“Towards a Risk Analysis of Antibiotic Resistance”

Berlin, Germany

November 11, 2003
Human illness:

- Caused by an antimicrobial-resistant bacteria,
- Attributable to an animal-derived food commodity, and
- Treated with the human antimicrobial drug of interest
Definition of the Hazard

Resistance Gene Reservoirs:
- Commensal organisms, e.g., Enterococcus transferring resistance genes or determinants to human commensals or human pathogens
- ESBLs
- Co-selection and induction of resistance -- e.g., tetracycline
Scope of the Problem

- Enteric zoonotic pathogens
- Commensal bacteria
- Proactive/Preventive approach rather than wait for conclusive evidence
Development of Antimicrobial Resistance in Humans

Veterinary use of antibiotics

Selection of resistant bacteria in animals

Food chain and/or direct contact

Resistance transfer to human intestinal flora

Cross resistance to human statistics
Antimicrobial Resistance as a Public Health Risk

Perceived Pathway

Antibiotic Drug Use in Food Animals

Resistant Bacteria

Antibiotic Resistance in Enteric Bacteria

Resistance Genes

Infection/Colonization in Humans

Adverse Health Events in Humans

Does antibiotic use in animals affect public health?
Lines of evidence that link resistant bacteria with food animals

- Deductions from the general epidemiology of foodborne infections
- Ecological studies of trends
- Outbreak investigations
- Case reports of farmers, their families, or other persons directly exposed to drug-resistant bacteria
- Subtyping of isolates
Evidence about transfer of resistance genes from food animals to humans

Under selective pressure, foodborne pathogens and commensal bacteria become reservoirs of resistance genes

- *Escherichia coli*, *Klebsiella*, *Enterobacter*, *enterococci*, *Salmonella*, *Bacterioides* etc

The public health dimensions of transfer of genes between commensals to pathogens are difficult to quantify

- Routine diagnostics only look after pathogens
- It is difficult to determine the direction of transfer
- It is difficult to determine where a gene came from
Deductions from the general epidemiology of foodborne infections

- Salmonella, nontyphi: 95%
- Campylobacter: 80%
- E. coli
  - Verocytotoxigenic: 85%
  - Enterotoxigenic: 70%
  - Other diarrhoeagenic: 30%
  - Uropathogenic and invasive: ?

(adapted from Mead et al, 1999)

Person-to-person transmission of nontyphoid Salmonella and Campylobacter is rare
Outbreaks of Salmonella have linked antimicrobial resistant bacteria back to farms:

- Mølbak et al., 23 patients with DT104 ACSSuTNx, Danish pig farm, treatment failures (N Engl J Med 1999). No evidence of recent use of FQ at the farm
- Walker et al., 86 patients with DT104 ACSSpSuTNx, milk from a dairy farm, FQs used at the farm in the month before the outbreak (Vet Rec 2000)
- Fey et al., child living on a farm, ceftriaxone res. MDR S. Typhimurium (N Engl J Med 2000). Ceftiofur widely used in cattle
Analysis of 52 outbreaks, 1971 to 1983:

- Case-fatality rate in 17 outbreaks with resistant Salmonella 13/312 (4.2%)
- In 19 outbreaks with sensitive isolates the case-fatality rate was 4/1912 (0.2%)
- In 16 outbreaks with unknown antibiogram the fatality was 4/1429 (0.3%)

Holmberg et al. Science 1984;225:833-5
Studies of treatment failures

- A least 13 reports describing reduced efficacy of fluoroquinolones in treating Salmonella infections with isolates resistant to nalidixic acid, but MIC values against cipro < 4 mg/L
- 5 S. Typhi, 7 non-typhoid Salmonella
- Endpoints included
  - Failure to clear the pathogen
  - Prolonged fever
  - Death
- Antimicrobial Agents Chemother (Aarestrup et al.)
Poor response to treatment

- Deaths reported in Denmark and Taiwan among patients with resistant Salmonella infections treated with fluoroquinolones
  - K Molbak et al. NEJM 1999
  - Emerging Infectious Diseases 2003
- Prolonged duration of diarrhea reported in Minnesota, Denmark, and US among patients with resistant Campylobacter infections
  - K Smith et al. NEJM 1999
  - J Engberg, et al. Submitted to journal
  - J Nelson, et al. Submitted to journal
  - J Neimann, et al., Submitted to journal
Invasive infection and hospitalization

- Patients infected Salmonella resistant to clinically important agents including quinolones associated with increased likely of invasive infections and being hospitalized, and longer duration of hospitalization
  - Adjusted for serotype
Increased transmission as a result of the unrelated use of antimicrobial agents to which the pathogen was resistant

- Antimicrobial drugs cause a transient decrease in the resistance to infection upon exposure to a foodborne pathogen
  - Competitive effect (general)
  - Selective effect (specific advantage for the resistant pathogen)
Deaths

- Patients infected quinolone-resistant Salmonella Typhimurium have marked increased risk of dying (than those infected with susceptible) in 2 years after infection
  - Adjusted for co-morbidity
- Relatively similar findings in patients infected with quinolone-resistant Campylobacter
Excess mortality associated with resistance

- To determine mortality associated with gastrointestinal infections, while adjusting for co-morbidity
- S. Typhimurium strains from 2,047 patients, 1995 to 1999
- To determine the survival of these patients, the registry was linked to the Danish Civil Registry System (CRS)
- To determine the survival of non-exposed individuals, we randomly selected 10 persons from the CRS per case - matched for age, sex and county (20,456 referents)
- Data on co-morbidity were obtained from the national registry of patients

Helms et el, Emerg Inf Dis J, 2002;8:490-5
Two years mortality according to antimicrobial resistance:

<table>
<thead>
<tr>
<th>Category</th>
<th>Relative mortality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-susceptible (953)</td>
<td>2.3 (95% CI 1.5 to 3.5)</td>
</tr>
<tr>
<td>R-type ACSSuT + other (283)</td>
<td>4.8 (95% CI 2.2 to 10.2)</td>
</tr>
<tr>
<td>R-type Nx + other (83)</td>
<td>10.3 (95% CI 2.8 to 37.8)</td>
</tr>
<tr>
<td>R-type ACSSuTNx (40)</td>
<td>13.1 (95% CI 3.3 to 51.9)</td>
</tr>
</tbody>
</table>

*all estimates compared with the general Danish population, and adjusted for co-morbidity
Risk of death or invasive illness associated with quinolone resistance in Salmonella Typhimurium and Campylobacter spp.

- Outcome: Death or invasive illness up to 90 days after diagnosis
  - survival data obtained from civil registry
  - data on complications obtained from the national discharge registry
- Used susceptible strains as reference
- Age was the underlying time-scale in the models
- Information on comorbidity obtained from the national discharge registry and the cancer registry
**Campylobacter spp:**  
(3,481 patients, 1995-2000, 13% comorbidity)

<table>
<thead>
<tr>
<th>R-type:</th>
<th>Number of patients</th>
<th>Invasive/death</th>
<th>Hazard ratio*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolone</td>
<td>768</td>
<td>6 (0.8%)</td>
<td>6.4 (1.2-32.9)</td>
<td>0.0270</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>109</td>
<td>4 (3.7%)</td>
<td>21.1 (0.9-470)</td>
<td>0.0542</td>
</tr>
<tr>
<td>Quin. + ery.</td>
<td>96</td>
<td>2 (2.1%)</td>
<td>3.6 (0.2-88.1)</td>
<td>0.4278</td>
</tr>
<tr>
<td>Susceptible</td>
<td>2,508</td>
<td>9 (0.4%)</td>
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* age underlying time scale, adjusted for comorbidity and sex
**Salmonella Typhimurium:**
*(1,346 patients, 1995-2000, 23% comorbidity)*

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<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Total</th>
<th>Invasive/death</th>
<th>Hazard ratio*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolone res.</td>
<td>102</td>
<td>9</td>
<td>(8.7%)</td>
<td>5.2 (1.9-14.3)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Pansusceptible</td>
<td>1,243</td>
<td>55</td>
<td>(4.4%)</td>
<td></td>
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</tr>
</tbody>
</table>

* age underlying time scale, adjusted for comorbidity and sex

This excess risk of adverse outcome was found to be independent of the outbreak in 1998, caused by a DT104 strain R-type ACSSuTNx
Conclusions

- The food chain contains an abundance of antimicrobial-resistant pathogens, including Salmonella and Campylobacter
- Growing evidence that this has significant public health consequences
- Hazards include increased risk of
  - Death
  - Invasive illness
  - Hospitalization
  - Increased duration of disease
  - Increased transmission due to enhanced receptivity
  - Increased risk of outbreaks in settings where antimicrobials are used
Recommendations

- Need to take a proactive/preventive approach rather than wait for conclusive evidence:
  - Reduce overall selection pressure from antimicrobial use by developing and adopting prudent drug use principles
  - Restrict FQ and 3rd generation cephalosporin use in animals to individual animal treatment and only if other treatments have failed
  - Improve animal production/animal husbandry practices to minimize need for antimicrobials
Recommendations, Cont’d

- Support and expand programs such as the WHO Global Salm-Surv to educate, train, and provide infrastructure to developing countries.

- Ultimate goal is to restrict the use of antimicrobials in food-producing animals in the absence of a diagnosis of infectious disease, where there is evidence of a hazard to public health.
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