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A Greener World Briefing Paper #2

Comments on Research from UK's Glasgow University on Antimicrobial Resistance

Certified Animal Welfare Approved by A Greener World (AGW) has the most rigorous standards for farm animal welfare currently in use by any organization in North America. Its standards have been developed in collaboration with scientists, veterinarians, researchers and farmers across the globe to maximize practicable, high-welfare farm management.

In recent research published in the *Proceedings of the Royal Society B*, Mather *et al* (2011) examined long-term surveillance data of *Salmonella* typhimurium DT104 from co-located humans and animals in Scotland. The researchers were trying to compare the development of antibiotic resistance in animals and people in Scotland in a major strain of salmonella. Their paper concluded that the local animal populations were unlikely to be the major source of antibiotic resistance in humans, and that in the majority of resistances which are common to both animals and humans the resistances appeared first in humans.

Several agricultural industry websites and magazines picked up on this report and subsequently used it to promote the position that antibiotic resistance does not result from the overuse of antibiotics in animal agriculture, and that further restrictions on antibiotics are therefore unnecessary. This is despite the fact that numerous published scientific papers already argue the exact opposite.

So how did the University of Glasgow researchers reach this conclusion and why are their results so at odds with almost all published research on salmonella? It is fair to say that the paper contains enough complex statistical analysis to evoke the old saying about "lies, damn lies and statistics." So, Animal Welfare Approved sought expert advice from Richard Young of the Alliance to Save Our Antibiotics.[1] Richard has been working on antibiotic use in farmed animals for over 10 years. As the author and major contributor to a number of reports on antibiotic use in farmed animals he is well placed to explain what's going on.

<u>Weaknesses in the Research</u>

[1] The Soil Association, Compassion in World Farming and Sustain are founder members of the Save Our Antibiotics Alliance. Richard Young is Policy Advisor to the Soil Association. Animal Welfare Approved would also like to thank Cóilín Nunan for his contribution to this analysis of Mather *et al* (2011).

According to Richard, Mather *et al* (2011) were essentially trying to compare the development of antibiotic resistance in animals and people in Scotland in a major strain of salmonella, one that mostly affects cattle but also pigs and poultry. Their conclusion was that animal and human DT104 populations differ significantly in several ways, such as prevalence, linkage, time of emergence and diversity. As a result, they infer that local animal populations are unlikely to be the major source of antibiotic resistant disease in humans. However, Richard has highlighted several weaknesses in the research which significantly undermine the validity of their conclusions.

The Omission of Key Data

The researchers focused on the different resistance profiles (in other words, the different lists of antibiotics to which the salmonella is resistant) which are found in humans only, in animals only, or in both. As Richard explains, one of their core arguments is that because they found more samples of salmonella with unique resistance profiles in humans than in animals, this means that more of the antibiotic resistance found in humans is coming from human rather than veterinary medicines.

In making their claim that the salmonella DT104 from humans are distinguishable from the animal salmonella, the researchers found that of the 52 profiles found in humans, 30 were unique to humans, whereas only 22 were also found in animals. Yet when Richard examined the research paper more closely he found that the 30 human-only profiles actually accounted for just a tiny fraction of all the human cases, while the 22 common profiles (shared between humans and animals) accounted for 2,707 of the 2,761 (or 98%) of the human cases – something that the researchers completely failed to mention in their paper. Richard feels that such highly relevant information should really have been clearly highlighted in the paper; yet the information is actually hidden away in Table S4 of the supplementary material, which is only available on the journal's website.

Insufficient Evidence

Richard explains that the researchers then looked at the 22 resistance profiles that are common to both humans and animals to see if they were first found in humans or in animals. The paper claims that 11 resistance profiles first emerged in humans, six appeared simultaneously in humans and animals, and just five first appeared in animals.

Yet the key question the researchers fail to answer is which of the different resistance profiles first emerged in humans and which in animals? The 65 different resistance profiles are listed in the supplementary data accompanying the report. From this list it is easy to pick out the 22 profiles that appear in both humans and animals. But there is nothing to further break down this list of 22 resistance profiles into the different categories noted above. In other words, which are the 11 resistance profiles that first emerged in humans? Which are the six profiles that appeared simultaneously? And which are the five that first appeared in animals? The researchers must know – yet they don't tell us.

It should be noted that one resistance profile alone accounts for 90% of animal cases and 70% of human cases. This has to be the most important profile for us to look at, but we aren't told where this resistance profile first emerged. Was it in humans or animals? In fact, the seven most common

resistance profiles in humans account for 2,676 of the 2,761 human cases (or 97% of the cases), and all these are also found in farm animals. So where did these resistance profiles first emerge – in animals or in humans? Again, the paper fails to say. Thus, on the basis of the information provided, we cannot even judge whether the overwhelming majority of cases are accounted for by resistance profiles which first emerged in animals or in humans. It seems extraordinary that this fundamental question is not addressed.

The paper also mentions that 13 of the 35 resistance profiles found in animals were *not* found in humans. This represents 37% of all resistance profiles found in animals. The researchers say that this percentage is too big; that if animals are the source of resistance for humans then with only a few exceptions the resistance profiles would be the same in both. The researchers suggest that finding 37% of animal profiles that don't appear in humans implies that the resistance can't be coming from animals.

However, what the researchers fail to declare is that these 13 animal resistance profiles together account for less than 1% of the salmonella cases found in animals. In other words, over 99% of the salmonella cases found in animals had resistance profiles that were also found in humans. Looking at actual cases rather than the percentage of profiles is obviously far more relevant to the transmission of resistance – and in doing so, we drop from 37% of animal resistance profiles that are not found in humans to less than 1%. As the researchers argue themselves, if the source of resistance was indeed animals then we wouldn't expect to find many resistance profiles that were detected in animals but not in humans. Less than 1% certainly isn't much! Clearly, this fact raises real concerns about the way the researchers chose to draw conclusions about antibiotic resistance.

<u>Neglecting the Potential Role of Imported Meat</u>

Richard goes on to explain that the greater diversity of resistance profiles which the study found in humans is likely to be due to a combination of two factors:

- No data on the impact of imported meat was considered. Humans frequently consume imported meat, but Scottish farm animals are only occasionally exposed to imported live animals
- Human antibiotic use may contribute to creating greater diversity of resistance profiles. As many studies have already shown, resistance in human salmonella comes mainly from farm-animal antibiotic use, but human antibiotic use may subsequently increase diversity. In contrast, diversity of resistance profiles in farm animals will only come from farm-animal antibiotic use.

In relation to imported food, we know that at least half of the pork and a significant proportion of the poultry meat eaten in Scotland would have been imported from elsewhere in the UK or EU, with additional poultry imports coming from South America and South East Asia. Although there is generally less *Salmonella* typhimurium DT104 (the salmonella they considered) in pork and poultry than in beef, we know that people were eating much more poultry and pork than beef during the period in question. Levels of resistance to some antibiotics in *Salmonella* typhimurium DT104 from turkeys in particular are higher than in cattle. In addition, it is known that poultry and pork are much more common sources of

food poisoning than beef, largely due the way the meat is slaughtered, eviscerated, stored, handled and cooked. Richard's point is that if the researchers failed to take into account the resistance profiles for *Salmonella* typhimurium DT104 in imported poultry and pork that Scottish people would have eaten during the period concerned then the results may be very misleading.

The authors attempt to get around this weakness by stating: "Given that Salmonella infections in humans are associated with the food chain and imported food is not derived from the sympatric [local] animal population, imported food as a source of infection and/or resistance must also be addressed." Yet they then completely fail to address this issue in the paper and fall back on the circular argument that because they only considered data for Scottish animals that their results remain valid for Scottish animals.

Irresponsible Conclusions

In conclusion, Richard contends that the University of Glasgow research is flawed. It starts from the perspective of "addressing the basic tenet that the use of antimicrobials in animal populations is the major influence on the emergence and maintenance of resistance in human pathogens." But the fact is that this "basic tenet" does not actually exist. No responsible campaign group is claiming that use of antimicrobials in animal populations causes resistance in *all* human infections. However, there is considerable scientific justification to claim that the overuse of antimicrobials in intensive farming is a significant cause of antimicrobial resistance for a significant proportion of serious human pathogens – including salmonella. Rather than try to disprove this, we must address it alongside efforts to reduce the unnecessary prescribing and inappropriate use of antibiotics in human medicine.

As a result, Richard is extremely concerned by the overall conclusions that Mather *et al* (2011) present at the end of their paper:

> *"'Furthermore, we infer that the sympatric [local] animal population is unlikely to be the major source of resistance diversity for humans. This suggests that current policy emphasis on restricting antimicrobial use in domestic animals may be overly simplistic. While these conclusions pertain to DT104 in Scotland, this approach could be applied to antimicrobial resistance in other bacteria–host ecosystems".*

Richard feels it is highly irresponsible for the researchers to make such sweeping claims based on just one study, especially since their conclusions contradict more than 50 years of research in this field. The statement is also unhelpful as it further encourages those who are seeking any justification to block efforts to promote the more responsible use of farm antibiotics. Indeed, this new research has already been used to bolster beliefs in the veterinary and farming sectors that antibiotic resistance in farm animals makes no significant contribution to resistance in humans – despite the significant weight of scientific evidence to the contrary.[2]

[2] See British Veterinary Association (2012).

Richard recognizes that some cases of salmonella will be caught from human sources rather than directly from meat, and that these will therefore reflect antibiotic use in human as well as animals. However, since people eat farm animals – and farm animals do not eat people – he feels it is counter-intuitive to suggest that one of the major causes of food poisoning would not also represent a major source of the antibiotic resistance genes in salmonella infections in people.

Richard's thorough analysis of Mather *et al* (2011) has revealed a number of weaknesses that raise significant questions about the validity of the results and conclusions presented. At the very least, this research paper should have been published with far more modest and balanced conclusions. Further research of a similar nature– albeit with more complete and reliable data – is needed before any clear conclusions can be drawn.

References and further reading

Alliance to Save Our Antibiotics (2011) *Case Study of a Health Crisis: How human health is under threat from over-use of antibiotics in intensive livestock farming*, Available at www.animalwelfareapproved.org/farmers/recommended-reading/

Mather, A.E., Matthews, L., Mellor, D.J., Reeve, R., Denwood, M.J., Boerlin, P., Reid-Smith, R.J., Brown, D.J., Coia, J.E., Browning, L.M., Haydon, D.T., and Reid, S.W. (2011). An ecological approach to assessing the epidemiology of antimicrobial resistance in animal and human populations, *Proceedings of the Royal Society B.* 2011 Nov 16. [Epub ahead of print]. Abstract available at http://rspb.royalsocietypublishing.org/content/early/2011/11/10/rspb.2011.1975.abstract

British Veterinary Association (2012) *New research suggests animals not to blame for human antimicrobial resistance,* press release, 6 January 2012, http://www.bva.co.uk/2651.aspx

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