QUANTIFYING HUMAN HEALTH RISKS FROM USE OF VIRGINIA MYCIN IN CHICKENS

L. Anthony Cox, Ph.D.
Cox Associates, Denver, CO

and

Kenneth W. Bafundo, Ph.D.
Phibro Animal Health
Fairfield, NJ
OBJECTIVE

- Familiarization with and simplification of some of the concepts associated with risk analyses.
- Review critical factors in the virginiamycin risk analysis.
OUTLINE

I. BACKGROUND
II. LITERATURE
III. ASSESSING RISK
IV. RESULTS
V. CONCLUSIONS
VIRGINIAMYCIN

- Streptogramin (Factor M and S)
- Affects protein synthesis, binding to two ribosomal sites
- Used for prevention of Clostridial enteritis and to enhance growth and feed efficiency in poultry, swine and cattle FOR 30 YEARS.
ANTIBIOTIC RESISTANCE AND VIRGINIAMYCIN

- *Enterococcus faecium* and *E. faecalis*
- Vancomycin and VRE
- Synercid (Quinupristin/Dalfopristin, QD)
  - Streptogramin for human *E. faecium* infections
- Concern over Virginiamycin use in animals influencing the response of Synercid in man
SYNERCI D
(quinupristin/dalfopristin)
‘QD’

- At launch, 99.8% of human *E. faecium* were sensitive (Jones *et al.*, 1998)
- NOT effective against *E. faecalis*
- NOT well tolerated by patients
- Emphasis and usage are currently in decline
ZYVOX
(Linezolid)

- Launched May 2000
- New antibiotic class
- Active against *E. faecium* and *E. faecalis*
- Very well tolerated
- Use expanding rapidly at the expense of Synercid
PROTOCOL FOR TREATING *E. FAECIUM* INFECTIONS

1998

I. Vancomycin
II. Synercid (QD)

2000 ONWARD

I. Vancomycin
II. *Zyvox* (L I N E Z O L I D)
III. Synercid (QD)
LITERATURE REVIEW

• Streptogramin resistant *E. faecium* in humans are extremely rare despite 30 years of virginiamycins use in animals.
# Prevalence of Human SREF from Worldwide Surveys

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<th>Author</th>
<th>Country/Region</th>
<th>% SREF or Comment</th>
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<td>JONES et al., 1998</td>
<td>USA &amp; CANADA</td>
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<td>SCHMITZ et al., 1999</td>
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• VR *E. faecium* is now recognized as host specific (Willems *et al.*, 2000).

  - Four genogroups were identified:
    A. Non hospitalized persons
    B. Chickens and turkeys
    C. Hospitalized patients
    D. Cattle
Attempts at cross-colonization have failed:
- Qaiyumi *et al.*, 2000. SREF from hospital ICUs did not colonize chickens.
- Sorensen *et al.*, 2001. “Transient intestinal carriage” occurred when human volunteers were given SREF of animal origin.
LITERATURE REVIEW

• The ‘esp’ gene has been shown to cause hospital outbreaks of *E. faecium* (Willems *et al.*, 2001).

  - The virulence gene.
  - Not recently acquired.
  - Common from hospital isolates in three distinct areas of the world.
  - **ABSENT** from all **ANIMAL ISOLATES**.
LITERATURE REVIEW

• The likelihood of genetic transfer is low (Sorensen *et al.*, 2001; McDonald *et al.*, 2001).
GENETIC TRANSFER

• *IN VITRO.*
  - Genetic transfer is easily demonstrated.

• Also demonstrated in specialized conditions:
  - Germ-free rats monocontaminated with *E. faecium* (Jacobsen *et al.*, 1999).
GENETIC TRANSFER

• **IN VIVO.**
  - Sorensen *et al.* (2001) could not demonstrate gene transfer even with massive doses of SR *E. faecium*.
  - McDonald *et al.*, 2001. If it occurs, it is a rare event.
GENETIC TRANSFER

• Virginiamycin usage:
  - Used worldwide for >30 years
  - Used in many species
    • Poultry, swine, cattle, fish, shrimp, horses, sheep, etc.

• Yet, SREF in man are extremely rare.
## Prevalence of Human SREF From Worldwide Surveys

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DOES GENETIC TRANSFER OCCUR IN MAN?

• JAPAN
  - Uncooked chicken is commonly consumed.
  - Virginiamycin used in Japan since 1974.
  - Imported chicken from countries where Virginiamycin is/has been used.
  - Synercid (QD) recently approved for use.
    • Government sponsored studies to investigate occurrence of SREF in man.
GENETIC TRANSFER

• Inoue et al., 1999.

Of 1,239 *E. faecium* isolates collected from Japanese hospitals

**ALL WERE SENSITIVE TO SYNERCID**
IF GENETIC TRANSFER OCCURS, IT IS A RARE EVENT

OUR RISK ANALYSIS ASSUMES THAT GENETIC TRANSFER OCCURS
1. *E. faecium* is now recognized as host specific (Willems *et al.*, 2000).

2. Attempts at cross-colonization have failed (Sorensen *et al.*, 2001; Qaiyumi *et al.*, 2000).
3. Identification of the ‘esp’ gene for virulence of *E. faecium* (Willems *et al.*, 2001)
   - GENE IS ABSENT FROM ALL ANIMAL ISOLATES OF *E. FAECIUM*

4. *In vivo* transfer of genes for streptogramin resistance is unproven (Sorensen *et al.*, 2001). If it occurs, it is rare (McDonald *et al.*, 2001).
ASSESSING RISK
ASSESSING RISK

DOES USING VIRGINIAMYCIN IN CHICKENS CAUSE QD RESISTANT *E. FAECIUM* LEADING TO DEATHS IN HUMAN PATIENTS?

OBJECTIVE:

To quantify the potential human health benefits of banning virginiamycin in 2002.
ASSESSING RISK

TO ESTABLISH UPPER BOUND RISK, A Vm ATTRIBUTABLE TREATMENT FAILURE IS DEFINED WHENEVER A PATIENT HAS:

1. A VREF infection
2. That is resistant to QD
3. That could have come from chicken
4. Patient is prescribed QD
5. QD therapy fails due to QD resistance
QUANTIFYING RISK

HUMAN TREATMENT FAILURES DUE TO VIRGINAMYCIN ARE A PRODUCT OF:

1. Total vanA *E. faecium* cases
2. Proportion not of hospital origin
3. Proportion with the genogroup found in chickens
4. Proportion that are QD resistant
5. Proportion that have treatment success with QD
QUANTIFYING RISK

STARTING POINT:

Total VRE caseload in the USA:

9371 CASES PER QUARTER

• Estimated from CDC NationalNosocomial Infections Surveillance System (NNIS)
1. Proportion of vanA *E. faecium* cases is: 61%  

- Only vanA VREF can be linked to food animals (*EAGAR, 2002*).  
- QD not used for vanB VREF (*Murray, 2000*).
2. Proportion of VREF not of hospital origin: 17%

- Thal et al. (1998); Bishoff et al. (1999); Austin et al. (1999).
3. Proportion with the genogroup found in chickens: 12.4%

- Willems *et al.* (2000) using AFLP described four genogroups of VREF.
- Genogroup B are common from poultry.
- 10 of 87 hospitalized patients in this study contained genogroup B strains.
- Assumes genetic transfer occurs.
4. Proportion that are resistant to QD:

1%

- Eliopolis *et al.* (1998); Jones *et al.* (1998); McDonald *et al.* (2001).
5. Proportion having treatment success: 71%

• QD is not completely effective.
  (Moellering et al., 1999; Linden, 2002)
### QUANTIFYING RISK

**Calculations:**

**Time Independent Reductions:**

1. VanA *E. faecium* 0.61 x
2. VRE not of hospital origin 0.17 x
3. Attributable to chickens 0.12 x
4. Proportion resistant to QD 0.01 x
5. QD effectiveness 0.71

**Product of Reductions**

.0001
QUANTIFYING RISK

TOTAL NUMBER OF VRE CASES/QUARTER
9371

X

TIME INDEPENDENT 0.0001

_____________

.9371

Treatment failures/quarter in the entire U.S. population
QUANTIFYING RISK

TIME DEPENDENT FACTORS:

• Due to linezolid, Synercid (QD) usage is declining at a rate of about **30%** per year or **7.8%** per quarter.
QUANTIFYING RISK

• TIME DEPENDENT FACTORS:

Assuming a ban were implemented, the level of resistance in chickens would decrease over time (DANMAP, 2000).

Danish data indicate that after 3 years, resistance is reduced by ~50%.
QUANTIFYING RISK

MORTALITY RATE ATTRIBUTION (conversion of treatment failures to mortality):

Assuming linezolid were not available, the mortality rate associated with QD failures (because of resistance):

15.5%

Linden et al., (1997)
RESULTS

WILL BANNING VIRGINIAMYCIN BENEFIT HUMAN HEALTH?
RESULTS

WILL BANNING VIRGINIAMYCIN BENEFIT HUMAN HEALTH?

If a ban had been implemented on January 1, 2002, 0.29 statistical mortalities would have been averted in the entire U.S. population over the next 5 years.
RESULTS

THIS IS EQUIVALENT TO AVERTING:

LESS THAN ONE STATISTICAL MORTALITY IN THE ENTIRE U.S. POPULATION OVER THE NEXT 15 YEARS.
RESULTS

This is approximately equivalent to:

**One statistical mortality averted per billion members of the U.S. population in the next 5 years**
RESULTS

• Because QD usage is declining at a rate of >30% per year, statistical mortality figures are declining as well.

• Thus, risk is decreasing over time.
CONCLUSIONS

• Despite scientific uncertainty on the occurrence and frequency of chicken to human transfer of resistance, this analysis places useful upper bounds on human health risk by use of virginiamycin in chickens.

• That risk is extremely low and could be zero if transfer of resistance does not occur.
CONCLUSIONS

- THE STUDY CONSTITUTES A WORST CASE ANALYSIS
  - Assume transfer of resistance from chickens to man does occur (has never been proven *in vivo*)
  - Assume that 12.4% of human QD resistant cases are acquired from chickens (unrealistically high)
  - Use an upwardly biased mortality figure of 15.5%
CONCLUSIONS

• In the context that all human activity involves risk, the degree of risk afforded to man by virginiamycin is greatly exceeded by many normal human endeavors.

  - Driving a Car
  - Flying in a Plane
  - Being Struck by Lightning
  - Consumption of Peanut Butter