



# Threats of antibiotic resistance: an obliged reappraisal

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## Abstract

We are living in a society of fear, where the objectivity in estimating risks is distorted by the media and the interested parties. During more than half of a century, the feeling of antibiotic resistance as an apocalyptic phenomenon able to push our society to the high mortality rates caused by infectious diseases in the dark pre-antibiotic ages has been steadily rising. However, at the current status of modern medicine, at least in the high-medium income countries, mortality by lack of efficacy of the antibiotic armamentarium in the therapy of infections is a problem, but not a catastrophe. The threat of antibiotic resistance has many other aspects than failures of therapy in the individual patient. Among them, the increase in the frequency of severe and potentially lethal infections, as bacteremia, the population biology alterations of the healthy microbiota, the global acceleration of bacterial evolution by selecting natural genetic tools mediating microbial interactions, and, most importantly, by modifying the equilibrium and composition of environmental microbial communities. All these threats have huge implications for human health as members of a Biosphere entirely rooted in a menaced microbiosphere.

**Keywords** Antibiotic resistance · Society of fear · One Health · Global Health · Risk evaluation

## Introduction

Along the last decades, research on bacterial antibiotic resistance has been steadily growing and now constitutes one of the fields with higher expansion in the frame of microbiological sciences. The main driver pushing research in that direction is the assumption of the urgency of solving a potentially catastrophic problem for human health. A curious epistemological problem is that scientific efforts are frequently directed to investigate and solve problems that have not been sufficiently scientifically dimensioned. Once science provide initial results, the door for new questions is opened, new knowledge opportunities are offered, and the unstoppable temptation of following the trend creates a powerful research stream that orientates the future of our endeavors. The case of antibiotic resistance fits with this

view. In this opinionated updated review, recapitulating a previous dissertation (Baquero 2016), we are examining the risks associated with antibiotic resistance in a critical way and trying to evaluate the dimension of the burden of resistance as a homeostatic reaction of the microbial world to the anthropogenic aggression resulting from the industrial production and medical (human, veterinary, agricultural medicine) use of antibiotics, which can affect the health of humanity.

## From ecstasy to fear

Few events in the history of microbiology have had such a wide impact in collective appreciation of the society as the discovery and extended use of antibiotics in the successful treatment of infectious diseases. Bacterial diseases were the highest cause of human mortality before the 40 s, probably including complications of viral diseases, as in the 1918's influenza pandemic (Klugman et al. 2009), and that following the “tragedy of tuberculosis” killing so many young and romantic people along the nineteenth century. Suddenly, antibiotics, the “miracle drugs” (Moore 1999), sharply reduced morbidity and mortality and certainly contributed (by reducing

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complications) to the progress of advanced surgery, from war surgery in the 1940s–1950s to organ transplantation, anti-cancer immunodepressive therapy, and in general intensive care facilities. All of this was perceived by the society at large as a spectacular achievement of microbiological and chemical research.

The discovery of antibiotic resistance appeared as a disturbing storm-cloud in this clear sky. However, the 1940–1980 period offered a continuous wealth of new antibiotics, with a crucial participation of Spain, even in later periods (Mochales 1994). Interestingly, such a continuous progress in discovery was mostly fostered by the necessity of “fighting new antibiotic resistances,” following a kind of Red Queen dynamics, where the new discoveries compensated for the emergence of new resistances in bacterial pathogens. There is no doubt that the marketing activities of pharma companies contributed to a “replacement dynamics” to outcompete “older” drugs that could become inactive because of resistance. This strategy has strongly influenced the notion of “the unbearable threat of resistance,” and in fact many international surveys on antibiotic resistance in the world were financed by pharma companies, mostly in order to demonstrate the “superiority” of their new drugs over the old ones, but also providing an extremely useful body of knowledge on the epidemiology and ecology of antibiotic resistance. In parallel, the antibiotic “replacement strategy” was also boosted by launching less-toxic drugs, sometimes overstating few and transient, or controllable, toxic events of the “older” ones.

From the mid-1980s of the past century, the rhythm of discovery of novel antibiotics was gradually slowing, in part due to pharma investments being directed mostly to other drugs either much more expensive (as anticancer drugs) or prescribed for life (as anti-hypertensive, anti-cholesterolemic). Note that implicitly this indicates that most infections could be successfully treated in practice with the current antibiotic armamentarium, and the demand for new miracle anti-infectives had been weakened. However, the fear of a catastrophic return to all the horrors of a pre-antibiotic era has not only been maintained but has significantly increased, and all national and international organizations, including the WHO, situate antibiotic resistance among the top risks for public health (World Health Organization 2019); ad-hoc public–private research organizations have been created by the European Union, as ENABLE, within the IMI initiative, to stimulate research for new anti-infectives active on multi-resistant (“bad-bugs”) pathogens (Kostyanov et al. 2016).

## Antibiotic resistance in the society of fear

In modern Western countries, in our developed world, a world of wonders, there is a dominant “culture of fear” which takes the form of the Alexis de Tocqueville (1805–1859) paradox: “plus tout va bien, plus on a peur” or “the better things are, the more fear we have.” Frank Furedi argues that most societal perceptions of risk, controversies over health, the environment, and technology have little to do with science or empirical evidence but are essentially shaped by cultural assumptions about human vulnerability, a kind of “kidulthood” of our society (Furedi 2007). Certainly, such a “kidulthood” favors the general manipulation of the society, either promising unfeasible “miracle” solutions or unnecessarily scaring our hopes of progress. The “threat” of antibiotic resistance is inserted in this global feeling of fear.

Of course, fear produces unwanted secondary effects. First, fear, as a cultural construct, tends to fix as proved the worse expectations. Second, it establishes a false equivalence, a fallacy, identifying situations to which we are scared of and those that are really dangerous. Third, the maintenance of a continuous fear without obvious solutions discredits scientific efforts; we have been speaking for too long (decades) about the urgent need to solve the problem of antibiotic resistance. Fourth, as a thought derived from the former, fear might convince us that “we are at the mercy of nature,” a deleterious thought for the societal appreciation of science. Fifth, and as suggested before, fear might be promoted, sustained, and exploited by interested parties, in the words (the parenthesis is mine) of one of my closest friends, “antibiotic resistance was a great career (and business) opportunity” (Levin 2017).

Fear has also positive aspects. First, it fosters the rapid analysis and counteractive responses of humans to confront microbial menaces, as occurred with AIDS, or currently with COVID-19 pandemics, but certainly it also contributed to open the golden age of antibiotic discovery. As early as in 1954, the British physician Lindsey W. Batten (1889–1981) declared: “We may come to the end of antibiotics. We may run clean out of effective ammunition, and then how the bacteria and moulds will lord it.” Second, the known interaction between emotion and creativity (Averill 2000) stimulates motivation and innovation in science. Third, fear improves social and organizational cooperation, and certainly fear to antibiotic resistance has significantly contributed to the interaction of scientists all around the world. Fourth, fear raises our awareness not to stop progress in any sense for the profit of a single humanity.

## The apocalyptic landscape and the problem of public communication

Fear in antibiotic resistance has been amplified by the news in the media, worldwide known as passionate apocalyptic lovers. An indicative random selection of press titles is: “Antibiotic apocalypse: doctors sound alarm over drug resistance (The Guardian), “Antibiotic apocalypse warning” (BBC News Health), “Antibiotic resistance could be much worse than EBOLA” (Yorkshire Post). But not only the media, also serious institutions and journals: “Return to a pre-antibiotic era?” (The World Academy of Sciences), “A return to the pre-antimicrobial era? (*Science*). “War against superbugs” is a metaphor also forming part of this catastrophe discourse, which has been analyzed both in its rhetorical form, and in the implicit political, and professional function (Nerlich 2009). Metaphors used by the media are easily understood, but the resulting understanding can be deeply biased (Brossard 2013). Scientific communication is frequently obliged to a distortive simplification (Ortín and Uranga 2021), which in alliance with our innate human attraction for tragedy produce apocalyptic mental “monsters” (Francisco de Goya *dixit*).

## The biased contribution of susceptibility testing, etiological attribution, and metagenomics

A main problem for the objective estimation of the consequences of a biological phenomenon is the accurateness of the methods measuring the biological parameters and criteria used to define the qualities of the system. Clearly, the burden of antibiotic resistance is estimated according to the definition of “resistance”. In vitro susceptibility testing provides “minimal inhibitory concentrations” (MICs), that, in practice, have been frequently taken as the single parameter for classifying a bacterial isolate into the “resistant” category. If the MIC is over a critical breakpoint, the organism is resistant. Therefore, the lower breakpoint, the higher the proportion of resistant strains in the species, and the feeling of “untreatable” bug. Of course, the advantage of establishing low breakpoints is to detect “first mutational steps” in the evolution of resistance, eventually preventing clinical resistance (Baquero 2001). But tagging such strains as resistant ones might have perverse consequences in the treatment of infections. In most cases infections caused by low-level resistant bacteria can be successfully treated with the antibiotic-in-case, and that obliged the international susceptibility testing agencies to “raise the breakpoint” to allow the use of the drug; typically, that has occurred for penicillins in *Streptococcus pneumoniae* with PBP mutations, or for carbapenems in *Escherichia coli* harboring carbapenemases.

A second problem was the common confusion (mostly for clinicians) between acquired resistance and natural antibiotic resistance. Many opportunistic non-commensal pathogens are intrinsically resistant to antibiotics, but, when they were listed among harmful human organisms, the feeling was that “antibiotic resistance” was widespread. In fact, in most cases these organisms have a low pathogenicity for patients but can be found in human mucosa, particularly in intensive care units where environmental members of the orders Pseudomonadales, Flavobacteriales, or Enterobacterales are present in water systems, not only from built environments (as sinks), but also medical equipment, as ventilators. The detection of these organisms in clinical samples is frequently a poor etiological value, but the alerted clinician might consider these (frequently intrinsically resistant) organisms at the time of therapy, increasing the awareness of “antibiotic resistance.”

Finally, the recent boom of microbial metagenomics has contributed to overstate the perception of a widespread antibiotic resistance, listing a number of resistance genes (genes whose loss increase susceptibility) probably approaching 10,000 in currently available curated databases. The ensemble of resistance genes in a microbiome is the “resistome,” accurately detectable by targeted capture metagenomics (Lanza et al. 2018). But resistance genes are simply everywhere and have been there for thousands of millions of years. The equivocal concept is “a bacterial organism carrying a resistance gene is a resistant organism.” The question is not “what is a resistance gene?” but “what is a resistance gene imposing a risk for therapy and public health?” (Martínez et al. 2015).

## Back to the pre-antibiotic era?

This statement is simply an over exaggeration. History never comes back again, and we will never be back in the dark ages of deadly infections. Not only antibiotics are responsible for the decline in infectious diseases. In fact, infectious diseases started declining much before the discovery of antimicrobial agents, because of the progress of hygiene-ecology and social welfare (McKeown 2016). On the other hand, except in rare cases of organisms producing deadly poisoning toxins, bacteria “start a pathogenic process” that is generally amplified by the reactive host pathophysiology, as in the case of potentially deadly processes (septic shock) following the immunological recognition of molecules present in bacterial envelopes, as lipopolysaccharides or teichoic acids, without any microbial active intervention. Progresses in medicine are able to control in our days most of these host

processes. In fact, many severe infectious diseases can now be cured without the need of antibiotics. A case-in-point is therapy of (once deadly) infectious diseases, as was cholera, where the lethality has almost disappeared just because of the introduction of oral rehydration therapy, without further need of antibiotics (Guerrant et al. 2003). At hospital level, progresses in the procedures of intensive care units care are able to compensate for most of the complications caused by either susceptible or resistant bacteria involved in severe infections. We will never be back in the pre-antibiotic era.

### Direct mortality attributed to antibiotic resistance

Direct mortality attributed to antibiotic resistance accounts for the cases of infected patients who could have been prevented from dying in the absence of antibiotic resistance in the causative organism. Human mortality directly attributed to antibiotic resistance remains based on a few “mantra” figures that are widely used in the introduction of most reports (and particularly grant proposals) concerning antibiotic resistance. “At least...” 25,000–33,000 deaths/year in Europe (European Medicines Agency Joint Report 2012, Boolchandani et al 2019; Cassini et al. 2019) or 23,000 deaths per year in the USA are due to antibiotic resistance (Centers for Diseases Control US 2019). In the world, it has been stated that antimicrobial resistance accounts for over seven million deaths/year, and it will probably reach ten million deaths by 2050 (O’Neill 2016; Hofer 2019). The accurateness of these alarmist estimations has been recently challenged, mostly on the bases of the absence of empirical data (Baquero 2016; Abat et al. 2017).

Indeed, it is extremely difficult to obtain the real figures. The key-difficulty is to discern between “deaths in infected patients *with* antibiotic-resistant bacteria” and “deaths in patients where the infection *is caused by* antibiotic-resistant bacteria and death results from resistance to standard therapy.” Of course, mortality is highly dependent on the age and the underlying diseases, so that critical patients dying from any cause, but carrying multi-drug resistant bacteria, and being under preventive or therapeutic antibiotic exposure might be falsely categorized as “deaths because of resistance.” The way to obtain reliable figures requires precise case–control studies, comparison of the mortality of patients of the same age, same underlying conditions, in the same setting, with the same infection caused by the same pathogen (either antibiotic-resistant or not), and treated in an identical way. Useful approximations to this ideal approach have been attempted in the Netherlands, for instance, matching (1:1) cohorts of patients with the same age, length of stay in the hospital

at infection onset with gram-negative infections attributed or not to multi-drug antibiotic-resistant organisms; 30-day mortality after the infection onset was almost identical (Rottier et al. 2020). A few years ago, the European Antimicrobial Resistance Surveillance Network (in the European Center for Disease Control) reported an extremely high frequency of bacteremic *Klebsiella pneumoniae* multi-resistant strains, including carbapenems, in Greece. Despite the alarm for the increase in mortality, no difference was found between patients attended in intensive care units with carbapenem susceptible or resistant strains (Vardakas et al. 2015). In addition, the burden of mortality attributable to antibiotic resistance should be weighted in comparison with other causes of mortality, to evaluate the “apocalyptic scenario.” Even considering as the right ones the data mentioned at the beginning of this section, mortality associated with antibiotic resistance was only able to account for 2–4% of the cardiovascular mortality in the European Union and the USA.

Of course, mortality by infectious diseases is much higher in low-income countries, where nutritional deficiency, lack of proper sanitation, and poor medical care, with low access to intensive care units, remind us of the social pre-antibiotic landscape in Europe two centuries ago. The current benefit of antibiotics in reducing overall mortality in these countries that until very recently were in the “pre-antibiotic era” seems clear (Abat et al. 2018). Under these circumstances, the mortality burden attributable not only to antibiotic resistance to accessible, cheap antibiotics but also to resistance to third generation cephalosporins and carbapenems could be much higher than in the USA or the EU (Huynh et al. 2015; Founou et al. 2017).

### Indirect mortality mediated by antibiotic resistance

Antibiotics alter the optimal (evolutionarily selected) proportions of microorganisms in the healthy human microbiota. For co-evolutionary reasons, the most abundant commensal species are non- or very poorly pathogenic towards their host, and antibiotic resistance in these species might in fact protect from the dangerous overgrowth of more pathogenic ones, increasing colonization resistance (microbiota resilience). In fact, the most prominent organisms causing deadly bacteremic infections, as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecium*, and *Enterococcus faecalis*, account for less than 1% of the intestinal organisms. Intensive exposure to antibiotics (for preventive purposes or therapy) is known to increase this relative proportion when these organisms are resistant to antibiotics, and this increase might result in undesirable consequences, even though the acquisition of antibiotic resistance does not increase (in fact might reduce) virulence.

Bacteremia is generally the result of bacterial translocation, the transit from the gut lumen or mucosa to extraintestinal sites, such as the mesenteric-lymph-node complex, liver, spleen, and bloodstream internal tissues (Berg 1995). Translocation is mostly a stochastic effect, so that the possibility of invasion is proportional to the absolute number of viable organisms (Taur et al. 2012). As the translocation rate of susceptible populations remains constant, but increases for resistant ones, the overall frequency of bloodstream infections increases when antibiotic-resistant strains are selected, and as a consequence, hospitalized patients have become progressively more severely ill over the last years (Ammerlaan et al. 2013), as was the case for the community-hospital spreading multi-resistant STc131 *E. coli* clone; however, it should be noted that mortality is also age-related (Rodriguez et al. 2021) or the presence of particular resistant *Enterococcus* clones (Bonten et al. 1998; Tedim et al. 2015).

Note that, particularly in elderly people, bacteremia often originates in urinary tract infections; also, in this case, the increased abundance of multi-resistant populations in the intestine facilitates transmission to the urinary tract. An interesting point is if the individual history of antibiotics uptake along life contributes to the cumulative density of antibiotic-resistant bacteria in the microbiota (Baquero 2007); in that case the individual attitude reducing antibiotic exposure might be a preventive of mortality, as occurs with tobacco, high salt, or hypercholesterolemic food for cardiovascular diseases.

More bacteremic episodes certainly mean a higher mortality rate; however, as was commented before, the risk of dying, at least in high-income countries, is similar for multi-resistant and susceptible *E. coli* populations (de Lastours et al. 2020). Probably a direct influence of antibiotic resistance in mortality is likely to occur in low-income countries with limited access to advanced medicine (Becker et al. 2009).

### Antibiotic resistance altering human-microbiota interactions

Ecological alterations of the microbiota (dysbiosis), occasionally with clinically intestinal complications, ranging from mild to severe, were described from the early stages in the use of antibiotics (Haenel 1961). The most important was the selection of harmful resistant organisms. Classical examples are enterococcal bacteremia during therapy with third-generation cephalosporins, or more recently the potentially lethal pseudomembranous colitis resulting from the selection of *Clostridium difficile* (Smits et al. 2016) frequently associated with the use of broad-spectrum antibiotics, particularly those influencing the predominant anaerobic populations.

Alterations of the microbiota are generally restored by surviving minorities and by the organisms of the surrounding human environment. In hospital, nursing homes, or in conditions of limited sanitation in low-income countries, particularly involving water environments (Baquero et al. 2008), restoration might involve the acquisition of antibiotic-resistant populations, substituting (without the need of antibiotic exposure) the old susceptible ones (Schwartz et al. 2020). The final effect is that antibiotic-resistant bacteria are increasingly integrated as “normal members of the microbiota,” and the long-term consequences of such replacements and the creation of a novel microbiota architecture remain unknown. This might be harmful, influencing inflammatory bowel diseases, allergies, asthma, obesity, diabetes, cardiovascular disease, neurobehavioral disorders, and eventually involving alterations in host immunity (Zhang and Chen 2019). Note that resistant populations (by either intrinsic or acquired antibiotic resistance) are poorly affected (resilient) by new antibiotic exposure, facilitating long-term colonization and host adaptation. The invasion of food animals by antibiotic-resistant bacteria and the increasing possibilities of human-animal microbiome coalescence (merging) might contribute to the evolution towards abnormal microbiomes with unpredictable consequences (Baquero et al. 2019).

### Antibiotic resistance modifying bacterial population biology and evolutionary biology

Antibiotics exert multi-level selection, that is, they independently select for particular genes, insertion sequences, integrons, transposons, plasmids, integrative-conjugative elements, and also for particular clones and clonal complexes within species, species, genus, and complex microbial communities (Baquero et al. 2013). The effect results in alterations in the relative abundance and diversity of these evolutionary entities. Considering that in a world without anthropogenic antibiotics the microbial (multilevel) entities tend to keep their historical co-evolutionary selected compositions inside their hosts, the disturbance of such equilibrium by antimicrobial agents might result in inadvertent risks. Of course, antibiotic selection of antibiotic-resistant bacteria implies the selection not only of the resistance genes, but of all the mobile genetic elements to which they are associated. In fact, the release in the environment of antibiotics, among other anthropogenic contaminants, increases the local density of harmful antibiotic resistance genes and also mobile genetic elements (Knapp et al. 2010; Wright et al. 2008; Gillings 2014). Increased density of mobile genetic elements implies an acceleration of the bacterial evolutionary rate (Souque et al. 2021). In other words, antibiotic resistance might significantly increase the density of tools involved in microbial genetic interactions, once more with unpredictable

consequences in shaping bacterial evolutionary trajectories that might influence human and animal health (Baquero et al. 2021a, 2021b).

## Antibiotic resistance and the planet microbiosphere

Human health is fully dependent on the health of the biological systems determining the main features of our environment. Antibiotics have historically been and are still constantly released into the environment; it has been estimated that the global annual production of antibiotics reaches 100–200 thousand tons, and one billion tons have been produced since 1940 (Serwecińska 2020), and many of them remain biologically active during extended periods of time. Considering that antibiotics can select antibiotic populations with relative decreases in susceptibility at concentrations of nanograms/ml, and/or interfere at such concentrations with the semiotic network of natural antibiotics, acting as interbacterial signaling agents (Linares et al. 2006), we can expect an effect on the natural microbiosphere. Possible ecological functional disturbances caused by the release of the antibiotics in the environment might include critical aspects for life, as oxygen production, nitrogen transformation, methanogenesis, or sulfate reduction. For instance, Cyanobacteria contribute with more than 25% of oxygen production and carbon dioxide fixation in Earth. Cyanobacteria are susceptible to most antibiotics and contain mobile genetic elements that might facilitate capture of antibiotic resistance, but how this might influence fitness and physiology of these organisms is unknown (Dias et al. 2019; Hernando-Amado et al. 2019). There is also an effect of environmental antibiotics on the bacterial components of the rhizosphere, essential for nitrogen fixation and plant health, on the biology of Protistan and protistan consumers in the soil, as well as the microbes-nematode interactions. It is known that low antibiotic exposure influences plant biology affecting plant germination, biomass allocation, and diversity (Minden et al. 2017). We can also expect harmful effects on insect vital endosymbionts (Koga et al. 2007), and probably microbe-originated cellular organelles mitochondria and chloroplasts could evolve to antibiotic resistance (Perasso 1974; Wang et al. 2015). A possible risk is the substitution of part of the key antibiotic-susceptible natural species by other intrinsically antibiotic-resistant organisms or selected variants, influencing primary producers, and potentially biogeochemical cycles in the Earth's surface systems. This certainly will approach an apocalyptic scenario for human health, not the one that we discussed in the first parts of this review.

## Final coda

Massive antibiotic industrial production, its use in humans, animals, and agriculture, and the resulting environmental pollution certainly influences the emergence and spread of antibiotic resistance, decreasing the effectiveness of chemotherapy, and constitutes a problem in public health that should be addressed by applying evolutionary principles (Andersson et al. 2020). However, it is highly improbable that antibiotic resistance could produce an apocalyptic landscape because of failing to control infections (Servitje 2019). In this review we suggest that other effects of antibiotics on the microbiotas and environmental microbiosphere can produce at long-term higher risks, deserving public awareness, by creating social norms to expand the protection of the individual health to the protection of one health and global health (Roca et al. 2015; Berendonk et al. 2015; Hernando-Amado et al. 2020). The threat of the spread of antibiotic-resistant organisms adverts us, once more, that the health of humans and the health of Earth are closely intertwined.

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