

ANTIMICROBIAL RESISTANCE

ANTIMICROBIAL RESISTANCE:
IN SEARCH OF A
COLLABORATIVE SOLUTION

Report of the Antimicrobial Resistance
Working Group 2013

Professor Dame Sally Davies,
Emiliano Rial Verde


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Professor The Lord Darzi



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Professor Dame Sally Davies

FOREWORD

As Chief Medical Officer I am the UK government's most senior advisor on health issues. The role dates back to 1855 and I am the sixteenth holder of the post – and the first woman, something that I am immensely proud of. Every year I publish my assessment of the public's health and advise the government on where action is required. In 2012 I decided to focus my first in-depth report on infectious diseases – partly as it seemed to be an uncontroversial topic. I was wrong. I am not easily rattled, but what I learnt scared me – not just as a doctor, but as a mother, a wife and a friend. Breaking from tradition, I engaged the expertise of a broad range of leading clinicians, academics, researchers and policymakers. Our findings were simple:

- We are losing the battle against infectious diseases.
- Bacteria are fighting back and are becoming resistant to modern medicine.
- In short, the drugs don't work.

Since the manufacture of penicillin in 1943, almost all of us have benefited from the medicinal effects of antimicrobial drugs – what we often colloquially and sometimes inappropriately refer to as antibiotics. These wonder drugs have stopped us dying from mundane infections such as a sore throat and have allowed us to routinely survive extraordinary operations, from hip replacements to heart transplants. Indeed, the World Health Organization estimates that antimicrobials add, on average, twenty years to everyone's lives.

If we allow resistance to increase, in a few decades we may start dying from the most commonplace of ailments that can today be treated easily. We will regress to the point where, in twenty years' time, when I need a hip replacement, the operation may be deemed too dangerous to even attempt due to the risk of catching an untreatable infection.

Our response needs to be global and multifaceted. This WISH report makes the case that if we do work together, bringing the ingenuity of humanity to this real, growing and often forgotten global threat, we can manage and mitigate the risk of antimicrobial resistance

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EXECUTIVE SUMMARY

Antimicrobial resistance is the ability of infectious organisms, including bacteria, to survive the agents designed to kill them and save patients from infection. Resistance can spread quickly across different bacterial species, from bacteria in animals to those in humans, and across national borders.

As a result, many types of bacteria causing human illnesses have become resistant to multiple antibiotics, leaving healthcare professionals in all countries with few treatment options. In fact, using a conservative estimate, more than half a million people die of resistant infections around the world every year, making antimicrobial resistance a threat that public health officials, politicians, healthcare professionals, and the public can no longer ignore.

TAKING ACTION TO TACKLE THE ROOT CAUSES

Five distinct fronts of action to tackle the antimicrobial resistance threat are discussed in this report. National action and international collaboration is needed in each of these five fronts:

1. AWARENESS

Every time an antibiotic is used inappropriately, the development of resistance accelerates. Often, inappropriate use stems from behaviors by healthcare professionals, patients, pharmacists, public health officials, and the broader community. To curb inappropriate use, we must ensure all stakeholders are aware of the severity of the antimicrobial resistance threat, of the importance of their own actions, and of what good behaviors look like.

2. ANTIBIOTIC CONSERVATION

Antibiotics are a public good with a limited effective lifetime. The more they are used, the higher the chance that resistance will develop. Hence, antibiotics should be reserved for those situations in which they are the most effective way to treat infection. However, lack of conservation is probably the leading root cause behind the antimicrobial resistance threat. To foster conservation, stronger regulation aimed at limiting non-prescription use in humans and use for growth promotion in farm animals is needed. Regulation should be complemented with diagnostics and treatment protocols to foster appropriate use in the healthcare setting, and with communications campaigns co-ordinated with the broader awareness efforts described above.

3. SANITATION, HYGIENE, INFECTION PREVENTION AND CONTROL

Avoiding infections is a public health priority that has the additional benefit of reducing the need for antibiotics. This, in turn, preserves antibiotic efficacy by delaying the development of resistance. Sanitation and hygiene in the community and the food industry, together with infection prevention and control mechanisms in healthcare settings, are the most effective ways to prevent infection. Awareness is again an essential step; a step that should be complemented with specific interventions like infection prevention and control task forces in healthcare environments, sanitary regulation for the food industry, and education at the community level.

4. SURVEILLANCE AND MONITORING

Understanding the magnitude of the antimicrobial resistance problem, its evolution, and the impact of our efforts to reduce antimicrobial resistance is essential to shape interventions and manage performance. Surveillance of resistance and monitoring of antibiotics usage in humans and agriculture are the main mechanisms to reach such an understanding. However, lack of compatible standards and fragmentation of efforts hamper the ability to complete a global picture of the antimicrobial resistance threat. International collaboration is needed to standardize guidelines for data gathering, to co-ordinate national and regional sharing and interpretation of antibiotic sales and usage data, and to develop a co-ordinated global surveillance and monitoring program.

5. RESEARCH AND DEVELOPMENT

Despite the clear need for new antibiotics, diagnostics, and vaccines, the current market incentives for research and development (R&D) are failing. A series of hurdles compound to reduce the potential return on investment in R&D: limited public funding for microbiology, challenging regulatory requirements, small patient populations—new antibiotics are reserved as the last line of treatment and treatment courses are short—and low prices compared to other disease areas. These hurdles have resulted in an exodus from the infectious disease space by large and mid-sized pharmaceutical companies, with the consequent reduction in the rate of new antibiotics introduction. To solve this market failure, four types of solutions are explored ranging from simple market mechanisms—increased prices or extended IP protection—to more complex solutions aimed at de-coupling R&D risk from commercial incentives.

As the antimicrobial resistance threat is already causing an alarming number of deaths across the globe and it is affecting all countries, no-regret moves at the national level and simple actions aimed at leveraging ongoing international efforts are hard to argue against. Indeed, a collaborative solution to tackle the antimicrobial resistance threat exists and the fronts of action are clear. It is now time to start moving forward.

ANTIMICROBIAL RESISTANCE: A GLOBAL THREAT

“Antimicrobial resistance” refers to the ability of infectious organisms, including bacteria, to survive the agents designed to kill them and save patients from infection (see Appendix). When the first bacteria resistant to penicillin were identified in the early 1940’s, the phenomenon was rare. 70 years on, the biological phenomenon of antimicrobial resistance is no longer a mere curiosity for scientists to study in the laboratory. With over 20 bacterial species showing resistance to multiple antibiotics¹, millions of people suffering from difficult-to-treat infections, and hundreds of thousands dying every year around the world², the global threat of antimicrobial resistance has reached a magnitude that cannot be ignored.

Resistance to antibiotics (the main type of antimicrobials used to cure bacterial infections) can occur in all bacterial species. It occurs when genetic mutation confers on a bacterium the ability to survive in the presence of an antibiotic. The mechanisms behind resistance are numerous; for example, a change in permeability preventing antibiotics from passing through the membranes that enclose bacteria, or a modification of a bacterial enzyme to equip it to destroy the molecules of an antibiotic and render them inert. Regardless of the mechanism, resistance to an antibiotic enables bacteria to survive and proliferate. So the more prevalent resistance to an antibiotic becomes, the less effective the antibiotic is at curing infection.

To aggravate the problem, many bacteria have the ability to exchange genetic material promiscuously across species, so resistance to an antibiotic developed by one bacterial species – such as *E. coli*, a common cause of food poisoning – can spread to another species – such as *K. pneumoniae*, a cause of pneumonia. That is also true for bacteria normally living in different environments; for example, bacteria from a farm animal can transmit antibiotic resistance to bacteria that infect humans. Resistance therefore spreads quickly among different bacteria, thereby rendering the particular antibiotic obsolete for the treatment of many illnesses.

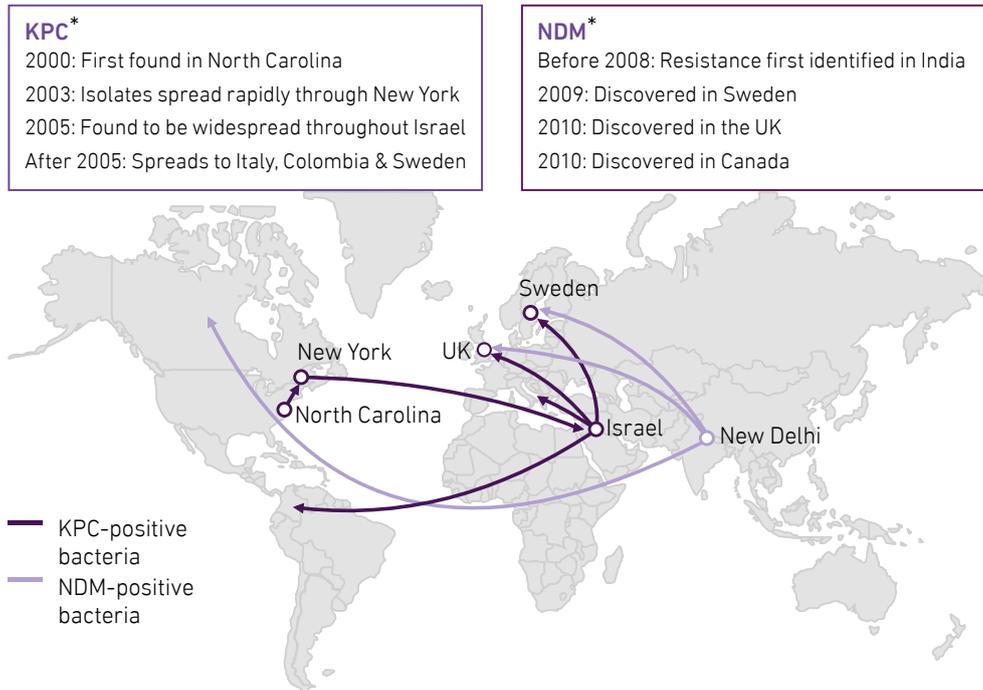
Furthermore, antimicrobial resistance knows no national borders, and affects all countries regardless of their economic status. Although developing countries show higher levels of resistance for some bacterial species, such as *Enterobacteriaceae*, developed and developing countries show similar resistance levels for other bacterial species, such as *A. baumannii*. In addition, the increased mobility of the global population means that resistance in one area of the world can be carried to another area with relative ease. For example, the New Delhi metallo- β -lactamase, an enzyme that enables bacteria to survive a particular type of antibiotic, was found for the first time in India in 2008, and by 2010 it had been discovered in antibiotic-resistant bacteria in Sweden, the UK, and Canada. Another similar, though unrelated, enzyme-related resistance was identified in the US in the year 2000, and by 2005 it had spread to Israel, several European countries, and Colombia, showing that the direction of spread can go both from developing to developed countries or vice versa³. The ease with which resistance spreads among the bacterial population, compounded by the ever-increasing international mobility of people, means that no country is immune to the threat of antimicrobial resistance.

Figure 1: Antimicrobial Resistance as a global threat

Source: McKenna M. Antibiotic resistance: The last resort. Nature. 2013. 499:394–39; McKinsey & Company analysis

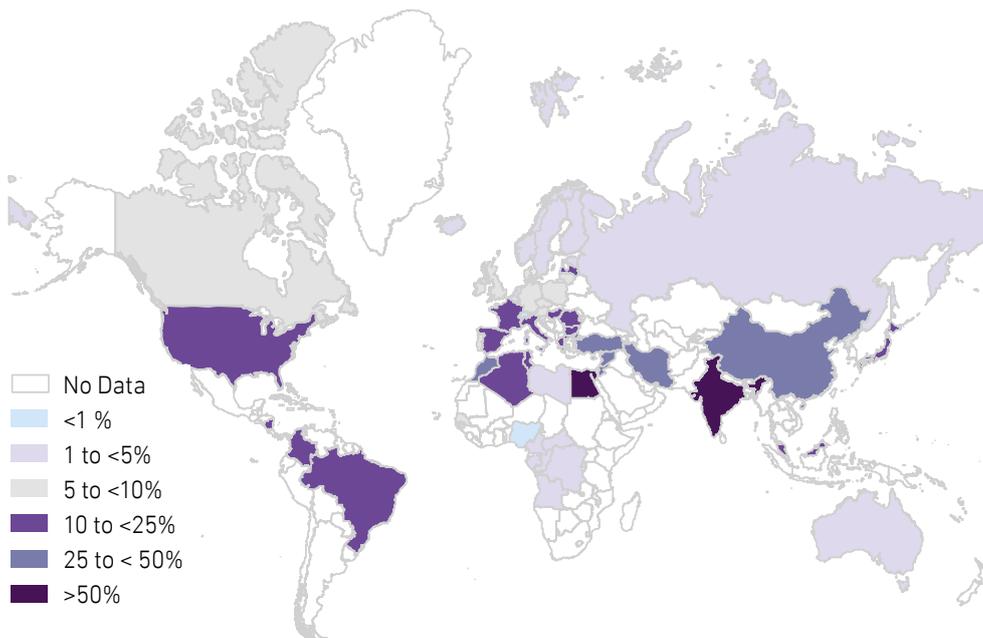
The increased mobility of the population makes antimicrobial resistance (AMR) a health threat without borders

Movement of two strains of Carbapenem-resistant *Klebsiella pneumoniae* (2000 - 2008)



AMR is a global threat that spans all continents

Escherichia coli resistance to third-generation cephalosporins (2007-2011)

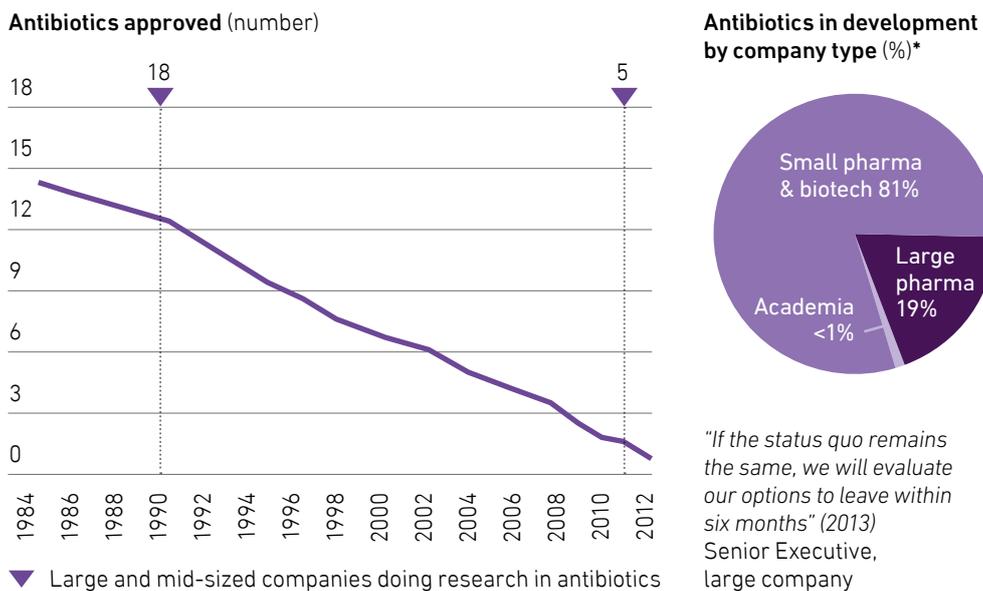


*KPC: *Klebsiella pneumoniae* carbapenemase.
 NDM: New-Delhi Metallobetalactamase

Healthcare systems until now have kept pace with antimicrobial resistance by means of introducing new antibiotics. This strategy worked well during the early years of the antibiotic revolution, but as resistance to more and more antibiotics developed, the pharmaceutical innovation engine has been unable to keep up. Over the past 25 years, while antimicrobial resistance has continued to rise, the number of new antibiotics has been in sharp decline, and 80 percent of the pharmaceutical companies that were conducting research and development in antibiotics have abandoned the quest (Figure 2).

Figure 2: A decreasing number of antibiotics reaches the market every year, and fewer large companies remain involved in antibiotic research

Source: Press search; McKinsey & Company analysis



With fewer large and mid-sized companies doing research in antibiotics, the R&D burden is shifting to smaller players with less financial muscle to foot high clinical development bills

* Includes all preclinical and Phase I-III antibiotics, excluding tuberculosis; Large pharma assigned for compounds currently active in R&D pipeline of one of top 20 pharma

The compounding effect of these two factors – increasing resistance to existing antibiotics and a slowdown of new antibiotics discovery – is that many bacterial infections today are very difficult to treat. A person contracting an infection caused by some of these “superbugs” has a 30-50 percent chance of dying⁴. Healthcare professionals look on helplessly, as unarmed spectators.

Indeed, infections resistant to antibiotics kill tens of thousands of people every year. A recent report by the US Centers for Disease Control and Prevention (CDC) estimates two million cases of antibiotic-resistant illnesses in the US each year, and at least 23,000 deaths¹. In Europe, the estimated figure was 25,000 deaths in 2007⁵. In developing countries, the data is scarce, but the level of drug-resistant infections and deaths are almost certainly comparable to, or higher than, that of developed countries. Furthermore, although at present most patients recover, resistant infections lead to longer stays in the hospital, higher risk of

side-effects, and much higher healthcare costs. The CDC has estimated the economic impact of antimicrobial resistance in the US alone is approximately US\$35 billion per year.

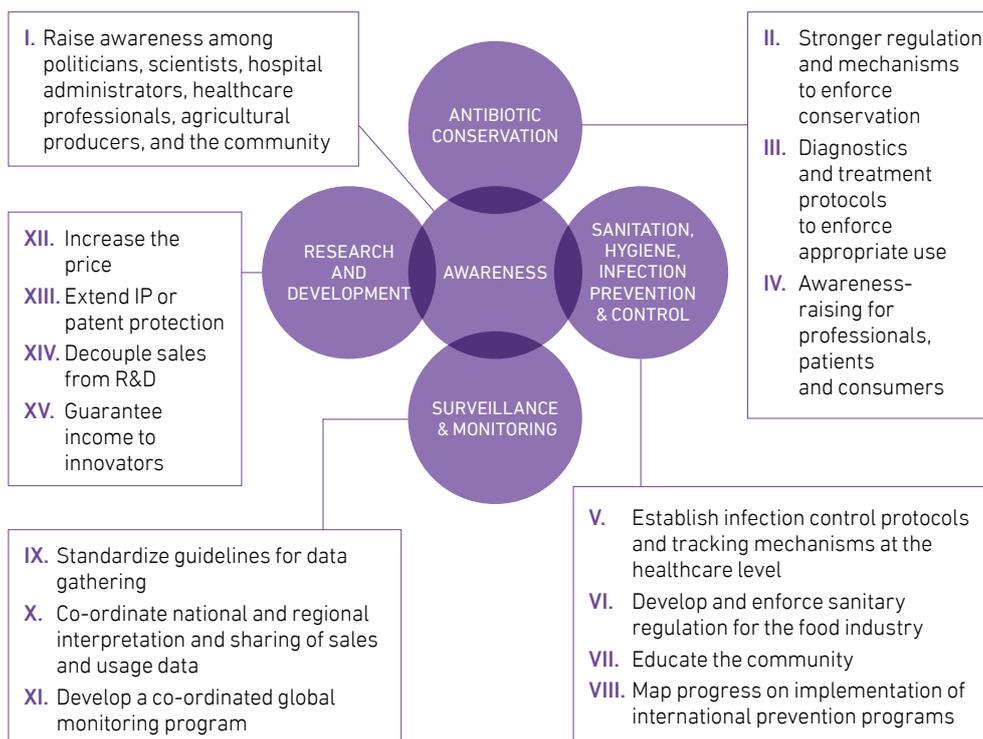
In 1900, pneumonia and tuberculosis were among the leading causes of death in the developed world. Great improvements in sanitation, together with the advent of effective antibiotics, changed that picture, and infectious diseases were replaced by cardiovascular disease and cancer as the main concern for public health authorities. Today it is difficult to imagine going back 100 years. The uncomfortable truth is that without action at the national and international level, we are at risk of taking that huge backward step.

ROOT CAUSES AND POTENTIAL SOLUTIONS

To avoid thousands of deaths and millions of illnesses, and to tackle a global challenge that spares no region of the world, simultaneous and collaborative action between policymakers, healthcare professionals, industry and the public is needed along five fronts (Figure 3):

1. Awareness
2. Antibiotic conservation⁶
3. Sanitation, hygiene, infection prevention and control
4. Surveillance and monitoring
5. Research and development

Figure 3: The five fronts of action



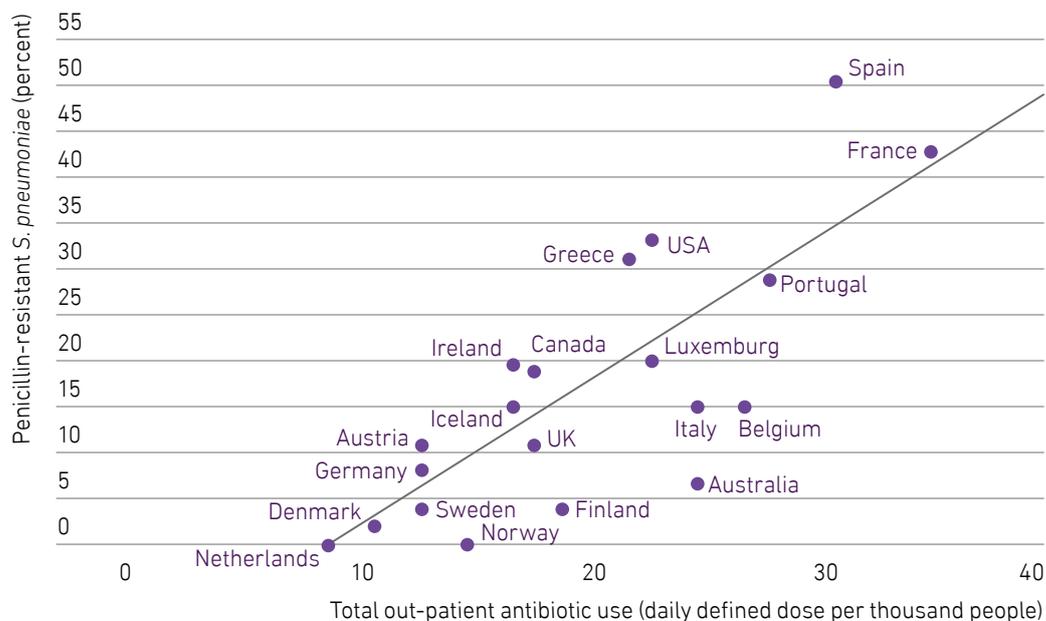
1. AWARENESS

The first step in tackling the antimicrobial resistance threat is raising awareness and understanding. All stakeholders needing to take action against antimicrobial resistance must be made fully aware of its existence, magnitude, and impact. This obvious first step is often neglected, in favor of an immediate engagement with the technical aspects of the solution. But without adequate awareness – by politicians, scientists, hospital administrators, healthcare professionals, agricultural producers and the community – antimicrobial resistance cannot be effectively tackled.

Antimicrobial resistance is an evolutionary process (see Appendix), so as more antibiotics are used, the more likely it is that resistance will emerge (Figure 4). In simple terms, bacteria abide by the motto “what does not kill you makes you stronger.”

Figure 4: Amounts of antibiotics used correlates with resistance

Source: Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in streptococcus pneumoniae and streptococcus pyogenes. *Emerging Infectious Diseases*. 2004.10(3):514-517



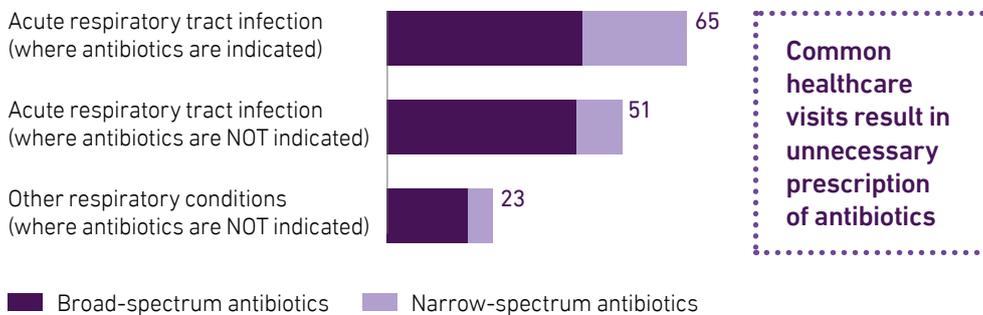
If use of an antibiotic increases by one daily dose per thousand people, the prevalence of resistance increases by ~1.5 percent

Every time an antibiotic is used inappropriately, the development of antimicrobial resistance can accelerate. Inappropriate use is driven by human behaviors that stem not from recklessness but from a short-term view or ignorance of the severity of the consequences. Indeed, too few people are aware that about half of all US patients visiting the doctor with an acute respiratory infection that does not require antibiotics (as it is viral in nature, and viruses do not respond to antibiotics) leave the doctor's office with an antibiotics prescription⁷ (see Figure 5), and in that way are actually contributing to antimicrobial resistance, or that resistant bacteria like MRSA (methicillin-resistant *S. aureus*) kill more US citizens every year than HIV/AIDS or the 2009 flu pandemic.⁸

Figure 5: Even prescription use of antibiotics might result in inappropriate use

Source: Shapiro DJ, Hicks LA, Paviva AT, et al. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09; Journal of Antimicrobial Chemotherapy. 2013. Get Smart CDC (www.cdc.gov/getsmart/)

Ambulatory care visits during which antibiotics were prescribed (percent)*



* Data is for the US from 2007 to 2009, from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.

Lack of awareness results in many seemingly uneventful behaviors that breed resistant bacteria that kill thousands of people every year. The consequences of these behaviors are not experienced immediately at the individual level, however, so people are seldom motivated to change their behavior. Consider these common examples:

- A patient starts feeling better, and decides to stop taking his antibiotics before the full course of treatment is over – he has thereby exposed the remaining bacteria in his body to a sub-lethal dose of the drug.
- A farmer gives antibiotics in feed to his cattle to promote growth – thereby exposing the bacteria in his animals to sub-lethal doses of the drug.
- A pharmacist sells antibiotics without prescription to a customer coming into the store with a fever – the customer may not need antibiotics.
- A doctor prescribes antibiotics without running a test to verify the bacterial origin of the symptoms and its sensitivity – she might be giving the wrong antibiotics, or the patient might not need any antibiotics at all.
- A public health official develops policies to improve access to antibiotics for the population, without regulating prescription procedures – he might be opening the door to antibiotics use for people that do not need antibiotics.
- Someone buys counterfeit/falsified medicines which even though may be prescribed and bought in good faith have a very low dose of effective antibiotic and therefore contribute to resistance.

This under-awareness of the magnitude of the antimicrobial resistance threat has serious effects. It not only fosters resistance at the local level, but it also prevents much-needed actions at the international level – actions such as controlling imports and exports of antibiotics, reducing the commercialization of counterfeits or sub-standard antibiotics, and limiting the use of antibiotics in a co-ordinated way

across the globe. Despite the various initiatives to raise awareness and promote action⁹, the level of international engagement on antimicrobial resistance has remained disappointingly low.

ACTION TO INCREASE AWARENESS

What is needed for this urgent first step is a concerted awareness campaign, supported by a broad range of countries, with international efforts being co-ordinated and complemented by national and local campaigns that take account of culture and context.

I. Raise awareness among politicians, scientists, hospital administrators, healthcare professionals, agricultural producers, and the community. A concerted awareness campaign should gather commitment at the international level, but must then be carried to the national level in order to reach and influence public health officials and politicians, scientists and scientific advisors, hospital administrators and healthcare professionals, agricultural producers and the food industry, and the community. Evidence from successful awareness campaigns suggests that successful action should include the following set of features:

- Commitment and constancy over time, including funding – behavioral change can take a long time; for example, the first appreciable reduction in cigarette consumption in the US was observed 20 years after the initial Surgeon General's report linking smoking to lung cancer.
- Awareness supported by regulatory change – incentives and enforcement accelerate behavioral change; for example, cigarette prices and smoking bans in public places supported the reduction in consumption observed during the 1990s and 2000s.
- Campaigns with tailored messages directed to each target group – different stakeholder groups need to make different behavioral changes, but together the results can be synergistic.
- Use of the appropriate channels to reach each stakeholder group – each target group convenes at different venues and is tuned to different sources of information.
- Prominent figures as champions within each stakeholder group – role models catalyze behavioral change.
- A small group of fully dedicated people, measured on their impact – planning and implementation of any campaign is a full-time job with the clear objective of changing behaviors in a measurable way.

2. ANTIBIOTIC CONSERVATION

Antibiotic conservation or stewardship⁶, in the context of antimicrobial resistance, refers to the preservation of the effectiveness of antibiotics by reducing, and ultimately eradicating, inappropriate use, while still maintaining access. As discussed in the previous section, usage of antibiotics drives the development of resistance. So usage should be responsible – that is, aimed at improving health in situations when antibiotics are the most effective way to treat an infectious disease. All other usage will foster the development of antimicrobial resistance without therapeutic benefit. Despite being a public good with limited effective lifespans, antibiotics are currently not well conserved, and inappropriate usage is rampant in developed and developing countries alike. In fact, lack of conservation is perhaps the strongest factor behind the antimicrobial resistance threat. Lack of knowledge and lack of care are serious issues in the healthcare setting, in the medicines distribution chain, in the community, and in agricultural production. Without committed public and political will to change the current situation, inappropriate antibiotics use could soon eradicate the effectiveness of antibiotics to treat many common infections.

Inappropriate antibiotic usage in the healthcare setting is severe in developed as well as developing countries. In the US, as mentioned, over half of ambulatory care visits for acute respiratory infections not needing antibiotic treatment do actually result in an antibiotics prescription (see Figure 5). In India and Kenya, even though the treatment of choice for diarrheal disease in children is oral rehydration, a high proportion of children with that condition are treated with antibiotics¹⁰. And a recent study in China found that two-thirds of hospitalized patients received antibiotics, when the rate of usage in other countries was 30 percent¹¹.

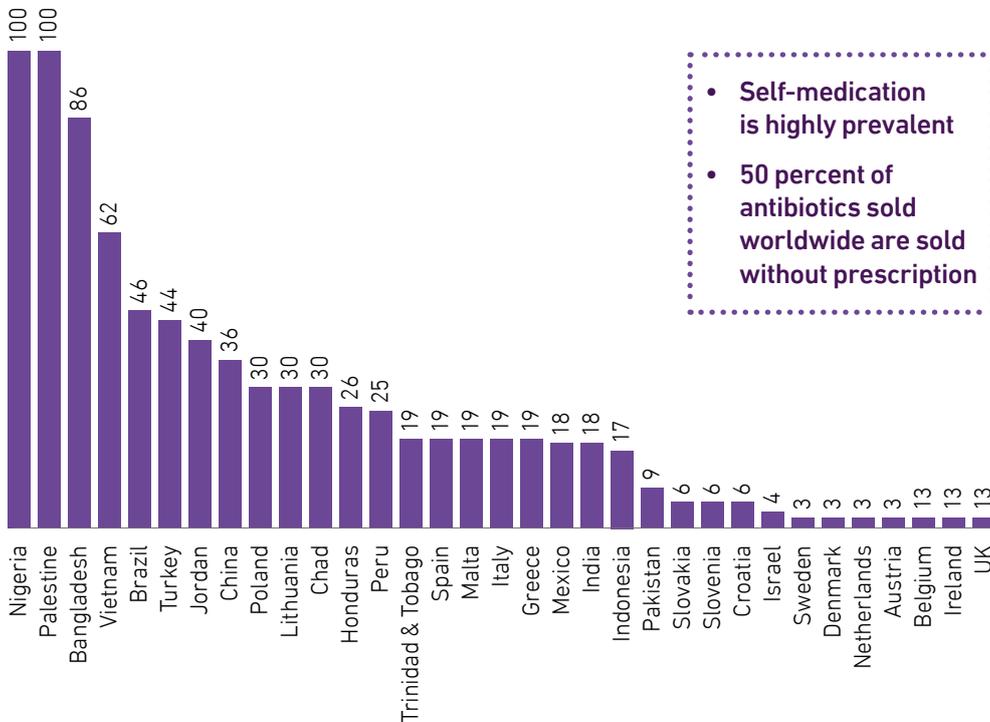
The key reasons for inappropriate prescription of antibiotics appear to be these: lack of knowledge, delay in laboratory results or lack of trust in them, desire to meet patient demand, and economic incentives based on prescription volume instead of patient outcomes^{11,12}. Until healthcare professionals acquire better awareness, the right incentives, and clear treatment guidelines, antibiotic conservation in the healthcare setting will not improve.

Another serious issue is lack of stewardship in the distribution and dispensing of antibiotics. When people are able to acquire antibiotics without prescription, or over the counter, the result is either sub-optimal treatment or increased use of antibiotics for cases in which they are not needed; and that promotes the development of resistance among potentially lethal bacteria. In some countries, including Nigeria, Sudan, and Bangladesh, nearly all antibiotics consumed are apparently acquired without a prescription. Developed countries are not exempt from the problem; Italy, Spain and Greece, for example, have levels of over-the-counter non-prescription use that approach 20 percent of the antibiotics courses sold (see Figure 6).

Figure 6: Non-prescription use of antibiotics is widespread, and reaches high levels even in some developed countries

Source: Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *Lancet Infectious Diseases*. 2011. 11:692-701

Frequency of non-prescription use of antibacterials in the general population (percent)



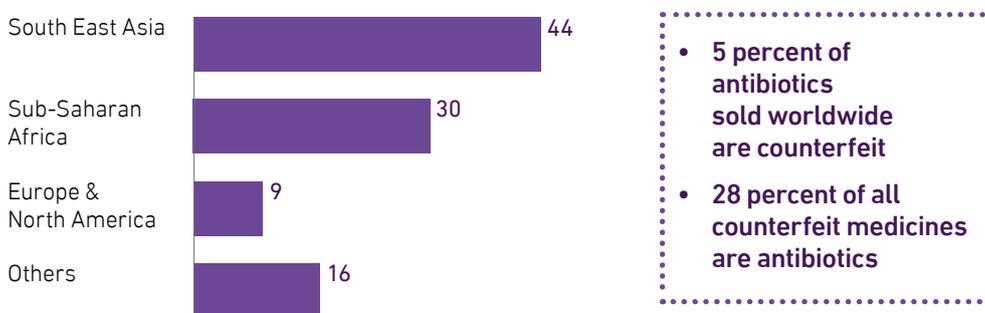
Some smaller countries with highly mobile populations, such as Qatar, might enforce prescription-only dispensing and control imports, but still face substantial inappropriate non-prescription use because residents purchase antibiotics without prescription when abroad, and then return with them. In larger countries with less mobile populations, an important source of non-prescription antibiotics is unregulated Internet purchasing: up to one-third of websites selling antibiotics in the US, Canada, and the UK do not require a prescription¹³.

One further issue related to the supply chain of antibiotics, and greatly fostering the development of resistance, is the widespread distribution of counterfeit antibiotics. Besides the illegal aspect of manufacturing, selling, and distributing counterfeit medicines, when counterfeit antibiotics reach the market, they endanger patients' lives both in the short term – owing to their partial or total inefficacy – and in the long term, because sub-therapeutic doses of antibiotics will greatly help resistant bacteria to flourish. The scale of the problem is severe in developing countries: an estimated 44 percent of all counterfeit antibiotics are distributed in South East Asia. But the problem affects developed countries too, where, by some accounts, close to 10 percent of all counterfeit antibiotics are consumed (Figure 7).

Figure 7: The high level of counterfeits in certain regions aggravates the AMR problem

Source: Delepierre A, Gayot A., Carpentier A. Update on counterfeit antibiotics worldwide; Public health risks. *Medecine et maladies infectieuses*. 2012. 42(6):247-255

Destination of counterfeit antibiotics (percent of total counterfeit antibiotics)



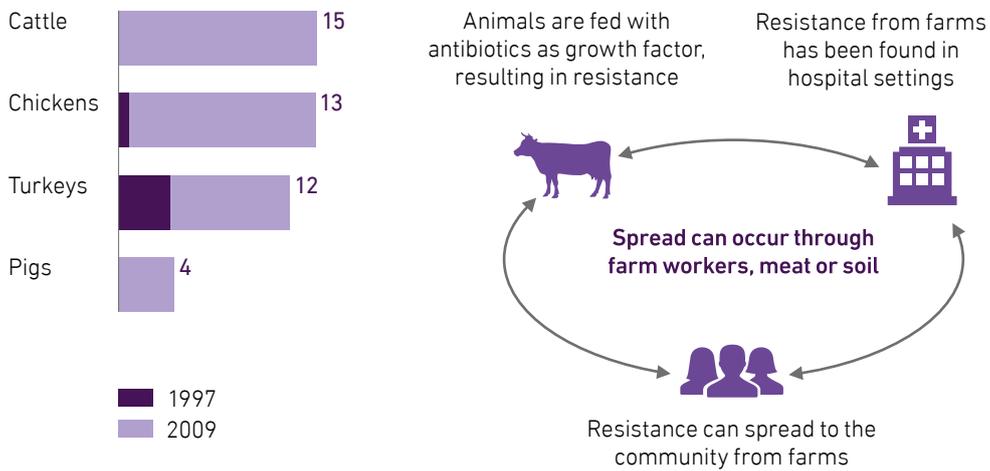
At the community level, stewardship is not deeply rooted in any country. Many people still believe that antibiotics can be used to treat flu-like symptoms that are viral in nature, when antibiotics have no effect on viruses. Furthermore, these beliefs manifest in patients demanding antibiotic prescriptions from their doctors, a practice identified as a driver of inappropriate prescription. It has in fact been shown that well-educated patients receive fewer antibiotic prescriptions during primary care visits¹¹. In the absence of education and awareness at the community level, and of mechanisms to restrict non-prescription availability of antibiotics, self-medication and inappropriate prescription are commonplace.

Conservation is not only required with regard to human use of antibiotics. More than 70 percent of all antibiotic production is probably destined for animal use¹⁴. Unlike in human use, most antibiotics for animals are not used for therapeutic purposes – that is, to cure infection – but instead are used to promote growth. The estimates are that almost 75 percent of all antibiotics¹⁵ given to animals are not used for treating infections. Antibiotics are widely used in cattle, poultry, swine, and fish at sub-therapeutic doses that increase the likelihood of resistance developing. As a result, an increase in resistant bacteria that can infect humans, like *Salmonella*, has been observed in cattle, chickens, turkeys, and pigs (see Figure 8).

Figure 8: Antibiotic resistance has been increasing among farm animals, posing an increasing risk to human health

Source: Frye JG, Fedorka-Cray PJ. Prevalence, distribution and characterisation of ceftiofur resistance in *Salmonella enterica* isolated from animals in the USA from 1999 to 2003. *International Journal of Antimicrobial agents*. 2007. 30(2):134-142

Ceftiofur-resistant *Salmonella* isolates (percent isolates)



Besides the unknown health effects on people consuming animals that have received antibiotics, there is a clear danger that bacteria from animals can spread to humans – whether from contact with the animals themselves, from farm soil, or even from processed meat. This transmission, coupled with the magnitude of inappropriate antibiotic usage, poses a significant threat to public health. Yet an economically viable food industry seems perfectly possible without use of antibiotics. When Denmark banned antibiotics for growth promotion in its swine industry, there was no negative impact on animal production¹⁶ or on the price of pork to the consumer¹⁷. Moreover, the Danish example has shown that after antibiotics are withdrawn from use for growth promotion, bacterial resistance to those antibiotics declines dramatically¹⁸.

ACTIONS TO IMPROVE CONSERVATION

While potential solutions vary from country to country, strong national action is needed in all countries. Many developed countries have stewardship guidelines and recommendations in the healthcare setting yet lack proper enforcement. Some countries, despite prohibiting over-the-counter antibiotic sales, still have a high proportion of non-compliance. Some countries have bans on agricultural use for growth promotion, but again lack the mechanisms to enforce those bans. At the same time, the supply chain is faulty at many levels: allowing counterfeit medicines in developing countries, for instance, or persisting in the use of growth-promoting antibiotics despite the data and the existing bans. In summary, it is clear that lack of stewardship is one of the main contributors to the development of antimicrobial resistance, and that co-ordinated action across multiple stakeholders is needed in order to curb the problem.

The difficulty is not in designing the solution but in implementing it – in all the sectors of society involved. The solution itself is relatively simple, with three key components:

II. Stronger regulation and mechanisms to enforce antibiotic conservation.

- Regulate sales of antibiotics, to ensure that they are dispensed only on valid prescription and are unavailable through over-the-counter sales.
- Set up track-and-trace mechanisms to reduce counterfeits in the market.
- Enforce more stringent penalties and controls in regard to distributors and sellers of counterfeit antibiotics.
- Engage pharmacies and drug stores by making them responsible for enforcing the regulations at the point of sale.
- Impose a ban or control internet sales of antibiotics.
- Agree and strengthen the World Health Organization (WHO) list of human-only antibiotics.
- Ban the non-therapeutic use of antibiotics in agriculture and aquaculture or, at a minimum, enforce testing and appropriate labeling of products containing antibiotic residues or derived from animals raised in the presence of antibiotics.

III. Diagnostics and treatment protocols to enforce appropriate use.

- Develop guidelines for appropriate treatment and prescription; for example, guidelines on avoiding the use of antibiotics to treat viral infections, or guidelines on ensuring that the appropriate antibiotic is prescribed. In Thailand, the antibiotics 'smart use program' combined guidelines with patient awareness to reduce dramatically the level of inappropriate antibiotics prescriptions.
- Align the incentives of healthcare professionals so as to support compliance with the guidelines.
- Incentivize the development of point-of-care diagnostics that could distinguish a bacterial infection from a viral infection, and that could diagnose specific resistance patterns within hours. This challenge remains a difficult one, but the existence of such diagnostics would prove transformational, by elevating appropriate, targeted antibiotics over empirical therapies¹⁹ and thereby preventing resistance.

IV. Awareness-raising for professionals, patients and consumers.²⁰

- Develop educational programs for professionals (doctors, veterinarians and nurses).
- Develop educational programs for patients, in order to increase awareness of the common conditions that are inappropriately treated with antibiotics, and thereby ensure that patients do not demand antibiotics when they are not needed.
- Adopt adherence schemes, incentives, and educational programs to ensure that patients take the full course of therapy prescribed, and are aware of the health risks involved if they fail to do so.
- Develop campaigns to publicize the inappropriate use of antibiotics in agriculture, so that consumer preference can drive changes in industry behavior.

3. SANITATION, HYGIENE, INFECTION PREVENTION AND CONTROL

While Awareness and Antibiotic Conservation are aimed at reducing the inappropriate use of antibiotics, we have to remember that appropriate use too can contribute to the development of resistance. The benefits of appropriate use, of course, far outweigh that risk. But far better still, for healthcare systems and for agriculture, is the prevention and control of infection in the first place. That reduces the requirement for antibiotics, and hence reduces the chance of resistance developing.

The various types of infection involved here are all of great concern: infections (sometimes already antibiotic-resistant) acquired in healthcare facilities and then transferred to the community; infections in the community that transfer to the healthcare setting; infections transmitted from farm animals to humans; and contamination of the food chain with infectious bacteria. In all these settings – healthcare facilities, farms, the food industry, and the community – behaviors are at the center of the problem. Even in countries with highly developed healthcare systems and infection prevention and control guidelines, compliant behaviors can and should be improved. One survey showed that 100 percent of student nurses in the UK had observed lapses in infection prevention and control measures during their training²¹.

Hygiene and sanitation in the food industry and at the community level are beyond the scope of this forum, but it is obvious that the standard measures – high-quality water, proper sewage, hand hygiene, decontamination of surfaces, and so on – are essential in animal production facilities, in food processing plants, and in the community. All such measures will ultimately prevent outbreaks of infection from happening, and will thereby reduce the need for antibiotics use. Moreover, even without changing the overall sanitary infrastructure, infection can be prevented by fostering simple behaviors like hand washing.

Action is needed to reduce infection and prevent transmission at the healthcare-facility level and the community level, and to prevent contamination of food with pathogenic bacteria. Such action is a no-regret move: simple guidelines, promotion of compliance, and periodic performance measurement – these are cost-effective ways of preventing and controlling infection. In the US, every resistant infection costs the healthcare system an extra US\$29,000²². In addition, as the behavioral changes are relevant to many of the same groups targeted on the Awareness and Antibiotic Conservation fronts (see the previous two sections), a single co-ordinated campaign is all that's needed: it can change behaviors on all three fronts with just a slightly larger investment.

This compliance-inducing approach to preventing and controlling infection is the main mechanism for reducing antibiotic usage, but there is another important one too: vaccination. By protecting people against infectious diseases, it reduces their need for antibiotics. Apart from their great value in human health, vaccines are valuable in agriculture too, where again they have the secondary effect of reducing the need for antibiotics. Salmon vaccination in Norway resulted in a 98 percent reduction in the use of antibiotics in fish farming, while actually helping to increase the production

volume and reduce the price to the consumer. Vaccines do tend to have a very narrow spectrum of effectiveness²³, but maximizing their use against bacterial diseases can still contribute significantly to stemming the surge of antibiotic resistance.

ACTIONS TO IMPROVE SANITATION, HYGIENE, INFECTION PREVENTION AND CONTROL

Concretely, action for sanitation, hygiene, infection prevention and control should begin with awareness campaigns at all stakeholder levels – campaigns to promote behaviors consistent with the guidelines and recommendations (see the Awareness section). Awareness should also be supported by specific actions targeted to each level:

V. Establish infection control protocols and tracking mechanisms at the healthcare level. Put in place hospital infection task forces or committees, with dedicated human resources for infection prevention and control, to establish, promote, and monitor compliance with guidelines on practices such as: decontamination of surfaces and equipment, hand hygiene, contact precaution and isolation, screening for infection upon admission, and readmission alert systems to identify patients recently discharged with a persistent hospital-acquired infection.

VI. Develop and enforce sanitary regulations for the food industry.

VII. Educate the community. Encourage education by healthcare professionals during primary care visits and at schools, to promote sanitation and hygiene at home and in the workplace.

VIII. Map progress on implementation of international prevention programs. Take collaborative action at the international level, such as the WHO First Global Patient Safety Challenge on hand-washing, which was endorsed by 125 member states.

4. SURVEILLANCE AND MONITORING

This action front in the war against antimicrobial resistance is based on understanding the magnitude of the problem and its evolution, and on measuring the impact of the previous three fronts of action – Awareness, Antibiotic Conservation, and Sanitation, Hygiene, Infection Prevention and Control. Although the terms “surveillance” and “monitoring” are often used interchangeably, they are considered distinct in this report. Surveillance is treated here as the set of activities aimed at tracking antibiotic resistance. It supports optimal guideline development and performance management. Monitoring, on the other hand, is the set of activities aimed at tracking the use of antibiotics in healthcare and agriculture. In essence, surveillance is about measuring the output, and monitoring is about measuring the input.

Both surveillance and monitoring activities are undertaken at the local level, but they generate data that can be aggregated and interpreted at the regional, national, and global level. At the local level, surveillance and monitoring rely on effective data-collection systems that operate under common standards allowing for data aggregation and comparison. At higher levels, surveillance and monitoring become

dependent on data analytics able to manipulate and visualize the data in a way that supports drawing insights and conclusions. For example, at the local level, hospitals in many developed countries and some developing countries will regularly collect data on resistance patterns, perhaps every week. These patterns are communicated to doctors in those hospitals so that they can decide accurately which antibiotics to prescribe to patients. At the regional and national level, all the data from these local hospitals will be aggregated, and can be analyzed to reveal resistance trends and correlate those with antibiotic usage. At the national level, surveillance detects rises in resistance for a particular pathogen, signaling a potential outbreak. Without surveillance mechanisms, an outbreak could go undetected until it is too late to act. For an example of the way that surveillance (combined with immediate action) averted a serious public health risk, consider the successful containment of an outbreak of carbapenem-resistant *K. pneumoniae* in Israel in 2006²⁴. At the global level, finally, effective surveillance can determine the source of new emerging “superbugs,” and support containment in the event of an epidemic. Surveillance and monitoring at all levels also help in optimizing the actions for tackling antimicrobial resistance, and in highlighting areas where more effort is needed.

Today, surveillance and monitoring still reveal significant gaps, which compromise the usability and comparability of the data. The main problems are a lack of common standards for data collection, and the persistence of areas where no data collection is conducted at all, for either surveillance or monitoring. In Europe, 77 percent of countries have a national antimicrobial-resistance surveillance system, but only 54 percent have standards for submitting samples to laboratories for analysis²⁵. If the situation is unsatisfactory for human pathogen surveillance and human antibiotics monitoring, it is all the more so in the case of animal antibiotics, where collection and analysis are even more fragmented. Nevertheless, there is a good base to build on. Three major regional surveillance networks exist. Each of them has created common standards across countries, and tracks several bacteria. ReLAVRA, the “Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos,” has been active in Latin America since 1996, and currently tracks 16 organisms. IDSR, the “Integrated Disease Surveillance and Response” network, covers Africa, and has been tracking eight organisms since 2002. EARS-Net, the “European Antimicrobial Resistance Surveillance Network”, is active in Europe, and has been tracking seven organisms since 2010. Although these networks are probably not directly compatible with each other, it could be valuable to bring them together: such co-ordination could create the first global antimicrobial resistance surveillance network, and could pave the way to an integrated surveillance and monitoring system.

ACTIONS TO IMPROVE SURVEILLANCE AND MONITORING

A concerted international effort to exploit the existing infrastructure and standards should take the following steps.

IX. Standardize guidelines for data gathering – leverage those that already exist, and maximize their compatibility; and make hospitals and agricultural facilities accountable for sample collection and laboratory submission.

X. Co-ordinate national and regional interpretation and sharing of sales and usage data – engage pharmaceutical companies, hospitals, pharmacies and veterinarians to ensure data availability.

XI. Develop a co-ordinated global surveillance and monitoring program – harmonize standards across existing regional networks and develop capabilities to analyze, interpret and report results.

5. RESEARCH AND DEVELOPMENT

R&D can take the credit for moving society from the pre-antibiotics world to the world of today, a world in which the great majority of bacterial infections can be treated with antibiotics, saving millions of lives each year. As these antibiotics are gradually rendered obsolete by the emergence of resistance, it is absolutely essential that development of novel antibiotics should continue. Similarly, as resistance patterns evolve, it is crucial to develop new vaccines to prevent infection, and to develop rapid diagnostic methods for detecting resistant bacteria and guiding treatment. Novel, more effective disinfectants and cleaning agents may also have an important role. As such, R&D remains a top priority, helping to equip healthcare professionals with the tools they need to tackle infection.

Alongside the pressing need for innovation, however, is a formidable set of hurdles for the organizations traditionally spearheading the development of new antibiotics. These hurdles are of four main types:

- Public and philanthropic funding for basic microbiology research is limited, so more of the R&D burden falls on the private sector. For example, the US National Institutes of Health (NIH) dedicates only 0.3 percent of its budget to antimicrobial resistance research, while resistant bacterial infections cause 1 percent of all deaths in the US²⁶. Limited funding results in the reduced size of US graduate research programs in microbiology – about 30 percent smaller than other, more popular programs like neuroscience²⁷ – or the overall tiny contribution that academic institutions make to development: they are taking the lead in less than 1 percent of current antibiotics development projects (see Figure 2 above).
- The regulatory requirements are challenging, making R&D even more difficult. However, some encouraging moves have recently taken place; notably, the changes to FDA regulations, as part of the GAIN act, and similar updates to EMA's requirements.
- Medications with reduced patient populations and short treatment courses will always have limited commercial potential. In the case of new-generation

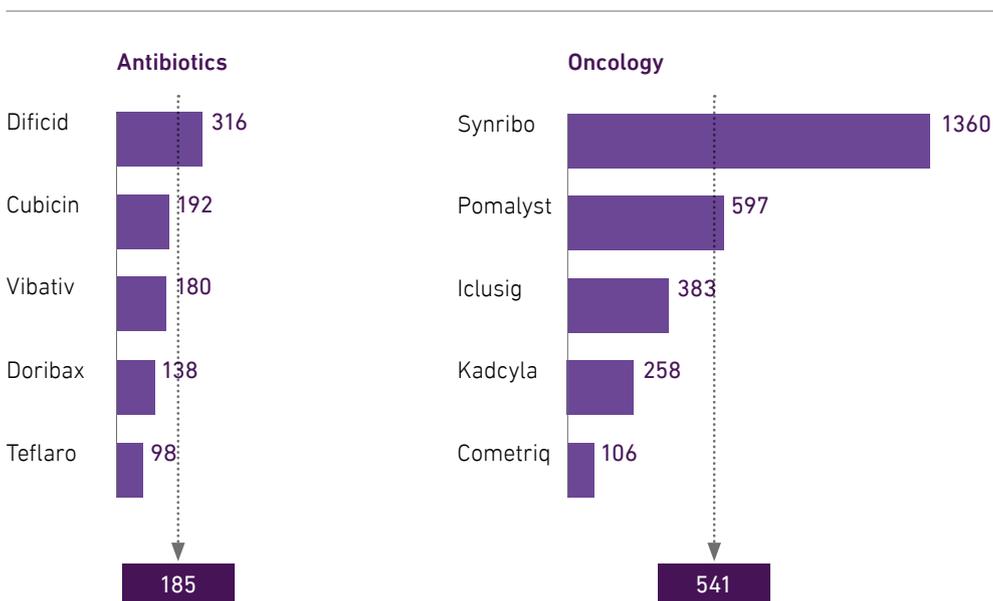
antibiotics, which tend to be used for severe or rare infections, patient numbers are low. Moreover, most antibiotic treatments tend to last only 14 days, whereas other types of medication are sometimes taken for much longer periods of time.

- To compound those commercial disincentives, the antibacterial space is commoditized, and characterized by low price points. Four out of the five most recent oncology drugs are priced above US\$ 200 per day of treatment, while only one out of the last five antibiotics launched is priced that high (Figure 9), even though all the drugs in question are life-saving. In addition, the oncology drugs are taken for longer periods, so their commercial appeal is greater still.

Figure 9: The antibiotics market is relatively commoditized, with lower prices than other therapeutic areas, even for life-saving drugs

Source: Zen Rx; PriceRx; press search

Price per day for the last five US launches in each therapeutic area (US\$, 2013)



The combined effect of these hurdles is to reduce the return on R&D investment in antibiotics. In other words, the pool of revenue that a new antibiotic can access after launch is much smaller than that for many other types of drugs. Accordingly, the number of large and mid-sized pharmaceutical companies developing antibiotics has dropped dramatically – from 18 in 1990 to just five today. What's more, the value of the market for existing anti-bacterial drugs has been shrinking (owing to loss of exclusivity, and the consequent competition from generics), with new product launches unlikely to compensate (Figure 10). Given the current economic equation, the question must be how long this area of R&D can retain even the few large and mid-sized pharmaceutical companies that still work on antibiotics.

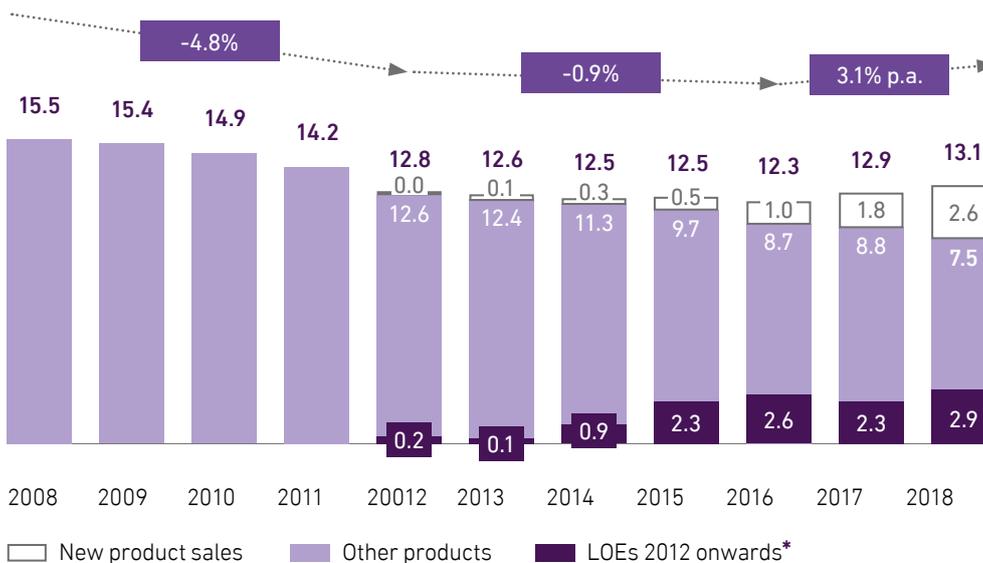
An alternative to antibiotics R&D is R&D on new vaccines. It would have the additional benefit of reducing the need for antibiotics use, thus extending the efficacy of the antibiotics that are still being prescribed today. However, despite successes with DTP (diphtheria, tetanus, pertussis) and pneumococcal vaccines, vaccine development for many bacterial species remains elusive. Furthermore, the financial case for vaccines seems no stronger than the one for antibiotics. In theory, the patient pool for vaccines is much larger, since everyone should get vaccinated to avoid infection, but it is highly

unlikely that governments and international organizations will agree to pay for a new protection regime – namely, the multiple vaccines needed for protecting humanity against the bacterial infections currently combated by antibiotics. And if governments are reluctant to foot the bill for vaccines, then pharmaceutical companies will lack the commercial incentive to work on such vaccines.

Figure 10: The market has been shrinking and new launches will not compensate for the value lost

Source: EvaluatePharma

Global antibacterial drugs market sales 2008-2018 (US\$ bn)



* LOE: loss of exclusivity, when the patent protecting a drug expires, opening the door for generics companies to produce and commercialize the drug

ACTIONS TO INCENTIVIZE R&D

It is clear that co-ordinated action is needed to provide incentives for R&D, or to develop alternative mechanisms to make the financial equation work again. To that end, there are four approaches to consider.

XII. Increase the price of antibiotics, or other types of therapy for which current commercial returns are insufficient, to incentivize R&D.

Ideally, new-generation antibiotics would be priced at similar levels to other life-saving drugs currently in the market. To guarantee acceptable returns, the new pricing would take into account the restricted patient pools and the short treatment courses. So, to match the returns obtained from a cancer drug, such as Herceptin, a novel antibiotic would need to be priced at an estimated US\$ 10,000 per treatment, or US\$ 700 per day. That is more than twice as much as the most expensive antibiotic currently in the market, Dificid, and over three times the price of Cubicin, the latest broad-spectrum antibiotic used for resistant infections (see Figure 9).

Increasing price is a relatively crude intervention, and with obvious affordability and access risks: although the price rise would be only two- or threefold, and a pricing mechanism would be fairly simple to implement, the new price level set out

above would likely make the drug inaccessible for large portions of the population, especially those in low- and middle-income countries.

XIII. Extend IP or patent protection to reward the developer of a new antibiotic with a longer period of exclusivity and thus higher overall returns.

How long would the patent protection need to last, in order to produce acceptable returns? To match the returns of drugs in other therapeutic areas, like oncology, a late-generation antibiotic would require patent protection in perpetuity. That is hardly practical. In any case, perpetual patent protection is not very attractive from a cash-flow perspective as the mechanism defers payback on the R&D investment too far into the future.

An alternative to perpetual patent protection could be an IP protection voucher, or transferable patent protection voucher, to be used by the innovator for another, more profitable product. The problem here is that although such a mechanism might suit large companies with extensive portfolios in which the voucher could be used, such a voucher might be useless to small pharmaceutical and biotech companies – and it is these companies that are responsible for most antibiotics innovation today (see Figure 2).

XIV. Decouple sales from R&D, and thereby separate the incentive to innovate from the incentive to sell.

Decoupling in this context means that R&D returns derive from a source other than the sales of the product for which R&D funds were spent. What other sources could there be? In other words, how could such a decoupling be operationalized? Essentially, a separate funding mechanism would have to be found for R&D. It could be a public-private partnership (PPP), a grant from an R&D granting agency, a prize, or a goal-specific investment by government or philanthropic organizations.

The PPP model has a particular advantage: if the PPP holds the IP in the drugs discovered, it could license the drugs to different manufacturers in ways that promote both access and appropriate use. But the model has some disadvantages too: the PPP would demand substantial public funding up front, as the R&D pipeline has to be large enough to ensure sustainable output; and the PPP would need rigorous governance and performance management, to ensure that the public funds are invested responsibly and produce the expected results.

XV. Guarantee income to innovators, by entering into long term contractual agreements – agreements ensuring a minimum level of return regardless of the volume of product sold.

To operationalize such a guarantee, various options are possible: a fixed fee, licensing fee, or an advanced market commitment.

The advantage of this guarantee mechanism is that the public funds would be spent only once the product is launched. The disadvantages are that appropriate safeguards have to be created to ensure access and appropriate use, and that the commitment needs to be negotiated upfront.

The last two of these approaches, despite the various disadvantages, address the R&D incentive problem holistically, and they could be implemented with design features to ensure access and appropriate use. Indeed, there are real examples of similar solutions, from which lessons and best practices could be derived (see Figure 11).

Figure 11: Examples of R&D and Innovation solutions

Source: IMI; MMV; BARDA; Gavi

	EXAMPLE	DESCRIPTION
Decouple sales from R&D		PPP between EU & EFPIA to speed up the development of medicines Launched ~€200mn program, New Drugs for Bad Bugs (ND4BB), in 2012
		Non-profit partnership to discover, develop and deliver safe and effective anti-malarial agents Largest pipeline of anti-malarial drugs globally, with over 50 projects, and ~US\$ 580 million pledged or received in 1999-2017
		Established in 2011 to develop counter-measures to potential bioterrorism agents US\$ 1 billion budget for development of antibiotics through PPPs with GSK, Basilea, Tetrphase, Cempra, etc.
Guarantee income		Advanced market commitment scheme to support vaccines for developing countries Donors subsidize the future sale of vaccines, and participating manufacturers agree to supply a fixed volume of vaccines per year

Finally, to complement R&D in new antibiotics, there is also a need for cost-effective rapid diagnostics. These diagnostics should be capable of making several distinctions: between bacterial infections and viral infections; between bacterial infections that indicate antibiotic treatment and those that don't; and between bacteria that are resistant to antibiotics and those that are susceptible. Several companies are now developing rapid diagnostics for infectious diseases, but further continuous investment in the area is needed in order to overcome the technological challenges. By developing rapid diagnostics that could be easily deployed in developed and developing countries alike, innovators will help to ensure appropriate use of antibiotics, as well as improving patient outcomes.

CONCLUSION

The antimicrobial resistance threat is already affecting our countries, our cities and our people. Every day, in both the developed and the developing world, people die from infections that do not respond to the drugs designed to treat them. In the face of this challenge, every public health official, politician, scientist, healthcare professional, agriculture minister, and industry representative has a responsibility to take action right away.

While the international community gets together to mount a co-ordinated response and develop initiatives on the R&D front, individuals can start working at the national level in a series of no-regret moves:

- **Engaging all levels of society in your country**
 - Assemble a group of influential stakeholders to design a comprehensive national program, to motivate action on three fronts – Awareness; Antibiotic Conservation; and Sanitation, Hygiene, Infection Prevention and Control – as described earlier in this report.
 - Start a dialogue between ministries of health and agriculture, to understand the level of antibiotic usage in farm animals, to explore alternatives, and to apply the lessons from other countries such as Denmark and Norway; that should help in the search for ways of reducing antibiotic usage in animals, without affecting the profitability of the agricultural industry and the price of food for consumers.
- **Linking up with ongoing efforts to avoid duplications and to achieve synergies**
 - Convene leaders of the existing surveillance and monitoring efforts, to start working towards unified standards and approaches.
 - If your country is not currently engaged in surveillance and monitoring, approach the network closest to your region and seek ways of joining.
 - If your country has no clear guidelines for bacterial infection treatment, prevention and control, reach out to your regional WHO office to procure appropriate guidelines, and then work with public health officials at the local and national level to develop a plan to implement these guidelines.

The antimicrobial resistance threat has to be addressed. A collaborative solution exists, and the fronts of action are clear. It is now in our hands to move forward and avert a public health catastrophe.

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APPENDIX

Antimicrobials are agents – chemical compounds or natural substances – that kill or slow down the growth of microorganisms, including bacteria, viruses, fungi, and parasites. When these organisms develop the ability to survive or continue growing in the presence of such agents, they are said to have become resistant.

“Antimicrobial resistance” is a generic term that applies to different kinds of microorganisms and several antimicrobial agents. Given the urgent need for action to prevent and treat bacterial infections that have become immune to many therapies, this report focuses on the specific threat of antibiotic resistance; that is, resistance developed by pathogenic bacteria to the antibiotics used to treat the infections that these bacteria cause. Such a focus does not imply that resistance developed by other microorganisms to other agents is not also a public health issue.

Resistance to antibiotics is developed by bacteria in an evolutionary process. Simply described, genetic mutations randomly occur in the bacteria’s genetic material, and some of these mutations might, by chance, alter a component of a bacterium that underpins its susceptibility to one or several related antibiotics. When that bacterium is exposed to the antibiotic, it will then survive and multiply, while all other bacteria – the ones that are not resistant – die or at least lose the ability to multiply, leaving them an easy prey of the immune system. In this way, the resistant bacterium is selected in the presence of the antibiotic, and all its progeny carry the mutation that enables resistance, thus creating a resistant strain. Although these events are very rare, the amount of bacteria in humans or animals is so great that some new strains are bound to emerge. When that happens in a bacterium that could cause a fatal illness, it is a very serious matter, as the antibiotics no longer work as intended, and treating the illness now becomes more difficult.

Here is a list of the common agents used in the fight against bacteria and bacterial infections.

- Soap and water is the traditional agent against bacteria on the skin; modern antibacterial soaps increase the efficacy of soap and water by adding an antibacterial agent to the soap.
- Chemical agents containing chlorine are traditionally used to kill bacteria and other microorganisms on surfaces, clothing, and skin.
- Chemical agents containing alcohol are used to kill bacteria on surfaces, clothing, and skin; they are not effective against certain bacteria that are able to form spores, like *Clostridium difficile* or *Bacillus anthracis* (the anthrax bacteria).
- Antibiotics are the main type of antibacterials currently used for treating infection.
- Vaccines are agents that enhance the reaction of the immune system against infectious agents; vaccines prevent infections rather than curing them.

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NOTES

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