18 november 2015

Europese Antibioticadag

Een Europees gezondheidsinitiatief

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"One Health Strategy" and International Initiatives

Herman Goossens

Voorzitter BAPCOC

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Agenda

- International initiatives
- One health
- Belgium
- BAPCOC

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International initiatives

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- Global:
  - Review on Antimicrobial Resistance
  - WHO HQ – WHA, Global Action Plan => UN General Assembly September 2016
  - G7 and G20
  - Global AMR Policy Science Summit (28-29 April 2016)
- Regional:
  - WHO regions: e.g. WHO Euro
  - US, EU
- Trans-regional:
  - Transatlantic Task Force on Antimicrobial Resistance (TATFAR)
  - Global Health Security Agenda (GHSA)
- Cross-country:
  - E.g. Nordic
- National
  - E.g. EU Member States, Turkey, China ...

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GLOBAL

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Review on Antimicrobial Resistance

David Cameron calls for action on antibiotic resistance

2 July 2014 Last updated at 02:14 BST

Prime Minister David Cameron has called for global action to tackle the growing threat of resistance to antibiotics.

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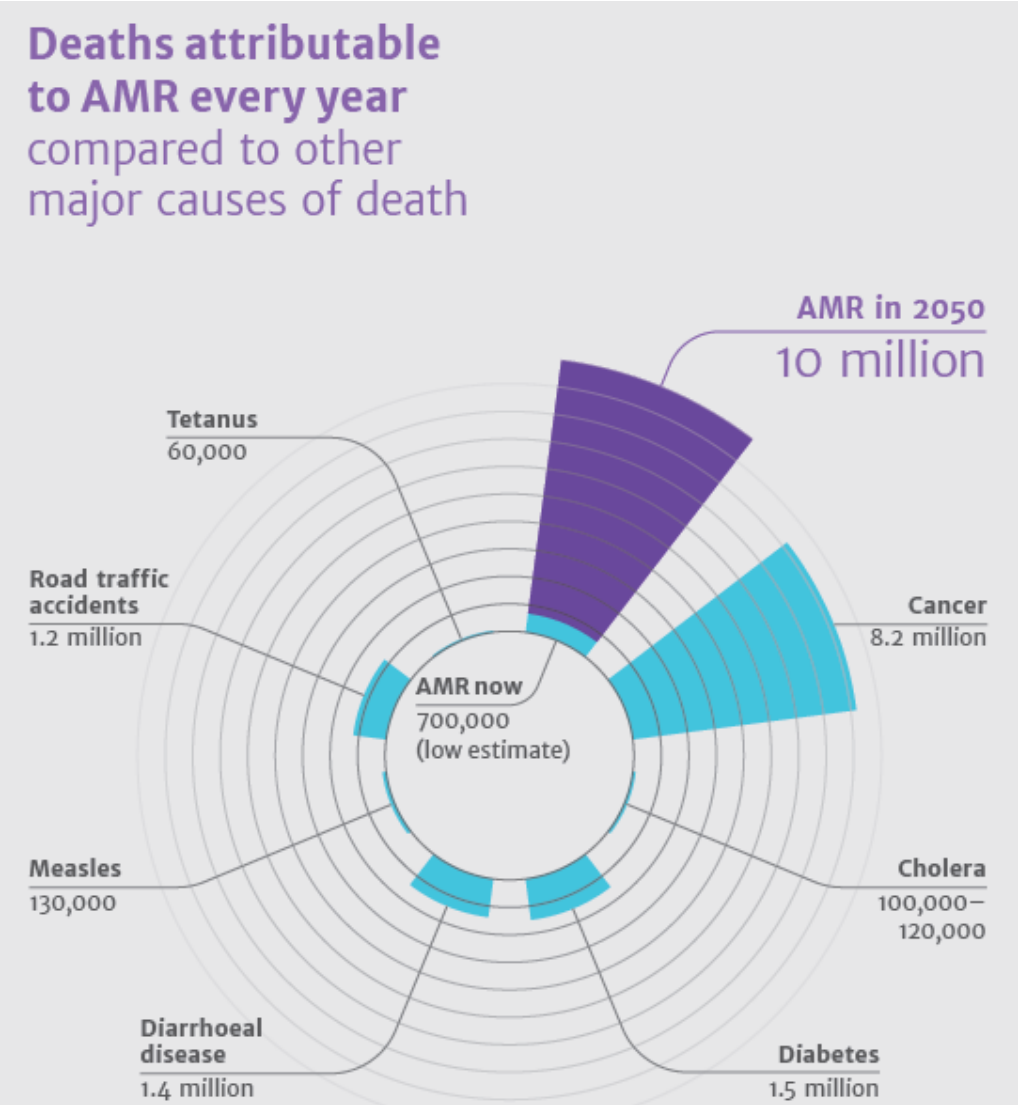
Review on Antimicrobial Resistance, Chaired by Jim O'Neil, December 2014



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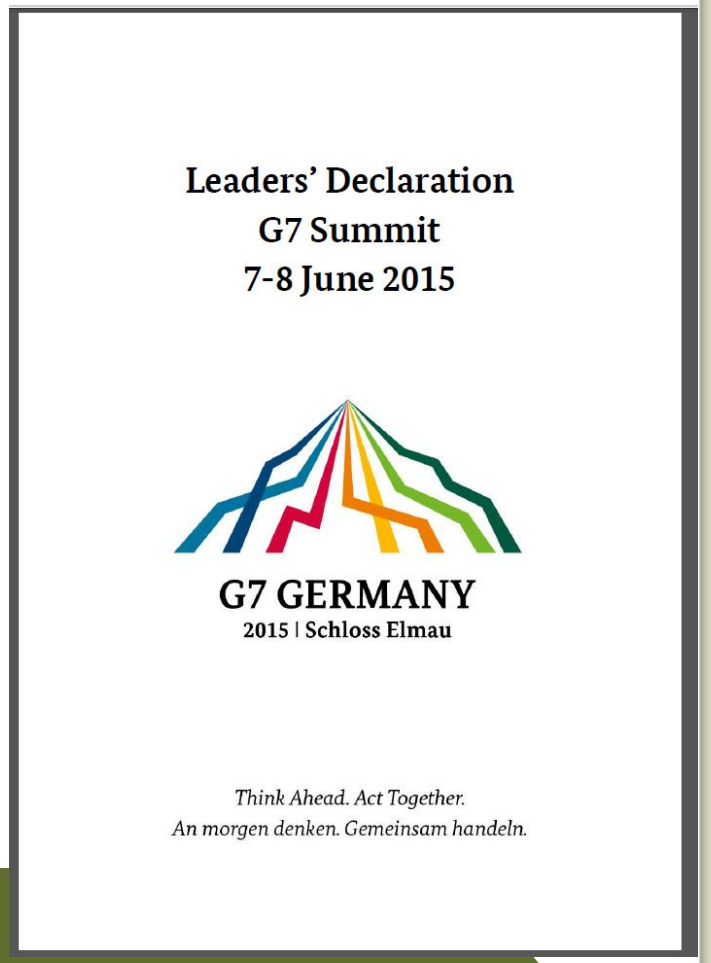
G7 Summit, 7-8 June 2015

- Stimulate innovation
- Intensify dialogue with
  - the pharmaceutical, biotechnology and food industries
  - WHO, OIE, and FAO
- Pool national efforts
- Hold a G7-Meeting to promote responsible use of antibiotics


Leaders' Declaration
G7 Summit
7-8 June 2015

G7 GERMANY
2015 | Schloss Elmau

Think Ahead. Act Together.
An morgen denken. Gemeinsam handeln.

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G7 Health ministers summit

Berlin, 8-9 October 2015

"Given the global nature of drug research, development and commercialisation and the global challenge antimicrobial resistance poses, we call for **greater interaction and synergies** between research initiatives. We see the need for **global access** to – and availability, affordability and rational use of – safe, effective and quality-assured antimicrobials. We will therefore explore the feasibility and need of setting up a **global antibiotic product development partnership** for new and urgently needed antibiotics, vaccine development, alternative therapies and rapid point of care diagnostics and seek collaboration with others such as WHO and Drugs for Neglected Disease Initiative (DNDi).

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G7 Health ministers summit ctd.

We are committed to explore **innovative economic incentives** to enhance the research and development of new antibiotics, other therapeutic options, and diagnostics. We will investigate various instruments, such as a **global antibiotic research fund** and a **market entry reward mechanism** for truly new antibiotics targeting the most important pathogens and most needed for global public health. We recognise and commend the work of various reviews on AMR, such as the OECD, and other independent Reviews on AMR, tackling the lack of new antibiotics internationally and the initial proposals on how governments around the world could act collectively to stimulate innovation from a range of organisations, private or public, big or small."

Next Meeting: Kobe September 2016

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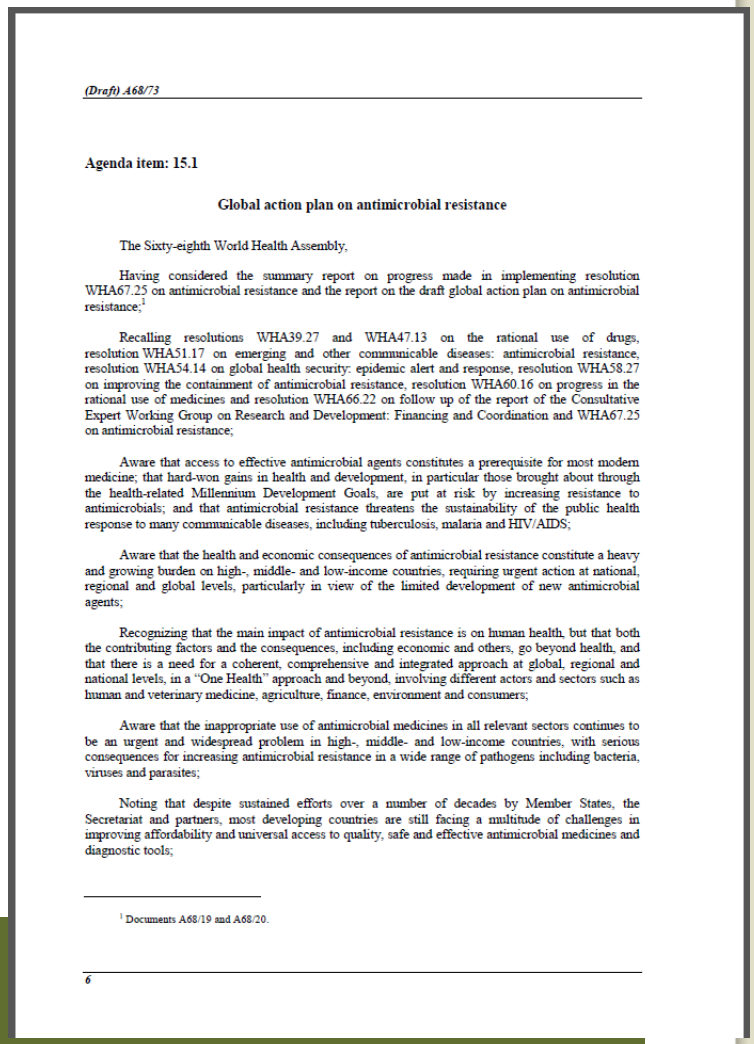
WHO Global Action Plan (WHA, May 2015)

Partnerships:

- Coordination of initiatives
- Identifying priorities
- Securing and managing investments
- Affordable and equitable access
- Open collaborative models of R&D

National Action Plan in place by mid 2017



(Draft) A68/73

Agenda item: 15.1

Global action plan on antimicrobial resistance

The Sixty-eighth World Health Assembly,

Having considered the summary report on progress made in implementing resolution WHA67.25 on antimicrobial resistance and the report on the draft global action plan on antimicrobial resistance;[1]

Recalling resolutions WHA39.27 and WHA47.13 on the rational use of drugs, resolution WHA51.17 on emerging and other communicable diseases: antimicrobial resistance, resolution WHA54.14 on global health security: epidemic alert and response, resolution WHA58.27 on improving the containment of antimicrobial resistance, resolution WHA60.16 on progress in the rational use of medicines and resolution WHA66.22 on follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination and WHA67.25 on antimicrobial resistance;

Aware that access to effective antimicrobial agents constitutes a prerequisite for most modern medicine; that hard-won gains in health and development, in particular those brought about through the health-related Millennium Development Goals, are put at risk by increasing resistance to antimicrobials; and that antimicrobial resistance threatens the sustainability of the public health response to many communicable diseases, including tuberculosis, malaria and HIV/AIDS;

Aware that the health and economic consequences of antimicrobial resistance constitute a heavy and growing burden on high-, middle- and low-income countries, requiring urgent action at national, regional and global levels, particularly in view of the limited development of new antimicrobial agents;

Recognizing that the main impact of antimicrobial resistance is on human health, but that both the contributing factors and the consequences, including economic and others, go beyond health, and that there is a need for a coherent, comprehensive and integrated approach at global, regional and national levels, in a "One Health" approach and beyond, involving different actors and sectors such as human and veterinary medicine, agriculture, finance, environment and consumers;

Aware that the inappropriate use of antimicrobial medicines in all relevant sectors continues to be an urgent and widespread problem in high-, middle- and low-income countries, with serious consequences for increasing antimicrobial resistance in a wide range of pathogens including bacteria, viruses and parasites;

Noting that despite sustained efforts over a number of decades by Member States, the Secretariat and partners, most developing countries are still facing a multitude of challenges in improving affordability and universal access to quality, safe and effective antimicrobial medicines and diagnostic tools;

[1] Documents A68/19 and A68/20.

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Global AMR Policy Science Summit

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- **Hosted by Wellcome Trust, supported by Department of Health, UK, and WHO**
- **Meeting 26 - 27 April 2016, London (tbc)**
- **Purpose:** The purpose is to bring together key leaders in the global scientific community and the key relevant policy makers, with a view to exploring the robustness of the science and evidence base behind the detail of the global AMR policy initiatives covering both the human and animal sectors.
- **Participants:** About 100-150 scientific and policy representatives from: Wellcome Trust, Royal Society/Academy of Medical Sciences, MRC, ARHAI and DARC expert committees, Regulatory representative, PHE & VMD, WHO/FAO/OIE/European Food Safety Authority, CDC, Center for Disease Dynamics, Economics & Policy, Washington DC, BRICs countries , Commonwealth Secretariat, NGOs, Industry, Médecins Sans Frontières & Vétérinaires Sans Frontiéres
- **Outcome:** A formal report and recommendations, which will summarise the available scientific evidence base for setting specific targets for combating antimicrobial resistance within national action plans.

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Joint Programming AMR

ARGENTINA
CANADA
BELGIUM
CZECH REPUBLIC
DENMARK
ESTONIA
FINLAND
FRANCE
GERMANY
GREECE
ISRAEL
ITALY
JAPAN
THE NETHERLANDS
NORWAY
POLAND
ROMANIA
SPAIN
SWEDEN
SWITZERLAND
TURKEY
THE UNITED KINGDOM

22 COUNTRIES
TO DATE HAVE JOINED FORCES
TO DEFINE A COMMON VISION

22 countries to date have joined forces to define a common vision, a strategic research agenda and joint planning as well as implementation of national research programmes

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Innovative Medicines Initiative (IMI): a new way to collaborate

- The largest public-private partnership in life science R&D
- IMI1 Started in 2008, ended in 2014
  - 11 Calls launched

EFPIA = **E**uropean **F**ederation of **P**harmaceutical **I**ndustries and **A**ssociations

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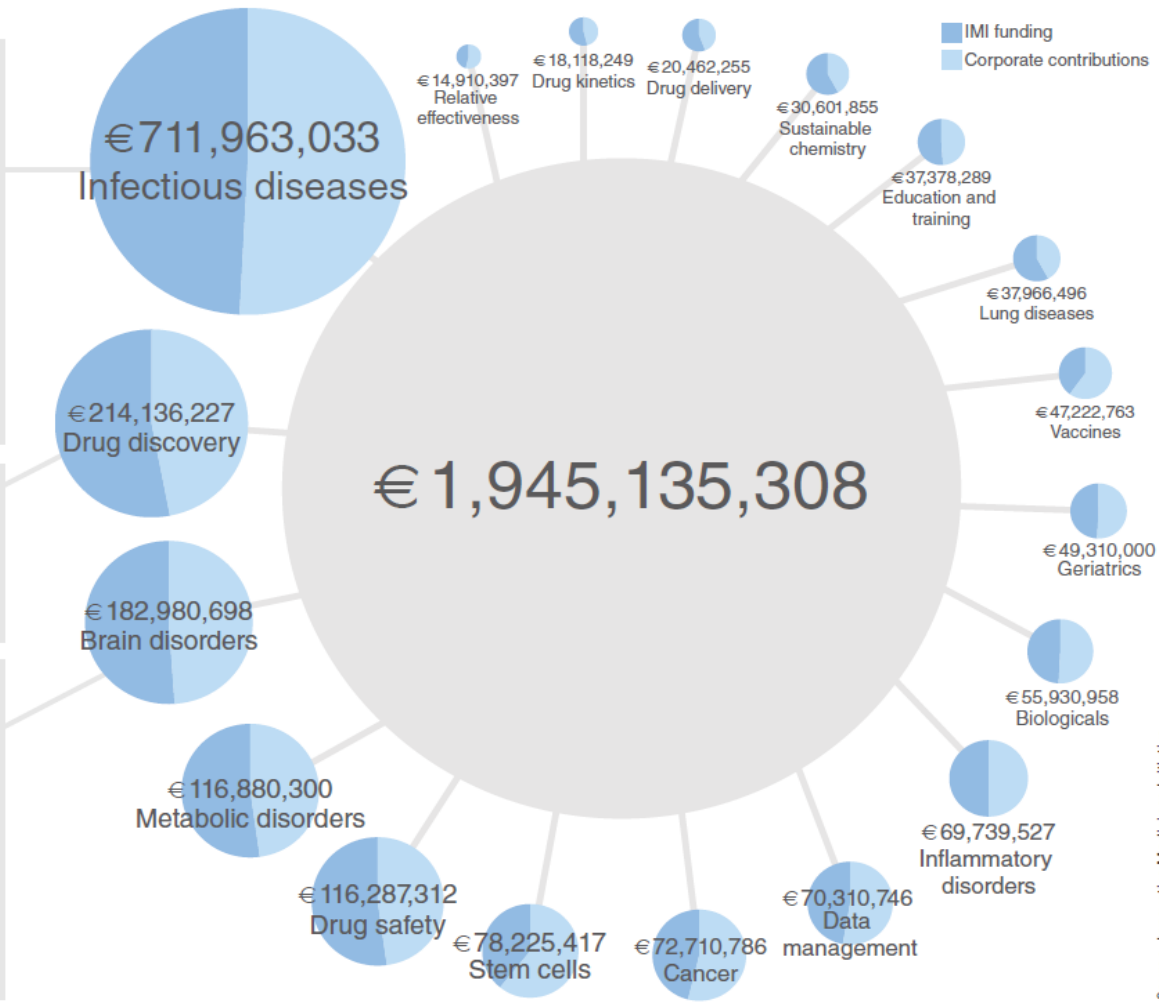
Infectious disease leads in first phase of Europe's IMI effort

Partners

AiCuris	GSK
Animal Health	**Janssen**
Division of Sanofi	Johnson & Johnson
Astellas	**MedImmune**
AstraZeneca	Merck
AstraZeneca/	**Merck Sharp &**
MedImmune	**Dohme**
Basilea	Merial
Boehringer	**Novartis**
Ingelheim Animal	Pfizer
Health	**Rempex**
Cubist	Sanofi

AstraZeneca	**Novartis**
Bayer	Pfizer
Janssen	**Sanofi**
Lundbeck	UCB
Merck	

Abbott	**Eli Lilly**
AbbVie	Esteve
AC Immune	**GRT**
Amgen	GlaxoSmithKline
Astellas	**HLU**
AstraZeneca	IDRS
Biogen Idec	**Janssen**
Boehringer	Lundbeck
Ingelheim	**Merck**
Eisai	



Source: Innovative Medicines Initiative

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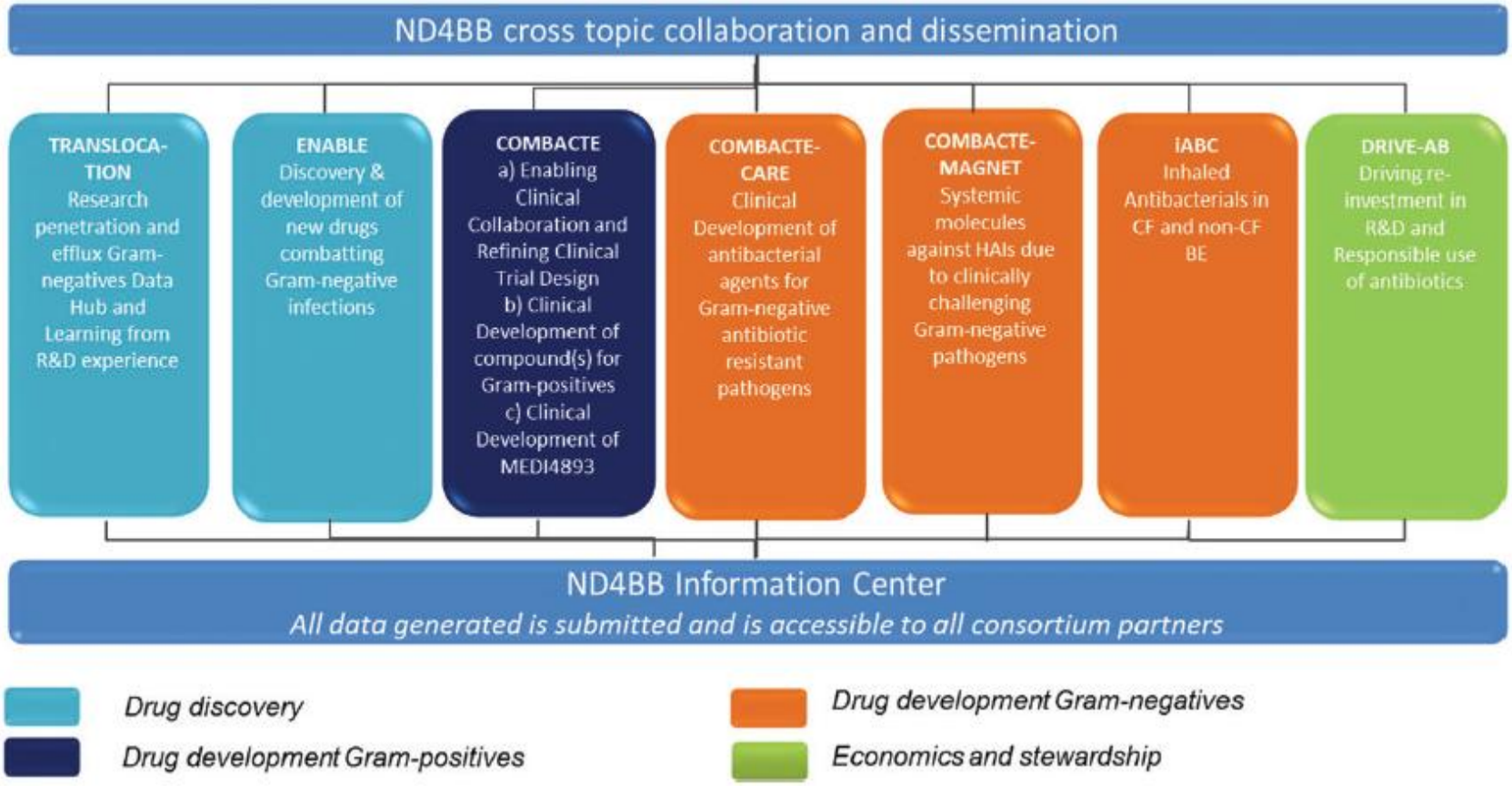
ND4BB Programme



Kostyanev, J Antimicrob Chemother, 16 November 2015

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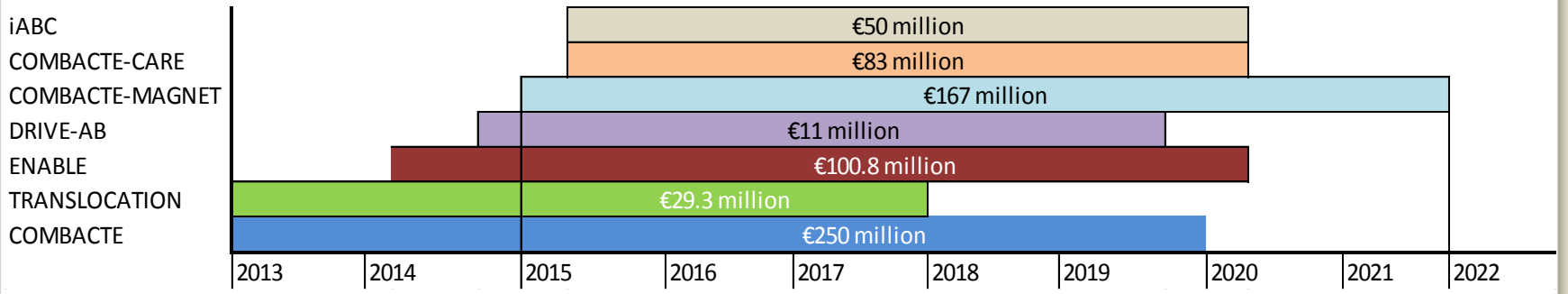
Timeline and total budget estimation of the seven topics of the ND4BB programme.

Total: €643.6M



NL EU Presidency – AMR event 2016

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Meeting of Ministers of Health and Agriculture on Antimicrobial Resistance, February 9 and 10, 2016 in Amsterdam

Objectives formulated by the Dutch EU-presidency:

- One health leadership
- Solid national action plans
- Commit to EU Action
- Legislate prudent use of antibiotics in animals in the interest of public health
- A next step in the development of new antibiotics

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US Presidential Initiatives: CARB

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State of the Union
Jan 2014

PCAST Report & National Strategy
18 Sept 2014

Executive Order on CARB
18 Sept 2014

National Action Plan for CARB
27 March 2015

CARB Presidential Advisory Council
Sept 2015

Combating
Antibiotic-
Resistant
Bacteria

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USA National Targets (2014 - 2020)

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- At least 95% of eligible hospitals will report antibiotic use data to the National Healthcare Safety Network (NHSN).
- Inappropriate inpatient antibiotic use for monitored conditions/agents will be reduced by 20% from 2014 levels.
- Inappropriate outpatient antibiotic use for monitored conditions/agents will be reduced by 50% from 2010 levels.
- Moreover: condition of Participation in Medicare
  Every hospital, ASC and LTC facility must have an antibiotic stewardship program by the end of 2017

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Agency Actions: Agriculture

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FDA Guidance 213 (Dec. 2013)

- Voluntary, but has led to permanent label changes
- Animal feed directive now requires prescribing by vet

USDA/agriculture well represented on CARB; 5/15 members

Leading companies are responding to consumer demand: Chipotle, McDonalds, Panera, Walmart & Sams Club US, Chick-Fil-A, Subway

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Trans Atlantic Task Force on Antimicrobial Resistance - TATFAR

The EU-US Summit Declaration called for the establishment of "*…a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us*".

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TATFAR Initiatives

TATFAR report was made public on 22 Sept 2011

Full report available at: http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/210911_TATFAR_Report.pdf

TATFAR has identified a set of 17 recommendations in key areas where future cooperation would prove fruitful:

-Common indicators of surveillance of antimicrobial use

-Joint EU-US clinical trials (CTTI, ARLI, ND4BB): Meeting 21-22 January 2016 in Stockholm

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Conclusions

- Most significant attention ***ever*** from senior global political leadership
- Access, conservation and innovation, in the context of One Health
- Innovation – growing consensus on need for strong pull incentive, including delinked post-approval payments
- National variations possible within a global framework

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National Targets in China

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OPEN ACCESS Freely available online

PLOS | MEDICINE

Health in Action

Changes in Chinese Policies to Promote the Rational Use of Antibiotics

Yonghong Xiao*, Jing Zhang, Beiwen Zheng, Lina Zhao, Sujuan Li, Lanjuan Li*

Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Target for general hospitals: “antibiotic utilization in inpatients should be less than 40 DDD/ per 100 patient days.“

Government policy, Initiation in May 2011 by vice-minster of China

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National targets in Sweden - 2011 - 2014

Antibiotic prescribing indicator: increased adherence to treatment guidelines for infections in outpatient care, and thereby a decrease in antibiotic prescribing.

- Long term target for 2014: 250 prescriptions/1000 inhabitants and year
- Target for 2011: decrease by 10% of the difference between current level and long term target

The indicator was based on calculations from a diagnosis-prescribing study about respiratory tract infections in primary care

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National targets in Norway - 2015-2020

Antibiotic use will be reduced by 30 percent measured in DDD/1000 inhabitants/days, compared with 2012

Norway will be one of the three European countries that uses the least antibiotics in humans, measured in DDD/1000 inhabitants/day

Prescription of antibiotics will be reduced from an average today of 450 prescriptions per 1000 inhabitants per year to 250 prescriptions per 1000 inhabitants per year.

Prescription of antibiotics for respiratory infections will be reduced by 20 percent measured in DDD/1000 inhabitants/day compared to 2012.

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National targets in the UK 2015 - 2019

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Primary care

Measures to reduce total antibiotic prescribing:

Total antibiotic prescribing to be reduced to 2010 levels at CCG level as measured by number of antibiotic prescriptions ("items") per 100 patients per year

Measures to encourage narrow spectrum antibiotic prescribing

Proportion of antibiotics from cephalosporin, quinolone or co-amoxiclav classes to be reduced to less than the current median for English CCGs as measured by the number of prescriptions ("items") from target classes in comparison with the total number of antibiotic prescriptions per year.

Hospital care

Measures to reduce total antibiotic prescribing

Total antibiotic consumption to be reduced by 1% per year 2015-2019 as measured by DDD per 1000 admissions per year.

Measures to encourage narrow spectrum antibiotic prescribing

Total carbapenem consumption to be reduced to 2010 consumption levels as measured by DDD per 1000 admissions per year.

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One Health

ESBLs is a One-Health problem

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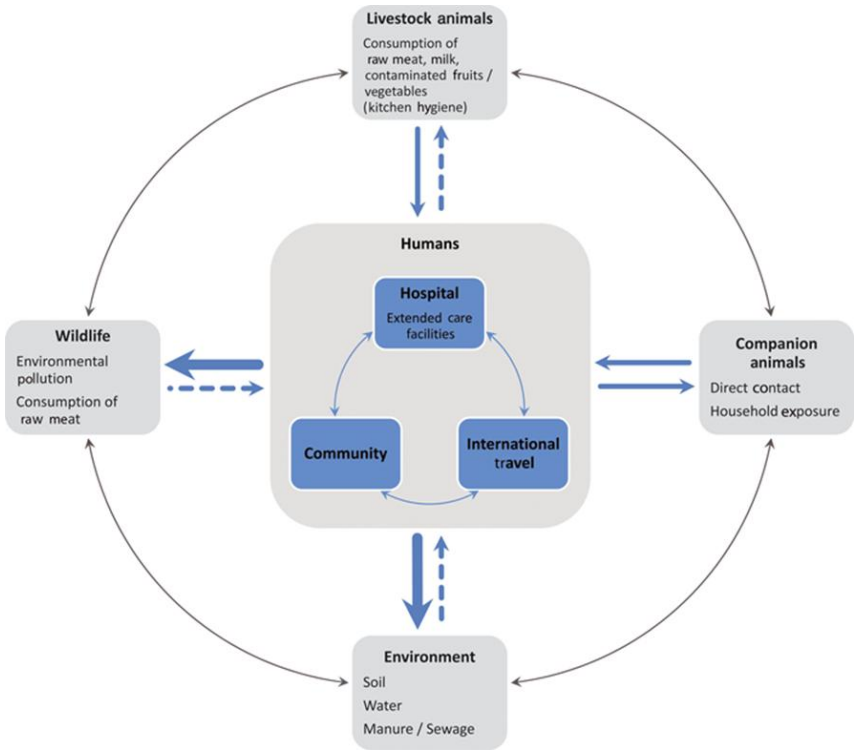
Dominated in humans by human to human transmission of successful "human-adapted-ESBL producing strains"

Attribution from animals by transfer of ESBL-genes on plasmids



Ewers et al. Clin Microbiol Infect. 2012; 18: 646-55

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ESBL-Producing Gram-Negatives in food

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

ELSEVIER

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 positive for ESBLs
- Pork/beef incidentally positive

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Association with humans

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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[1], 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

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

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

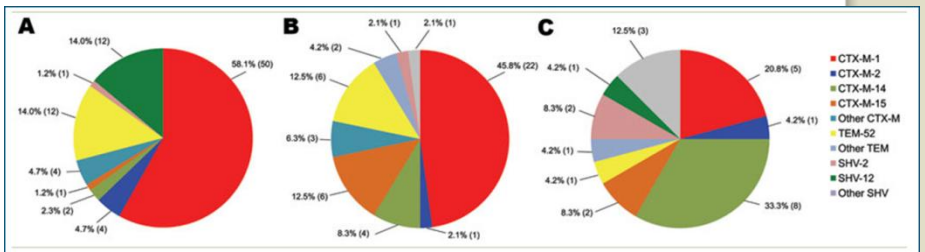

Figure 1. Distribution of extended-spectrum β-lactamase genes in chicken meat (A), human rectal swabs (B), and human blood cultures (C), the Netherlands. Values in parentheses are no. positive.

CMI, 2011

EID 2011

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Antibiotic use in animals in the Netherlands

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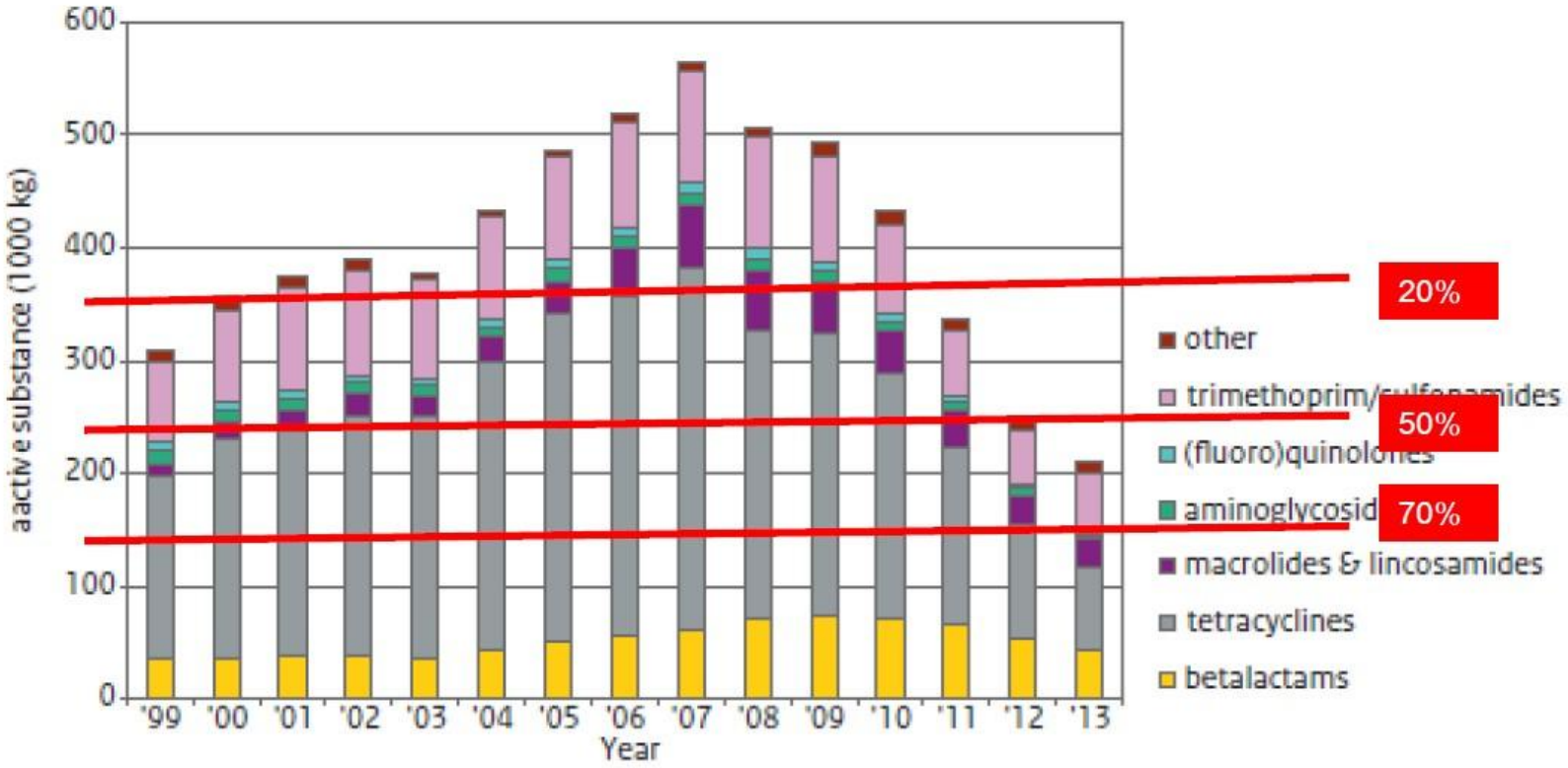
Figure ABuse 01. Antimicrobial veterinary medicinal product sales 1999-2013 in kg (thousands)



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

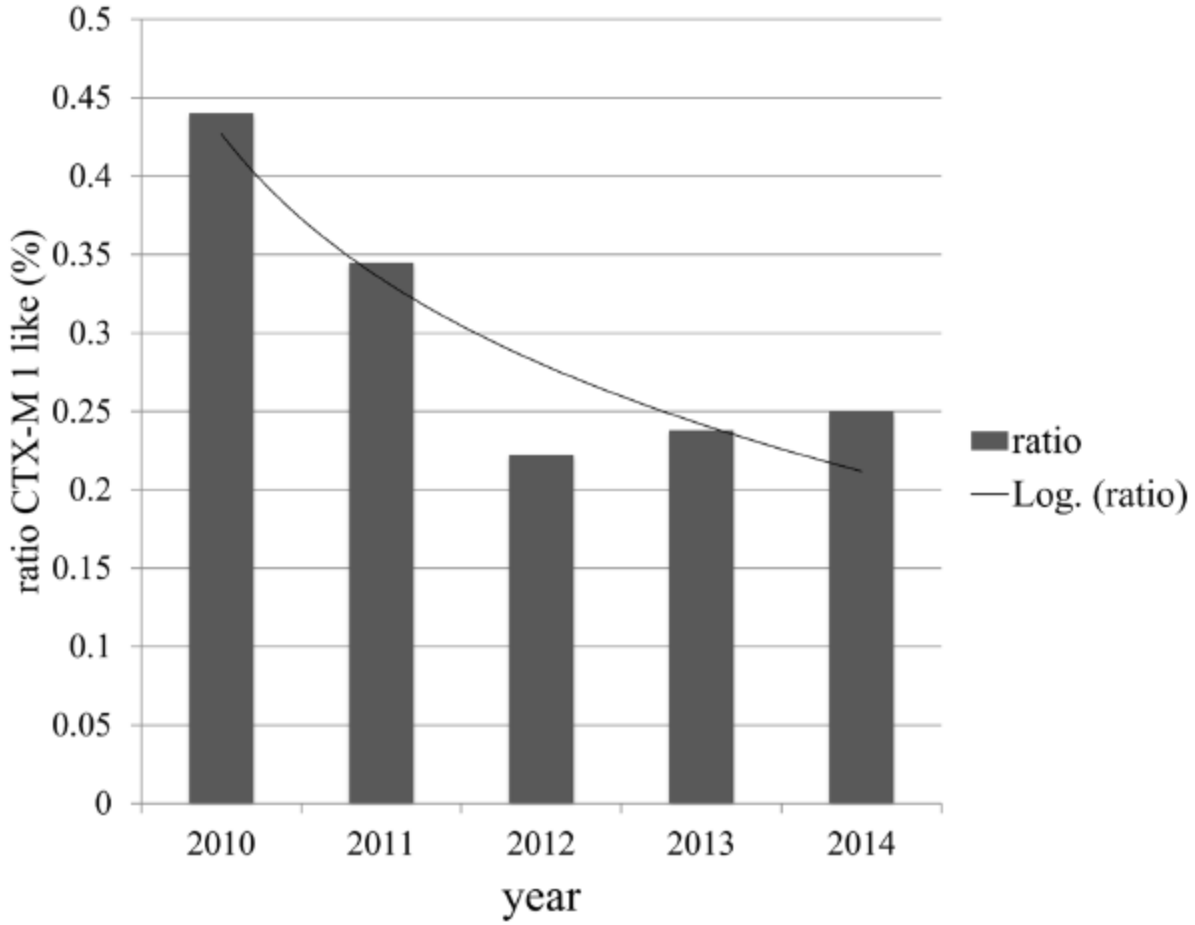


Fig 3. Proportion of CTX-M-1 like ESBL genes over time. The vertical bars represent the percentage of CTX-M-1 like ESBL genes divided by the total number of ESBL genes. The line represents the logarithmic trendline.

Willemsen et al, PLOS One 2015; November 3

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(Partially) Successful Initiatives

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Belgian National Public Campaigns

When: since November 2000, annually during winter season

Organised by: BAPCOC (Belgian Antibiotic Policy Coordination Committee)

Budget:

400,000 EUR/annual campaign

Interventions targeting the public:

Ads on TV, radio and newspaper

Information booklets

Folders

Posters

Internet campaigns: www.antibiotics-info.be

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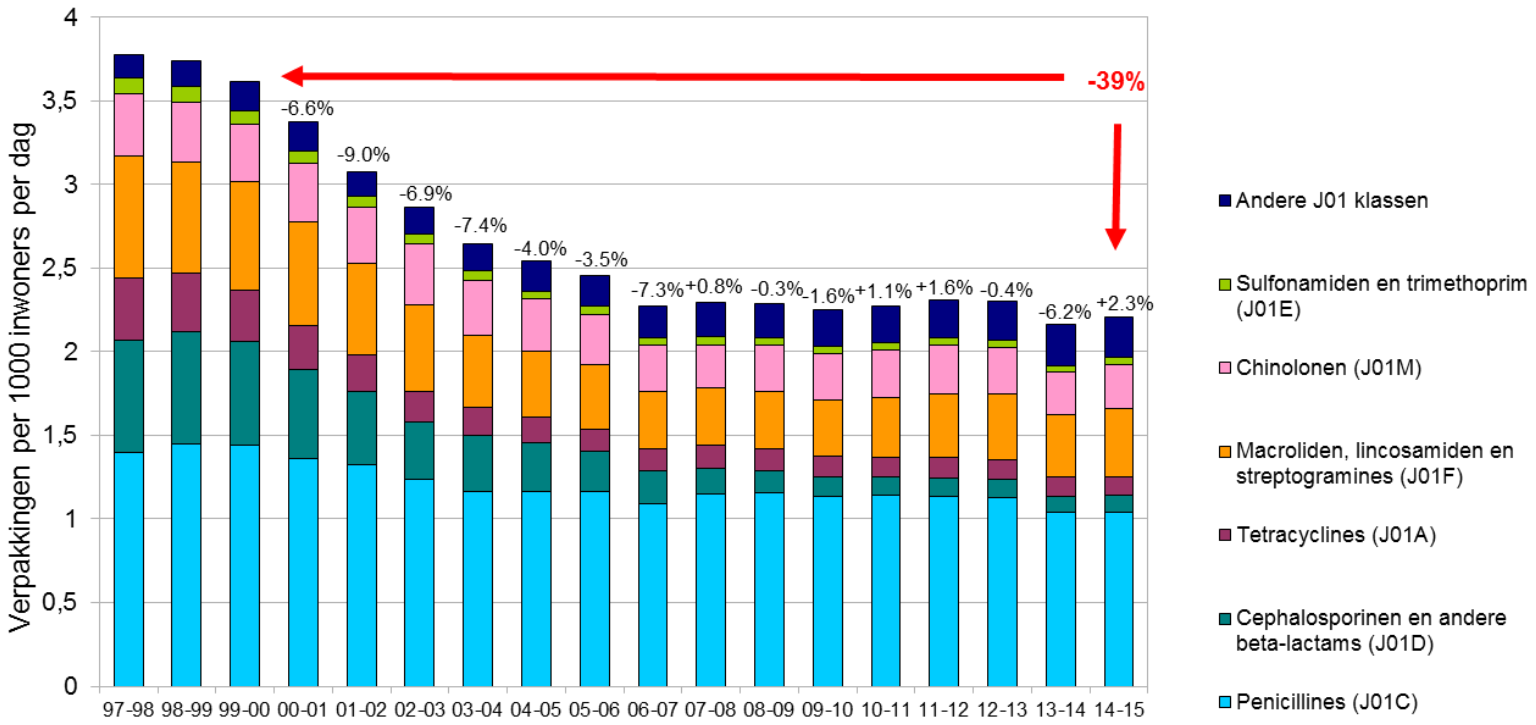
Outpatient antibiotic use in Belgium in PID



Farmanet gegevens voor België zonder zelfstandigen

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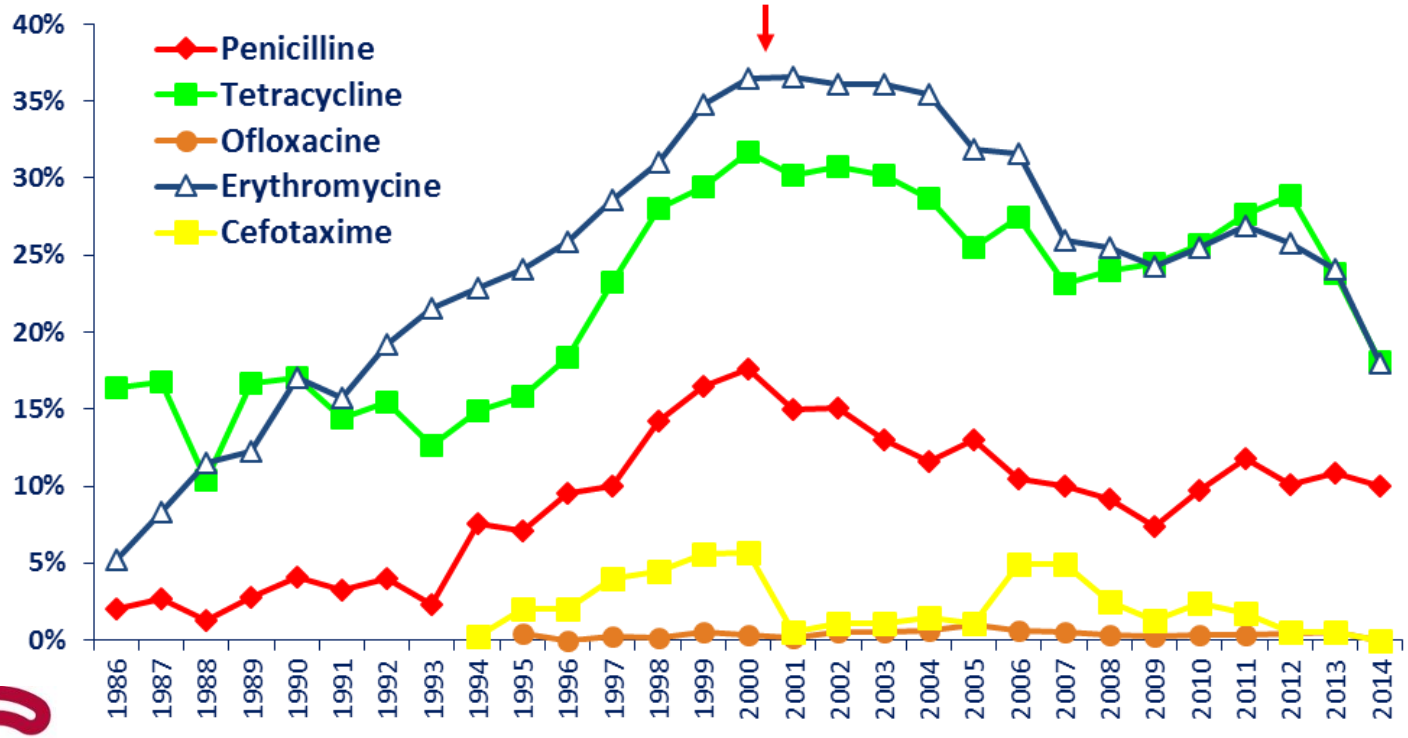
Resistance of *S. pneumoniae* in Belgium



Courtesy: Jan Verhaegen, Nationaal Referentiecentrum *Streptococcus pneumoniae*

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Cost Savings

Total cost for reimbursement of antibiotics decreased with 21 million Euro (-16.7%) from 125.555.454 Euro in 2002-03 to 104.529.213 Euro in 2008-09.

Cumulative savings between 2002 and 2009: 90.154.345 Euro (two thirds were due to reduced prescribing; one third was due to reduction in price of antibiotics).

For every EUR invested in the campaign, 25 EUR were saved

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Hand hygiene compliance before vs after campaign

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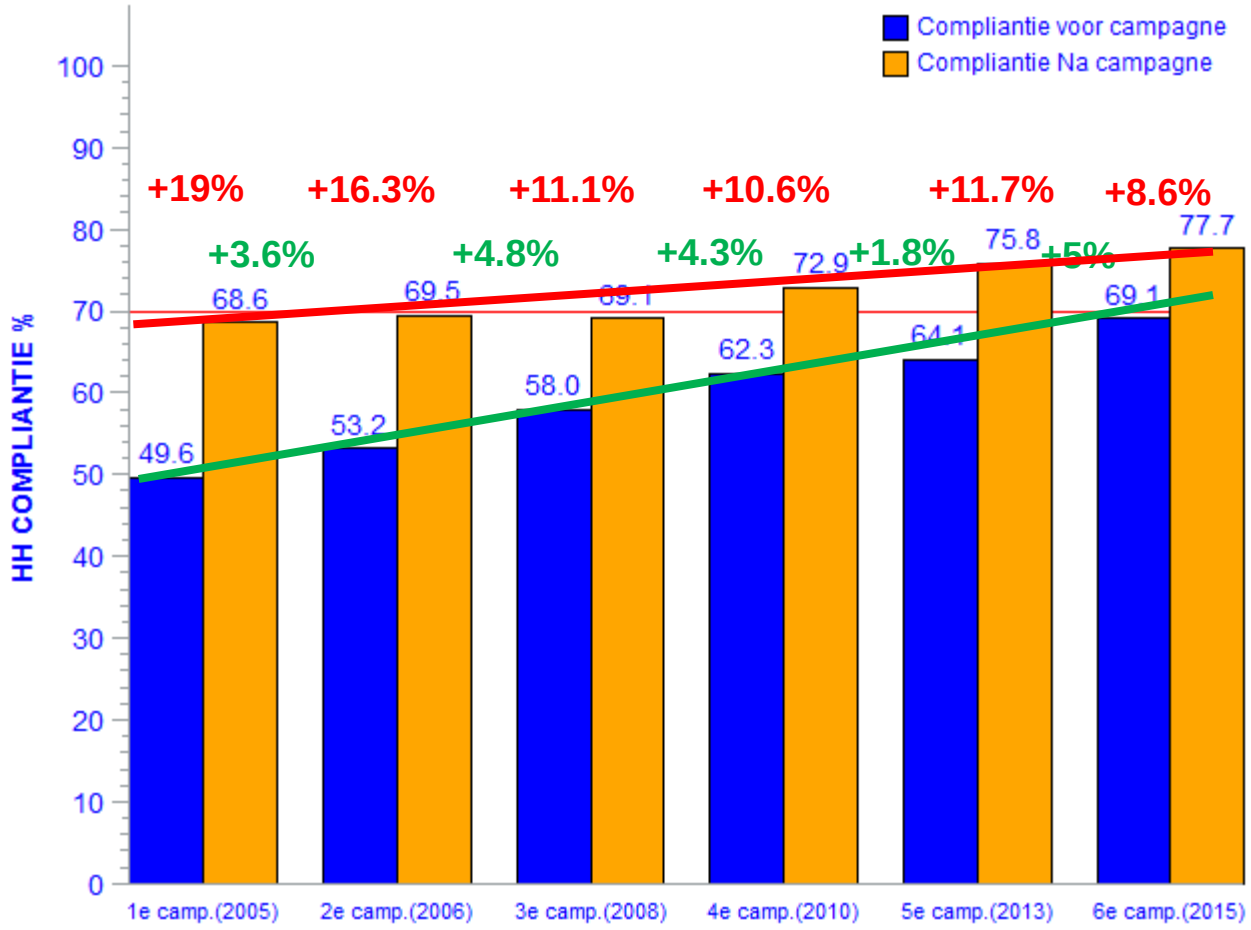

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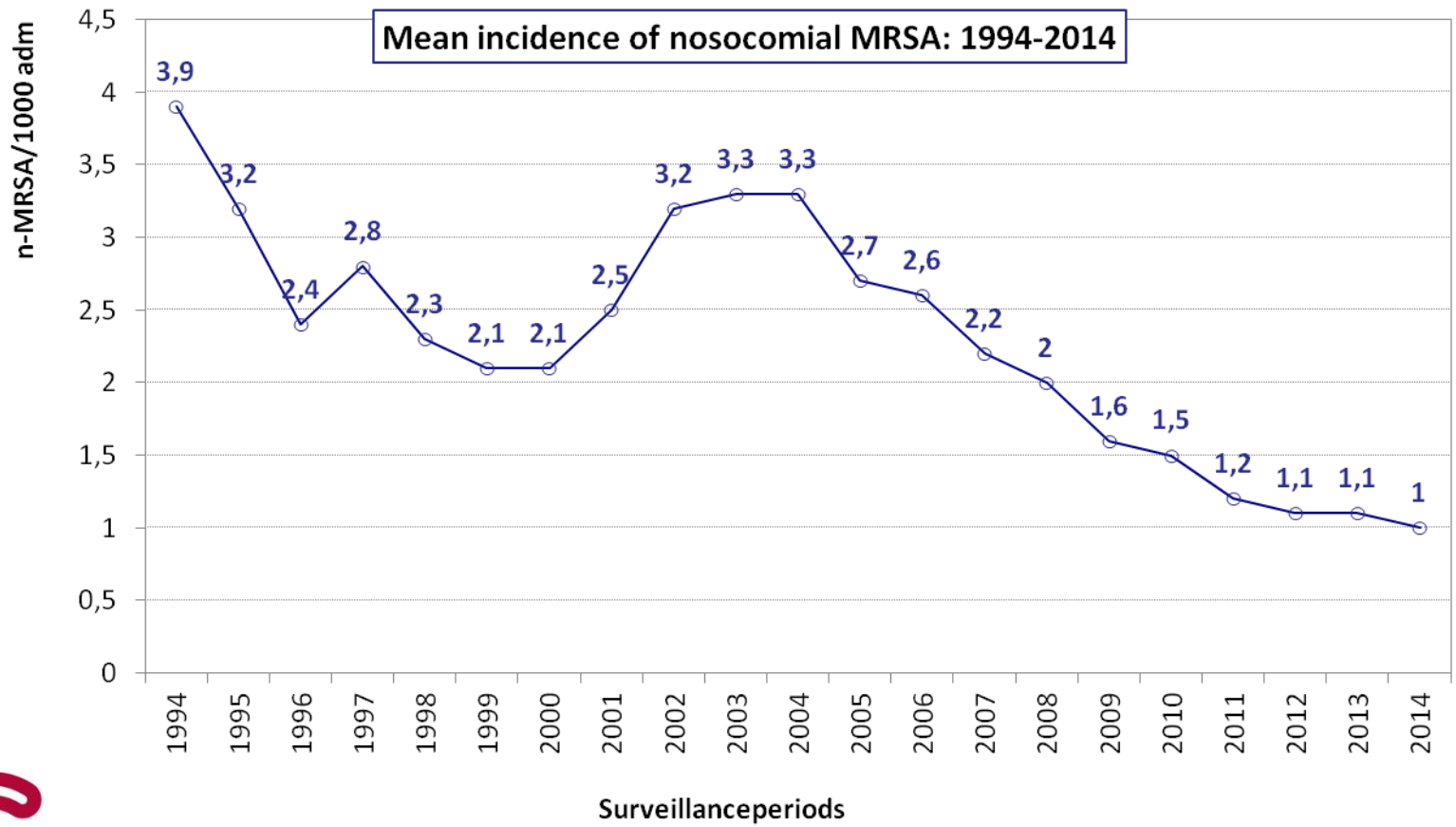
Infections MRSA



Source: *Epidemiological surveillance of MRSA: WIV-ISP (B. Jans) and National Reference Lab, Erasmus Hospital (O. Denis)*

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Conclusions

- National public campaigns since 1999-2000 to reduce antibiotic use and resistance in the community have been very successful, with huge cost savings
  - However, plateau in 2006-2007 and significant increase of moxifloxacin use
- National multimodal campaigns since 2005 to promote hand hygiene in Belgian hospitals were very successful, which most likely resulted on a reduction of MRSA infections in hospitals
  - However, HH compliance can still be improved

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Challenges

Outpatient quinolone use in Europe in 2011

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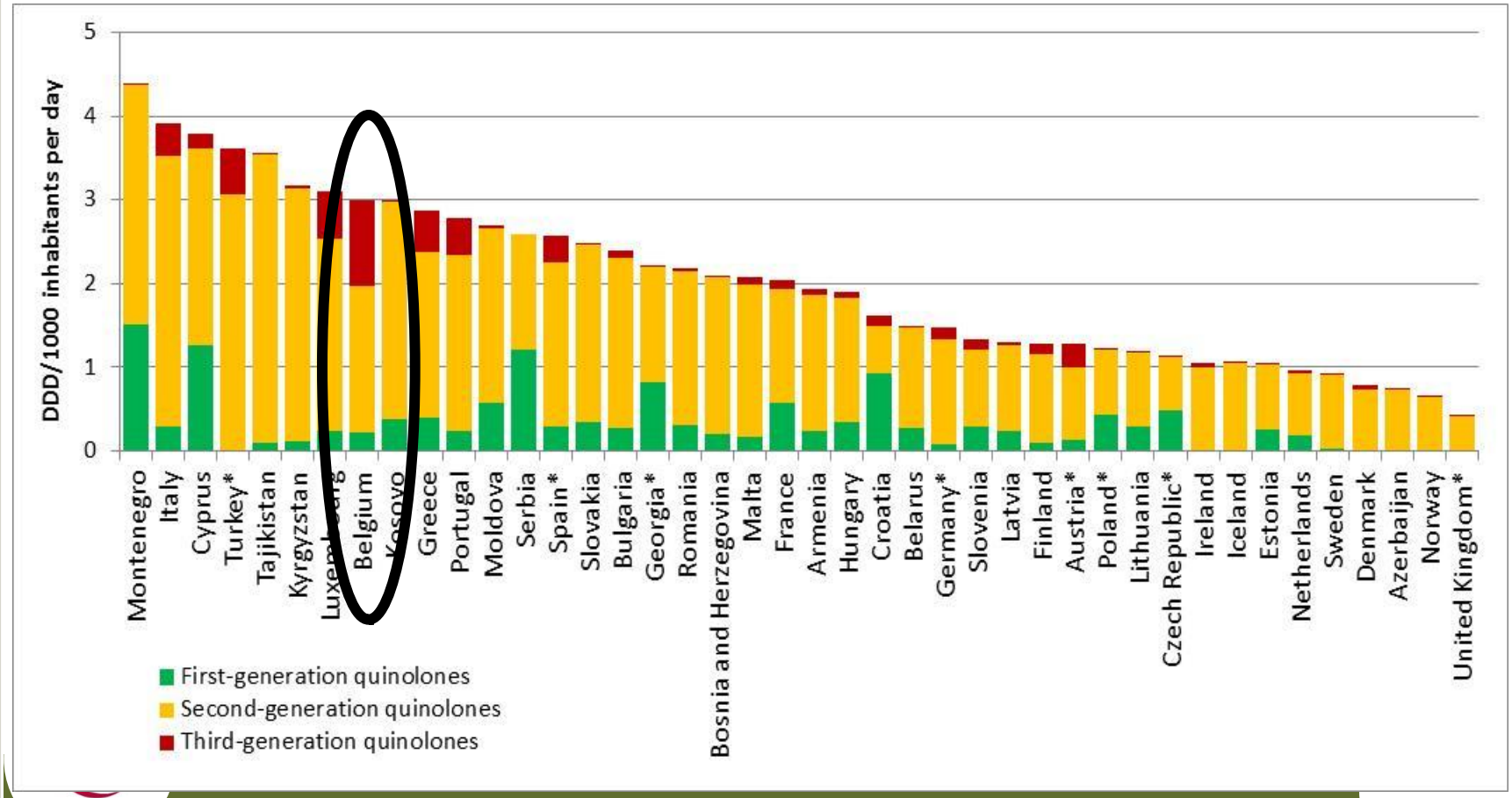

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Antibiotic consumption in Belgium and the Netherlands in 2013

	Total population	Total pills consumed	Total costs	Pills/ Person	Cost/ Person
Belgium	11,140,000	141,000,070	€134,524,191	12.66	€12.08
Netherlands	16,770,000	99,476,775	€43,046,397	5.93	€2.57

Source: IMS Health MIDAS; IMS Health Belgian National Retail Data

With a 30% smaller population in Belgium than in The Netherlands, antibiotic spending in Belgium is two times higher and related cost is 5 times higher.

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Conclusions

"By comparing Belgium's prescription patterns to the Netherlands, we estimated important potential savings due to antibiotics mis-use/over-use (€71 Million). The additional health and cost implications of antibiotics resistance were not taken into account. These savings could then be reinvested in covering innovative drugs."

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Evolution of resistance mechanisms among Enterobacteriaceae: 2005 - 2014

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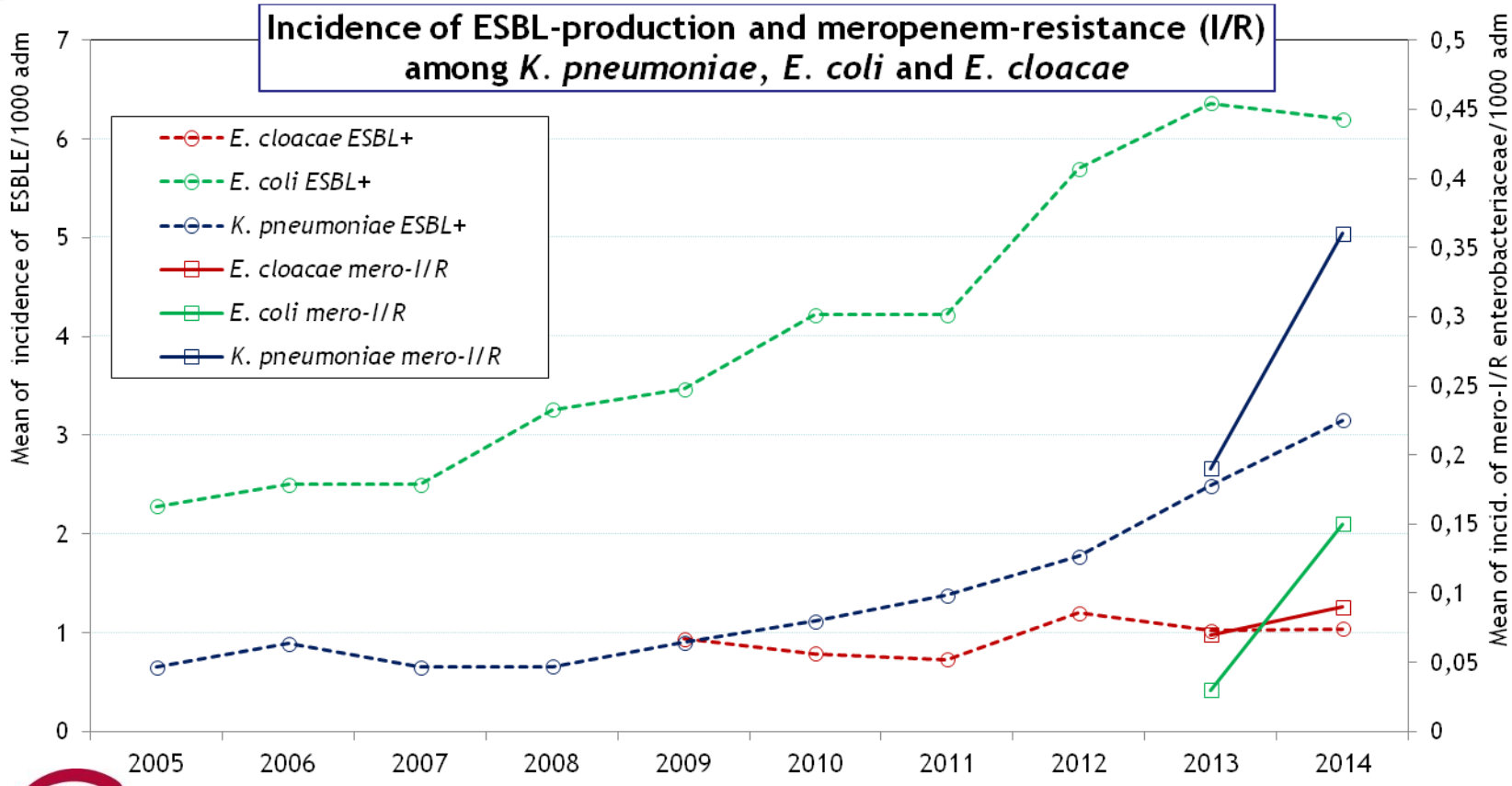

Source: Epidemiological surveillance of resistant enterobacteriaceae: WIV-ISP (B. Jans) and National Reference Lab, UCL, Mont-Godinne (Y. Glupczynski)

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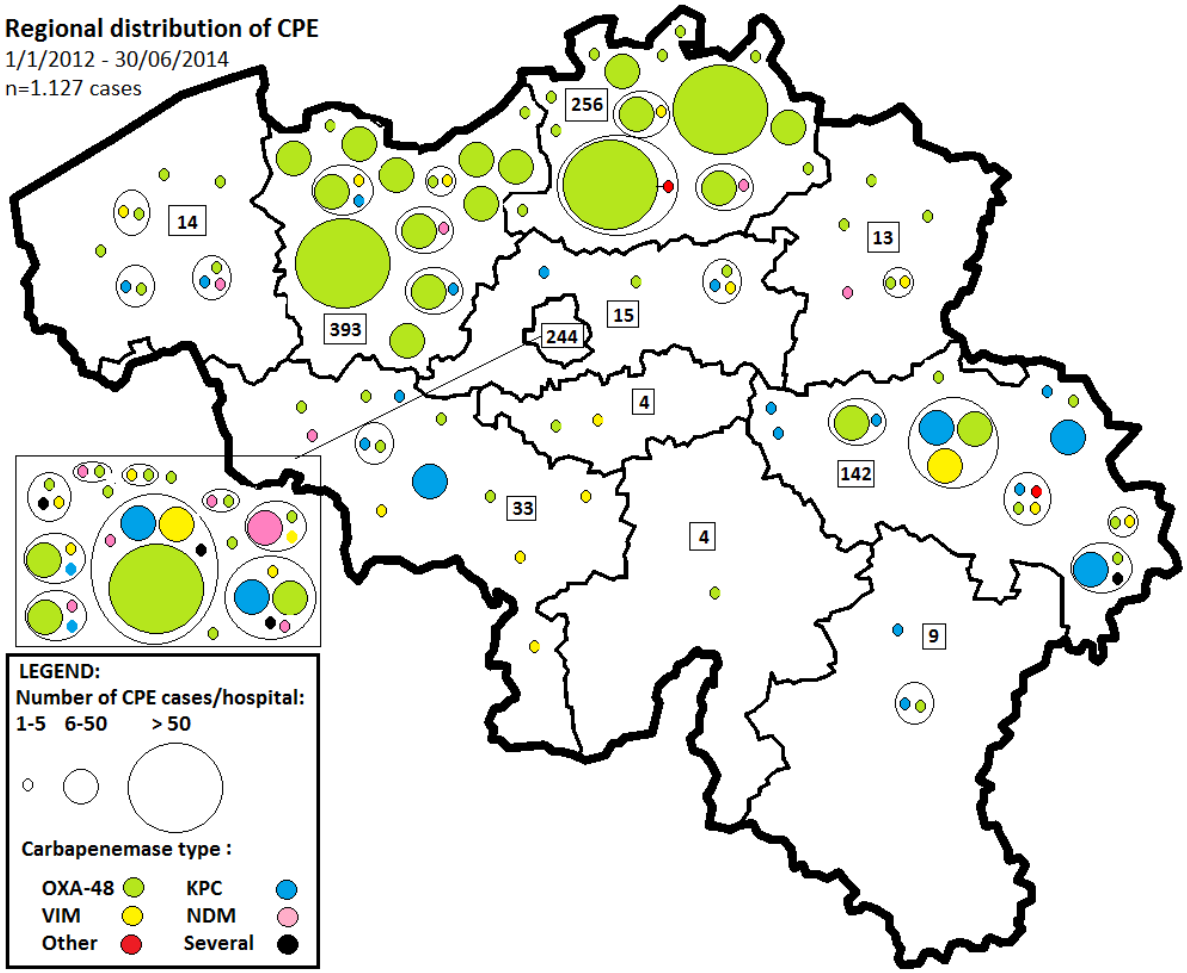

- 22/103 hospitals with clusters/outbreaks
- Local/inter-regional spread in 5 provinces
- 11% associated to international travel

Courtesy from B. Jans, SIPH
NSIH report year 2013-2014
(D/2014/2505/68)

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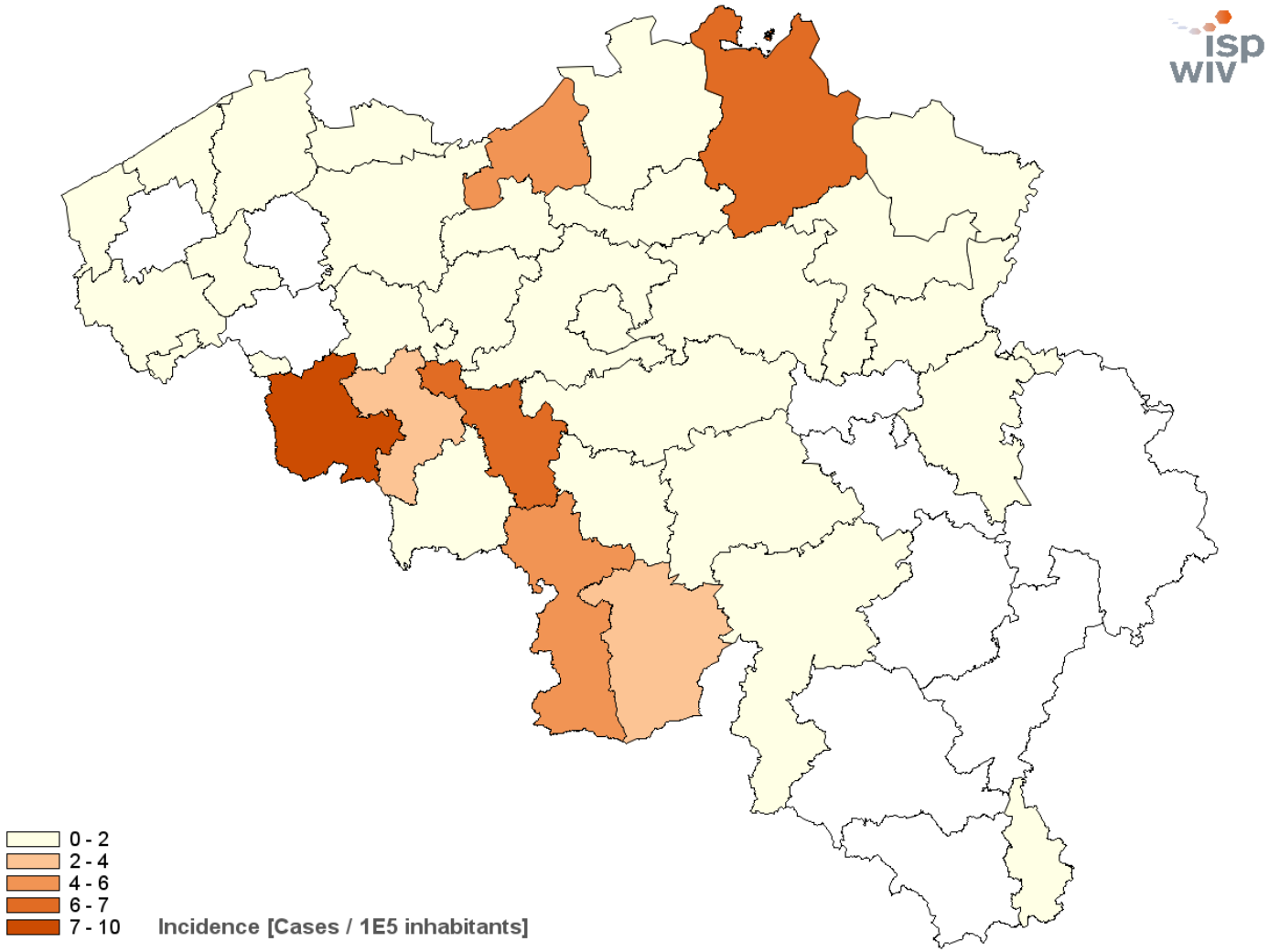
Enterococcal strains received at the NRC (01/01/2009-30/09/2015)

	2009	2010	2011	2012	2013	2014	2015
Nr of strains received	32	27	81	131	178	300	462
UNK	0	4	2	0	0	0	0
E. faecium	18	19	47	104	95	215	386
E. faecalis	12	3	18	15	67	68	60
E. cass/gall	2	1	13	9	12	12	11
Other Ent. spp	0	0	1	3	4	4	4
Nr of VRE (%)	18 (56.3)	21 (77.8)	61 (75.3)	103 (77.4)	85 (47.8)	198 (65.8)	381 (82.5)
vanA (%)	5 (27.8)	8 (38.1)	24 (39.3)	84 (81.6)	61 (71.8)	163 (82.3)	349 (91.6)
*van*B (%)	11 (61.1)	12 (57.1)	24 (39.3)	11 (10.7)	12 (14.1)	20 (10.1)	18 (4.7)
*van*C (%)	2 (11.1)	1 (4.8)	13 (21.3)	8 (7.7)	12 (14.1)	11 (5.6)	11 (2.9)
Other (%)	0	0	0	0	0	3 (1.5)	3 (0.8)
Nr of outbreaks	1 (n=6)	1 (n=3)	3 (n=4, 12, 16)	4 (n=3, 4, 6, 39)	1 (n=36)	10 (n=2, 3, 3, 3, 6, 6, 8, 14, 35, 46)	9 (n=3, 5, 8, 9, 12, 24, 36, 67, 112)

Geographical distribution of Enterococci (2014)



Antimicrobial use in animals in Europe

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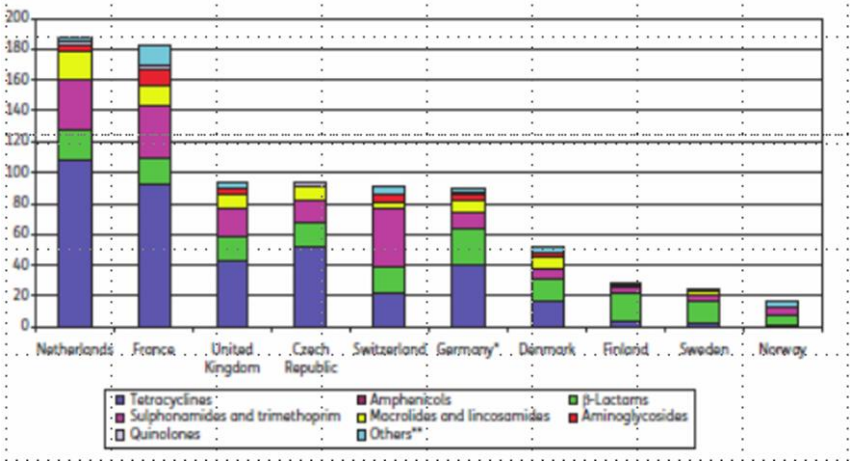
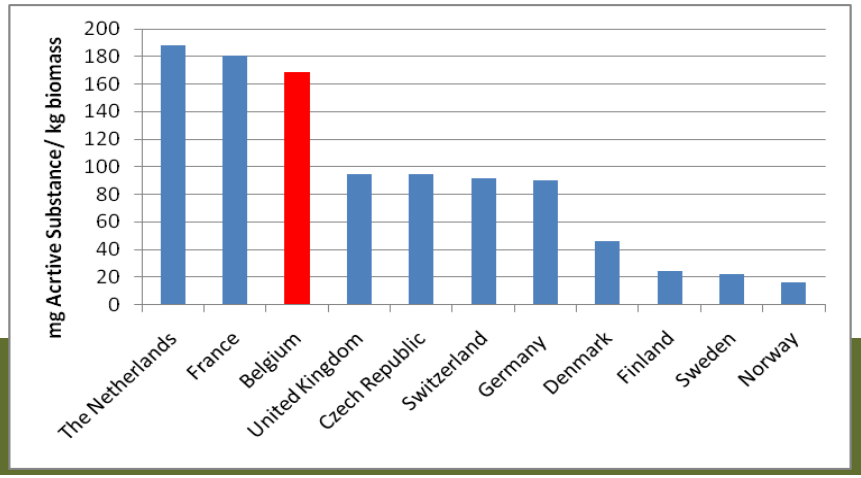


ESVAC report 2007



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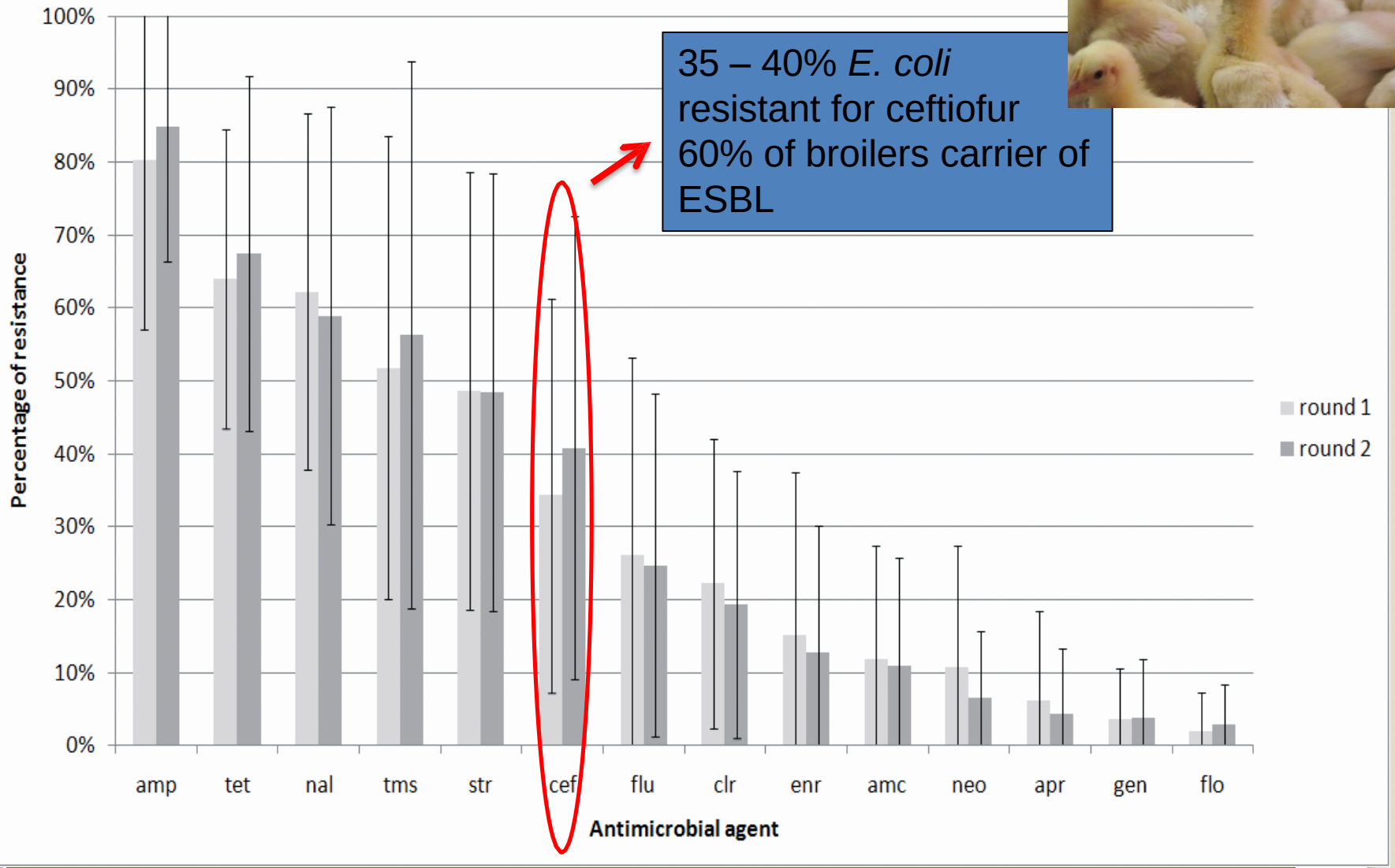
Belgian broilers (E. coli)



35 – 40% *E. coli* resistant for ceftiofur
60% of broilers carrier of ESBL

Persoons et al., 2010

BelVet-Sac
Antibiotic use in animals in Belgium

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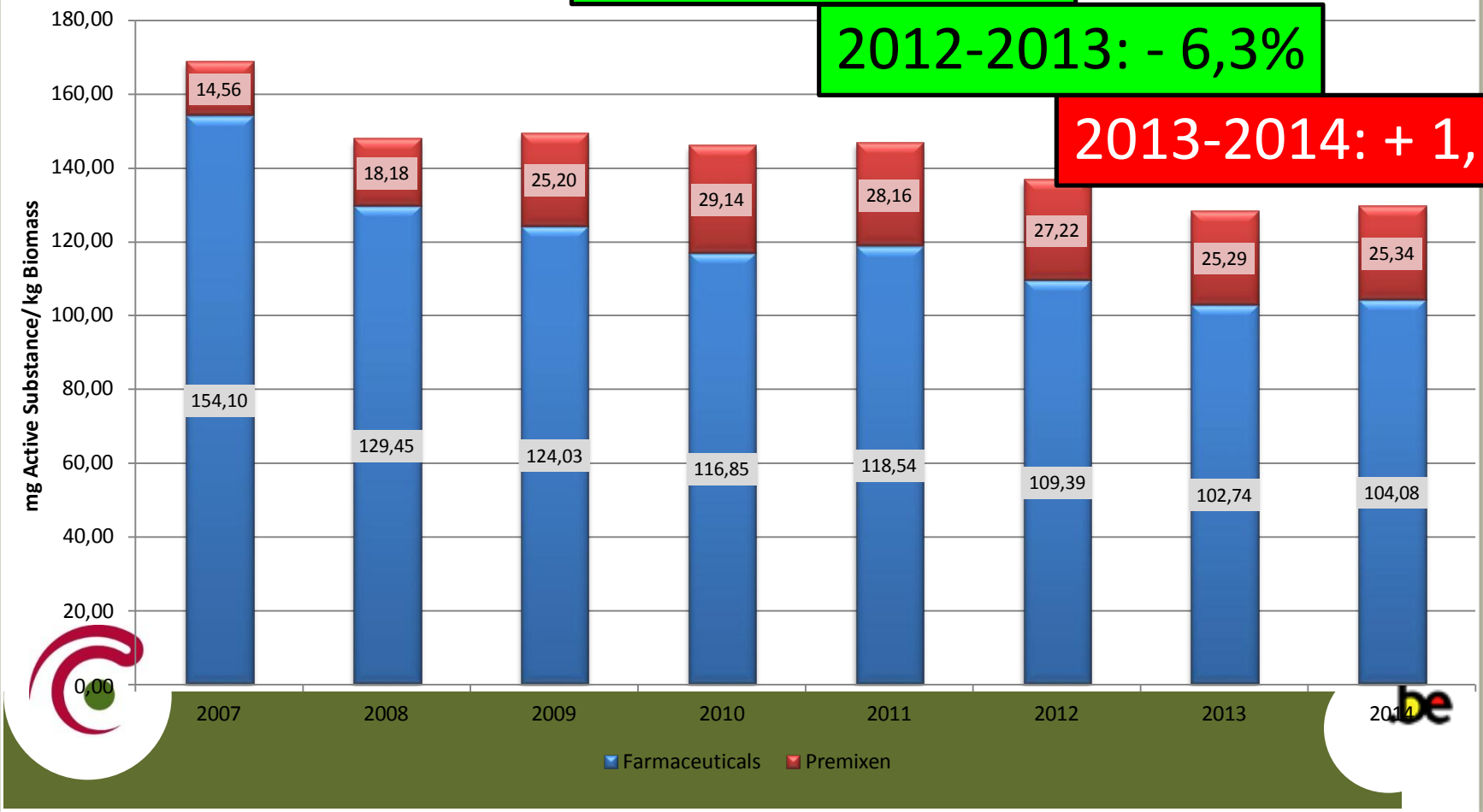
2011-2012: - 6,9%

2012-2013: - 6,3%

2013-2014: + 1,1%



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New BAPCOC National Action Plan 2014-2019

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One health approach: integrated programmes and datasets on antimicrobial utilisation and resistance
Targets for outpatients and inpatient antibiotic use
Quality measures/Audits
Education and Training
Better integration and coordination (MDRO Working group; National Reference Centres; INAMI/RIZIV; WIV/ISP)
Engage with stakeholders
Develop methods to monitor effects of antimicrobial stewardship strategies, policy and guidance interventions across the healthcare economy

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Budget 2015 (15 November 2015)

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- Sensibilisatiecampagne ter promotie van het verantwoord antibioticagebruik – winter 2015-2016 [RIZIV : 400.000€]
- Financiering antibiotherapiebeleidsgroepen [BFM ziekenhuizen B5: 4.261.873 €]
- Financiering ziekenhuishygiëne [BFM B4]:
  - verpleegkundigen: 9.696.521 €
  - artsen: 6.897.554 €
- Financiering regionale platformen [BFM B4: 22.310 €]
- Financiering Noso-info [BFM B4: 35.000 €]
- Verspreiding van bedrijfsgezondheidsgidsen voor verantwoord gebruik van diergeneeskundige antibacteriële middelen die werden ontwikkeld door AMCRA [RIZIV art 56: 15.000€]
- CPE prevalentiestudie in de populatie [RIZIV art 56: 25.000€]
- Updaten van de guidelines profylactisch en therapeutisch gebruik van antibiotica in ziekenhuizen door het BVIKM [RIZIV art 56: 50.000€]
- Organisatie van de studiedag “One health strategie” op 18/11/2015 [RIZIV art 56: 6.000€]

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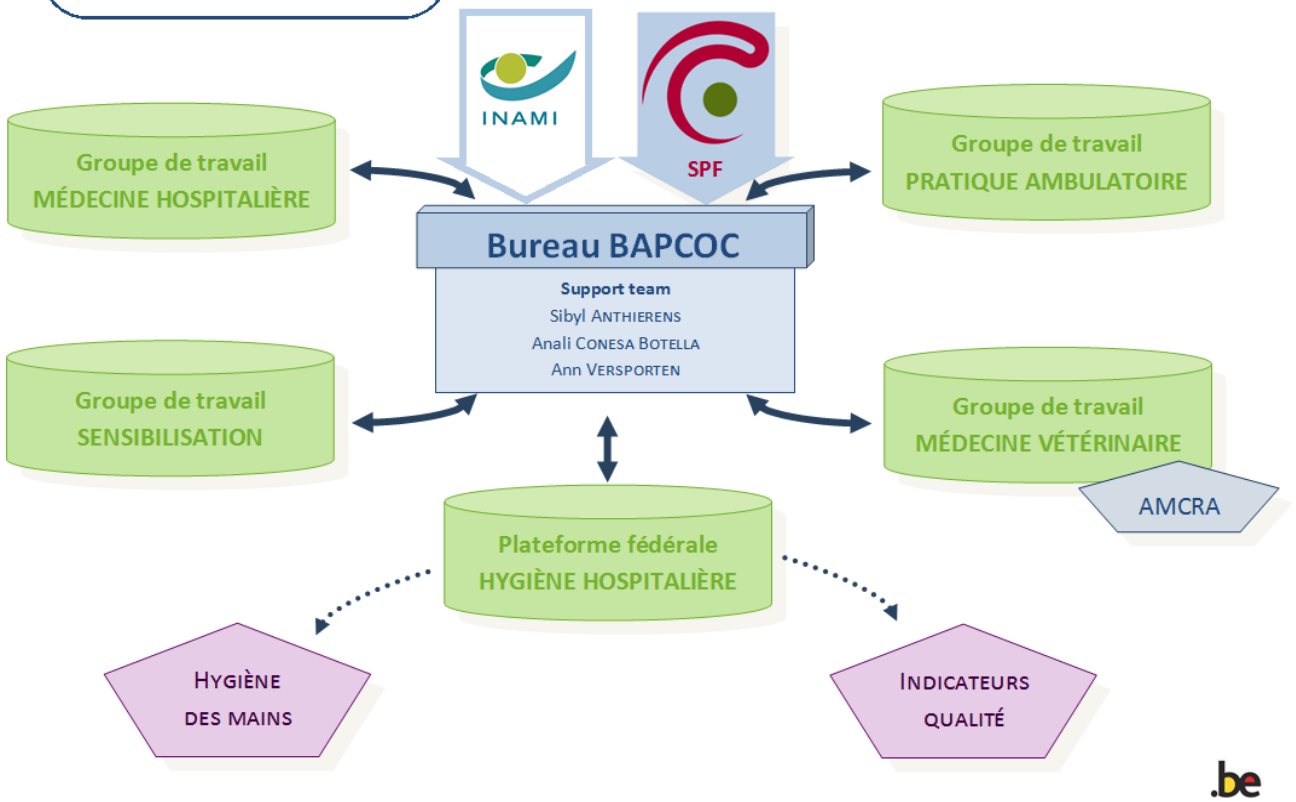
ORGANIGRAMME



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Lancering BAPCOC Strategisch Plan 2015 – 2019: Persconferentie 18/11/2014

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Changing behavior and culture requires perseverance

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