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IFPMA Position on Antimicrobial Resistance (AMR)

Summary

- The introduction and widespread use of antibiotics led people to believe that we could successfully treat all infections - the rise in antimicrobial resistance has shown that thinking to be wrong.
- A continuous pipeline of new classes of antibiotics that can overcome increasing bacterial resistance is essential, but the current pipeline is insufficient due to a range of scientific, regulatory and financial factors. Solutions will require creative partnership between our industry, governments, the WHO and other stakeholders.
- In parallel with this effort, effective antibiotic stewardship is also required: antibiotics must be prescribed and used responsibly in order to maximize their benefit. Here too partnership is required - between governments, the pharmaceutical industry (R&D-based *and* generic), WHO and healthcare professionals.

1. Background

Antibiotics made modern medicine possible. Before the introduction of antibiotics, such as penicillin in the 1940s, infectious diseases as simple as common skin infections claimed countless victims. In the early 1900s, 90% of children with bacterial meningitis died. Complex medical interventions like organ transplants, hip replacements and even chemotherapy are all made possible or better by the use of antibiotics. But a hallmark of antibiotics is that they lose their effectiveness over time as bacteria naturally evolve and mutate and so become resistant to the medicine's power.

The problem of AMR is growing¹, and seventy years after their introduction the rise of bacterial resistance to popular and historically effective antibiotics has become a grave threat to global public health. We now face the possibility of a future without effective antibiotics for several types of bacteria that cause life-threatening infections in humans.

A challenge facing both developed and developing countries

The problem of AMR extends across the globe. In the US, hospital-acquired, drug-resistant bacterial infections kill 63,000 patients² each year, and drug-resistant bacterial infections place a \$34 billion drain on society. In the EU, multidrug-resistant bacteria cause about 400,000 infections a year and at least 25,000 deaths annually, and generate healthcare costs and productivity losses of €1.5 billion³. But while there are high levels of resistance in developed countries, the most alarming levels of resistance are in developing countries.

In 2004, WHO identified infectious diseases as the top priority for new medicines based on the potential public health impact. Their World Health Report (2004) estimated that 15 million people

¹ "Streptococcus pneumoniae (*S. pneumoniae*), another common pathogen, causes bacterial meningitis and bacterial pneumonia, among other conditions. In 1987, only 2 of every 10,000 *S. pneumoniae* infections—0.02 percent—were resistant to penicillin, the antibiotic of choice. By 2004, this figure had risen to 1 in 5—20 percent—a 1,000-fold increase (CDC 2005)."
<http://www.extendingthecure.org/executive-summary>

² Gerberding, J. The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment – Workshop Summary. Washington, DC: National Academies Press, Pages 210-15.

³ Bacterial Challenge: Time to React, ECDC/EMA Joint Technical Report. Stockholm, 2009.

died of infectious and parasitic disease in the preceding year. To put that number in perspective, 7.4 million died of cancer in the same year. Outside the US and EU the disease burden from infection is greater than the total of all other therapy areas combined.

There is a dearth of new antibacterial medicines

The growth in antimicrobial resistance has been accompanied by a sharp decline in the development of new antibacterial medicines. Over the past three decades only two new classes of antibacterial medicines have been discovered, compared to 11 in the previous 50 years. While there are now a very small number of new, resistance-breaking antibiotics in the late stages of clinical development, a recent report from the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) entitled “The Bacterial Challenge – Time to React” (2009) highlights the clear gap between society’s urgent need for novel antibiotics and the current biopharmaceutical pipeline. It is now widely accepted that the increase in resistance and the decline in the number of new drugs coming to market together pose a major threat to health in all countries. We must act soon to boost antibiotic development or face a growing crisis.

2. Causes of the growth in AMR

Antimicrobial resistance is a naturally occurring phenomenon. Bacteria have always possessed the ability to protect themselves from naturally occurring antibiotics by acquiring resistance through the exchange of genetic material with other bacteria. This survival mechanism, which bacteria have developed over billions of years, eventually enables them to develop a resistance to most antibiotics. As a result, even our most recently approved and most effective drugs will gradually decline in efficacy; the healthcare industry must therefore constantly develop new antibiotics. Two further factors have accelerated the development of this resistance: widespread use of antibiotics, and time-consuming diagnostic tools leading to the inappropriate use of antibiotics.

a) Widespread use of antibiotics

Over the last twenty years the resistance problem has increased as antibiotic-resistant bacteria have become more prevalent and multidrug-resistant strains have emerged in many species that cause disease in humans. Over-prescription, misprescription and non-compliance have made the situation even worse. Numerous studies confirm that increased antibiotic consumption is associated with the worldwide emergence of antibiotic resistance⁴. Stopping AMR might be biologically impossible, but the healthcare community can refine, develop and adopt practices to slow resistance and ensure that the global stock of antibiotics remains viable for a longer period.

b) Time-consuming diagnostic tools

The ability to identify targeted pathogens with rapid diagnostic tests (RDTs) could greatly improve appropriate treatment involving the use of antibiotics as well as reduce the cost and time needed to conduct clinical trials. Currently, the most accurate and widespread identification of bacteria takes 36–48 hours to provide results. As delays in initiation of effective therapy can lead to increased sickness or even death of the patient, physicians frequently must treat patients empirically while still waiting for test results, or may not even undertake those tests at all. This may lead to inappropriate prescription of antibiotics or even the misdiagnosis of viral infections as bacterial. The absence of effective RDTs has also led physicians to rely on broad spectrum antibiotics as opposed to more targeted treatments. We must be realistic about what can be achieved through improved diagnostics: even the latest tools can take 24 hours or more to produce a result, and they often require a level of resources that in developing country settings limit their use. Nevertheless, improved diagnostic tools are an important part of the response to the AMR challenge.

⁴ These include a study collecting data from the EARSS project, the telithromycin surveillance (PROTEKT) project⁴, and the pan-European project⁴.

3. Why the lack of new antibiotics?

The R&D-based pharmaceutical industry continues to invest billions of dollars in the development of new antibiotics, and there remains considerable expertise in this field within the industry and some promising pipeline candidates. However, we are not seeing sufficient development of new and novel classes of antibiotics to treat infections. There are scientific, regulatory and financial reasons for this.

a) Antibiotic discovery is difficult

The discovery of new antibiotics is not a simple task. Bacteria have multiple mechanisms of resistance and it is difficult to find drug candidates to fight them. As a result, progress depends on sustained efforts by industry over a period of many years, combined with the existence of, as well as scientific progress by, diverse groups of trained scientists within academia and industry. Much of the research infrastructure required for this process was lost during the 1990s when, mistakenly, there was a sense that new antibiotics were not needed.

b) Challenging regulatory requirements

Because placebo-controlled superiority trials of anti-infectives for serious bacterial infections are unethical, the more challenging active-control non-inferiority design must be used for trials of new antibiotics. Furthermore, increasingly stringent regulatory requirements in some countries for non-inferiority studies have decreased the incentive to conduct clinical research in this area. A recent statement by the Infectious Disease Society of America regarding a proposed FDA guidance on trial design highlights the dilemma: "*Extreme statistical conservatism must be balanced with physician and patient needs if the public health need is to be addressed*".⁵

c) Inadequate financial incentives

Antibiotics generally provide a low return on investment and are therefore not seen as an attractive investment opportunity by the pharmaceutical industry. This is explained by a number of factors:

- the limited use of new antibiotics because they are kept in reserve as medicines of last resort
- the relatively short period for which antibiotics are taken compared with drugs for chronic diseases
- the cost of drug development for new antibacterials can be very high where highly selective patient populations are required, as they often are where patients with resistance to existing treatments are required for clinical trials

4. Key part of the solution: more antibiotics, responsibly prescribed

The AMR challenge is broad, and any solution will need to encompass measures such as improved hygiene in hospitals. Options to strengthen the antibiotics we already have to resistance also need to be pursued to the full. However, if we are to avoid the crisis of growing resistance we will need to overcome the challenges holding back the discovery of new antibiotics, and ensure those antibiotics are prescribed only when appropriate.

a) Pipeline invigorated by new ways of working

In order to address the scientific challenges holding back the discovery of new antibiotics, basic science in antibiotics must be stimulated. Rebuilding the drug discovery infrastructure will require sustained efforts and funding by governments, academia and industry.

The regulatory environment also has to change so that new antibiotics can more easily be approved and brought to market, without reducing the level of quality, safety and efficacy. Regulators and industry need to work closely together to update the requirements to bring new classes of antibacterials via feasible, informative, and clinically relevant clinical trial programs.

⁵ Letter from IDSA to FDA Division of Dockets Management. The Infectious Diseases Society of America's Commentary on Food and Drug Administration Draft Guidance HFA-305. 17 November 2010.

We also need to incentivise companies to invest in the infection area. Incentives may take a variety of forms: both “push” rewards that offset the costs of development (e.g. tax credits, grants, liability protection); and “pull” rewards that increase the potential return on investment (e.g. advanced market commitments, rewards for completion of milestones, transferrable IP). These incentives should also seek to boost investment in new diagnostic tools.

b) Responsible prescription and use

The benefits to be gained by having a continuous pipeline of new antibiotics need to be complemented by ensuring that the medicines are prescribed appropriately and used properly. All participants in the healthcare system have a role to play in ensuring this happens:

- pharmaceutical companies who manufacture and market antibiotics
- payers who pay for those antibiotics
- physicians who undertake diagnostic tests and prescribe antibiotics
- the pharmacists who sell antibiotics
- the patients who take them

The IFPMA’s member companies adhere to the conditions of the IFPMA Code of Pharmaceutical Marketing Practices⁶, supplemented by member association and company Codes, which set standards for the ethical promotion of medicines. The IFPMA calls on other stakeholders to adopt codes of practice with regard to the marketing and prescribing of medicines. Responsible use of antibiotics may also require new financial mechanisms to allow companies to receive a return on their investment while limiting the use of the new drugs to situations of greatest need.

⁶ <http://www.ifpma.org/ethicalpromotion>

About the IFPMA:

The International Federation of Pharmaceutical Manufacturers & Associations is the global non-profit NGO representing the research-based pharmaceutical industry, including the biotech and vaccine sectors. Its members comprise 26 leading international companies and 45 national and regional industry associations covering low, middle and high income countries. The industry's R&D pipeline contains hundreds of new medicines and vaccines being developed to address global disease threats, including cancer, heart disease, HIV/AIDS and malaria. The IFPMA Clinical Trials Portal (www.ifpma.org/ClinicalTrials), the IFPMA's Ethical Promotion online resource (www.ifpma.org/EthicalPromotion/) and its Developing World Health Partnerships Directory (www.ifpma.org/HealthPartnerships) help make the industry's activities more transparent. The IFPMA supports a wide range of WHO technical activities, notably those relating to medicine efficacy, quality and safety. It also provides the secretariat for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

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