Veterinary drug residues:
implications for international food trade

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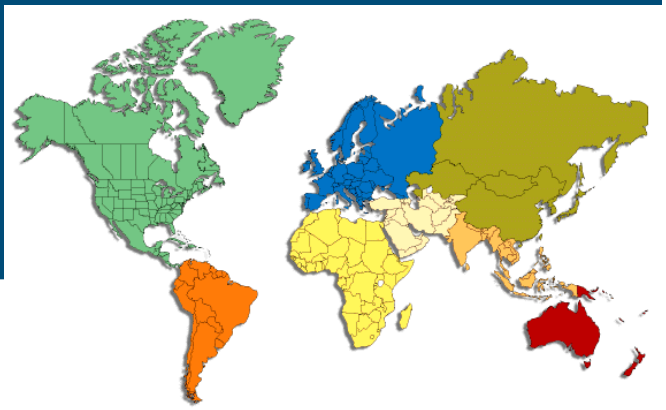
Veterinary drug residues

Consumer protection

International trade

Animal welfare



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Outline

- Veterinary drug residues: the EU perspective
- Banned/unauthorized drugs
  - Hormonal substances for growth promotion
  - Chloramphenicol & nitrofurans
- “MRL” drugs
  - Antibiotic resistance

Veterinary drug residues

- The EU has adopted detailed legislation on use of and monitoring for veterinary drugs
  - Council regulation 2377/90
    - Each pharmacologically active substance must have a Maximum Residue Limit (MRL)-status before it can be registered for use in a food producing species
    - Annexes of CR 2377/90
      - Annex I - final MRLs
      - Annex II - no MRLs needed
      - Annex III - provisional MRLs
      - Annex IV - forbidden substances
    - Safety evaluation > ADI > MRL > withdrawal times

Veterinary drug residues

- EU legislation on use of and monitoring for veterinary drugs (cont'd)
  - Council directive 96/23/EC
    - "On measures to monitor certain substances and residues thereof in live animals and animal products" > National monitoring programs
    - Establishment of a network of community and national reference laboratories
  - Commission decision 2002/657/EC
    - Method performance criteria
    - Introduction of Minimum Required Performance Limits (MRPL)

Import requirements

- Detailed EU legislation on imports of live animals and products of animal origin from third countries
  - With respect to residues:
    - Effective legislation (authorisation, distribution, administration, inspection)
    - Laboratory facilities
    - Monitoring program established
- Basically:

  compliance with EU regulations and standards

Banned veterinary drugs

- Categories defined in 96/23/EC
  - A1-A5: substances having anabolic effects
  - A6: unauthorized substances
  - B1: antibacterials
  - B2: other veterinary medicinal products
  - B3: other substances & environmental contaminants

Banned veterinary drugs - hormones

- (81/602/EC) 88/146/EC EU (96/22/EC)

  prohibit use of substances having a hormonal action for growth promotion in farm animals
- US: import measures on EU export from 1989-1996
- 1996-1997: dispute settlement (WTO)
  - Initially: non-conformity with SPS agreement
  - Appeal: measures should be based on assessment
  - But:

Banned veterinary drugs - hormones

- A WTO member has the right to choose level of appropriate health protection
- Not obliged to assess risk only in quantitative manner to be able to take protective measures
- Not obliged to follow majority and mainstream scientific views

⇨ Precautionary principle

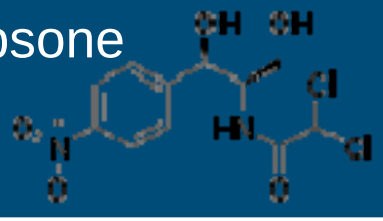
Banned veterinary drugs - hormones

- EU carried out complementary risk assessment
  - No conclusive evidence
  - Conflict of opinion remains
  - Protectionism or consumer concerns?

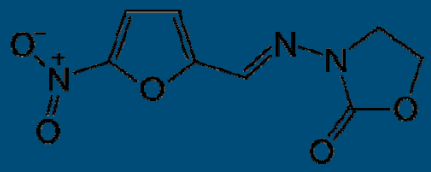
Banned veterinary drugs

- 96/23/EC category A6: unauthorized or banned substances

- *Aristolochia*
- Chloramphenicol
- Chlorpromazine
- Colchicine
- Dapsone



- Dimetronidazole
- Furazolidone
- Metronidazole
- Nitrofurans
- Ronidazole



Crisis 2002-2003

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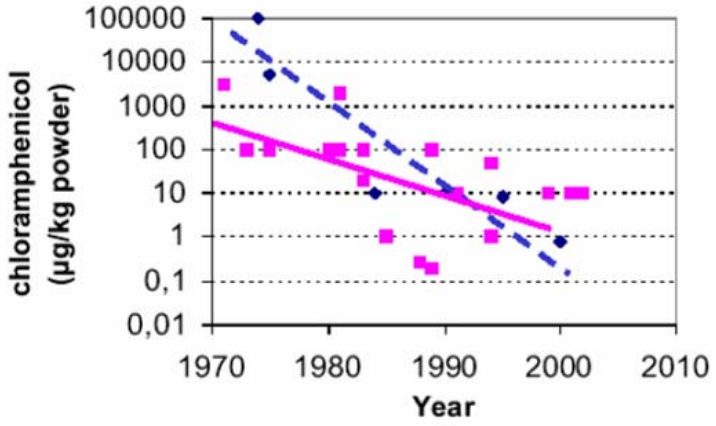
Improved detection methods

- Detection levels have become extremely low
- Nitrofurans: detection of the metabolites
  - Availability in developing countries limited
    - Knowledge
    - Equipment
    - Trained personnel



Hanekamp & Wijnands, 2004

Nitrofuran and chloramphenicol crisis

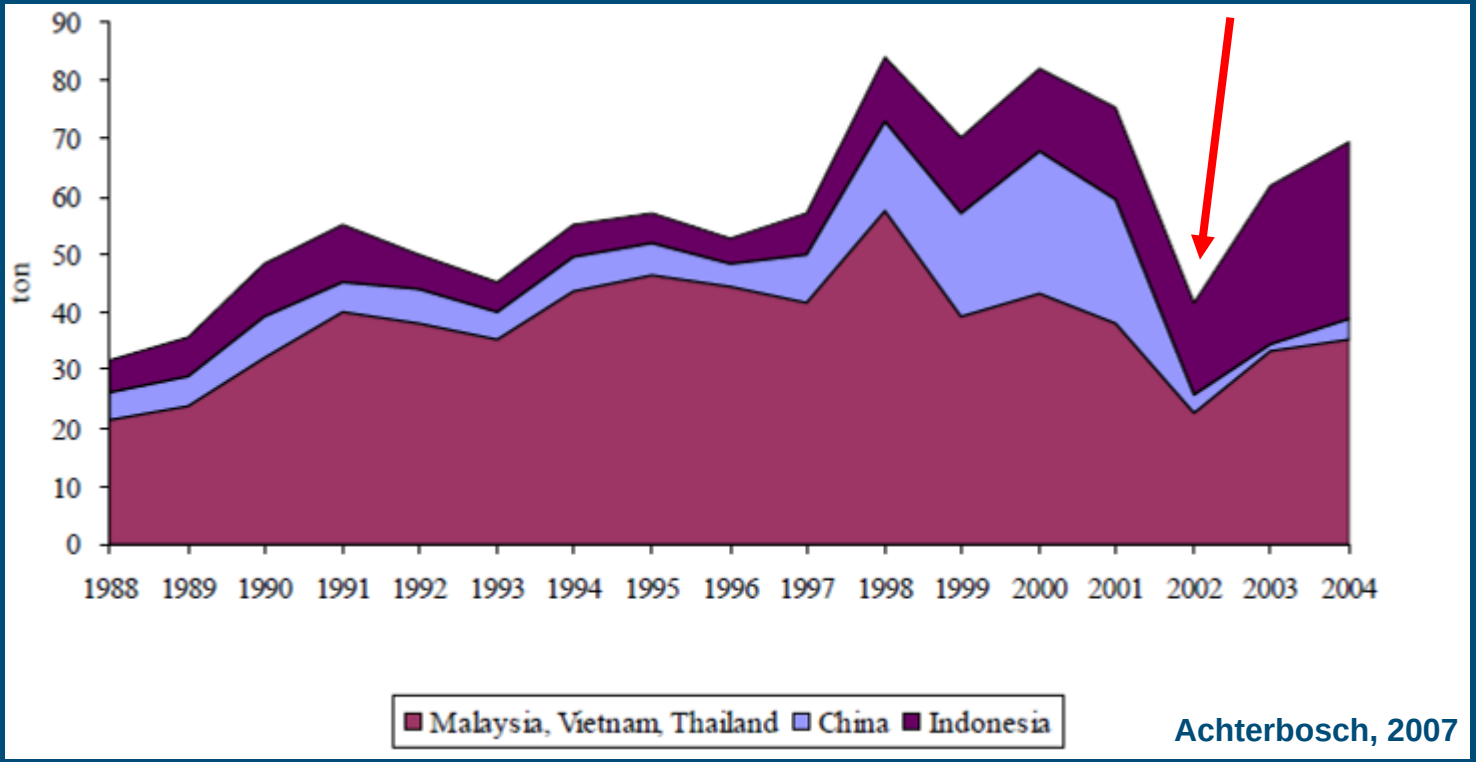
- NF residues in poultry and aquaculture products imported to EU from Thailand, China, Taiwan, India, Vietnam, Ecuador and Brazil
- Poultry and pork produced in Portugal, Italy, Greece, Romania and Bulgaria
- CAP in milkpowders (baltic states), shrimp (Asia) casings (China)

Nitrofuran and chloramphenicol crisis

- EU took restrictive measures
  - 2002: ban on import from China (lifted Aug'04)
  - Sept '02-march '03 complete control of all imports from several countries
- Countries involved were forced to improve legislation/registration of drugs, tracing, residue control etc.

Nitrofuran and chloramphenicol crisis

Import of shrimp into EU



Achterbosch, 2007

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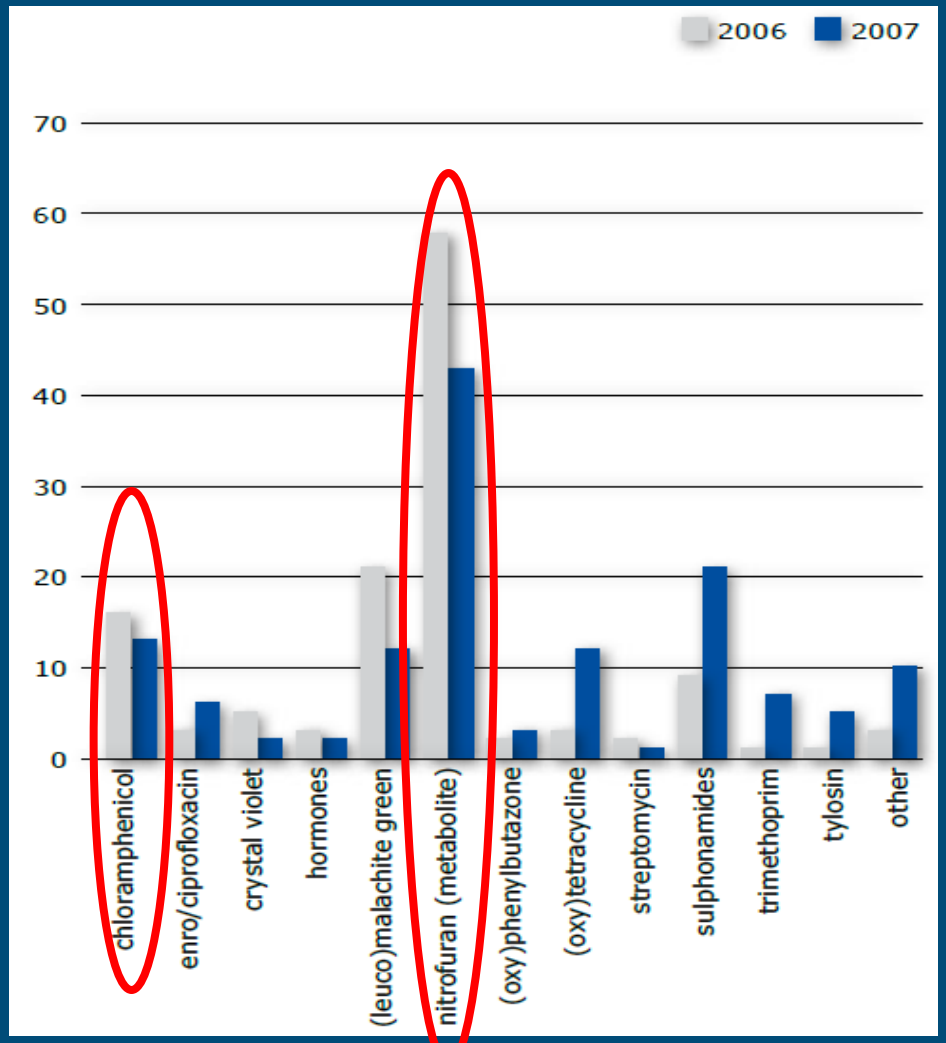
Rapid Alert System for Food and Feed



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“MRL”-drugs

- Council regulation 2377/90
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Determining the Acceptable Daily Intake (ADI)

- Adverse systemic effects
- Reproduction and developmental effects
- Mutagenic effects
- Carcinogenic effects
- Effects on human intestinal flora
- Immunologic effects
- Pharmacological properties
- Endocrine effects

Theoretical Maximum Daily Intake

- The TMDI is the sum of residues present in a standard food basket (daily consumption of) :
  - 300 g muscle
  - 100 g liver
  - 50 g fat
  - 50 g kidney
  - 1500 g milk
  - 100 g eggs
  - 20 g honey

TMDI

ADI

MRL needed!

Determining an MRL

- Chemical identity and properties
- Uses and recommended doses in food animals
- Pharmacokinetic, metabolism and pharmacodynamic data
- Total residue (radiolabel) studies
- Residue depletion studies in food animals
- Available routine method of analysis including method performance

“MRL”-drugs

- Safety and residue studies to be provided by the applicant
- → In practice these studies are only performed on major food producing species
  - Major problem for minor species
  - Very limited number of drugs (or none at all) available for treating e.g. laying hens, fish, bees
  - Off-label use
  - Dilemma with regard to tolerance levels

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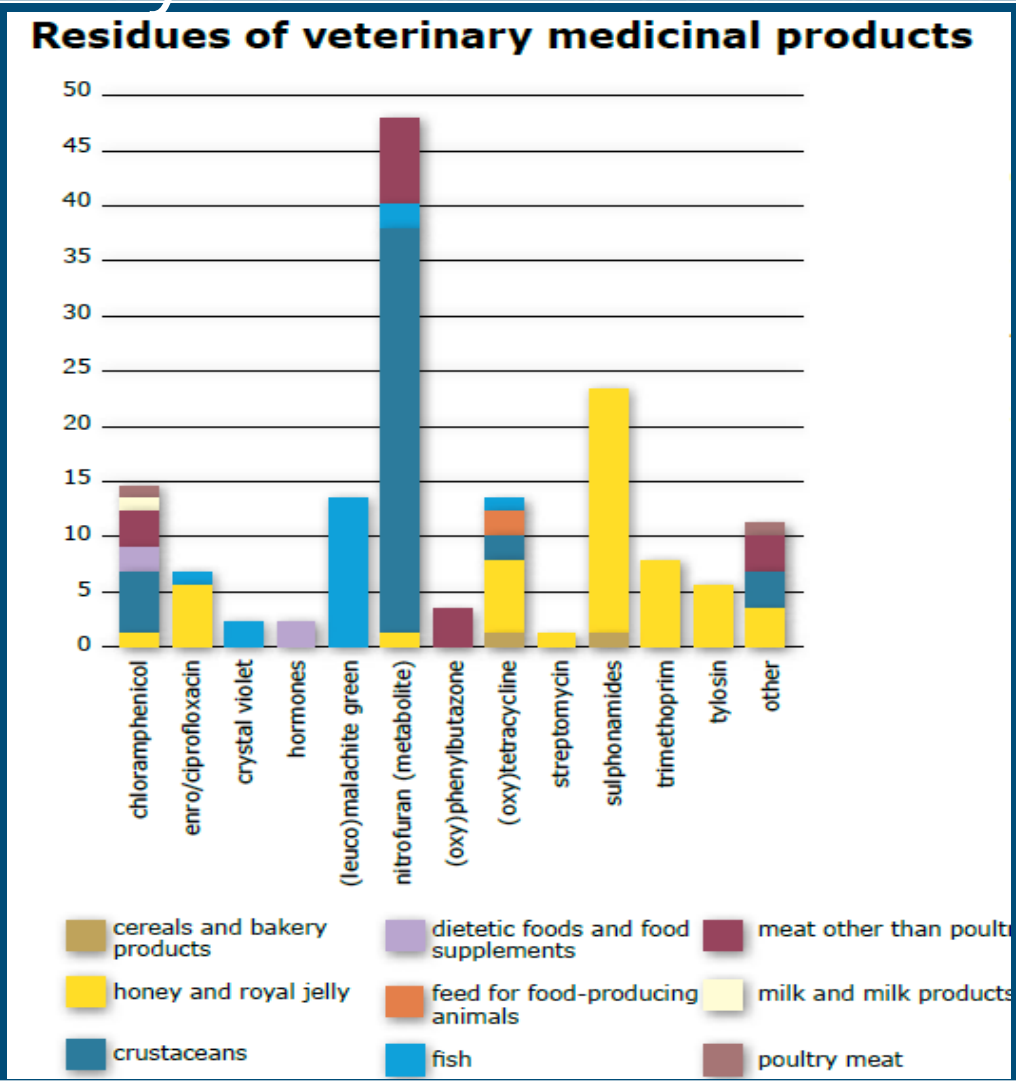

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Rapid Alert System for Food and Feed

- Number of MRL violations very limited
  - EU monitoring programs indicate ~ 0.05 – 0.1 % non-compliant
  - Import control on approved drugs is limited

MRLs differ throughout the world !

Accepted Residue Limits

Tetracycline standards in beef

EU, New Zealand	0.1 ppm
Japan	0.2 ppm
Australia, Canada	0.25 ppm
Codex	0.6 ppm
US	2.0 ppm

J. Int. Trade & Economic Development 12:4 377–402

Routledge
Taylor & Francis Group

Balancing food safety and risk: do drug residue limits affect international trade in beef?

John S. Wilson, Tsunehiro Otsuki and Baishali Majumdsar

The World Bank

Modelling trade flow effects of harmonizing standards

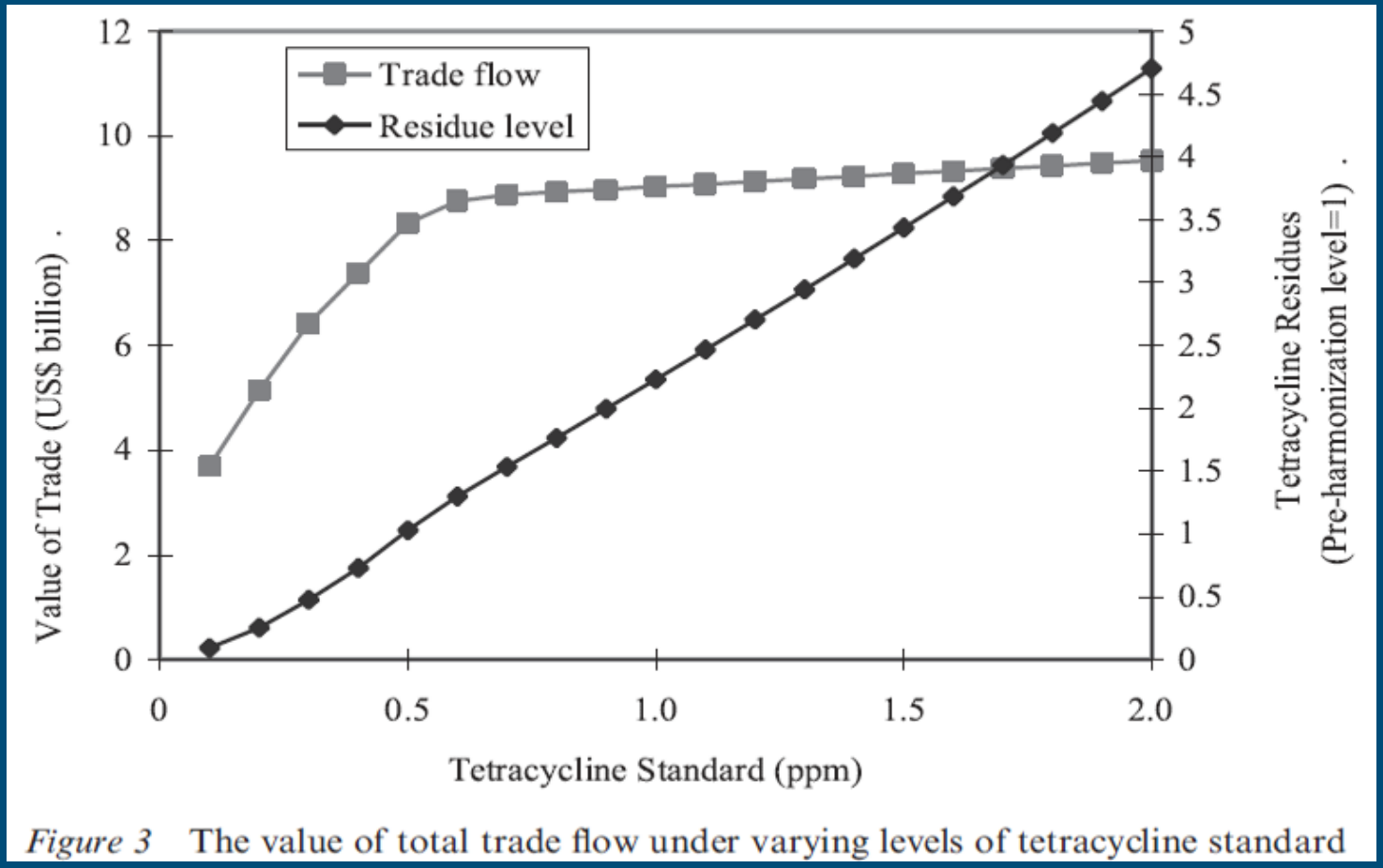

Figure 3 The value of total trade flow under varying levels of tetracycline standard

Wilson et al. J. Int. Trade & Economic Development 2003, 12:377

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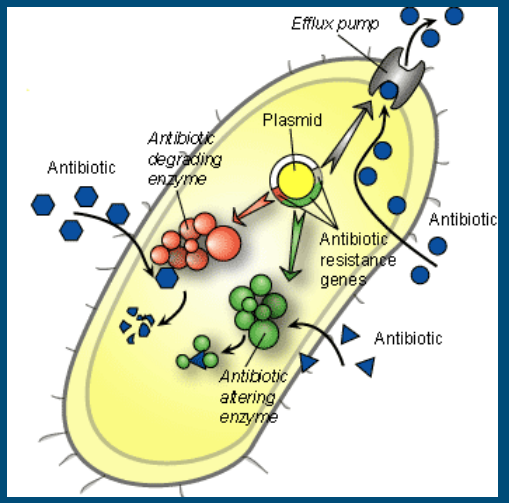
Problems associated with antibiotic (over-)use

- Technological
- Allergy
- Composition of the intestinal flora
- Resistance



- Unrestrained use
- Application as growth promoting substance

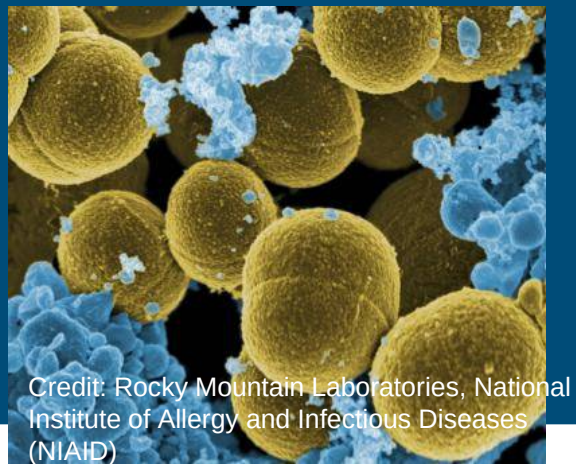
MRSA in the Netherlands

- Meticillin-resistant *Staphylococcus aureus* (MRSA) was found in:

  < 1% normal population

  23% of pig farmers

  40% pigs (80% herds)



Credit: Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases (NIAID)

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Export of pigs…..and more?

- From residue perspective samples are compliant, but…..
- Wulf et al (2008) Clin. Microbial. Infect. 14:29-34 MRSA prevalence in pig veterinarians
  - Highest % Italy, Germany and Netherlands
  - Countries with high trade volume

International trade and antibiotic resistance

- Significant problem?
  - Very low prevalence among danish vets….
- Depending on situation in “human area”
- Very limited monitoring
- Calls for prudent use

Thank you for your attention

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