The Dutch model for reduction of antibiotic use in Livestock
Why, How and What

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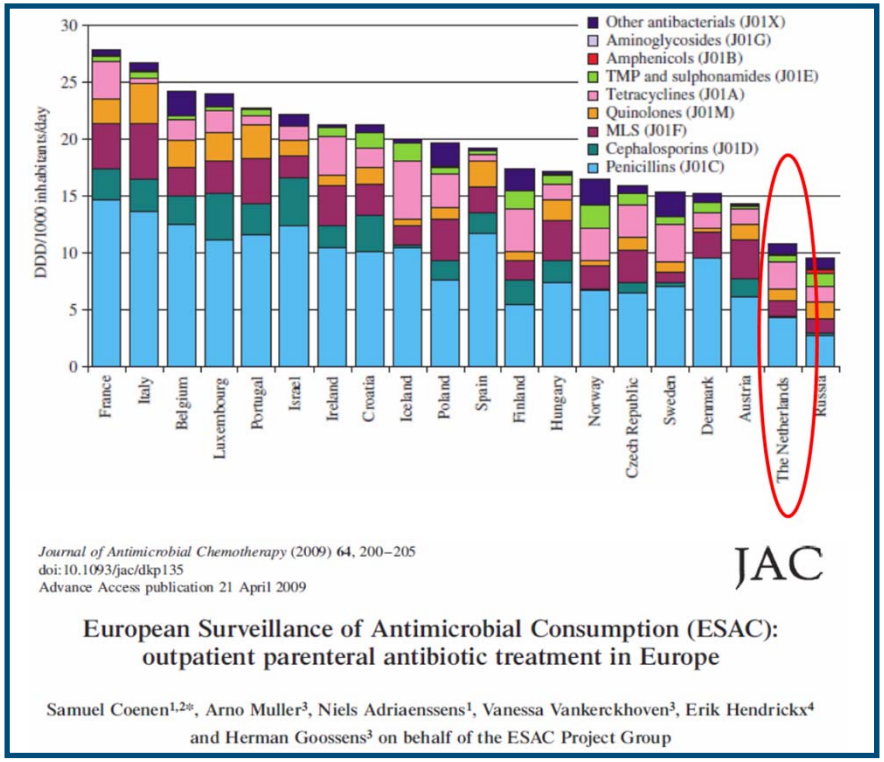
CENTRAL VETERINARY INSTITUTE
WAGENINGEN UR

Universiteit Utrecht

Antibiotic usage in humans and animals in Europe



Journal of Antimicrobial Chemotherapy (2009) **64**, 200–205
doi:10.1093/jac/dkp135
Advance Access publication 21 April 2009

JAC

European Surveillance of Antimicrobial Consumption (ESAC): outpatient parenteral antibiotic treatment in Europe

Samuel Coenen[1,2]*, Arno Muller[3], Niels Adriaenssens[1], Vanessa Vankerckhoven[3], Erik Hendrickx[4] and Herman Goossens[3] on behalf of the ESAC Project Group

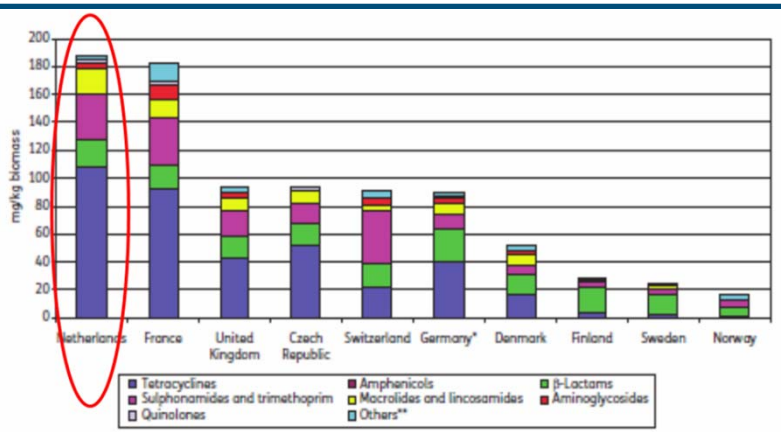


Figure 1. Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.

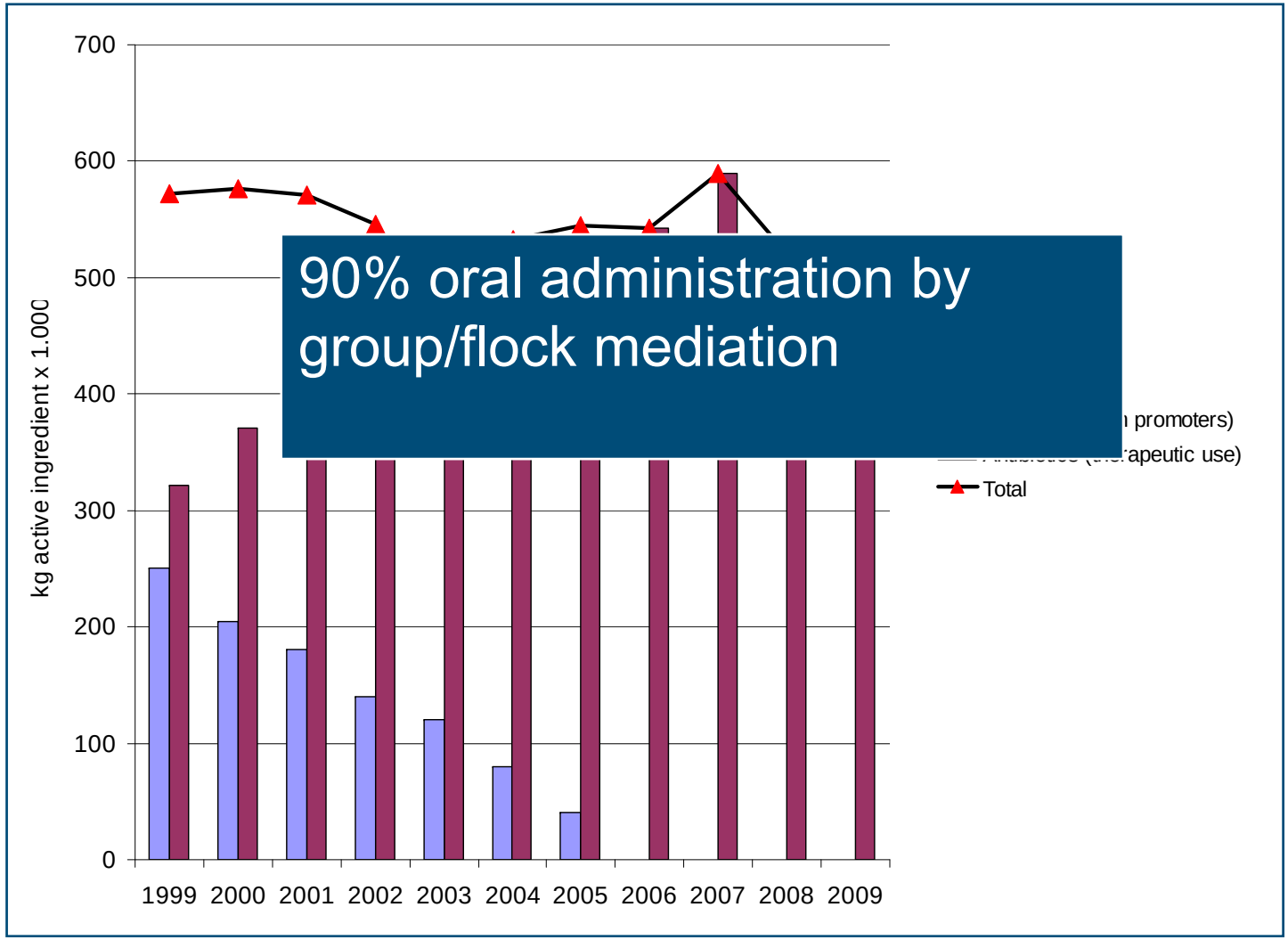
J Antimicrob Chemother 2010; **65**: 2037–2040
doi:10.1093/jac/dkq247 Advance Access publication 29 June 2010

Journal of Antimicrobial Chemotherapy

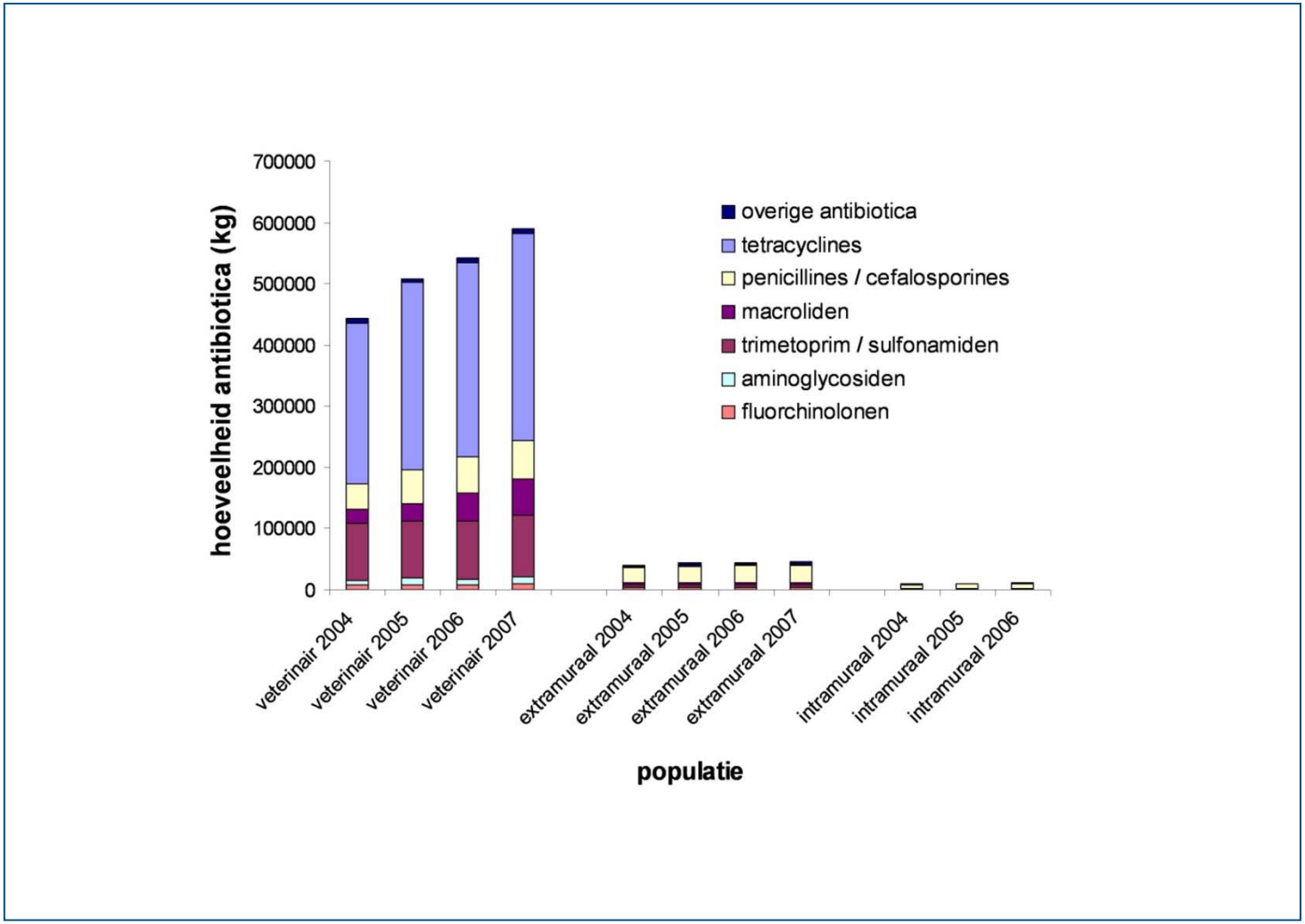
Comparison of the sales of veterinary antibacterial agents between 10 European countries

Kari Grave*, Jordi Torren-Edo and David Mackay

Antibiotic use in animals in NL (Source FIDIN)

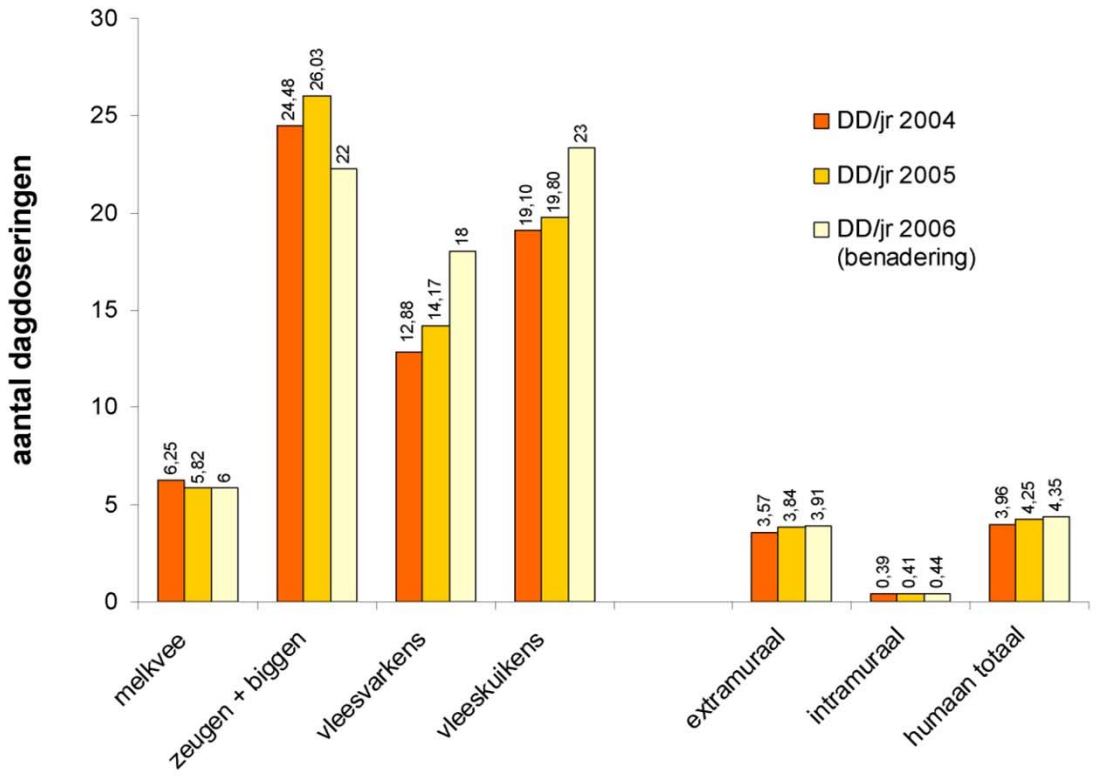


Animal versus human use in kg



van Geijlswijk, et al, TvD, 2009

Number of antibiotic administrations to the average animal/human per year



van Geijlswijk, et al, TvD, 2009

What does this mean

- In Dutch food-producing animals ideal environment for selection of multidrug resistant organisms

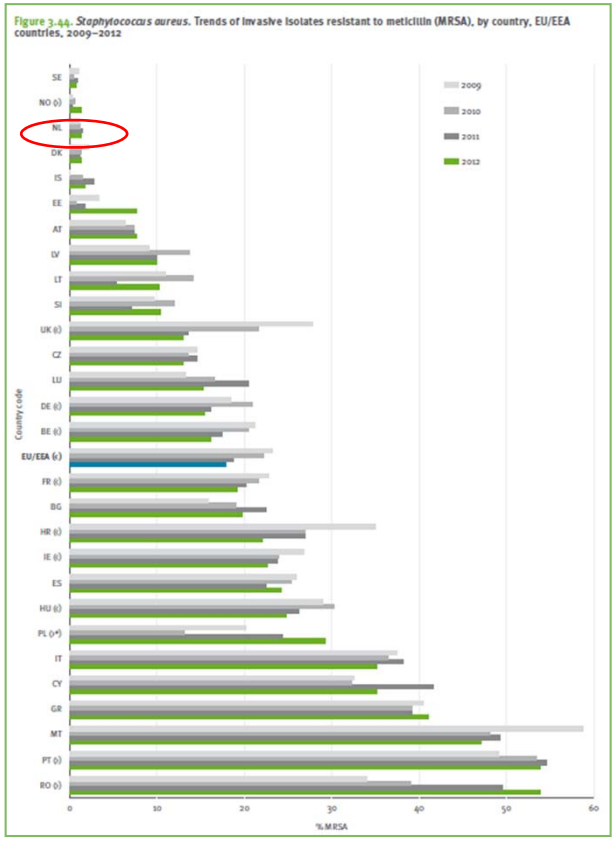
  - Risk??
    - Animal health?
      - Yes, if they cause infections
    - Public health?
      - Yes if:
        - » **Food-borne pathogens**
        - » **Zoonotic organisms**
        - » **Transferable genes**

Relation between resistance in animals and humans?

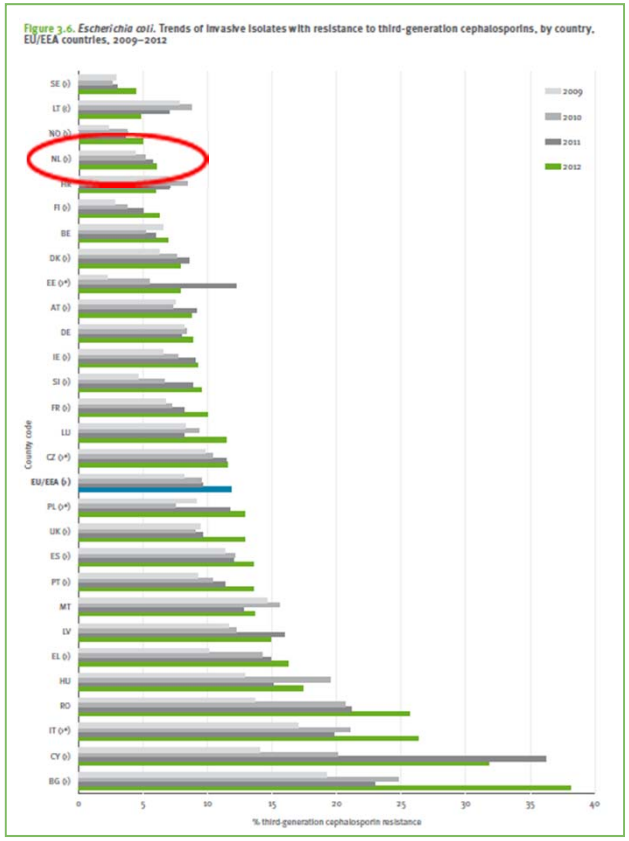
- In spite of long term differences in use, the resistance levels in Dutch Health care are low!
- So does a relation with resistance in animals exist?
  - Unfortunately, yes
    - MRSA!
    - ESBLs!

EARSS-net 2012 report (ECDC)

MRSA



ESBLs



Livestock associated MRSA (ST398)

Methicillin-resistant *Staphylococcus aureus* in Pig Farming

Andreas Voss,*† Frans Loeffen,* Judith Bakker,*
Corne Klaassen,† and Mireille Wulf*

Live Stock associated MRSA (ST398)

- Many pigs and veal calves carry LA-MRSA in their noses
(poultry, horses, companion animals…)

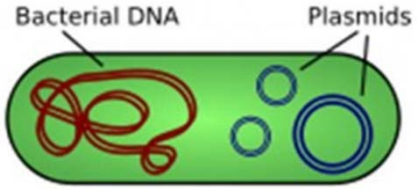
- Increased risk for carriership of farmers and vets
  - Contact infection, no human to human spread,
  - Food products not considered to be an important source

- Global problem

- In NL, measurable effects in human health care
  - Infections
  - Increased costs

Extended Spectrum Beta-lactamases (ESBLs)

- Enzymes that inactivate beta-lactam antibiotics
  - Penicillin, ampicillin, amoxicillin
  - All cefalosporins
- Consequence for infections with ESBL-producers:
  - Impaired treatment, increased risk for patients
- Genes are transferable on plasmids (E. coli/Salmonella)
  - Transmission of ESBLs also via the food-chain!!!

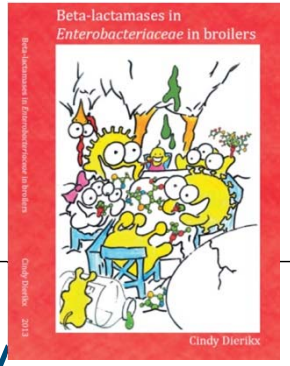


Types of Beta-Lactamases

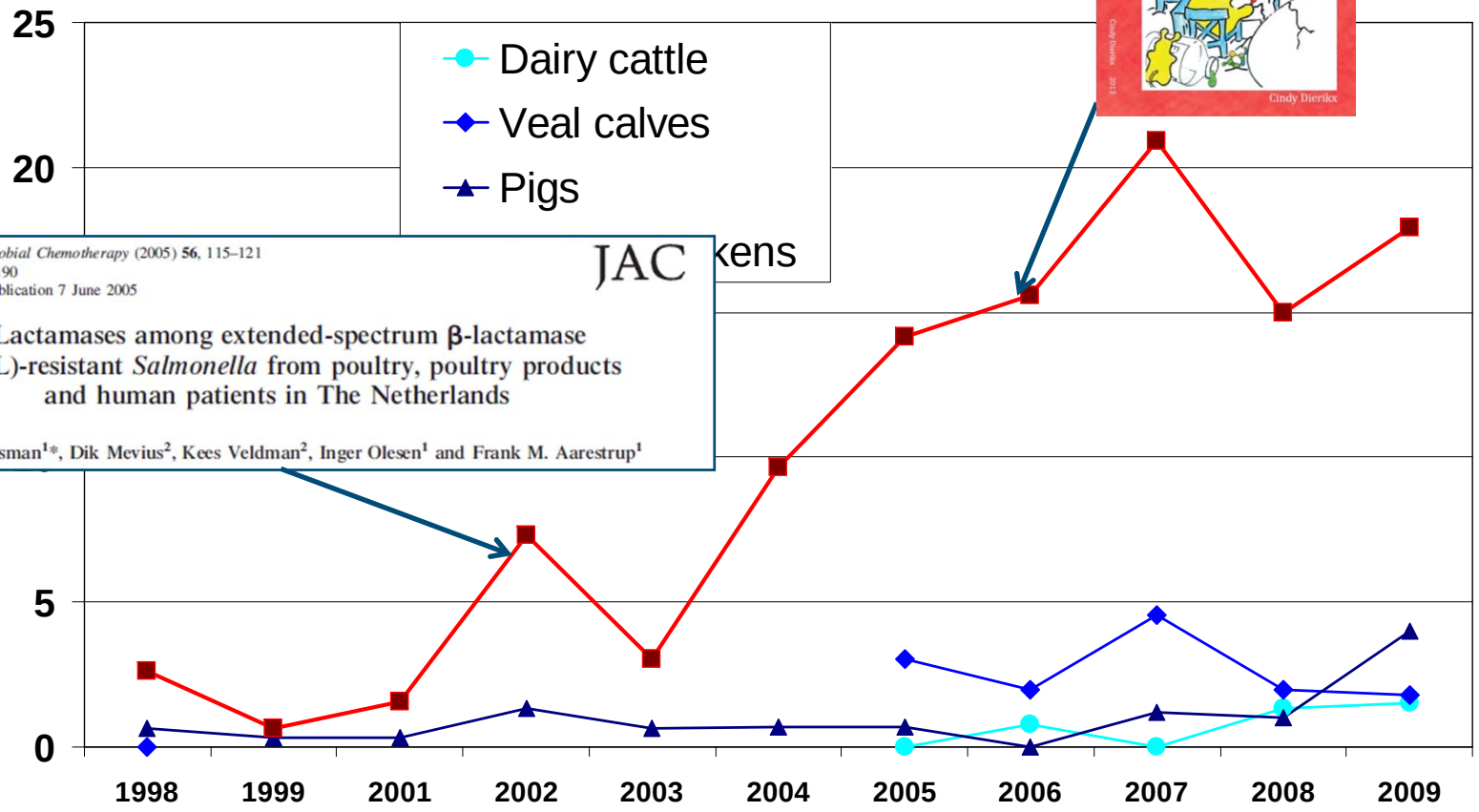
- Beta-Lactamase
  - Penicillinase *bla*$_z$ (S. aureus)
  - TEM-1, SHV-1 (Enterobacteriaceae)
- ESBLs
  - TEM-derivatives, SHV-2 and derivatives, CTX-M, OXA, PER, VEB, GES
- AmpC-group (CMY, DHA etc)
- Carbapenemases (KPC, OXA, IMP, VIM, NDM)

> 1000 variants known
Human: CTX-M-15 (9, 14, 3...)
Animals: CTX-M-1, TEM-52 (CMY-2, SHV-12)

Cefotaxime resistance in E. coli (MARAN-reports)



Cefotaxime R% in E. coli



Journal of Antimicrobial Chemotherapy (2005) **56**, 115–121
doi:10.1093/jac/dki190
Advance Access publication 7 June 2005

JAC

β-Lactamases among extended-spectrum β-lactamase (ESBL)-resistant *Salmonella* from poultry, poultry products and human patients in The Netherlands

Henrik Hasman[1]*, Dik Mevius[2], Kees Veldman[2], Inger Olesen[1] and Frank M. Aarestrup[1]

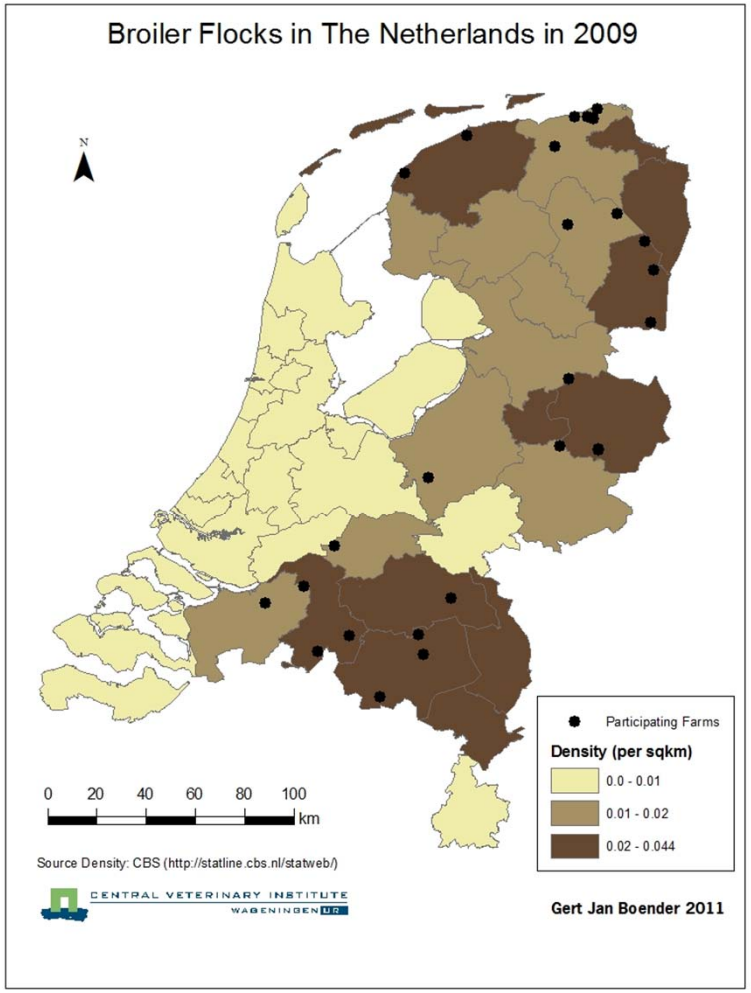
Prevalence of ESBLs in broilers

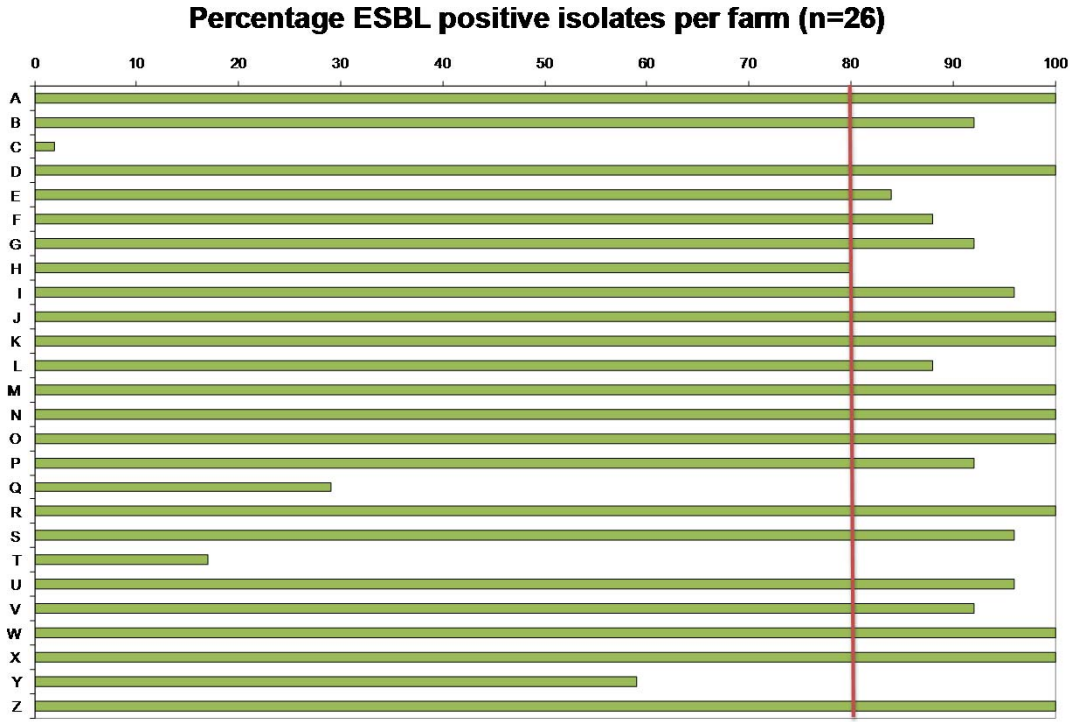
J Antimicrob Chemother 2013; **68**: 60–67
doi:10.1093/jac/dks349 Advance Access publication 4 September 2012

Journal of Antimicrobial Chemotherapy

Extended-spectrum-β-lactamase- and AmpC-β-lactamase-producing *Escherichia coli* in Dutch broilers and broiler farmers

Cindy Dierikx[1]*, Jeanet van der Goot[1], Teun Fabri[2], Alieda van Essen-Zandbergen[1], Hilde Smith[1] and Dik Mevius[1,3]





- All farms ESBL-positive
- > 90% broilers positive

Genetic association with human isolates

ORIGINAL ARTICLE — EPIDEMIOLOGY

Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains

M. A. Leverstein-van Hall[1,2], C. M. Dierikx[3], J. Cohen Stuart[1], G. M. Voets[1], M. P. van den Munckhof[4], A. van Essen-Zandbergen[3], T. Platteel[1,4], A. C. Fluit[1], N. van de Sande-Bruinsma[2], J. Scharinga[1], M. J. M. Bonten[1,5] and D. J. Mevius[3,6]; on behalf of the national ESBL surveillance group*

1) Department of Medical Microbiology, University Medical Centre Utrecht, Utrecht, 2) Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, 3) Department of Bacteriology and TSEs, Central Veterinary Institute of Wageningen UR, Lelystad, 4) SALTRO, Primary Health Care Laboratory, Utrecht, 5) Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht and 6) Department of Infectious Diseases & Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands

CMI, 2011

Level of genetic typing	% of human isolates with poultry associated genetic element[a]
ESBL genes ($bla_{CTX\text{-}M\text{-}1}$, $bla_{TEM\text{-}52}$, $bla_{SHV\text{-}12}$, $bla_{SHV\text{-}2}$ and $bla_{CTX\text{-}M\text{-}2}$)	35% (see Table 1)
$bla_{CTX\text{-}M\text{-}1}$ and $bla_{TEM\text{-}52}$ genes	30% (23.7% $bla_{CTX\text{-}M\text{-}1}$; 6.2% $bla_{TEM\text{-}52}$)
$bla_{CTX\text{-}M\text{-}1}$ and $bla_{TEM\text{-}52}$ genes on IncI1 plasmid	20% (14.2% $bla_{CTX\text{-}M\text{-}1}$; 6.2% $bla_{TEM\text{-}52}$)
$bla_{CTX\text{-}M\text{-}1}$ and $bla_{TEM\text{-}52}$ genes on IncI plasmid belonging to complex CC7 or CC3 and CC5 resp.	19% (12.6% $bla_{CTX\text{-}M\text{-}1}$; 6.2% $bla_{TEM\text{-}52}$)
$bla_{CTX\text{-}M\text{-}1}$ and $bla_{TEM\text{-}52}$ genes on IncI plasmid belonging to complex CC7 or CC3 and CC5 resp. in a poultry-associated MLST strain (ST10, ST58 or ST117)	11% (9.5% $bla_{CTX\text{-}M\text{-}1}$; 2.0% $bla_{TEM\text{-}52}$)

152 citations since 2011

Association with humans

RESEARCH

Extended-Spectrum β-Lactamase Genes of *Escherichia coli* in Chicken Meat and Humans, the Netherlands

Ilse Overdevest, Ina Willemsen, Martine Rijnsburger, Andrew Eustace, Li Xu, Peter Hawkey, Max Heck, Paul Savelkoul, Christina Vandenbroucke-Grauls, Kim van der Zwaluw, Xander Huijsdens, and Jan Kluytmans

EID, 2011

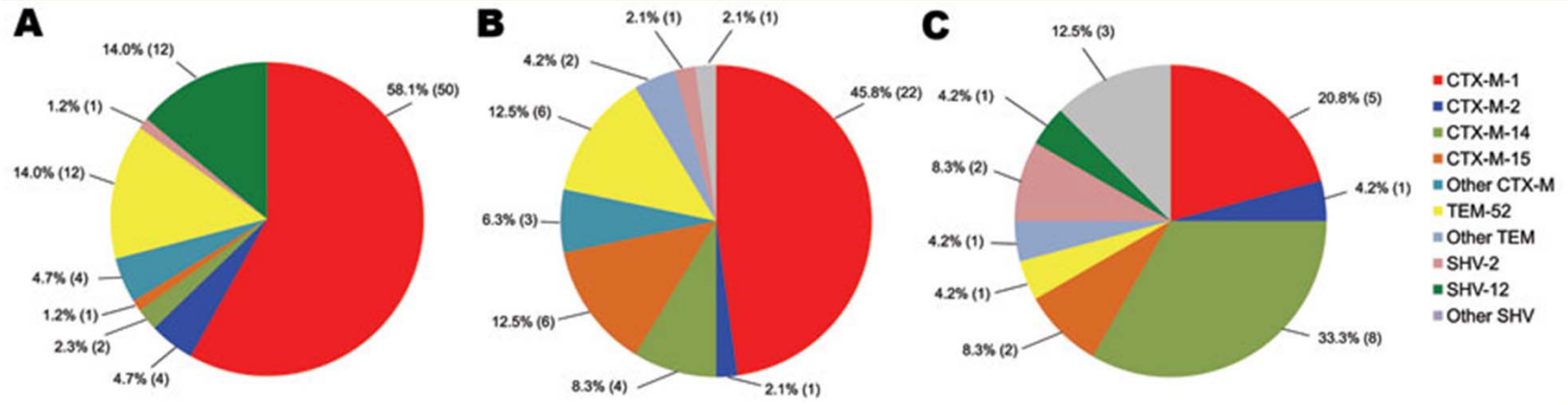


Figure 1. Distribution of extended-spectrum β-lactamase genes in chicken meat (A), human rectal swabs (B), and human blood cultures (C), the Netherlands. Values in parentheses are no. positive.

International Journal of Food Microbiology 154 (2012) 212–214

Contents lists available at SciVerse ScienceDirect

International Journal of Food Microbiology

journal homepage: www.elsevier.com/locate/ijfoodmicro

Short Communication

Comparison of ESBL contamination in organic and conventional retail chicken meat

James Cohen Stuart [a,*], Thijs van den Munckhof [a], Guido Voets [a], Jelle Scharringa [a], Ad Fluit [a], Maurine Leverstein-Van Hall [a,b]

[a] Department of Medical Microbiology, University Medical Center Utrecht, The Netherlands
[b] Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

84 – 100% of poultry meat pos for ESBLs

Pork/beef incidentally pos

- Conclusion:
  - Yes an animal attribution is apparent
  - Poultry meat was considered to be the most likely source

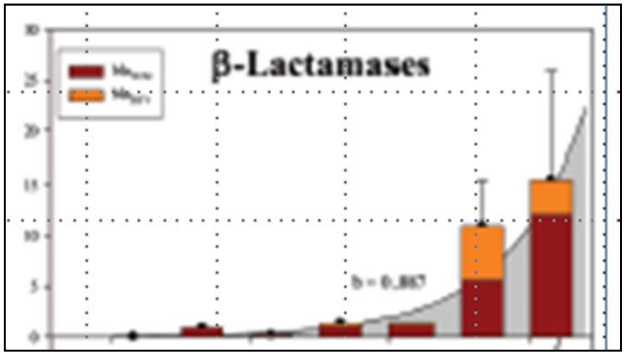
Prevalences in the Netherlands

> 50% in (herds) animals

- Broilers
- Layers
- Veal calves
- Fattening pigs
- Turkeys
- Dogs
- Cattle 41%

Environment

- Soil
- Surface water



Knapp, Dolfing et al. 2009

13% birds (waders)

ESBL-positive


AEM

Characteristics of Cefotaxime-Resistant *Escherichia coli* from Wild Birds in The Netherlands

Kees Veldman,[a] Peter van Tulden,[a] Arie Kant,[a] Joop Testerink,[a] Dik Mevius[a,b]

Department of Bacteriology and TSEs, Central Veterinary Institute of Wageningen UR, Lelystad, The Netherlands[a]; Department of Infectious Diseases and Immunology, Utrecht University, Utrecht, The Netherlands[b]

Is poultry the source or part of the problem??

Determinants for change in policy

- Consecutive crises with PH impact in animal production
  - BSE, Q-fever, MRSA, ESBLs
  - Debate about effects of increase in farm sizes

Reduction targets defined 2010 in Dutch Parliament

- Mandatory reduction of antibiotic usage of 20% in 2012 and 50% in 2013 (compared to 2009)
  - New target = 70% for 2015
  - Preventive use not legal
  - Use of fluoroquinolones, cephalosporins restricted
- No separation between prescription and sales
- One-in-one relationship between farmer and vet
  - No more free distribution of antibiotics
    - Vet is responsible and accountable
  - Health and treatment plan on each farm

Private measures

- All antibiotic use on farms registered
  - Mandatory since 2012 , implemented by private parties involved in two years
  - Transparency and benchmarking
- Independent control institute
  - Netherlands Veterinary Medicines Authority (SDa, www.autoriteitdiergeneesmiddelen.nl)
    - Tasks
      - Report usage data publically,
      - Define target for usage
      - Identify frequent users
      - Control measures to improve usage

BENCHMARKINDICATORS

ACTION LEVEL

Direct measures necessary to reduce antibiotic usage

SIGNALING LEVEL

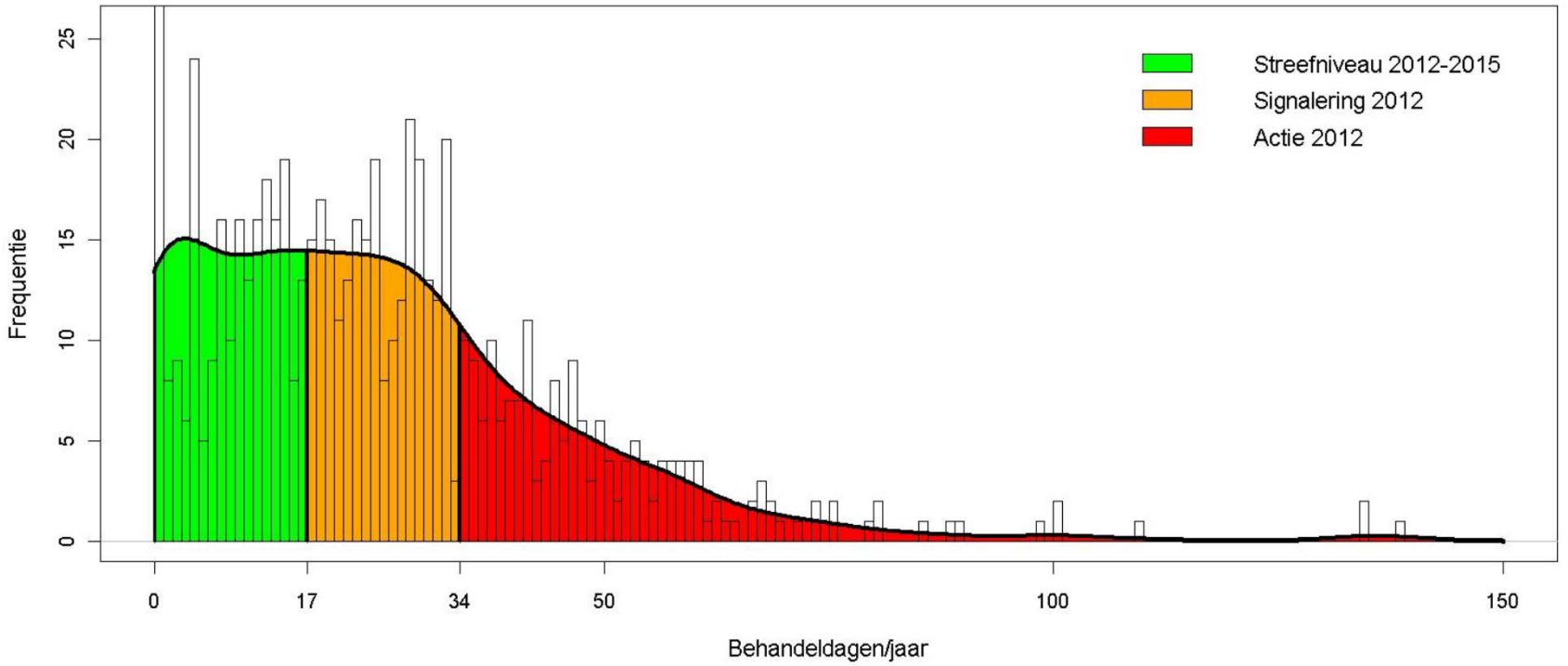
Please be aware

TARGET LEVEL

No direct measures necessary to reduce antibiotic usage

SDa Autoriteit Diergeneesmiddelen

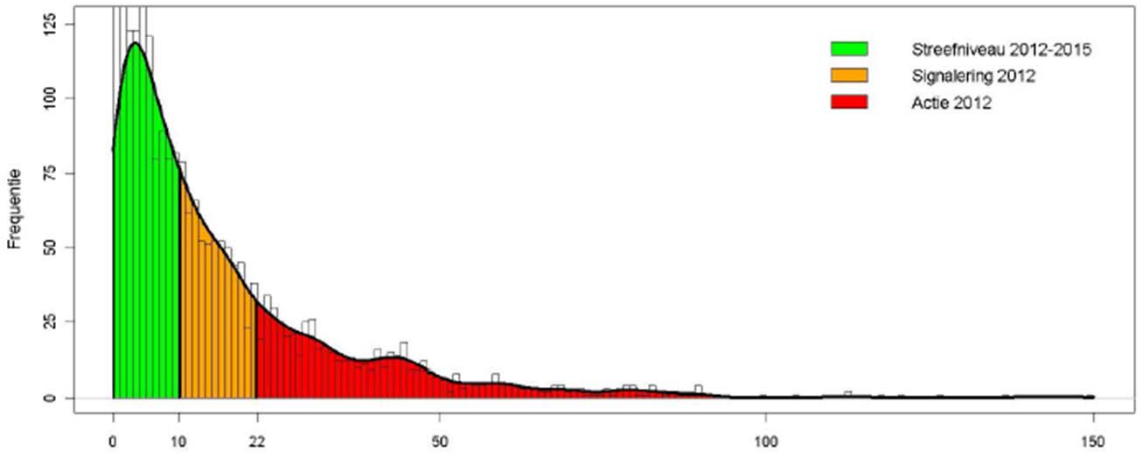
Broilers usage data 2011 (N = 737)



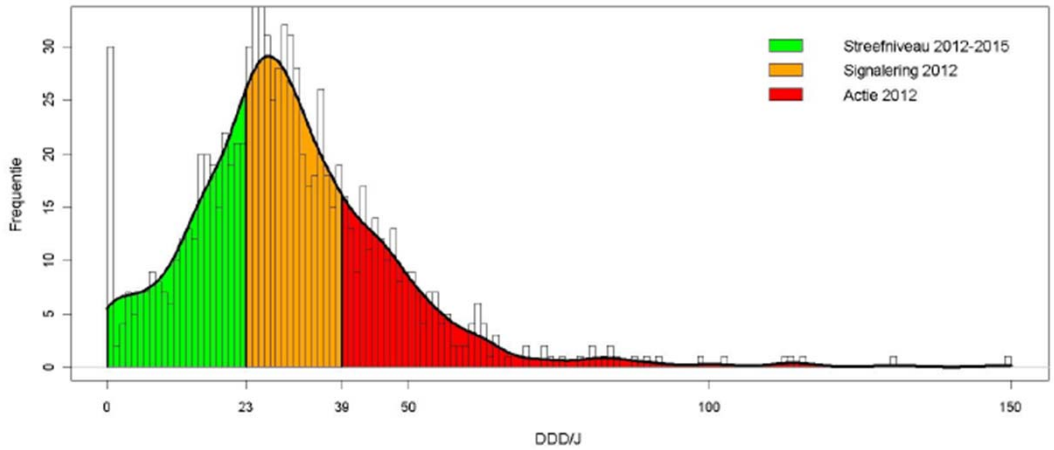
SDa Autoriteit Diergeneesmiddelen

Pig-production farms (top), veal calves (bottom)

Figuur 3A. Frequentieverdeling van DDD/J zoals berekend voor zeugenbedrijven in 2011. De doorgetrokken lijn is de berekende afgevlakte verdeling op basis van het histogram, gebaseerd op de bedrijven met een DDD/J van 0 tot 150.



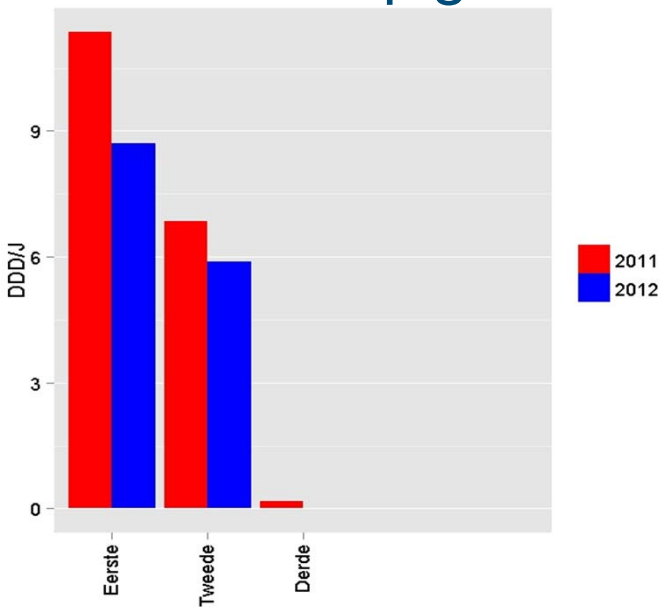
Figuur 2A. Frequentieverdeling van DDD/J zoals berekend voor blankvleesbedrijven in 2011. De doorgetrokken lijn is de berekende afgevlakte verdeling op basis van het histogram, gebaseerd op de bedrijven met een DDD/J van 0 tot 150.



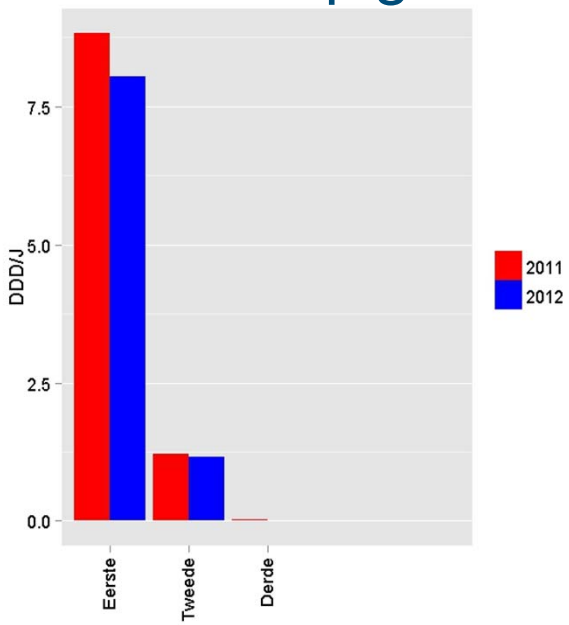
SDa Autoriteit Diergeneesmiddelen

Trends 1st, 2nd 3rd choice antibiotics 2011-2012

Sows and piglets

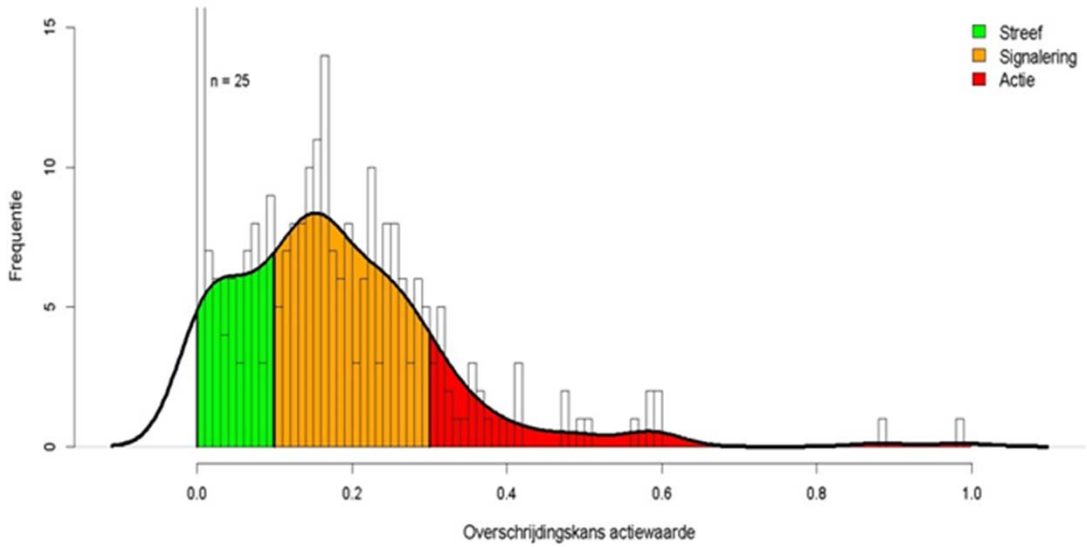


Finisher pigs



SDa Autoriteit Diergeneesmiddelen

Bechmarking of veterinarians



- Based on population of farms it can be identified if vets prescribe systematically more than others
- VBI = veterinary benchmarkindicator

SDa Autoriteit Diergeneesmiddelen

Effect on reduction in sales

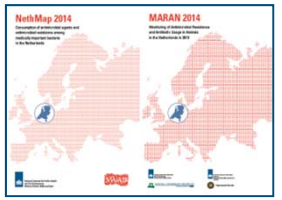
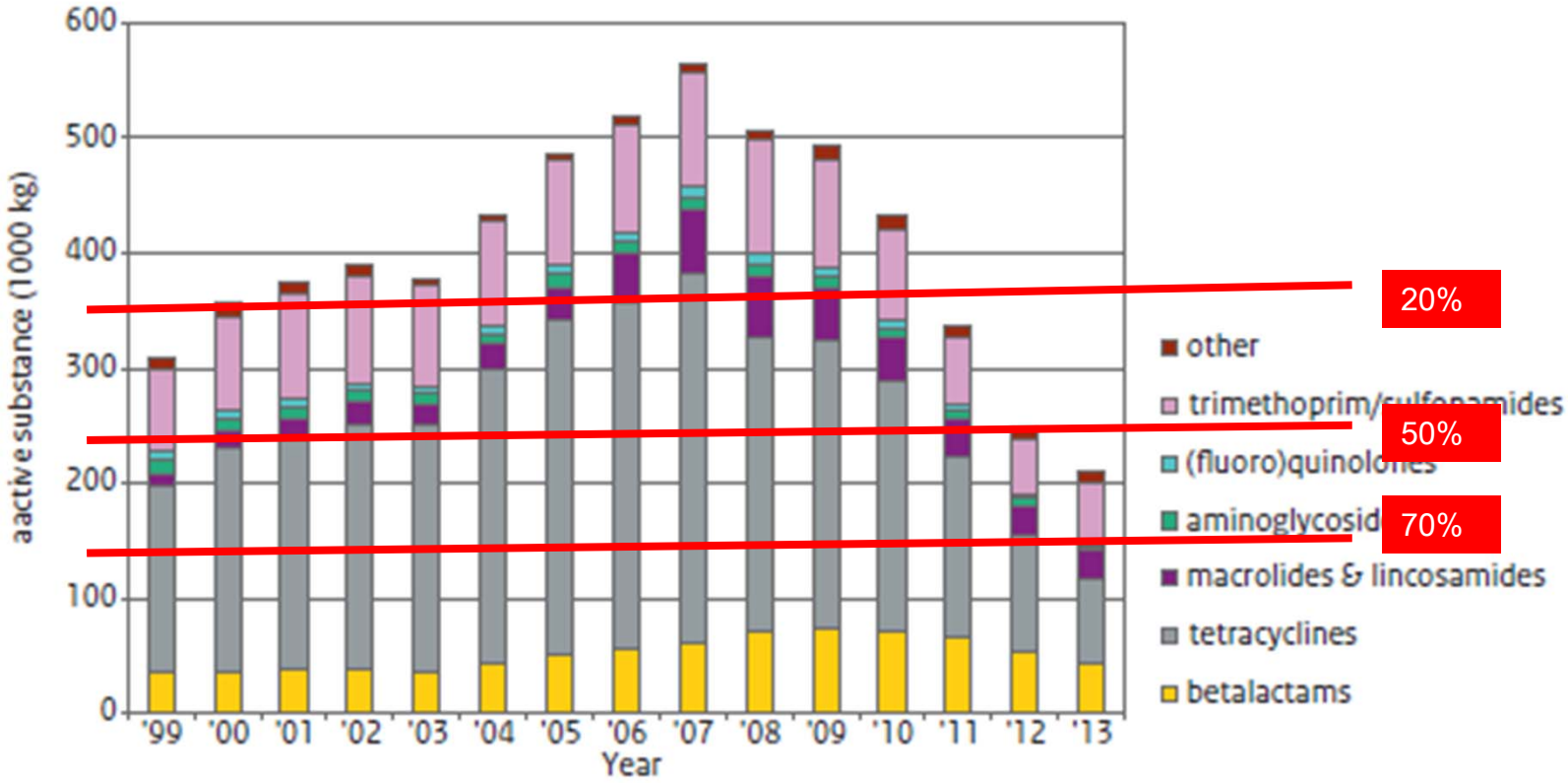


Figure ABuse 01. Antimicrobial veterinary medicinal product sales 1999-2013 in kg (thousands)



(MARAN-2014)
www.maran.wur.nl

Effect of reductions of antibiotic use in animals on the occurrence of antimicrobial resistance in commensal E. coli

Effect of reductions of antibiotic use in animals on the occurrence of antimicrobial resistance in commensal E. coli

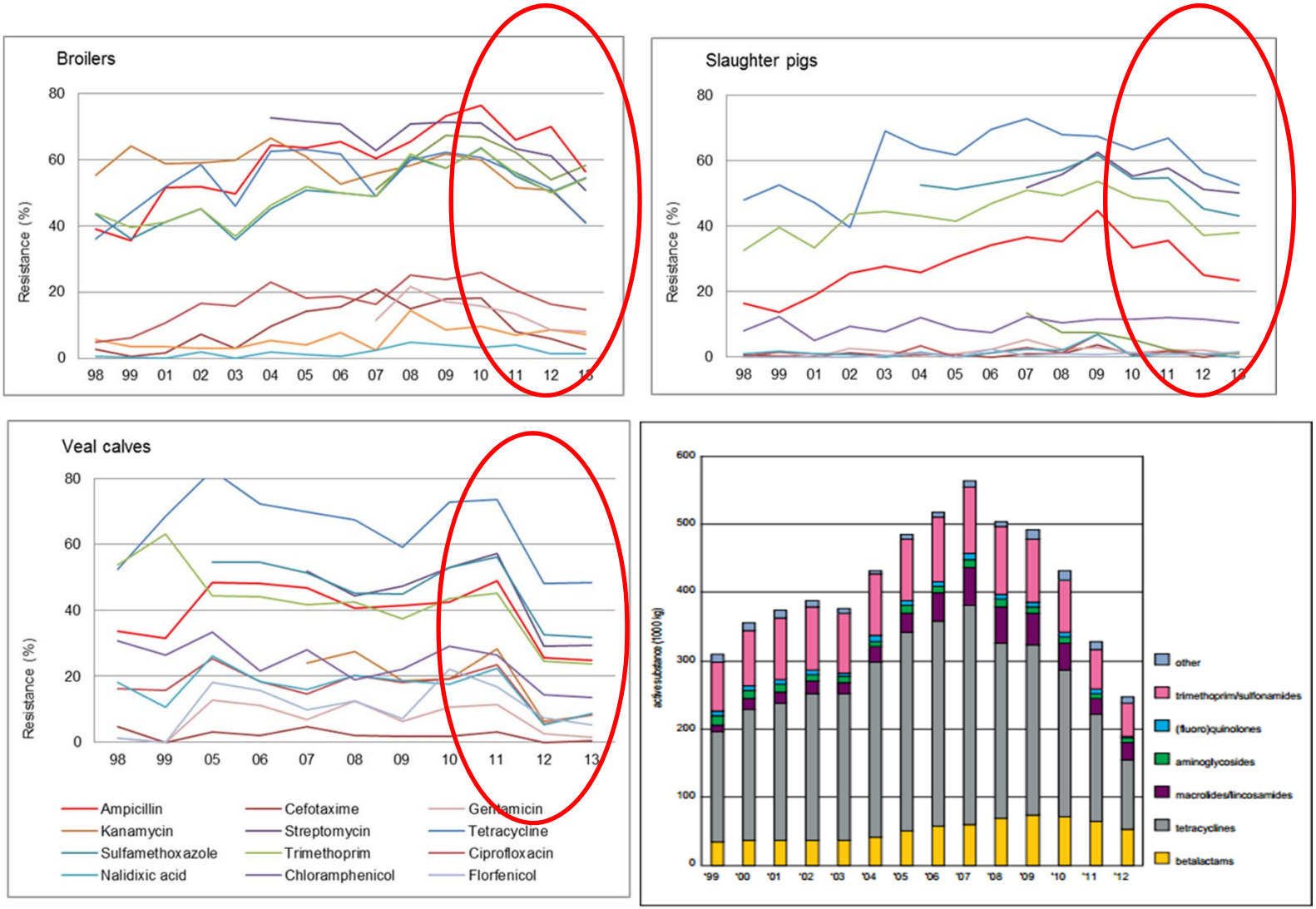
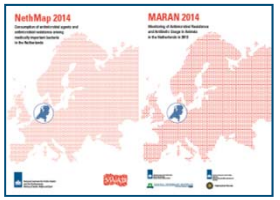
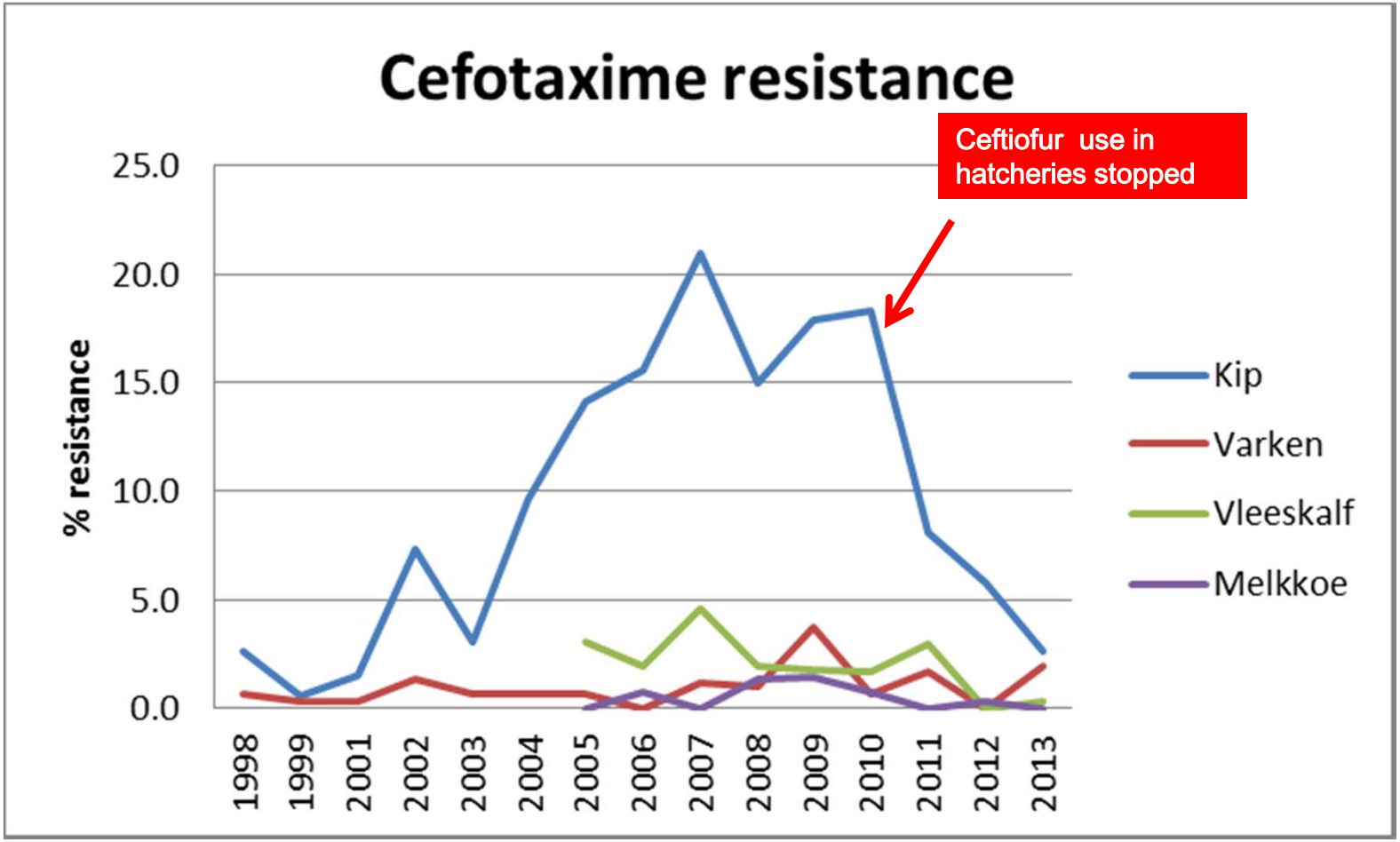


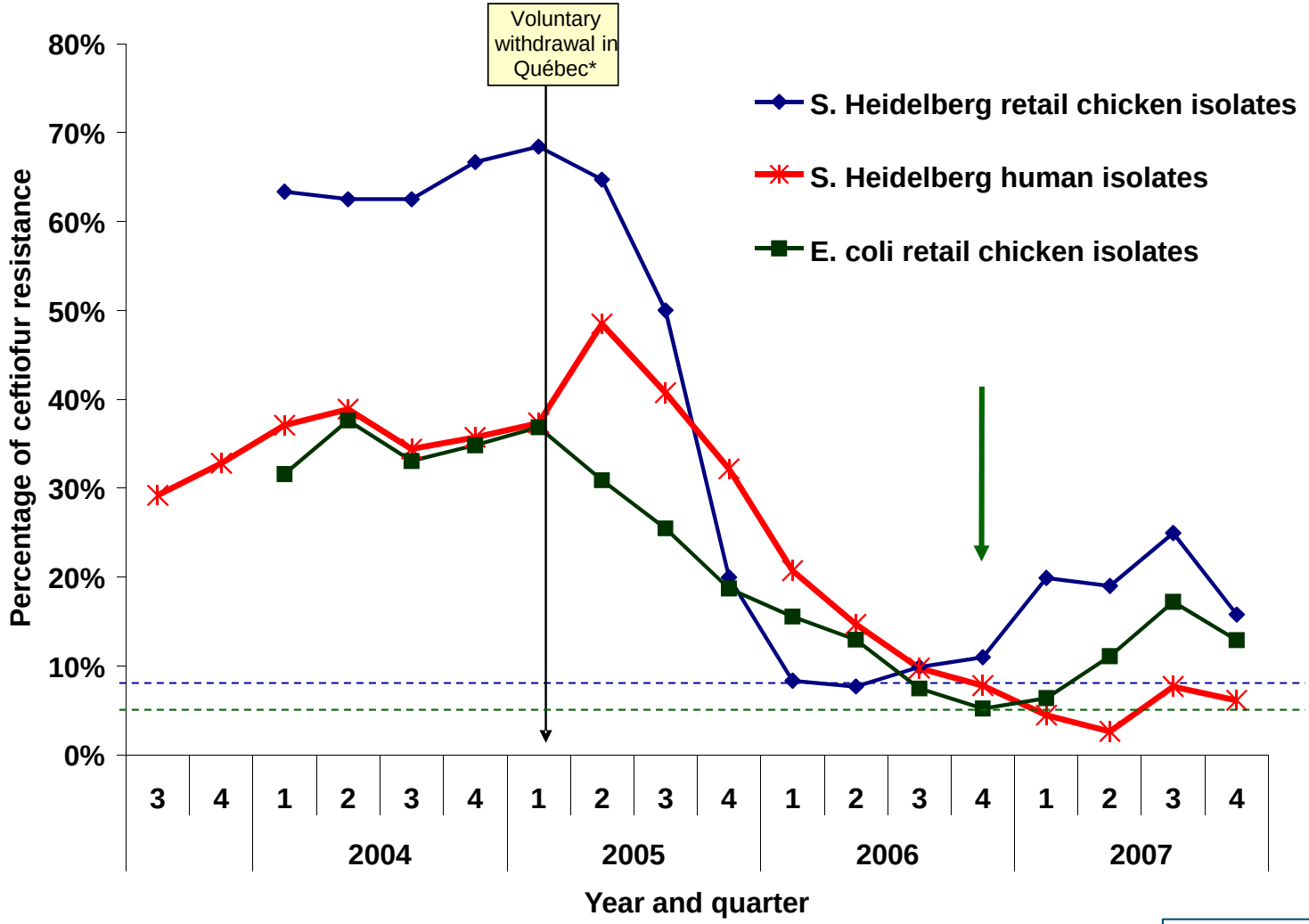
Figure ABuse01. Veterinary therapeutic sales from 1999-2012 (FIDIN-2012).

Effect of reduction of 3e-gen cephalosporins





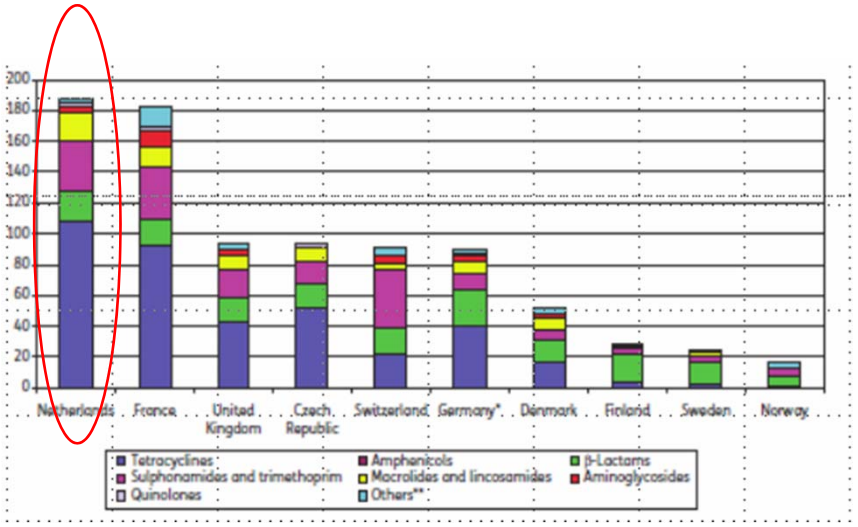
Impact of withdrawal of in ovo use of ceftiofur in Québec



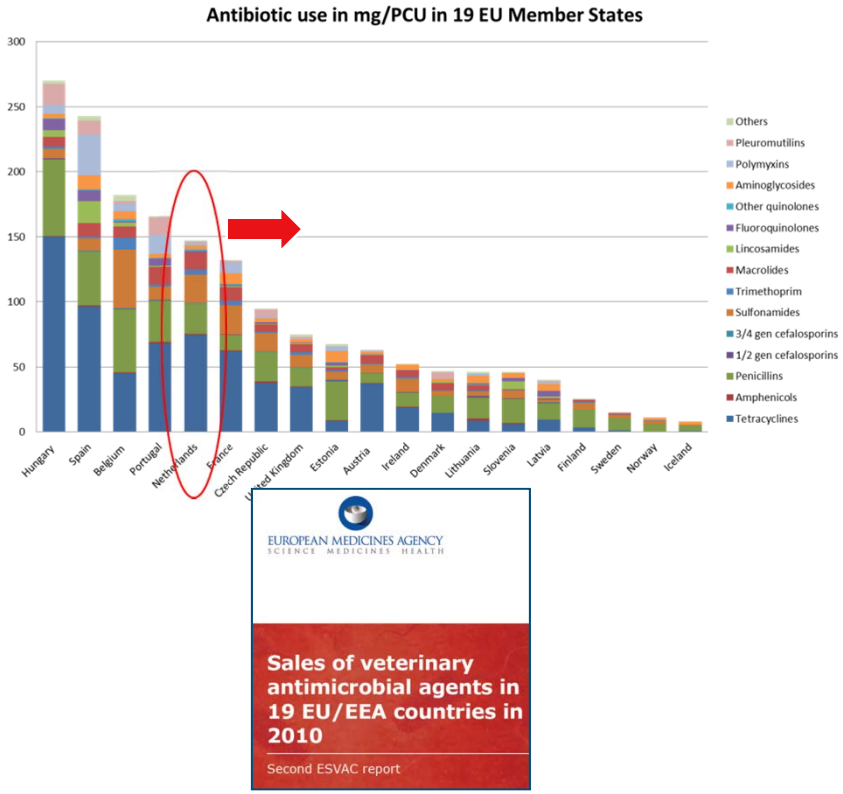
Dutil et al 2010 EID.

Sales of antibiotics for (mg) per kg biomass produced (PCU) in Europe

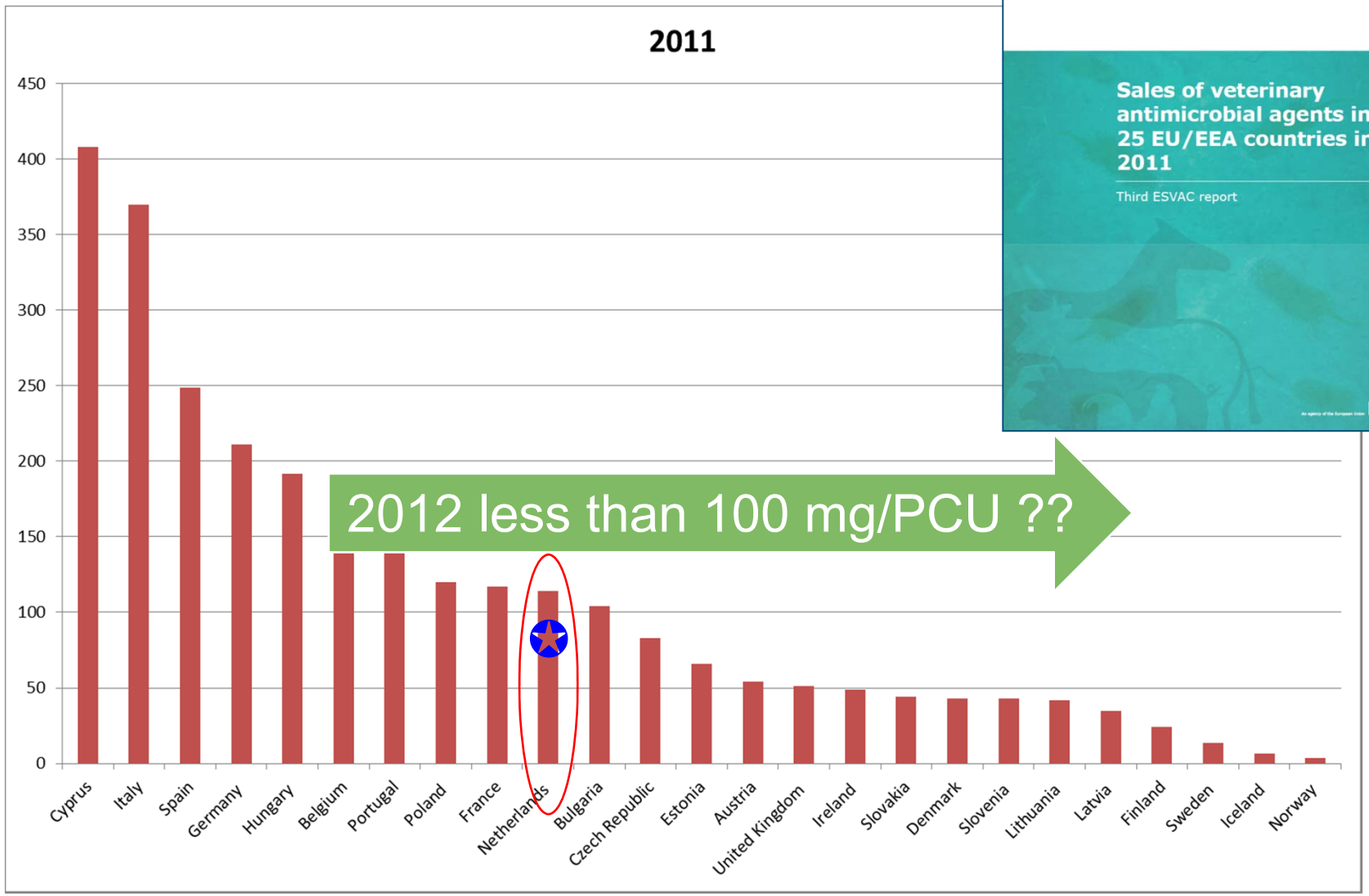
2007



2010



ESVAC 2011


2011
450
400
350
300
250
200
150
100
50
0
Cyprus
Italy
Spain
Germany
Hungary
Belgium
Portugal
Poland
France
Netherlands
Bulgaria
Czech Republic
Estonia
Austria
United Kingdom
Ireland
Slovakia
Denmark
Slovenia
Lithuania
Latvia
Finland
Sweden
Iceland
Norway
2012 less than 100 mg/PCU ??

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011
Third ESVAC report

Critical success factors were

- Clear targets defined by the authorities
- Adaptation of the animal drug law
- Measures initiated by private animal production sectors icw veterinary association aimed at prudent use and transparency
- Independent control institute (SDa)
  - Benchmarking of farms and vets

Carbepenemases in animals.

Are we prepared?

J Antimicrob Chemother 2013
doi:10.1093/jac/dkt260
Advance Access publication 30 June 2013

NDM-1 carbapenemase-producing *Salmonella enterica* subsp. *enterica* serovar Corvallis isolated from a wild bird in Germany

Jennie Fischer, Silvia Schmoger, Silke Jahn, Reiner Helmuth and Beatriz Guerra*

5th Symposium ARAE 2013

012 **The first outbreak of a multidrug resistant *Acinetobacter baumannii* strain on a Dutch animal intensive care unit**
Leendertse M 1,2, Wagenaar JA 1,3, Hordijk J 1, Robben JH 4, Broens E 1

Full Text (PDF)

Emergence of OXA-48 carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* in dogs

J. Antimicrob. Chemother. (2013) 68 (12): 2802-2808
first published online July 5, 2013

Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Advies
Preventie en bestrijding van carbapenemresistentie in Nederland

J Antimicrob Chemother
doi:10.1093/jac/dks108

***Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm**

Jennie Fischer[1], Irene Rodríguez[1], Silvia Schmoger[1], Anika Friese[2], Uwe Roesler[2], Reiner Helmuth[1] and Beatriz Guerra[1]*

[1]Federal Institute for Risk Assessment, BfR, Department for Biological Safety, Max-Dohm Strasse 8–10, D-10589 Berlin, Germany; [2]Free University Berlin, FU, Institute of Animal Hygiene and Environmental Health, Philippstr. 13, D-10115 Berlin, Germany

J Antimicrob Chemother 2013
doi:10.1093/jac/dks393
Advance Access publication 2 October 2012

***Salmonella enterica* subsp. *enterica* producing VIM-1 carbapenemase isolated from livestock farms**

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