COMMENTARY

Ominous projections for global antibiotic use in food-animal production

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Alexander Fleming famously warned that the ignorant may someday misuse his life-saving discovery—penicillin—and select for resistant bacteria (1). This was prescient given the widespread use of subtherapeutic antibiotics by food-animal producers today. According to the findings of Van Boeckel et al. (2) in PNAS, the proliferation of ignorance is only poised to increase. Using global datasets of veterinary antibiotic use, livestock densities, and economic projections of meat demand, Van Boeckel et al. (2) estimate that from 2010 to 2030 antibiotic use in food-animal production will increase by 67%, from 63,151 ± 1,560 tons to 105,596 ± 3,605 tons.

The study by Van Boeckel et al. (2) is the first to estimate global use of antibiotics in livestock production, and to disaggregate that global figure into estimates for each of 228 countries. However, their estimate is based on data from only 32 countries. Using a clear framework and a state-of-the-art Bayesian statistical model, the authors extrapolate from the most reliable data available to arrive at the global sum. This is an admirable approach to a difficult problem, but it raises a question: Why not derive the values more simply, by summing data from all 228 countries, using the actual records of antibiotic use in livestock production? After all, this is how we quantify global fossil fuel use (3), livestock production and trade (4, 5), and the use of fertilizers in agriculture (4). For many assessments of global economic activity, including these, the actual data exist. However, for antibiotics in livestock production, a statistical model is the best option because comprehensive data on the use of antibiotics in livestock production are not available. Most countries do not record the sale and use of antibiotics, in part because practitioners may be reluctant to release those data. Despite this limitation, Van Boeckel et al. (2) provide the first global assessment of antibiotic use in livestock production. Their estimate is important: The figure is large and has been notoriously difficult to extract (6), and it sets the stage for understanding the global impacts of profligate use of these powerful drugs.

New Data for Answering Tough Questions

This estimate fills a fundamental knowledge gap in understanding the interplay between antibiotic-resistant bacteria in the food-animal production sector and in the human medical sector. Also, importantly, these data enable researchers to tackle bold new questions: What are the relative selective pressures on bacteria imposed by antibiotic use on the farm and in human medicine? Does antibiotic use in food-animal production correlate with the prevalence and types of mobile resistance elements circulating among farm animals and humans? How does the level of antibiotic use in food-animal production and in human medicine influence the expansion of bacterial clones and resistance elements exchanged between humans and livestock?

With a global estimate of antibiotic use in food-animal production, one pressing question should now be answerable: What proportion of total global antibiotic use is devoted to humans and to animals? Using sales records, the same authors tabulated global antibiotic use in human medicine (7). Although those data are expressed in "standard units" of pharmaceuticals rather than in kilograms, there is now the potential to directly compare medical and veterinary antibiotic use on a country-by-country basis.

Geographically explicit estimates of antibiotic use in food animals, when combined with similar high-resolution data on the magnitude of antibiotic use in human medicine (7), lay a quantitative foundation for testing the ecological factors that regulate the spread of antibiotic resistance. For instance, there may be a vicious synergy of antibiotic use in food animals and in humans, whereby antibiotic-resistant bacteria that spill over to humans from livestock can ignite a blaze of resistant pathogens when medical antibiotic use is high (8). Together with estimates of antibiotic use in animals and in people, existing data from a select number of countries that monitor trends of antibiotic resistance (9, 10) can now be used to test that hypothesis. Similarly, elevated antibiotic use on the farm can rapidly amplify resistance among human pathogens that find their way into livestock. Whole-genome sequencing of human- and livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) has revealed that this has already occurred in the MRSA CC398 lineage (11), but how widespread is this phenomenon? The findings of Van Boeckel et al. (2) suggest that the BRICS countries (Brazil, Russia, India, China, and South Africa) may be the places to look for this pattern in the coming decades.

Human populations increasingly demand more animal-based protein, which in turn leads to more industrialized methods of food-animal production, including subtherapeutic antibiotics for growth promotion and disease prevention (12). According to Van Boeckel et al. (2), this cascading demand will be most profound in the BRICS nations, where massive human populations, rapidly growing economies, and a rising demand for meat will escalate antibiotic consumption by 99%—up to seven times the projected population growth for these countries.

Antibiotic resistance has already reached a crisis (13). Antibiotics discovery has plummeted (14), yet resistance to existing antibiotics is increasing rapidly (15). These trends should be a warning, demanding immediate action to curb unnecessary antibiotic use around the world. However, curbing unnecessary antibiotic use requires political and scientific leadership. Whereas the politics of antibiotics in food-animal production has a mixed record of success, the scientific community has also come up short on some

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counts. Policymakers have repeatedly asked researchers to quantify the public health burden of antibiotic use in food-animal production, but we have failed to credibly estimate the attributable mortality. Without such a number, it is difficult for policymakers to defend precautionary legislation.

However, is this an answerable question? Can we actually quantify the number of antibiotic-resistant human infections arising from antibiotic use in food-animal production? It is, after all, an ecological problem, where antibiotic use in one sector may fuel the resistant bacteria acquired from the other.

Some of the most troublesome antibiotic-resistant bacteria are capable of colonizing humans and animals and of flowing seamlessly between them, such as extraintestinal pathogenic *Escherichia coli* and *S. aureus*. With the right techniques, such as whole-genome phylogenetic analyses, we can quantify these transmission events with regular bacterial sampling of food animals and people (16). However, antibiotics have been used in food-animal production since the 1940s, and therefore one would need a Wellsian time portal to truly quantify the full public health burden of such antibiotic use. As it stands in the United States, we do not sufficiently monitor antibiotic resistance to answer this question for the present day.

Furthermore, there is no clear algorithm for assigning attribution even in a counterfactual world of complete knowledge of transmission between food animals and humans. For example, consider this hypothetical but probable scenario: A bacterium acquires a multidrug-resistance determinant in food-animal production; it becomes prevalent under antibiotic selection in that environment; it then becomes established in the human population through a single animal-to-human transmission event; it expands among humans under selection pressure from human antibiotic use; and it subsequently causes 100 human infections. In this case, do we attribute 1 or 100 infections to antibiotic use in food-animal production? What if a mobile multidrug-resistance element evolves on the farm but is only potentiated after being transferred to a well-adapted human pathogen? What about a bacterium that carries multiple resistance determinants, some acquired in relation to antibiotic use in food-animal production, others in relation to human medicine?

Although difficult questions remain, we must remind ourselves of one basic fact: Antibiotics are potent selectors of antibiotic-resistant bacteria; with increased antibiotic use, the incidence of drug resistance also rises. If we delay action as we try to quantify the total human health burden of antibiotic use in food-animal production, Van Boeckel et al. (2) estimate that such use will continue to increase.

Strong Global Leadership Is Needed

Methods exist for raising food animals efficiently and profitably without the use of nontherapeutic antibiotics. Denmark has become the classic example. The Danes banned all nontherapeutic antibiotics more than a decade ago and have maintained their status as one of the world's largest pork exporters, demonstrating that such production can be achieved at a competitive price (17). Today, food-animal production companies in other countries are responding to consumer demands and raising cattle, chickens, pigs, and turkeys without nontherapeutic antibiotics (18). It can be done.

However, this is a global problem, and without a global governing body we have only national leaders to help guide our way. Sadly, this is one area where the United States lags behind other more developed countries. On March 27, 2015, President Obama issued his "National Action Plan for Combating Antibiotic-Resistant Bacteria" (19). In this plan, he shows strong leadership in antibiotic innovation and rapid diagnostics, offering practical plans for improved stewardship of antibiotic use in human medicine, along with time-bound, measurable goals for reductions. In contrast, the President's plan offers no measurable goals for antibiotic reductions in food-animal production and, importantly, no practical steps for tackling antibiotic use for routine disease prevention. Without leadership on this issue from the United States, it is hard to imagine that the leaders of the BRICS nations will oblige their food-animal producers to forgo nontherapeutic antibiotics.

Van Boeckel et al. (2) provide an objective, data-driven estimate of antibiotic use in food-animal production around the world and a baseline for evaluating intervention. The question remains whether meaningful interventions will be attempted.

The study's results, and the collective knowledge from more than 80 y of research since the discovery of penicillin, argue that scientists must add their voices to the public discourse surrounding antibiotic stewardship. We must help inform policymakers and demand global leadership to ensure that the trends predicted in this paper do not come to pass.

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