

# Geeft minder antibiotica-gebruik minder resistentie? *Of is dit een fabeltje waarin we graag geloven?*



**Paul M. Tulkens, MD, PhD**

Vorige voorzitter van ISAP (1998-2000)

Emeritus Hoogleraar  
*Pharmacologie cellulaire et moléculaire*  
*Louvain Drug Research Institute*  
*Health Sciences Sector*  
*Université catholique de Louvain*  
Brussel, België



# Belangenconflicten

## (Degenen die betaald hebben voor ons onderzoek en gesprekken)

- Onderzoekssubsidies
  - Industrie: Cempra, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Melinta, Debiopharm, Eumedica
  - Publiek: *Fonds de la Recherche Scientifique (F.R.S.-FNRS)*, Belgische Federale Overheidsdienst "Volksgezondheid", *Région Wallonne*, *Région Bruxelloise/Brusselse Gewest*, Europese Unie (FP7 en JPIAMR)
- Spreker honoraria
  - Industrie: Bayer, GSK, OM-Pharma, Vifor, Dong A,
  - Publiek: Opleidingsprogramma Antibioticabeleid Vlaanderen
- Adviesraden en/of besluitvormingsorganen
  - Industrie: Bayer, Trius, The Medicines Company
  - Publiek: *US National Institutes of Health (grant reviewing)*; *EUCAST General Assembly and Steering committee*; *European Medicines Agency (as external expert)*; Belgische Commissie voor tegemoetkoming van geneesmiddelen; *Belgian Antibiotic Policy Coordination Committee (BAPCOC)*; *EU program "DRIVE AB" governance (new economical framework for antibiotics)*

Dias beschikbaar op <http://www.facm.ucl.ac.be/> → Lectures → in het Nederlands

# Waar zal ik het over hebben?

- oude "klassieke" voorbeelden (zeer kort):
  - gentamicine tegen amikacine ...
  - vancomycin en *S. aureus* / *Enterococci*
  - verbod op cefalosporinen ...
  - $\beta$ -lactamen en *S. pneumoniae*
- antibiotica gebruik en resistentie in verschillende EU landen...
- resistentie onder controle houden op Intensieve Zorgen: aspecten belangrijker dan het aantal antibiotica

Dias beschikbaar op <http://www.facm.ucl.ac.be/> → Lectures → in het Nederlands

# Disclaimer ...

- Dit is een persoonlijke blik ...
- Ik zal zeker veel punten missen en de belangrijkste acteurs vergeten...
- Wat ik zal presenteren is zowel op openbare (web zoals publicaties) als op privé documenten gebaseerd ... wat betekent dat de werkelijkheid anders zou kunnen zijn ...

Dias beschikbaar op <http://www.facm.ucl.ac.be/> → Lectures → in het Nederlands

# Oude publicatie over gentamicine vs. amikacine

## Antibiotic Resistance Patterns During Aminoglycoside Restriction

BY EDWARD J. YOUNG, MD, C. MACK SEWELL, DrPH, MAUREEN A. KOZA, RN,  
AND JILL E. CLARRIDGE, PhD

Am J Med Sci. 1985; 290:223-7 - PMID: [3936358](#).



# Oude publicatie over gentamicine vs. amikacine

## Antibiotic During An

BY EDWARD J. YOUNG, M  
AND JILL E. CLARRIDGE, P

Am J Med Sci. 1985; 290:2

### Antibiotic Resistance Patterns

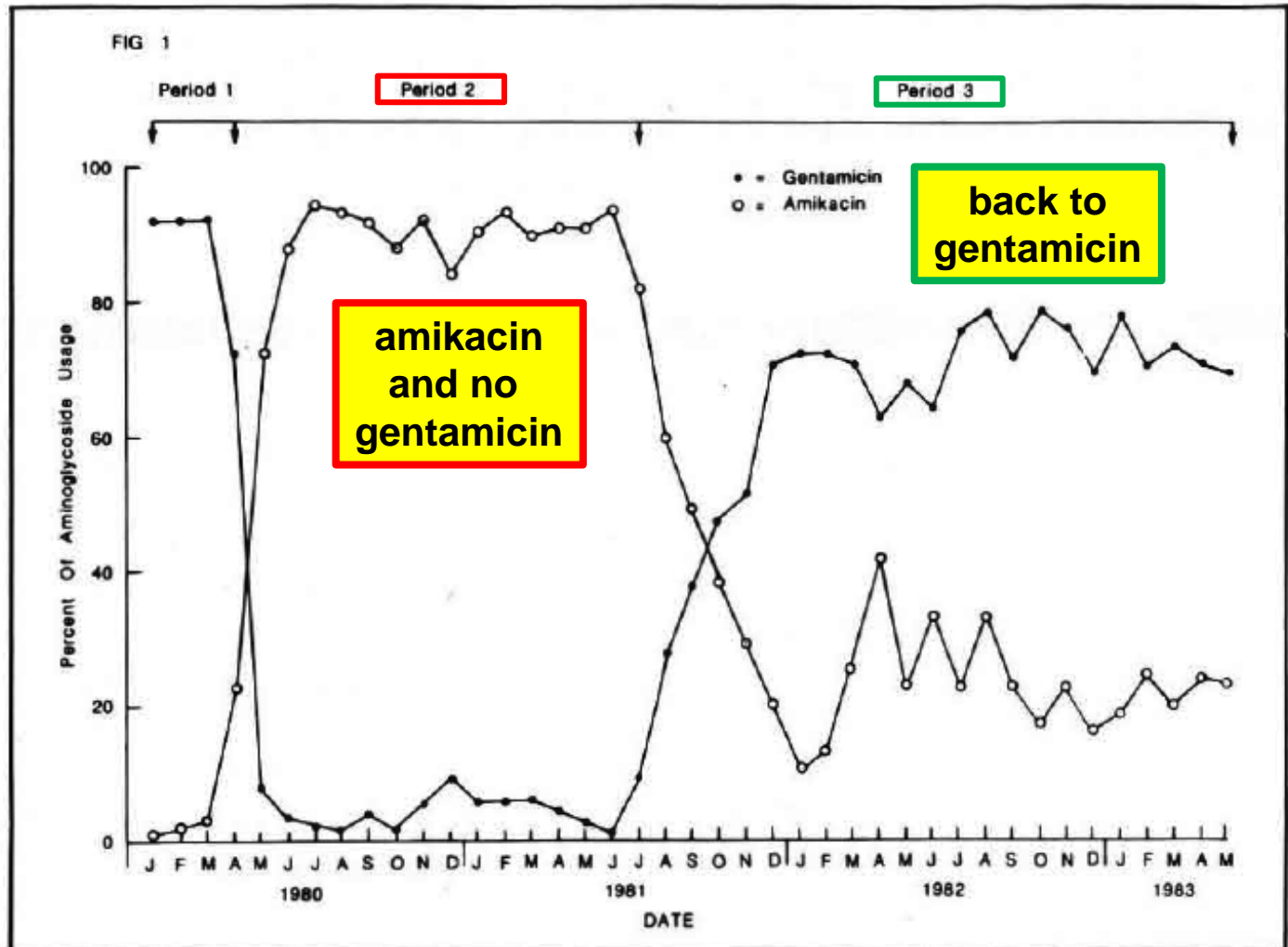


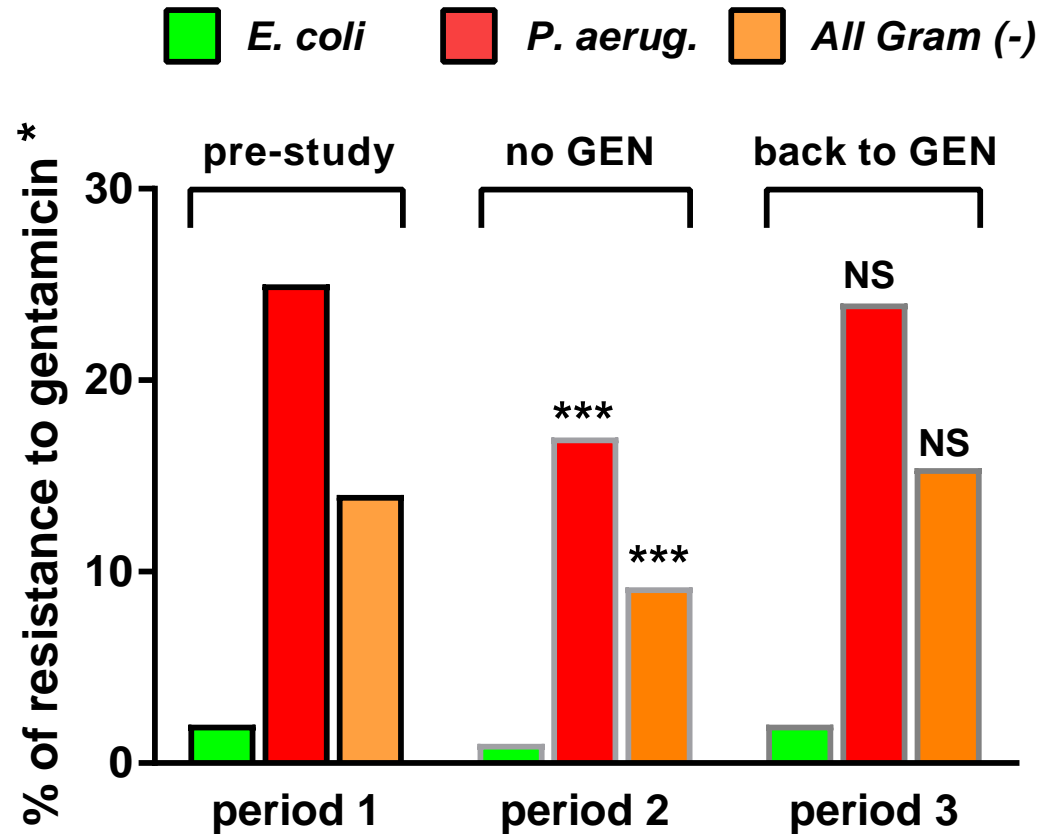
Figure. Aminoglycoside usage patterns.

# Oude publicatie over gentamicine vs. amikacine

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Am J Med Sci. 1985; 290:223-7 - PMID: [3936358](https://pubmed.ncbi.nlm.nih.gov/3936358/).



\* most of the isolates were susceptible to amikacin

Statistical analysis: comparison of period 2 or period 3 vs period 1 using Mantel-Haenzel technique based on the logarithms of the odds ratios (*E. coli*: n= 270/1402/1735; *P. aeruginosa*: n=199/1033/1460; all Gram(-): n=1053/5374/7873)  
Ref.: Fleiss JL: Statistical Methods for Rates and Proportions. New York, John Wiley, 1973.

# "Oude" Publicaties en vancomycine ...



1980's:

Large scale re-introduction of vancomycin \*

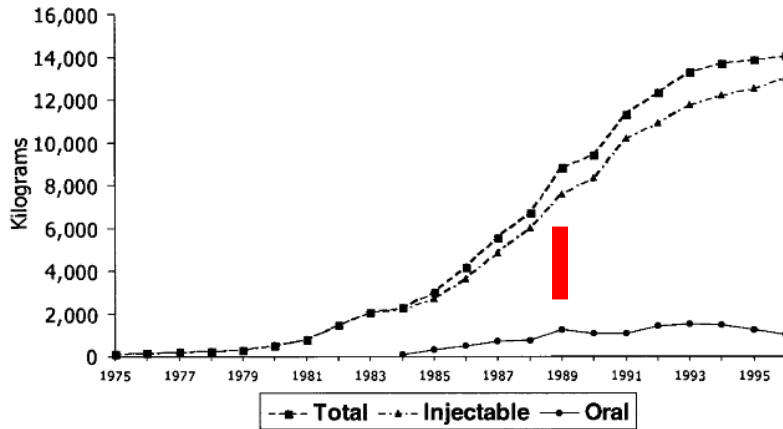


FIG. 1. Usage of vancomycin (in kilograms) in the United States, France, Italy, Germany, United Kingdom, and The Netherlands.

Kirst et al. Antimicrob Agents Chemother. 1998; 42:1303-4.

\* Vancomycin was described in 1955-57  
(Antibiot Annu. 1955-1956;3:606-322 and 1956-57;4:75-122)

1989:

## Vancomycin-resistant Enterococci

*Epidem. Inf.* (1989) 103, 173-181 Printed in Great Britain

### High-level vancomycin-resistant enterococci causing hospital infections

A. H. C. UTTLEY<sup>1</sup>, R. C. GEORGE<sup>2</sup>, J. NAIDOO<sup>2</sup>, N. WOODFORD<sup>2</sup>,  
A. P. JOHNSON<sup>2</sup>, C. H. COLLINS<sup>1</sup>, D. MORRISON<sup>3</sup>, A. J. GILFILLAN<sup>2</sup>,  
L. E. FITCH<sup>1</sup>, AND J. HEPTONSTALL<sup>1</sup>

*Public Health Laboratory, Dulwich Hospital, East Dulwich Grove,  
London SE22 8QF<sup>1</sup>, Antibiotic Reference Laboratory<sup>2</sup> and  
Streptococcus Reference Laboratory<sup>3</sup>, Division of Hospital Infection,  
Central Public Health Laboratory*

(Accepted 12 March 1989)

#### SUMMARY

Nosocomial infection or colonization due to enterococci with high-level resistance to vancomycin (minimal inhibitory concentrations [MICs] between 64 and > 2000 mg/L) has occurred in 41 patients with renal disease. These vancomycin-resistant enterococci were cultured from many sources including blood. All but one strain contained one or more plasmids ranging in molecular weight from 1.0 to 40 Megadaltons (MDa). Vancomycin resistance was transferable by conjugation to a susceptible recipient strain of *Enterococcus faecalis* but this was not always associated with plasmid DNA. The emergence of transferable high-level vancomycin resistance in enterococci causing significant clinical infections is of particular importance since vancomycin is widely regarded as a reserve drug for the management of infections with multi-resistant Gram-positive organisms.



# "Oude" Publicaties en vancomycine ...



**1980's:**

Large scale re-introduction of vancomycin \*

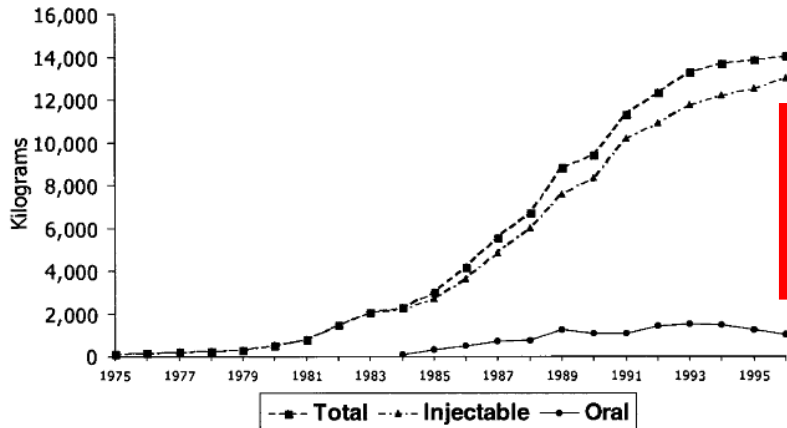


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\* Vancomycin was described in 1955-57  
(*Antibiot Annu.* 1955-1956;3:606-322 and 1956-57;4:75-122)

**1997:**

*S. aureus* strains with reduced susceptibility to vancomycin

*Journal of Antimicrobial Chemotherapy* (1997) **40**, 135-146

## Correspondence

**Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility**

*J Antimicrob Chemother* 1997; **40**: 135-136

K. Hiramatsu<sup>a\*</sup>, H. Hanaki<sup>a</sup>, T. Ino<sup>b</sup>, K. Yabuta<sup>b</sup>,  
T. Oguri<sup>c</sup> and F. C. Tenover<sup>d</sup>

<sup>a</sup>Department of Bacteriology; <sup>b</sup>Department of Pediatrics, Juntendo University, Tokyo; <sup>c</sup>Clinical Laboratory, Juntendo Hospital, Tokyo, Japan; <sup>d</sup>Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA

# Een andere "oude" publicatie over $\beta$ -lactams en *S. pneumoniae*

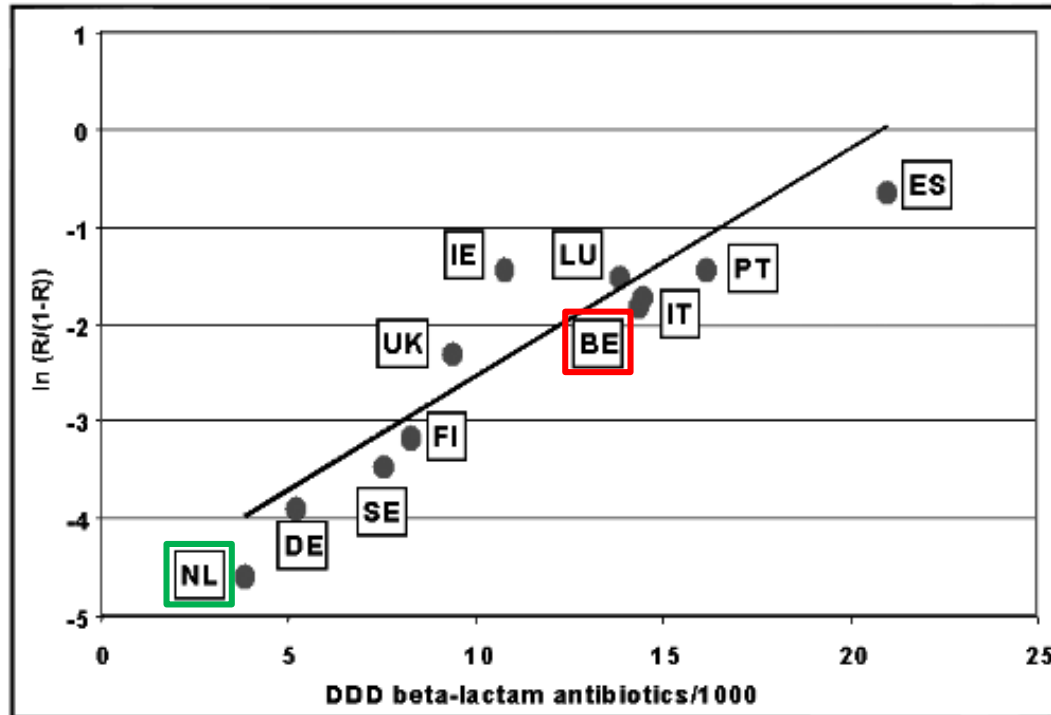


Figure 2. The logodds of resistance to penicillin among invasive isolates of *Streptococcus pneumoniae* (PNISP;  $\ln(R/[1-R])$ ) is regressed against outpatient sales of beta-lactam antibiotics in 11 European countries; antimicrobial resistance data are from 1998 to 1999 and antibiotic sales data are from 1997. DDD = defined daily dose; BE = Belgium; DE = Germany; FI = Finland; IE = Ireland; IT = Italy; LU = Luxembourg; NL = the Netherlands; PT = Portugal; ES = Spain; SE = Sweden; UK = United Kingdom.

Bronzwaer *et al.* Emerg Infect Dis. 2002;8:278-82. PubMed PMID: [11927025](https://pubmed.ncbi.nlm.nih.gov/11927025/)

# Maar een vroegtijdige waarschuwing...



## Class Restriction of Cephalosporin Use to Control Total Cephalosporin Resistance in Nosocomial *Klebsiella*

James J. Rahal, MD; Carl Urban, PhD; David Horn, MD; Katherine Freeman, DrPH;  
Sorana Segal-Maurer, MD; James Maurer, MD; Noriel Mariano, BS; Sheila Marks, RN;  
Janice M. Burns, RN; Dana Dominick, RPh, MS; Mimi Lim, RN, MPA

JAMA. 1998; 280:1233-7 – PMID [9786372](https://pubmed.ncbi.nlm.nih.gov/9786372/)

# Maar een vroegtijdige waarschuwing...



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James J. Rahal, MD  
Sorana Segal-Maurer, MD  
Janice M. Burns, PhD

JAMA. 1998; 280:

Table 1.—Change in Parenteral Cephalosporin and Imipenem/Cilastatin Use From 1995 to 1996 Following Cephalosporin Restriction in 1996

Antibiotics	Year	Unpaired Median Monthly Gram Use (Range)			Change, %	P	Paired Median Monthly Gram Use (Range)		P
		1995	1996	Change, %			1995	1996	
All cephalosporins	1995	5558	1106	-80.1	<.001	-4709	(-7168 to -3208)	<.001	
	1996	(4452 to 8858)	(259 to 1690)						
Ceftazidime	1995	383	66	-72.5	<.001	-248	(-494 to 80)	<.005	
	1996	(60 to 523)	(0 to 189)						
Cefotaxime	1995	253	227	-10.3	>.05	-96	(-750 to 208)	>.05	
	1996	(129 to 910)	(6 to 350)						
Ceftriaxone sodium	1995	155	94	-39.4	<.05	-78	(-151 to 81)	<.05	
	1996	(61 to 296)	(8 to 249)						
Cefotetan	1995	1450	63	-95.7	<.001	-1390	(-2386 to 899)	<.001	
	1996	(1068 to 2443)	(5 to 187)						
Cefuroxime	1995	2210	192	-91.3	<.001	-1928	(-4117 to -821)	<.001	
	1996	(995 to 4494)	(34 to 377)						
Cefazolin	1995	1428	440	-69.2	<.001	-1050	(-1898 to 568)	<.001	
	1996	(1177 to 2145)	(106 to 676)						

# Maar een vroegtijdige waarschuwing...



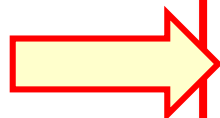
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Imipenem	1995	197 (76 to 463)	140.6	<.05	258 (-140 to 551)	.05
	1996	474 (119 to 627)				



# Maar een vroegtijdige waarschuwing...



Table 3.—Change in Number and Incidence of Patient-Related Ceftazidime-Resistant *Klebsiella* From 1995 to 1996 Following Cephalosporin Restriction in 1996\*

Site	Year	No. of PR-CRK	Change, %	Incidence by Unpaired Median PR-CRK/ADC Ratio (Range)	P	Incidence by Paired Median Monthly PR-CRK/ADC Ratio Difference (Range)	P
Hospital-wide	1995	150	-44.0	0.032 (0.015-0.054)	<.01	-0.019 (-0.037-0.014)	<.05
	1996	84		0.019 (0.006-0.039)			
All intensive care units	1995	55	-70.9	0.137 (0.036-0.237)	<.001	-0.098 (-0.237-0.048)	<.01
	1996	16		0.034 (0-0.121)			
Surgical intensive care unit	1995	40	-87.5	0.293 (0.083-0.636)	<.001	-0.194 (-0.636-0.043)	<.005
	1996	5		0 (0-0.143)			
Medical intensive care unit	1995	17	-58.8	0.100 (0-0.300)	>.05	-0.100 (-0.214-0.200)	>.05
	1996	7		0 (0-0.200)			
Cardiac intensive care unit	1995	2	100	0 (0-0.091)	>.05	0 (-0.091-154)	>.05
	1996	4		0 (0-0.231)			

\*PR-CRK/ADC indicates number of patient-related ceftazidime-resistant *Klebsiella* (PR-CRK) per 1000 average daily census (ADC), hospital-wide; and per 100 ADC for individual and all intensive care units.

opmerkelijke daling  
van patiënten met  
resistente organismen ...

# Maar een vroegtijdige waarschuwing...



Table 4.—Change in Number and Incidence of Patient-Related Imipenem-Resistant *Pseudomonas aeruginosa* From 1995 to 1996 Following Cephalosporin Restriction in 1996

Site	Year	No. of PR-IRP	Change, %	Incidence by Unpaired Median PR-IRP/ADC* Ratio (Range)	P	Incidence by Paired Median Monthly PR-IRP/ADC Ratio Difference (Range)	P																																							
Hospital-wide	1995	67	68.7	0.015 (0.003-0.026)	<.01	0.010 (-0.008-0.031)	<.01																																							
	1996	113		0.025 (0.016-0.042)				All intensive care units	1995	20	75.0	0.032 (0-0.161)	<.05	0.033 (-0.027-0.157)	<.01	1996	35	0.080 (0.033-0.182)	Surgical intensive care unit	1995	12	33.3	0.100 (0-0.429)	>.05	0.067 (-0.286-0.250)	>.05	1996	16	0.143 (0-0.429)	Medical intensive care unit	1995	8	37.5	0 (0-0.300)	>.05	0.019 (-0.209-0.200)	>.05	1996	11	0.095 (0-0.200)	Cardiac intensive care unit	1995	0	...	0 (0-0.0)	<.05
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\*PR-IRP/ADC indicates number of patient-related imipenem-resistant *P aeruginosa* (PR-IRP) per 1000 average daily census (ADC), hospital-wide and per 100 ADC for individual and all intensive care units

# Maar een vroegtijdige waarschuwing...

1998

knijp de ballon!



opmerkelijke stijging van patiënten met imipenem-R organismen

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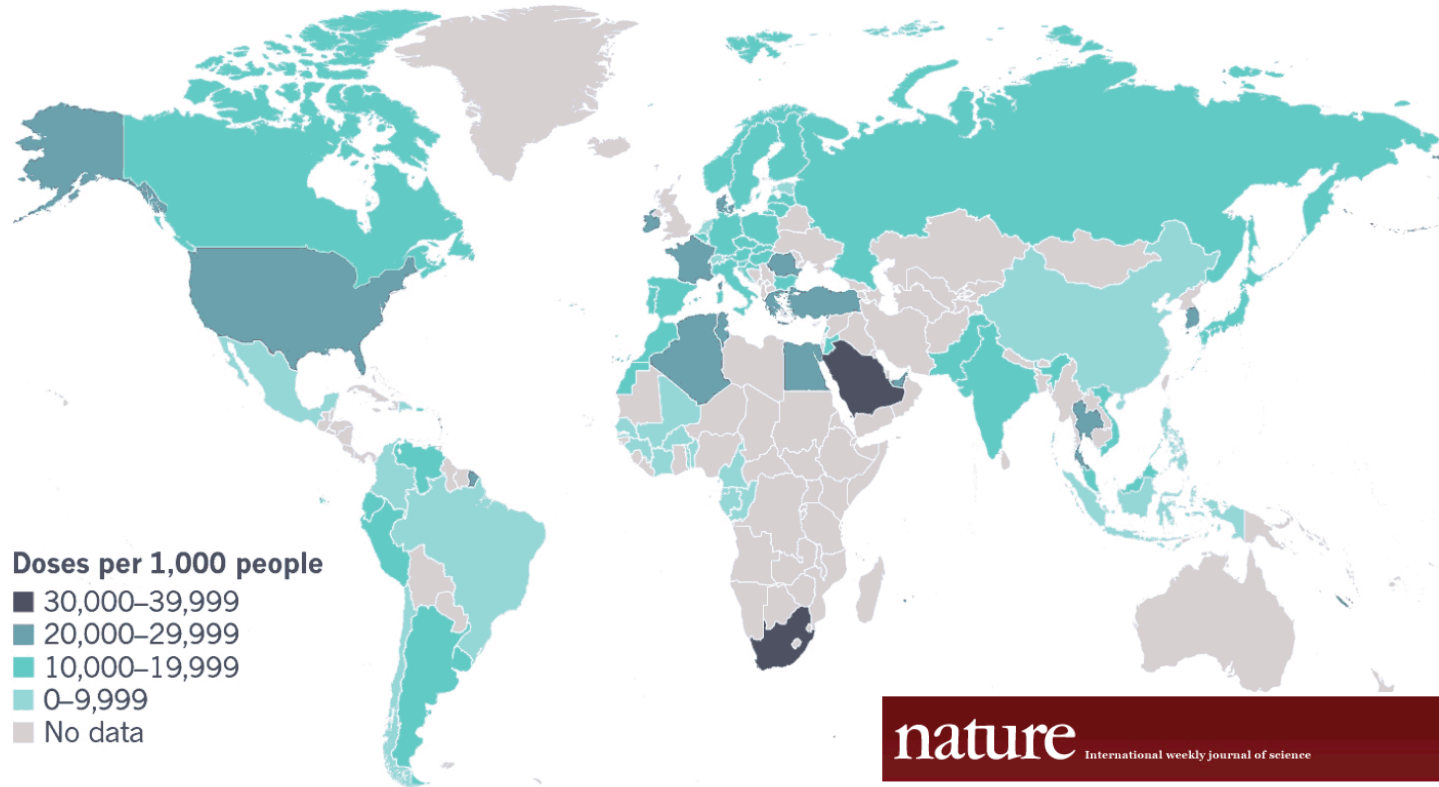
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# Antibiotica gebruik is nog aan het stijgen

## TREATMENT TRENDS

The first comprehensive, global report on antibiotic use shows that the drugs are increasingly popular in low- and middle-income countries.



**nature** International weekly journal of science

### Dramatic rise seen in antibiotic use

New report provides the most comprehensive picture yet of antibiotic use and resistance worldwide.

Sara Reardon

17 September 2015

<http://www.nature.com/news/dramatic-rise-seen-in-antibiotic-use-1.18383>

Laatst bezocht: 3 sep 2017

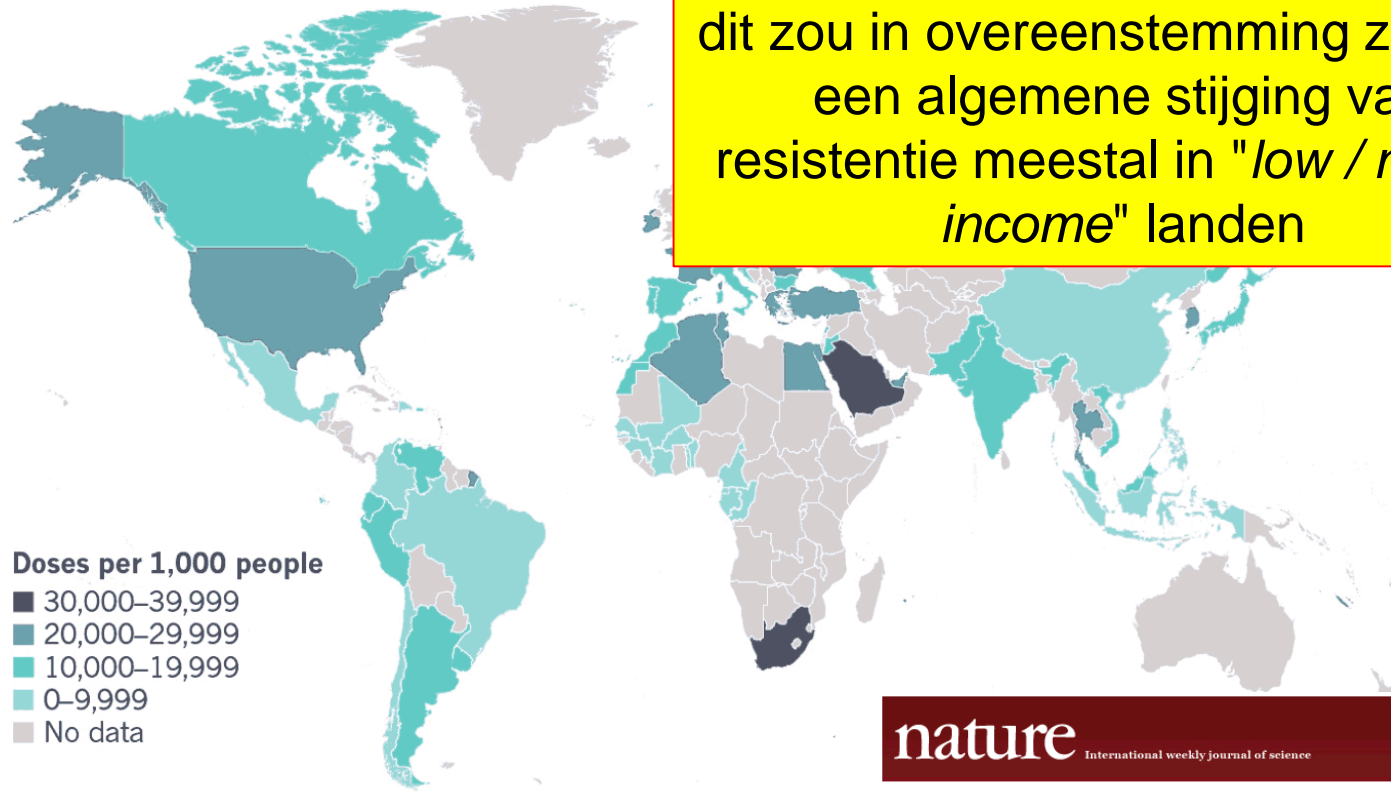
# Antibiotica gebruik is nog aan het stijgen

## TREATMENT TRENDS

The first comprehensive, global report on antibiotic use shows that the drugs are increasingly popular in low- and middle-income countries.



dit zou in overeenstemming zijn met een algemene stijging van resistentie meestal in "low / middle income" landen



### Doses per 1,000 people

- 30,000–39,999
- 20,000–29,999
- 10,000–19,999
- 0–9,999
- No data



### Dramatic rise seen in antibiotic use

New report provides the most comprehensive picture yet of antibiotic use and resistance worldwide.

Sara Reardon

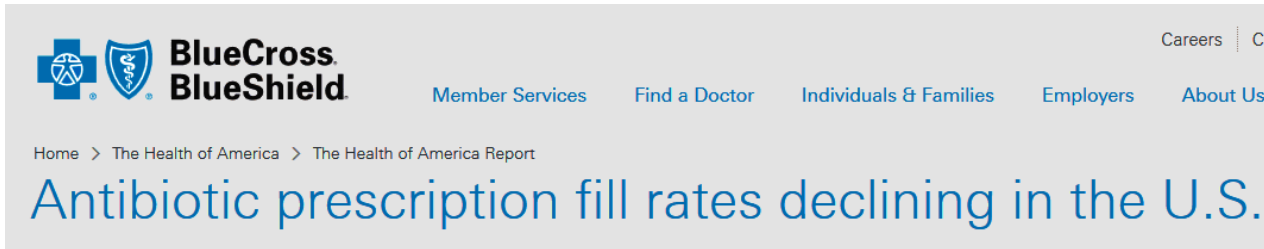
17 September 2015

<http://www.nature.com/news/dramatic-rise-seen-in-antibiotic-use-1.18383>

Laatst bezocht: 3 sep 2017

# Maar andere studies tonen een belangrijke vermindering van het aantal antibiotica voorschriften...

2015



The screenshot shows the BlueCross BlueShield website header with navigation links: Member Services, Find a Doctor, Individuals & Families, Employers, and About Us. Below the header, the breadcrumb trail reads: Home > The Health of America > The Health of America Report. The main heading of the report is "Antibiotic prescription fill rates declining in the U.S."

een wijd gepubliceerde studie...

<https://www.bcbs.com/the-health-of-america/reports/antibiotic-prescription-rates-declining-in-the-US>

Laatst bezocht: 5 sep 2017

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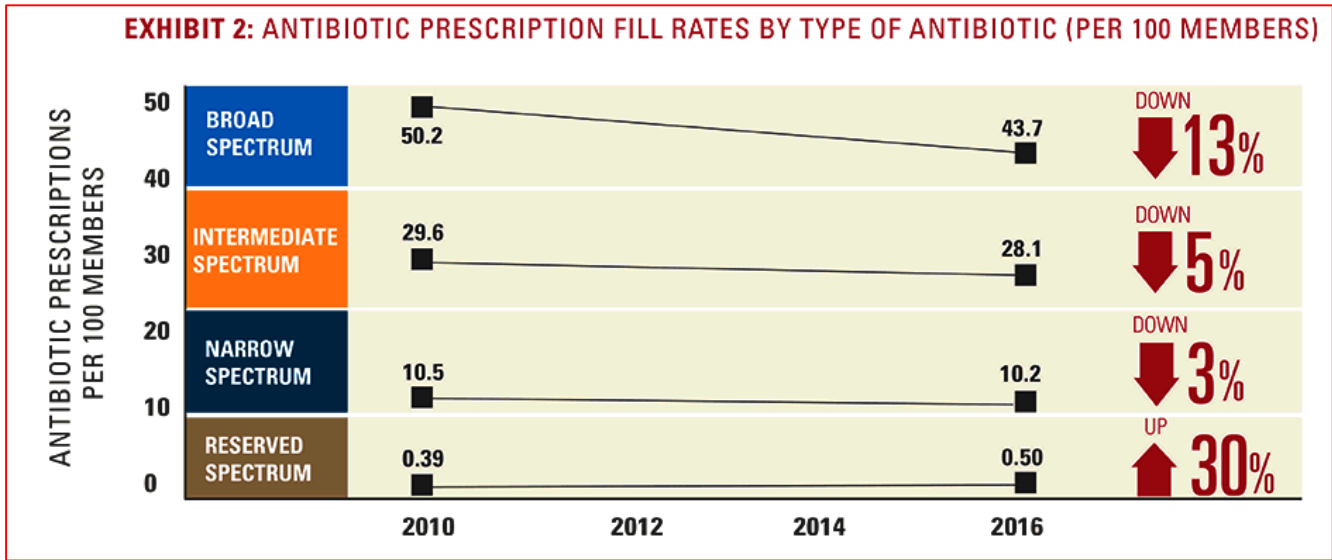
een wijd gepubliceerde studie...

BlueCross BlueShield  
 Member Services Find a Doctor Individuals & Families Employers About Us  
 Home > The Health of America > The Health of America Report  
 Antibiotic prescription fill rates declining in the U.S.

**9% DECLINE** NOTABLE PROGRESS IN REDUCING ANTIBIOTIC USE OVER THE PAST SEVEN YEARS

**CHANGE IN ANTIBIOTIC FILL RATES**

- BROAD-SPECTRUM **DOWN 13%**
- ADULT **DOWN 6%**
- CHILDREN **DOWN 16%**
- INFANT **DOWN 22%**



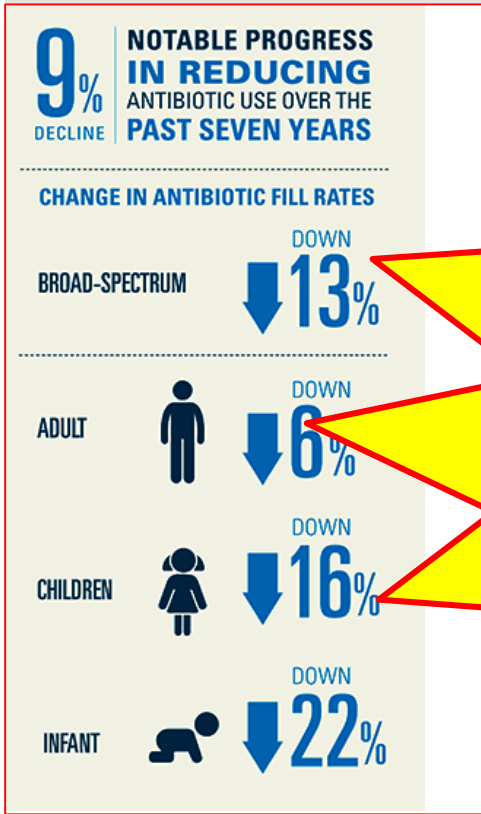
<https://www.bcbs.com/the-health-of-america/reports/antibiotic-prescription-rates-declining-in-the-US>  
 Laatste bezocht: 5 sep 2017

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2015

BlueCross BlueShield  
Member Services Find a Doctor Individuals & Families Employers About Us  
Home > The Health of America > The Health of America Report

een wijd gepubliceerde studie...



maar geen vergelijking met een daling (of een stijging) van de resistentie...

<https://www.bcbs.com/the-health-of-america/reports/antibiotic-prescription-rates-declining-in-the-US>  
Laatst bezocht: 5 sep 2017

# Een andere recente studie...



Clinical Infectious Diseases



ACCEPTED MANUSCRIPT

## **Antibiotic Expenditures by Medication, Class, and Health Care Setting in the United States, 2010–2015**

KJ Suda, PharmD, M.S. ✉, Lauri A Hicks, DO, Rebecca M Roberts, M.S.,  
Robert J Hunkler, Linda M Matusiak, Glen T Schumock, PharmD, MBA, PhD

*Clinical Infectious Diseases*, cix773, <https://doi.org/10.1093/cid/cix773>

**Published:** 25 August 2017 **Article history** ▼

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Clinical Infectious Diseases



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KJ Suda, PharmD, M.S.  
Robert J Hunkler, Linda

*Clinical Infectious Diseases*

**Published:** 25 August 2015

**Table 1. Antibiotic Expenditures Overall and by Year in Healthcare Settings in the United States, 2010-2015\***

	Antibiotic Expenditures (in millions)	% Growth
2010	\$10,569	--
2011	\$9,788	-7.4
2012	\$8,436	-13.8
2013	\$9,163	8.6
2014	\$9,095	-0.7
2015	\$8,810	-3.1
<b>Total expenditures, 2010-2015</b>	<b>\$55,861</b>	<b>-16.6</b>

\*p=0.1119 for trend

# Een andere recente studie...



Clinical Infectious Diseases



ACCEPTED MANUSCRIPT

Antibiotic Expenditure by Class, and Health Care Setting, United States, 2010-2015

KJ Suda, PharmD, M.S., Robert J Hunkler, Linda

Clinical Infectious Diseases  
Published: 25 August

Table 1. Antibiotic Expenditures Overall and by Year in Health Care Settings in the United States, 2010-2015\*

Year	Expenditures	% Growth
2010		--
2011		-7.4
2012		-13.8
2013		8.6
2014		-0.7
2015	\$8,810	-3.1
<b>Total expenditures, 2010-2015</b>	<b>\$55,861</b>	<b>-16.6</b>

\*p=0.1119 for trend

maar ook hier geen vergelijking met een daling (of een stijging) van de resistentie...



# Is er een relatie in Europa ? Globale gegevens



APPROVED: 28 June 2017 doi: 10.2903/j.efsa.2017.4872

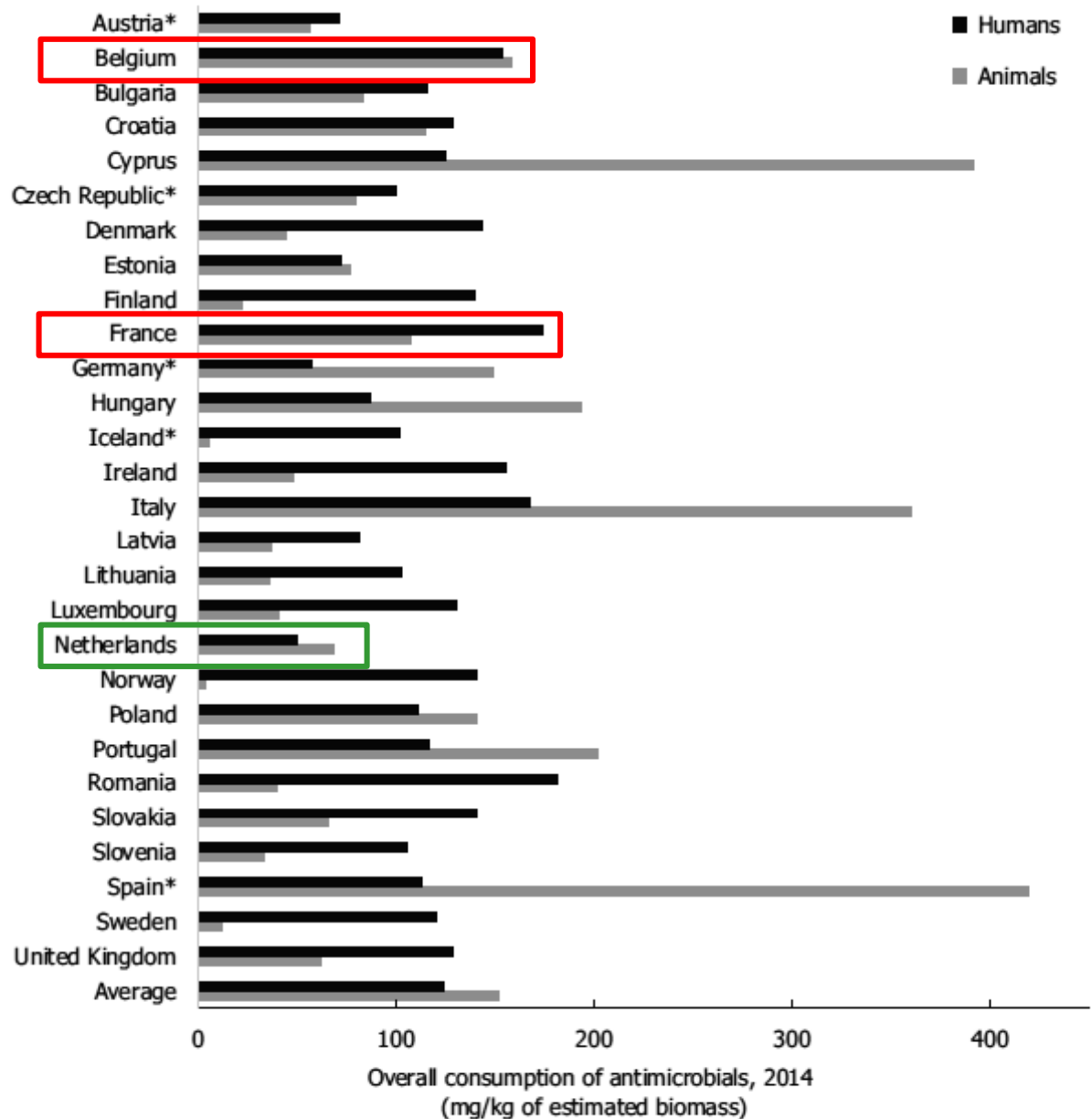
## **ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals**

### **Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report**

European Centre for Disease Prevention and Control (ECDC),  
European Food Safety Authority (EFSA) and  
European Medicines Agency (EMA)

Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. EFSA Journal 2017;15(7):4872, 135 pp.  
<http://dx.doi.org/10.2903/j.efsa.2017.4872>

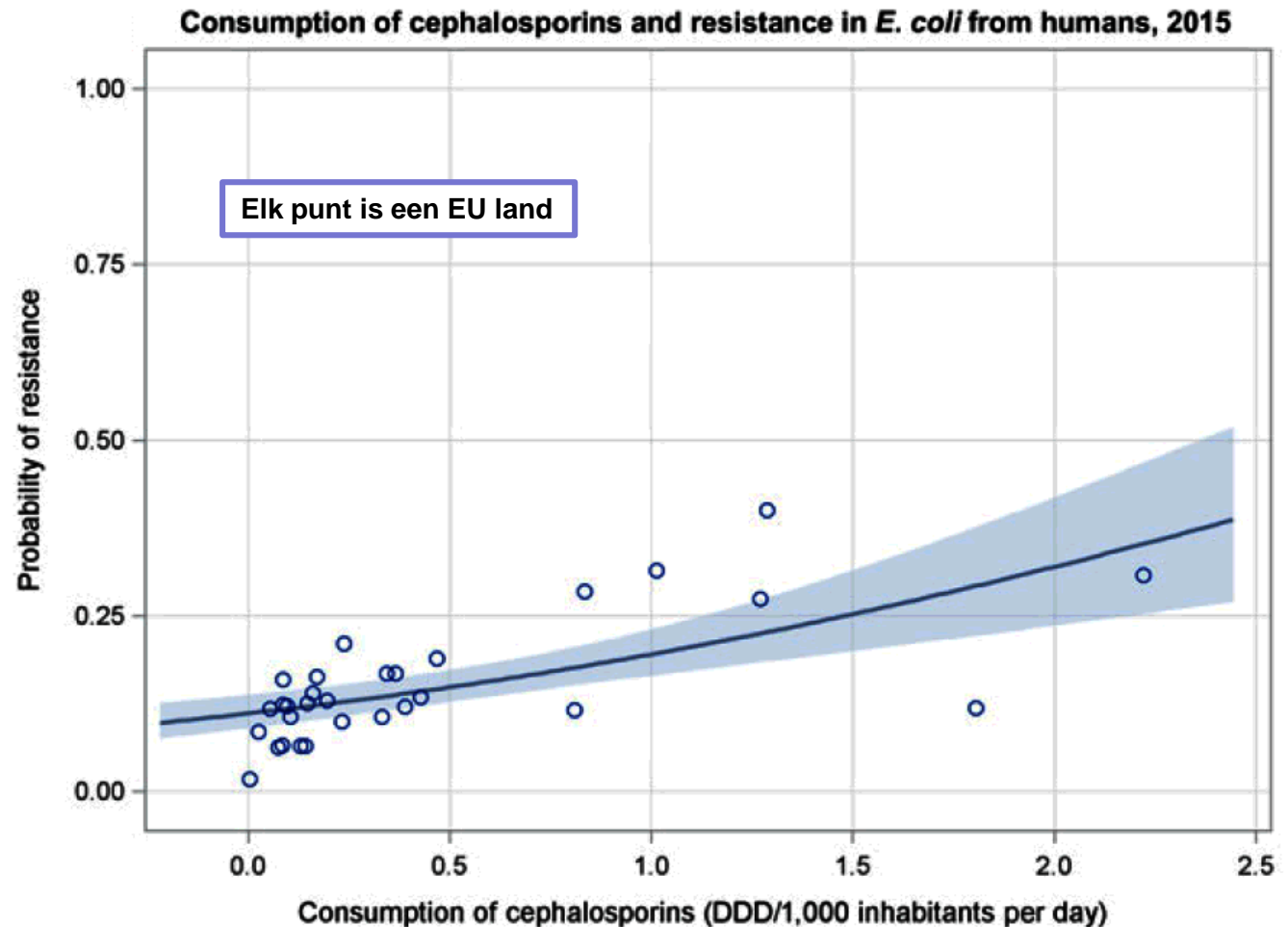
# Europa: Globale gegevens voor gebruik



Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. EFSA Journal 2017;15(7):4872, 135 pp. <http://dx.doi.org/10.2903/j.efsa.2017.4872>

**Figure 6:** Comparison of biomass-corrected consumption of antimicrobials (mg/kg of estimated biomass) in humans and food-producing animals by country, EU/EEA MSs, 2014

# Europa: Globale relatie gebruik – resistentie voor *E. coli* en cefalosporines

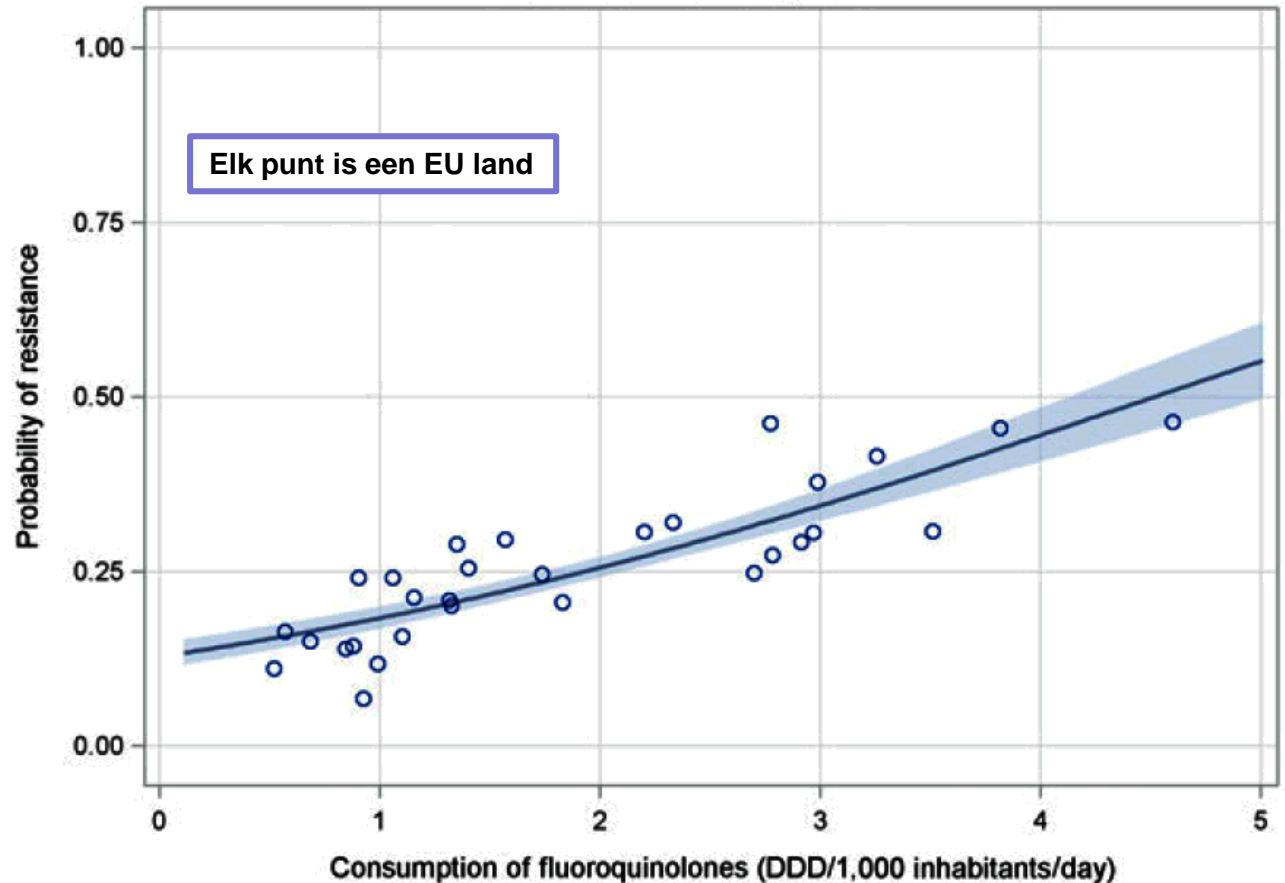


Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. EFSA Journal 2017;15(7):4872, 135 pp. <http://dx.doi.org/10.2903/j.efsa.2017.4872>

**Logistic regression analysis curves of the total (community and hospital) consumption of 3rd- and 4th-generation cephalosporins in humans and the probability of resistance to 3rd-generation cephalosporins in invasive *E. coli* from humans**

# Europa: Globale relatie gebruik – resistentie voor *E. coli* en chinolonen

Consumption of fluoroquinolones and resistance in *E. coli* from humans, 2015

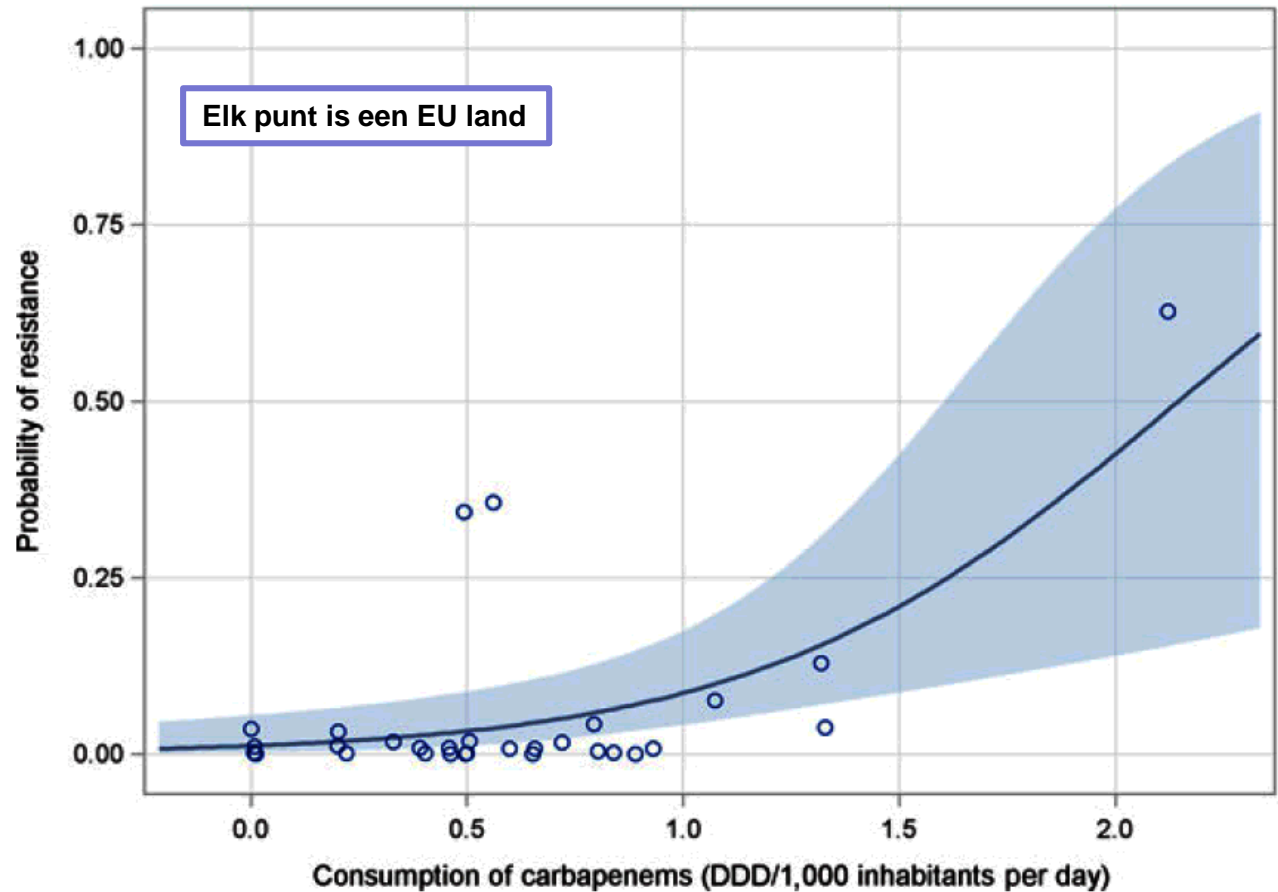


Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. EFSA Journal 2017;15(7):4872, 135 pp. <http://dx.doi.org/10.2903/j.efsa.2017.4872>

**Logistic regression analysis curves of the total (community and hospital) consumption of fluoroquinolones in humans and the probability of resistance to fluoroquinolones in human invasive *E. coli***

Europa:  
Globale relatie  
gebruik –  
resistentie  
voor  
*K. pneumoniae* en  
carbapenems

Consumption of carbapenems and resistance  
in *K. pneumoniae* from humans, 2015



Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. EFSA Journal 2017;15(7):4872, 135 pp. <http://dx.doi.org/10.2903/j.efsa.2017.4872>

**Logistic regression analysis curves of the total (community and hospital) consumption of carbapenems and the probability of resistance to carbapenems in invasive *K. pneumoniae* from humans**

# Meer granulaire en overtuigende relaties in Europa ? Nederland vs. België vs. Frankrijk

## Antibiotic Use

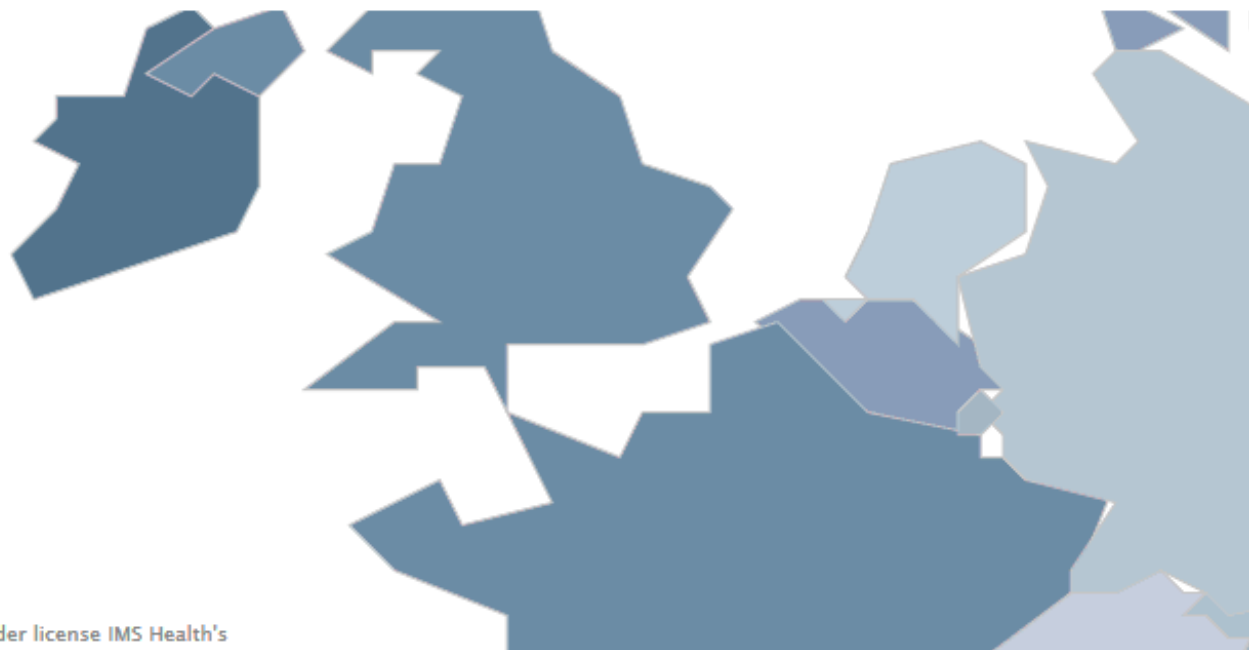
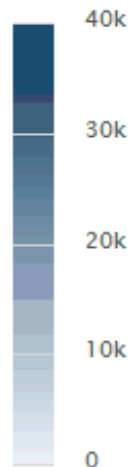
Map Trend Chart

- +

### Use of All Antibiotics in 2015

Source: IMS Health

Std Units/  
1000 Pop



Data obtained under license IMS Health's  
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Center for Disease Dynamics, Economics & Policy (cddep.org)

<https://resistancemap.cddep.org/AntibioticUse.php>  
Laatst bezocht: 3 sep 2017

# Nederland en België zijn zeer verschillend...

## Antibiotic Use

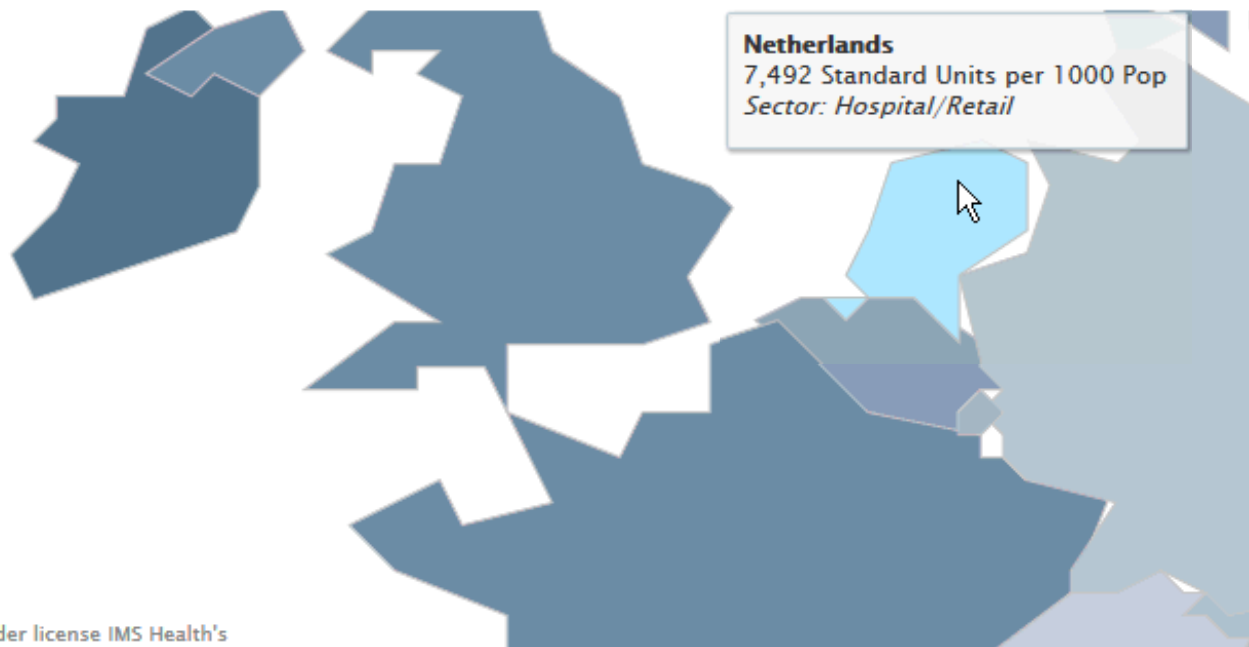
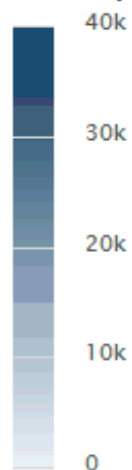
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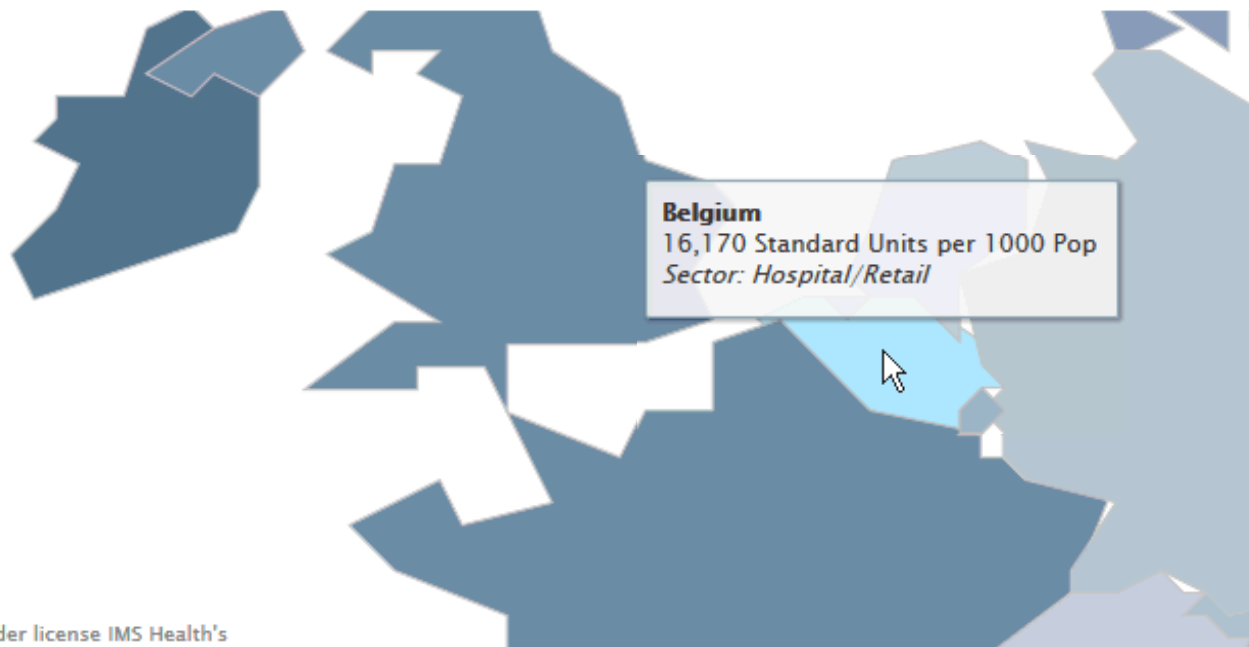
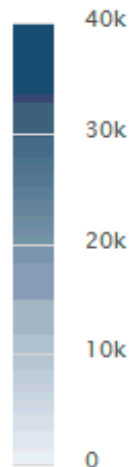
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<https://resistancemap.cddep.org/AntibioticUse.php>  
Laatst bezocht: 3 sep 2017



# Maar Frankrijk is nog verrassender...

## Antibiotic Use

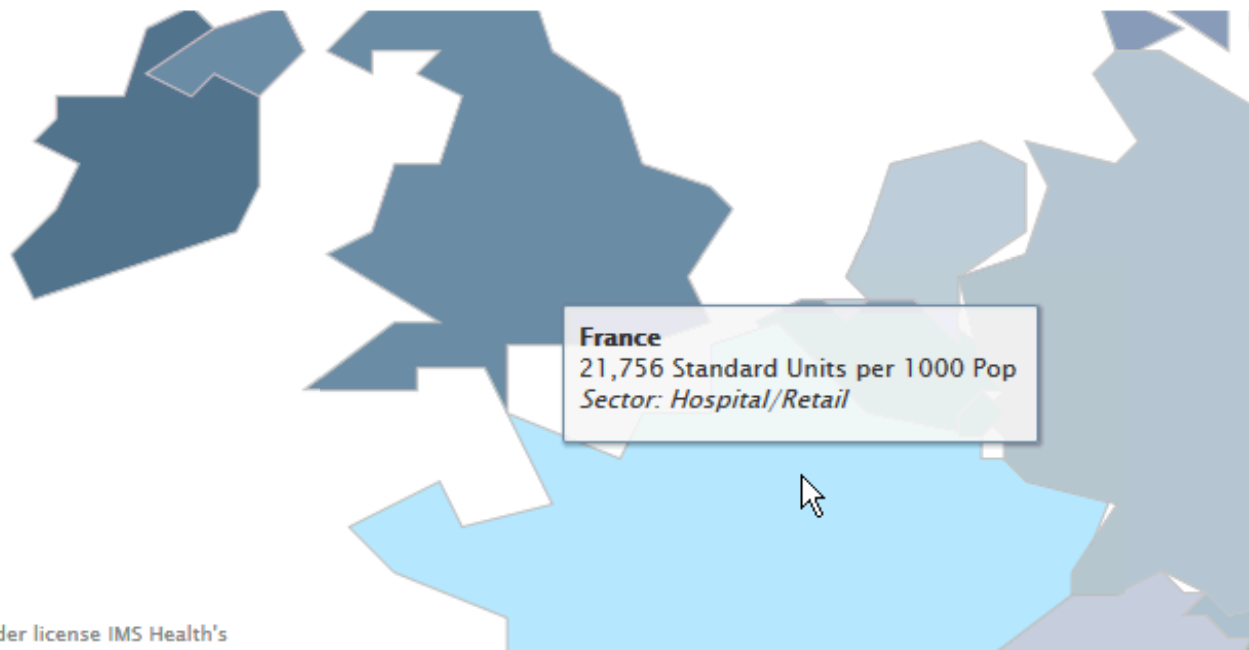
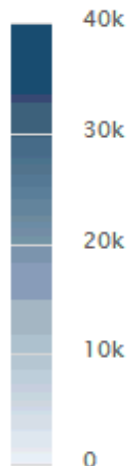
Map Trend Chart

- +

### Use of All Antibiotics in 2015

Source: IMS Health

Std Units/  
1000 Pop



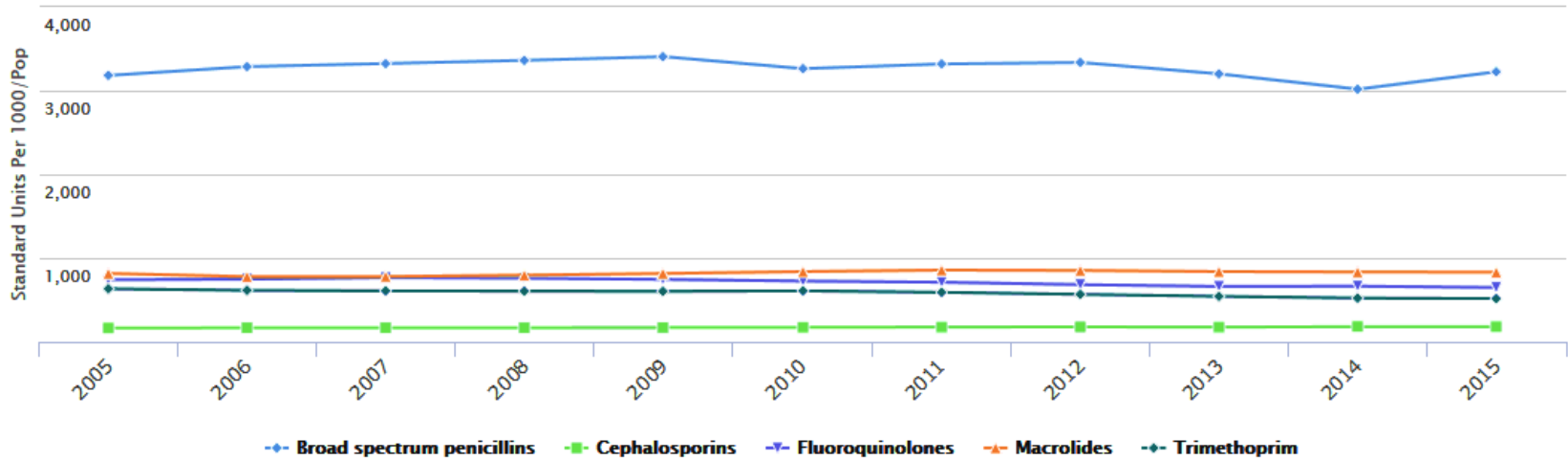
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<https://resistancemap.cddep.org/AntibioticUse.php>  
Laatst bezocht: 3 sep 2017

# Welke antibiotica ?

## Antibiotic Use in Netherlands

Source: IMS Health



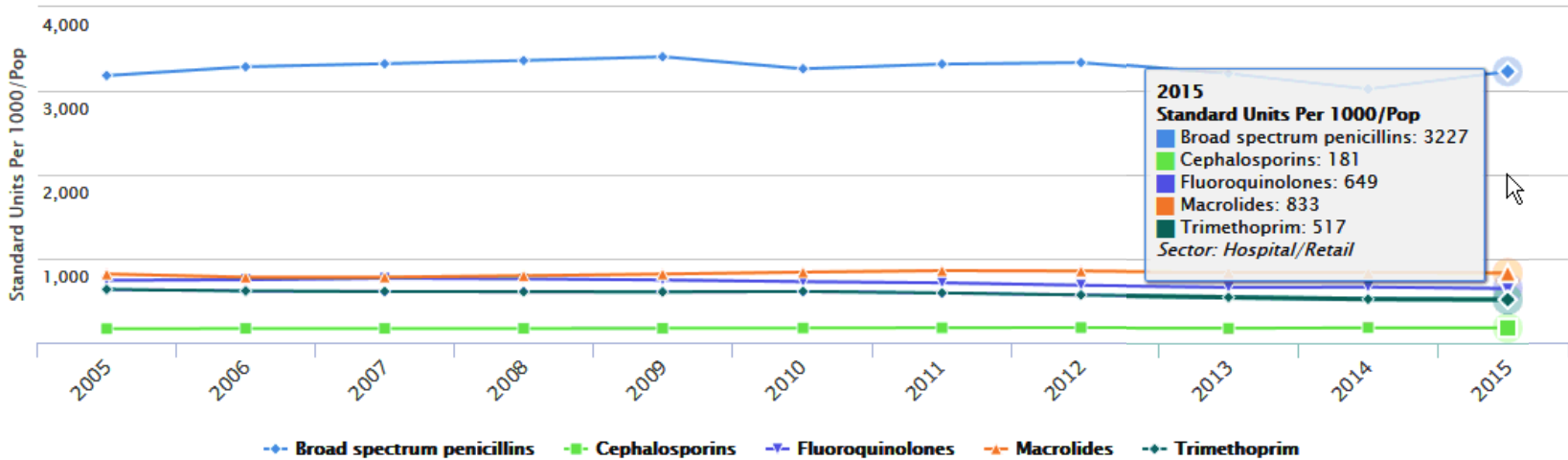
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Center for Disease Dynamics, Economics & Policy (cddep.org)

# Welke antibiotica ?

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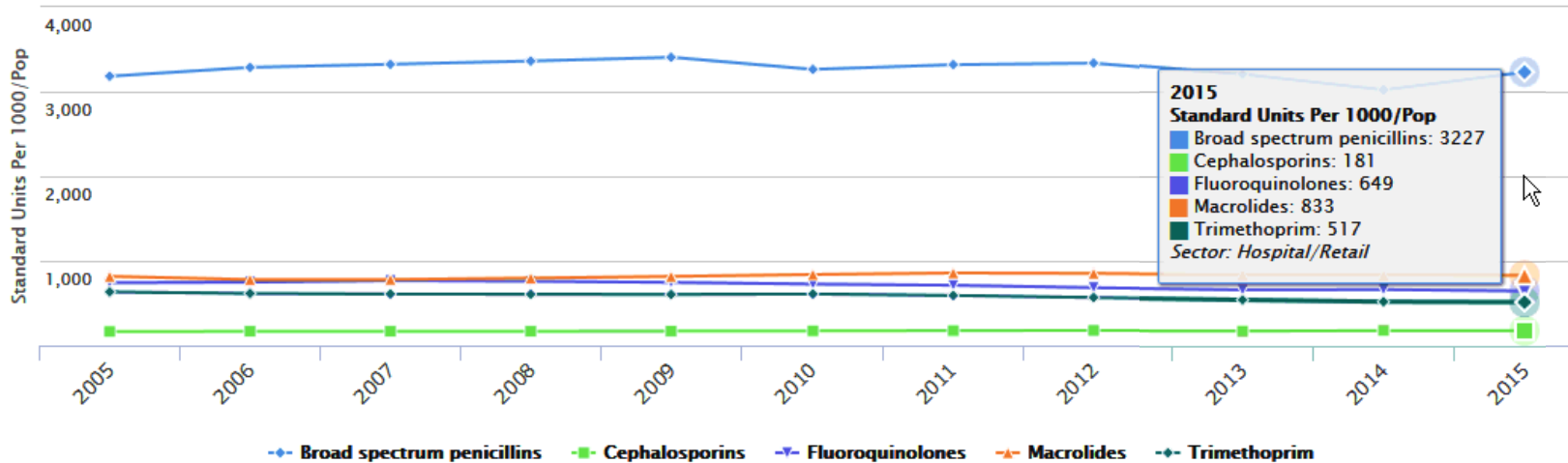
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# Welke antibiotica ?

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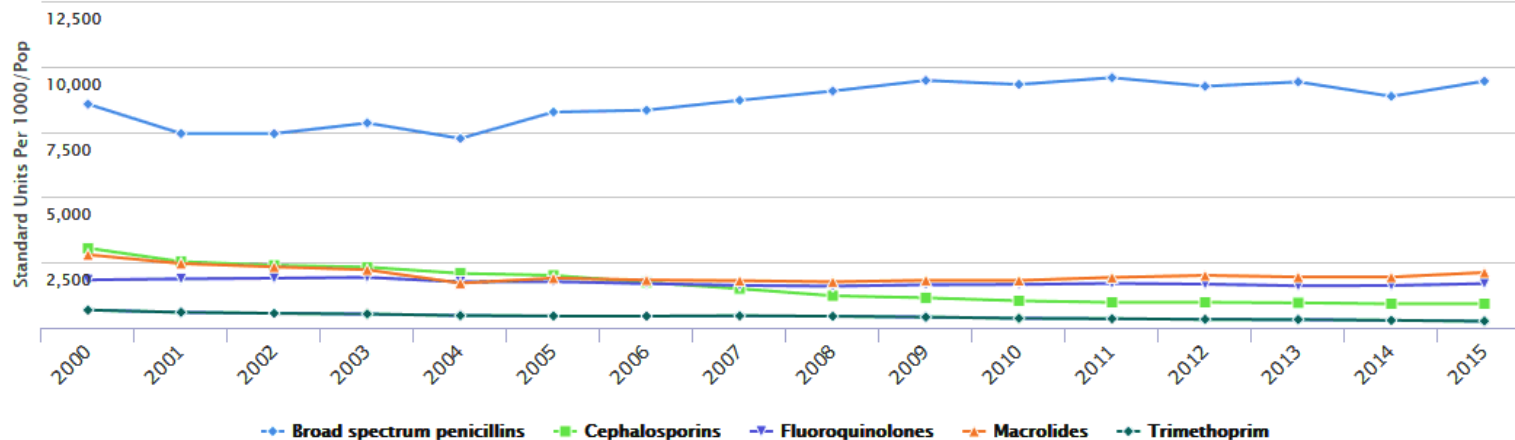
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Center for Disease Dynamics, Economics & Policy (cddep.org)

## Antibiotic Use in Belgium

Source: IMS Health

<https://resistancemap.cddep.org/AntibioticUse.php>  
 Laatste bezocht: 3 sep 2017



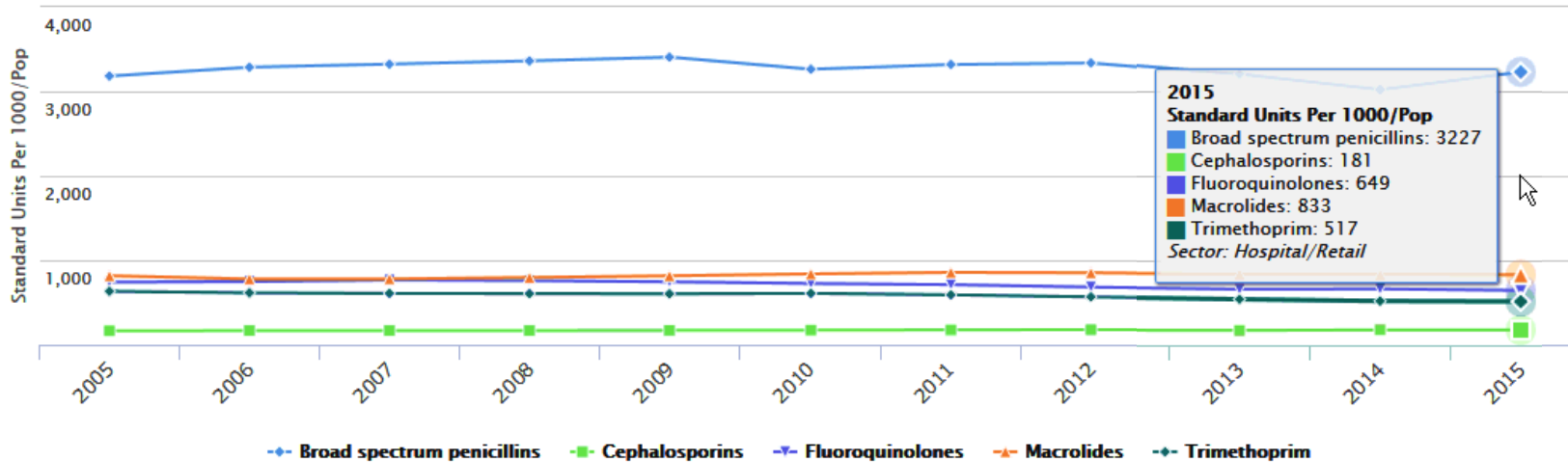
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Center for Disease Dynamics, Economics & Policy (cddep.org)

# Welke antibiotica ?

## Antibiotic Use in Netherlands

Source: IMS Health



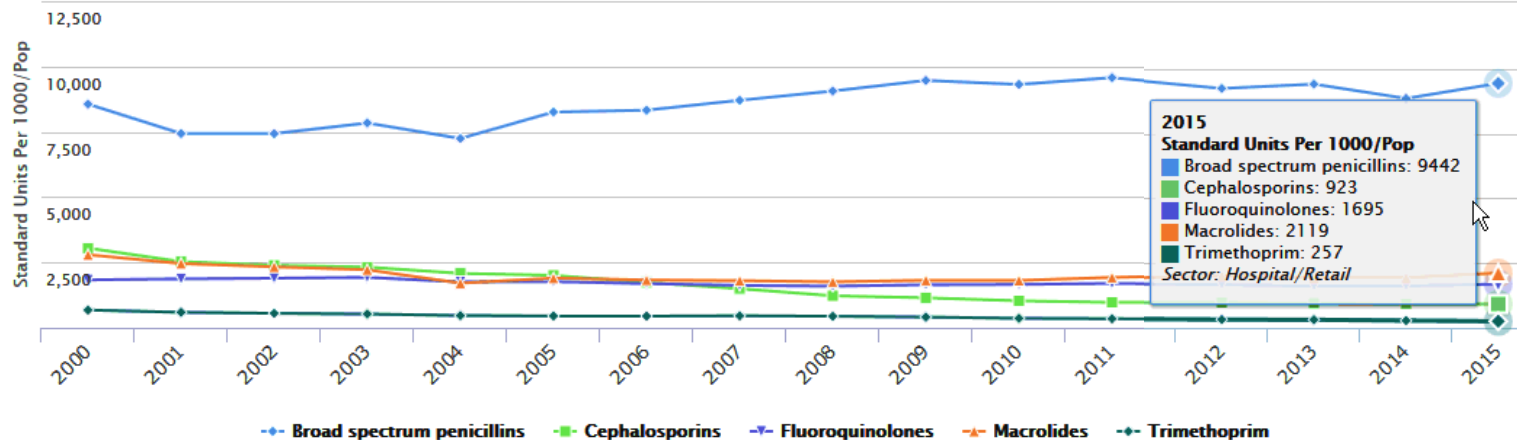
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 Laatst bezocht: 3 sep 2017



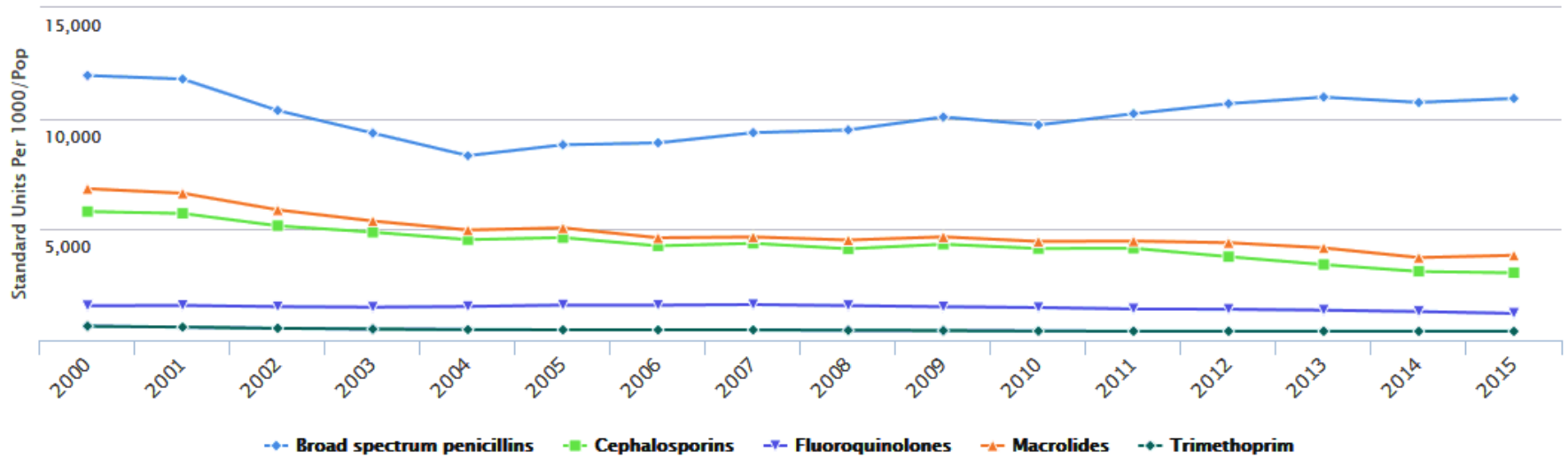
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Center for Disease Dynamics, Economics & Policy (cddep.org)

# Welke antibiotica ?

## Antibiotic Use in France

Source: IMS Health



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Center for Disease Dynamics, Economics & Policy (cddep.org)

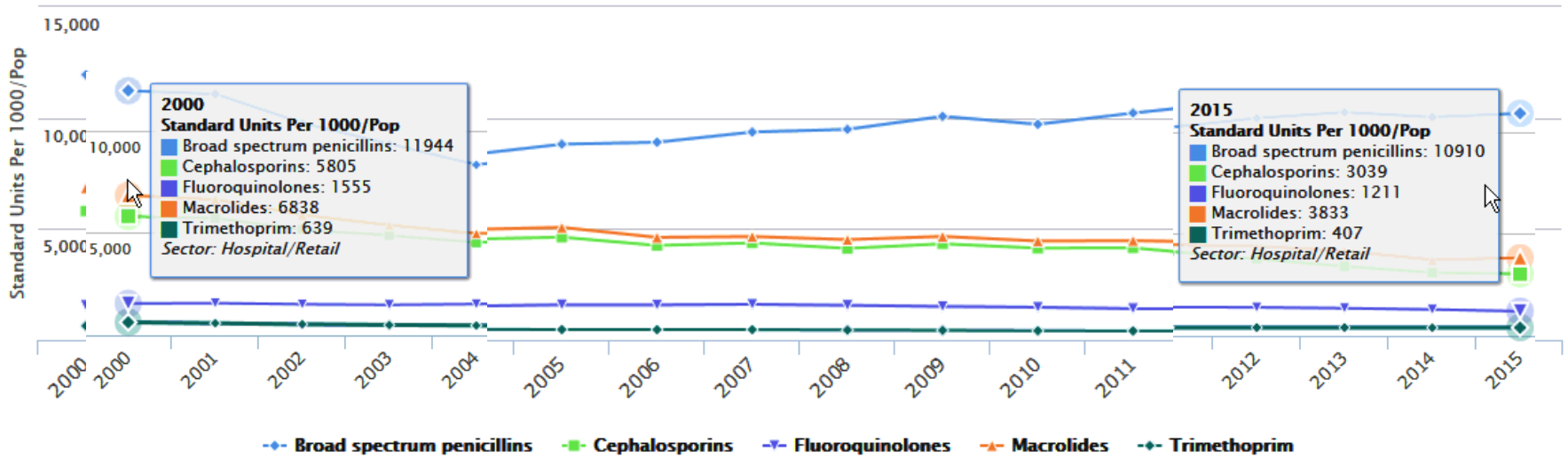
<https://resistancemap.cddep.org/AntibioticUse.php>

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# Welke antibiotica ?

## Antibiotic Use in France

Source: IMS Health



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Center for Disease Dynamics, Economics & Policy (cddep.org)

<https://resistancemap.cddep.org/AntibioticUse.php>

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# Wat nu met resistentie ?

## *S. pneumoniae* en penicilline

Country	2015			Trend 2012-2015
	N	%IR	(95% CI)	
Belgium	1361	0.6	(1-2)	
Netherlands	1163	1.8	(1-2)	
France	1068	22.9	(21-26)	

European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report.  
<http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf>  
 Laatste bezocht: 3 sep 2017

**BE ≤ NL << FR**

## *S. pneumoniae* en macroliden

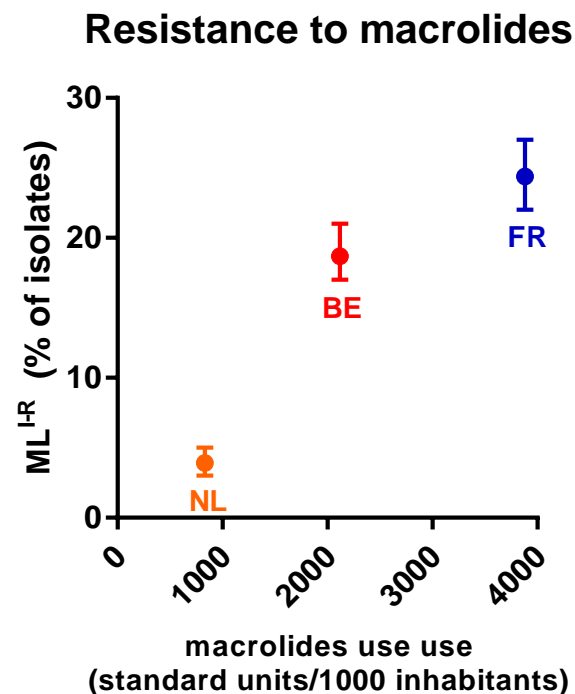
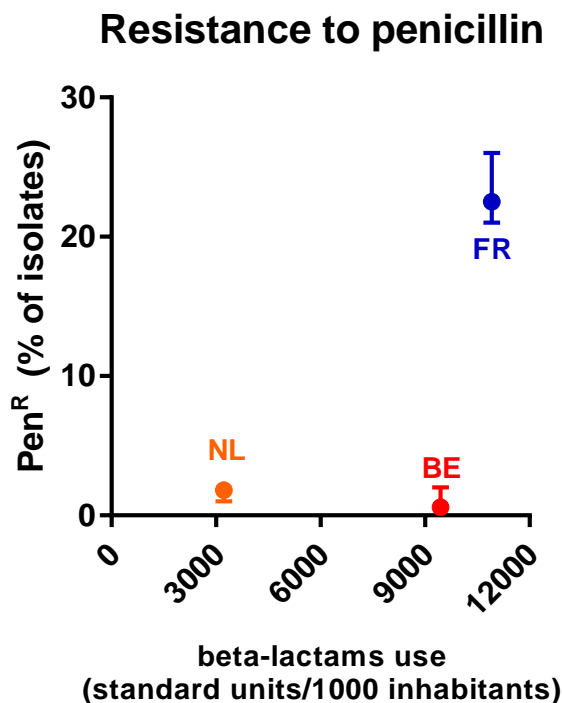
Country	2015			Trend 2012-2015
	N	%IR	(95% CI)	
Netherlands	1168	3.9	(3-5)	
Belgium	1361	18.7	(17-21)	
France	1068	24.4	(22-27)	

**NL << BE ≤ FR**



# NL-BE-FR relatie resistentie / antibiotica gebruik

## *S. pneumoniae*



Resistentie gegevens: European Centre for Disease Prevention and Control: Antimicrobial resistance surveillance in Europe 2015. Annual Report.

<http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf>

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Antibiotica gebruik gegevens:

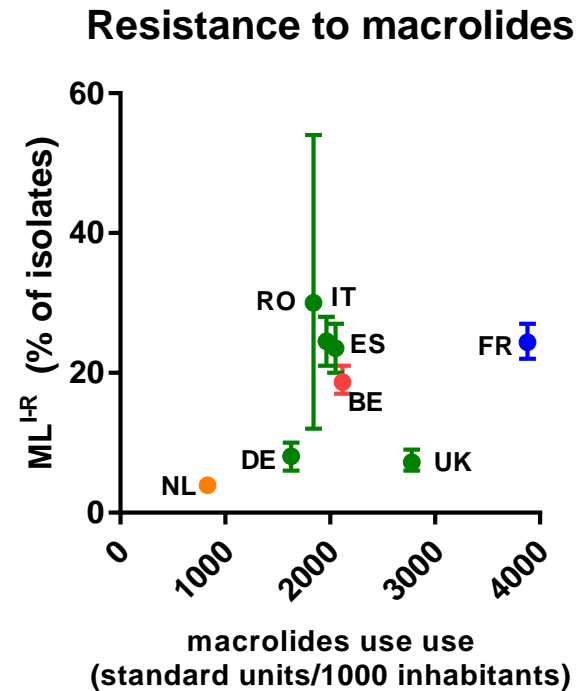
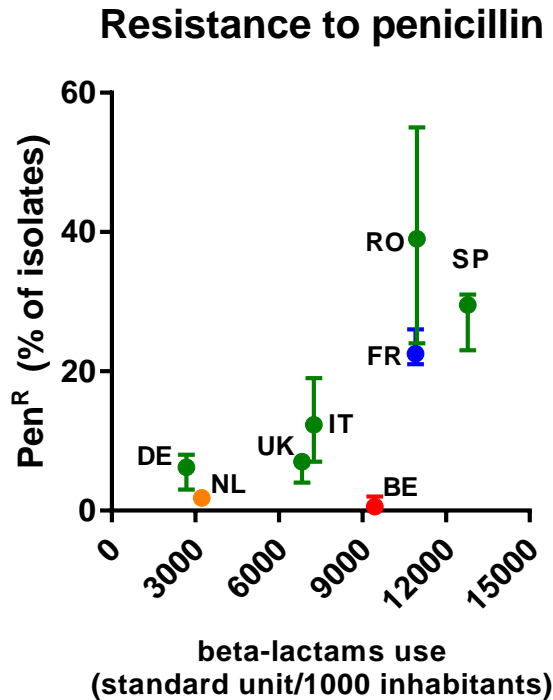
<https://resistancemap.cddep.org/AntibioticUse.php>

Laatst bezocht: 3 sep 2017

- Er is zeker een duidelijke correlatie tussen antibiotica gebruik en de oorsprong van resistentie...
- Maar de relatie tussen het gebruik en het niveau van resistentie is niet lineair en veel complexer...

# Maar wat met andere EU landen...

## *S. pneumoniae*



Resistentie gegevens: European Centre for Disease Prevention and Control: Antimicrobial resistance surveillance in Europe 2015. Annual Report.

<http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf>

Laatst bezocht: 3 sep 2017

Antibiotica gebruik gegevens:

<https://resistancemap.cddep.org/AntibioticUse.php>

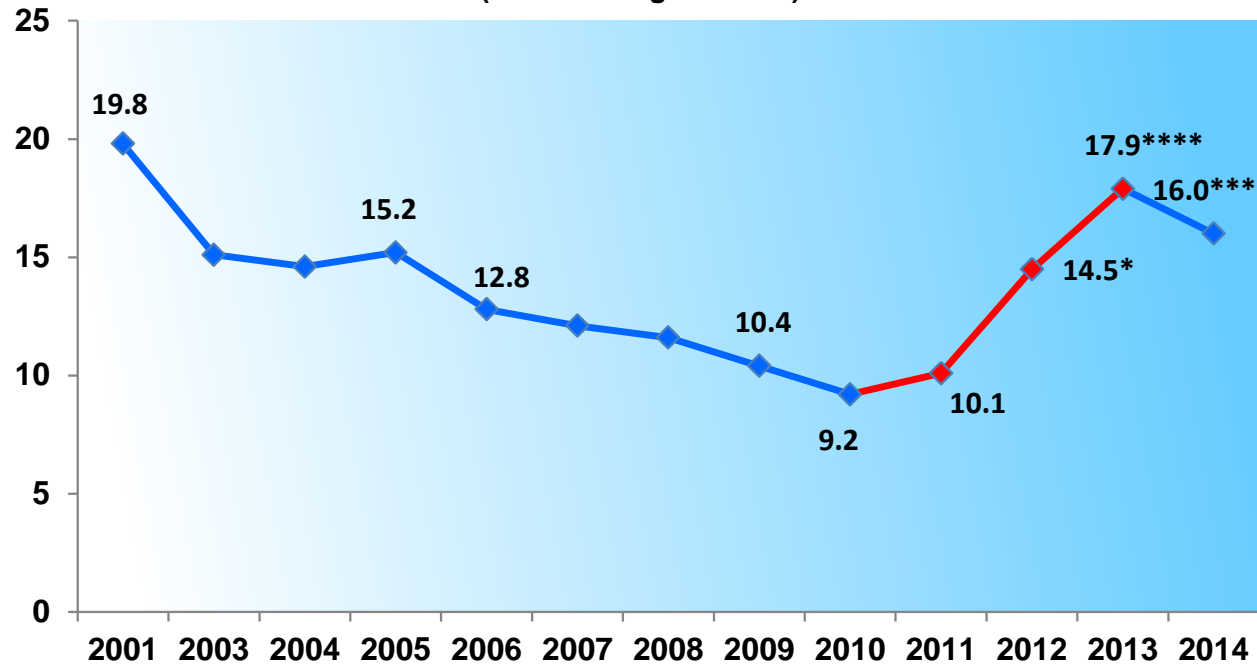
Laatst bezocht: 3 sep 2017

- De relatie is niet meer duidelijk en varieert tussen antibiotica...

# Variatie van resistentie over tijd ...

*S. pneumoniae* – Belgische gegevens

Fig. 14: Evolution of Penicillin Non-susceptibility Rates (%)  
(\*: level of significance)



WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID  
INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE

<http://bacterio.wiv-isp.be/reporting/reportspdf/SP3013avec%20couverture.pdf>

# Belgische campagnes: ieder jaar sedert 2000...



<http://www.red-antibiotica.org/> (Nederlands)  
<http://www.antibiotiques.org/> (Frans)



[http://www.belgium.be/fr/actualites/2013/news\\_campagne\\_antibiotiques\\_2013](http://www.belgium.be/fr/actualites/2013/news_campagne_antibiotiques_2013)

**LES  
ANTIBIOTIQUES**

**PRENEZ-LES COMME IL FAUT  
ET UNIQUEMENT QUAND IL LE FAUT !**

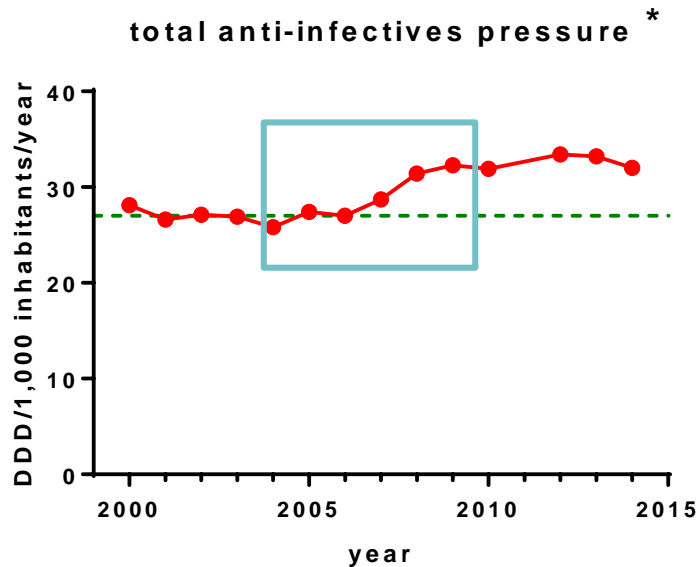
Une mauvaise utilisation des antibiotiques rend les bactéries plus résistantes. Par conséquent, les maladies graves ne peuvent plus être traitées correctement. Veillez donc à ce que les antibiotiques agissent encore lorsque vous en aurez réellement besoin

<http://www.usagecorrectantibiotiques.be/fr>



<http://www.gebruikantibioticacorrect.be/nl/lees-tante-biotica-online>

# Magere lange termijn (officiële) resultaten qua antibiotica gebruik...



\* defined as DDD's of ATC class J drugs (anti-infectives for systemic use) reimbursed in the community (~ 85% antibiotics)

Oorspong:

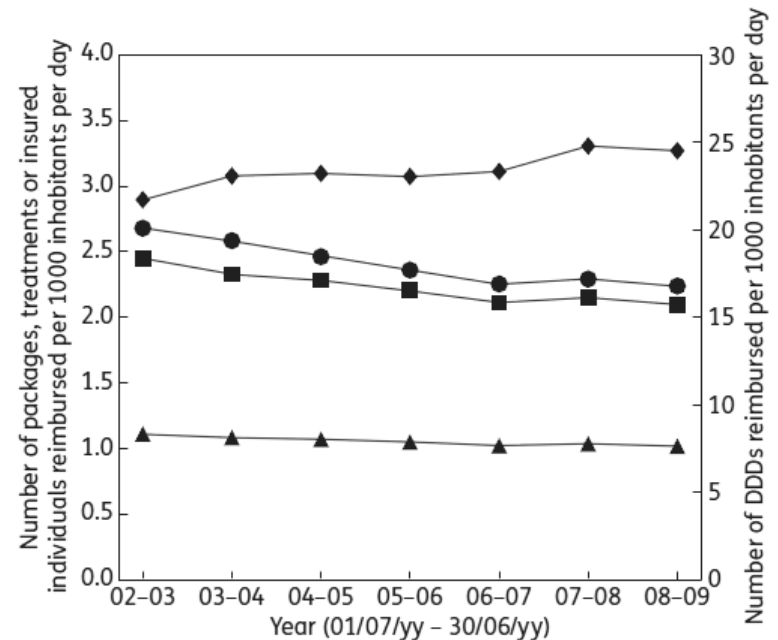
<http://www.inami.fgov.be/fr/statistiques/medicament/Pages/statistiques-medicaments-pharmanet-01.aspx#.V1wBn6JYyE0>

(Frans)

<http://www.inami.fgov.be/nl/statistieken/geneesmiddel/Paginas/statistieken-geneesmiddelen-farmanet-01.aspx#.V1wDHKJYyE0>

(Nederlands)

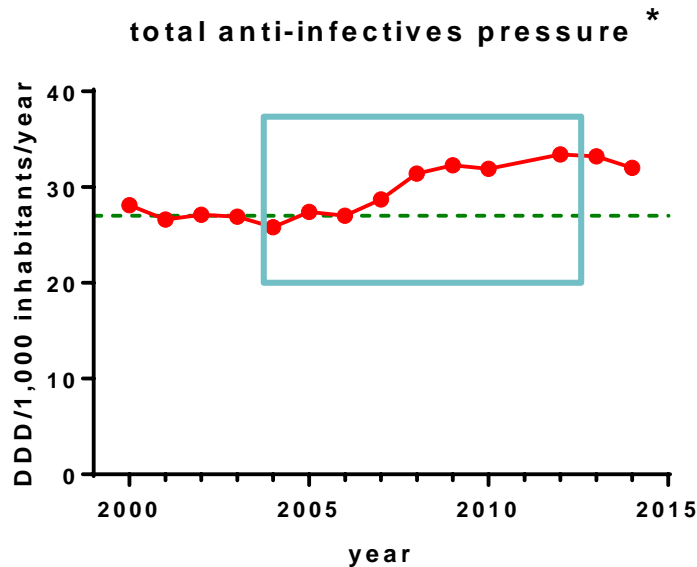
## Or estimation of no. of prescription?



**Figure 1.** Outpatient antibiotic use in Belgium per July-June year expressed as the number of DDDs (diamonds), packages (circles), treatments (squares) and insured individuals (triangles) reimbursed per 1000 inhabitants per day.

Coenen *et al.* J Antimicrob Chemother 2014; 69: 529-534 – PMID: [24084641](https://pubmed.ncbi.nlm.nih.gov/24084641/)

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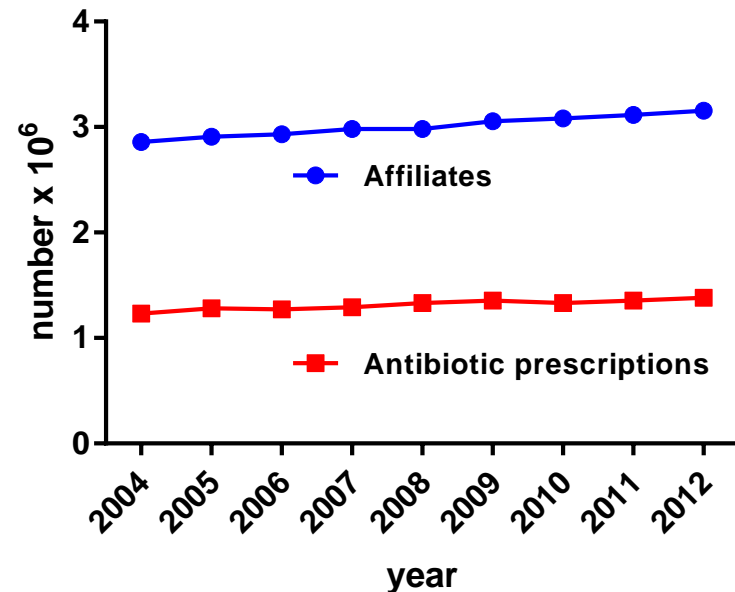
(Frans)

<http://www.inami.fgov.be/nl/statistieken/geneesmiddel/Paginas/statistieken-geneesmiddelen-farmanet-01.aspx#.V1wDHKJYyE0>

(Nederlands)

Or estimation of no. of prescription?

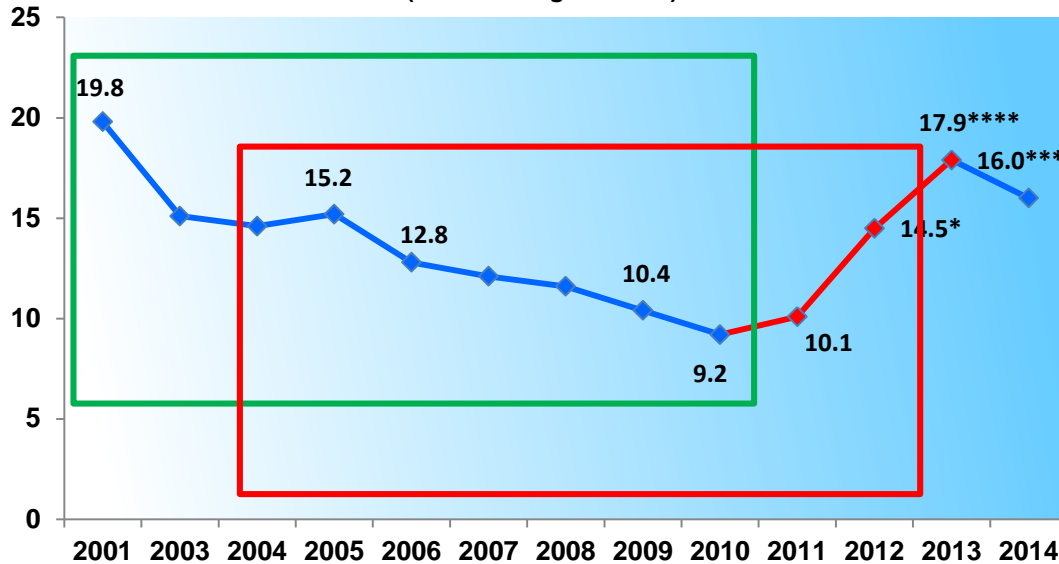
Numbers of affiliates and of antibiotic prescriptions (Solidaris)



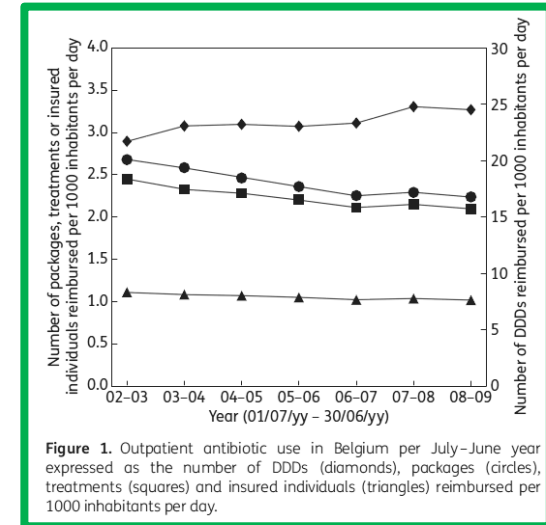
Gegevens van de Socialiste Mutualiteiten (ongeveer 40% of populatie)  
 Moreau *et al.* Poster P1140 - 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna, Austria, 22-25 April 2017 - <http://www.facm.ucl.ac.be/posters/2017/ECCMID-2017/Moreau-et-al-ECCMID-2017-P1140.pdf> - Laatst bezocht: 3 sep 2017

# Dus, waarom een daling en daarna een stijging in resistentie ?

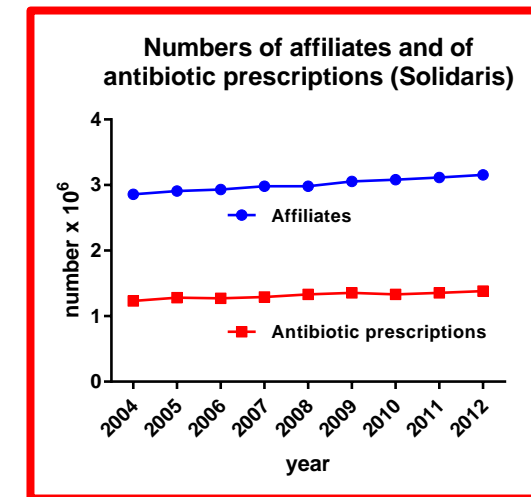
**Fig. 14: Evolution of Penicillin Non-susceptibility Rates (%)**  
(\*: level of significance)



**Relaties zijn zeker niet lineair ...**

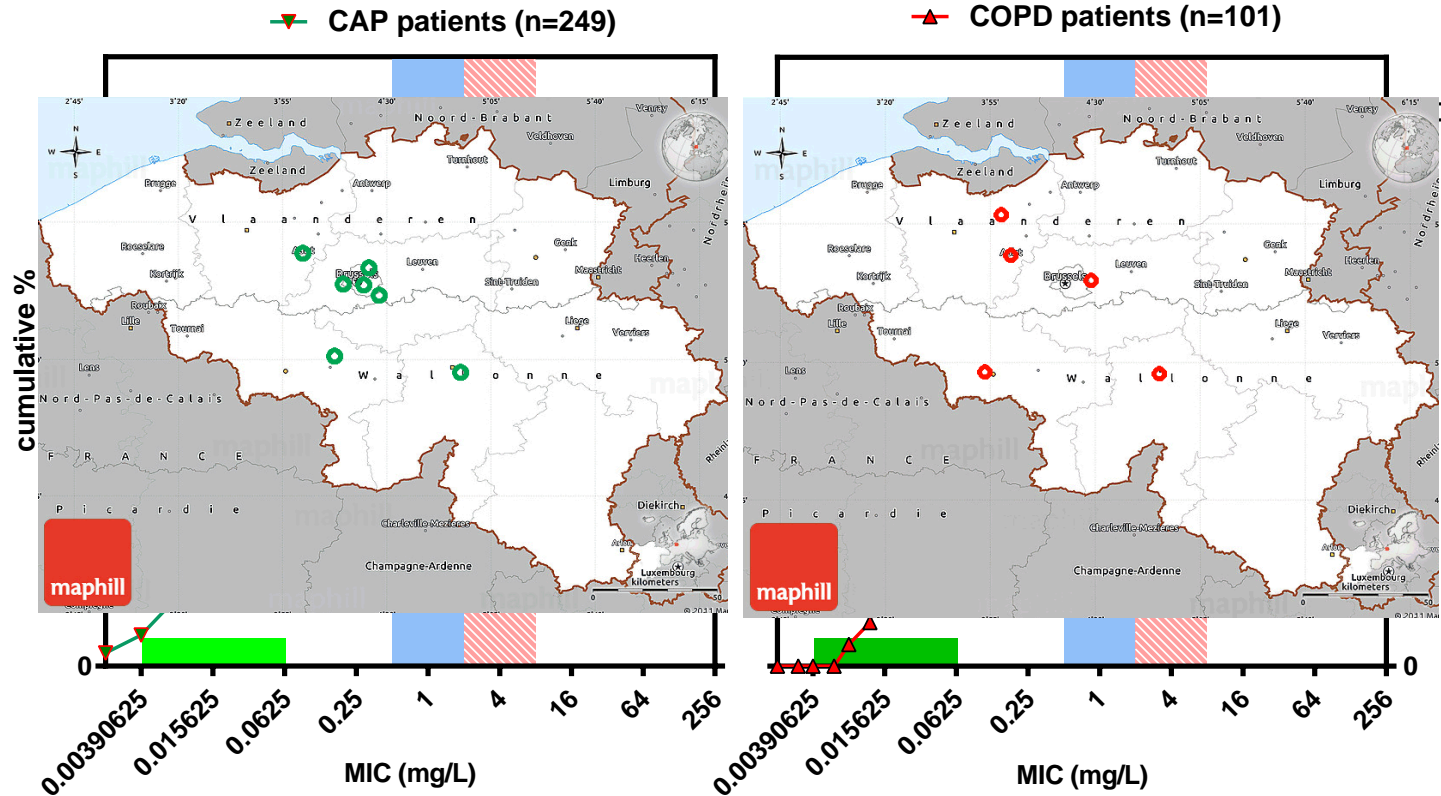


**Figure 1.** Outpatient antibiotic use in Belgium per July-June year expressed as the number of DDDs (diamonds), packages (circles), treatments (squares) and insured individuals (triangles) reimbursed per 1000 inhabitants per day.



# Maar welke patiënten ?

## *S. pneumoniae* amoxicilline gevoeligheid in België



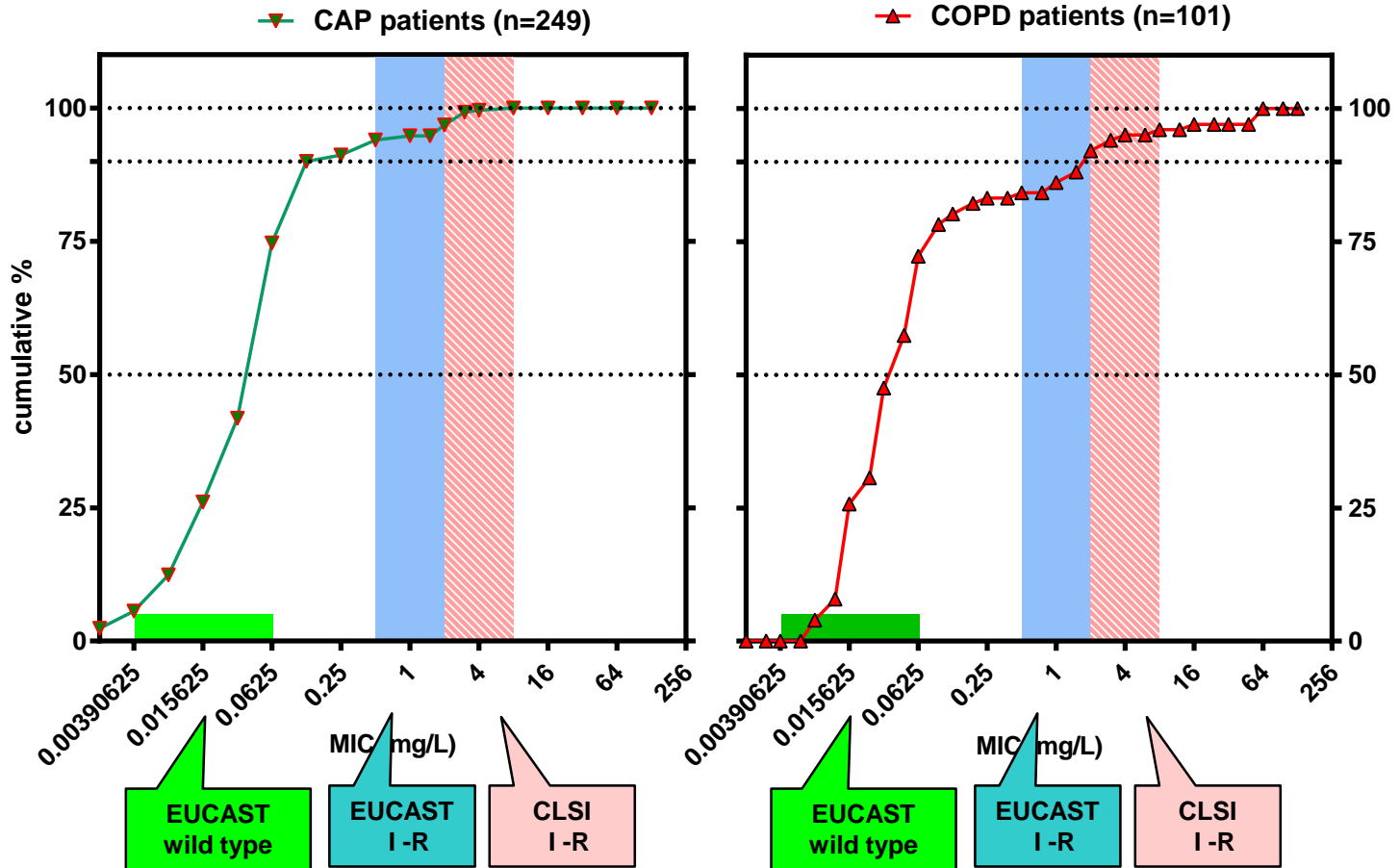
Lismond *et al.* Int J Antimicrob Agents 2012;39:208-16 - PMID: [22245497](https://pubmed.ncbi.nlm.nih.gov/22245497/)

Vandevelde *et al.* Int J Antimicrob Agents 2014;44:209-17 - PMID: [25123808](https://pubmed.ncbi.nlm.nih.gov/25123808/)



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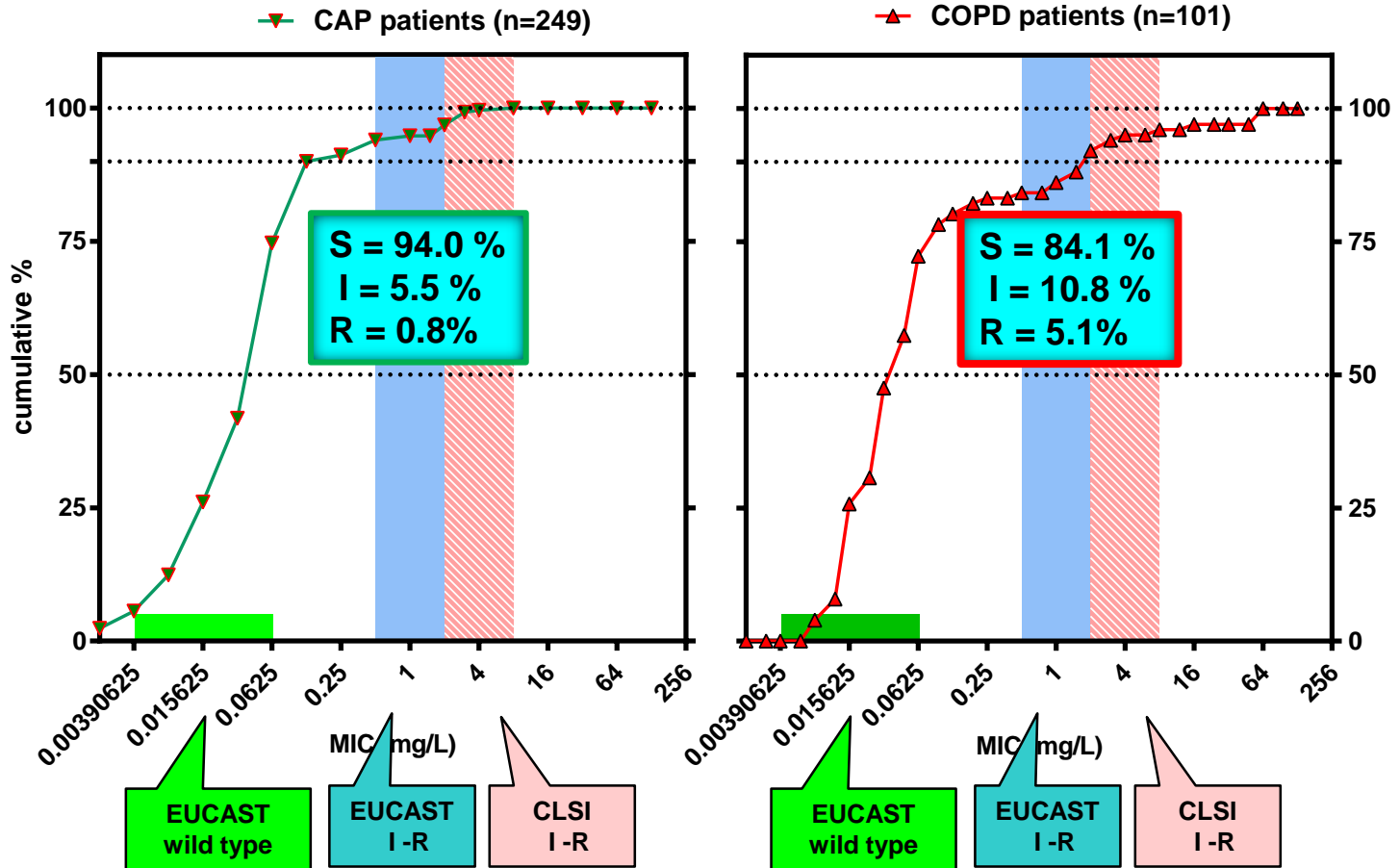


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Vandevelde *et al.* Int J Antimicrob Agents 2014;44:209-17 - PMID: [25123808](https://pubmed.ncbi.nlm.nih.gov/25123808/)

# Vragen over resistentie statistieken...

1. Wat doet U daarmee ? Wanneer stopt U met een antibioticum te gebruiken op een empirische basis?
2. Kan lokale variabiliteit gegeneraliseerd worden naar nationaal vlak?
3. Wat is de correcte noemer (collectie isolaten, geïnfecteerde patiënten, ...)?
4. Zijn datasets bevooroordeeld (ziekenhuis, moeilijk om te behandelen patiënten, ...)?
5. Wie is de gebruiker van de gegevens?

Aangepast en vertaald uit Dalhoff A. Infection (2012) 40:239–262 – PMID: [22460782](#)

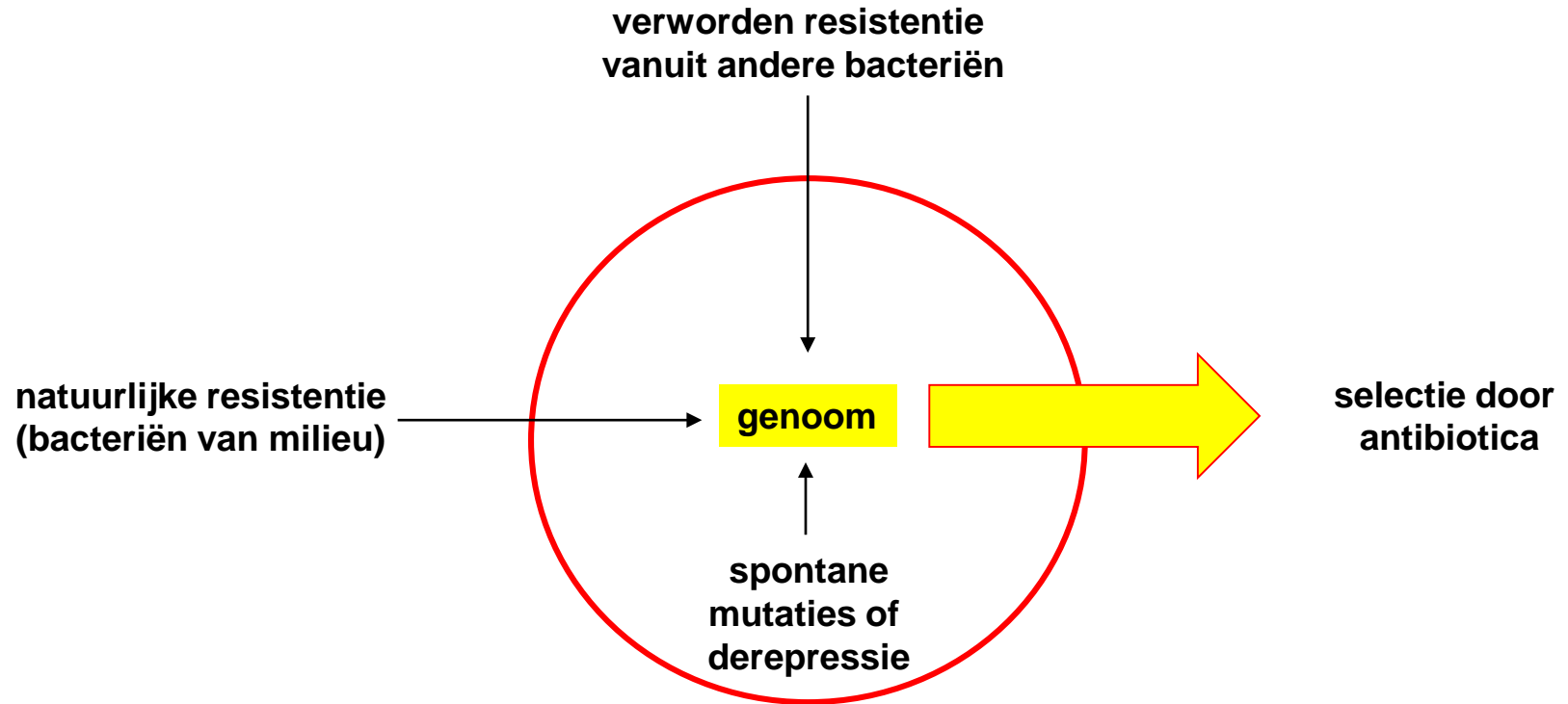
# Een korte (voorlopige) conclusie

- Een directe (eenvoudige) relatie tussen gebruik en resistentie bestaat waarschijnlijk niet...
- **Betere meetschalen** dan het aantal verkochte DDD's of terugbetaalde voorschriften zijn nodig om **meer granulaire relaties** te kunnen ontdekken tussen echt antibioticagebruik en resistentie ...
- Bovendien, het is essentieel de aard (en reden) van de verschillende resistentie mechanismen afzonderlijk te beoordelen...
- Ten laatste, de situatie is totaal verschillend tussen intensieve zorgen (ziekenhuis) en de huisartspraktijk ... waar het grootste aantal van antibiotica gebruikt wordt...

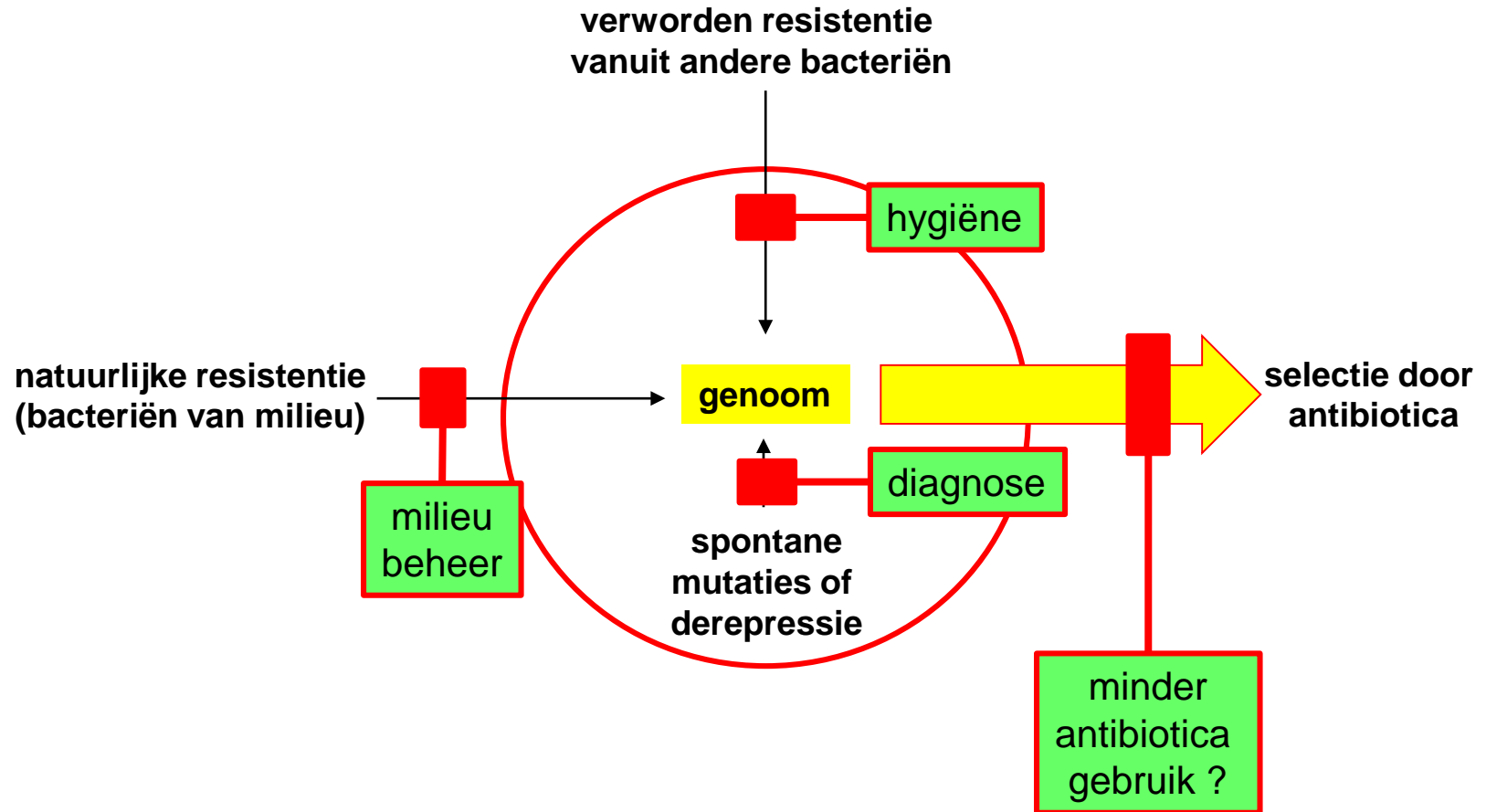
Geen meer globale (blinde ?) resistentie gegevens maar patiëntgeoriënteerde data ...



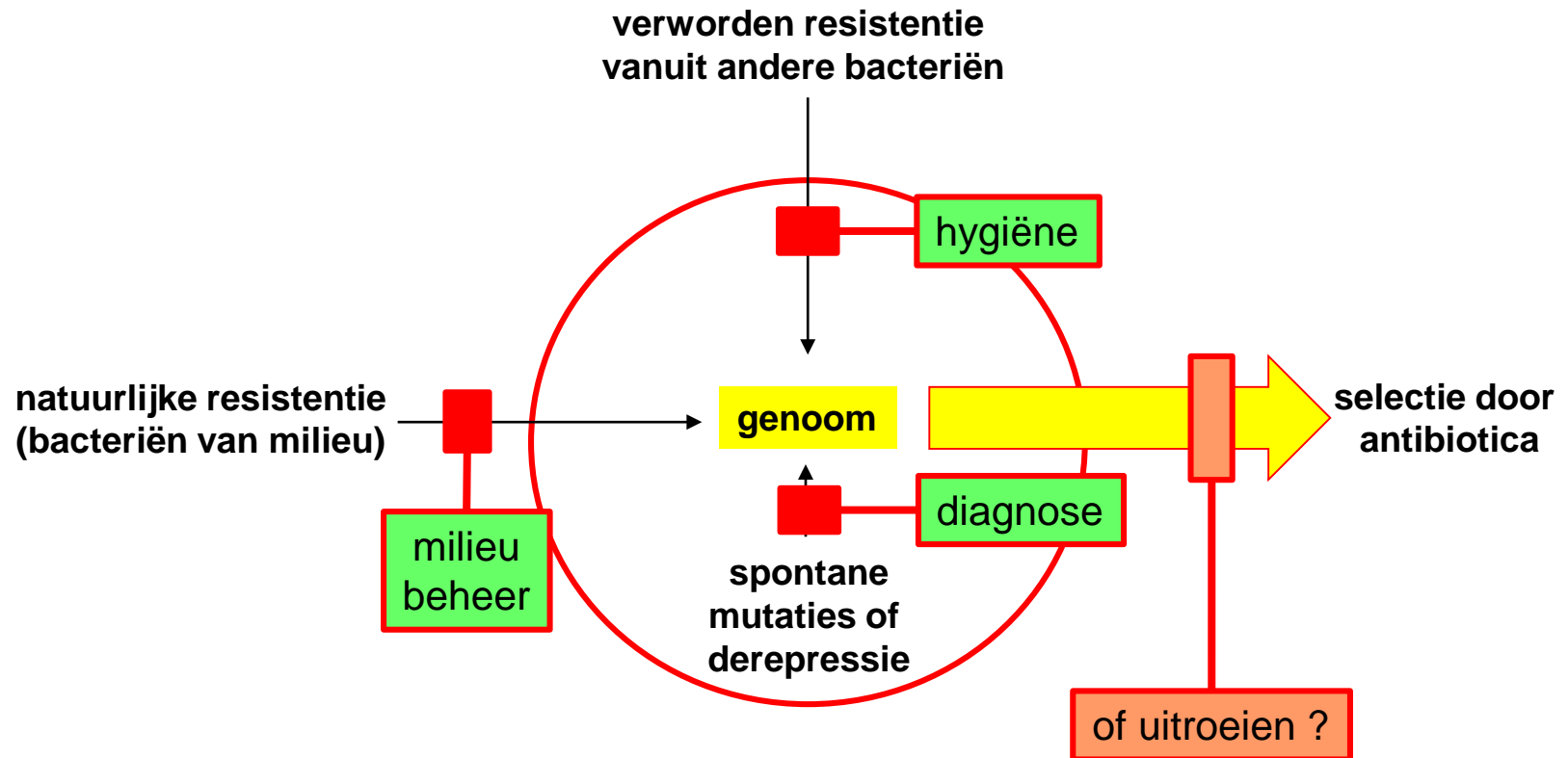
# Hoe ontstaat resistentie?



# Hoe ontstaat resistentie?



# Hoe ontstaat resistentie?

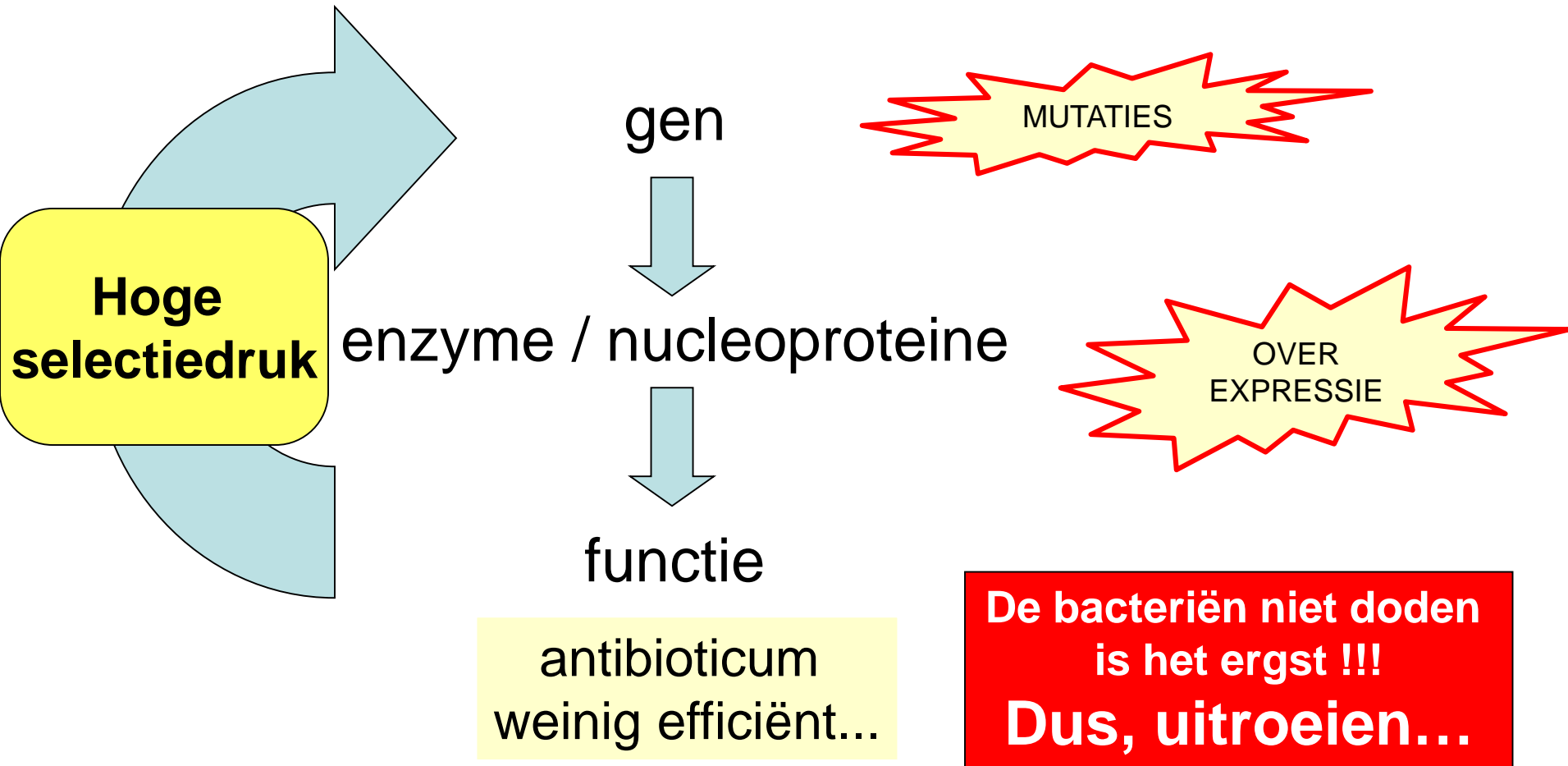


# De vier redenen om bacteriën uit te roeien...

- Dode bacteriën muteren niet meer...  
(eenvoudige toepassing op de principes van Darwin...)
- Als ze dood zijn kunnen ze hun buur niet meer contamineren...  
(basisprincipe van acties in de epidemiologie...)
- Hoe dan ook, als Pasteur gelijk heeft (*en hij heeft gelijk...*), moet men de ziekteverwekker niet uitschakelen om te genezen?  
(fysiopathologisch principe van infectieziekten...)
- Wenst u niet dat uw patiënt veel sneller geneest en voor goed?  
(een tevreden patiënt is er één die niet terugkomt... voor hetzelfde probleem)

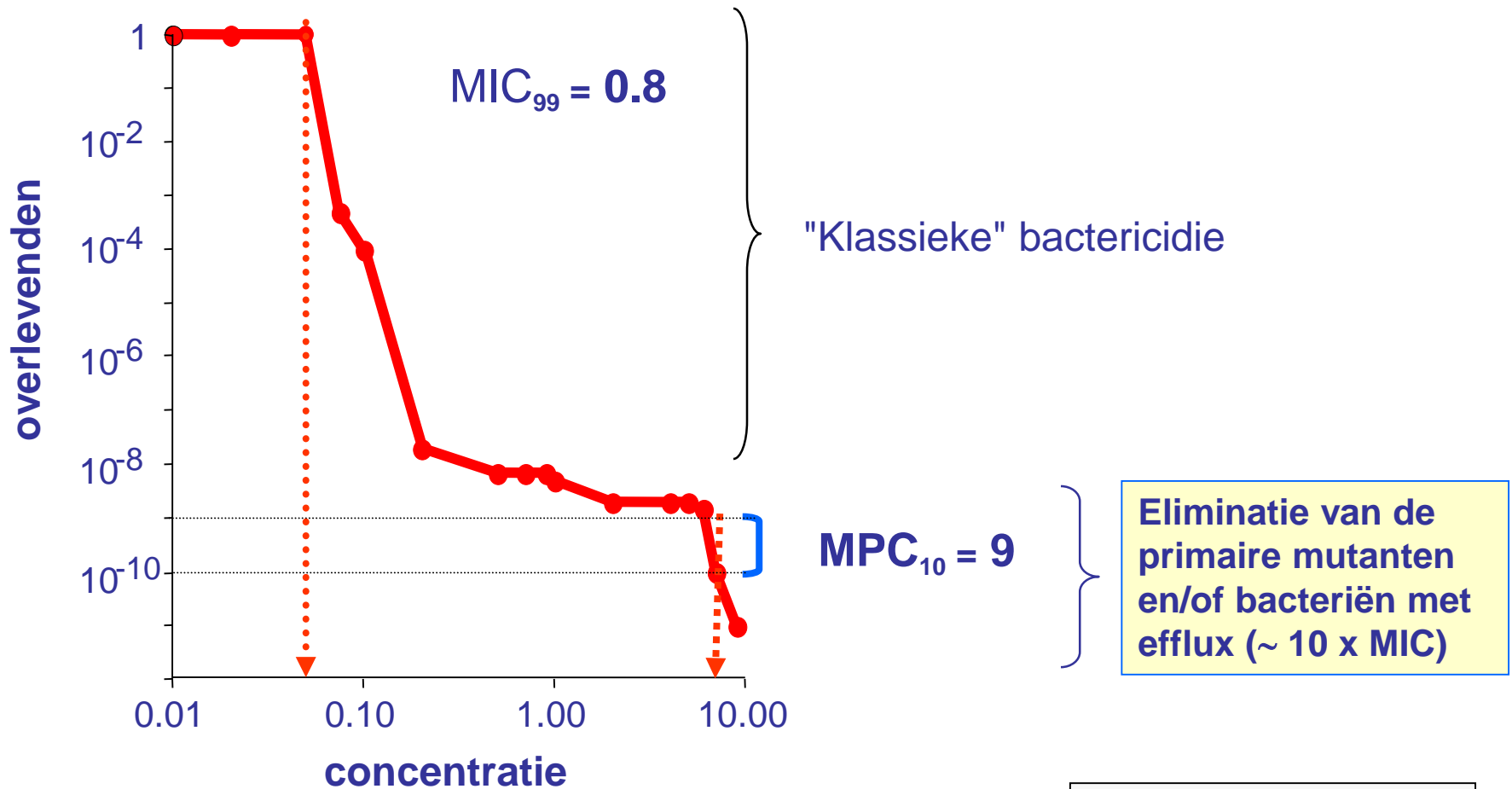


# Selectie van mutanten: de rol van antibiotica...



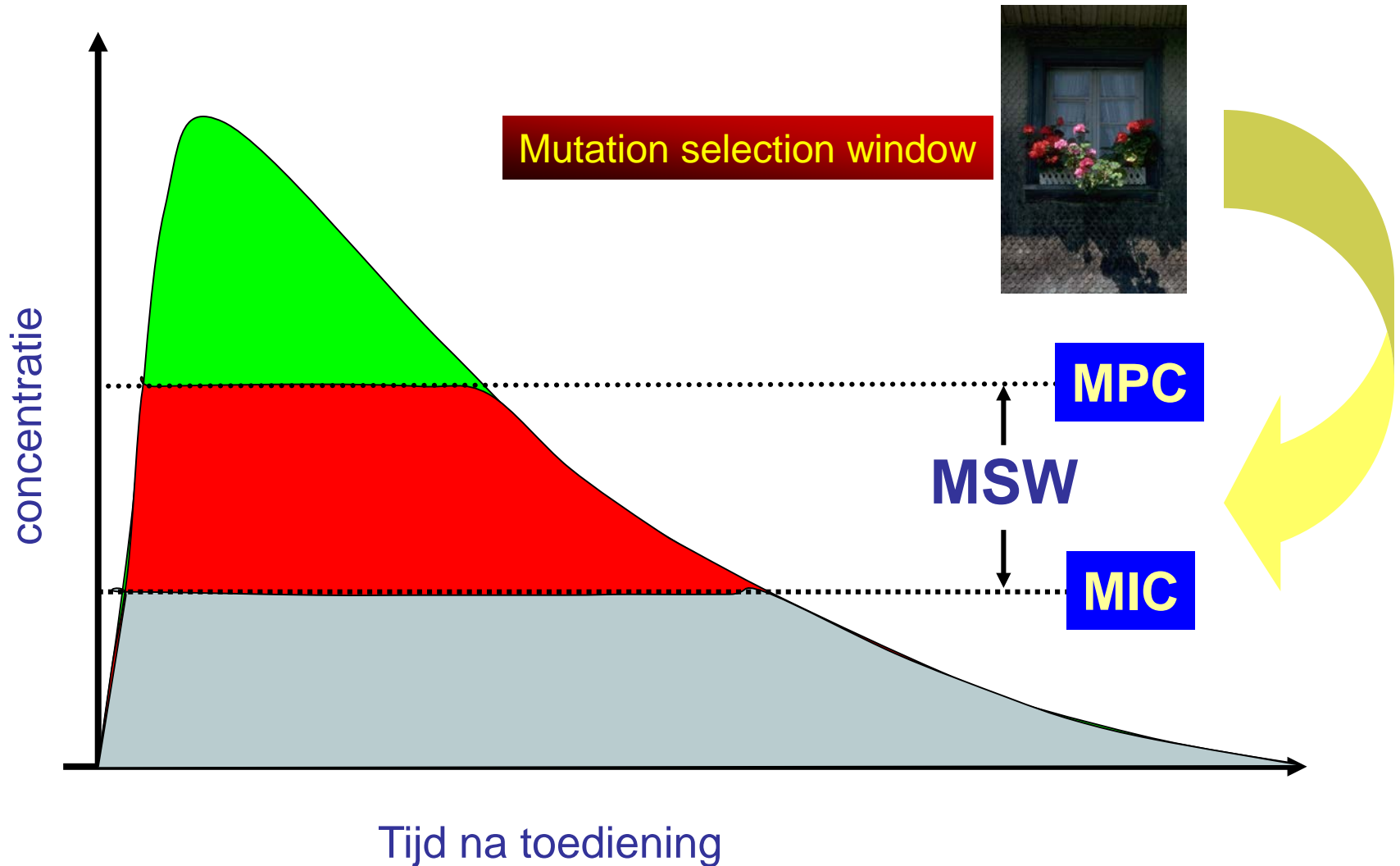
# Concentratie die mutaties / efflux voorkomt... (Mutation Preventing Concentration [MPC])

Voorbeeld: bactericide werking van een FQ tegenover *Mycobacterium bovis*



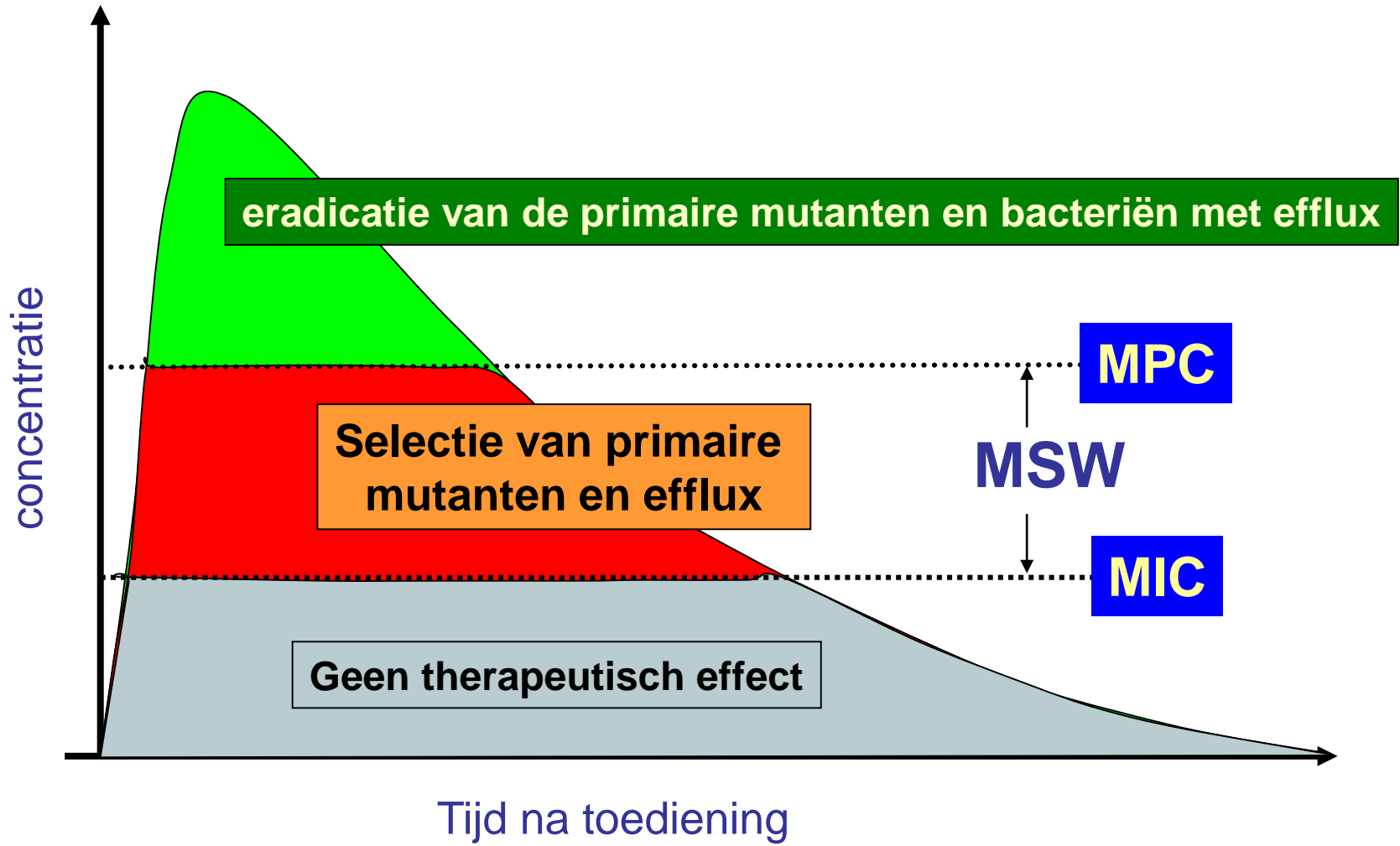
Dong *et al*; AAC 43:1756-1758

# Venster waarbinnen selectie van mutaties en efflux plaats vindt...



concept overgenomen van Drlca & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

# Venster waarbinnen selectie van mutaties plaats vindt...



concept overgenomen van Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

# Oorsprong van resistentie gedurende de behandeling

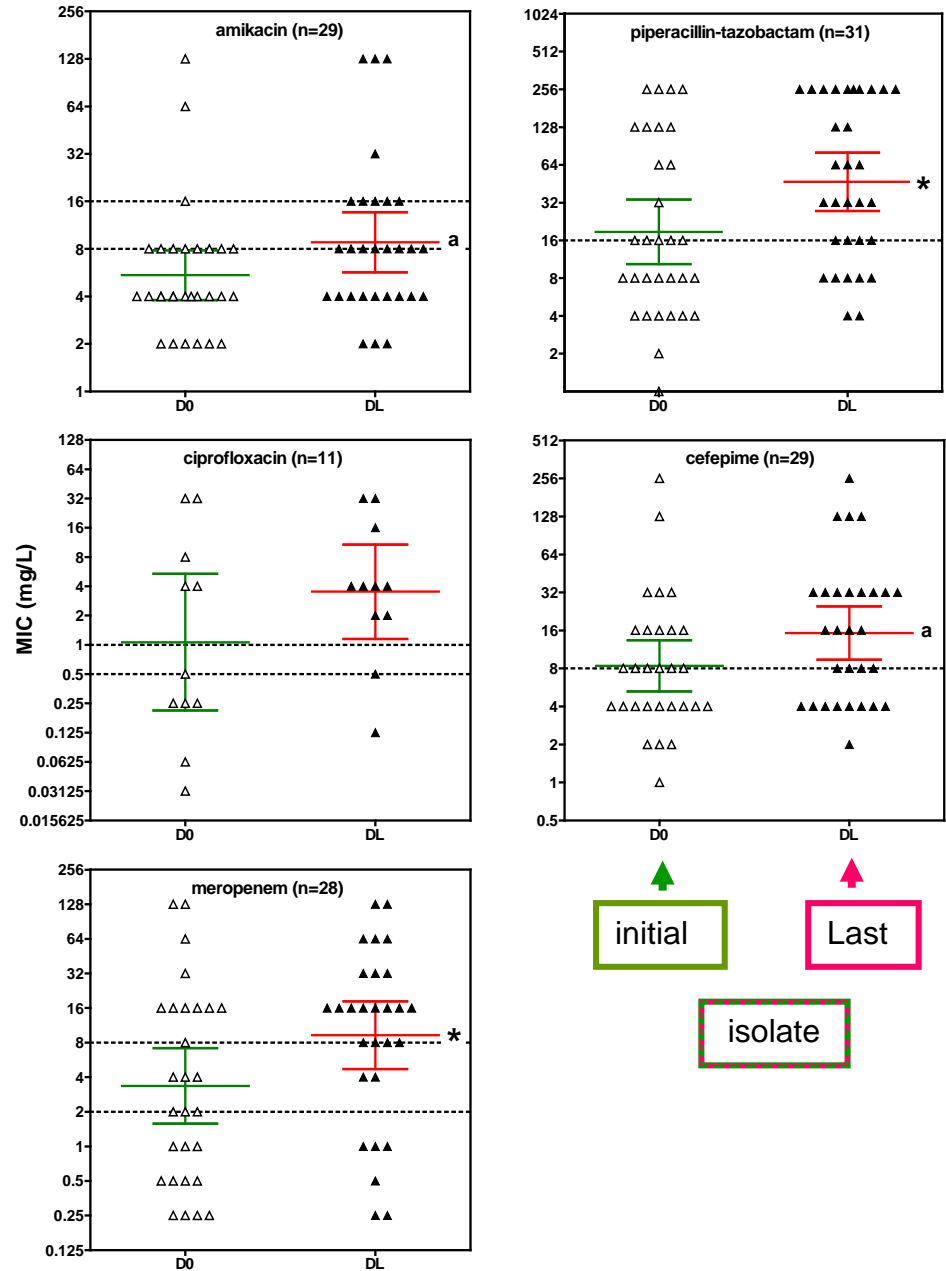
*P. aeruginosa* successive clonal isolates from the same patient (all patients treated with large doses of 1 to 3 antibiotics)

- D0: initial isolate
- DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

\*  $p < 0.05$  by paired t-test (two-tailed) and Wilcoxon non-parametric test

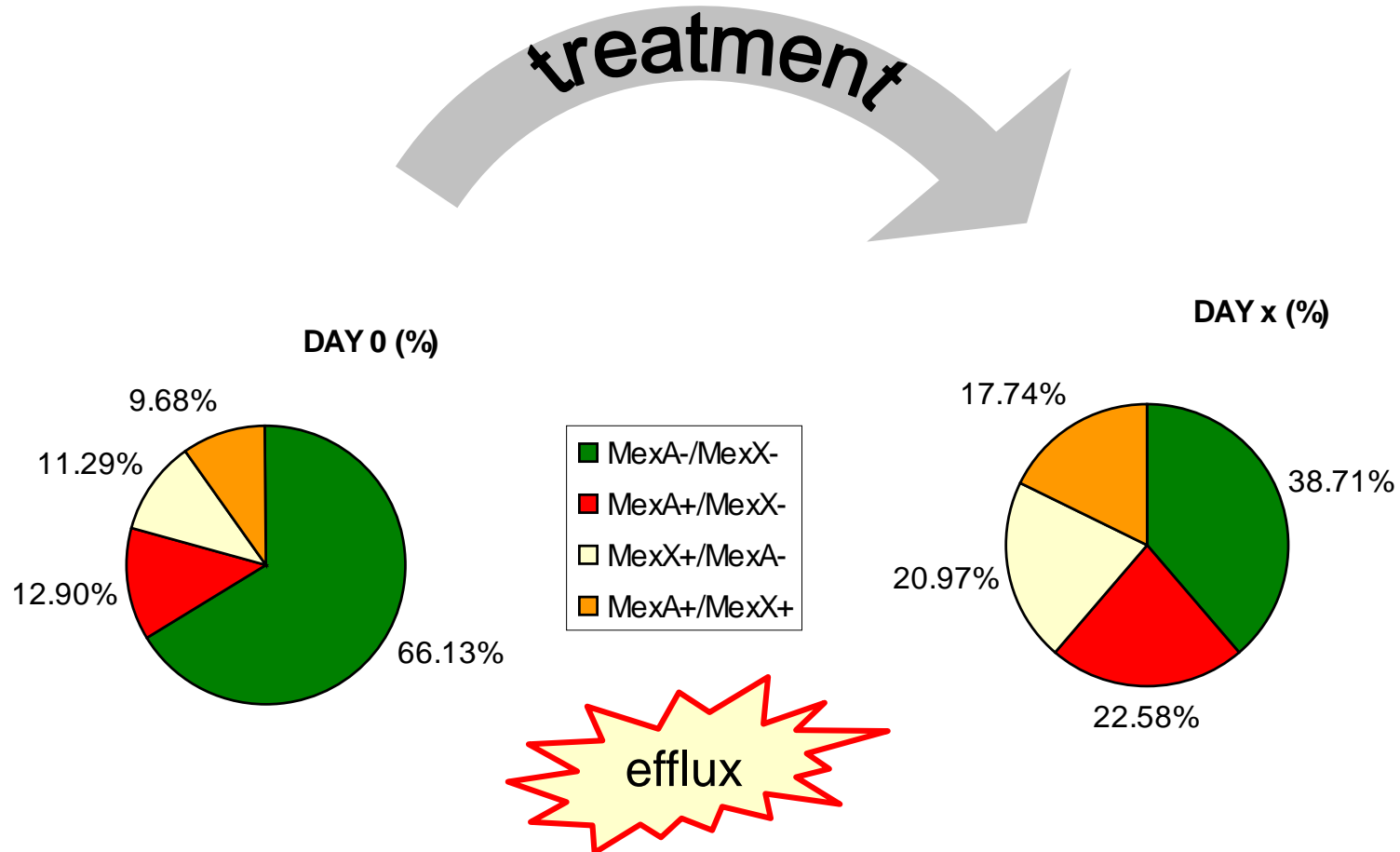
<sup>a</sup>  $p < 0.05$  by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)



# Een mechanisme van MIC verhoging tijdens antibiotica behandeling

Prevalence of MexA and MexX overexpressers in 62 phylogenetically-related pairs of *P. aeruginosa* isolated from ICU patients (VAP)



Riou *et al.* Int J Antimicrob Agents 2016;47:77-83 - PMID: [26691019](https://pubmed.ncbi.nlm.nih.gov/26691019/)

# PK/PD en resistentie: toepassing voor chinolonen

## Preventie van resistentie en doeltreffendheid:

- $\text{piek} / \text{MIC} > 10$   
(om de MPC te bereiken)
- $\text{AUC} / \text{MIC} > 100$   
(niet volledig immuuncompetente patiënt)



pieken en bruggen ...

Nota: dit kan ook het geval zijn door te lage  $\text{AUC}_{24\text{h}}$  voor

- vancomycine (selectie van zogenaamd "hetero-VISA")
- tigecycline en macroliden (over-expressie of efflux pompen)

# AUC<sub>24h</sub> / MIC = 125 en Piek / MIC > 10 als limietwaarden voor de gevoeligheid aan FQ

Drug	Typical daily dosage <sup>a</sup>	Typical PK values		Proposed PK/PD upper limit of sensitivity (µg/ml) for	
		C <sub>max</sub> in mg/L total/free (dose)	AUC <sub>24 h</sub> (mg × h/L) total/free	Efficacy <sup>b</sup>	Prevention of resistance <sup>c</sup>
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.  
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423



# Resistentie... *The last frontier* ?

## **Application of a mathematical model to prevent in vivo amplification of antibiotic-resistant bacterial populations during therapy**

Nelson Jumbe,<sup>1,2</sup> Arnold Louie,<sup>1</sup> Robert Leary,<sup>3</sup> Weiguo Liu,<sup>2</sup> Mark R. Deziel,<sup>1</sup> Vincent H. Tam,<sup>1</sup> Reetu Bachhawat,<sup>2</sup> Christopher Freeman,<sup>2</sup> James B. Kahn,<sup>4</sup> Karen Bush,<sup>5</sup> Michael N. Dudley,<sup>6</sup> Michael H. Miller,<sup>2</sup> and George L. Drusano<sup>1</sup>

<sup>1</sup>Ordway Research Institute, Albany, New York, USA

<sup>2</sup>Center for Immunology and Microbial Diseases, Albany Medical College, Albany, New York, USA

<sup>3</sup>San Diego Supercomputer Center, University of California, San Diego, San Diego, California, USA

<sup>4</sup>Ortho-McNeil Pharmaceutical, Raritan, New Jersey, USA

<sup>5</sup>Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey, USA

<sup>6</sup>Essential Therapeutics Inc., Mountain View, California, USA

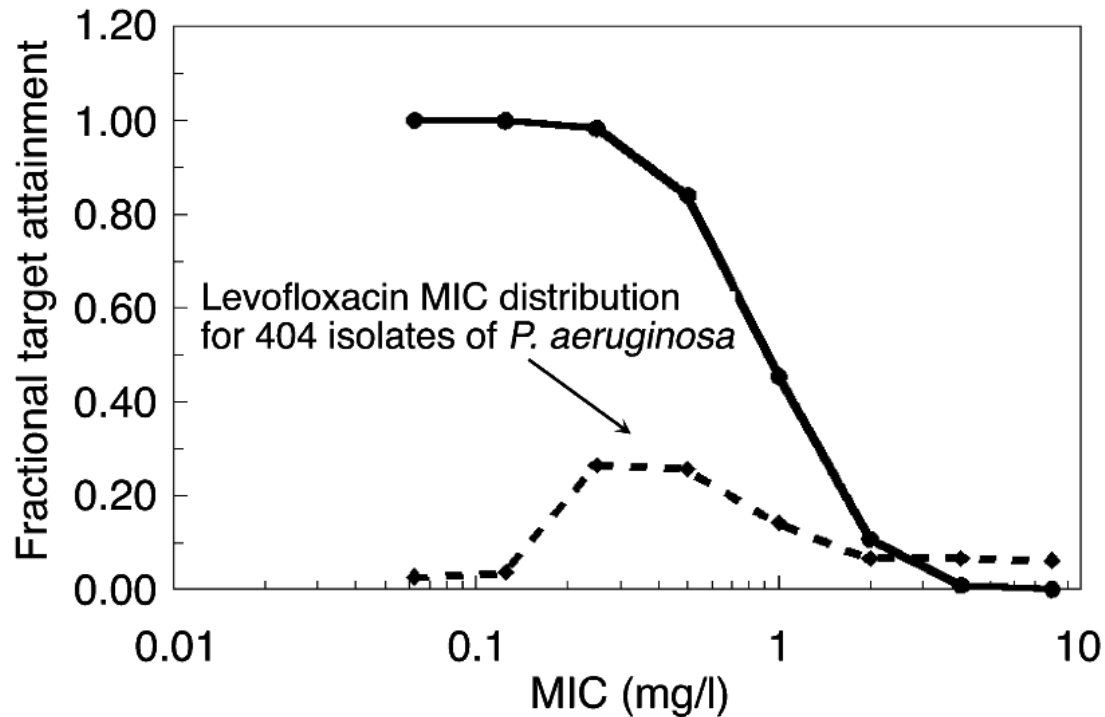
Jumbe *et al.* J Clin Invest. 2003;112:275-85 - PMID: [12865415](https://pubmed.ncbi.nlm.nih.gov/12865415/)

# Resistentie... *The last frontier?*

## Application of a mathematical model to prevent in vivo amp bacterial po

Nelson Jumbe,<sup>1,2</sup>  
Vincent H. Tam,<sup>3</sup>  
Karen Bush,<sup>5</sup> Mic

<sup>1</sup>Ordway Research Instit  
<sup>2</sup>Center for Immunolog  
<sup>3</sup>San Diego Supercompu  
<sup>4</sup>Ortho-McNeil Pharma  
<sup>5</sup>Johnson & Johnson Ph  
<sup>6</sup>Essential Therapeutics



**Figure 6**

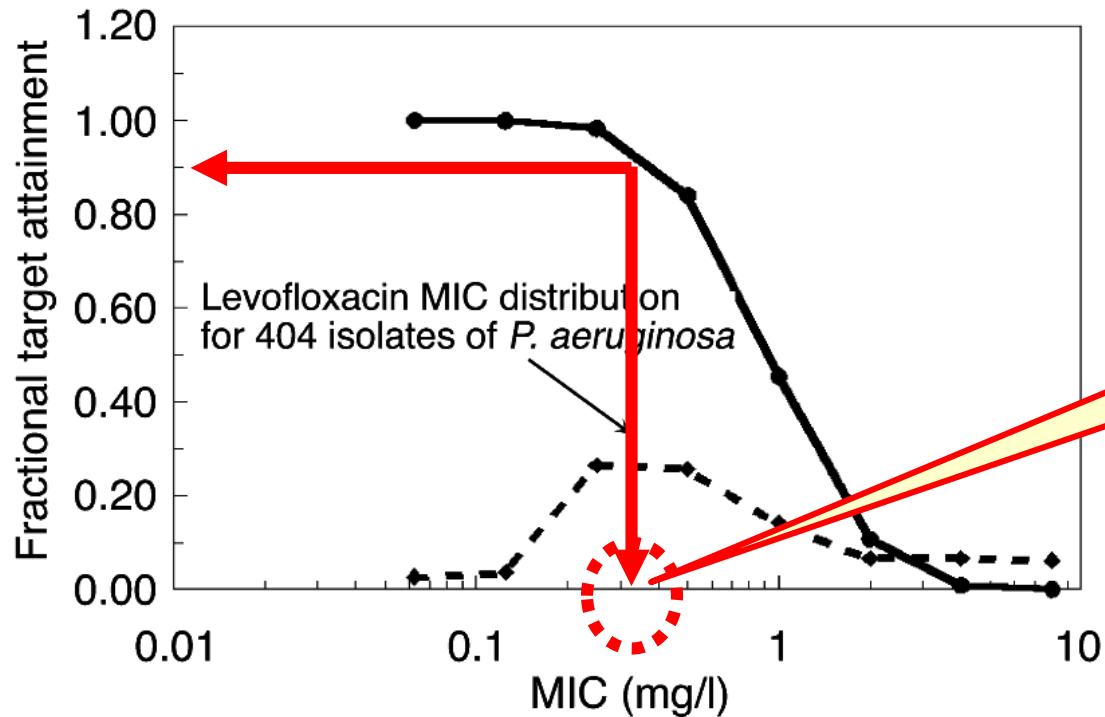
Target-attainment analysis. The fraction of 10,000 simulated subjects that attained an AUC/MIC ratio of 157:1 (target for suppression of resistance) is displayed as a function of the MIC for a distribution of 404 isolates of *P. aeruginosa*.

# Resistentie... *The last frontier?*

## Application of a mathematical model to prevent in vivo amp bacterial po

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**Figure 6**

Target-attainment analysis. The fraction of 10,000 simulated subjects that attained an AUC/MIC ratio of 157:1 (target for suppression of resistance) is displayed as a function of the MIC for a distribution of 404 isolates of *P. aeruginosa*.

# Resistentie... *The last frontier* ?

EUCAST Clinical Breakpoint Tables v. 7.1, valid from 2017-03-10  
*Pseudomonas* spp.

Fluoroquinolones	MIC breakpoint (mg/L)	
	S ≤	R >
Ciprofloxacin <sup>1</sup>	0.5	0.5
Levofloxacin <sup>2</sup>	1	1

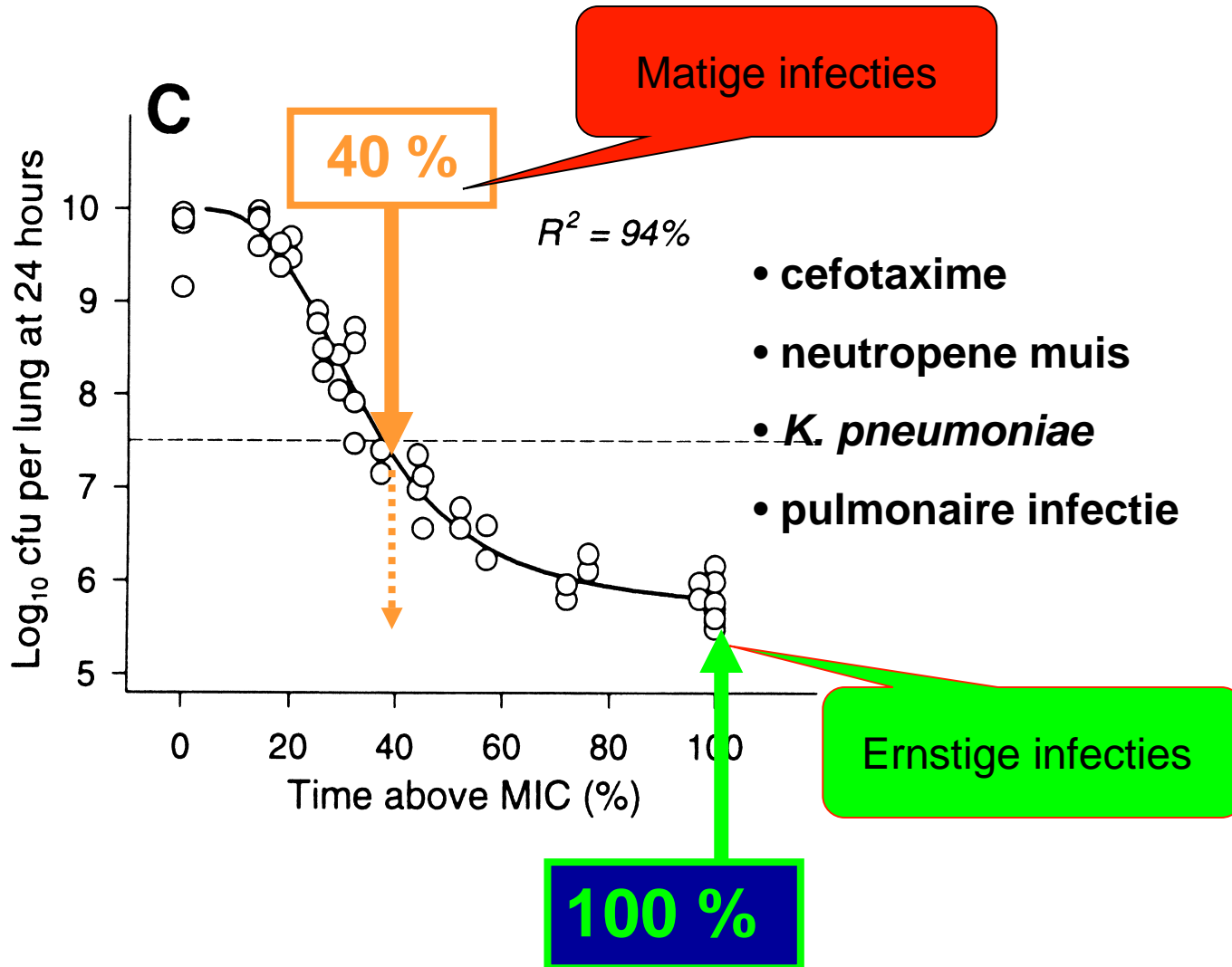
het probleem is dat het "resistentie" breekpunt van 0.3 mg/L voor levofloxacin **VEEL lager** zal worden dan de CLSI en/of EUCAST doeltreffendheid breekpunten ...

Table 2B-1  
*Pseudomonas aeruginosa*  
 M02 and M07

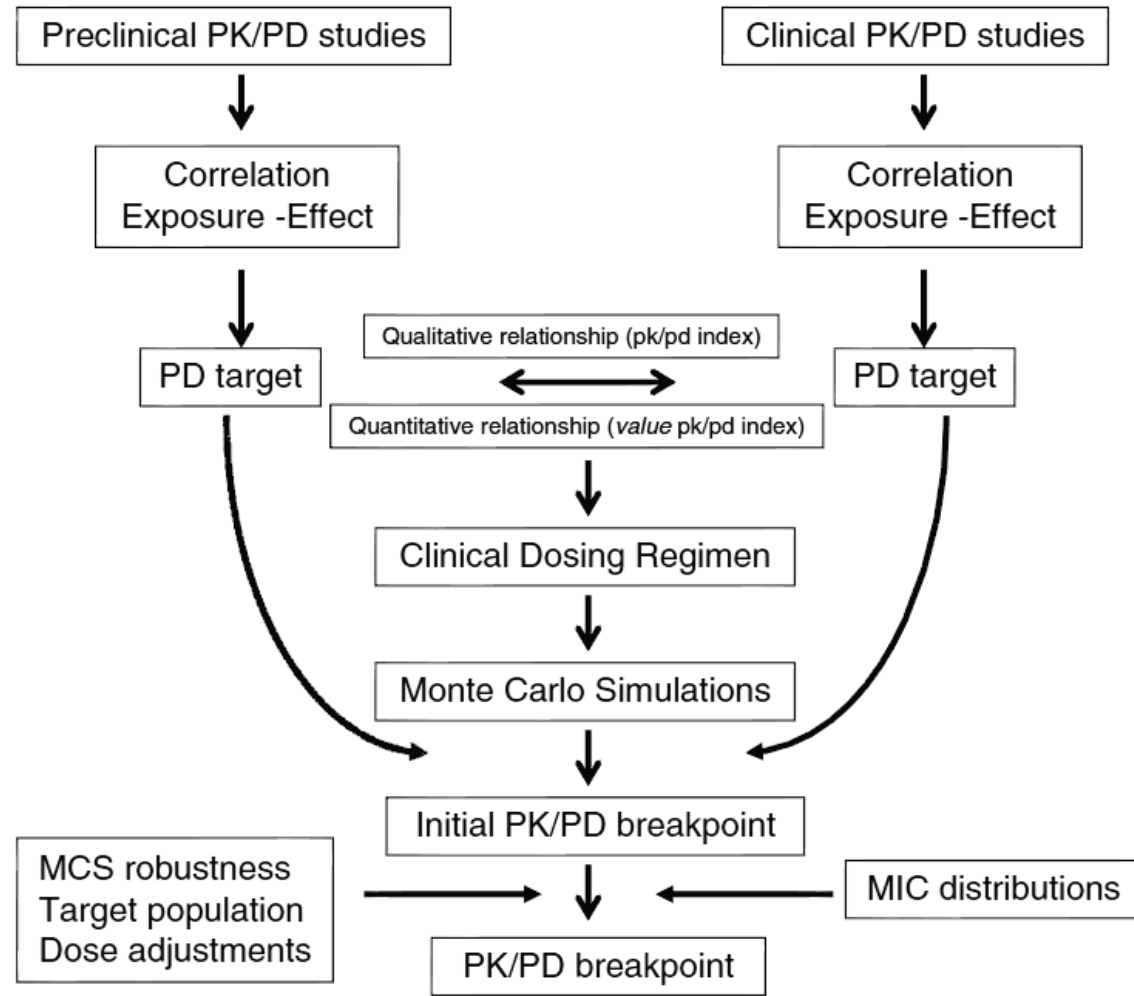
Table 2B-1. (Continued)

Antimicrobial Agent	MIC Interpretive Criteria (µg/mL)		
	S	I	R
<b>FLUOROQUINOLONES</b>			
Ciprofloxacin	≤ 1	2	≥ 4
Levofloxacin	≤ 2	4	≥ 8

# β-lactams: aanpak

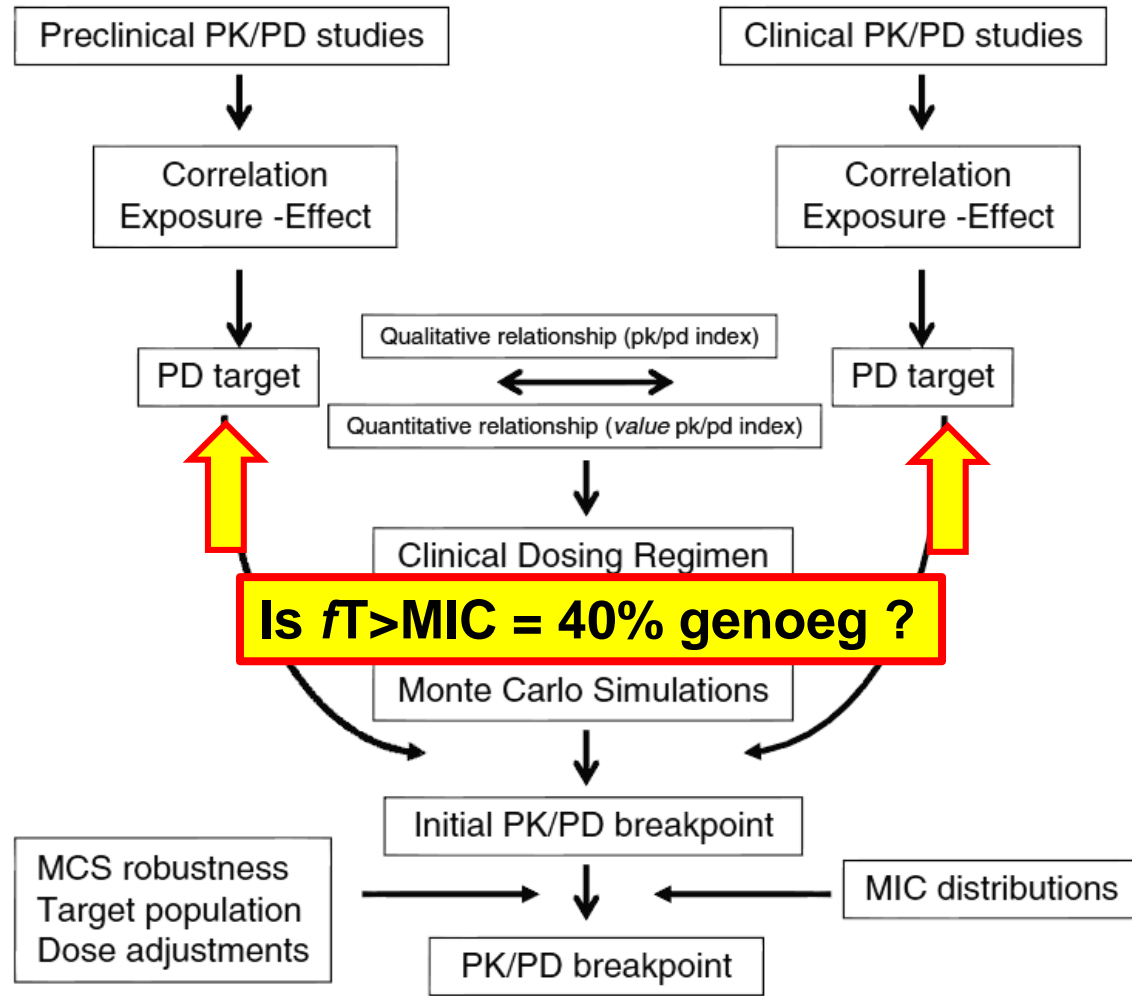


# Breekpunten instelling: de EUCAST weg



**Fig. 3.4** Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

# Breekpunt instelling...



**Fig. 3.4** Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

# Een voorstel voor $\beta$ -lactams?

*J Antimicrob Chemother* 2017; **72**: 1421–1428  
doi:10.1093/jac/dkx001 Advance Access publication 31 January 2017

Journal of  
Antimicrobial  
Chemotherapy

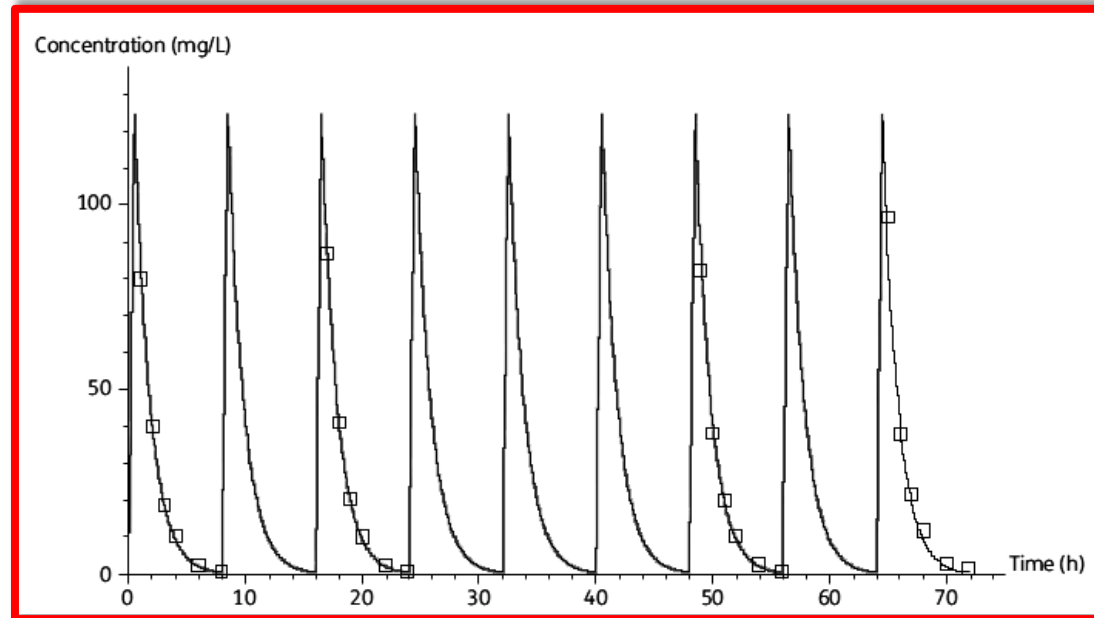
## Determining $\beta$ -lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam<sup>1\*</sup>, Kai-Tai Chang<sup>1</sup>, Jian Zhou<sup>1</sup>, Kimberly R. Ledesma<sup>1</sup>, Kady Phe<sup>1</sup>, Song Gao<sup>1</sup>,  
Françoise Van Bambeke<sup>2</sup>, Ana María Sánchez-Díaz<sup>3</sup>, Laura Zamorano<sup>4</sup>, Antonio Oliver<sup>4</sup> and Rafael Cantón<sup>3</sup>

<sup>1</sup>University of Houston, Houston, TX, USA; <sup>2</sup>Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; <sup>3</sup>Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; <sup>4</sup>University Hospital Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain

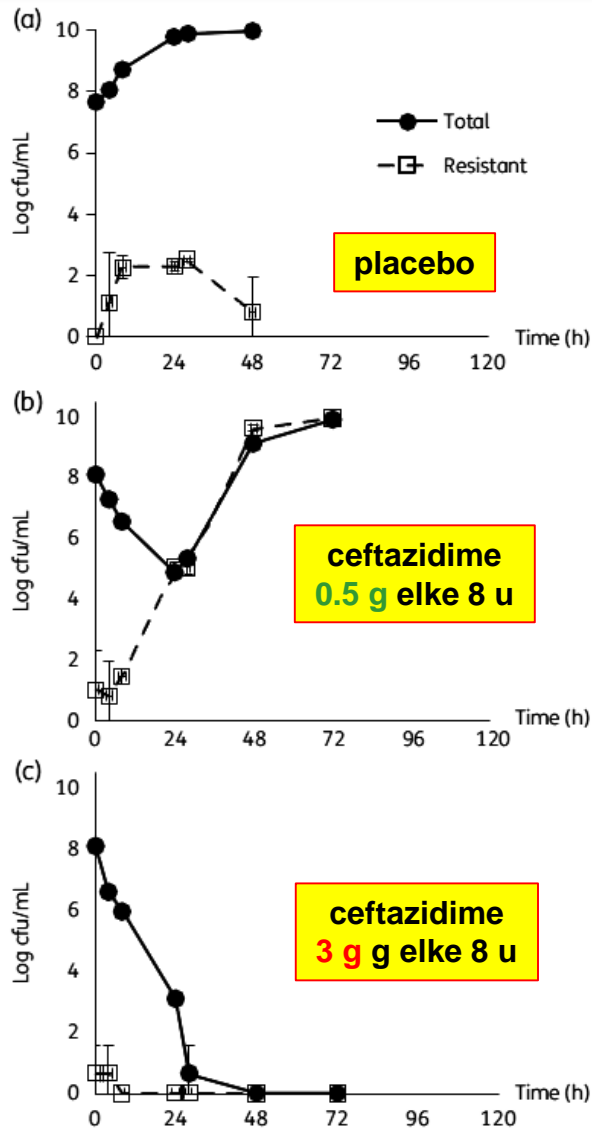
Tam *et al.* *J Antimicrob Chemother* 2017;72:1421-1428 - PMID: [28158470](https://pubmed.ncbi.nlm.nih.gov/28158470/)

Verschillende doses en blootstellingen van  $\beta$ -lactams werden gesimuleerd in een holvezel (*hollow fiber*) infectiemodel

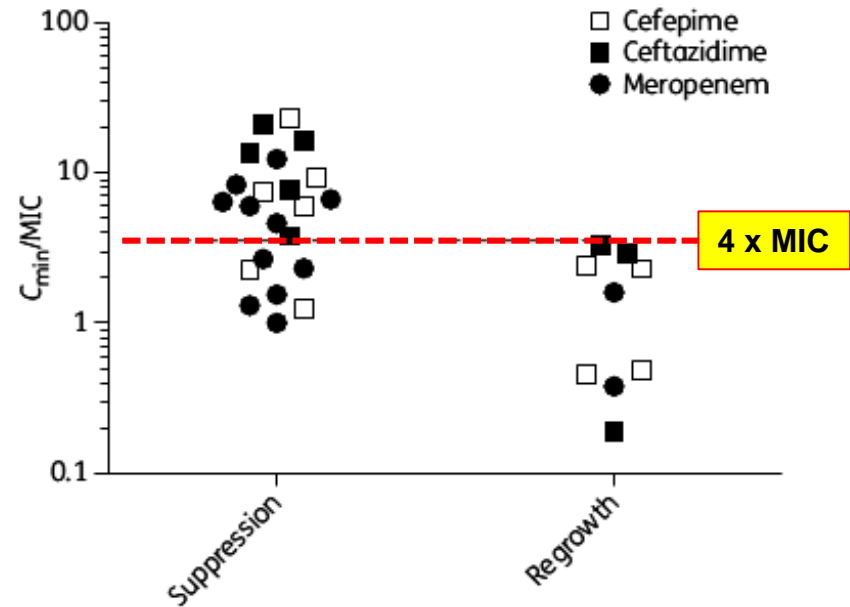




# Een voorstel voor $\beta$ -lactams?



**Figure 2.** Typical bacterial profiles for WT *P. aeruginosa*. Placebo control (a). Ceftazidime at 500 mg every 8 h ( $C_{min}/MIC = 2.9$ ) (b). Ceftazidime at 3000 mg every 8 h ( $C_{min}/MIC = 7.7$ ) (c). Data are shown as mean  $\pm$  SD.



**Figure 3.** Drug exposures ( $C_{min}/MIC$ ) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold ( $C_{min}/MIC \geq 3.8$ ) is depicted by the horizontal broken line.

**Om resistentie te voorkomen, moet de  $C_{min}$  van  $\beta$ -lactams  $> 4 \times MIC$  (gemiddelde) blijven ... wat hogere doseringen dan goedgekeurd vraagt...**

# Wat kan resistentie op Intensieve Zorgen veroorzaken ... en wat kunt U daar doen ?

- Totaal aantal antibiotica ?

**Ja, maar niet de enige reden...**

- Te breed spectrum antibiotica ?
  - neveneffecten op de commensaal flora
  - resistentie in "non-target" doelwitten

**Het is nu tijd voor betere en sneller diagnostica...**

- Te lage dosering ?
  - onvoldoende uitroeien van het "target" doelwit
  - gemakkelijke selectie van een laag niveau van resistentie (efflux, bv.) die tot een hoog niveau van resistentie kan leiden

**Denk aan TDM...**

- $\beta$ -lactamen
- chinolonen
- linezolid

- Te lange behandeling ?
  - meer kans voor selectie van resistente organismen
  - accumulatie van mutaties en expressie veranderingen

**Gebruik van voorspellende infectie biomarkers**



# Biomarkers ?

---

## Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial



*Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lenneke E Haas, Bert G Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Elsen, Jeroen A Schouten, Jörn O Streefkerk, Hans G Krabbe, Hans Kieft, Georg H Kluge, Veerle C van Dam, Joost van Pelt, Laura Bormans, Martine Bokelman Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Ewoudt MW van de Garde, Anne Marie G A de Smet, Jozef Kesecioglu, Armand R Girbes, Maarten W Nijsten, Dylan W de Lange*

Lancet Infect Dis. 2016; 16:819-827 - PMID: [26947523](https://pubmed.ncbi.nlm.nih.gov/26947523/)

# Biomarkers ?

Efficacy  
duration  
a rare

Evelien de  
Gertrude C  
Hans Kieft  
Jos W Twiss

Lancet Infect

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
<b>Antibiotic consumption (days)</b>				
Daily defined doses in first 28 days	7.5 (4.0 to 12.8)	9.3 (5.0 to 16.5)	2.69 (1.26 to 4.12)	<0.0001
Duration of treatment	5.0 (3.0 to 9.0)	7.0 (4.0 to 11.0)	1.22 (0.65 to 1.78)	<0.0001
Antibiotic-free days in first 28 days	7.0 (0.0 to 14.5)	5.0 (0 to 13.0)	1.31 (0.52 to 2.09)	0.0016
<b>Mortality (%)</b>				
28-day mortality	149 (19.6%)	196 (25.0%)	5.4% (1.2 to 9.5)	0.0122
1-year mortality	265 (34.8%)	321 (40.9%)	6.1% (1.2 to 10.9)	0.0158
<b>Adverse events</b>				
Reinfection	38 (5.0)	23 (2.9)	-2.1% (-4.1 to -0.1)	0.0492
Repeated course of antibiotics	175 (23.0)	173 (22.0)	-1.0% (-5.1 to 3.2)	0.67
Time (days) between stop and reinstitution of antibiotics	4.0 (2.0 to 8.0)	4.0 (2.0 to 8.0)	-0.22 (-1.31 to 0.88)	0.96
<b>Costs</b>				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33.6 (2.5 to 64.8)	0.0006
<b>Length of stay (days)</b>				
On the intensive care unit	8.5 (5.0 to 17.0)	9.0 (4.0 to 17.0)	-0.21 (-0.92 to 1.60)	0.56
In hospital	22.0 (13.0 to 39.3)	22.0 (12.0 to 40.0)	0.39 (-2.69 to 3.46)	0.77

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA=not applicable.

**Table 2: Primary and secondary outcome measures**

# Biomarkers en vermindering van antibiotica gebruik

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)
Daily defined doses in first 28 days	7.5 (4.0 to 12.8)	9.3 (5.0 to 16.5)
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**Table 2: Primary and secondary outcome measures**

# Waar zijn we nu ?



# Wat doe wij nu ?

Tijdens een wandeling door Rotterdam...



# Het was misschien een fabeltje... en ik heb (zeker) veel belangrijke punten vergeten...

stel dus  
maar  
vragen !



Dias beschikbaar op <http://www.facm.ucl.ac.be/> → Lectures → in het Nederlands