



# Should We Forbid the Consumption of Antibiotics to Stop the Spread of Resistances in Nature?

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## Abstract

The appearance and diffusion of antibiotic resistance are at the moment seen as an inevitable characteristic of bacterial development succeeding the consumption of antibiotics. This spectacular event is completely clarified by the link present among the manifestation of resistances and the consumption of antibiotics. In terms of mechanisms, the augmenting appearance of antibiotic-resistant bacteria (ARB) has been largely assigned to the selection of resistant variants that pre-exist in sensitive communities. Lately, Merlin [1] published an excellent review on the secondary influences of antibiotics at sub-inhibitory levels and trace metal elements, which obviously call attention to the reality that the antibiotic resistance danger has not to be related to the only antibiotic therapy applications, and must to some extent be viewed as a multifactorial issue where co-selection and stimulation of horizontal gene transfer as well completely applies. This work focuses on the main conclusions of Merlin [1] report. More in-depth epidemiological investigations have to let defining the range of these secondary impacts outside the scene of a Petri dish and may interpret why many antibiotic resistances run away any decrease of presence while lowering the corresponding antibiotic consumption. In addition, defining thoroughly which antibiotic molecules manifest secondary influences, and at which levels, would be a supplementary stage toward antibiotic hazard evaluation, whether for therapeutic applications or for the impact of antibiotics once liberated in the downstream mediums.

## Subject Areas

Public Health

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## Keywords

Antibiotic-Resistant Bacteria (ARB), Antibiotic Resistant Gene (ARG)

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### 1. Controlling the Consumption of Antibiotics

The appearance and diffusion of antibiotic resistance are at the moment seen as an inevitable characteristic of bacterial development succeeding the consumption of antibiotics [1] [2]. This spectacular event is completely clarified by the link present among the manifestation of resistances and the consumption of antibiotics [3] [4] [5]. In terms of mechanisms, the augmenting appearance of antibiotic-resistant bacteria (ARB) [6] [7] has been largely assigned to the selection of resistant variants that pre-exist in sensitive communities [8]. These resistant bacteria are perhaps surpassing the rest of the microbial communities in a context where antibiotics are administrated at relatively high levels, which implies that local concentrations are well-over the Minimum Inhibitory Concentrations (MICs). Regardless of the augmenting presence of antibiotic resistance between bacteria that has been known decades ago as resulting from antimicrobial drug consumption, only lately has the gravity of the situation been regarded by international, national and local health organizations/agencies. This realization conducted to series of decisions and recommendations aiming to educate and ameliorate exercises of health professionals and consumers, with a view to keeping the performance of the therapeutic potential [9] [10] [11]. Taking into account the link among antibiotic consumption and presence of resistances in bacteria [4], most suggestions offered to take action in the public health and veterinary/farming fields via restricting the unsuitable exposure of bacteria to antibiotics with a view to decelerate a natural evolution toward resistance and its diffusion in the downstream environment in a One Health context [9] [12]. Restricting the unsuitable exposure of bacteria to antibiotics tacitly implies 1) decreasing the necessity for antibiotics, which can be attained with infection control actions that would restrict the epidemic diffusion of resistant bacteria, and 2) a better usage of antibiotics so as to decrease the overall antibiotic consumption if unneeded [1]. Even if there is a huge inequality among nations concerning the consumption of antibiotics [13], modification in practice stays hard to apply if public health is about. Besides, taking measures to decrease antibiotic resistance needs a coordinated and multi-sectorial procedure joining political commitment, resources, specific governance mechanisms, and practical management [14]. Two years ago, the ECDC illustrated that the total consumption of antibiotics in the EU did not importantly vary in the community and the hospital sectors; however, a small decreasing and increasing tendencies were noted for some nations over the 2013-2017 period. Alterations in consumption were likely more apparent in veterinary medicine. In an account including the 2011-2016 period on veterinary antibiotics sale, the European Surveillance of Veterinary Antimi-

crobial Consumption communicated a global diminution of 20% combined for 25 nations [15]. This was temporarily interpreted by the application of policies and actions targeting at decreasing the abuse of antibiotics. Even if the examined period is too short yet to draw robust conclusion, the first impacts of such responsible-use campaigns start to be apparent. Even if the investigated period is too brief until now to extract the right deduction, the primary impacts of such responsible-use campaigns begin to be clear. As an example, In France, an unmatched national plan to decrease antibiotic consumption in the animal sector has been commenced [16]. This conducted to an impactful 39% diminution of antibiotic prescription in veterinary medicine in 6 years, all animals considered. The decrease was even more powerful for dangerous antibiotics like fluoroquinolones (81% reduction) and last generation cephalosporin (75% reduction). Such actions were pursued by a clear reduction of pathogenic ARBs [17]. As noted by the French National Public Health Agency [18], employing information as well furnished by the European Food Safety Agency (EFSA), the fraction of resistant *Escherichia coli* for C3G went down from 16% to <2% in poultry among 2010 and 2017, which was greatly augmenting prior 2010 [18] [19] [20]. While more findings are required to support such findings, they are inclined to reveal that a better usage conducting to a decreased consumption of antibiotics may quickly lead to a net diminution of the relative existence of ARBs. While numerous different publications are actually promising to continue in that orientation [21] [22] [23], the link among the presence of resistance and antibiotic consumption does not constantly obey this tendency. In fact, even if it is not the large plurality of the published instances, ending or augmenting the consumption of a specific antibiotic does not constantly lead to the accompanying diminution or augmentation of the corresponding resistances, and this may change following to the examined environment, the public/animal analyzed, and the antibiotic and bacteria considered. For example, researchers [24] mentioned a negative association among a diminishing consumption of cefotaxime and the rate of cefotaxime resistant—*E. coli* pathogens isolated in a Taiwanese university hospital. Identical tendencies were noted for the consumption of ceftriaxone and ceftriaxone-resistant *E. coli* and *Klebsiella* spp. in a Turkish hospital setting [25]. Negative associations among antibiotic consumptions and the expansion of resistances may as well function the other way around and may depend on the bacterial species considered. In a Korean investigation including six university hospitals, researchers [26] noted contrasted findings following an augmented consumption of fluoroquinolones, where the resistance rate for ciprofloxacin in *E. coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, either augmented, remained stable or decreased, respectively over an 8-year period.

Astonishingly, the identical researchers [26] as well discovered a negative association among diminishing consumptions of aminoglycosides and the resistance rate for third-generation cephalosporins and ciprofloxacin; therefore, separating a specific drug consumption from its influence on the corresponding

antibiotic resistance, at least for a few documented situations. In addition, carbapenem-resistant *P. aeruginosa* could be isolated from animals that have not been already treated with carbapenems. In such condition, the resistance to carbapenem was related to an efflux pump dysregulation (rather than a carbapenemase) conducting from mutations likely selected via disinfectants [27]-[37] and additional antibiotics in veterinary practices [38]; therefore depicting that resistant phenotypes can arise independently from the existence of the corresponding antibiotics. In addition, the identification of antibiotic resistance genes in metagenomes from 30,000-years old sediments recalls that resistance phenotypes and their corresponding genes possibly existed before the so-called antibiotic era [39]. Such remarks distinctly show that the appearance and the diffusion of antibiotic resistances in bacteria cannot only be interpreted by a simple selection phenomenon taking place throughout antibiotics therapy, even if the latter is a significant driving factor in numerous cases [1].

## 2. Antibiotic Secondary Impacts

Dealing with the diffusion of antibiotic resistance will certainly need a better utilization of antibiotics with a view to decelerate the appearance of resistant variants related to antibiotic therapies [1]. However, taking into account the indispensability of antibiotics in new medicine, antibiotic resistance will persist to be liberated in an anthropogenically-impacted medium where ARBs may continue, collect, transfer their resistant genes (ARGs) to indigenous microorganisms, and lastly re-enter the food chain and pollute human and animal bowels for a novel round of selection [5]. It has to be mentioned here that nature has been defined as a reservoir of ARGs in numerous times [40]. Taking into account that the spreading of antibiotic resistance depends on the acquisition of resistance; however, as well involves a transmission, and thus a contact, among people, or with wastewater, or manure, or animals, tackling the dissemination of ARB and ARGs [6] [7] will without question need controlling both the usage of antibiotics but as well the path of transmission, particularly at the ecological level. In this context, researchers [41] suggested that the transmission of ARB and ARGs [6] [7] was possibly the controlling factor to consider for dominant antibiotic resistance, which involves functioning at diverse degrees than the antibiotic consumption as well [1].

The worldwide lowering of consumption is not the only significant action applied by national and international organizations for better use of antibiotics [1]. The categorization of antimicrobial agents as critically substantial molecules for human health (WHO classification list), the limitation of their accessibility/delivery and the confinement of particular antibiotic usages to human medicine are crucial actions aiming at preventing the appearance of specific resistances in the animal husbandry sector and their diffusion in the human health sector [11] [42] [43]. Even so, limiting the use of a particular antibiotic is probably to be of a restricted influence if collateral effects were to be noted among an-

tibiotics of diverse nature on the appearance and the spread of unrelated ARGs. Recently, researchers [44] established that Tn916, a mobile genetic element implicated in the diffusion of an ARG for tetracycline, could manifest a 1000-fold increase of its transfer frequency when exposed to sub-inhibitory levels of tetracyclines, but as well as macrolides, lincosamides, and streptogramins. This indicates that not only sub-inhibitory levels of an antibiotic could stimulate the spread of its corresponding resistant gene, but that collateral stimulation by different antibiotics is also possible. This tends to rule out the effectiveness, at least partially, of any action that would be founded on confining the use of cross-reacting antibiotics. In addition, the usage of trace metal elements like zinc oxide or copper sulfate is usually employed as an antibiotic alternative to promote the growth of livestock and poultry. Therefore, numerous scientists noted a concomitant augmentation of ARB and ARGs that are possible to result from co-selective processes, as ARGs and metal resistance genes can collocate on the identical genetic entities (mobile genetic elements) [45] [46] [47].

### 3. Conclusions

From this work, the following conclusions can be drawn:

- 1) Secondary influences of antibiotics at sub-inhibitory levels and trace metal elements obviously call attention to the reality that the antibiotic resistance danger has not to be related to the only antibiotic therapy applications, and must to some extent be viewed as a multifactorial issue where co-selection and stimulation of horizontal gene transfer as well completely applies.
- 2) More in-depth epidemiological investigations have to let defining the range of these secondary impacts outside the scene of a Petri dish and may interpret why many antibiotic resistances run away any decrease of presence while lowering the corresponding antibiotic consumption.
- 3) In addition, defining thoroughly which antibiotic molecules manifest secondary influences, and at which levels, would be a supplementary stage toward antibiotic hazard evaluation, whether for therapeutic applications or for the impact of antibiotics once liberated in the downstream mediums [1].

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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