GACETA MÉDICA DE MÉXICO

Resistance to antibiotic: A serious global problem

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Abstract

An important piece of improvement in public health standards, medicine achievements, and development is based on the impressive effect of vaccines and antibiotics on infectious diseases. However, the last three or so decades have witnessed how an unsound use of antibiotics has resulted in antibiotic multi-resistant clones in hospitals and community environments. It also has been said that antibiotic research and the development pipeline has crashed, leading to no new antibiotic molecules to be tested at a time of treatment failure, manifest with unacceptable frequency as an increased economic and human cost in lives. Like the name of the series, antibiotic resistance is a global problem with clear evolutionary roots and a broad local impact. In that sense, this review explores the interaction among resistant mechanisms, underlying motives of expansion and actual trends in antibiotic resistance upgrade to limit the problem. Conceivably, only the involvement of players at every level, and coordinated actions accordingly constitute the necessary elements for effectively intervention. (Gac Med Mex. 2015;151:632-9)
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KEY WORDS: *Public health. Resistance. Antibiotic. Disease.*

Introduction

The development of resistance to antibiotics is a natural and unavoidable process. This is because microorganisms are living beings that throughout their evolution have developed strategies that allow for them to explore new niches and survive. Antibiotics are not a human invention; they have been present for hundreds of million years before humans started populating the planet[1]. For centuries, microorganisms have been faced with different compounds, out of which now we derive our current antibiotics and, consequently, can currently have resistance from the start[2]. The discovery of antibiotics is one of the wonderful results of the scientific development summarized in the works by Louis Pasteur and Robert Koch, by establishing the microbial theory of disease the former, and the postulates on causality the latter.

In a historical context, knowledge of the association between disease and infections led initially to the discovery and production of vaccines, currently the most extraordinary development of science considering its direct utility in mankind. Eventually, Ehrlich set the bases of chemotherapy and enabled the recognition of the potential of antibiotics in the cure and prevention of sequels due to transmittable diseases[3]. However, since their earliest moments it became clear that the development of resistance would represent the end of their usefulness. Looking ahead of his time, Alexander

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Fleming emphasized that indiscriminate use of penicillin would lead to a quick development of resistance. Soon, the production of penicillinase was identified, an enzyme of which more than 100 types have been described and that inactivates penicillin, by the formerly universally sensitive staphilococci[4,5]. Thus started a race that was lost since the start, where the volume of industrial production of molecules with antibiotic effect has no parallel, as does the dissemination of the determinants of resistance among bacteria, with these determinants exceeding, sooner or later, the production of new antibiotic products.

Over almost seven decades, mankind has participated of the benefit of antibiotics. Today, the vast majority of infectious processes are resolved with short courses of treatment, but everytime is more common finding in our practice and in scientific reports examples of a broad resistance to antibiotics. In the world, there are multiple reports on increasing resistance reaching alarming levels[6-9]. Although there are regional variations, the trend is clear for any country with the capability to analyze antimicrobial sensitivity in bacterial isolates. The situation is so serious, that the World Health Organization (WHO) has qualified it as "worldwide emergency" and has urged its country members to take measures to mitigate its explosive development and to encourage the serch and design of new antimicrobial molecules. In different economic analysis and global politics forums, the situation is described as potentially catastrophic.

In its plan of action against resistance, the WHO outlines activities at different levels, including: generating and sharing epidemiological information; implementation of infection prevention measures; optimizing the use of antibiotics through the development of national and global policies on the consumption and production of antibiotics; restrictions on the consumption of antibiotics as growth promoting agents in cattle, and rational use for human consumption, in addition to simuli for study and development in the area[10]. Evidently, drastic measures have to be implemented because if we fail to do so, soon we will be living in the "post-antibiotics era".

Current trends

In 1945, Alexander Fleming warned in an interview with the New York Times that excessive use of penicillin would cause the selection of resistant bacteria. By 1946, only a few years after penicillin had become available for open medical use, 14% of *S. aureus* strains were resistant, in 1950, resistance had increased to 59%, and now, in 2014, it is 99%[11,12].

Since the industrial development of penicillin, the pharmaceutical industry grew in parallel to its production and that of other antibiotics. Penicillinase-resistant antibiotics were developed, as well as other useful for mycobacteria *(M. tuberculosis),* for Gram-negative (G-), for fungi, and so on up to the novel antiretrovirals.

Table 1 shows the different groups of antibiotics according to their structure and a summary on the global situation of resistance. Most of them are compounds resulting from research on naturally-obtained molecules. Penicillins are derived from fungi, aminoglycosides from actinomycetes and polypeptides from bacteria, with only a few being biosynthetic (phenoxymethylpenicillin), semi-synthetic (ampicillins) or synthetic (chloramphenicol). According to their structure and mode of action, antibiotics can have activity against several bacterial species (wide spectrum) or limited to one or a few species (narrow spectrum). Similarly, according to their structure, their action can be bactericidal, causing cell lysis as a result of their direct action, or can be bacteriostatic, stopping bacterial multiplication and thus facilitating for the human body's defense mechanisms to eradicate the infection[13].

From 1945 to present days, 7 decades have barely elapsed, and in this brief period, multiple molecules with antibiotic activity have been developed. Now we know that, sooner or later, each new development implicitly entails the appearance of resistance, as well as the development of clones, some more successful than others, that when disseminated evolve locally, as demonstrated by the acquisition of virulence factors by methicillin-resistant *Staphylococcus aureus* (MRSA) clones associated with community-acquired infection[14], or the dispersion of CTX-M enzymes across Latin America[15].

Mechanisms of resistance

From the history of the discovery of penicillin described by Fleming we can infer that as he returned from a vacation period, when checking over his Petri dishes with staphilococci cultures, he found areas where bacterial colonies had dissappeared; these, same as previous cultures, were not resistant to what Fleming discovered to be the product of a fungus, which he named penicillin owing to its origin. Resistance appears when non-lethal doses induce a rise in the mutation rates and/or genetic material horizontal transference[16]. Hence, the selection of the mutant results from a physiological mechanism that is employed in a different environment or organism conferring it higher probabilities of survival. With regard to the origin

Table 1. Main classes, targets and time to resistance report

Target/Structural class	Antibiotic	Resistance	Years to resistance identification
Cell wall			
Beta-lactams	Penicillin Cephalosporin Carbapenems Monobactams	Beta-lactamases, PBP mutants	3
Membrane disruptors			
Polypeptides	Polymyxin Vancomycin	Substitution by D-Ala-D-Lac or D-Ala-D-Ser	36
Protein synthesis			
Aminoglycosides	Streptomycin Kanamycin	Antibiotic modification	16 12
Rifamycin	Rifampicin		
Nitroimidazole	Metronidazole		
Oxazolidinone	Linezolid	Unknown	2
Tetracycline	Tetracycline	Efflux	5
Chloramphenicol	Chloramphenicol		16
Macrolides	Erythromycin	rRNA methylation/ efflux pumps	36
Folic acid-synthesis competitive inhibitors			
Sulfonamides	Co-trimoxazole	Others	
DNA synthesis			
Fluoroquinolones		Mutations in DNA gyrase	

and dispersion of resistance-determining genes, we can assume that, based on the exposure to different antibiotics, there are at least three environments. In an undisturbed soil or in a cave not visited for the last 4 million years there is the highest diversity of codifying-genes that might act as mechanisms of resistance (resistome) and the lowest number of resistant microorganisms[4]. In the opposite extreme, there are environments where a high density of microorganism, resistance genes and selective pressure by antibiotics converge, as in the intestine of animals bred for consumption. Interestingly, in spite of the large amounts of antibiotics employed, this doesn't appear to be proportional to the number of strains that more problems cause, although it is certain that the reserve of resistance genes is significant both in residual water[17,18] and animal manure fertilized soil[19] and even in the human microbiota[20]. Some of the results with high rates of resistance are shown in figure 1. Thus, it is evident that resistance precedes our pharmacological developments.

The consequences

Although the reduction in mortality due to the use antibiotics occurred simultaneously with improvements in sanitary conditions in the West, it is undeniable that the use of antibiotics had an impact on the reduction of mortality due to infectious diseases and enabled countless medical and surgical advances[11,21]. It is not difficult imagining what would we have to face should we not have useful antibiotics at present. The smallest lacerations would be life-threatening in case of infection. With an older population, critically ill patients, immunosuppressed patients, among others, would be a prey for infections. Current medicine requires complete control of the risk for infection to make its impressing achievements effective; transplantations, different invasive procedures, placement of implants and even the simplest surgery would be of much higher risk and even unconceivable without useful antibiotics. The effects of antimicrobial resistance are measurable as an increase in
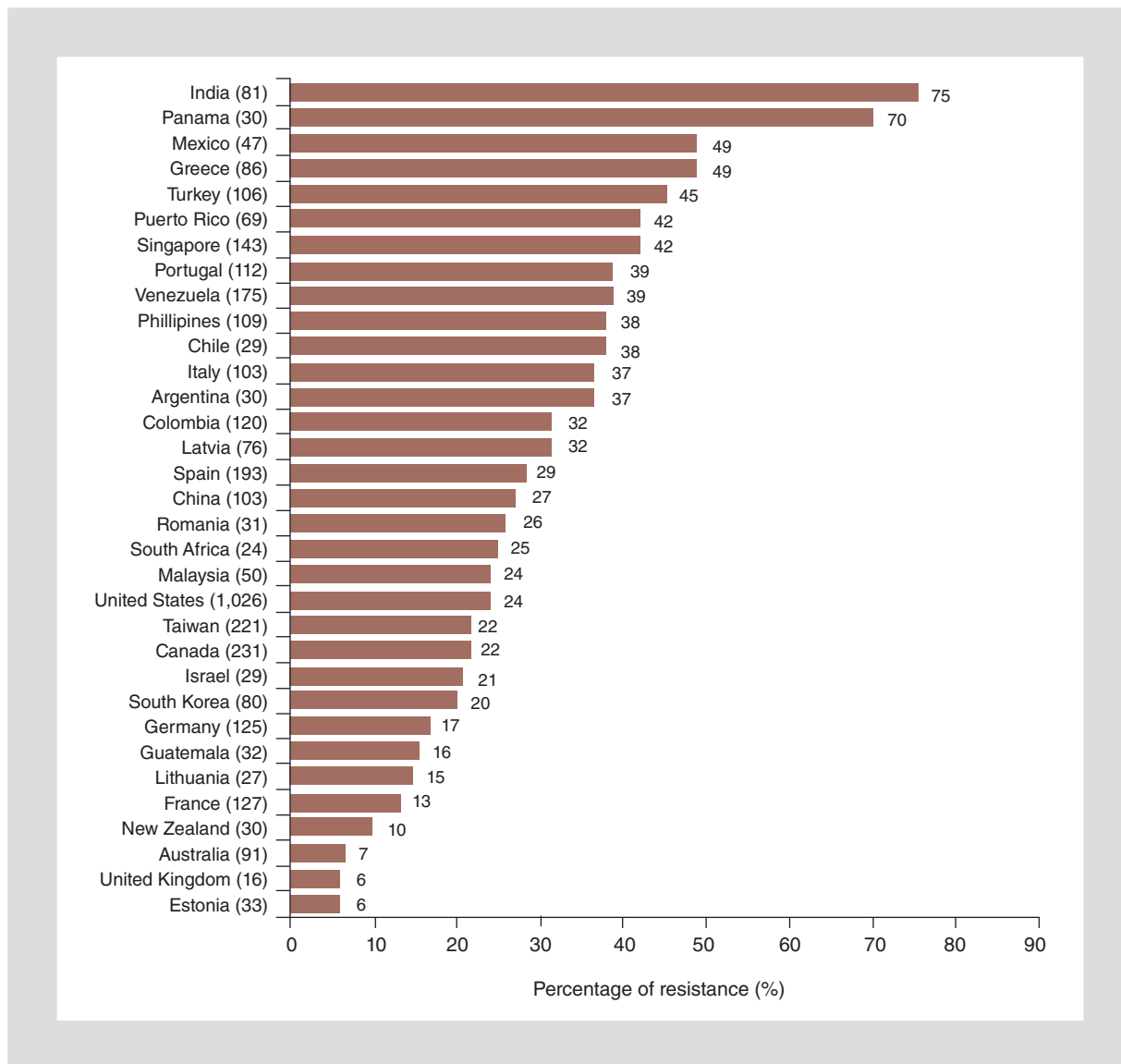
Figure 1. *Percentage of resistance by country in urinary tract infections* (taken from Bouchillon, et al., 2012).

treatment costs, higher hospital length of stay and increased mortality and morbidity due to formerly non-pathogenic microorganisms[22,23], whereas in the closest clinical setting, antimicrobial resistance contributes to treatment failure, complicates the implementation of guidelines, limits empirical treatment and leads to the use of less effective antibiotics or with poorly studied side-effects[24,25]. In more than one sense, the problem of resistance genes dispersion is global, since, in theory, products and persons carrying strains with resistance determinants, including medical personnel, usually travel across countries. In the USA, up to 37 thousand people ate calculated to die as a consequence of infections by multi-resistant bacteria[26]. It is not strange that in nations with emerging economies such as the BRICs

(Brazil, Russia, India and China), which are the countries that have increased more the overall consumption of antibiotics over the last decade[27]; either due to poor regulatory consumption control or to the prevailing unhealthy conditions in a large number of cities in India, the highest rates of carriers of beta-lactam-resistant bacteria are found there[28]. It is also in India where these pathogens were first identified in water, as well as determinant pathogens such as NMD1, which confers resistance to carbapenems. In countries of Africa and Asia, where the highest burden of infectious disease is concentrated together with lower capacity of response and access to new antimicrobials, there is evidence, resumed by Okeke et al., 2005[29], of reports on ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole-resistant *S. typhy*

global dissemination, which might be associated with more seriousness of the infection. As also notes the same author, treatment costs may be significantly increased. Today, the percentage of cases caused by multi-resistant TB account for a very small fraction of the total; the cost of one treatment can be up to 122 times higher than when targeting a sensitive strain. An important obstacle in some middle-sized economies is the lack of specific information and with adequate resolution to gauge the magnitude of infections by community-acquired resistant microorganisms. Since most Latin American countries lack efficacious surveillance programs to measure antimicrobial resistance, accessible information stems from a few cohort studies, which implies limited epidemiological information and a distribution that might not represent the population as a whole. Nevertheless, the results of regional and local studies can serve as a guideline with regard to the prevalence of the most common resistance genes in nosocomial infections and the use of combinations they might be sensitive to. This way, the resistance rate of vancomycin-resistant enterococcus in Latin America is found to have escalated up to 14%, which is still a lower rate than that in the USA[30], but following the trends in Brazil and Mexico, it might increase. Hospital-treatment-associated meticillin-resistant *Staphylococcus aureus* (HA-MRSA) shows a mean resistance of 48%[31], and 21% in healthy carriers of strains isolated in the community (CA-MRSA) in Mexico[32]. However, comparatively, enterobacteria constitute a larger problem than in USA. A significant number of extraintestinal resistant infections is divided between *Klebsiella* (KPC) and *Escherichia coli* (ESBL phenotype). In Mexico, when *Escherichia coli* strains obtained from hospitalized patients and from serious community-acquired infections are analyzed, infection by this resistant microorganism appears to be much more common, reaching a rate close to 50% of isolates[33].

A decade ago, we conducted an analysis to find out the impact of inadequate antimicrobial treatment on mortality in seriously ill patients treated in intensive care units. Antibiotic resistance was the most common cause of inadequate therapy associated to very elevated mortality[34]. In current practice it is increasingly common to find multi-resistant infections. What would the reader answer to the question: when was the last time you diagnosed an infection with no significant resistances?

Causes

Although the original cause of resistance is intrinsic to bacterial evolution in the world, it is a fact that

Table 2. Practices and conditions resulting in resistance increase

Practices associated with the development of resistance:
– Antibiotic overuse in practice with outpatients and hospitalized patients, even if it is therapeutic
– Use of antibiotics in the agriculture and livestock industry, particularly in the production of foods
– Increased survival of severely ill patients
– Increase of life expectancy with increased use of antibiotics at old age

Advances in medical science have resulted in survival of numerous patients with:
– Critically ill patients
– Immunosuppression
– Congenital diseases (e.g., cystic fibrosis)
– Lack of use of proven and effective measures for prevention and control of infections such as hand washing and restrictions in – the use of antibiotics and adequate isolation of patients with resistant infections
– Increased use of invasive procedures
– Increased use of prosthetic devices and foreign objects prone to superinfections with resistant bacteria

indiscriminate/inadequate use of antimicrobials amplifies and accelerates this process. The use of atibiotics in medicine occurs for a significant continuous increase, and this can be followed in longitudinal studies in hospital centers. Conversely, when the use of antibiotics is controlled, resistance increase can be modulated. In 1986, in the National Institute of Nutrition, the resistance of G-bacilli to gentamicin was close to 18%, and to tobramycin, higher than 11%, while to amikacin it was only 3.2%. Thus, the use of gentamicin and tobramycin was completely discontinued, with amikacin being used as the only aminoglycoside. The result after 3 years showed a reduction to 7.4% of resistance to G- and down to 0.8% to tobramycin[35-37]. Use intensity maintains a selection pressure and it is possible modifying it. The risk factors for the development of resistance are described in table 2.

It is important highlighting that the highest consumption of antibiotics occurs outside medicine, in the agribusiness sector, as growth promoters. This sector, being the main consumer of antibiotics, is also the main generator of resistance[38]. It should be noted that there is a clear relationship between the cattle-breeding use and resistance; it is therefore urgent to develop public policies limiting the generation of resistance to clinically used antibiotics[39]. Figure 2 shows the proportion corresponding to the consumption of antibiotics in USA for human use and cattle-breeding use. In view of the magnitude of the problem, it is clear that laws should be issued prohibiting the "industrial" use of
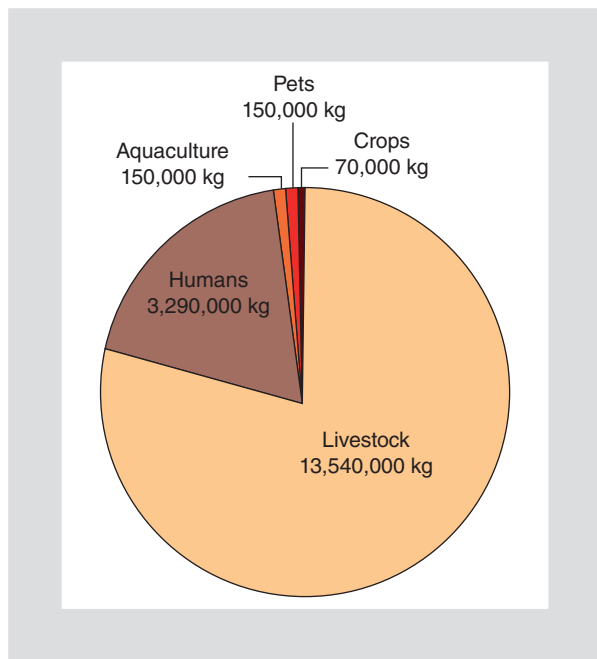
Figure 2. *Estimated consumption of antibiotics in USA.* (Taken from Hollis & Ahmed [2013] with permission).

Figure 3. *Antibiotic agents approved by the USA Food and Drug Administration (FDA).* (Taken from Shlaes et al. [2013] with permission).

antibiotics in the production of foods as already has been done in European countries[40]. The use of antibiotics must be restricted exclusively to humans, and for veterinary use, only for therapeutical purposes (Box 1).

Production

A factor that critically irrupts in this scenario where resistance is increasingly higher is the declining investigation and development and subsequent approval of new antibiotics (Fig. 3). Three arguments outline the d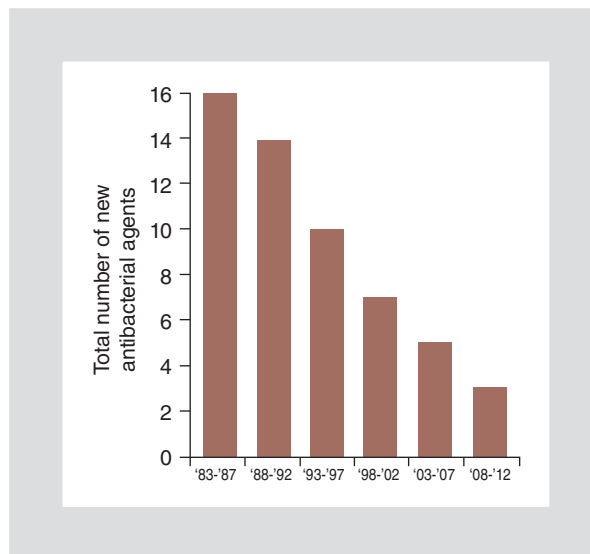ramatic decrease in the number of new antibiotics and account for the exit of big pharmaceutical companies in the production of new antibiotics[41]:

– Mechanisms of action and effective molecules have already been discovered.
– Regulatory factors and competence keep new antibiotics from reaching the last phases in clinical trials.
– Essentially economic reasons. The production of new therapeutic molecules implies an enormous investment in terms of money and time, and there is always the risk for the molecule not being able to be marketed. The industry looks to maintain maximum cost-benefit, and the trend is to direct research for the production of drugs that require continuous use (antihypertensive drugs, diuretics, hypoglycemic drugs, hypolipemic drugs, antiin-

Box 1. Perspectives arising from research: Beginning of a new paradigm?

– Some time ago, theree fundamental aspects were identified, which stand out among the maelstrom of publications and developments around antimicrobial resistance.
– First, the capacity of antibiotics to interfere in bacterial metabolism. From an evolutive perspective, antibiotics probably acted since its very origin as messenger molecules. Regardless of the known mechanisms of action, there are strong arguments favoring that antibiotics play a relevant role in the induction of lysis in bacterial cells through the production of oxygen free-radicals. If proven, as now is suggested, alteration of the redox mechanism could be a link between the environment and bactericidal efficacy and/or hypermutagenic states[49].
– Second. The comparative metagenomic study of the genomic architecture, bacterial ecology and the formation of stable communities, together with available knowledge on the determinants of the efficiency horizontal transference occurs with, are only some of the factors that enable for the probability of a particular evolutive trajectory occurrence to be calculated, i.e., the capacity to share mobile genetic elements that confer multi-resistance among bacteria is better known every day. This implies predicting the appearance of resistance against an antibiotic, before even entering the market, and enables the design of molecules with antibiotic effect "free of resistant strains"[50].
– The third milestone that will directly benefit infected patients is the capacity to know the resistance profile of a strain in an hour by monitoring resistance in real time based on a single cell in microchannels and electrokinetic charge[51].

flammatory drugs) against drugs that are required for few days (few weeks' courses)[22,42,43]. In this era it is not good business investing in the development of antibiotics. It is for these reasons that participation of the State should be promoted in the search for a solution. Joint investments, tax incentives, patent extensions and prizes have been proposed. Truth is that some type of solution will have to be sought in order to stimulate the production and development of new antibiotics[44].

While the studies with the new omic technologies promise to facilitate the identification of new targets and influence on the design of new molecules with more than one active site, in the short-term, the best opportunities are found in the identification and development of inhibitors that restore antibiotics their capacity[45,46]. Whichever the case, beyond the non-inferiority demonstration, it is clear that we have to assess in which cases resistance translates into treatment failure and what the likelihood of possible outcomes is[47].

A retrospective study in the United Kingdom found that antimicrobial resistance in primary care stabilized over the last decade in a relative low average of 12%; however, this value implies, in terms of treatment failure, an important burden[48].

Treatment failure as an index includes factors from both the pathogen and the host. Good news is that the risk can be mitigated by applying relatively simple measures, some associated with hygiene and vaccination. To what extent is it possible to preserve first-line antibiotics' efficacy and construct treatment regimens based on the distribution of resistance, microbiological knowledge and seriousness of infections, remains to be clarified.

Necessary interventions

The problem of resistance is acknowledged as a natural phenomenon that threatens many of the advances in global health. However, it has to be locally gauged; in this sense, some key points are briefly mentioned:
- Surveillance of pathogens has to be more effective. In a country like Mexico it is possible to carry out systematic analyses in different scenarios, through the use of laboratory networks that facilitate the communication of data for treatment decision making.
- The use of antibiotics for industrial purposes (agriculture and livestock) should be prohibited as soon as possible.
- Sufficient resources should be directed to basic research for the development of new antibiotics and other alternatives for the treatment of infections.

Table 3. International recommendations to face an antibiotic crisis

PCAST
- Federal investment (US)
- Systematic monitoring and surveillance
- Development of antibiotics for human care
- Search for alternatives for agricultural use
- Establishment of networks for clinical tests
- Regulatory improvement
- Reward antibiotics development and promote governmental association
- Responsibility in the use of antibiotics and rapid diagnosis

WHO
- Improve alertness and understanding of antimicrobial resistance through communication, education and training
- Strengthen evidence-based knowledge, research and surveillance
- Reduce the incidence of infection through hygiene and preventive measures
- Optimize the use of antimicrobials in human and animal health
- Develop sustainable plans taking into account the needs of the countries; diagnostic tools, vaccines
- Implementation, monitoring and assessment of national plans

- For new antibiotics to be available, it is necessary to develop new regulatory routes and improve the capacity to assess them in clinical trials.
- To improve antibiotics shelf life, its use in agriculture should be limited and education programs and vigorous regulation should be established; in addition, early diagnosis and rational use of antibiotics should be promoted.
- None of the above can be carried out without providing stimuli to the antibiotics chain of development.

Table 3 describes interventions proposed by different entities.

Conclusions

Resistance is an unavoidable phenomenon, but it should not constitute a sentence.

The introduction of antibiotics is the technology that has achieved the highest reduction in mortality. Loss of effectiveness can result in an increase in deaths by infections and impact on different fields of medicine.

It is urgent to avoid the use of antibiotics with non-medical purposes.

It is necessary to have widely distributed studies on resistance.

It is necessary to improve technical capacity and timing of diagnosis.

Control has to be established at all levels and fields of antibiotic use.

Stimulate antibiotic development and production.

Of particular importance is general population education, including healthcare personnel, on appropriate use of antibiotics.

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