

Antibiotic resistance – The faceless threat

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1. Introduction

A potential post-antibiotic era is threatening present and future medical advances. The current world-wide increase in resistant bacteria and, simultaneously, the downward trend in the development of new antibiotics have serious implications. Resistant bacteria dramatically reduce the possibilities of treating infectious diseases effectively and multiply the risks of complications and a fatal outcome for patients with infections of the blood. Most vulnerable are those with weakened immune defences, such as cancer patients, malnourished children and people who are HIV-positive, for whom adequate therapy to prevent and treat severe infections is often necessary for their survival. In addition, antibiotic resistance jeopardises advanced medical procedures such as organ transplantations and implants of prostheses, where antibiotics are crucial for patient safety and to avoid complications.

Mortality as a result of infectious diseases represents one-fifth of global deaths [18]; respiratory infections are the leading killer, causing nearly four million deaths annually (Fig. 1). These deaths are to some extent regarded as preventable with increased access to health care and medicines. However, the global emergence and spread of bacteria that resist antibiotics is raising the question as to whether this is still the case, especially in parts of the world where second and third line antibiotics are unavailable. Considering that the escalating medical and economic consequences of antibiotic resistance are generally well known by medical professionals and political actors, the inertia surrounding the issue is difficult to explain. The vagueness of the international response and the failure to translate existing knowledge into concrete action are serious problems. This complacency on the part of global society needs urgently to be replaced by concerted action to reduce the present and future consequences of antibiotic resistance.

2. A global problem

In the late 1940s, after less than a decade of penicillin being used to treat patients with infectious diseases, unresponsive strains of the bacterium *Staphylococcus aureus*, the leading cause of hospital-acquired infections, were detected in English hospitals [3]. A striking example of biological evolution had begun: bacterial strains with natural and acquired resistance were being selected as a result of the use of antibiotics. About a decade later the first report on resistance to the second generation of peni-

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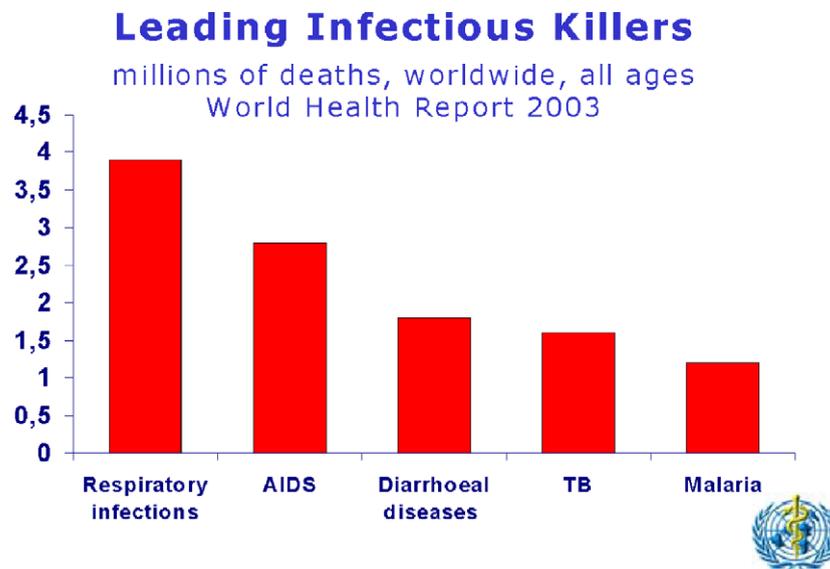


Fig. 1. Global mortality from infectious diseases. Source [18].

cillins arrived; it came from a Boston hospital, where methicillin-resistant strains of *Staphylococcus aureus* (MRSA) had been identified [1]. MRSA has become a symbol of antibiotic-resistant bacteria and is without doubt one of the best-studied pathogens. Since the 1980s the frequency of isolates of MRSA among *Staphylococcus aureus* has increased from close to zero to nearly 70% in Japan and the Republic of Korea, 30% in Belgium and around 40% in the United Kingdom and the United States. It was discovered that mechanisms of resistance could be spread horizontally between different strains and different bacteria and that, consequently, clones with multiresistant qualities could develop. The problem soon became serious for other pathogens as well. Infections caused by multiresistant bacterial strains such as *Acinetobacter* and *Stenotrophomonas* can in some cases no longer be treated with modern antibiotics and the only available treatment is an old antibiotic, colistin, earlier rejected for clinical purposes due to its toxic side effects. Globally, escalating levels of the multiresistant intestinal pathogens *Salmonella* and *Shigella* cause severe infections that are difficult to treat, especially in children. In *Shigella* strains from Indonesia, Thailand and India 80–90% resistance is seen for two or more antibiotics [8]. Resistance to remaining effective therapy, such as fluoroquinolones, is steadily increasing, and the industry pipeline for antibiotics against important intestinal pathogens is running dry.

No country on its own can isolate itself from resistant bacteria. Antibiotic resistance is a growing international problem affecting both current and future generations. Resistance that develops in one area of a country may easily spread nationwide. Globalisation, with increased migration, trade and travel, has widened the range for infectious diseases. A resistant strain of *Streptococcus pneumoniae*, first identified in Spain, was soon afterwards found in Argentina, Brazil, Chile, Taiwan, Malaysia, the USA, Mexico, The Philippines, the Republic of Korea, South Africa and Uruguay (Fig. 2) [12]. Such examples underline the fact that no single country can protect itself from the threat of resistant bacteria as pathogens are spreading across international, cultural and ethnic boundaries. Although the effects of antibiotic resistance are more documented in industrialised countries, there is a greater potential for harm in the developing world, where many of the second and third line therapies for drug-resistant infections are unavailable and unaffordable.

Transmission of international epidemic clones

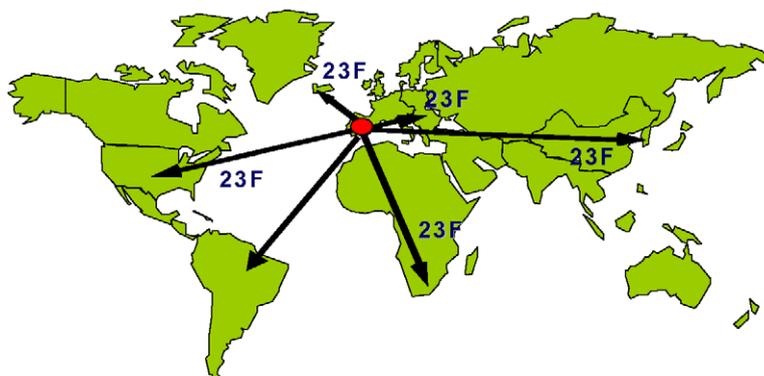


Fig. 2. Global spread of a penicillin-resistant *Pneumococcus* strain.

3. System failure

A thorough inventory of biological compounds with antibiotic activity followed the introduction of penicillin. Substances with different target mechanisms to attack bacteria were developed into new categories of antibiotics by the pharmaceutical industry and were eagerly used by medical professionals in their clinical practice. For many years, society's medical needs for antibacterial drugs were met by the pharmaceutical industry. An apparent symbiosis between the interests of the community and those of the industry prevailed. In the 1970s, innovative research to develop new antibiotics gradually waned, and the focus of research and development shifted to the fine-tuning of existing products. As resistance to antibiotics accelerated, the fragile relationship between the community and the pharmaceutical industry began to break down.

New antibiotics almost instantly faced the problem of the evolution of bacterial resistance after being put on the market and the short durability of antibacterial drugs was giving pharmaceutical companies cold feet. The industry began increasingly to weigh up its liabilities towards shareholders on the one hand and public trust and accountability to the community at large on the other. Difficulties arose as financial performance confronted the common good. The cleft between public and private interests grew wider with the development of national and international drug policies aimed at containing resistance and restricting and rationalising the use of antibiotics. Sharpened demands from regulatory bodies have increased the development cost of new medicines, and prioritising measures to secure optimal returns on investment have driven the industry into other pharmaceutical areas with bigger and safer markets. At present, the industry's ventures are shifting from therapy for acute conditions towards long-term treatment of chronic diseases. Prospective investments in antibiotics are more than ever competing with drugs for musculo-skeletal and neurological diseases with 10 or 15 times greater "net present value", a measure used by the industry to predict the potential success of products. However, the need for antibiotics is anticipated to remain consistently high. From a broad societal perspective, the industry might be expected to supply communities with good drugs at affordable prices and provide reliable information on them. Today, this is not the case.

4. The causes of resistance

Resistance is a natural biological outcome of antibiotic use. The more we use these drugs, the more we increase the speed of emergence and selection of resistant bacteria. In human use, around 80% of antibiotic consumption takes place in the community and at least half of this is considered based on incorrect indications, mostly viral infections [20]. The mechanisms behind this overuse are many and intricate. The short-term advantages of antibiotic use for patients, health care workers and drug distributors seem to outweigh concerns about future consequences (Fig. 3). The almost overwhelming complexity of factors influencing antibiotic consumption includes cultural conceptions, patient demands, diagnostic uncertainty, economic incentives, the level of training among health staff and pharmacists, and advertising to prescribers, consumers and providers from the pharmaceutical industry. In Europe, antibiotic consumption is four times higher in France than in the Netherlands [2] although the burden of disease is very similar in the two countries. Studies from some developing countries show that several antibiotics are generally prescribed at each consultation [10].

The relationship between antibiotic use and resistance is complex. Underuse, through lack of access to antibiotics, inadequate dosing and poor adherence to therapy, may play as important a role in driving resistance as overuse [19]. The use of broad-spectrum antibiotic agents as a substitute for precise diagnostics or to enhance the likelihood of therapeutic success increases the rate of selection of resistant bacteria. In addition, counterfeit and substandard drugs contribute to sub-optimal concentrations of antibiotics, failing to control bacterial populations that are considered a risk factor for developing resistance. It is estimated that over 50% of antibiotics worldwide is purchased privately, from pharmacies or in the informal sector from street vendors, without prescriptions. Half of the purchases are for one-day treatments or less, an example reflecting the magnitude of the problem [16].

Once resistant strains are selected, their spread is promoted by factors such as overcrowding and poor hygiene. One example is day care centres, which provide ample opportunities for the transmission of infectious diseases and, in particular, the emergence of resistant *Streptococcus pneumoniae*. The combination of the presence of young, susceptible children suffering from recurrent infections and the use of multiple, often broad-spectrum antibiotics makes such environments ideal for the carriage and transmission of these bacteria. In the hospital setting, some bacterial clones have been more successful than others in spreading extensively. One example of the rapid dissemination of such epidemic clones is the

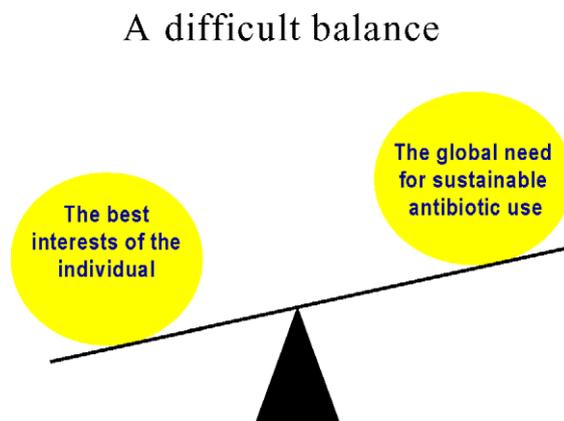


Fig. 3. Individual advantages versus future consequences. Source Cars/Nordberg.

**Blood cultures with growth of *Staphylococcus aureus*.
The share of Methicillin-resistant strains (MRSA)
England & Wales 1989-2002**

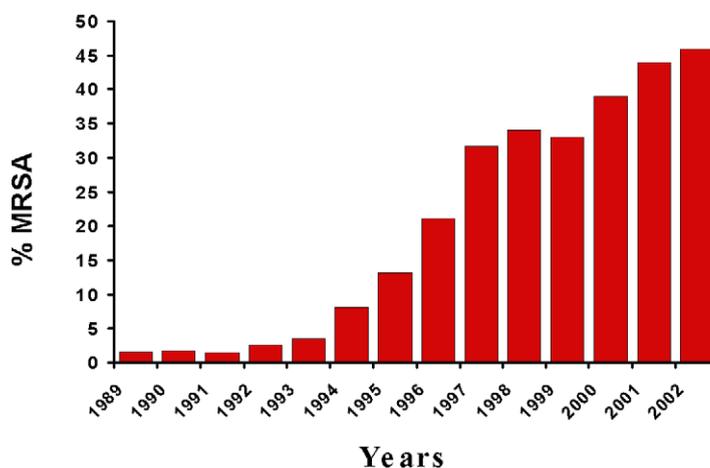


Fig. 4. The frequency of MRSA among blood cultures with *Staphylococcus aureus*.

MRSA epidemic in England and Wales where the frequency of MRSA among *Staphylococcus aureus* in blood cultures increased from less than 5% in 1994 to present levels of just below 50% (Fig. 4) [6].

5. Antibiotics for non-human use

Following their success in medicines for human beings, antibiotics have been increasingly used to treat and prevent diseases in animals, fish and plants. Besides this, sub-therapeutic doses of antibiotics have been shown to have growth-enhancing effects and have for decades been intensively used in animal-rearing practices. In Europe and North America, antibiotic use in the animal sector constitutes around half of the total consumption [17]. In 1987 more than 90% of the drugs used on animals in the United States was administered without veterinary consultation [13]. Within the European Union most antibiotics in feedstuff have been prohibited for a number of years, but in many countries large numbers of animals, irrespective of their health status, are exposed daily to sub-therapeutic concentrations of antibiotics. Some growth promoters belong to groups of antibiotics, such as glycopeptides, that are essential drugs in human medicine for the treatment of serious, potentially life-threatening infections. Emerging multiresistant bacteria from farm animals are transmitted to humans mainly through the food chain or by direct contact. The parallel emergence in animals of resistant strains, especially of *Salmonella* and *Campylobacter*, is continuously bringing in new clones that cause infections in human beings.

6. The consequences

For many years, medical professionals have defined antibiotic resistance as a major public health problem. The issue has also received increased attention from several international bodies and is now more generally recognised as a threat to global health. Still, the consequences have not been sufficiently convincing to place this issue high on the political agenda. There may be several reasons for this.

Firstly, public funding for research on antibiotic resistance has been low. In most industrialised countries the problem has been considered an annoying but inevitable side effect of antibiotic use, and the epidemiological and societal aspects of antibiotic resistance have been neglected while the research agenda has been decided by the pharmaceutical industry. This way of looking at the problem has been detrimental and has caused a situation where today we face many fundamental knowledge gaps including the health and economic consequences of antibiotic resistance, especially in the community.

Secondly, to describe the public health consequences of antibiotic resistance is difficult and challenging because the problem of resistance involves diverse pathogens, transmitted in unique ways, which cause a wide range of diseases. The consequences for the patient, such as a prolonged disease or increased mortality, which could be attributable to antibiotic resistance, are hidden within a variety of clinical syndromes and the present difficulties of measuring this resistance. Since antibiotic resistance is not of itself a disease entity, invisibility characterises the issue, making it unknown and faceless for many people outside the medical field.

Thirdly, because of the previously continuous development of new antibacterial agents it has been possible, in countries where new drugs are affordable, to change the therapy to new antibiotics when resistance levels to older ones have become “uncomfortably” high. This has not been possible in poor countries where many of the second and third line therapies for drug-resistant infections are unavailable, making the potential harm of resistance to first line antibiotics considerably greater. The limited numbers of antibiotics in these countries are becoming increasingly inadequate for treating infections, and necessary antibiotics to deal with infections caused by resistant pathogens are absent from many essential drug lists [5]. The situation is now changing in industrialised countries, too. Because of the virtually empty pipeline of new drugs, clinicians are now facing a situation where the likelihood of success from empiric antibiotic treatment is reduced and where patients are sometimes infected with bacteria resistant to all available antibiotics.

7. Mortality, costs and ecology

Through the selection pressure caused by antibiotic use, a large pool of resistance genes has been created. Today, we are starting to see the tip of the iceberg. Slowly, the health impact is emerging. In the case of bloodstream infections from MRSA, mortality is repeatedly being shown to be two to three times higher than in infections with non-resistant strains [4,14,15]. Failure of the initial antibiotic regimen due to resistant bacteria increases the risks of secondary complications and a fatal outcome, underscoring the clinical dilemma of empirical therapy and the prevailing lack of rapid diagnostic tests. Recently, a study in intensive care demonstrated significantly higher mortality among patients that received inadequate empirical therapy, compared with those given adequate therapy (42 vs. 17%) [7]. Consequently, there is a clear justification for initial broad-spectrum therapy in severe infections. This moves us into a vicious circle where increasing levels of resistance necessitate the use of broader, more potent antibiotics to secure patient survival but where using these reserve antibiotics escalates the problem as resistance develops and creates a situation where effective antibiotics are lacking [9].

Besides the medical consequences of antibiotic resistance, the problem is associated with large societal costs. The most concrete example is the cost of drugs, as new empirical treatments are needed to combat resistant pathogens. In 1997, estimates of the annual health care costs associated with the treatment of resistant infections in the US reached over USD 7 billion. In a district general hospital in the United Kingdom, the cost of containing an MRSA outbreak in 1995 was greater than £400,000. The

figures produced so far probably underestimate the total current costs of resistance as they are limited to health care costs, the majority of these being incurred by the health care system [11]. Further, none of these calculations include any estimate of costs to be incurred by future generations, which almost certainly will be larger than those being experienced currently. The economic and health costs of resistance, serious enough in the industrialised world, are often made more severe in developing countries. The economic, health and infrastructure systems of these countries, resulting in irregular supply and availability of drugs and often a dependence on unofficial sources, have led to extensive and inappropriate use of drugs, resulting in infections from strains far more resistant than those currently encountered in industrialised countries.

Antibiotic resistance is a global and intergenerational issue. The ecological consequences are basically still unknown. Use of antibacterial drugs during the last 60 years has upset the balance in which microorganisms coexisted for millions of years. Antibiotic compounds can currently be detected in liquid waste at animal feedlots and fish-breeding locations, in lakes and ground-water supplies. Ecological niches outside the health care sector are changing, as bacteria formerly susceptible to antibiotics develop resistance to them. What are the long-term health consequences and potential environmental effects of reduced microbial diversity in the global microbial flora through antibiotic use? Similarities with other environmental problems can be seen, such as global warming and the reduction of the ozone layer where the approaching impact is difficult to predict.

8. What now?

Although the full magnitude of the consequences for society is still unclear, awaiting more data before taking further action to contain the development of resistant bacteria is not an appealing option. Continued complacency is unjustifiable and even unethical in contexts where the lack of effective antibiotics is most imminent.

International collective action is essential, yet responsibility for health remains predominantly national. Consequently, there is a potentially significant disparity between the problems and potential solutions associated with antibiotic resistance and the institutions and mechanisms available to deal with them. Comprehensive recommendations on rationalising antibiotic use, from the World Health Organization, the European Union and other multilateral organisations, get lost when it comes to translating them into action plans in individual countries. The difficulties of enforcing these recommendations on a global level are evident. Presently, the links between the well-formulated strategies at the level of global society and their acceptance by national policy makers are weak. To identify these barriers so as to prevent the message from repeatedly being returned to sender is a major challenge. To reverse the downward trend in research and development of new antibiotics is another.

The prevailing perplexity of governments in the face of the need to balance commercial and community interests in this issue must be resolved. At present, public and private interests are at odds – society's continuously high needs contrasting with the diminished accountability of the pharmaceutical industry. Incentives for the development of new antibacterial drugs with novel mechanisms of action are essential. But how to get out of this impasse? To attract the industry sufficiently to return to investing in new antibiotics may require concrete measures, including reducing the costs of research and development as well as securing the longer use of products. These ideas are not new. In the area of neglected diseases an 'orphan drug system' has developed to stimulate production of necessary drugs. Extended patents have also been discussed as a way of directing industry investments. Increasing the returns on investment is

the obvious key factor in promoting drug development within the existing framework; but can alternative options be found outside the existing structures? Using a public health approach to fill preventive and curative gaps in respect of diseases where the industry has lost interest would be an attractive path to explore.

How do we prevent the same pattern from continuously repeating itself: one in which medical experts meet and compare escalating figures of resistant bacteria from different parts of the world, discuss worst-case scenarios but fail to reach out successfully either to politicians or to society as a whole? Obviously, current efforts are not enough to make the problem of antibiotic resistance a national political priority in any country; therefore, other ways must be explored. Politicians are predictable. They will certainly remain inactive as long as political passivity outweighs the will to initiate action on this issue. Building strong public awareness is vital if policy makers are to be stirred from their present dormant state into taking action.

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