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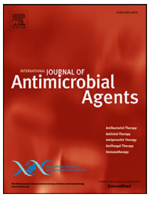

Hot Topic

The living croquet theory: The *Staphylococcus aureus* paradigm

Some time ago, we proposed the hypothesis of living croquet, which postulates that when three different living beings are constitutive elements of a multifactorial phenomenon [1], it is impossible to predict their future. This is illustrated in the novel *Alice in Wonderland* by the fact that Alice, a little girl, plays croquet with a mallet that is a pink flamingo moving by itself in all directions, and the ball is a hedgehog that has its own destiny and makes its own choices. The chance that Alice, by using the mallet and this ball, can direct it through the hoop as she wants or predict in what direction it will go is simply unreasonable. This is true for all predictive models in which the elements are multiple, from our point of view. This illustrates the Yiddish proverb 'man predicts, God laughs' [2].

Thus, in the evolution of bacterial resistance to antimicrobials, most of the evolutionary elements have been incomprehensible because the partners are of different nature. An example of interest is that of *Staphylococcus aureus* (Fig. 1A). The restriction of our field of vision led us to believe that there are only two partners for selection of resistance in *S. aureus*, i.e. the bacterium itself and humans, and that only the use of drugs invented by humans (extended-spectrum penicillins) would have selected resistance. Such resistance would be the direct result of human activity.

This reflection is part of a fear common to all mankind called Anthropocene, that is to say the modification of our ecosystem by the human species. In fact, antibiotics have extremely diverse and natural sources. They are mainly derived from non-ribosomal peptide synthetases, which are themselves non-ribosomal proteins made from a combination of typical and atypical amino acids (not assembled by ribosomes). These secondary metabolites were created probably more than 4 billion years ago [3] in an intermicrobial conflict. Traces of genes that code for antibiotics and genes that encode for enzymes such as β-lactamases have been found in archaic samples in various ecosystems, including vertebrates and humans [3–6]. Indeed, antibiotics are natural products, especially β-lactams, as well as resistance to β-lactam antibiotics, whether it is resistance to β-lactams by β-lactamases or antibiotic resistance by genes pre-dating the use by humans of antibiotic molecules and probably the very appearance of man. It should be noted that penicillin can be secreted by an arthropod [7]. Therefore, the purely human vision that only use of antibiotics by humans is responsible for antimicrobial resistance is false and needs to be revisited, because staphylococci are not only human commensals. A great evolution of recent knowledge shows that many wild animals are infected, including birds (perhaps the flamingos of *Alice in Wonderland*), and therefore human carriage of *S. aureus* is rather banal. Finally, to complete the picture, it has recently been shown that *S. aureus* is present in wildlife, including *mecC*-MRSA (methicillin resistance gene *mecC*-positive methicillin-resistant *S. aureus*) in wild hedgehogs (the croquet ball in *Alice in Wonderland*) in Sweden, with similar *spa* types of such isolates with human isolates likely suggesting possible zoonotic transmission [8].

The time has come to understand that areas including multifactorial data in complex ecosystems are not predictable. It is naïve to think that simply establishing a doctor in charge of antimicrobial stewardship will change the story of a fight that has lasted for millions of years between different microbes. In fact, there are several key examples of predictable and unpredictable evidence linked to antimicrobial resistance in *S. aureus* as well as evidence of adaptation in humans. Although the role of humans and prescription of antibiotics is undeniable and predictable in specific and restricted ecosystems where antibiotic selection pressure is high (e.g. farm animals), the results are unpredictable in larger ecosystems such as the environment or in human beings in the community.

For example, although it was predicted that MRSA will spread worldwide owing to the acquisition of various mobile staphylococcal cassette chromosome *mec* (SCC*mec*) elements, the worldwide decrease of MRSA over the last 15 years could not be predicted [9]. Similarly, the first description of a plasmid containing the vancomycin resistance gene *vanA* transferred from *Enterococcus faecalis* to *S. aureus* was believed to become a nightmare scenario when it was reported in the USA in 2002 [10]. However because of plasmid instability, such vancomycin-resistant *S. aureus* has not been successful, and this was fortunate but also unpredictable. Emergence of different clones with heteroresistant vancomycin-intermediate *S. aureus* (hVISA) and vancomycin-intermediate *S. aureus* (VISA) phenotypes by genome adaptation was predictable and worrying, however the clinical implications remain unclear since these strains are usually not associated with an increase mortality [11]. Conversely, there is scientific evidence that the human microbiome can contain many microbes able to synthesise secondary metabolites that could help humans to adapt to and fight against other microbes, and this dynamic process is also unpredictable since it depends on many different factors including our diet and/or genetic predisposition [12]. In this perspective, the living croquet theory (Fig. 1B) is a new way of thinking of the evolution of antimicrobial resistance as a complex set of living beings with each having its own destiny and that the consequences of this complex dynamic process cannot be solved taking into account only the microbe itself and the use of antibiotics by humans. Thus, based on this theory of complexity of living cells, we believe that we need to continue to survey not only resistance to antibiotics at local, national and international levels but also the emergence of new clones that could be more invasive but less resistant. A better understanding of the complexity of the different ecosystems

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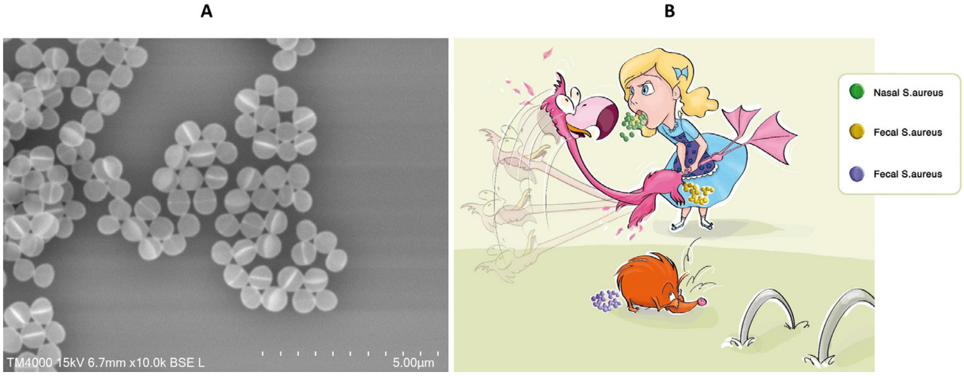

Fig. 1. (A) Electron microscopy image of *Staphylococcus aureus* (TM4000 microscope; Hitachi, Tokyo, Japan). (B) The theory of Alice's living croquet is to explain that *S. aureus* from human nasal carriage and those from faecal flamingo or hedgehog have their own biological evolution and it is impossible to predict the future of resistance because some clones and/or genetic exchanges between *S. aureus* may lead to an unexpected new clone. By analogy, the outcome of this game is also unpredictable because each of the partners (Alice, the flamingo and the hedgehog) in this game are biological entities with their own behaviour.

involved (animals, food, environment, our microbiome, etc.) in this dynamic process may help in the future to adapt our strategies for the treatment of infectious diseases to the reality and not to prediction and fantasies.

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Competing interests

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References

[1] Raoult D. Alice's living croquet theory. Int J Antimicrob Agents 2016;47:249. doi:10.1016/j.ijantimicag.2016.01.013.
[2] Coben H. Shelter. New York, NY: G.P. Putnam's Sons; 2011.
[3] D'Costa VM, King CE, Kalan L, Morar M, Sung WW, Schwarz C, et al. Antibiotic resistance is ancient. Nature 2011;477:457–61.
[4] D'Costa VM, McGrann KM, Hughes DW, Wright GD. Sampling the antibiotic resistome. Science 2006;311:374–7.
[5] Marshall CG, Lessard IA, Park I, Wright GD. Glycopeptide antibiotic resistance genes in glycopeptide-producing organisms. Antimicrob Agents Chemother 1998;42:2215–20.
[6] Keshri V, Panda A, Levasseur A, Rolain J-M, Pontarotti P, Raoult D. Phylogenomic analysis of β-lactamase in Archaea and bacteria enables the identification of putative new members. Genome Biol Evol 2018;10:1106–14. doi:10.1093/gbe/evy028.
[7] Suring W, Marien J, Broekman R, van Straalen NM, Roelofs D. Biochemical pathways supporting β-lactam biosynthesis in the springtail *Folsomia candida*. Biol Open 2016;5:1784–9. doi:10.1242/bio.019620.
[8] Bengtsson B, Persson L, Ekstrom K, Unnerstad HE, Uhlhorn H, Borjesson S. High occurrence of *mecC*-MRSA in wild hedgehogs (*Erinaceus europaeus*) in Sweden. Vet Microbiol 2017;207:103–7. doi:10.1016/j.vetmic.2017.06.004.
[9] Rolain J-M, Abat C, Brouqui P, Raoult D. Worldwide decrease in methicillin-resistant *Staphylococcus aureus*: do we understand something? Clin Microbiol Infect 2015;21:515–17. doi:10.1016/j.cmi.2015.04.017.
[10] Perichon B, Courvalin P. VanA-type vancomycin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2009;53:4580–7. doi:10.1128/AAC.00346-09.
[11] Howden BP, Peleg AY, Stinear TP. The evolution of vancomycin intermediate *Staphylococcus aureus* (VISA) and heterogenous-VISA. Infect Genet Evol 2014;21:575–82. doi:10.1016/j.meegid.2013.03.047.
[12] Fritz S, Rajaonison A, Chabrol O, Raoult D, Rolain J-M, Merhej V. Full-length title: NRPPUR database search and in vitro analysis identify an NRPS-PKS biosynthetic gene cluster with a potential antibiotic effect. BMC Bioinformatics 2018;19:463. doi:10.1186/s12859-018-2479-5.