

$\text{Pr}(\text{ingested dose} > \text{MID} \mid \text{AS-}) = e^{-a \cdot \log(\text{MID})} = 3.23\text{E-}5$ and rearranging, this becomes:

$$a \cdot \log(\text{MID}) = -\ln(3.23\text{E-}5) = 10.34, \text{ or, on substituting the estimate } a = 0.3984:$$

$$a \cdot \log(\text{MID}) = 10.34/a = 10.34/0.3984 = 25.954.$$

At present, with a near-zero percentage of AS+ flocks, these estimates give the current risk as:

$$\text{Pr}(\text{ingested dose} > \text{MID} \mid \text{AS-}) = \exp[-a \cdot \log(\text{MID})] = \exp(-25.954 \cdot 0.3984) = 3.23\text{E-}5.$$

But now suppose that a changes to reflect an average tenfold increase in microbial load per processed carcass, from $a = 1/\ln(10^{1.09}) = 0.3984$ for AS- flocks to $a^+ = 1/\ln(10^{2.09}) = 0.2078$ (based on the data of [Russell, 2003](#)). Then risk per serving will become:

$$\text{Pr}(\text{ingested dose} > \text{MID} \mid \text{AS+}) = \exp[-a^+ \cdot \log(\text{MID})] = \exp(-25.954 \cdot 0.2078) = 0.0045.$$

The relative risk of human illness due to untreated airsacculitis in chickens is therefore:

$$\text{RR} = \text{Pr}(\text{exposure} > \text{MID} \mid \text{AS+})/\text{Pr}(\text{exposure} > \text{MID} \mid \text{AS-}) = 0.0045/3.23\text{E-}5 = 139.3.$$

It is a convenient mathematical fact that this relative risk RR does not depend on the assumed dose-response threshold MID (the effective minimum infective dose, if any), due to a well-known property of exponential distributions. Thus, the increase in human health risk if a fraction F of currently AS- flocks become AS+ is:

$$\text{Risk from } F = F \cdot (\text{RR} - 1) = 138.3 \cdot F.$$

The multiplier of 138.3 can be interpreted as a product of two components: (a) A *microbial load ratio factor* of **10** reflecting the average ten-fold greater microbial load of *Campylobacter* on chicken carcasses from AS+ flocks compared to those from AS- flocks ([Russell, 2003](#)); and (b) A *dose-response ratio factor* of **13.83** reflecting the log-exponential model's assumption that *higher doses have a higher average risk-per-cfu* than low doses, i.e., a ten-fold increase in the *mean* microbial load corresponds to a more than 10-fold increase in the *highest* microbial loads (the right tail of the distribution, which is disproportionately hazardous to human health).

By contrast, [Rosenquist et al., 2003](#) estimate that a 100-fold change in mean *Campylobacter* cfu count per chicken carcass would produce only a 30-fold change in human illness rates, corresponding to a *less* than proportional change in risk. This is based on a Beta-Poisson population dose-response model fit to experimental data ([Teunis et al., 1999](#); [Teunis and Havelaar, 2000](#)) in which each cfu ingested is assumed to have the *same* probability of causing infection, independent of the size of the dose received (i.e., the number of other CFUs ingested at the same time), although this probability can be different for different people. The simulated dose-response curve is approximately linear on a log-log scale around current estimated exposures, so that a 10-fold increase in *C. jejuni* cfu per chicken carcass, as in [Russell, 2003](#), would be expected to produce only about a 3-fold increase in risk. This multiplier of 3 can be interpreted as the product of (a) A microbial load ratio factor of 10; and (b) A dose-response ratio factor of 0.3, reflecting the assumption that highly sensitive people will still respond even to ten-fold lower doses, while highly insusceptible people will not respond in either case (current microbial load or reduced load), so that the overall change in response in a highly heterogeneous population will be less than proportional to the change in mean dose.

An intermediate model is the linear non-threshold model, according to which the risk of campylobacteriosis is proportional to dose ingested and the dose-response ratio factor is **1**. In this model, a 10-fold increase in microbial load creates a 10-fold increase in expected number of illnesses. In this case, we have the apparently simple formula:

$$P^+ = 10 * P^-.$$

However, we are now considering *total* campylobacteriosis cases caused by eating Campylobacter-contaminated chicken, rather than only severe cases, in order to quantify the total human health harm caused by additional microbial load. Therefore, the preceding value for P^- must be adjusted to account for (a) Greater underreporting assumed for all cases than for severe ones. We assumed a factor of 8 cases per reported case for severe cases, compared to 38 total cases per reported case estimated by Mead et al., 1999; in addition, we estimated that 0.00595 of total cases were severe (Buzby et al., 1996). Thus, the value of P^- for total cases becomes:

$(38/8) * (P^- \text{ for severe cases}) / (\text{fraction of total cases that are severe}) = (38/8) * (1.6583E-8 \text{ from above}) / (0.00595) = 1.324E-5$. For the linear model, the value of P^+ is now:

$$P^+ = 10 * P^- = 1.324E-4$$

Hence $(P^+ - P^-) = (1.324E-4 - 1.324E-5) = 1.19E-4$ is the excess individual risk of campylobacteriosis (*C. jejuni* or all strains – the factor of 0.99 can be neglected at this level of precision) per serving from an airsacculitis-positive (AS+) bird.

Given the sensitivity of risk predictions to the assumed dose-response model, i.e., convex (upward-curving, as in the FDA-CVM 2001 log-exponential model), concave (sub-linear, as in the Rosenquist et al. 2003 model), or linear, we will use the linear model for baseline calculations, while recognizing that it may give predicted excess risks that are high by a factor of 3 (if the Rosenquist model is accurate) or low by a factor of 14 (if the log-exponential model is correct). Use of the linear model also obviates the need to model the variability of microbial loads in chicken carcasses from AS+ compared to AS- flocks: the mean cfu counts per carcass suffice when risk is assumed to be proportional to dose.

In summary, the baseline model for risk from chicken servings from AS+ carcasses has the form:

Risk per serving from AS+ bird = (microbial load ratio factor) * (dose-response ratio factor) * (Risk per serving from AS- bird) = (10 from Russell, 2003) * (1 for linear no-threshold model) * (P^-).

The dose-response ratio factor of 1 would be replaced by values of 0.3 or 14 in the other dose-response models examined. For the baseline calculation, the excess risk of campylobacteriosis per serving from an AS+ bird is $(P^+ - P^-) = 1.19E-4$.

*Estimated human health effects of ceasing antibiotic use in chicken: ?F and $(P^+ - P^-) * ?F * M * N$*

Now suppose that some macrolide uses in chickens were restricted or terminated. Assuming that, after the change, poultry veterinarians would have to use less effective alternatives such that half of those chickens with airsacculitis currently prevented or treated with macrolides would remain airsacculitis positive, then about half a percent ($?F = 0.005$) of current AS- flocks processed per year would be expected to be replaced with AS+ flocks. The corresponding increase

in human campylobacteriosis cases caused by chicken consumption under our baseline assumptions above (i.e., for $(P^+ - P^-) = 1.19E-4$) would thus be about:

$(0.005 \text{ fraction of chicken flocks becoming AS+}) * (38 \text{ average number of fresh chicken servings per capita-year in US}) * (292,000,000 \text{ people in US}) * (1.19E-4 \text{ estimated average excess risk of campylobacteriosis per serving from AS+ flock}) = 0.005 * 38 * 292,000,000 * 1.19E-4 = 6602.1 \text{ excess cases per year if macrolide antibiotics are withdrawn.}$

This number assumes that airsacculitis prevalence rates remain unchanged following a ban; if they increase, the excess cases predicted for the human population will increase proportionally.

Similarly for macrolides and other animal antibiotics that reduce or eliminate the prevalence of AS+ flocks, a ban is expected to cause an average of $(2 * 6602.1) = 13,204$ excess campylobacteriosis cases per year in the human population for each 1% increase in chicken servings from AS+ flocks. These additional illnesses must be weighed against any human health benefits from reduced resistance.

Estimating (1 - s): Antibiotic-resistant fraction

The fractions of chicken-caused severe *C. jejuni* illnesses that are resistant to different antibiotics have not been well studied in the United States. Overall, about 1% of *C. jejuni* illnesses were reported as being erythromycin-resistant in 2000, and the number has been relatively stable or declining for many years (CDC, 2000). In the absence of data specifically for severe cases caused by chicken consumption, we will use the overall **erythromycin-resistance rate of $(1 - s) = 1\%$** among *C. jejuni* in 2000, with an uncertainty factor of 4 for future values.

Estimating p: Preventable resistant fraction

If use of macrolides in food animals ceased, what would be the effects on *future resistance rates* among severe *C. jejuni* cases in human patients, and how long would these effects take to occur? This is a different question from estimating the fraction of current resistance levels that are statistically associated with or attributable to past antibiotic use in animals, and retrospective attributable fraction estimates cannot answer it. For example, in discussing the effects of withdrawing the animal antibiotic avoparcin in order to reduce vancomycin-resistant enterococci (VRE) in food animals and people, Aarestrup et al. (2001) warned that “It is not possible to foresee whether the occurrence of resistance will decrease to an undetectable level in the future.” Heuer et al., 2002 started more bluntly that the withdrawal appeared to have led to “no significant decrease in the proportion of VRE-positive [broiler] flocks” in Denmark within five years and concluded that “This study demonstrated the extensive occurrence of VRE in broiler flocks more than 5 years after the avoparcin ban in Denmark, and indicates that VRE may persist in the absence of the selective pressure exerted by avoparcin.” (Heuer et al., 2002.) Similar findings have been reported for Norway (Borgen et al., 2000) and Sweden, where VRE were still commonly found in sewage more than fifteen years after avoparcin stopped being used in food animals, possibly due to continued human antibiotic use and hospital runoff (Iversen et al., 2002). Thus, the avoparcin experience, though not directly relevant to the US, warns that withdrawing animal antibiotics to reduce resistance levels in animals and humans may be less than completely effective, corresponding to a preventable resistance fraction $p < 1$.

For macrolides, the ban in Denmark on macrolides used as animal growth promoters was followed by an unexpected increase in human resistance rates. Erythromycin resistance rates in

domestically acquired human *C. jejuni* isolates had been low (< 2%) and steady or decreasing in 1997 and 1998. In general, erythromycin resistance in human isolates, as measured by a variety of laboratory procedures, had remained fairly low and stable in most European countries for several decades, with levels of around 0-3% for *C. jejuni* commonly reported (e.g., 2% in Belgium in isolates from stool samples collected in 1972; [Vanhoof et al., 1980](#); 3% in Finland during the 1980s ([Rautelin et al., 1991, 2003](#); <1% in Norway in 1998-9 ([Afset and Maeland, 2001](#)); 2.3% in Spain in 1998-92 ([Sanchez et al., 1994](#)); 6.4% with an increasing trend in Sweden when foreign travel cases are included ([Sjogren et al., 1992, 1997](#)), but not when they are excluded ([Osterlund et al., 2003](#))). In Denmark, however, erythromycin rates in human isolates abruptly reversed their previous declining trend immediately following the ban, increasing by more than 5-fold (from < 1% to > 5%) from 1998 to 2001 ([Hayes and Jensen \(2003\)](#), Figure 2). How, if at all, the 1998 ban affected this ensuing rise in human resistance levels is not known, as aggregate temporal trend information alone does not reveal causality. Nonetheless, this history suggests that the preventable resistance fraction, p , for a macrolide ban may be less than 1.

The above data taken together do not suggest a specific non-zero numerical value for the fraction of antibiotic resistance among chicken-caused severe *C. jejuni* cases that would be prevented by a ban. To be conservative, i.e., to maximize the estimated human health benefit of a ban in [Table 4](#), we will use a non-informative baseline interval estimate of $p \leq 100\%$, corresponding to an assumption that a ban could render all such cases susceptible to human antibiotics, while recognizing that the true value could also be as low as 0%. Again, we will use sensitivity analysis to study the effects of this uncertainty.

This interval estimate does not adequately represent the discrete probability that the correct value is 0, but may be interpreted as an approximate conditional probability distribution for the value of p if it is not zero. (If $p = 0$, then the remainder of the analysis becomes irrelevant, as the total direct human health benefit from a ban, $p(1 - s)f(Q_r - Q_s)(P^-)MN$, would then be zero.)

Estimated prescription rate, r

To be conservative, we assume that 100% of severe *C. jejuni* cases seek treatment and are prescribed antibiotics. However, for severe and dangerous cases, e.g., for immunocompromised patients and/or patients with increasing bloody diarrhea that has lasted more than a week, antibiotics other than erythromycin and ciprofloxacin may be indicated. Prescriptions of erythromycin or ciprofloxacin in such cases may not be made until diagnostic and resistance tests have been completed, making it less likely that a patient will be assigned a drug to which the infection is resistant ([Ang and Nachman, 2003](#)). Even without improvement in testing technology, there is less than 100% probability that a severe case with resistance to a specific antibiotic (e.g., erythromycin) will be prescribed that antibiotic, since another antibiotic (e.g., ciprofloxacin) may be prescribed instead. According to FoodNet survey data, about 55% of campylobacteriosis patients who were prescribed antibiotics received fluoroquinolones (usually, ciprofloxacin) ([FDA-CVM, 2001](#)). Recent concern over emergence of fluoroquinolone resistance may help to shift prescriptions toward erythromycin. In any case, it appears that a patient who has resistance to only one antibiotic currently has at most on the order of a $r = 50\%$ chance of being prescribed that antibiotic. This fraction may decrease as better testing technologies are developed. However, the emergence of multiresistant *C. jejuni* strains, such as a jointly macrolide- and fluoroquinolone-resistant cluster of cases among male homosexuals in Quebec ([Gaudreau and Michaud, 2003](#)), place a lower bound on the probability that a patient with resistance to one antibiotic will not be resistant to another assigned as treatment. Given the prescription rate data reported in [FDA-CVM, 2001](#), we will take 0.5 as the approximate current probability that a patient with severe campylobacteriosis

resistant to a specific human antibiotic is treated with an antibiotic to which the illness is resistant. However, we will include an uncertainty factor of 2, corresponding to the interval estimate [0,25, 1], to acknowledge the possibility of increasing multiresistant strains in future as well as to allow for improvements in rapid resistance testing and prescription practices that would reduce the frequency of treatment with resisted antibiotics.

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Variable	Values, Uncertainty Factors (UF)
Total campy cases reported per 100,000 people/year	<u>13.37</u> , <u>CDC, 2003</u>
Fraction severe (treatment with antibiotic is indicated)	<u>0.00595</u> , USDA: <u>Buzby, et al., 1996</u>
Under-reporting factor	<u>8</u> (2-38; UF = 5), (<u>Mead et al. 99</u>)
US population, N	<u>292E6</u> = 2,920 x 100,000 people in US, UF ≈ 1, <u>US Census Bureau</u>
Fraction of severe cases caused by chicken products (including cross-contamination)	<u>0.10</u> , UF = 10 , from <u>genetic, competing risk, epi, historical data</u> (<u>Stern and Robach, 2003</u>)
Fraction of severe cases that are antibiotic-resistant,	<u>0.01</u> for erythromycin resistance, UF = 2 , <u>CDC, 2000</u>
Resistant severe <i>C. jejuni</i> cases per year caused by chicken products = (P̄)*(MN)*(1- s) = product of above	1.84 cases/yr. for macrolides = Product of above = (<u>13.37E-5</u>) * <u>0.00595</u> * <u>8</u> * <u>292E6</u> * <u>0.10</u> * <u>0.01</u> ; UF = 18 (from UFs of 5, 10, 2)
Preventable fraction	< 1 (EU experience)
Excess treatment failure fraction	< fraction treated with resisted antibiotic*fraction experiencing treatment failure from resistance