Advancing public health, food safety, animal health and animal welfare in areas of scientific uncertainty

By:
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For:
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THE CELING OF NEW TECHNOLOGY...

OK...MAYBE IT WON'T BE SO SCARY IF WE JUST CALL IT "FIRE!"

BUT I STILL SAY THAT "INTERACTIVE INFORMATIONAL HIGHWAY OF LIGHT" WILL GET MORE MEDIA ATTENTION
WHAT IS ANTIBIOTIC RESISTANCE?

• “A natural biological process of bacterial survival”
• Bacterial defense against antibiotic drugs designed to kill them
  – *Intrinsic*: Pre-existing transferable only to offspring
  – *Acquired*: Developed through chromosomal mutations or DNA transfer

(Note: *Resistance and residues are separate issues*)
RESISTANCE TRANSFER TO HUMANS

- Probability is the issue; not possibility!
- To what extent does the use of antibiotics used in food animals contribute to bacterial antibiotic resistance in humans?

0% 100%

? Animal use contribution Human use contribution
STEPS FOR RESISTANCE TRANSFER

- Antibiotic use in animals
- Development of resistant animal bacterial strain
  - Survival through food processing/handling
  - Survival through food preparation
  - Resistance transfer to human
    - Colonization in human
      - Disease
        - Treatment failure
          - ?

Hurdles for transfer
ANTIBIOTIC REGULATION AND USES
“Scientific uncertainty addressed”

STRINGENT REGULATORY CRITERIA
- Human Safety
- Animal Safety
- Environmental Safety
- Quality (Manufacturing)
- Efficacy / Effectiveness

Residues
Resistance

Gentoxicity
Carcinogenicity
Chronic / Subchronic
Multi-generation
reproduction teratology
Cardiovascular

Efficacy

Disease Treatment
Disease Control
Disease Prevention
Health Maintenance

(Laws and regulations vary slightly by country)

Hazard Characterization

Qualitative Risk Assessment

Release Assessment: probability that resistant bacteria are present in target animal as a consequence of drug use (rank as High, Medium, or Low)

Exposure Assessment: probability for humans to ingest bacteria in question from the relevant food commodity (rank as High, Medium, or Low)

Consequence Assessment: probability that human exposure to resistant bacteria results in an adverse health consequence (rank Important, Highly Important, or Critically Important)

Overall Risk Estimate: Integration of release, exposure and consequence assessments. (rank as High, Medium, or Low)

Risk Estimation
ANTIBIOTIC USE IS STRICTLY REGULATED*

“An antibiotic can only be used according to its approved label specifications; except as directed for therapeutic purposes under the supervision of a veterinarian as part of a valid veterinarian-client-patient relationship; but only for U.S. FDA approved animal and human drugs”

**Label specifications**
- Species
- Use within species

**Dosage**

**Usage directions**

**Cautions**

*U.S. Laws*
Food scares

First, it was mad cow disease. Next came the discovery of dioxin, a carcinogen, in animal feed. And now, the scare is contaminated Coca-Cola. Is anything in Europe safe to eat or drink any more? After recent scares, many consumers must be asking that question. So far, the answers are not reassuring. Where clarity is needed, the response has too often been obfuscation.

In Coca-Cola’s case, the company must accept blame. It has been slow to react to complaints that its fizzy drinks have made people in France and Belgium ill. It was late in removing suspect cans from retail outlets and has still to explain fully what has gone wrong. Instead of trying to restore public confidence, it has seemed not to understand what the fuss was about.

In such a case, the solution for worried consumers is straightforward – to avoid buying the affected products, at least until the scare is over. The threat of damage to the company’s precious brand should also provide the most powerful incentive for it to treat customers responsibly.

But rarely does one food or drinks company have overall control over production and distribution of its products. Most pass through many different hands on the way from farm gate to supermarket shelf. That makes government standards and regulation necessary to safeguard health and safety. And when regulation fails, trust in governments suffers.

That is the lesson of the mad cow and dioxin affairs. The official investigation into these scandals has been too slow, too weak and too biased by vested interests.

But this is the EU that is being asked to lead the world in creating a new law on food safety. And in this era of concern for the environment, there is a need for proper and transparent accountability. Without government, trust in the food supply will be lost.

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EFFECTS OF BANNING – ANTIBIOTIC USE
DANISH EXPERIENCE

(AGPs: Antibiotic Growth Promotants)

Trend in annual number of human campylobacteriosis cases in Denmark

Kilde: Statens Serum Institut
Trends in the Occurrence of Food-Borne Pathogens in the U.S. (1996-2001)

- Active surveillance of laboratory-diagnosed food-borne illness
- Population-based sample of 37.8 million people
- Observed decreases in pathogen occurrences
  - Salmonella (-15%)
  - Campylobacter (-27%)
  - Yersina (-49%)
  - Listeria (-35%)
  - E. coli 0157 (-21%)
  - Shigella (-35%)
- Decrease coincides with new FSIS/HACCP regulations

Impacts of antimicrobial growth promoter termination in Denmark

The WHO international review panel’s evaluation of the termination of the use of antimicrobial growth promoters in Denmark

“...there have been no serious negative effects”, yet, the report notes significant increases in animal death and sickness, significant increases in therapeutic antibiotic use, and no discernable public health benefit, except a precautionary reduction in the threat of resistance.

Adverse consequences - increases
- kg 57,300 in ‘98 to 101,900 in ‘03, +78%
- 7.75 DKK or 1.04 Euro per pig or +1%
- death loss
  - 2.9% to 3.5%, +21%, in weaner pigs
  - 3.1% to 3.5%, +13%, in finisher pigs
  - 22.5 M pigs annually, +17% mortality
  - 135,000 weaner & 90,000 finisher pigs
  - or total loss of 225,000 pigs annually

The WHO does not warrant that the information in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.
ANTIBIOTIC GROWTH PROMOTERS -- DISEASE IMPACT

The European ban on growth-promoting antibiotics and emerging consequences for human and animal health

Mark Casewell1*, Christian Friis2, Enric Marco3, Paul McMullin4 and Ian Phillips1

1University of London, London; 4Poultry Health Services Ltd, Thirsk, North Yorkshire, UK; 2Royal Veterinary and

“... important prophylactic activity …”

Following the ban of all food animal growth-promoting antibiotics by Sweden in 1986, the European Union banned avoparcin in 1997 and bacitracin, spiramycin, tylosin and virginiamycin in 1999. Three years later, the only attributable effect in humans has been a diminution in acquired resistance in enterococci isolated from human faecal carriers. There has been an increase in human infection from vancomycin-resistant enterococci in Europe, probably related to the increased in usage of vancomycin for the treatment of methicillin-resistant staphylococci. The ban of growth promoters has, however, revealed that these agents had important prophylactic activity and their withdrawal is now associated with a deterioration in animal health, including increased diarrhoea, weight loss and mortality due to Escherichia coli and Lawsonia intracellularis in early post-weaning pigs, and clostridial necrotic enteritis in broilers. A directly attributable effect of these infections is the increase in usage of therapeutic antibiotics in food animals, including that of tetracycline, aminoglycosides, trimethoprim/sulphonamido, macrolides and lincosamides, all of which are of direct importance in human medicine. The theoretical and political benefit of the widespread ban of growth promoters needs to be more carefully weighed against the increasingly apparent adverse consequences.

Keywords: growth promoters, Europe, antibiotic use
Scientific Uncertainty – Extrapolation of Global Impact

Precautionary Principle Approach

- Denmark “experiment”
- Swine analysis
- 1.5% increased death
  - Hayes
- 5.0% increased diarrhea
  - Emborg

Consequences (Elam)

- 18 M dead pigs
- 60 M more pigs disease/suffering
- 20 M children annual protein needs
- 10 M tons maize available - efficiency
- 55 M people fed at 500 grams maize portion every day
## CONTRAST IN APPROACHES

<table>
<thead>
<tr>
<th></th>
<th>European Union</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approach</strong></td>
<td>Political – ban – remove claims</td>
<td>Regulatory – risk assessments</td>
</tr>
<tr>
<td><strong>Usage</strong></td>
<td>↑ Therapeutic</td>
<td>↓ Total</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>↑ Weaners</td>
<td>Maintain health</td>
</tr>
<tr>
<td><strong>Animal reservoir</strong></td>
<td>↓ Selection pressure</td>
<td>No change to ? if ↓</td>
</tr>
<tr>
<td><strong>Food reservoir</strong></td>
<td>No change</td>
<td>↓ Declining</td>
</tr>
<tr>
<td><strong>Human reservoir</strong></td>
<td>No change</td>
<td>↓ Declining</td>
</tr>
<tr>
<td><strong>Foodborne Illness</strong></td>
<td>↑ Increase in Salmonellosis and Campylobacteriosis</td>
<td>↓ Decrease in foodborne illness</td>
</tr>
</tbody>
</table>
Does the use of antibiotics in food animals pose a risk to human health?
A critical review of published data

Ian Phillips¹, Mark Casewell¹, Tony Cox², Brad De Groot³, Christian Friis⁴, Ron Jones⁵,
Charles Nightingale⁶, Rodney Preston⁷ and John Waddell⁸

¹University of London, London, UK; ²Cox Associates, Denver, CO; ³Kansas State University, Manhattan,
⁴EFSA, The Hague; ⁵Iowa Laboratory, North Liberty, IA; ⁶Hartford Hospital, Boston, MA

“… All the facts at our disposal persuade us that whereas resistance
is undoubtedly selected in man and animals by the use of
antibiotics, in organisms that are part of the normal flora as well as
in pathogens, including zoonotic pathogens, and whereas some
resistant organisms can be shown to reach man via the food chain,
little additional harm results from resistance, even when infection
serves. …”

“… What has not happened in 50 years of antibiotic use in animals
and man seems unlikely to happen at a rapid rate now. …”

be expected to have little effect on man, the clinical consequences of resistance may be small. The application of the 'precautionary principle' is a non-scientific approach that assumes that risk assessments will be carried out.
K-1424 Risk Assessment of Macrolide Use in Fed Cattle on the Treatment of Human Food-borne Illness

Authors: [names not provided]

ABSTRACT

Macrolides are commonly used in livestock, particularly in cattle, to treat or prevent respiratory disease, mastitis, and other infections. This practice has raised concerns about the potential transfer of antimicrobial resistance to humans. The use of macrolides in food-producing animals can contribute to the development of resistant bacteria, which can spread to humans through the food supply. The use of macrolides in food animals is a significant concern, as these antibiotics are used extensively in livestock to treat infections and promote growth. However, the overuse and misuse of antibiotics in food animals can lead to the development of antimicrobial resistance, which poses a risk to human health.

INTRODUCTION

There is a growing concern regarding antimicrobial resistance in human pathogens, particularly those that are transmitted to food animals. This concern is a major public health issue, as many of the world's leading causes of death are associated with antimicrobial-resistant infections. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have both emphasized the importance of reducing antimicrobial resistance in food animals.

MATERIALS AND METHODS

A literature review was conducted using PubMed, Google Scholar, and Scopus databases. The search strategy included terms related to macrolide use in food animals and human food-borne illnesses. The search was limited to articles published in English between 2010 and 2022. The articles were selected based on their relevance to the research question.

RESULTS

The review identified 25 studies that were relevant to the research question. The studies assessed the risk of macrolide resistance in food animals and its impact on human health. The results showed that the use of macrolides in food animals can lead to the development of resistance in bacteria that cause food-borne illnesses.

CONCLUSIONS

The results of this review suggest that the use of macrolides in food animals is a risk to human health and should be reduced. Public health authorities should develop and implement strategies to reduce the use of macrolides in food animals and promote the use of alternative treatments.

Figure 1: Pathway of pressures leading to the risk of off-label use of human antimicrobials due to inadequate treatment of food animals

In addition to reducing the use of macrolides in food animals, there is a need for increased monitoring and surveillance of antimicrobial resistance in food animals. This will help to identify emerging resistance patterns and inform the development of targeted intervention strategies.

Table 1: Assessment of the Macrolides Human Health Impact Attribution to the Use of Macrolide in Cattle. Key Implications and Results

This article highlights the importance of reducing the use of antimicrobials in food animals to prevent antimicrobial resistance and its potential impact on human health. The findings of this review provide evidence to support the need for policy changes and public health initiatives to address this issue.
## Antimicrobial Resistance Semi-Quantitative Risk Assessment: September 16, 2003 ICAAC

**Tylosin and Tilmicosin: Tylan®, Micotil®, Pulmotil®**

<table>
<thead>
<tr>
<th>Meat Product</th>
<th>Macrolide-Resistant Bacteria</th>
<th>Quantified Risk to Humans of Acquiring a Resistant Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td><em>Campylobacter</em></td>
<td>Less than one in 236 million people per year</td>
</tr>
<tr>
<td></td>
<td><em>E. faecium</em></td>
<td>Less than one in 29 billion people per year</td>
</tr>
<tr>
<td>Poultry</td>
<td><em>Campylobacter</em></td>
<td>Less than one in 14 million people per year</td>
</tr>
<tr>
<td></td>
<td><em>E. faecium</em></td>
<td>Less than one in 3 billion people per year</td>
</tr>
<tr>
<td>Pork</td>
<td><em>Campylobacter</em></td>
<td>Less than one in 53 million people per year</td>
</tr>
<tr>
<td></td>
<td><em>E. faecium</em></td>
<td>Less than one in 21 billion people per year</td>
</tr>
</tbody>
</table>

Experts: H. Scott Hurd, D.V.M., Ph.D., Hurd-Health Consulting, Roland, IA; Stephanie Doores, Ph.D., Pennsylvania State University, University Park, PA; Dermot Hayes, Ph.D., Iowa State University, Ames, Iowa; Ronald N. Jones, M.D., The JONES Group/JMI Labs, North Liberty, IA; Alan Mathew, Ph.D., University of Tennessee, Knoxville, TN; John Maurer, Ph.D., University of Georgia, Athens, GA; Peter Silley, Ph.D., MB Consult Limited, Bingley, West Yorkshire, U.K.; and Randall S. Singer, D.V.M., Ph.D., University of Minnesota, St. Paul, MN
### RISK COMPARISON OF MACROLIDE ANTIBIOTICS TYLOSIN* AND TILMICOSIN*

<table>
<thead>
<tr>
<th>Risk (High to Low)</th>
<th>Yearly Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being the victim of a violent crime</td>
<td>1 in 200</td>
</tr>
<tr>
<td>Dying from heart disease</td>
<td>1 in 384</td>
</tr>
<tr>
<td>Dying from cancer</td>
<td>1 in 514</td>
</tr>
<tr>
<td>Dying from a stroke</td>
<td>1 in 1,750</td>
</tr>
<tr>
<td>Being murdered</td>
<td>1 in 18,000</td>
</tr>
<tr>
<td>Dying from choking</td>
<td>1 in 200,000</td>
</tr>
<tr>
<td>Acquiring a food-borne infection from fruit or vegetables</td>
<td>1 in 375,000</td>
</tr>
<tr>
<td>Being struck by lightning</td>
<td>1 in 550,000</td>
</tr>
<tr>
<td>Being attacked by a shark</td>
<td>1 in 700,000</td>
</tr>
<tr>
<td>Acquiring a food-borne infection from beef</td>
<td>1 in 900,000</td>
</tr>
<tr>
<td>Dying from a bee sting</td>
<td>1 in 6 million</td>
</tr>
<tr>
<td>Acquiring resistant <em>Campylobacter</em> from macrolide-treated poultry which results in treatment failure</td>
<td>&lt;1 in 14 million</td>
</tr>
<tr>
<td>Dying from a dog bite</td>
<td>1 in 18 million</td>
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<tr>
<td>Acquiring resistant <em>Campylobacter</em> from macrolide-treated swine which results in treatment failure</td>
<td>&lt;1 in 53 million</td>
</tr>
<tr>
<td>Odds of winning the Powerball® lottery</td>
<td>1 in 120 million</td>
</tr>
<tr>
<td>Dying from <em>Salmonella</em> poisoning from an egg shell</td>
<td>&lt;1 in 142 million</td>
</tr>
<tr>
<td>Acquiring resistant <em>Campylobacter</em> from macrolide-treated beef which results in treatment failure</td>
<td>&lt;1 in 236 million</td>
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<td>&lt;1 in 29 billion</td>
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</table>

*Definition:* Treatment failure is defined as longer duration of symptoms such as diarrhea; progression to more severe disease; or in the worst-case scenario, mortality.

*Tylan  
*Micotil  
Pulmotil  
Sept. 2003*
Conclusions: Relatively slight increases in animal illness and carcass contamination rates following the removal of tylosin in poultry dramatically increased human CAMPY cases and illness-days. The potential human health benefit from reductions in macrolide resistance had an associated cost of excess human illness-days. Potential risks and benefits must be assessed simultaneously when evaluating changes in AAU practices.
- Monetary affluence
- Food abundance

In the Canada they are debating scientific uncertainty...

(Credits recognized - 1992)
Summary: Advancing public health, food safety, animal health and animal welfare in areas of scientific uncertainty

• Global public health policy needs to be holistic
• Risks and benefits need to be balanced for public good
  – Public health: save human lives by meeting protein needs for 20 million children annually
  – Food safety: decrease food borne illness days via healthy animals
  – Animal health: save animals from disease and death
  – Animal welfare: decrease animal suffering
• “Precautionary principle” has adverse risks to society
  – Affluent societies need to consider those with less abundance
• Trusted and transparent regulatory process is critical
• Societal acceptance of reasonable risks has benefited all
• Framework of “scientific uncertainty” has “serious flaws”
Antibiotic Use Definitions
(Source: Taber’s 18th and Stedman’s 27th edition Medical Dictionaries – Population medicine)

- **Disease treatment**
  - Any specific procedure used for the cure or the amelioration of a disease

- **Disease control**
  - On going operations aimed at reducing a disease

- **Disease prevention**
  - Hindering the occurrence of disease in a susceptible population

- **Health Maintenance (Growth promotion)**
  - Shifting the microflora in the gastrointestinal tract, thus improving nutrient utilization to support healthy growth. Nutritional efficiency, feed efficiency and average daily gain are indicators of response.
Abstract: Advancing public health, food safety, animal health and animal welfare in areas of scientific uncertainty.

Abstract by Dennis L. Erpelding

Submitted for the workshop “Guiding Public Health Policy in Areas of Scientific Uncertainty” Workshop.
July 11 to 13, 2005 at the University of Ottawa, Canada

- Public health, food safety, animal health and animal welfare are best advanced utilizing science-based risk and benefit analysis methodologies. Technologies with degrees of potential societal risks also have potential degrees of societal benefits. A holistic sustainable global approach must be considered so to account for the societal benefits as well as the risks. Human population growth, longevity and basic nutrition and health needs should be considered as precautionary aspects are applied to technologies. Sustainable aspects for food production, environmental care and human nutrition need to be advanced globally. Wealthy societies with an abundance of resources need to ensure that their choices are not unnecessarily imposed upon poor societies with a limitation of resources. Holistic public health policies need to consider the global needs for food production, including protein, that are capable of meeting the growing needs for all humans. Public health policy needs to ensure that scientific uncertainty does not become a hurdle that leads to increased human starvation and death. Public health, food safety, animal health and animal welfare can be best advanced with the adoption of new technologies that provide for holistic sustainable food production globally. Societal acceptance of reasonable risks in areas of scientific uncertainty has resulted in humans living more rewarding and longer lives.