COVID-19 and Antimicrobial Resistance: the case for a One Health approach

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[1] Responsible Use of Medicines in Agriculture Alliance

Abstract

The impact of COVID-19 on global One Health issues, such as antimicrobial resistance is still unravelling but could have far reaching consequences. However, the disruptive nature of the pandemic could also produce beneficial outcomes. Here we discuss the potential impact of COVID-19 on another key One Health area – the veterinary profession - its efforts to reduce antibiotic use in the fight against antimicrobial resistance and the role a One Health approach plays in addressing this global challenge in a post-pandemic UK.

Antibiotics are a key part of the approach to treat secondary infections in patients hospitalised with COVID-19. A review of data from COVID-19 cases, mostly in Asia, found that over 70% received mostly broad-spectrum antibiotics as part of their treatment.[1] This pattern is predicted to be similar in Europe and North America [2] despite studies suggesting that only 10-15% of COVID-19 patients have bacterial co-infections.[1,3,4] In the UK, remote healthcare consultations have increased, which have previously been associated with greater precautionary antibiotic prescribing.[5] The ramifications of COVID-19 on the fight against antimicrobial resistance (AMR) could, therefore, be significant.

A similar effect may also be seen in veterinary health care. The impact of COVID-19 on veterinary prescribing is still emerging but one consequence of the pandemic has been changes to the provision of veterinary care to companion and food-production animals. This includes remote prescribing of antibiotics to safeguard animal health and welfare.[6] The British Veterinary Association has voiced concerns about the potential impact on AMR from excessive/irresponsible prescribing in the absence of a physical examination.[7]

Moreover, COVID-19 has been diagnosed in a small number of domestic dogs, cats, captive felines and pet ferrets, however, it is believed to be transmitted by close contact with their owners/handlers.[8] A matter of graver concern is the spread of COVID-19 in farmed mustelids like mink.[9] This highlights the importance of veterinarians in protecting public health and working with health professionals – part of the concept of One Health. The One Health concept was defined in 2008 as "the collaborative effort of multiple disciplines – working locally, nationally, and globally – to attain optimal health for people, animals and our environment."[10] The World Health Organisation, World Animal Health Organisation, Food and Agriculture Organisation and the United Nations Environmental Programme have all committed to applying such a One Health approach to AMR. In this viewpoint, we weigh up the current evidence on drivers of AMR and put forward the case for encouraging One Health collaborations and breaking down professional silos for tackling global health challenges.

The Responsible Use of Medicines in Agriculture (RUMA) Alliance have been coordinating industry efforts to promote prudent use of antimicrobials since 1997 due to the risk of AMR to human and animal health from irresponsible antimicrobial use. While there is substantial antibiotic use in livestock farming globally, the UK has seen a decreasing trend across all livestock sectors over the past 5 years. In 2017, only 36% of national antibiotic consumption went to animals (26% for livestock species) compared to 64% for human health.[11] Irrespective of the quantities of

antibiotics used, evidence that antibiotic use in farming contributes significantly to resistance in human bacterial infections remains unclear but working collaboratively across animal, human and planetary health will be key to further our understanding.[12]

The strongest link between AMR in farmed animals and humans remains via foodborne pathogens, particularly *Campylobacter* spp. and *Salmonella* spp. Around 50% of *C. jejuni* isolates from UK retail chicken are resistant to ciprofloxacin,[13] a level which has not changed substantially over the past 7 years. This is despite reduced antibiotic use in the poultry meat sector (76% reduction between 2012-2019) and minimal use of quinolones.[14] These figures suggest that blanket removal of antibiotics from livestock production systems will not necessarily reduce AMR genes in bacterial pathogens. When resistance occurs due to gene mutations, there may not be a fitness cost or bacterial fitness may be enhanced, meaning resistance is more likely to become fixed in a population.[15] Unfortunately, food production has been reliant on antimicrobials in the past with notable examples of misuse in the form of antibiotics as growth promoters - a legacy of post-war industrialisation and rapid expansion of food production across Europe in the aftermath of World War 2. This practice has been prohibited in the EU since 2006 but it is the view of RUMA that use of antibiotics in food-producing animals should still be minimised to reduce the risk of AMR in foodborne pathogens.

Regarding other major pathogens such as MRSA, pathways of transmission and drivers of resistance between animals and humans remain elusive. There are several contradictory studies pertaining to livestock-associated MRSA (LA-MRSA) Clonal Complex 398, which has been found in people through screening.[16] LA-MRSA has been associated with individuals with direct contact with pigs/cattle, suggesting transmission mainly occurs between animals and their handlers.[16] However, a Danish study suggested spill-over of LA-MRSA strains from pig handlers to people with no contact with pigs.[17] A study from the UK [18] (which has a very different pig sector) did not repeat this finding, and so the route of transmission from animals to humans is still to be fully elucidated.

The transmission of commensal bacteria like *Enterococcus* spp. and *E. coli* through animal products has also been of considerable interest. A range of studies examining multi-drug-resistant infections in humans have found the bacteria involved not only have different genome sequences to those found in livestock[19], but are often of different species, suggesting bacterial resistance in humans is quite distinct.[20] Studies on plasmid-mediated resistance, (e.g., extended-spectrum beta-lactamases) also show limited evidence of links with animal sources,[21] casting doubt on antibiotic use in livestock farming as the primary driver of AMR.

A recent review by Tang and colleagues found the implications for human populations of reducing antibiotics in food-producing species were "unclear".[22] The role of environmental reservoirs of bacteria on transmission of resistance genes between different populations is also an emerging picture.[23] In a comprehensive review article on AMR in the environment, Singer and colleagues conclude that there is insufficient science to inform policy in this area.[23] This uncertainty makes clear the importance of a One Health research approach to determine which interventions - medical and shared environmental - are likely to yield the greatest impact in reducing AMR.

Despite the uncertainties, there is a risk that wherever antibiotics are used, bacteria develop resistance with the potential for transmission in the environment and between species. It is partly due to this risk that UK farming has driven down unnecessary use.[24] Ongoing surveillance between 2015-2019 shows not only a 74% reduction in highest-priority critically important antibiotic use but also decreased antibiotic resistance in the indicator strains taken from both livestock and raw animal products. [24] This decreasing trend in the UK is testament to how seriously the farming sectors under the leadership of the RUMA have taken the AMR crisis.

While the veterinary profession and aligned industries continue working towards maximal reductions without negative animal health and welfare repercussions, the question remains: How low can use be driven and how can this be achieved? The farming industry continually strives for better farm biosecurity, hygiene and husbandry practices to prevent and control disease, which often requires capital investment at a time when profit margins are being increasingly eroded.

The more specialised UK livestock sectors – poultry, pigs and fish – already produce affordable animal protein efficiently while meeting some of the highest animal welfare regulations and broadly adopted farm assurance standards in the world. In 2018 the UK food-producing sector was the fifth lowest consumer of antibiotics in the EU at 29.6 mg/PCU (Population Correction Unit), behind the Nordic countries.[25] Hence, UK antibiotic consumption is one of the lowest in the world even while remaining a major animal protein-producing country.[26]

System-level changes allowing livestock production to exceed these current achievements are likely to increase production costs, and such increased prices must be borne somewhere in the supply chain. With most farmers operating on minimal margins and many struggling to make a profit,[27] wider society may need to pay for such additional measures. Political pressure for affordable food could prevent the emergence of such systems unless they become part of an emerging post-COVID, post-Brexit economy. As with any change, an appreciation of the challenges and drivers of changing

behaviour is necessary. By working with behaviour change scientists using a One Health approach, we stand to make more progress.

The challenge of tackling climate change and the impacts of global food production on the environment and biodiversity are also important drivers for change. If targets are to be met, animal protein must be produced as efficiently as possible, minimising losses from disease, while overall production and consumption of animal-derived products will need to reduce (in Europe at least).[28] If additional costs are levied on consumers, this must be examined in the context of social deprivation and its impacts on diet and nutrition. This returns the focus to COVID-19 and how diet-related disease has influenced the severity of infection and consequent mortality.

Achieving further antibiotic reductions across the UK livestock industry is a complex issue, but one the sector is committed to finding ways of achieving. Encouragingly, many farms in each sector already have very low antibiotic use. Hopefully, the public's support for British farmers and local produce during the pandemic will enable the sector to invest and realise further reductions in our emerging post-COVID, post-Brexit economy, whilst recognising the critical connectedness of human, animal and planetary health.

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