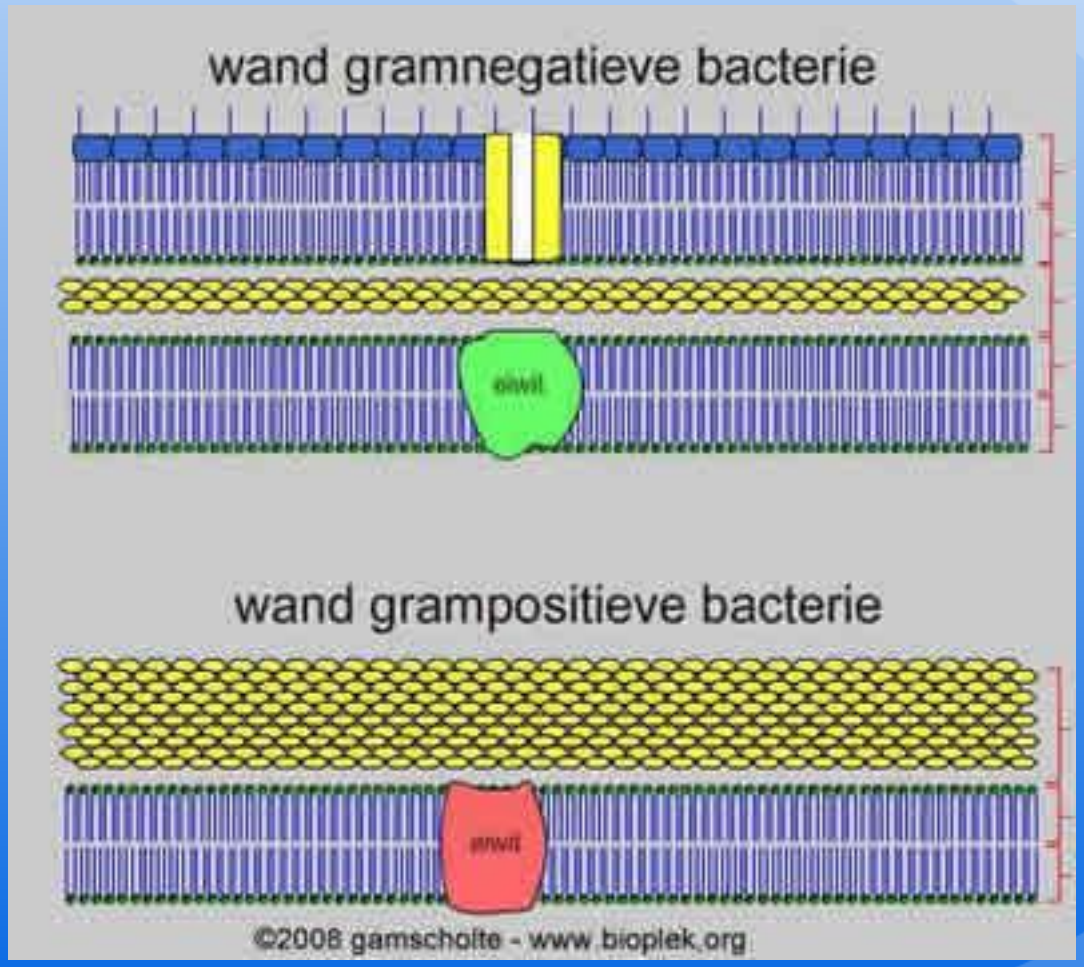
Resistentie

Toegespit[illegible]nze regio

Een internationaal probleem

Indeling bacteriën



Indeling bacteriën

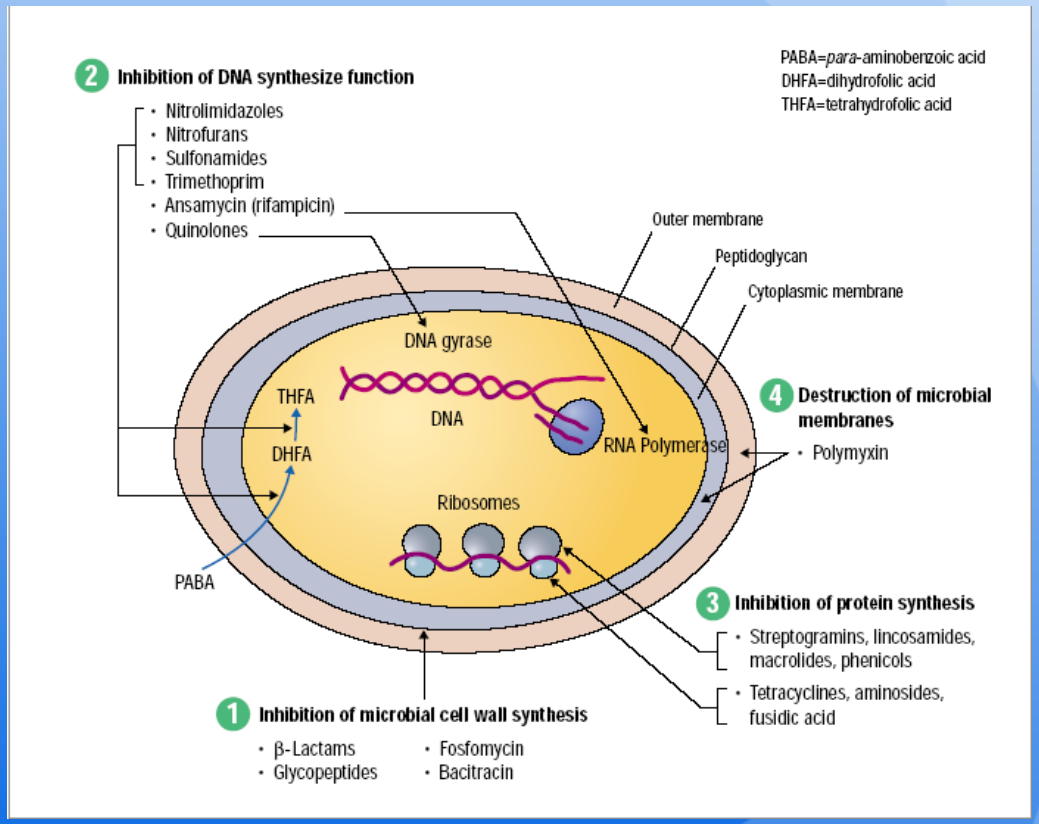
	Gram positief	**Gram negatief**
Coccen	Staphylococcen Streptococcen Pneumococ Enterococcen	Meningococ Gonococ
Staven	Bacillus Listeria Nocardia	E.coli Salmonella Shigella Pseudomonas

Antibiotica klassen (> 150 preparaten, 64 in FTK)

- B-lactam
- Quinolonen
- Aminoglycosiden
- Glycopeptiden
- Tetracyclines
- Chlooramphenicol
- Macroliden/lincosamiden
- Sulfonamide
- Overige

Werkingsmechanismen van antibiotica

- Celwand synthese
- DNA synthese
- Eiwit synthese



Resistentie mechanismen van bacteriën

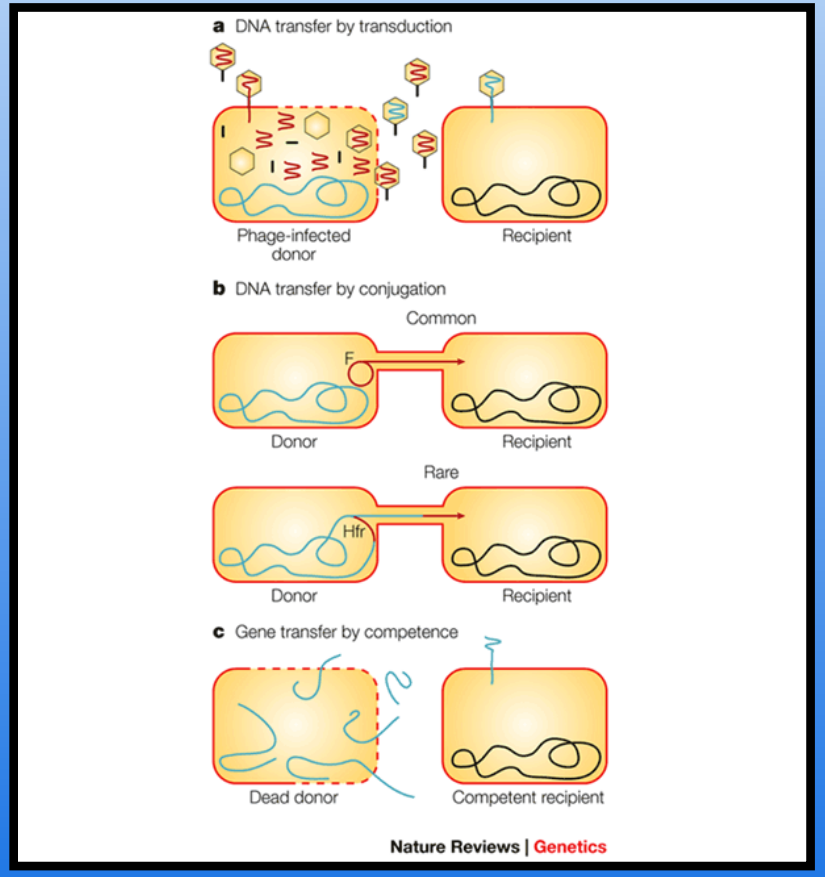
- Veranderd aangrijpingspunt
- Verminderde concentratie op plaats van activiteit
  - Permeabliteit
  - Efflux
- Inactivatie antibioticum
  - Afbraak
  - Modificatie

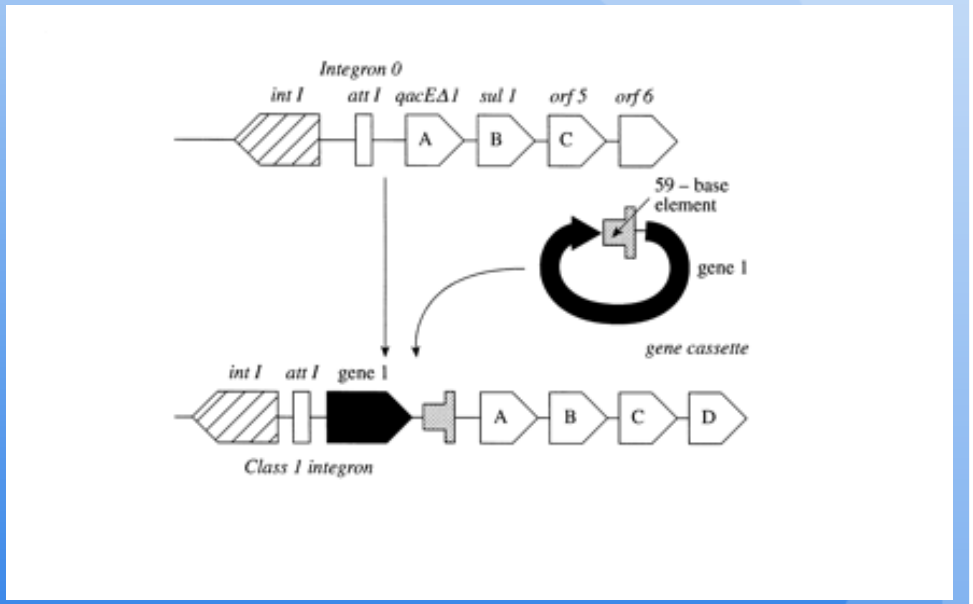
Intrinsieke en verworven resistentie

- Natuurlijke ongevoeligheid
  - Mycoplasma: beta-lactam R
  - Gram-positieven: Colistine R
  - Gram-negativen: Glycopeptide resistent
- Natuurlijke (chromosomale) resistentie
  - K.pneumoniae: AML R
  - E.cloacae: AMC R
  - S.maltophilia: Betalactams R
- Verworven resistentie
  - mutatie
  - DNA acquisitie

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

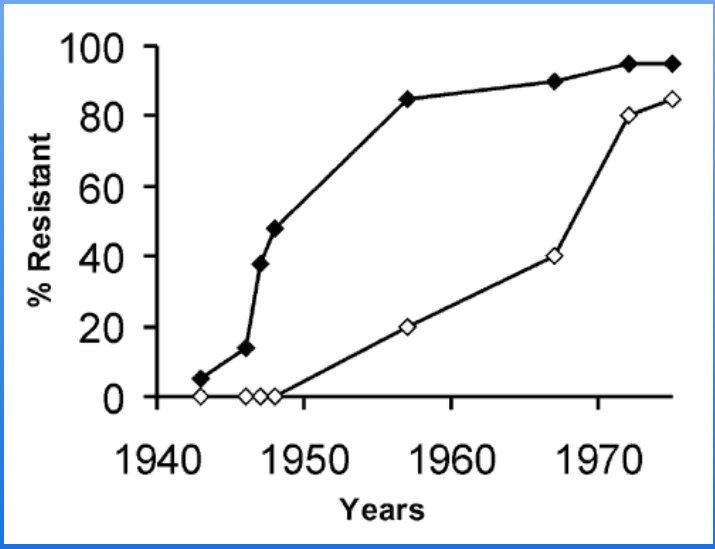
DNA acquisitie



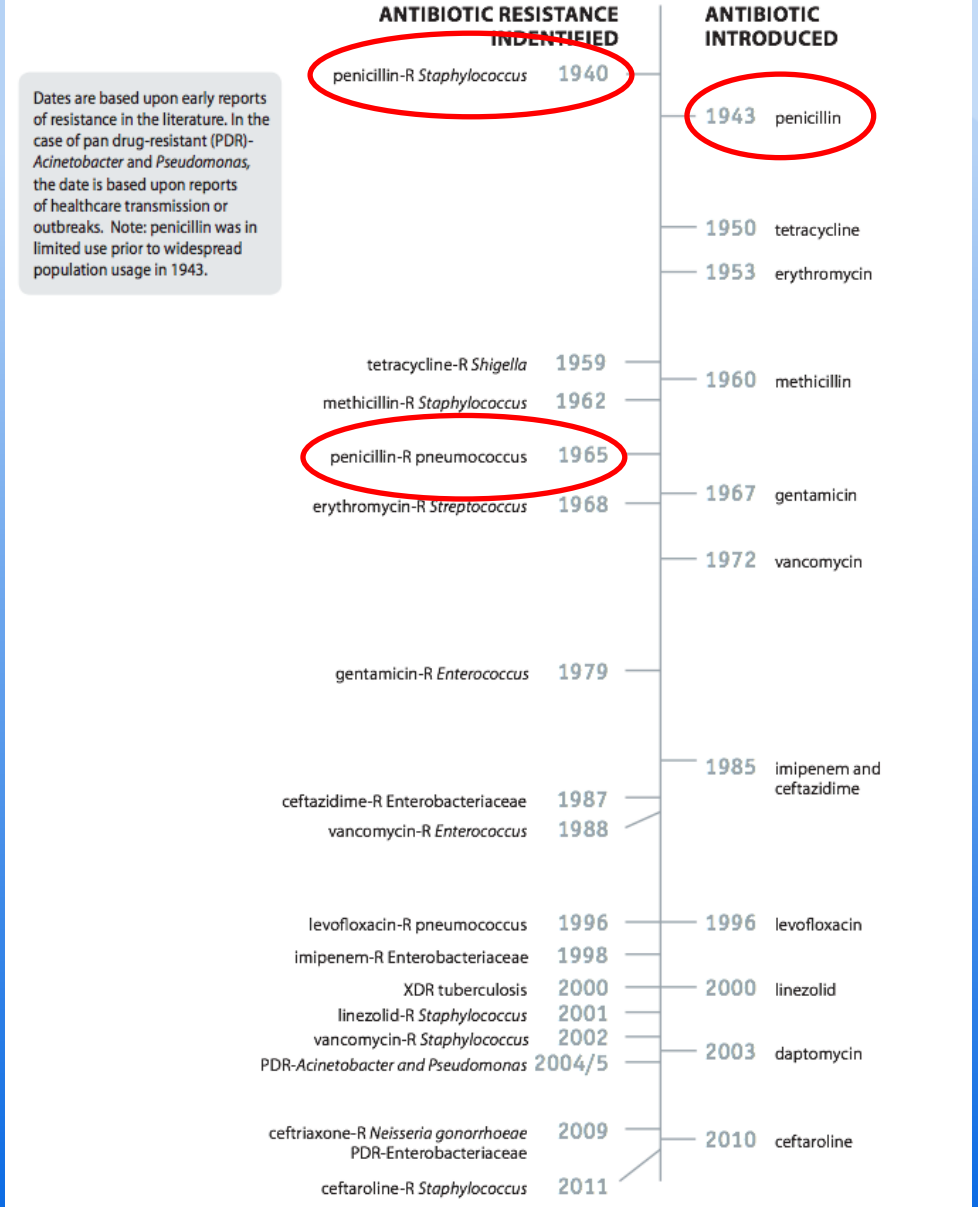


Resistentie niet nieuw!!

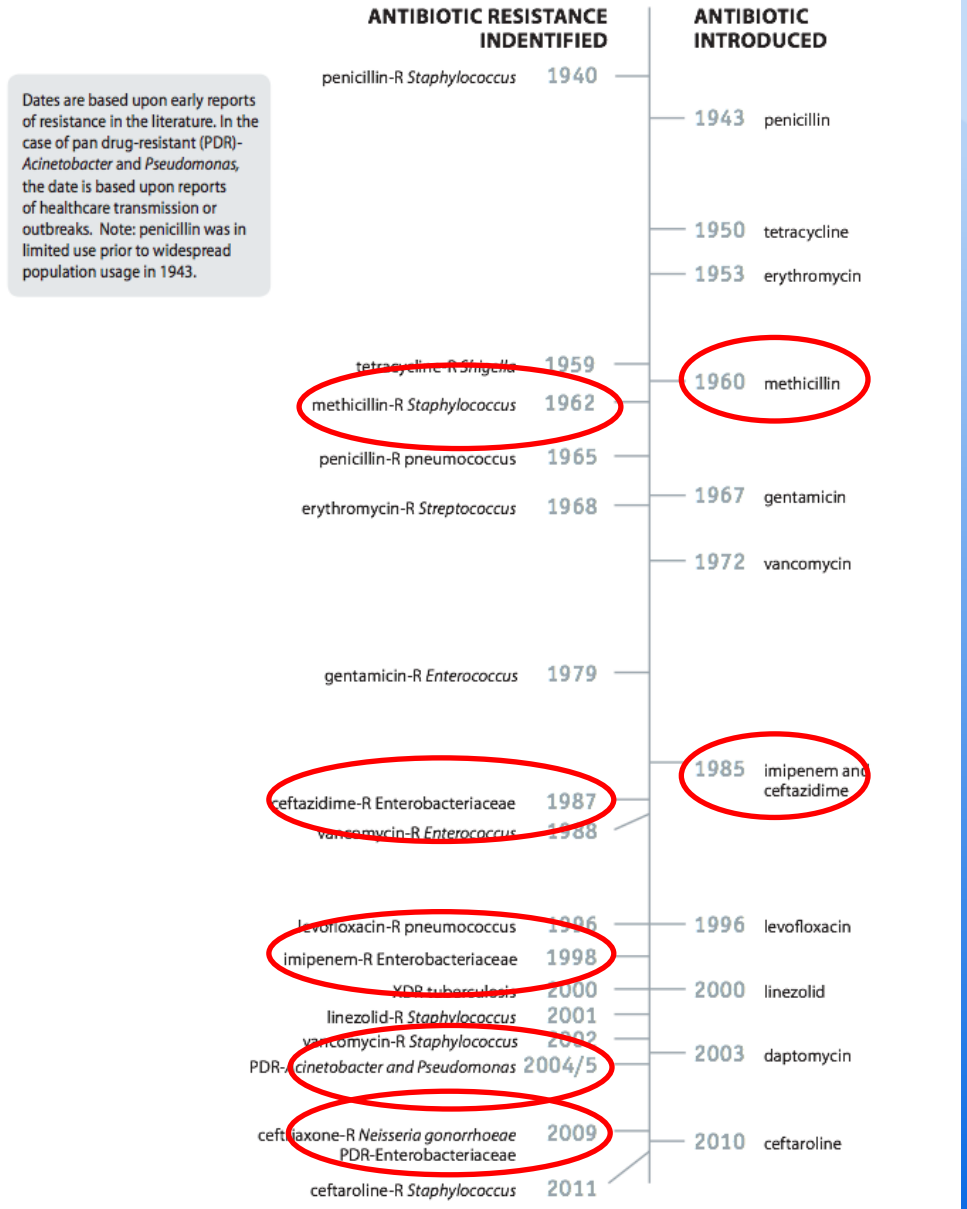
"There is probably no chemotherapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring 'fastness' [resistance]."
—Alexander Fleming, 1946



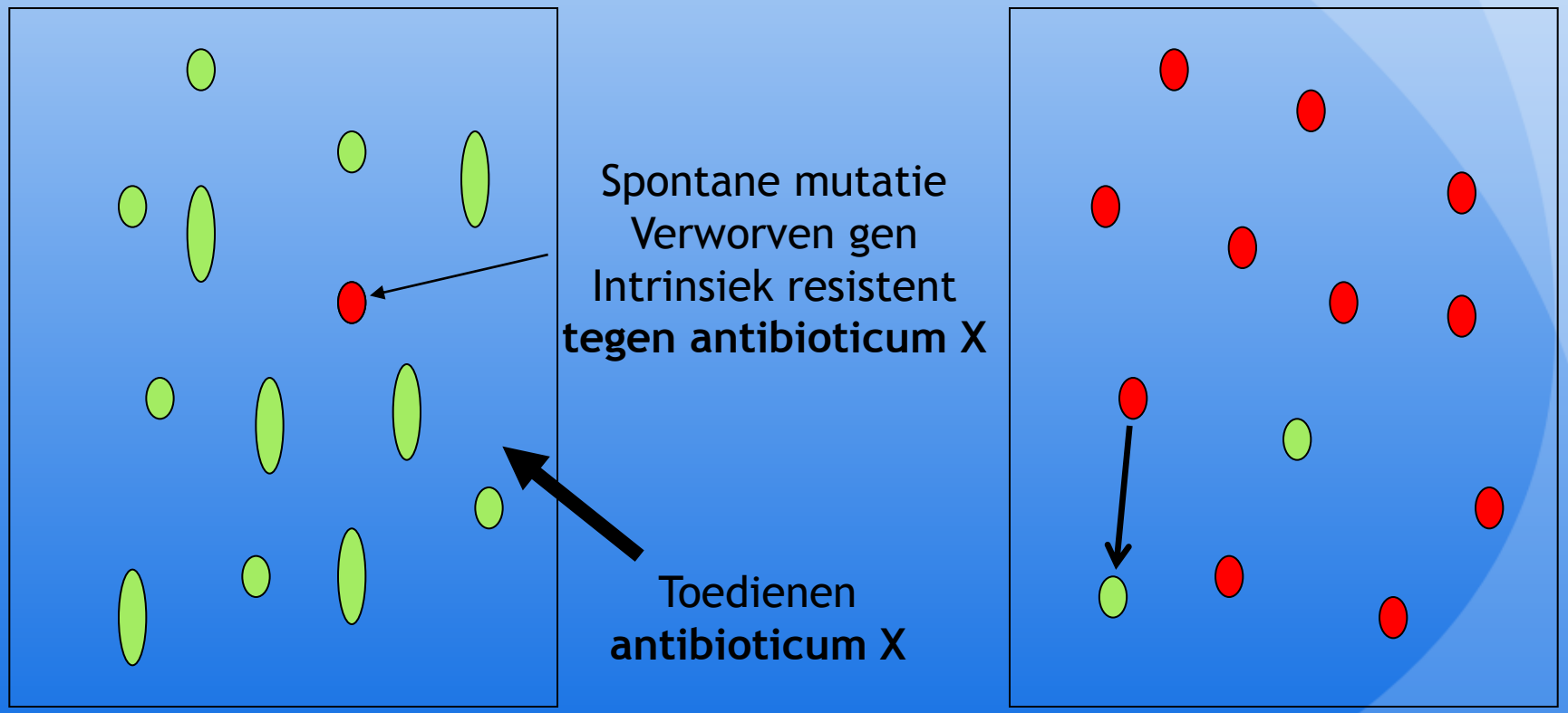
Timeline of Key Antibiotic Resistance Events



Timeline of Key Antibiotic Resistance Events



Selectie van resistentie



populatie voor antimicrobiele therapie

populatie tijdens antimicrobiele therapie

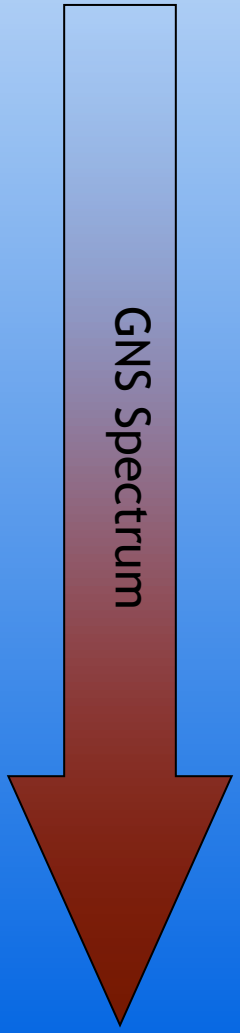
Selectie

- Resistentie ontwikkeling = selectie

- Het toevoegen van een antibiotisch middel leidt ALTIJD tot selectie van die microben die resistent zijn voor het betreffende middel

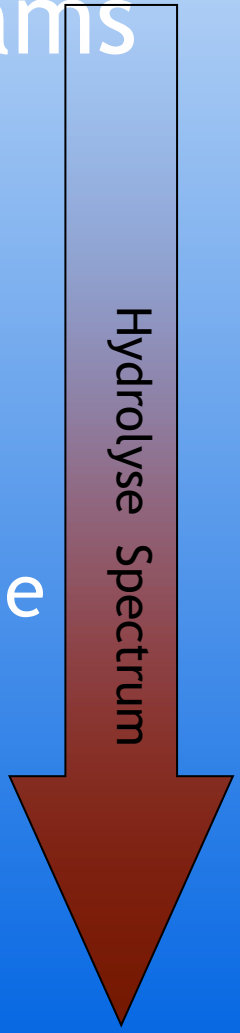
Hiërarchie beta-lactams

- Penicillins
  - SSP
  - BSP
  - ESP
- Inhibitors
- Cephalosporins
  - 1e
  - 2e
  - 3e
  - 4e
- Carbapenems



Klinisch relevante beta-lactamase houdt tred met introductie van beta-lactams

- Penicilline — penicillinase Gram +ve
- Amoxicilline — klassieke beta-lactamase (TEM, SHV)
- Cephalosporine — Cephalosporinase (ESBLs, AmpC)
- Carbapenems — Carbapenemases



Beta-lactamases

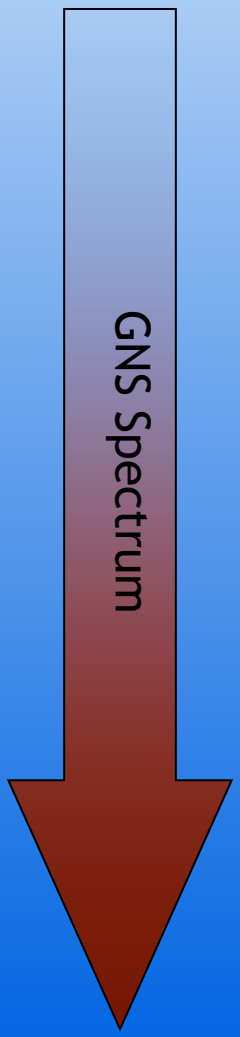
TABLE 1. Classification schemes for bacterial β-lactamases, expanded from Bush et al. (16)

Bush-Jacoby group (2009)	Bush-Jacoby-Medeiros group (1995)	Molecular class (subclass)	Distinctive substrate(s)	Inhibited by		Defining characteristic(s)	Representative enzyme(s)
				CA or TZB[a]	EDTA		
1	1	C	Cephalosporins	No	No	Greater hydrolysis of cephalosporins than benzylpenicillin; hydrolyzes cephamycins	*E. coli* AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
1e	NI[b]	C	Cephalosporins	No	No	Increased hydrolysis of ceftazidime and often other oxyimino-β-lactams	GC1, CMY-37
2a	2a	A	Penicillins	Yes	No	Greater hydrolysis of benzylpenicillin than cephalosporins	PC1
2b	2b	A	Penicillins, early cephalosporins	Yes	No	Similar hydrolysis of benzylpenicillin and cephalosporins	TEM-1, TEM-2, SHV-1
2be	2be	A	Extended-spectrum cephalosporins, monobactams	Yes	No	Increased hydrolysis of oxyimino-β-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam)	TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1
2br	2br	A	Penicillins	No	No	Resistance to clavulanic acid, sulbactam, and tazobactam	TEM-30, SHV-10
2ber	NI	A	Extended-spectrum cephalosporins, monobactams	No	No	Increased hydrolysis of oxyimino-β-lactams combined with resistance to clavulanic acid, sulbactam, and tazobactam	TEM-50
2c	2c	A	Carbenicillin	Yes	No	Increased hydrolysis of carbenicillin	PSE-1, CARB-3
2ce	NI	A	Carbenicillin, cefepime	Yes	No	Increased hydrolysis of carbenicillin, cefepime, and cefpirome	RTG-4
2d	2d	D	Cloxacillin	Variable	No	Increased hydrolysis of cloxacillin or oxacillin	OXA-1, OXA-10
2de	NI	D	Extended-spectrum cephalosporins	Variable	No	Hydrolyzes cloxacillin or oxacillin and oxyimino-β-lactams	OXA-11, OXA-15
2df	NI	D	Carbapenems	Variable	No	Hydrolyzes cloxacillin or oxacillin and carbapenems	OXA-23, OXA-48
2e	2e	A	Extended-spectrum cephalosporins	Yes	No	Hydrolyzes cephalosporins. Inhibited by clavulanic acid but not aztreonam	CepA
2f	2f	A	Carbapenems	Variable	No	Increased hydrolysis of carbapenems, oxyimino-β-lactams, cephamycins	KPC-2, IMI-1, SME-1
3a	3	B (B1)	Carbapenems	No	Yes	Broad-spectrum hydrolysis including carbapenems but not monobactams	IMP-1, VIM-1, CcrA, IND-1
		B (B3)					L1, CAU-1, GOB-1, FEZ-1
3b	3	B (B2)	Carbapenems	No	Yes	Preferential hydrolysis of carbapenems	CphA, Sfh-1
NI	4	Unknown					

[a] CA, clavulanic acid; TZB, tazobactam.
[b] NI, not included.

Hiërarchie beta-lactams

- Penicillins
- ESP
- Inhibitors
- Cephalosporins
- Carbapenems

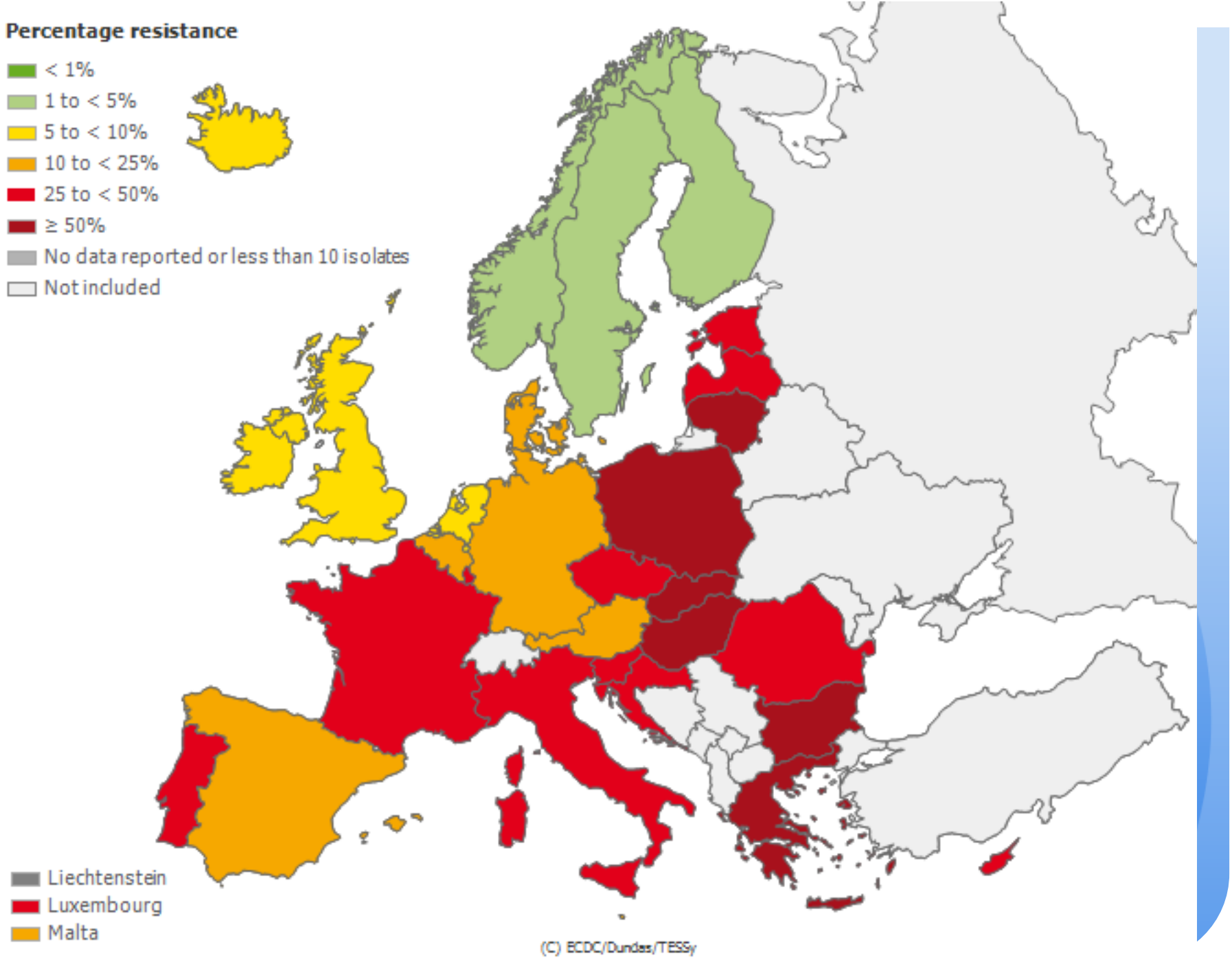


ESBLs

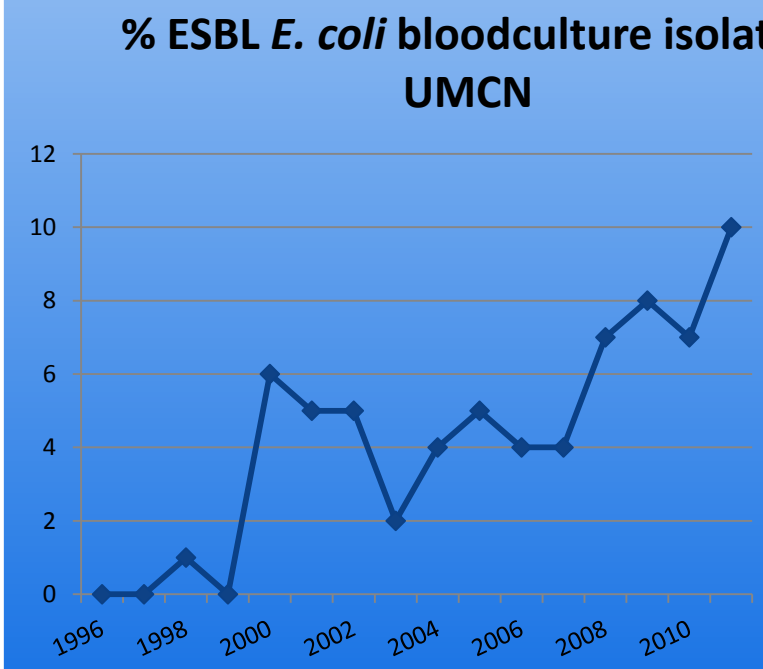
ESBLs: CTX-M-15

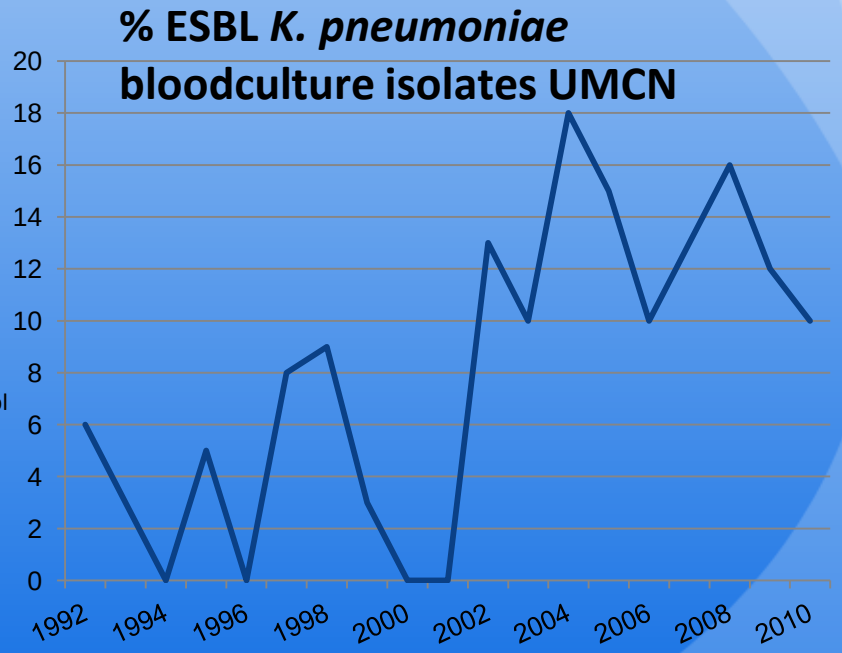
- Chromosomaal in Kluyvera spp.
- Midden ‘90s; Op plasmide in E.coli
- Momenteel meest voorkomende ESBL wereldwijd

- 70-90% Enterobacteriaceae in India ESBL
- Prevalentie elders sterk toenemend


Percentage resistance
< 1%
1 to < 5%
5 to < 10%
10 to < 25%
25 to < 50%
≥ 50%
No data reported or less than 10 isolates
Not included
Liechtenstein
Luxembourg
Malta
(C) ECDC/Dundas/TESSy

ESBLs in bloedkweken





ESBL Kolonisatie studies

Prevalence of carriage of ESBL producing enterobacteriaceae in a Dutch teaching hospital

G Moen*, I Willemsen, M Kluytmans, C Verhulst, J Kluytmans

From International Conference on Prevention & Infection Control (ICPIC 2011)
Geneva, Switzerland. 29 June – 2 July 2011

2010: 4,5 % ESBL in opgenomen patiënten

Clin Microbiol Infect. 2013 Jun;19(6):542-9. doi: 10.1111/j.1469-0691.2012.03947.x. Epub 2012 Jul 3.

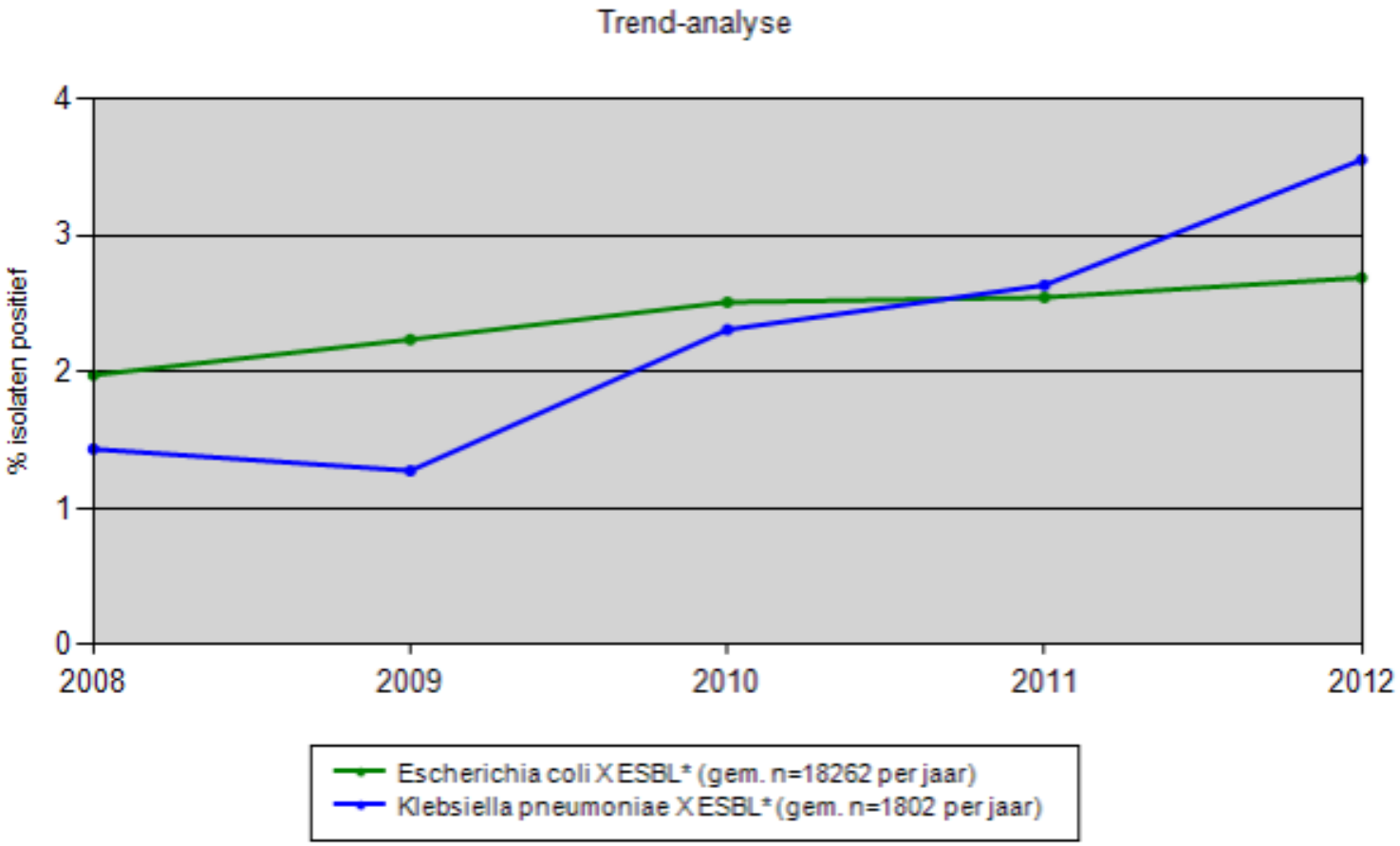
High prevalence of ESBL-producing Enterobacteriaceae carriage in Dutch community patients with gastrointestinal complaints.

Reuland EA, Overdevest IT, Al Naiemi N, Kalpoe JS, Rijnsburger MC, Raadsen SA, Ligtenberg-Burgman I, van der Zwaluw KW, Heck M, Savelkoul PH, Kluytmans JA, Vandenbroucke-Grauls CM.

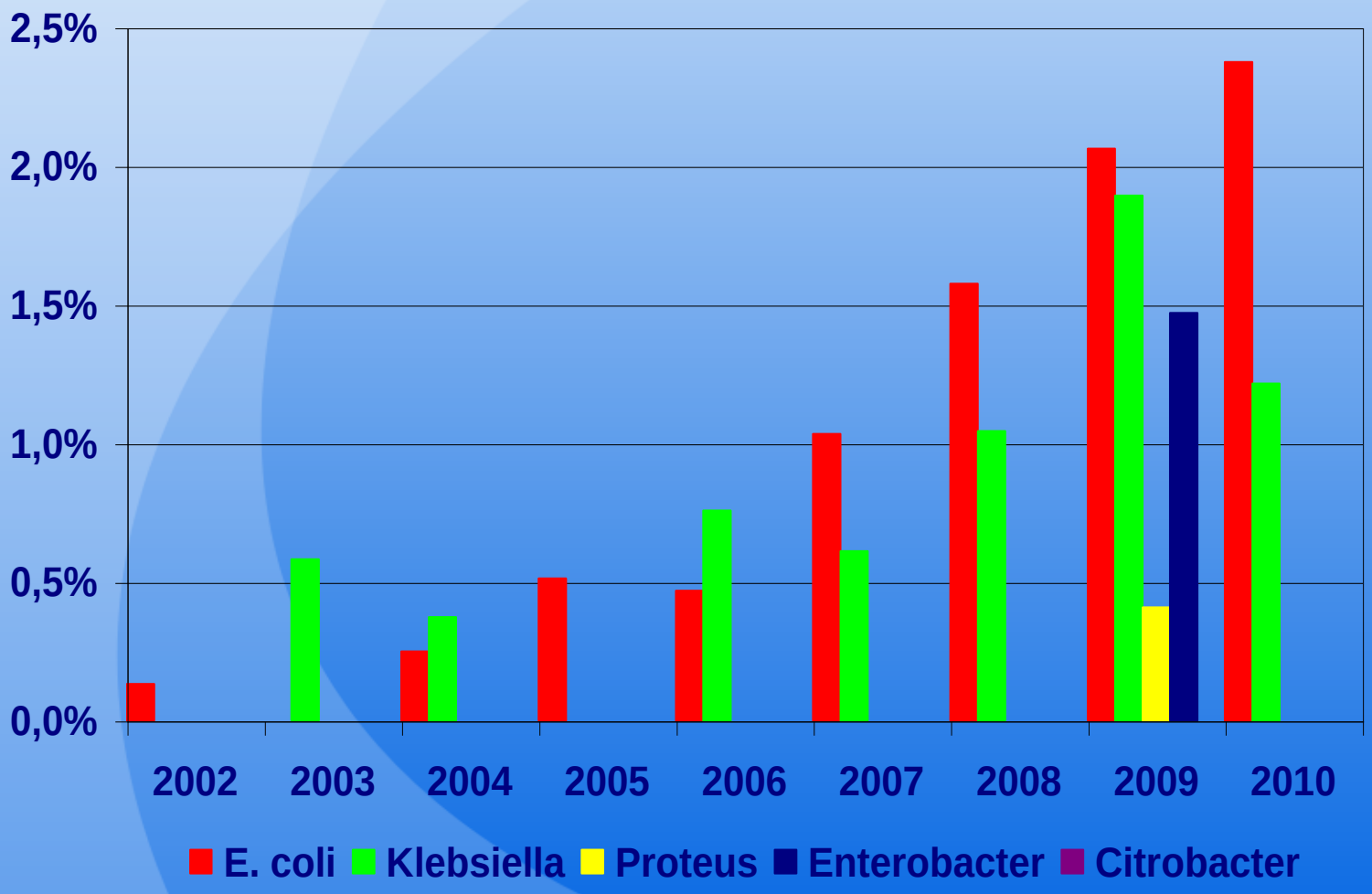
Medical Microbiology and Infection Control, VU University Medical Centre, Amsterdam, the Netherlands. e.reuland@vumc.nl

2010: 10,1 % ESBL in patiënten bij huisarts met GI klachten

Landelijk HA ESBL

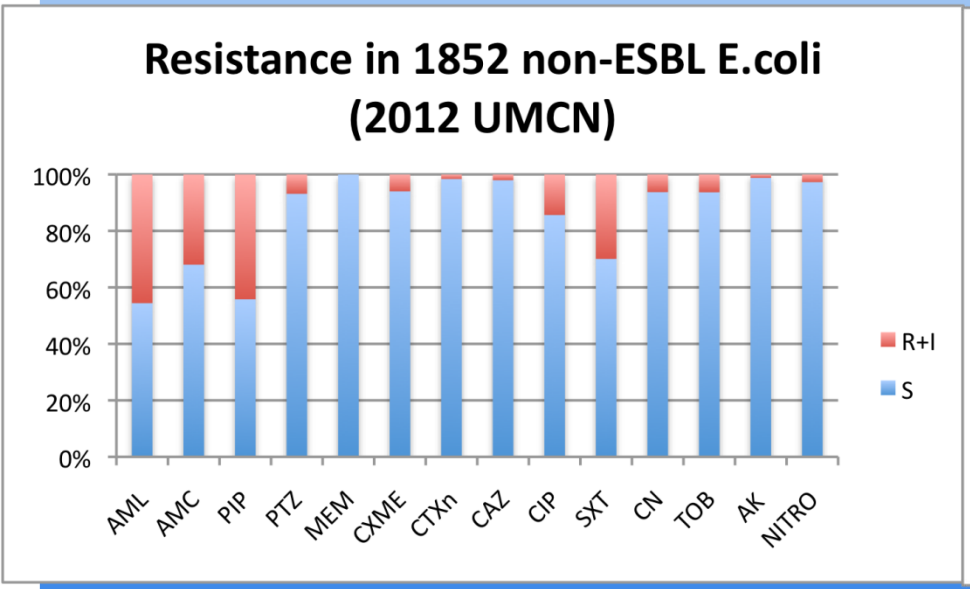


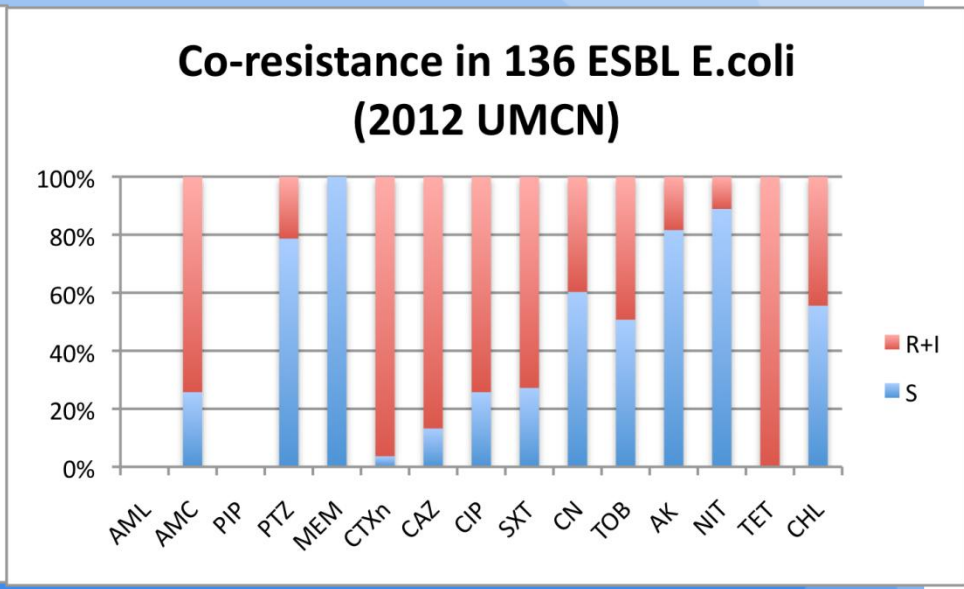
ESBLs in PAMM regio



PAMM database 2002 t/m oktober 2010

Co-resistentie ESBL Radboud





Hierarchie beta-lactams

- Penicillins
- ESP
- Inhibitors
- Cephalosporins
- Carbapenems

GNS Spectrum

Overig [illegible]delen

ESBLs

Carbapenemases

Carbapenemases

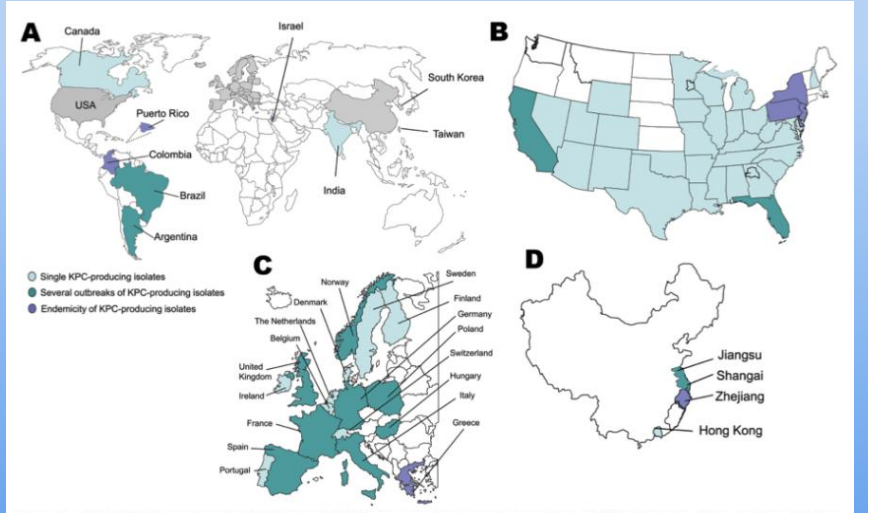


Figure 1. A) Worldwide geographic distribution of *Klebsiella pneumoniae* carbapenemase (KPC) producers. Gray shading indicates regions shown separately: B) distribution in the United States; C) distribution in Europe; D) distribution in China.

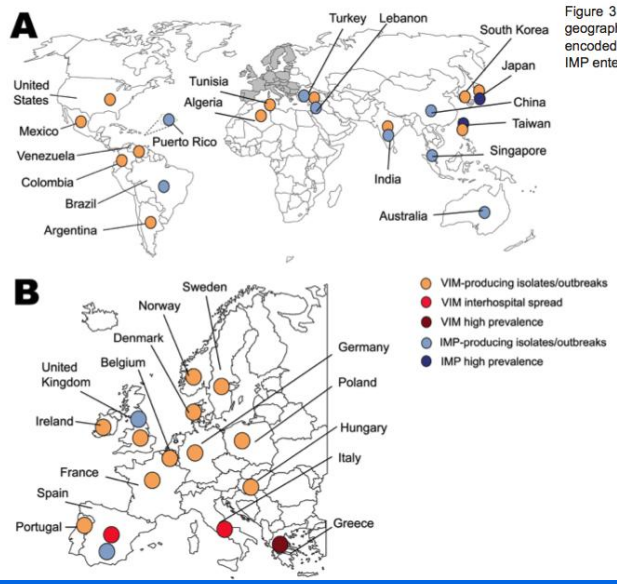


Figure 3. Worldwide (A) and European (B) geographic distribution of Verona integron–encoded metallo-β-lactamase (VIM) and IMP enterobacterial producers.

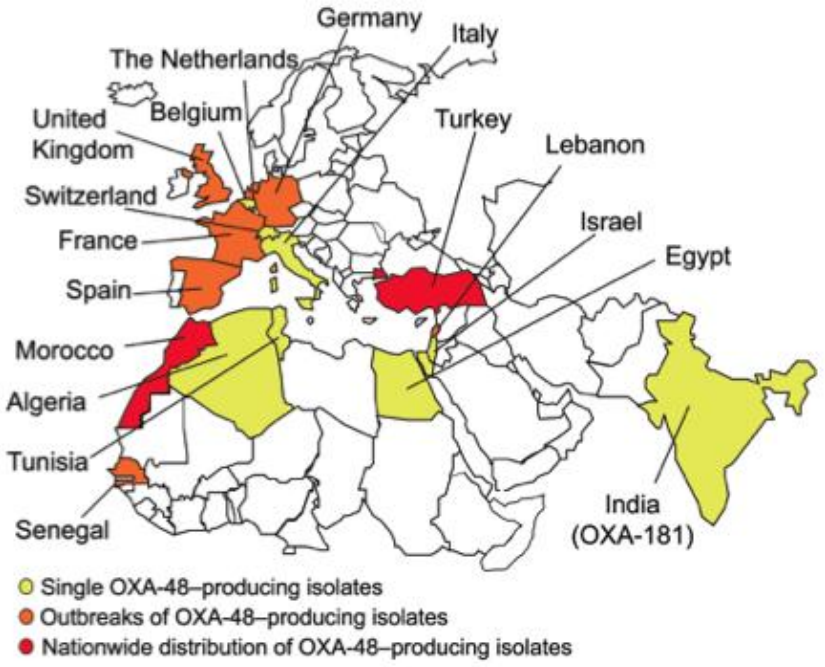


Figure 5. Geographic distribution of oxacillinase-48 (OXA-48) type producers.

Carbapenemase-producing *Enterobacteriaceae*

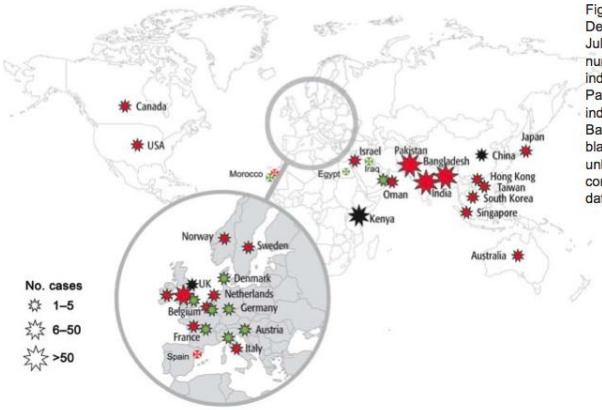
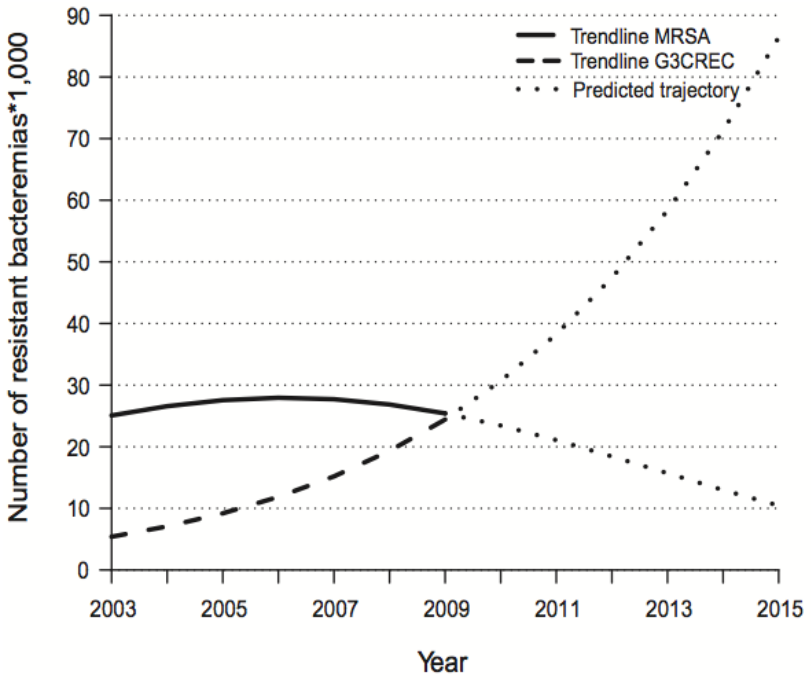


Figure 4. Geographic distribution of New Delhi metallo-β-lactamase-1 producers, July 15, 2011. Star size indicates number of cases reported. Red stars indicate infections traced back to India, Pakistan, or Bangladesh; green stars indicate infections traced back to the Balkan states or the Middle East; and black stars indicate contaminations of unknown origin. (Most of the information corresponds to published data; other data are from P. Nordmann.)

Huidig probleem

- Snelle toename MDR/PDR Gram-negatieven

Burden of Resistant Bacteremias in Europe



2007	MRSA	G3CREC
BSI	27.711	15.183
Excess deaths	5.503	2.712
Excess hospital days	255.683	120.065
Costs € million	44	18.1

Figure 1. Trends in the estimated number of MRSA and G3CREC bacteremias in the European region. Extrapolated EARSS numbers 2003–2009, and future trajectories based on regression analysis for 2010–2015.
doi:10.1371/journal.pmed.1001104.g001

OPEN ACCESS Freely available online PLoS MEDICINE

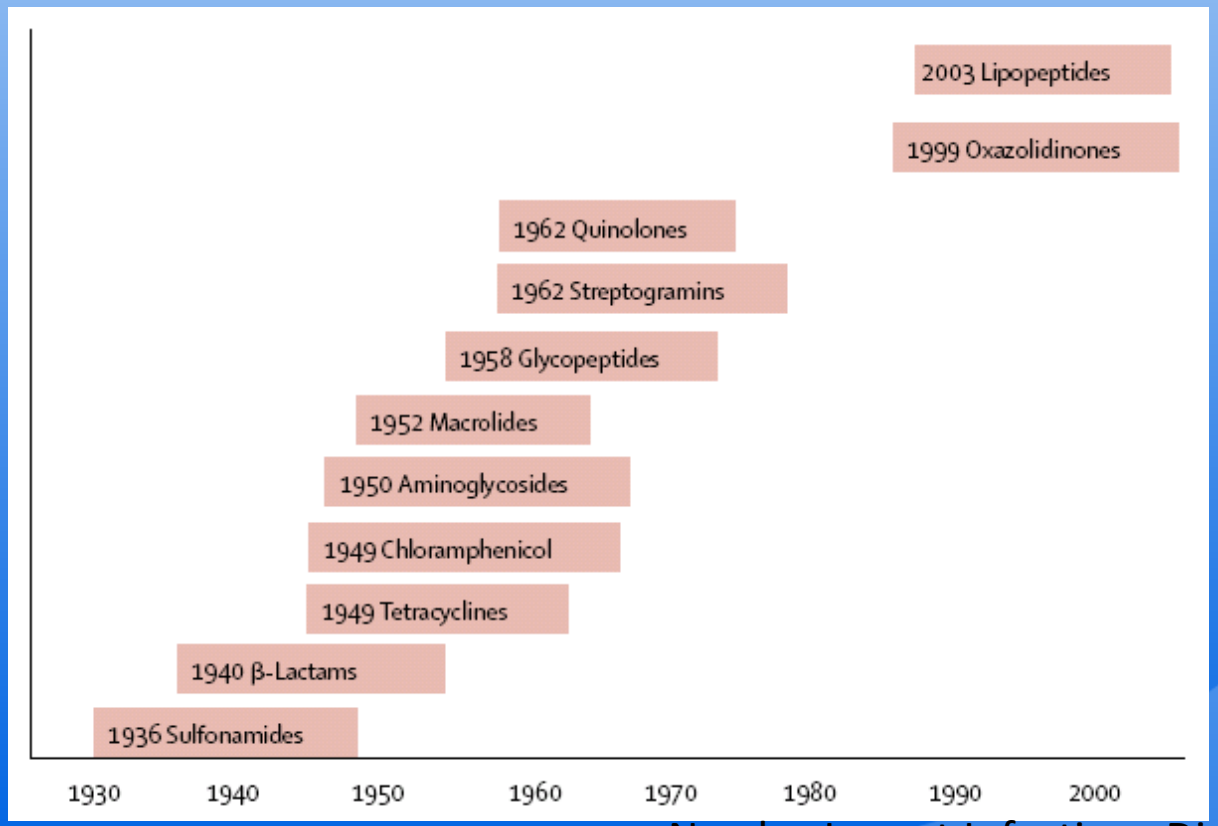
Mortality and Hospital Stay Associated with Resistant *Staphylococcus aureus* and *Escherichia coli* Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe

Marlieke E. A. de Kraker[1,2]*, Peter G. Davey[3], Hajo Grundmann[1,2], on behalf of the BURDEN study group

1 Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, 2 Department of Medical Microbiology, Academic Medical Centre Groningen, Groningen, The Netherlands, 3 Quality, Safety and Informatics Research Group, Dundee, United Kingdom

Huidig probleem

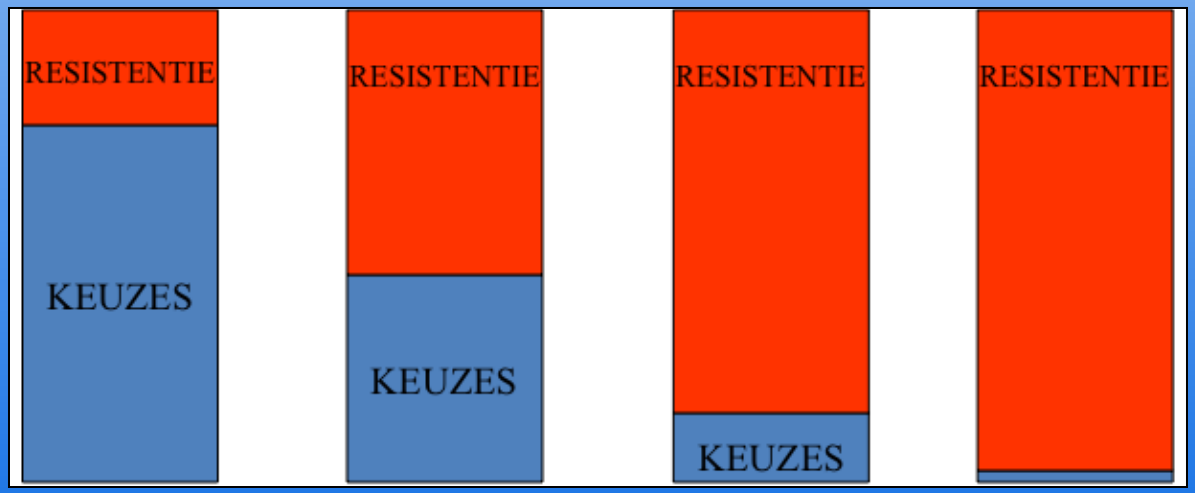
- Geen nieuwe middelen



Norrby, Lancet Infectious Diseases 2005

Huidig probleem

- Geen nieuwe middelen
- Snelle toename MDR Gram-negatieven



Huidig probleem

- Geen nieuwe middelen
- Snelle toename MDR Gram-negatieven
- Slechtere uitkomst/toxiciteit

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

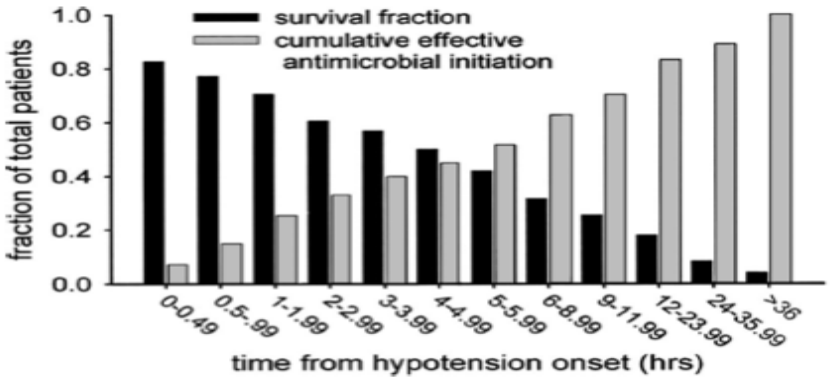


Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. *Black bars* represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The *gray bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

Drijvende krachten resistentie

- Toename therapeutisch gebruik totaal

Nethmap/Maran-rapport 2013 in het kort:

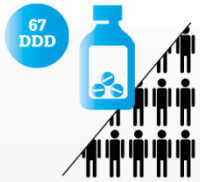
	huisarts	ziekenhuis	verpleeghuis
gebruik antibiotica	 **1000 inwoners/dag** Sinds een jaar stabiel, na jarenlange stijging.	 **100 patiëntdagen** Sinds een jaar stabiel, na jarenlange stijging.	 **1000 bewoners/dag** Varieert enorm van 3 tot 175 DDD/1000 bewoners/dag. Voor het eerst gemeten.
gebruik breedspectrum-antibiotica	Stijgt, met name Augmentin, azitromycine en ciprofloxacine.	Stijgt, met name carbapenems, chinolonen en glycopeptiden.	Veel Augmentin, nitrofurantoïne en fluorchinolonen.
resistentie	Stijging resistentie tegen derde generatie cefalospo-rinen.	Veel resistentie tegen 3e generatie cefalosporines en multidrugresistentie.	Veel resistentie tegen *E Coli*. Veel resistentie van *S aureus* tegen ciprofloxacine.

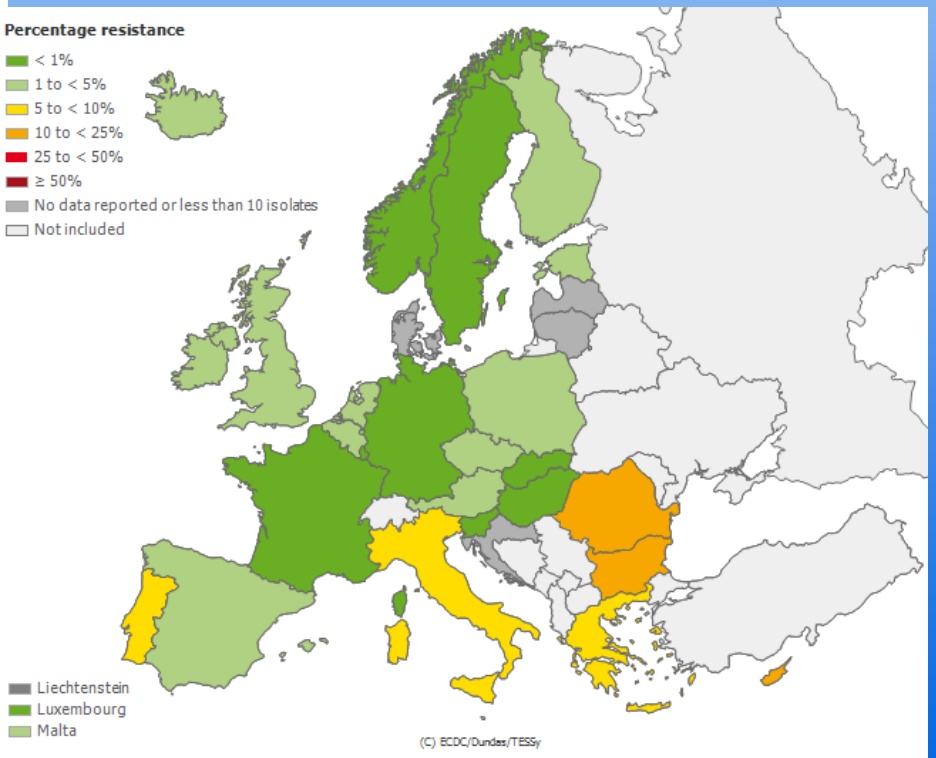
Table 1. Swedish Data on Outpatient Antibiotic Prescribing, 2012.*

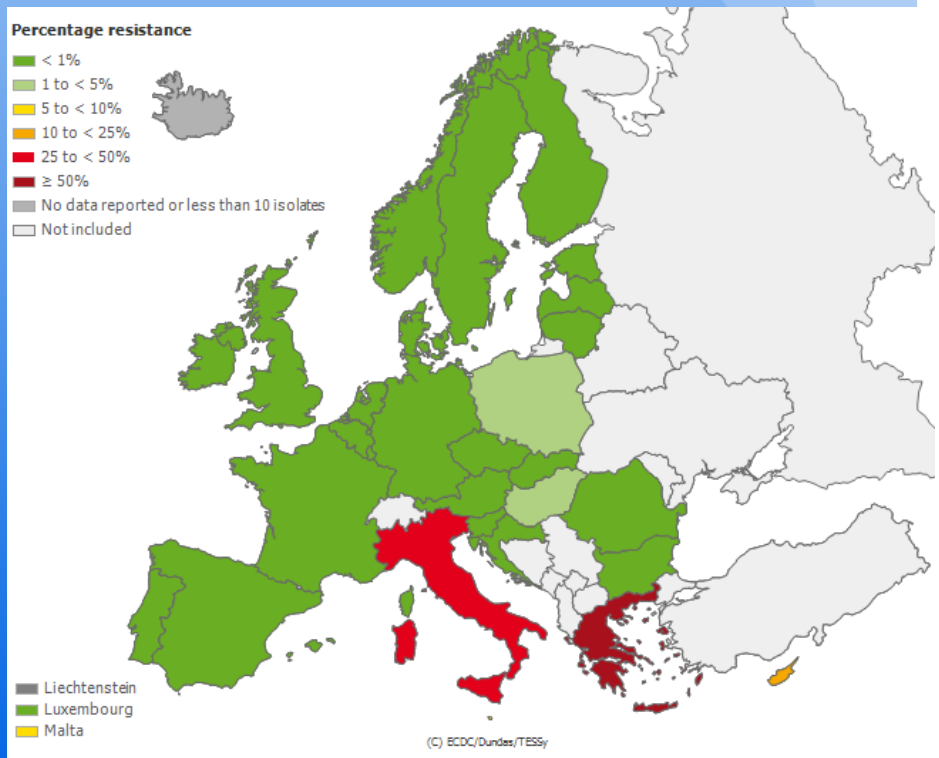
Variable	Prescriptions in Millions	Prescriptions/ 1000 Inhabitants
	no./total no. (%)	*no.*
Antibiotic category		
Beta-lactamase–sensitive penicillins	1.10/3.68 (30)	116
Penicillins with extended spectrum	0.53/3.68 (14)	55
Tetracyclines	0.49/3.68 (13)	52
Beta-lactamase–resistant penicillins	0.37/3.68 (10)	40
Quinolones	0.24/3.68 (7)	25
Nitrofurantoin	0.22/3.68 (6)	23
Lincosamides	0.15/3.68 (4)	16
Other antibacterials	0.14/3.68 (4)	14
Macrolides	0.11/3.68 (3)	12
Cephalosporins	0.11/3.68 (3)	12
Trimethoprim	0.09/3.68 (2)	10
Trimethoprim with sulfonamides	0.06/3.68 (2)	7
Combinations of penicillins	0.06/3.68 (2)	6
Other types of antibiotics	0.01/3.68 (<1)	1
Top five antibiotic agents		
Penicillin V	1.10/2.38 (46)	116
Doxycycline	0.38/2.38 (16)	40
Floxacillin	0.37/2.38 (16)	40
Pivmecillinam	0.31/2.38 (13)	33
Nitrofurantoin	0.22/2.38 (9)	23
Geographic health care region		
North	0.28/2.91 (10)	315
Uppsala-Örebro	0.68/2.91 (23)	344
Stockholm	0.88/2.91 (30)	408
Southeast	0.34/2.91 (12)	344
West	0.07/2.91 (2)	384
South	0.66/2.91 (23)	386
Patient age group		
0 to <3 yr	0.16/3.50 (5)	462
3 to <10 yr	0.31/3.50 (9)	414
10 to <20 yr	0.27/3.50 (8)	252
20 to <40 yr	0.73/3.50 (21)	296
40 to <65 yr	1.04/3.50 (30)	339
≥65 yr	0.99/3.50 (28)	556
Provider specialty or clinical setting		
Health care center	2.05/3.48 (59)	216
Acute care hospital	0.61/3.48 (18)	65
Dentistry	0.23/3.48 (7)	24
Other health care unit	0.42/3.48 (12)	44
Unspecified	0.18/3.48 (5)	19

* Data are from the Swedish Institute for Communicable Disease Control.[3]

Drijvende krachten resistentie

- Resistentie: toename gebruik breed-spectrum AB: Vicieuze cirkel

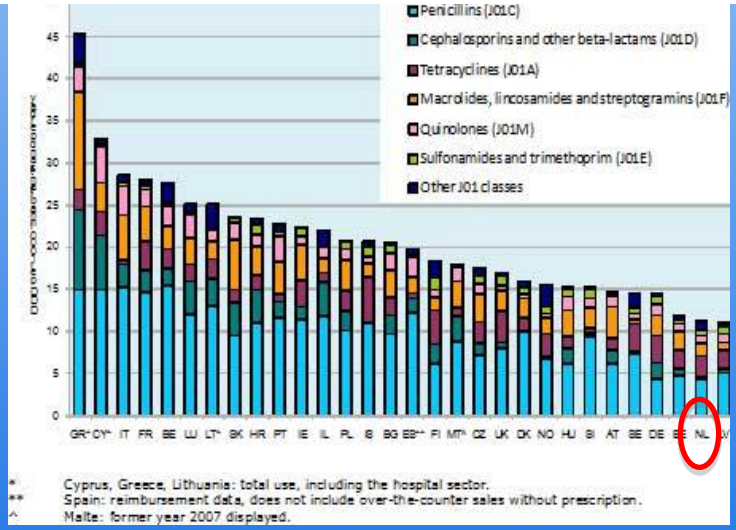




Drijvende krachten resistentie

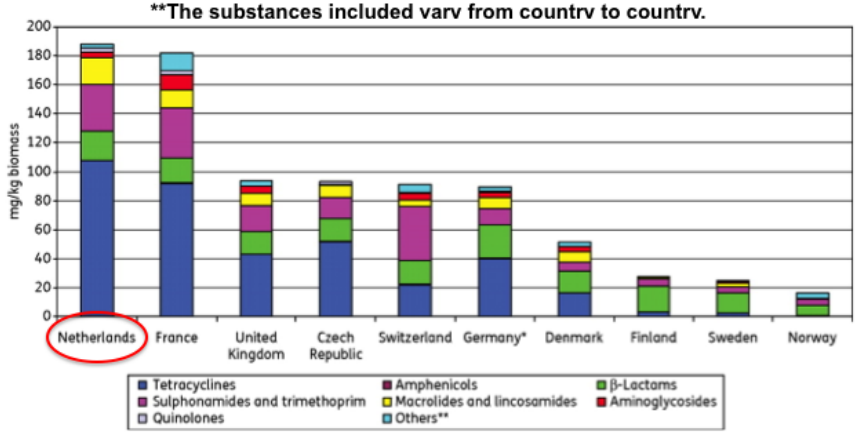
- Niet-therapeutisch gebruik andere sectoren

Outpatient use by pharmacological subgroup according to ATC classification, year 2008

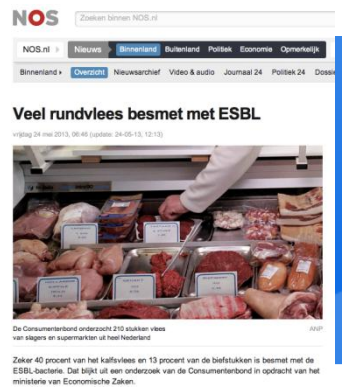


The European Surveillance of Antimicrobial Consumption (ESAC)

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.



Grave K et al. J. Antimicrob. Chemother. 2010;65:2037-2040



Drijvende krachten resistentie

- Contaminatie omgeving met resistente bacteriën, genen, en antibiotica

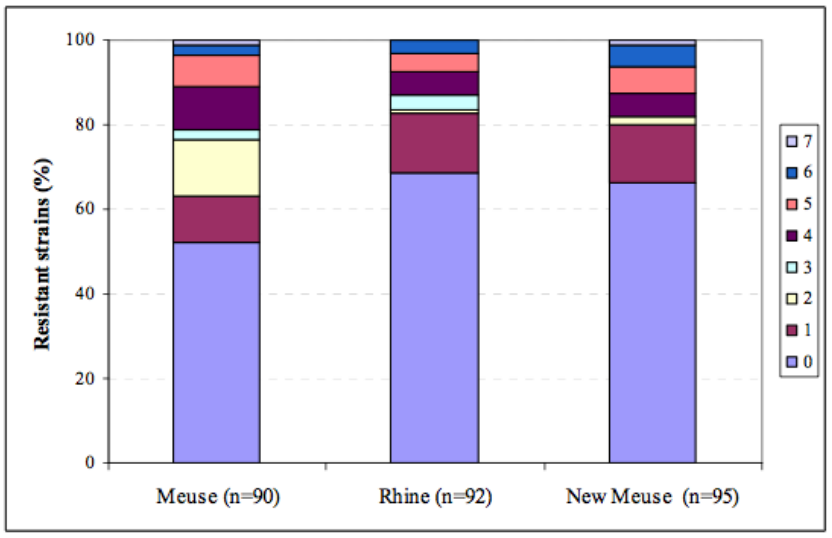
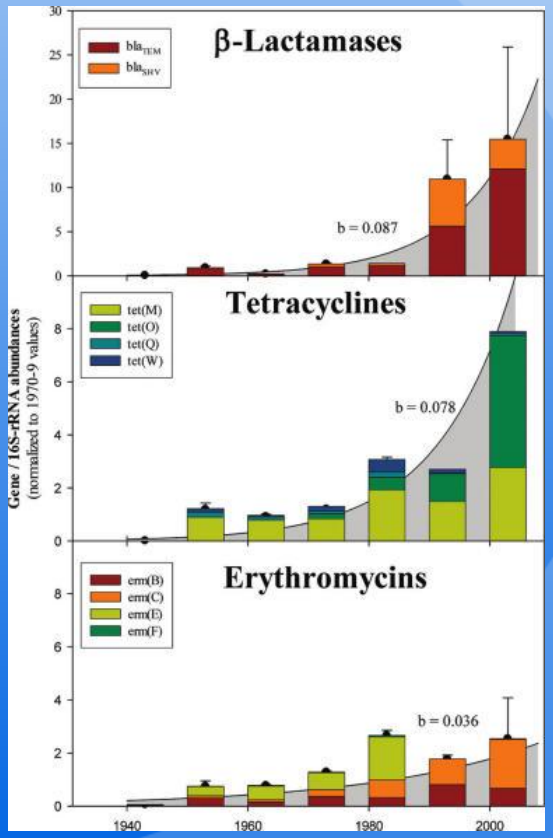
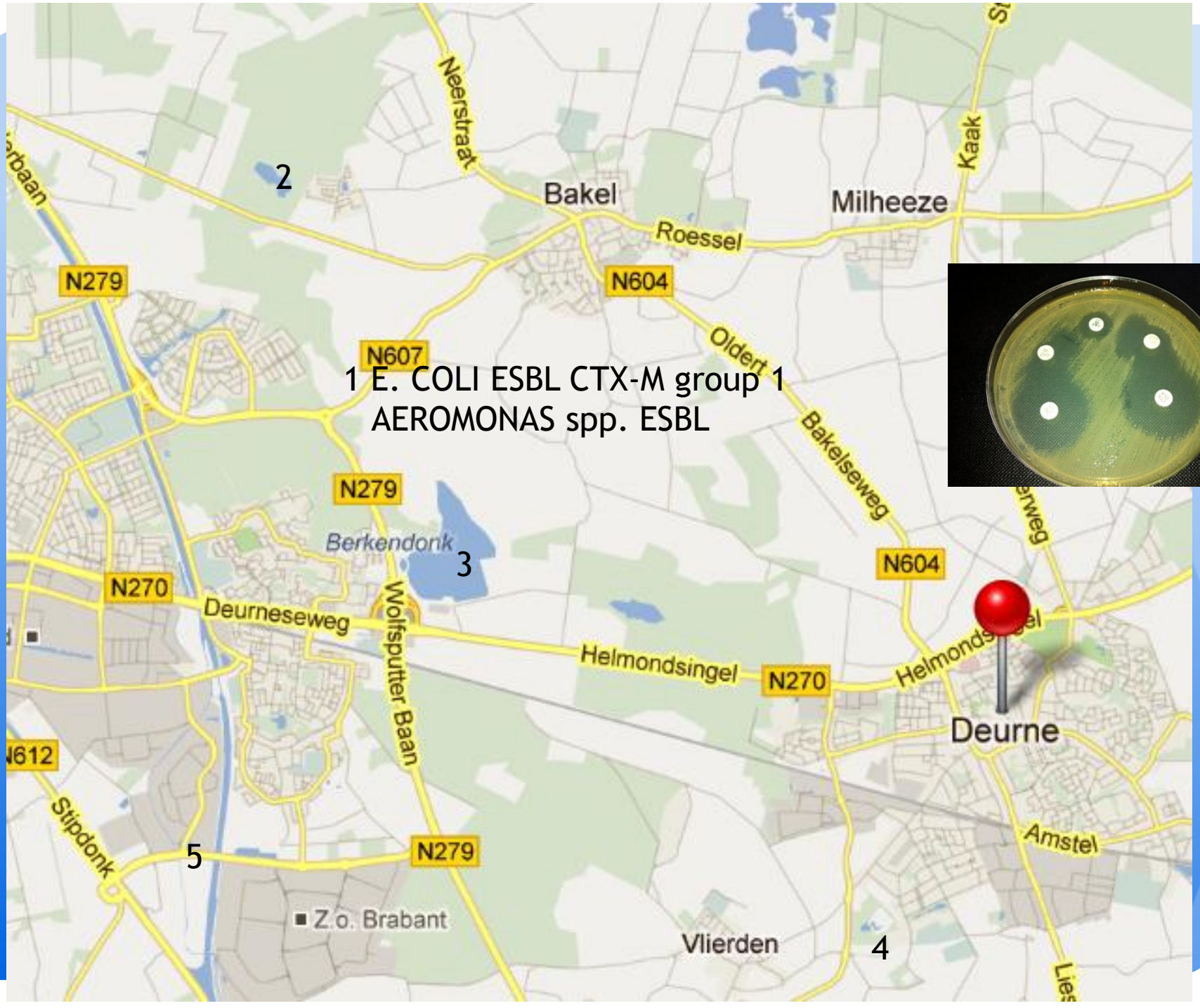


Figure 5 Percentages of sensitive, monoresistant and multiresistant E. coli strains observed in Dutch rivers




2
Neerstraat
Bakel
Milheeze
Kaak
Roessel
N279
N604
N607
Oldert
Bakelseweg
1 E. COLI ESBL CTX-M group 1
AEROMONAS spp. ESBL
N279
Berkendonk
3
N604
N270
Deurneseweg
Wolfsputter Baan
Helmondsingel
N270
Deurne
N612
Stipdonk
5
N279
Amstel
Z.o. Brabant
Vlierden
4

Scholieren vinden resistente bacteriën in de Bakelse Aa

29 februari 2012 | Laatste update: 29 februari, 06:00

Rayna de Wit en Cas van der Putten bij het water van de Bakelse Aa. Foto Rene Manders.

DEURNE - Door monsters te nemen in oppervlaktewateren voor hun profielwerkstuk, kwamen twee leerlingen uit 6 VWO van het Peellandcollege in Deurne er achter, dat resistente bacteriën ook heel dichtbij te vinden zijn.

Cas van der Putten (18) en Rayna de Wit (17), vonden in het water van de Bakelse Aa twee bacteriestammen die beide resistent zijn voor verschillende soorten antibiotica.

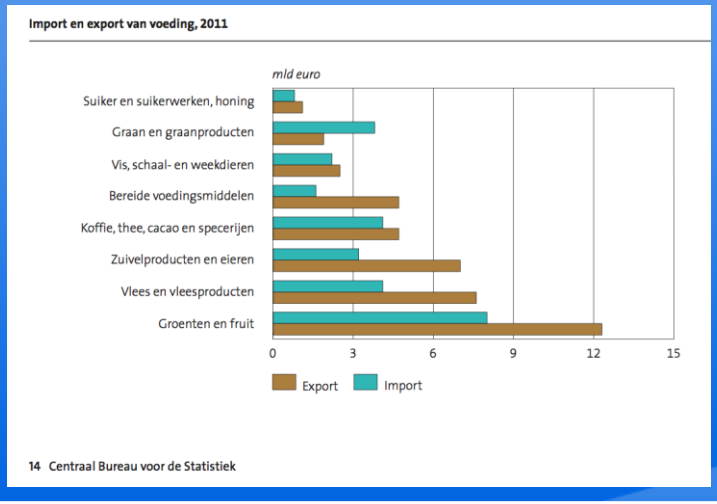
Ook lijkt dat de e.coli (darmbacterie) die door het duo werd gevonden een ESBL-vormende bacterie is. Dit kan gevaarlijk zijn voor de gezondheid, omdat antibiotica dan

Drijvende krachten resistentie

- Globalisering

Table. Global estimates of annual migrant populations

Administrative category	Population estimates and year	Reference
Refugees	16 million in 2007	(*18*)
Asylum seekers or refugee claimants	650,000 in 2007	(*18*)
Internally displaced persons	51 million in 2007, includes those displaced by natural disasters and conflict	(*18*)
Temporary (recreational or business travel) movement	924 million in 2008	(*19*)
Regular immigrants	Annual flow of 2.4 million, reported in 2005 (from a stock of 200 million immigrants worldwide)	(*20*)
International students	2.1 million in 2003	(*21*)
Migrant workers	81–86 million in 2005	(*22*)
Trafficked (across international borders) persons	Estimated 800,000 in 2006	(*23*)
Domestic arrivals, by air	Estimated 900 million in 2007	(*24*)



Drijvende krachten resistentie

- Globalisering met intercontinentale verspreiding

TABLE 2. Distribution of CTX-M genes detected in 24 strains of *Escherichia coli* isolated from rectal swabs after foreign travel[a]

Continent or region	No. of isolates				
	Group I		Group IV		
	CTX-M-1	CTX-M-15	CTX-M-9	CTX-M-14	CTX-M-27
Africa		1			
Asia (India excluded)		2	1	5	2
India		7			
Southern Europe	1	1			
Middle East		2	2		
Total	1	13	3	5	2

[a] PCR amplification with subtype-specific primers was used.

TABLE 3. Travel destinations of travelers who were negative for ESBL-producing strains before the trip and rate of fecal colonization with ESBL-producing *E. coli* strains upon return[a]

Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

[a] The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0.001$). Three participants visited more than one continent, and therefore, the sum of travelers in this table exceeds the actual number of 100.

Hierarchie beta-lactams

- Penicillins
- ESP
- Inhibitors
- Cephalosporins
- Carbapenems

GNS Spectrum

Overig

delen

Carbapenemases

OXA-48 carbapenemase

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Binnenland | Overzicht | Nieuwsarchief | Video & audio | Journaal 24 | Politiek 24 | Dossie

Opnieuw besmette patiënten Rotterdam overleden

woensdag 20 jul 2011, 08:11 (Update: 20-07-11, 20:51)

Het Maasstad Ziekenhuis nam onvoldoende maatregelen NOS

Door redacteur gezondheidszorg Rinke van den Brink

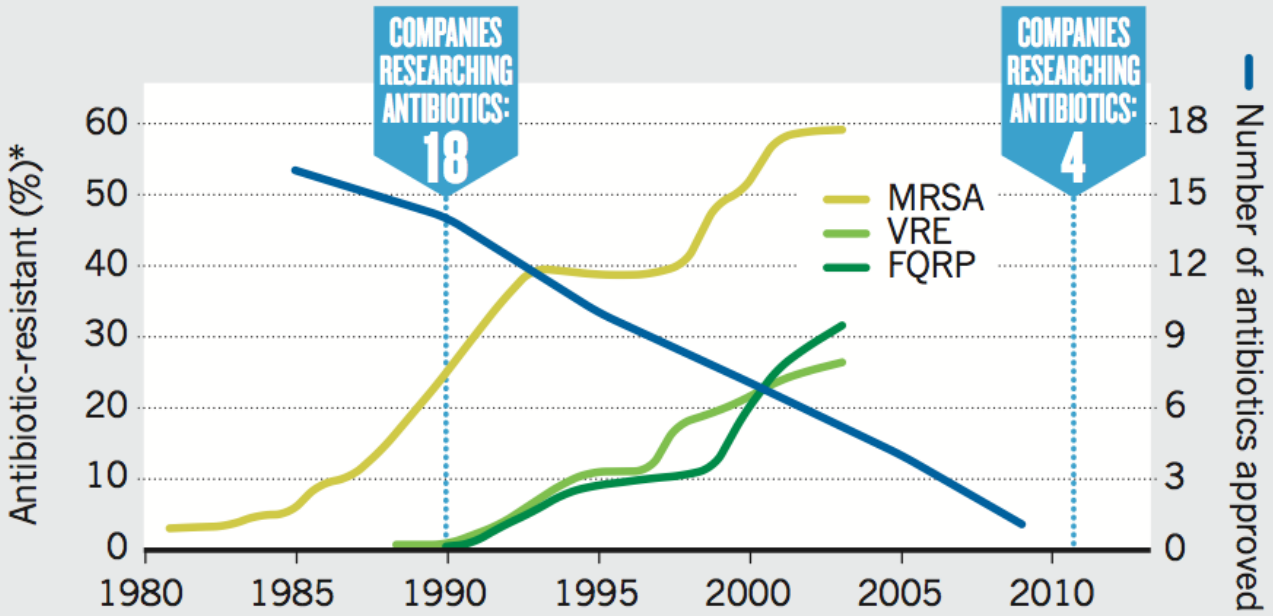
In het [redacted]erdam zijn opnieuw vier patiënten overleden die de multiresistente bacterie hadden opgelopen waarmee het ziekenhuis al zeker sinds afgelopen september kampt.

Fix the antibiotics pipeline

As resistance mushrooms, governments must make development of new antibiotics financially viable for industry, say **Matthew A. Cooper** and **David Shlaes**.

A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.



*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

Hoe verder?

- Hygiëne
- Rationeel antibiotica beleid

Rationeel antibiotica voorschrijven en preventie resistentie

- Infectie?
- Klinische DD?
- Microbiologische DD?
- Gevoeligheid?

In deze situatie en in deze patient

- Juiste empirie
- Versmallen
- Tijdig stoppen
- Goed doseren
- Hygiene
- ‘Combinatie therapie’

Inspectie voor de Gezondheidszorg
Ministerie van Volksgezondheid, Welzijn en Sport

Voor gerechtvaardigd vertrouwen in verantwoorde zorg

Samenwerking bij Antibiotic stewardship

21 juni 2013

Dr. Merel F. M. Langelaar
Coördinerend specialistisch senior inspecteur
IGZ

Toetsing antibiotic stewardship

Vanaf 2014, wanneer antibiotic stewardshipprogramma's professionele standaard zijn, toetsing door IGZ:

- Antibioticumbeleid in orde
  (lokaal ab-boekje geïmplementeerd, voorbehouden lijst gebruikt, diagnostiek uitgevoerd etc.).
- Er is een functionele structuur in het ziekenhuis verantwoordelijk voor de kwaliteit van het uitgevoerde antibioticabeleid.
- Die structuur is gemandateerd en wordt gefaciliteerd door de verschillende afdelingen en de RvB van het ziekenhuis.

Resistentie wordt voornamelijk in de hand gewerkt door het antibioticagebruik in de ziekenhuizen en de verpleeghuizen.

Versmallen van therapie is niet noodzakelijk (niet haalbaar) in de huisartsen praktijk.

Empirische behandeling zou minder plaatsvinden door point of care testen (bv. CRP), snellere kweek resultaten of actieve rapportage.

Het gebruik van antibiotica zou verbeterd kunnen worden door in het antibiogram alleen dat antibioticum te rapporteren dat op basis van de klinische gegevens en het micro-organisme de eerste keus is.

Een vroege switch naar orale antibiotica kan een belangrijke kostenbesparing opleveren voor het ziekenhuis.