



UiO : Det medisinske fakultet



Vi har tenkt på fremtiden i 200 år



Is it possible to reverse antibiotic resistance?

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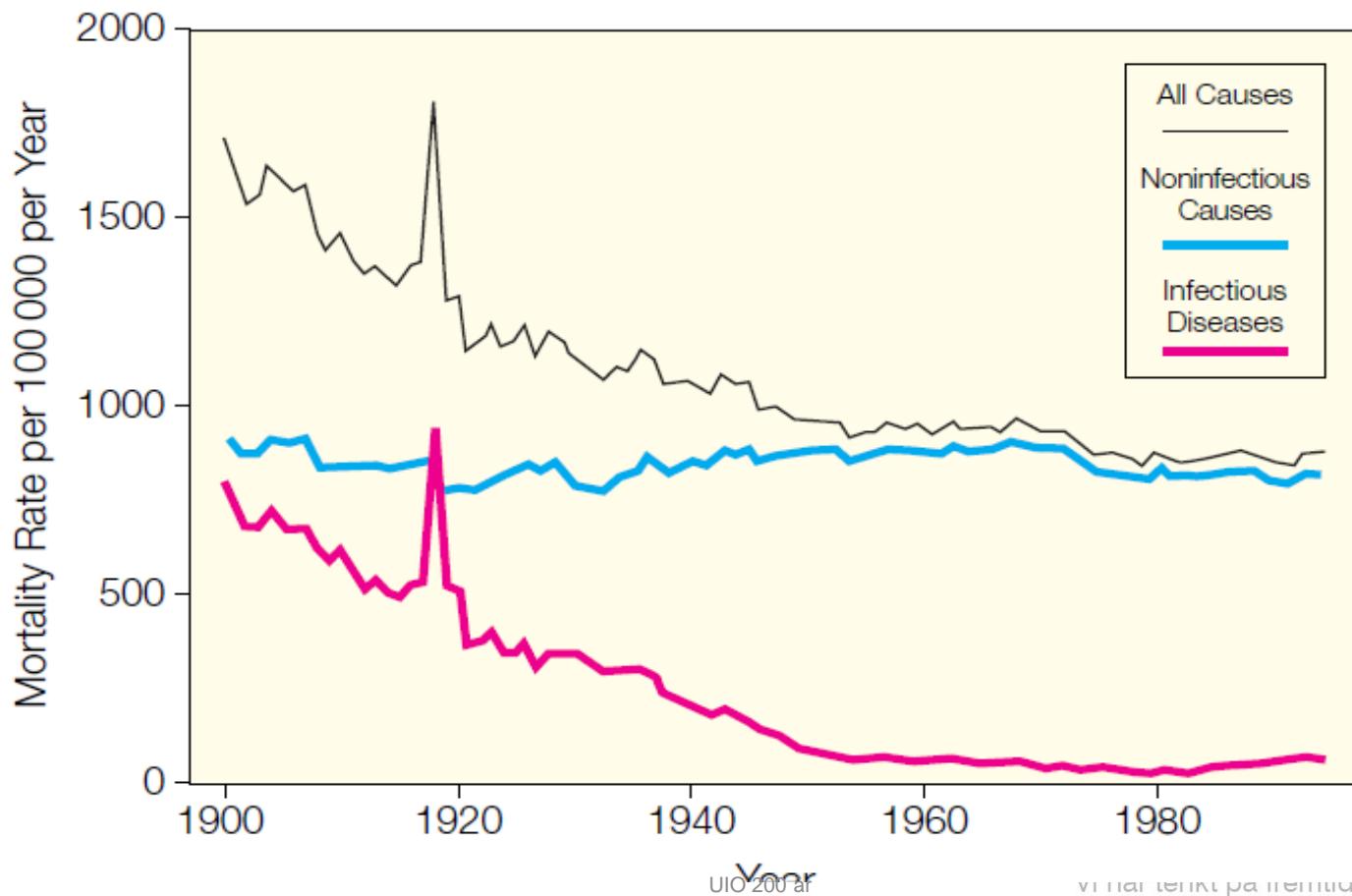
«Take home messages»

- All use of antibiotics (AB) leads to resistance
- All antibiotic changes the normal bacteriological flora
- It is unethical to overuse AB
- We probably can reverse AB-resistance



Mortality rate USA 1900-2000. Armstrong. JAMA

Figure 2. Crude Mortality Rates for All Causes, Noninfectious Causes, and Infectious Diseases



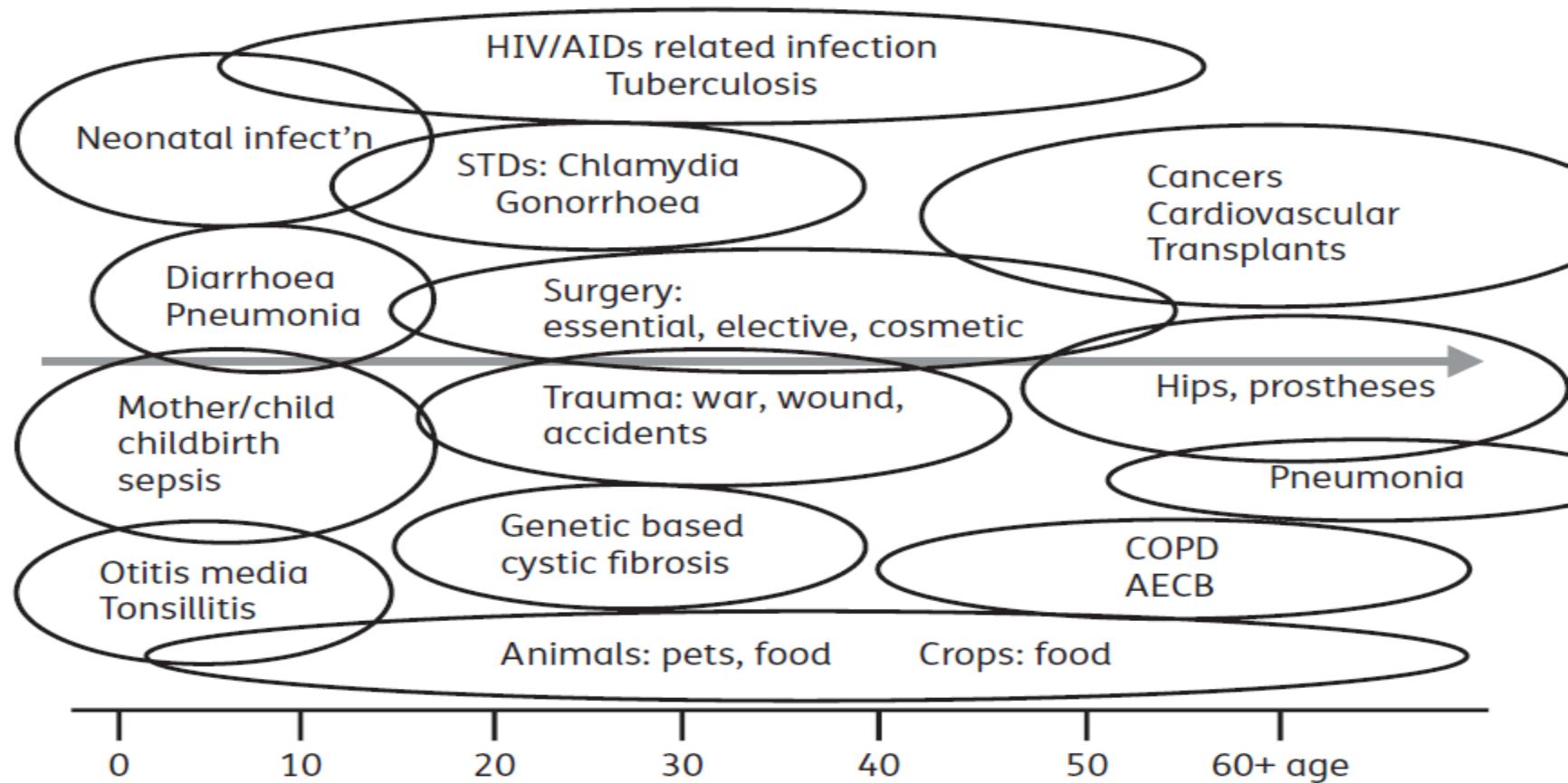


Antibiotic mediated reduction in mortality

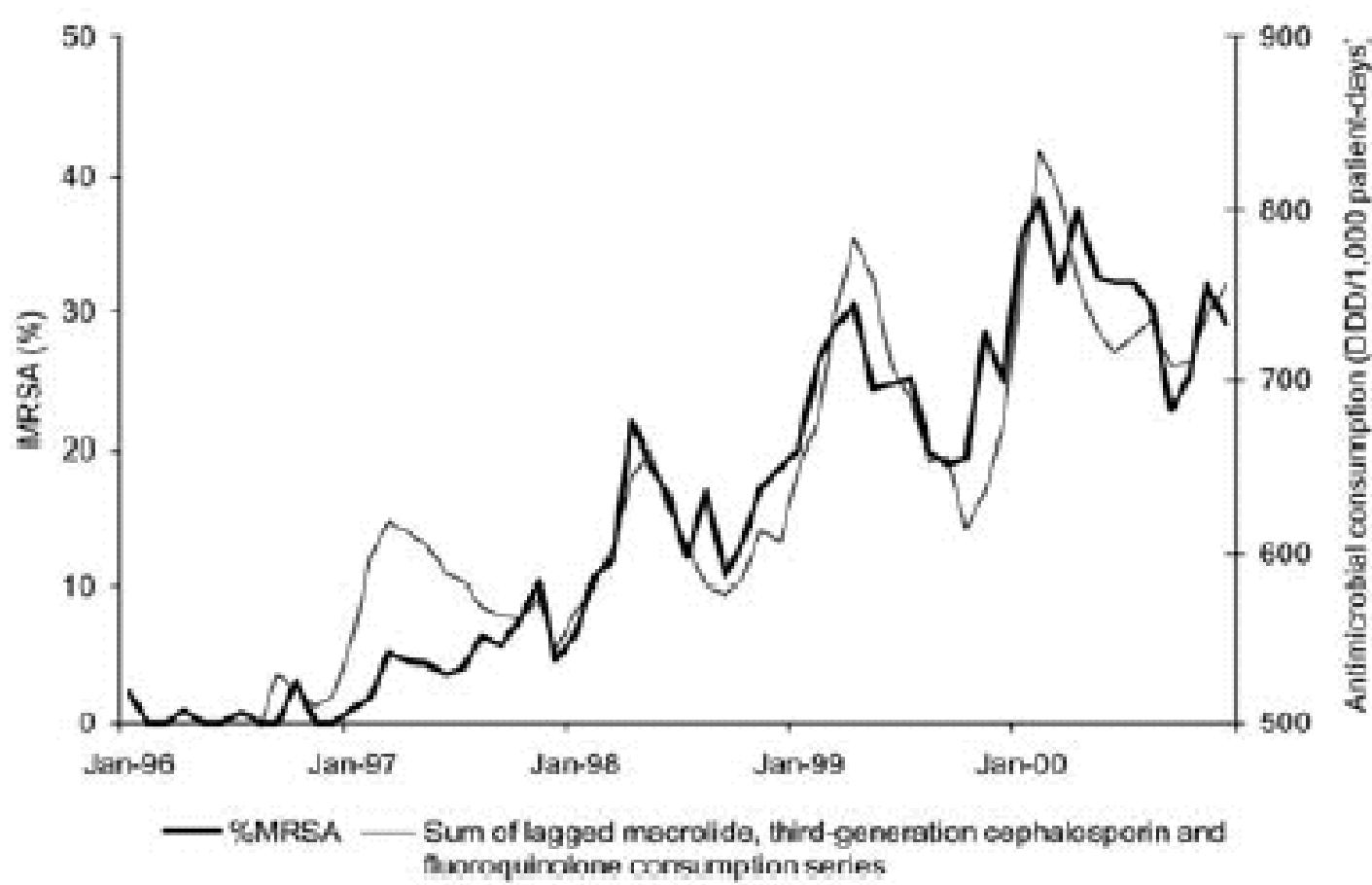
Table 3. Antibiotic-Mediated Mortality Reductions for Specific Infections

Disease	Pre-Antibiotic Mortality Rate	Antibiotic Mortality Rate	Change in Mortality
Community Pneumonia [53]	~23%	~7%	-16%
Nosocomial Pneumonia [54]	~60%	~30%	-30%
Bacterial Endocarditis [112–115]	~100%	~25%	-75%
Bacterial Meningitis [116–117]	>80%	<20%	-60%
Skin Infection [55, 118]	~11%	<.5%	-10%
By comparison, treatment of myocardial infarction (i.e., heart attack) with aspirin or streptokinase [119]			-3%

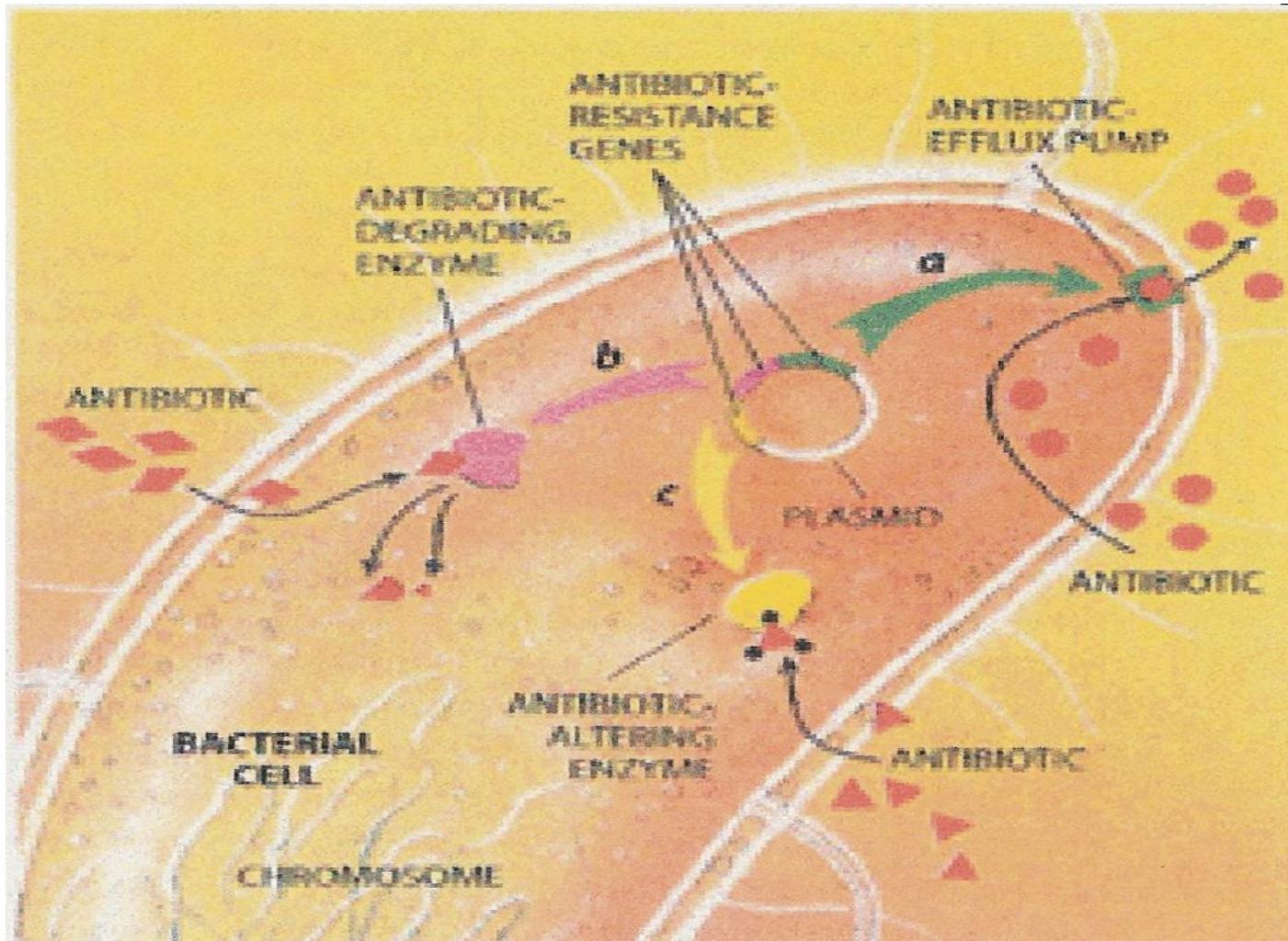
Antibiotics, from cradle to grave



The correlation between antibiotic use and resistance. Monnet DL et al. Emerg Inf Dis 2004



Mechanisms of resistance



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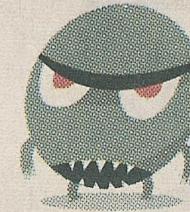
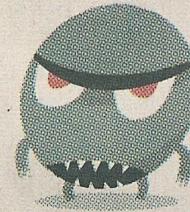
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Sådan opstår resistens

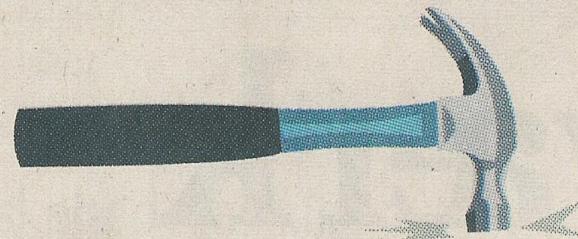
En gruppe bakterier har forårsaget en infektion.



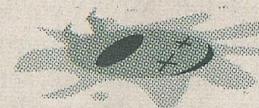
Mutation

Bakterier, der har forårsaget en infektion

Man angriber bakterierne
med **Antibiotikum 1**.



Én har en naturlig mutation, der gør den modstandsygtig over for antibiotikum 1.
I en enhver infektion vil der være mange millioner bakterier til stede. Derfor vil der
ofte være nogle, der har en mutation, der gør, at de overlever angrebet.



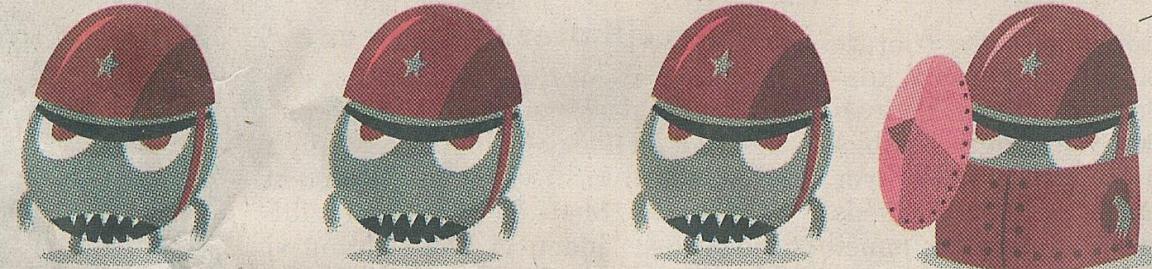
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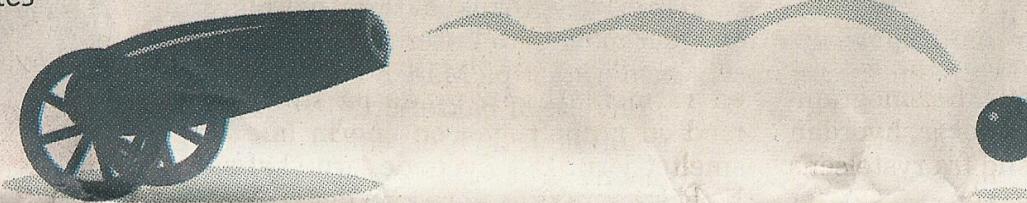


De overlevende bakterier har nu mulighed for at brede sig og sprede deres gener for resistens. Undervejs sker der igen nye mutationer.

Ny mutation



Antibiotikum 2 sættes ind mod bakterierne.

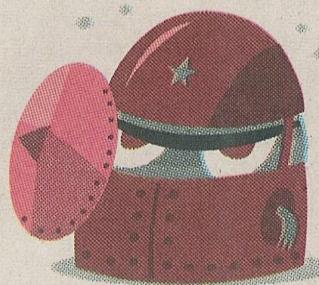
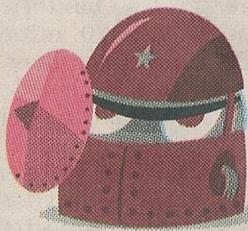
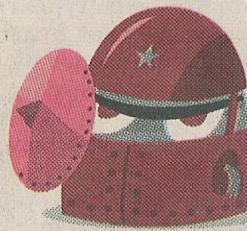
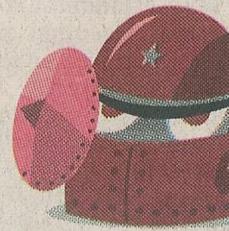


Det virker på en anden måde end det første antibiotikum og dræber derfor de fleste. Men bakterien med den nye mutation overlever...



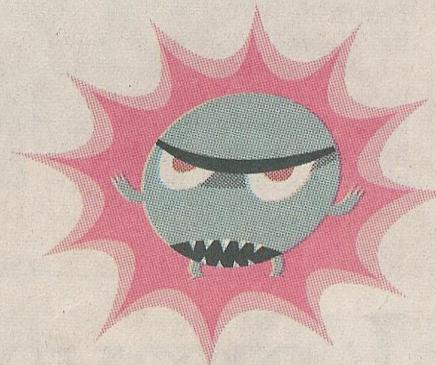


Fri for de andre bakterier kan den reproducere sig selv til en ny stamme af bakterier, der kan modstå både antibiotika 1 og 2. Den er blevet multiresistent. I flere tilfælde er der ikke gået mere end få år fra et antibiotikum er sendt i handlen for de første resisterente bakterier dukker op.



MRSA

Hidtil har resistens først og fremmest været et problem på hospitaler, hvor man bruger meget antibiotika. I verden udenfor er de multiresistente bakterier hæmmet af deres eget forsvar. Panser og plade er for tungt at slæbe rundt på, når man alligevel ikke bliver angrebet. Inden for de senere år er der dog dukket flere stammer af bakterier op, der både har beskyttelse over for antibiotika og som kan klare sig i konkurrencen med deres ubeskyttede slægtninge. Deres forsvar hæmmer dem ikke nær så meget.



CAMRSA

... Bakterier bryder sidste bolværk





Solution to Killer Superbug Found in Norway.

New York Times December 30, 2009

OSLO, Norway (AP) -- Aker University Hospital is a dingy place to heal.

The floors are streaked and scratched. A light layer of dust coats the blood pressure monitors. A faint stench of urine and bleach wafts from a pile of soiled bedsheets dropped in a corner.

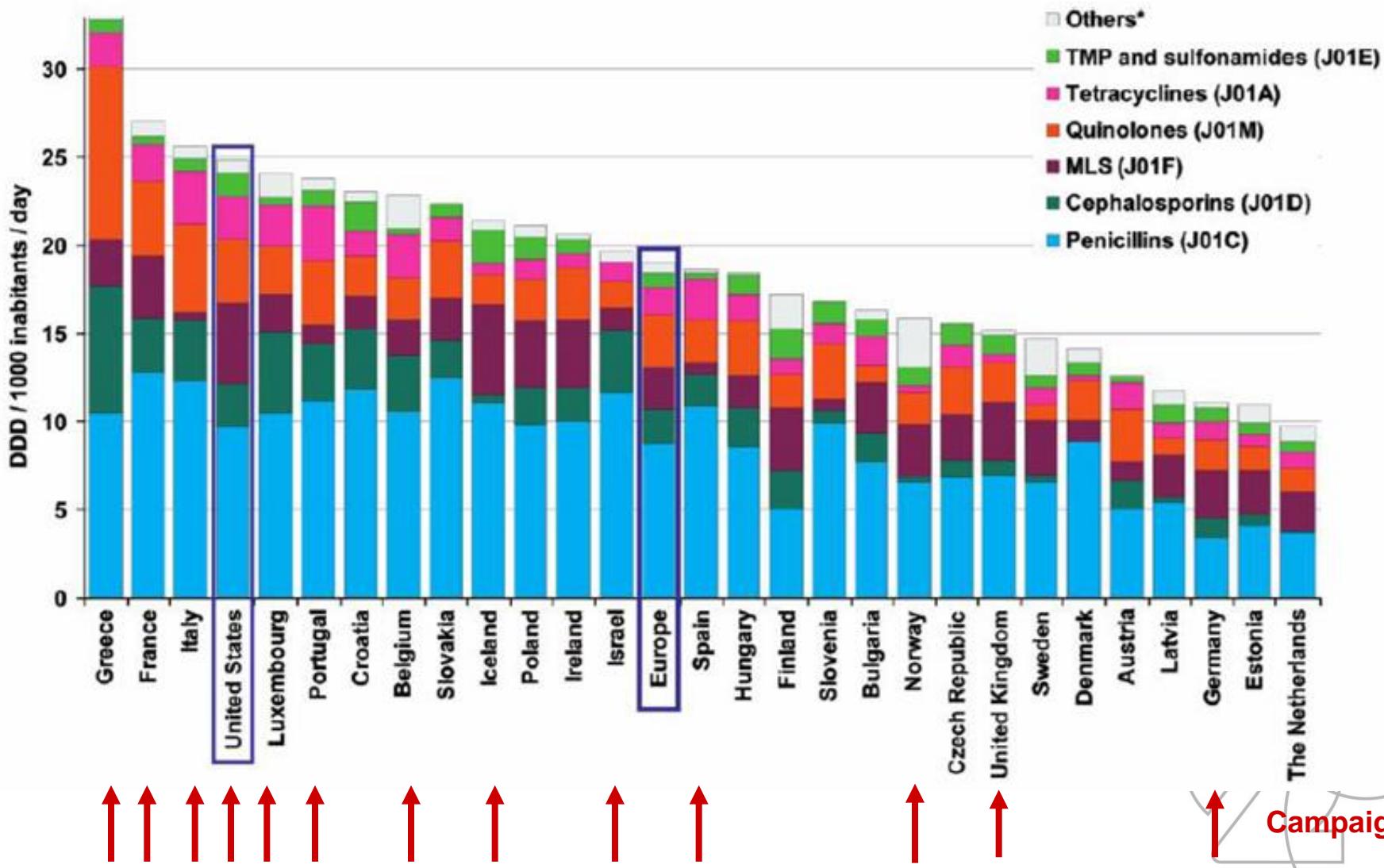
Look closer, however, at a microscopic level, and this place is pristine.

There is no sign of a dangerous and contagious staph infection that killed tens of thousands of patients in the most sophisticated hospitals of Europe, North America and Asia this year, soaring virtually unchecked.

The reason: Norwegians stopped taking so many drugs.

Twenty-five years ago, Norwegians were also losing their lives to this bacteria. But Norway's public health system fought back with an aggressive program that made it the most infection-free country in the world. A key part of that program was cutting back severely on the use of antibiotics.

Outpatient antibiotic use in European countries



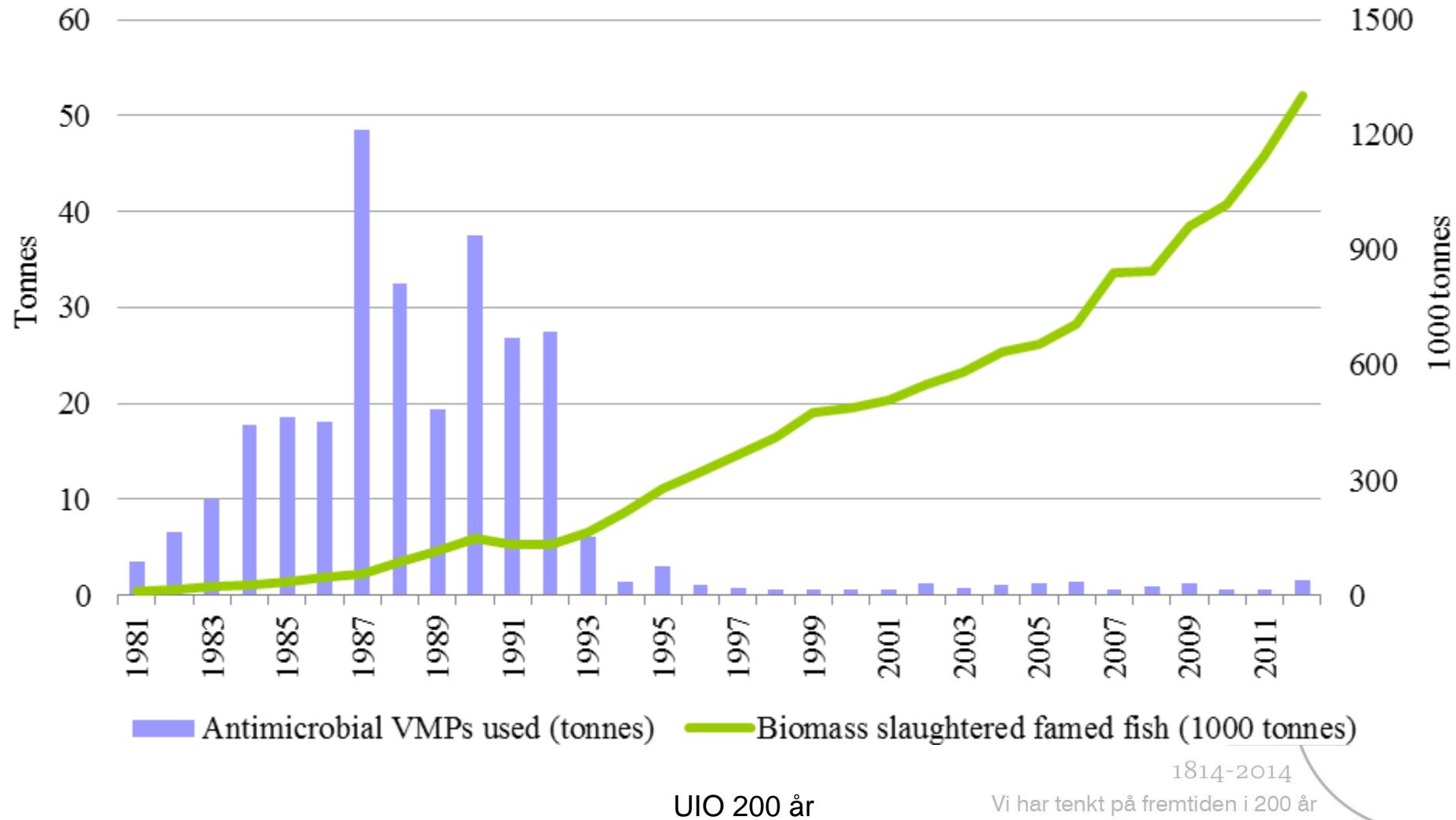
Total outpatient antibacterial use in the United States and 27 European countries in 2004



How can we preserve antibiotics?

- Stop (prophylactic) AB-use in agriculture
- Follow national guidelines for AB-use
- Use e-health and mobile health
- Public campaigns
- Campaigns and education of health personnel

Antibiotic use in fish farming



Reduction of AB-resistant enterococci after the ban of

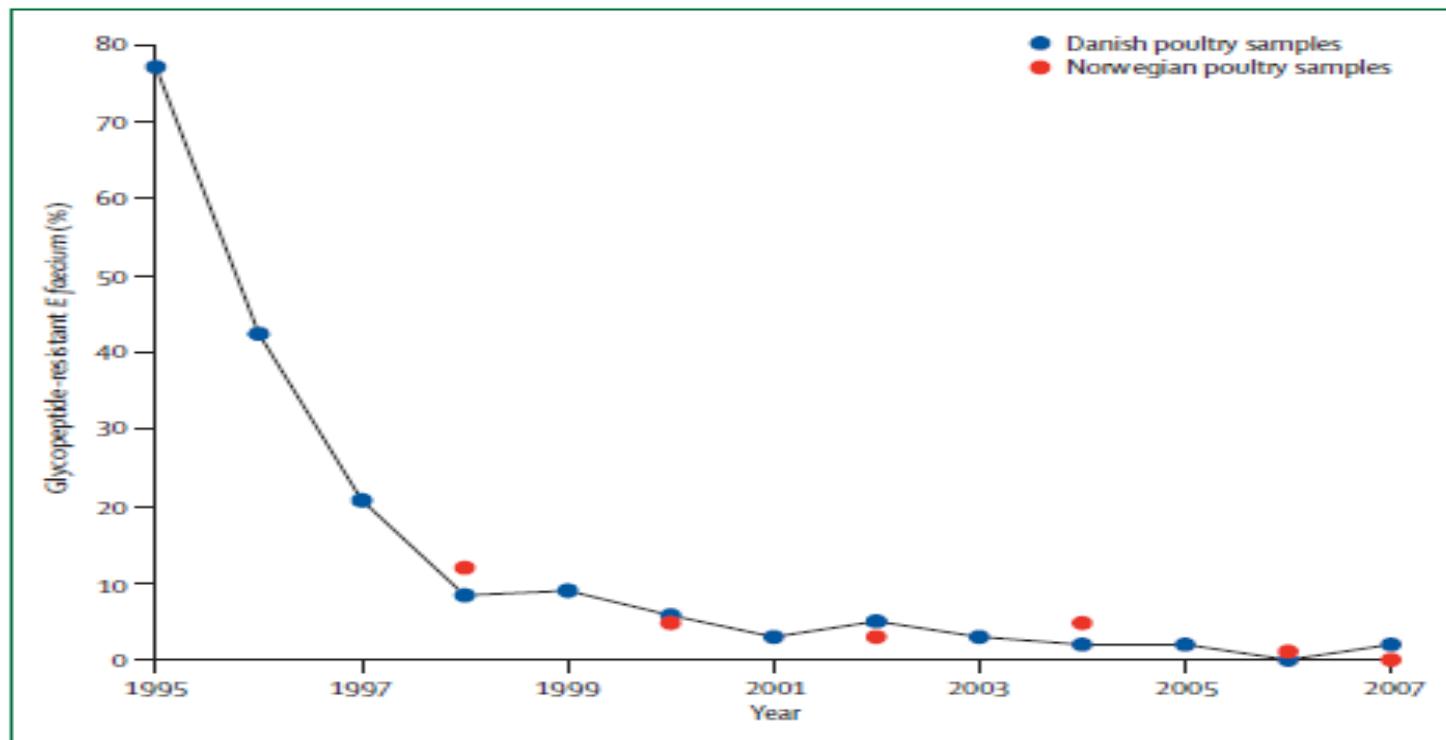
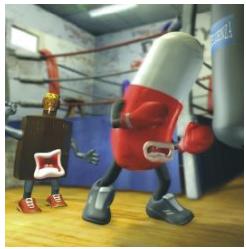
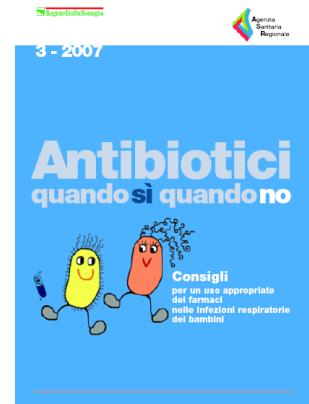
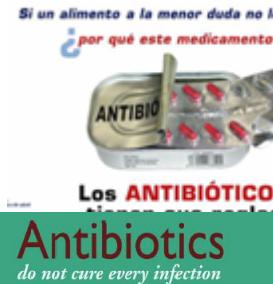


Figure 2: Occurrence of glycopeptide-resistant *Enterococcus faecium* in Danish and Norwegian poultry samples
Percentage of glycopeptide resistant *E faecium* (GREF) in Danish and Norwegian poultry samples following the 1995 ban on the glycopeptide growth promoter avoparcin. The plotted line is based on the complete Danish data sets where *E faecium* were isolated from cloacal-swab samples before susceptibility testing.⁸ The Norwegian proportions of GREF among collected *E faecium* isolates were determined from both faecal and meat samples.⁶ *E faecium* isolated from meat are of faecal origin and the GREF proportions in infected meat are most likely directly reflecting the proportions in faeces. No GREF were detected among Danish faecal *E faecium* samples in 2006.⁸ However, GREF were isolated from Danish poultry meat samples in 2006, suggesting that GREF occurrence below 1–2% is close to the detection limit of the surveillance programme.⁸

Det medisinske fakultet

Overview over single campaigns





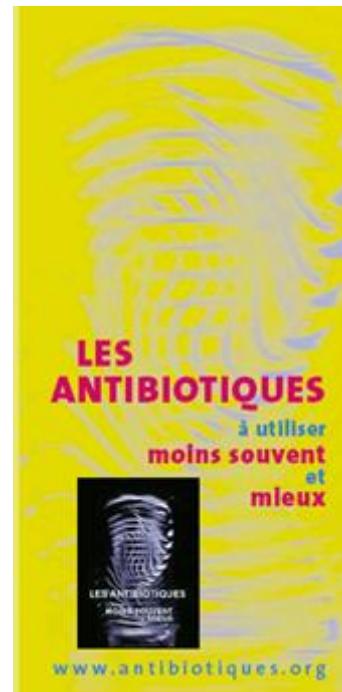
Belgium

www.antibiotics-info.be



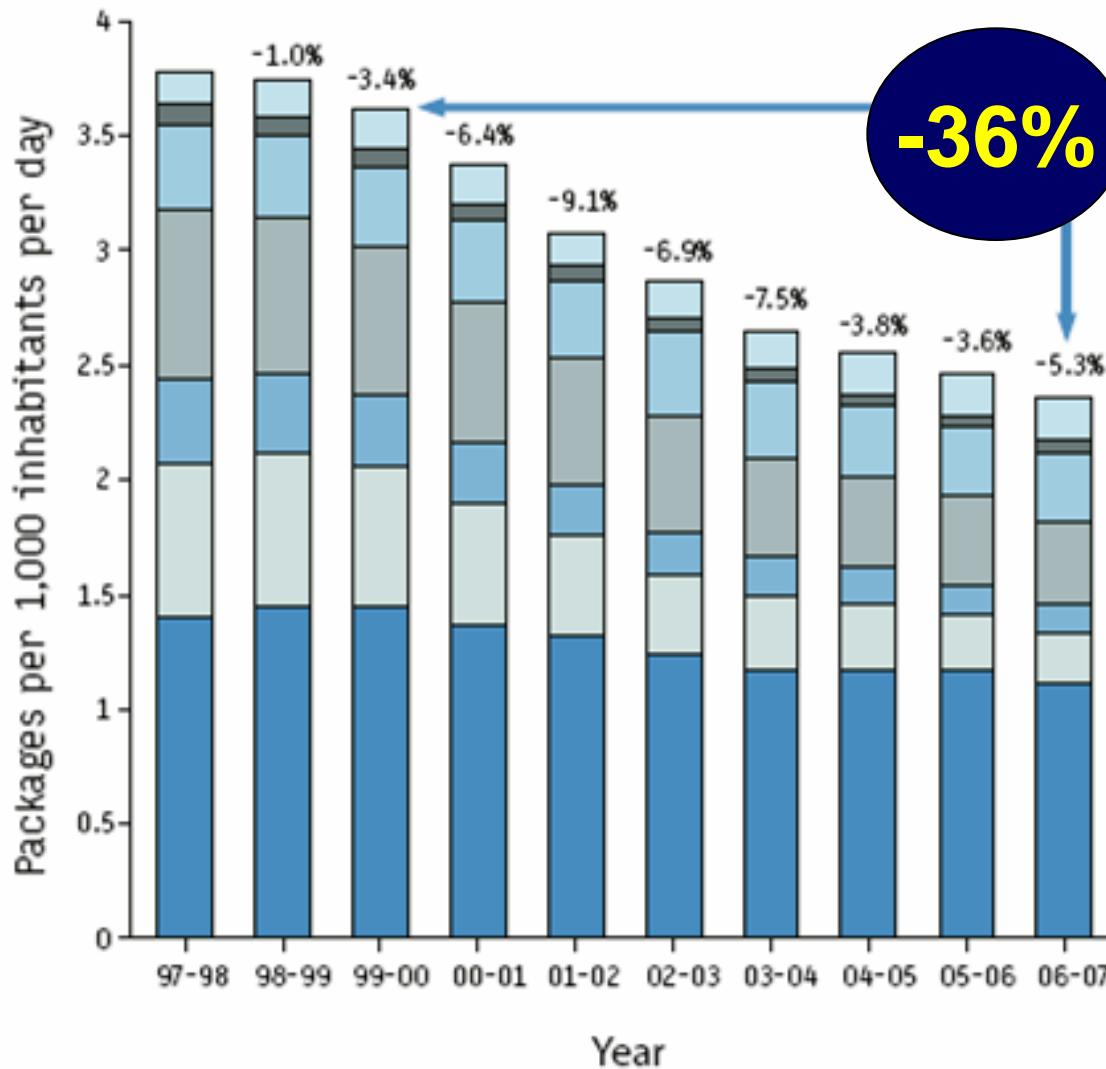
Population
10.5 million

- **Yearly campaign since 2000**
 - about 385'000 €/year
- **Interventions**
 - Information material
 - Treatment guidelines
 - TV and radio spots



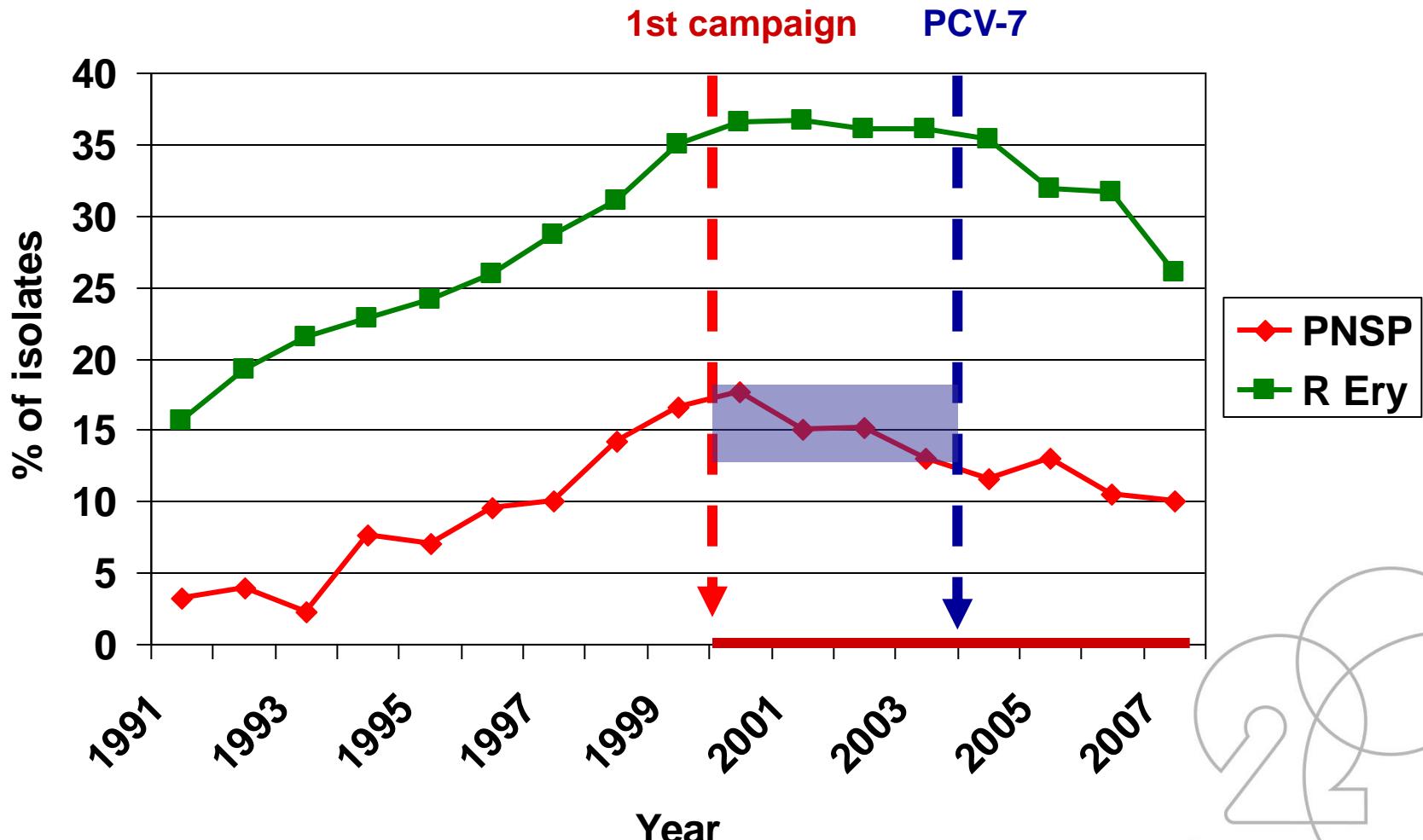


Belgium



Belgium

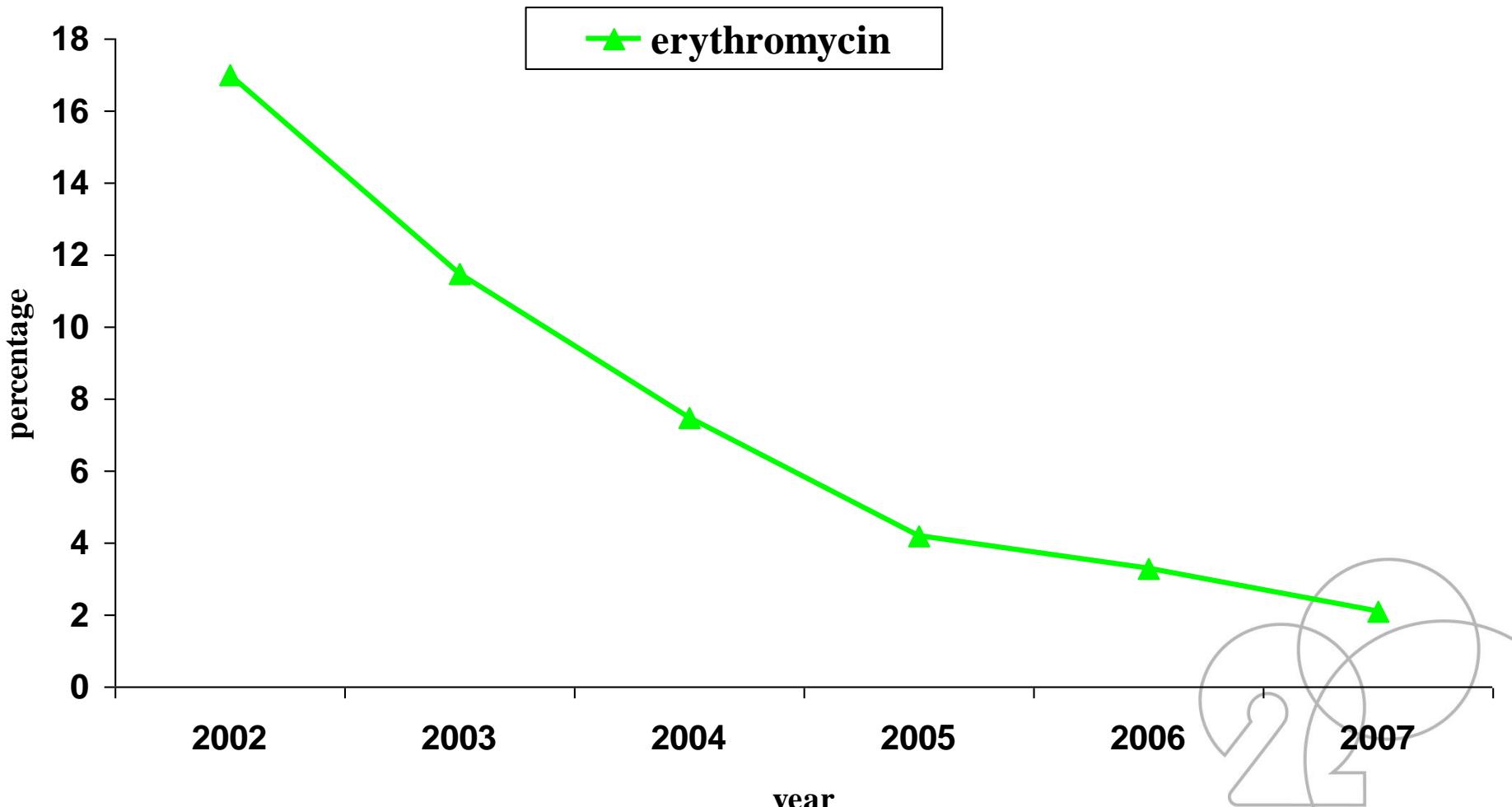
Evolution of bacterial resistance of pneumococci



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Antibiotic Resistance of Throat Isolates of *Streptococcus pyogenes* in Belgium (2002 – 2007)



National Reference Centre *S. pyogenes* (University of Antwerp)
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France

www.antibiotiquespasautomatiques.com



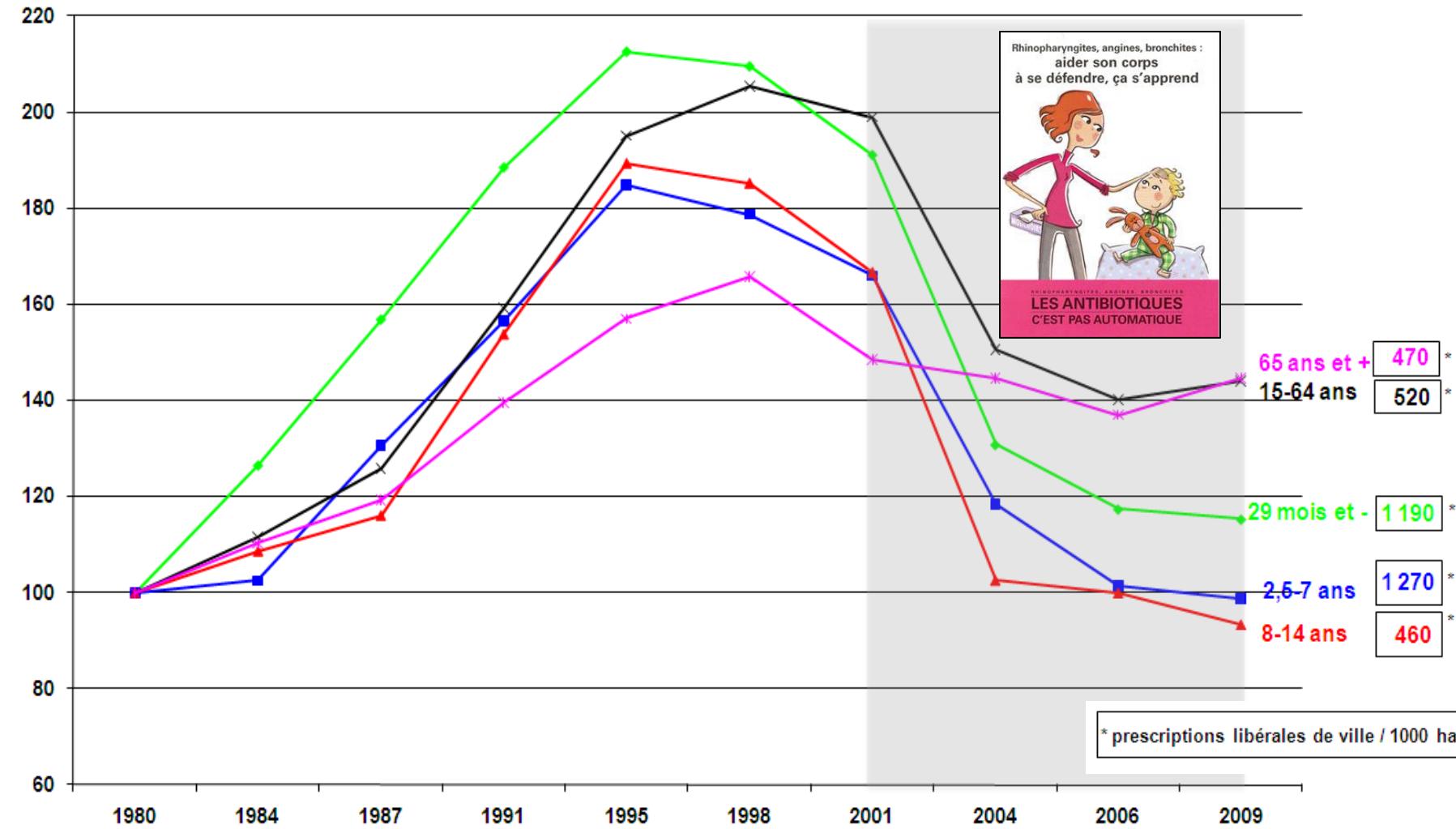
Population
64.5 million

- “Antibiotics Are Not Automatic”
- Yearly campaign since 2002
 - About 4 million €/year
- Interventions
 - Ads on TV, radio, newspaper
 - Information leaflets, internet campaign, exhibitions
 - Academic detailing, promotion of streptococcal rapid antigen test, treatment guidelines



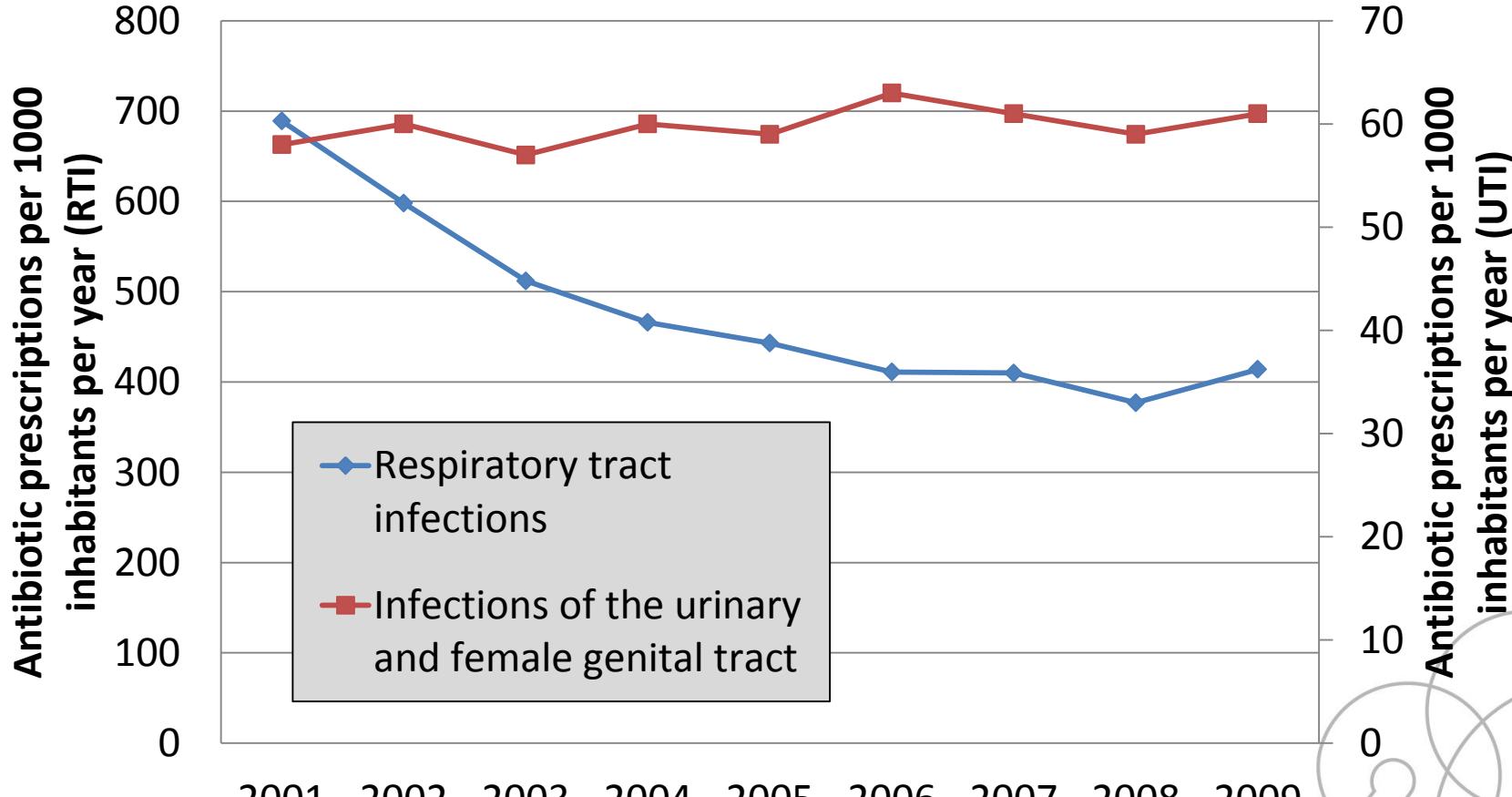
Evolution des prescriptions antibiotiques de ville en France, en fonction de l'âge (1980 – 2009)

BASE 100 = 1980



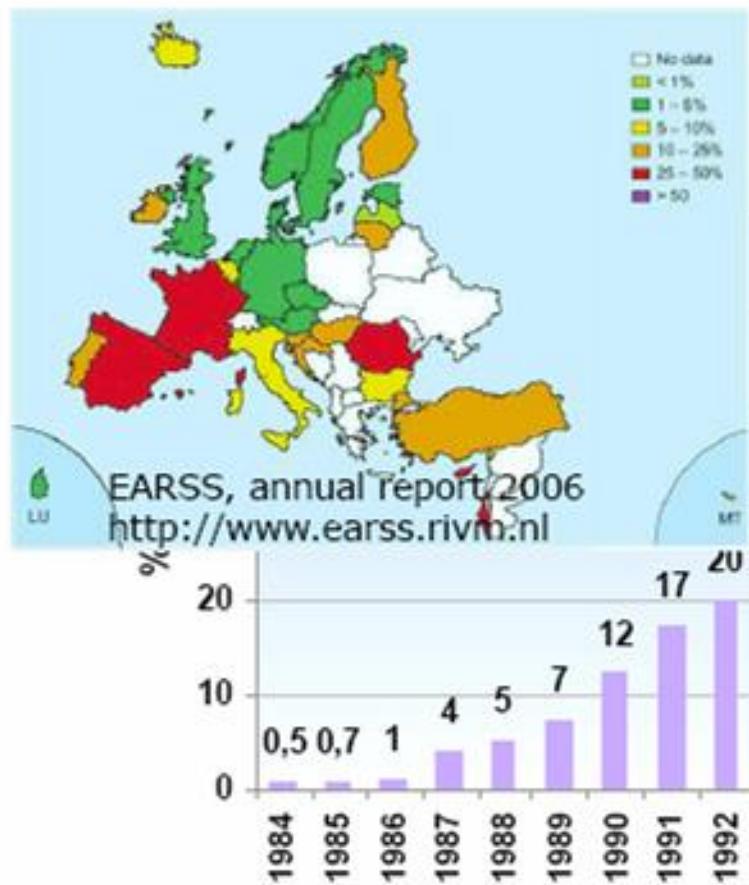
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Reduction in AB-use only in respiratory tract infections...



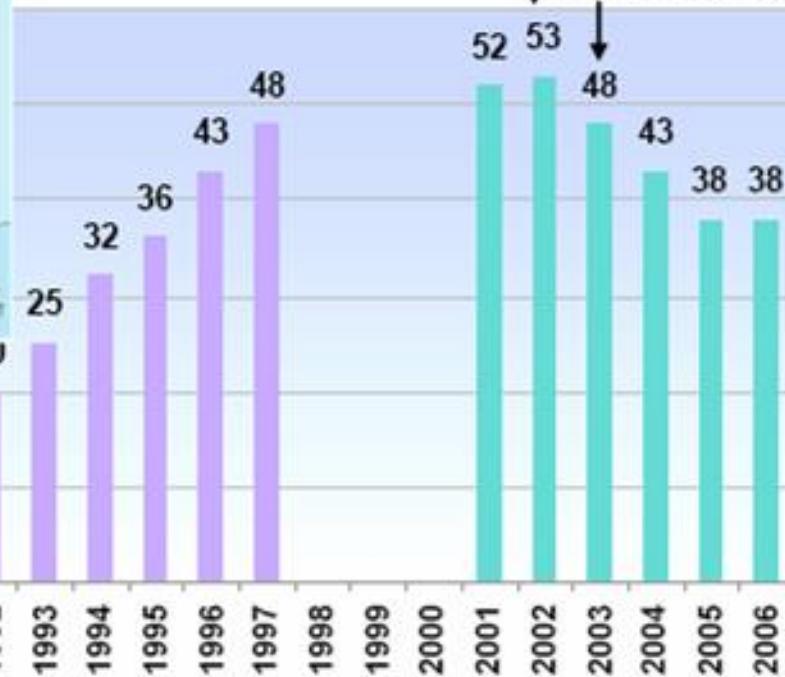
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Penicillin non susceptible *S. pneumoniae* in France



National plan for a rational use of antibiotics

↓ PCV7 introduction



1984-1997: GEEP - P. Geslin; 2001-2006: CNRP-ORP

CNRP

CNRP, Annual report 2007



Informationen
zum Problem der
Antibiotika-Resistenz
und zum richtigen
Umgang mit Antibiotika

viamedica
STIFTUNG FÜR EINE GESEHNE MEDIZIN

Germany

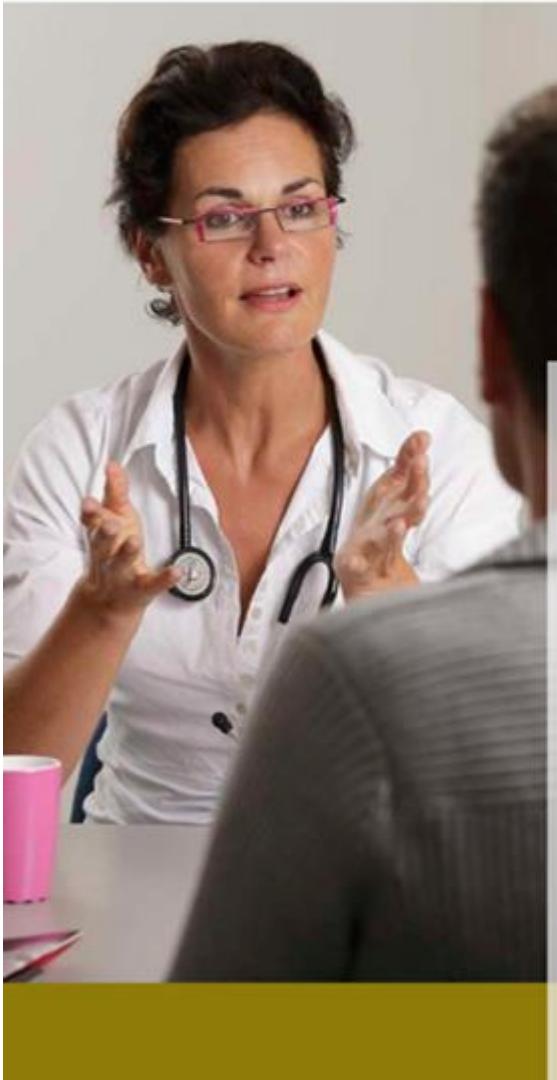
Informationskampagne Antibiotika-Resistenz
www.viamedica-stiftung.de

- Campaign since 2007
- Private Foundation to promote: "Equilibrium between medicine, man and nature"
- Few interventions, no evaluation

- "**Use herbal remedies first**"
- "**Patients should always ask their doctor if a herbal remedy can be prescribed instead of antibiotics**"

Antibiotica

Gebruik ze goed en alleen als 't moet!



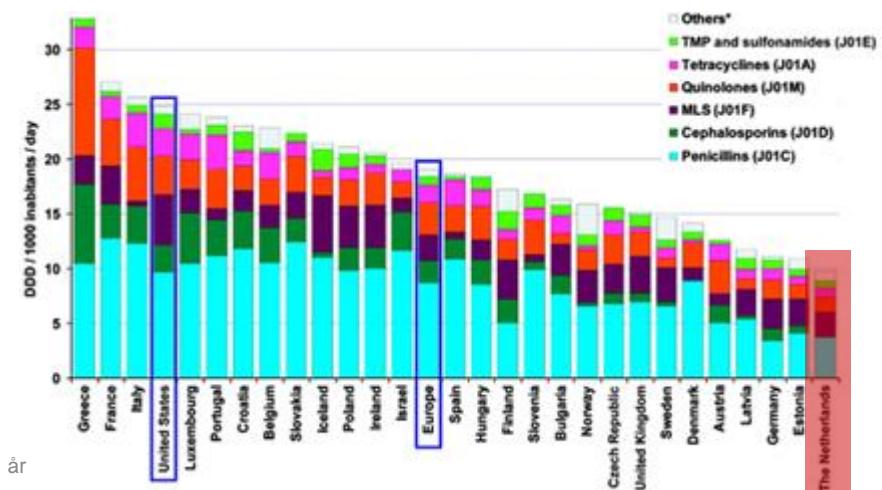
Vragen & Antwoorden over antibioticagebruik

Antibiotica blijven effectief als we ze verstandig gebruiken: niet te vaak en op de goede manier. Uw arts weet wanneer u antibiotica nodig hebt en hoe u ze moet innemen.

Volg het advies van uw arts, dan bestrijdt u de infectie goed. Zo houden we antibiotica werkzaam.

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Even the Netherlands...





- “Campaign for the responsible use of antibiotics”
- Yearly campaign since 2006
 - 6.5 million € (2006)
- Target population
 - General population, parents
 - GPs, paediatricians, pharmacists
- Interventions
 - Mass mailing to physicians
 - Ads on TV, radio, print-media



ESTATE
DEPT

LET'S GO

GO!



GO!

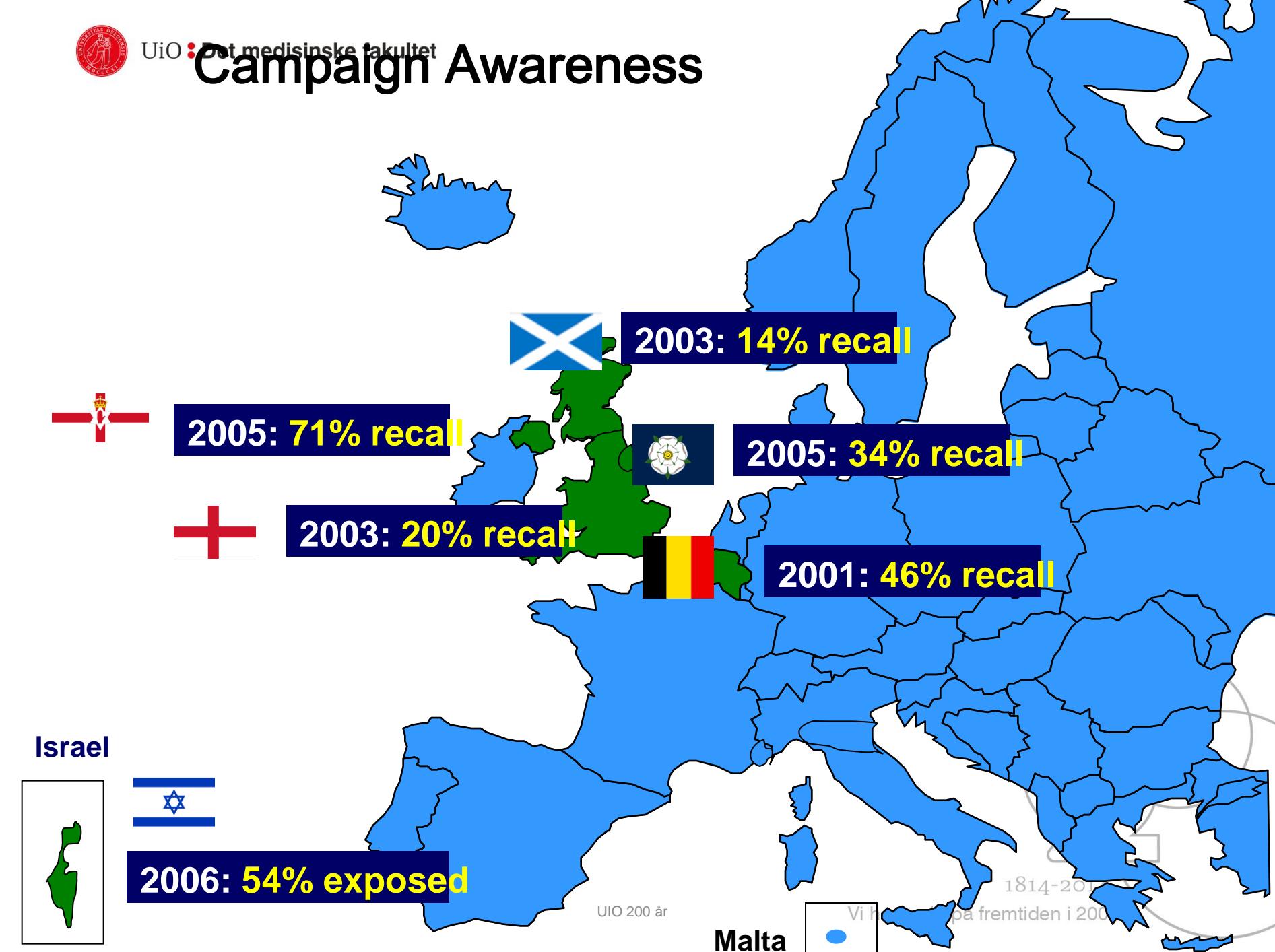


תְּלַבֵּג אֲסָרִים יְמִינָה



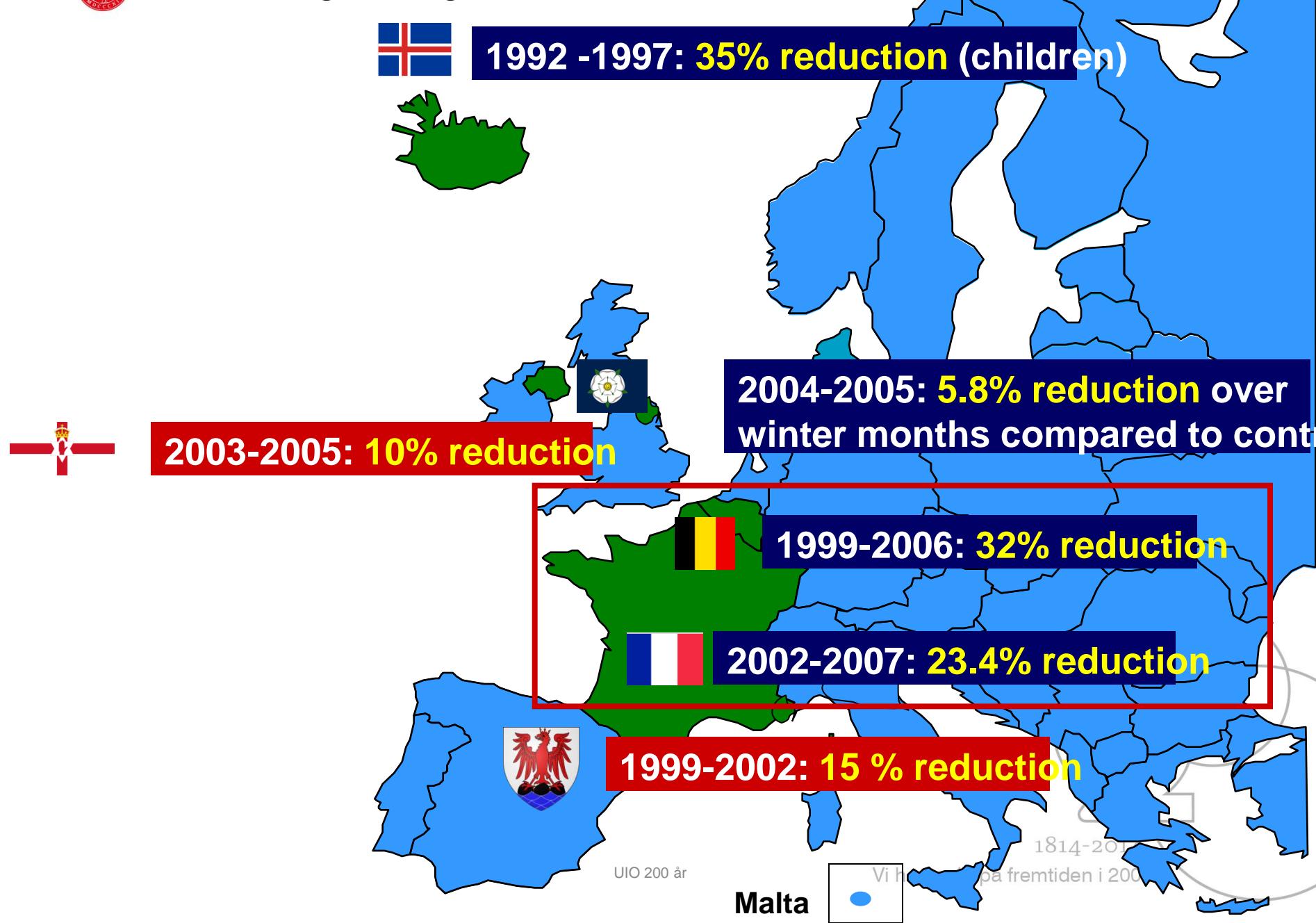


Campaign Awareness



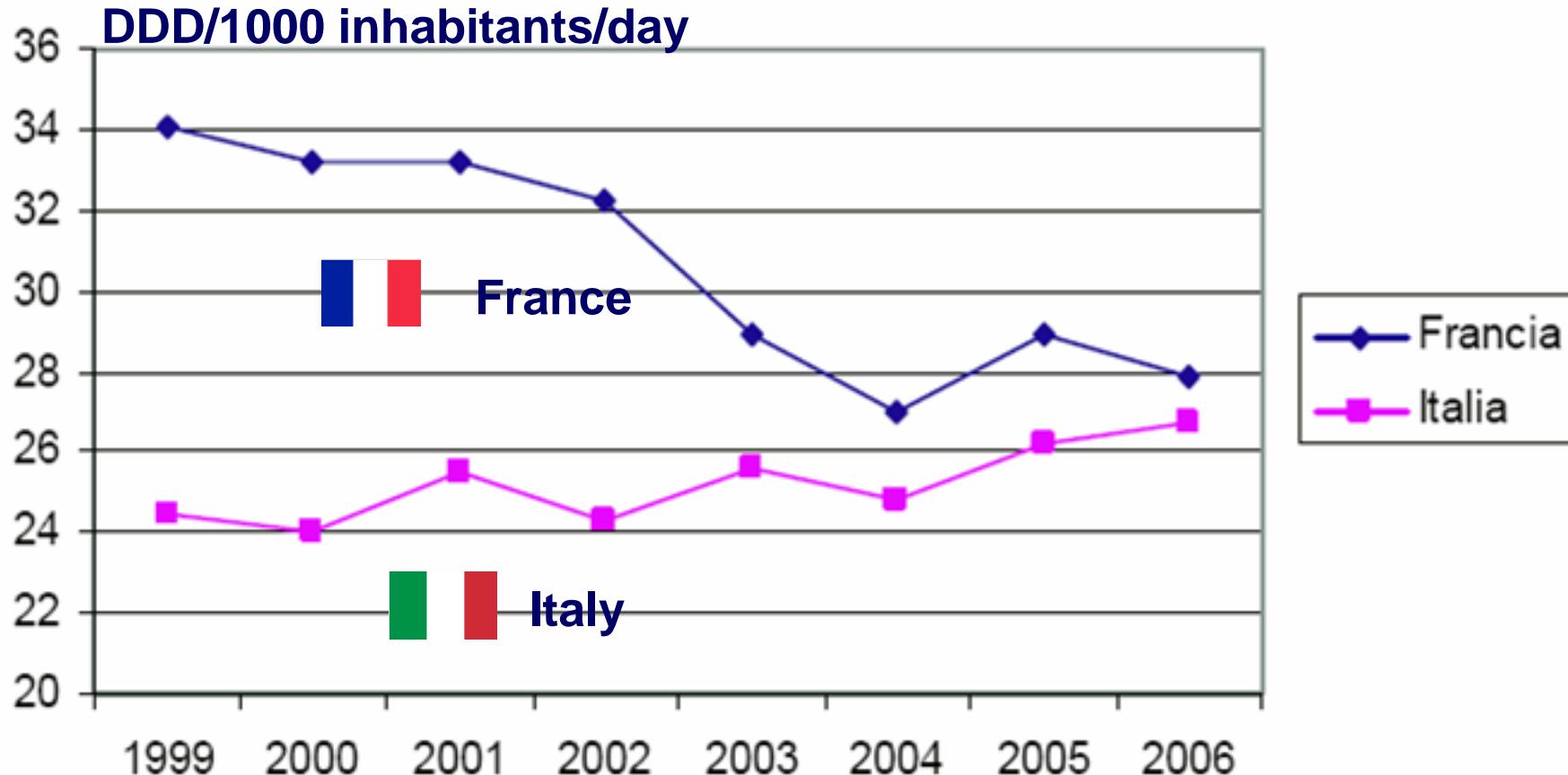


Outcome regarding antibiotic use



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Trends in antibiotic consumption France and Italy (1999-2006)



Fonte: ESAC aggiornato anno 2006



Er det farlig å redusere antibiotikabruken?

Neppe





Potential adverse effects of reduced prescribing



**Not routinely
monitored**





Potential adverse effects of reduced prescribing?

- **England**

- 1992-2002: admissions for peritonsillar abscesses, mastoiditis and rheumatic fever in children stable

Sharland et al. (2005). *BMJ* 331:328-9

- **Sweden**

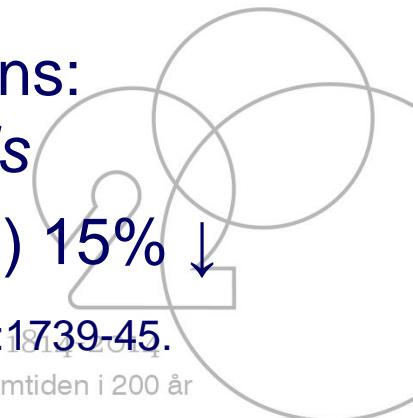
- 1987-2003: no increase in admissions for acute sinusitis, peritonsillar abscess and acute mastoiditis
 - 1995-2004: outpatient antibiotic use ↓20%

Mölstad et al. (2008). *Lancet Infect Dis* 8:125-32.

- **Alpes-Maritimes**

- 1998-2003: stable rates of invasive infections: *S. pneumoniae*, *S. pyogenes*, *N. meningitidis*
 - 1999-2002: AB use in children (self reported) 15% ↓

Blanc et al. (2008). *Presse Med* 37:1739-45.





To eksempler på at resistens begrenser våre behandlingsmuligheter

Følg med





Executive Summary: International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Kalpana Gupta,¹ Thomas M. Hooton,² Kurt G. Naber,⁹ Björn Wullt,¹⁰ Richard Colgan,³ Loren G. Miller,⁴ Gregory J. Moran,⁵ Lindsay E. Nicolle,⁸ Raul Raz,¹¹ Anthony J. Schaeffer,⁶ and David E. Soper⁷

¹Department of Medicine, Veterans Affairs Boston Health Care System and Boston University School of Medicine, Boston, Massachusetts; ²Department of Medicine, University of Miami Miller School of Medicine, University of Miami, Miami Florida; ³Department of Family and Community Medicine, University of Maryland, Baltimore, Maryland; ⁴Division of Infectious Diseases, Harbor-UCLA Medical Center, Torrance, and ⁵Department of Emergency Medicine and Division of Infectious Diseases Olive View-UCLA Medical Center, Slymar, California; ⁶ Department of urology, Northwestern University, Chicago, Illinois; and ⁷Departments of Obstetrics and Gynecology and Medicine, Medical University of South Carolina, Charleston, South Carolina; ⁸Department of Internal Medicine and Department of Medical Microbiology University of Manitoba, Winnipeg, Canada; ⁹Technical University of Munich, Munich, Germany; ¹⁰Lund University Hospital, Lund, Sweden; and ¹¹Infectious Diseases Unit, Ha'Emek Medical Center, Afula, and Rappaport Faculty of Medicine, Technion, Haifa, Israel

Only two treatment options in urinary tract infections.
Nitrofurantoin OR Fosfomycin

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Treat UTI in 2012 with antibiotics of the 1960s!



Super-heros never die!!

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Gonorrhea is not a serious disease, but...

J Antimicrob Chemother 2012; **67**: 2059–2061
doi:10.1093/jac/dks188 Advance Access publication 17 May 2012

**Antimicrobial
Chemotherapy**

The ticking time bomb: escalating antibiotic resistance in *Neisseria gonorrhoeae* is a public health disaster in waiting

David M. Whiley^{1,2*}, Namraj Goire^{1,2}, Monica M. Lahra³, Basil Donovan^{4,5}, Athena E. Limnios³, Michael D. Nissen^{1,2,6} and Theo P. Sloots^{1,2,6}





Conclusion: It is possible to improve AB-use and preserve ABs as useful drugs in Norway

- Reduce total and broad spectrum AB by
 - Using official guidelines for AB use
 - Implement e-health and mobil health
 - Education
- This will reduce resistance, costs and side effects
- Improve hospital hygiene



Number of molecular entity for systemic antibiotics

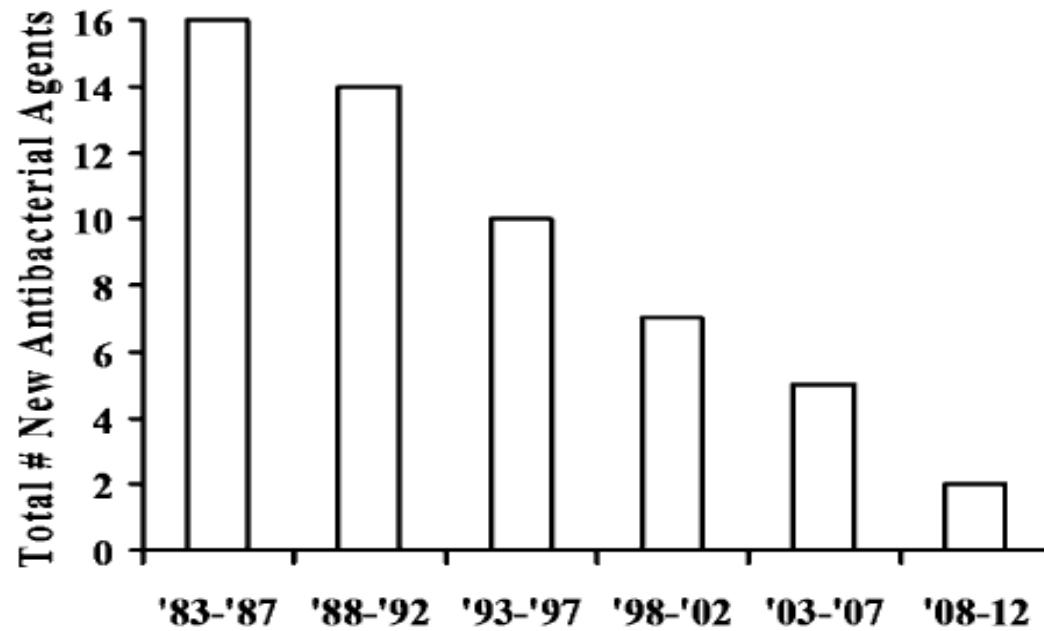
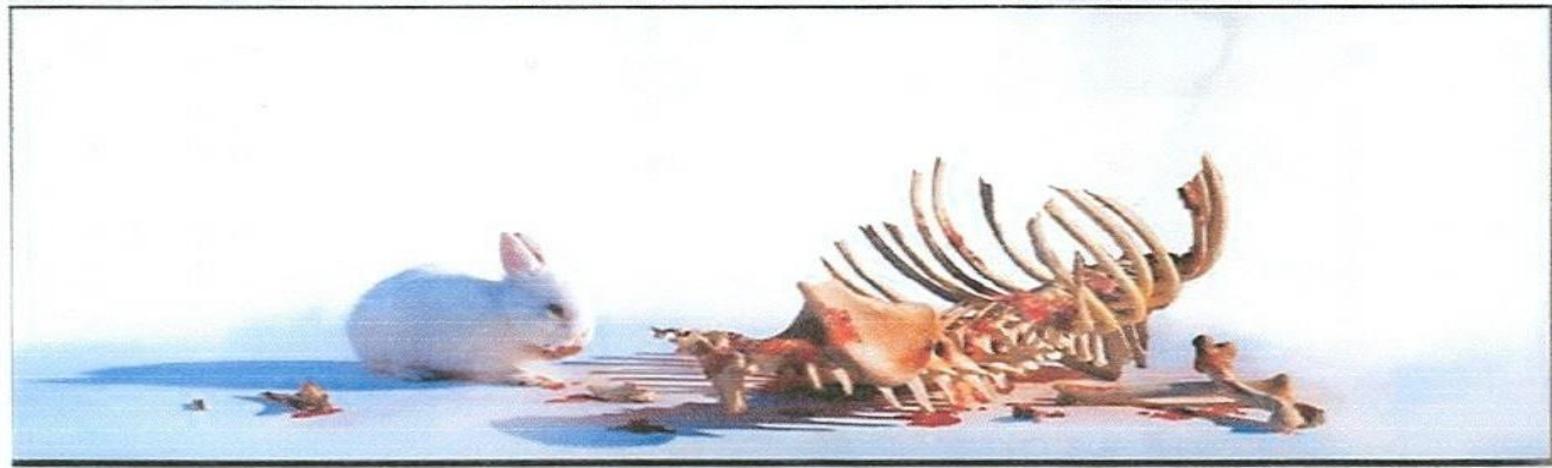


Figure 1. Number of New Molecular Entity (NME) Systemic Antibiotics Approved by the US FDA Per Five-year Period, Through 3/11.



Thank you



Jernlunge bruk fram til våre dager
for hjelp til åndedrett.



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But, we can face an apocalypse because of:

- Political neglect
- Ignorant, unethical and poor educated doctors
- Greed (false drugs, legalisation)
- Agriculture, live stock, fruits
- Lack of basic resources in dev. countries
- Inadequate infection control
- No new antibiotics





Perspectives

- Average age increased from 50 to 80 years from y1900 to y2000
- 20 y because of better standard of living
- 10 y due to modern medicin
- 7/10 y due to antibiotics and vaccines
- Resistance is a threat to modern medicine
- **There is no new AB in the pipelines**



Use of macrolide antibiotics in Finland

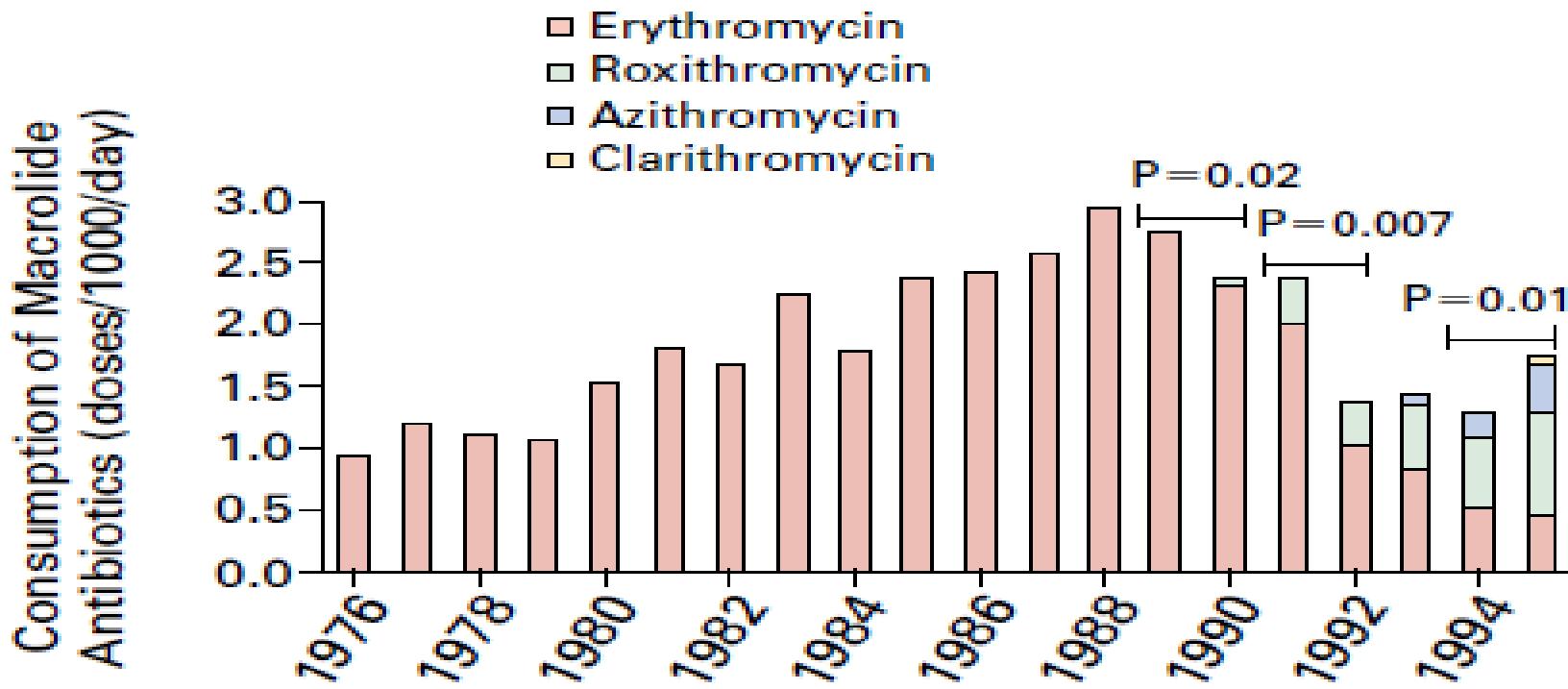


Figure 1. Total Consumption of Macrolide Antibiotics by Outpatients in Finland from 1976 through 1995.

Reduction of macrolide resistance after

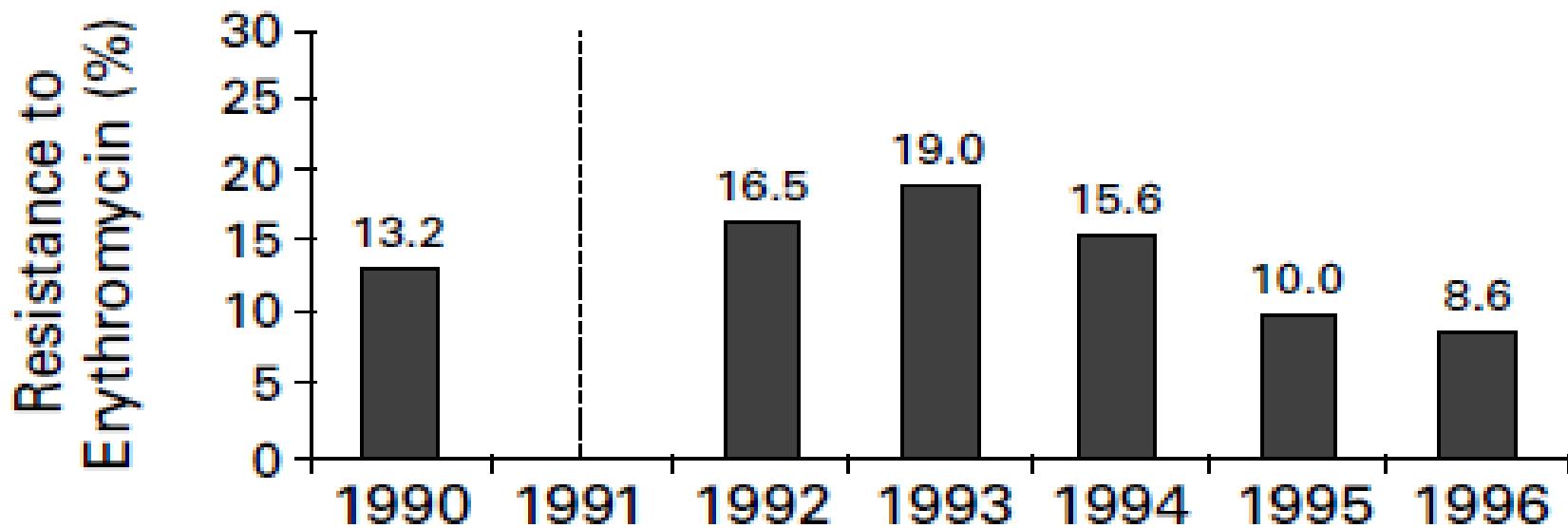


Figure 2. Frequency of Resistance to Erythromycin among Group A Streptococcal Isolates from Throat-Swab and Pus Samples in Finland in 1990 and in 1992 through 1996.

The change of the normal flora

Price & Sligh, Lancet 1970, Des 12;2 (7685):1213-5

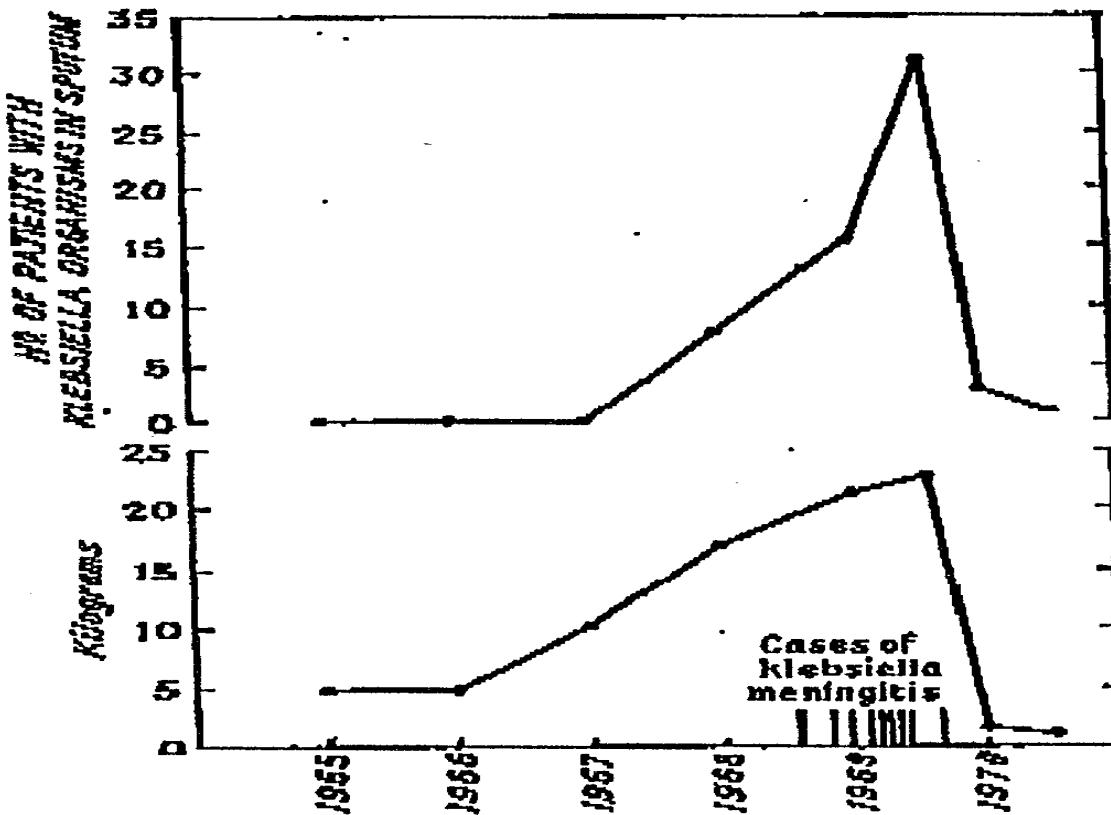


Fig. 3—Isolation of Klebsiella from sputum specimens (first 100 patients admitted to intensive-care ward each year), and annual consumption of ampicillin and cloxacillin.

Reduction of antibiotics

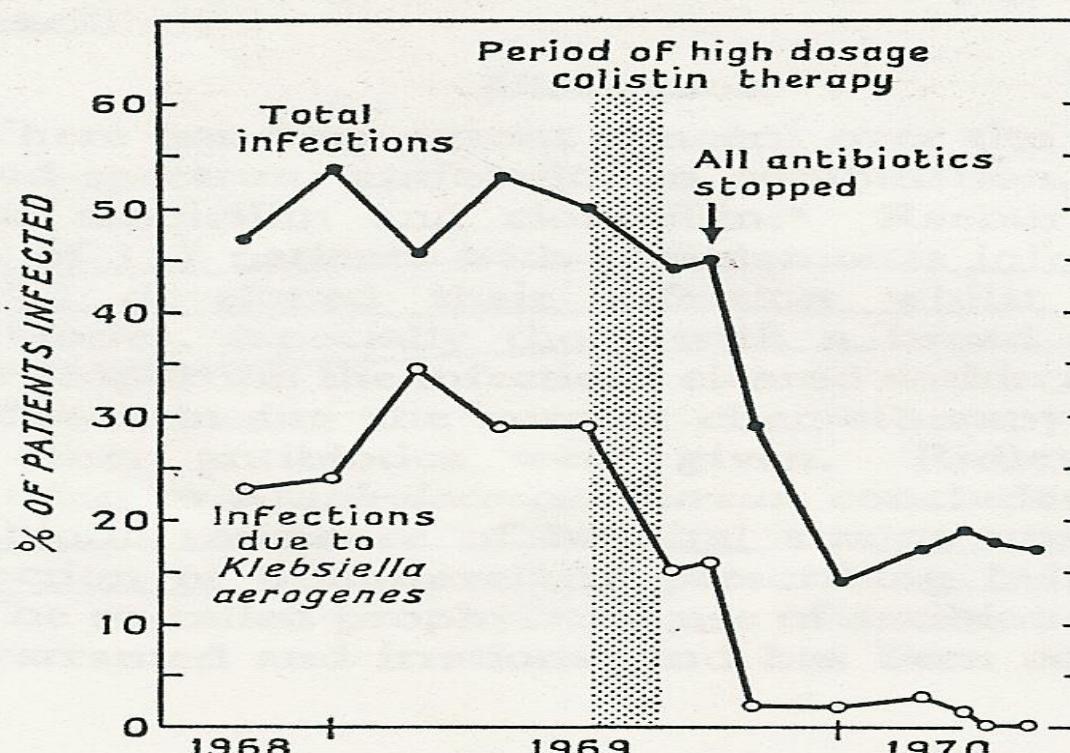


Fig. 1—% of patients in intensive-care ward with purulent sputum.

Fleming A.

Penicillin's finder assays its future. New York Times 1945; 21.



... the public will demand [penicillin]...then will begin an era...of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save.

In such a case **the thoughtless person playing with penicillin** treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism.

- I hope the evil can be averted.



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