reinvested into drug discovery.

A grand challenge in antibiotic discovery would be one place to start. This idea is based upon the grand challenges used by the Gates Foundation. Grants, be they from government or charity, would be given with a low entry threshold to academia and SMEs that had new ideas of antibiotic discovery. There may be an insufficient number of SMEs to cope with the need for new compounds—academics could be encouraged to set up their own companies and SMEs could be encouraged to embed in universities to foster collaboration with legal agreements to protect both parties.

Preclinical development would be done by SMEs, and would aim to mature the drug to be phase 1 ready. A central facility would need to be set up to provide advice to academics and SMEs about preclinical development. Funding could derive from government loans or grants. Phase 1/2 and phase 2 clinical trials would be done by SMEs funded by loans and grants. The central facility would provide advice about clinical development.

For more on the **Global Fund to Fight AIDS, Tuberculosis, and Malaria** see http://www.theglobalfund.org/en/

SMEs would usually falter at the phase 3 stage of development, which are often too expensive for such companies. Possible ways forward are to partner with a major pharmaceutical company, or with a large financial institution. Another way is to reduce the cost of trials by using microbiological endpoints,[6] which can make trials up to ten-times cheaper than those using clinical endpoints.

For more on the **World Bank** see http://www.worldbank.org/en/about

In summary, regeneration of antibiotic discovery could be achieved by collaboration between academia and the pharmaceutical industry. The infrastructure of antibiotic discovery in both academia and in industry is dangerously weakened and needs to be rebuilt.

Part 8: Beyond antibiotics—alternative strategies for prevention and treatment

Antibiotics today

Most antibiotic chemical scaffolds in present clinical use were discovered more than 50 years ago. These discoveries mainly came as a result of mining the bioactive chemicals produced by soil bacteria. The large effect of these new antibiotics in treating infections and enabling new medical procedures was tempered somewhat early in their use by the emergence of resistant strains of pathogens and eventually their spread, along with their genes, across the globe.[4] Later, many antibiotic scaffolds derived from microbial secondary metabolism were chemically modified to improve efficacy and circumvent resistance, leading to regular availability of plentiful new medicines to address emerging challenges from increasingly multidrug-resistant pathogens.

The ability of the pharmaceutical sector to reliably deliver new drugs to the clinic to address the resistance-mediated obsolescence of old medicines is very limited in the 21st century. A general paucity of investment and activity in antibiotic drug discovery exists, and consequently few new drugs are on the horizon.[340] This fact has frankly taken the public, clinicians, regulators, and politicians by surprise. Where will the new antibiotics come from that are needed to address the growing problem of resistance? Both conventional and non-conventional approaches are needed to address this pressing clinical problem.[341]

New antibiotics

Once dismissed as old thinking, a renaissance in natural product discovery is needed. We have not exhausted the chemical space of traditional single molecules with potent antibiotic activity and drug potential. However, the days of highly potent, non-toxic, broad-spectrum, and inexpensive

drugs might be over. These were the criteria that traditionally benchmarked antibiotic drug discovery and are increasingly difficult to achieve. In fact, the desire for broad-spectrum agents, active against most Gram-positive and Gram-negative pathogens, has selected for drugs with the capacity for serious deleterious effects on the human microbiota. The result has been unwanted side-effects and, in the emergence of antibiotic associated colitis due to *C difficile*, even increased morbidity and mortality.[342] The clinical reasoning driving the search for broad-spectrum drugs is the fact that very often, the microorganisms causing the infection are unknown to the clinician at the time of presentation. Therefore physicians opt for empirical treatment to cover all the bases, leading to a desire for broad-spectrum drugs. A new focus on very narrow spectrum or even organism-specific antibiotics accompanied by advances in molecular diagnostics to guide infectious disease specialists in drug deployment could provide a new, more selective antibiotic arsenal. However, the discovery of such drugs will need new approaches and chemicals in step with innovation in diagnostics and changes to the regulatory frameworks governing new antibiotic approval.[343]

The chemical matter and drug discovery strategy dominant in the antibiotic sector over the past 25 years has been focused on synthetic chemical libraries and in-vitro target-based approaches. Although this strategy has enjoyed success in various therapeutic areas, its use in antibiotic discovery is a well documented failure.[344] Modern target-based drug discovery seems to have missed the mark because of an incomplete understanding of the bacterial targets selected and of the chemistry needed for success in the development of antibacterial drugs. However, natural products, in particular from microbial sources, have been an outstanding source of antibiotic chemical scaffolds. More than 25 000 such molecules have already been discovered and the genome sequences of producing organisms have provided a glimpse of a huge potential for new compounds.[345,346] Reinvestigation of this bioactive chemical wealth should prove useful, especially with cell-based screens on either multidrug-resistant organisms to avoid identification of known drug scaffolds or strains engineered to favour discovery of desired targets—for example using antisense RNA strategies to deplete key enzymes or pathways thereby sensitising cells to compounds affecting privileged targets.[347]

The success of the lipopeptide daptomycin (marketed as Cubicin), is an instructive lesson to emphasise some of the above points.[348] Daptomycin is a natural product produced by the soil bacterium *Streptomyces roseosporus* first discovered in the 1980s at Eli Lilly. Initial exploration of its promise as a new antibiotic was halted because of muscle toxic effects. Furthermore, daptomycin had a narrow spectrum, effective only against selected Gram-positive pathogens, a deal-breaker for conventional antibiotic development strategies. Nevertheless creative re-examination of dosing obviated the muscle toxic effects and increased clinical need spurred by the emergence of MRSA as an important pathogen resulted in re-examination of daptomycin by Cubist, a medium sized pharmaceutical company, and subsequent clinical approval of daptomycin in 2003. Sales of the drug are on track to top $1 billion per year in the near future, showing that even narrow-spectrum natural product agents have the potential to provide excellent return on investment. Indeed, measures such as the GAIN Act, signed into law recently by the US Government, provide for additional market exclusivity and a favourable regulatory framework for new antibiotic drugs.[349]

Therefore, with the appropriate chemical matter, clever screens that avoid prevailing chemical scaffolds, and a willingness to forego broad-spectrum coverage for a more limited field of susceptible organisms, there is great reason to be optimistic that traditional single agent antibiotics can continue to be identified and brought to market. However, there are also grounds to be optimistic that alternative approaches to traditional antibiotics can offer alternative strategies for new medicines. These include, but are not limited to, antibiotic adjuvants, antivirulence strategies, and biologicals.

Adjuvants

Compounds that potentiate the activity of antibiotics, antibiotic adjuvants, can increase the efficacy of drugs in both antibiotic susceptible and resistant pathogens.[350] The combination of antibiotics, often empirically to cover the spectrum of possible infections and to avoid possible resistance, has been a mainstay of infectious disease medicine for decades. Indeed, the first-line treatment of some bacterial diseases, such as tuberculosis, requires multidrug treatment, as do common treatments for cancer and viral diseases like hepatitis and HIV/AIDS. However, combination of antibiotics with non-antibiotic compounds with adjuvant activity is a relatively novel strategy that can reveal unexpected biology and overcome resistance.

Antibiotic adjuvants can take the form of compounds that directly target resistance mechanisms and compounds that exploit chemical genetic interactions that potentiate antibiotic activity. Directly targeting resistance mechanisms is a clinically proven strategy that extends the spectrum of antibiotics by inhibiting resistance and rescuing antibiotic activity. Various inhibitors of Ser-β-lactamases in combination with penicillins have been in clinical use for decades.[351] Important among these is a combination of amoxicillin with the β-lactamase inhibitor clavulanic acid, a natural product produced by *Streptomyces calvuligerus*, marketed as Augmentin (GlaxoSmithKline). Other similar combinations in clinical use include ticarcillin with clavulanic acid (Timentin; GlaxoSmithKline), piperacillin with tazobactam (Zosyn; Pfizer) and ampicillin with sulbactam (Unasyn; Pfizer). Experimentally, clavulanic acid inhibits the intrinsic β-lactamase that renders *Mycobacterium tuberculosis* impervious to β-lactam antibiotics and thus a combination with meropenem has

excellent killing activity against this deadly pathogen offering a new treatment strategy.[352]

The β-lactamase inhibitor combinations in current clinical use have little effect on strains producing AmpC or ESBLs (figure 8). To address this clinical need, the novel β-lactamase inhibitor avibactam in combination with cephalosporins (ceftaroline and ceftazidime) is in late-stage clinical trials and is showing great promise.[353] The notion of directly inhibiting resistance elements, thereby rescuing antibiotic activity, is not confined to the β-lactam antibiotics. Efforts to block aminoglycoside-inactivating enzymes[354] and antibiotic efflux pumps[355] have also proven effective in vitro, though none have progressed to clinical trials yet.

Antibiotic adjuvants are not restricted to inhibitors of resistance. In a screen of off-patent drugs for potentiators of the tetracycline analogue minocycline against *E coli*, *S aureus*, and *P aeruginosa*, several non-antibiotic compounds were identified with adjuvant properties. One of these was loperamide (Immodium; McNeil Consumer Healthcare).[356] This compound is a μ-opioid receptor agonist in people. In Gram-negative bacteria (that do not have this receptor), loperamide disrupts the electrical component (Δψ) of the proton motive force across the bacterial membrane. The bacteria respond by increasing the pH gradient (ΔpH) to maintain the ATP-generating capacity of the proton motive force. It is this pH gradient that enables tetracycline to enter the cell. Therefore loperamide increases antibiotic influx, even in otherwise resistant cells. The combination was highly effective in vitro and in animal models of infection, providing a proof-of-principle of the adjuvant approach and screening to identify non-obvious drug combinations. Similar screens in pathogenic yeast uncovered unexpected cell-killing synergy between the fungistatic antifungal drug fluconazole and the selective serotonin reuptake inhibitor sertraline (Zoloft; Pfizer).[357]

In recently published work,[358] the approach identified a new combination of the cephalosporin cefuroxime and the antiplatelet aggregation drug ticlopidine (Ticlid; Roche). Here an unexpected inhibition of TarO, an enzyme essential for early stage wall teichoic acid biosynthesis, by ticlopidine was recorded. This inhibition results in particularly powerful synergy with β-lactam antibiotics that target PBP2 in MRSA, which otherwise is insensitive to cefuroxime. Thus, the combination achieves both suppression of antibiotic resistance and narrow pathogen selectivity, both key attributes of 21st century antibiotic medicines.

The antibiotic adjuvant idea can also be applied to overcome bacterial functions that are commonly associated with drug resistance. In particular, bacteria can adhere to surfaces such as medical devices and epithelial cells, where they continue to grow but become insensitive to antibiotics. These biofilms are implicated in numerous bacterial infections and are often the reason that antibiotic treatment fails. Several efforts to combine antibiotics with agents that prevent biofilms from forming, disrupt them, or otherwise block their antibiotic insensitivity have been reported.[359,360] Some of these are quite potent in their effects in vitro, suggesting that the approach has merit for clinical assessment.

Antivirulence strategies

One of the reasons that antibiotic resistance is such a challenge is that the evolutionary bottleneck of cell death is so stringent, and the numbers of bacteria in one infection are so large that even rare mutational events can result in resistant mutants that break through. Coupled with the ability to receive DNA horizontally from other species or even genera, the massive adapt or die selective pressure steers evolution towards the selection of ever more resistant pathogens. An alternative notion is not to kill bacteria, but rather impair their ability to establish an infection in the first place. These antivirulence strategies have been aided by genetic screens to identify virulence determinants for a number of pathogens.[361] In principle, such virulence targets are less prone to selection for resistance to antivirulence agents, and mutants that do occur are much more likely to be impaired in their ability to cause infection. To the extent that some antivirulence approaches will place a selective pressure on pathogens, one clearly needs to be cautious about the question of drug resistance and virulence. Nevertheless, this approach will benefit from the fact that antivirulence compounds tend to be narrow in spectrum and this will restrict any selective pressures for drug resistance. Here again, the benefit of species-specific treatment defines an imperative for a new generation of antibiotics.

Among the more promising antivirulence targets are quorum sensing, type 3 secretion systems, toxins, and the biosynthesis of glycolipid surface structures. Quorum sensing refers to the production of diffusible small molecules by bacteria that act as autoinducers of various cellular factors at high cell densities. These compounds, such as homoserine lactones produced by Gram-negative

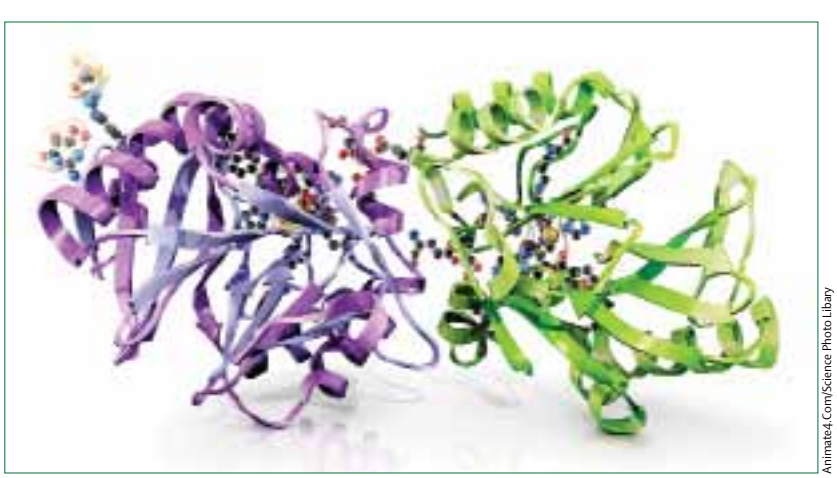

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Figure 8: **Potential targets of new drugs include resistance enzymes such as ESBLs**

pathogens and small peptides by Gram-positive organisms, trigger various responses including the formation of biofilms. Inhibition of quorum sensing disrupts this process. Several such inhibitory compounds have been identified that block virulence and quorum sensing in *P aeruginosa*[362] and *S aureus*,[363,364] for example.

Bacterial colonisation of tissue is essential to the establishment of infection and interference with this process is a high-quality target for antivirulence compounds. Among the first small molecules shown to prevent virulence was virstatin.[365] This molecule blocks the activity of the *V cholerae* transcription factor ToxT that controls the expression of TCP, a pillus protein that is essential for colonisation of the intestine. Similarly type 3 secretion systems are extracellular proteins that facilitate bacterial binding to cells and injection of virulence proteins into the cytosol. Several small molecule inhibitors of type 3 secretion systems have been identified including salicylidene acylhydrazides that are effective against several pathogens including *Chlamydia* spp, *E coli*, *S enterica*, and *Shigella flexneri*.[366]

Many pathogens, such as *C difficile*, *V cholerae*, *Bordetella pertussis*, *E coli*, and *Bacillus anthracis*, secrete extracellular toxins that contribute greatly to virulence. These toxins are often enzymes and have been targeted by screening campaigns to identify inhibitors that attenuate virulence. For example, a series of small molecules have been recently reported that block ADP-ribosyltransferases that are known extracellular bacterial toxins associated with cholera, diphtheria, and pertussis.[367]

Disruption of the production of glycolipid surface structures, such as lipopolysaccharide in Gram-negative pathogens and lipoteichoic acids in Gram-positive bacteria, are promising antivirulence strategies. In terms of the former, the essential in-vitro early steps of lipopolysaccharide assembly—namely lipid A and 3-deoxy-D-*manno*-oct-2-ulosonic acid biosynthesis—have long been indicated as valid targets. However, late steps in lipopolysaccharide synthesis are dispensable in vitro, but are associated with substantial reductions in virulence and increased antibiotic sensitivity. Data from proof-of-principle efforts to find late-step inhibitors[368,369] suggest that these are targets of high potential. Lipoteichoic acid biosynthesis, a polyanionic glycolipid common to most Gram-positive pathogens has also been the target of recent small molecule screening efforts that have generated interesting new leads.[370] Additionally, data from feasibility studies in *M tuberculosis* have suggested that the synthesis of acyltrehalose-containing glycolipids is crucial to host invasion,[371] setting the stage for antivirulence drug discovery efforts aimed at the cell surface of this organism.

Although antivirulence strategies are expanding the target base for new antibiotics, several challenges are unique to this approach. First, antivirulence agents are probably highly specific to individual pathogens and there will be a requirement for great confidence in identification of the causative agent of disease. In addition to the challenge of diagnosis, to be fully effective such agents might need to be provided before infection becomes well established. In some cases—for example, where *C difficile* is a known and serious risk—the argument for prophylaxis will be relatively straightforward, but in other cases, it will not be. Further, these challenges will make clinical trial design especially complex. It is nevertheless imaginable that the first implementation of such drugs may be in combination with conventional antibiotics.

Biological therapeutics

With growing concern over the failing antibiotic drug-discovery pipeline, there is a great deal of interest and efforts in progress to investigate alternatives to small molecule drugs. Where biological medical products have had remarkable effect on modern medicine, this class of therapeutics is increasingly touted as a viable alternative to antibiotics. Indeed, there has been remarkable success in the area of biologicals (eg, insulin, erythropoietin, monoclonal antibodies, and other engineered receptor constructs) to provide therapeutic options in which there were no or few effective alternatives in other areas of medicine. Thus, although biologicals might not form the mainstay of future strategies to deal with multidrug resistance, substantial interest exists in various areas including monoclonal antibodies, modifiers of the immune system, and age-old phage treatment. We deem the first two of these approaches to be particularly exciting new directions for therapeutics to treat bacterial infection. On the whole, these approaches are not being thought of in isolation of antibiotic treatments but as adjunctive therapies to increase the efficacy of antibiotic treatment. Efforts on biologicals in the form of monoclonal antibodies and immune modulators are particularly innovative directions that will benefit from new understanding of the host–pathogen interactions. These are more long-term solutions to the challenge of antibiotic resistance, but they are driven by the urgent and growing need for new treatments.

The past couple of decades have seen many successful monoclonal antibody-based products introduced in the areas of rheumatology and oncology. Collectively, these efforts have made the discovery, manufacture, and clinical development for monoclonal antibodies a mature pharmaceutical approach for consideration in an increasing variety of therapeutic areas. This general approach was formerly the exclusive domain of treatments for infection. Passive vaccination, the provision of readymade antibodies to treat infectious disease, was developed by the likes of Paul Ehrlich and Emil Behring in the late 19th century and was the standard of care until it was supplanted by antibiotic treatment. However, today, only one anti-infective monoclonal antibody is on the market—palivizumab for the prevention of respiratory syncytial virus infections in high-risk neonates.[372]

Modern discovery and development efforts in monoclonal antibodies for bacterial diseases have been largely focused on bacterial toxins or on cell surface structures.[373] The protective antigen of *B anthracis*, for example, has been a popular target as are the toxins of *C difficile*. Lipid A and lipoteichoic acid have likewise been targets for monoclonal antibody treatment development, as have surface proteins and carbohydrates from various important pathogens. Although it is relatively early days for these approaches, a consensus is emerging that success in animal models of infection is not always predictive of clinical success.[374] Furthermore, combinations of monoclonal antibodies, perhaps in addition to antibiotic treatment, might be a preferred approach.

Modulation of host immunity is another exciting and emerging approach for the application of biological medicine products to treat bacterial infections. Here, the natural defence mechanisms of the host are targeted for enhancement to derive therapeutic benefit. Immune modulators under investigation include host defence regulator peptides and agonists of the innate immune system—eg, Toll-like receptors and NOD-like receptors.[375] Innate defence regulator peptides are a particularly interesting subset of these modulators, and are often cationic peptides (10–50 aminoacids) with a high proportion of hydrophobic residues that impart amphiphilic physical properties, are generally membrane-active, and have antimicrobial activity in vitro.[376] Nevertheless, these peptides often have only weak antimicrobial activity under host physiological conditions and have convincing effects in modulating the host immune response. The clinical development of such molecules to treat bacterial infections has commonly focused on the antimicrobial activities with subsequent recognition during development of the immunomodulatory properties.[377] Thus, these seem to be combination treatments with immune and antibiotic activities in one medicine.

Also in this category of immune modulating biologicals are probiotics. A mounting recognition of the role of host microbiota in shaping and modulating our immune systems has led to the therapeutic application of probiotics for various diseases, most notably the treatment of *C difficile*.[378] Such treatments have intuitive appeal to patients and are growing in popularity. Indeed, the science of probiotics remains a mysterious one at present, but the potential is clearly there for this approach and for immune modulation treatments generally. The specialty is well positioned for transformational insights from breakthroughs in mechanistic understanding of how to control the immune system in treatment.

Other antibiotic alternatives that in particular have potential effect on *C difficile* infections are the use of microbiome transplantation and the therapeutic application of antibiotic resistance proteins. The transplantation of intestinal microbiomes (also known as faecal transplants) for the treatment of severe gastrointestinal disease caused by *C difficile* infection has promise. A recent systematic review and meta-analysis[379] of available clinical data reported remarkable resolution of disease in most cases, but cautioned that further randomised controlled trails and long-term follow-up are now needed to confirm the usefulness of the approach. Another creative approach that seeks to prevent *C difficile* overgrowth and infection resulting from antibiotic use is the oral administration of antibiotic resistance enzymes. The biotechnology company Synthetic Biologics is developing a treatment of β-lactamases that when taken orally will degrade β-lactam antibiotics in the intestine that otherwise could degrade the normal microbiome and facilitate *C difficile* infection.

Finally, vaccines remain powerful agents for disease prevention. Their use obviates the need for antibiotic by preventing infection in the first place, and they have been in clinical use for decades. This is an area in which epidemiological studies that identify key circulating pathogens are essential to continuously revise vaccine formulations. The effectiveness of the new seven-valent pneumococcal conjugate vaccine in reducing disease burden and consequent unintended selection for the rise of serotypes that are not covered by the vaccine shows the importance of vaccination and continuous monitoring of target organisms.[380] Vaccines directed against organisms for which antibiotic resistance is especially challenging is a strategy that could have great clinical effect. Recent efforts to develop vaccines for important drug resistant pathogens such as MRSA[381] and *M tuberculosis*[343,382] are promising, but have yet to generate viable candidates for late stage clinical trials.

Part 9: Call to action

Measuring the extent of the problem and its consequences

The generation of reliable, relevant, and up-to-date information will be essential to respond to the negative effects of antibiotic resistance on public health. The poor understanding of the unique features and risks of antibiotic resistance is an important cause for the global complacency paving the way for the present crisis. Few studies have been done on the magnitude of the burden of antibiotic resistance and its contributions to excess mortality to convince policy makers of the need to react. Although antibiotic resistance is undermining the effective treatment of many important bacterial diseases with high mortality, especially in LMICs, it lacks the profile of HIV, tuberculosis, and malaria. Clear information on the health and economic burden of antibiotic resistance is urgently needed to make this complex problem tangible to policy makers. Studies in the EU[383] and USA[36] provide some data, but need to be scaled up worldwide, and the results from such data collection and analysis should be communicated to decision makers, prescribers, dispensers, and the general public. Likewise, a global surveillance system for

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antibiotic resistance, including outbreak reporting and an early warning system to detect new resistance mechanisms and their global spread, is still lacking, despite the obvious need of such a system and several proposals for potential models.[384,385] Absence of essential local epidemiological data also leads to delayed or suboptimum revisions of treatment guidelines, thereby driving the vicious circle of injudicious empirical use of antibiotics by prescribers based on anecdotal evidence or experience without a firm evidence base. One large hurdle is the insufficient laboratory capacity in LMICs, which need to be strengthened. Meanwhile, sentinel population-based studies are needed to get a rapid global assessment of the scale of antibiotic resistance in key pathogens. Likewise, data for antibiotic use in human medicine, veterinary medicine, agriculture, and horticulture need to be monitored globally and regionally. All countries should set up systems for the monitoring of antibiotic use and comparable units of measurements should be agreed and implemented.

Regulation, rational use, and infection control in human medicine

Antibiotics are different from all other medicines in that the effects of their use extend way beyond individual patients. The societal effects of antibiotic use justifies that they should belong to a special regulatory category. Antibiotic use should be strictly monitored and legislation to prevent over-the-counter sales without a prescription enforced, unless this would cause an unacceptable access problem (eg, in rural areas). Financial incentives to prescribers and dispensers leading to irrational use need to be removed. Regular revision of standard treatment guidelines into clear, simple, updated, evidence-based, locally relevant, and accessible documents is essential. Motivational measures include pay-for-performance policy, the audit-feedback mechanism on antibiotic prescribing rates of individual prescribers, and public disclosure on antibiotic prescribing rates of health-care facilities. To reduce patients' perceived need for antibiotics and reduce demand and change social norms, well designed and contextualised educational campaigns should be done. Implementation of basic hygienic routines is still largely absent in many hospitals and health-care settings worldwide. Cultural and other barriers for their implementation need much more study. Infection control interventions need to be reassessed and improved in an era with rapid transmission of multidrug-resistant bacteria and mobile antibiotic resistance genes.

The need for rapid diagnostics

A fundamental obstacle in the management of antibiotic resistance in LMICs is the inadequate capacity and infrastructure to do basic microbiological laboratory analyses. These deficiencies need to be addressed—eg, by mechanisms similar to the World Bank supported East Africa Public Health Laboratory Networking Project[386] and the Danish supported Antibiotic Drug Use Monitoring and Evaluation of Resistance (ADMER) in Ghana. Rapid point-of-care diagnostic tests providing information on the pathogen and its susceptibility to antibiotics have enormous potential to minimise inappropriate antibiotic use and to increase patients' safety. Additionally, cost savings from diagnostic testing might motivate their development. So far, efforts to develop such technology have been fragmented, with a lack of corporate learning and inadequate identification and sharing of multidisciplinary expertise. The present diagnostic development landscape is scattered, leading to tests of suboptimum overall quality and insufficient clinical relevance. Challenges exist at every step from ideas for rapid diagnostic tests to uptake by health-care systems.

A multidisciplinary, multistakeholder, multiregional, long-term platform should be created with the task of developing a living road map for diagnostic development, identifying the clinical need and associated (technical) requirements in view of market and technology forecasts. The road map should identify the present and future clinical needs and diagnostic requirements, which would enable test developers to bring together appropriate technologies to provide a clinically useful answer. In addition to technology developers (commercial and academic), experts in clinical, statistical, regulatory, behaviour change, and social and health economic sciences, the platform should include the end users—clinical microbiologists, infectious diseases specialists, and other health-care providers—who will base treatment decision on the results of these tests. Factors that affect the introduction of new diagnostic technologies and delivery into health systems should be identified, and barriers to acceptance of rapid diagnostic tests addressed. End-users should develop diagnostic algorithms for major infectious diseases where rapid diagnostics could be used to target patients who really need antibiotics. The road map should be developed in three steps: first, reach a consensus about a set of clinical needs and the technologies needed to satisfy those needs; second, provide a mechanism to help forecast technology developments; and third, provide a framework to help plan and coordinate technology development. The creation of target product profiles for novel diagnostic tests would provide useful guidance for industry. Product development partnerships like FIND or PATH could potentially embrace this area of work.

The animal sector and the environment

Antibiotics and antibiotic resistance needs to be seen from an ecological and environmental perspective. Strong local and global partnerships in which policy makers, academia, and professionals from all sectors work together to improve present systems are needed to ensure multifaceted action, sharing of experiences, transparency, and continuous improvement. Unnecessary antibiotic use in all sectors needs to be removed and the spread to the

environment minimised. For the animal sector and the environment, we propose the following policy actions.

Use of antibiotics, which is unnecessary (eg, for growth promotion) or where alternatives exist (eg, routine prevention) should be phased out. The international organisations WHO, OIE, and FAO should provide a clear definition of "unnecessary routine prevention". Governments across the globe should then revise existing legislation or draft new legislation accordingly. The transition should be supported by extension services providing advice on alternatives and on how to tackle potential negative animal health problems. Resources should be allocated for a dialogue between all stakeholders and for monitoring of compliance with the new legislation. WHO, OIE, and FAO should monitor progress

All countries should monitor use of antimicrobials for animals in a comparable way. Guidance on collection of data and units of measurement should be agreed on by WHO, OIE, and FAO. Governments should set up systems for data collection and analysis of antibiotic use by species and production type. The pharmaceutical industry, farmers, and veterinarians should contribute by providing access to data. WHO, OIE, and FAO should monitor progress jointly.

The need for antimicrobials in animals should be reduced. WHO, OIE, and FAO, governments, and key stakeholders (pharmaceutical industry, farmers, veterinarians, academics, among others) should work together to identify and implement incentives for development of health-orientated systems for rearing of animals for food production and for development and implementation of other disease preventive measures. Additionally, all key stakeholders should commit to prudent and rational use of antimicrobials. The environmental release of antibiotics from all sectors needs to be monitored and controlled. Strategies need to identify and focus control on hot spots for horizontal resistance gene transfer such as wastewater treatment facilities.

New antibiotics and alternative strategies

The rapid pandemic spread of multiresistant bacteria and the paucity of new effective antibiotics is placing patients' safety at risk worldwide. The infrastructure of antibiotic discovery both in academia and in industry is at a dangerously low level and needs to be rebuilt. A new sustainable global model for the discovery, development, and distribution of antibiotics needs be developed in which the private and public sectors work in partnership and the large scientific bottlenecks for discovery of antibiotics with new mechanisms of action are solved in collaboration between academia, SMEs, and major pharmaceutical companies. In the EU, substantial public funding for antibiotic research has been put into the Innovative Medicines Initiative, and the Joint Programming Initative on Antimicrobial Resistance is strengthening collaboration within the academic sectors in 18 of the EU member states. These important initiatives need to be moved to structured sustainable global collaboration. Beyond the much needed substantial push funding for antibiotic discovery and development, incentives are needed to secure the rational use of new antibiotics and prevent them from being heavily marketed. Financing models that delink research and development investment from revenue returns need to be developed and piloted. By such delinkage, the return on investment for pharmaceutical firms should be divorced from volume-based market sales of antibiotics and access to new antibiotics will need to be controlled through regulation, procurement, and distribution. Such approaches should empower consumers and providers alike to tackle antibiotic resistance as well as ensure that those in need benefit from affordable, effective antibiotics.

Intensive research efforts need to be directed to retain the efficacy of our present antibiotics by substantial investment in antibiotic adjuvants. Alongside antibiotic research, increased investments need to be made in alternatives to antibiotics. The goal is to encourage researchers and biotech to reconsider the reliance on antibiotics and to explore other means of controlling bacterial infection, such as virulence blockers, monoclonal antibodies, immune modulators, and bacterial vaccines.

Governmental coordination and action

The ultimate responsibility for the provision of equitable and affordable access to effective antibiotics for those in need lies with national governments. The consequences of antibiotic resistance reach far beyond the human health sector and thus no one governmental ministry or agency can be held solely responsible. National task forces with a broad intersectoral coordinating role, including all relevant stakeholders, with governmental mandate, are needed. Task forces should produce annual action plans and milestones in different areas, such as surveillance, regulation, treatment guidelines, infection control, education, and awareness raising. Health professionals and university academics have an important catalytic role and should engage with community leaders, civil society organisations, and students.

Global governance

The serious threat to public health caused by the rapid loss of antibiotic effectiveness calls for global concerted actions. We advocate for a health systems thinking approach in the efforts to contain antibiotic resistance. Treatment for bacterial infections is a fundamental prerequisite for fulfilment of health related Millennium Development Goals and access to effective antibiotics should be included in the discussions of the post-2015 Developments Goals. We call for a coalition of governments with a strong representation from LMICs that will work with WHO, UNICEF, UN Development Programme, other UN agencies, other international bodies, science academies, development aid agencies, philanthropists, and civil society organisations to develop a global plan to tackle the antibiotic crisis and share responsibilities for its implementation. This governmental coalition should also

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initiate processes to create global funding mechanisms for needs driven research and development of antibiotics, alternative treatments, diagnostics, and vaccines. A global code of conduct should be developed for antibiotic use and implementation of strategies against antibiotic resistance.

Contributors

A list of the contributors to each section can be found in the panel on page 1 of the Commission. Part 1: RL did the literature search and wrote the section, AKMZ, AD, and CW contributed to the writing and read the final paper. Part 2: all authors contributed to the reference search for the piece, writing, revisions, and final approval. Part 5: ADS drafted the original piece; all authors participated in all subsequent phases and approved the final manuscript. Part 6: FNQ and FM contributed equally.

Conflicts of interest

AC holds an European Commission FP7 grant(BacAttack) and an Innovative Medicines Initiative grant (Predict TB) and is the founder, director, chief scientific officer, shareholder of Helperby Therapeutics Ltd which makes new antibiotics. All other authors declare no conflicts of interest. IMG has received consultancy and lecture and as president of the International Society of Chemotherapy frequently requests meeting support from various companies involved in the development of diagnostics and antibiotics for MRSA.

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References

1 Centers for Disease Control and Prevention (CDC). Vital signs: carbapenem-resistant Enterobacteriaceae. *MMWR Morb Mortal Wkly Rep* 2013; **62:** 165–70.

2 Laxminarayan R, Heymann DL. Challenges of drug resistance in the developing world. *BMJ* 2012; **344:** e1567.

3 Abraham EP, Chain E. An enzyme from bacteria able to destroy penicillin. 1940. *Rev Infect Dis* 1988; **10:** 677–78.

4 Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010; **74:** 417–33.

5 Holmes KK, Johnson DW, Floyd TM. Studies of venereal disease. I. Probenecid-procaine penicillin G combination and tetracycline hydrochloride in the treatment of "penicillin-resistant" gonorrhea in men. *JAMA* 1967; **202:** 461–73.

6 Rasnake MS, Conger NG, McAllister K, Holmes KK, Tramont EC. History of U.S. military contributions to the study of sexually transmitted diseases. *Mil Med* 2005; **170** (suppl)**:** 61–65.

7 Nordmann P, Naas T, Poirel L. Global spread of Carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* 2011; **17:** 1791–98.

8 Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis* 2011; **11:** 355–62.

9 Ruiz J, Pons MJ, Gomes C. Transferable mechanisms of quinolone resistance. *Int J Antimicrob Agents* 2012; **40:** 196–203.

10 Holden MT, Hsu LY, Kurt K, et al. A genomic portrait of the emergence, evolution, and global spread of a methicillin-resistant *Staphylococcus aureus* pandemic. *Genome Res* 2013; **23:** 653–64.

11 Ammerlaan HS, Harbarth S, Buiting AG, et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. *Clin Infect Dis* 2013; **56:** 798–805.

12 Allegranzi B, Bagheri Nejad S, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011; **377:** 228–41.

13 Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005; **365:** 1175–88.

14 Waters D, Jawad I, Ahmad A, et al. Aetiology of community-acquired neonatal sepsis in low and middle income countries. *J Glob Health* 2011; **1:** 154–70.

15 Viswanathan R, Singh AK, Ghosh C, Dasgupta S, Mukherjee S, Basu S. Profile of neonatal septicaemia at a district-level sick newborn care unit. *J Health Popul Nutr* 2012; **30:** 41–48.

16 Saleem AF, Ahmed I, Mir F, Ali SR, Zaidi AK. Pan-resistant Acinetobacter infection in neonates in Karachi, Pakistan. *J Infect Dev Ctries* 2010; **4:** 30–37.

17 Perry JD, Naqvi SH, Mirza IA, et al. Prevalence of faecal carriage of Enterobacteriaceae with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. *J Antimicrob Chemother* 2011; **66:** 2288–94.

18 Khan E, Ejaz M, Zafar A, et al. Increased isolation of ESBL producing Klebsiella pneumoniae with emergence of carbapenem resistant isolates in Pakistan: report from a tertiary care hospital. *J Pak Med Assoc* 2010; **60:** 186–90.

19 Perovic O, Singh-Moodley A, Smith M, Lowman W. Antimicrobial resistance of *Klebsiella pneumoniae* and *Staphylococcus aureus* at sentinel sites in South Africa. 52nd interscience conference on antimicrobial agents and chemotherapy; San Francisco; Sept 9–12, 2012.

20 Lowman W, Sriruttan C, Nana T, et al. NDM-1 has arrived: first report of a carbapenem resistance mechanism in South Africa. *S Afr Med J* 2011; **101:** 873–75.

21 NICD-NHLS. Update on carbapenemase-producing Enterobacteriaceae. *NICD Communicable Diseases Communiqué* 2012; **12:** 5–6.

22 Hollyway K, Mathai E, Sorensen T, Gray T. Community-based surveillance of antimicrobial use and resistance in resources-constrained settings: report on five pilot projects. Geneva: World Health Organization, 2009.

23 Datta S, Wattal C, Goel N, Oberoi JK, Raveendran R, Prasad KJ. A ten year analysis of multi-drug resistant blood stream infections caused by *Escherichia coli* and *Klebsiella pneumoniae* in a tertiary care hospital. *Indian J Med Res* 2012; **135:** 907–12.

24 Ko KS, Suh JY, Kwon KT, et al. High rates of resistance to colistin and polymyxin B in subgroups of *Acinetobacter baumannii* isolates from Korea. *J Antimicrob Chemother* 2007; **60:** 1163–67.

25 Capone A, Giannella M, Fortini D, et al, for the SEERBIO-GRAB network. High rate of colistin resistance among patients with carbapenem-resistant Klebsiella pneumoniae infection accounts for an excess of mortality. *Clin Microbiol Infect* 2013; **19:** 23–30.

26 Kontopidou F, Plachouras D, Papadomichelakis E, et al. Colonization and infection by colistin-resistant Gram-negative bacteria in a cohort of critically ill patients. *Clin Microbiol Infect* 2011; **17:** 9–11.

27 Antoniadou A, Kontopidou F, Poulakou G, et al. Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multiclonal cluster. *J Antimicrob Chemother* 2007; **59:** 786–90.

28 Baadani AM, Thawadi SI, El-Khizzi NA, Omrani AS. Prevalence of colistin and tigecycline resistance in *Acinetobacter baumannii* clinical isolates from 2 hospitals in Riyadh Region over a 2-year period. *Saudi Med J* 2013; **34:** 248–53.

29 Napier BA, Burd EM, Satola SW, et al. Clinical use of colistin induces cross-resistance to host antimicrobials in *Acinetobacter baumannii*. *MBio* 2013; **4:** e00021–13.

30 Klein EY, Sun L, Smith DL, Laxminarayan R. The changing epidemiology of methicillin-resistant *Staphylococcus aureus* in the United States: a national observational study. *Am J Epidemiol* 2013; **177:** 666–74.

31 Anupurba S, Sen MR, Nath G, Sharma BM, Gulati AK, Mohapatra TM. Prevalence of methicillin resistant *Staphylococcus aureus* in a tertiary referral hospital in eastern Uttar Pradesh. *Indian J Med Microbiol* 2003; **21:** 49–51.

32 Zafar A, Stone M, Ibrahim S, et al. Prevalent genotypes of meticillin-resistant *Staphylococcus aureus*: report from Pakistan. *J Med Microbiol* 2011; **60:** 56–62.

33 Malik N, Butt T, Arfan-ul-Bari. Frequency and antimicrobial susceptibility pattern of methicillin resistant *Staphylococcus aureus*. *J Coll Physicians Surg Pak* 2009; **19:** 287–90.

34 ECDC/EMEA. Technical Report. The bacterial challenge: time to react. Sept 2009. http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (accessed Oct 31, 2013).

35 Klevens RM, Morrison MA, Nadle J, et al, for the Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA* 2007; **298:** 1763–71.

36 US Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. April 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf (accessed Oct 31, 2013).

37 Lambert ML, Suetens C, Savey A, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis* 2011; **11:** 30–38.

38 Wolkewitz M, Frank U, Philips G, Schumacher M, Davey P, for the BURDEN Study Group. Mortality associated with in-hospital bacteraemia caused by *Staphylococcus aureus*: a multistate analysis with follow-up beyond hospital discharge. *J Antimicrob Chemother* 2011; **66:** 381–86.

39 de Kraker ME, Davey PG, Grundmann H, for the BURDEN study group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med* 2011; **8:** e1001104.

40 Kayange N, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza-Tanzania. *BMC Pediatr* 2010; **10:** 39.

41 Office of Technology Assessment. Impacts of antibiotic-resistant bacteria: a report to the US Congress. Washington DC: Government Printing Office, 1995.

42 Reed S, Sullivan S, Laxminarayan R. Socioeconomic issues related to antibiotic use. In: Low DE, ed. Appropriate antibiotic use. London: The Royal Society of Medicine Press, 2001. 41–46.

43 Holmberg SD, Solomon SL, Blake PA. Health and economic impacts of antimicrobial resistance. *Rev Infect Dis* 1987; **9:** 1065–78.

44 The Genesis Report. The real war on drugs: bacteria are winning. New Jersey; December 1994.

45 Howard D, Rask K. The Impact of resistance on antibiotic demand in patients with ear infections. In: Laxminarayan R, ed. Battling resistance to antibiotics and pesticides: an economic approach. Washington DC: RFF Press, 2002. 119–33.

46 O'Brien KL, Wolfson LJ, Watt JP, et al, for the Hib and Pneumococcal Global Burden of Disease Study Team. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; **374:** 893–902.

47 Gu B, Kelesidis T, Tsiodras S, Hindler J, Humphries RM. The emerging problem of linezolid-resistant *Staphylococcus*. *J Antimicrob Chemother* 2013; **68:** 4–11.

48 Patel SN, Memari N, Shahinas D, Toye B, Jamieson FB, Farrell DJ. Linezolid resistance in *Enterococcus faecium* isolated in Ontario, Canada. *Diagn Microbiol Infect Dis* 2013; published online Oct 2. DOI:10.1016/j.diagmicrobio.2013.08.01

49 López-Salas P, Llaca-Díaz J, Morfin-Otero R, et al. Virulence and antibiotic resistance of *Enterococcus faecalis* clinical isolates recovered from three states of mexico. Detection of linezolid resistance. *Arch Med Res* 2013; **44:** 422–28.

50 Laxminarayan R, Malani A, Howard D, Smith DL. Extending the cure: policy responses to the growing threat of antibiotic resistance. Washington DC: Resources for the Future, 2007.

51 Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ* 2013; **346:** 1493.

52 Goossens H, Ferech M, Vander Stichele R, Elseviers M, for the ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365:** 579–87.

53 Braykov NP, Eber MR, Klein EY, Morgan DJ, Laxminarayan R. Trends in resistance to carbapenems and third-generation cephalosporins among clinical isolates of *Klebsiella pneumoniae* in the United States, 1999–2010. *Infect Control Hosp Epidemiol* 2013; **34:** 259–68.

54 Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999–2005. *Emerg Infect Dis* 2007; **13:** 1840–46.

55 Steinman MA, Landefeld CS, Gonzales R. Predictors of broad-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care. *JAMA* 2003; **289:** 719–25.

56 Nitzan O, Low M, Lavi I, Hammerman A, Klang S, Raz R. Variability in outpatient antimicrobial consumption in Israel. *Infection* 2010; **38:** 12–18.

57 Filippini M, Masiero G, Moschetti K. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: evidence from Switzerland. *Health Policy* 2006; **78:** 77–92.

58 Glass SK, Pearl DL, McEwen SA, Finley R. Canadian province-level risk factor analysis of macrolide consumption patterns (2000–2006). *J Antimicrob Chemother* 2010; **65:** 148–55.

59 Matuz M, Benko R, Doro P, et al. Regional variations in community consumption of antibiotics in Hungary, 1996–2003. *Br J Clin Pharmacol* 2006; **61:** 96–100.

60 ECDC. Summary of the latest data on antibiotic consumption in the European Union. Nov 2012. http://ecdc.europa.eu/en/eaad/Documents/ESAC-Net-summary-antibiotic-consumption.pdf (accessed Oct 31, 2013).

61 Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *Lancet Infect Dis* 2011; **11:** 692–701.

62 Sweidan M, Zhang Y, Harvey K, Yang Y, Shen X, Yao K. Proceedings of the 2nd national workshop on rational use of antibiotics in China. Beijing: Beijing Children's Hospital, 2005.

63 Dong H, Bogg L, Rehnberg C, Diwan V. Association between health insurance and antibiotics prescribing in four counties in rural China. *Health Policy* 1999; **48:** 29–45.

64 Bennett D, Lauderdale T-L, Hung C-L. Competing doctors, antibiotic use, and antibiotic resistance in Taiwan. Sept 16, 2008. http://chess.uchicago.edu/events/hew/fall08/bennett.pdf (accessed Nov 1, 2013).

65 Apisarnthanarak A, Tunpornchai J, Tanawitt K, Mundy LM. Nonjudicious dispensing of antibiotics by drug stores in Pratumthani, Thailand. *Infect Control Hosp Epidemiol* 2008; **29:** 572–75.

66 Wise R. Antimicrobial resistance: priorities for action. *J Antimicrob Chemother* 2002; **49:** 585–86.

67 Glad T, Bernhardsen P, Nielsen KM, et al. Bacterial diversity in faeces from polar bear (*Ursus maritimus*) in Arctic Svalbard. *BMC Microbiol* 2010; **10:** 10.

68 Levy SB, FitzGerald GB, Macone AB. Spread of antibiotic-resistant plasmids from chicken to chicken and from chicken to man. *Nature* 1976; **260:** 40–42.

69 Harrison EM, Paterson GK, Holden MT, et al. Whole genome sequencing identifies zoonotic transmission of MRSA isolates with the novel mecA homologue mecC. *EMBO Mol Med* 2013; **5:** 509–15.

70 Fleming A. Penicillin, its practical application. London: Butterworth & Co, 1946.

71 Kunin CM. This is medical progress? Trends and consequences of antibiotic use in the United States. In comment. *JAMA* 1974; **227:** 1030–32.

72 Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. *Lancet Infect Dis* 2012; **12:** 774–80.

73 Thriemer K, Katuala Y, Batoko B, et al. Antibiotic prescribing in DR Congo: a knowledge, attitude and practice survey among medical doctors and students. *PLoS ONE* 2013; **8:** e55495.

74 Global Antibiotic Resistance Partnership, Public Health Foundation of India. Situation analysis. Antibiotic use and resistance in India. March 2011. http://www.cddep.org/sites/cddep.org/files/publication_files/India-report-web.pdf?issuusl=ignore (accessed Nov 4, 2013).

75 Food and Drug Administration Department of Health and Human Services. 2010 summary report on antimicrobials sold or distributed for use in food-producing animals. http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm277657.pdf (accessed April 29, 2013).

76 WHO. The evolving threat of antimicrobial resistance: option for action. 2012. http://www.who.int/patientsafety/implementation/amr/publication/en/index.html (accessed May 24, 2013).

77 Stone SP, Fuller C, Savage J, et al. Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. *BMJ* 2012; **344:** e3005.

78 Schwaber MJ, Lev B, Israeli A, et al, for the Israel Carbapenem-Resistant Enterobacteriaceae Working Group. Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. *Clin Infect Dis* 2011; **52:** 848–55.

79 Brinsley K, Srinivasan A, Sinkowitz-Cochran R, et al. Implementation of the Campaign to Prevent Antimicrobial Resistance in Healthcare Settings: 12 steps to prevent antimicrobial resistance among hospitalized adults-experiences from 3 institutions. *Am J Infect Control* 2005; **33:** 53–54.

80 Ghafur A, Mathai D, Muruganathan A, et al. The Chennai Declaration: a roadmap to tackle the challenge of antimicrobial resistance. *Indian J Cancer* 2013; **50:** 71–73.

81 Gould IM, Wang GH, Wu J-J, et al. Global burden of multi drug resistant organisms current antimicrobial resistance problems in the Asia-Pacific. MDRO Beijing Consensus Meeting Report. *J Global Antimicrob Resistance* (in press).

82 Paterson DL. The role of antimicrobial management programs in optimizing antibiotic prescribing within hospitals. *Clin Infect Dis* 2006; **42** (suppl 2): 90–95.

83 Lawes T, Edwards B, Lopez-Lozano JM, Gould I. Trends in *Staphylococcus aureus* bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006–2010: retrospective cohort study and time-series intervention analysis. *BMJ Open* 2012; **2:** 3.

84 Vernaz N, Hill K, Leggeat S, et al. Temporal effects of antibiotic use and Clostridium difficile infections. *J Antimicrob Chemother* 2009; **63:** 1272–75.

85 Dellit TH, Owens RC, McGowan JE Jr, et al, for the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; **44:** 159–77.

86 Nabyonga Orem J, Bataringaya Wavamunno J, Bakeera SK, Criel B. Do guidelines influence the implementation of health programs? Uganda's experience. *Implement Sci* 2012; **7:** 98.

87 Wertheim HFL, Chandna A, Vu PD, et al. Providing impetus, tools, and guidance to strengthen national capacity for antimicrobial stewardship in Viet Nam. *PLoS Med* 2013; **10:** e1001429.

88 Millar M. Constraining the use of antibiotics: applying Scanlon's contractualism. *J Med Ethics* 2012; **38:** 465–69.

89 Apisarnthanarak A, Mundy LM. Comparison of methods of measuring pharmacy sales of antibiotics without prescriptions in Pratumthani, Thailand. *Infect Control Hosp Epidemiol* 2009; **30:** 1130–32.

90 Radyowijati A, Haak H. Improving antibiotic use in low-income countries: an overview of evidence on determinants. *Soc Sci Med* 2003; **57:** 733–44.

91 Thorgeirsson T, Kawachi I. Behavioral economics: merging psychology and economics for lifestyle interventions. *Am J Prev Med* 2013; **44:** 185–89.

92 Sumpradit N, Chongtrakul P, Anuwong K, et al. Antibiotics Smart Use: a workable model for promoting the rational use of medicines in Thailand. *Bull World Health Organ* 2012; **90:** 905–13.

93 McDonnell Norms Group. Antibiotic overuse: the influence of social norms. *J Am Coll Surg* 2008; **207:** 265–75.

94 MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. *Clin Microbiol Rev* 2005; **18:** 638–56.

95 Choi S, Reich M. Report cards and prescribing behavior: assessing the impacts of public disclosure on antibiotic prescribing rates in South Korea. Third International Conference in Improving Use of Medicines; Antalya, Turkey; Nov14–18, 2011. 13 AD.

96 Masiero G, Filippini M, Ferech M, Goossens H. Socioeconomic determinants of outpatient antibiotic use in Europe. *Int J Public Health* 2010; **55:** 469–78.

97 Mintzes B. Pharmaceutical promotion and prevention of antibiotic resistance. Mastering anti-infective therapies. Paris: 2005.

98 Hawkings NJ, Butler CC, Wood F. Antibiotics in the community: a typology of user behaviours. *Patient Educ Couns* 2008; **73:** 146–52.

99 Grigoryan L, Burgerhof JG, Degener JE, et al, for the Self-Medication with Antibiotics and Resistance (SAR) Consortium. Determinants of self-medication with antibiotics in Europe: the impact of beliefs, country wealth and the healthcare system. *J Antimicrob Chemother* 2008; **61:** 1172–79.

100 Planta MB. The role of poverty in antimicrobial resistance. *J Am Board Fam Med* 2007; **20:** 533–39.

101 Zarb P, Goossens H. Human use of antimicrobial agents. *Rev Sci Tech* 2012; **31:** 121–33.

102 Wirtz VJ, Dreser A, Gonzales R. Trends in antibiotic utilization in eight Latin American countries, 1997-2007. *Rev Panam Salud Publica* 2010; **27:** 219–25.

103 Earnshaw S, Monnet DL, Duncan B, O'Toole J, Ekdahl K, Goossens H, for the European Antibiotic Awareness Day Technical Advisory Committee, and the European Antibiotic Awareness Day Collaborative Group. European Antibiotic Awareness Day, 2008–the first Europe-wide public information campaign on prudent antibiotic use: methods and survey of activities in participating countries. *Euro Surveill* 2009; **14:** 19280.

104 Blozik E, Wildeisen IE, Fueglistaler P, von Overbeck J. Telemedicine can help to ensure that patients receive timely medical care. *J Telemed Telecare* 2012; **18:** 119–21.

105 Minzi O, Manyilizu V. Application of basic pharmacology and dispensing practice of antibiotics in accredited drug-dispensing outlets in Tanzania. *Drug Healthc Patient Saf* 2013; **5:** 5–11.

106 WHO. Promoting rational use of medicine: core components. WHO policy perspectives on medicine. Number 5. Sept 2002. http://apps.who.int/medicinedocs/en/d/Jh3011e/ (accessed Nov 1, 2013).

107 Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. *Virulence* 2013; **4:** 192–202.

108 Laxminarayan R, Klugman KP. Communicating trends in resistance using a drug resistance index. *BMJ Open* 2011; **1:** e000135.

109 Huttner B, Goossens H, Verheij T, Harbarth S, for the CHAMP consortium. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis* 2010; **10:** 17–31.

110 Park S, Zhang Y, Lin S, Wang TH, Yang S. Advances in microfluidic PCR for point-of-care infectious disease diagnostics. *Biotechnol Adv* 2011; **29:** 830–39.

111 Diekema DJ, Pfaller MA. Rapid detection of antibiotic-resistant organism carriage for infection prevention. *Clin Infect Dis* 2013; **56:** 1614–20.

112 Galar A, Leiva J, Espinosa M, Guillén-Grima F, Hernáez S, Yuste JR. Clinical and economic evaluation of the impact of rapid microbiological diagnostic testing. *J Infect* 2012; **65:** 302–09.

113 Kerremans JJ, Verboom P, Stijnen T, et al. Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. *J Antimicrob Chemother* 2008; **61:** 428–35.

114 Cantón R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. *FEMS Microbiol Rev* 2011; **35:** 977–91.

115 Johnson AP, Davies J, Guy R, et al. Mandatory surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in England: the first 10 years. *J Antimicrob Chemother* 2012; **67:** 802–09.

116 Okeke I. Divining without seeds. The case for strengthening laboratory medicine in Africa. Ithaca: Cornell University Press, 2011.

117 European Centre for Disease Prevention and Control (ECDC). European Antimicrobial Resistance Surveillance Network. http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx (accessed Nov 1, 2013).

118 WHO. Impacts of antimicrobial growth promoter termination in Denmark. The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark. Foulum, Denmark, Nov 6–9, 2002. Geneva: World Health Organization, 2003.

119 Food and Agriculture Organization (FAO), WHO, and World Organisation for Animal Health (OIE). Report of the FAO/WHO/OIE expert meeting on critically important antimicrobials. Nov 26–30, 2007, Rome: FAO; Geneva: World Health Organization, 2008.

120 Bouki C, Venieri D, Diamadopoulos E. Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review. *Ecotoxicol Environ Saf* 2013; **91:** 1–9.

121 Shi P, Jia S, Zhang XX, Zhang T, Cheng S, Li A. Metagenomic insights into chlorination effects on microbial antibiotic resistance in drinking water. *Water Res* 2013; **47:** 111–20.

122 Davey P, Brown E, Charani E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013; **4:** CD003543.

123 DeNap JC, Hergenrother PJ. Bacterial death comes full circle: targeting plasmid replication in drug-resistant bacteria. *Org Biomol Chem* 2005; **3:** 959–66.

124 Kurinčič M, Klančnik A, Smole Možina S. Epigallocatechin gallate as a modulator of Campylobacter resistance to macrolide antibiotics. *Int J Antimicrob Agents* 2012; **40:** 467–71.

125 Potera C. Phage renaissance: new hope against antibiotic resistance. *Environ Health Perspect* 2013; **121:** a48–53.

126 Allerberger F, Gareis R, Jindrák V, Struelens MJ. Antibiotic stewardship implementation in the EU: the way forward. *Expert Rev Anti Infect Ther* 2009; **7:** 1175–83.

127 Bodansky D. Whither the Kyoto Protocol? Durban and beyond. Aug 2011. http://belfercenter.ksg.harvard.edu/publication/21314/whither_the_kyoto_protocol_durban_and_beyond.html (accessed Oct 7, 2013)

128 Cantón R, Akóva M, Carmeli Y, et al, for the European Network on Carbapenemases. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin Microbiol Infect* 2012; **18:** 413–31.

129 Butler CC, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ* 2009; **338:** 2242.

130 Little P, Stuart B, Moore M, et al, for the GRACE consortium. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; **13:** 123–29.

131 Kang CI, Kim SH, Kim HB, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. *Clin Infect Dis* 2003; **37:** 745–51.

132 Ishengoma DR, Rwegoshora RT, Mdira KY, et al. Health laboratories in the Tanga region of Tanzania: the quality of diagnostic services for malaria and other communicable diseases. *Ann Trop Med Parasitol* 2009; **103:** 441–53.

133 Kreft R, Costerton JM, Ehrlich GD. PCR is changing clinical diagnostics. *Microbe* 2013; **8:** 15–20.

134 Ritzi-Lehnert M. Development of chip-compatible sample preparation for diagnosis of infectious diseases. *Expert Rev Mol Diagn* 2012; **12:** 189–206.

135 Okeke IN, Peeling RW, Goossens H, et al. Diagnostics as essential tools for containing antibacterial resistance. *Drug Resist Updat* 2011; **14:** 95–106.

136 Peeling RW, Smith PG, Bossuyt PMM. A guide for diagnostic evaluations. *Nat Rev Microbiol* 2008; **6:** 2–6.

137 Loens K, Beck T, Ursi D, et al. Two quality control exercises involving nucleic acid amplification methods for detection of Mycoplasma pneumoniae and Chlamydophila pneumoniae and carried out 2 years apart (in 2002 and 2004). *J Clin Microbiol* 2006; **44:** 899–908.

138 Loens K, van Loon AM, Coenjaerts F, et al, for the GRACE Study Group. Performance of different mono- and multiplex nucleic acid amplification tests on a multipathogen external quality assessment panel. *J Clin Microbiol* 2012; **50:** 977–87.

139 World Economic Forum. The financial sustainability of health systems. A case for change. 2012.

140 Loens K, Van Heirstraeten L, Malhotra-Kumar S, Goossens H, Ieven M. Optimal sampling sites and methods for detection of pathogens possibly causing community-acquired lower respiratory tract infections. *J Clin Microbiol* 2009; **47:** 21–31.

141 Gazin M, Paasch F, Goossens H, Malhotra-Kumar S, for the MOSAR WP2 and SATURN WP1 Study Teams. Current trends in culture-based and molecular detection of extended-spectrum-β-lactamase-harboring and carbapenem-resistant Enterobacteriaceae. *J Clin Microbiol* 2012; **50:** 1140–46.

142 Livermore DM, Andrews JM, Hawkey PM, et al. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? *J Antimicrob Chemother* 2012; **67:** 1569–77.

143 Falagas ME, Tansarli GS, Rafailidis PI, Kapaskelis A, Vardakas KZ. Impact of antibiotic MIC on infection outcome in patients with susceptible Gram-negative bacteria: a systematic review and meta-analysis. *Antimicrob Agents Chemother* 2012; **56:** 4214–22.

144 Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibioitic prescribing rates for acute respiratory-tract infection: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013; **382:** 175–82.

145 Mitsuma SF, Mansour MK, Dekker JP, et al. Promising new assays and technologies for the diagnosis and management of infectious diseases. *Clin Infect Dis* 2013; **56:** 996–1002.

146 Nicks BA, Manthey DE, Fitch MT. The Centers for Medicare and Medicaid Services (CMS) community-acquired pneumonia core measures lead to unnecessary antibiotic administration by emergency physicians. *Acad Emerg Med* 2009; **16:** 184–87.

147 Stokstad ELR, Jukes TH. Further observations on the animal protein factor. *Proc Soc Biol Exp Med* 1949; **73:** 523–28.

148 Swedish Ministry of Agriculture. Antimicrobial feed additives. Report from the commission on antimicrobial feed additives. Stockholm, 1997. 139.

149 Robinson P. Controlled trial of aureomycin in premature twins and triplets. *Lancet* 1952; **259:** 52.

150 Swann MM. Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine. London: Her Majesty's Stationery Office, 1969.

151 Grave K, Jensen VF, Odensvik K, Wierup M, Bangen M. Usage of veterinary therapeutic antimicrobials in Denmark, Norway and Sweden following termination of antimicrobial growth promoter use. *Prev Vet Med* 2006; **75:** 123–32.

152 Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. *Clin Microbiol Rev* 2011; **24:** 718–33.

153 Witte W. Selective pressure by antibiotic use in livestock. *Int J Antimicrob Agents* 2000; **16** (suppl 1): 19–24.

154 Aarestrup FM, Jensen VF, Emborg HD, Jacobsen E, Wegener HC. Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark. *Am J Vet Res* 2010; **71:** 726–33.

155 Pagel SW, Gautier P. Use of antimicrobial agents in livestock. *Rev Sci Tech* 2012; **31:** 145–88.

156 European Medicines Agency. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2011. Third ESVAC report. Oct 15, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf (accessed Oct 16, 2013).

157 European Food Safety Authority (EFSA) and European Centre for Disease Prevention and Control (ECDC). The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2011. *EFSA J* 2013; **11:** 3196.

158 Kruse H, Sørum H. Transfer of multiple drug resistance plasmids between bacteria of diverse origins in natural microenvironments. *Appl Environ Microbiol* 1994; **60:** 4015–21.

159 Wellington EM, Boxall AB, Cross P, et al. The role of the natural environment in the emergence of antibiotic resistance in gram-negative bacteria. *Lancet Infect Dis* 2013; **13:** 155–65.

160 Catry B, Van Duijkeren E, Pomba MC, et al, for the Scientific Advisory Group on Antimicrobials (SAGAM). Reflection paper on MRSA in food-producing and companion animals: epidemiology and control options for human and animal health. *Epidemiol Infect* 2010; **138:** 626–44.

161 Holmberg SD, Osterholm MT, Senger KA, Cohen ML. Drug-resistant Salmonella from animals fed antimicrobials. *N Engl J Med* 1984; **311:** 617–22.

162 Hald T, Lo Fo Wong DM, Aarestrup FM. The attribution of human infections with antimicrobial resistant *Salmonella bacteria* in Denmark to sources of animal origin. *Foodborne Pathog Dis* 2007; **4:** 313–26.

163 Nordstrom L, Liu CM, Price LB. Foodborne urinary tract infections: a new paradigm for antimicrobial-resistant foodborne illness. *Front Microbiol* 2013; **4:** 29.

164 Chee-Sanford JC, Mackie RI, Koike S, et al. Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. *J Environ Qual* 2009; **38:** 1086–108.

165 Chaslus-Dancla E, Lafont JP, Martel JL. Spread of resistance from food animals to man: the French experience. *Acta Vet Scand Suppl* 2000; **93** (suppl): 53–60.

166 Lester CH, Frimodt-Møller N, Sørensen TL, Monnet DL, Hammerum AM. In vivo transfer of the vanA resistance gene from an *Enterococcus faecium* isolate of animal origin to an *E. faecium* isolate of human origin in the intestines of human volunteers. *Antimicrob Agents Chemother* 2006; **50:** 596–99.

167 Seiffert SN, Hilty M, Perreten V, Endimiani A. Extended-spectrum cephalosporin-resistant Gram-negative organisms in livestock: an emerging problem for human health? *Drug Resist Updat* 2013; **16:** 22–45.

168 Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, et al, for the National ESBL surveillance group. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin Microbiol Infect* 2011; **17:** 873–80.

169 Börjesson S, Jernberg C, Brolund A, et al. Characterization of plasmid-mediated AmpC-producing E. coli from Swedish broilers and association with human clinical isolates. *Clin Microbiol Infect* 2013; **19:** 309–11.

170 Fischer J, Rodríguez I, Schmoger S, et al. *Salmonella enterica* subsp. enterica producing VIM-1 carbapenemase isolated from livestock farms. *J Antimicrob Chemother* 2013; **68:** 478–80.

171 Codex Alimentarius Commission. Guidelines for risk analysis of foodborne antimicrobial resistance. http://www.foedevarestyrelsen.dk/SiteCollectionDocuments/25_PDF_word_filer%20til%20download/04kontor/resistens%20codex.pdf (accessed Nov 1, 2013).

172 Ashbolt NJ, Amézquita A, Backhaus T, et al. Human Health Risk Assessment (HHRA) for environmental development and transfer of antibiotic resistance. *Environ Health Perspect* 2013; **121:** 993–1001.

173 WHO. Critically important antimicrobials for human medicine. 3rd revision 2011. http://www.who.int/foodborne_disease/resistance/cia/en (accessed Nov 1, 2013).

174 Smith DL, Harris AD, Johnson JA, Silbergeld EK, Morris JG Jr. Animal antibiotic use has an early but important impact on the emergence of antibiotic resistance in human commensal bacteria. *Proc Natl Acad Sci USA* 2002; **99:** 6434–39.

175 Bowen M. Antimicrobial stewardship: Time for change. *Equine Vet J* 2013; **45:** 127–29.

176 Cars O, Högberg LD, Murray M, et al. Meeting the challenge of antibiotic resistance. *BMJ* 2008; **337:** a1438.

177 Carlet J, Jarlier V, Harbarth S, Voss A, Goossens H, Pittet D, for the Participants of the 3rd World Healthcare-Associated Infections Forum. Ready for a world without antibiotics? The Pensières Antibiotic Resistance Call to Action. *Antimicrob Resist Infect Control* 2012; **1:** 11.

178 WHO. The rational use of drugs. Report of the Conference of Experts, Nairobi, Nov 25-29, 1985. Geneva: World Health Organization, 1987. 67.

179 Li Y, Xu J, Wang F, et al. Overprescribing in China, driven by financial incentives, results in very high use of antibiotics, injections, and corticosteroids. *Health Aff (Millwood)* 2012; **31:** 1075–82.

180 Bigdeli M, Jacobs B, Tomson G, et al. Access to medicines from a health system perspective. *Health Policy Plan* 2013; **28:** 692–704.

181 So AD, Gupta N, Brahmachari SK, et al. Towards new business models for R&D for novel antibiotics. *Drug Resist Updat* 2011; **14:** 88–94.

182 So AD, Ruiz-Esparza Q, Gupta N, Cars O. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards. *BMJ* 2012; **344:** e1782.

183 Morones-Ramirez JR, Winkler JA, Spina CS, Collins JJ. Silver enhances antibiotic activity against gram-negative bacteria. *Sci Transl Med* 2013; **5:** 190ra81.

184 Fischbach MA. Combination therapies for combating antimicrobial resistance. *Curr Opin Microbiol* 2011; **14:** 519–23.

185 Cottarel G, Wierzbowski J. Combination drugs, an emerging option for antibacterial therapy. *Trends Biotechnol* 2007; **25:** 547–55.

186 Mishra RPN, Oviedo-Orta E, Prachi P, Rappuoli R, Bagnoli F. Vaccines and antibiotic resistance. *Curr Opin Microbiol* 2012; **15:** 596–602.

187 Goodman C, Gould C, Karnes E, et al. The value of diagnostics innovation, adoption and diffusion into health care. The Lewin Group Reports. July 2005. http://www.lewin.com/~/media/Lewin/Site_Sections/Publications/ValueofDiagnostics.pdf (accessed Nov 1, 2013).

188 WHO. Increasing access to diagnostics through technology transfer and local production. Geneva: World Health Organization, 2011.

189 Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010; **363:** 1005–15.

190 Lim YW, Steinhoff M, Girosi F, et al. Reducing the global burden of acute lower respiratory infections in children: the contribution of new diagnostics. *Nature* 2006; **444** (suppl 1)**:** 9–18.

191 Rinaldi A. Drug and a syphilis test offer hope of yaws eradication. SciDevNet. April 24, 2013. http://www.scidev.net/global/disease/news/drug-and-a-syphilis-test-offer-hope-of-yaws-eradication.html (accessed Nov 1, 2013).

192 Mitjà O, Hays R, Ipai A, et al. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. *Lancet* 2012; **379:** 342–47.

193 Michel CE, Solomon AW, Magbanua JP, et al. Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative study. *Lancet* 2006; **367:** 1585–90.

194 Save the Children. Surviving the first day: state of the world's mothers. May 2013. http://www.savethechildren.org.uk/sites/default/files/images/State_of_World_Mothers_2013.pdf (accessed Sept 24, 2013).

195 Johansson EW, Carvajal L, Newby H, Young M, Wardlaw T. Pneumonia and diarrhoea: tackling the deadliest diseases for the world's poorest children. June 2012. New York: UNICEF, 2012.

196 Baqui AH, Black RE, El Arifeen S, et al. Zinc therapy for diarrhoea increased the use of oral rehydration therapy and reduced the use of antibiotics in Bangladeshi children. *J Health Popul Nutr* 2004; **22:** 440–42.

197 Rutschmann OT, Domino ME. Antibiotics for upper respiratory tract infections in ambulatory practice in the United States, 1997–1999: does physician specialty matter? *J Am Board Fam Pract* 2004; **17:** 196–200.

198 Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *J Antimicrob Chemother* 2013; published online July 25. DOI:10.1093/jac/dkt301.

199 Mainous AG 3rd, Everett CJ, Post RE, Diaz VA, Hueston WJ. Availability of antibiotics for purchase without a prescription on the internet. *Ann Fam Med* 2009; **7:** 431–35.

200 Blomberg B, Manji KP, Urassa WK, et al. Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. *BMC Infect Dis* 2007; **7:** 43.

201 Siegel RM, Kiely M, Bien JP, et al. Treatment of otitis media with observation and a safety-net antibiotic prescription. *Pediatrics* 2003; **112:** 527–31.

202 Schiff GD, Wisniewski M, Bult J, Parada JP, Aggarwal H, Schwartz DN. Improving inpatient antibiotic prescribing: insights from participation in a national collaborative. *Jt Comm J Qual Improv* 2001; **27:** 387–402.

203 Otrompke J. Public and private partnership helps to set the standard of care for multi-drug resistant tuberculosis. Case studies for global health. Oct 30, 2009. http://casestudiesforglobalhealth.org/post.cfm/public-and-private-partnership-helps-to-set-the-standard-of-care-for-multi-drug-resistant-tuberculosis-1 (accessed Nov 1, 2013).

204 Bisoffi Z, Sirima BS, Angheben A, et al. Rapid malaria diagnostic tests vs. clinical management of malaria in rural Burkina Faso: safety and effect on clinical decisions. A randomized trial. *Trop Med Int Health* 2009; **14:** 491–98.

205 Bastiaens GJH, Schaftenaar E, Ndaro A, Keuter M, Bousema T, Shekalaghe SA. Malaria diagnostic testing and treatment practices in three different Plasmodium falciparum transmission settings in Tanzania: before and after a government policy change. *Malar J* 2011; **10:** 76.

206 Batwala V, Magnussen P, Nuwaha F. Antibiotic use among patients with febrile illness in a low malaria endemicity setting in Uganda. *Malar J* 2011; **10:** 377.

207 Nanyonjo A, Nakirunda M, Makumbi F, Tomson G, Källander K, for the inSCALE Study Group. Community acceptability and adoption of integrated community case management in Uganda. *Am J Trop Med Hyg* 2012; **87** (suppl 5)**:** 97–104.

208 Mukanga D, Tiono AB, Anyorigiya T, et al. Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. *Am J Trop Med Hyg* 2012; **87** (suppl 5)**:** 21–29.

209 Hamer DH, Brooks ET, Semrau K, et al. Quality and safety of integrated community case management of malaria using rapid diagnostic tests and pneumonia by community health workers. *Pathog Glob Health* 2012; **106:** 32–39.

210 Waters HR, Rehwinkel JA, Burnham G. Economic evaluation of Mectizan distribution. *Trop Med Int Health* 2004; **9:** 16–25.

211 Sturchio JL. The case of ivermectin: lessons and implications for improving access to care and treatment in developing countries. *Community Eye Health* 2001; **14:** 22–23.

212 Trehan I, Goldbach HS, LaGrone LN, et al. Antibiotics as part of the management of severe acute malnutrition. *N Engl J Med* 2013; **368:** 425–35.

213 Bole K. UCSF teams tackle childhood mortality and river blindness: $16 million from Bill & Melinda Gates Foundation supports international projects. UCSF News. Jan 10, 2013. http://www.ucsf.edu/news/2013/01/13394/ucsf-teams-tackle-childhood-mortality-and-river-blindness (accessed Nov 1, 2013).

214 Rinaldi A. Drug and a syphilis test offer hope of yaws eradication. April 24, 2013. http://www.scidev.net/global/disease/news/drug-and-a-syphilis-test-offer-hope-of-yaws-eradication.html (accessed Nov 1, 2013).

215 Khadem TM, Dodds Ashley E, Wrobel MJ, Brown J. Antimicrobial stewardship: a matter of process or outcome? *Pharmacotherapy* 2012; **32:** 688–706.

216 The Center for Disease Dynamics, Economics and Policy. Resistance map. Antibiotic use and resistance: what's new? http://www.cddep.org/ResistanceMap/key-findings#.UksSsmSG0Vk (accessed Oct 1, 2013).

217 Institute for Healthcare Improvement. Science of improvement: how to improve. April 24, 2011. http://www.ihi.org/knowledge/Pages/HowtoImprove/ScienceofImprovementHowtoImprove.aspx (accessed Nov 1, 2013).

218 Kilo CM. A framework for collaborative improvement: lessons from the Institute for Healthcare Improvement's Breakthrough Series. *Qual Manag Health Care* 1998; **6:** 1–13.

219 California Department of Public Health.The California antimicrobial stewardship program initiative. http://www.cdph.ca.gov/programs/hai/Pages/AntimicrobialStewardshipProgramInitiative.aspx (accessed Nov 1, 2013).

220 WHO. The evolving threat of antimicrobial resistance: options for action. Geneva: World Health Organization, 2012.

221 Nugent R, Back E, Beith A. The race against drug resistance. Washington DC: Center for Global Development Washington, 2010.

222 O'Brien TF. Emergence, spread, and environmental effect of antimicrobial resistance: how use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. *Clin Infect Dis* 2002; **34** (suppl 3): 78–84.

223 Liu L, Johnson HL, Cousens S, et al, for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012; **379:** 2151–61.

224 Okeke IN, Klugman KP, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part II: strategies for containment. *Lancet Infect Dis* 2005; **5:** 568–80.

225 Monjur F, Rizwan F, Asaduzzaman M, et al. Antibiotic sensitivity pattern of causative organisms of neonatal septicemia in an urban hospital of Bangladesh. *Indian J Med Sci* 2010; **64:** 265–71.

226 Nepal HP, Acharya A, Gautam R, Shrestha S, Paudel R. Bacteriological profile of neonatal septicemia cases and the antimicrobial resistance pattern in a tertiary care hospital of central Nepal. *Internat J Biomed Research* 2013; **4:** 26–31.

227 Shitaye D, Asrat D, Woldeamanuel Y, Worku B. Risk factors and etiology of neonatal sepsis in Tikur Anbessa University Hospital, Ethiopia. *Ethiop Med J* 2010; **48:** 11–21.

228 Chiabi A, Djoupomb M, Mah E, et al. The clinical and bacteriogical spectrum of neonatal sepsis in a tertiary hospital in yaounde, cameroon. *Iran J Pediatr* 2011; **21:** 441–48.

229 Acquah SEK, Quaye L, Sagoe K, Ziem JB, Bromberger PI, Amponsem AA. Susceptibility of bacterial etiological agents to commonly-used antimicrobial agents in children with sepsis at the Tamale Teaching Hospital. *BMC Infect Dis* 2013; **13:** 89.

230 Viswanathan R, Singh AK, Basu S, Chatterjee S, Sardar S, Isaacs D. Multi-drug resistant gram negative bacilli causing early neonatal sepsis in India. *Archives of Dis in Childhood-Fetal and Neonatal Ed* 2012; **97:** 182–87.

231 Muhammad Z, Ahmed A, Hayat U, Wazir MS, Rafiyatullah WH. Neonatal sepsis: causative bacteria and their resistance to antibiotics. Journal of Ayub Medical College. *J Ayub Med Coll Abbottabad* 2010; **22:** 33–36.

232 Awoniyi DO, Udo SJ, Oguntibeju OO. An epidemiological survey of neonatal sepsis in a hospital in Western Nigeria. *Afr J Microbiol Research* 2009; **3:** 385–89.

233 Al-Shamahy HA, Sabrah AA, Al-Robasi AB, Naser SM. Types of Bacteria associated with Neonatal Sepsis in Al-Thawra University Hospital, Sana'a, Yemen, and their Antimicrobial Profile. *Sultan Qaboos Univ Med J* 2012; **12:** 48–54.

234 Kruse AY, Thieu Chuong DH, Phuong CN. Neonatal bloodstream infections in a pediatric hospital in Vietnam: a cohort study. *J Trop Pediatr* 2013; published online July 18. DOI:10.1093/tropej/fmt056.

235 Elham AM. EL-Feky, Zeinab A, Rahman Y, Mansi YA. Retrospective analysis of neonatal bacteremia and antimicrobial resistance pattern in neonatal intensive care unit. *Res J Med Med Sci* 2011; **6:** 62–68.

236 Zaidi AK, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. *Pediatr Infect Dis J* 2009; **28** (suppl 1): 10–18.

237 West BA, Peterside O. Sensitivity pattern among bacterial isolates in neonatal septicaemia in port Harcourt. *Ann Clin Microbiol Antimicrob* 2012; **11:** 7.

238 Lubell YAE, Ashley EA, Turner C, Turner P, White NJ. Susceptibility of community-acquired pathogens to antibiotics in Africa and Asia in neonates--an alarmingly short review. *Trop Med Int Health* 2011; **16:** 145–51.

239 Lynch JP 3rd, Zhanel GG. Streptococcus pneumoniae: does antimicrobial resistance matter? *Semin Respir Crit Care Med* 2009; **30:** 210–38.

240 Zafar A, Hussain Z, Lomama E, Sibille S, Irfan S, Khan E. Antibiotic susceptibility of pathogens isolated from patients with community-acquired respiratory tract infections in Pakistan–the active study. Journal of Ayub Medical College. *J Ayub Med Coll Abbottabad* 2008; **20:** 7–9.

241 Borg MA, Tiemersma E, Scicluna E, et al, for the ARMed Project members and collaborators. Prevalence of penicillin and erythromycin resistance among invasive *Streptococcus pneumoniae* isolates reported by laboratories in the southern and eastern Mediterranean region. *Clin Microbiol Infect* 2009; **15:** 232–37.

242 Benouda A, Ben Redjeb S, Hammami A, Sibille S, Tazir M, Ramdani-Bouguessa N. Antimicrobial resistance of respiratory pathogens in North African countries. *J Chemother* 2009; **21:** 627–32.

243 Tali-Maamar H, Laliam R, Bentchouala C, et al. Serotyping and antibiotic susceptibility of *Streptococcus pneumoniae* strains isolated in Algeria from 2001 to 2010. *Med Mal Infect* 2012; **42:** 59–65.

244 Agudelo CI, Castañeda E, Corso A, et al, for the Grupo Sireva II. Resistance to non-beta-lactam antibiotics in the clinical isolates of *Streptococcus pneumoniae* of children in Latin America. SIREVA II, 2000-2005. *Rev Panam Salud Publica* 2009; **25:** 305–13 (in Spanish).

245 Arifeen SE, Saha SK, Rahman S, et al. Invasive pneumococcal disease among children in rural Bangladesh: results from a population-based surveillance. *Clin Infect Dis* 2009; **48** (suppl 2): 103–13.

246 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2095–128.

247 Abera B, Bezabih B, Dessie A. Antimicrobial suceptibility of *V. cholerae* in north west, Ethiopia. *Ethiop Med J* 2010; **48:** 23–28.

248 Balaji K, Okonjo PA, Thenmozhi R, Karutha Pandian S. Virulence and multidrug resistance patterns of *Vibrio cholerae* O1 isolates from diarrheal outbreaks of South India during 2006–2009. *Microb Drug Resist* 2013; **19:** 198–203.

249 Karki R, Bhatta DR, Malla S, et al. Resistotypes of *Vibrio cholerae* 01 Ogawa Biotype El Tor in Kathmandu, Nepal. *Nepal Med Coll J* 2011; **13:** 84–87.

250 Marin MA, Thompson CC, Freitas FS, et al. Cholera outbreaks in Nigeria are associated with multidrug resistant atypical El Tor and non-O1/non-O139 Vibrio cholerae. *PLoS Negl Trop Dis* 2013; **7:** e2049.

251 Sang WK, Oundo V, Schnabel D. Prevalence and antibiotic resistance of bacterial pathogens isolated from childhood diarrhoea in four provinces of Kenya. *J Infect Dev Ctries* 2012; **6:** 572–78.

252 Kiiru JN, Saidi SM, Goddeeris BM, Wamae NC, Butaye P, Kariuki SM. Molecular characterisation of *Vibrio cholerae* O1 strains carrying an SXT/R391-like element from cholera outbreaks in Kenya: 1994–2007. *BMC Microbiol* 2009; **9:** 275.

253 Mwansa JCL, Mwaba J, Lukwesa C, et al. Multiply antibiotic-resistant *Vibrio cholerae* O1 biotype El Tor strains emerge during cholera outbreaks in Zambia. *Epidemiol Infect* 2007; **135:** 847–53.

254 Rashed SM, Mannan SB, Johura FT, et al. Genetic characteristics of drug-resistant *Vibrio cholerae* O1 causing endemic cholera in Dhaka, 2006-2011. *J Med Microbiol* 2012; **61:** 1736–45.

255 Charles RC, Ryan ET. Cholera in the 21st century. *Curr Opin Infect Dis* 2011; **24:** 472–77.

256 Borkakoty B, Biswas D, Devi U, Yadav K, Mahanta J. Emergence of classical ctxB genotype 1 and tetracycline resistant strains of *Vibrio cholerae* O1 El Tor in Assam, India. *Trans R Soc Trop Med Hyg* 2012; **106:** 382–86.

257 Shakoor S, Zaidi AK, Hasan R. Tropical bacterial gastrointestinal infections. *Infect Dis Clin North Am* 2012; **26:** 437–53.

258 Gu B, Cao Y, Pan S, et al. Comparison of the prevalence and changing resistance to nalidixic acid and ciprofloxacin of *Shigella* between Europe-America and Asia-Africa from 1998 to 2009. *Int J Antimicrob Agents* 2012; **40:** 9–17.

259 Ghosh S, Pazhani GP, Chowdhury G, et al. Genetic characteristics and changing antimicrobial resistance among *Shigella* spp. isolated from hospitalized diarrhoeal patients in Kolkata, India. *J Med Microbiol* 2011; **60:** 1460–66.

260 Ahmed D, Hoque A, Elahi MSB, Endtz HP, Hossain MA. Bacterial aetiology of diarrhoeal diseases and antimicrobial resistance in Dhaka, Bangladesh, 2005–2008. *Epidemiol Infect* 2012; **140:** 1678–84.

261 Okeke IN, Laxminarayan R, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis* 2005; **5:** 481–93.

262 Shea KM, and the American Academy of Pediatrics Committee on Environmental Health, and the American Academy of Pediatrics Committee on Infectious Diseases. Nontherapeutic use of antimicrobial agents in animal agriculture: implications for pediatrics. *Pediatrics* 2004; **114:** 862–68.

263 Srikantiah P, Girgis FY, Luby SP, et al. Population-based surveillance of typhoid fever in Egypt. *Am J Trop Med Hyg* 2006; **74:** 114–19.

264 Kumar S, Rizvi M, Berry N. Rising prevalence of enteric fever due to multidrug-resistant *Salmonella*: an epidemiological study. *J Med Microbiol* 2008; **57:** 1247–50.

265 Khan MI, Soofi SB, Ochiai RL, et al. Epidemiology, clinical presentation, and patterns of drug resistance of *Salmonella* Typhi in Karachi, Pakistan. *J Infect Dev Ctries* 2012; **6:** 704–14.

266 Lunguya O, Lejon V, Phoba M-F, et al. *Salmonella typhi* in the democratic republic of the congo: fluoroquinolone decreased susceptibility on the rise. *PLoS Negl Trop Dis* 2012; **6:** e1921.

267 Kariuki S, Revathi G, Kiiru J, et al. Typhoid in Kenya is associated with a dominant multidrug-resistant *Salmonella enterica* serovar Typhi haplotype that is also widespread in Southeast Asia. *J Clin Microbiol* 2010; **48:** 2171–76.

268 Mills-Robertson F, Addy ME, Mensah P, Crupper SS. Molecular characterization of antibiotic resistance in clinical *Salmonella typhi* isolated in Ghana. *FEMS Microbiol Lett* 2002; **215:** 249–53.

269 Molyneux EM, Walsh AL, Malenga G, Rogerson S, Molyneux ME. *Salmonella* meningitis in children in Blantyre, Malawi, 1996–1999. *Ann Trop Paediatr* 2000; **20:** 41–44.

270 Tabu C, Breiman RF, Ochieng B, et al. Differing burden and epidemiology of non-Typhi *Salmonella* bacteremia in rural and urban Kenya, 2006–2009. *PLoS One* 2012; **7:** e31237.

271 Feasey NA, Dougan G, Kingsley RA, Heyderman RS, Gordon MA. Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. *Lancet* 2012; **379:** 2489–99.

272 Kariuki S, Revathi G, Kariuki N, Kiiru J, Mwituria J, Hart CA. Characterisation of community acquired non-typhoidal *Salmonella* from bacteraemia and diarrhoeal infections in children admitted to hospital in Nairobi, Kenya. *BMC Microbiol* 2006; **6:** 101.

273 Gordon MA, Graham SM, Walsh AL, et al. Epidemics of invasive *Salmonella enterica* serovar enteritidis and *S. enterica* Serovar typhimurium infection associated with multidrug resistance among adults and children in Malawi. *Clin Infect Dis* 2008; **46:** 963–69.

274 Kingsley RA, Msefula CL, Thomson NR, et al. Epidemic multiple drug resistant *Salmonella* Typhimurium causing invasive disease in sub-Saharan Africa have a distinct genotype. *Genome Res* 2009; **19:** 2279–87.

275 Bachou H, Tylleskär T, Kaddu-Mulindwa DH, Tumwine JK. Bacteraemia among severely malnourished children infected and uninfected with the human immunodeficiency virus-1 in Kampala, Uganda. *BMC Infect Dis* 2006; **6:** 160.

276 Ikumapayi UN, Antonio M, Sonne-Hansen J, et al. Molecular epidemiology of community-acquired invasive non-typhoidal *Salmonella* among children aged 2 29 months in rural Gambia and discovery of a new serovar, *Salmonella enterica* Dingiri. *J Med Microbiol* 2007; **56:** 1479–84.

277 Vandenberg O, Nyarukweba DZ, Ndeba PM, et al. Microbiologic and clinical features of *Salmonella* species isolated from bacteremic children in eastern Democratic Republic of Congo. *Pediatr Infect Dis J* 2010; **29:** 504–10.

278 Lunguya O, Lejon V, Phoba M-F, et al. Antimicrobial resistance in invasive non-typhoid *Salmonella* from the Democratic Republic of the Congo: emergence of decreased fluoroquinolone susceptibility and extended-spectrum beta lactamases. *PLoS Negl Trop Dis* 2013; **7:** e2103.

279 Menezes GA, Khan MA, Harish BN, et al. Molecular characterization of antimicrobial resistance in non-typhoidal salmonellae associated with systemic manifestations from India. *J Med Microbiol* 2010; **59:** 1477–83.

280 Byarugaba DK. A view on antimicrobial resistance in developing countries and responsible risk factors. *Int J Antimicrob Agents* 2004; **24:** 105–10.

281 Paruk F, Richards G, Scribante J, Bhagwanjee S, Mer M, Perrie H. Antibiotic prescription practices and their relationship to outcome in South Africa: findings of the prevalence of infection in South African intensive care units (PISA) study. *S Afr Med J* 2012; **102:** 613–16.

282 Datta S, Wattal C, Goel N, Oberoi JK, Raveendran R, Prasad KJ. A ten year analysis of multi-drug resistant blood stream infections caused by *Escherichia coli* & *Klebsiella pneumoniae* in a tertiary care hospital. *Indian J Med Res* 2012; **135:** 907–12.

283 Rosenthal VD, Maki DG, Rodrigues C, et al, for the International Nosocomial Infection Control Consortium Investigators. Impact of International Nosocomial Infection Control Consortium (INICC) strategy on central line-associated bloodstream infection rates in the intensive care units of 15 developing countries. *Infect Control Hosp Epidemiol* 2010; **31:** 1264–72.

284 Laxminarayan R, Bhutta ZA, Duse A, et al. Drug resistance. In: Jamison DT, Breman JG, Measham AR, et al, eds. Disease control priorities in developing countries, 2nd edn. New York: Oxford University Press, 2006. 1031–51.

285 Byarugaba DK. Antimicrobial resistance and its containment in developing countries. In: Antibiotic policies: theory and practice. Gould IM, van der Meer JWM, eds. New York: Springer, 2005. 617–47.

286 Ashley EA, Lubell Y, White NJ, Turner P. Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Saharan Africa and Asian low and middle income countries. *Trop Med Int Health* 2011; **16:** 1167–79.

287 Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics-systematic review and meta-analysis. *Arch Dis Child* 2013; **98:** 146–54.

288 Nugent R. Food and agriculture policy: issues related to prevention of noncommunicable diseases. *Food Nutr Bull* 2004; **25:** 200–07.

289 Nugent R, Back E, Beith A, Center for Global Development's Drug Resistance Working Group. The race against drug resistance. June 14, 2010. http://www.cgdev.org/publication/race-against-drug-resistance (accessed Nov 1, 2013).

290 Nugent R, Okeke IN. When medicines fail: recommendations for curbing antibiotic resistance. *J Infect Dev Ctries* 2010; **4:** 355–56.

291 Transparency International. Global corruption report 2006: corruption and health. London: Pluto Press, 2006.

292 Raka L. Prevention and Control of Hospital-Related Infections in Low and Middle Income Countries. *Open Infect Dis J* 2010; **4:** 125–31.

293 Goossens H. The Chennai declaration on antimicrobial resistance in India. *Lancet Infect Dis* 2013; **13:** 105–06.

294 Leung E, Weil DE, Raviglione M, Nakatani H, for the World Health Organization World Health Day Antimicrobial Resistance Technical Working Group. The WHO policy package to combat antimicrobial resistance. *Bull World Health Organ* 2011; **89:** 390–92.

295 Nishtar S. Choked pipes: reforming Pakistan's mixed health system. Oxford: University Press Oxford, 2010.

296 Ghana Statistical Service. Public expenditure tracking surveys. 2007. http://www.statsghana.gov.gh/nada/index.php/catalog/57 (accessed Aug 13, 2013).

297 Lewis M, Pettersson G, The World Bank Development Economics Department and Human Development Department. Governance in health care delivery: raising performance. Oct 2009. http://www-wds.worldbank.org/servlet/WDSContentServer/WDSP/IB/2009/10/13/000158349_20091013151915/Rendered/PDF/WPS5074.pdf (accessed Oct 7, 2013)

298 Koziol M, Tolmie C. Using public expenditure tracking surveys to monitor projects and small-scale programs: a guidebook. Aug 2010. http://elibrary.worldbank.org/doi/abs/10.1596/978-0-8213-8519-7 (accessed Nov 1, 2013).

299 Freedominfo.org. Mexico. Freedom of information. http://www.freedominfo.org/regions/latin-america/mexico/mexico2/ (accessed Aug 13, 2013).

300 Ramkumar V. Our money, our responsibility: a citizens' guide to monitoring government expenditures. Washington DC: International Budget Project, 2008.

301 Transparency International. Corruption perceptions index 2012. http://www.transparency.org/ cpi2012/results (accessed Aug 12, 2013).

302 WHO. Developing health management information systems: a practical guide for developing countries. Geneva: The World Health Organization, 2004.

303 Fraser HS, Biondich P, Moodley D, Choi S, Mamlin BW, Szolovits P. Implementing electronic medical record systems in developing countries. *Inform Prim Care* 2005; **13:** 83–95.

304 Dagan R. Impact of pneumococcal conjugate vaccine on infections caused by antibiotic-resistant *Streptococcus pneumoniae*. *Clin Microbiol Infect* 2009; **15** (suppl 3)**:** 16–20.

305 Ganguly NK, Arora NK, Chandy SJ, et al, for the Global Antibiotic Resistance Partnership (GARP)–India Working Group. Rationalizing antibiotic use to limit antibiotic resistance in India. *Indian J Med Res* 2011; **134:** 281–94.

306 Levin A, Kaddar M. Role of the private sector in the provision of immunization services in low- and middle-income countries. *Health Policy Plan* 2011; **26** (suppl 1)**:** 4–12.

307 Joice R, Lipsitch M. Targeting imperfect vaccines against drug-resistance determinants: a strategy for countering the rise of drug resistance. *PLoS One* 2013; **8:** e68940.

308 Gouws E, Bryce J, Habicht JP, et al. Improving antimicrobial use among health workers in first-level facilities: results from the multi-country evaluation of the Integrated Management of Childhood Illness strategy. *Bull World Health Organ* 2004; **82:** 509–15.

309 Contessotto Spadetto C, Cámara Simón M, Avilés Inglés MJ, Ojeda Escuriet JM, Cascales Barceló I, Rodríguez Sánchez F. Rational use of antibiotics in pediatrics: impact of a rapid test for detection of beta-haemolytic group A streptococci in acute pharyngotonsillitis. *An Esp Pediatr* 2000; **52:** 212–19 (in Spanish).

310 Coates AR, Halls G, Hu Y. Novel classes of antibiotics or more of the same? *Br J Pharmacol* 2011; **163:** 184–94.

311 Powers JH. Antimicrobial drug development—the past, the present, and the future. *Clin Microbiol Infect* 2004; **10** (suppl 4)**:** 23–31.

312 Fenton C, Keating GM, Curran MP. Daptomycin. *Drugs* 2004; **64:** 445–55.

313 Zappia G, Menendez P, Monache GD, Misiti D, Nevola L, Botta B. The contribution of oxazolidinone frame to the biological activity of pharmaceutical drugs and natural products. *Mini Rev Med Chem* 2007; **7:** 389–409.

314 Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48:** 1–12.

315 Coates AR, Halls G. Antibiotics in phase II and III clinical trials. *Handb Exp Pharmacol* 2012; **211:** 167–83.

316 Bax R and Griffin D. Introduction to antibiotic resistance. *Handb Exp Pharmacol* 2012; **211:** 1–12.

317 Hernandez V, Crépin T, Palencia A, et al. Discovery of a novel class of boron-based antibacterials with activity against gram-negative bacteria. *Antimicrob Agents Chemother* 2013; **57:** 1394–403.

318 Chen YH, Ko WC, Hsueh PR. Emerging resistance problems and future perspectives in pharmacotherapy for complicated urinary tract infections. *Expert Opin Pharmacother* 2013; **14:** 587–96.

319 Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of *Escherichia coli* from community-acquired urinary tract infections in Europe: the ECO·SENS study revisited. *Int J Antimicrob Agents* 2012; **39:** 45–51.

320 Widerström M, Wiström J, Ek E, Edebro H, Monsen T. Near absence of methicillin-resistance and pronounced genetic diversity among Staphylococcus epidermidis isolated from healthy persons in northern Sweden. *APMIS* 2011; **119:** 505–12.

321 Mossialos E, Morel CM, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D, World Health Organization 2010, on behalf of the European Observatory on Health Systems and Policies. Policies and incentives for promoting innovation in antibiotic research. 2010. http://www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.pdf (accessed Aug 17, 2013).

322 McKenna M. Antibiotic resistance: Scandinavia gets it. Sept 8, 2010. http://www.superbugtheblog.com/2010/09/antibiotic-resistance-scandinavia-gets.html (accessed Nov 1, 2013).

323 Ministry of Health and Social Affairs, Sweden. Innovative incentives for effective antibacterials. http://www.lakemedelsverket.se/upload/nyheter/2009/Rapport%20fr%C3%A5n%20m%C3%B6tet.pdf (accessed Nov 1, 2013)

324 European Commission. Communication from the Commission to the European Parliament and the Council. Action plan against the rising threats from antimicrobial resistance. http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf (accessed Nov 1, 2013).

325 Bergström R. The role of the pharmaceutical industry in meeting the public health threat of antibacterial resistance. *Drug Resist Updat* 2011; **14:** 77–78.

326 Haverfield S. New approaches to antibacterial drug development; request for comments. May 31, 2013. http://phrma.org/phrmapedia/publications/testimony-public-comments/new-approaches-antibacterial-drug-development (accessed Nov 1, 2013).

327 Spellberg B. New antibiotic development: barriers and opportunities in 2012. Alliance for the prudent use of antibiotics. Newsletter vol 30, issue 1. http://www.tufts.edu/med/apua/news/news-newsletter-vol-30-no-1-2.shtml (accessed Nov 1, 2013).

328 Infectious Diseases Society of America. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clin Infect Dis* 2010; **50:** 1081–83.

329 Davies S, Chief Medical Officer, UK. Independent.co.uk, March 26, 2013.

330 Towse A, Sharma P. Incentives for R&D for new antimicrobial drugs. *Int J Econ Bus* 2011; **18:** 331–50.

331 Infectious Diseases Society of America. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. *Clin Infect Dis* 2012; **55:** 1031–46.

332 Goldfarb NM. Clinical operations: accelerating trials, allocating resources and measuring performance. *J Clin Res Best Practices* 2006; **2:** 12.

333 Coates A. Antibiotic discovery. Pan European Networks: Science and Technology 2012; **4:** 1–2.

334 Tralau-Stewart CJ, Wyatt CA, Kleyn DE, Ayad A. Drug discovery: new models for industry-academic partnerships. *Drug Discov Today* 2009; **14:** 95–101.

335 Jenks S. New NIH center broadens scope of translational research. *J Natl Cancer Inst* 2012; **104:** 728–31.

336 Williams RJ, Walker I, Takle AK. Collaborative approaches to anticancer drug discovery and development: a Cancer Research UK perspective. *Drug Discov Today* 2012; **17:** 185–87.

337 Cohen J. Infectious disease. Approval of novel TB drug celebrated–with restraint. *Science* 2013; **339:** 130.

338 Coates ARM. Antibiotic Resistance-them or us? Pan European Networks. Science and Technology 2012. http://www.helperby.com/wp-content/uploads/2013/08/ST5-A-Coates-2023-CE-Atl.pdf (accessed Nov 1, 2013).

339 Ballell L, Bates RH, Young RJ, et al. Fueling open-source drug discovery: 177 small-molecule leads against tuberculosis. *ChemMedChem* 2013; **8:** 313–21.

340 Cooper MA, Shlaes D. Fix the antibiotics pipeline. *Nature* 2011; **472:** 32.

341 Fernebro J. Fighting bacterial infections-future treatment options. *Drug Resist Updat* 2011; **14:** 125–39.

342 Bartlett JG. Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. *Ann Intern Med* 2006; **145:** 758–64.

343 Rex JH, Eisenstein BI, Alder J, et al. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. *Lancet Infect Dis* 2013; **13:** 269–75.

344 Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov* 2007; **6:** 29–40.

345 Bérdy J. Bioactive microbial metabolites. *J Antibiot (Tokyo)* 2005; **58:** 1–26.

346 Bérdy J. Thoughts and facts about antibiotics: where we are now and where we are heading. *J Antibiot (Tokyo)* 2012; **65:** 385–95.

347 Donald RG, Skwish S, Forsyth RA, et al. A *Staphylococcus aureus* fitness test platform for mechanism-based profiling of antibacterial compounds. *Chem Biol* 2009; **16:** 826–36.

348 Eisenstein BI, Oleson FB Jr, Baltz RH. Daptomycin: from the mountain to the clinic, with essential help from Francis Tally, MD. *Clin Infect Dis* 2010; **50** (suppl 1): 10–15.

349 Brown ED. Is the GAIN Act a turning point in new antibiotic discovery? *Can J Microbiol* 2013; **59:** 153–56.

350 Kalan L, Wright GD. Antibiotic adjuvants: multicomponent anti-infective strategies. *Expert Rev Mol Med* 2011; **13:** 5.

351 Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. *Clin Microbiol Rev* 2010; **23:** 160–201.

352 Hugonnet JE, Tremblay LW, Boshoff HI, Barry CE 3rd, Blanchard JS. Meropenem-clavulanate is effective against extensively drug-resistant Mycobacterium tuberculosis. *Science* 2009; **323:** 1215–18.

353 Shlaes DM. New β-lactam-β-lactamase inhibitor combinations in clinical development. *Ann N Y Acad Sci* 2013; **1277:** 105–14.

354 Shakya T, Stogios PJ, Waglechner N, et al. A small molecule discrimination map of the antibiotic resistance kinome. *Chem Biol* 2011; **18:** 1591–601.

355 Lomovskaya O, Bostian KA. Practical applications and feasibility of efflux pump inhibitors in the clinic–a vision for applied use. *Biochem Pharmacol* 2006; **71:** 910–18.

356 Ejim L, Farha MA, Falconer SB, et al. Combinations of antibiotics and nonantibiotic drugs enhance antimicrobial efficacy. *Nat Chem Biol* 2011; **7:** 348–50.

357 Spitzer M, Griffiths E, Blakely KM, et al. Cross-species discovery of syncretic drug combinations that potentiate the antifungal fluconazole. *Mol Syst Biol* 2011; **7:** 499.

358 Farha MA, Leung A, Sewell EW, et al. Inhibition of WTA synthesis blocks the cooperative action of PBPs and sensitizes MRSA to β-lactams. *ACS Chem Biol* 2013; **8:** 226–33.

359 Rogers SA, Huigens RW 3rd, Cavanagh J, Melander C. Synergistic effects between conventional antibiotics and 2-aminoimidazole-derived antibiofilm agents. *Antimicrob Agents Chemother* 2010; **54:** 2112–18.

360 Wenderska IB, Chong M, McNulty J, Wright GD, Burrows LL. Palmitoyl-DL-carnitine is a multitarget inhibitor of *Pseudomonas aeruginosa* biofilm development. *ChemBioChem* 2011; **12:** 2759–66.

361 Escaich S. Antivirulence as a new antibacterial approach for chemotherapy. *Curr Opin Chem Biol* 2008; **12:** 400–08.

362 Mattmann ME, Blackwell HE. Small molecules that modulate quorum sensing and control virulence in *Pseudomonas aeruginosa*. *J Org Chem* 2010; **75:** 6737–46.

363 Mansson M, Nielsen A, Kjærulff L, et al. Inhibition of virulence gene expression in *Staphylococcus aureus* by novel depsipeptides from a marine photobacterium. *Mar Drugs* 2011; **9:** 2537–52.

364 Nielsen A, Nielsen KF, Frees D, Larsen TO, Ingmer H. Method for screening compounds that influence virulence gene expression in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2010; **54:** 509–12.

365 Hung DT, Shakhnovich EA, Pierson E, Mekalanos JJ. Small-molecule inhibitor of *Vibrio cholerae* virulence and intestinal colonization. *Science* 2005; **310:** 670–74.

366 Duncan MC, Linington RG, Auerbuch V. Chemical inhibitors of the type three secretion system: disarming bacterial pathogens. *Antimicrob Agents Chemother* 2012; **56:** 5433–41.

367 Turgeon Z, Jørgensen R, Visschedyk D, et al. Newly discovered and characterized antivirulence compounds inhibit bacterial mono-ADP-ribosyltransferase toxins. *Antimicrob Agents Chemother* 2011; **55:** 983–91.

368 De Leon GP, Elowe NH, Koteva KP, Valvano MA, Wright GD. An in vitro screen of bacterial lipopolysaccharide biosynthetic enzymes identifies an inhibitor of ADP-heptose biosynthesis. *Chem Biol* 2006; **13:** 437–41.

369 Langsdorf EF, Malikzay A, Lamarr WA, et al. Screening for antibacterial inhibitors of the UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC) using a high-throughput mass spectrometry assay. *J Biomol Screen* 2010; **15:** 52–61.

370 Richter SG, Elli D, Kim HK, et al. Small molecule inhibitor of lipoteichoic acid synthesis is an antibiotic for Gram-positive bacteria. *Proc Natl Acad Sci USA* 2013; **110:** 3531–36.

371 Brodin P, Poquet Y, Levillain F, et al. High content phenotypic cell-based visual screen identifies *Mycobacterium tuberculosis* acyltrehalose-containing glycolipids involved in phagosome remodeling. *PLoS Pathog* 2010; **6:** e1001100.

372 Reichert JM. Marketed therapeutic antibodies compendium. *MAbs* 2012; **4:** 413–15.

373 Oleksiewicz MB, Nagy G, Nagy E. Anti-bacterial monoclonal antibodies: back to the future? *Arch Biochem Biophys* 2012; **526:** 124–31.

374 Bebbington C, Yarranton G. Antibodies for the treatment of bacterial infections: current experience and future prospects. *Curr Opin Biotechnol* 2008; **19:** 613–19.

375 Hancock RE, Nijnik A, Philpott DJ. Modulating immunity as a therapy for bacterial infections. *Nat Rev Microbiol* 2012; **10:** 243–54.

376 Hancock RE, Sahl HG. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. *Nat Biotechnol* 2006; **24:** 1551–57.

377 Easton DM, Nijnik A, Mayer ML, Hancock RE. Potential of immunomodulatory host defense peptides as novel anti-infectives. *Trends Biotechnol* 2009; **27:** 582–90.

378 McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. *Am J Gastroenterol* 2006; **101:** 812–22.

379 Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108:** 500–08.

380 Falup-Pecurariu O. Lessons learnt after the introduction of the seven valent-pneumococcal conjugate vaccine toward broader spectrum conjugate vaccines. *Biom J* 2012; **35:** 450–56.

381 McKenna M. Vaccine development: Man vs MRSA. *Nature* 2012; **482:** 23–25.

382 Prabowo SA, Gröschel MI, Schmidt ED, et al. Targeting multidrug-resistant tuberculosis (MDR-TB) by therapeutic vaccines. *Med Microbiol Immunol (Berl)* 2013; **202:** 95–104.

383 European Centres for Disease Prevention and Control and European Medicines Agency. The bacterial challenge: time to react. Sept 2009. http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (accessed Nov 1, 2013).

384 Wernli D, Haustein T, Conly J, Carmeli Y, Kickbusch I, Harbarth S. A call for action: the application of The International Health Regulations to the global threat of antimicrobial resistance. *PLoS Med* 2011; **8:** e1001022.

385 Grundmann H, Klugman KP, Walsh T, et al. A framework for global surveillance of antibiotic resistance. *Drug Resist Updat* 2011; **14:** 79–87.

386 World Bank. East Africa Public Health Laboratory Networking Project. http://www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2010/02/24/000020953_20100224150202/Rendered/PDF/531990PID0AFR0public0health0rev.pdf (accessed Nov 1, 2013).