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EXAMPLES OF RISK ASSESSMENTS FOR FOOD SAFETY POLICY ANALYSIS

(Prepared by WHO Collaborating Center for Risk Assessment and Hazard Identification in Foods of Animal Origin)

Introduction

This center has been functioning since 1992, under the directorship of Dr George Beran, Emeritus Professor, Iowa State University College of Veterinary Medicine. In 2005, Scott Hurd became the Director and the center's emphasis was changed slightly to the following areas:

- Provide critical skills in the area of food and veterinary risk analysis, including risk communication, risk management, and especially risk assessment.
- Determine the most effective intervention points to control microbiological and chemical hazards in foods of animal origin
- Adapt risk analysis techniques to problems and situations relevant to PAHO.
- Interpret global risk analysis initiatives for situations and food safety problems of PAHO countries.
- Develop and apply statistically accurate surveillance tools to obtain critical data for risk assessment
- Provide technical cooperation in surveillance and assessment of food-borne hazards

Some examples of the recent work that may be applied to improve the effectiveness of national policy for food safety in the Americas and Caribbean are described below. Additionally, opportunities exist for training in quantitative risk assessment skills through graduate programs and web-based courses offered by this Center in collaboration with Iowa State University's Institute for Food Safety and Security. (www.ifss.iastate.edu).

Example of Macrolide Antibiotic Resistance: Comparative Risk Assessment

Introduction

Concerns abound regarding antibiotic resistance in bacteria affecting humans, including pathogens assumed to be of food-borne origin. Administration of antibiotics to food animals for subtherapeutic use (namely, disease prevention and growth promotion) has been suggested as a significant cause of this developing resistance (Aarestrup, 2001). To address these concerns, many government regulatory authorities and decision makers propose applying risk assessment methods. However, experience with risk assessment shows that risk quantification alone is insufficient for decision making. Instead, comparison of the risk and benefits – or a comparative risk assessment – leads to a more informed decision. This paper briefly describes two related analyses that provide a fully transparent quantitative attempt to address decision makers' needs: a quantitative risk assessment of

macrolide use in food animals, consistent with Food and Drug Administration (FDA) Guidance; and a comparative assessment of the public health impacts of feed additive tylosin use in chickens.

Quantitative Risk Assessment

The objective of this first study was to conduct a quantitative risk assessment (RA) consistent with the newly published FDA Guidance 152 (U.S. FDA, 2003) to estimate the risk of macrolide use in livestock, in relation to human campylobacter infection, and compare with other societal risks. The scope of this RA included all label claim uses for both tylosin and tilmicosin (Elanco Animal Health, Greenfield, IN) in swine, poultry and beef cattle (Hurd, *et al.*, 2004).

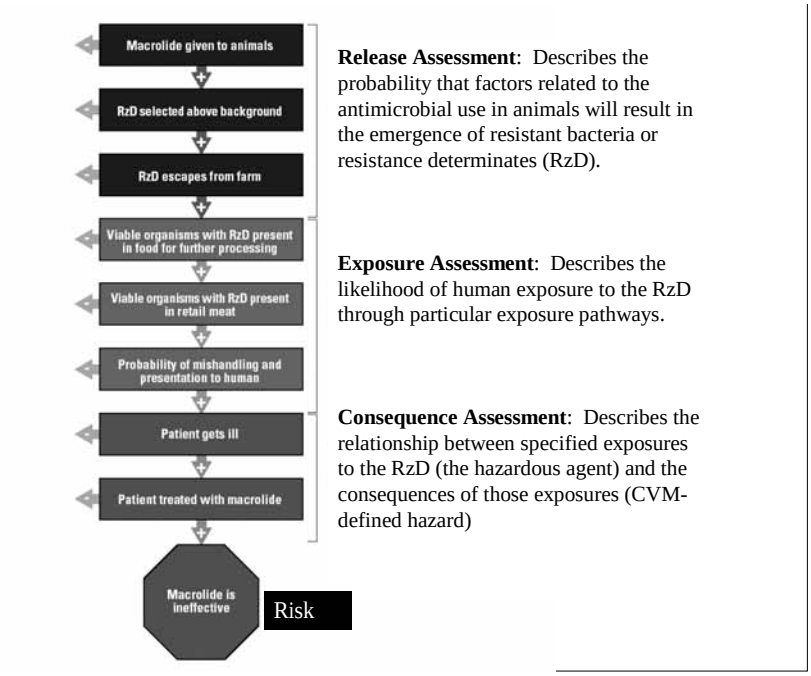
For this assessment, the hazard was defined in accordance with Guidance Document 152 as "human illness" that is: 1) caused by macrolide-resistant *Campylobacter* spp., 2) attributable to consumption of contaminated pork, poultry or beef, and 3) treated with a human antibiotic of the macrolide class. The risk was defined and modeled as the yearly probability that an average American would be affected by the defined hazard and, as a result, experience an adverse therapeutic event (*i.e.*, poorer efficacy than usual as manifested by longer duration of diarrhea, progression to more severe disease, or mortality).

The FDA recommends a "qualitative" risk assessment, which applies high, medium, and low estimates for each of the three analyzed components: release-, exposure- and consequence-assessment. However, this assessment used a determinist quantitative model, recognizing that some data might be limited and may need to be approximated. This approach provides greater transparency regarding calculations and assumptions at each point in the chain of events. Additionally, this approach allows for revision with new data and for the consequences of human drug use to be based on the actual probability of treatment.

Figure 1 graphically summarizes the modeled chain of events (steps) necessary to lead to the defined risk. A number of events are required for human illness to occur as a result of tylosin or tilmicosin (T-T) administration. First, T-T must be administered to food animals. An increased prevalence of resistant determinant (RzD) must then occur in the intestinal bacterial flora of the animals due to T-T administration. Next, the resistant bacteria must leave the place of administration, *e.g.*, farm or feedlot. The RzD must move from the intestinal or fecal material in the treated animal and contaminate the carcass, rinse fluids, and/or neighboring carcasses during slaughter and processing operations. The RzD must remain on contaminated carcasses after processing, storage, and placement into the retail sales environment. The meat product must then be mishandled, undercooked or otherwise improperly prepared such that human infection or colonization can occur. For *Campylobacter* spp., the inoculating dose must be sufficient to cause the person to become ill, to seek medical treatment, and be treated with a macrolide which consequently fails due to the RzD. As shown in Figure 1, this event model is consistent with the FDA-defined hazard. Additionally, it provides addition of an estimate of the probability that treatment would be ineffective, the calculated risk.

Each event or "Node" was represented in a separate worksheet of an Excel® spreadsheet software program (Microsoft, Richmond, WA). Quantities or probabilities associated with each Node were entered into the worksheet, combined with output or calculations from the previous sheet, and carried forward to the final estimate: expected illness per capita-year in the U.S. for human macrolide treatment failure or to be compromised from the presence of resistant bacteria due to administration of T-T to food animals. A copy of the workbook is available from (www.ifss.iastate.edu/macrolide/).

Figure 1. Pathway of Events Leading to the Risk



Quantitative Risk: Results and Discussion

This model estimated that the probability of human illness in the U.S. due to macrolide-resistant campylobacteriosis for all meat commodities combined was slightly less than 1 in 10 million. For pork and beef, the probabilities were 1 in 53 million and 1 in 236 million, respectively. For poultry it was slightly less than 1 in 14 million. The risk from poultry use was the highest of the three commodities, mostly due to high *Campylobacter* spp. carcass contamination rates.

Using a rigorous quantitative model and conservative assumptions, the direct risk of a macrolide use in swine and other livestock was estimated to be very low in comparison to other societal risks. However, the risk is not zero. Therefore, in order to warrant continued use, it must be outweighed by some potential benefit, particularly public health benefit. Mechanisms for producing this public health benefit include decreased subclinical illness (e.g. airsacculitis, necrotic enteritis), fewer adhesions resulting in better evisceration, less carcass trim, and more size uniformity, all of which may lead to reduced levels of pathogen (*Salmonella* spp., *Campylobacter* spp.) carcass contamination.

Comparative risk assessment

To estimate these benefits, a comparative risk assessment was conducted. This assessment quantifies changes in human health risks due to changes in tylosin use in chickens (Singer *et al., 2005).* Antibiotic use was assumed to affect animal health, and animal health was assumed to affect carcass contamination, which is known to affect public health risk. A mathematical model of ordinary differential equations was derived to provide a "systems dynamics" approach. These equations model changes in human illness (resistant and non-resistant) as a function of changes in carcass contamination rates, which change with animal illness rates which are affected by antibiotic use.

The use of a macrolide antibiotic, tylosin, in poultry production was chosen for evaluation in this initial model. It is on the only macrolide feed additive approved for use in broiler chicken production that can select for chromosomal point mutations conferring resistance in *Campylobacter*. Members of this antibiotic class are sometimes used to treat human campylobacteriosis. Macrolide antibiotics can be administered as a feed additive in chicken production for performance gains. This use may reduce the incidence of necrotic enteritis by modulating *Clostridium perfringens* colonization as well as mucolytic activity of the intestinal bacterial population. Thus, the use of antibiotics, such as

tylosin, is considered to contribute to intestinal integrity and size uniformity of birds in the flock as well as to the maintenance of the health status of the chicken flock. Because tylosin has the potential to decrease *Clostridium perfringens* levels resulting in decreases in necrotic enteritis, the model allowed the simultaneous assessment of the potential human health risks and benefits of macrolide use in chickens.

When applied to *Campylobacter* from poultry meat, the model predicts that small increases in animal illness can lead to increased *Campylobacter* contamination on chicken meat which then causes large increases in human campylobacteriosis. It shows that the use of tylosin as a feed additive in chickens increases the incidence of human macrolide-resistant *Campylobacter* infections but also reduces total human illness days per year caused by all *Campylobacter*. For example, only a 1% increase in the incidence of animal illness following the removal of tylosin from chickens is predicted to cause an additional 2.4 to 53.7 excess campylobacteriosis illness days for every illness day prevented due to decreased macrolide resistance. This translates to an annual increase in the incidence of campylobacteriosis ranging from 0.3 to 8.9%. A mathematical sensitivity analysis showed small improvements in chicken health result in significant reductions in human illness.

Conclusions:

These analyses suggest that policies regarding antibiotic use in food animals should be analyzed on a case-by-case basis as antibiotics have different; 1) uses, 2) animal health impacts, 3) resistance development probabilities, and 4) human treatment probabilities. Secondly, they show that information from risk assessments must be comparative as antibiotic use in agricultural animals may have significant benefits to human health that must be weighed against their theoretical risk.

Acknowledgment

These analyses were prepared independently following meetings sponsored by Elanco Animal Health, Greenfield, IN. The authors attest that the opinions and work contained herein accurately reflect their opinions and not necessarily those of Elanco Animal Health.

Example o*f Risk-based analysis of the Danish pork Salmonella program, past and future*

Introduction

The question of where in the production system to best implement control Salmonella policies often ends up between the farm or the abattoir, as control policies further downstream e.g. the kitchen are difficult to implement. The Danish on-farm program involves classification of herd Salmonella status based on statistically based serological sampling. Herds with high seroprevalence levels receive special attention and financial penalties that encourage the reduction of Salmonella levels. As the program moves into its second decade, it is beneficial to evaluate the impact it has had on human risk of salmonellosis due to Danish pork.

All public policy efforts directed to the farm or the abattoir assume there is a connection between Salmonella in pigs and pork and salmonellosis in humans. It is assumed that reduction in pathogen prevalence on-farm and in the abattoir will result in reduced illness attributable to that pathogen-food combination, even if that attribution is not directly measurable. Every carcass tested, every HACCP implemented assumes there is a connection between efforts made on the farm or in the abattoir and human health. The goal of this analysis was to use that assumed connection and to evaluate some long range (10 year) control options for the Danish pork production system.

Materials And Methods

The method used was to generate a computer simulation model constructed of a series of Excel workbooks; one for each simulated year and scenario (Figure 1). Each workbook had four modules representing the key processes affecting Salmonella levels in pigs leaving the farm, on carcasses after slaughter, and pork attributed human cases of Salmonella (PAHC).

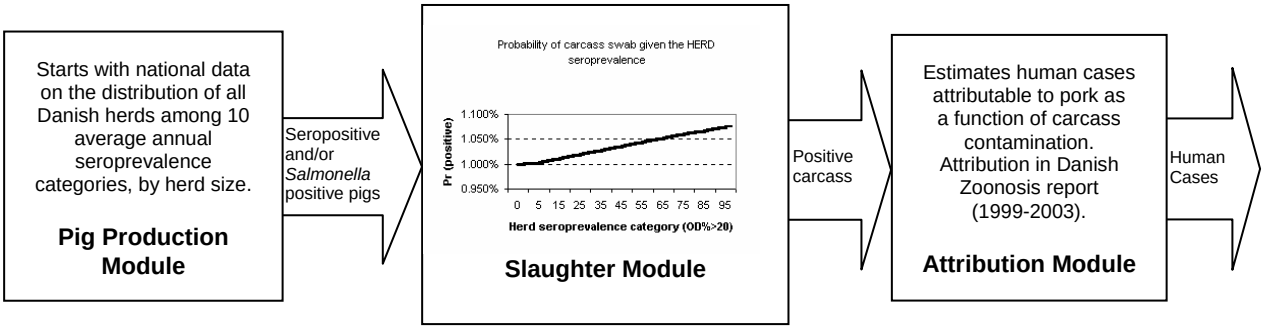


Figure 1: A Systems model of the production pork attributed Danish human salmonellosis cases from Danish produced pork.

There were two types of analysis conducted **retrospective** and **prospective**. The objective of **retrospective** analysis (1994-2003) was to isolate the separate effects of reductions in on-farm seroprevalence levels from improvements in the abattoir processes.

Results

In the **retrospective** analysis, the **Historical** scenario shows a reduction of PAHC from 351 to 202 (42%) comparing 1995 to 2003. This scenario reflects the effects of changes in the on-farm seroprevalence in combination with abattoir process improvements. Looking at the effect of on-farm interventions only (**Abattoir95**) shows there was an early significant decrease in number of positive carcasses due solely to the on-farm control program; reduction of approximately 73 (21%) mean number PAHC (1995 versus 1998). However, the effect of this on-farm program alone did not continued much beyond 1998; the annual number of PAHC staying around the 1998 level of 278. In the scenario of no on-farm control program beyond 1995 levels (**Farm95**), i.e. all improvements in the abattoir, there was downward trend similar to that simulated in the **Historical** scenario; reduction from 351 cases per year to 234.

The **prospective** analysis showed that continued reductions on-farm (**ImpF**) will result in minimal reductions in positive carcasses or human risk (159 PAHC/yr in 2004 to 144 in 2013). Also, there is little predicted change in risk if on-farm levels do not revert back (**RevF**) beyond the high levels of the early years (1995 to 1997). These data also show that continued improvement in abattoir methods, with no further changes on-farm (**Farm2003ImpAb**) will continue to reduce positive carcasses and expected human cases at a slow steady rate. With no more changes on-farm, the predicted number of PAHC in 2013 is around 110; significantly less than the 152 predicted in 2003. For on-farm improvements only, the predicted number of PAHC in 2013 was not significantly less than the 2003 starting point.

This study compared the relative impact of *Salmonella* control efforts implemented on-farm since 1994 with efforts occurring at the same time in the abattoir. Overall, this study demonstrates that, except for the first few years (1994-1998), the on-farm program had minimal impact in reducing the number of positive carcasses and pork attributable human cases (PAHC). Most of the reductions in the PAHC up to 2003 were, due to ill-defined improvements in slaughter hygiene. The various **prospective** scenarios out to 2013 show a similar conclusion that on-farm efforts at *Salmonella* reduction, similar to

those in the past, will not markedly improve public health. This is largely due to the fact that herds in the low seroprevalence categories still sell *Salmonella* infected pigs. These results are in agreement with Alban and Stark (2005), who look in more detail at the effect of various slaughter processes on carcass positivity.

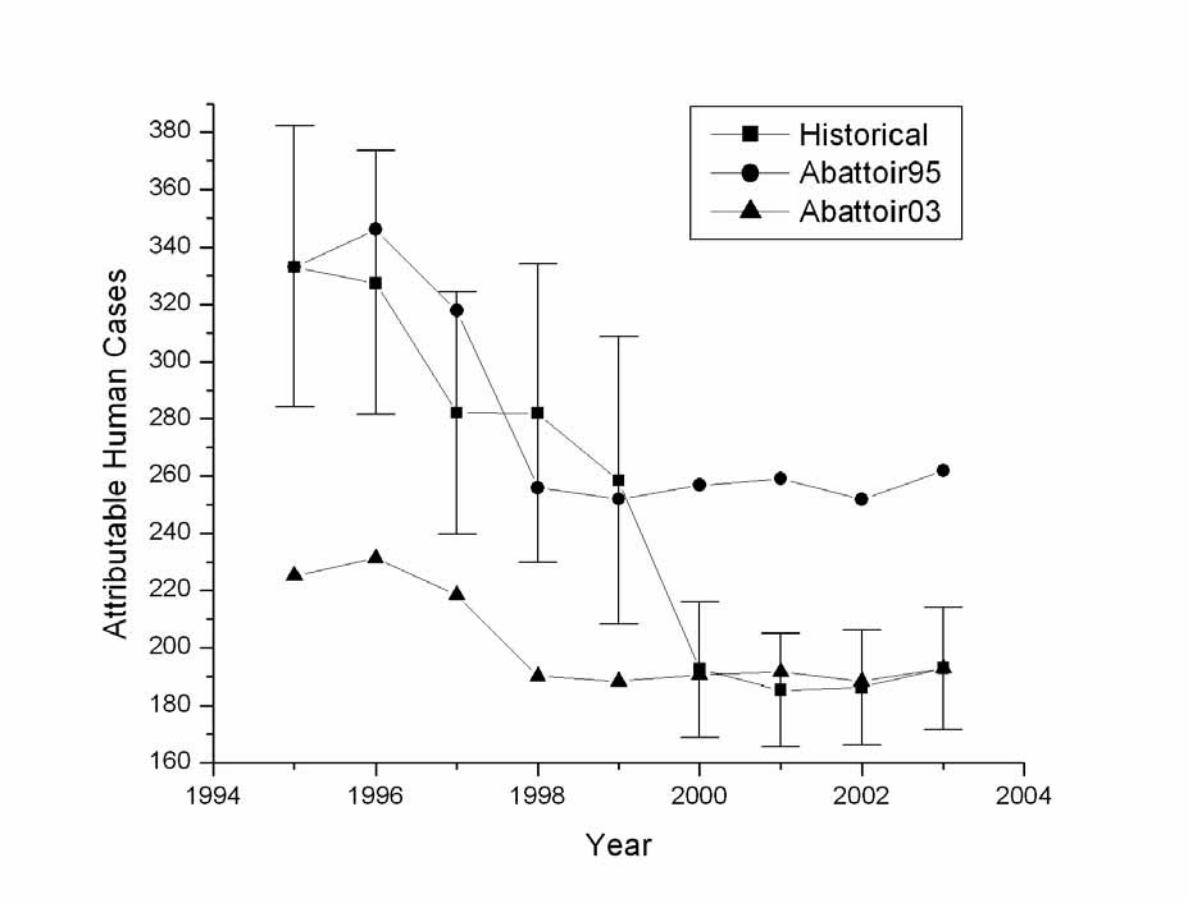


Figure 2: Comparison of simulated total annual number of pork attributable human cases if on-farm control methods were used with 1995 (**Abattoir95**) or 2003 (**Abattoir03**) slaughter quality parameters.

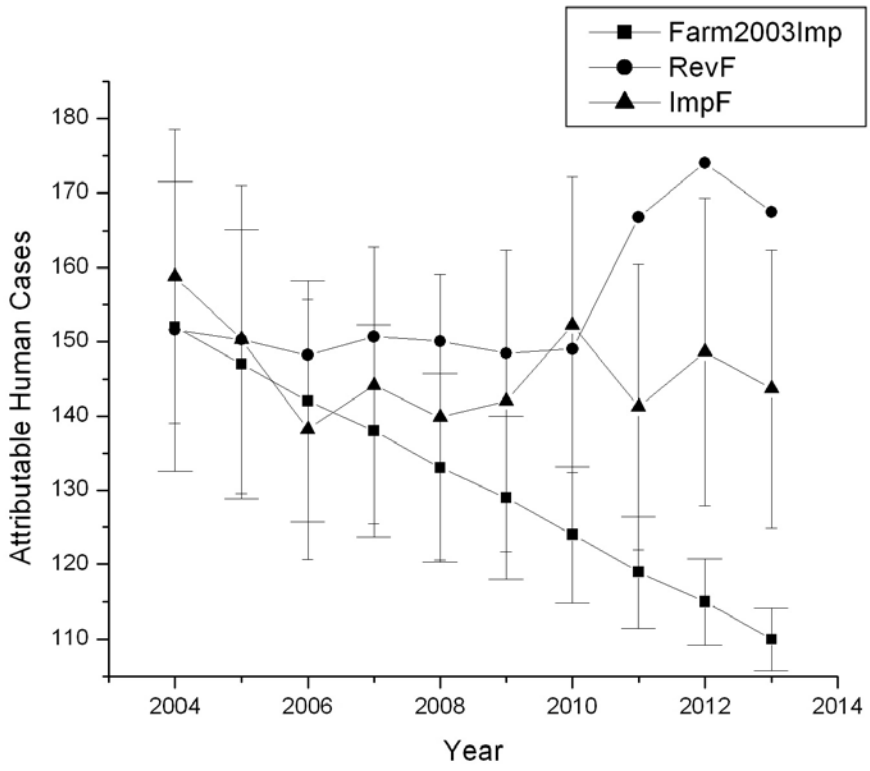


Figure 3: Comparison of simulated pork attributable human cases per year based on holding on-farm seroprevalence levels at 2003 levels and improving abattoir methods (**Farm2003ImpAb**); reverting on-farm methods to 1995 values while keeping abattoir values constant (**RevF**); and continuing to improve on-farm methods while keeping abattoir values constant (**ImpF**).

A few recommendations for Denmark, may be deduced from this analysis:

- Consider a limited or reduced investment in on-farm control; just enough to maintain the current infection status.
- Remain open to new on-farm technologies that may make Salmonella control more cost-effective.
- Explore and invest in new abattoir specific interventions.
- Consider carcass decontamination options for all carcasses.
- Continue to refine this model and other systems models that connect underlying current policy options.

REFERENCES

For a full report with references, see the International Epi Lab, www.dfvf.dk

Hurd, H. S., Doores, S., Hayes, D., Mathew, A., Maurer, J., Silley, P., Singer, R., & Jones, R.N. (2004). The public health consequences of macrolide use in food animals: A deterministic risk assessment. *Journal of Food Protection* 67:5, 980-992.

Singer, R.S, Cox, L.A., Dickson, J.S., Hurd, H.S., Phillips, I., Miller, G.Y. (2005). Improved Food Animal Health May Lead to Decreased Human Food-borne Illness. *Proceedings of the National Academy of Science* (submitted).

United States Food and Drug Administration. Center for Veterinary Medicine. 2002. Draft guidance for industry: evaluating the safety of antimicrobial new animal drugs with regard to their microbiological

effects on bacteria of human health concern. Document no. 152. Available at: http://www.fda.gov/cvm/guidance/dguide152.pdf. Accessed 29 July 2003.