Resistance to antibiotics of bacteria in tropical countries

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Key words: Antibiotic resistance, tropical countries, natural antibiotic compounds

The identification of the source of resistance of bacteria to antibiotics is, in my opinion, too naïve and too much based on the guilt of human-related activity. This perception of the world yields analyses that claim to establish an exclusive link between the use of man-made antibiotics and the resistance of microorganisms to antibiotics. This illusion neglects the importance of the source of natural antibiotics. Most antibiotics are secreted naturally by microorganisms, bacteria, of the actinomycetes phylum, or fungi(1). These antibiotics are naturally present in the environment and the antibiotic resistance of microorganisms existed long before their medical use. Beta-lactamases are found in genetic sequences of microorganisms from the Middle Ages, and the resistance of *Staphylococcus aureus* in the 19th century has recently been demonstrated (2). Antibiotics are assembled in microorganisms by non-ribosomal protein synthases and polyketides synthases, which are the only known translation devices outside the ribosome. Their existence may have preceded that of ribosomes and may be archaic translation machineries. Since biodiversity in general is much higher in the humid intertropical zone, it is also likely to be the place where the most diverse microorganisms are found, as evidenced by the richness of the human microbiota in rural intertropical areas compared to urban or temperate areas(3). This biodiversity can be accompanied by a biodiversity of molecules with antibiotic activity. Finally, the molecules secreted by non-ribosomal protein synthase and polyketide synthase have multiple activities, not only antimicrobial but also antifungal. Against eukaryotes, some molecules are used as anti-cancer treatments. Some human beta lactamases have anticancer drug inhibitory activity as with mitomycin(4). The spectrum of activity of beta lactamases far exceeds the anti-beta lactamine activity, playing a role in the digestion of nucleic acid (4).

Antibiotic resistance is a global concern and, interestingly, the source of resistance is often found in the world's intertropical or hottest regions (5). This specificity has not been satisfactorily explained and has just been confirmed by a very extensive study carried out in this journal(6) which shows that a country's overall antibiotic consumption is not correlated with the level of bacterial resistance. On the contrary, there is an inverse relationship, the lower the prescription rate, the higher the

resistance level. We have confirmation of this in France, where antibiotic consumption is one of the highest in the world, and where the level of resistance is one of the lowest in the world, particularly in Marseille(7).The same is true in the United States, where difficult-to-treat Gram-negative bacteria represent a very small proportion of the bacteria isolated from the blood cultures of hospitalized patients(8). The reason for these differences remains poorly explained. One of the explanations proposed was the poor management of antibiotics prescribing in humans, which could explain this discrepancy(5). This seems to overlook the idea that man-made antibiotics are the only source of antibiotics, neglecting those produced in the environment. Antibiotics can eventually be used as food by other microorganisms, which in turn develop enzymes to digest them for consumption(9). It has been evaluated that most families of antibiotics can be used as growth factors for soil microorganisms, and the digestion of penicillin and its use as a sole source of carbon has been demonstrated in *Escherichia coli* transformed in vitro. This shows that antibiotics do not only kill microorganisms, but can also serve as a nutrient, especially in areas particularly rich in environmental microorganisms. In addition, it has recently been shown that some arthropods are capable of secreting penicillins and cephalosporins, leading to a less simplistic view of antibiotics, of selection pressure exclusively from human-made drugs, and resistance(10). Thus, beta-lactam resistance genes are detected in all vertebrates, including humans, but also in archaea, which are not sensitive to beta-lactams (11).The work conducted in this journal on Kenya shows that in a city where antibiotic prescribing is extremely low, the level of resistance of *Escherichia coli* is particularly high, not only in humans but also in wildlife. This study must put into perspective a much less anthropocentric approach but integrate the fact that antibiotics are probably more than 3 billion years old, as are antibiotic resistance enzymes, and that we can only understand, and therefore combat antibiotic resistance, if we have a more scientific vision of this world.

In conclusion, public health considerations lead to a significant simplification, in particular for sending simple messages that can be understandable to all, but partially false. This needs to be acknowledged. Control measures should not prevent the integration of recent scientific data for fear

of misuse of antibiotics. Such a line of thought might end up being dangerous for humans and more emphasis should be put on the complexity of the relationships between antibiotics and the enzymes that, among others, digest them.

Funding

No funding was received for this work.

Competing interests

There are no conflicts of interest.

Reference List

(1) Angelakis E, Merhej V, Raoult D. Related actions of probiotics and antibiotics on gut microbiota and weight modification. Lancet Infect Dis 2013 October;13(10):889-99.

(2) Raoult D, Rolain JM. The Living Croquet Theory: The Staphylococcus aureus Paradigm. Int J Antimicrob Agents 2019 April 12.

(3) Angelakis E, Bachar D, Yasir M, Musso D, Djossou F, Melenotte C et al. Comparison of the gut microbiota of obese individuals from different geographic origins. New Microbes New Infect 2019 January;27:40-7.

(4) Lee SY, Brem J, Pettinati I, Claridge TD, Gileadi O, Schofield CJ et al. Cephalosporins inhibit human metallo beta-lactamase fold DNA repair nucleases SNM1A and SNM1B/apollo. Chem Commun (Camb) 2016 May 10;52(40):6727-30.

(5) Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health 2018 September;2(9):e398-e405.

(6) Hassell JM, Ward MJ, Muloi D, Bettridge JM, Robinson TP, Kariuki S et al. Epidemiology of Clinically Relevant Antimicrobial Resistance at the Wildlife-Livestock-Human Interface in Nairobi. The Lancet Global Health. In press 2019.

(7) Le Page S., Dubourg G, Baron SA, Rolain JM, Raoult D. No global increase in resistance to antibiotics: a snapshot of resistance from 2001 to 2016 in Marseille, France. Eur J Clin Microbiol Infect Dis 2018 December 4.

(8) Raoult D, Rolain JM. The paradigm of the Shadoks and antibiotic resistance. Clin Infect Dis 2019 March 6.

(9) Hibbing ME, Fuqua C, Parsek MR, Peterson SB. Bacterial competition: surviving and thriving in the microbial jungle. Nat Rev Microbiol 2010 January;8(1):15-25.

(10) Pontarotti P, Raoult D. Why do arthropods secrete beta-lactams? Int J Antimicrob Agents 2019 April;53(4):370.

(11) Keshri V, Panda A, Levasseur A, Rolain JM, Pontarotti P, Raoult D. Phylogenomic Analysis of beta-Lactamase in Archaea and Bacteria Enables the Identification of Putative New Members. Genome Biol Evol 2018 April 1;10(4):1106-14.