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Surveillance of AMR and AMU in Denmark

Robert Skov, MD, Senior Consultant
National AMR coordinator
Statens Serum Institut
Denmark

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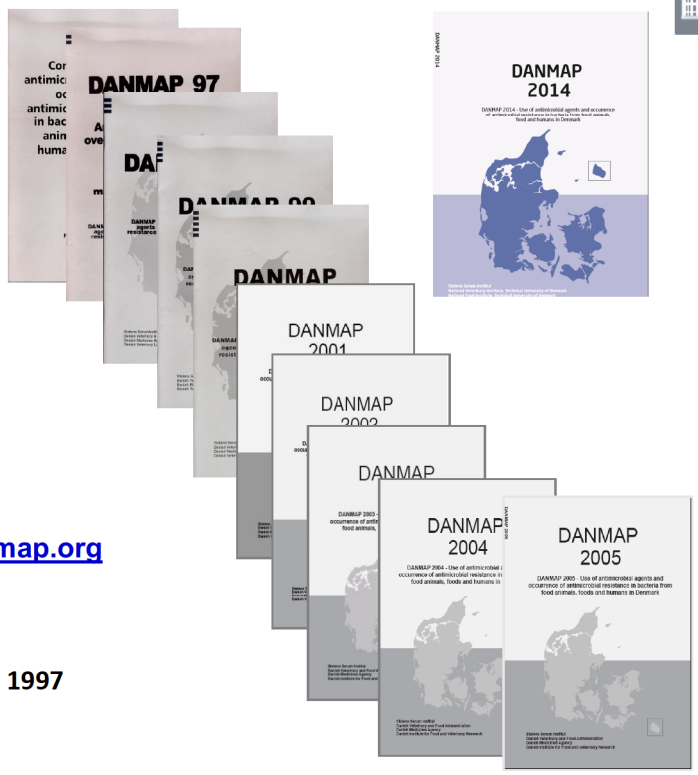
DANMAP

Danish Integrated
Antimicrobial
Resistance
Monitoring And
Research Programme



http://www.danmap.org

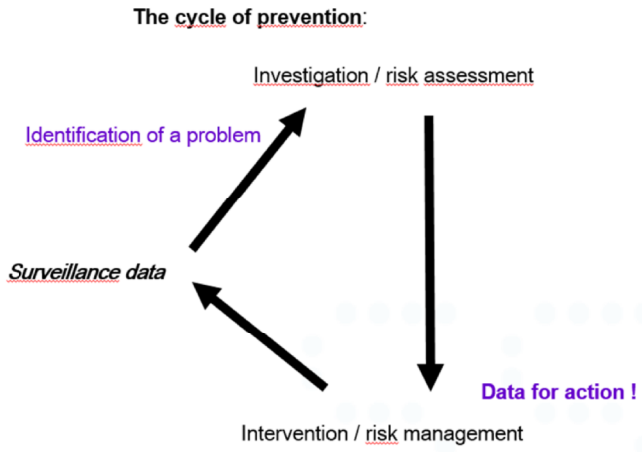
Annual report since February, 1997

Public health surveillance – the basic principles

Systematic, ongoing

- Collection
- Analysis
- Interpretation
- Dissemination
- Link to public health practice

with in a legal framwork



Denmark - demographics

- Population 5.7 million, 43.000 km^2
- 5 geographical health care regions - responsible for hospitals
- Few private hospitals – mainly specialized
- 99 municipalities – responsible for elderly care, child care, schools
- 10 Departments of Clinical microbiology (DCM)
- Unique personal identification number for all citizens used for all health care services

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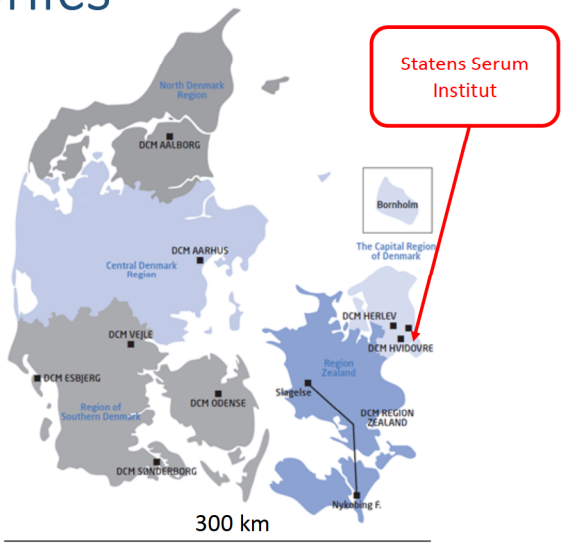
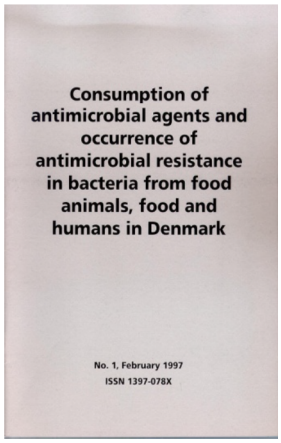
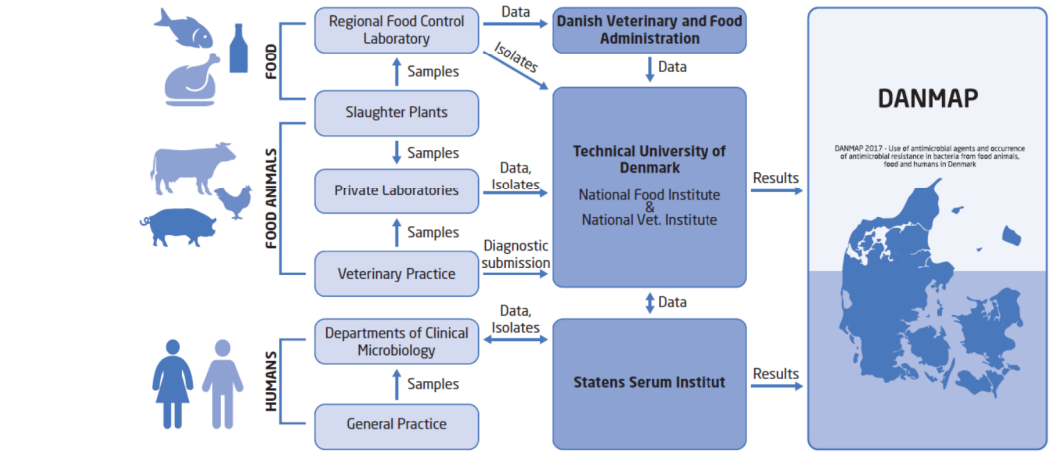


AMR surveillance in Denmark

- 1995: “The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme” – DANMAP
- Established by the Danish Ministry of Food, Agriculture and Fisheries and the Danish Ministry of Health in 1995
- Aim: “Investigate associations between use of antimicrobial agents in animals and humans and occurrence of resistance among bacteria from animals, food, and humans” – “Farm to table”
- Today more reflecting the increasing problems of resistant bacteria in humans



AMR data collection - humans



DANMAP established

1995

AMR data collection 1995 - paper reports from DCMs

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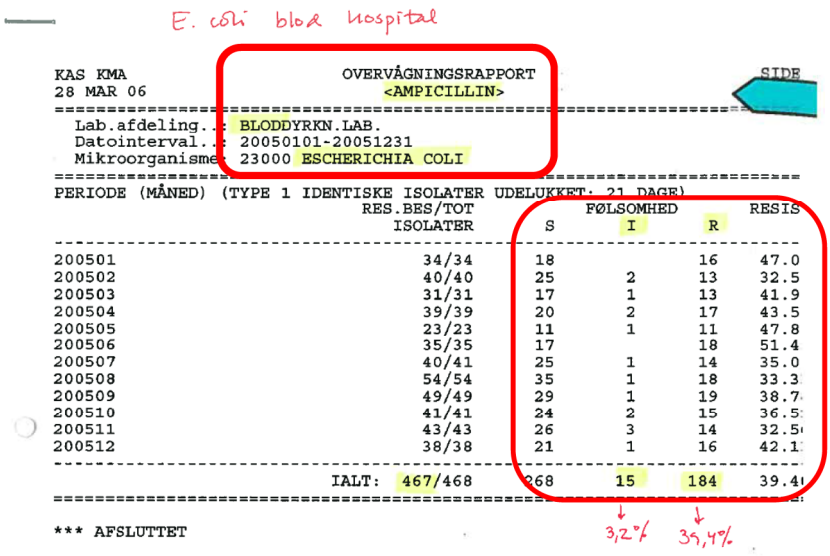
- Data submitted annually to SSI as paper reports printed from local laboratory information systems
- Reported "as is" from DCMs – analysis options very limited



E. coli blod Hospital

KAS KMA OVERVÅGNINGSRAPPORT SIDE
28 MAR 06 <AMPICILLIN>

Lab.afdeling..: BLODDYRKN.LAB.
Datointerval..: 20050101-20051231
Mikroorganisme: 23000 ESCHERICHIA COLI

PERIODE (MÅNED) (TYPE 1 IDENTISKE ISOLATER UDELUKKET: 21 DAGE)

	RES.BES/TOT ISOLATER	FØLSOMHED S	I	R	RESIS
200501	34/34	18		16	47.0
200502	40/40	25	2	13	32.5
200503	31/31	17	1	13	41.9
200504	39/39	20	2	17	43.5
200505	23/23	11	1	11	47.8
200506	35/35	17		18	51.4
200507	40/41	25	1	14	35.0
200508	54/54	35	1	18	33.3
200509	49/49	29	1	19	38.7
200510	41/41	24	2	15	36.5
200511	43/43	26	3	14	32.5
200512	38/38	21	1	16	42.1
IALT:	467/468	268	15	184	39.4

3,2% 39,4%

*** AFSLUTTET

DANMAP established

1995

2007 – data files on isolate level

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- Reporting from DCM changed to computerized data submission on isolate level with information on patient, hospital, hospital ward, sample date, full antibiogram etc.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	Year	SampleID	SampleType	PatientID	Hospital Ward	SampleDate	RecvDate	ReplDate	ExaminationType	SampleType2	Sex	Species	Antibiotic	SIR	ZoneMM
2	2013	32	BH1	Patient 1	HH25.00542	20121231	20130101	20130105	10230	10050	M	23000	12600	R	14
3	2013	32	BH1	Patient 1	HH25.00542	20121231	20130101	20130105	10230	10050	M	23000	13000	R	
4	2013	32	BH1	Patient 1	HH25.00542	20121231	20130101	20130105	10230	10050	M	23000	13510	S	20
5	2013	85	BH1	Patient 2	HH55.00222	20121231	20130101	20130103	10210	10050	M	23000	17400	S	
6	2013	85	BH1	Patient 2	HH55.00222	20121231	20130101	20130103	10210	10050	M	23000	28160	S	23
7	2013	85	BH1	Patient 2	HH55.00222	20121231	20130101	20130103	10210	10050	M	23000	36400	x	22
8	2013	85	BH1	Patient 2	HH55.00222	20121231	20130101	20130103	10210	10050	M	23000	36460	S	
9	2013	522	BH1	Patient 3	AH40.8ST2	20121231	20130101	20130103	10210	10050	M	23000	12600	S	22
10	2013	522	BH1	Patient 3	AH40.8ST2	20121231	20130101	20130103	10210	10050	M	23000	13000	S	19
11	2013	522	BH1	Patient 3	AH40.8ST2	20121231	20130101	20130103	10210	10050	M	23000	13510	S	23

DANMAP established

1995

Paper / PDF reports
hand held analysis

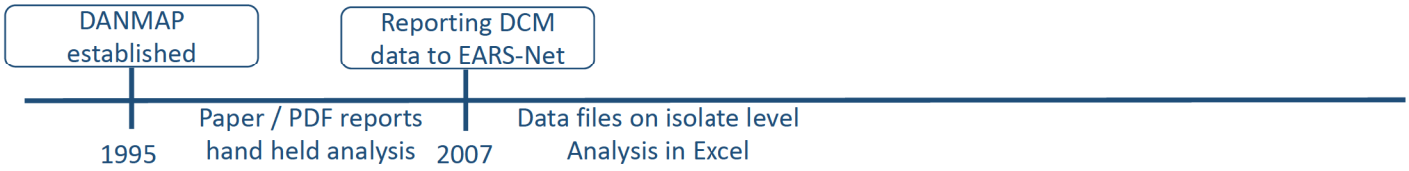
Reporting DCM data to EARS-Net

2007

Data files on isolate level
Analysis in Excel

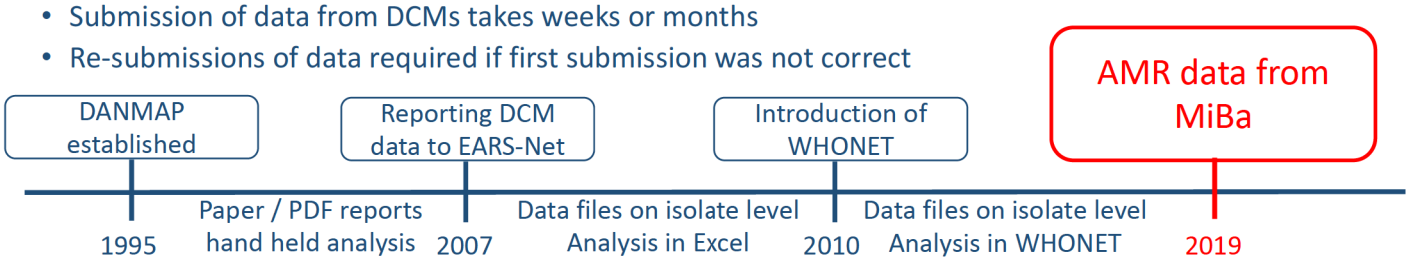
2007 – data files on isolate level

- Reporting from DCM changed to computerized data submission on isolate level with information on patient, hospital, hospital ward, sample date, full antibiogram etc.
- Streamlining of bacterial species and antibiotics under surveillance
- Extra information e.g. patient age and gender, hospital and hospital ward made more detailed analyses possible.
- Data were analyzed in Excel
- Isolate based data gave a much better understanding of susceptibility testing procedures in the DCMs



Analysis of AMR data today - overview

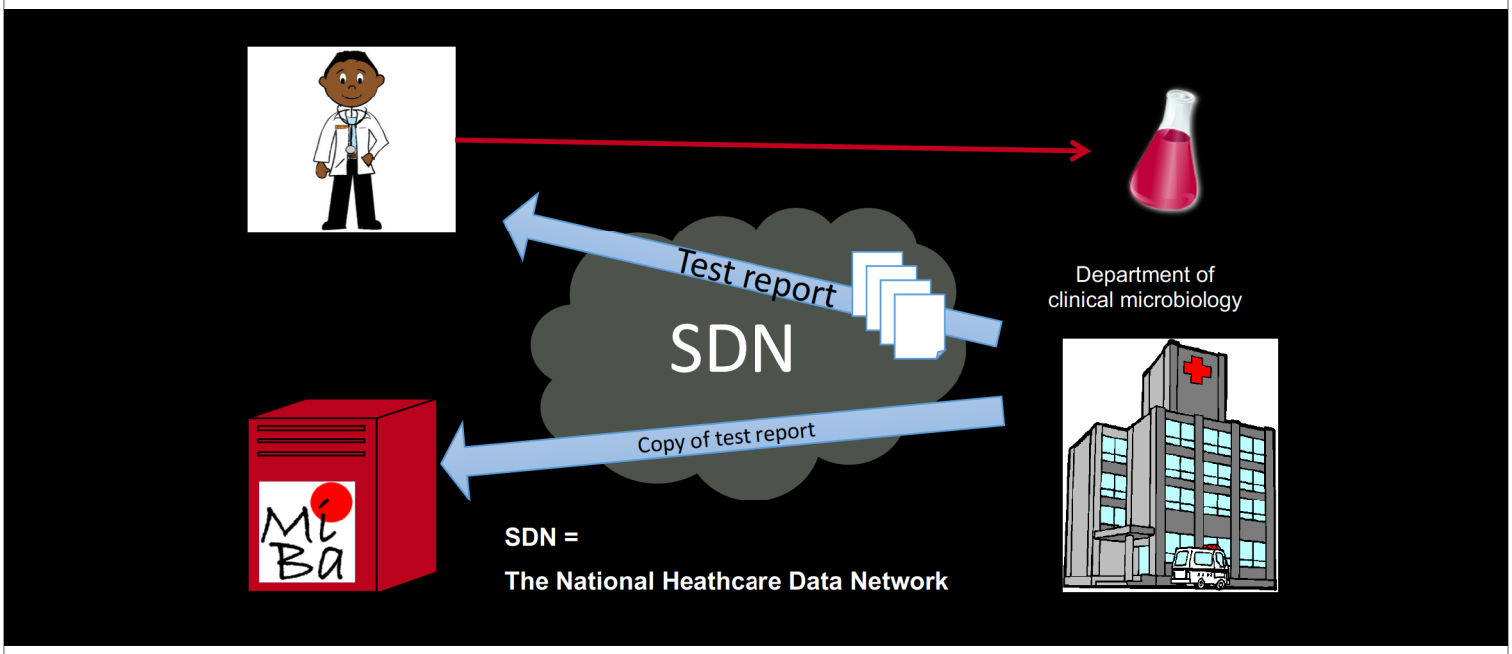
- Data format submitted by DCMs identical to 2007 – analyses made in WHONET
- Pros:
  - DCMs get a better understanding of what they submit when they do it manually
  - DCMs feel more like a part of the national surveillance
  - Discussing data submissions, data, susceptibility testing and finding errors improves the collaboration with the DCMs
- Cons:
  - Human error very likely in data export at DCM
  - Difficult for us to identify errors in data
  - Submission of data from DCMs takes weeks or months
  - Re-submissions of data required if first submission was not correct



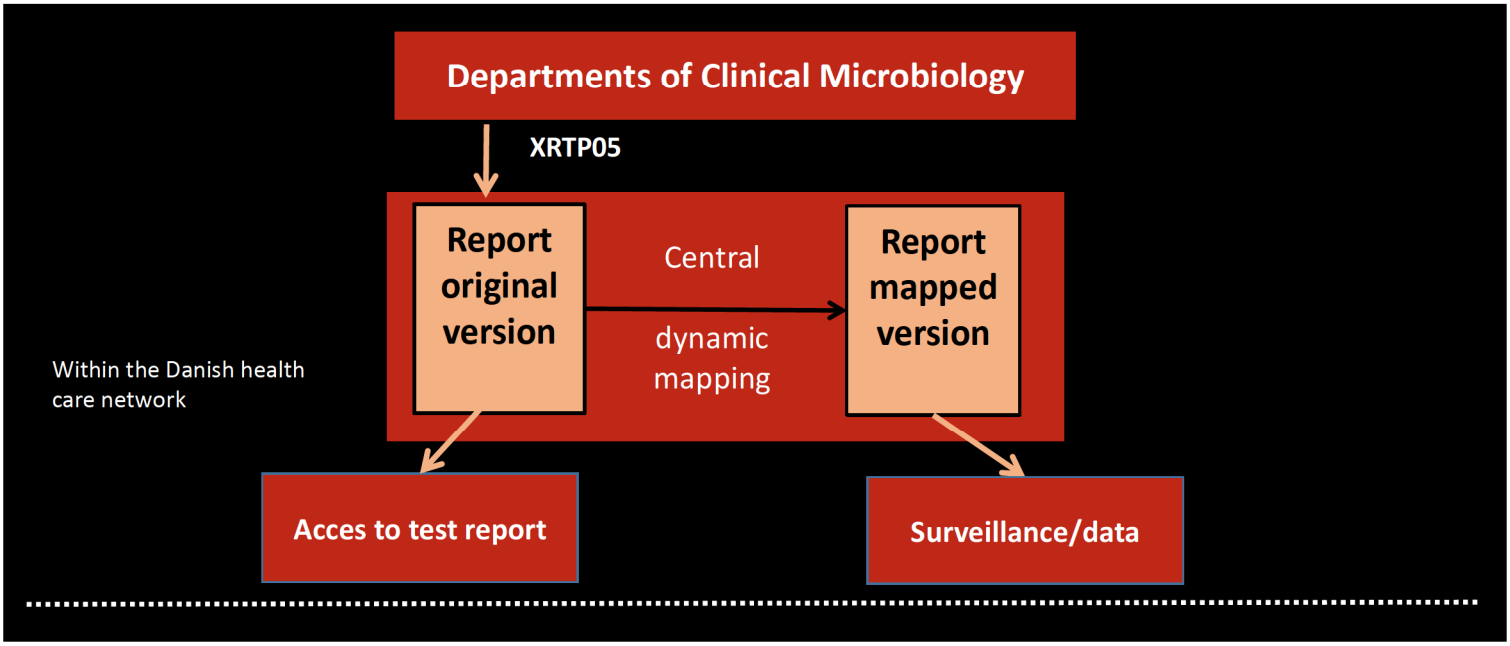
The evolution of Danish surveillance systems

- Surveillance of infectious diseases – history, evolution
- The key components of our digital infection preparedness system
  - MiBa
  - HAIBA
  - MiBalert
  - MiBa II
  - eRES – the digital platform for AMR surveillance
- The next steps and current vision
- Choices, challenges and lessons learnt

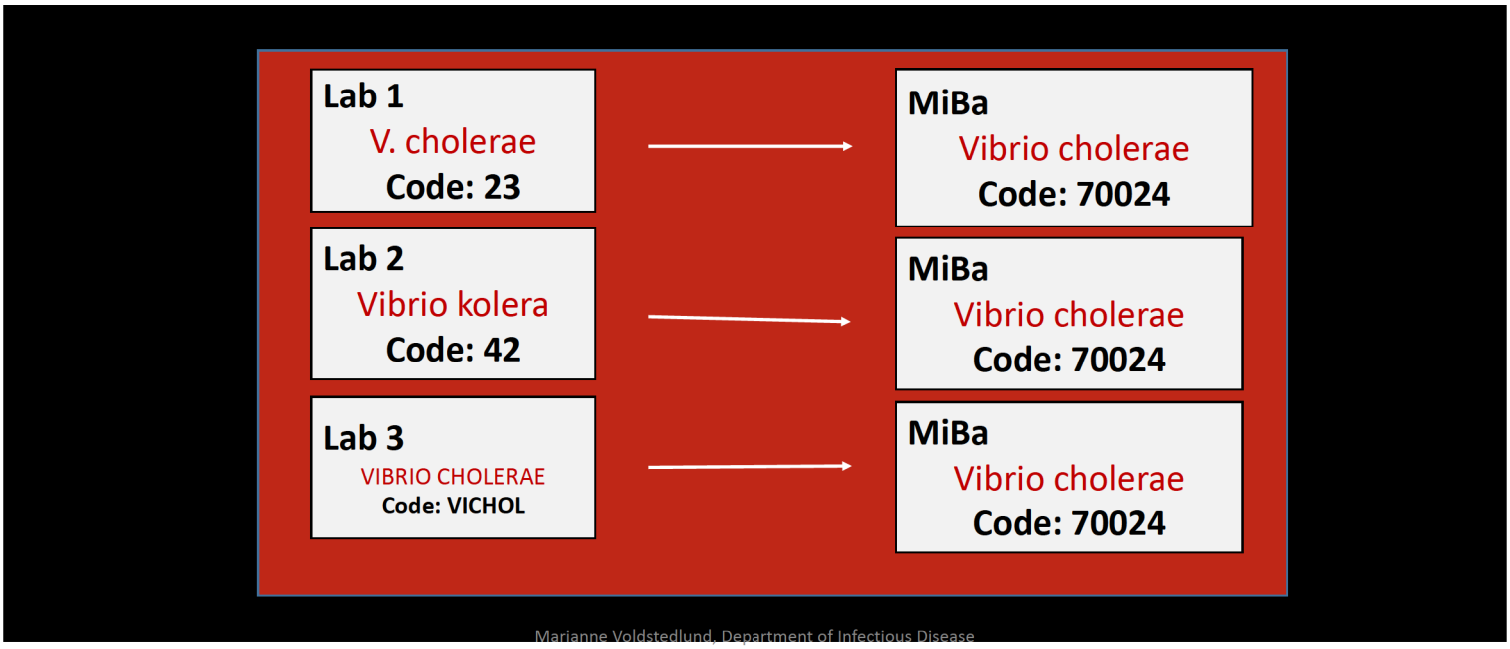
Basic principles of MiBa



Data model



Central Dynamic Mapning



Marianne Voldstedlund, Department of Infectious Disease Epidemiology, Statens Serum Institute, Copenhagen, Denmark

MiBa in Clinical care

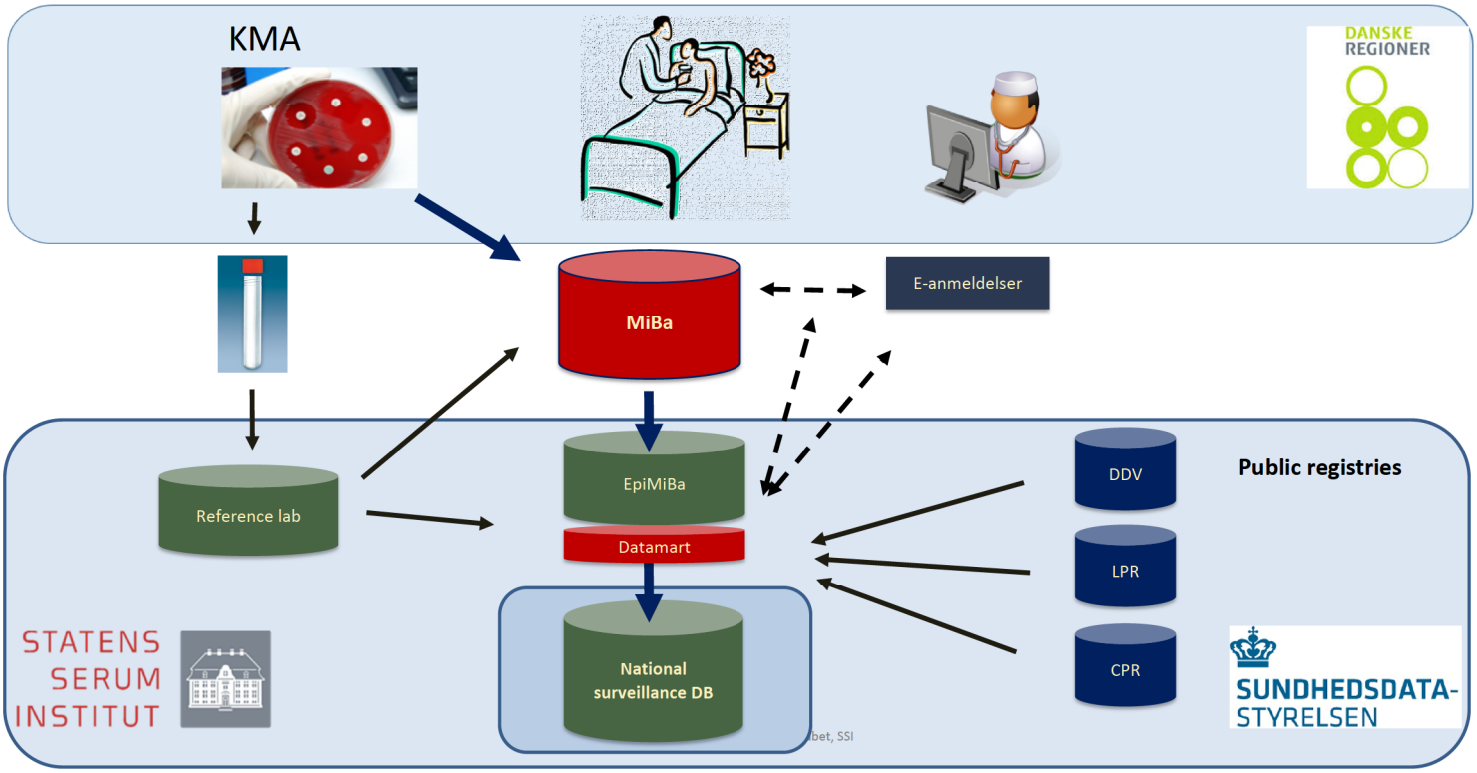
Before MiBa

- No sharing of reports between hospitals and/or GPs

After MiBa

- Nationwide acces to all test reports

MiBa based surveillance: coherent data flows



What is a datamart - KID

- Easy and fast search of full information from MIBA.
  - Only saves conclusions and keys.
- Standardized used of software, algorithms and codes.
  - Makes mass production easier
- Streamlines data updates
  - Delta oriented – Only new or changed test results are loaded daily (close to real-time).

The MiBALert project

Background:

- When patients are re-admitted or transferred between hospitals, information on multiresistant microorganisms is often recognized late or lost
- Proper isolation precautions is often delayed
- Infection or colonization of fellow patients or even hospital outbreaks follows

Benefits of a new surveillance system based on MiBa

- DANMAP used to be reported manually and non-standardized from the DCM to SSI - a time consuming, cumbersome task demanding manual reporting from the labs and data cleaning at SSI.
- The new MiBa based system automatically receives and harmonises data and allows data to be analysed consecutively.
- Can be automated.
- Selection criteria can be used uniformly for all DCM's when performed centrally, this will further increase data quality.

Animal isolates

- Follow the EU scheme
- In 2018, most of the sampling for DANMAP was allocated to the mandatory sampling of broilers (examined for *Campylobacter jejuni*, indicator *E. coli* and ESBL/AmpC/Carbapenemaseproducing *E. coli*).
- Additionally, sampling of slaughter pigs
  - *Salmonella* and indicator *E. coli*
- cattle <1 year
  - *Campylobacter jejuni* and indicator *E. coli*

Meat

- Follow the EU scheme
- In 2018, ESBL/AmpC/Carbapenemase-producing *E. coli* were isolated from packages of fresh, chilled broiler meat collected in Danish wholesale and retail outlets throughout the year
- *Salmonella* isolates were surveyed from pork originating from the national control programme at the slaughterhouses
  - *Salmonella* from broiler meat and beef are not included in DANMAP 2018 due to low numbers of isolates available from the national surveillance programmes
- *Campylobacter* from broiler meat originated from the national control program

AMU

In Denmark, all antimicrobial agents used for treatment are available on prescription only.

Humans

Reported to The Register of Medicinal Product Statistics
Data for primary sector
- Since 1994
- Prescription sales to individuals
- Prescription sales to medical clinics

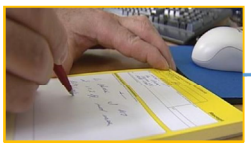
Data for hospital sector
- Since 1997
- Sales per departments

Veterinary

- Veterinarians are required by law to report all use of antibiotics and prescriptions for production animals to VetStat monthly.
- data on coccidiostatics as feed additives (non-prescription) is also collected by VetStat,
- Comparison of antimicrobial use is performed taking into account their potency, formulation, route of administration and the age of the animals (where relevant) generating defined animal daily doses (DADDs).

Private Pharmacy

Primary sector



Prescription sales from private pharmacies

Hospital sector

Sales from Hospital Pharmacies to departments

Human

Veterinary

The Register of Medicinal Product Statistics

Sales of antimicrobials for veterinary use from manufacturers not through pharmacies

Sales of veterinary medicines to Vetstat at The Danish Veterinary and Food Administration

Data are reported every month by the 10th the following month

AMR IN DENMARK 2019

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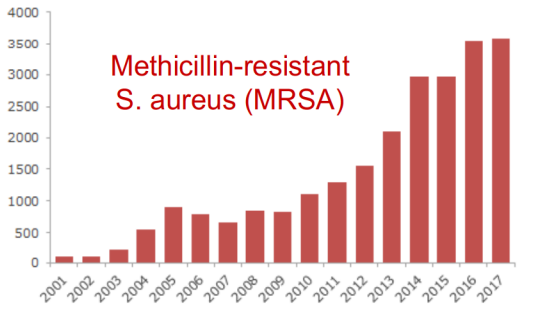
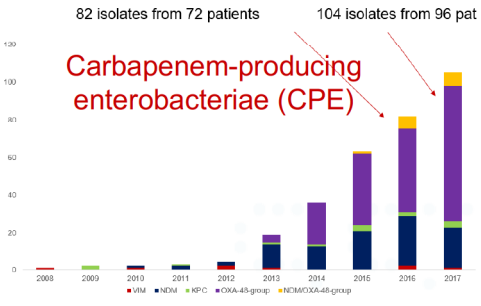
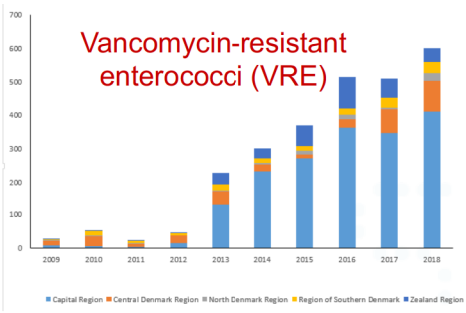
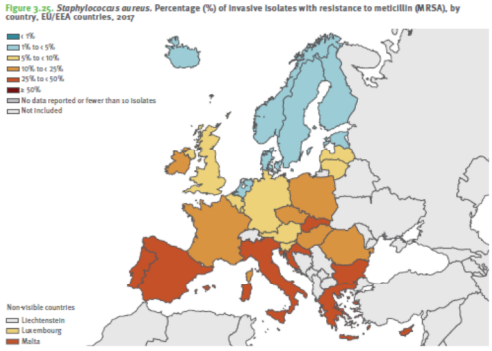


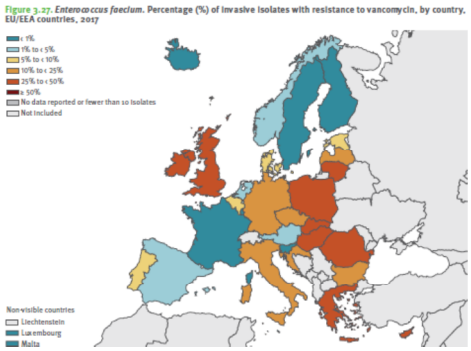




AMR: DENMARK COMPARED TO EUROPE



MRSA: DK low-prevalence



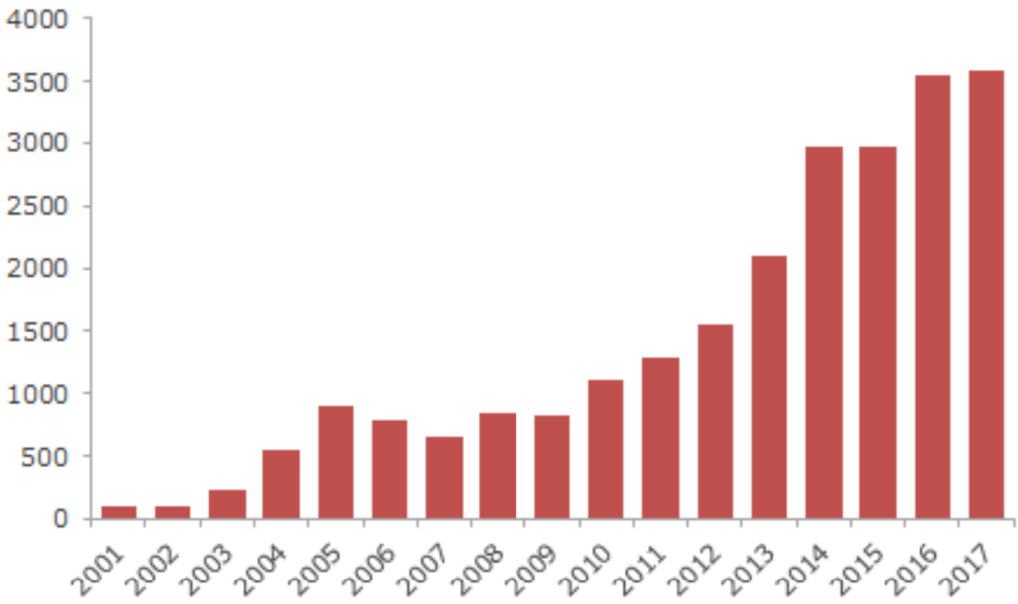
VRE: DK medium-prevalence

CPE: DK low-prevalence

ANTIBIOTIC RESISTANCE AND INFECTION CONTROL

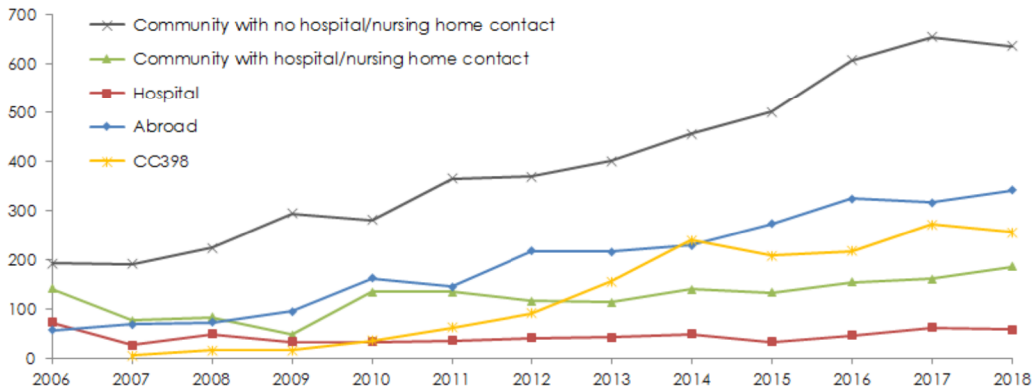
	Screening	Isolation	Outbreak and HCW	Year	Typing/ Surveillance	Regu-lation	Guide-lines	Trend
MRSA	mandatory	mandatory	mandatory	2006	mandatory	Yes	Yes	Limited transmis sion hospitals
VRE	Optional	Optional	No	-	Voluntary	No	(Yes)	Endemic at hospitals
ESBL	No	No	No	-	Voluntary	No	(partly)	Endemic at hospitals
CPO	mandatory	mandatory	mandatory	2018	mandatory	Yes	Yes	Sporadic cases
CD 027	mandatory	mandatory	mandatory	2010	Mandatory	Yes	Yes	Endemic, limited transmis sion in hospitals
C. auris	Optional	Optional	No	-	Voluntary	No	(Yes)	Not seen in Denmark

MRSA



ANNUALLY REPORT ON MRSA 2019

Figure 2. Number of clinical MRSA infections by epidemiological classification, 2006-2018



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Thank you for your attention

Happy to take any questions

Antimicrobial Resistance is an Ecological Challenge

All sectors contribute to the problem

Each time we use antibiotics, we risk fueling the growth of resistant bacteria

3,400,000 kg
Human Medicine

5,560,000 kg
Animal Production

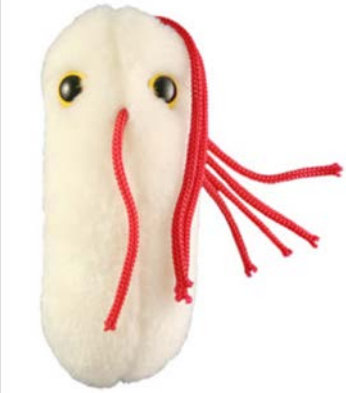
Routine antibiotic use is an essential part of the industrialized livestock production model

Big Question

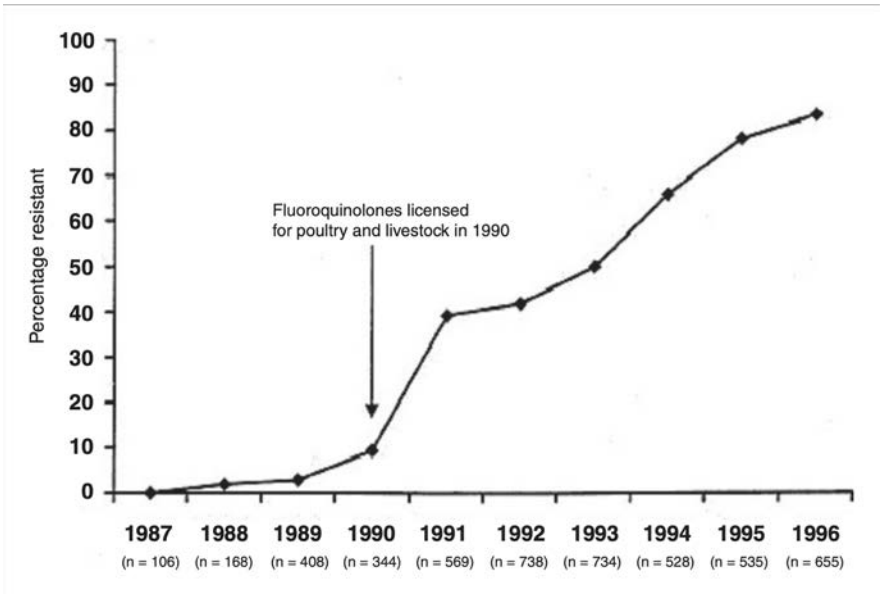
What proportion of antimicrobial-resistant human infections can be attributed to antimicrobial use in food animals?

Human health can be impacted by both direct infection and horizontal gene transfer

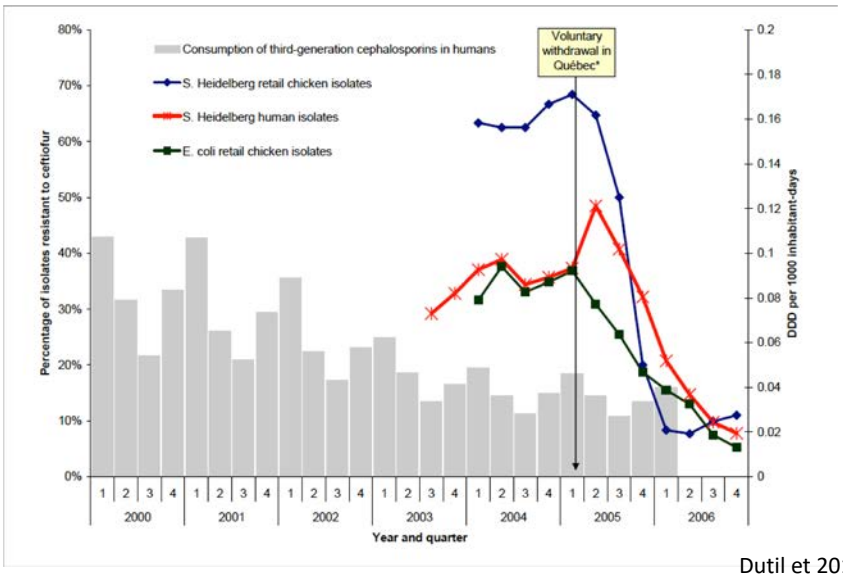
Salmonella



Campylobacter



Silbergeld et 2008



Dutil et 2010

XDR Gonorrhea

XDR TB

Animals are not involved

S. aureus

E. coli

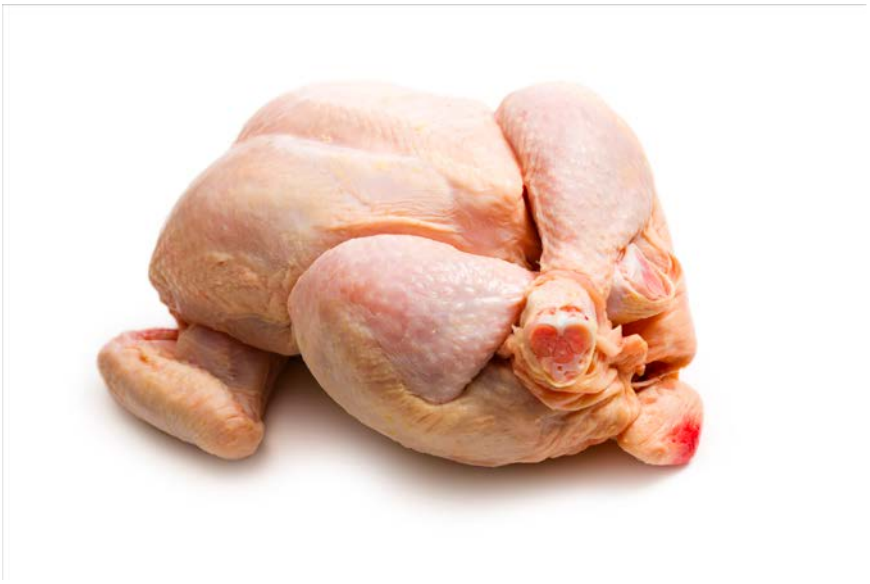
Colonizing Opportunistic Pathogens "COPs"

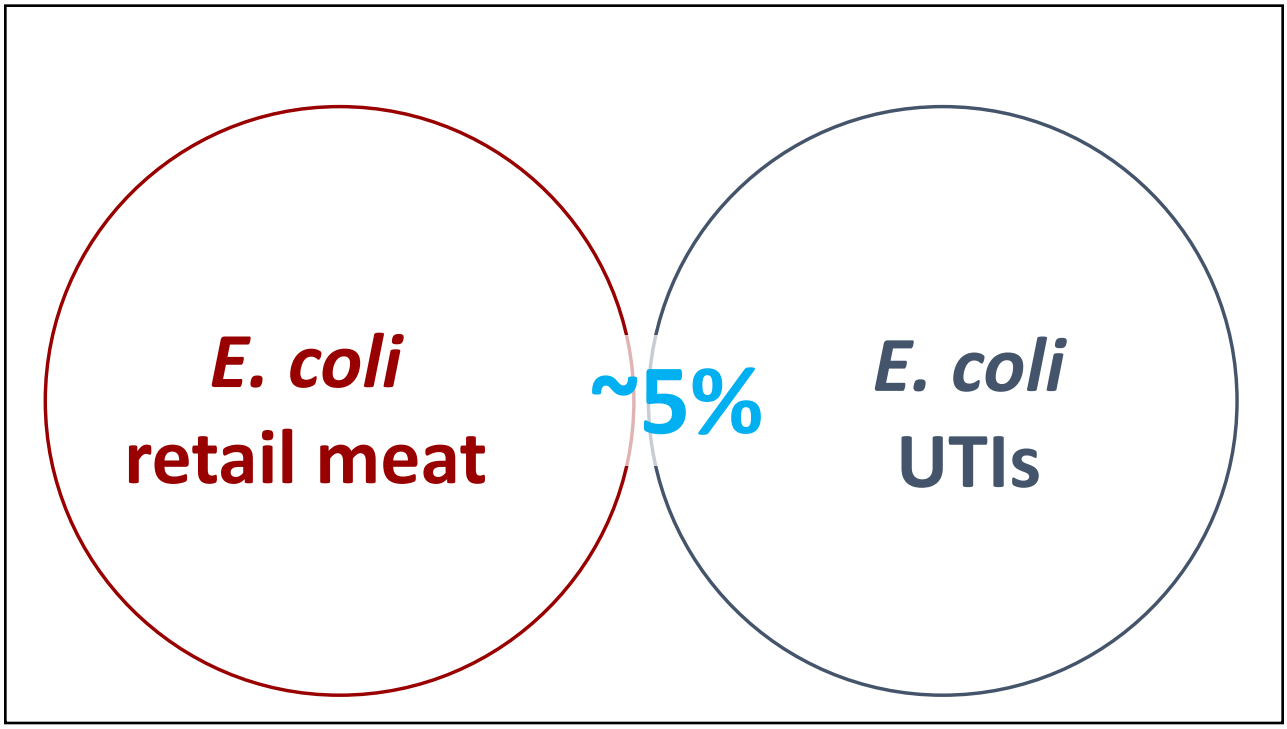
E. coli

E. coli's Multiple Personalities

E. coli cause most urinary tract infections

- UTI-causing *E. coli* strains can live in our guts without any symptoms
- We get UTIs when these *E. coli* strains make the short trip from the anus to the urethra
- The urinary tract is a major gateway to the blood
- How do UTI-causing *E. coli* get in our guts?!





In the U.S., we conservatively estimate that there are 300,000 to 400,000 UTIs per year from recent foodborne exposure

S. aureus

Livestock-associated MRSA ST398

Staphylococcus aureus CC398: Host Adaptation and Emergence of Methicillin Resistance in Livestock

RESEARCH ARTICLE

Meticillin-resistant *Staphylococcus aureus* CC398 is an increasing cause of disease in people with no livestock contact in Denmark, 1999 to 2011

Clinical Infectious Diseases

MAJOR ARTICLE

Emergence of Livestock-Associated Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in Denmark

Jesper Larsen,[1] Andreas Petersen,[1] Anders R. Larsen,[1] Raphael N. Sieber,[1] Marc Stegger,[1,2] Anders Koch,[1] Frank M. Aarestrup,[3] Lance B. Price,[2,4] and Robert L. Skov[1]; for the Danish MRSA Study Group*

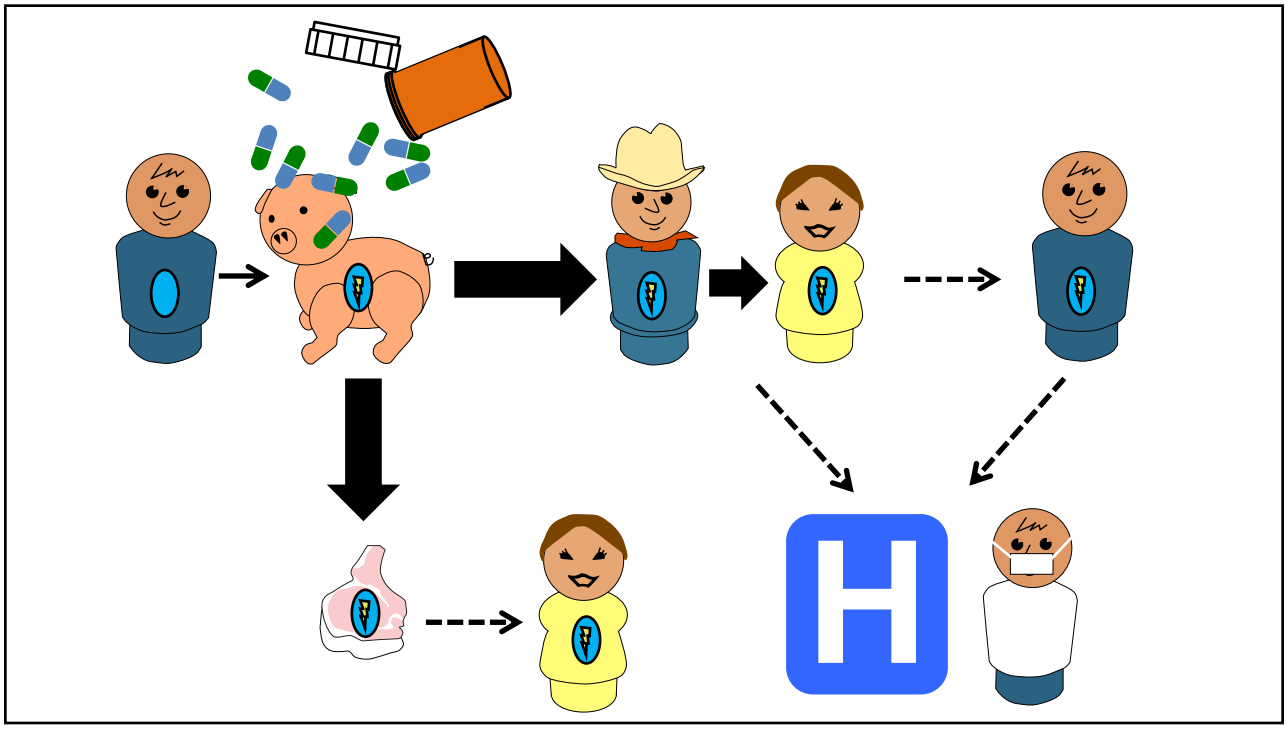
[1]Statens Serum Institut, Copenhagen, Denmark; [2]Translational Genomics Research Institute, Flagstaff, Arizona; [3]Technical University of Denmark, Kongens Lyngby; and [4]George Washington University, District of Columbia

Clinical Infectious Diseases

BRIEF REPORT

Evidence for Human Adaptation and Foodborne Transmission of Livestock-Associated Methicillin-Resistant *Staphylococcus aureus*

Jesper Larsen,[1] Marc Stegger,[1,5] Paal S. Andersen,[1,2] Andreas Petersen,[1] Anders R. Larsen,[1] Henrik Westh,[2,3] Yvonne Agerso,[4] Alexandra Fetsch,[7] Britta Kraushaar,[7] Annemarie Käsbohrer,[7] Andrea T. Feßler,[8] Stefan Schwarz,[8] Christiane Cuny,[9] Wolfgang Witte,[9] Patrick Butaye,[10,12] Olivier Denis,[11] Marisa Haenni,[13] Jean-Yves Madec,[13] Eric Jouy,[16] Frederic Laurent,[14,15] Antonio Battisti,[17] Alessia Franco,[17] Patricia Alba,[17] Caterina Mammina,[19] Annalisa Pantosti,[18] Monica Monaco,[18] Jaap A. Wagenaar,[20,22] Enne de Boer,[21] Engeline van Duijkeren,[23] Max Heck,[23] Lucas Dominguez,[24] Carmen Torres,[25] Myriam Zarazaga,[25] Lance B. Price,[5,6,a] and Robert L. Skov[1,a]



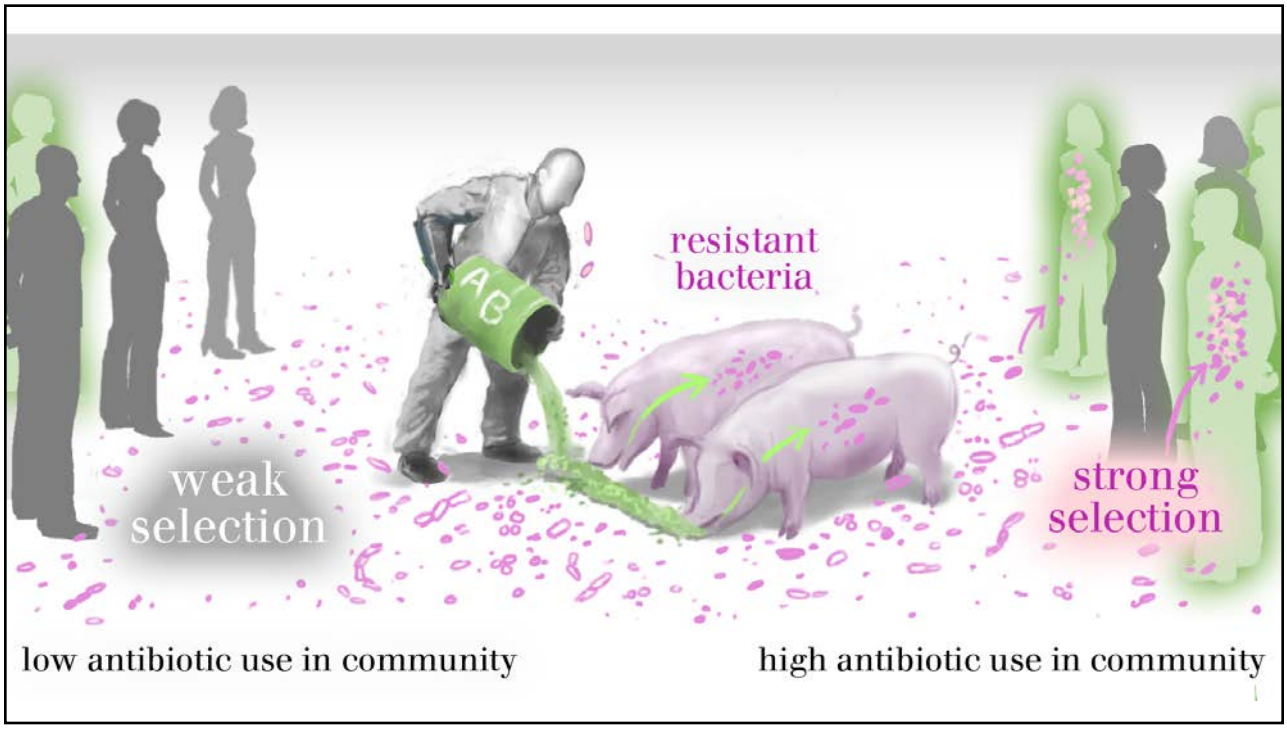
ST398 reflections

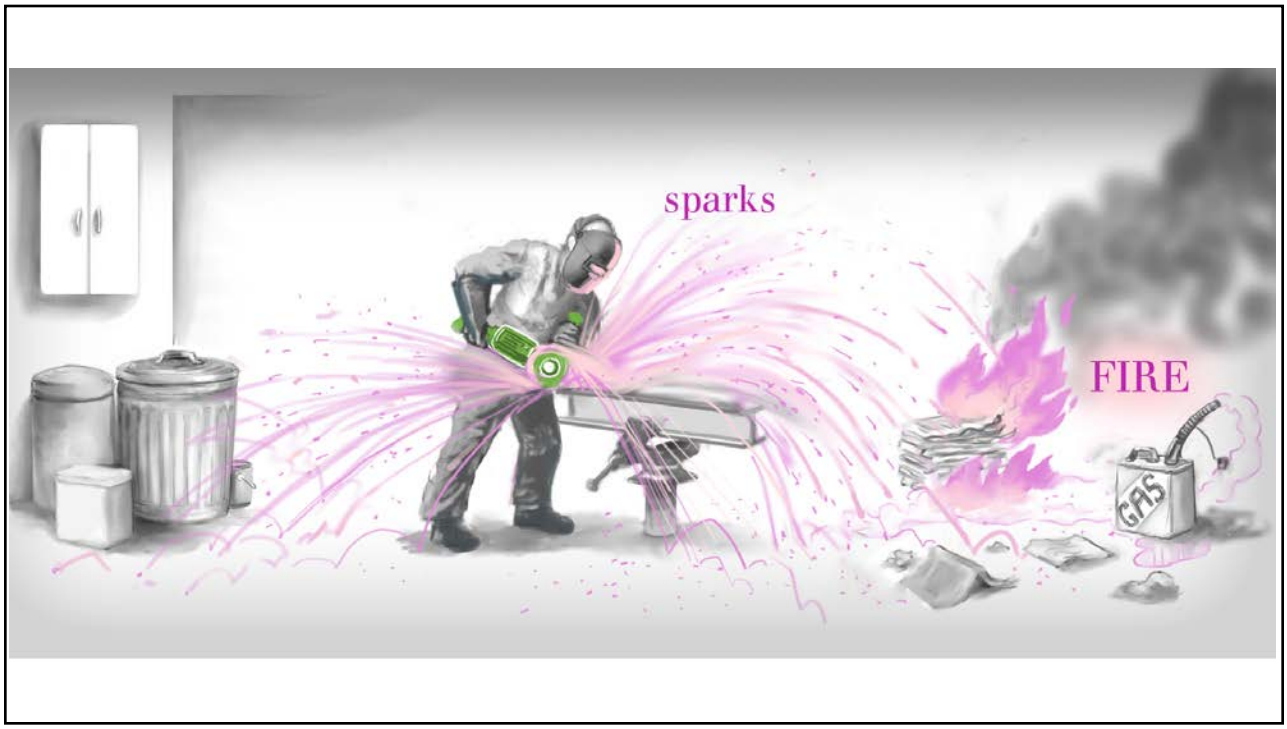
- It has spread rampantly among pigs in northern Europe and beyond
- It spread widely among Dutch swine herds that were, at the time, given lots of non-therapeutic antibiotics
- It also spread among Danish pigs, which are often held up as an example of industrial production without routine antibiotics
- In both countries, LA-ST398 has made or makes up a substantial portion of their MRSA cases; however, the overall MRSA incidence in those countries is extremely low

Today, ST398 has become a textbook example of livestock-to-human MRSA transmission

But just like any textbook, it doesn't translate everywhere

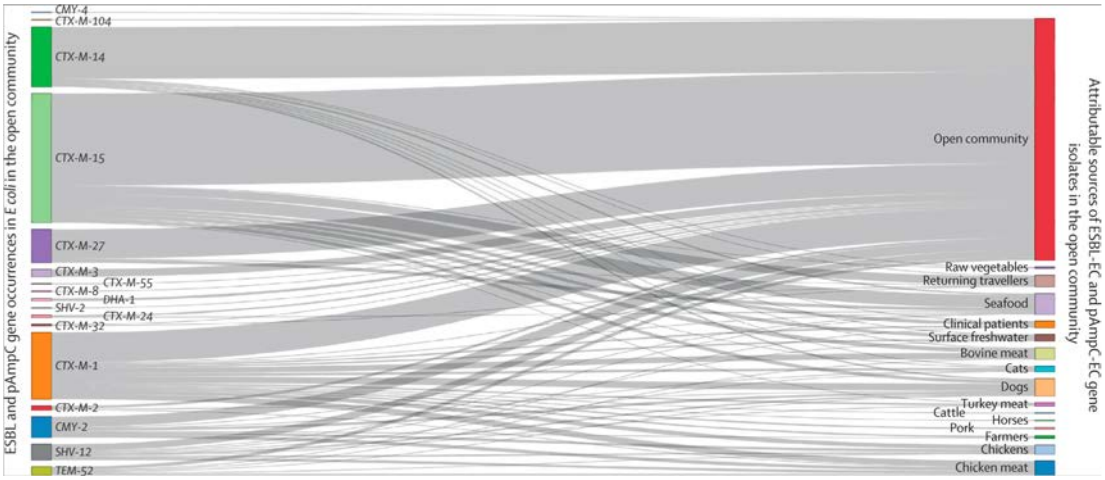
Sparks, fuel and fire


resistant
bacteria
weak
selection
strong
selection
low antibiotic use in community
high antibiotic use in community


sparks
FIRE
GAS

Human health can be impacted by both direct infection and horizontal gene transfer

Attributable sources of community-acquired carriage of *Escherichia coli* containing β-lactam antibiotic resistance genes: a population-based modelling study

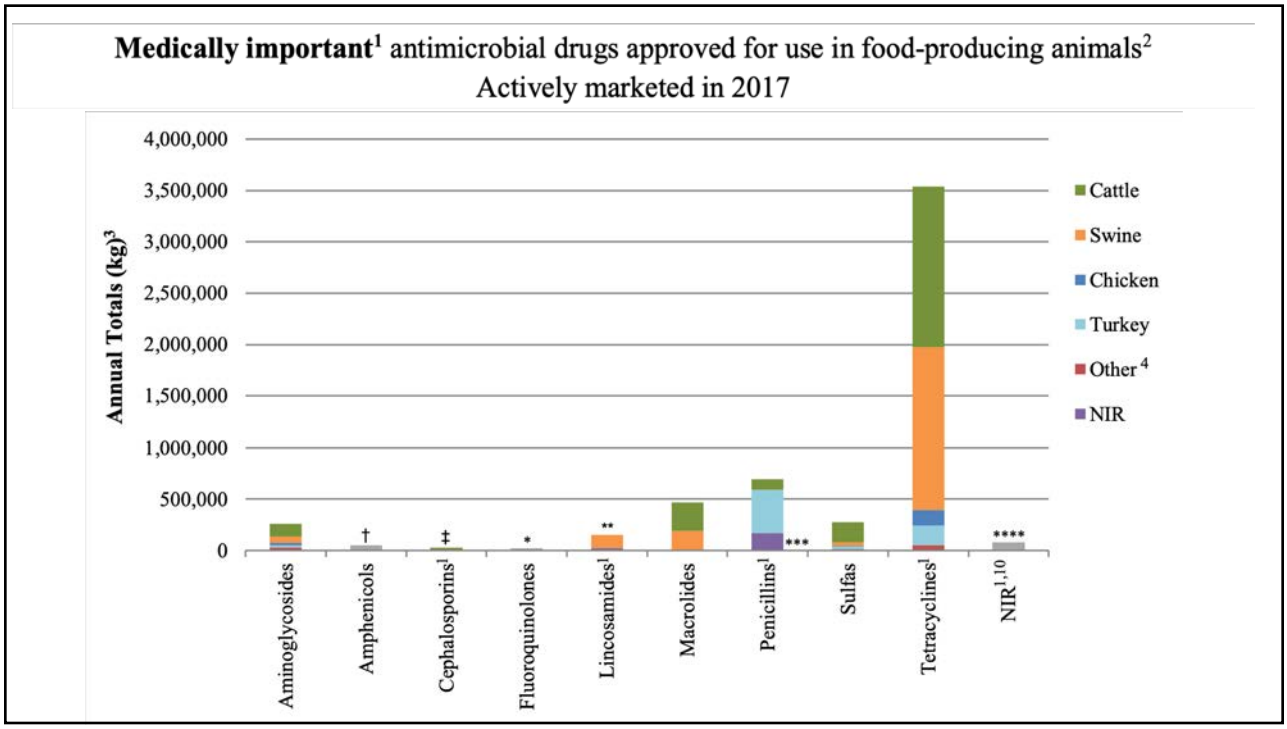


	Mean (95% CrI)	Median	SD
Human sources			
Human-to-human transmission in the open community	60·1% (40·0–73·5)	61·3%	8·7
Secondary transmission from high-risk groups	6·9% (4·1–9·2)	6·9%	1·3
Returning travellers	3·9% (2·3–5·5)	3·9%	0·8
Clinical patients	2·0% (1·2–2·6)	2·0%	0·4
Poultry and pig farmers	1·0% (0·5–1·6)	1·0%	0·3
Food consumption and preparation	18·9% (7·0–38·3)	17·6%	8·1
Seafood	6·6% (0·3–21·6)	5·1%	5·8
Chicken meat	4·5% (0·2–13·1)	3·7%	3·5
Bovine meat	3·6% (0·1–12·5)	2·7%	3·3
Turkey meat	1·8% (0–6·1)	1·3%	1·6
Raw vegetables	1·1% (0–3·9)	0·8%	1·1
Pork	0·9% (0–3·3)	0·6%	0·9
Sheep or goat meat	0·4% (0–1·6)	0·3%	0·4
Animals			
Contact with companion animals	7·9% (1·4–19·9)	7·0%	4·9
Dogs	5·1% (0·2–16·3)	3·9%	4·4
Cats	2·4% (0·1–8·0)	1·9%	2·2
Horses	0·5% (0–1·7)	0·3%	0·5
Non-occupational contact with farm animals	3·6% (0·6–9·9)	3·0%	2·5
Chickens	2·8% (0·1–9·0)	2·1%	2·4
Cattle	0·4% (0–1·4)	0·3%	0·4
Sheep or goats	0·3% (0–1·1)	0·2%	0·3
Pigs	0·1% (0–0·5)	0·1%	0·1
Environment	2·6% (0·2–8·7)	1·9%	2·3
Swimming in surface freshwater	2·3% (0·1–8·4)	1·6%	2·3
Contact with wild birds	0·3% (0–1·1)	0·2%	0·3

The percentage attributions of intestinal carriage of ESBL or pAmpC gene detections in *E coli* isolates from individuals of the open community (n=454) to the different human and non-human sources. ESBL=extended-spectrum β-lactamase. pAmpC=plasmid-mediated AmpC. CrI=credible interval.

Table: **Estimated attributions of each considered source of intestinal carriage of ESBL or pAmpC gene-carrying *Escherichia coli* detected in the open community in the Netherlands, 2005–17**

Special attention has to be paid to the type of antimicrobials being used in animal production


Medically important[1] antimicrobial drugs approved for use in food-producing animals[2]
Actively marketed in 2017
Annual Totals (kg)[3]
4,000,000
3,500,000
3,000,000
2,500,000
2,000,000
1,500,000
1,000,000
500,000
0
Cattle
Swine
Chicken
Turkey
Other[4]
NIR
†
‡
*
**
***
****
Aminoglycosides
Amphenicols
Cephalosporins[1]
Fluoroquinolones
Lincosamides[1]
Macrolides
Penicillins[1]
Sulfas
Tetracyclines[1]
NIR[1,10]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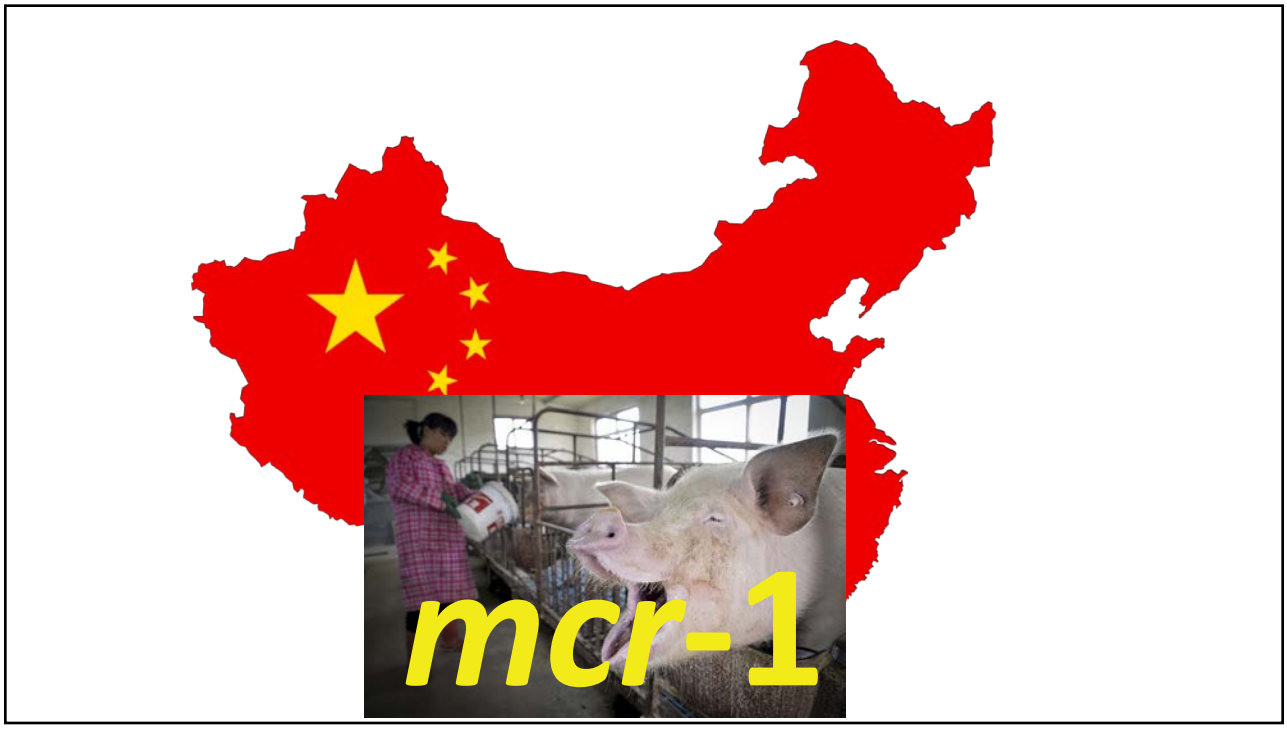
nations



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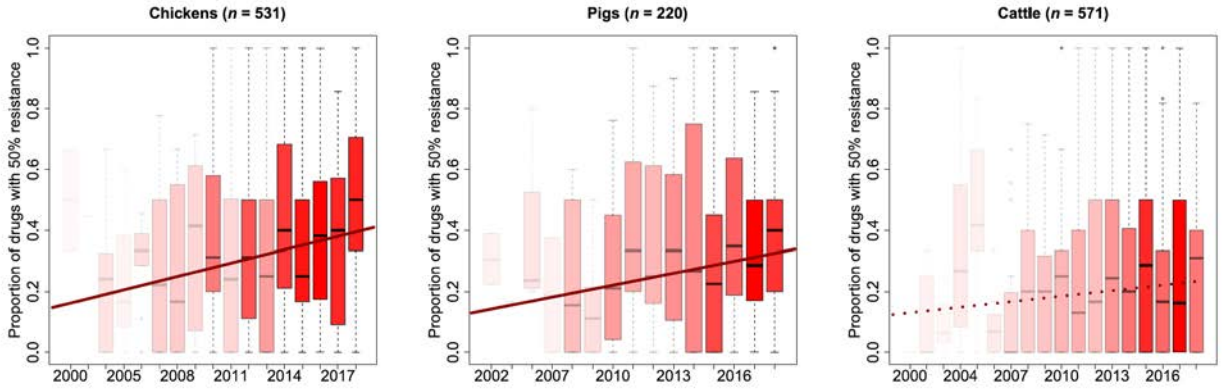


Fig. 2. Increase in antimicrobial resistance in LMICs. Proportion of antimicrobial compounds with resistance higher than 50% (P50) is shown. Solid lines indicate statistically significant (5% level) increases of P50 over time; shading indicates the number of surveys per year relative to total number of surveys per species.

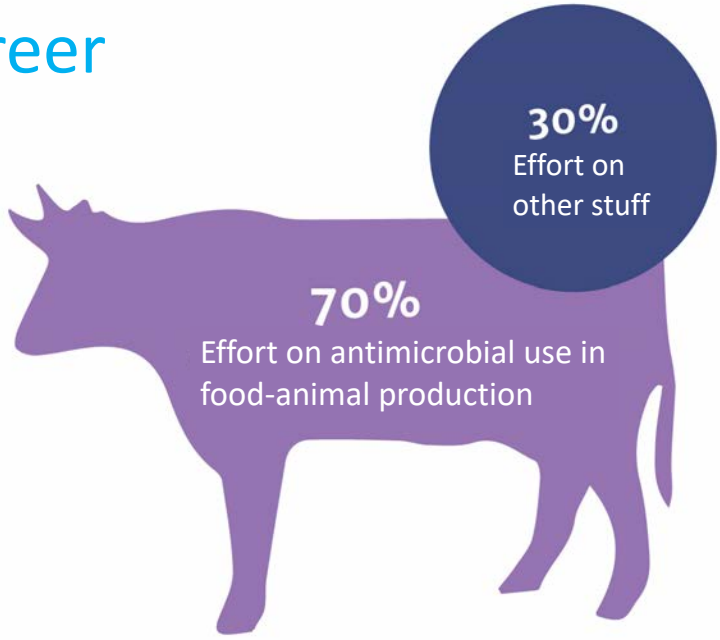
van boeckel 2019

The misuse of antimicrobials in food animals also threatens animal welfare

Back to our big question

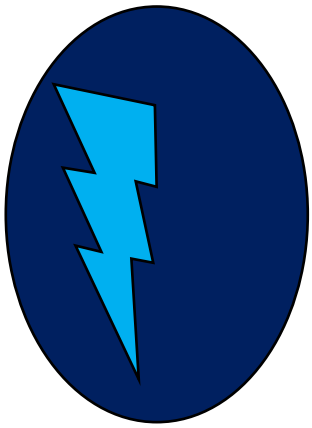
What proportion of antimicrobial-resistant human infections can be attributed to antimicrobial use in food animals?

My career

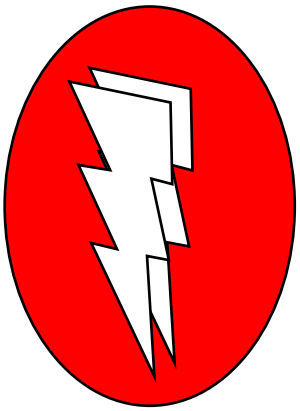

30%
Effort on other stuff
70%
Effort on antimicrobial use in food-animal production


Can we quantify *blame*?

CRE in people



mcr-1 in livestock



The agriculture industry is essential

And it needs constant oversight

Azole use in Dutch agriculture has been associated with deadly azole-resistant fungal infections

A key element to curbing antimicrobial resistant infections is eliminating unnecessary antimicrobial use in agriculture and human medicine