

Antimicrobial Resistance: A Global Public Health Challenge Requiring a Global One Health Strategy

Guy H. Palmer, D.V.M, Ph.D., and Douglas R. Call, Ph.D., The Paul G. Allen School for Global Animal Health, Washington State University*

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The first test of penicillin on a human, Constable Albert Alexander in 1941, illustrated the remarkable power of antibiotics to control bacterial infection, only to end in tragedy when all available penicillin was exhausted and Alexander's infection recrudesced (McKenna, 2010). Since then, antibiotics have saved millions of lives and, due to their efficacy, their use has become ubiquitous in human and veterinary medicine. Unfortunately, any use of antibiotics, whether defined as prudent or not, will inevitably invoke Darwinian selection that favors the emergence, amplification, and persistence of antibiotic resistance. Thus, while Constable Alexander's death resulted from an insufficient supply of antibiotics, the threat today is the lack of effective antibiotics due to widespread resistance. During the past 70 years, the health impact of antibiotic resistance has been held at bay primarily by the continual development of new classes of antibiotics and by new generations of existing classes. As has been widely reported, however, there are a number of issues limiting the pipeline of new antibiotics needed to continue to stay ahead of widespread resistance (Spellberg et al., 2008). A recent review identified 20 new antibiotic compounds in development since 2000, of which 8 out of 9 synthetic compounds are derived from quinolones—a class of antibiotic that may only require

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minor chromosomal mutations to gain resistance (Butler and Cooper, 2011).

Exacerbating the lack of new antibiotic classes to combat antibiotic resistance is an unprecedented increase in the ability of microbes to move around the world. Global travel aids the rapid spread of emerging pathogens and the expansion of pandemics (Tatem et al., 2006). Enteric bacteria carrying plasmid-encoded resistance to multiple antibiotics are carried surreptitiously, like Trojan Horses, connecting even remote communities to tertiary-care hospitals in a global network. Movement of people, however, is not the only means of spread, because resistance is also carried by microbes present in food and on fomites. The statement that any pathogen can move around the globe within 24 hours also holds for the spread of antibiotic resistance. In fact, the dissemination of antibiotic-resistance traits through travel and trade likely occurs at levels orders of magnitude higher than pathogens (Okeke and Edelman, 2001). There is no question that the emergence and maintenance of

* G.H.P. was a participant in the Forum on Microbial Threats symposium on "Sustaining Public Health Capacity in an Age of Austerity."

antibiotic resistance *anywhere* is a threat to health *everywhere*.

Although these basic concepts have been understood for some time now, what is new is the realization of the role that the environment itself plays in the maintenance and potential spread of antibiotic resistance. At local scales, we have only limited understanding of how the ecology of interactions enhances or deters the dissemination of antibiotic resistance. For example, analysis of *Salmonella* DT104 in Scotland revealed that antibiotic-resistant bacteria in humans represented a distinct pool from those found in local cattle populations (Mather et al., 2011). This is likely to be very different in countries where people, animals, and wildlife interact directly or through food and water at an intimate level (Kalter et al., 2010). The contamination of water and soil with active metabolites of antibiotics excreted in the urine of treated individuals, humans, and livestock creates a previously unrecognized reservoir for resistance (Forsberg et al., 2012; Subbiah et al., 2012). These problems are exacerbated where antibiotic use is unregulated and widespread both in human use and animal production.

So, where do we go from here? We emphasize the need for a global approach—both in terms of countries and sectors. The former is illustrated by Denmark, which has one of the most, if not *the* most, proactive and coordinated efforts toward prudent use of antibiotics in the world. However, travel and trade make it difficult to capture local benefits in the absence of global control. For example, a comparison of poultry broiler meat produced in Denmark with broiler meat imported to the country found significantly higher resistance levels for *Campylobacter jejuni*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Escherichia coli* in the imported meat (DANMAP, 2011). Similarly, human travel

continually reintroduces resistant strains, despite best local practices.

There is also the need to work across sectors. The use of antibiotics in livestock remains widespread, and the increasing demand for dietary protein in rapidly growing low- and middle-income countries—expected to double animal production by 2050 (FAO, 2011)—creates a powerful incentive for their continued use unless alternatives and incentivized policies are developed and implemented.

Denmark's leadership in reducing the use of antibiotics in animal production should be applauded and, wherever feasible, including in the United States and other wealthy countries, followed. However, the political will, regulatory structures, and needed resources are not universally available, particularly in low-income countries, where the competing pressures for inexpensive food are greatest. Thus, although stricter regulation has an important role, we should be cautious about unintended consequences. If there is increased production cost associated with local policies, consumers are likely to shift preferences to cheaper, imported foods that may exacerbate the problem. Furthermore, even if strict controls on antibiotic access could be implemented in rapidly growing developing countries, there may be profound health consequences due to malnutrition if the supply of affordable meat and milk protein became static or was reduced, given that antibiotics may be necessary to maintain production levels. Only improved preventive health and production practices are likely to reduce demand for antibiotics without shifting the costs of antibiotic externalities to the poorest people.

Voltaire's aphorism that we should not let "the perfect be the enemy of the good" is applicable here. To the list of interventions recently proposed by Spellberg et al. (2013), we would add and emphasize the need for

cross-sector commitment. Calls to limit antibiotic use in food animal production are best accomplished by reducing demand with improved vaccination, husbandry practice, sanitation, and biosecurity. Similarly, expanded research investment in livestock probiotics, immunostimulants, and vaccines will provide alternatives that can reduce the need for antibiotics with less chance of unintended consequences for food availability and access. Regulation accompanied by viable alternatives will have a much higher likelihood of success.

We should also consider control through other selective compartments, such as in soils where excreted antibiotics may exert most of their unintended selective pressure (Subbiah et al., 2012). This is important because when selection occurs in the environment, engineered solutions may still preserve the efficacy of the antibiotics. Similarly, understanding the ecology of resistance may provide opportunities to block resistance transmission at key intersections between sources and communities. Finally, there is significant need to coordinate surveillance efforts for antibiotic resistance at a global scale. If surveillance can be coupled with early and decisive intervention policies, then it may be possible to keep antibiotic resistance at lower levels of prevalence and best preserve our armamentarium (Austin et al., 1999).

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