FOODBORNE PATHOGENS AND DISEASE
Volume 9, Number 8, 2012

DOI: 10.1089/fpd.2012.1160

Letter to the Editor

Confusion over Antibiotic Resistance: Ecological Correlation Is Not Evidence of Causation

Louis A. Cox Jr.[1,2] and Randall S. Singer[3]

Dear Editor:

Vieira *et al.* (2011) noted that, across 11 countries, "Resistance in *E.* [*Escherichia*] *coli* isolates from food animals (especially poultry and pigs) was highly correlated with resistance in isolates from humans. This supports the hypothesis that a large proportion of resistant *E. coli* isolates causing blood stream infections in people may be derived from food sources." Is this causal interpretation of ecological correlations justified?

Consider the following hypothetical analogy: a study examines levels of radioactivity in animals and humans in 11 countries, observes that some countries have higher levels of radioactivity in both humans and poultry than others, and concludes that, "This supports the hypothesis that a large proportion of radioactivity in people may be derived from food sources" (or, with equal logical validity, that "a large proportion of radioactivity in poultry may be derived from people.") Either inference is a non sequitur: an alternative explanation is that both animals and people have higher levels of radiation in countries with higher background levels. The same logic applies to resistant *E. coli*. An ecological correlation is unsurprising, given the global prevalence of multidrug resistance plasmids, even in areas and epochs without anthropogenic influence (Singer et al., 2006b; D'Costa et al., 2011).

Viera *et al.* (2011) stated that "when usage of antimicrobials in humans was analyzed with antimicrobial resistance among human isolates, only correlations between fluoroquinolones ($r = 0.90$) and third-generation cephalosporins ($r = 0.75$) were significant." One might equally well explain the significantly correlated resistance prevalences between the human and animal isolates by assuming that use of these critically important antibiotics in humans selects for resistance in human isolates of *E. coli*, which are then disseminated into animal production units, as by assuming transmission from animals to people.

The authors also asserted that, "Studies have shown (1) that multi-resistant *E. coli* can be frequently found in food animals…, (2) widespread carriage of multi-resistant *E. coli* in the community with no healthcare association…, and (3) indications that most resistant *E. coli* in the bowel of people are derived from food animals …" (p. 1296), but these studies do not address directionality of transmission. The one-directional flow posited by the authors is not the only—or most likely—pattern consistent with the data (Singer et al., 2006a). Correlations of resistances warrant no such causal interpretation.

Methods for sound causal inference, and guidance for refuting plausible alternative explanations, have been extensively developed in epidemiology (e.g., Maclure, 1985). It would be well to apply them before announcing causal interpretations of ambiguous ecological correlations.

References

D'Costa VM, King CE, Kalan L, Morar M, Sung WLW, Schwarz C, Froese D, Zazula G, Calmels F, Debruyne R, Golding GB, Poinar HN, and Wright GD. Antibiotic resistance is ancient. Nature 2011;477:457–461.

Maclure M. Popperian refutation in epidemiology. Am J Epidemiol 1985;121:343–350.

Singer RS, Reid-Smith R, and Sischo WM. Stakeholder position paper: epidemiological perspectives on antibiotic use in animals. Prev Vet Med 2006;73:153–161.

Singer RS, Ward MP, and Maldonado G. Can landscape ecology untangle the complexity of antibiotic resistance? Nature Rev Microbiol 2006;4:943–952.

Vieira AR, Collignon P, Aarestrup FM, McEwen SA, Hendriksen RS, Hald T, and Wegener HC. Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: an ecological study. Foodborne Pathog Dis 2011;8:1295–1301.

Address correspondence to:
Randall S. Singer, D.V.M., MPVM, Ph.D.
Department of Veterinary and Biomedical Sciences
University of Minnesota
1971 Commonwealth Avenue
St. Paul, MN 55108

E-mail: rsinger@umn.edu

[1]Cox Associates, Denver, Colorado.
[2]Department of Biostatistics and Informatics, University of Colorado, Denver, Colorado.
[3]Department of Veterinary and Biomedical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, Minnesota.