International Symposium

"Towards a Risk Analysis of Antibiotic Resistance"

Session 1

Hazard Identification

Conclusions of Working Group 1

Hazard Identification

Hazard: a biological, chemical or physical agents that may have an adverse effect on the health of humans/animals

→ antimicrobial agents used in food animals

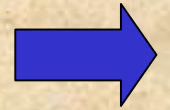
Risk: the probability of an agent (hazard) to cause an adverse effect and the magnitude of this effect

Hazard identification: identification of known or potential adverse effects on health associated with a particular hazard (antimicrobial agents used in food animals)

Hazard Identification

Adverse effects on human health arising from the use of antimicrobial agents in food-producing animals:

1. antimicrobial resistance disseminates in bacteria of animal origin,
2. resistant bacteria from animals infect humans indirectly and/or directly,
3. resistant bacteria from animals transfer their resistance genes to bacteria of medical importance,
4. propagation of resistant strains in food animals and humans



failure of treatment for serious infections in humans

Dissemination of resistant bacteria in animals

Factors favouring the selection and dissemination of resistant bacteria in animals
following the application of antimicrobials to animals:

subtherapeutic dosing

mass medication

long-term treatment

broad-spectrum antibiotics / combinations vs. narrow-spectrum antibiotics

prophylactic/metaphylactic application without proper microbiological diagnostics (incl. antibiogram)

Dissemination of resistant bacteria in animals

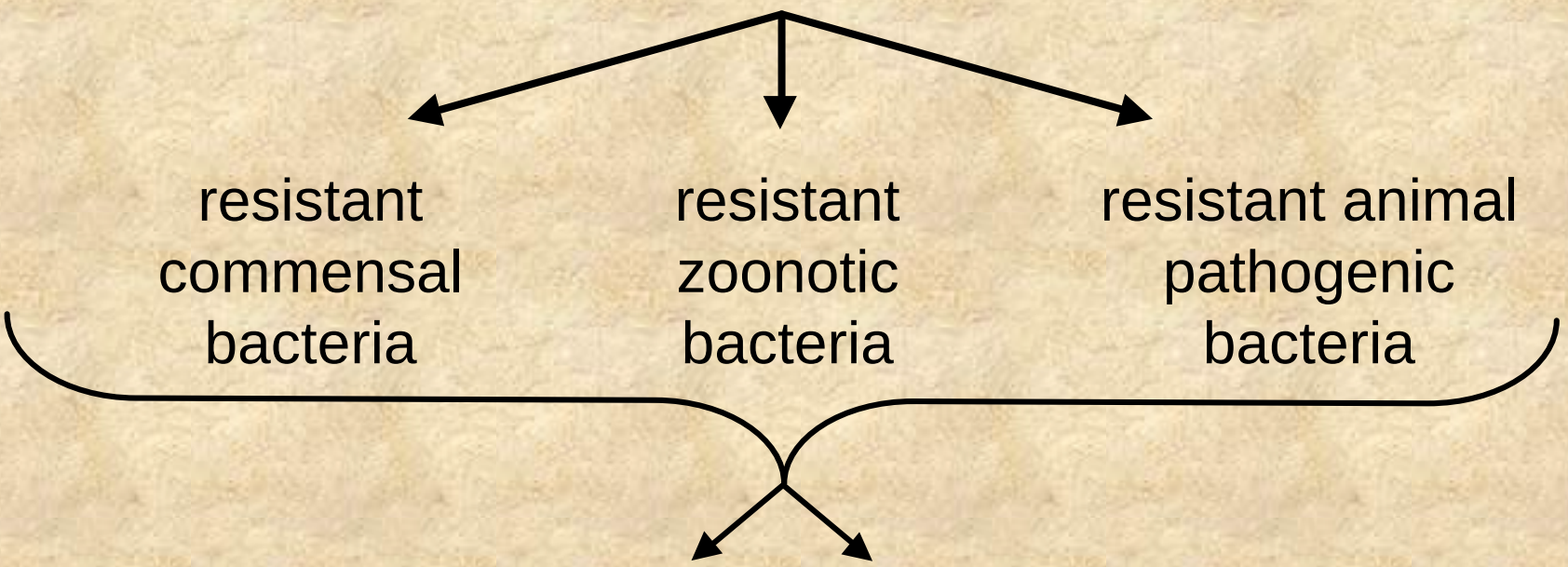
Food-producing animals receive antimicrobial agents for therapeutic, metaphylactic and prophylactic purposes, and to a lesser extend for growth promotion

Exposure to antimicrobial agents kills susceptible bacteria and allows to resistant bacteria to multiply at the expense of the susceptible ones

Enrichment of resistant bacteria by selection

Dissemination of resistant bacteria in animals

Enrichment of resistant bacteria by selection



Spread of resistant bacteria between individual animals of the same herd

Horizontal transfer of resistance genes between bacteria of the same animal

Spread of resistant bacteria from food-producing animals to humans

indirectly via food of animal origin

(e.g. carcasses contaminated during slaughter or contamination during food processing)

or

directly by contact with food-producing animals or their excretions

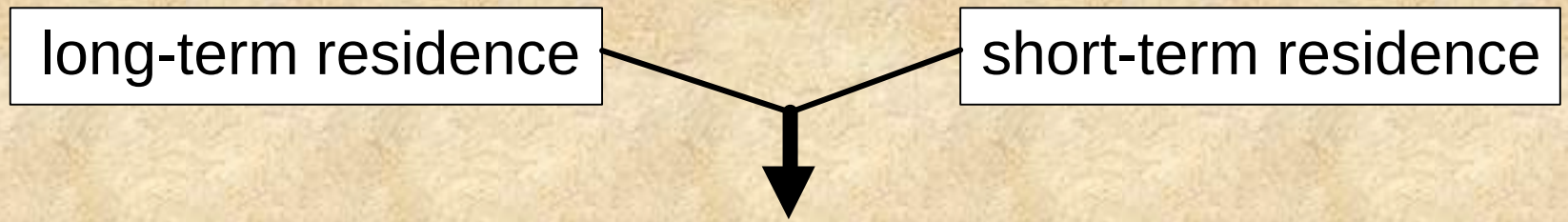
(e.g. farmers, veterinarians, abattoir workers)

Spread of resistant bacteria from food-producing animals to humans

The fate of the resistant animal bacteria in the human host depends on various bacterial and host factors

long-term residence	short-term residence
colonization ↓ initiation of an infection (pathogens)	passage through the human gut transient carriage on the skin or on mucosal surfaces

Spread of resistant bacteria from food-producing animals to humans



horizontal transfer of resistance genes from animal bacteria to:

human commensal bacteria

and/or

human pathogenic bacteria

presence of resistance genes from bacteria of animal origin in bacteria of humans

Clinical disease in humans

humans carrying resistant bacteria

(either resistant bacteria of animal origin or bacteria of human origin harbouring resistance genes obtained from bacteria of animal origin)

develop clinical diseases from these bacteria

treatment with antimicrobial agents to which the causative bacterium is resistant causes adverse effects:

prolonged / more severe illness

treatment failure

death

Key questions

1. Does the use of antimicrobial agents in animals contribute to the dissemination of resistant bacteria ?
2. Do these resistant strains spread from animals to humans ?
3. Do the resistance determinants in these bacteria transfer to human pathogenic strains ?
4. Do resistant bacterial strains from animals cause clinical diseases in humans ?

Different situations with regard to the antimicrobial agents applied, the resistance genes/mutations selected and the bacteria involved.

Does the use of antimicrobial agents in animals contribute to the dissemination of resistant bacteria ?

Salmonella:	fluoroquinolone resistance (*gyr*, *par, grl* mutations) apramycin/gentamicin resistance (*aac(3')-IV*) multidrug resistance (DT104, 204c, etc.)
Campylobacter:	fluoroquinolone resistance (*gyr*, *par* mutations) macrolide resistance (23S rDNA mutations)
E. coli:	fluoroquinolone resistance (*gyr*, *par, grl* mutations) apramycin/gentamicin resistance (*aac(3')-IV*) streptothricin resistance (*sat1, sat2*)
Enterococci:	glycopeptide resistance (*vanA* gene cluster) macrolide resistance (*ermB*) streptogramin resistance (*vat*(D), *vat*(E))

Do resistant strains from animals spread to humans ?

Salmonella:	yes	fluoroquinolone resistance
	yes	apramycin/gentamicin resistance
	yes	multidrug resistance
Campylobacter:	yes	fluoroquinolone resistance
	?	macrolide resistance
E. coli:	?	fluoroquinolone resistance
	yes	apramycin/gentamicin resistance
	yes	streptothricin resistance
Enterococci:	yes	glycopeptide resistance
	yes	macrolide resistance
	yes	streptogramin resistance

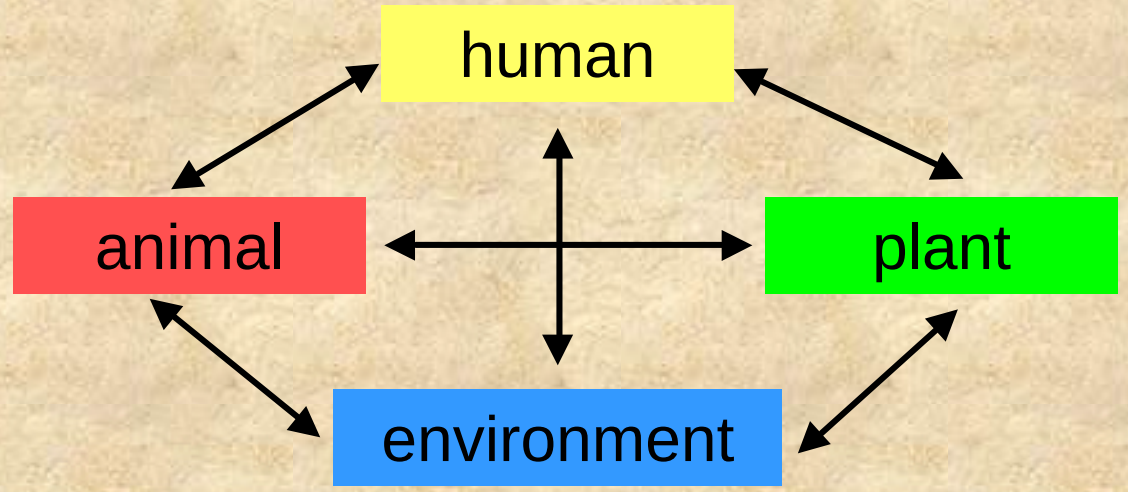
Do the resistance determinants of these strains transfer to other human pathogenic bacteria ?

Salmonella:	no	fluoroquinolone resistance
	yes	apramycin/gentamicin resistance
	yes	multidrug resistance
Campylobacter:	no	fluoroquinolone resistance
	no	macrolide resistance
E. coli:	no	fluoroquinolone resistance
	yes	apramycin/gentamicin resistance
	yes	streptothricin resistance
Enterococci:	yes	glycopeptide resistance
	yes	macrolide resistance
	yes	streptogramin resistance

Do the resistance determinants of these strains transfer to other human pathogenic bacteria ?

Problem: Occurrence of the same resistance genes in bacteria from animal and human origin

Many antimicrobial agents (tetracyclines, erythromycin, penicillins, chloramphenicol, gentamicin, streptomycin) have been used in human and veterinary medicine, horticulture and aquaculture since the 1950s.



Various transfer processes **in any direction** have taken place since then

Origin of resistance genes ?

Do the resistant strains of animal origin cause clinical diseases in humans ?

Both, resistant and susceptible strains of zoonotic bacteria, such as *Salmonella* or *Campylobacter* are well-documented in the literature as causes of infections in humans.

Human infections due to bacterial genera/species carrying resistance genes of presumable animal origin have also been reported.

- *vanA*-carrying *E. faecium*
- uropathogenic *E. coli* carrying *sat* or *aac(3')-IV* genes

Treatment implications of resistant strains causing clinical diseases in humans ?

Salmonella : Nontyphoidal *Salmonella* infections usually do not require antibiotic treatment - treatment failures (e.g. fluoroquinolones) have been documented in single cases

Campylobacter : antibiotic treatment only for prolonged and severe cases of gastroenteritis or for invasive diseases; macrolides (1st choice), fluoroquinolones (2nd choice)

Enterococci : infections occur mainly in patients with compromised host defence / invasive surgery treatment failures have been documented occasionally when multiresistant strains were involved

Further aspects

1. Importation of resistant strains / resistance genes (free trade - open markets - global control)
2. Other (co-)selective pressures (biocides, disinfectants, heavy metals, etc.)
3. Residues - possible selective pressure
4. Hazard identification for single species (*Salmonella enterica*, *Campylobacter jejuni*) - or general approaches for e.g. zoonotic bacteria
5. Slow reversibility of resistant strains to susceptibility

Most important factor in “Hazard Identification”:

Transfer of resistant strains from food animals to humans