

Ruwen Jou,* Pei-Chun Chuang,*
Ying-Shun Wu,† Jing-Jou Yan,‡
and Kwen-Tay Luh§

*Center for Disease Control, Taipei, Taiwan, Republic of China; †Chest Hospital, Tainan, Taiwan, Republic of China; ‡National Cheng Kung University Hospital, Tainan, Taiwan, Republic of China; and §National Association of Tuberculosis, Taipei, Taiwan, Republic of China

References

1. Anti-tuberculosis drug resistance in the world report no. 3 [monograph on the Internet]. [cited 2006 Mar 3]. Available from http://www.who.int/tb/publications/who_hm_tb_2004_343/en/index.html
2. Center for Disease Control, Department of Health, Executive Yuan, Taiwan. Statistics of communicable diseases and surveillance report in Taiwan area, 2003 [monograph on the Internet]. [cited 2006 Mar 3]. Available from <http://www.cdc.gov.tw/en/index.asp>
3. Chiang IH, Yu MC, Bai KJ, Wu MP, Hsu CJ, Lin TP, et al. Drug resistance patterns of tuberculosis in Taiwan. *J Formos Med Assoc.* 1998;97:581-3.
4. Chiang CY, Hsu CJ, Huang RM, Lin TP, Luh KT. Antituberculosis drug resistance among retreatment tuberculosis patients in a referral center in Taipei. *J Formos Med Assoc.* 2004;103:411-5.
5. Lu PL, Lee YW, Peng CF, Tsai JJ, Chen YH, Hwang KP, et al. The decline of high drug resistance rate of pulmonary *Mycobacterium tuberculosis* isolates from a southern Taiwan medical centre, 1996-2000. *Int J Antimicrob Agents.* 2003;21:239-43.

Address for correspondence: Ruwen Jou, Reference Laboratory of Mycobacteriology, Center for Research and Diagnostics, Center for Disease Control, Department of Health, 161 Kun-Yang Street, Nan-Kang, Taipei, 115, Taiwan, Republic of China; email: rwj@cdc.gov.tw



Enrofloxacin in Poultry and Human Health

To the Editor: Following logic similar to that recently used by the US Food and Drug Administration to withdraw approval for enrofloxacin, a recent letter estimated that fluoroquinolone use in poultry could compromise responses to antimicrobial drugs in >24,000 persons per year in the United States (1). However, >99.9% of this estimated risk appears to result from incorrect assumptions. Potentially important corrections include the following: 1) not attributing resistance from foreign travel and human ciprofloxacin use to domestic use of enrofloxacin in poultry (this could reduce the estimated risk by $\approx 1/3$) (2); 2) updating the estimated fraction of human foodborne *Campylobacter* infections caused by poultry to reflect declines in microbial loads on chicken carcasses since 1992 reduces the estimated risk by a factor of perhaps $1/10$ (3) (the cited 90% estimate by Hurd et al. [1] was intended for use as part of a conservative upper-bounding analysis, not as a realistic point estimate); 3) replacing an assumption that 10% of infected persons would benefit from antimicrobial drug therapy with a more data-based value of 0.6% (4) would reduce the estimated risk by a factor of $0.6/10 = 0.06$; 4) replacing an assumption that fluoroquinolones are prescribed for *all* affected patients receiving antimicrobial drug treatment (rather than, for example, erythromycin) by a more realistic value of fluoroquinolones being prescribed for perhaps $\approx 50\%$ of patients (2) reduces the estimated risk by a factor of $\approx 50\%$; 5) replacing an assumption that *all* such cases lead to compromised responses with a more data-driven estimate that perhaps $\approx 17\%$ of patients have compromised responses would reduce the estimated risk by a

factor of $1/6$ (5); and 6) recognizing that reducing enrofloxacin use may not decrease fluoroquinolone resistance in all *Campylobacter* spp. from food animals (effect not quantified) (6). Together, such changes reduce the estimated risk by a factor of at least $(1/3) \times (1/10) \times (0.6/10) \times (1/2) \times (1/6) = 0.00017$, or by >99.9%.

More notably, the calculation in (1) also wrongly assumes that the fraction of patients with fluoroquinolone-resistant infections times the fraction of infections caused by poultry gives the fraction of patients with compromised response caused by fluoroquinolone use in poultry. As a simple counterexample, suppose that 80% of all infections were caused by poultry, with the rest caused by something else (e.g., water), and that all and only the 20% of infections caused by the latter source are resistant. Then the procedure in (1) would estimate (80% of infections caused by poultry) \times (20% of infections resistant) = 16% as the fraction of resistant infections caused by poultry, even though the correct answer is zero. Thus, the basic logic of the calculation is flawed.

Louis Anthony Cox, Jr*†

*Cox Associates, Denver, Colorado, USA; and †University of Colorado Health Sciences Center, Denver, Colorado, USA

References

1. Collignon P. Fluoroquinolone use in food animals [letter]. *Emerg Infect Dis.* 2005;11:1789-80.
2. Cox LA Jr. Quantitative health risk analysis methods: modeling the human health impacts of antibiotics used in food animals. New York: Springer; 2005.
3. Stern NJ, Robach MC. Enumeration of *Campylobacter* spp. in broiler feces and in corresponding processed carcasses. *J Food Prot.* 2003;66:1557-63.
4. Busby JC, Roberts CT, Lin J, MacDonald JM. Bacterial foodborne disease: medical costs and productivity losses. 1996 [cited 2006 Mar 22]. Washington: US Dept of Agriculture, Economic Research Service. Agricultural economics report 741. Available from <http://www.ers.usda.gov/publications/aer741/>

5. Sanders JW, Isenbarger DW, Walz SE, Pang LW, Scott DA, Tamminga C, et al. An observational clinic-based study of diarrheal illness in deployed United States military personnel in Thailand: presentation and outcome of *Campylobacter* infection. *Am J Trop Med Hyg.* 2002;67:533–8.
6. DANMAP—Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. 2005 Jul [cited 2006 Mar 22]. Available from http://www.dfvf.dk/Files/Filer/Zoonosecentret/Publikationer/Danmap/Danmap_2004.pdf

Address for correspondence: Louis Anthony Cox, Jr, Cox Associates, 503 Franklin St, Denver, CO 80218, USA; email: tcxdenver@aol.com

In response: Cox's letter (1) contains a number of false assumptions, errors, misleading assertions, and misquotations. Cox asserts that annually 1 person or fewer in the United States will experience an adverse effect because of fluoroquinolone use in poultry. He reduces 10-fold my referenced risk for persons acquiring *Campylobacter* infections from poultry (2). His unrealistically low estimate is not given in his referenced citation. His estimated risk is also much lower than in the reference 2, which Cox himself quotes, "Poultry is the most common cause of sporadic cases of campylobacteriosis in the United States" (Economic Research Service of the US Department of Agriculture) (3). Cox knows that his assertion (4) that poultry make little or no contribution to human *Campylobacter* infections has been extensively examined and found to be wrong. Indeed, an entire section in a recent US Food and Drug Administration (FDA) determination was written about the unreliability of Cox's testimony and these assertions, a finding made by both the FDA commissioner and an administrative law judge (5,6).

Cox also misquotes Busby et al. (3) when he asserts that only 0.6% of persons with *Campylobacter* infections benefit from antimicrobial drugs. The Busby article states that 0.6% of persons with *Campylobacter* infections need "hospitalization," not how many would benefit from antimicrobial drug therapy. Cox has thus made a misleading attribution (something he has previously been found to do [5]).

Busby et al. (3) estimated that in 1993, ≈1,500,000 persons in the United States acquired *Campylobacter* infections from food sources. Even if the proportion who can benefit from receiving antimicrobial drugs is as low as 2%, this translates to 30,000 persons. If 20% of these infections were caused by fluoroquinolone-resistant *Campylobacter* spp., then 6,000 persons would potentially have their therapy and outcome compromised, rather than the 1 person that Cox would have us believe. More realistic is the figure of 24,000 persons estimated previously to be at risk of having an adverse outcome (or ≈285 persons for every 1 million chickens treated with fluoroquinolones) (1). Cox's assumptions and calculations thus seem flawed and unrealistic.

Peter Collignon*

*The Canberra Hospital, Woden, Australian Capital Territory, Australia

References

1. Cox LA. Enrofloxacin in poultry and human health [letter]. *Emerg Infect Dis.* 2006;12:872–3.
2. Collignon P. Fluoroquinolone use in food animals [letter]. *Emerg Infect Dis.* 2005;11:1789–80.
3. Busby JC, Roberts T, Jordan Lin C-T, MacDonald JC. Bacterial food-borne disease: medical costs and productivity losses. [cited 2006 Mar 8]. *Agricultural Economics Report No. (AER741)*. Washington: United States Department of Agriculture; 1996. Available from <http://www.ers.usda.gov/publications/aer741/>
4. Phillips I, Casewell M, Cox T, DeGroot B, Friis C, Jones RN, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. *J Antimicrob Chemother.* 2004;53:28–52.
5. US Food and Drug Administration. Final decision of the commissioner. Proposal to withdraw the approval of the new animal drug application for enrofloxacin for poultry [cited 2006 Mar 8]. Docket no. 2000N-1571. p. 16–7; 108–19. Available from <http://www.fda.gov/oc/antimicrobial/baytri1.pdf>.
6. US Food and Drug Administration. Initial decision. Withdrawal of approval of the new animal drug application for enrofloxacin for poultry [cited 2006 Mar 8]. Docket no. 00N-1571. p. 13–5. Available from <http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031604/00n-1571-idf0001-vol389.pdf>

Address for correspondence: Peter Collignon, Infectious Diseases Unit and Microbiology Department, The Canberra Hospital, Australian National University, PO Box 11, Woden, ACT 2607, Australia; email: peter.collignon@act.gov.au

Biodefense Shield and Avian Influenza

To the Editor: In defending against avian influenza virus H5N1, the possibility of adopting treatments being developed for biodefense should not be overlooked. Biodefense medicine primarily concerns respiratory infections because bioweapons in their deadliest form disperse *Bacillus anthracis* and *Yersinia pestis*, the causes of anthrax and plague, and highly contagious viruses like smallpox, Ebola, and Marburg as aerosols. The National Institutes of Health and Department of Defense have funded developing novel biodefense medications designed to stimulate innate mucosal immunity by using interferons (IFNs) and interferon inducers.