Antimicrobials: access and sustainable effectiveness 1

Access to effective antimicrobials: a worldwide challenge

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

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Recent years have seen substantial improvements in life expectancy and access to antimicrobials, especially in low-income and lower-middle-income countries, but increasing pathogen resistance to antimicrobials threatens to roll back this progress. Resistant organisms in health-care and community settings pose a threat to survival rates from serious infections, including neonatal sepsis and health-care-associated infections, and limit the potential health benefits from surgeries, transplants, and cancer treatment. The challenge of simultaneously expanding appropriate access to antimicrobials, while restricting inappropriate access, particularly to expensive, newer generation antimicrobials, is unique in global health and requires new approaches to financing and delivering health care and a one-health perspective on the connections between pathogen transmission in animals and humans. Here, we describe the importance of effective antimicrobials. We assess the disease burden caused by limited access to antimicrobials, attributable to resistance to antimicrobials, and the potential effect of vaccines in restricting the need for antibiotics.

Antimicrobials are crucial to global health

Antimicrobials, particularly antibiotics, have been a mainstay of modern medicine for the last eight decades. Penicillin lowered mortality associated with pneumococcal pneumonia from 20–40% to 5%,[1–3] and mortality from pneumococcal bacteraemia from 50–80%[4] to 18–20%.[3,5,6] In the past few decades, antibiotics have been used to support modern medical care, including the ability to do surgeries and organ replacements and treat cancer. The twin pressures of the remaining burden of infectious disease in many low-income and lower-income countries and high rates of nosocomial infections in aging populations with increased time spent in long-term health-care settings sets us on course for a continued dependence on antibiotics while also placing substantial selection pressure on bacteria for resistance to evolve.

Despite increases in worldwide antibiotic consumption, access to antibiotics is a problem: more than a million children with untreated pneumonia and sepsis die each year.[7] At the same time, the effectiveness of these drugs is declining worldwide, driven by ever-higher rates of antibiotic use and selection pressure for resistance.[8] Solving the challenge of providing effective antibiotics requires balancing the issues of access and resistance. Resistance could be most easily dealt with by restricting access, but that is neither feasible nor desirable. For the millions who have never had the opportunity to use an antibiotic, the failure of affordable, first-line drugs would be tragic.

In this Series on antimicrobial access and resistance, we discuss the health effect of limited access to antimicrobials and the emergence of resistance (Laxminarayan and colleagues), the drivers and mechanisms of development and transmission of resistance (Holmes and colleagues),[9] enablers for increased and appropriate access to antimicrobials (Mendelson and colleagues),[10] the evidence base for policy interventions combatting resistance (Dar and collegues),[11] and finally the worldwide collaboration necessary to improve access to and sustain effectiveness of antimicrobials (Ardal and colleagues).[12] Here we examine the case for urgent action to secure human and animal

Key messages

Access

- Antibiotic consumption in humans is increasing worldwide, driven by rising incomes, health insurance, and a large remaining burden of infectious disease. Between 2000 and 2010, antibiotic consumption in 71 countries increased by 36%, with Brazil, Russia, India, China, and South Africa (BRICS) accounting for three-quarters of this increase.
- No access and delays in access to antibiotics kill more people than antibiotic resistance. Using the Latin Hypercube Sampling (LHS) model, we estimate that universal provision of antibiotics could avert a mean of 445 000 (332 000 LHS minimum, 541 000 LHS maximum) community-acquired pneumonia deaths in children aged younger than 5 years, a 75·4% (60·7% LHS minimum, 85·0% LHS maximum) reduction across the 101 countries in our analysis.

Resistance

- Resistance to antibiotics threatens improvements made in child survival. Globally, an estimated 214 000 neonatal sepsis deaths (139 000 LHS minimum, 318 000 LHS maximum) are attributable to resistant pathogens each year.

Vaccines

- Scaling up vaccines against pneumococcus and *Haemophilus influenzae* type b (Hib) could avert the need for antibiotics worldwide and reduce selection pressure. We estimate that universal coverage with a pneumococcal conjugate vaccine could avert up to 11·4 million days of antibiotics for pneumonia caused by *Streptococcus pneumoniae* in children younger than 5 years per year, a 47% reduction in days on antibiotics in the 75 countries included in our analysis.

Animal health

- Antibiotics are an essential element of animal health, but the increasing use of antibiotics in subtherapeutic concentrations for growth promotion and disease prevention (as a substitute for hygiene) is placing substantial selection pressure for resistance to evolve. Worldwide antimicrobial consumption in animals is projected to rise by 67% from 63 151 (±1560) tons in 2010 to 105 596 (±3605) tons in 2030, and by nearly double in the BRICS countries over that period, placing a great selection pressure on susceptible bacteria. A one-health approach to improving animal health that recognises the interlinked nature of animal and human health is essential.

health informed by estimates of the disease burden avertable through increased access to antimicrobials or attributable to resistance to antimicrobials, and the potential effect of existing vaccines in restricting the need for antibiotics.

Antibiotic consumption is increasing worldwide but limited access to these medicines is still an issue

Between 2000 and 2010, worldwide consumption of antibiotics by humans increased by 36%, with Brazil, Russia, India, China, and South Africa (BRICS) accounting for three-quarters of this increase despite collectively representing only 40% of the world's population.[13] In BRICS countries, 23% of the increase in the retail sales volume was attributable to India where regulations to control over-the-counter sales of antibiotics are poorly enforced. Antibiotic consumption in hospitals is increasing rapidly in China, which accounted for 57% of the increase in hospital sales of antibiotics in the BRICS countries. The pattern of antibiotic consumption has shifted towards newer broad-spectrum antibiotics, including cephalosporins, broad-spectrum penicillins, and fluoroquinolones. Substantial relative increases in consumption rates were noted for two last-resort classes of antibiotics: carbapenems (45%) and polymixins (13%).

This increase in antibiotic consumption is driven by economic growth and prosperity, particularly in low-income and middle-income countries,[14] but improvements in access have not been uniform. Irrational prescribing and over-the-counter sales of antibiotics without a prescription have resulted in a massive increase in antimicrobial use, particularly of carbapenems, in urban areas.[8]

The increase in antibiotic consumption notwithstanding, access to antibiotics is a continuing problem and more deaths are caused by the limited access and delays in access to antibiotics than to antibiotic resistance. Improving access to antibiotics is particularly challenging in many rural and remote areas where frontline health workers employed in government programmes are unable to deploy antibiotics.[15]

Many of the estimated 6·3 million children aged younger than 5 years who died in 2013 died of preventable infectious diseases.[7] 15% of these child deaths were caused by pneumonia (935 000 deaths), 7% by neonatal sepsis or meningitis (421 000) and 2% by non-neonatal meningitis (151 000). Prior studies suggest that a large proportion of these deaths could be averted by increasing access to antibiotics, as shown by the declines in mortality rates associated with pneumococcal pneumonia and pneumococcal bacteraemia due to penicillin. Our analysis also shows that under-5 pneumonia deaths are strongly correlated with availability of antibiotics (figure 1, Panel 1; more details on methods can be found in the appendix). An estimated 169 760 deaths in India and 49 407 deaths in Nigeria could potentially be averted through prompt access to effective antibiotics. By averting 444 536 present deaths of the estimated mean total of 589 549 community-acquired bacterial pneumonia deaths across the 101 countries in our sample, universal provision of antibiotics could reduce these deaths in children aged younger than 5 years by an estimated 75·4% (60·7% LHS minimum, 85·0% LHS maximum). According to our calculations, an estimated 40·4 million episodes of acute febrile illnesses in children aged younger than 5 years are caused by three common bacterial pathogens, with only 27·5 million of these illnesses being treated with antibiotics. Therefore, increasing antibiotic access could benefit the remaining 12·9 million children who are not at present being treated with antibiotics for acute febrile illnesses (appendix).

The loss of antibiotic effectiveness has important consequences for human health

The declining effectiveness of antibiotics in treating bacterial infections is now a worldwide phenomenon driven by ever-higher rates of antibiotic use, poor water, sanitation and public health measures to tackle infections, demographic changes with more elderly people, and increased use of medical procedures, hospital admissions, and tertiary care. The absence of sufficient access to basic public health and sanitation is a serious issue, particularly in countries where diarrheal disease is common and a major driver of antibiotic use.[23] In high-income countries, the burden of infections has been reduced largely through improved nutrition, chlorination of water, sanitation, and the establishment of public health departments, but in low-income and many lower-middle income countries, antibiotics are being used as a substitute for these measures. For example, infectious disease mortality had already declined to 200 per 100 000 people when antibiotics were introduced in the USA in 1942,[24] but they are being used in countries with higher rates of infectious disease.

In high-income countries, where the burden of infectious diseases is modest, the decreasing effectiveness of first-line antibiotics is overcome by more expensive second-line and third-line antibiotics, driving up health-care costs. In low-income and middle-income countries, patients with resistant pathogens are frequently unable to obtain or afford expensive second-line treatments, and this contributes to greater morbidity and mortality.[14]

Deaths attributable to resistance are caused by delays in recognition and ineffective treatment. Deaths are also caused by misdiagnosis and incorrect treatment of malaria with antibiotics, and vice versa, particularly in areas where both diseases are common.[25] Increasingly, there are patients who do not respond to any known class of antibiotics.

Infections caused by Gram-positive bacteria in high-income countries are being tackled by new antibiotics and better hospital infection control. A new wave of community-acquired strains of MRSA are now common in health-care settings.[26] High rates of MRSA

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See Online for appendix

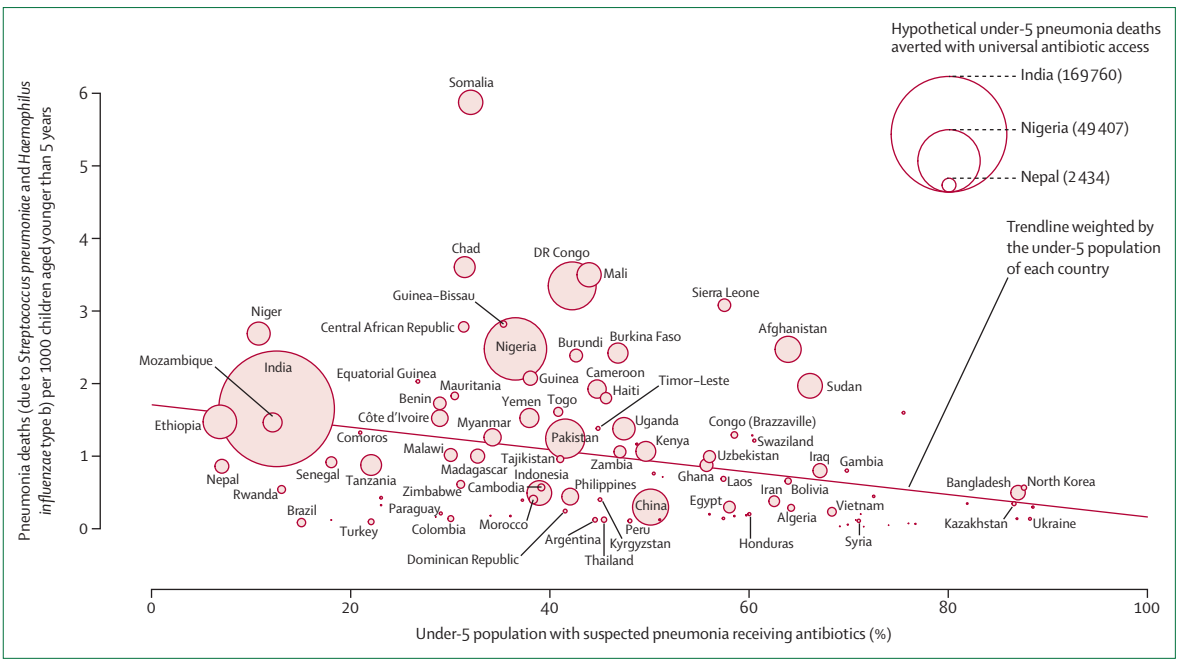

Figure 1: **Estimated pneumonia deaths avertable in under-5 populations with improved antibiotic access**
Countries with less than 100 deaths averted are not labelled. Data on under-5 population with suspected pneumonia receiving antibiotics are from 1990 to 2013; data from the most recent year reported is used, when available.

have been documented by various studies from Asia: a multi-country analysis estimated the average prevalence of MRSA in Asian hospitals at 67·4%, with the lowest rate of 22·6% in India and the highest rate of 86·5% in Sri Lanka.[27] Community-acquired MRSA averaged 25·5% across the eight countries in the study, with the lowest rate of 2·5% in Thailand and the highest rate of 38·8% in Sri Lanka.

Gram-negative organisms are by far the biggest threat because of growing resistance to carbapenems, which until recently were effective against multidrug-resistant strains. Carbapenem-resistant Enterobacteriaceae (CRE) have now been detected worldwide. New Delhi metallo-β-lactamase (NDM) enzymes, first reported in 2008, are now reported worldwide.[28] In the USA in 2012, 4·6% of acute-care hospitals reported at least one CRE healthcare-associated infection. Carbapenem resistance in common Enterobacteriaceae has increased sharply over the past decade: the proportion of Enterobacteriaceae that were CRE increased from 0% in 2001 to 1·4% in 2010, with most of the increase observed in *Klebsiella* spp.[29] The rapid international spread of resistance genes, such as extended-spectrum β-lactamase (ESBL), NDM-1, and *Klebsiella pneumoniae* carbapenemase (KPC), suggests the nature of the serious threat of antimicrobial resistance. The sharp increase in resistance is clear in the case of β-lactamase antibiotics. Nearly 1000 resistance-related β-lactamases, including novel classes of genes, have been identified, a ten-fold increase since 1990.[30]

Hospital data from developing countries suggest that pathogens causing neonatal infections (in the first 28 days of life) are frequently resistant to the WHO-recommended regimen of ampicillin and gentamicin: 71% of *Klebsiella* spp and 50% of *Escherichia coli* were resistant to gentamicin.[17] Resistance has also been reported as high in early-onset, presumably maternally acquired neonatal infections reported from hospital series in developing countries; 60–70% of *E coli* and nearly 100% of *Klebsiella* spp are ampicillin-resistant, and 40–60% of *Klebsiella* spp are resistant to gentamicin (appendix).[31] High rates of ESBL production in *E coli* have restricted use of second-line therapy with extended-spectrum cephalosporins.[32] Many newborns in hospitals in South Asia are now treated with carbapenems as first-line therapy for sepsis or presumed sepsis. The emergence of pan-resistant untreatable CRE and *Acinetobacter* spp infections associated with high mortality in neonatal nurseries is of most concern.[33]

Figure 2 shows the estimated number of neonatal deaths attributable to resistant sepsis infections in the five countries with the highest numbers of neonatal deaths in the world. Resistance-attributable neonatal sepsis deaths are greatest in India, where 56 524 neonates (33 683 LHS minimum, 89 620 LHS maximum) die each year owing to neonatal sepsis caused by bacteria resistant to first-line antibiotics. These deaths are also high in Pakistan (25 692 deaths; 16 486 LHS minimum, 39 660 LHS maximum), Nigeria (19 405 deaths; 6797 LHS minimum, 35 490 LHS maximum),

the Democratic Republic of Congo (7095 deaths; 3938 LHS minimum, 11735 LHS maximum), and China (2807 deaths; 1448 LHS minimum, 4795 LHS maximum; panel 1, appendix).

Gonorrhoea, which was entirely susceptible to penicillin in the 1970s, developed widespread resistance to penicillin and tetracycline during the 1980s, and by the mid-2000s acquired high-levels of resistance to quinolones.[34] In response, countries have started using third-generation oral cephalosporins (eg, ceftriaxone) but now, growing resistance in *Neisseria gonorrhoeae* to these drugs is limiting therapeutic options.[35,36]

Quantifying the burden of resistance is challenging both because of the paucity of the data and the multi-dimensionality of the issue. Data on antibiotic use and resistance are needed at the country and sub-country level. Data from networks such as the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) maintained by the European Center for Disease Control (ECDC) for the European Union countries[37,38] and ResistanceMap[39] maintained by the Center for Disease Dynamics, Economics & Policy (CDDEP) in the USA have enabled greater understanding of antibiotic use patterns in high-income countries. Data are available in other countries from private sector laboratory networks, but public sector reporting systems are weak.

The attributable burden of resistant infections is a useful metric to assess the effects of continuing treatment with antibiotics that no longer work, but does not tell us much about whether sufficient value was derived from antibiotics in the process of attaining that level of resistance. In other words, our aim should be to maximise the value derived from antibiotics (through enabling appropriate access and adopting strategies to reduce resistance) rather than attempting to minimise resistance (which is best achieved by not using antibiotics). Effective antibiotics also have other economic values, including option value (in addressing influenza pandemics), enablement value (in allowing other medical procedures to be done) and diversity value (in reducing selection pressure on existing drugs).[40]

Effective antibiotics are a crucial part of influenza preparedness because epidemiological and clinical interactions between influenza and the secondary bacterial respiratory pathogens that cause pneumonia have been a major cause of death in influenza pandemics (including in 1918).[41,42] Antibiotics are frequently prescribed during winter months to treat secondary bacterial pneumonia, a common cause of death in people with seasonal influenza; co-infections have been reported with roughly a quarter of all influenza-related deaths.[43]

With aging populations, antibiotics are needed to enable complex surgeries, transplants and procedures on immune-compromised patients.[44] Therefore, the consequences of increased bacterial resistance are both directly in the form of higher infectious disease, but also in the form of lost opportunities for surgeries because of concerns about resistant infections. Patients with high risk of infection, either because of their age or other complications, might be advised against medical procedures that could otherwise benefit them because the risk of potentially untreatable post-operative

Panel 1: **Summary of estimates from new models in this study**

A) Proportion of pneumonia-attributable deaths potentially avertable through universal provision of antibiotics

We estimated the potential effect of increasing antibiotic access on reducing pneumonia-related deaths in children aged younger than 5 years. Our analysis shows that universal provision of antibiotics could avert 0·445 million (0·332 million LHS minimum, 0·541 million LHS maximum) deaths out of the estimated 0·590 million community-acquired pneumonia deaths in children aged younger than 5 years across the 101 countries in our analysis. India, with a low reported percentage of children with suspected pneumonia receiving antibiotic treatment (12·5%) and an estimated 0·210 million under-5 community-acquired bacterial pneumonia deaths, could reduce the number of present community-acquired bacterial pneumonia deaths by 80·7% to 40 691 with universal provision of antibiotics. Similarly, Ethiopia, which had the lowest reported percentage of children with suspected pneumonia receiving antibiotic treatment (6·8%) in our analysis with 17 480 deaths, had the highest mean proportion of such deaths averted at 81·6% (figure 1; appendix).

B) Estimated burden of neonatal deaths attributable to resistance

Infectious diseases are the leading cause of death in children younger than 5-years old in low-income and middle-income countries, with neonates bearing the highest burden. Out of 2·9 million annual neonatal deaths in 2012, an estimated 0·68 million (0·46–0·92 million) deaths were associated with possible severe bacterial infection.[16] Nearly 60% of neonatal infections are caused by Gram-negative bacteria.[17] There is a documented increase in the incidence of *Klebsiella* spp and *Staphylococcus* spp infections resistant to the WHO recommended guideline of ampicillin or penicillin plus gentamicin.[18] We estimated the population attributable fraction (PAF), an estimate of the proportion of cases of a disease that could theoretically be averted by modifying or removing exposure to a specific risk factor (resistance).

PAFs were estimated for resistant Gram-negative and Gram-positive infections for India, Nigeria, the Democratic Republic of the Congo, Pakistan, and China—the five countries that account for a half of premature deaths worldwide[19]—and resistance attributable deaths were aggregated across the countries. An estimated 56 500 (33 700 LHS minimum, 89 600 LHS maximum) neonatal sepsis deaths in India and 19 400 (6800 LHS minimum, 35 500 LHS maximum) neonatal sepsis deaths in Nigeria were attributable to pathogens resistant to first-line antibiotics. Taking into account that these five countries account for 52% of global neonatal sepsis deaths,[19] an estimated 214 500 (139 100 LHS minimum, 318 400 LHS maximum) neonatal sepsis deaths were attributable to resistant pathogens (figure 2, appendix).

C) Proportion of antibiotic prescriptions (or antibiotic days) potentially reduced through universal pneumococcal vaccination

We estimated the annual number of days of antimicrobial therapy that could potentially be reduced through universal pneumococcal conjugate vaccine (PCV) availability worldwide. Our analysis included a total of 75 countries, with PCV coverage (3rd dose) less than 80% as of 2013,[20] for which county-specific data on the incidence of under-5 pneumonia cases caused by *Streptococcus pneumoniae*[21] and the proportion of under-5 suspected pneumonia cases receiving antibiotic treatment[22] were available.

We estimate that about 11·4 million antibiotic days could be avoided annually as a result of PCV for pneumonia caused by pneumococcal infections in children aged younger than 5 years. This equates to roughly a 47% reduction in the amount of antibiotics used for pneumonia cases caused by *S pneumoniae* in the 75 countries included in this analysis (figure 3; appendix).

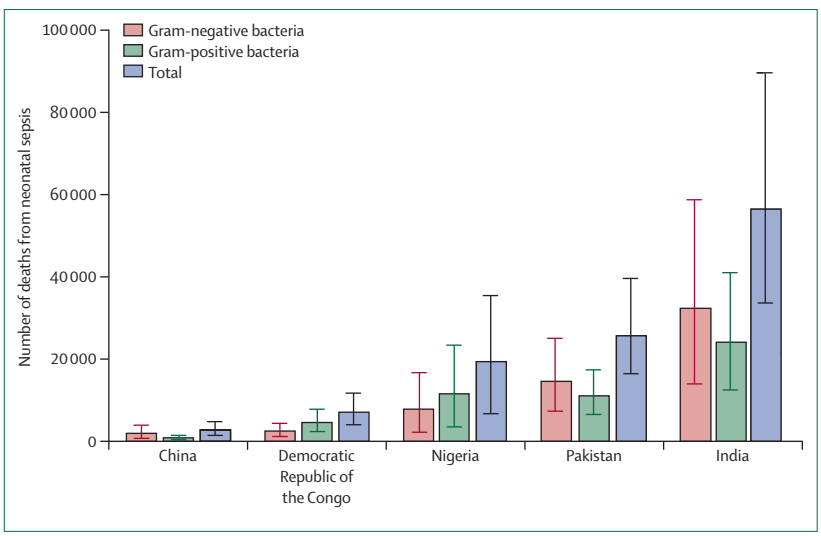

Figure 2: **Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries**
Bars represent maximum and minimum values from Latin Hypercube Sampling model in appendix.

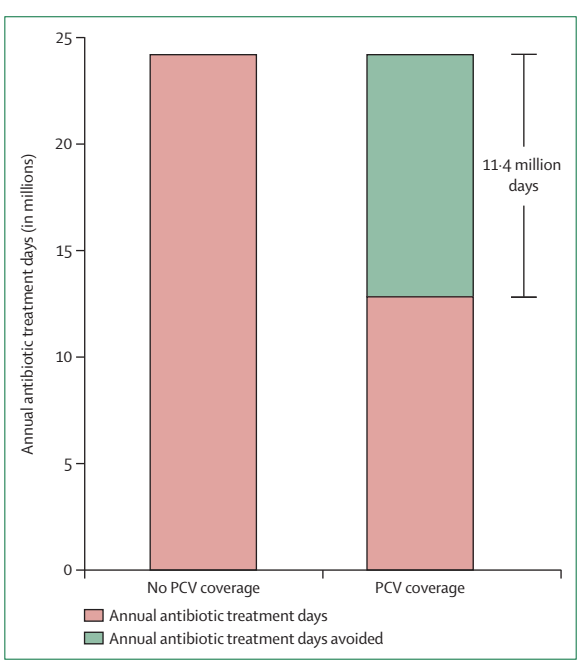

Figure 3: **Days on antibiotics for suspected pneumonia, averted by provision of pneumococcal conjugate vaccine (PCV)**
Bar represents antibiotic days avoided with PCV coverage.

infections might skew the risk-benefit tradeoff for such patients, especially those with several complications (appendix). Even a modest scale-back in procedures that depend on antibiotics, such as surgeries and transplants, because of the risk of untreatable infections could substantially compromise life and health.

New antibiotics with novel mechanisms of action are needed. Reliance on a multiplicity of drugs at both the individual and the population scale could reduce selection pressure.[40,45] However, in view of the many antibiotics (often close substitutes for each other) in the market, the economic value of new antibiotics with new mechanisms of action does not become apparent until other antibiotics start failing. In the absence of a perceived value and willingness to pay for new antibiotics, however, reimbursements are low and the pharmaceutical sector does not sufficiently invest in developing new antibiotics.

Present and future vaccines reduce the need for antibiotics and curb selection pressure

Effective antibiotics are needed to treat childhood pneumonia, which accounts for roughly 493 000 (15·8%) of under-5 child deaths in sub-Saharan Africa.[7] Pneumococcal conjugate (PCV) and *Haemophilus influenzae* type b (Hib) vaccines are useful instruments to reduce the roughly 935 000 worldwide under-5 deaths from pneumonia, but they are not sufficiently deployed. PCVs have yet to be adopted for widespread public sector use in China, India, Nigeria, Bangladesh, Afghanistan, and Indonesia.[7,46] In the USA, the introduction of the pneumococcal conjugate vaccine has resulted in reduced antibiotic consumption and lowered rates of invasive disease caused by penicillin-non-susceptible strains, whereas strains not susceptible to multiple antibiotics decreased by 59% between 1999 and 2004 to 1·7 cases per 100 000 in the USA.[47] Despite such benefits that have now been reported from many other countries including South Africa,[48] Denmark,[49] and Gambia,[20] worldwide coverage is low. In 2012, of the 71 countries reporting data on infant immunisation coverage with vaccines including PCV, 14 countries reported coverage of less than 50%, 8 countries reported 50–79% coverage, 17 countries reported 80–89% coverage, and 32 countries reported coverage of 90% or greater.[20]

The Hib vaccine has been instrumental in reducing the burden of pneumonia worldwide. In South Africa, the number of Hib cases in under-5 children declined within the 5-year period after introduction of Hib vaccine, but Hib isolates were more likely to be multidrug-resistant.[50] The Hib vaccine has been introduced in nearly all low-income countries as part of the pentavalent vaccine, but coverage is low in key countries such as India and South Africa.

With a universal pneumococcal conjugate vaccine, the mean number of antibiotic days for pneumonia caused by *Streptococcus pneumoniae* in children aged younger than 5 years avoided per year is about 11·4 million (a 47% reduction in the 75 countries used in the analysis; figure 3, panel 1, appendix). Similarly, reductions can be achieved through expansions in coverage of Hib vaccine where the pentavalent vaccine (including DTP, Hib, and Hepatitis B antigens) has not yet been introduced. A vaccine against *Staphylococcus aureus*, the most common cause of postoperative infections, has yet to be developed. The most recent candidate vaccine V710 did not prevent invasive *S aureus* infections, including surgical site infections.[51] Hib is the only major vaccine-preventable

Gram-negative pathogen; broad-spectrum vaccines against other Gram-negative infections such as Enterobacteriaceae that target endotoxins could alter the present situation with respect to resistant pathogens.

Use of antibiotics in subtherapeutic concentrations is increasing in response to higher demand for animal protein worldwide

The use of antibiotics in animals at subtherapeutic concentrations for growth promotion (and ostensibly, disease prevention) is growing rapidly in response to a massive increase in the production of meat and animal products for human consumption. This process, a result of rising incomes, particularly in southeast Asia and China, is placing selection pressure for resistance to evolve. It is also threatening access to effective antibiotics for treatment of animal disease, essential both for food security for society at large and livelihood security for the roughly 12% of the world's population that is entirely dependent on livestock.[52]

Global meat production in 2012 was 304 million tons with average annual meat consumption of 42·9 kg per person.[53] The latest estimates of antibiotic use in the animal sector conservatively estimate the total consumption of antibiotics in 2010 at 63 151 (±1560) tons.[54] Antimicrobial consumption is projected to rise by 67% to 105 596 (±3605) tons by 2030, and by nearly double in the BRICS countries. Consumption in hotspots like India is expected to grow by 312% by 2030 and is likely to be driven by the growth in consumer demand for livestock products in middle-income countries and a shift to large-scale farms where antimicrobials are used routinely.[54]

There is a high degree of correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing pigs, poultry, and cattle.[55] Previous studies suggest that improved safeguards for judicious use in animals do not necessarily harm animal populations. Following on from the Swedish ban in 1986 and the Danish ban in 1994, in 2006, the European Union banned the use of all antibiotics used for growth promotion in food animals.[56] In the USA, the Food and Drug Administration has called for the withdrawal of medically important antibiotics in subtherapeutic concentrations.[57] There is growing consensus that specific medically important classes of antimicrobials, in particular the critically important antimicrobials classified by WHO with highest priority for human medicine,[58] should be restricted.

Data from Denmark since 1995 show that there have been vast decreases in the use of antimicrobials since the ban: between 1992 and 2008, use of antibiotics for pigs decreased by 51% and use for poultry decreased by 90%.[59] Danish regulations require prescriptions for the use of antibiotics in food animals, regular audits of veterinarians overseeing food animals, and caps on the profits to veterinarians selling antibiotics.[56] No evidence exists that bans of avoparcin and virginiamycin in Sweden between 1995 and 1998 increased overall antimicrobial consumption. Similarly, bans of antimicrobial growth promoters (AGPs) have not affected mortality of weaning pigs or the size of the pig industry in Denmark[60,61] or of the poultry industry.[59]

Despite 50 years of antimicrobial use as growth promoters, reliable data on the effect of AGP use on productivity are absent. There is substantial variability in the growth response to subtherapeutic antimicrobials, according to the species, the age of animals, their genetic potential, and the specific hygiene and management

Panel 2: **Key priorities to avert or delay a post-antibiotic era**

Prioritise access for children and neonates

Achieving child survival goals will depend on continued and expanded access to effective antibiotics. Although there are ambitious targets for pneumococcal and rotavirus immunisation that have the potential to reduce antibiotic use, it might be some time before vaccines reach all children who need them. Additionally, even with universal vaccine coverage, vaccine effectiveness is often less than 100% (eg, PCV13 effectiveness ranges from 73 to 90% according to serotype).[64] Improvement of access to antibiotics for many, particularly neonates with multidrug-resistant Gram-negative pathogens, is an urgent priority.

Encourage innovation in markets and medicine and repurposing of existing instruments

Sufficient evidence now exists that gentamicin, a first-line drug effective against most bacteria that cause newborn sepsis, is as effective as third-line cephalosporins in culture-proven sepsis. Provision of gentamicin by front-line health workers can reduce deaths from neonatal sepsis and lower the unnecessary use of newer-generation antibiotics by private practitioners and hospitals. Similar concerns about limited access to effective antimalarials that could also delay the emergence of resistance prompted the establishment of the Affordable Medicines Facility for malaria. Despite evidence that innovative financing to leverage private markets and public facilities to deliver lifesaving medicines works, this mechanism has been largely abandoned for political reasons rather than being explored further on the basis of scientific evidence.[65,66]

Balance universal access with effective oversight and investment in basic public health

The increase in universal health coverage including through insurance represents both an opportunity for, and threat to, access to effective antibiotics. Programmes of free or subsidised antimicrobials are being planned or are underway in many countries, but without adequate regulatory oversight they could lead to increases in inappropriate antibiotic use without the commensurate decline in infectious diseases. Studies have shown associations between health insurance and use of antibiotics in settings as diverse as the USA,[67] China,[68] and Indonesia[69] because insured patients are less affected by antibiotic costs.

Advocate for multisectoral attention and inclusive public health practices

The issue of access to effective antibiotics is on the periphery of discussions about global health spending. The report by the UN high-level panel on the post-2015 development agenda had no mention of antimicrobial resistance in their illustrative goals for health. The new UN Commission on Life-Saving Commodities for Women and Children recommended bulk buying, local manufacturing, and innovative marketing to help transform the supply, demand, and use of quality life-saving products including amoxicillin.[70] The Global Action Plan for Prevention and Control of Pneumonia recognises that despite interventions including vaccines, promotion of exclusive breastfeeding, and reducing indoor air pollution, effective case management with antibiotics using trained community health workers is of critical need and can save lives.[71] Although insufficient evidence exists that use of community workers leads to increased use of antibiotics for treatment of infectious diseases, this could be a focus of community case management programmes.

conditions.[62] Although studies done before the 1980s reported improvement in feed efficiency and growth rates of pig, poultry, and cattle fed subtherapeutic antimicrobials were as high as 5–15%, studies done in the USA, Denmark, and Sweden after the 2000s point to reduced effects: less than 1% improvement or no statistically significant improvement, except for nursery pigs, in which a 5% improvement in growth rate has been reported.[63] A common explanation is that the growth response to antimicrobials is less important when nutrition, hygiene practices, the genetic potential of animals, and the health status of animal herd and flock are optimum. A report from the Organisation for Economic Co-operation and Development modest shows losses of production and meat value after a ban on antimicrobial growth promoters worldwide.[62]

The future of effective antibiotics

Worldwide, we are relying more heavily on antibiotics to ensure our medical, nutritional, and economic security while simultaneously causing the decline of their usefulness with overuse and ill-advised use. To avert or at least delay the crisis of a real postantibiotic era, we identify a few key priorities (panel 2). Specific policy actions and related strategies are discussed later in this series.

Antibiotic resistance is a nuanced and multisectoral problem that threatens to erase decades of progress in medicine, food security, and public health. Like climate change, the issue of antimicrobial resistance is worldwide, and connects priorities across the globe regardless of a country's level of development. Almost every instance of drug resistance has arisen in a single country before spreading internationally. Without better national health systems and worldwide coordination and cooperation between human and animal health sectors, we stand on the edge of an era of vastly greater antibiotic prices for those who can afford newer drugs and of higher morbidity and mortality consequences for those who cannot. Worldwide collective action rooted in national responses is necessary and in this *Lancet* Series we will analyse and recommend policies to be considered at both national and worldwide levels.

Contributors

The study and analysis was conceptualised by RL who also wrote the first draft of the manuscript. SP and CHB implemented the analytical models and analysed data to present the new estimates reported in this study. SD, KK, JA-R, and PM provided input on the policy sections of the Series paper and reviewed the manuscript. All authors were responsible for critical revision of the manuscript for important intellectual content and approved the final version.

Declaration of interests

We declare no competing interests.

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