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Review Article

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Myths and Misconceptions around Antibiotic Resistance: Time to Get Rid of Them

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ABSTRACT

The antibiotic resistance arena is fraught with myths and misconceptions, leading to wrong strategies to combat it. It is crucial to identify them, discuss them in light of current evidence, and dispel those that are unequivocally wrong. This article proposes some concepts that may qualify as misconceptions around antibiotic resistance: the susceptible–resistant dichotomy; that incomplete antibiotic courses cause resistance; that resistance "emerges" in patients and hospitals; that antibiotics are mostly abused clinically; that resistance is higher in countries that use more antibiotics; that reducing antibiotic usage would reduce resistance; that financial incentives would "jumpstart" research and development of antibiotics; that generic and "original" antibiotics are the same; and that new anti-infective therapies are just around the corner. While some of these issues are still controversial, it is important to recognize their controversial status, instead of repeating them in specialized literature and lectures and, especially, in the planning of strategies to cope with resistance.

Keywords: Antibiotic resistance; Antibiotic usage; Treatment adherence; Generic antibiotics; Antibiotic R&D

INTRODUCTION

For some decades, a phrase has been repeated as a symbol of arrogance and ignorance concerning infectious diseases, and even as a cause of the stalled research and development (R&D) of new antibiotics: "It is time to close the book on infectious diseases and declare the war against pestilence won". This phrase is attributed to William H. Stewart, the Surgeon General of the United States in 1969. Although it is certainly a sad example of arrogance and ignorance, it appears that Dr. Stewart never said those words, or anything of the sort [1], canceling its relevance as an infamous quote. The field of antibiotic resistance is plagued by myths like this, often repeated in prestigious journals and by public health authorities, but without any supporting evidence. For example, an infographic on the "causes of antibiotics resistance" issued by the Pan-American Health Organization (PAHO) and the World Health Organization (WHO) lists among the six causes of resistance, "patients not finishing their treatment" and the "lack of new antibiotics being developed", aside from the peculiar definition of resistance occurring "when bacteria change and become resistant" (https://

www.paho.org/en/node/52899). The first listed cause, as will be discussed below, is a growingly contentious notion; and the second is absurd, as it is impossible that the lack of new antibiotics causes resistance (albeit it is a reason for resistance to be a cause of concern).

The purpose of this article is to review some of the concepts that, according to current evidence, should be carefully analyzed before being repeated, in specialized literature and lectures. Each time clinicians act upon these concepts, they are potentially missing an opportunity at changing pernicious behavior. Furthermore, as these notions pervade even regulatory efforts, their persistence jeopardizes the adequate design of public policies aimed at controlling the growing threat of antibiotic resistance. Of course, many of the issues discussed here are still controversial, but it is very important to realize their controversial status, instead of accepting old opinions as fundamental truths. As this review is not aimed to be comprehensive, many of the references are to be taken merely as examples of a point that has been reported by several other authors.

SUSCEPTIBLE OR RESISTANT: IS THAT ALL THERE IS?

In the clinical milieu, bacteria are characterized as being either susceptible or resistant to a given antibiotic, with the occasional “intermediate susceptibility” being reported. This dichotomy is entirely artificial, as is the operational definition of acquired resistance: an increase in the minimal inhibitory concentration (MIC) of a given antibiotic, that leads to therapeutic failure when using the antibiotic. The MIC breakpoints change from time to time, and between countries; and it is difficult to make the assessment when dealing with non-pathogenic bacteria, as the definition itself becomes irrelevant [2]. But even for clinical purposes, the susceptible–resistant dichotomy is an incomplete picture, at best, of the complexity of bacterial responses to antibiotics. Some bacteria can withstand high, typically bactericidal concentrations of antibiotics, resulting in their inability to grow, but not die; if a whole population displays this phenotype it is called “tolerance”, while if this affects only a subpopulation, they are called “persisters”. By increasing the number of surviving cells during antibiotic exposure, tolerance and persistence may foster the emergence of actual resistance through mutation [3], or by increasing the chances of conjugal transfer of resistance plasmids [4]. As virtually all methods used in the clinical laboratory to assess antibiotic susceptibility only measure growth inhibition, these phenotypes cannot be detected. Another phenotype outside the binary paradigm is heteroresistance: a mix of resistant and sensitive subpopulations within a genetically homogeneous strain [5]. This can be detected by the trained eye, either as small colonies growing within the inhibitory halo when using the disk diffusion method, or as a constant slight turbidity in liquid serial dilutions. Moreover, “subsistence” is the ability of bacteria to use antibiotics as carbon source and “dependence” is a bacterial population’s need for an antibiotic to keep growing [6]. Furthermore, there is the “MIC creep”, a gradual increase in the MIC that is still below the resistance breakpoint that can jeopardize the clinical efficacy of an antibiotic if the infection is occurring in tissues (or in patients) where the antibiotic does not reach high enough concentrations [6] (**Fig. 1**). How common are these phenomena, what are the underlying mechanisms, how does each of them impact the therapeutic activity of antibiotics and the emergence of actual resistance, are questions yet to be resolved. However, to imagine that bacteria can only be either susceptible or resistant, and especially, that therapeutic failure is only a consequence of resistance (or of a wrong laboratory report of susceptibility), is an oversimplification of the problem, and plainly wrong.

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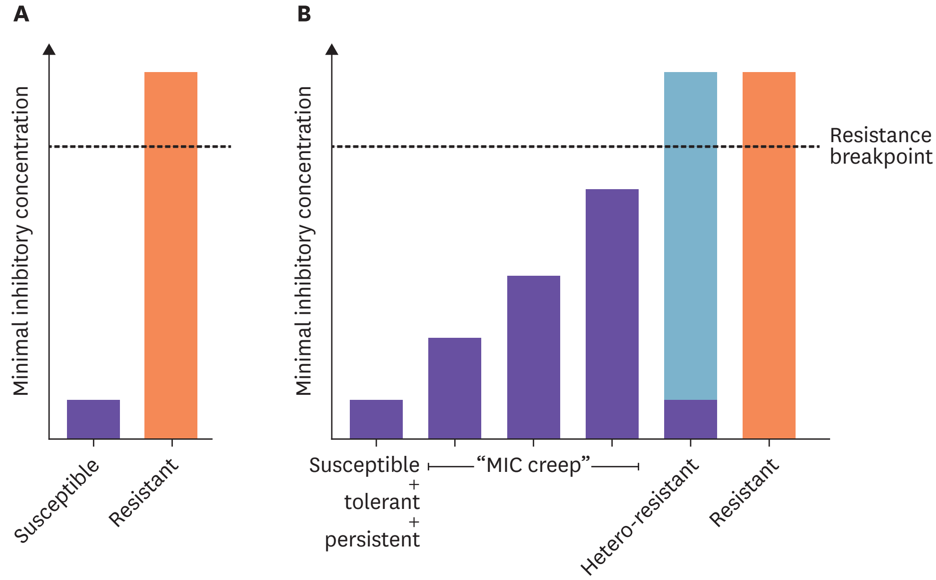

Figure 1. Susceptibility, resistance, and more.
(A) The typical dicothomic view of susceptible and resistant phenotypes, related to a minimal inhibitory concentration (MIC) breakpoint. (B) Some of the actual phenotypic varieties behind: within the "susceptible" group, several other variants could be silently present, such as tolerance and persistence (see text). Other organisms can have increased MICs, still below the designated breakpoint, but potentially causing clinical problems; this is called "MIC creep". Hetero-resistance has been detected for some antibiotics in some bacteria: a small fraction of a mostly susceptible population, has a high MIC; if a sample of this sub-population is re-grown, again most are susceptible and only a few display the resistance phenotype. All these variations are of clinical or epidemiological relevance, yet most studies only report either susceptible or resistance prevalences.

THE LENGTH OF ANTIBIOTIC TREATMENTS, AND THE INTERRUPTION OF COURSES

Most of the antibiotics currently in use were developed more than half a century ago, or are mere derivatives of such old drugs — the so-called "generations" of cephalosporins, fluoroquinolones, macrolides, etc. The clinical trials used to test their efficacy and safety were developed under the premise that an excess of treatment, if not useful, would neither be harmful. Once antibiotics became cheap to produce, long treatments, often of one or several weeks, were deemed ideal without any evidence that it would take that long for them to work. A recent paper [7] mocks the typical length of antibiotic treatments, of one or several weeks, calling this the "Constantine unit", after Constantine the Great, in 321 AD, pronounced a 7-day duration as a week. In terms of efficacy, a growing number of short-term antibiotic treatments have proven to be equally efficacious to their long, 1 - 2 "Constantine unit" counterparts [7]. Unfortunately, the baseless need for long treatments became gradually reinforced with an even more baseless claim: that cutting short such treatments (often by the patient him/herself, once the symptoms receded) is a cause of resistance, as the WHO/PAHO infographic states. "Resistance is much more likely to occur with long antibiotic courses" [8], as resistance seldom emerges at the site of infection [9]. A common argument behind the purported increased risk of resistance related to lack of compliance is the repeated exposure to sub-inhibitory antibiotic concentrations, which are known to foster the emergence of resistance [10]. However, this argument neglects the fact that, for most antibiotic dosing (except for continuous infusion, for which there are limited clinical trials), there is always a period of time between each dose where antibiotics concentrations are below the MIC. For instance, for so-called time-dependent antibiotics, like the beta-lactams, it is considered enough to have plasma concentrations above the MIC for 40 – 50% of the time between doses

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[11]. Therefore, even when patients rigorously adhere to their treatments, the concentration of antibiotics in their bodies remains sub-inhibitory for a significant amount of time. Therefore, every use of antibiotics, whether or not a part of a "complete course", poses a selective pressure for resistance.

Perhaps the only reason for resistance being fostered due to incomplete antibiotics courses, is that the remaining pills are often saved by the patient, and self-prescribed when a similar ailment emerges [12]. It is therefore crucial to put to rest the fallacy of resistance developing because patients do not complete their antibiotic treatments, and perhaps even encouraging stopping the use of antibiotics when symptoms resolve [13]. This would certainly shorten the use of antibiotics in the outpatient setting, avoiding the unnecessary exposure of bacteria to antibiotics, which is the actual selective pressure for resistance.

RESISTANCE EMERGENCE IN PATIENTS AND HOSPITALS

In different, mostly informal medical contexts, it is often said that a number of practices around antibiotic usage (*e.g.*, using antibiotics when not needed, cutting short an antibiotic treatment) will "cause" resistance, or make resistance to "emerge". These imply that, among a formerly completely susceptible bacterial population, somehow, a resistant variant arises because of these practices. Indeed, mutations or the transient decrease in antibiotic susceptibility caused by several stress-induced mechanisms can cause resistance to emerge during antibiotic exposure. However, the bulk of resistance determinants in clinically-relevant bacteria (with few exceptions, such as *Mycobacterium tuberculosis*, or *Pseudomonas aeruginosa* in cystic fibrosis [14], a peculiar condition that induces hypermutability in that bacterial species [15]) are ancient genes that can be traced down to antibiotic-producing organisms or other environmental bacteria that were likely exposed to natural antibiotics or related compounds [16]. Therefore, what the exposure to human-made antibiotics is doing, is to select the few bacteria that already carry such genes in clinical settings, and perhaps foster their horizontal transmission from innocuous to pathogenic bacteria (**Fig. 2**). This difference could be seen as subtle, or only of a semantic nature; but in the opinion of this author, phrasing the emergence of resistance like this reflects a deep misconception of the evolutionary processes behind the origin and spread of antibiotics resistance.

A burst of papers reporting "ancient" resistance traits (*e.g.*, [17]), do not show any such genes in clinically-relevant bacteria, indicating that these determinants do exist, but have so far failed to reach human pathogens. However, much older reports [18] have shown that, at least biochemically (as extensive sequencing was not yet available), resistance in pathogens can be traced down to corresponding antibiotic-producing bacteria. This proposed source of resistance genes has not been widely demonstrated, perhaps due to "sampling bias", *i.e.*, the resistance gene simply does not come from the bacterial strain used industrially to manufacture antibiotics. The *van* resistance clusters mediating glycopeptide resistance, may have originated from glycopeptide producing organisms, such as *Streptomyces toyocaensis* and *Amycolaptis orientalis* [19]. Furthermore, a number of currently critical resistance genes, such as $bla_{\text{CTX-M}}$ (encoding a prevalent extended-spectrum beta-lactamase), *qnr* (a plasmid-borne determinant of low-level fluoroquinolone resistance), and perhaps even *mcr-4* (a plasmid-borne determinant of polymyxin resistance) have been tracked down to environmental bacteria of the genus *Kluyvera* or *Shewanella* [2]. The staphylococcal cassette chromosome *mec* (SCC*mec*) that mediates the so-called methicillin-resistance in *Staphylococcus aureus*, seems

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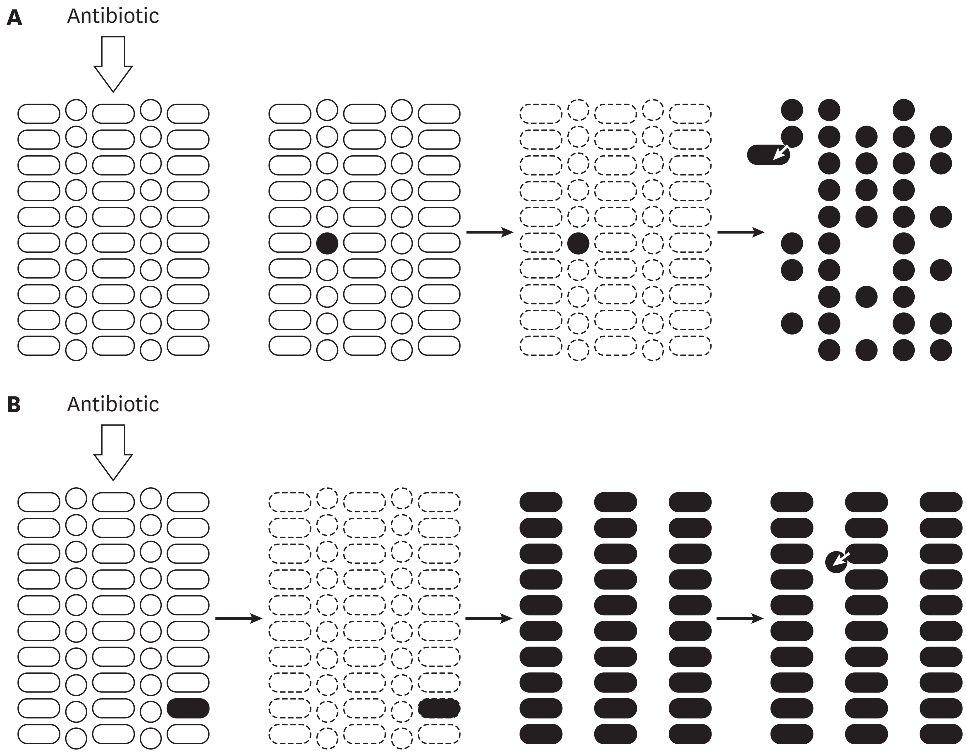

Figure 2. Antibiotics "causing" or "selecting" resistance.
(A) The typical explanation of resistance within a patient or a hospital: first, a homogeneously susceptible (open figures), mixed population of bacteria (with round "cocci" being the pathogens) is exposed to an antibiotic; somehow, perhaps through mutation, an organism becomes resistant (black figure) after the initial exposure. Most susceptible organisms die (broken outlines) and after multiplication, the resistant pathogen occupies the place of the formerly susceptible population. Occasionally, the resistant pathogen can transfer the resistance gene to another upcoming bacteria. While this can happen, it is not the origin of most resistance determinants found in current pathogenic bacteria. (B) The actual phenomenon: a pre-existing resistant organism, perhaps not even a pathogen, is a minority member of an otherwise susceptible population. When exposed to an antibiotic, susceptible bacteria die, including the pathogen (which is seen as therapeutic success), but the multiplication of the resistant one allows the colonization of the empty niche. Occasionally, the resistant bacteria can transfer the resistance gene to a surviving or upcoming pathogen. The origin of the initial resistance trait in this scenario is often the environmental bacteria that has carried it for millennia, and/or that has been selected by the reckless dumping of antibiotics into the environment.

to have originated from *Staphylococcus fleurettii*, a common animal-related bacteria [20]. This all is to say that most resistance genes that are clinically relevant have existed for thousands or millions of years (serine beta-lactamases are two billion years old [21]), and human-made antibiotics have only selected them to the point that they are now prevalent among pathogens. Hence, antibiotic use and abuse did not and does not "cause" resistance, and resistant bacteria do not "emerge" because of antibiotic usage. The actual process is much more complicated than that.

THE CLINICAL ABUSE OF ANTIBIOTICS

Antibiotics have been abused by physicians almost as early as they were introduced into clinical use. It is often said that about half of medical prescriptions of antibiotics are wrong (or perhaps even as much as 77%, in USA ambulatory clinics, considering drug of choice and dosing regimen [22]); and that the main risk for receiving a needless course of antibiotics is to consult a physician. Self-prescription, a rampant practice in many countries, can also be considered as "clinical" use (as the objective is to cure an ailment), and the fraction of it that amounts to abuse may be higher than the fraction of wrongful medical prescription. Although these notions are essentially true, the real impact of such abuse must be analyzed

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in the context of the entirety of antibiotic usage. With more than 63,000 tons of antibiotics being used worldwide for agricultural purposes [23], between 50 – 80% of all antibiotics produced in the world are used in this form of abuse: "growth promotion" of farm animals, aquaculture, beekeeping, fruit and grass infection control, etc. In the USA alone, 10,000 tons of antibiotics were sold for animal use while only 3,290 tons were sold for human use. There is an astounding 1: 30 ratio of humans: animals receiving antibiotics. Some of these antibiotics are administered to animals, as happens with pigs and chickens; and some directly reach the environment, as happens in flow-through aquaculture, and the spraying of plants and soils. Drugs administered to animals are often excreted in active form, and ultimately end up in the environment, in manure and wastewater (along with a significant fraction of antibiotics consumed by humans, especially in low- and middle-income countries with absent or scarce wastewater treatment plants [16]). Therefore, even if half the antibiotic prescriptions that are deemed wrong disappear, it would only account for 10 – 25% of all antibiotic usage. Considering that resistance does not emerge in clinical settings, as discussed above; and that the clinical use of antibiotics does not seem to correlate to resistance; nor does reducing antibiotic usage lead to reduced resistance, as will be discussed below; the reduction of the clinical use of antibiotics does not seem to be a particularly effective way to tackle the problem of resistance.

This is not to say that the clinical abuse of antibiotics should not be vigorously discouraged: if not "causing" resistance, it may be affecting the expression of pathogenic traits in bacteria during treatment, perhaps even pushing them into hypervirulent states (as antibiotic exposure can induce the expression of toxins, adhesins and other virulence determinants, and biofilm-forming factors [24]). Furthermore, antibiotics cause harmful adverse effects in some patients, and represent an economic burden to public health systems (solely in the USA, $10.7 billion was spent on antibiotics in 2009 [25]). However, to expect significant results in controlling resistance from purely or mostly promoting the prudent use of antibiotics in the clinical setting seems naïve. As with many other environmental problems — antibiotic resistance is, in the end, an environmental problem — when power structures call for individuals to modify their behaviors, be this by reducing private car usage (10% of global CO_2) or plane traveling (2.1%), the use of plastic straws (0.02% of plastic waste), or the prescription of antibiotics, a much larger fraction of the problem that these measures are supposedly tackling, comes from financial interests that such power structures are not willing to affect. In the end, antibiotic resistance is a "profit-driven plague" [26], and there is very little that individuals can do to fight it.

ANTIBIOTIC RESISTANCE AND COUNTRY-WIDE USAGE

Assuming that clinical antibiotic use and abuse are the main "cause of resistance", it is reasonable to also assume that resistance will be higher in those countries where antibiotics are used the most. With antibiotic usage and resistance measured in many different ways, it seems like a difficult task to actually correlate usage and resistance in a country-wide fashion. A report measuring outpatient consumption of antibiotics (defined as daily doses per 1,000 inhabitants per day, DDD/TID), and contrasting it to the prevalence of penicillin non-susceptibility in *Streptococcus pneumoniae*, and macrolide resistance in *S. pneumoniae* and *Streptococcus pyogenes*, in some European countries (plus USA and Australia), showed significant correlations [27]. A further European study, now including, in addition to penicillin- and erythromycin-nonsusceptible *S. pneumoniae*, fluoroquinolone-resistant

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Escherichia coli; and contrasting specifically to penicillin- and fluoroquinolone-usage, also showed a direct usage–resistance correlation, except for the macrolide pair [28]. It is worth mentioning here that none of these resistant pathogens is considered to be a critical public health threat. (Interestingly, resistance in commensal bacteria does not seems to correlate to antibiotic usage [29].) However, for fluoroquinolone-resistant *E. coli*, especially those isolated from blood cultures (a particular health problem), human consumption of fluoroquinolones did correlate with resistance prevalence in high-income countries, but not in middle-income ones [30]. For the latter group of countries, sanitation, corruption, and access to and quality of health care, were more clearly associated with resistance. Country income was shown to be inversely associated with resistance prevalence in infections caused by the most critical multi-resistant pathogens (carbapenem-resistant *P. aeruginosa* and *Acinetobacter* spp., cephalosporin-resistant enteric bacteria, methicillin-resistant *S. aureus* [MRSA], and vancomycin-resistant *Enterococcus faecium* [31]). In a previous, Europe-only study including several key resistant pathogens (*e.g.*, MRSA, multi-resistant enteric bacteria and *P. aeruginosa*, vancomycin-resistant enterococci), overall antibiotic usage only had a correlation coefficient of 0.40 when graphed against overall antibiotic usage (in DDD/TID); but control of corruption had a correlation coefficient of -0.77 [32]. While factors such as “control of corruption” and “quality of governance”, used in this paper, are rather subjective and difficult to measure, the strong correlation — stronger than the one observed for antibiotic usage, suggests that there are many more issues at play. Sanitation, health-care quality, and agricultural use of antibiotics are all affected by poor governance and corruption; perhaps even counterfeit and substandard generic antibiotics have a role in the higher rates of antibiotic resistance [33]. A simple example could illustrate the point: USA and Mexico, countries sharing the 8th largest border in the world, differ substantially in clinical antibiotic usage (approximately 28 DDD/TID in USA and 7 DDD/TID in Mexico, by 2015 [34]). Yet patients initially hospitalized on the Mexican side of the border, and then transferred to hospitals in the USA, carry with them a significantly higher amount of resistant bacteria, compared to similar patients that have been hospitalized in the USA from the beginning [35, 36]. Should country-wide antibiotic usage be the main driver of resistance, the results of this comparison would be precisely the opposite.

As with many other issues regarding antibiotic resistance, to assume that it is only driven by clinical antibiotic usage is an oversimplification. Therefore, to try to address the resistance problem by only diminishing such usage, especially in low- and middle-income countries, is fallacious. However, perhaps it is important to emphasize here, especially for readers in rich countries, that (1) most people live in low- and middle-income countries; and (2) resistant bacteria do not recognize political borders.

REDUCING CLINICAL ANTIBIOTIC USE TO REDUCE RESISTANCE

If the clinical use and abuse of antibiotics is the main driver of the emergence and spread of antibiotic resistance, then curbing such usage should reduce resistance rates. This notion drives the efforts towards the rational use of antibiotics, and antibiotic stewardship: *e.g.*, “Numerous strategies have been developed to encourage improved antibiotic stewardship internationally in primary and secondary care. Many assume that bacteria with resistance genes are less ‘fit’ than susceptible strains, and therefore reducing the antibiotic exposure should reduce resistance” [37]. The concept is also behind the idea of antibiotic cycling in hospitals. From the biological point of view, for this to be true, at least two conditions need

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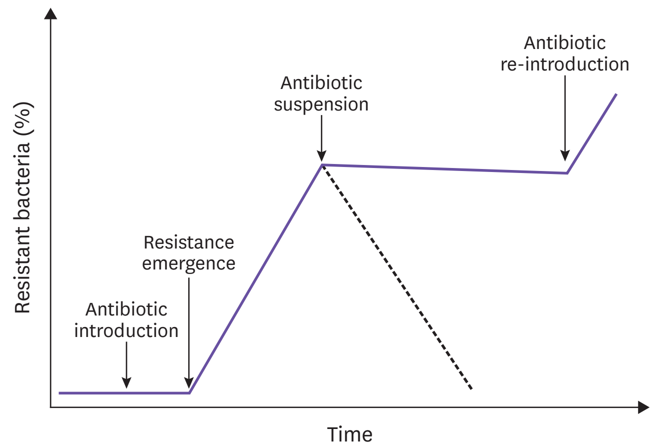

Figure 3. The effect of antibiotic usage reduction upon resistance.
Before the introduction of a new antibiotic, most or all pathogens within its spectrum of activity are susceptible. After the introduction of the drug and for a while thereafter, resistance is undetectable. However, a resistance trait is acquired, either by mutation or by horizontal gene transfer (usually from environmental bacteria) and resistance prevalence starts to grow. If the clinical use of the antibiotic is reduced (*e.g.*, by rational usage policies) or even suppressed (*e.g.*, during hospital antibiotic "cycling"), the expected effect should be a rapidly diminishing rate of resistance (broken line). However, the stabilization of the rate, perhaps with a slim decrease, is most commonly observed. If cycling, when the antibiotics is reintroduced, resistance increases rapidly, starting from the point left when use was stopped; hence there was no gain (modified from [47]).

to be fulfilled: (1) antibiotic resistance should reduce the fitness of bacteria in an antibiotic-free environment, so that, when antibiotics are not present, susceptible bacteria would out compete their resistant counterparts; and (2) antibiotics should be the only (or, at least, main) selective and maintenance pressure for antibiotic resistance. As will be discussed in the following paragraph, these conditions do not apply for most cases of clinically-relevant antibiotic resistance. Furthermore, societal aspects, in addition to biological ones, as have been discussed above, bear an equally, or perhaps even stronger pressure for selecting and/or maintaining antibiotic resistance unrelated to the actual amount of antibiotics present in the clinical setting. Hence, although reducing the abuse of antibiotics is always a good goal, that would certainly reduce the incidence of adverse effects and, possibly, curtail the emergence and spread of more resistant bacteria; it is very unlikely that it would result in a reduced rate of resistance in the short- or mid-term (**Fig. 3**).

The notion that resistant bacteria is less fit than the susceptible counterpart in the absence of antibiotics, was proposed as the consequence of carrying resistance plasmids that would be of no use in antibiotic-free environments [38]. The classic experiments of Bouma and Lensky [39] showed that plasmids and their bacterial hosts co-evolve so that the pair has even enhanced fitness, compared to plasmid-free bacteria. High-rate conjugation can also maintain costly plasmids in the absence of antibiotics [40]. Resistance mutations that reduce fitness have been documented for a few antibiotics, such as nitrofurantoin [41]; for most others, either there is little or no cost, or compensatory mutations can alleviate such cost [42]. Some resistance traits that, when expressed, are very costly to the cell, such as the VanA vancomycin resistance operon, can minimize this fitness cost by being inducible [43]. In any case, the fact that resistance is resistant to elimination has been known for some time [44], and precludes the expectation of diluting resistant organisms with susceptible ones if antibiotics are not present. In addition to not becoming, or being able to circumvent the fitness cost, co-selection by other antibiotics can nullify the effect of such a cost on the maintenance of the trait: this was observed for trimethoprim resistance despite a significant

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reduction in the use of that antibiotic [45], for instance. The cross-effects of antibiotics are not limited to co-selection: in an experimental setting, for instance, an antibiotic (streptomycin), by changing cell density and quorum sensing responses, increased the conjugative transfer of vancomycin resistance in *Enterococcus faecalis* by 30-fold [46].

There are many other agents that contribute to the selective and maintenance pressure of antibiotic resistance. Various causes of non-antibiotic agents selecting for resistance are biochemical, phenotypic and genetic cross-resistance [47]. Therapeutically, a number of "unintentional" antibiotics, *i.e.*, compounds that are used for non-infectious diseases, but that are toxic to bacteria, can therefore be selecting for antibiotic resistance. In the environment, along with widespread release of many of these drugs [48], a variety of other agents that exert an indirect selective pressure, or that modify the bacterial response to antibiotics (*e.g.*, herbicides, disinfectants, heavy metals [16]), compound the issue affecting the microbiota of water and soils in unpredictable ways. Hence, by just reducing the clinical use of antibiotics, even if resistance were to become a fitness burden, an extremely wide variety of agents and conditions would still be selecting and/or maintaining antibiotic resistance traits.

As to antibiotic "cycling" in hospitals, most evidence suggests that the practice is, as would be expected, not useful for reducing resistance [49, 50], for the same reasons as discussed above [51], and could even worsen the problem [52]. This is a clear example of how a misconception (*i.e.*, reduced antibiotic use reduces resistance) leads to useless strategies, wasting time and money.

DISCOVERING NEW ANTIBIOTICS

A trend attributed to the seemingly apocryphal quote from Dr. Stewart mentioned at the beginning, is the abandonment of antibiotic R&D by pharmaceutical companies. This is false because the phrase was never said by the US Surgeon General, and because it is not the actual reason for drug companies to reduce or cease antibiotic R&D. Despite being the most profitable business there is [53], large pharmaceutical companies (hereafter called *Big Pharma*) have abandoned the field of antibiotics because there are other kinds of drugs from which even more profit can be derived. Hence, under the free market logic, *Big Pharma* is no longer pursuing antibiotic R&D, and is devoting their efforts towards cancer and rare diseases, where drugs fetching astronomical prices are the norm. With the objective to lure back *Big Pharma* to antibiotic R&D (and, by the way, against the defended principles of free market), a variety of "bribes" have been devised as financial "incentives": extended or "wild card" patents, contractual increased prices, fast-track approvals, etc. These incentives have only managed to sponsor a number of rehashed drugs (*i.e.*, new "generations" of older scaffolds), most of them not even targeting critical microorganisms, as was originally established in the incentives' regulation [54]. The reasons for this positive (carrot) incentives to fail and perhaps even be counterproductive, have been discussed before [6], as well as the need for negative (stick) incentives, a sort of punishment for *Big Pharma* companies that do not engage in antibiotic R&D. As, again, governments and international organizations are not willing or capable to design and enforce negative incentives, it may be necessary for the organized society to devise such "sticks" [55], as has been done for forestry and fishery resources, for example. In any case, either by carrots or sticks, *Big Pharma* is not returning to antibiotic R&D anytime soon, nor do not-for-profit institutions that used to provide the

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basis for antibiotic discovery at the beginning of the "antibiotic era". The shrinking antibiotic arsenal that we currently have would not improve in the foreseeable future.

Having said that, and supposing that antibiotic R&D can be somehow jumpstarted, the number of new targets against which new kinds of antibiotics can be directed, may be very limited. A study on *Salmonella* detected 64 essential enzymes, conserved across a number of other pathogens, but that are already targets of old antibiotics; eight new potential targets detected by this study are homologs of human enzymes, suggesting a potential for poor selectivity and toxicity of any inhibitor to be discovered [56]. A more recent screen combining essential targets (in *M. tuberculosis*) and compound libraries, yielded only about 40 molecules potentially capable of affecting known bacterial targets (*e.g.*, cell wall, folate or RNA synthesis, DNA gyrase [57]); considering that many of them are likely to be unstable, toxic, or otherwise unusable as drugs, the approach does not seems particularly promising.

GENERIC ANTIBIOTICS: THE SAME BUT CHEAPER?

The issue of generic drugs is politically charged, and it is not the intention of this article to get into this particular controversy. However, there are plenty of reports of generic antibiotics not having the same antimicrobial effects, both *in vitro* and *in vivo* [58-60] (along with just as many pointing at contaminants and other sub-standard conditions; [61-63]). At least two further papers associate the use of generic antibiotics with increased resistance: the amplification of an initial 1% resistant inoculum in an animal infection model when using generic piperacillin-tazobactam [64]; and another that links the introduction of generic ciprofloxacin with increased resistance, attributed to increased use of the drug fostered by lower price [65]. The problem with generic antibiotics goes beyond the efficacy and safety issues of individual brands or formulations: the industrial conditions in which most of them are manufactured is, perhaps, of much more concern. To keep generics cheap, their production has been centralized in countries where low wages and, most especially, minimal regulation and disregard for environmental protection, are the norm. Industrial residues containing active antibiotics are usually dumped into water bodies without prior treatment, creating large selection "hotspots" in such bodies that also receive wastewater containing resistant bacteria of human or animal origin. This combination results in a high prevalence of resistant bacteria, that easily return to human populations in the form of multi-resistant pathogens [66]. Therefore, by choosing generic antibiotics, there is a risk of reduced efficacy and higher resistance selection, while enabling manufacturing conditions that pollute the environment both, with antibiotics and, indirectly, antibiotic-resistant bacteria. While "choosing" may not be the adequate word in the sentence above, as generic drugs are often the only choice because of price or availability, for those that can actually chose, it may be important to keep these factors in mind. It would also be in the interest of public health to review the regulation behind generic manufacturing, and perhaps even the recommendation to prefer generic drugs that "disincentive the development of new medicines" [67].

NEW ANTI-INFECTIOUS STRATEGIES FOR THE "POST-ANTIBIOTICS ERA"

A number of non-antibiotic candidates have been mentioned and explored as future therapeutic options for bacterial diseases, should antibiotics become useless — the "post-

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antibiotic era". Some of them are older than industrial antibiotics themselves, such as the use of bacteriophages; some specifically address the antibiotic resistance issue, such as plasmid elimination [68]; and some combine old and new notions, such as the interference with adherence, virulence, biofilm formation and quorum sensing, which are often different views of the same phenomena [69]. Most of them face important barriers to become viable commercial options: the spectrum tends to be narrow, reducing the number of clinical indications, hence the market share would be minimal; and entirely new laboratory tests would be necessary to assess their therapeutic activity, as the typical antibiogram would not be useful. Phage therapy, which has shown interesting results and is already in use in farm animals, could rapidly follow the same path of antibiotics, with the pursue of wide spectrum and agricultural usage, and lacking the necessary knowledge to understand the complex interactions between phages and bacteria, as we did with antibiotics [70]. Phages could instead be used for other interesting but limited purposes, such as the eradication of specific strains linked to non-infectious diseases (*e.g.*, alcoholic liver disease related to cytolyic *E. faecalis* [71]). Resistance towards other potential anti-infective strategies, such as quorum-sensing inhibitors, seems to arise easily [72]; a number of quorum-sensing inhibitors have been successfully explored against plant pathogens, but functioning animal models are scarce [73]. Perhaps vaccines, in the preventive rather than therapeutic side of the problem, could offer an entirely different anti-infectious avenue; a number of them, against *Clostridioides difficile*, *P. aeruginosa* and *S. aureu*s, are at different developmental stages [74]. *C. difficile* infections, ironically linked to the use of antibiotics, affect a defined niche of patients, which could receive the vaccine in a timely way; but to identify which populations are at risk for most other bacterial infections, in order to have them vaccinated, sounds like a difficult task, not to mention the irrational hate that vaccines tend to elicit in many people. In any case, non-antibiotic strategies do not seem to be "just around the corner", with still too many hurdles ahead to become viable options.

CONCLUSION

This review has been written almost exactly two years from the declaration of coronavirus disease 2019 (COVID-19) being a pandemic; officially, about six million people have died of the disease worldwide — a three-million yearly average. This is indeed higher than the estimated 700,000 yearly deaths caused by resistance by 2016 [75], and the 1.27 million reported by 2019 [76]; but not much higher. And it is certainly well below the predicted 10 million yearly deaths to be caused by antibiotic resistance by 2050 (although, as did happen with climate change and COVID-19 itself, there are people considering these figures as "myths" [77]). Drastic interventions are certainly needed in order to harness the rapid spread of antibiotic resistance; but it is also imperative to correctly assess the targets of such interventions if they are to be successful. To keep aiming at the reduction of clinical use, while agricultural use grows rampantly; to keep expecting local, incomplete, disjoined strategies to effectively fight a worldwide public health threat; to keep searching for new antibiotics or new strategies to fight infection, without previously correcting the societal vices that led to the waste of antibiotics; to keep recommending patients and physicians useless or counterproductive measures to fight resistance; these are all recipes for failure. Curiously enough, these are the measures that governments, international organizations and *Big Pharma* are proposing and implementing, to no avail. It is time to realize that the solution will not come from them.

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