Trends in Microbiology

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Opinion

Assessing the Risk of Antibiotic Resistance Transmission from the Environment to Humans: Non-Direct Proportionality between Abundance and Risk

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The past decade has witnessed a burst of study regarding antibiotic resistance in the environment, mainly in areas under anthropogenic influence. Therefore, impacts of the contaminant resistome, that is, those related to human activities, are now recognized. However, a key issue refers to the risk of transmission of resistance to humans, for which a quantitative model is urgently needed. This opinion paper makes an overview of some risk-determinant variables and raises questions regarding research needs. A major conclusion is that the risks of transmission of antibiotic resistance from the environment to humans must be managed under the precautionary principle, because it may be too late to act if we wait until we have concrete risk values.

Risk Associated with the Environmental Antibiotic Resistome

The risks associated with the environmental antibiotic resistome have been discussed under three different perspectives: at the microbial community level, the genome level, and the transmission of resistance. One refers to the risks of the emergence and evolution of clinically relevant antibiotic resistance from the environment and that may be enhanced by exogenous factors, such as chemical contaminants or physicochemical conditions [1–4]. This kind of insight, approached mainly at the bacterial community level, using either culture-based or culture-independent methods, is essential to understand how processes such as wastewater treatment, water disinfection, manure application in soils, or environmental pollution may contribute to enrich the environment in antibiotic-resistant bacteria (ARB). Another perspective of risk, approached essentially at the genome level, focuses on the threat imposed by genes that can confer resistance to antibiotics, but which differ on the spectrum of drugs against which they may be active and on the potential to be transferred by horizontal gene transfer. These traits affect their clinical relevance and therefore the associated human risk [5,6]. A third perspective of risk refers to the transmission of ARB or antibiotic-resistance genes (ARG) from the environment to humans [7–9]. Curiously, although the ultimate goal of most studies about the environmental antibiotic resistome is associated with human health, this is probably the least explored type of risk. This is due, in part, to some major gaps that hamper reliable risk assessments, in particular, the nonexistence of databases that cross human- and environmental-related resistome data [10]. Nonetheless, the risk of transmission to

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The absence of a significant overlap of antibiotic-resistant bacteria (ARB) and antibiotic-resistance genes (ARG) between the human microbiome and potential environmental sources should not be interpreted as an indication of risk absence. Hence, screening of ARG pools cannot be used as an accurate measure of the risk for transmission to humans.

The risks of transmission of antibiotic resistance from the environment to humans must be assessed based on ARB (not only on ARG) that are able to colonize and proliferate in the human body. The risk is a function of their fitness in the human body and the presence of resistance and virulence genes.

Even at extremely low abundance in environmental sources, ARB may represent a high risk for human health. The limits of quantification of methods commonly used to screen for ARG in environmental samples may be too high to allow reliable risk assessments.

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humans may surpass the level of comparative analyses of epidemiological data. This paper aims to discuss critical aspects that govern the transmission of ARB and ARG from the environment to humans and proposes the identification of some key risk determinant factors.

A Transmission Chain of Reservoirs, Carriers, and Vectors

Although the pathways and modes of transmission of antibiotic resistance to humans are still poorly understood, there are multiple instances of evidence of the wide and rapid spread of both ARB clones and ARG variants. The current knowledge suggests that a complex combination of variables referring to different environmental compartments, ubiquitous bacteria, and human–bacteria interaction may rule the risks of transmission to humans [9,11]. These aspects are discussed in this section.

Natural versus Contaminant Antibiotic Resistome

The environmental resistome comprises both the natural antibiotic-resistance pool and that resulting from human activities, herein designated contaminant (Figure 1, Key Figure). The natural resistome, where genes have been found with significant identity to those of clinically relevant multidrug-resistant (MDR) pathogens, probably represents the beginning of the whole antibiotic-resistance cycle [12]. Hence, these ARB, most of which are probably strictly environmental, can be considered reservoirs [13,14]. Reservoirs comprise phylogenetically diverse bacteria, belonging to phyla such as Actinobacteria, Proteobacteria, or Bacteroidetes, often antibiotic producers or with the capacity to transform or metabolize antibiotics [12–16]. However, it is unlikely that all ARG that have arisen in clinical pathogens and continue to spread are only due to a direct transfer from reservoirs. Thus, it can be hypothesised that some intermediary agents are required to complete this process. This role can be attributed to bacteria that are abundant in the contaminant resistome, have high genome plasticity, and are able to spread ARG over different environmental compartments and among different bacterial populations. While the transfer of ARG from reservoirs (natural) to other bacteria may be a rare and random event, contaminant ARB and ARG may be able to spread rapidly and widely (e.g., New Delhi metallo-β-lactamase, *bla*NDM-1; extended-spectrum beta-lactamase $bla_{CTXM-15}$; methicillin-resistant *Staphylococcus aureus*, MRSA) [17–19]. Therefore, the risks of transmission of ARB from the environment to humans are probably higher in the contaminant than in the natural resistome.

The contaminant antibiotic resistome comprises two major types of player: (i) carriers that are ARB with a role in the spread of ARG in the environment, but which cannot colonize or infect the human body, and (ii) vectors that are ARB that can colonize and sometimes invade the human body (Figure 1). Carriers and vectors are not necessarily members of distinct taxonomic groups, and the difference between both may be at the level of ecology or at the physiological level. That is, vectors, but not carriers, have the chance to be in contact with humans; or vectors, but not carriers, have the ability to colonize the human body (Figures 2 and 3). According to the available literature, among the most active potential carriers and vectors seem to be members of the classes Gammaproteobacteria and Betaproteobacteria and of the phyla Actinobacteria and Firmicutes [20,21]. Members of the family Enterobacteriaceae, and of genera such as *Aeromonas*, *Acinetobacter*, *Pseudomonas*, *Enterococcus*, or *Staphylococcus*, have been frequently described as carriers, and some of them are also recognized vectors [20,22]. In the conceptual model proposed, vectors would be the end-of-the line for antibiotic resistance transmission to humans. Even though carriers are not able to colonize and infect humans, their spread and proliferation in the environment would increase the abundance and diversity of ARG in vectors. Hence, it may increase the risks of transmission of ARB to humans.

Vector Bacteria: A Vehicle for ARG from the Environment to Humans

The risks of transmission of antibiotic resistance from the environment to humans must be assessed based on bacteria, rather than on their resistance genes – in particular, bacteria that