Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

Human health impacts of antibiotic use in agriculture: A push for improved causal inference

Randall S Singer[1,2] and Jessica Williams-Nguyen[1,3]

Resistant bacterial infections in humans continue to pose a significant challenge globally. Antibiotic use in agriculture contributes to this problem, but failing to appreciate the relative importance of diverse potential causes represents a significant barrier to effective intervention. Standard epidemiologic methods alone are often insufficient to accurately describe the relationships between agricultural antibiotic use and resistance. The integration of diverse methodologies from multiple disciplines will be essential, including causal network modeling and population dynamics approaches. Because intuition can be a poor guide in directing investigative efforts of these non-linear and interconnected systems, integration of modeling efforts with empirical epidemiology and microbiology in an iterative process may result in more valuable information than either in isolation.

Addresses
[1] Department of Veterinary and Biomedical Sciences, University of Minnesota, 1971 Commonwealth Ave., St. Paul, MN 55108, USA
[2] Instituto de Medicina Preventiva Veterinaria, Facultad de Ciencias Veterinarias, Universidad Austral de Chile, Valdivia, Chile
[3] Department of Epidemiology, School of Public Health, University of Washington, 1959 NE Pacific Street, Health Sciences Building F-262, Box 357236, Seattle, WA 98195-7236, USA

Corresponding author: Singer, Randall S (rsinger@umn.edu)

Current Opinion in Microbiology 2014, **19**:1–8

This review comes from a themed issue on **Ecology and industrial microbiology**

Edited by **Kornelia Smalla** and **James Tiedje**

http://dx.doi.org/10.1016/j.mib.2014.05.014

Introduction

Bacterial infections in humans that are resistant to antibiotics continue to pose a significant challenge globally [1]. The role of antibiotic use in agriculture as a causal factor in this ongoing problem has received considerable discussion over many years. There is no denying that many resistant bacteria are present in agricultural environments and can affect humans through food consumption or through more complex environmental routes of exposure. While agricultural antibiotic use (AAU) can influence resistance in specific bacterial populations, the real challenge is determining which agricultural practices are having the greatest contribution to the emergence, amplification, persistence and dissemination of antimicrobial resistance (AMR). Stated another way, how do we identify those practices that are truly contributing significantly to the antibiotic resistance problem and how do we accurately predict the net benefit to human health that modification or elimination of these practices would have? Incorrectly believing that these links are causal [2], rather than simply correlation, and failing to appreciate the relative importance of the diversity of potential causes, together represent a significant barrier to effective intervention in the agricultural arena.

Without sound science to establish and quantify these causal links, we often rely on assumptions about causality to infer which interventions will be effective. As an example, a recent publication quantified the number of deaths from bloodstream infections caused by third-generation cephalosporin-resistant *Escherichia coli* (G3CREC) that were due to the use of antibiotics, mainly the third-generation cephalosporins, in poultry production [3]. The data on which these calculations were based came predominantly from two sources. One study estimated the excess mortality and prolongation of hospital stay associated with G3CREC bloodstream infections in humans in Europe. A second study in the Netherlands [4] found that '56% of the resistance genes in G3CREC in humans were identical to genes derived from *E. coli* isolated from retail chicken samples' (p. 1339). Collignon *et al.* [3] then calculated the number of excess deaths from G3CREC-associated bloodstream infections caused by antibiotic use in poultry as 56% of the total estimated excess deaths due to G3CREC-associated bloodstream infections.

This simplistic calculation makes several strong and unacknowledged assumptions. First, the authors assumed that all human isolates that have identity to poultry strains (56% for the Netherlands study) were derived from poultry. Second, the authors implicitly assumed that AAU within the poultry production system was the sole cause of all third-generation cephalosporin resistance in these *E. coli*. Finally, the authors assume that the relationship between isolates in the Netherlands can be extrapolated to all of Europe. The need for making such assumptions when attempting to estimate risk is understandable given the challenges of collecting strong, quantitative evidence. However, failure to acknowledge and

validate these assumptions can lead to inaccurate inferences and misguided interventions [5].

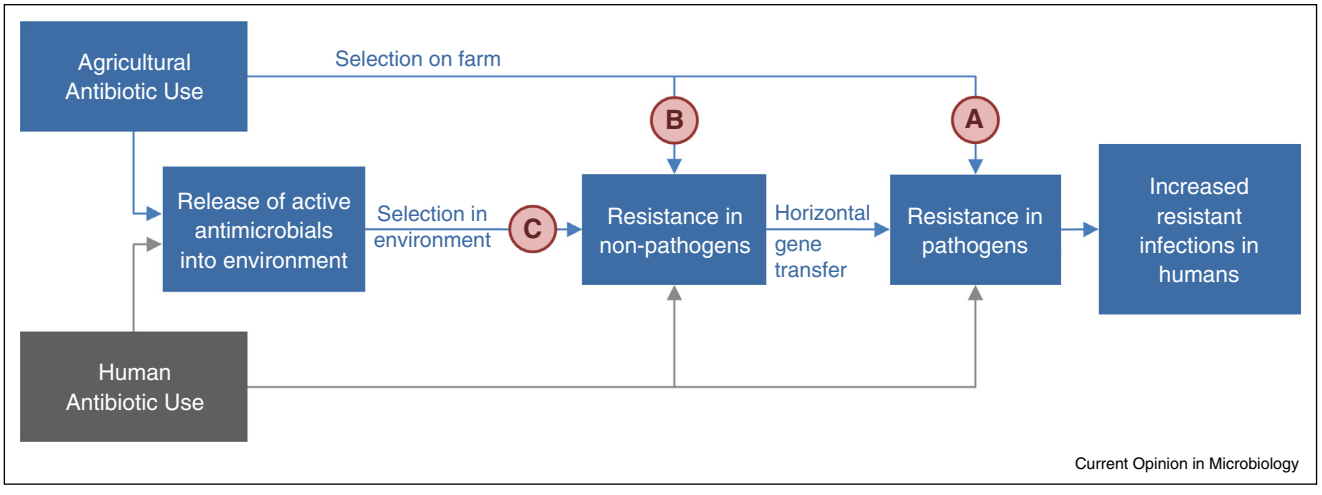
While it is generally acknowledged that much of the resistance in human pathogens is associated with human uses of antibiotics [1], the purpose of this paper is to explore scientific approaches for evaluating and quantifying the causal link between the use of antibiotics in animal agriculture and human health. Specifically, this paper will focus on the theme of attribution, because in effect we are performing attribution analyses on different levels. For example, we are attempting to attribute the observed resistance to specific selection forces. We are also attempting to attribute the human illness to specific sources. The latter has received considerable attention and is a growing area of investigation [6–10], but the former is still in its infancy with respect to the ecology of antimicrobial resistance.

Linking AAU to human health

To motivate this discussion, we first consider the ways in which the exposure (AAU) can cause resistance to increase above background levels and then lead to a negative outcome (human health harm) (Figure 1). We will consider the predominant risk to human health posed by AAU to be treatment failure due to the bacterium being resistant, which then results in increased morbidity, increased duration of illness, or mortality. To link AAU to increased human health impacts, the following three scenarios should, in a general form, provide a sufficient structure for this discussion. In Scenario A, AAU leads to an increase in resistant pathogens which are then transmitted to humans via the food chain or the environment. The selection pressure exerted by the AAU in this scenario occurs on the farm. In Scenario B, AAU selects for resistance in non-pathogens, perhaps commensals or environmental microbes, which then transfer resistance genes to pathogens leading to more resistant infections in humans. Again selection in this case occurs on the farm. Finally, Scenario C involves the release of active antimicrobial compounds into the environment where selection occurs predominantly in non-pathogens, such as soil microbes, and resistance is transferred horizontally to pathogens as in B. Scenarios B and C might be referred to as forces increasing the size of the resistance gene pool.

To estimate the risk to human health in each of these scenarios (or combinations of them), we must establish quantifiable, causal links and determine what the current state of evidence tells us about the relative importance and interconnectedness of these links. For example, knowing that a human illness was caused by a resistant bacterium that originated from an agricultural facility (the proverbial smoking gun) does not necessarily inform the causal relationship between AAU and human health. The resistance in this bacterium was unlikely to have been created *de novo* by the AAU on the source farm. Many of the resistance genotypes, particularly when associated with multidrug resistance plasmids, are conserved and have a global distribution [11,12,13•,14]. The cumulative effect of the AAU over large geographic areas over extended durations of time is likely aiding in the spread of this resistance, but appropriate data and improved analytical approaches are needed to estimate this relationship accurately [13•,15]. Finding resistance genes in the environment, even if it is known that they are emanating

Figure 1



Conceptual model of the ways in which agricultural antibiotic use (AAU) can cause increased resistant infections in humans. In Scenario A, AAU leads to an increase in resistant pathogens which are then transmitted to humans via the food chain or the environment. In Scenario B, AAU selects for resistance in non-pathogens which then transfer resistance genes to pathogens leading to more resistant infections in humans. In Scenario C, active antimicrobial compounds are released into the environment where selection occurs predominantly in non-pathogens, and resistance is transferred horizontally to pathogens as in B. Human antibiotic use is shown for reference but not discussed.