HAZARD CHARACTERIZATION

“Towards a Risk Analysis of Antibiotic Resistance”

Berlin, Germany

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Definition of the Hazard

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:

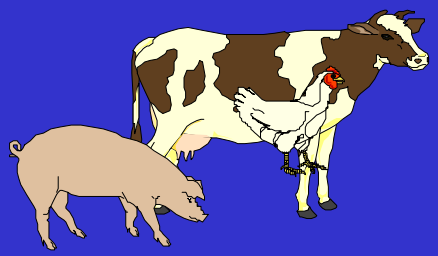
- Commensal organisms, e.g., Enterococcus transferring resistance genes or determinants to human commensals or human pathogens
- ESBLs
- Co-selection and induction of resistance -- e.g., tetracycline

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

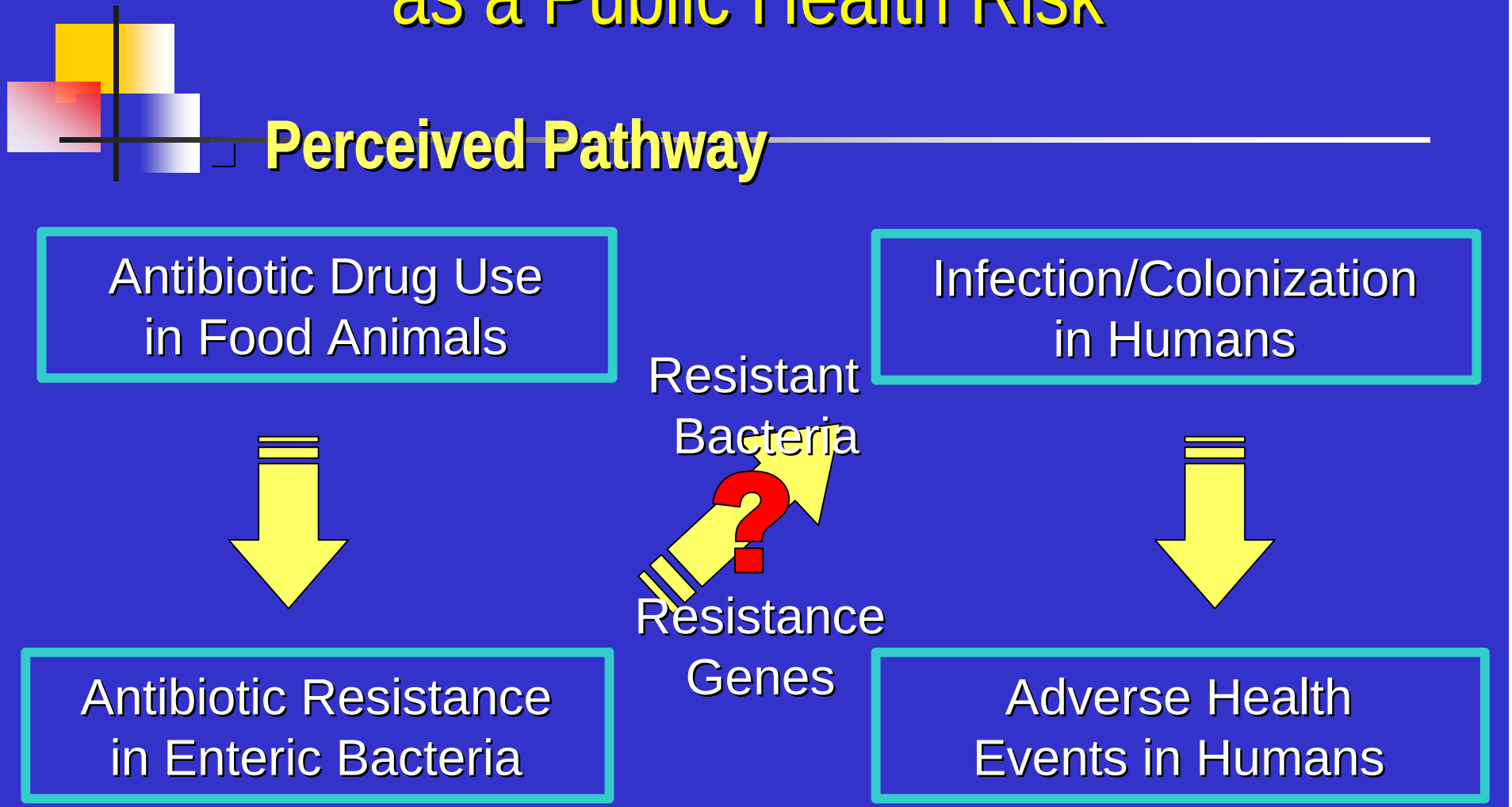
Food chain and/or direct contact

Resistance transfer to human intestinal flora ?

Cross resistance to human statistics

Antimicrobial Resistance as a Public Health Risk

Perceived Pathway



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

	Foodborne
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

Evidence from outbreaks

- Outbreaks of *Salmonella* have linked antimicrobial resistant bacteria back to farms:
  - Holmberg et al., 18 patients with MDR S. Newport. Source: Hamburger from SD cattle fed chlortetracycline (N Engl J Med 1984)
  - 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 unkown 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.)

Scientific Evidence

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

Scientific Evidence

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
  - J Varma, et al. In preparation.

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
  - Competetive effect (general)
  - Selective effect (specific advantage for the resistant pathogen)

Scientific Evidence

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-morbitity
  - M. Helms, et al. *Emerging Infectious Dis* 2002.
- Relatively similar findings in patients infected with quinolone-resistant *Campylobacter*
  - K. Molbak, et al. In preparation.

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:

	Relative mortality*
Pan-susceptible (953)	2.3 (95% CI 1.5 to 3.5)
R-type ACSSuT + other (283)	4.8 (95% CI 2.2 to 10.2)
R-type Nx + other (83)	10.3 (95% CI 2.8 to 37.8)
R-type ACSSuTNx (40)	13.1 (95% CI 3.3 to 51.9)

*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)

	Number of patients			
R-type:	Total	Invasive/death	Hazard ratio*	P
Quinolone	768	6 (0.8%)	6.4 (1.2-32.9)	0.0270
Erythomycin	109	4 (3.7%)	21.1 (0.9-470)	0.0542
Quin. + ery.	96	2 (2.1%)	3.6 (0.2-88.1)	0.4278
Susceptible	2,508	9 (0.4%)		

* age underlying time scale, adjusted for comorbidity and sex

Salmonella Typhimurium: (1,346 patients, 1995-2000, 23% comorbidity)

	Number of patients			
	Total	Invasive/death	Hazard ratio*	P
Quinolone res.	102	9 (8.7%)	5.2 (1.9-14.3)	0.0013
Pansusceptible	1,243	55 (4.4%)		

* 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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