A one-health approach to antimicrobial resistance

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Widespread use of antibiotics in animals either as growth promoters or for metaphylaxis may drive the spread of clinically relevant drug resistance genes and pathogens. New work uncovers drug resistance gene patterns from livestock across European farms and finds a correlation with agricultural antibiotic use.

The face of antimicrobial resistance (AMR) has changed rapidly. Fifteen years ago, our focal point rested on Gram-positive pathogens that were being circulated in hospitals, such as methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant pneumococcus (PRP) and vancomycin-resistant enterococci (VRE). Clinical management of PRP and MRSA, for example, was relatively straightforward and focused on infection control and hospital containment (at least before the emergence of community-acquired MRSA)[1]. Today, however, the spotlight has shifted to Gram-negative pathogens — particularly multidrug-resistant (MDR) or extensively drug-resistant (XDR) Enterobacteriaceae. Specifically, over the last 15 years, extended-spectrum β-lactamases and, in the last 10 years, mobile carbepenmases (for example, New Delhi metallo-β-lactamase 1 (NDM-1)) have now become globally ubiquitous in Gram-negative pathogens[2,3]; and in the last 3 years, the discovery of a mobile colistin resistance mechanism, MCR[4], has meant that some strains are virtually untreatable with our current pharmacopoeia.

The rapid increase in Gram-negative antibiotic resistance has changed how we perceive AMR. In particular, many of the Enterobacteriaceae normally reside within human and animal gut microbiomes, and thus resistance genes and pathogens can be widely disseminated in agricultural and human waste. While long-ignored, we are now — arguably too late — considering how contaminated potable water, domestic and industrial waste management and use of antibiotics in animals are contributing to AMR dissemination[5]. For example, the emergence of MCR has almost certainly been exacerbated by the use of colistin on Chinese and Southeast Asian farms[6]; and in this issue

of Nature Microbiology, Munk and colleagues now show that such antibiotic-associated resistance selection is also occurring throughout European farms[7].

Munk et al. quantified and characterized the acquired-resistance gene pools (resistomes) of 181 pig and 178 poultry farms from 9 European countries, sequencing more than 5,000 gigabases of DNA using shotgun metagenomics[7]. They subsequently quantified acquired AMR using the ResFinder database and a second database constructed for this study that consists of AMR genes identified through screening 'environmental DNA'. These data showed that the pig and poultry resistomes were very different in their composition and their abundance of AMR genes. There was a significant country-specific effect on the resistomes, which is hardly surprising when the type and amount of antibiotics used on farms is quite heterogeneous. Interestingly, Monk and colleagues found higher AMR loads in pigs, while poultry resistomes were more diverse; disconcertingly, they also saw that the abundance of several critical AMR genes, including mcr-1 and optrA, were highly varied between host species and country. For example, the levels of MCR appeared higher in Bulgaria, which did not accord with the apparent colistin usage. Generally, however, the study showed that the total acquired-AMR level was associated with the overall country-specific antimicrobial usage in livestock and that countries with comparable antibiotic usage patterns had similar resistomes.

The advantage of assessing the whole resistome is that the total burden of AMR can be theoretically assessed. However, such approaches do have some limitations and rely on certain assumptions. First, the total effect of the resistome across the entire microbiome is not fully understood (that is, phenotypic resistance may be different than the individual components). Second, such resistance prediction relies on gene homology but relevant flanking sequences such as promoters are rarely considered, which may lead to overestimation of resistance. Third, we are limited by our knowledge of existing resistance genes and the drugs to which they confer resistance. Only after the characterization of mcr as a colistin resistance gene was mcr'discovered' in genomic databases across numerous countries[4]. This example highlights the continued need for classical microbiology to inform bioinformatics and expand our knowledge on novel resistance mechanisms. Additionally, there is a need to compare the resistant bacteria that can be

grown with the overall resistome, which will provide a better measure of the 'phantom resistome', that is, the resistome that cannot be cultured, which is very different from unculturable bacteria. For example, in Wang et al., the difference between the sequence- and culture-based methods in detecting mcrand blaNDM was usually close to two-fold, suggesting that the resistance phenotype did not reflect the genotype or resistome[8] and that the resistome is often considerably larger than what we may believe.

The emergence of widespread resistance has also forced us to consider the 'one-health' approach to understanding AMR and how it spreads across all community sectors (such as hospitals, communities (for example, human carriage of AMR), farming animals (including fish), other animal vectors (including insects, human and animal waste, wastewater systems), and so on (Figure 1)). But, while monitoring MRSA spread on an intensive care or post-surgical ward is relatively simple — patients are confined to beds and the contagion can be assessed by swabbing of anterior nares or axilla — extensively sampling for carbapenem- and colistin-resistant Enterobacteriaceae, for example, in one-health sectors poses major challenges. First, what is a representative sample given the vastness of the number of potential sampling sites? Second, how do you measure resistance prevalence in such a space? Third, do you detect both phenotypic and genotypic resistance (thereby capturing the phantom resistome), and what relevance do they have to each other? Fourth, how do you factor in climatic and anthropogenic effects (for example, flooding, antibiotic usage, pollution) on AMR? Fifth, if you are calculating associations with resistance prevalence, how accurate is the epidemiological data (for example, local antibiotic feed consumption, temperatures, rainfall)? One approach to deal with these confounders would be to focus on a small number of sites and systematically collect a defined set of samples to cater for seasonal variation[8], but this approach would present challenges in ever larger studies.

Munk and colleagues have used new technologies to address an old problem and importantly deliver an expansive, unique set of data in a unique way. These types of large datasets will be critical for understanding how AMR is spread and intersects with human health. However, to truly examine cause and effect using microbiomes across all one-health sectors, the data required in the future will need to be even vaster and its subsequent analysis will be even more challenging.

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FIGURE 1: COMPLEX AMR INTERACTIONS ACROSS ONE-HEALTH SECTORS.

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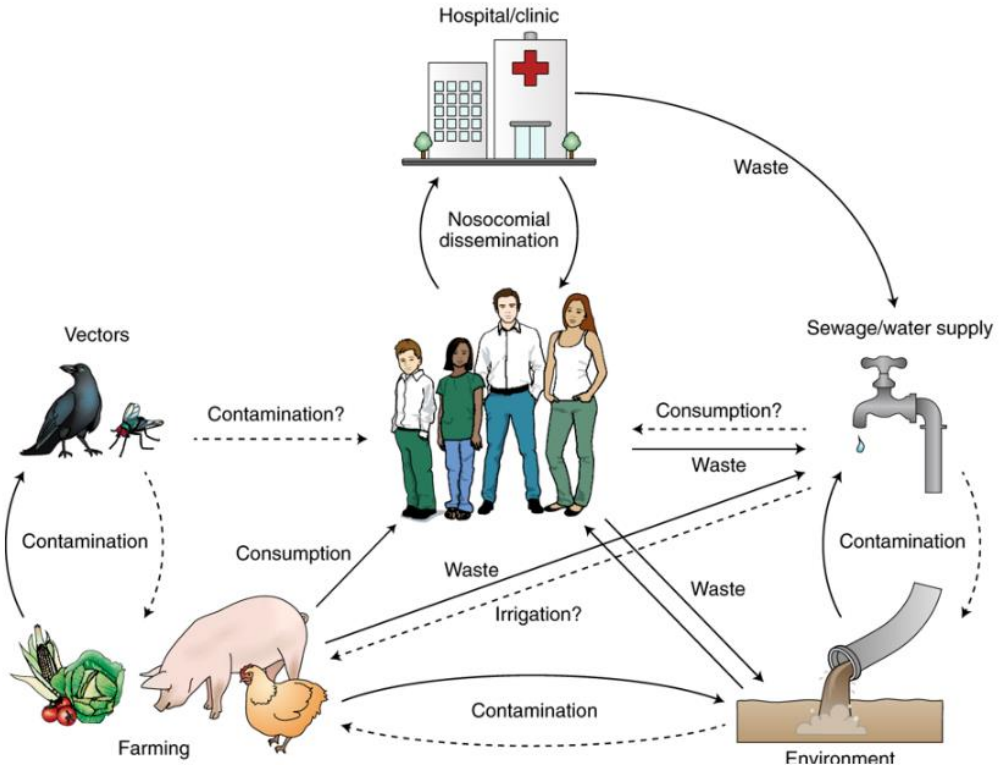

A potential schematic for complex transmission paths between human, environmental, agricultural and clinical reservoirs of AMR genes and drug-resistant pathogens. Dashed lines indicate putative transmission paths.