Name of the Project: Effect of Antibiotics on bacterial population

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Department: Microbiology

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OBJECTIVE:

Antibiotics are among the most successful drugs used in human therapy. In addition, they have been used for several decades in animal growth promotion, prophylaxis, metaphylaxis, treatment, and general farming production. This wide antibiotic use has led to different habitats becoming polluted by a large range of concentrations of antibiotics. Since antibiotics are inhibitors of bacterial growth, this situation has an impact on the structure and the activity of bacterial populations. The effect of antibiotics on bacterial populations has mainly focused on the aspects related to human health, in particular the selection of antibiotic-resistant mutants and the acquisition, selection, and spread of antibiotic resistance genes. While this has obvious relevance to the treatment of infectious diseases, other aspects of the roles that antibiotics may play in bacterial populations are much less studied in comparison. In the field of human health, some studies have addressed the impact of antibiotic treatment on the global structure of the human gut microbiome. These articles focus particularly on the general description of changes at the population level as well as on the selection of resistance genes. However, with recent work considering the gut microbiome itself as an organ, and taking into consideration that microbial composition may impact human physiology at different levels, more information on the consequences that changes to the human microbiome in the presence of antibiotics have on human health is still needed. One aspect to be taken into con sideration is that, when antibiotic treatment is needed, the effects of the antimicrobial on the microbiome should be considered as unavoidable side effects. Nevertheless, some work indicates that these effects can be mitigated by using compounds able to adsorb antibiotics in the gut. By using these compounds together with antibiotics, the concentration of the drug at the point of infection (unless in gut infections) will not change; however, it will be much lower at the gut and the microbiome should not be strongly altered. One aspect that has received more attention in the last few years is the effect of antibiotics in environmental microbiota. Also, in this case, most studies focus on the aspects of this topic closer to human health, in particular how natural ecosystems, polluted or not with antibiotics, may be involved in the acquisition, selection, and spread of antibiotic resistance among human pathogens. This "one-health" approach is, of course, needed if we wish to fully understand the spread and maintenance of clinically relevant antibiotic-resistant microorganisms. Nevertheless, it is worth mentioning that fewer studies focus on the overall effect of antibiotics on the structure and productivity of environmental, not pathogenic, bacteria. Taking into consideration that all basic nutrient cycles in nature (carbon, nitrogen, oxygen, etc.) are based on the metabolism of microorganisms, learning whether or not antibiotic pollution may alter the right functioning of these cycles is of relevance. However, only some studies have addressed this relevant topic. It is true that the concentrations of antibiotics are low in most ecosystems, but even low concentrations of antibiotics may trigger specific bacterial responses, and analysing such responses is a topic of interest.

OUTCOME:

This panorama has changed in the last few years. The classical view indicates that the selection of resistance can happen in a range of concentrations from the minimal inhibitory concentration, under which susceptible and resistant bacteria will grow, to the minimal preventive concentration, which inhibits the growth of resistant mutants. However, recent information indicates that subinhibito

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concentrations of antibiotics can select antibiotic resistant microorganisms. While selection at high concentrations of antibiotics is based on the inhibition of the susceptible cells and hence a resistant population can be selected after few duplication events, both susceptible and resistant microorganisms grow at subinhibitory concentrations and selection is based on the differential fitness they present in the presence of the antimicrobial. This means that the selection of resistance requires, in this case, several duplications to allow the displacement of the susceptible population by the resistant one, which is fitter in the presence of an antibiotic. While it is true that there are several situations in which bacteria are under subinhibitory concentration, such as in the human body after treatment, these concentrations tend to be transient and it is difficult for a resistant population to be selected unless a constant selection pressure is implemented. There are, however, some situations in which this type of selection can be foreseen. One is in waste-water from hospitals or from antibiotic producing plants. Another is in animal production when antibiotics are used as growth promoters. Indeed, the study of the metagenomes of pigs treated with antibiotics for long periods of time has shown their guts present an increase in Proteobacteria as well as in abundance and diversity of resistance genes, even some of them conferring resistance to antibiotics not administered in the study. These results raise the possibility that non-therapeutic use of antibiotics can be a major element in the selection of antibiotic-resistant bacteria in animals, which will eventually be more important than their therapeutic use. Work on the effect of antibiotics on the behaviour of bacterial populations usually takes into consideration just the antibiotic itself. However, recent work has shown that the presence of other stressors may modulate such effects. Usually, a second stressor increases the chances of acquiring resistance, but on other occasions the stressor antagonizes the selective pressure of the antibiotic. In the case of human health, this is particularly relevant when resistance to one antibiotic enhances the susceptibility to another (collateral sensitivity) because the use of such antibiotics together or in combination should reduce the chances of antibiotic resistance acquisition by human pathogens.

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