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Causal regulations vs. *political will*: Why human zoonotic infections increase despite precautionary bans on animal antibiotics

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Abstract

Using precautionary principles when facing incomplete facts and causal conjectures raises the possibility of a Faustian bargain. This paper applies systems dynamics based on previously unavailable data to show how well intended precautionary policies for promoting food safety may backfire unless they are informed by quantitative cause-and-effect models of how animal antibiotics affect animal and human health. We focus on European Union and United States formulations of regulatory precaution and then analyze zoonotic infections in terms of the consequences of relying on *political will* to justify precautionary bans. We do not attempt a political analysis of these issues; rather, we conduct a regulatory analysis of precautionary legal requirements and use Quantitative Risk Assessment (QRA) to assess a set of policy outcomes. Thirty-seven years ago, the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (the Swann Report) warned that uncontrolled use of similar antibiotics in humans and food animals could promote the emergence of resistant strains of foodborne bacteria that could endanger human health. Since then, many countries have either banned or restricted antibiotics as feed additives for promoting animal growth. Others, including the United States, have relied on *prudent use* guidelines and programs that reduce total microbial loads, rather than focusing exclusively on antibiotic-resistant bacteria. In retrospect, the regulatory strategy of banning or restricting animal antibiotic uses has had limited success: it has been followed in many cases by deteriorating animal health and increases in human illnesses and resistance rates. Conversely, a combination of continued prudent use of antibiotics to prevent and control animal infections, together with HACCP and other improvements, has been followed by large improvements in the microbial safety of chickens and other food animals in the United States, leaving both animals and people better off now than they were decades ago. A quantitative risk assessment model of microbiological risks (*Campylobacter* because of data availability) suggests that these outcomes may be more than coincidental: prudent use of animal antibiotics may actually improve human health, while bans on animal antibiotics, intended to be precautionary, inadvertently may harm human health.

Keywords: Zoonotic diseases; Infections; Risks; Precautionary principles; System dynamics; E.U. and U.S. law

1. Introduction

Histories of perceived public health threats, public health interventions, and subsequent changes in health status provide a rich source of data for understanding the causal relations between public choices and their consequences. Sometimes, the results are surprising and counterintuitive. Quantitative risk assessment (QRA) is a powerful framework for understanding and explaining interventions and results causally, identifying ways to manage future hazards effectively. This paper has two objectives. The first is to sketch the legal basis of public actions that can result in *all-or-none* risk management interventions, such as bans, which are justified by a legally enforceable precautionary principle. We then illustrate and explain some surprising trends in the long history of efforts to ban or restrict animal antibiotics to preserve the efficacy of similar antibiotics for humans, focusing on antibiotic resistance and human illnesses from the foodborne bacterium *Campylobacter*.

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2. The European Union context

We deal with a legally enforceable precautionary principle and consequent public health choices concerning human resistance to antibiotics administered to animals, as way of illustrating issues and results, focusing on *Campylobacter*. Those choices are mandated by EU Treaties beginning with the European Treaty of Union (Treaty of Maastricht, Art. 130r), the EC Treaty Art. 174 renumbering Art. 130r; the EU Constitution (not ratified), the Reform Treaty Draft of 2007, and decisions of the European Court of Justice (ECJ) and its Court of First Instance (CFI). The most recent EU Treaty does not modify EC Treaty Art. 174, which was amended by the 2004 ICG, and thus Art. 130r remains in force, as does case law developed under it. Article 130r states (*inter alia*) that:

2. Community policy on the environment shall aim at a high level of protection… (and) shall be based on the precautionary principle…
3. In preparing its policy on the environment, the Community shall take account of:
   (i) available scientific and technical data;
   (ii) environmental conditions in various regions of the Community;
   (iii) the potential benefits and costs of action or lack of action;
   (iv) the economic and social development of the Community as a whole and the balanced development of its regions.

This mandate now extends beyond its early scope (Art. 130r dealt with only environmental policy), for example to general food laws. A question that remains open (it will be decided in the works inherent to the Reform Treaty (Draft) of 2007) is how the *high level of protection and improvement of the quality of the environment* of Art 2 of the EU Treaty (to be renumbered as Art. 3), which concerns the EU's objectives, will affect precautionary actions. Clearly, the normative aspect of *achieving a high level of protection based on the precautionary principle* is unassailable. However, the Treaties (and Art. 130r) do not define the precautionary principle. Moreover, achieving the *high level of protection* (Art. 130(r)(2)) requires meeting the conditions set forth in (Art. 130(r)(3)). Assessing the implications of policy involves the analysis of risks and their management, representations of uncertainty, variability, and causal reasoning that differ from traditional statistical-probabilistic analysis characterized by *small k*, *large n situations* (where the sample sizes can increase, and studies can be replicated and studied for internal and external validity at relatively low cost). Thus, actions justifiable by appeal to Art. 130r Precautionary Principle may often not benefit from traditional causal statistical modeling (partly because the standard assumptions do not apply).

The historical basis for the precautionary principles was reviewed by Harremoes et al. (2001), Ricci et al. (2003, 2004a,b, 2006). What happened in the US regarding exposure to benzene is particularly relevant to precautionary regulation, when there is no information at low doses. Briefly, the US Supreme Court held that OSHA (the US agency that administers the OSH Act) must use the best scientific evidence to support its finding of *significant risk* for a given occupational carcinogen that it wants to regulate. As the record showed, OSHA had done an unacceptable job as to the scientific justifications for their assumption of the linear, no-threshold cancer model, LNT, (Ricci and Molton, 1981). As the Court stated (footnotes and citations omitted for brevity):

The Court of Appeals was correct in refusing to enforce the 1-ppm exposure limit on the ground that it was not supported by appropriate findings. OSHA's rationale for lowering the permissible exposure limit from 10 ppm to 1 ppm was based, not on any finding that leukemia has ever been caused by exposure to 10 ppm of benzene and that it will not be caused by exposure to 1 ppm, but rather on a series of assumptions indicating that some leukemia might result from exposure to 10 ppm and that the number of cases might be reduced by lowering the exposure level to 1 ppm.

The issue is not that an agency cannot change (up or down) permissible exposures when science is unable to provide incontrovertible proof of danger. Incontrovertible scientific proof probably cannot be achieved – certainly not at the incidence levels discussed by Harremoes et al. (2001) – yet waiting can be dangerous for society because of the continued exposure to the conjectured, at very low doses, hazard. The issue is therefore whether the expected costs from waiting outweigh the expected costs of acting now.

Legally, actions based on the Art. 130r Precautionary Principle must account for economic welfare effects. For example, if the EU lowers its standards for aflatoxin exposure and affects agricultural production in Africa, implementing the standard within the EU might reduce cancers in the EU but cause unemployment and possible structural changes to the economies of the African exporters of peanuts. The basis for the standard has to be looked at not only in terms of the potential for reducing the burden of diseases within the EU, but also the increase in the burden of disease its trading partners' countries via a change in local employment, multiplier effects associated with the employment change, and so on. If a EU subsidy to offset the change in employment occurs, its effect has to be studied as well.

Peel (2004) argues that lack of normative yardsticks (e.g., acceptability of risk criteria, how to deal with uncertainty) results in a *normative vacuum*. (p. 9) She focuses on the WTO sanitary and phytosanitary, WTO-SPS, Agreement and its effect on *national SPS measures* and suggests that the WTO-SPS Agreement has focused on the fact that the US believes that policy based *sound science* should drive regulations, unlike the EU's focus on a policy of precaution that seemingly deemphasizes science, as we have discussed. The WTO-SPS Agreement includes risk-based regulations (Peel, op. cit., footnote 23):

The SPS Agreement specifically allows for this possibility in Article 3.3, although Members must be able to show a *scientific justification* or that SPS measures are in *consequence of the level of sanitary or phytosanitary protection a Member determines to be appropriate in accordance with the relevant provisions of paragraphs 1 through 8 of Article 5* (Art. 5 is the risk assessment article). This rather confusing provision was interpreted by the WTO Appellate Body in the *Beef Hormones*

case (para. 175) as requiring a Member to undertake a risk assessment in accordance with Article 5 of the SPS Agreement in order to demonstrate a scientific justification for its measures.

As Peel summarizes (p. 13):

> ... Article 2.2, one of the 'basic rights and obligations' WTO Members have under the SPS Agreement. ... requires WTO Members to base any SPS measures they wish to introduce on "scientific principles" and to ensure that their SPS measures are "not maintained without sufficient scientific evidence." Article 2.2 is subject to an 'exception' set out in Article 5.7 of the Agreement, which allows Members to adopt SPS measures "on the basis of available pertinent information" in circumstances where "relevant scientific evidence is insufficient." However, measures may only be adopted pursuant to Article 5.7 "provisionally" as Members are subject to ongoing requirements "to seek to obtain the additional information necessary for a more objective assessment of risk" and to "review the sanitary or phytosanitary measure accordingly within a reasonable period of time.

Under Art. 130r Precautionary Principle regulation there is concern with the effect of such regulation on domestic (e.g., Member States of the EU) and international trade (e.g., WTO). Peel writes that:

> An important component…(is)…whether "available scientific evidence" has been taken into account in the carrying out of the risk assessment, …to meet the 'basic obligation' in Article 2.2 not to maintain SPS measures without sufficient scientific evidence, as well as the more specific requirements for risk assessment in Article 5.40 …The final part of the enquiry will generally turn to the trade impacts of the SPS measures and whether they are "not more trade-restrictive than required to achieve [the Member's] appropriate level of sanitary or phytosanitary protection, taking into account technical and economic feasibility." p.18

> The second important provision is Article 5, which establishes obligations for Members to ensure that their SPS measures are "based on" a risk assessment. In carrying out an assessment of SPS risks, Members must take into account "available scientific evidence" and risk assessment techniques developed by the international organizations whose standards are referenced in the Agreement." (footnote omitted)

Art. 130r results in a sequence of events. The first is the political decision to act by the relevant Institution of the EU (e.g., via a Council Regulation), through an appeal to the Precautionary Principle, and make a policy choice. This is a choice that must be informed by scientific facts and knowledge (as commanded by Art. 130r(3)(i) and (iii)). The second, when a scientific answer confirms *a* causal link consistent with the intent of Art. 130r(3)(i), relates to the choice of action by that Institution, e.g., a ban. The EU Commission (EU Com2000 1, Pub07_en)) clarified the implications of Art. 130r Precautionary Principle as follows:

> The precautionary principle is relevant only in the event of a potential risk, even if this risk cannot be fully demonstrated or quantified or its effects determined because of the insufficiency or inclusive nature of the scientific data. … The precautionary principle can under no circumstances be used to justify the adoption of arbitrary decisions. … Any assessment … should be based on the existing body of scientific and statistical data. Most decisions are taken where there is sufficient information available for appropriate preventive measures to be taken but in other circumstances, these data may be wanting in some respects. Whether or not to invoke the Precautionary Principle is a decision exercised where scientific information is insufficient, inconclusive, or uncertain and where there are indications that the possible effects on the environment, or human, animal or plant health may be potentially dangerous and inconsistent with the chosen level of protection.

The Communication (EU Com2000 1, Pub07_en), among its 4 objectives, wants to *avoid unwarranted recourse to the precautionary principle, as a disguised form of protectionism.* (EU Com2000 1, Pub07_en), regarding the *identification of potentially negative effects,* states that:

> Before the precautionary principle is invoked, the scientific data relevant to the risks must first be evaluated. However, one factor logically and chronologically precedes this evaluation, namely identification of the potentially negative effects of a phenomenon. To understand these effects more thoroughly it is necessary to conduct a scientific examination. The decision to conduct this examination without awaiting additional information is bound up with a less theoretical and more concrete perception of the risk.

However, human perceptions are biased by framing, cognitive, computational and other issues (Kahneman et al., 1982). Thus, reliance on *concrete perception* for making assessments of causal relation, is fraught with dangers, one of which is that *political will* takes over and leads to more harm than benefit, regardless of the good intentions on which it may be predicated. Com2000 also states some of the relevant conditions affecting use of Art. 130r Precautionary Principle that include:

> *Examining costs and benefits* entails comparing the overall cost to the Community of action and lack of action, in both the short- and long-term. This is not simply an economic cost–benefit analysis: its scope is much broader, and includes non-economic considerations, such as the efficacy of possible options and their acceptability to the public.

> *Subject to review* in the light of new scientific data, means measures based on the precautionary principle should be maintained so long as scientific information is incomplete or inconclusive, and the risk is still considered too high to be imposed on society, in view of the chosen level of protection. Measures should be periodically reviewed in the light of scientific progress, and amended as necessary.

> *Assigning responsibility for producing scientific evidence* is already a common consequence of these measures. Countries that impose a prior approval … requirement on

products that they deem dangerous *a priori* reverse the burden of proving injury, by treating them as dangerous unless and until businesses do the scientific work necessary to demonstrate that they are safe.

2.1. Implications of the management of hazards within the context of Art 130r precautionary principle

Art. 130r Precautionary Principle-based policy occurs when *scientific information is insufficient, inconclusive, or uncertain*. Unfortunately, these phrases are vague. The Commission punts on what these phrases mean (e.g., what are *insufficient* or *inconclusive*, and what defines *uncertain*?). How can a judge differentiate between the two? Does a lexical analysis (e.g., the *plain meaning* standard) suffice for their judicial interpretation, when these phrases are part of scientific – not colloquial – language and thus have specific meaning? Does the balancing of the entire scientific evidence, of a case, and the more likely than not test (>50%) define what is *sufficient*, or should the test consist of a lesser probability, given the potentially irreversible or serious nature of the outcomes? Alternatively, should it be a larger evidentiary burden, given the nature of the scientific conjectures that support causal reasoning?

Social decision-makers must be able to find specific guidance that would answer the amount and quality of the evidence necessary to trigger Art 130r precautionary action. In US civil law, the general legal test is the *more-likely-than-not*. In this test, *conclusive legal evidence* is the result of applying it to the entirety of the probative evidence of causation, 'witnesses' are deposed under oath, cross-examined, and so on. A legal test of the probative value of the scientific evidence has little to do with scientific tests of causation. To illustrate the implications of balancing the evidence, we turn to the judicial evaluation of the probative values of scientific evidence in civil litigation. It is likely that, in environmental health, even when the relationship between disease and exposure is known, the expected magnitude of the *RR* is generally below 2.00. And yet, for actions resolved by appeal to precautionary principles, it is unlikely that there will enough data to make those calculations. Although the EU is silent on what to do in even this simple case, the US is clear.

The EU Regulation on General Food Law (Art. 7) states that (Van Der Haegen, 2003):

> In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment.

Additionally, it also states that precautionary measures (Van Der Haegen, 2003):

> Shall be proportionate and no more restrictive of trade than is required to achieve the high level of health protection chosen in the EU, regard being had to technical and economic feasibility and other factors regarded as legitimate in the matter under consideration.

In COM (2002), the Commission on the Impact Assessment, clarifies their thinking regarding scientific information: *it is an aid to decision-making, not a substitute for political judgment*.

The European Court of Justice, regarding the legal standard for prohibiting non-approved nutrients additives in health drinks, has stated that (as reported in Marchant and Mossman, 2005, p.38):

> A decision to prohibit … is in fact the most restrictive obstacle to trade in products lawfully manufactured and marketed in other Member States, can be adopted only if the alleged real risk for public health appears to be sufficiently established on the basis of the latest scientific data available at the date of the adoption of such decision."

However, if (Marchant and Mossman, 2005, p. 38):

> …scientific uncertainty persists as regards the existence or extent of real risks to human health it must be accepted that a Member State may, in accordance with the precautionary principle, take protective measures without having to wait until the existence and gravity of those risks are fully demonstrated.

2.2. Risks, ambiguity, and vagueness

Both EU and US jurisdictions have dealt with ambiguity and vagueness. In the EU (C-236/01, C-236/98, *Monsanto* v. *Presidenza del Consiglio dei Ministri*, 2003):

> …the advocate general…stated that, "[a]ccording to the precautionary principle, …conclusive scientific evidence of the reality of risk is not required. Action is therefore appropriate even where cause for concern is based on preliminary scientific findings… [O]n the other hand…not every claim or scientifically unfounded presumption of potential risk to human health or the environment can justify the adoption of national protective measures. Rather, the risk must be adequately substantiated by scientific evidence."

Finally, consider the AG's statement (C-236/98, *Monsanto* v. *Presidenza del Consiglio dei Ministri*, 2003) that the precautionary principle applies:

> Under the precautionary principle…the Community must take action even in cases where there is not an existing, but a potential risk to the environment.… when no concrete threat to [the environment or human, animal, or plant life] has yet been demonstrated but initial scientific findings indicate a possible risk.

Judicial ambiguity in risk-based reasoning is evident from phrases such as *potential risk* and *possible risk* by the AGs. Similarly, the phrase *plausible public health risk*, used by an AG in the case involving adding vitamin C in Ocean Spray cranberry juice, is vague. In this case, the ECJ found that the

appropriate standard is *real risk*, not the AG's *plausible public health risk*, and handed down an opposite judgment. We summarize the diversity of legal statements about risk, by the judicial institution of the EU, in Table 1.

Both the EU's ECJ and the US Supreme Court interpret their own constitutional guides (the US Constitution for US courts, the appropriate Treaty for the ECJ) and must resolve ambiguities, as well as policy, factual, and substantial legal issues. Although neither Court ostensibly adopts the reasoning of the other, the fundamentals of their reasoning are similar, particularly when facing science-policy issues. For example, the two lower judicial bodies of the ECJ (the Advocate General, AG, and the Court of First Istance, CFI) have stated that:

- "In accordance with the precautionary principle, **any discharge should**, broadly speaking … **be avoided**." (AG, Case C-184/97, *Commission* v. *Germany*, 1999),
- The precautionary principle compels reducing risks "to the **lowest level reasonably imaginable**." (CFI, Case T-13/99, *Pfizer Animal Health SA v. Council*, 1999)
- "[T]o withdraw the products until it can be **conclusively demonstrated** that they pose no present or future risk to human health" (CFI, Case T-13/99, *Pfizer Animal Health SA v. Council*, 1999).

They are questionable because these statements are specious or vacous:

- *any discharge should, broadly speaking…be avoided* is equivalent to *zero risk* which is legally inconsistent with the case law of the EU;
- a level of risk that is *the lowest level reasonably imaginable* is vacuous (it might even contradict the Treaty's language);
- *conclusive demonstration* is well beyond the domain of the overall evidentiary legal standards of civil law, such is *more-likely-than-not*, and appear to invoke a standard that go even beyond the traditional criminal law standard of proof *beyond a reasonable doubt*. This is clearly contradictory to the precepts of any precautionary principle found in the literature.

As Marchant and Mossman (2005, pp. 63–64) have remarked, judicial opinions vacillate between what appears to be a personal view of Art. 130r Precautionary Principle and the legal command of Art. 130r as a whole.

Table 1
Examples of judicial statements about Art. 130r precautionary principle and QRA

CFI	CFI		ECJ	
"[w]here scientific evaluation does not make it possible to determine the existence of a risk with sufficient certainty, … recourse to the precautionary principle depends as a general rule on the level of protection chosen by the competent authority in the exercise of its discretion… That choice must, however, comply with the principle that the protection of public health, safety and the environment is to take precedence over economic interests."	The precautionary principle applies only where there is a risk to human health which, "although it is not founded on mere hypotheses that have not been scientifically confirmed, has not yet been fully demonstrated."		Member State seeking to ban the import of a food product must find that the product presents a "real risk sufficiently established on … the latest scientific data."	
"whilst it is undisputed that Article 130r(2) of the treaty requires Community policy in environmental matters to aim for a high level of protection, such a level of protection, to be compatible with that provision, does not necessarily have to be at the highest that is technically possible."	The precautionary principle does not require moving as close to zero risk as possible, because "it is not possible to prove scientifically that there is no current or future risk associated with" a given product.	Approved the Commission's decision "to withdraw … products until it can be conclusively demonstrated that they pose no present or future risk to human health".	"Where it proves … impossible to determine with certainty the existence or extent of the alleged risk because of the insufficiency, inconclusiveness or imprecision of the results of studies conducted, but the likelihood of real harm to public health persists…, the precautionary principle justifies the adoption of restrictive measures."	
Judicial decisions must consider that the precautionary principle "would be undermined if the national legislature were to use modes of proof such as statutory presumptions which had the effect of restricting the scope" of the applicable regulations.	"the precautionary principle has been infringed" by the EU's approval of deferoxamine because "the conclusions of the ad hoc working group note that the data which she provided reinforce the already existing doubts" about the drug. The EU argued that "the precautionary principle is incorporated into the concepts of safety and efficacy which have to be taken into account" The court held for the EU.	Regulators "enjoy a broad discretion" to adopt measures "on the basis of as yet incomplete scientific knowledge."	"…the need to … balance … the objectives and principles … in Article 130r … the… review by the Court must … be limited to the question whether the Council in adopting the regulation, committed a manifest error of appraisal regarding the conditions for the application of Article 130r …."	The court did not agree with Commission's reliance on the precautionary principle and other factors to balance against the expert scientific opinions. It held that the Commission acted unlawfully by refusing to list progesterone as recommended by the Commission's own expert … committee.

2.3. Ubiquity of uncertainty

According to the Commission (Com2000):

> There is a controversy as to the role of scientific uncertainty in risk analysis, and notably as to whether it belongs under risk assessment or risk management. This controversy springs from a confusion between a prudential approach and application of the precautionary principle. These two aspects are complementary but should not be confounded. The prudential approach is part of risk assessment policy which is determined before any risk assessment takes place and which is based on the elements described in 5.1.3; it is therefore an integral part of the scientific opinion delivered by the risk evaluators. On the other hand, application of the precautionary principle is part of risk management, when scientific uncertainty precludes a full assessment of the risk and when decision-makers consider that the chosen level of environmental protection or of human, animal and plant health may be in jeopardy.

These comments are puzzling. Both scientific and managerial decisions are affected by uncertainty. For prospective choices and decisions, the triplet *actions*, *consequences*, *states-of-nature* is inherently probabilistic. Thus, uncertainty does not have a *role*, as the Commission suggests, rather it is a property of prospective choices. Regarding the statement that *scientific uncertainty precludes a full assessment of the risk*, it is unlikely that we can ever have a full risk assessment. Given costs and time available in practical situations, all assessments are contingent on available information. Decision and risk analysis are often most useful precisely when full assessment is impossible, and techniques such as value of information (VoI) analysis can then help to make effective decisions even when assessment is incomplete.

When predicting adverse health outcomes from hazardous situations with deterministic models, (such as systems of algebraic and/or differential equations), uncertainty can often be accounted by forms of sensitivity analysis. Practical risk assessment and risk management are data driven. In both, variability of the samples and limitations of causal models (uncertainty about the form of the *best* model) cause some of the uncertainties. Uncertainty in the management of hazards occurs in modeling actions, consequences, states-of-nature, loss and in selecting the criterion that determines the optimal choice (such as the maximization of the net expected benefits). A policy decision under Art. 130r Precautionary Principle must consider multiple casual factors and heterogeneous dimensions (economic, social and so on) that should be accounted for under Art. 130r. Thus, the optimal choice has a probability of being chosen – thus becoming a decision – that can be independent of modeled optimal choice because of the exercise of *political will*; however, this does not mean that the decision-maker should not be informed of that optimal choice.

2.4. Antibiotics risks and the extension of Art. 130r precautionary principle: Pfizer and Alpharma

A European Council Regulation (Dec. 17, 1998) withdrew four antibiotics, including virginiamycin, from the list of additives in animal feed. Some of the scientific evidence was that pathogen bacteria, which become resistant to the antibiotics due to the feeding to livestock of antibiotic additives, could transfer from animals to humans. It triggered regulatory action via secondary legislation (the Council Regulation). Pfizer and Alpharma, directly affected by the ban, sued in the CFI to annul that Regulation because of the danger that it would cause *serious and irreparable damage* to them. The CFI found against these two companies because they could sell their products on markets outside the Community, two of their European plants would probably not be closed, and the ban was not final.

2.4.1. Pfizer (Virginiamycin)

Although the CFI held that *preventive measures can be adopted without having to wait until the reality and seriousness of the risks being fully apparent*, nonetheless, preventive measures cannot be based on a scientific conjecture, but can be taken where there is a *real risk*. Such risk entails some probability that the negative effects, which the measure should prevent, will occur, but such probability cannot be *zero risk*. The CFI held that an agency must develop a risk assessment, based on both science ("risk assessment") and policy ("risk management") to decide on the appropriate action. The role of science is held to be essential; however, the ultimate outcome is based on policy, informed by science. For Virginiamycin, the Scientific Committee for Animal Nutrition, SCAN, an expert committee specifically established to provide scientific advice to the EU to animal feedstuffs, concluded that there was insufficient scientific evidence that Virginiamycin would cause the alleged hazard, and thus did not advise the EU to withdraw it from the market.

2.4.2. Alpharma (Bacitracin zinc)

Here, SCAN was not asked to review the scientific evidence, before the Council wrote the Regulation; nonetheless, the Council concluded that it was risky to human health. Not referring to SCAN is only appropriate in *exceptional circumstance and when there are adequate guarantees*, as the CFI stated, of *scientific objectivity*. The CFI upheld the Regulation, stating that EU Institutions could take a *horizontal approach* to an *entire class of antibiotics by systematically excluding the use as additives in feedingstuffs of products also used in human medicine*. The CFI found those "exceptional circumstances," and held that SCAN's advice is not binding, unless explicitly stated to be so in the legislation, and that it was not mandatory for the Commission to seek such advice.

Peel (2004) concludes that:

> Despite the limited nature of the scientific evidence available to the Community institutions and the lack of anything indicating an immediate health threat, the CFI found that the Commission and Council had not committed any manifest errors in their review of scientific studies and assessment of the risks to health prior to adopting the measure. Although the Court stressed that regulatory authorities must have at their disposal scientific information which is sufficiently reliable and cogent to allow them to understand the ramifications of

the scientific questions raised and to make a decision on policy measures in full knowledge of the facts, the CFI displayed a strongly deferential attitude when reviewing the institutions' interpretation of the scientific material and their judgments as to the existence of genuine scientific uncertainty.

The CFI found that the uncertainty in the use of antibiotics as additives to animal diets and human resistance to those antibiotics, justified their ban by appeal to the Precautionary Principle of Art. 130r as such ban was consistent (proportionate) with protecting human health.

2.5. Summary on the US regulatory perspective

In US federal statutes, precautionary regulatory action often requires evidence of causation and risk assessments. The range of federal legislative pronouncement is much more ample than the EU's; for example, the FDA (whose zero-risk policy is discussed later) and the EPA have dealt with:

- "In the case of threshold effects an additional ten-fold margin of safety for the pesticide chemical residue shall be applied for infants and children... (Federal Food, Drugs, and Cosmetics Act, FFDCA, §408 (b)(2)(C))(b)."
- "The Administrator shall specify, to the extent practicable: 1) Each population addressed by any estimate of public health effects; 2) The expected risk or central estimate of risk for the specific populations; 3) Each appropriate upper-bound or lower-bound estimate of risk... (Safe Drinking Water Act, § 300 g-1 (b)(3))."

For certain food additives, the principle of precaution adopted by the Congress was the *reasonable certainty of no harm* (FFDCA, sect. 409; (c)(3)(A)). This is defined as (21 CFR 170.3(i)) "A reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."

The legislative history of the FFDCA (House Committee on Interstate and Foreign Commerce Report) states that "[t]he concept of safety…involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive."

By these terms, causation – or at least judgments about potential causation – constrains allowed interventions. Still in the context of the FDA, the Delaney Clause (marketing of foods and cosmetics that contain carcinogenic chemical additives, Section 408, FFDCA; 21 U.S.C. 348(c)(3)(A), states that "[n]o food additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal."

Even this ban (the *zero-risk* principle) is causal in the sense that sufficient evidence (animal bioassays or epidemiology) must exist before it is triggered. This Clause was changed (in 1992, via the *Diethylstilbestrol* (*DES*) *Proviso*) to permit approval of carcinogenic compounds in food-producing animals, if residual exposure to them causes a *de minimis* risk of human cancer. The FDA then approved Red 8, 9, 19, and Orange 17 under the *de minimis* cancer risk policy: additives which posed a lifetime cancer risk of less than $1.0 * 10^{-6}$ are *de minimis,* and insignificant for regulation. However, *Public Citizen* v. *Young* held that the FDA's *de minimis* policy violated the Delaney Clause: in 1989, four colors acceptable under this *de minimis* policy were withdrawn because the scientific evidence triggered action based on the zero-risk principle of the Delaney Clause.

3. Animal antibiotics and human risk: A surprising history

Whether animal antibiotics increase resistance among human bacterial infections of zoonotic origin has been of concern since the 1960s. In the absence of clear empirical support (NAS, 1999), it was not until the 1990s that pressure from concerned regulators, activists, and scientists (Wegener et al., 1997) – sometimes described as a manifestation of "political will" (Wallinga, 2005) based on the Precautionary Principle – gained enough political traction in Europe to achieve widespread bans of animal antibiotics.

In the US, some called for regulation or legislation to stem continued uses of many animal antibiotics in food animal production, including streptogramins, macrolides, and fluoroquinolones. Bills were proposed banning animal antibiotics from use in chickens purchased by school lunch programs; McDonalds and other large buyers promised that they would buy chicken raised without antibiotic growth promoters. However, the legal culture of data-driven risk assessment and need to show evidence of causation, juxtaposed with a lack of data clearly showing that antibiotic use in animals causes measurable adverse effects on public health or clinical rates of compromised treatments in human patients, prevented the progress of such efforts. As of 2007, the US FDA has withdrawn only one antibiotic, enrofloxacin, a fluoroquinolone used to cure fatal respiratory illnesses in chickens.

In contrast, in 1998, the European Union banned five antibiotics (as growth-promoters) including streptogramins, macrolides, and fluoroquinolones by appeal to the Precautionary Principle (Pugh, 2002). Others were banned in 2006. Unlike the US, in the EU no QRA predicting human (or animal) health consequences was considered necessary. These EU bans have been widely viewed as a successful act of "political will" that circumvented data collection and causal modeling:

> "U.S. regulation of agricultural antimicrobials today is very reliant on risk assessment. While more data can be useful for use in risk assessment, microbial risk assessment itself may not be well suited to the purpose of reducing antimicrobial overuse. Among other recognized shortcomings, current microbial risk assessment models typically fail to account for the essential ecological nature of antimicrobial resistance. This makes it inadequate for fully characterizing the human health or ecological risks of animal antimicrobials. European success at phasing out unnecessary antimicrobial usage in agriculture, on the other hand, has derived from decisions based on public health concerns and political will,

and not on the collection of usage data or on the successful completion of a risk assessment." (Wallinga, 2005)

The EU's reasoning creates a dilemma. Lack of *full* scientific knowledge, as a trigger for pure policy decisions magnifies the effect of having to prove a negative while bearing the burden of persuasion of no harm. For example, the EU states (Commission of the European Communities, CEC, 2001) that "[r]esponsibility to generate knowledge about chemicals should be placed on industry. Industry should also ensure that only chemicals that are safe for the intended purposes are produced." Importantly, the CEC also states that "precautionary measures must not be applied to address conjectured risks" and that "…scientific evaluation of the potential adverse effects should be undertaken based on the available data… [T]his requires reliable scientific data and logical reasoning, leading to a conclusion which expresses the possibility of occurrence and the severity of a hazard's impact on the environment, or health of a given population…."

On this account (and equating *possibility* with probability), public choices justified by political will alone do not pass muster; as the EU Court of First Instance (an agency of the ECJ) held that "It is necessary…to define the 'risk' which must be assessed when the precautionary principle is applied… A preventive measure cannot properly be based on a purely hypothetical approach…founded on mere conjecture which has not been scientifically verified…"

Yet, the effect on a party of proving a negative (an impossibility) and bearing the burden of persuasion absent sufficient causal evidence must be weighted against the equitable rule that those with superior knowledge are held to a higher standard than those without such knowledge. Because those at risk may not have the knowledge and expertise to assess complex and uncertain factual issues, the producers of risk justly bear the burden of showing that their products are safe, particularly if they benefit from selling them. A potential solution to this dilemma is to use causal models to bound risks under a variety of either alternative or concurrrent scenarios.

Regardless of the criterion that justifies the final regulatory choice (e.g., select the option that maximizes the expected net discounted benefits; or is minimax, or other), the greater the social stakes, the heavier the policy analysis burden on policymakers who advocate an all-or-none solution as to the antibiotics being prohibited for one or more uses. Thus, although an antibiotic can be authorized for other uses its ban, relative to the prohibited use, is all-or-none. The legal fact that the burden of persuasion (that exposure is not deleterious) rests on producers of that hazard does not excuse lack of causal assessments by policy-makers who must make the final choice for society. Accountability requires it. *A fortiori*, if the basis for a social choice is unscientific and inconsistent with the facts, ext ante and ex post of the ban, then the criteria that led to such a choice and the credibility of those advocating it are undermined. Thus, if *political will* becomes the societal criterion and the resulting act is a ban, and if that ban causes more injuries than it prevents, then accountability requires that the criterion of political will be evaluated as one that may, in at least some cases, do more harm than good.

The contrast between EU and US risk management histories of antibiotics in animal feeds raises a question with theoretical, empirical, and moral dimensions:

How well have the European bans based on "political will" and the Precautionary Principle worked in protecting public health and in reducing antibiotic resistance rates in human isolates?

There also is a serious technical challenge: *How should microbial risk assessment models account for the essential ecological nature of antimicrobial resistance?*

The answers are surprising and perhaps counter-intuitive. Although the data necessary to provide final answers is not yet complete, there is sufficient information to bound the answers via theoretical and empirical reasoning, including sensitivity analyses. Specifically, some QRA models for resistant bacteria have treated bacterial ecologies implicitly, starting with the *total* health effects of microbial hazards (e.g., human illness cases per year), regardless of the (often unknown) ecological pathways involved, and using genetic and other data to bound the maximum preventable fraction by removing animal antibiotic uses (Cox, 2006). Here, we use a QRA dynamic model of the flows of susceptible and resistant bacterial populations among animals and humans as a complementary approach.

3.1. Comparing human health histories with and without precautionary interventions

EU's act of precautionary "political will" banning use of animal antibiotics was followed by undesirable and long-lasting health changes in animals and people in many countries. These included: (a) Large transient increases in animal morbidity, lasting for at least several years, due to increased bacterial illnesses such as necrotic enteritis in chickens and infections with *Escherichia coli* and *Lawsonia intracellularis* in pigs (VLA, 2004; Casewell et al., 2003); (b) Enduring increases in animal mortality due to increased bacterial infections, e.g., a 25% increase in pig mortality rates in Denmark that persisted at least through 2005 (KeepMedia, 2005); (c) Continuing increases in human foodborne bacterial illness rates (campylobacter and foodborne pathogens other than salmonella) throughout most of Europe, although not in every country in every year (Eurosurveillance, 2002; Patrick et al., 2004; EFSA, 2006); and (d) Unexpected *increases* in antimicrobial resistance rates in clinical isolates from human patients in the years immediately following the bans (see Fig. 2). Initial decreases in resistant bacteria in *healthy* animals and humans were also reported, as hoped (Wegener, 2003), but both human and animal health deteriorated significantly. Resistance rates between hospitalized patients, those at risk, in fact increased (Phillips, 2007). Some, but not all, of these changes persisted through at least 2005, the most recent year for which data are available. The high initial surge in animal illness rates, such as necrotic enteritis, appears to have been successfully controlled within five years by increased use of therapeutic antibiotics and other countermeasures (VLA, 2004). Years of increases in campylobacteriosis reversed in 2002 and 2003, (Eurosurveillance, 2005), but campylobacteriosis increased again throughout

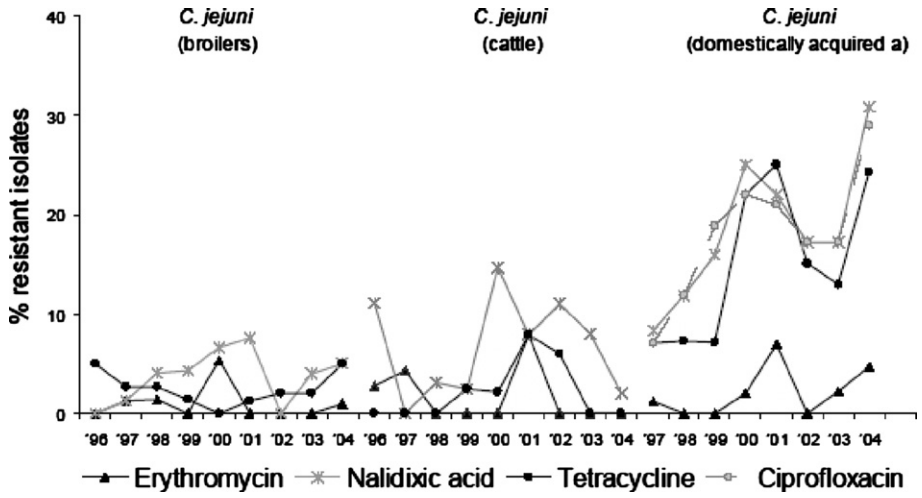

Fig. 1. Trends in resistance to selected antimicrobials among *Campylobacter jejuni* isolates from broilers, cattle and human domestic cases, Denmark. Includes cases where origin of infection is not documented and may therefore include isolates acquired abroad but not documented as such. *Source:* DANMAP, 2004, http://www.dfvf.dk/Files/Filer/Zoonosecentret/Publikationer/Danmap/Danmap_2004.pdf.

most of Europe between 2003 and 2004 (EFSA, 2006; ElAmin, 2006). Wegener's (2003) statement that "recent experience from a number of European countries shows that the use of antimicrobials for growth promotion provides insignificant benefits to agriculture and that it can be terminated. Ending the use of antimicrobial growth promoters has led to reductions in the prevalence of resistant bacteria in food and food animals, as well as in humans, in countries where this has happened" seems to ignore data that contradict these beliefs (Cox, 2007).

Denmark, which led much of the scientific concern and pressure for the bans (Wegener et al., 1997), has provided annual reports (DANMAP) summarizing surveillance data on antibiotic resistance rates among *Campylobacter* and other zoonotic bacteria in isolates from humans and food animals. Fig. 1, from the latest available (2004) DANMAP annual report, shows human and animal resistance rates before and after the 1998 ban on animal antibiotics used as growth promoters and to prevent illnesses. Fig. 2 depicts the human data for the few years around 1998, when effects of the ban might be clearest. The main finding was that *antibiotic resistance rates in human isolates increased dramatically* (by several hundred percent) in the wake of the ban, at a rate far greater than might have been expected based on trends before the ban. They remained elevated through 2004, the most recent year for which human data are available, despite an intensive program (including animal slaughter) that reduced unacceptable salmonellosis rates (Wegener et al., 2003).

Resistance rates in animals also showed some unanticipated changes. The DANMAP, 2004 report stated that: "Among *C. coli* from pigs ciprofloxacin/nalidixic acid resistance increased significantly (*P value*=0.04) from 3% in 2003 to 16% in 2004. [T]his increase coincides with a decrease in fluoroquinolones consumption since 2001 due to legislation changes. The reason for the increase in ciprofloxacin/nalidixic acid resistance remains unknown. In *C. coli* isolates from pigs resistance to erythromycin was unchanged from 2003 to 2004 despite a substantial increase in macrolide consumption in weaned pigs in the same period." This suggests that the causal relation between antibiotic use in animals and antibiotic resistance in bacteria isolated from animals is more complex than once supposed. The decrease in infections due to a number of concurrent controls does not change the point because the ban was supposed to reduce resistance. The effect of other measures on reducing infections is not relevant to assessing the effect of the ban.

Fig. 2 depicts annual cases of campylobacteriosis in Norway. Illness rates trending upward since an initial withdrawal of animal antibiotics in 1992, increased rapidly again after 1997. This trend was reversed by 2003, after increased use of therapeutic antibiotics and other countermeasures controlled necrotic enteritis in chickens. Surveillance found "A parallel

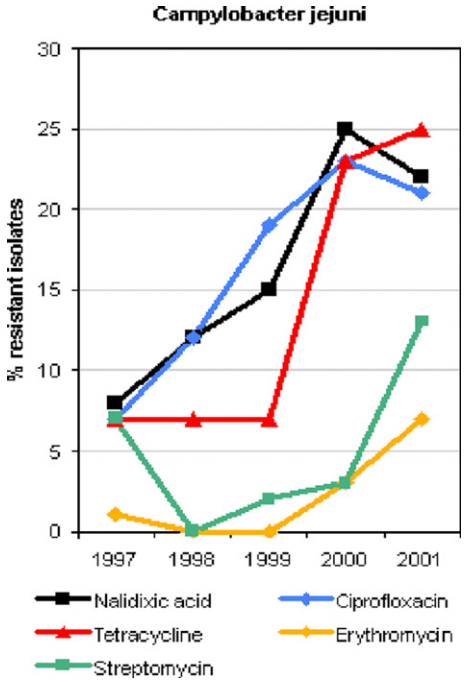

Fig. 2. Antimicrobial resistance rates among domestically acquired *C. jejuni* campylobacteriosis cases for human patients in Denmark. (*Source:* Hayes and Jensen, 2003).

increase [in] several other countries in Europe, including Austria, Denmark, Finland, Ireland, Spain, and Sweden" (Eurosurveillance, 2002).

Clearly, *post hoc* does not necessarily imply *propter hoc.* In the absence of a control group, it might be impossible to determine whether the trends in Figs. 1 and 2 simply reflect global (or northern hemisphere) numbers and changes that are unrelated to the bans. However, US data during the same period provides for a comparison for what happened there without bans. While campylobacteriosis and other foodborne bacterial illness rates (other than salmonellosis) were climbing in Europe (ElAmin, 2006), they fell significantly (by over 30%, for campylobacteriosis) in the United States (CDC, 2005; Samuel et al., 2004). Microbial loads of campylobacter in chickens also fell (by perhaps 90% between 1995 and 2001, based on a study in Georgia, Stern and Robach, 2003). While resistance rates for macrolides, streptogramins, and fluoroquinolones in human isolates exploded in parts of Europe immediately following the bans, (Fig. 2), they remained relatively stable or fell for domestically acquired cases in the US (CDC, 2005; Cox, 2006). Possible contributors to these outcome include: implementation of Hazard Analysis Critical Control Point (HACCP) principles to identify and control bacterial contamination throughout the food chain; increasing public awareness and education; and perhaps the continued prudent use of key animal antibiotics by US farmers to reduce animal illnesses and promote uniform animal weights. In the EU, there have been extensive efforts as wells.

Rival causal explanations and interpretations have provoked controversy over the most effective approaches to regulatory risk management for animal antibiotics (NAS, 1999). Despite some disappointing outcomes following the EU bans, results from simple theoretical models suggested that animal antibiotic use increased treatment failure rates in humans and that withdrawing animal antibiotic uses should reduce human resistance rates (Smith et al., 2005). A highly precautionary stance might be that the analysis of the effect of a ban on animal antibiotics should be based on such models, even when the real-world effects of doing so are not fully understood. But enthusiasm for such a stance must be tempered by recognition that, in practice, it may not be precautionary at all: it may cause more harm than good to public health. In such a setting, uncertainty about causation – the very difficulty that the Precautionary Principle is often invoked to help bypass – makes it impossible to identify what interventions will truly be "precautionary".

4. QRA modeling for human and animal illness and resistance

It is paradoxical that increased resistance has often followed reducing animal antibiotic use: How can removing the selection pressure from an animal antibiotic fail to reduce the resistance levels in humans and in animals? Perhaps human antibiotic resistance rates would have increased with or without animal antibiotic use, e.g., because of human use of similar drugs. Terminating animal antibiotic use would then slow the increase (or have no effect, if the increase is entirely driven by other factors). But, although this explanation might be plausible for some drugs, it appears to be inconsistent with data for others. Fig. 2 shows that resistance to erythromycin and streptomycin among human *Campylobacter* isolates appears to increase specifically after the ban on macrolides and other growth promoters. A systems dynamics model of bacterial flows (for both susceptible and resistant bacteria) suggests an explanation for this apparent paradox.

Deterministic "causation" is described straightforwardly in systems dynamics models in terms of changes in a system's outputs produced (i.e., caused) by changing its inputs, with the help of systems of equations (typically differential or partial differential equations and/or algebraic equations) describing how changes in inputs propagate through the system to cause changes in outputs. These equations predict how the system's observed quantities change following interventions that affect its inputs. Applied to animal antibiotics and human health, systems dynamics modeling can help to clarify, and to suggest potential explanations for, the undesirable trends seen in Figs. 1 and 2.

4.1. Systems dynamic modeling

A model of the human health impacts of animal antibiotic uses should account for at least the following variables:

- IH(t) = fraction of the human population with a specified foodborne illness, e.g., campylobacteriosis, at any time t; IH = "ill humans" fraction.
- IA(t) = fraction of *servings* of a food from animals with a specified illness (e.g., airsacculitis) that the animal antibiotic could help to prevent, reduce, or control. IA = "ill animal" fraction for servings from processed animals. Animals not slaughtered and animal carcasses removed during processing are excluded when IA is calculated, (presumably do not affect IH).
- RH(t) = Fraction of human illnesses resistant to the human antibiotic, at time t. RH = "resistant human" fraction.
- RA(t) = Fraction of isolates from foods (ingested servings of meat) resistant to the antibiotic, at time t.

We study six causal relations, formulated as a system of ordinary differential equations (Appendix A) that describe how the levels of the quantities affect each other's rates of change:

1. Animal Drug Use Increases Animal Health: Animal drug use ↓ → IA↑
2. Animal Drug Use Increases Animal Resistance: Animal drug use ↓ → RA↓
3. Animal Illnesses Increase Human Illnesses: IA↑ → IH↑
4. Human Illnesses and Antibiotic Use Increase Human Resistance: IH↑ → RH↑
5. Conjecture 1, antibiotic use in ill humans leads to increased resistance in the environment and, eventually, in food animals: IH↑ → RA↑?
6. Conjecture 2, resistance determinants flow from food animals to humans via one or more pathways (environmental, food chain, or other): RA↑ → RH↑ ?

4.2. Animal drug use increases animal health: (Animal drug use)↓ → IA↑

Casewell et al. (2003) noted that "The ban of growth promoters has…revealed that these agents had important prophylactic activity and their withdrawal is now associated with a deterioration in animal health, including increased diarrhea, weight loss and mortality due to *E. coli* and *L. intracellularis* in early post-weaning pigs, and clostridial necrotic enteritis in broilers." Van Immerseel et al. (2004) noted that "The incidence of *Clostridium perfringens*-associated necrotic enteritis in poultry has increased in countries that stopped using antibiotic growth promoters." A size of the initial increase in IA can be estimated from historical data for some animal illnesses: necrotic enteritis (NE) in the United Kingdom following the bans initially increased from about 0% to a transient high of about 15%, (Veterinary Laboratories Agency (VLA), 2005). A high initial increase is typically brought under control by increased use of non-banned antibiotics, such as new ionophore growth promoters (Williams, 2005): historical records do not show the idealized response to a one-time perturbation in which antibiotics are withdrawn and no other exogenous changes take place (substituting therapeutic antibiotics and non-banned growth promoters). Moreover, responses are heterogeneous across countries (Patrick et al., 2004): In Denmark, NE prevalence increased from perhaps 1–2 flocks out of 1700 flocks monitored before the ban to 25 out of 1700 after the ban (Madsen and Pederson, 2000), but this rate is still far lower than in countries further south (Van Immerseel et al., 2004). Nonetheless, an initial increase of perhaps 15% for NE provides a useful point for the possible size of the initial response of NE illness rates in chicken flocks to a decrease in animal antibiotic before the compensating effects of countervailing measures (e.g., increased use of non-banned antibiotics) are known. For pigs, available data are limited, but a lasting increase in mortality rate in Denmark, from about 17% prior to the bans to about 21% after has been reported in trade journals (KeepMedia, 2005).

4.3. Animal drug use increases animal resistance: (Animal drug use)↓ → RA↓

Withdrawing animal antibiotics should reduce resistance to them in animals, although the rate of reduction may vary greatly across different "bug/drug" pairs. Bywater et al. (2005) found that, for *E. faecium* isolates from pigs and chickens in Europe, "Resistance prevalence [for spiramycin, tylosin and virginiamycin] declined rapidly following removal of growth promoters in pigs and chickens, suggesting that in the absence of selective pressure, a susceptible population began to replace phenotypically resistant strains". A reduction is not guaranteed for all antibiotics: there was no apparent decrease in resistance to bacitracin (Bywater et al., 2005). Declines in vancomycin-resistant *E. faecium* (VRE) in Europe, following bans on avoparcin in animals, have also been gradual. In Denmark, recent decreases in fluoroquinolone use in pigs were unexpectedly followed by large (>500%) *increases* in fluoroquinolone resistance in *C. coli* isolates between 2003 and 2004 (DANMAP 2004), suggesting that resistance rates in these animals may respond to forces in addition to direct selection pressures from use of fluoroquinolones in pigs.

4.4. Animal illnesses increase human illnesses: IA↑ → IH↑

Increased animal illness rates and/or withdrawal of animal antibiotics that prevent animal bacterial infections may increase human illness rates by creating larger microbial loads of zoonotic pathogens in meats (NAS, 1999). For example, NE caused by the bacterium *C. perfringens* can lead to contaminated food that causes human illnesses (food poisoning), typically manifested as type A diarrhea, but also in serious infections (Van Immerseel et al., 2004). Chicken carcasses from flocks with bacterial illnesses, such as airsacculitis, have higher rates of processing errors, cuts, fecal contamination, and microbial loads of human pathogens such as *Campylobacter* and *Salmomella* (Dawe, 2004; Russell, 2003). Thus, increased microbial loads of pathogens on chicken carcasses can cause increased rates of human food poisoning and resulting illnesses such as campylobacteriosis and salmonellosis; this is plausible but has not yet been demonstrated. However, the strength of the IA → IH link can be estimated from historical data. Wingstrand et al. (2006) reported that, in Denmark, "In the 1990s, the national consumption of poultry meat increased by ≈40% (1991: 63,900 tons, 1998: 93,200 tons). [T]he increase was observed for almost all types of chicken and turkey products but most markedly in fresh cuts. In the same period, the incidence of campylobacteriosis increased by >400%, from 20 to 86 cases per 100,000 inhabitants. Bacteriologic data, which show higher loads of *Campylobacter* in fresh poultry, suggest that the exposures to *Campylobacter* spp. have increased much more than the general increase in poultry consumption and thus explains why the increase in human disease incidence has exceeded the increase in poultry consumption." This assumption refers specifically to animal drug use refers specifically to use for either prevention or as an AP.

4.5. Human illnesses and antibiotic use increase human resistance

4.5.1. IH↑ → RH↑

An important source of emerging resistance to human antibiotics, in isolates of bacteria from human patients, is likely to be use of these antibiotics in human medicine. Treatment of patients with antibiotics sometimes results in an initially susceptible infection becoming resistant. Yet, discharges of antibiotics and antibiotic-resistant bacteria via hospital runoff and sewage can spread resistant bacteria and resistance determinants to other humans and, perhaps, animals (Teale, 2002), and to water and soil (Kummerer, 2004). Iversen et al. (2004) concluded, for ampicillin- and ciprofloxacin-resistant *E. faecium* strain in Sweden, that "…a possible transmission route for nosocomial *E. faecium* from patients in hospitals to hospital sewage and urban sewage, and further via treatment plants to surface water and possibly back to humans. This proposed route of circulation of drug-resistant enterococci might

be further amplified by antibiotic usage in human medicine. In contrast, such transmission from food animals seems to play a negligible role in Sweden." Kuhn et al. (2005) found that, in Europe, "… animal-associated VRE [vancomycin-resistant enterococci] probably reflect the former use of avoparcin in animal production, …VRE in human-associated samples may be a result of antibiotic use in hospitals".

It is unnecessary to specify all of the environmental pathways from IH to RH (or from these to RA). Instead, we postulate that increases in IH *might* lead to increases in RH, for example, and then estimate the empirical coefficient relating them (i.e., relating changes in RH to changes in levels of IH) from data on how RH changes (see Fig. 2) after IH changes (see Fig. 3). IH↑ → RH↑ is plausible because more cases of food poisoning are likely to lead to more use of antibiotics as empiric treatment or therapy for diagnosed foodborne infections, and hence increased selection pressure for resistance in human isolates; the quantitative size of this effect must be empirically determined.

4.5.2. *IH↑ → RA↑?*

If antibiotics, resistant bacteria, resistance determinants, and resistant bacteria from hospitals and human medical uses enter the environment, then they can potentially lead to resistant strains in animals. However, based on Iversen et al. (2004) and Kuhn et al. (2005), it appears that this possibility may be of little practical importance, at least for *E. faecium* and VRE.

4.5.3. *RA↑ → RH↑?*

A possibility that dominates political, regulatory and public health concerns (Wallinga, 2005) is that increased resistance in animal bacteria might lead to increased resistance in isolates from human patients, thus increasing treatment failures for human antibiotics. Evidence suggests that this link is relatively weak because animal bacteria do not easily flow to humans at significant rates (e.g., Iversen et al., 2004; Kuhn et al., 2005; Pugh, 2002; Phillips et al., 2004). Yet, this link is of such central concern that it is included to assess how strong it could be.

The QRA model (Appendix A) suggests that *a ban in animal drug use can indeed increase resistance levels in isolates from humans*, even while reducing resistance levels in animal isolates, *if* it leads to a sufficiently large increase in sick animals, and hence in sick people. We test this explanation with historical data, checking whether the frequency of microbial loads of bacteria sufficient to cause human illness increased after bans. The QRA model shows that, contrary to good intentions, a ban may increase resistance to bacteria in humans (by increasing the number of illnesses, some of which are treated with antibiotics). Thus, we do not consider other longer term issues (namely, preventing the selection of resistant bacteria against antibiotics that might be necessary for humans treatment in the future). Another testable prediction is that, if animal antibiotic bans have caused increase resistance levels in human isolates by this mechanism (i.e., via the causal path: animal antibiotic use ↓ → IA↑ → IH↑ → RH↑), then there should be contemporaneous increases in both the ill animal fraction IA (e.g., in animal illnesses such as NE) and also in the human illness fraction IH. These testable implications are confirmed for the European Union, where animal illnesses such as necrotic enteritis and human campylobacteriosis rates (see Fig. 2) increased sharply (e.g., Veterinary Laboratory Agency, 2004). It may be possible to generalize, by using QRA models to future data, our more limited results.

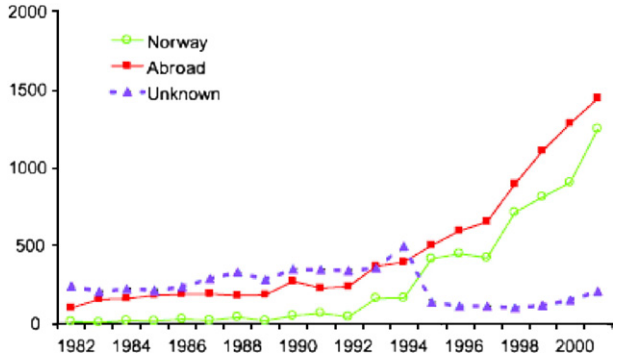

Fig. 3. Antimicrobial resistance rates among domestically acquired *C. jejuni* campylobacteriosis cases for human patients in Denmark. (*Source:* Hayes and Jensen, 2003). *Source:* Eurosurveillance Weekly, 2002 http://www.eurosurveillance.org/ew/2002/020613.asp.

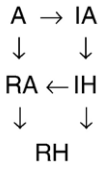

Fig. 4. Model structure.

4.6. Quantitative analysis

The model structure, with dependencies summarized by the directed acyclic graph (DAG) depicted in Fig. 4 (Appendix A) is:

The DAG implies (under smoothness assumptions) the following recursive model structure:

$$\begin{aligned} d\mathrm{IA} &= (\partial \mathrm{IA}/\partial A)/dA \\ d\mathrm{IH} &= (\partial \mathrm{IH}/\partial \mathrm{IA})d\mathrm{IA} \\ d\mathrm{RA} &= (\partial \mathrm{RA}/\partial A)dA + (\partial \mathrm{RA}/\partial \mathrm{IH})d\mathrm{IH} \\ d\mathrm{RH} &= (\partial \mathrm{RH}/\partial \mathrm{IH})d\mathrm{IH} + (\partial \mathrm{RH}/\partial \mathrm{RA})d\mathrm{RA}, \end{aligned} \tag{5}$$

where dA = change in the fraction, A, of animals receiving antibiotics that reduce animal illnesses. These equations combine to give:

$$\begin{aligned} d\mathrm{RH} = [&(\partial \mathrm{RH}/\partial \mathrm{IH})(\partial \mathrm{IH}/\partial \mathrm{IA})(\partial \mathrm{IA}/\partial A) + (\partial \mathrm{RH}/\partial \mathrm{RA})(\partial \mathrm{RA}/\partial A) \\ &+(\partial \mathrm{RH}/\partial \mathrm{RA})(\partial \mathrm{RA}/\partial \mathrm{IH})(\partial \mathrm{IH}/\partial \mathrm{IA})(\partial \mathrm{IA}/\partial A)]dA. \end{aligned} \tag{6}$$

For finite changes:

$$\begin{aligned} \Delta\mathrm{RH} = [&(\Delta \mathrm{RH}/\Delta \mathrm{IH})(\Delta \mathrm{IH}/\Delta \mathrm{IA})(\Delta \mathrm{IA}/\Delta A) \\ &+ (\Delta \mathrm{RH}/\Delta \mathrm{RA})(\Delta \mathrm{RA}/\Delta A) \\ &+(\Delta \mathrm{RH}/\Delta \mathrm{RA})(\Delta \mathrm{RA}/\Delta \mathrm{IH})(\Delta \mathrm{IH}/\Delta \mathrm{IA})(\Delta \mathrm{IA}/\Delta A)]\Delta A \end{aligned} \tag{7}$$

The ratios represent average slope factors. A ban that changes antibiotic use from $A=1$ to $A=0$ corresponds to $\Delta A=-1$. If the effect of increasing IH on RA is negligible, $\Delta RA/\Delta IH \approx 0$, this formula simplifies to:

$$\Delta RH = [(\Delta RH/\Delta IH)(\Delta IH/\Delta IA)(\Delta IA/\Delta A) + (\Delta RH/\Delta RA)(\Delta RA/\Delta A)]\Delta A$$

Because $\Delta A=-1$ for a ban, we obtain the structural linear regression model:

$$\Delta RH = (\Delta RH/\Delta IH)(\Delta IH/\Delta IA)\Delta IA - (\Delta RH/\Delta RA)\Delta RA, \quad (8)$$

(ΔIA is the increase in IA; $-\Delta RA$ is the decrease in animal resistance caused by the ban); $(\Delta RH/\Delta IH)(\Delta IH/\Delta IA)$ and $(\Delta RH/\Delta RA)$ become regression parameters. The data to fit these regression models to RH, IA, and RA values (observed in multiple countries and time periods) are becoming available (EFSA, 2006), but are not yet adequate. Nonetheless, estimates are:

- $(\Delta RH/\Delta RA)\Delta RA \approx 0$, i.e., relatively large observed decreases in the fraction of resistance in isolates from food animals (Bywater et al., 2005 for VREF) have not produced detectable reductions in the fractions of resistant isolates among human patients (e.g., Iversen et al., 2004; Kuhn et al., 2005 for VRE and VREF), see Fig. 2.
- $(\Delta RH/\Delta IH) \approx 0.003$, (when DIH is in units of cases per 100,000 person-years (rather than being converted to a pure fraction based on duration of illness)), estimated from cross-sectional data (Fig. 5) on ciprofloxacin resistance fractions among human isolates and corresponding campylobacteriosis incidence rates in several countries (EFSA, 2006). The regression between campylobacteriosis rate and fraction of ciprofloxacin-resistant *Campylobacter* isolates, Fig. 5, suggests that $\Delta RH \gg 0.003 + // \Delta IH$, when ΔIH is measured in units of cases per 100,000 person-years.
- $(\Delta IH/\Delta IA)\Delta IA \approx 23.5$ excess cases per 100,000 person-years, estimated increase in human campylobacteriosis rates from banning animal antibiotics, (e.g., from increases in bacterial illnesses (NE) and/or weight loss in animals, increasing the frequencies of exceptionally high microbial loads of campylobacter reaching consumers (Dawe, 2004)). Longitudinal campylobacteriosis data for Denmark, Fig. 6, can be used for estimation. Campylobacteriosis rates increased dramatically after 1992 (Norway implemented antibiotic bans), probably in part because of greater consumption of fresh chicken (Wingstrand et al., 2006). In 1998, they jumped again following antibiotic bans in Denmark and other countries, and remained elevated for several years. Campylobacteriosis increased from 20 to 86 cases per hundred thousand person-years as consumption of fresh chicken increased from approximately 4000 to 12500 tons/year (Wingstrand et al., 2006). If campylobacteriosis is caused almost entirely by consumption of fresh chicken (since the microbial load on frozen chicken is reduced by approximately 100-fold), then this increase in fresh chicken consumption would have increased the campylobacteriosis incidence rate from 20 to $(12{,}500/4000)+20=62.5$ cases per hundred thousand person-years in the absence of any change in probability of illness per serving. But the actual incidence rate increased to 86 cases per hundred thousand person-years, implying that the average probability of illness per serving of chicken increased by $86/62.5 \approx 1.4$. Tentatively attributing this increase in the "illness potency" of servings to increased microbial loads due to reduced use of animal antibiotics yields a suggested baseline value of a 1.4-fold increase in human campylobacteriosis illnesses due to the ban, corresponding to an absolute increase of $(86-62.5)=23.5$ excess cases per hundred thousand person-years.

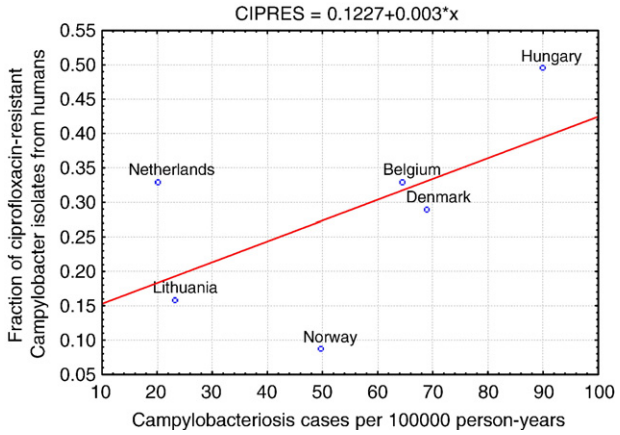

Fig. 5. Ciprofloxacin resistance (RH) vs. campylobacteriosis rates (IH). *Source:* Plot of data from EFSA, 2006.

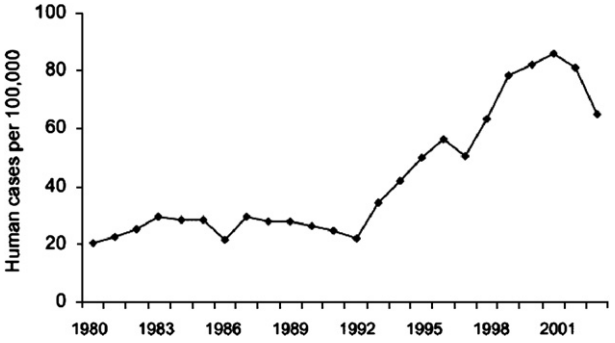

Fig. 6. Laboratory-confirmed human campylobacteriosis in Denmark, 1980–2003. *Source:* Wingstrand et al., 2006.

Given the limitations of past surveillance programs, adequate data to support more precise and confident estimates will probably not be available for at least another year. However, our preliminary values suggest how data can be used to validate and refine assumptions. For instance, using the estimated values $(\Delta RH/\Delta RA)\Delta RA \approx 0$, $(\Delta RH/\Delta IH) \approx 0.003$, and $(\Delta IH/\Delta IA)\text{-}\Delta IA \approx 23.5$, Eq. (8) becomes:

$$\Delta RH = (\Delta RH/\Delta IH)(\Delta IH/\Delta IA)\Delta IA - (\Delta RH/\Delta RA)\Delta RA \approx 0.003 \times 23.5 = 0.07.$$

This appears reasonable for streptomycin and erythromycin in Fig. 2, but RH increased by much more than 7% for nalidixic acid and ciprofloxacin. To explain the larger increase in RH within the model, it is necessary to drop the simplifying assumptions that $\Delta RA/\Delta IH \approx 0$ and that $\Delta RH/\Delta RA \approx 0$ in Eq. (7), to the following more complete model for human health effects of a ban:

$$\begin{aligned}\Delta RH &= (\Delta RH/\Delta IH)(\Delta IH/\Delta IA)\Delta IA \\ &\quad - (\Delta RH/\Delta RA)\Delta RA \\ &\quad + (\Delta RH/\Delta RA)(\Delta RA/\Delta IH)(\Delta IH/\Delta IA)\Delta IA \\ &= (\Delta IH/\Delta IA)\Delta IA[(\Delta RH/\Delta IH) \\ &\quad + (\Delta RH/\Delta RA)(\Delta RA/\Delta IH)] \\ &\quad - (\Delta RH/\Delta RA)\Delta RA \qquad (9)\end{aligned}$$

(Terms such as $(\Delta RH/\Delta RA)\Delta RA$ are analogies to $(\partial RH/\partial RA)dRA$). For example, if $(\Delta IH/\Delta IA)\Delta IA = 23.5$, $(\Delta RH/\Delta IH) = 0.003$, $(\Delta RH/\Delta RA)\Delta RA = 0.5$, and $(\Delta RH/\Delta RA)(\Delta RA/\Delta IH) = 0.03$, then Eq. (9) becomes:

$$\Delta RH = 23.5^*[0.003 + 0.03] - 0.5 = 0.26,$$

Close to the peak value in Fig. 2. Thus, the quantitative data for ciprofloxacin in Fig. 2 can be reconciled or explained by the model in Fig. 4 *if* $(\Delta RH/\Delta RA)(\Delta RA/\Delta IH) > 0$, i.e. there is a significant flow of resistance from ill humans to food animals ($\Delta RA/\Delta IH > 0$, perhaps due to antibiotics in sewage entering the environment) and a flow from animals back to people ($\Delta RH/\Delta RA > 0$, e.g., due to resistant bacteria in fresh meat products or in animal waste products entering the environment). It underscores the importance of the DANMAP 2004 observation that "Among *C. coli* from pigs ciprofloxacin/nalidixic acid resistance increased significantly ($P = 0.04$) from 3% in 2003 to 16% in 2004. [T]his increase coincides with a decrease in fluoroquinolones consumption [in animals] since 2001 due to legislation changes." It suggests that continued discharges to the environment of ciprofloxacin from human usage may play a role in selecting resistant bacteria that are later found in food animals (e.g., pigs) and people.

5. Discussion and conclusions

We have suggested, based on Campylobacter data and theoretical modeling, how a relatively simple systems dynamics model can help to understand and interpret historical data on the relations among animal antibiotic use, animal illness and resistance rates, and human illness and resistance rates describes how these variables affect each other over time, acting through environmental pathways, the food chain, and other (possibly unspecified and unknown) pathways. We have not used data for other organisms, such as Salmonella, for example, because of the number of concurrent efforts to reduce salmonellosis (including the slaughtering animals) that confound before and after analyses.

Although data to validate the model and to estimate its parameters with useful precision and confidence are only now starting to be obtained, our initial results show that the logical structure of the model in Fig. 4 is consistent with the initially surprising historical result that several antibiotic resistance rates in isolates from human campylobacteriosis patients *increased* significantly following bans on several animal antibiotics used as growth promoters (and reductions in other antibiotics, such as fluoroquinolones). One possible explanation is that reduced animal antibiotic use increases human illnesses (e.g., due to increased microbial loads in fresh meat products), leading to increased resistance in human isolates (e.g., due to increased use of human antibiotics to treat illnesses). For some antibiotics, an additional partial explanation may be that human antibiotics entering the environment result in increased resistant bacteria in food animals and fresh meat products. Fundamentally, the new data are consistent with our theoretical predictions. Although we cannot yet demonstrate cause and effect, we raise doubt (beyond the 50%) that suggests revisiting the ban because antibiotics in animal feeds are helpful, rather than damaging, as was presupposed under the scenario dictated by *political will* (Singer, 2007).

As surveillance data accumulate, with improved consistency, detail, and completeness, the model proposed can be further tested and refined. Until then, our results suggest that the link between animal antibiotic use and human health is more complex than has often been assumed, with the non-negligible effect being that banning animal antibiotic uses may actually increase human illness rates and antibiotic resistance rates among pathogens infecting human patients. A possible link between antibiotic use, animal health and human illness rates has previously been proposed based on experimental investigations of microbial loads in chickens from infected and non-infected flocks. Our results complement these microbiological approaches by using available aggregate epidemiological, cross-sectional, and trend data (Figs. 1, 2, and 5), rather than microbial load data. These data are explained within the model structure (Fig. 4) by assuming that maintaining animal health can significantly benefit human health and resistance levels.

This model is consistent with the policy commands of Article 130r, because it provides an essential component of cost–benefit analysis – the causal link between interventions and their consequences over time – as well as a framework to include new information and describe the net effects of policy interventions over time. Even when data and knowledge are incomplete or conjectural, the model can be used to bound the potential magnitude and direction of adverse outcomes that are consistent with historical data (and with modeling assumptions), before policy is enacted, and the results can be used to assess the potential full effect of that policy, such as a ban, and its alternatives, such as a delayed or phased ban.

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Appendix A

This appendix develops a quantitative risk assessment (QRA) model in which the controllable input, $A(t)$, indicates animal drug use: $A(t)=1$ if the animal drug is used at time t, else $A(t)=0$ (A="animal antibiotic use" or "action"). The model describes the potential human health consequences of changes in $A(t)$. The systems dynamics model is:

$$\mathrm{IA}(t) = A \times \mathrm{IA}_1 + (1-A) \times \mathrm{IA}_0 \quad (1)$$

or, equivalently, $\mathrm{IA}=\mathrm{IA}_0+\mathrm{A}(\mathrm{IA}_1-\mathrm{IA}_0)$, where short-run transients and within-flock dynamics of animal illnesses are ignored. (This states that the fraction of ill animals is IA_1 when $A=1$ and IA_0 when $A=0$.)

$$d\mathrm{IH}/dt = [a_1 + b_1(1-\mathrm{IA}) + c_1\mathrm{IA} + d_1\mathrm{IH}](1-\mathrm{IH}) - r_1\mathrm{IH} \quad (2)$$

$$d\mathrm{RA}/dt = [a_2 + b_2A + c_2\mathrm{IA}^*A + d_2\mathrm{IH} + e_2\mathrm{RH}](1-\mathrm{RA}) - r_2\mathrm{RA} \quad (3)$$

$$d\mathrm{RH}/dt = [a_3 + b_3A + c_3\mathrm{IA}^*A + d_3\mathrm{IH} + e_3\mathrm{RH} + f\mathrm{RA}] \times (1-\mathrm{RH}) - r_3\mathrm{RH} \quad (4)$$

The rate of change of each dynamic quantity X (for X=IH, RA, or RH) is of the form:

$$dX(t)/dt = k[1-X(t)] - rX(t), \text{ abbreviated as : } dX/dt = k(1-X) - rX.$$

Interpretively, $(1-X)$ is proportional to the pool of "susceptibles," the fraction of units (people, animals, or bacteria) without undesirable condition (illness or resistance) but that may acquire it. k=fractional rate per unit time at which susceptible units acquire the undesirable condition, r="recovery rate" at which units with the undesirable condition make a transition back to not having it.

Coefficients a_1, a_2, and a_3, are background rates of spontaneous transition from the susceptible to the affected groups (per susceptible unit, per unit time); b_1=the rate at which servings from healthy animals, represented by $(1-\mathrm{IA})$ (the fraction not ill) make healthy people (represented by $(1-\mathrm{IH})$) sick; c_1 is the analogous coefficient for servings from ill animals. If the disease is infectious, $d_1>0$ represents the rate at which ill humans, IH, infect healthy ones, $(1-\mathrm{IH})$. If b_2 is positive, the use of the animal antibiotic contributes to the flow of animal bacteria from the pool susceptible to the antibiotic, $(1-\mathrm{RA})$, to the resistant pool, RA. b_3 accounts for direct contribution to selection of resistant strains in human (e.g., from farm leads into surface water), selection of resistant strains in the environment, and hence an increase in the resistant fraction RH among isolates from affected humans. c_2 and c_3 allow for therapeutic uses of the animal antibiotic in ill animals to contribute to resistance selection in animals and human, respectively. d_2 and d_3 allow for treatment of ill humans to select for resistant strains then found in animals (Iversen et al., 2004) and in humans, respectively; e_2 and e_3 allow for patients with resistant strains who excrete them and contribute differently to such strains in animals and humans. f describes the possibility that resistant bacteria are transferred from animals to humans, (e.g., directly via food, or indirectly through transfer of resistance determinants).

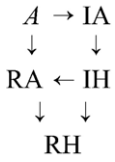
The fraction of people with resistant illnesses=$\mathrm{IH}(t)*\mathrm{RH}(t)$. As appropriate for animal antibiotics, growth promoters, prophylactics, and bacteria, for which the spread of resistant strains is potentially driven by animal antibiotic use (via b_2A) and by empiric treatment of ill humans (whether or not they have resistant strains, via d_2IH), perhaps followed by entrance of the prescribed human antibiotic into sewage and consequent selection and spread of resistant strains to animals and humans (via fRA) (Iversen et al., 2004), d_1, b_3, c_2, e_2 and e_3 become "structural zeros", obtaining:

$$d\mathrm{IH}/dt = [a_1 + b_1(1-\mathrm{IA}) + c_1\mathrm{IA}](1-\mathrm{IH}) - r_1\mathrm{IH} \quad (2')$$

$$d\mathrm{RA}/dt = [a_2 + b_2A + d_2\mathrm{IH}](1-\mathrm{RA}) - r_2\mathrm{RA} \quad (3')$$

$$d\mathrm{RH}/dt = [a_3 + d_3\mathrm{IH} + f\mathrm{RA}](1-\mathrm{RH}) - r_3\mathrm{RH} \quad (4')$$

As discussed in the text, this system can explain the patterns in the European historical data, Figs. 1 and 2. Dependencies are summarized in the following directed acyclic graph:



Model structure

Equilibria of human illness and resistance before and after a change in A can be assessed by replacing each equation $\mathrm{d}X/\mathrm{d}t=k(1-X)-rX$ with the equilibrium condition $(\mathrm{d}X/\mathrm{d}t=0)$:

$$k(1-X) = rX; \text{ thus } X = k/(k+r)$$

Any change that increases k increases the steady-state value of X (i.e., $k/(k+r)$ tends to 1, for $k>0$ and $r>0$). Accordingly:

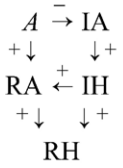
$$\mathrm{IH} : k_1 = a_1 + b_1(1-\mathrm{IA}) + c_1\mathrm{IA} = (a_1+b_1) + (c_1-b_1)\mathrm{IA}$$

$$\mathrm{RA} : k_2 = a_2 + b_2A + d_2\mathrm{IH}$$

$$\mathrm{RH} : k_3 = a_3 + d_3\mathrm{IH} + f\mathrm{RA}$$

Thus, if $d_3>0$ and $f>0$, then RH increases with both IH and RA. If $b_2>0$ and $d_2>0$, then RA increases with both IH and A. IA decreases with A, if the animal antibiotic use either reduces or prevents animal illnesses. IH increases with IA if and only if $c_1>b_1$, (e.g., if servings from ill animals carry higher microbial loads and hence greater risk-per-serving than servings from well animals).

The impact on human health from changes in animal drug use are studied by assigning signs:



Model: Qualitative impacts

Changing the value of input A from $A=1$ to $A=0$ (i.e., implementing a ban on an existing use) *increases* IA (from IA_1 to IA_0). However, it tends to *decrease* RA. Therefore, while the impact of the change in A on the equilibrium value of IH is an unambiguous increase (reduced A increases IA and increased IH), the impact on RH depends on the relative strengths of the impacts from decreases in RA due to lower A (transmitted via b_2 and f) and the impacts from increases in IH (via d_2, f, and d_3). If the impact of IH on RA is negligible ($d_2 \approx 0$), then the steady-state equilibrium equations become:

- $IH = \{a + c[IA_0 + A^*(IA_1 - IA_0)]\} / \{r_1 + a + c[A^* IA_1 + (1-A) IA_0]\}$
- $RA = (a_2 + b_2 A)/(a_2 + b_2 A + r_2)$
- $RH = (a_3 + d_3 IH + f^* RA)/(r_3 + a_3 + d_3 IH + f\, RA)$

For brevity, we use the coefficients $a = (a_1 + b_1)$ and $c = (c_1 - b_1)$, working with steady-state, equilibrium levels. A change in A on RH is positive iff it increases the variable component of the numerator, $d_3 IH + f^* RA$ (increasing the ratio defining RH, moving it closer to 1.) Changing A from 1 to 0 *reduces* RA by an amount ΔRA, from $(a_2 + b_2)/(a_2 + b_2 + r_2)$ to $a_2/(a_2 + r_2)$ and *increases* IH by an amount ΔIH from $(a + cIA_1)/(r_1 + a + cIA_1)$ to $(a + cIA_0)/(r_1 + a + cIA_0)$. Thus, the impact on RH is an increase if and only if $d_3 \Delta IH > f^* \Delta RA$, i.e., $\Delta IH > (f/d_3)\Delta RA$.

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