TRANSMISSION OF ANTIMICROBIAL RESISTANCE FROM PIGS TO HUMANS: TRUES AND LIES

Luca Guardabassi
DVM, PhD, ECVH Diplomate
Affiliated Professor, Faculty of Life and Medical Sciences, University of Copenhagen

Through the years, use of antimicrobials in livestock has been the subject of an endless debate about the appropriateness of using these important medicines in the veterinary sector. This is a highly controversial topic involving ethical issues on animal welfare and human health, as well as economic interests by the pharmaceutical industry, the food industry and various professional categories, including farmers, veterinarians, pharmacists and researchers. As a consequence of all these factors, the debate has been often vigorous but not always scientifically unbiased. The aim of this lecture is to review the state-of-the-art on transmission of antimicrobial resistance (AMR) from pigs to humans with particular emphasis on specific risks that were overestimated by the scientific community in the past.

The human health risks associated with consumption of pork contaminated with resistant bacteria are highly dependent on the bacterial species and the type of AMR involved. Historically, the main risks have been associated with foodborne pathogens such as Salmonella and Campylobacter. However, the public health burden attributable to AMR in these species is limited, since infections are generally self-limiting and, in most cases, managed without antimicrobial therapy. Moreover, resistance to clinically-relevant antimicrobial agents is generally low among both porcine and human clinical isolates, although there are significant geographical differences.

Pigs are also a reservoir of other types of resistant bacteria that may colonize the human body without causing disease, transfer AMR genes to the commensal microbiota, and eventually cause opportunistic infections by taking advantage of specific host factors such as immunosuppression, altered microbiota or breached integumentary barriers. Vancomycin-resistant enterococci (VRE) belong to this category. The risk of foodborne transmission of VRE was highly debated during the 1990s in relation to the use of avoparcin in livestock, which was banned in the EU in 1997. However, the use of highly discriminatory typing methods based on DNA sequencing has shown that the VRE lineages causing infections in humans are not epidemiologically related to those occurring in pigs and other types of livestock. Moreover, the countries where VRE are a frequent cause of human infections (e.g. USA) have never used avoparcin in livestock but have extensively used vancomycin and other glycopeptides in human medicine, suggesting that human use of these antibiotics is the main driver for the spread of VRE.

In recent years, methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum β-lactamase (ESBL)-producing Escherichia coli are the most important multidrug-resistant bacteria that have emerged in pig production. These bacteria are, by definition, resistant to cephalosporins, which are first-line agents in the therapy of severe E. coli and S. aureus infections, and therefore resistance has a considerable impact on morbidity, mortality and healthcare costs. Human infections caused by LA-MRSA clearly originate from pigs but their public health impact is negligible in countries with high MRSA prevalence, and their widespread occurrence in countries with high pig production and low MRSA prevalence in the human population has not resulted in an increase of the overall mortality rate due to S. aureus infections, which is
mainly impacted by methicillin-susceptible strains. In these countries, the main impact of LA-MRSA is economic since their spread among farm workers has increased the costs associated with active surveillance and decolonization, and represents a potential threat to the sustainability of the national ‘search and destroy’ control policies.

Notably, the risk that ESBL-producing *E. coli* are transmitted by food is higher than for LA-MRSA, since this route of transmission is unusual and largely unknown for *S. aureus*. Furthermore, while LA-MRSA have limited ability to transfer methicillin resistance to other human pathogenic *S. aureus* lineages, ESBL-encoding genes spread by horizontal transfer of plasmids that can readily be exchanged between *E. coli* of animal and human origins. Consequently, foodborne transmission of ESBL-producing *E. coli* is more insidious and difficult to assess and control compared to LA-MRSA, and the actual burden of human infections attributable to ESBL-producing *E. coli* of animal origin remains poorly assessed. Based on recent whole genome sequencing studies, such burden appears to be smaller than previously predicted by the scientific community, as confirmed by the low prevalence of the predominant ESBL type in pigs (CTX-M-1) among human clinical isolates and by the structural differences observed between the plasmid vectors carrying this resistance determinant in human and pig populations within a defined geographical area. Various modelling studies have estimated that the contribution of pork to human exposure to ESBL-producing *E. coli* is significantly lower than for poultry meat and beef.

Other multidrug-resistant bacteria responsible for treatment failure and high mortality in human medicine, such as carbapenem- and colistin-resistant Enterobacteriaceae, are increasingly reported in livestock in some Asian countries but these bacteria are much less frequent in pig production systems in the rest of the world, and display significant differences in comparison with those isolated from human patients. In general, remarkable geographical differences exist in the prevalence of AMR resistance and such differences often, not always, reflect national patterns of antimicrobial usage. Accordingly, the type and extent of the interventions needed for prevention and control of AMR are not the same for all countries. Each country should define specific objectives based on the national context, and develop an adequate action plan that is able to accomplish them in line with the available resources. Establishing national One Health surveillance programs is a good starting point to understand the complex interactions between antimicrobial usage and the occurrence of AMR, but adequate resources should also be allocated to ensure efficient communication and education of antimicrobial prescribers and users, effective infection prevention, and optimization of antimicrobial use, which in turn requires investment for updating and implementing national guidelines on prudent antimicrobial use as well as for developing new medicines, diagnostic tools, vaccines and interventions.