Invited reply

The diversity of antimicrobial resistance is different in Salmonella Typhimurium DT104 from co-located animals and humans

In our paper, we set out to examine antimicrobial resistance patterns in animals and humans, using an existing extensive dataset of Salmonella Typhimurium DT104 in Scotland. We concluded, based on a variety of novel and statistically robust analyses, that the Scottish animal population was unlikely to be the major source of resistance diversity for DT104 in humans. Far from concluding that there was no association between antimicrobial-resistant Salmonella in animals and humans, we set out to dissect the nature of this association using new analytical tools and techniques applied to one of the largest datasets available. We summarize Professor Collignon’s criticisms of our paper as follows: (i) most isolates had a resistance profile that was common to both animals and humans; (ii) we over-emphasized the importance of rare profiles; (iii) we ignored the issue of imported food; and (iv) the passively sampled animal isolates in our study were biased in some way.

Given the clonal nature of S. Typhimurium DT104, it is unsurprising that the majority of isolates exhibit the same phenotypic resistance profiles. This may well indicate an association between isolates from animals and humans, but no objective interpretation of this observation alone would conclude that it is informative of any predominance in the direction of transmission between the two populations.

Second, and in Professor Collignon’s view, most importantly, he states that we have selectively given similar weights to rare profiles as to more common profiles. This is not the case. We examined the diversity of resistance profiles found in these two populations across a spectrum of ecological diversity measures that include all possible weightings of rare profiles from equal contribution to no contribution (fig. 2c,d in our original paper). For all of these possible weightings, the phenotypes found in the human population are more diverse than those found in the animal population.

Third, we reiterate the important distinction between the food products consumed in Scotland (much of which is imported), and the focus of our study—the local animal population that might comprise the Salmonella reservoir, and of which our sample is much more representative. The previous research on DT104 we reference does not demonstrate that DT104 is predominantly spread from food animals to humans via food; many of these studies include only human isolates [1–3], and therefore explicit examination of their association with animal isolates is not possible. Although there are studies that have indicated food items as sources of DT104 infection [4–7], or contact with livestock [7–9], the majority of Salmonella infections in humans are sporadic, not outbreak related, and the source is rarely identified [10].

We explicitly recognize the potential importance of alternative sources throughout our paper, particularly, the potential contribution of imported food to the resistance burden in humans. The dataset we analysed included only animal isolates from Scotland, and we therefore restrict our conclusions to animals from Scotland. We acknowledge that DT104 from foreign animal populations, via imported food, may be a significant source of antimicrobial resistance and antimicrobial resistance diversity for humans in Scotland, and we therefore call for greater investigation into these other potential sources of resistance and other routes of origin, diversity and spread, including the environment.

Fourth, it is true that data from passive surveillance are almost certainly biased—be it from animals or humans, but our conclusions are arguably robust to many of these biases. For example, we cannot exclude the possibility that sick calves may be overrepresented in our dataset. However, if they were, this would increase the diversity in animals, as it has been demonstrated that younger animals have greater diversity in antimicrobial resistance phenotypes than older animals [11,12], in which case our conclusions are conservative. Regarding the issue of whether or not isolates obtained from clinically ill individuals represent those found in asymptomatic cases, work by Wiesner et al. [13] on S. Typhimurium suggests that isolates from clinical and non-clinical cases are similar. Perron et al. [14], examining DT104 from clinical and asymptomatic pigs, demonstrated that while isolates from asymptomatic cases were more genetically diverse with respect to the organism, the clinical isolates were more diverse with respect to antimicrobial resistance phenotype, thus increasing the likelihood that the resistance profiles of DT104 from the animal population in our study, which were derived from clinical samples, will be found to be more diverse. However, we find that, on the contrary, human isolates are more diverse.

Our results do challenge some established views on resistance in DT104; such is the nature of science, and the process by which collective knowledge is advanced. Clearly, antimicrobial resistance is a complex issue, and the results we presented relate to S. Typhimurium DT104 in Scotland. It is important to investigate other
organisms in other settings to increase our understanding of the ecology of resistance. As a group of researchers across the spectrum of the medical and life sciences, independent of any industry or political grouping, we recognize the need for and emphatically support the prudent use of antimicrobials in both humans and animals. If use in a local animal population is not the major driver of resistance diversity in human enteric pathogens, then we must strive to identify what other sources are responsible.

We agree with Professor Collignon on one point, that antimicrobial resistance is one of the most important challenges to human and animal health. This challenge transcends not only taxonomic boundaries, but also national and disciplinary divides. Solutions will only be found through the synergistic application and integration of diverse methods that exploit the whole evidence base. This will require interdisciplinary communication and understanding, a willingness to explore and understand different approaches, to listen and to learn. Our work is intended as a single contribution to this process.

Readers may also wish to refer to our response to Price et al. [15] and Nunan & Young [16] in the e-letter section of this journal.

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