

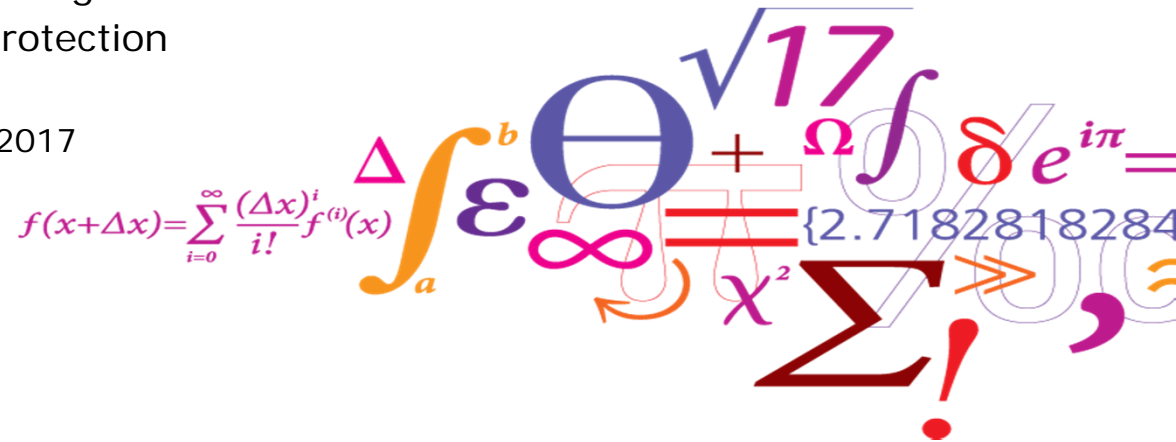
Antimicrobial resistance I: Situation and strategies in Europe

Joint International Symposium

Global Past, Present and Future Challenges in Risk Assessment
– Strengthening Consumer Health Protection

Berlin, November 30th – December 1st, 2017

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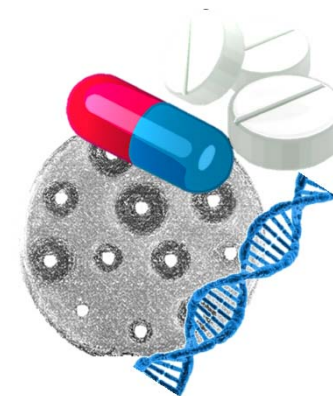
National Food Institute (DTU FOOD) Division for Genomic Epidemiology

Genomic Epidemiology

- 40 employees
- Aim: global surveillance of infectious diseases and AMR
- WHO Collaborating Centre and
EU Reference Laboratory for Antimicrobial Resistance in Foodborne Pathogens

Outline

- Antimicrobial resistance (AMR) in EU
- What is Europe doing about AMR?
- A snapshot of current projects on AMR at Div. Genomic Epidemiology
 - The EFFORT project
- Challenges in AMR risk assessment



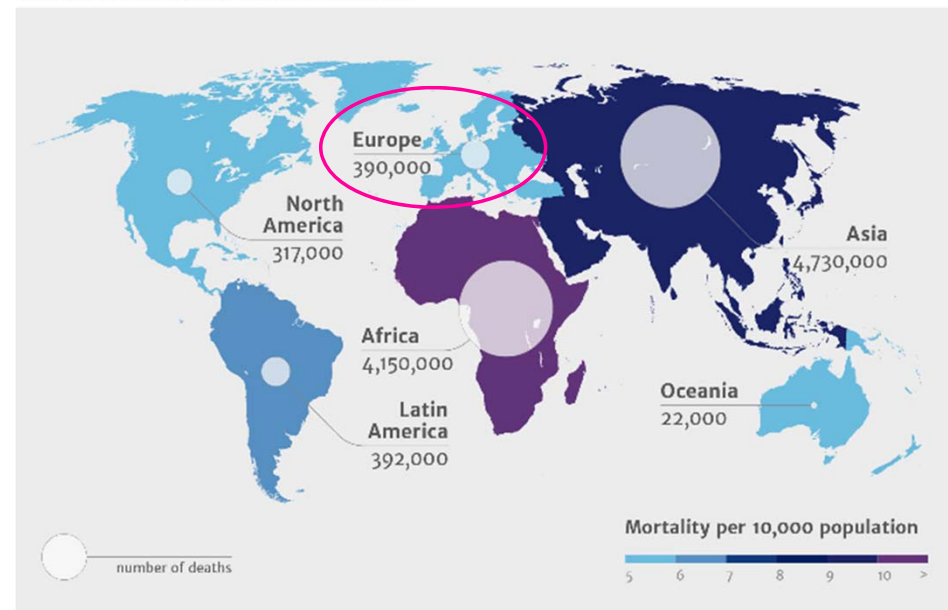
Antimicrobial Resistance in EU

Present:

- 25,000 deaths/year
- 2.5 million extra hospital days
- €1.5 billion/year in healthcare costs and productivity losses

Future:

Deaths attributable to AMR in 2050***



* Source: [The Bacterial Challenge Time to React \(ECDC\)](#) Figures from 2009, underestimated as take into account 5 multidrug resistant bacteria and 4 types of infections. Figures to be updated in 2018.

** Source: World Health Organization [factsheet](#).

*** Source: [J. O'Neil, 2014. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations.](#)

Source: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/11/WC500238133.pdf

What is Europe doing about AMR?

European Commission:

- AMR research funding
- EU Guidelines for AM use
- One Health action plan

EFSA – EMA - ECDC

- Public awareness
- Surveillance



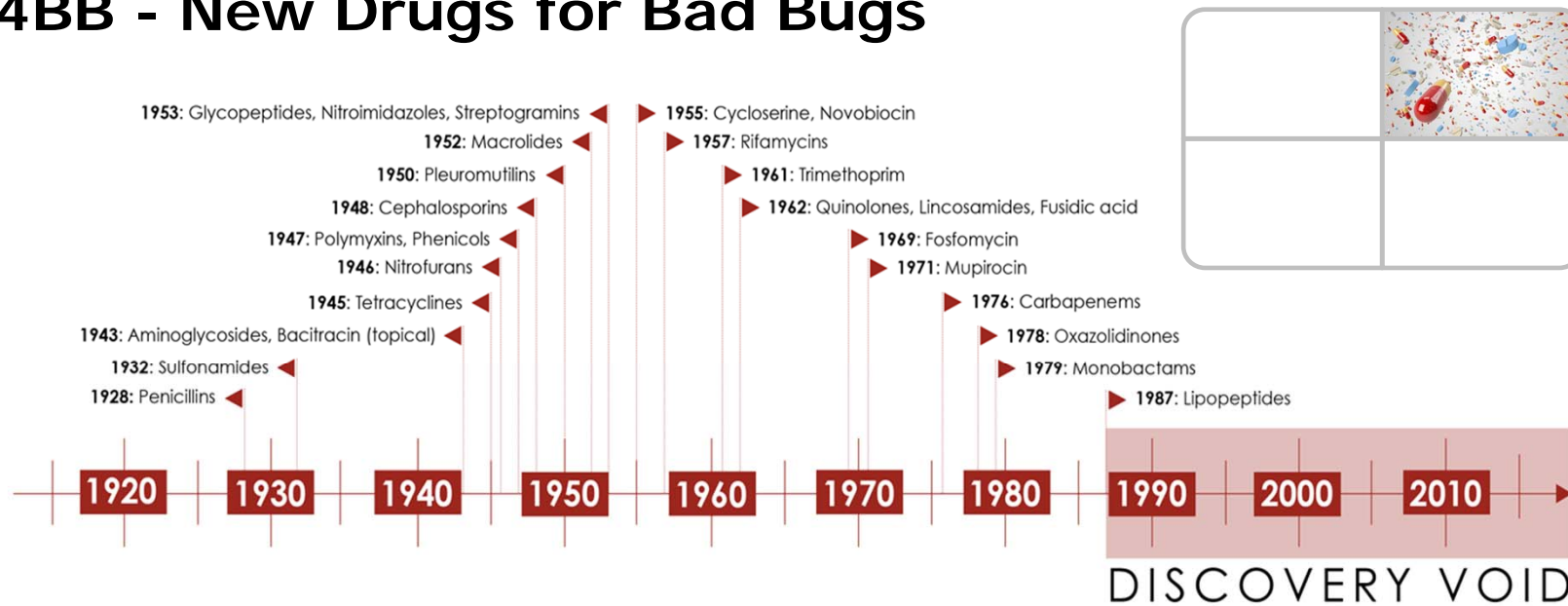
AMR Research - EC Funded projects (e.g. first hits for search on "resistance" in CORDIS)

Since 1999, the Commission has invested over €1.3 billion in AMR research

PROJECT	FUNDING	START	END
debugIT	FP7	2008	2011
BIOHYPO	FP7	2009	2012
PAR	FP7	2010	2013
RESISTOME	FP7	2010	2015
R-GNOSIS	FP7	2011	2017
EVOTAR	FP7	2011	2015
RESISTEVO	FP7	2012	2016
SPECRESEVO	FP7	2012	2014
TRAIN-ASAP	FP7	2012	2016
ARISE	FP7	2012	2018
RARE	FP7	2012	2016
COEVOCON	FP7	2013	2018
EFFORT	FP7	2013	2018
TAILORED-TREATMENT	FP7	2013	2017
RESISTANCE EVOLUTION	H2020	2015	2020
CARTNET	H2020	2018	2021



ND4BB - New Drugs for Bad Bugs



© ReAct Group 2015

It tackles scientific, regulatory, and **business challenges** that hamper the development of new antibiotics

Part of the ***Innovative Medicines Initiative***, funded jointly by the European Union and the European pharmaceutical industry

JPIAMR – Joint Programming Initiative on Antimicrobial Resistance

Joint Programming - European Member States agree on a common **Strategic Research Agenda**, to be implemented jointly



Year	Topic	Supported projects
2014	InnovaResistance	7 supported Projects/ 41 partners
2015	Repurposing Neglected Antibiotics	3 Projects/17 partners
2016	Transnational Working Groups Call	13 working Groups/ 160 partners 42 projects/WGs
2016	Transmission and Selection of Resistance in Humans, Animals, and the Environment (ERAnet Cofund)	19 Projects/96 partners

The European One Health Action Plan against Antimicrobial Resistance

Goals:

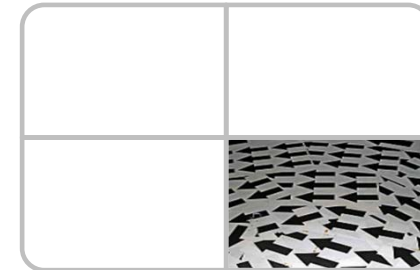
- Include the role of the **environment**
- Improved **data collection, monitoring** and **surveillance**
- Boost **research, development and innovation**
- Make the EU a **best practice region**
- Shape the **global agenda**



EU guidelines for AM use

EU Guidelines for the prudent use of antimicrobials in human health

to reduce inappropriate use and promote prudent use of antimicrobials in humans



EU Advice on the use of colistin products in animals

The larger abundance of the *mcr-1* gene in veterinary isolates and animal environments compared to human isolates, together with the much higher use of colistin in livestock compared to human medicine *suggest a **flow of resistance from animals to humans.***



EFSA – EMA – ECDC on AMR

Public awareness



15th November

The collage features several key public awareness materials:

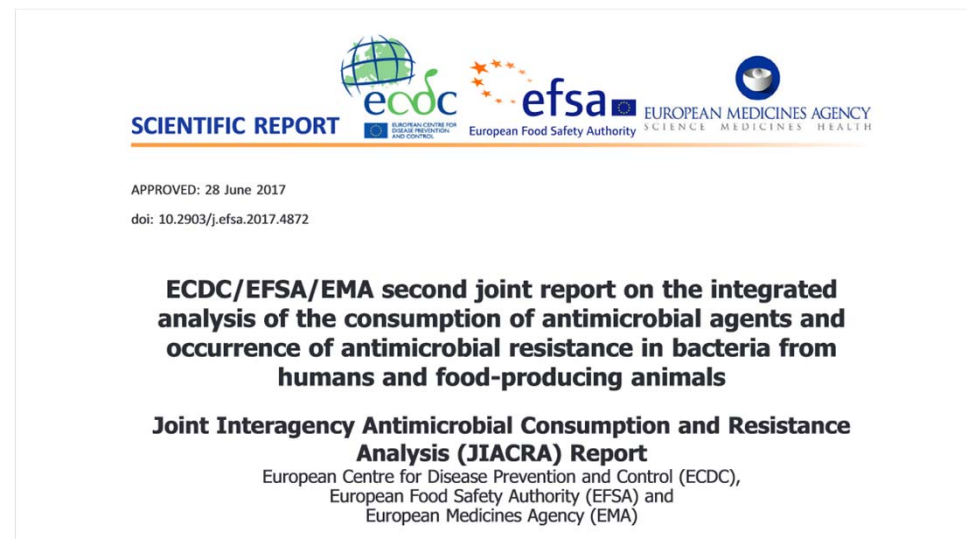
- EMA Website:** A screenshot of the European Medicines Agency website showing the 'Antimicrobial resistance' section. It includes a news release titled 'Combined resistance to multiple antibiotics: a growing problem in the EU' and a call to action for a live Twitter event on November 15th.
- EFSA Report:** A screenshot of an EFSA report titled 'EU report: more evidence on link between antibiotic use and antibiotic resistance'. It includes a video thumbnail and a circular infographic titled 'Antimicrobial resistance in Europe'.
- Infographic:** A circular infographic titled 'Visual guide: Working Together to Fight Antibiotic Resistance'. It shows a central 'Tetracycline' node connected to various antibiotic classes and regions like 'Northern Europe'.
- Information Session:** A flyer for an 'Information session on antimicrobial resistance' presented by EMA, featuring a circular diagram of antibiotic classes.
- EFSA Infographic:** A large infographic titled 'How can we reduce the use of antimicrobials in food-producing animals?' showing a farm scene and a circular diagram of antibiotic classes.

EFSA – EMA – ECDC on AMR

Surveillance

Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA)

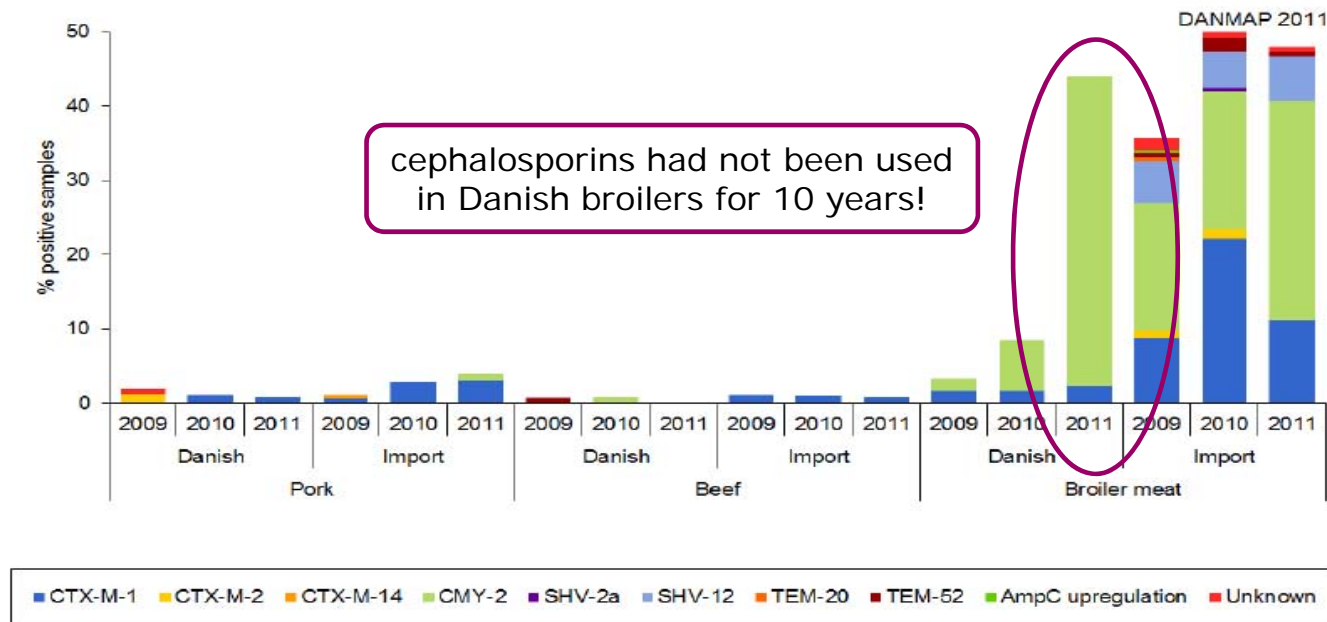
Joint report on consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals (2015, 2017)



Why is a pan-European approach necessary?

Example: The Danish broiler production

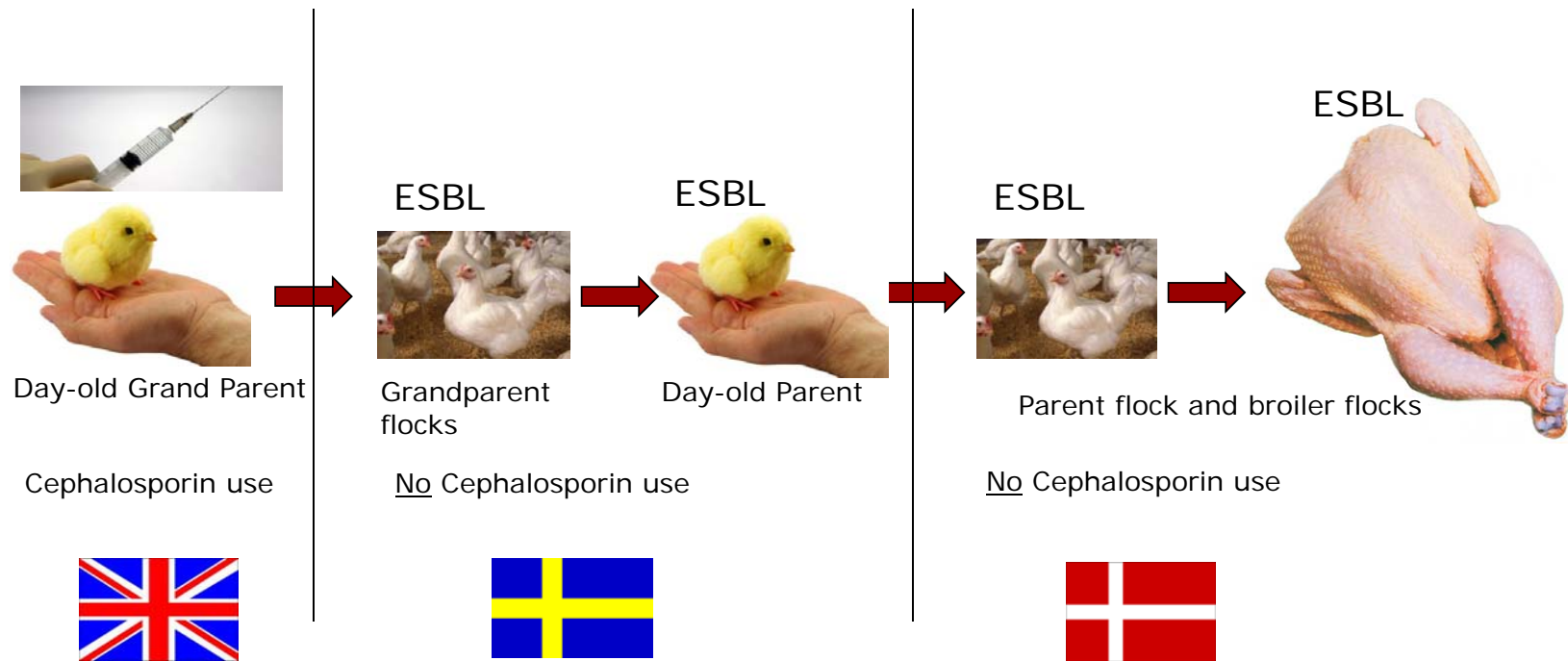
Figure 2. Occurrence (%) of ESBL-producing *Escherichia coli* and genes in meat^(a,b), Denmark



Source: DANMAP 2011

Why is a pan-European approach necessary?

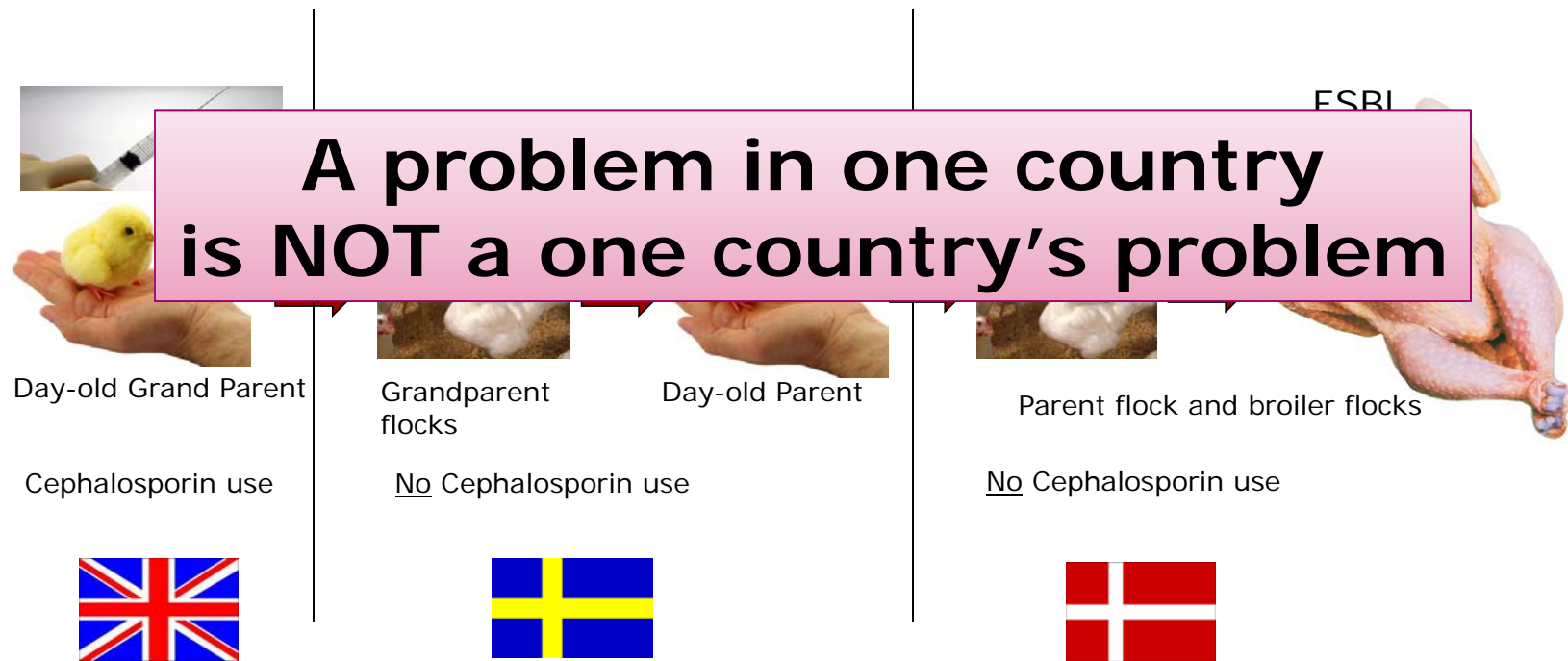
Example: The Danish broiler production



Source: Tine Hald

Why is a pan-European approach necessary?

Example: The Danish broiler production



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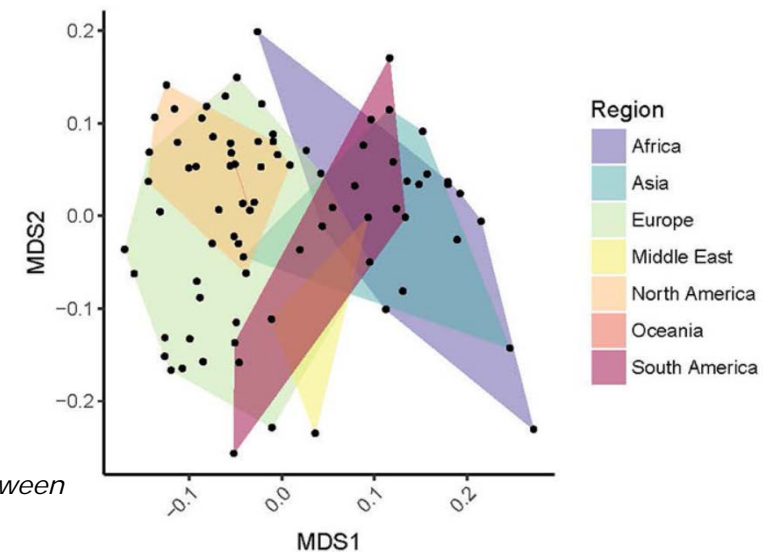
A snapshot of current projects on AMR at the Division of Genomic Epidemiology (DTU-FOOD)

1. Global Sewage Surveillance Project

A proof-of-concept for applying metagenomic analysis of sewage in the global surveillance and prediction of human infectious diseases and antimicrobial resistance



- **Human sewage** collected in major cities around the world
- **Metagenomic** sequencing and quantification of **AMR genes**
- Quantification of **AM residues**
- Associations between AMR and **global risk factors**



Global Sewage resistomes: dissimilarities between samples of different geographical regions

2. The EFFORT project – facts and objectives

- Ecology from **Farm to Fork** Of microbial drug **Resistance** and **Transmission**
- 5 years (Dec 2013- Nov 2018)
- EU FP7/2007-2013
- 10 countries, 20 institutions



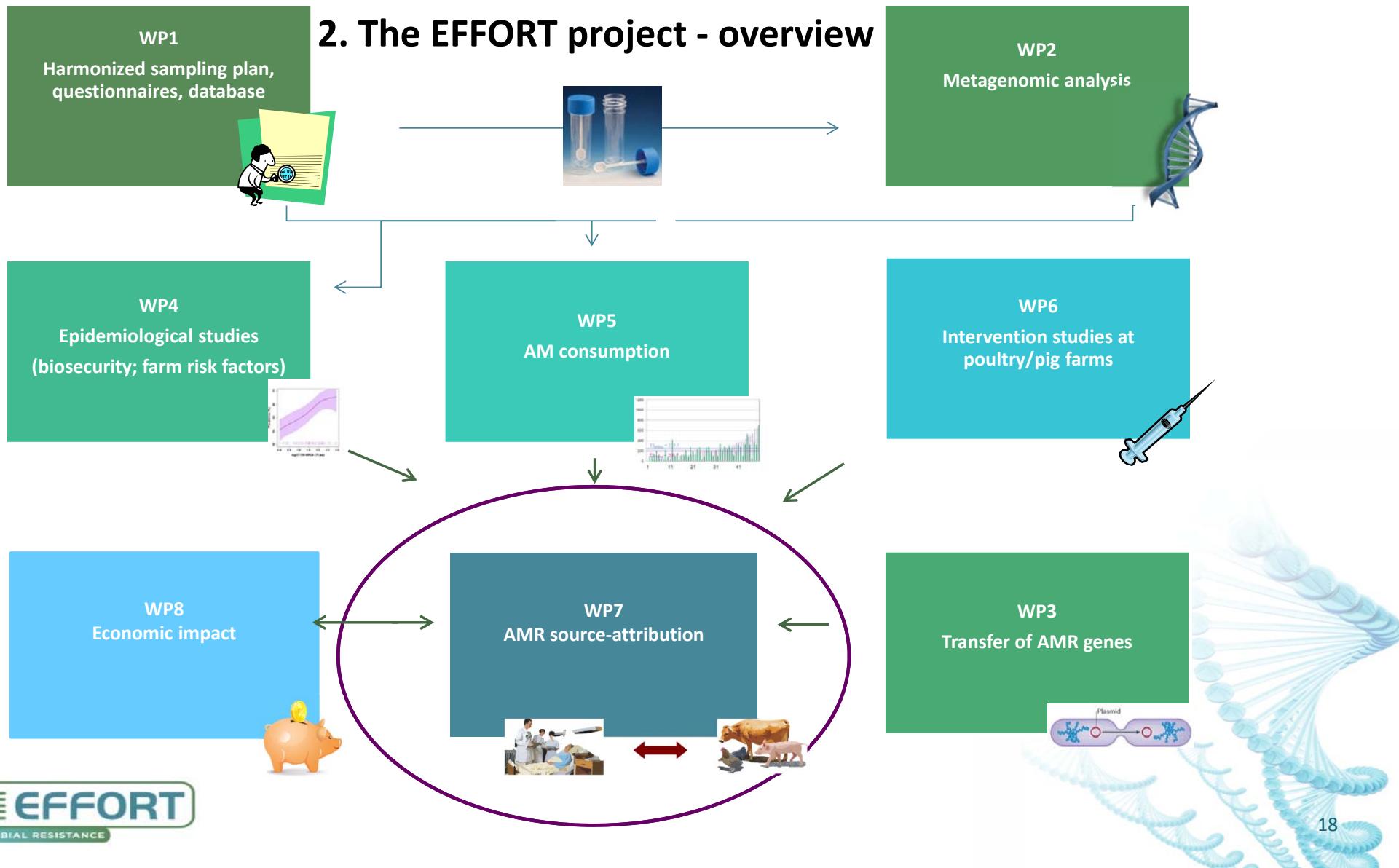
To understand:

- The epidemiology of AMR in the food chain
- The ecology of AMR in the microbial communities
- **The relative contribution of different exposure routes of AMR from animals to humans**
- The economic impact and animal welfare aspects of AMR in the food chain

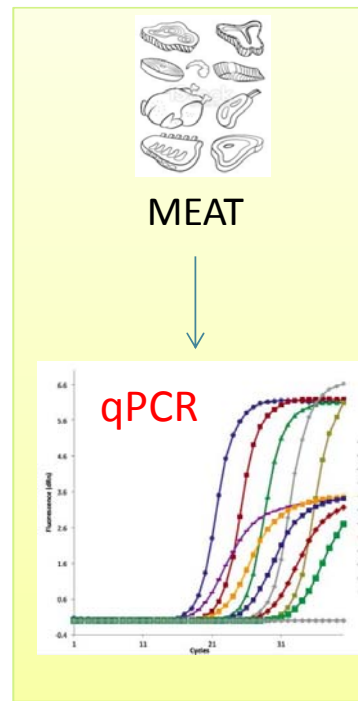
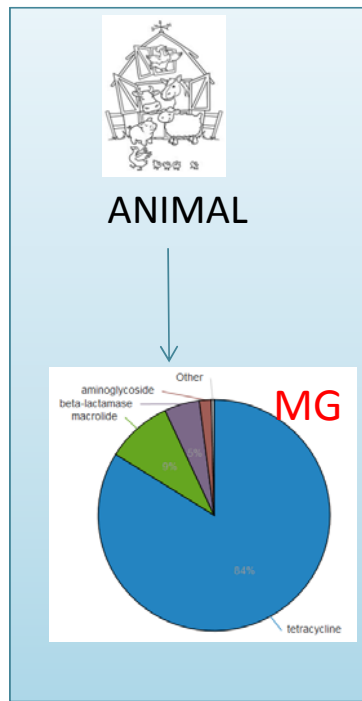


The research leading to these results has received funding from the European Community's Seventh Framework Programme [FP7/2007-2013] under grant agreement n° 613754.

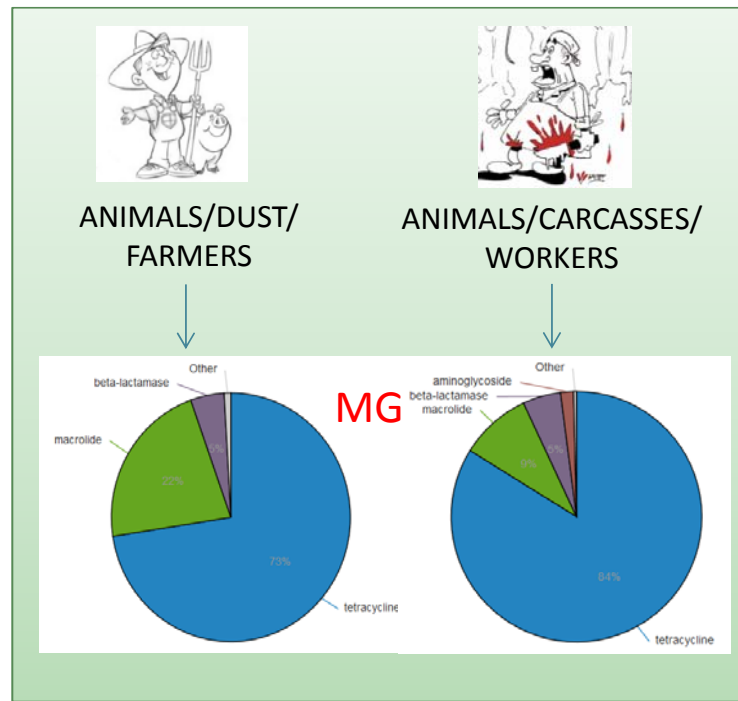
2. The EFFORT project - overview



2. The EFFORT project – AMR source-attribution



Task 7.1: Quantification of human exposure through food and animal transmission routes to AMR determinants in the overall population



Task 7.2 : Quantification of human exposure to AMR determinants for the occupational risk groups

2. The EFFORT project – AMR source-attribution Preliminary results

Comparative Exposure Assessment Framework

$$F_{sp} = C \times P \times Q \times Fr_{cc}$$

F_{sp} = exposure per person per day (whole population) (e.g. F_{po} =pork)

C = consumption of food product per person per day (C)

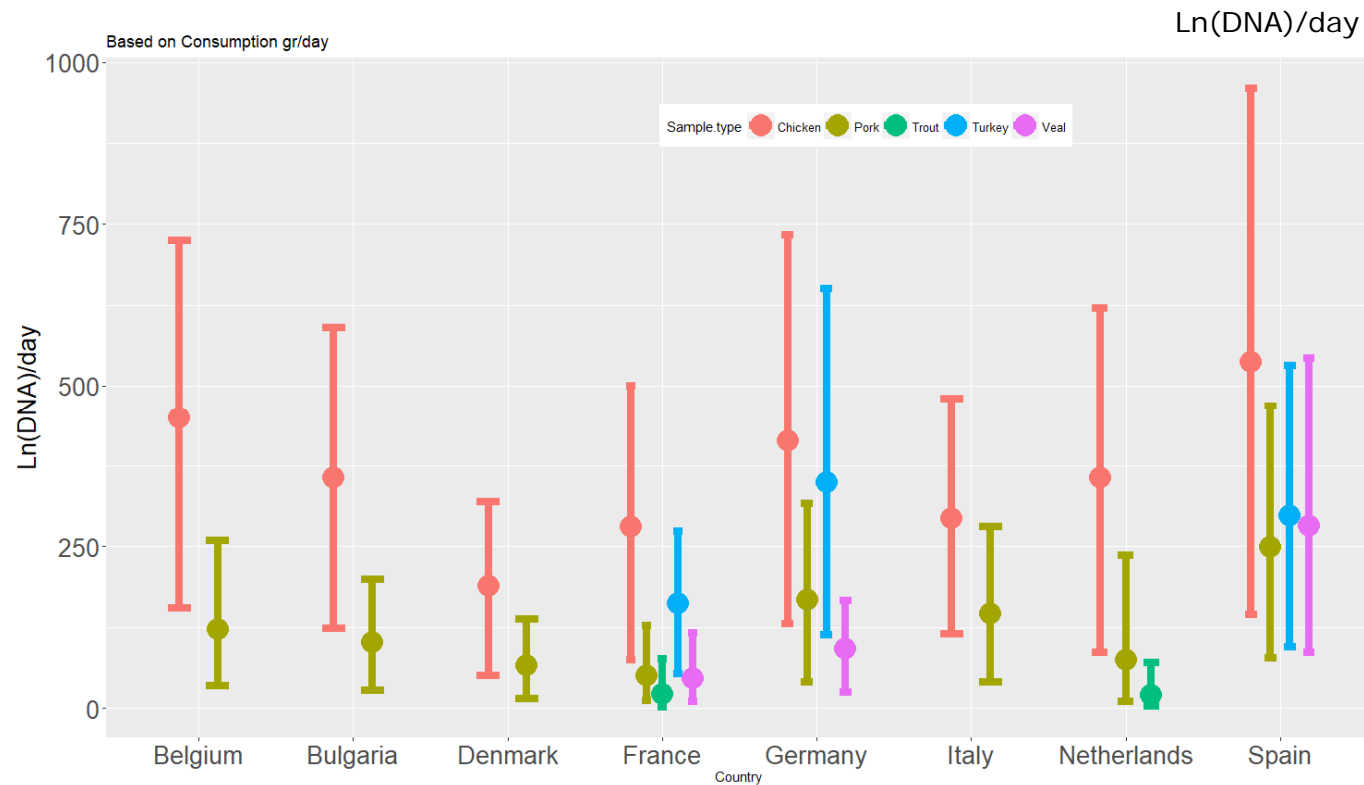
P = prevalence of products with AMR determinant at retail

Q = quantity of AMR determinant in contaminated products

Fr_{cc} = fraction of cross contamination (depends on transference rate from product to environment (Tr_{pe}) and transference rate from environment to product (Tr_{ep}))

2. The EFFORT project – AMR source-attribution Preliminary results

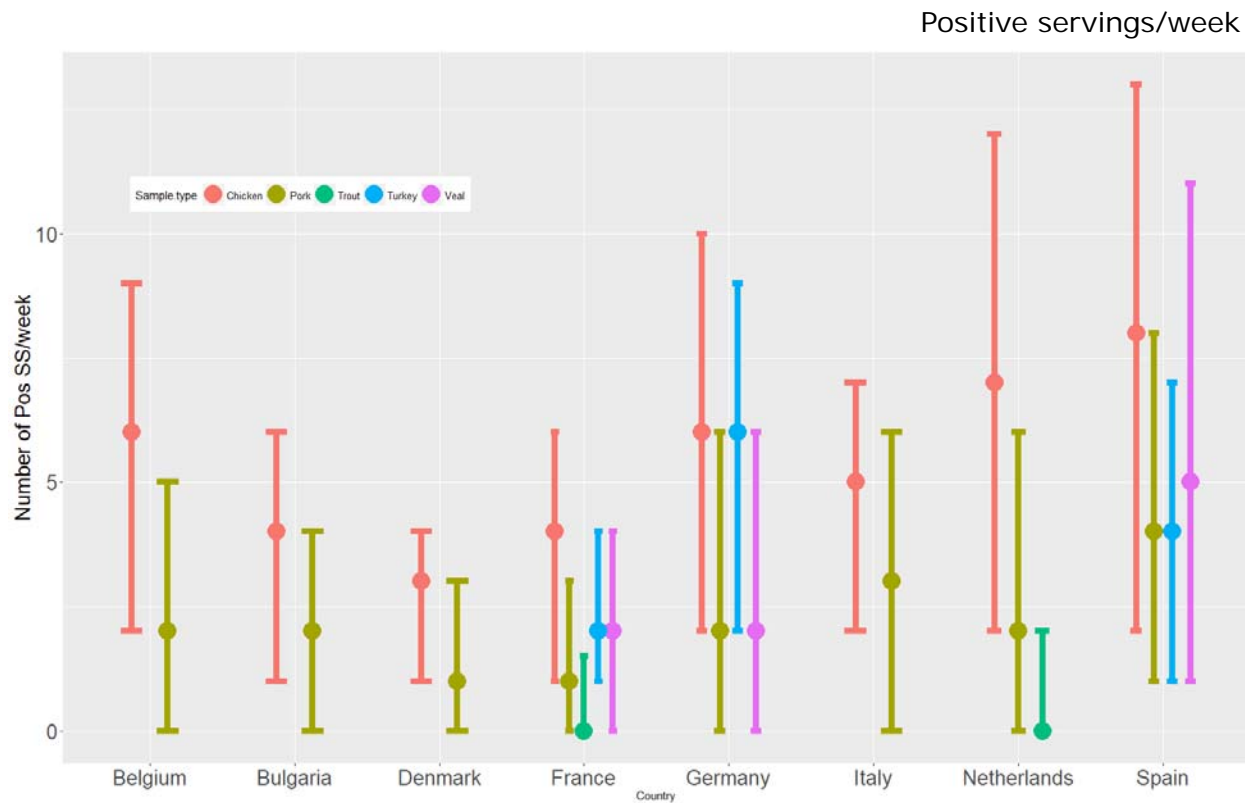
Comparative Exposure Assessment Framework



Source: Javier Sanchez, UPEI (guest researcher at SAFOSO)

2. The EFFORT project – AMR source-attribution Preliminary results

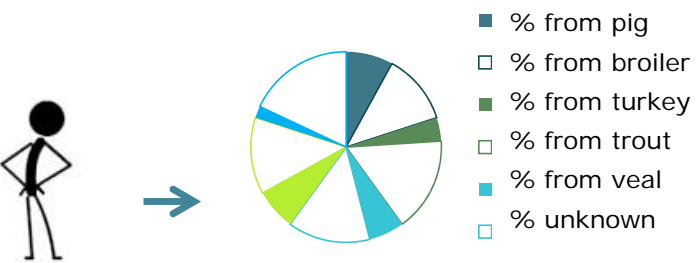
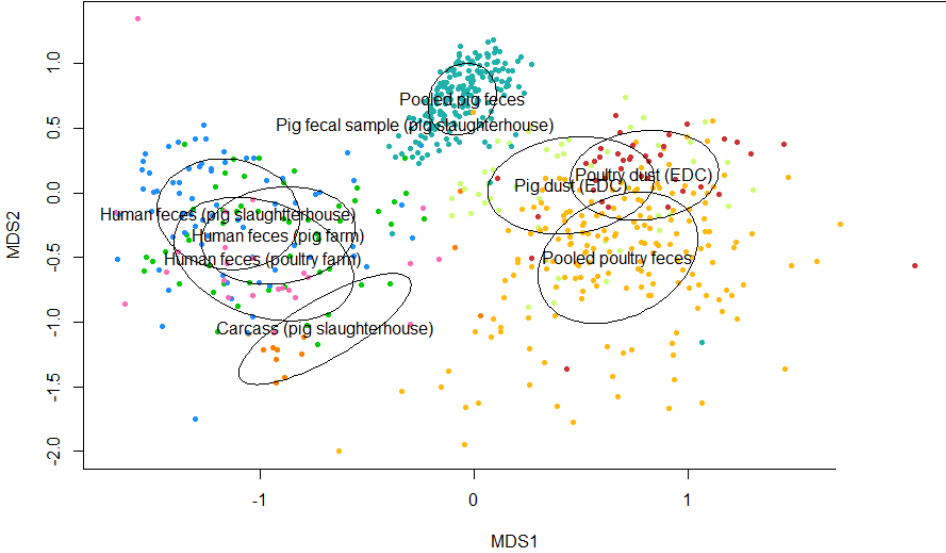
Comparative Exposure Assessment Framework



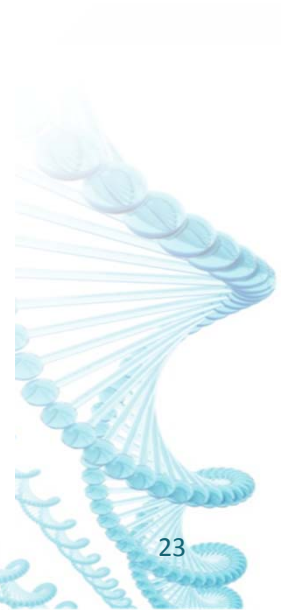
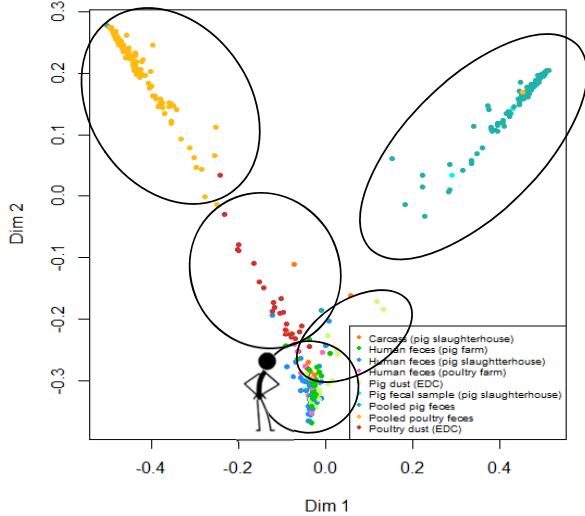
Source: Javier Sanchez, UPEI (guest researcher at SAFOSO)

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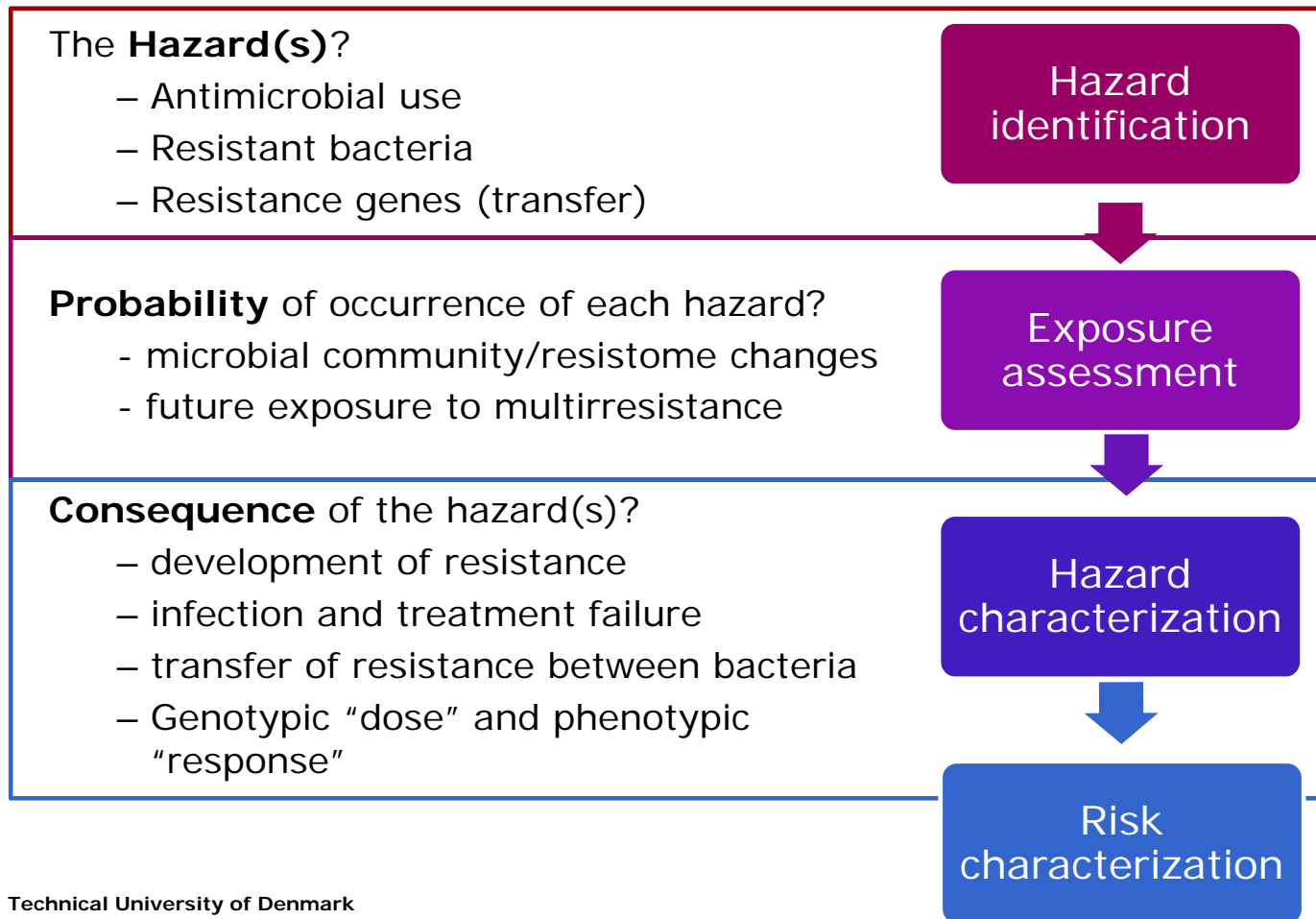
Ordination of all data by sample type



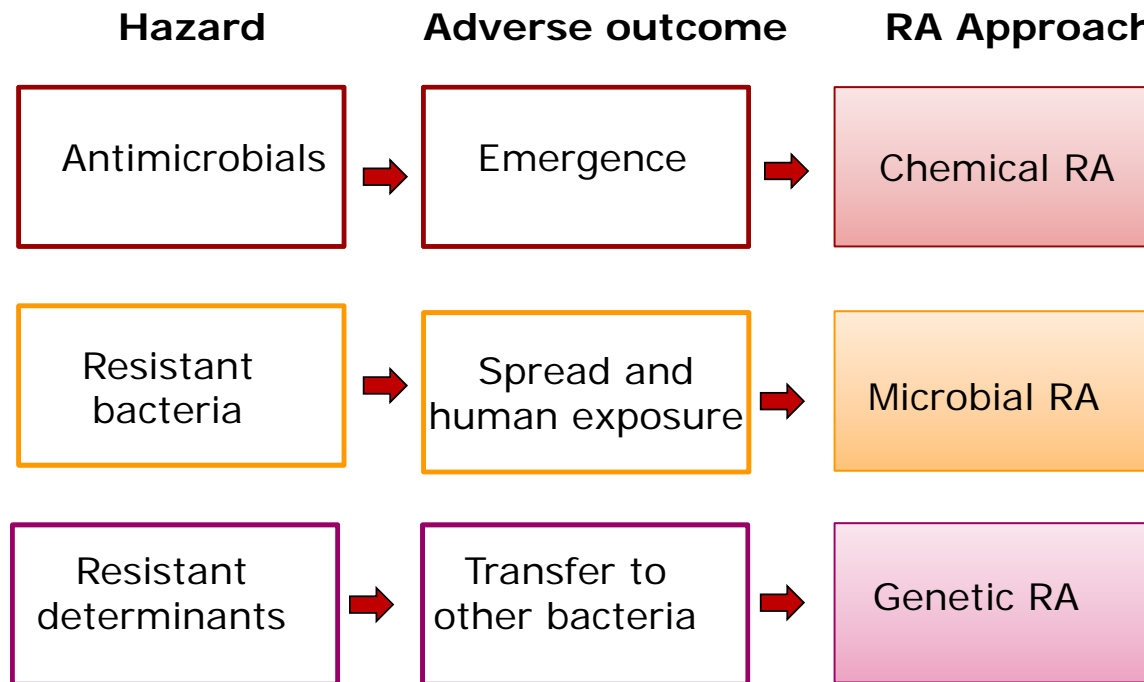
Random Forest classification model



Challenges in AMR risk assessment



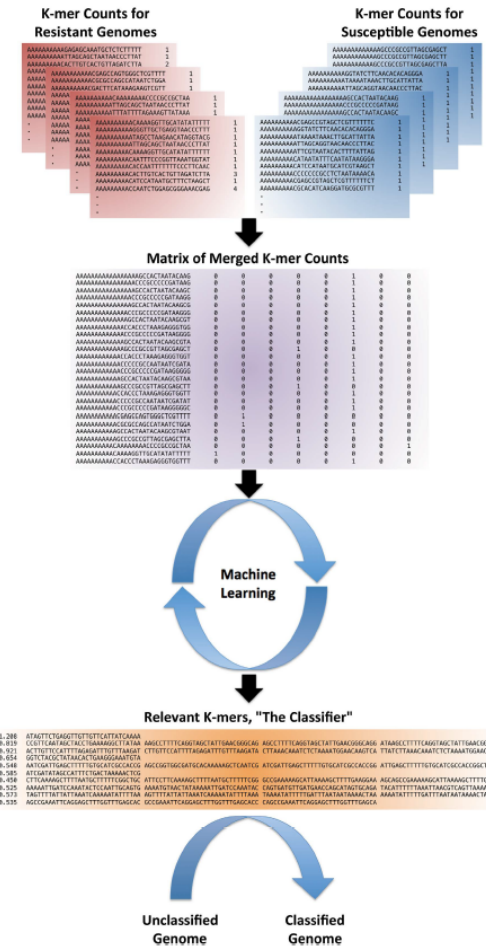
A possible framework for AMR risk assessment



Source: Salisbury et al., 2002. A risk analysis framework for the long-term management of antibiotic resistance in food-producing animals.

One step forward in AMR hazard characterization

- Predicting phenotypic resistance from WGS
- Susceptible vs resistant
- Whole genome considered
- Supervised machine learning

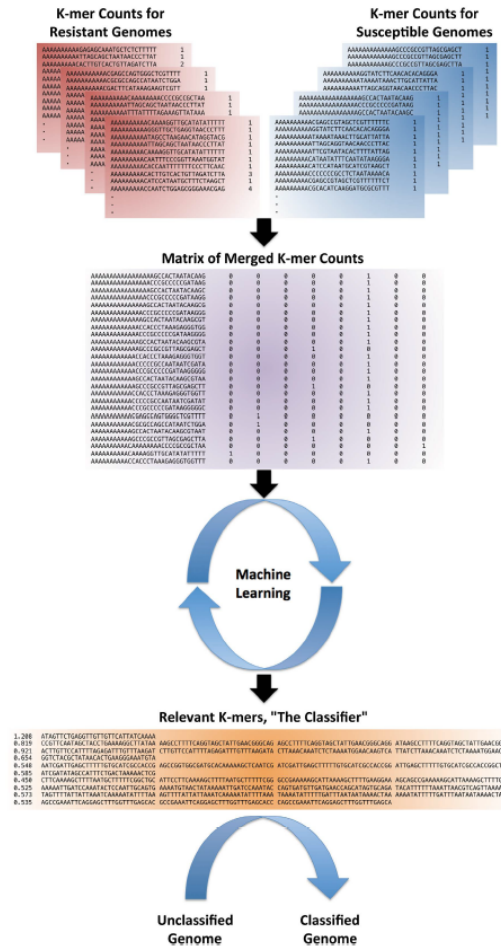


Source: Davis et al. 2016. *Antimicrobial Resistance Prediction in PATRIC and RAST*

One step forward in AMR hazard characterization

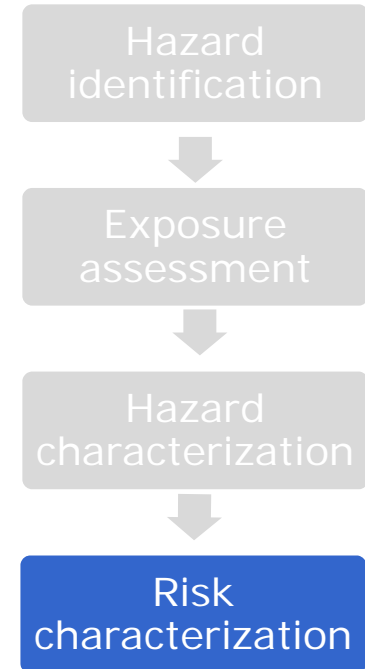
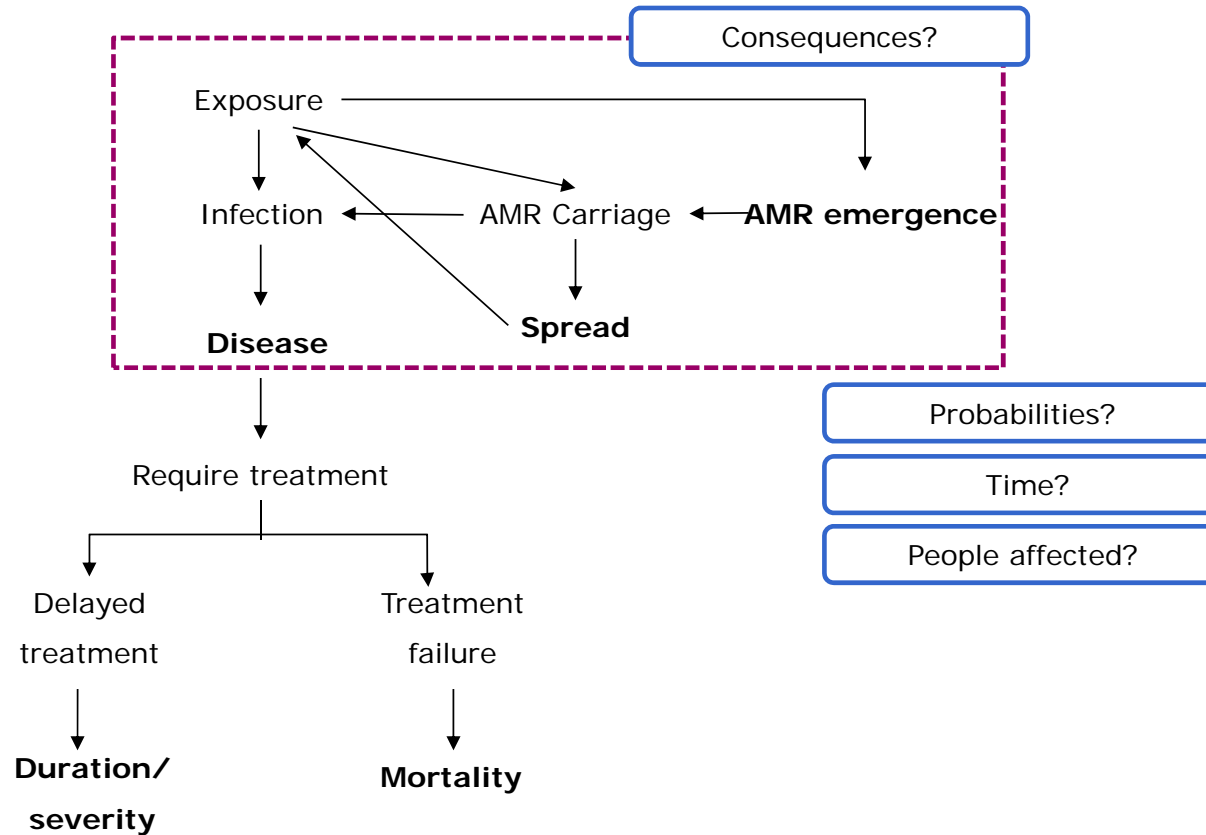
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What about metagenomics ?



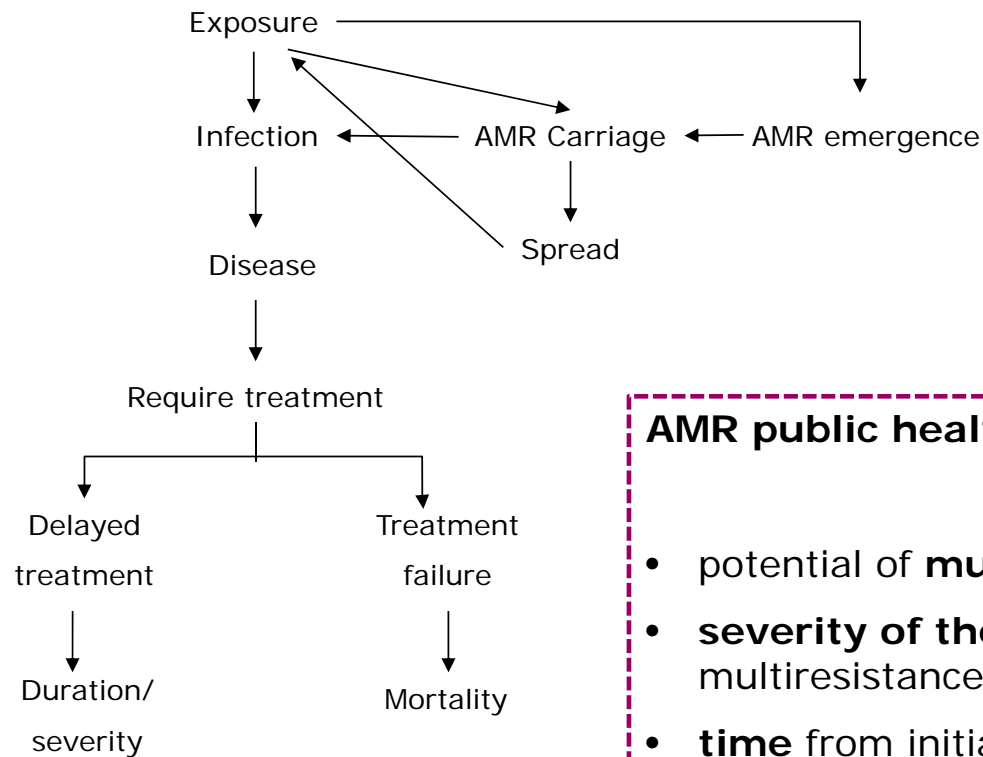
Source: Davis et al. 2016. *Antimicrobial Resistance Prediction in PATRIC and RAST*

AMR risk characterization



Adapted from Tine Hald

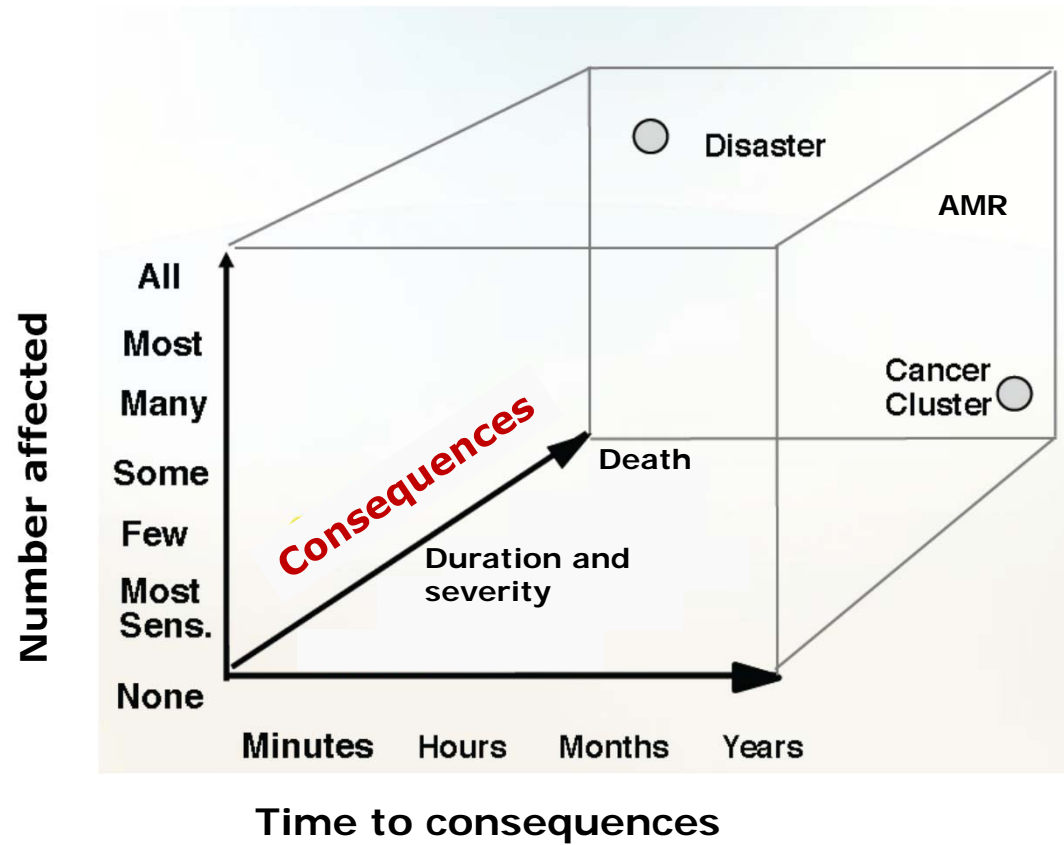
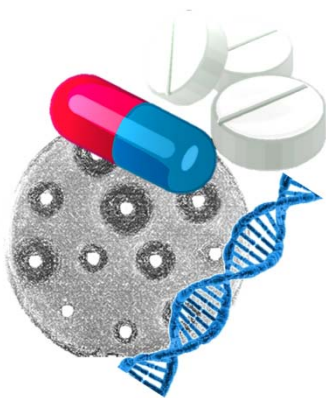
AMR risk characterization



AMR public health risk assessment to estimate:

- potential of **multiresistance emergence and spread**
- **severity of the consequences** of exposure to multiresistance
- **time** from initial exposure to the emergence, spread and consequences of multiresistance

Thank you for your attention



References/links

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