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EDITORIAL

Preventing and managing antimicrobial resistance: imperative for chest physicians

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World Health Day is celebrated every year on the 7th of April as a major advocacy event promoted by the World Health Organization (WHO) for all ministries of health worldwide. The aim is to bring a specific topic of great importance to national and international attention. This year, the selected theme is antimicrobial resistance (AMR), which is a serious threat to the care and control of all infectious diseases. AMR not only affects the three major pandemics of tuberculosis (TB), malaria and HIV, but most other infectious diseases, including widespread hospital-acquired infections, particularly after the emergence of ''superbugs'' resistant to all currently available major antibiotics [1, 2].

AMR BURDEN

The identification of AMR as a serious international health issue comes at a crucial point in the global attempt to contain its impact. Strategies have been defined by WHO in the past decade, but rarely implemented [3]. In the past few years, the appearance of multidrug-resistant organisms capable of resisting the most potent latest-generation antibiotics and chemotherapeutic agents has generated substantial apprehension among clinicians and public health experts (fig. 1).

In 2006, the first description of extensively drug-resistant (XDR)-TB, *i.e.* a disease caused by *Mycobacterium tuberculosis* strains resistant to the most important first- and second-line anti-TB drugs, prompted international attention [4, 5], particularly following the appearance and spread of XDR-TB amongst people living with HIV in South Africa, which resulted in an unprecedented high case-fatality rate [6]. XDR-TB has been reported in nearly 70 countries worldwide, and strains resistant to all first- and second-line drugs are circulating in Europe [7].

Multidrug-resistant (MDR)-TB, a disease that is caused by strains that are at least resistant to the two most potent first-line drugs, is present everywhere; the highest percentage amongst new cases has been observed in the countries of the former Soviet Union [8].

Equally concerning is the emergence of resistant *Plasmodium falciparum* malaria parasites in South-East Asia, which present a delayed response to artemisinin-based medicines [9]. Resistance to traditional antimalarials, such as chloroquine and sulfadoxine-pyrimethamine, is affecting nearly all endemic countries. It also has consequences for chemoprophylaxis recommended to international travellers.

In the case of antiretroviral drugs used to treat HIV infection, the emergence and transmission of resistant viruses results in failure to suppress HIV and the need for more expensive drug combinations [10].

Beyond the three major pandemics, extensively drug-resistant bacteria have now emerged that threaten millions of human lives, as well as the achievements of antibiotic therapy over the past 70 years. Hospital-acquired infections are today often caused by highly resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). In 2008, this organism caused 44% of the 380,000 reported hospital-acquired infections in the European Union (EU), and it may result in double the mortality produced by methicillin-sensitive *S. aureus* [11]. Even more concerning is the recent appearance among intensive care unit patients of different species of Gram-negative bacilli that are resistant to the carbapenems, the most potent β-lactam drugs currently available [12]. Lately, the world's attention has focused on the appearance of a new β-lactamase enzyme, the New Delhi metallo-β-lactamase (NDM)-1, originally described in India and Pakistan and recently traced in a dozen European countries [1, 12]. This carbapenemase, which hydrolyses virtually all penicillins, cephalosporins and carbapenem compounds, is the product of a genetic element that encodes resistance genes, which can be rapidly transferred among different species of *Enterobacteriaceae* [1, 2]. This observation follows the identification of nearly 900 β-lactamase enzymes in recent decades [2, 12].

The AMR problem is not only a clinical one: it is also a major cause of health expenditures, illustrated by the costs of treating XDR-TB or dealing with hospital-acquired infections. In the EU, for example, the attributable extra in-hospital costs caused by MRSA infections is ~€380 million annually [11]. In addition, AMR threatens health security and damages trade and economy; the recent emergence of NDM-1-related infections in India may have unjustified economic repercussions on medical ''tourism''.

AN INADEQUATE RESPONSE THUS FAR

Thus far, the response of governments and key organisations, including professional societies, to this huge challenge has often been weak, incoherent, lacking in structure and late. There are

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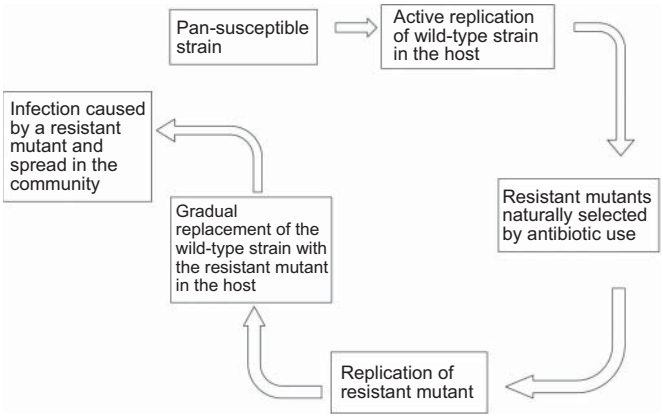

FIGURE 1. Simplified mechanism of the development of antimicrobial resistance.

very few countries that have comprehensive plans and budgets allocated to AMR containment; communities and consumers are essentially unaware and unengaged; surveillance systems in most developing countries, but also in several industrialised countries, are inadequate for the provision of accurate and timely information on the emergence of new forms of AMR; the quality of medicines is not controlled in many countries, thus exposing patients to the risk of inadequate or insufficient treatment and creating conditions for the emergence of AMR; and infection prevention and control practices are virtually absent in the clinical facilities of most developing countries, but also in the EU, as recently shown in the case of TB [13]. Importantly, in addition to all of these points, the behaviour of health professionals is likely to be a major determinant in the generation of AMR: prescription practices by physicians are sometimes irrational and inappropriate, pharmacists provide access to antibiotics favouring self-medication, and some pharmaceutical companies promote antibiotic sales indiscriminately [14–16].

These various problems, compounded by a limited arsenal of new medicines and diagnostics for infectious diseases that is failing to grow, make AMR is one the biggest clinical and public health challenges that must be urgently faced worldwide. Unless health authorities (governmental, non-state, and influential professional societies) make bold policy decisions to contain AMR, the problem will continue to grow and take us back potentially to the ''pre-antibiotic'' era. European countries will not be spared, as multidrug resistance for most pathogens has already been reported widely in this continent [12], showing once again that knowledge and science are not enough if they are not backed by clear policies about the use of antibiotics as well as joint implementation with all other necessary actions to contain AMR [17]. A move in this direction has been pursued within the EU, though various recommendations made by the European Council nearly a decade ago have not yet been satisfactorily implemented by EU Member States [18].

THE NEED FOR A BOLD RESPONSE

On the occasion of World Health Day 2011, WHO is proposing a six-point policy package for the containment and prevention of AMR (table 1) [19].

The implementation of this package relies, first and foremost, on a clear understanding of the various drivers of AMR that are common for all diseases and may vary in importance and intensity in different settings. AMR requires a response that is applied across the health system. The first step is the design of comprehensive national plans and the allocation of sufficient resources to implement all measures necessary to contain AMR. An accountability line must also be established, since AMR containment is a complex intervention that does not rely on a single programme but on various branches within the ministry of health and even beyond it. Surveillance is essential and laboratories using modern rapid technologies are key. Strict control of the quality of medicines should not be negotiable. Rational and informed drug prescription must be enforced, coupled with education of consumers and adequate regulations impeding irrational prescription or inappropriate dispensing practices and abuse of antibiotics. Infection control measures are inevitable to prevent the spread of drug-resistant organisms in clinical settings. Finally, research towards better diagnostics and new antimicrobials should be promoted by governments in harmony with the non-state sector, since new tools are one of the ways of containing ever-evolving micro-organisms.

LEARNING FROM MDR- AND XDR-TB

Sir John Crofton (fig. 2) was among the first to recognise the importance of AMR in TB treatment. His use of rational combinations of antimicrobial drugs to treat TB while preventing drug resistance has inspired the introduction of multidrug regimens in the treatment of other infectious diseases. Indeed, in the pursuit of implementation of a new AMR package, lessons can be learnt from TB control, as global strategic directions to face MDR- and XDR-TB have been clearly identified [20] and effectively implemented in a few countries, including Estonia and Latvia [8]. For example: drug-resistance surveillance has

TABLE 1 The World Health Organization's (WHO) comprehensive six-point policy package to contain and prevent antimicrobial resistance

1) Commit to a comprehensive, financed national plan with accountability and civil society engagement
2) Strengthen surveillance and laboratory capacity
3) Ensure uninterrupted access to quality essential medicine
4) Regulate and promote rational use of medicines, including those used in animal husbandry, and ensure proper patient care
5) Enhance infection prevention and control
6) Foster innovations, and the research and development of new tools

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FIGURE 2. Sir John Crofton (1910–2009) was among the first to recognise the importance of antimicrobial resistance in tuberculosis treatment. As a response, in the early 1950s, he established the principles of multidrug therapy through what became known as the ''Edinburgh Method''.

been organised globally since the 1990s [21, 22]; policies have been formulated and effectively introduced in some settings to protect key antibiotics, such as rifampicin [23], or to ban the sale of selected medicines in the non-state sector [24]; rational use of anti-TB medicines by non-programme care providers has been achieved through mechanisms such as contracting and accreditation [25]; and a research agenda has been designed and promoted jointly by all stakeholders [26].

A similar pragmatic approach is now necessary to face AMR *sensu lato*, since most measures are across the health system, and the clearer the package, the easier it is to implement. Thus, World Health Day 2011 provides a unique opportunity to gain the attention of all stakeholders on the urgent need for action. It is therefore important for the European Respiratory Society (ERS) to take a bold position *vis-à-vis* AMR. The ERS has a responsibility to inform and promote good practices. First, training of medicine consumers, patients and physicians is a must. Due to its very large audience and the impact it has on practitioners across the world, the ERS needs to be a leader in promoting education among the various constituencies. Secondly, chest physicians and ERS members need to be well aware of the measures available to confront such a challenging problem. All chest specialists must be prepared to provide adequate patient care, beginning with correct diagnosis and, where necessary in the case of infections, proper use of antibiotics [27]. This should be guided as much as possible by the drug-susceptibility pattern of the infecting pathogen. The Infectious Diseases Society of America has issued antibiotic stewardship guidelines to promote rational use [28], and international standards already exist for TB care [29, 30]; both documents need to be promoted more vigorously by the ERS and, ideally, incorporated into a new set of AMR containment guidelines for ERS members. Every practicing physician should contribute to surveillance by reporting the required information to the public health system in such a way that can introduce rapid containment measures. Chest physicians need to advocate for, and adopt, proper infection control practices in all facilities where the spread of drug-resistant organisms is likely, whether they will cause TB or hospital-acquired infections. Finally, preventing drug resistance is key to preserving the efficacy of drugs that are still in the discovery-and-development pipeline. Fluoroquinolones like moxifloxacin and gatifloxacin, which may become first-line drugs for TB in the near future, need to be used rationally in today's management of respiratory infections to preserve their effectiveness tomorrow.

In conclusion, it will only be through the wide adoption of the highest standards of care, bold health policies, and, where necessary, strict and enforced regulations that AMR can be controlled. It would be unforgivable to miss the opportunity of World Health Day 2011 to make the case. The ERS can and must address the AMR threat in such a way that, at least among chest physicians worldwide, the various measures to face the challenge are well known and, consequently, are put into practice.

STATEMENT OF INTEREST

None declared.

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