

# **Mechanisms of acquired antibiotic-resistance in bacteria from very remote human communities with minimal antibiotic exposure**

## **INTRODUCTION**

The selective pressure generated by the use of antibiotics (in clinical, veterinary, husbandry and agricultural practices) has been the major driving force leading to the emergence and spread of resistance traits among pathogenic bacteria observed since the beginning of the antibiotic era. A reduction of unnecessary antibiotic use and the introduction of rigorous antibiotic stewardship policies have been advocated as mandatory measures to control the global dissemination of resistance (1). However, the relationship between use of antibiotics and development/maintenance of resistance is complex, as evidenced by the fact that resistance is not always reversible following restriction of antibiotic use, and by the finding of acquired antibiotic resistance (i. e. resistance to antibiotics to which the bacterial species is intrinsically susceptible) among commensal bacteria isolated from humans and wild animals not subjected to significant antibiotic exposure and living in remote areas of the planet (2). These unexpected observations underscore the complexity of the mechanisms involved in the emergence and spread of antibiotic resistance, and suggest that a better understanding of these mechanisms is crucial to improve strategies for antibiotic resistance control.

## **THE STUDY**

Following a research project aimed at describing antibiotic use and resistance in Bolivia and Peru (ANTRES Project), we found that faecal carriage of *Escherichia coli* with acquired antibiotic resistance traits was widespread in subjects living in urban areas (3;4), and showed relevant levels also in individuals from a very remote Chayahuita Indian community of the Peruvian Amazonas with very low levels of antibiotic exposure and limited exchanges with exterior. The patterns and rates of resistance found in the Chayahuita community were similar to those we previously observed in a very remote Guaraní Indian community in the Bolivian Chaco (high levels of

acquired resistance to the oldest antibiotics, e. g. tetracycline, ampicillin, trimethoprim-sulfamethoxazole, streptomycin, and chloramphenicol) (5; 6).

The general objective of this study was to investigate the resistant bacterial population from the remote Amazonas community and to compare the resistant isolates from that setting with those from the nearest urban areas and from the remote Bolivian community.

Findings from this study showed a remarkable diversity of resistant clones and resistance genes and plasmids (7). Overall, the population structure of resistant bacteria and the nature of resistance genes were similar to those observed in the previously surveyed remote community of Bolivia, located in a completely unrelated geographic and climatic context, where the level of isolation and antibiotic exposure was comparable. Present findings therefore suggest that antibiotic resistance observed in remote communities with minimal antibiotic exposure is a general phenomenon contributed by complex mechanisms which follow a consistent pattern.

In this study, it was also possible to compare data obtained in the remote Peruvian community with those obtained in the nearest urban area, which had been investigated in the same research project. In both settings, the highest resistance rates were observed for the oldest antibiotics, with resistance rates surprisingly comparable between the two settings. Similarities between the remote community and the nearest urban area were also observed for the most prevalent MDR phenotype and the nature of resistance genes.

Overall, these findings suggest that the limited contacts with the urban areas (e.g. sporadic travellers, animals) could be enough to provide an influx in the remote communities of resistant isolates and resistance genes. Occasional introduction of resistant strains from the exterior would be followed by both clonal expansion of resistant strains and horizontal transfer/recombination of mobile genetic elements harbouring resistance genes, even in the absence of a sustained antibiotic exposure.

Results from this study suggest that, although crucial for decreasing the emergence and dissemination of resistance, strategies based only on antibiotic restriction policies are unlikely to

fully succeed for some type of resistant strains and resistance genes. It is now clear that antibiotic resistance should be viewed as a complex ecological problem and also be addressed by applying a landscape ecology approach, which allows taking into account the multitude of factors affecting this phenomenon (e. g. type and level of selective pressure, routes of transmission, mechanisms of persistence).

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