Multiresistente bacteriën: waar komen ze vandaan, en waar gaan we naar toe?

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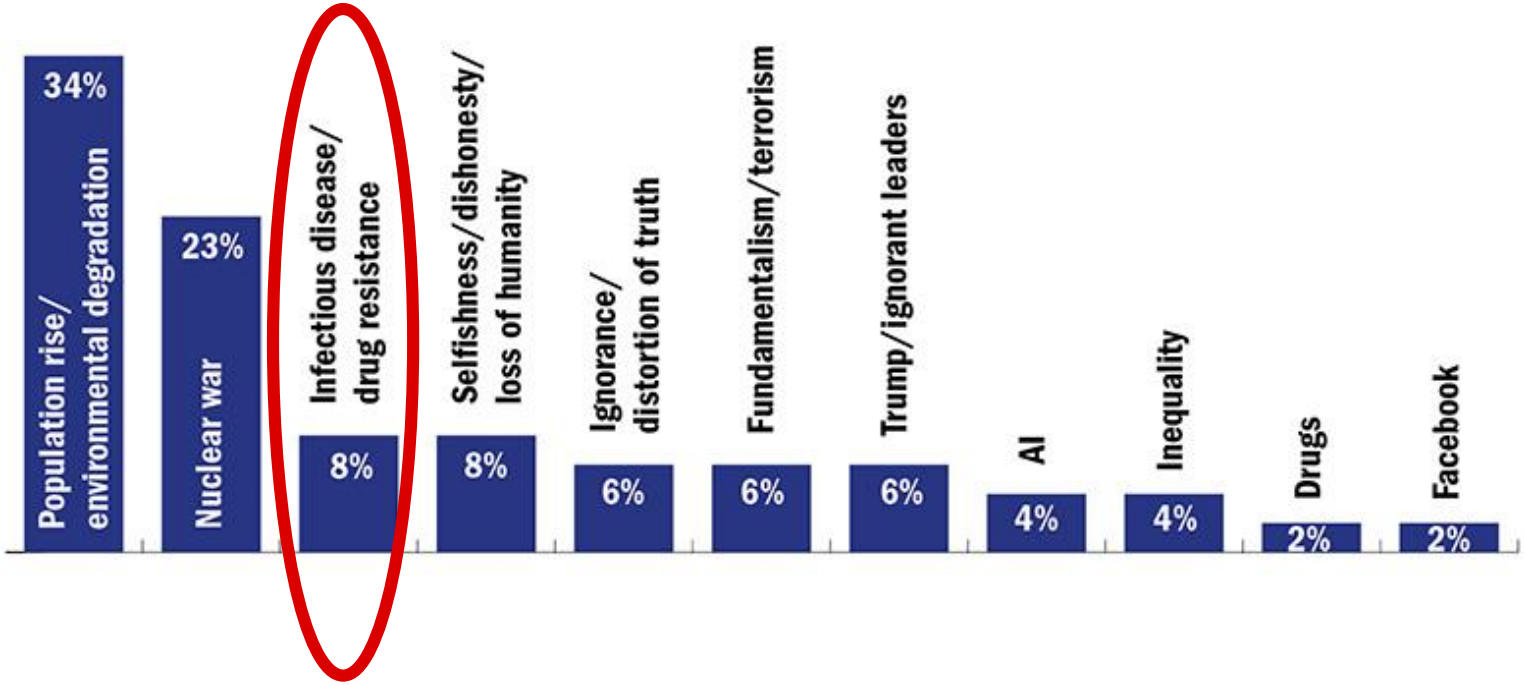
Voorzitter BAPCOC
Voorzitter Technical Advisory Committee EAAD

What is the biggest threat to humankind according to 50 Nobel prizewinners?



Note: some respondents listed more than one threat

Source: Times Higher Education, 29 August 2017

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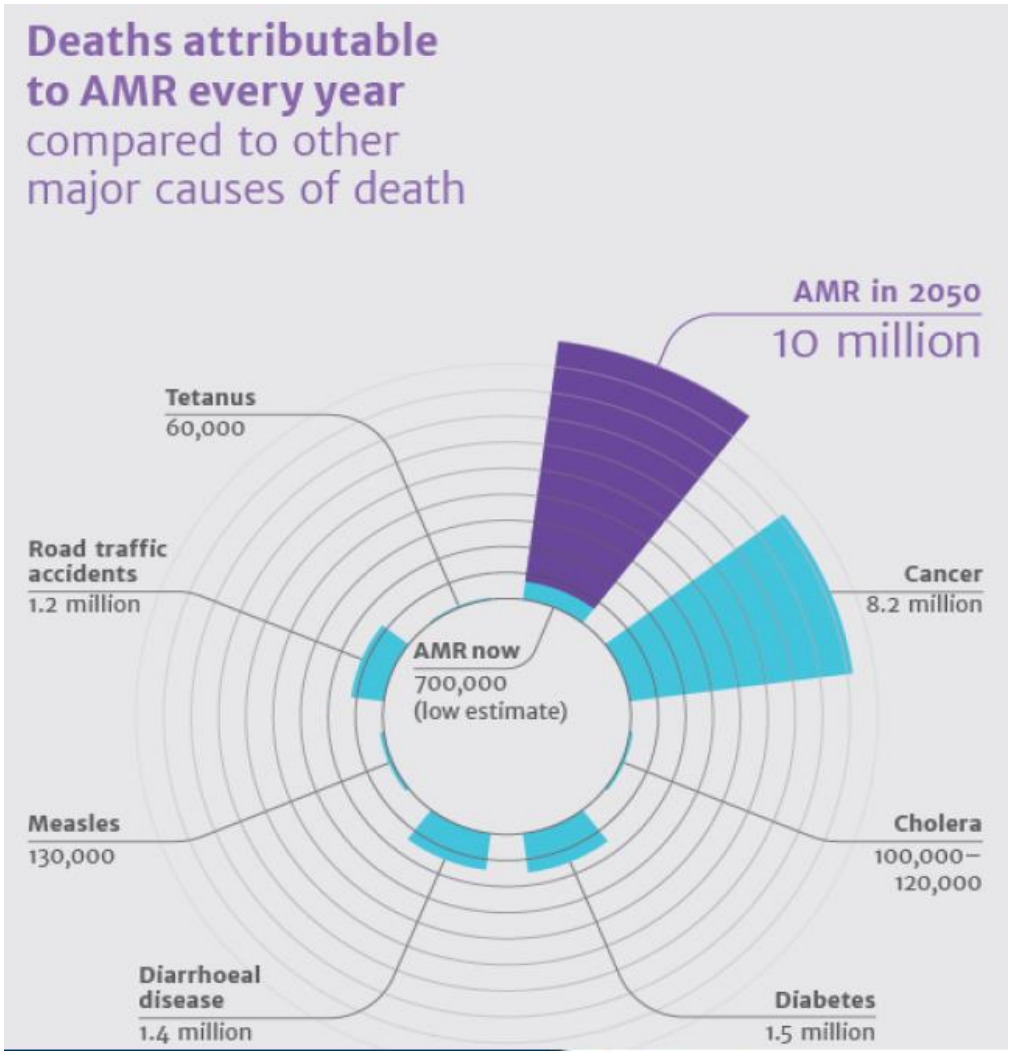
Antimicrobial resistance a 'greater threat than cancer by 2050'

UK chancellor George Osborne to tell IMF that 10m people a year could die without radical action

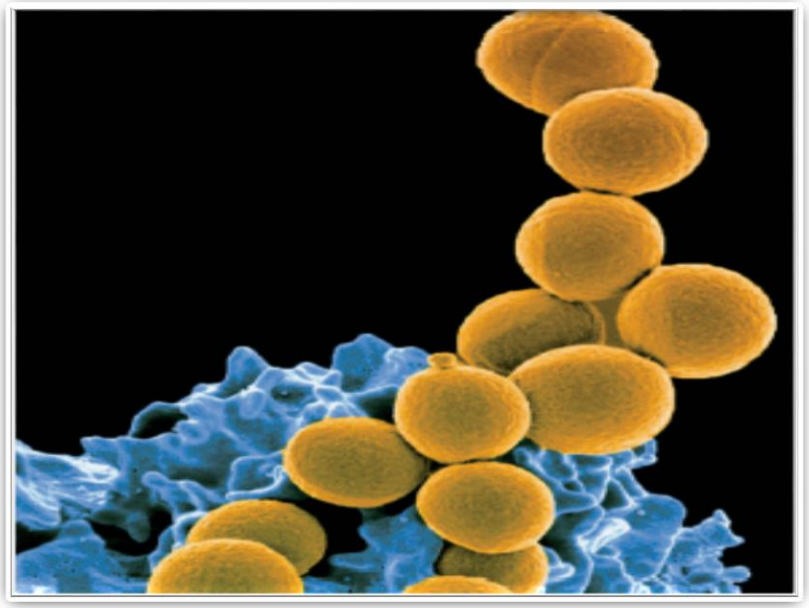
The chancellor will call for incentives for pharmaceutical companies to develop new antibiotics. Photograph:



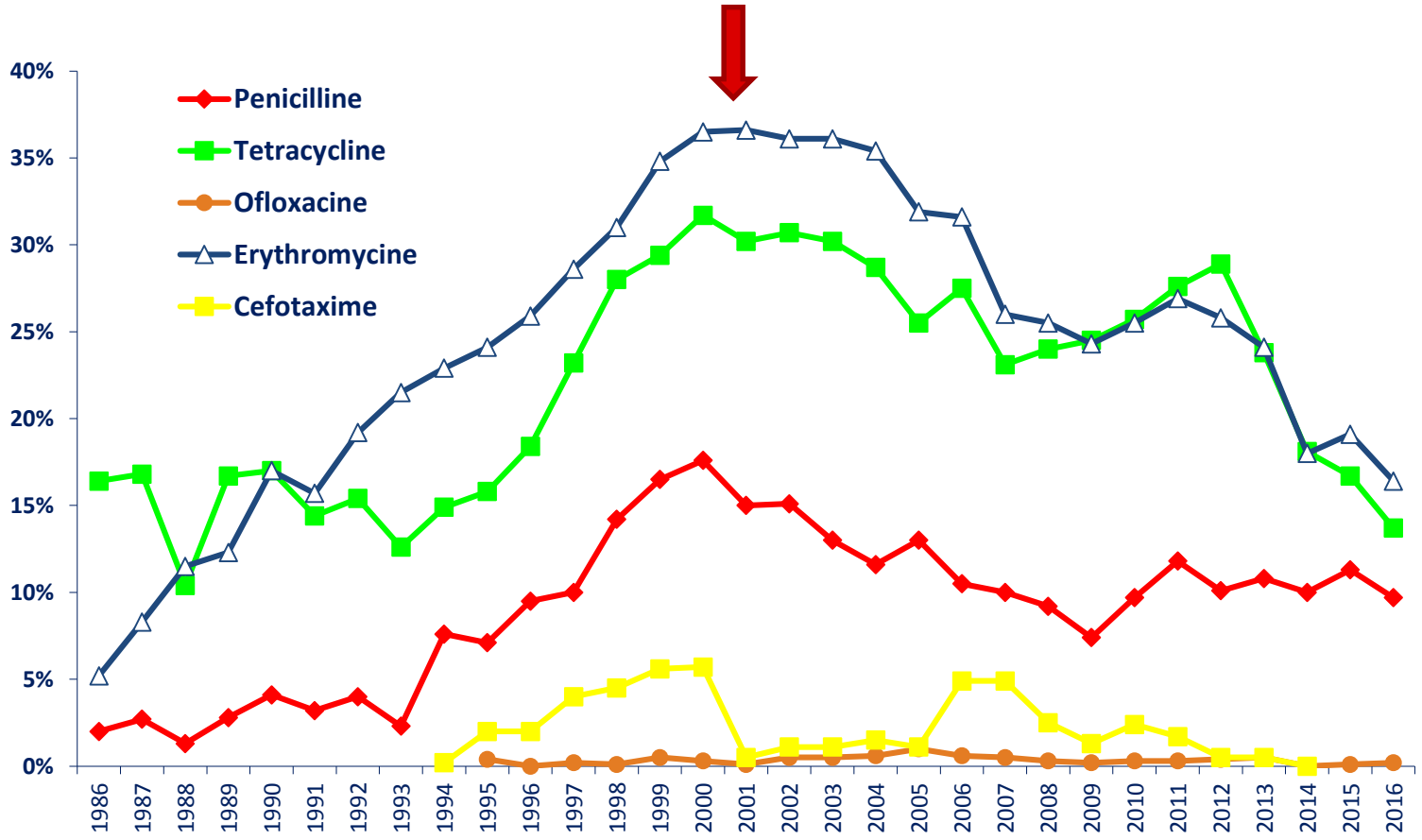
O'Neill J. The Review on Antimicrobial Resistance. December 2014.

Waar komen ze vandaan? (Trends)

Resistentie bij Gram-positieve bacteriën

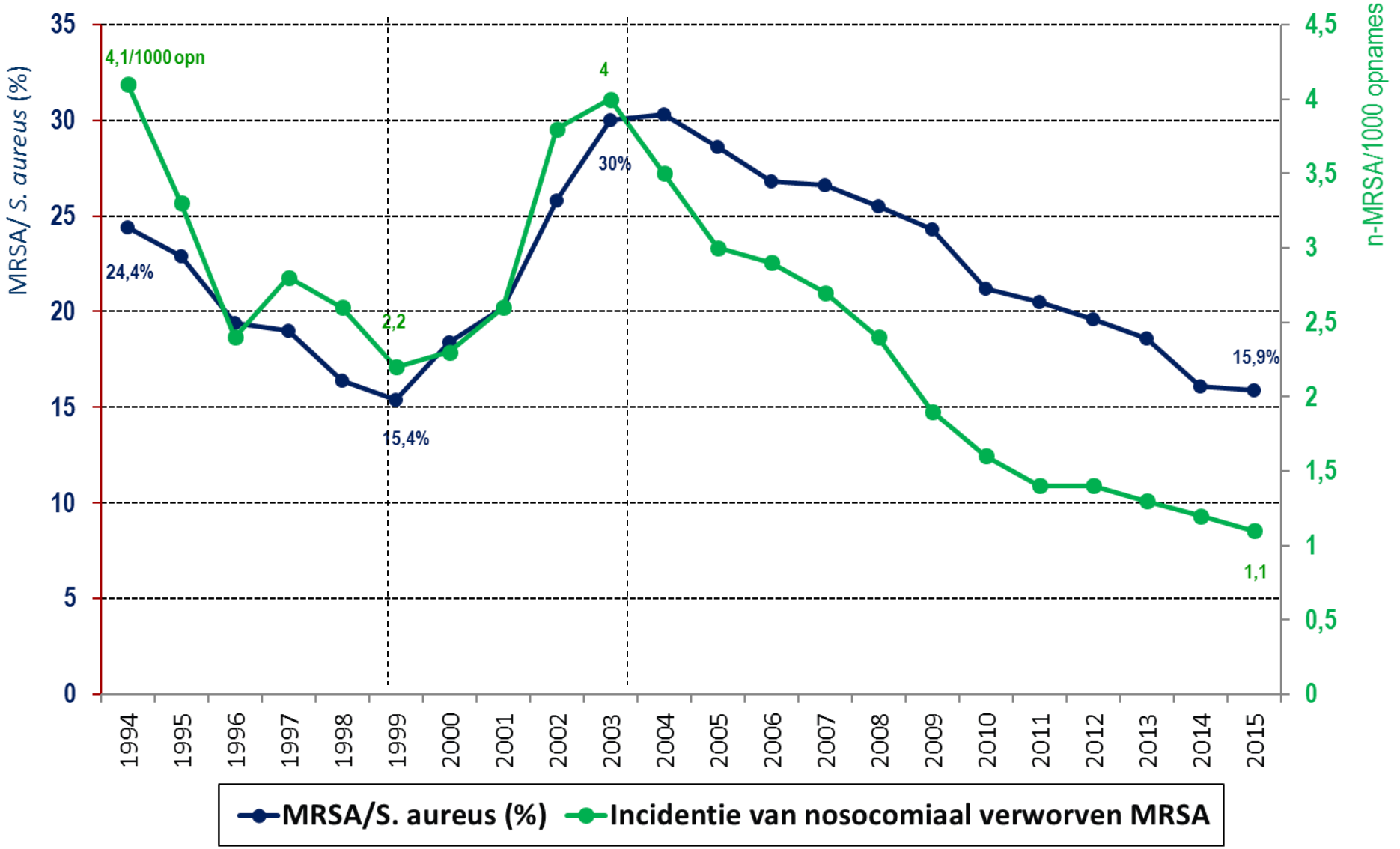


Evolutie van de resistentiecijfers van *Streptococcus pneumoniae* isolaten in België: 1986 - 2016



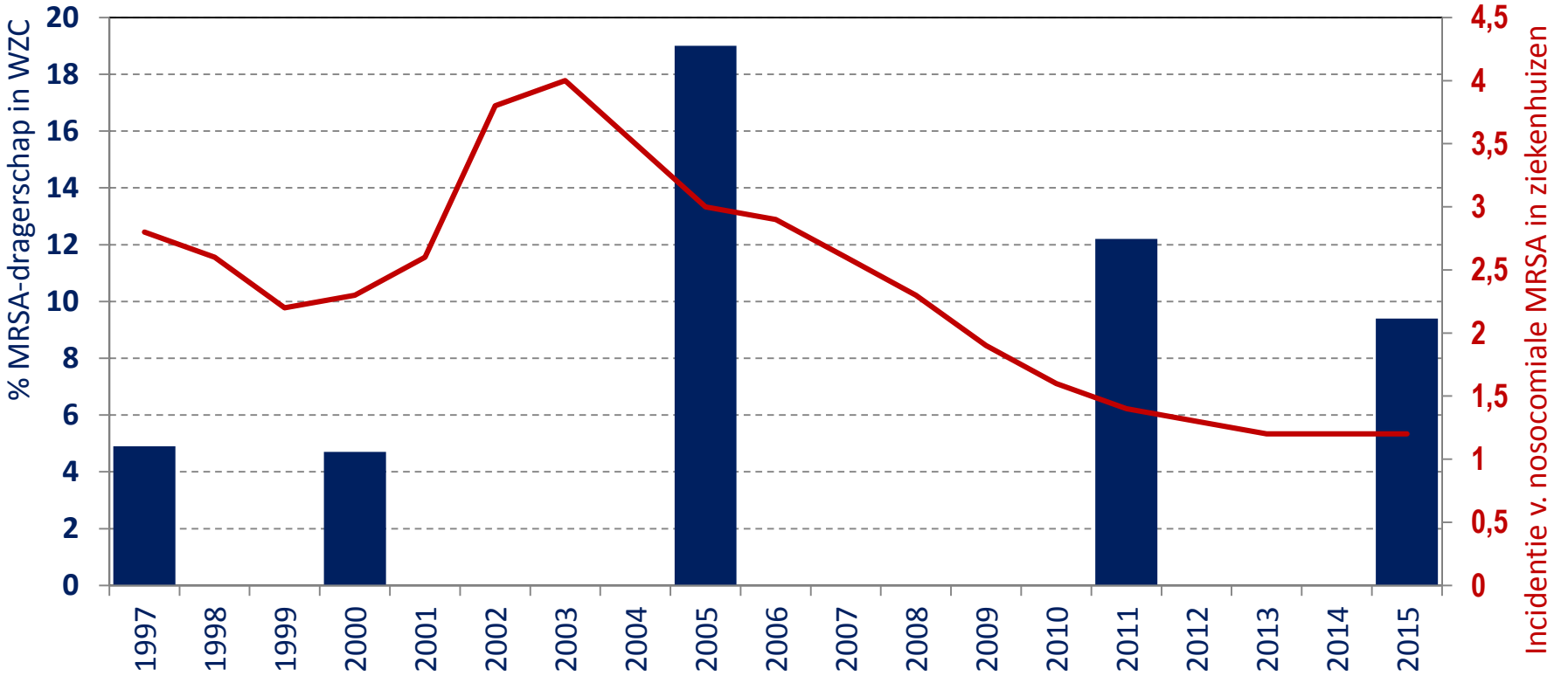
Bron: Laboratorium Microbiologie, Universiteit Leuven, Nationaal Referentiecentrum voor *S. pneumoniae*.

Evolutie van de resistentiecijfers en incidentie van n-MRSA in acute ziekenhuizen in België: 1994 - 2015



Bron: Epidemiologische surveillance van MRSA in Belgische ziekenhuizen (WIV), 2015

Evolutie van MRSA-dragerschap (%) bij bewoners van woonzorgcentra in België: 1997 - 2015



17 WZC (1997)	24 WZC (2000)	60 WZC (2005)	60 WZC (2011)	29 WZC (2015)
4.9 % MRSA	4.7 % MRSA (0% - 14%)	19 % MRSA (2% - 43%)	12.2 % MRSA (0% - 36%)	9.0% (0% - 22%)

Acute ziekenhuizen en woonzorgcentra zijn «communicerende vaten»

Bron: Prevalentiestudies ivm dragerschap van MDRO in Woonzorgcentra in België: 1997, 2000, 2005, 2011 en 2015

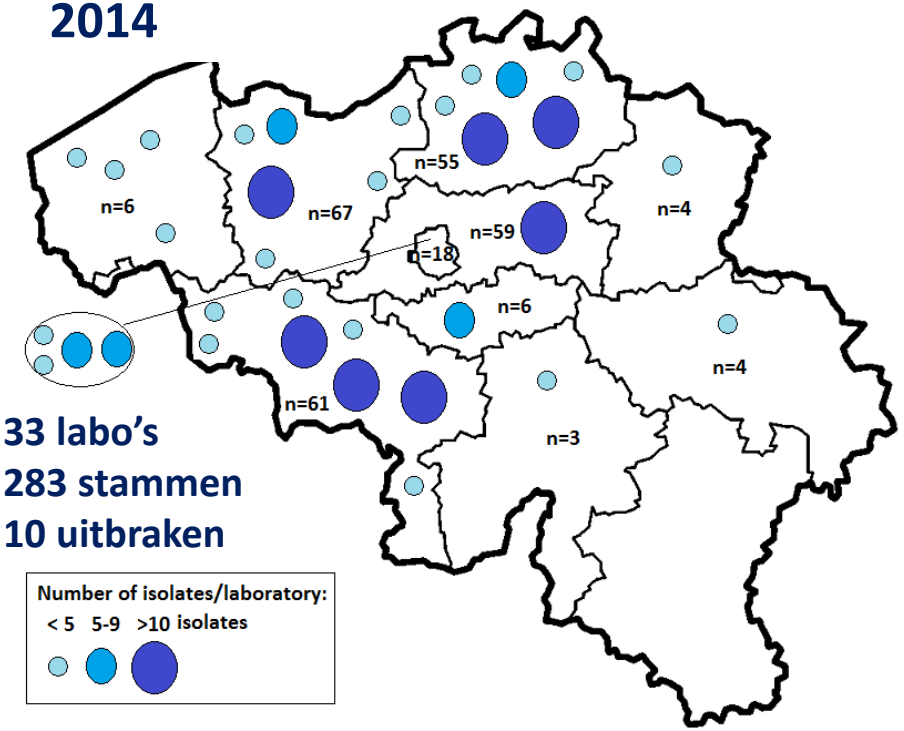
Aantal ontvangen Enterokokken stammen NRC, UZA: 2009 -2016

Year	2009	2010	2011	2012	2013	2014	2015	2016
Nr of strains received	32	27	81	131	178	300	578	530
UNK	0	4	2	0	0	0	0	0
E. faecium	18	19	47	104	95	215	447	448
E. faecalis	12	3	18	15	67	68	111	67
E. cass/gal	2	1	13	9	12	12	14	12
other Ent. Spp	0	0	1	3	4	4	4	3
Nr of VRE (%)	18 (56,3)	21 (77,8)	61 (75,3)	103 (77,4)	85 (47,8)	198 (65,8)	444 (76,1)	444 (83,8)
vanA (%)	5 (27,8)	8 (38,1)	24 (39,3)	84 (81,6)	61 (71,8)	163 (82,3)	402 (90,5)	417 (93,9)
vanB (%)	11 (61,1)	12 (57,1)	24 (39,3)	11 (10,7)	12 (14,1)	20 (10,1)	24 (5,4)	15 (3,4)
vanC (%)	2 (11,1)	1 (4,8)	13 (21,3)	8 (7,7)	12 (14,1)	10 (5,1)	13 (2,9)	12 (2,7)
other (vanAB, vanBC, vanAC, vanD) (%)	0	0	0	0	0	3 (1,5)	5 (1,1)	0
Nr of outbreaks*	1 (n=6)	1 (n=3)	3 (n=4, 12, 16)	4 (n=3, 4, 6, 39)	1 (n=36)	n=10 (2, 3, 3, 3, 6, 6, 8, 14, 35, 46)	n=22** (2, 3, 3, 3, 3, 3, 4, 4, 5, 5, 6, 6, 9, 11, 12, 12, 15, 18, 20, 37, 54, 76)	n=36** (2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3, 3, 3, 4, 4, 4, 5, 6, 7, 8, 8, 8, 8, 9, 12, 12, 13, 25, 28,36, 37)

•All except 1due to *E. faecium; ** 1 clone in several hospitals in the same region; outbreak: if indicated by local lab*
•and confirmed by NRC-typing

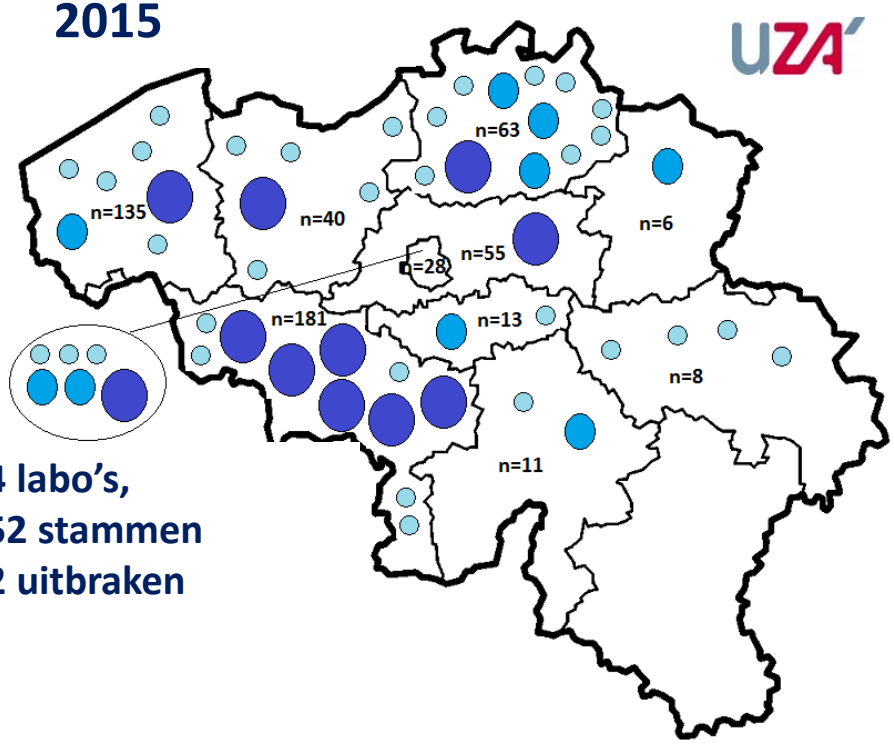
Bron: Laboratorium Microbiologie, Universitair Ziekenhuis Antwerpen, Nationaal Referentiecentrum Enterokokken

2014



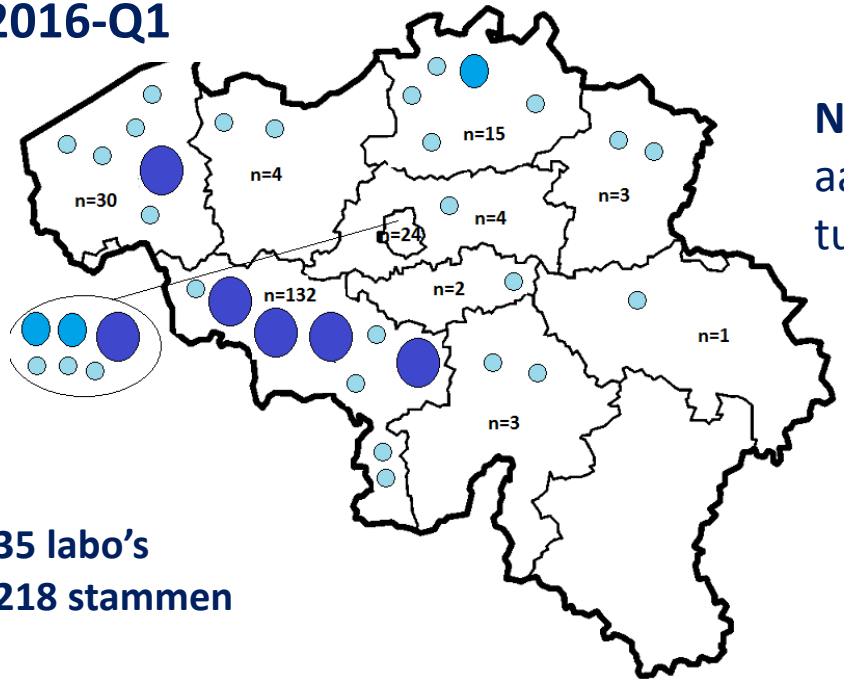
33 labo's
283 stammen
10 uitbraken

2015



54 labo's,
552 stammen
22 uitbraken

2016-Q1



35 labo's
218 stammen

Nationaal Referentiecentrum:
aantal ontvangen stammen
tussen 1/1/2014 en 30/04/2016

Resistentie bij Gram-negatieve bacteriën

Classification of β-Lactamases

Class A	Class B	Class C	Class D
PC			
SHV-1, TEM-1, 2			
SHV->1	IMP	AmpC	OXA-1, 10,
TEM->2	**VIM**	CMY	OXA-11, 15
CTX-M	KHM	ACT	OXA-23/27
PER	SPM	DHA	24/40
VEB	GIM	ACC	**48,** 51/66/69
CARB	SIM	FOX	**58**, 143
RTG	**NDM**		
CepA	AIM		
SME	DIM		
IMI	BEL		
SME			
NMC			
IND			
KPC			
GES			
BIC			

ESBL

Carbapenemases

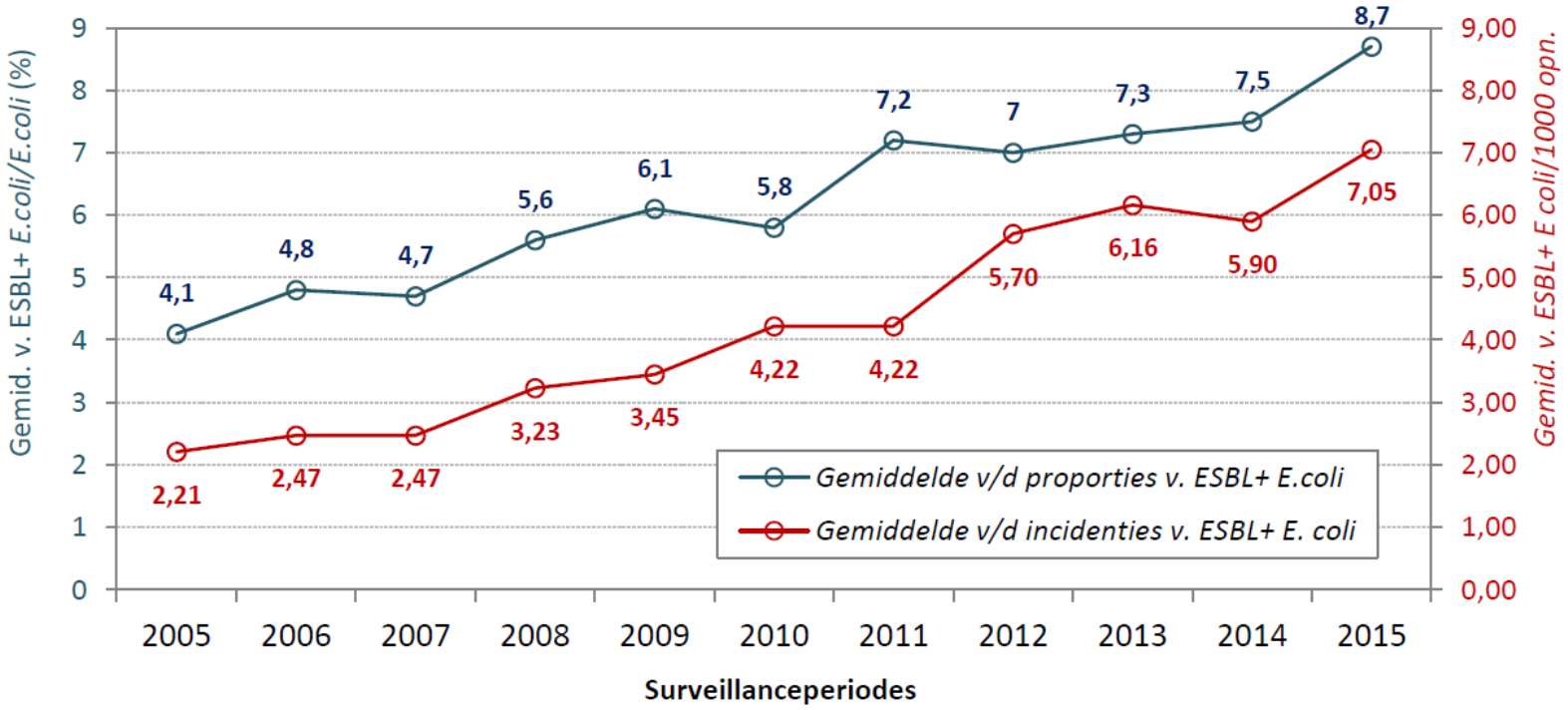
Metallo-β-Lactamases (MBLs)

Bush & Jacoby, Antimicrob Agents Chemother 2010; 54: 969 – 76
Patel & Bonomo, Expert Rev Anti Infect Ther 2011; 9: 555 - 70

Incidentie en proportie van ESBL+ *E. coli* in België (NSIH)

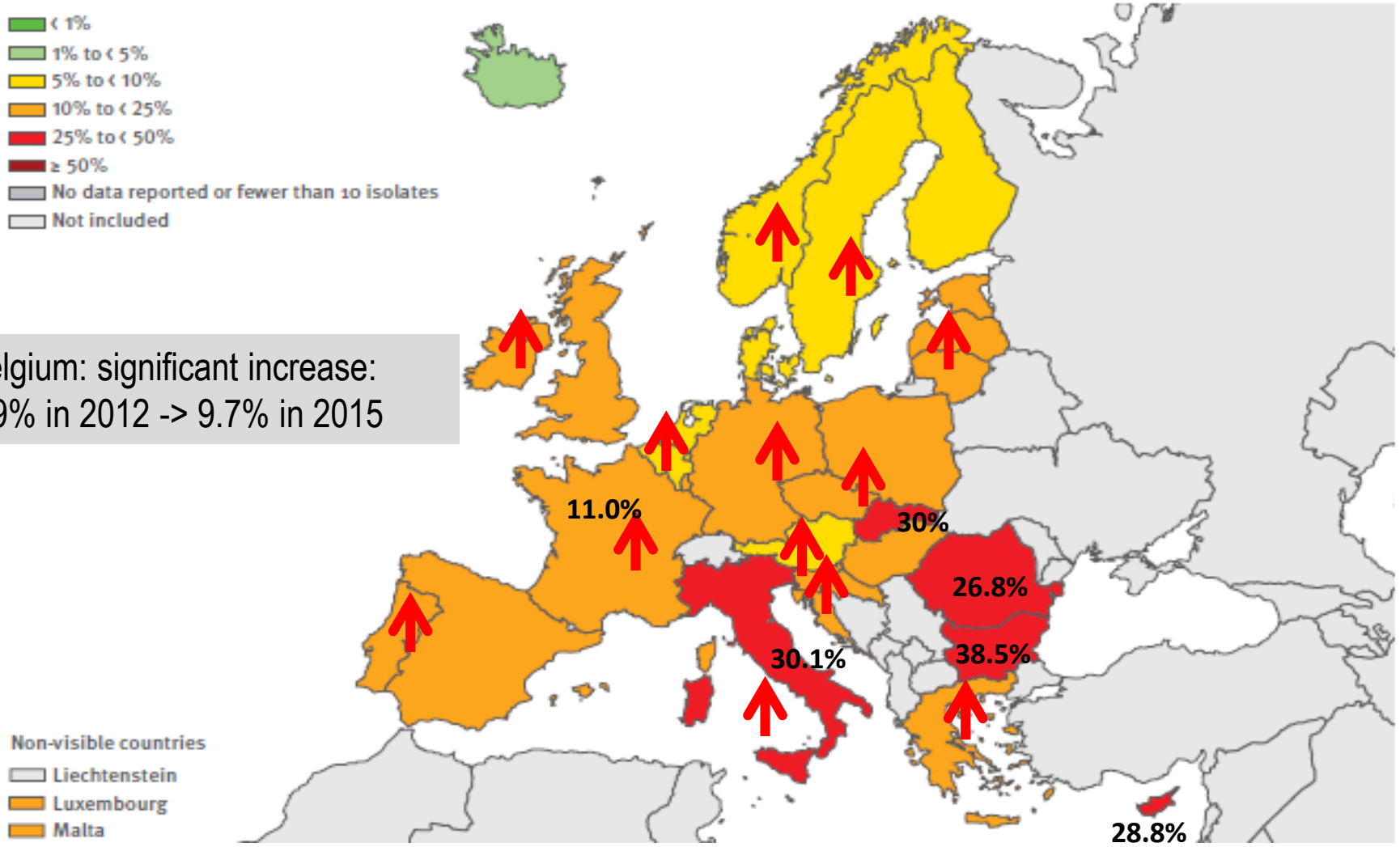
Acute hospitals + chronic health sector; All types of specimens (blood, urine, pus, sputum,…); Community acquired + hospital acquired

Figuur 28: Evolutie van het gemiddelde van de proporties en incidentiecijfers van ESBL+ Escherichia coli: min. 3 deelnames sinds 2005



Bron: Surveillance van antibioticaresistente bacteriën in Belgische ziekenhuizen: Rapport 2015

Escherichia coli: Percentage of invasive isolates (Blood/CSF) with resistance to 3rd gen. cephalosporins in Europe (2015)



Belgium: significant increase:
6.9% in 2012 -> 9.7% in 2015

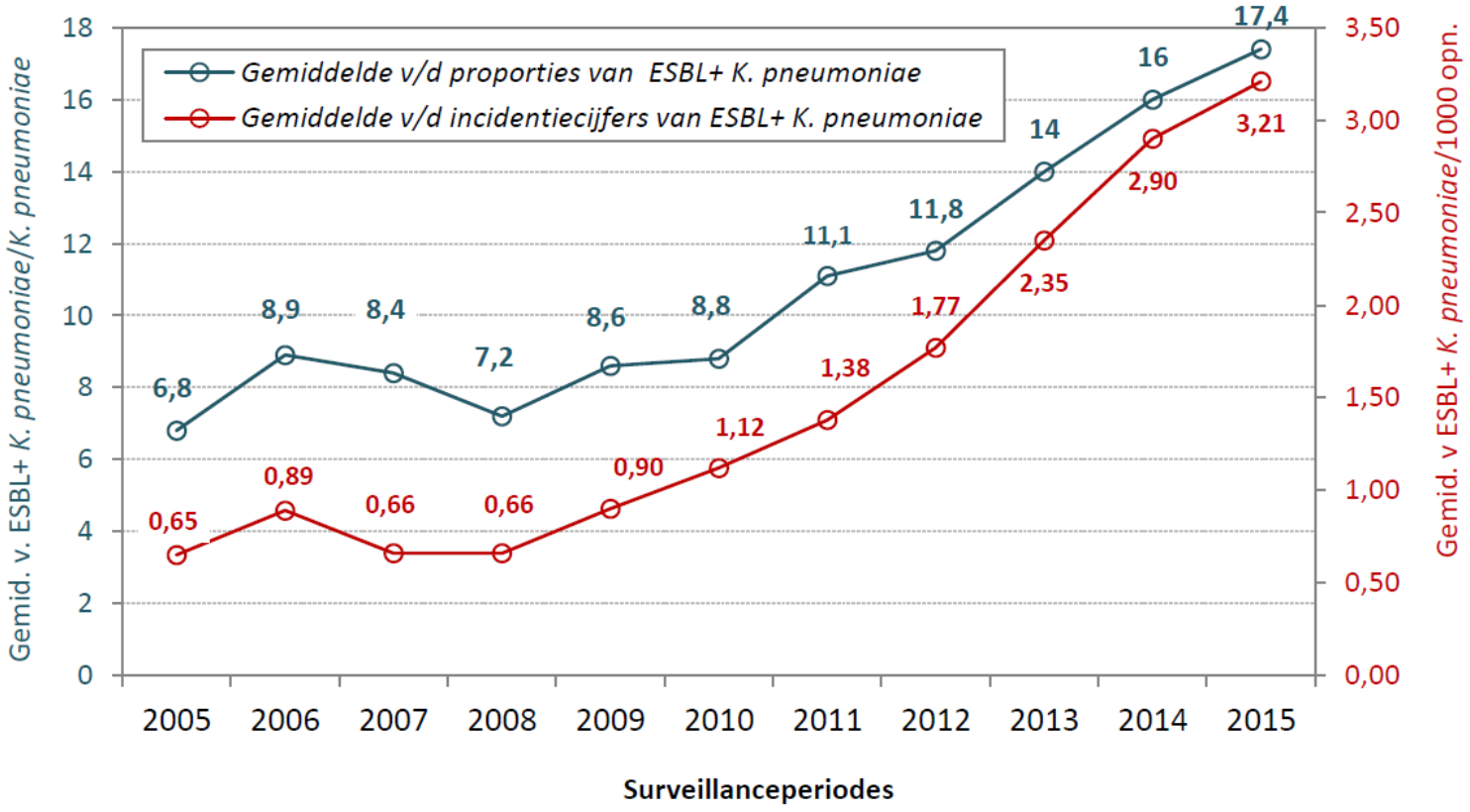
Mean weighed Resistance: 11.9% in 2012 -> 13.1% in 2015
Increasing resistance trend in 12 countries
90% of C3G-R *E. coli*: ESBL-positive

EARS-Net Report 2015
www.ecdc.europa.eu

Incidentie en proportie van ESBL+ *K. pneumoniae* in België

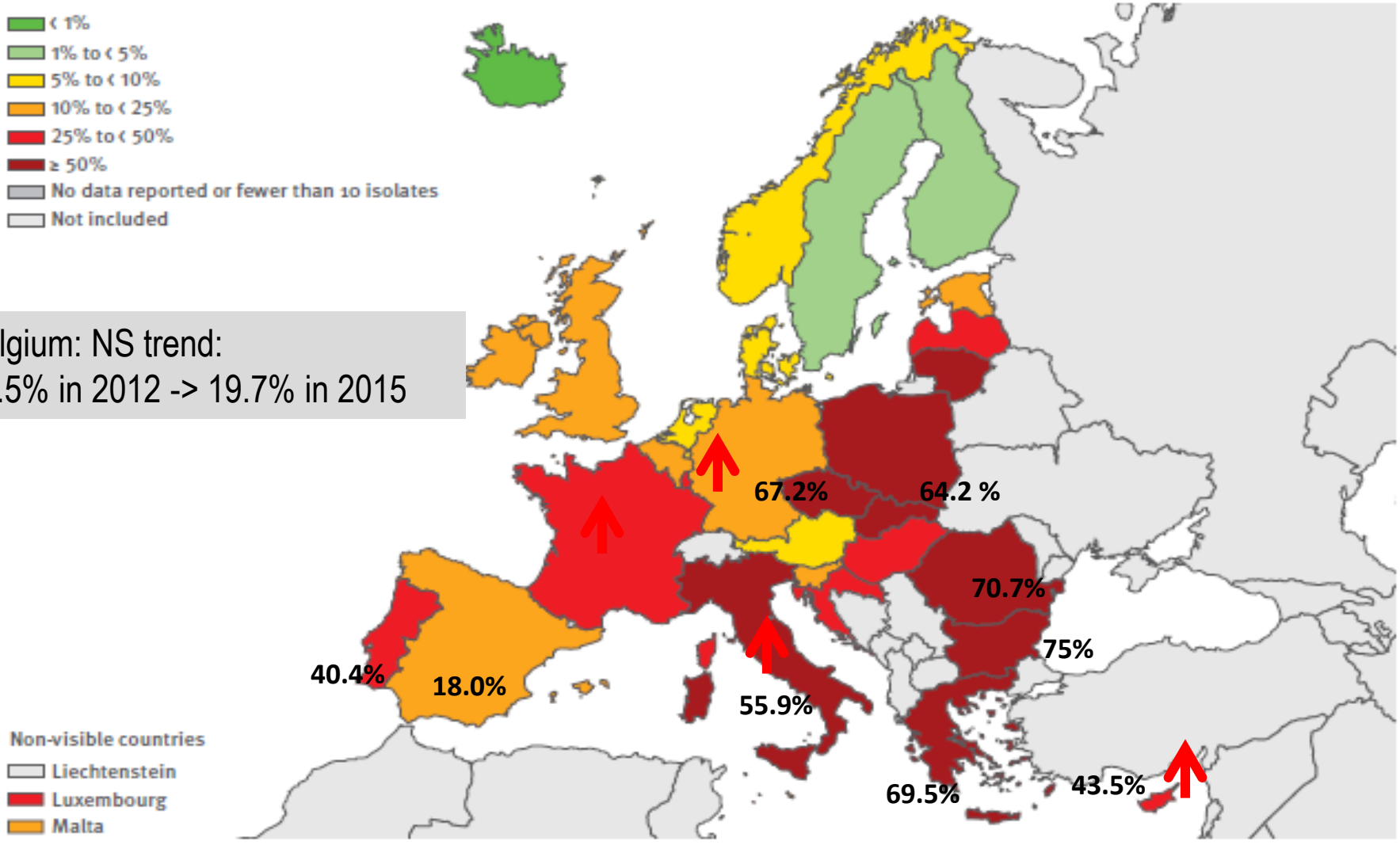
Acute hospitals + chronic health sector; All types of specimens (blood, urine, pus, sputum,…); Community acquired + hospital acquired

Figuur 34: Evolutie van het gemiddelde van de proporties en incidentiecijfers van ESBL-producerende Klebsiella pneumoniae: ziekenhuizen met min. 3 deelnames sinds 2005



Bron: Surveillance van antibioticaresistente bacteriën in Belgische ziekenhuizen: Rapport 2015

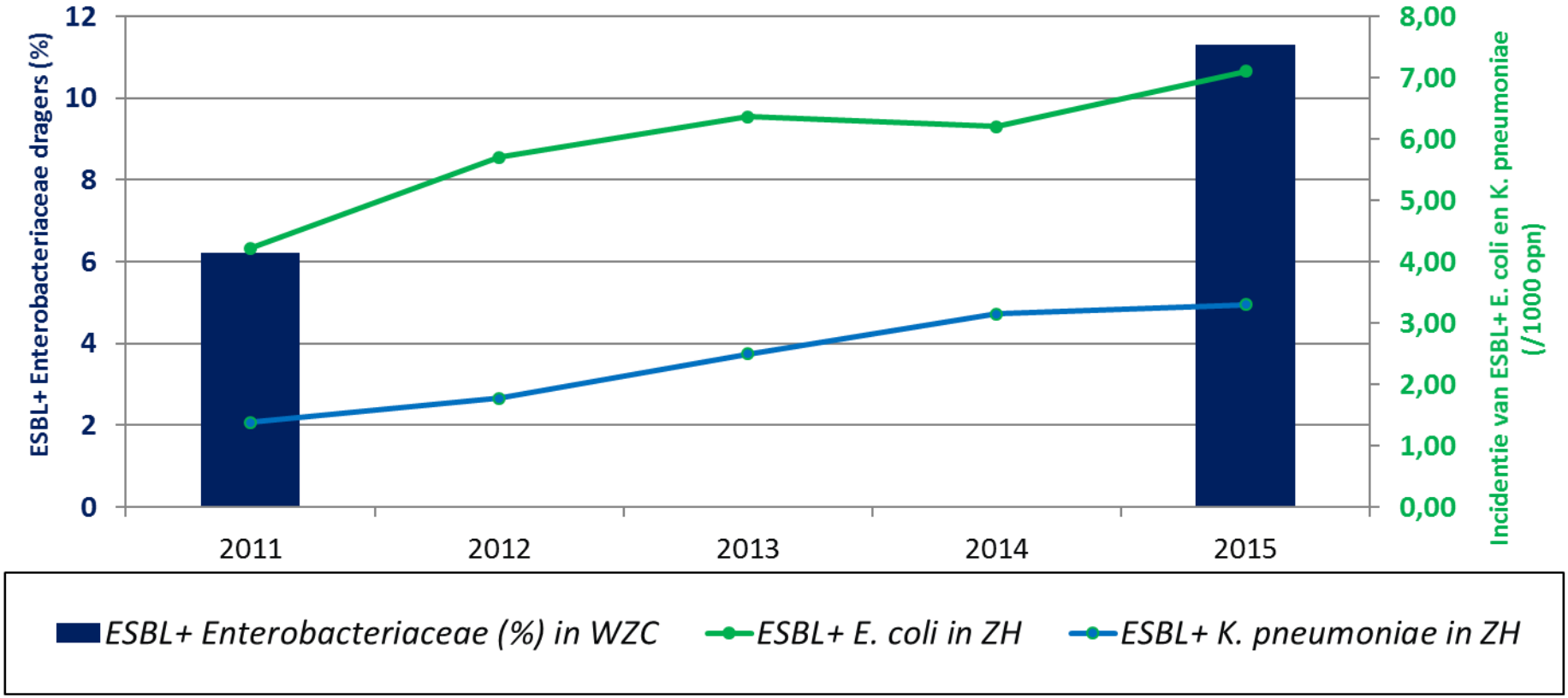
Klebsiella pneumoniae: Percentage of invasive isolates with resistance to C3G in Europe (2015)



Significantly increasing trend in 3 countries (25.8% in 2012 -> 30.3% in 2015)
85% C3G-R *K. pneumoniae* are ESBL+

EARS-Net Report 2015
www.ecdc.europa.eu

ESBL-producerende *Enterobacteriaceae* in WZC in België: % dragerschap 2011 - 2015



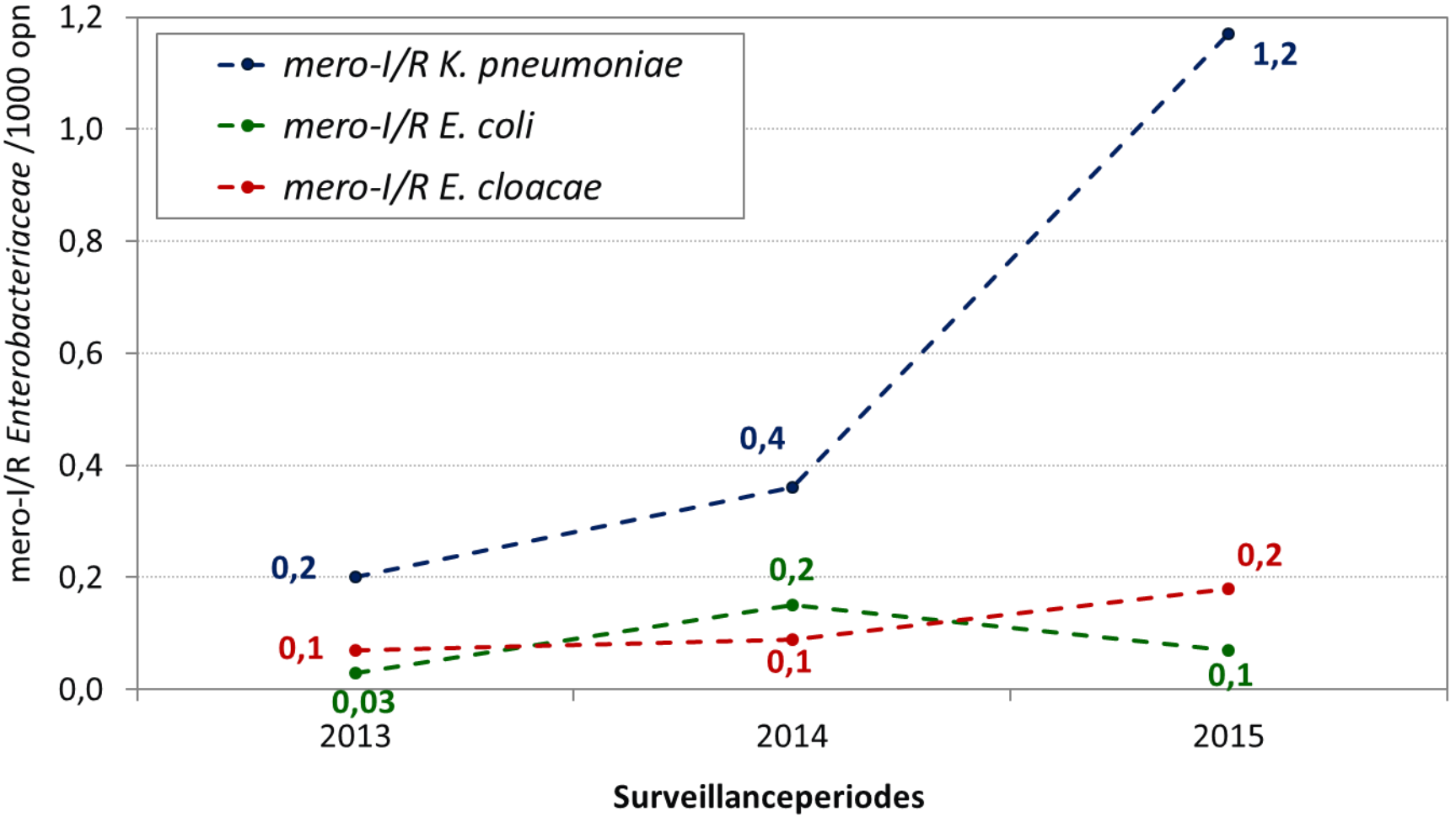
60 WZC (2011)
6.2 % ESBL+
(0% - 20%)

29 WZC (2015)
11.3 % ESBL+
(0% - 45.8%)

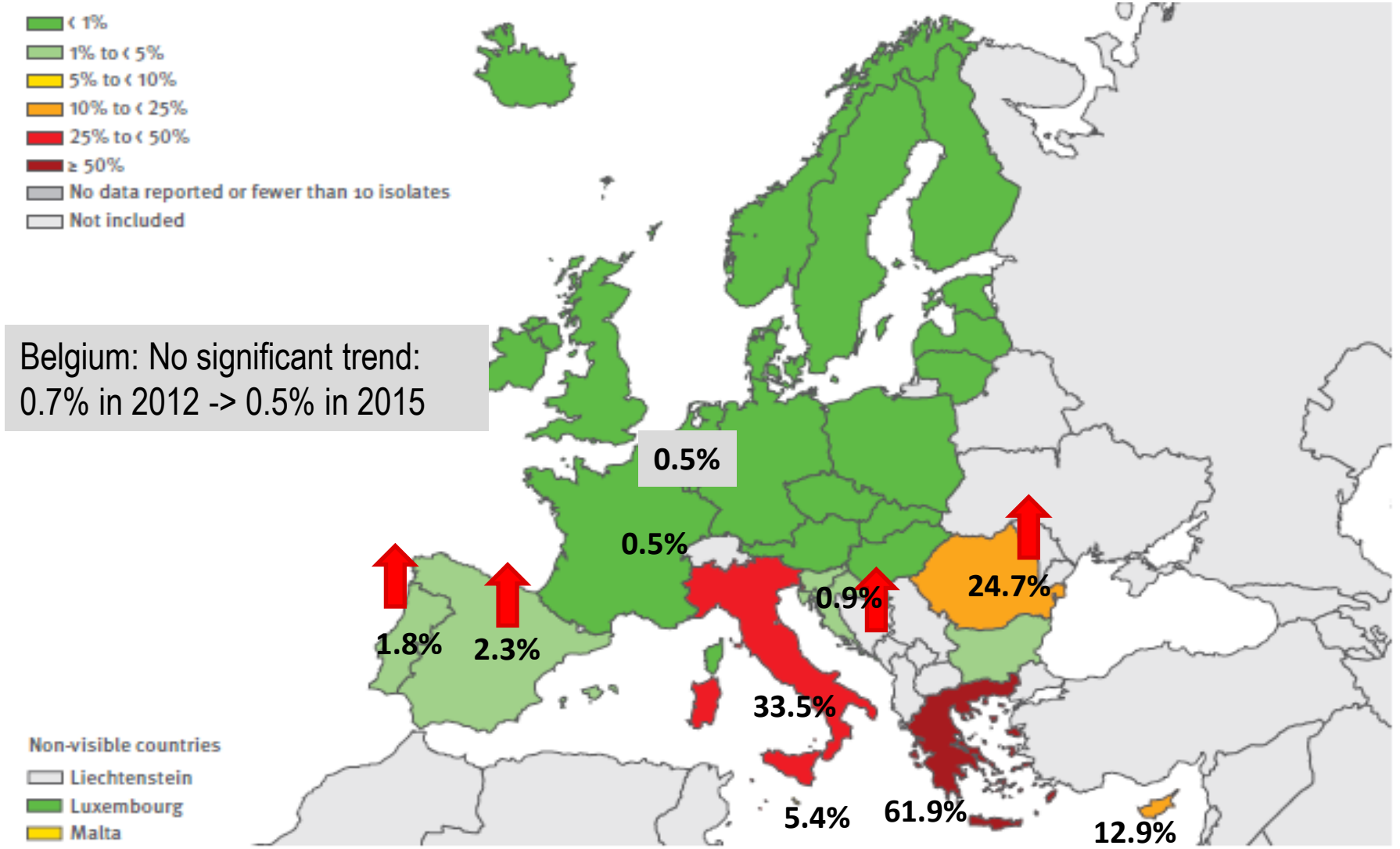
Bron: Prevalentiestudies in verband met dragerschap van MDRO in Woonzorgcentra in België: 2011 en 2015

Evolutie van de incidentiecijfers van mero-I/R *E. cloacae*, *E. coli* en *K. pneumoniae* (per 1000 opnames): 2013-2015

E. cloacae, E. coli en *K. pneumoniae*: uit klinische- en screeningstalen



K. pneumoniae: Proportion of invasive isolates resistant to carbapenems in Europe (2015)

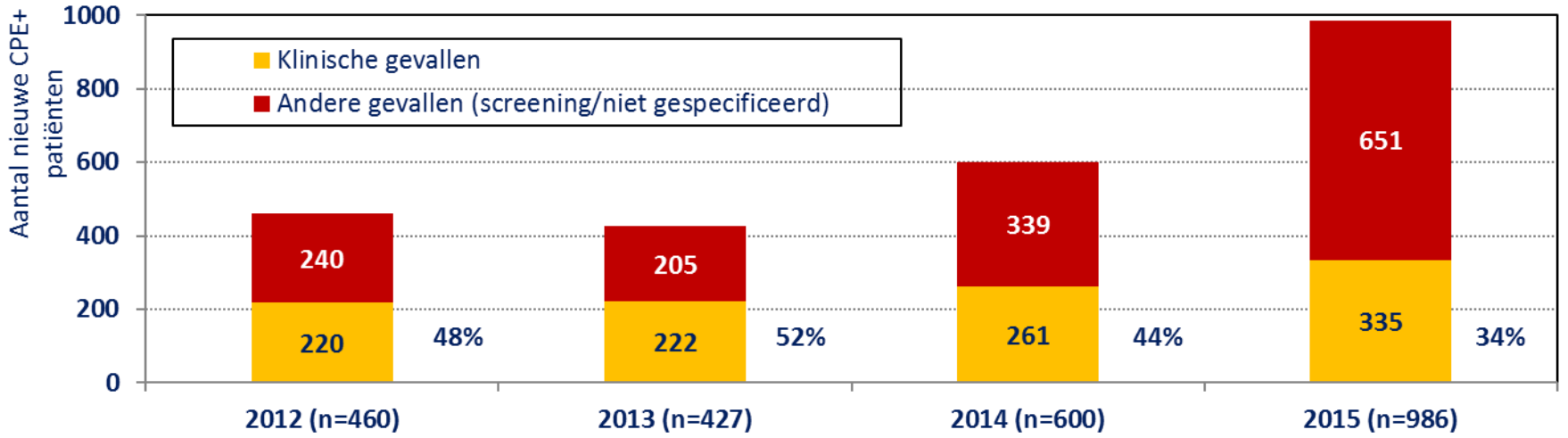


Belgium: No significant trend:
0.7% in 2012 -> 0.5% in 2015

Significant increasing trend in 4 countries
(HR, P, RO, SP)

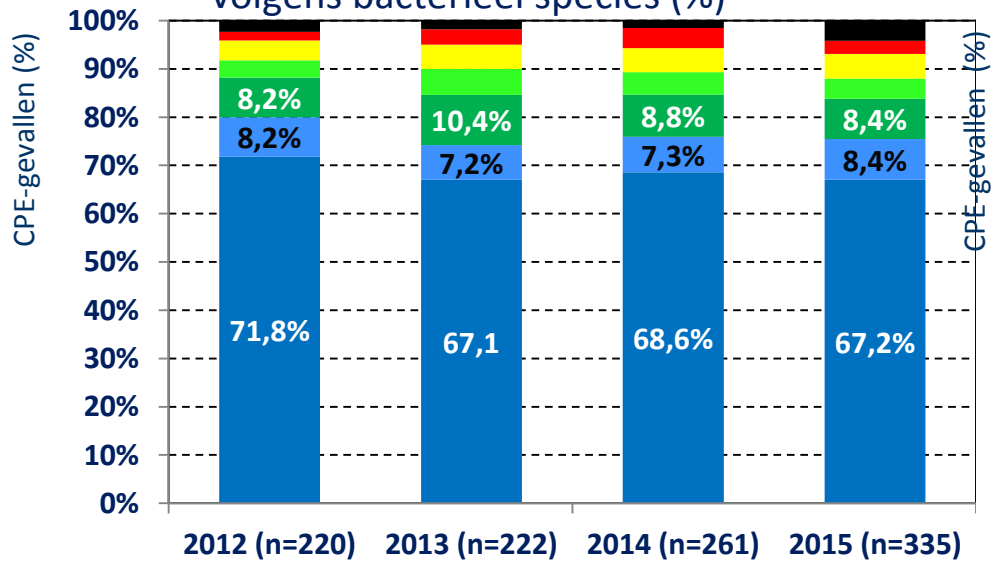
EARS-Net Report 2015, www.ecdc.europa.eu

Jaarlijks aantal CPE-gevallen: 1/1/2012 - 31/12/2015

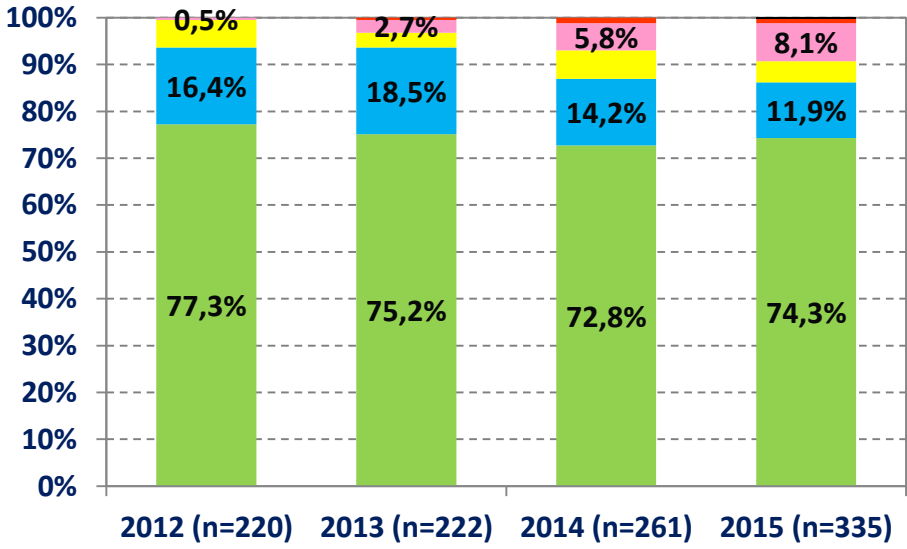


Evolutie van het jaarlijks aantal klinische CPE-gevallen (n=1038): 1/1/2012 – 31/12/2015

volgens bacterieel species (%)



volgens carbapenemase-type (%)



K. pneumoniae *E. cloacae* *E. coli* *C. freundii* *K. oxytoca* *Andere species* *Multi-species*

OXA-48 KPC VIM NDM Meerdere Andere

Bron: WIV/NRC-surveillance

2
1

Jaarlijks aantal ziekenhuizen met één of meerdere CPE-clusters: verdeling volgens type carbapenemase (2012 – 2015)

Aantal ziekenhuizen met:	2012	2013	2014	2015
CPE-clusters met één enkel type carbapenemase:	**15**	**15**	**15**	**16**
OXA-48	11	11	9	11
KPC	3	3	3	2
NDM	1	1	2	3
VIM			1	
CPE-clusters met meerdere types carbapenemasen	**1**	**1**	**3**	**4**
KPC + VIM	1			
NDM + VIM		1		1
OXA + VIM			1	1
OXA + KPC			1	1
OXA + NDM			1	
OXA + KPC + NDM				1
Totaal aantal ziekenhuizen in epidemische situatie tijdens het surveillancejaar	**16**	**16**	**18**	**20**

Bron: Surveillance van antibioticaresistente bacteriën in Belgische ziekenhuizen: Rapport 2015

Wat drijft ze?


sex&
drugs&
rock&roll

1. Sex

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3365–3370 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.00126-09

Molecular Epidemiology of KPC-Producing *Klebsiella pneumoniae* Isolates in the United States: Clonal Expansion of Multilocus Sequence Type 258[▽]

Brandon Kitchel,[1]* J. Kamile Rasheed,[1] Jean B. Patel,[1] Arjun Srinivasan,[1] Shiri Navon-Venezia,[2] Yehuda Carmeli,[2] Alma Brolund,[3] and Christian G. Giske[3]

Worldwide Diversity of *Klebsiella pneumoniae* That Produces β-Lactamase bla_{KPC-2} Gene[1]

Gaëlle Cuzon, Thierry Naas, HaVy Truong, Maria-Virginia Villegas, Karin T. Wisell, Yehuda Carmeli, Ana. C. Gales, Shiri Navon-Venezia, John P. Quinn, and Patrice Nordmann

Spreading of ESBL and Carbapenemases in same clone in Greece

Detection of the new metallo-β-lactamase VIM-19 along with KPC-2, CMY-2 and CTX-M-15 in *Klebsiella pneumoniae*

Spyros Pournaras[1]*, Aggeliki Poulou[2,3], Evangelia Voulgari[3], Georgia Vrioni[3], Ioulia Kristo[1] and Athanassios Tsakris[3]

2. Drugs

Defined daily doses

(DDD) per 1000 inh. and per day

Country	2015	Trends in antimicrobial consumption, 2011–2015
Netherlands	10.7	↓
Estonia	11.6	
Sweden	12.3	↓
Latvia	13.3	
Austria	14.0	
Germany	14.3	
Slovenia	14.5	
Norway	15.8	
Denmark	16.1	
Lithuania	16.7	
Hungary	17.0	
Finland	17.2	↓
Czech Republic	19.6	
Iceland	19.9	
United Kingdom	20.1	
Portugal (a)	21.3†	
Bulgaria	21.4	
Croatia	21.8	
Malta	22.2	
Spain	22.2†	
EU/EEA	**22.4**	
Slovakia	24.5	
Ireland	25.6	
Poland (a)	26.2	
Luxembourg	26.3	
Italy	27.5	
Belgium	29.2	
France	29.9	
Cyprus	31.1*	
Romania	33.3*	
Greece	36.1	

Packages

per 1000 inh. and per day

Country	2015	Trends in consumption of antibiotics, 2011–2015
Sweden	0.99	↓
Denmark	1.58	↓
Estonia	1.68	↓
Latvia	1.71	
Austria	1.73	
Finland	1.79	↓
Slovenia	1.94	
Spain	1.95†	↓
Lithuania (a)(b)	1.98	
Czech Republic	2.00	
Iceland (a)(b)	2.09	
Portugal	2.14†	
Luxembourg	2.48	↓
Ireland	2.53	
Croatia	2.65	
Belgium	2.76	
Bulgaria	3.01	
Slovakia (a)(b)	3.05	
EU/EEA	**3.13**	
Italy	3.65	
Greece	3.89	
France	4.74	

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Update with 2016 data: 15 Nov. 2017

* Total care data, including the hospital sector.

† Reimbursement data (i.e. not including consumption without a prescription and other non-reimbursed courses).

(a) Countries that changed the type of reported data (reimbursement versus sales data) between 2011 and 2015.

(b) Countries that did not report data for all years during the period 2011–2015.

Consumption of antibiotics for systemic use (ATC group J01) in the community, EU/EEA, 2011-2015

Source: ESAC-Net, 2016. The symbols ↑ and ↓ indicate a significant increasing or decreasing trend for the period 2011-2015, respectively.

Antibioticumgebruik in de Ambulante Praktijk in België en Nederland in 2013

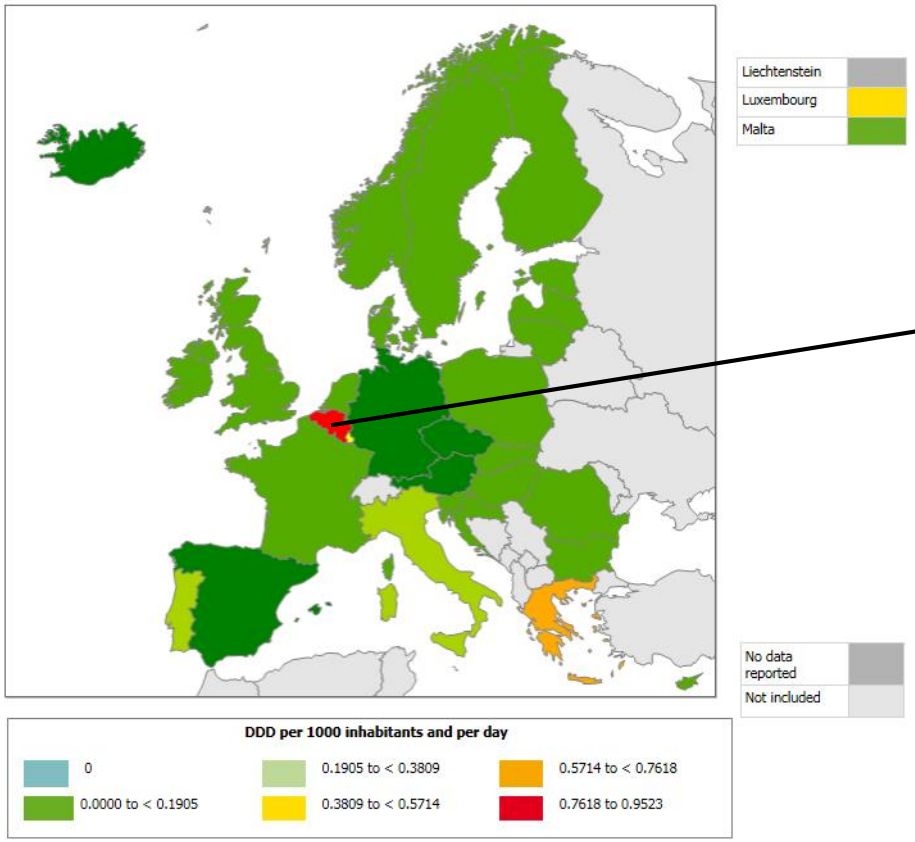
	Total population	Total pills consumed	Total costs	Pills/ Person	Cost/ Person
Belgium	11,140,000	141,000,070	€134,524,191	12.66	€12.08
Netherlands	16,770,000	99,476,775	€43,046,397	5.93	€2.57

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.

Caekelbergh et al, ISPOR Congress 7-11 November 2015

Geographical distribution of the consumption of Third-Generation Quinolones (ATC group J01M) in the community and hospital sector in Europe, reporting year 2014



MOXIFLOXACIN

See: ESAC-Net

3. Pandemische verspreiding

Global dissemination of CTX-M-15 producing ST131 *E. coli*

Clin Microbiol Rev. 2014 Jul; 27(3): 543–574.

Global dissemination of a clone: KPC-producing ST258 *K. pneumoniae*

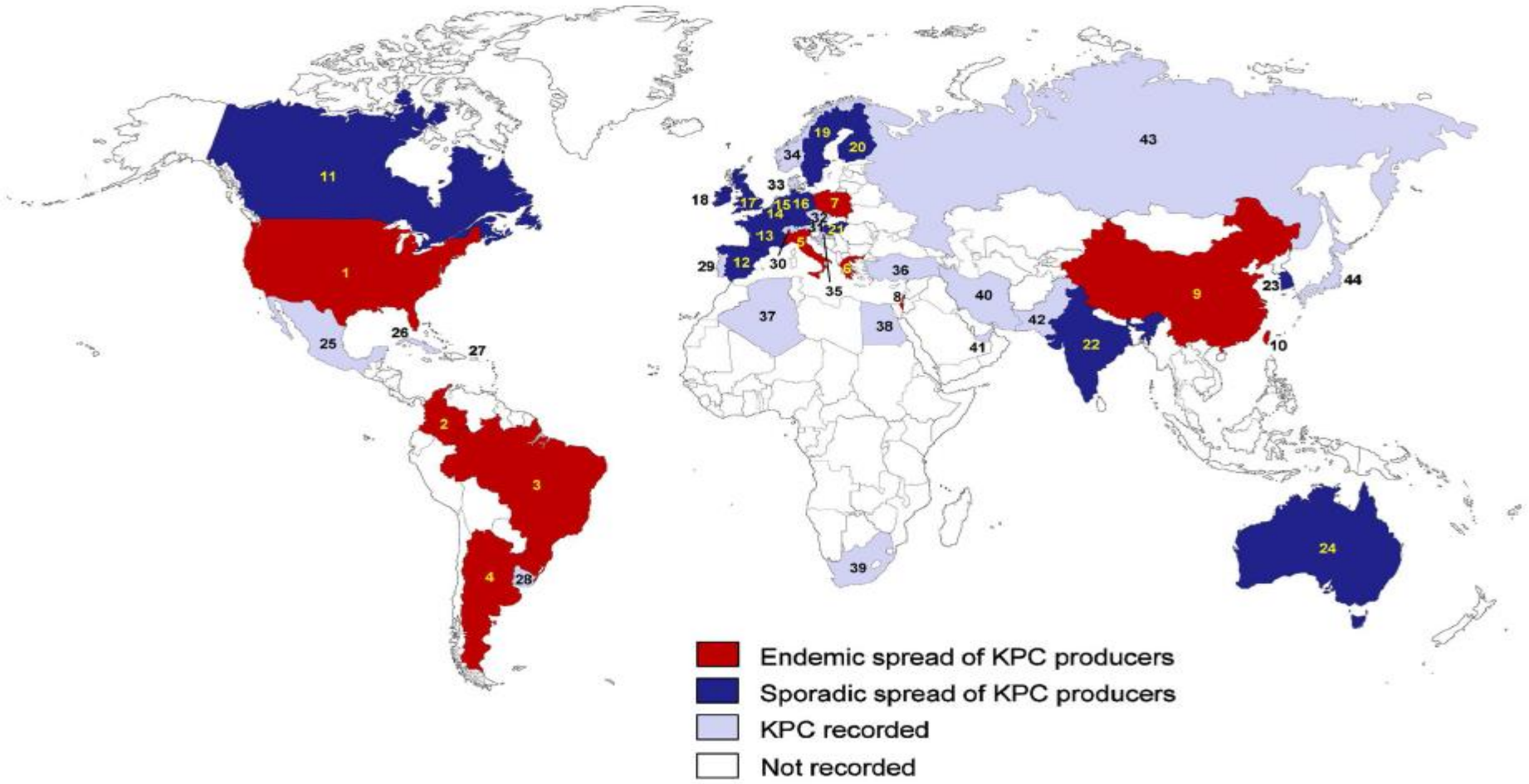


FIGURE 1 | Epidemiological features of KPC-producing *Klebsiella pneumoniae*. (1) USA; (2) Colombia; (3) Brazil; (4) Argentina; (5) Italy; (6) Greece; (7) Poland; (8) Israel; (9) China; (10) Taiwan; (11) Canada; (12) Spain; (13) France; (14) Belgium; (15) Netherlands; (16) Germany; (17) UK; (18) Ireland; (19) Sweden; (20) Finland; (21) Hungary; (22) India; (23) South Korea; (24) Australia; (25) Mexico; (26) Cuba; (27) Puerto Rico; (28) Uruguay; (29) Portugal; (30) Switzerland; (31) Austria; (32) Czech Republic; (33) Denmark; (34) Norway; (35) Croatia; (36) Turkey; (37) Algeria; (38) Egypt; (39) South Africa; (40) Iran; (41) United Arab Emirates; (42) Pakistan; (43) Russia; (44) Japan.

Lee et al. Front Microbiol. 2016; 7: 895.

Global dissemination of a resistance gene: *ndm*-harboring *K. pneumoniae*

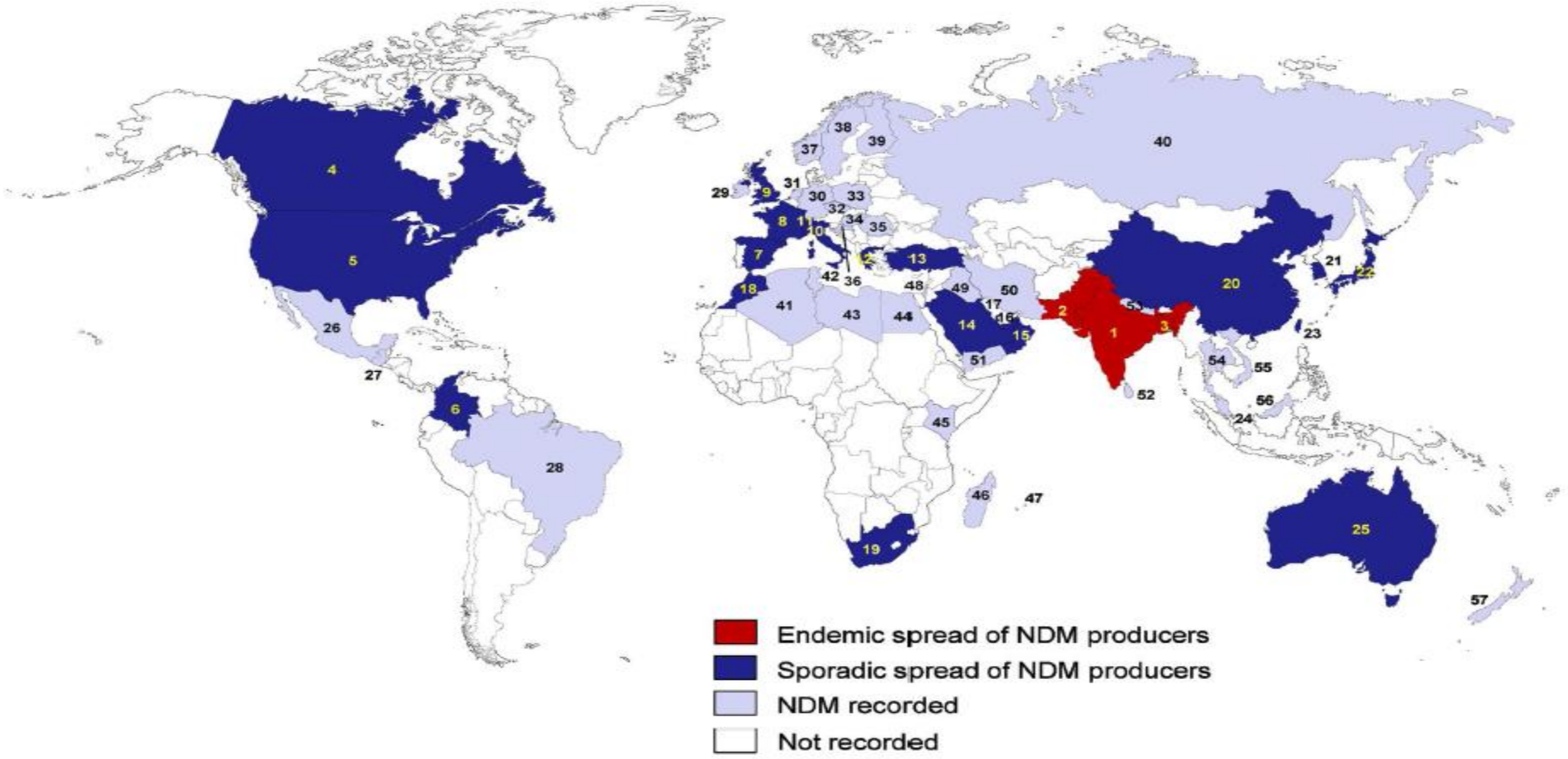


FIGURE 3 | Epidemiological features of NDM-producing *K. pneumoniae*. (1) India; (2) Pakistan; (3) Bangladesh; (4) Canada; (5) USA; (6) Colombia; (7) Spain; (8) France; (9) UK; (10) Italy; (11) Switzerland; (12) Greece; (13) Turkey; (14) Saudi Arabia; (15) Oman; (16) United Arab Emirates; (17) Kuwait; (18) Morocco; (19) South Africa; (20) China; (21) South Korea; (22) Japan; (23) Taiwan; (24) Singapore; (25) Australia; (26) Mexico; (27) Guatemala; (28) Brazil; (29) Ireland; (30) Germany; (31) Netherlands; (32) Czech Republic; (33) Poland; (34) Hungary; (35) Romania; (36) Croatia; (37) Norway; (38) Sweden; (39) Finland; (40) Russia; (41) Algeria; (42) Tunisia; (43) Libya; (44) Egypt; (45) Kenya; (46) Madagascar; (47) Mauritius; (48) Israel; (49) Iraq; (50) Iran; (51) Yemen; (52) Sri Lanka; (53) Nepal; (54) Thailand; (55) Vietnam; (56) Malaysia, (57) New Zealand.

Lee et al. Front Microbiol. 2016; 7: 895.

Global dissemination of resistance plasmid: pOXA-48a-harboring *K. pneumoniae*

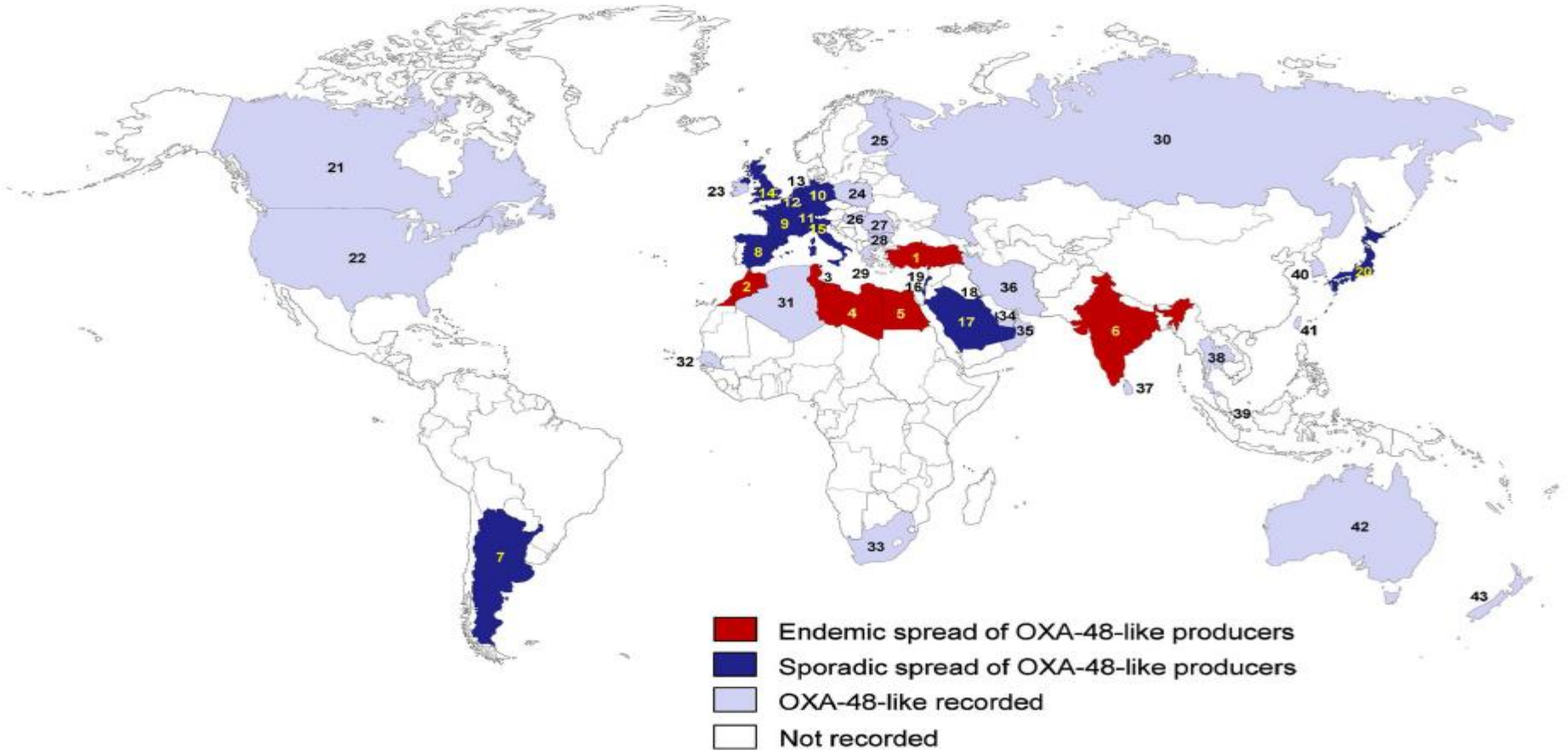


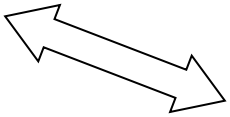
FIGURE 4 | Epidemiological features of OXA-48-like-producing *K. pneumoniae*. (1) Turkey; (2) Morocco; (3) Tunisia; (4) Libya; (5) Egypt; (6) India; (7) Argentina; (8) Spain; (9) France; (10) Germany; (11) Switzerland; (12) Belgium; (13) Netherlands; (14) UK; (15) Italy; (16) Israel; (17) Saudi Arabia; (18) Kuwait; (19) Lebanon; (20) Japan; (21) Canada; (22) USA; (23) Ireland; (24) Poland; (25) Finland; (26) Hungary; (27) Romania; (28) Bulgaria; (29) Greece; (30) Russia; (31) Algeria; (32) Senegal; (33) South Africa; (34) United Arab Emirates; (35) Oman; (36) Iran; (37) Sri Lanka; (38) Thailand; (39) Singapore; (40) South Korea; (41) Taiwan; (42) Australia; (43) New Zealand.

Lee et al. Front Microbiol. 2016; 7: 895.

4. Transmissie

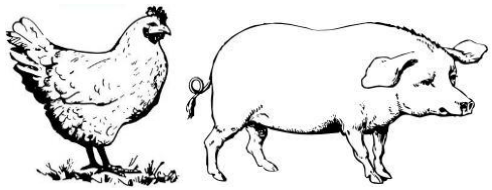
One Health

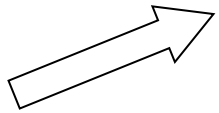
household members
& pets

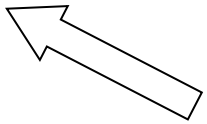


travel

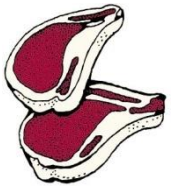
animals



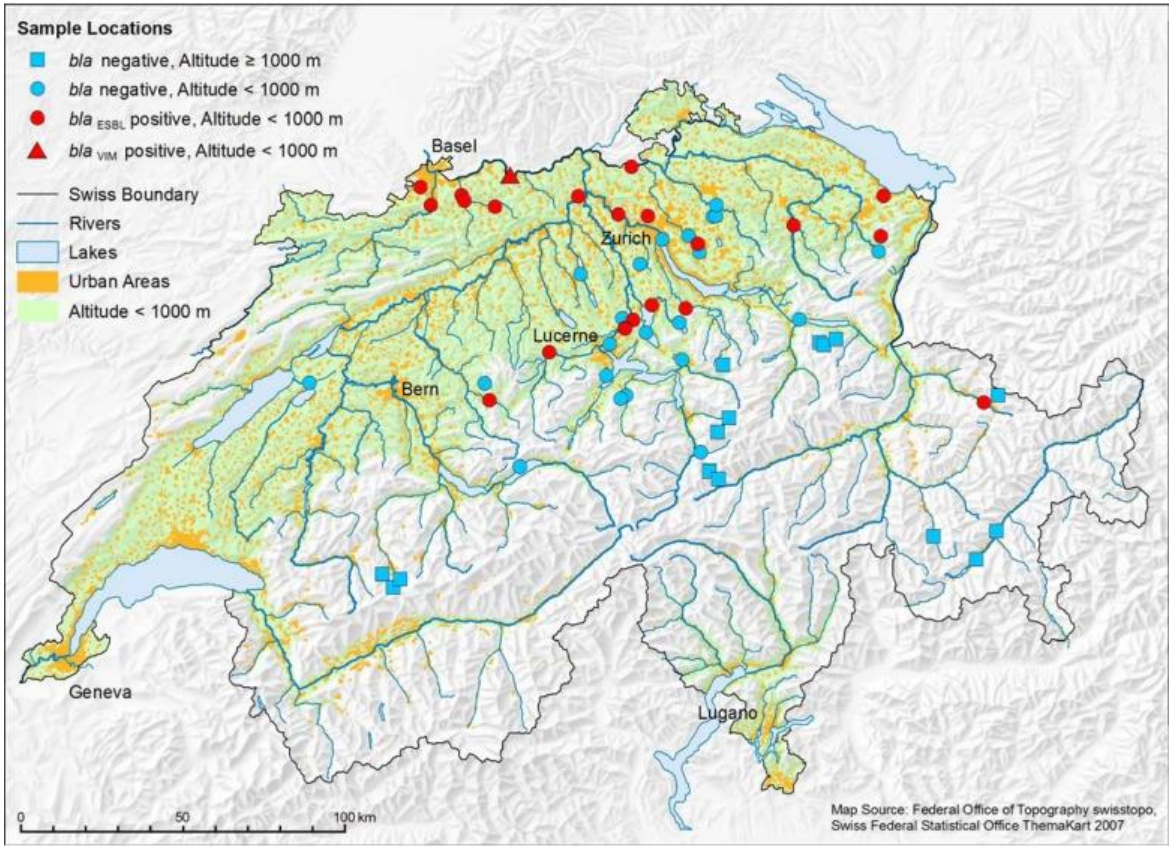




food



ESBL-Producing Gram-Negatives in the Environment



Characteristics of Extended-Spectrum β-Lactamase- and Carbapenemase-Producing Enterobacteriaceae Isolates from Rivers and Lakes in Switzerland

Zurfluh et al., Appl Environ Microbiol. May 2013; 79: 3021–3026

Waar gaan we naartoe?

Two world leaders and AMR advocacies have disappeared

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.

UK lost global AMR leadership in 2016

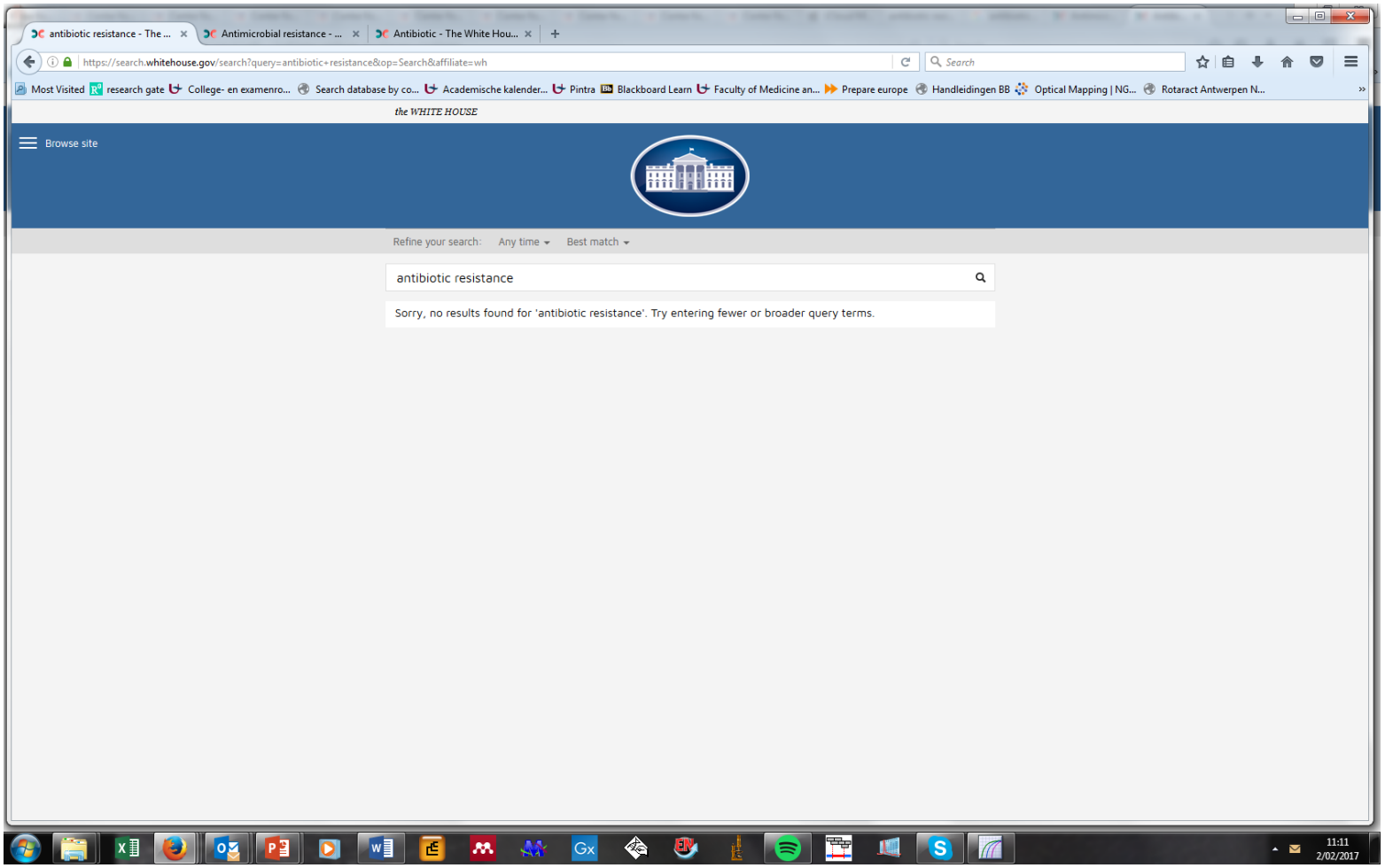
Obama battles 'superbugs' with national plan

By Sandee LaMotte, CNN

Updated 5:11 PM ET, Fri March 27, 2015

President Barack Obama announces a five-year plan to fight antibiotic-resistant bacteria.

Future role of US unclear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Refine your search:
Any time
Best match
antibiotic resistance
Sorry, no results found for 'antibiotic resistance'. Try entering fewer or broader query terms.
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2/02/2017

High-level meeting of the UN General Assembly on antimicrobial resistance on 21 September 2016

Unprecedented level of attention.

For the first time, Heads of State committed to taking a broad, coordinated approach to address the root causes of AMR across multiple sectors, especially human health, animal health and agriculture.

Recognized “One Health” approach as overarching principle for addressing AMR and emphasized that this requires coherent, comprehensive and integrated multi-sectoral action

Recognized that human, animal and environmental health are interconnected

Political Declaration of the high-level meeting of the UN General Assembly on antimicrobial resistance

21 September 2016, New York, USA

- Countries reaffirmed their commitment to develop national action plans on AMR, based on the Global Action Plan on Antimicrobial Resistance developed in 2015 by the World Health Organization (WHO) in coordination with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).
- UNGA called upon the Tripartite (and other intergovernmental organizations), to support the development and implementation of national action plans and antimicrobial resistance activities at the national, regional and global levels.
- Leaders at the UN meeting called on WHO, FAO and OIE, in collaboration with development banks such the World Bank other relevant stakeholders, to coordinate their planning and actions and to report back to the UN General Assembly in September 2018.

Germany's new leadership in 2017 on Global Health, including our fight against AMR

G20 GERMANY 2017
HAMBURG

The G20 in July 2017 under Germany's presidency has pledged to invigorate research and development efforts to find new drugs.

GARDP
Global Antibiotic Research & Development Partnership
A joint DNDi / WHO initiative

Germany hosts pledging event for GARDP, a new initiative to develop new antibiotic treatments, on 4 September 2017: EUR 56.5 million raised (EUR 51.3 million from German government!)

Department of Health

UNITED NATIONS FOUNDATION

wellcome

Meeting in October in Berlin to start the process of greater alignment and coordination of global stakeholders

A Call to Action on AMR

12th and 13th October 2017

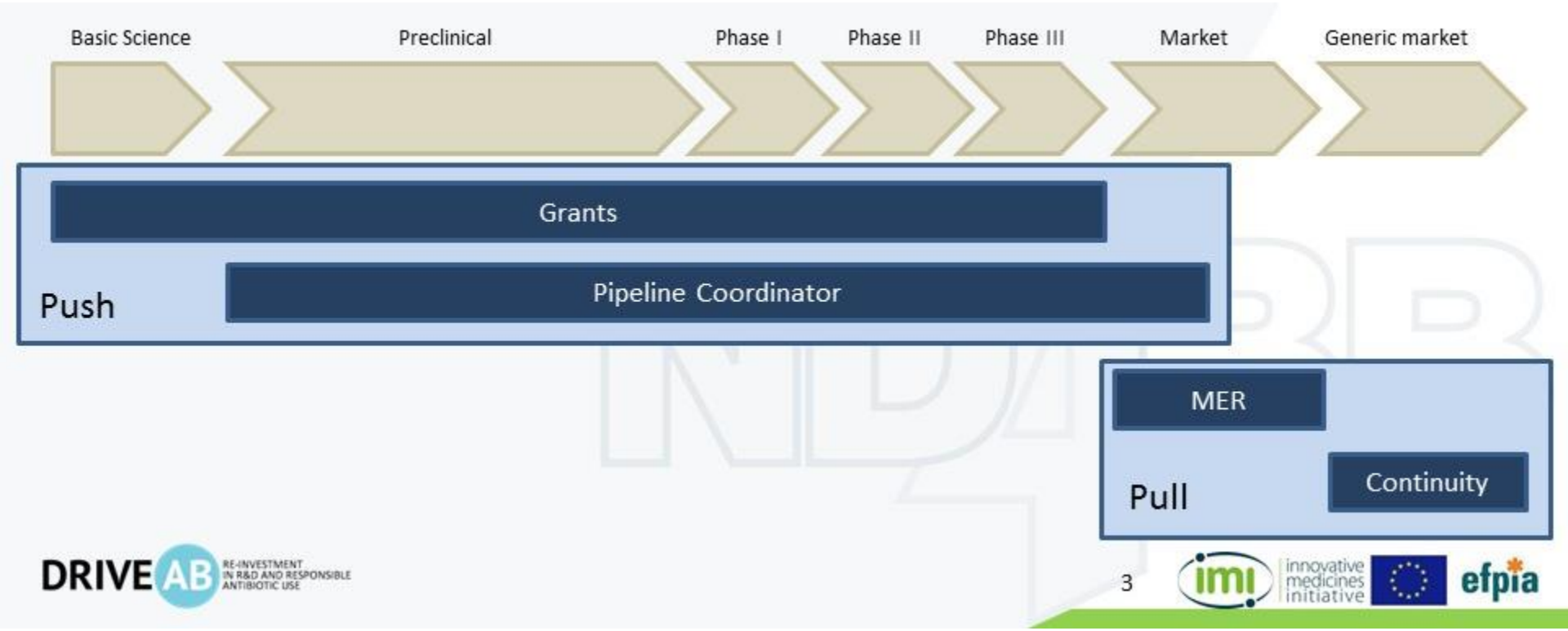
Novel antibiotic candidates

Bacteria (WHO category)	WHO (2017)	# in clinical development	# likely to register
Acinetobacter baumannii, carbapenem-R	Critical	4	~1
Pseudomonas aeruginosa, carbapenem-R	Critical	3	~1
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	9	3-4
Enterococcus faecium, vancomycin-R	High	9	~4
Staphylococcus aureus, methicillin-R, vancomycin-I/R	High		
Helicobacter pylori, clarithromycin-R	High	0	0
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High	2	~0.6

Candidate tallies per WHO pipeline review (publishing soon). Likelihood of success using industry standard estimates (Czaplewski 2016).

Source: DRIVE-AB summary for ASM-ESCMID conference, 5 September 2017

DRIVE-AB: 4 types of incentive tools



Source: DRIVE-AB summary for ASM-ESCMID conference, 5 September 2017

BAPCOC: Budget 2016

- Sensibilisatiecampagne ter promotie van het verantwoord antibioticagebruik – winter 2016-2017 [RIZIV : 400.000€]
- Campagne handhygiëne [BFM B4: 125.000€]
- Financiering antibiotherapiebeleidsgroepen [BFM B5: 4.346.371€]
- Financiering ziekenhuishygiëne [BFM B4]:
  - verpleegkundigen: 9.748.327€
  - artsen: 6.968.890€
- Financiering regionale platformen [BFM B4: 22.310€]
- Financiering Noso-info [BFM B4: 35.000€]
- Studie PPS MDRO in WZC [RIZIV art 56: 125.135€]
- Updaten guidelines ziekenhuisgeneeskunde BVIKM [RIZIV art 56: 50.000€]
- Sensibilisatiecampagne AMCRA [RIZIV art 56: 38.600€]

Dank u