



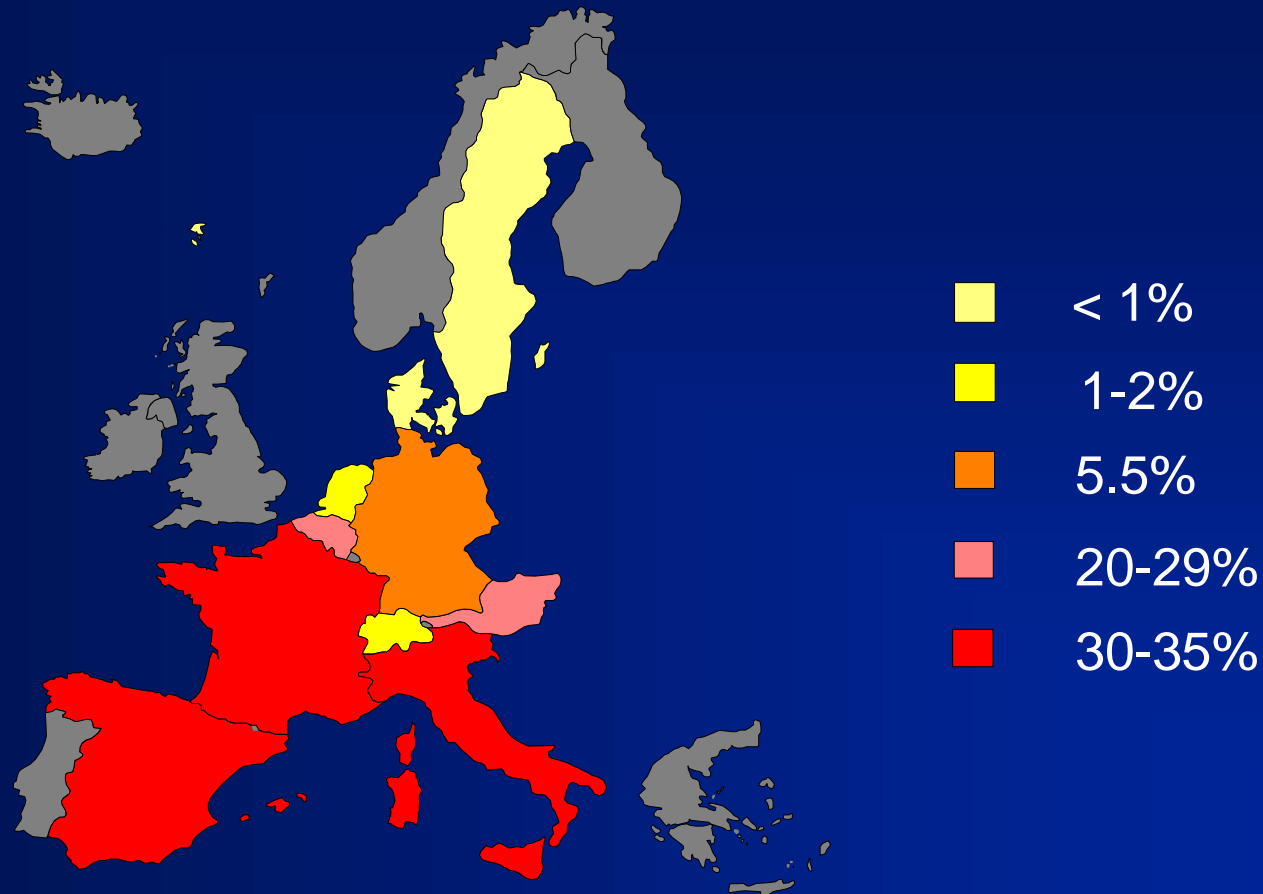
Antimicrobial Resistance and Usage Patterns in Europe:

Focus on Dutch-Belgian Differences and Complementarity & Lessons for the Future

Dominique L. Monnet

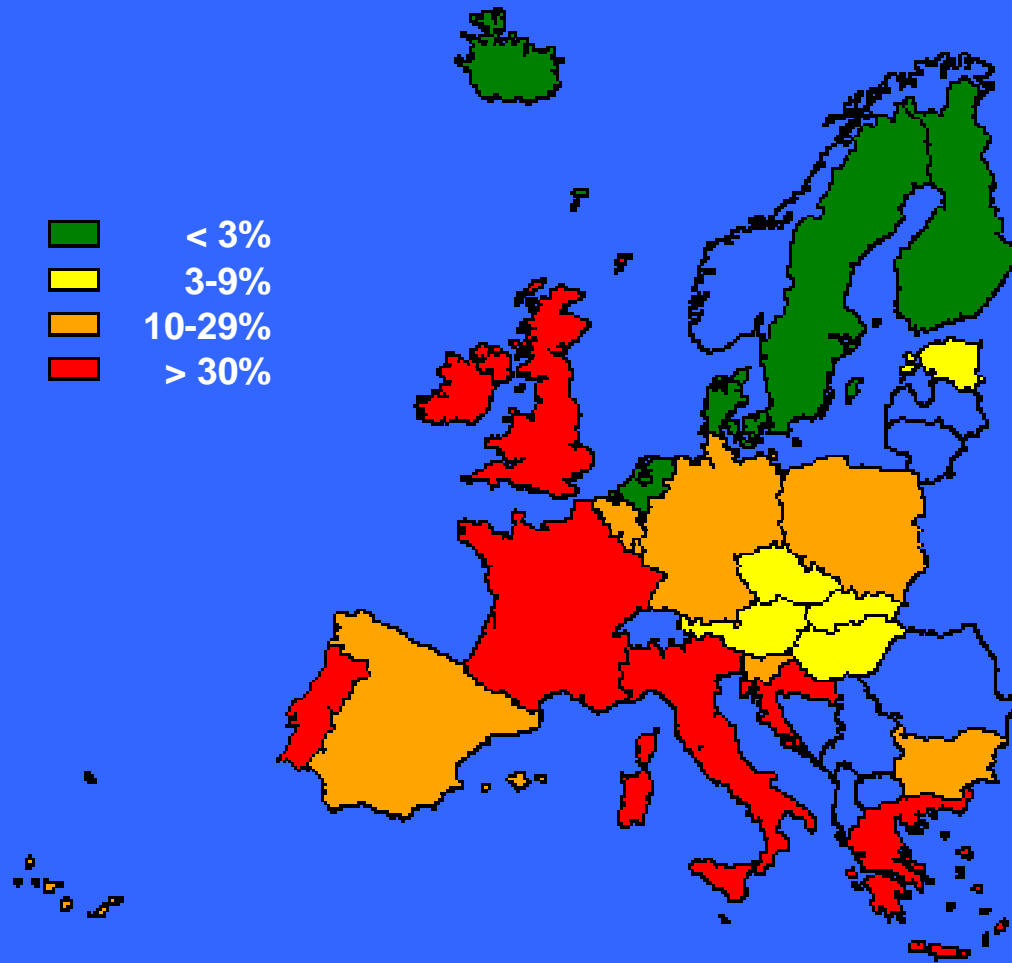
Antimicrobial Resistance Surveillance Unit,
Dept. of Antimicrobial Resistance & Hospital Hygiene,
Statens Serum Institut, Copenhagen, Denmark

MRSA in Europe, 1990-1991

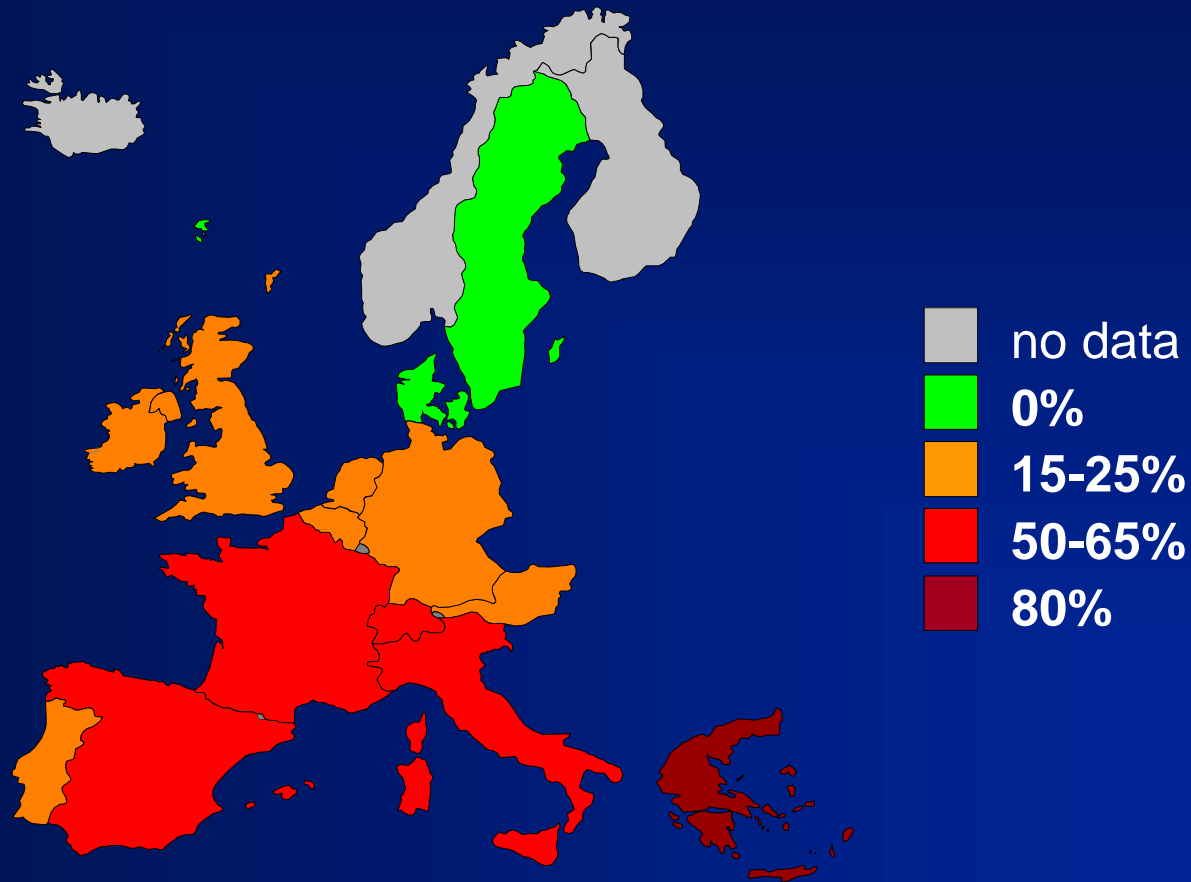


Source: Voss A, et al. Eur J Clin Microbiol Infect Dis 1994;13:50-55.

Methicillin-Resistant *Staphylococcus aureus* (MRSA) from Blood, 2001

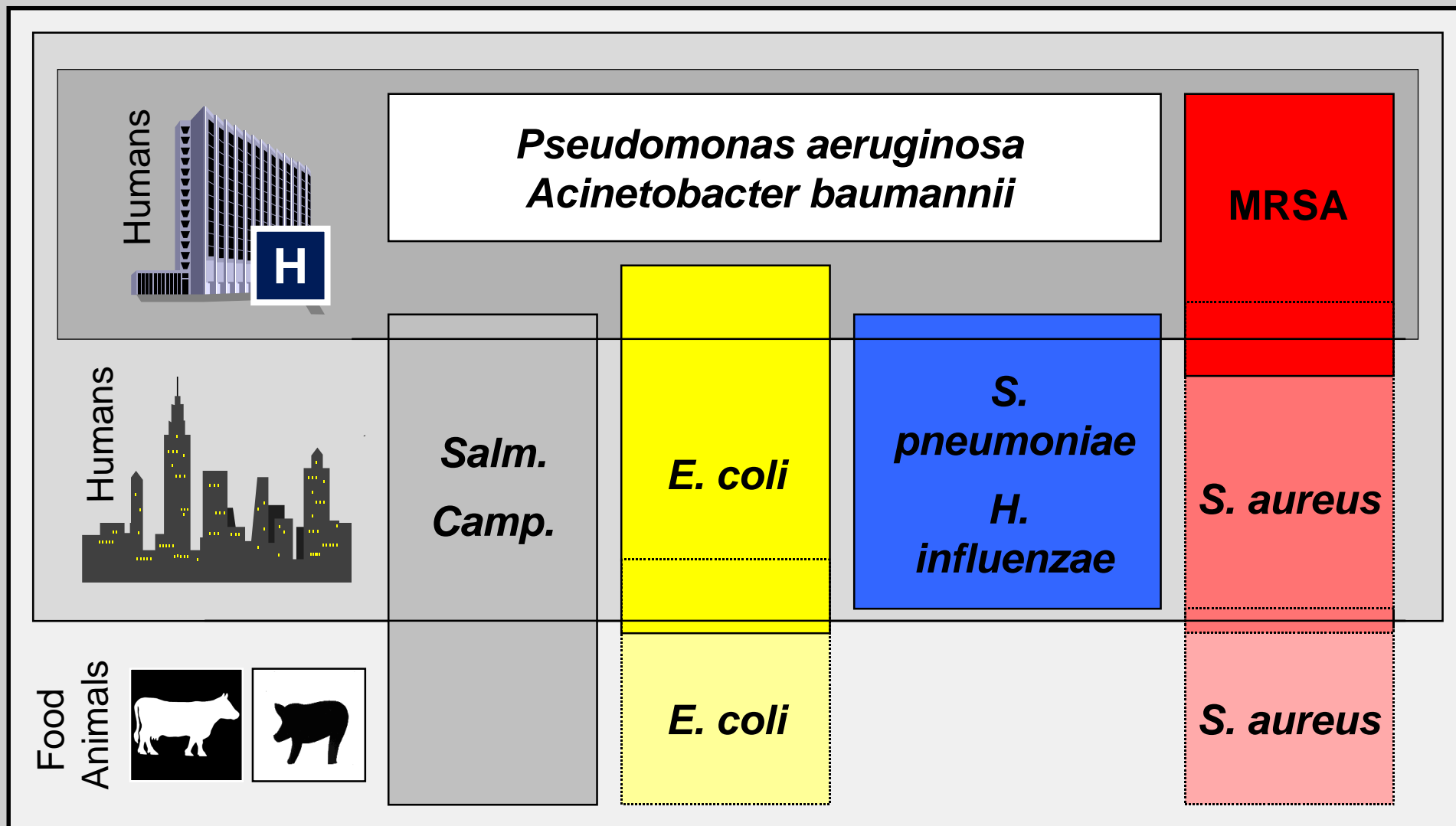


Ticarcillin-Resistant *Pseudomonas aeruginosa* in Europe (ICU NIs only), 1992



Source: EPIC Study (Régnier B. Pathol Biol 1996;44:113-23).

The World According to... Human Bacterial Pathogens and Their Habitat

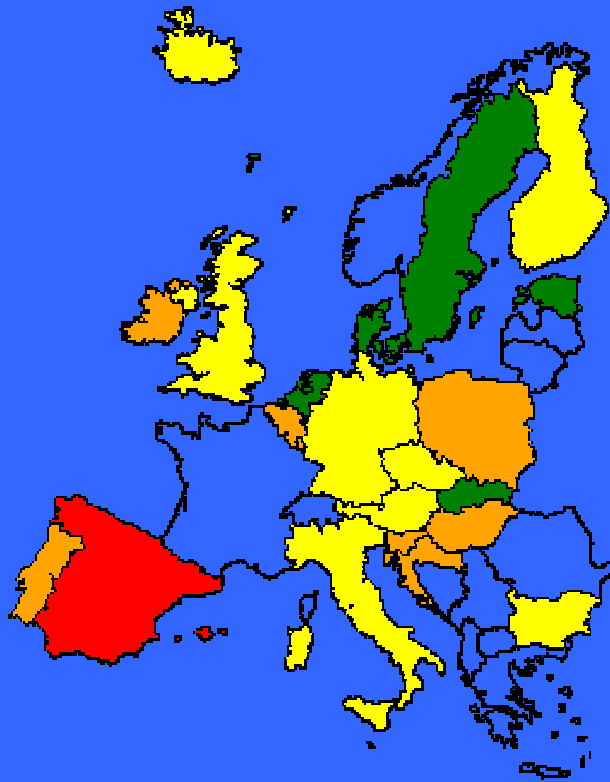
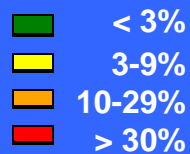


le MONDe de la Résistance Intrinsèque et Acquisée aux ANTibiotiques ;-).

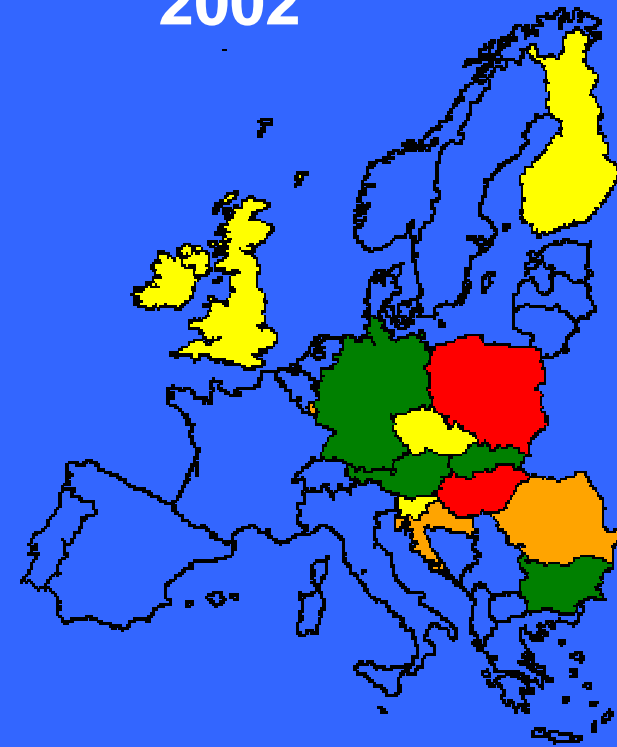
Penicillin-Non Susceptible *Streptococcus pneumoniae* (PNSP) from Sterile Sites



2001



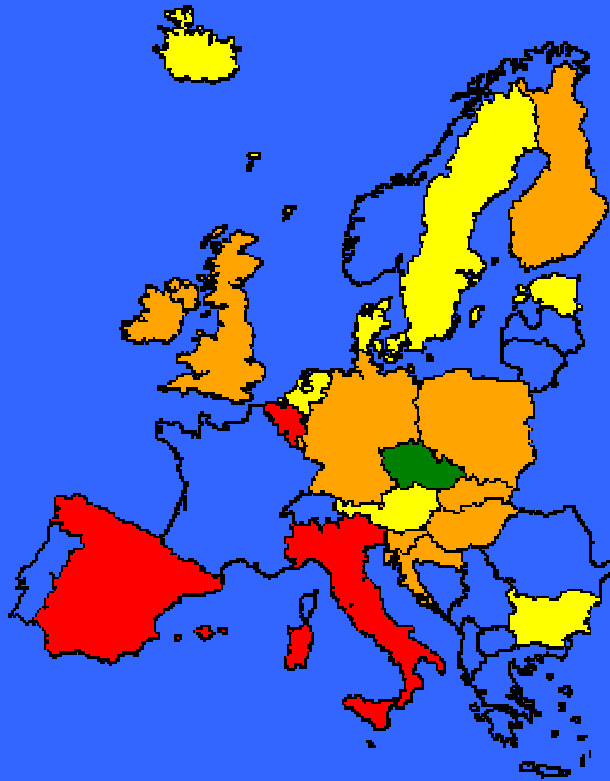
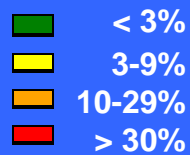
2002



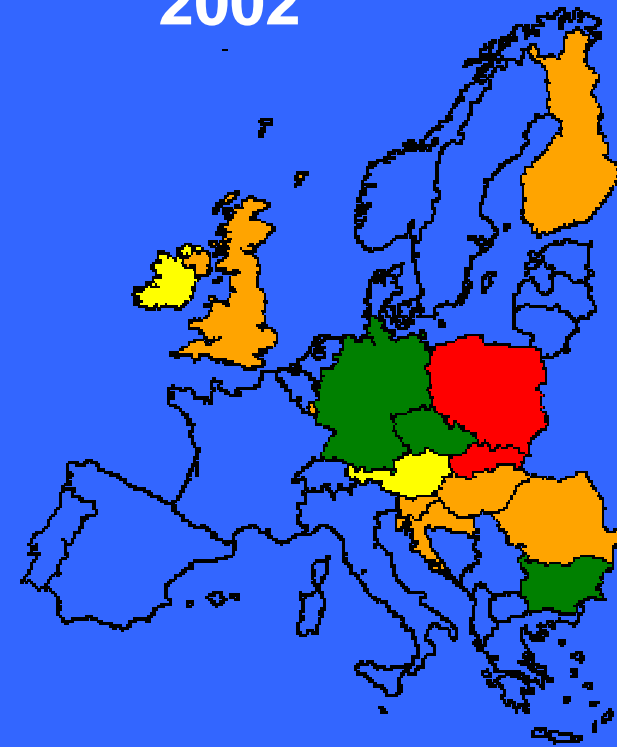
Erythromycin-Resistant *Streptococcus pneumoniae* from Sterile Body Sites



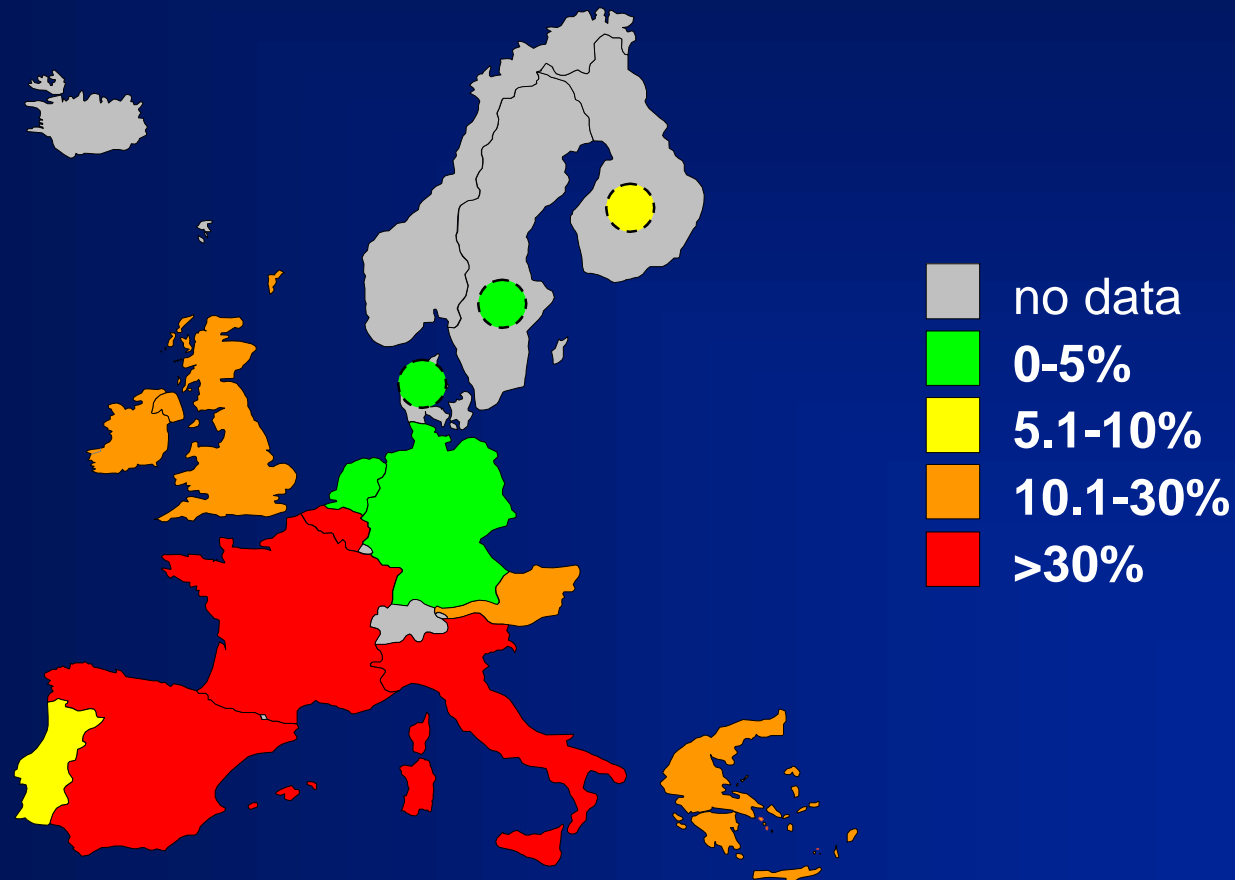
2001



2002



Erythromycin-Resistant *Streptococcus pneumoniae* from Community-Acquired Respiratory Tract Infections, 1998



Sources: Alexander Project, FINRES, STRAMA and DANMAP.

- Lower use of macrolides
(less exposed, shorter duration)
- Lower use of other antimicrobials
- Better compliance (dose, intervals)

More rational utilization of antimicrobials?

Lower Percentage of Erythromycin-R *S. pneumoniae* in Community-Acquired RTIs

Different population?

- Age (extremes)
- Respiratory and other diseases

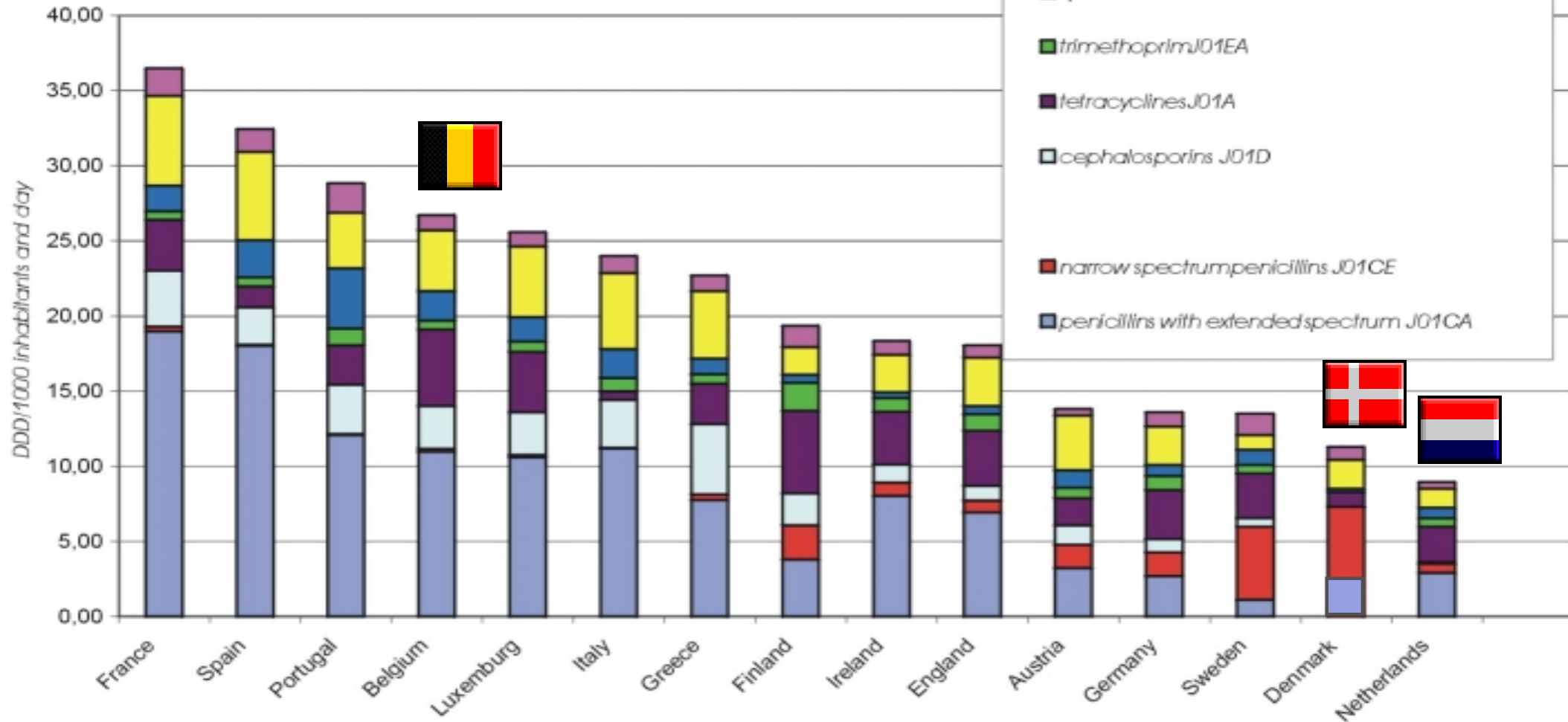
- Pre-school facilities
- Long-term care?
- Better living conditions
- Socio-economic status
- Climate?
- Less travel
- Different clones

Less cross-transmission?

Better protection against disease?

- Vaccination
- Breast feeding

Sales of different classes of antibiotics to outpatients 1997 in the EU



Source: Cars O, et al. Lancet 2001; 357: 1851-3.



Is It Relevant to Examine Overall Antibiotic Consumption? (1)

- Overall antibiotic consumption (no. DDD) is related to no. antibiotic prescriptions and no. persons exposed to antibiotics
- It only accounts for some aspects of antibiotic misuse, e.g. prescribed when not indicated, duration too long, but cannot account for errors in dosing or low compliance
- Nevertheless, if the antibiotic course prescribed is not completed, then it is probably used at another occasion

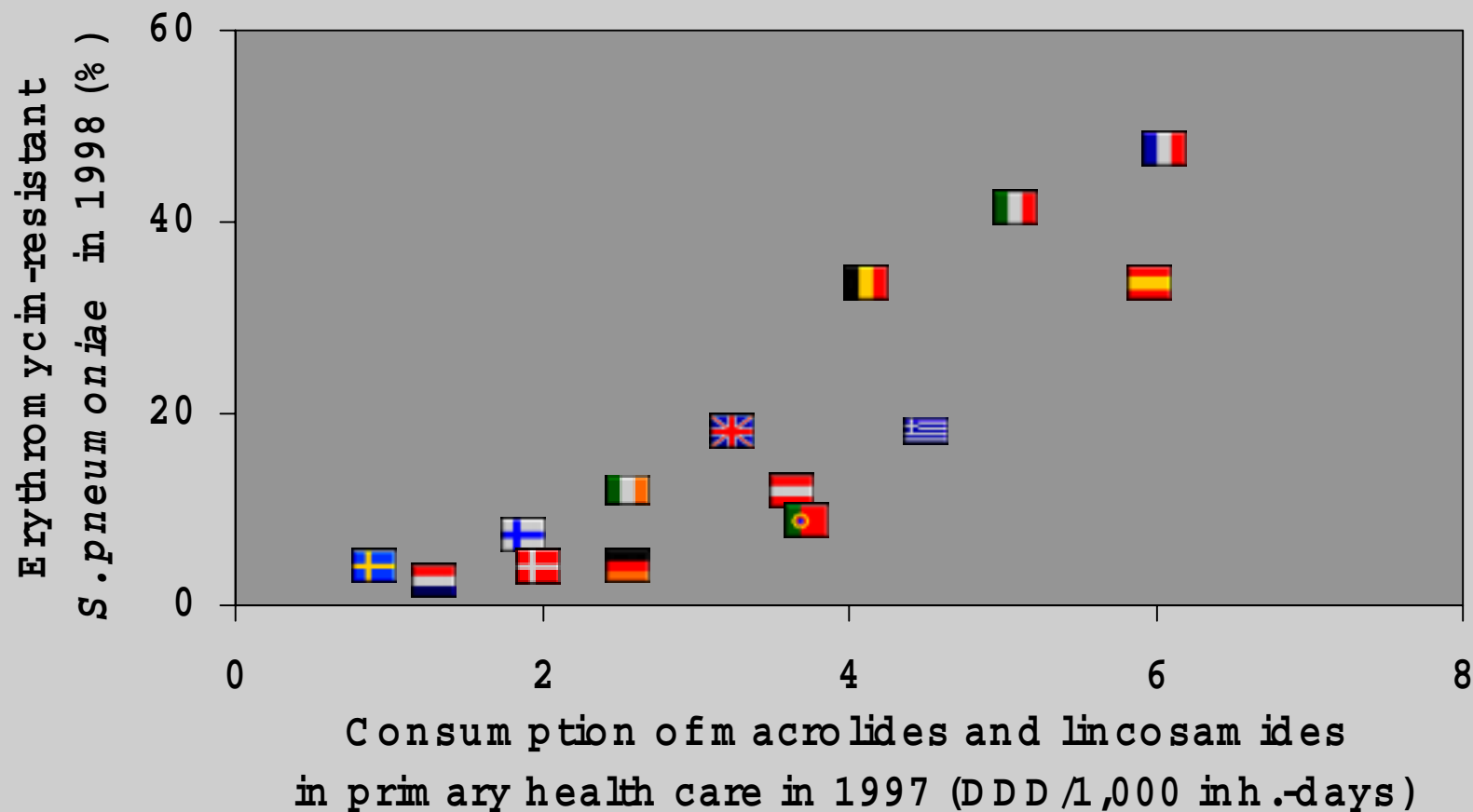


Is It Relevant to Examine Overall Antibiotic Consumption? (2)

- Antibiotics have an effect not only on the patients who are treated but also an effect on other patients and the environment
- Relationship between antibiotic use and resistance is an ecological problem!
- There is room for improvement considering the extent of variations both in the amount and the pattern of use among European countries



Erythromycin-Resistant *Streptococcus pneumoniae* and Macrolide Consumption in EU Member States, 1997-1998



Sources: Alexander Project, FINRES, STRAMA, DANMAP, and Cars O, et al. Lancet 2001; 357: 1851-3.

%Erythromycin-R *S. pneumoniae* (Logodds transf.) and Antimicrobial Consumption in Europe

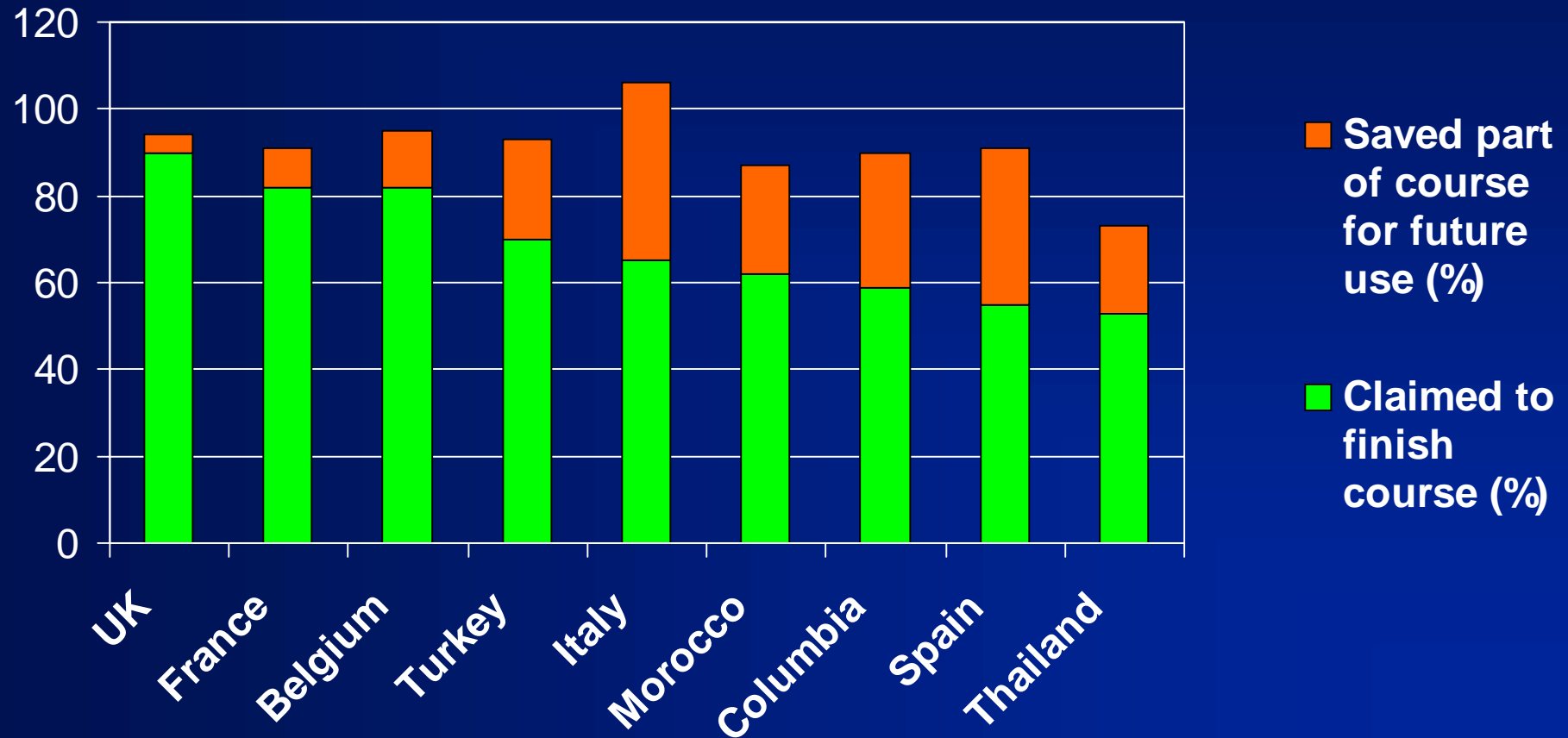


Independent variable (ATC group)	No. EU countries	R ²	P
Tetracyclines (J01A)	14	<0.1	NS
Extended spectrum penicillins (J01CA , Ln tr.)	14	0.74	<0.001
Beta-lactamase sensitive penicil. (J01CE, Ln tr.)	14	0.49 (-)	0.005
Beta-lactamase resistant penicillins(J01CF)	14	<0.1 (-)	NS
Cephalosporins (J01DA)	14	0.55	0.003
Trimethoprim (J01EA, Ln tr.)	14	<0.1	NS
Macrolides and lincosamides (J01F)	14	0.82	<0.001
Fluoroquinolones (J01MA, Ln tr.)	14	0.32	0.04
Other antibacterials (from ATC group J01)	14	0.14	NS

Source for resistance data: Alexander Project.

Source for antimicrobial consumption data: Cars O, et al. Lancet 2001; 357: 1851-3.

Patients' Interviews and Misuse of Antibiotics, 1993-



Source: Pechère J-C. Clin Infect Dis 2001; 33 (Suppl 3): S170-S173.

%Erythromycin-R *S. pneumoniae* (Logodds transf.) and Factors That Might Facilitate Cross-Transmission



Independent variable	No. EU countries	R ²	P
Preschool children taking up offers of preschool services (%)	10	0.39	0.06
Population whose daily caring activities prevent them from undertaking the same amount of paid work (%)	14	0.12 (-)	NS
Persons living in households with children (%)	14	0.33	0.03
Persons in overcrowded households (% , Ln transf.)	14	0.29	0.05
Households lacking at least one of three basic amenities, i.e. bath, toilet or hot water (% , Ln transf.)	12	<0.1	NS
Persons living below the "poverty line" (% , Ln tr.)	12	0.32	0.06
Nights spent in EU countries with high %Ery-R <i>S.p.</i> (per 1,000 inh.-days, incl. domestic, Ln transf.)	14	0.27	0.06

Sources: Danish National Institute of Social Research, EC Eurostat, and European Travel Commission (ETC) Tourism Statistics.



%Erythromycin-R *S. pneumoniae* (Logodds transf.) and Susceptibility to/Protection against Disease

Independent variable	No. EU countries	R ²	P
Population whose age is ≤ 4 years (%)	14	<0.1 (-)	NS
Population whose age is >65 years (%)	14	0.13	NS
Daily cigarette smokers (%)	14	0.12	NS
Households that cannot afford to keep home adequately warm (%; Ln transf.)	13	0.22	NS
Distributed doses of pneumococcal vaccine (per 10,000 inhabitants, 1996, Ln transf.)	14	<0.1	NS
Infants breastfed at 3 months of age (%; Ln tr.)	13	0.47 (-)	0.01
Persons with at least 3 hours of physical activity (leisure) in a typical week (%)	14	0.29 (-)	0.05

Sources: U.S. Bureau of the Census, EC Eurostat, WHO Regional Office for Europe, and Fedson DS. Clin Infect Dis 1998;26:1117-23.



Multiple Linear Regression Models for Prediction of %Erythromycin-R *S. pneumoniae* (Logodds transf.): Preliminary Results

Independent variable	β	t	P
(Constant)	-	-12.398	<0.001
Macrolides and lincosamides (J01F)	0.904	7.329	<0.001

$R^2=0.817$

Independent variable	β	t	P
Macrolides and lincosamides (J01F)	0.840	6.796	0.012
Infants breastfed at 3 months of age (% , Ln tr.)	-1.619	-13.100	0.011

$R^2=0.959$

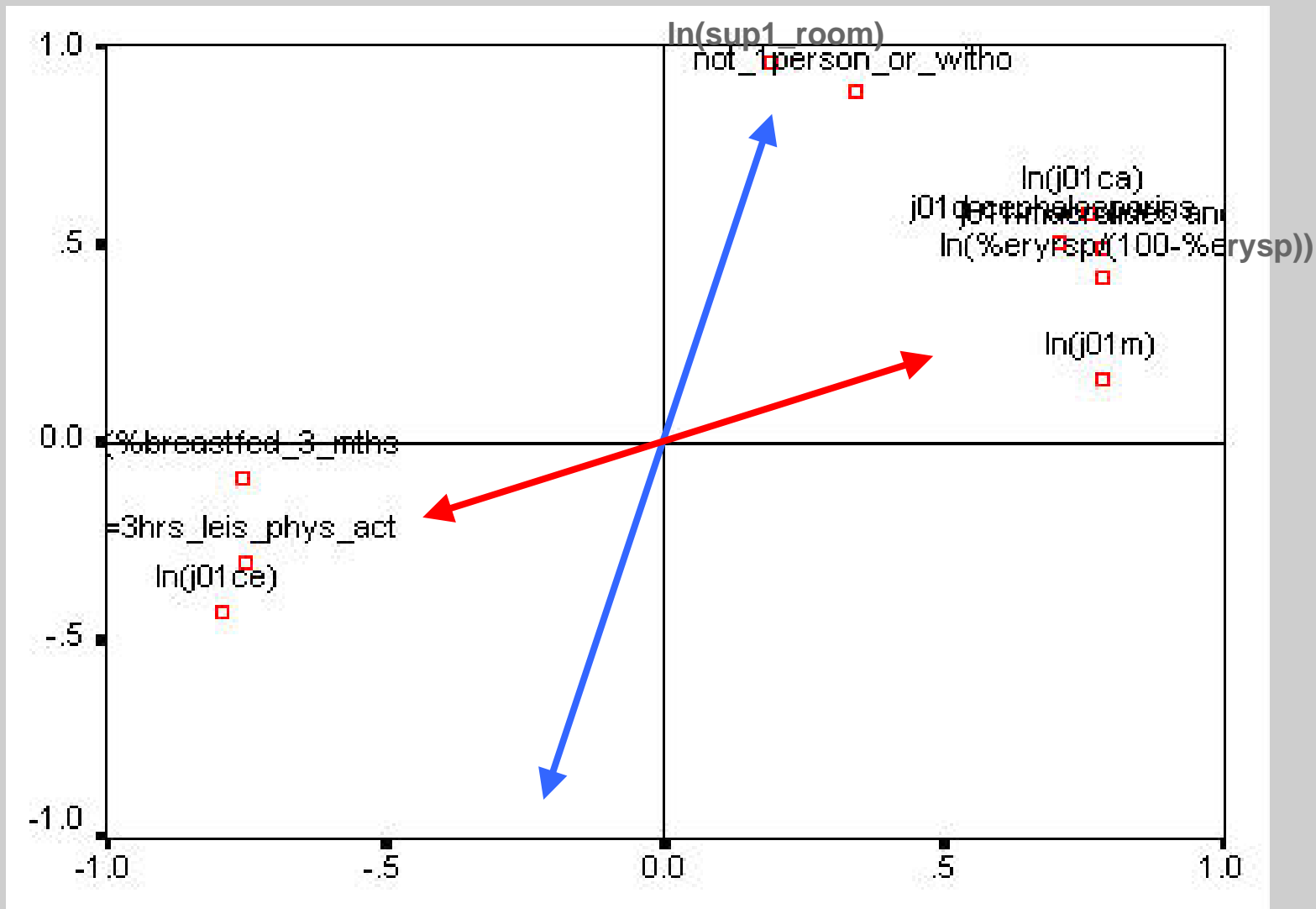
**Factor Analysis (PCA) of %ERSP (Logodds transf.)
and Other Variables: Preliminary Results (1)**



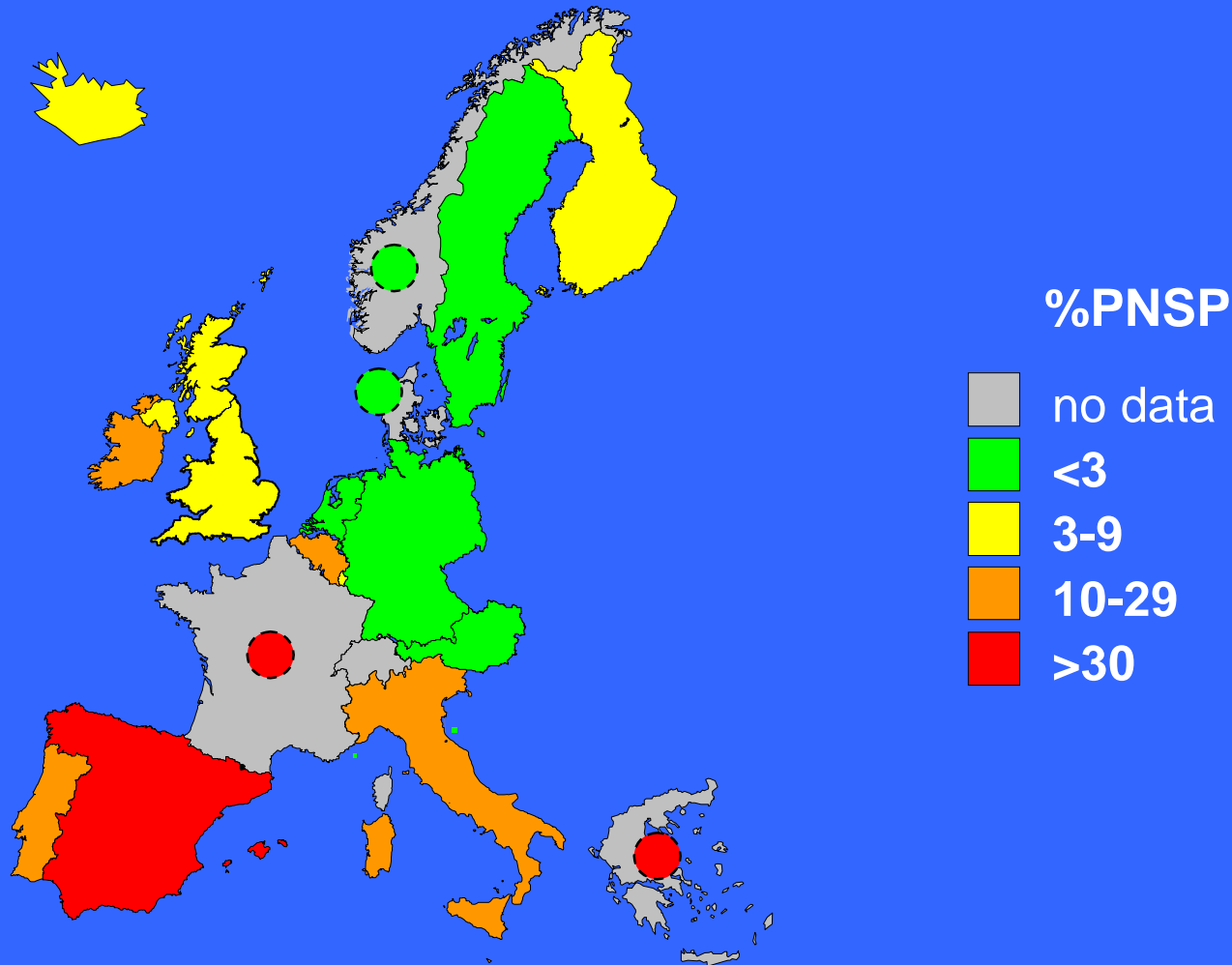
Variable	Component	
	1	2
%Erythromycin-R <i>S. pneumoniae</i> (Logodds tr.)	0.779	0.410
Macrolides and lincosamides (J01F)	0.781	0.489
Cephalosporins (J01DA)	0.702	0.502
Extended spectrum penicillins (J01CA , Ln transf.)	0.755	0.574
Beta-lactamase sensitive penicil. (J01CE, Ln trsf.)	-0.795	-0.428
Fluoroquinolones (J01MA, Ln transf.)	0.784	0.159
Persons with at least 3 hours of physical activity (leisure) in a typical week (%)	-0.750	-0.303
Infants breastfed at 3 months of age (% , Ln transf.)	-0.755	-0.090
Persons in overcrowded households (% , Ln transf.)	0.189	0.954
Persons living in households with children (%)	0.342	0.879



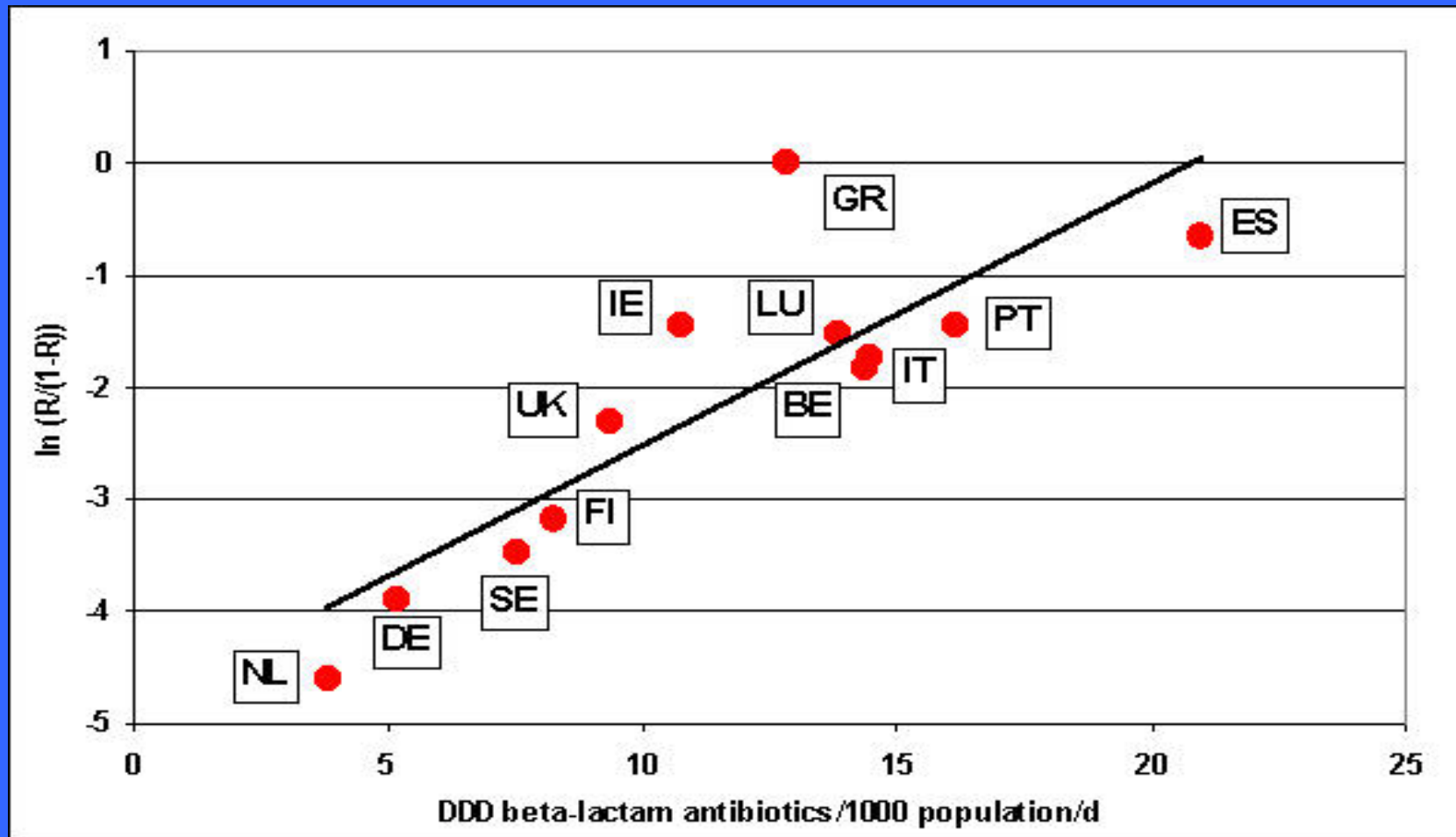
Factor Analysis (PCA) of %ERSP (Logodds transf.) and Other Variables: Preliminary Results (2)



Penicillin-Non Susceptible *Streptococcus pneumoniae* (PNSP) from Sterile Sites, 2000



Penicillin-Non Susceptible *S. pneumoniae* from Sterile Sites (1998-99, log odds transf.) & Consumption of Beta-Lactams (1997) in the EU



Source: Bronzwaer SLAM, et al. Emerg Infect Dis 2002; 8: 278-282.



%PNSP (Logodds transf.) and Antimicrobial Consumption in Europe

Independent variable (ATC group)	No. EU countries	R ²	<i>P</i>
Tetracyclines (J01A)	14	<0.1	NS
Extended spectrum penicillins (J01CA , Ln tr.)	14	0.66	<0.001
Beta-lactamase sensitive penicil. (J01CE, Ln tr.)	14	0.31 (-)	0.04
Beta-lactamase resistant penicillins(J01CF)	14	<0.1 (-)	NS
Cephalosporins (J01DA)	14	0.74	<0.001
Trimethoprim (J01EA, Ln tr.)	14	<0.1	NS
Macrolides and lincosamides (J01F)	14	0.71	<0.001
Fluoroquinolones (J01MA, Ln tr.)	14	0.26	0.06
Other antibacterials (from ATC group J01)	14	0.18	NS

Source for resistance data: EARSS.

Source for antimicrobial consumption data: Cars O, et al. Lancet 2001; 357: 1851-3.

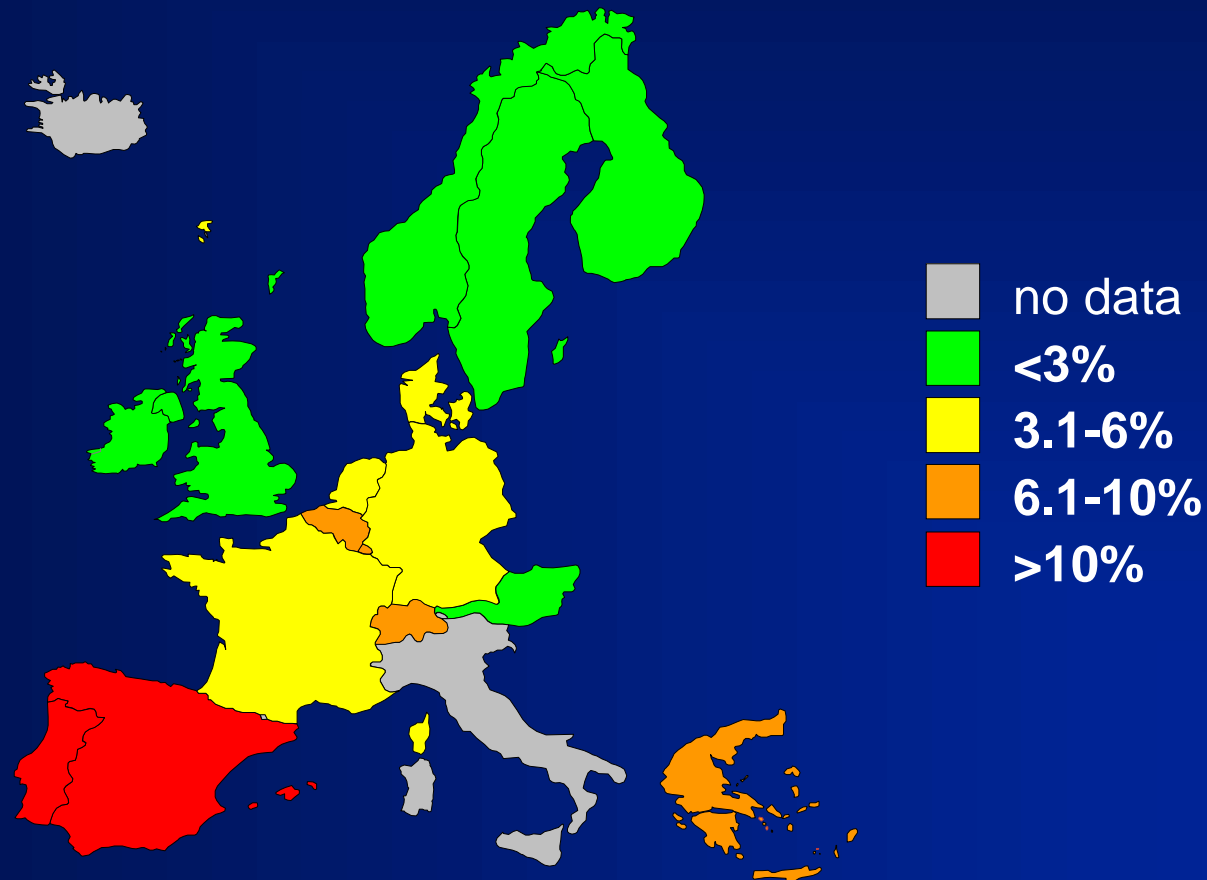


Multiple Linear Regression Model for Prediction of %PNSP (Logodds transf.): Preliminary Results

Independent variable	β	t	P
(Constant)	-	-10.386	<0.001
Cephalosporins (J01DA)	0.860	5.839	<0.001

$R^2=0.740$

Nalidixic Acid-Resistant *Escherichia coli* from Community-Acquired Uncomplicated UTIs in Women, ECO-SENS Project, 1999-2000



Source: Kahlmeter G. Clin Microbiol Infect 2001;7(Suppl 1): 86.



%Nalidixic Acid-Resistant *E. coli* (Logodds transf.) and Antimicrobial Consumption in Europe

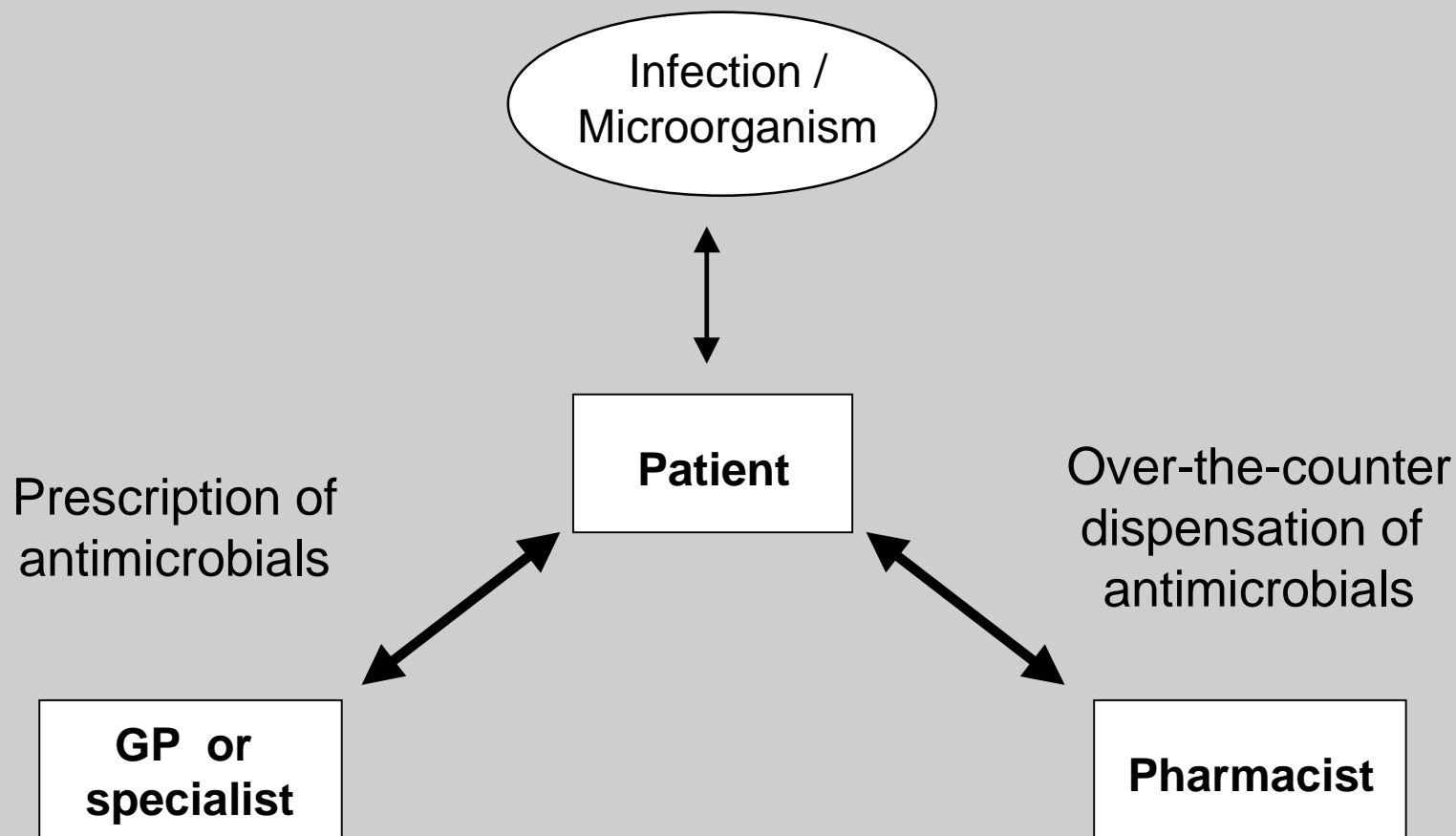
Independent variable (ATC group)	No. EU countries	R ²	P
Tetracyclines (J01A)	14	0.11	NS
Extended spectrum penicillins (J01CA , Ln tr.)	14	0.31	0.04
Beta-lactamase sensitive penicil. (J01CE, Ln tr.)	14	0.64 (-)	0.001
Beta-lactamase resistant penicillins(J01CF)	14	<0.1 (-)	NS
Cephalosporins (J01DA)	14	0.20	NS
Trimethoprim (J01EA, Ln tr.)	14	<0.1 (-)	NS
Macrolides and lincosamides (J01F)	14	0.35	0.03
Fluoroquinolones (J01MA, Ln tr.)	14	0.49	0.005
Other antibacterials (from ATC group J01)	14	0.15	NS

Source for resistance data: Kahlmeter G, et al. ECO.SENS.

Source for antimicrobial consumption data: Cars O, et al. Lancet 2001; 357: 1851-3.

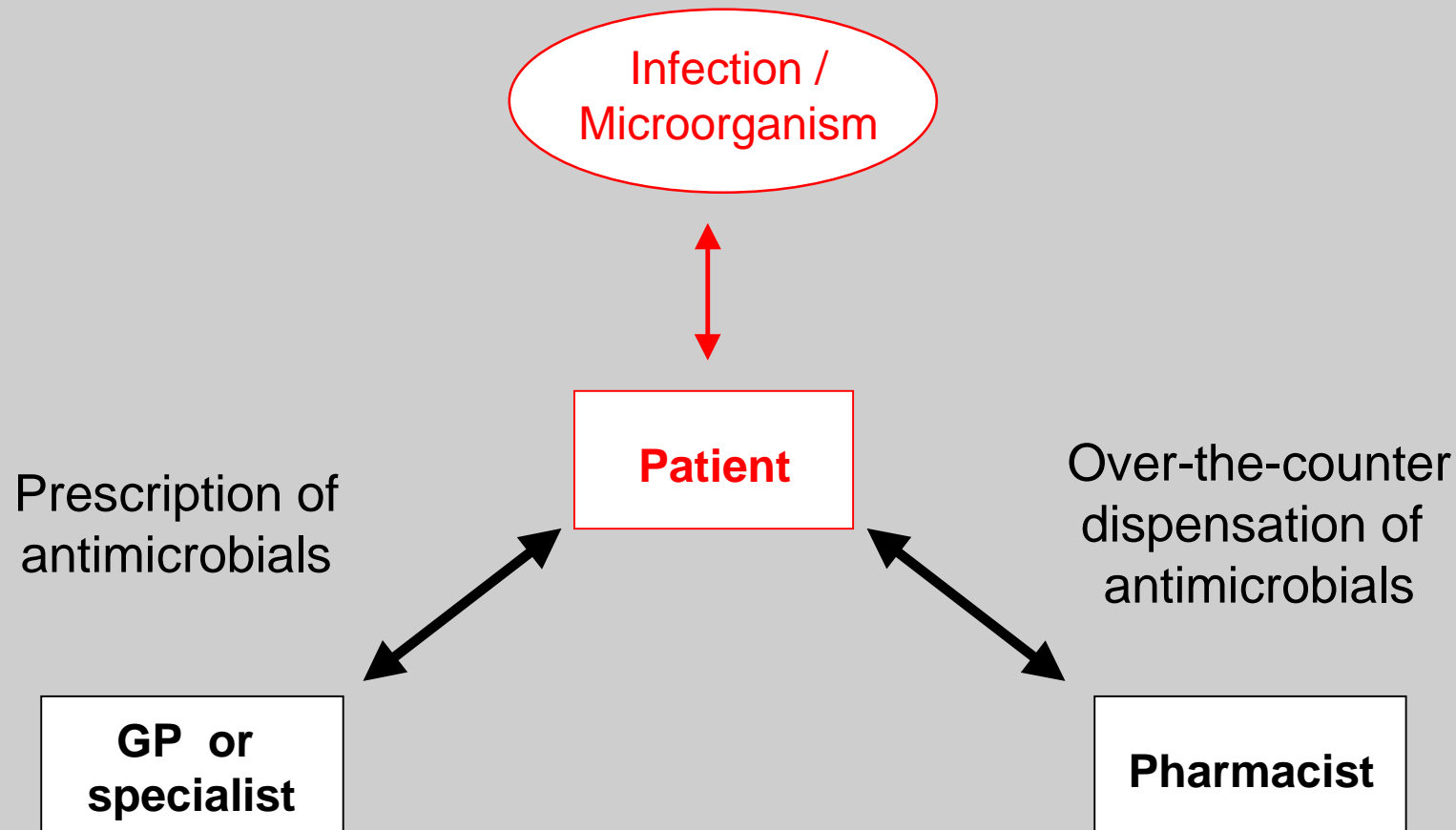


Pathways of Antimicrobial Use in Primary Health Care





Pathways of Antimicrobial Use in Primary Health Care (1)








Different Susceptibility to/Protection Against Infectious Diseases or Incidence of Community-Acquired Infectious Diseases?

- Demography
- Incidence of certain diseases, e.g. diabetes, cancer
- Living conditions: overcrowding, day care, hygiene
- Protecting factors: breastfeeding, vaccinations

- Incidence of community-acquired infections: bacterial RTIs, influenza-like illness
- Prevalence of resistance among community-acquired bacteria

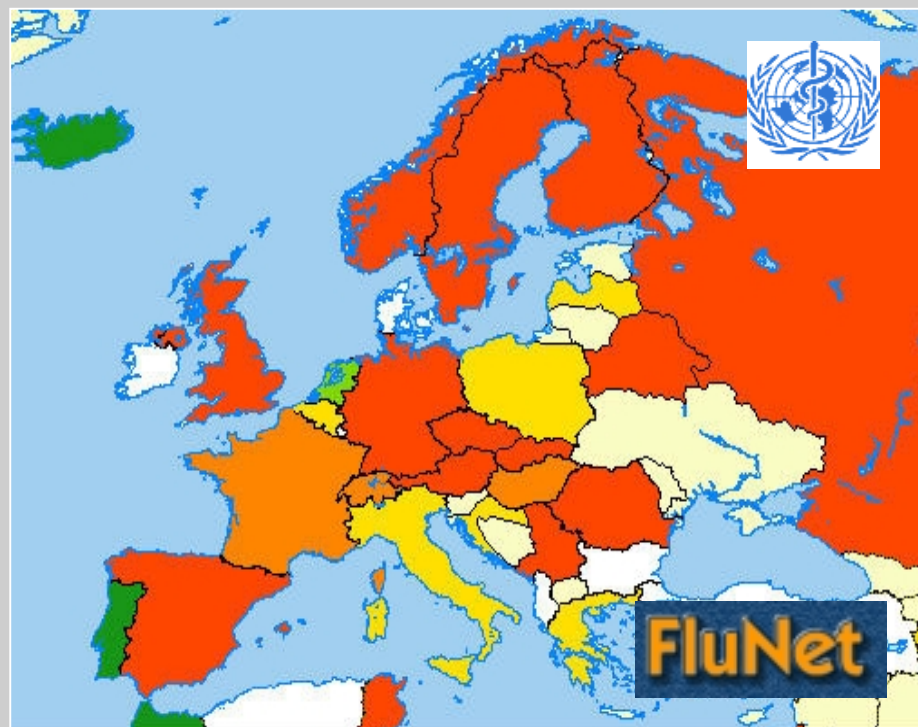


Characteristics of the Population of 3 EU Member States, 1996-1999 (1)

	Belgium 	Netherlands 	Denmark 
Population (million inhab.)	10.2	15.7	5.3
Pop. 0-4 year old (%)	6	6	6
Pop. > 65 year old (%)	17	14	15
Urban population (%, WHO)	97	89	86
Pop. density (inhab./km ²)	336	464	125
Pop. in overcrowded homes (%)	10	3	9
Pop. below "poverty line" (%)	17	12	11
Pop. cannot afford to keep home adequately warm (%)	3	2	3
Pop. without at least one of bath, toilet or hot water (%)	7	1	3



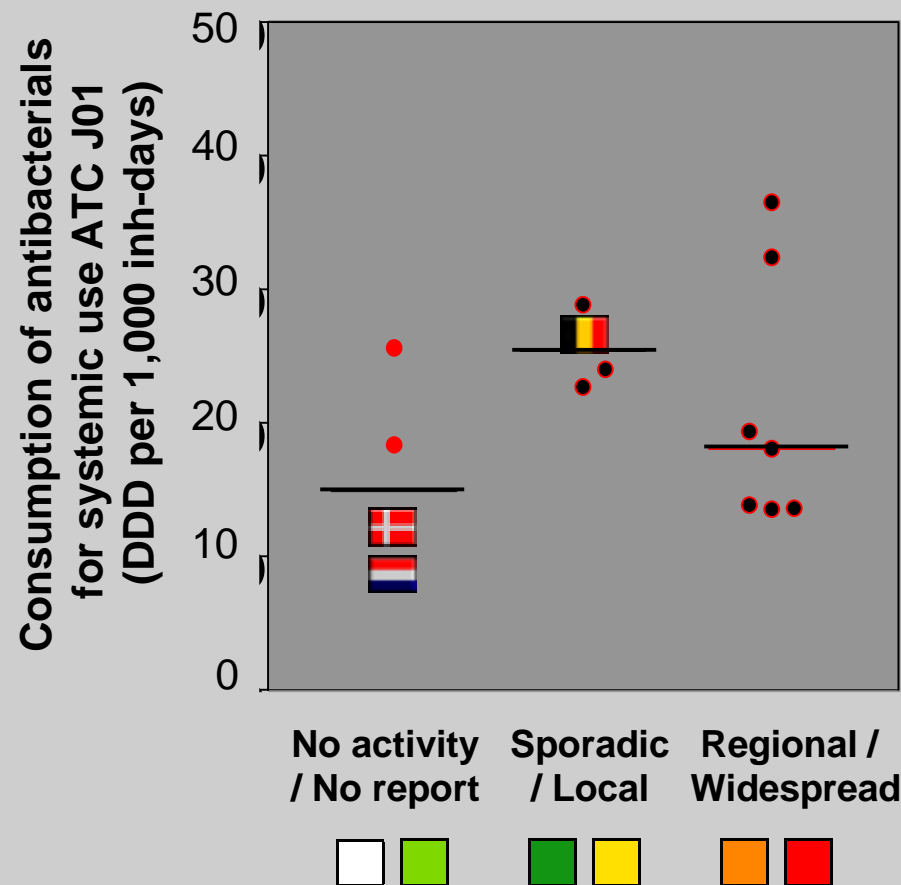
Influenza-Like Illness Activity and Overall Consumption of Systemic Antibacterials (ATC J01) in Primary Health Care, EU Member States, 1997



Influenza-Like Illness Activity, 1997

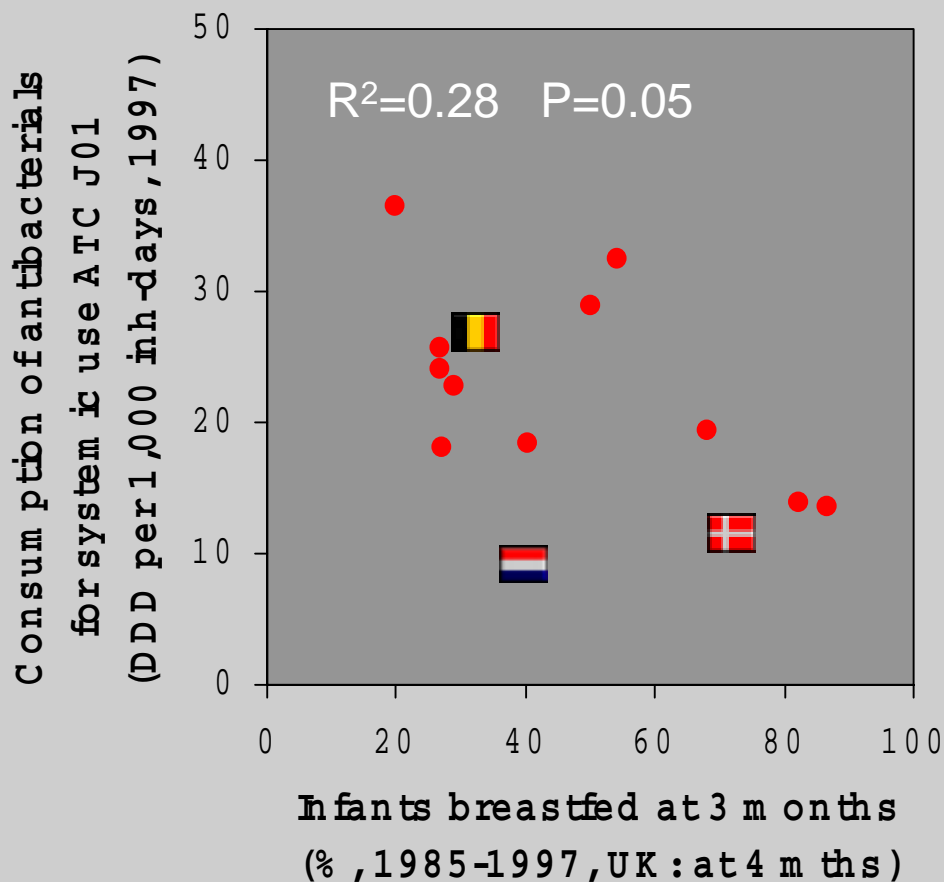
Source: FluNet. Available from:

<http://oms2.b3e.jussieu.fr/flunet/activity.html>





Overall Consumption of Systemic Antibacterials (ATC J01) in Primary Health Care and Breastfeeding, EU Member States, 1985-1997






See also:

Breastfeeding & Respiratory Illness During Childhood

Wilson AC, et al. *BMJ* 1998;316:21-25.



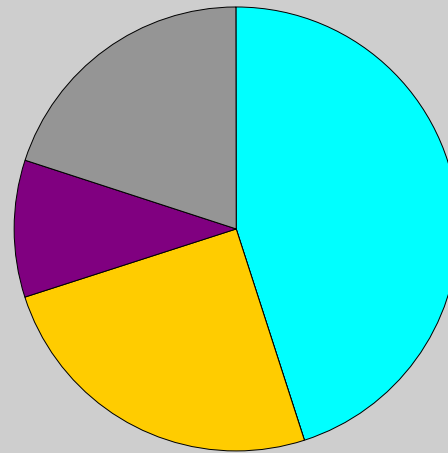
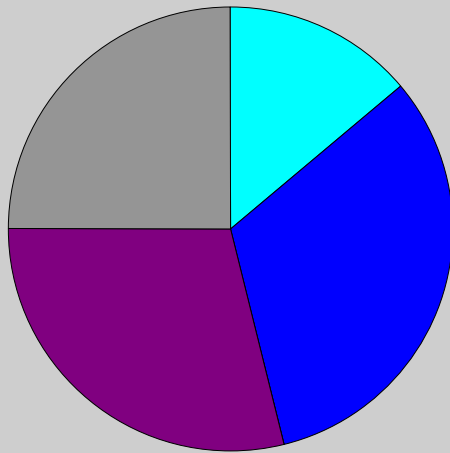
Characteristics of the Population of 3 EU Member States, 1996-1999 (2)






	Belgium 	Netherlands 	Denmark 
Daily smokers (%)	31	34	38
Persons living in households with children (%)	65	60	55
Preschool children taking up offers of preschool services (%)	95	47	80
Respiratory diseases (no./100,000)	1,319	704	1,448
Distrib. doses pneumococcal vaccine (no./10,000 inhab., 1996)	150	3	11
Pop. with at least 3 hours of physical activity (leisure) in typical week (%)	30	57	52
Infants breastfed at 3 months (%)	31	41	70

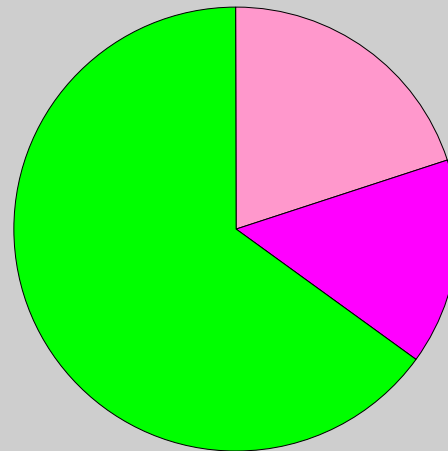
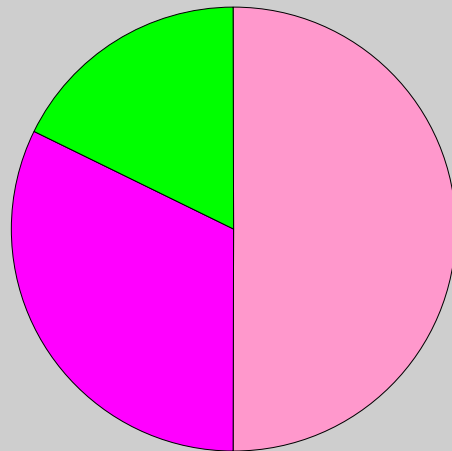
Labelling of Disease and Attitude Towards Upper Respiratory Tract Infections




Flanders 

Netherlands 





-  "A cold"
-  "Bronchitis"
-  "Flu"
-  Unlabelled (e.g., coughing, runny nose)
-  Other (e.g., "sinusitis", "angina")



-  Consulting a doctor
-  Self-medication
-  Nursing one's illness

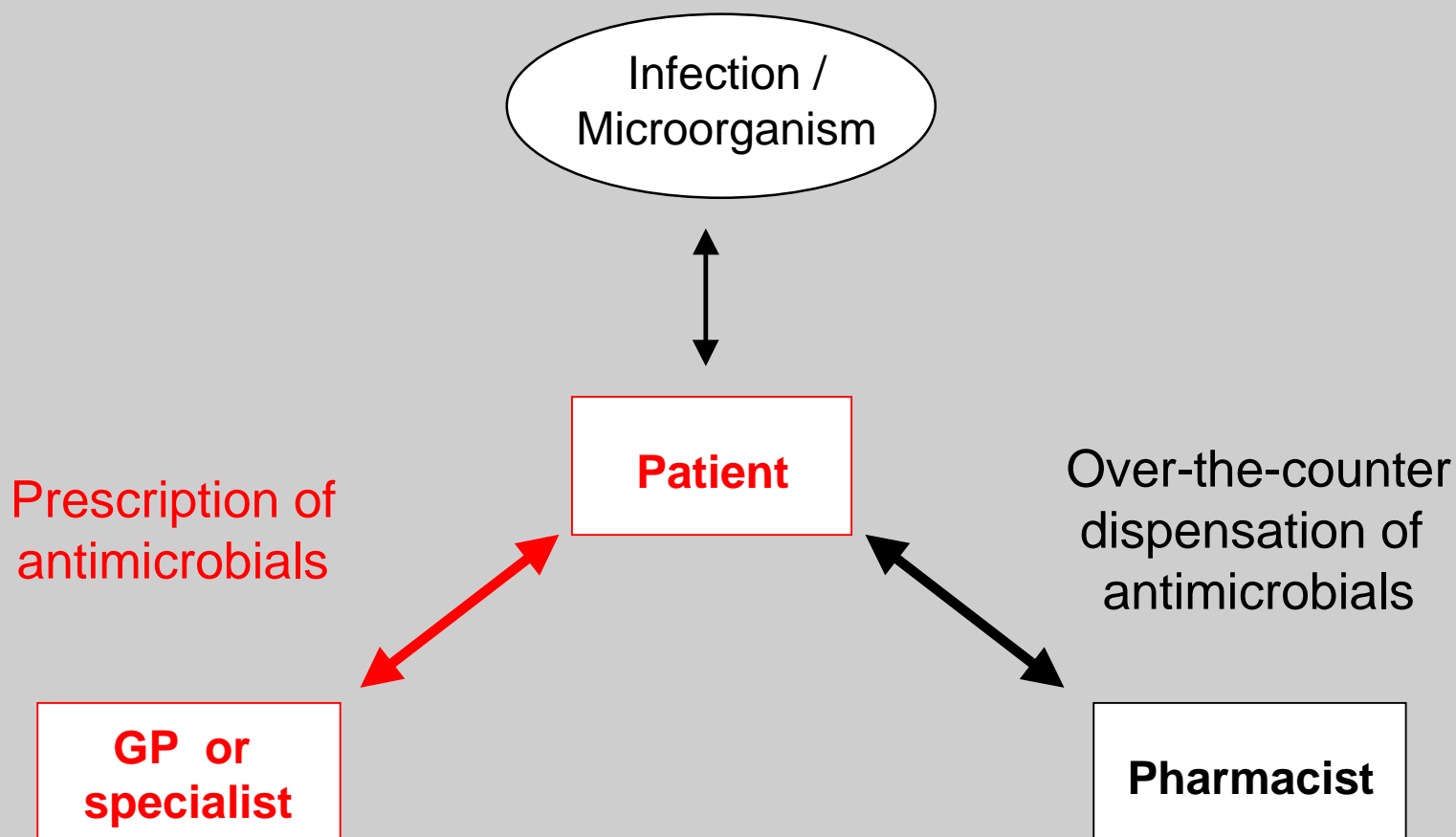


Prescription of Antimicrobials and Bacteriological Testing for Acute Tonsillitis, 1989-1990

	Belgium  (n=44 pts)	Netherlands  (n=62 pts)
Prescribed antibiotics (%)	100	68
- penicillin V (%)	5	86
- amoxicillin (%)	60	14
- macrolide (%)	21	0
Bacteriological tests (%)	13	2
No test, prescribed antibiotics (%)	80	52



Pathways of Antimicrobial Use in Primary Health Care (2)





Factors that Influence Prescription (1): Related to the Patient






- Cultural differences: perceived severity of illness
- Social issues: pressure to be back at work/day care
- Economical issues: income vs. price
- Education and information: information campaigns
- Health care system and regulation: cost of GP consultation, price of antimicrobials after reimbursement, direct access to specialists(?)
- Promotion: direct-to-consumer advertising



Factors that Influence Prescription (2): Related to the GP or the Specialist

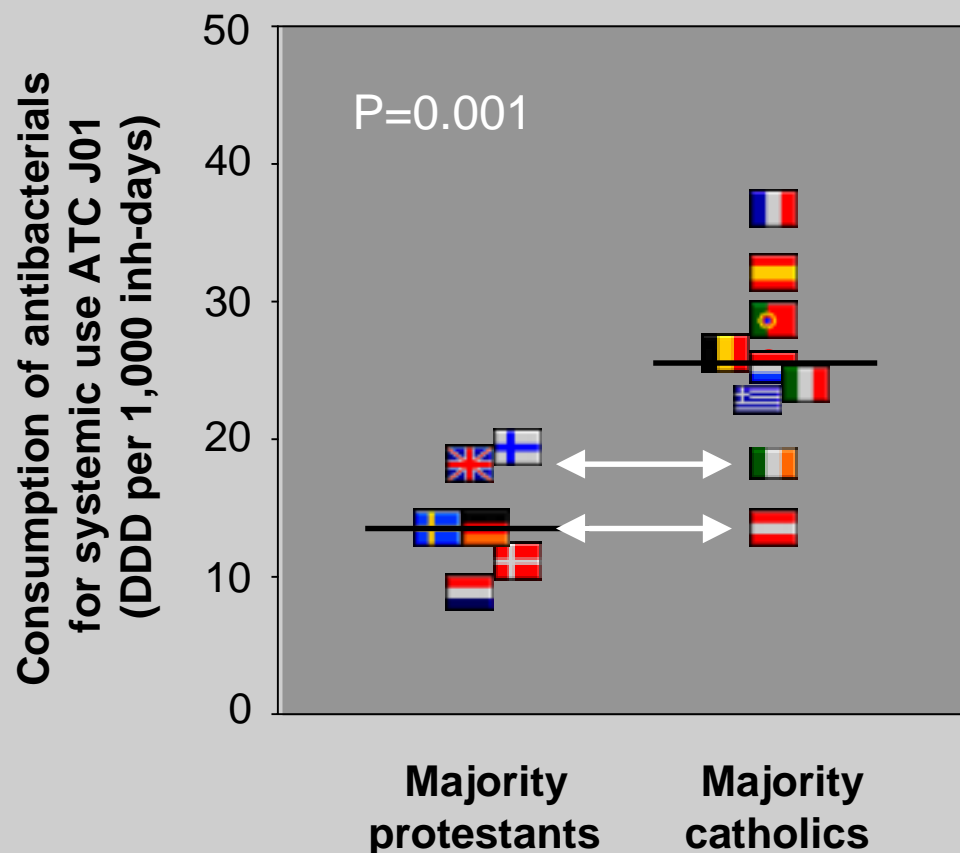
- Cultural differences: willingness to help
- Education and information: information campaigns, guidelines, drug compendia, registered indications for a specific antibiotic, promotional material provided by representatives
- Health care system and regulation: type of healthcare system, rostering of patients, GP remuneration, working hours, point-of-care diagnostic tests, economical incentives, fear of litigation
- Pharmaceutical industry and promotion: competition among pharmaceutical companies, intensity of promotional activity to GPs/specialists

Attitude Towards Upper Respiratory Tract Infections, by Region and Religion

	Catholic, FL  (n=6)	Catholic, NL  (n=3)	Protestant, NL  (n=8)	Non- churchg., FL  (n=9)	Non- churchg., NL  (n=4)
Healing power of body (%)	0	33	88	0	75
Fear of complications (%)	83	0	0	56	0
Belief in antibiotics					
- sceptic (%)	0	33	63	11	25
- strong believer (%)	50	0	0	44	0
Use of antibiotics during the past 5 years					
- none/low (%)	17	67	88	44	25
- high/very high (%)	50	0	0	44	0






What About Cultural Differences in the European Union?



WELL..., INSTEAD OF ALWAYS POINTING AT CULTURAL DIFFERENCES TO EXCUSE OUR LACK OF ACTION OR PREVIOUS MISTAKES, MAY BE... WE COULD LEARN FROM (OTHER) DIFFERENCES AMONG COUNTRIES OR REGIONS AND IDENTIFY AREAS FOR IMPROVEMENT!

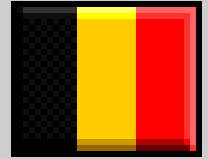


Antimicrobial Prescribing Attitudes of GPs Can Be Modified Through Peer-Review/Education!

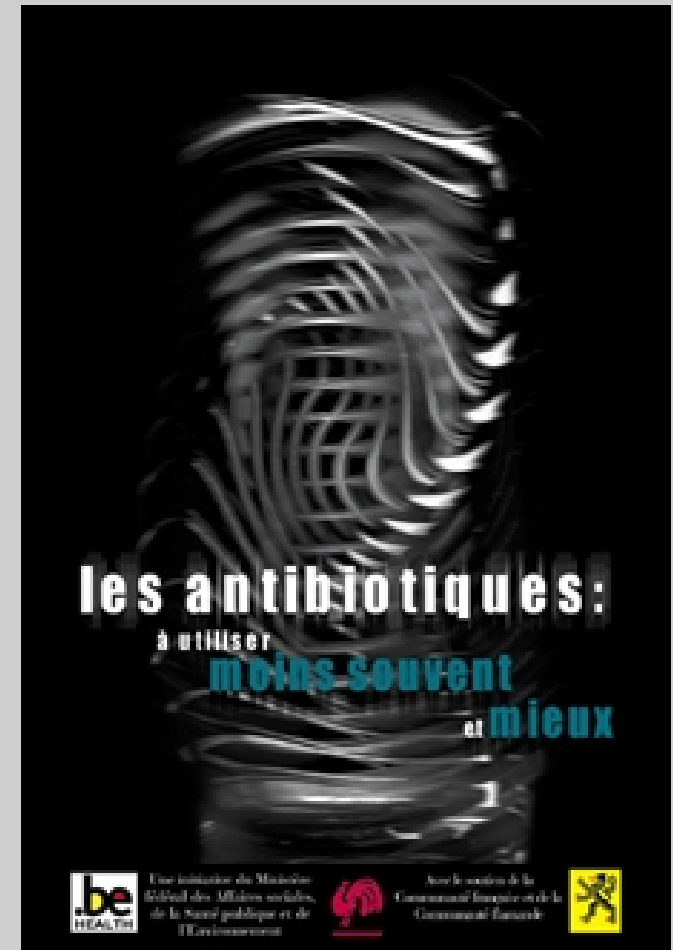
-  Netherlands: peer-review groups (incl. collaborating pharmacist), mandatory clinical audits every 2 or 4 weeks (pharmacist reviews prescriptions)
-  Belgium: **no such peer-review groups**
-  Denmark: Audit Project Odense (APO), voluntary audits and reviews, originally for Danish counties, now expanding in other European countries

Source: Coenen S, et al. Lancet 2001;358:1272; Thiadens HA, et al. Lancet 2001;358:1272-3; Audit Project Odense, 2001 report.

Impact of a Public Campaign for a More Rational Use of Antibiotics in Belgium, 11/2000-03/2001



- **Expect antibiotic for 'flu':**
49% resp. (before) vs. 30% (after)
- **Expect antibiotic for sore throat:**
32% (before) vs. 18% (after)
- **Less antibiotic to avoid resistance:**
64% (before) vs. 75% (after)
- **Antibiotics must be protected:**
13% (before) vs. 25% (after)
- **Total antibiotic sales decreased by approx. 10%**



Source: Beauraind I, et al. Personal communication.

<http://www.antibiotiques.org/>



Characteristics of Spanish vs. Danish Compendia



Dimensions

30x21x7 cm

30x21x5 cm

17x11x2.5 cm

Weight

3.1 kg

1.8 kg

380 g

Main classif.

by company

by disease+alph.

by disease

Financing

pharm. industry

pharm. industry

med. assoc.

Guidelines

no





no

yes

(27 pages)

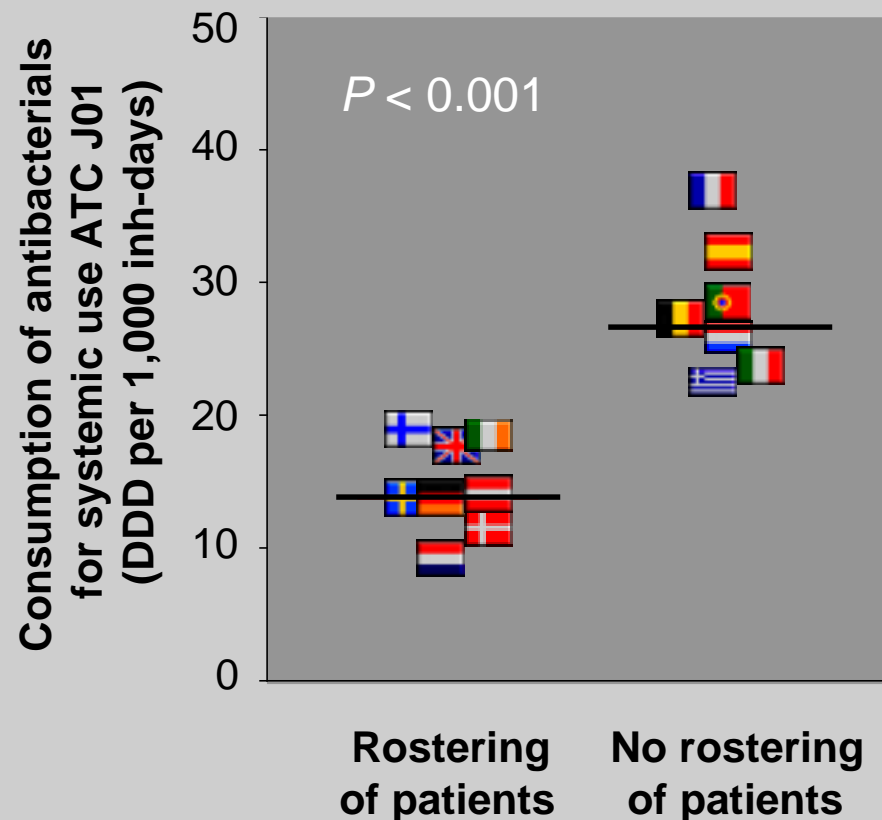
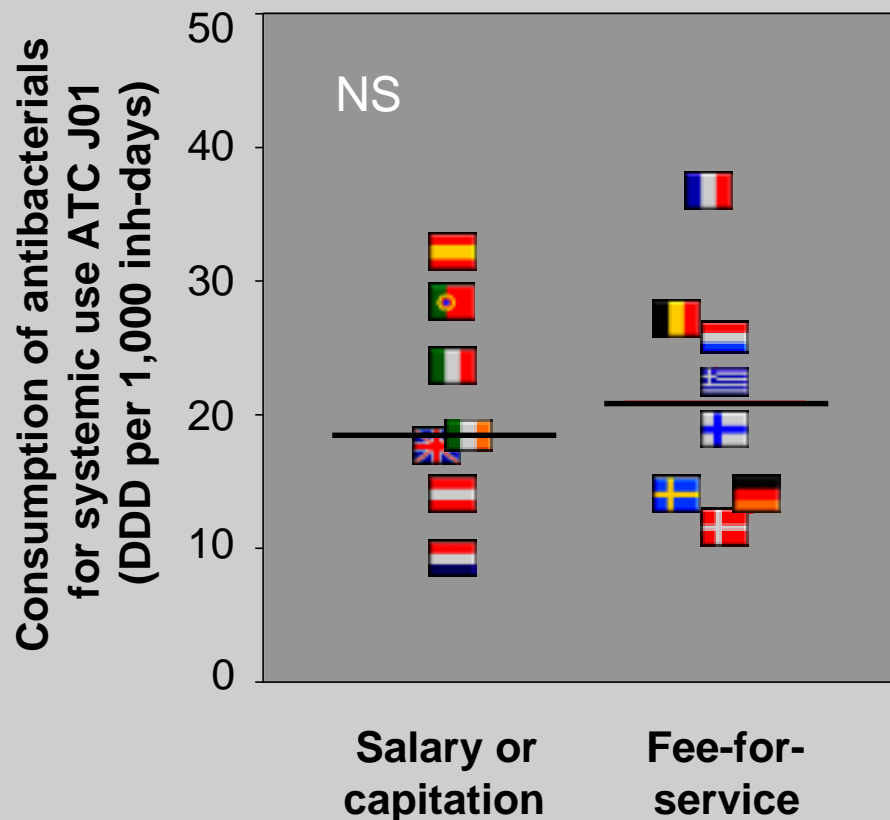


Characteristics of Primary Health Care Systems in Four EU Member States, 1997

	Belgium 	Netherlands 	Denmark 	Sweden 
GP/100,000 inh.	153	48	64	56
Remuneration GPs	Fee	Capitation/Fee	Fee	Salary/Fee
Rostering of patients	No	Yes	Yes	Yes
Referral to specialists	No	Yes	Yes	Yes
Patient pays for:				
- consultations	Partially	No	No	Max./year
- antibiotics	15 – 25%	No	50 – 100%	Max./year

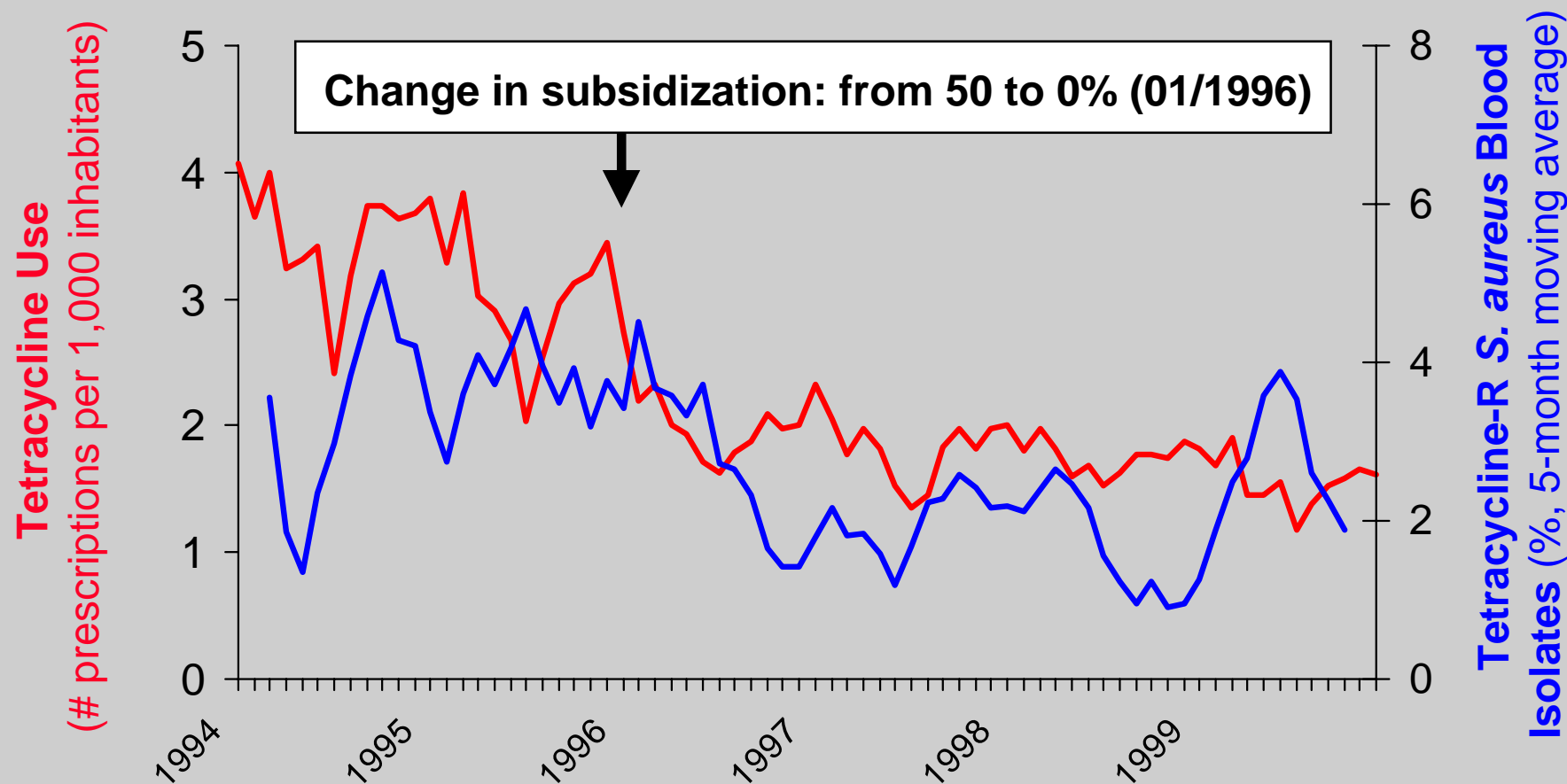


Overall Consumption of Systemic Antibacterials (ATC J01) in Primary Health Care, Fee-for-Service and Rostering of Patients by GPs, EU, 1997



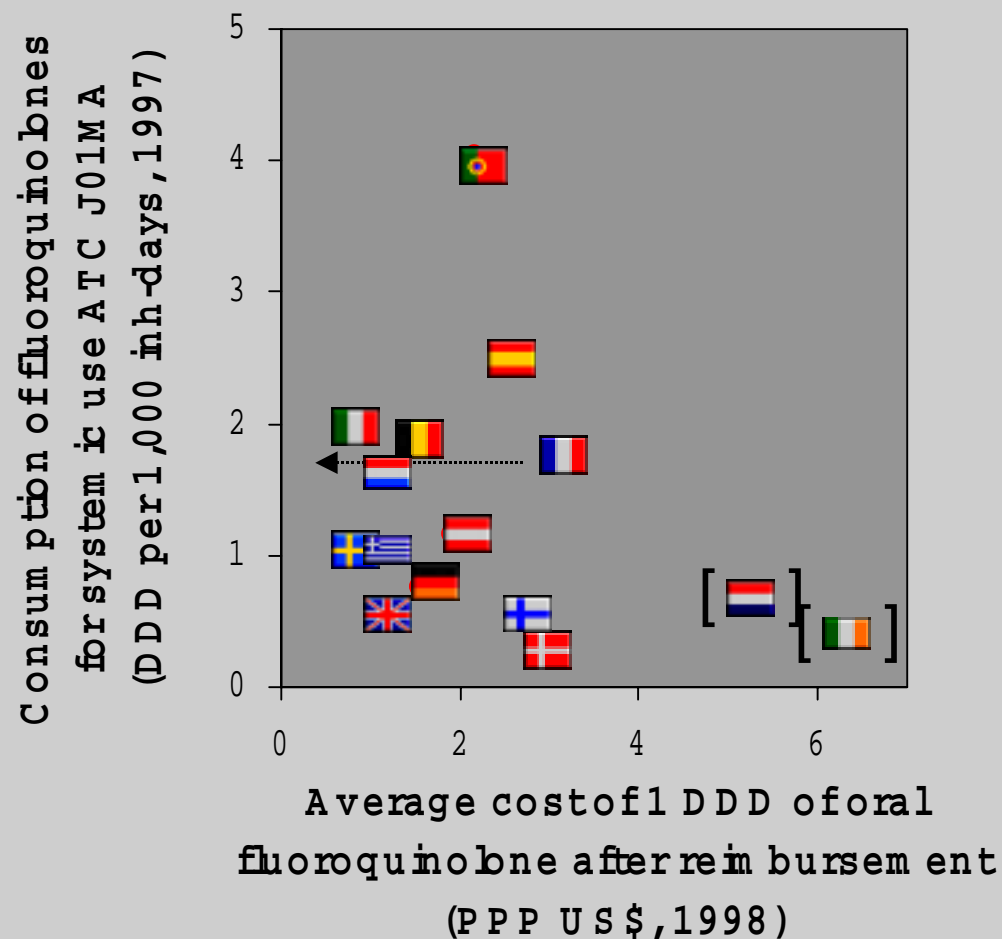
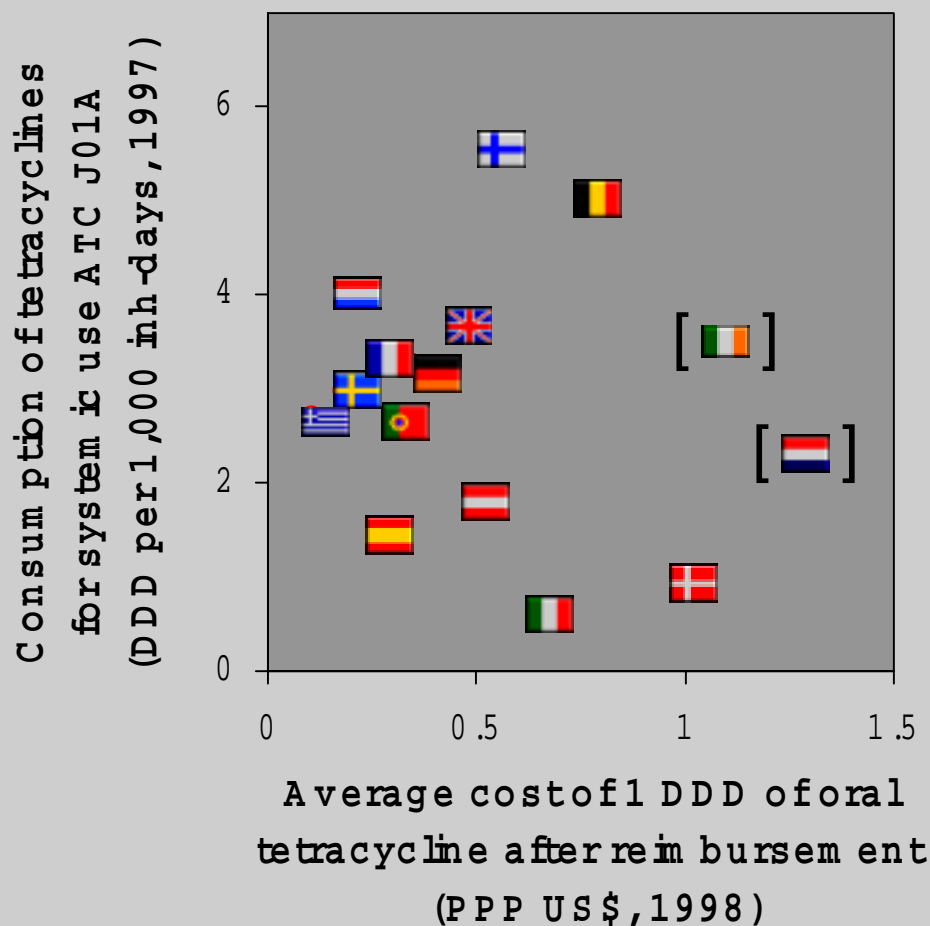


Monthly Tetracycline Prescription Rate and Tetracycline Resistance in *S. aureus* Blood Isolates, Denmark, 01/1994-12/1999



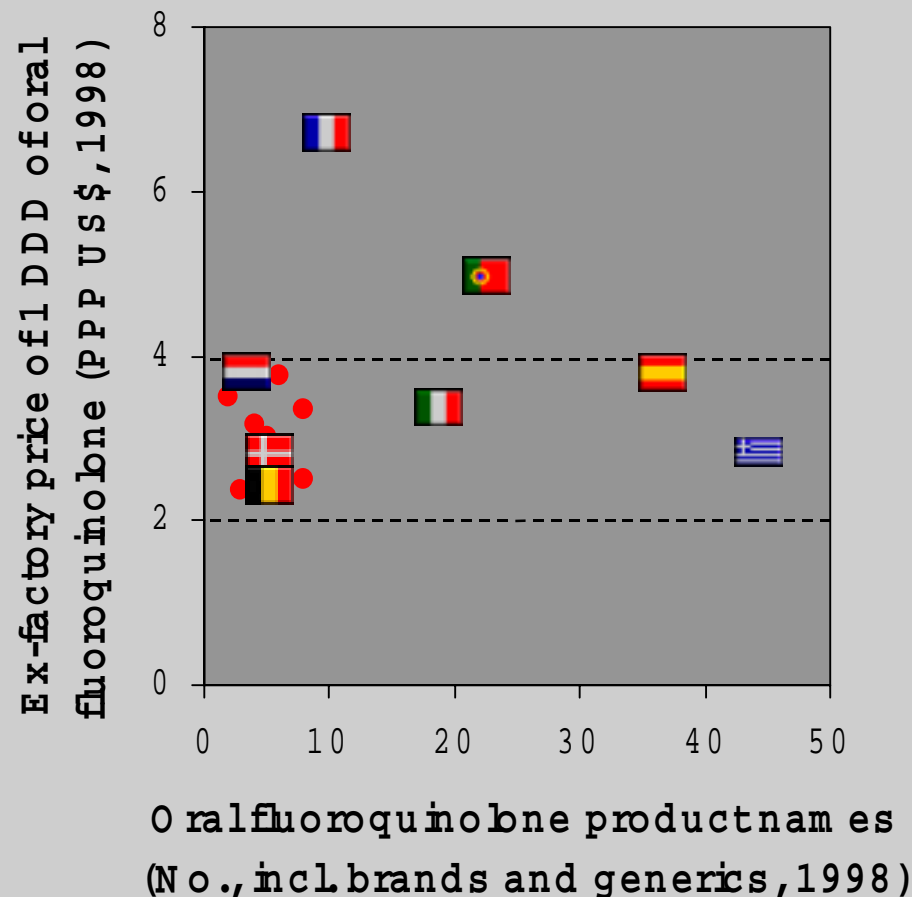
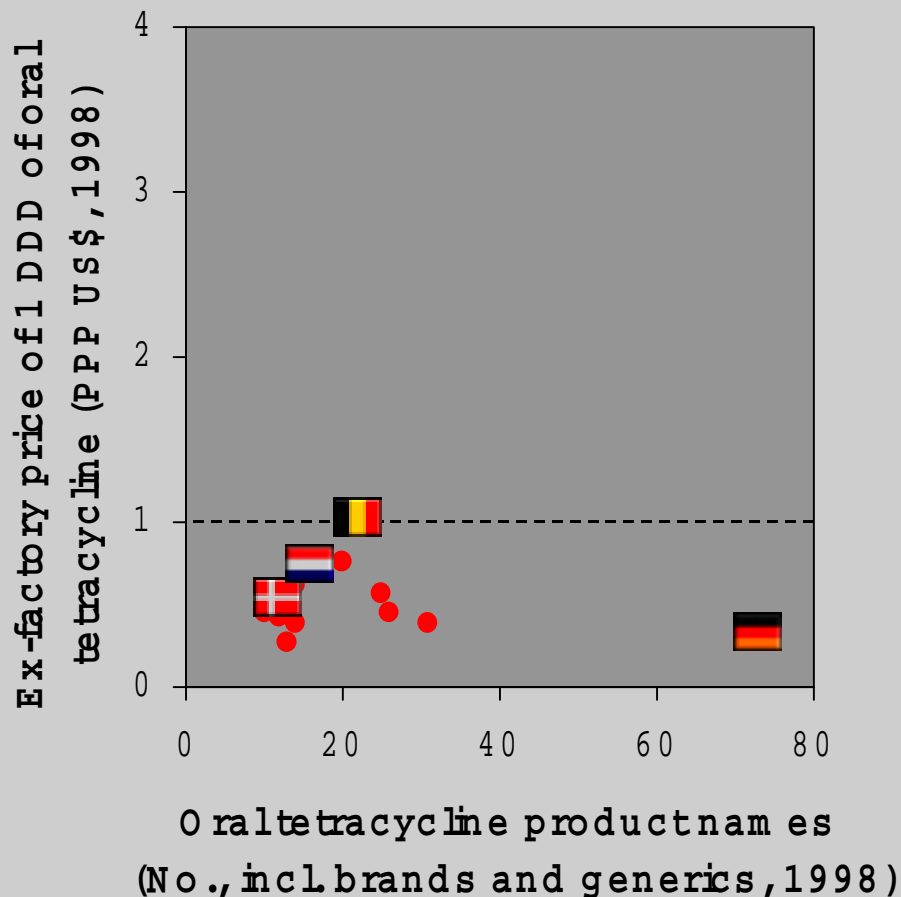


Cost After Reimbursement and Consumption of Tetracyclines and Fluoroquinolones in Primary Health Care, EU Member States, 1997



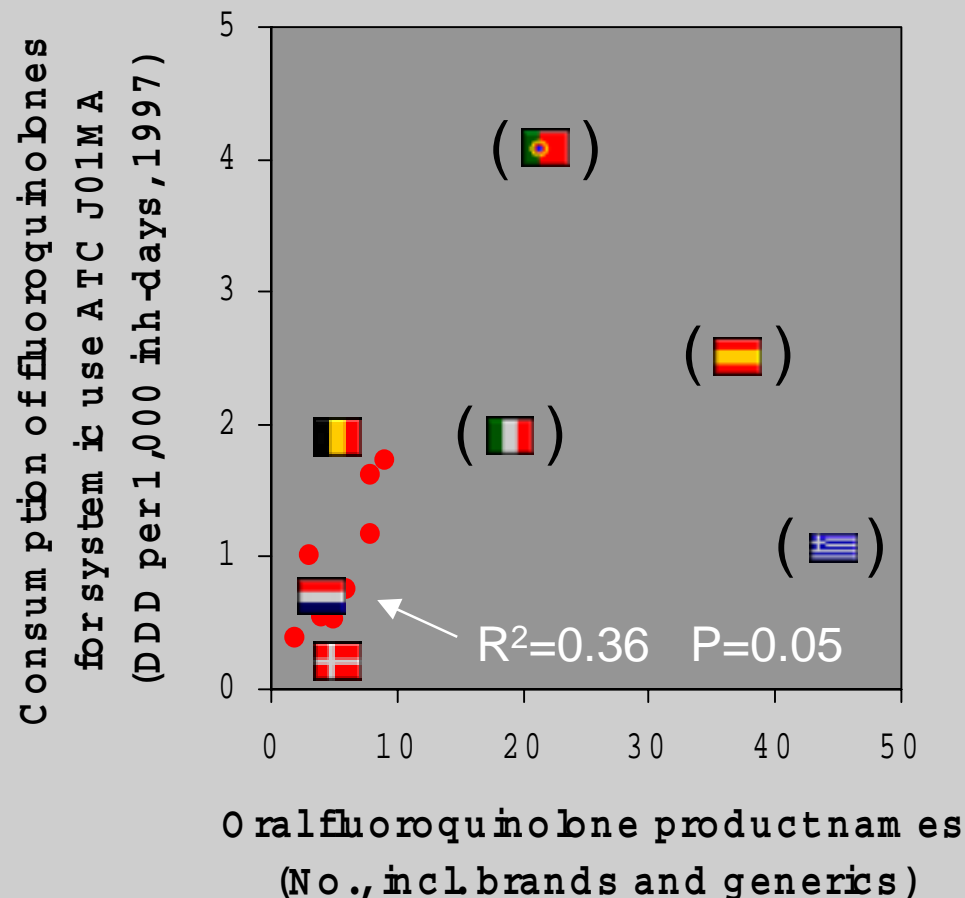
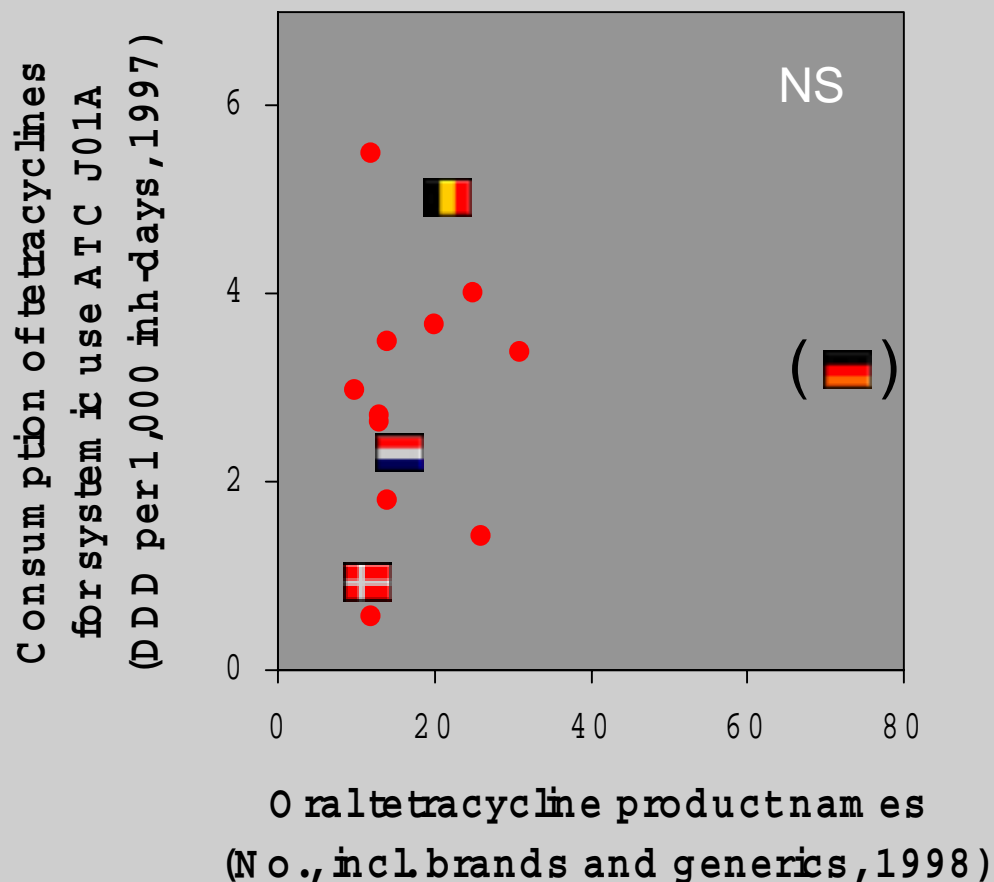


Ex-Factory Price and Number of Brands of Tetracyclines and Fluoroquinolones on Market, EU Member States, 1998



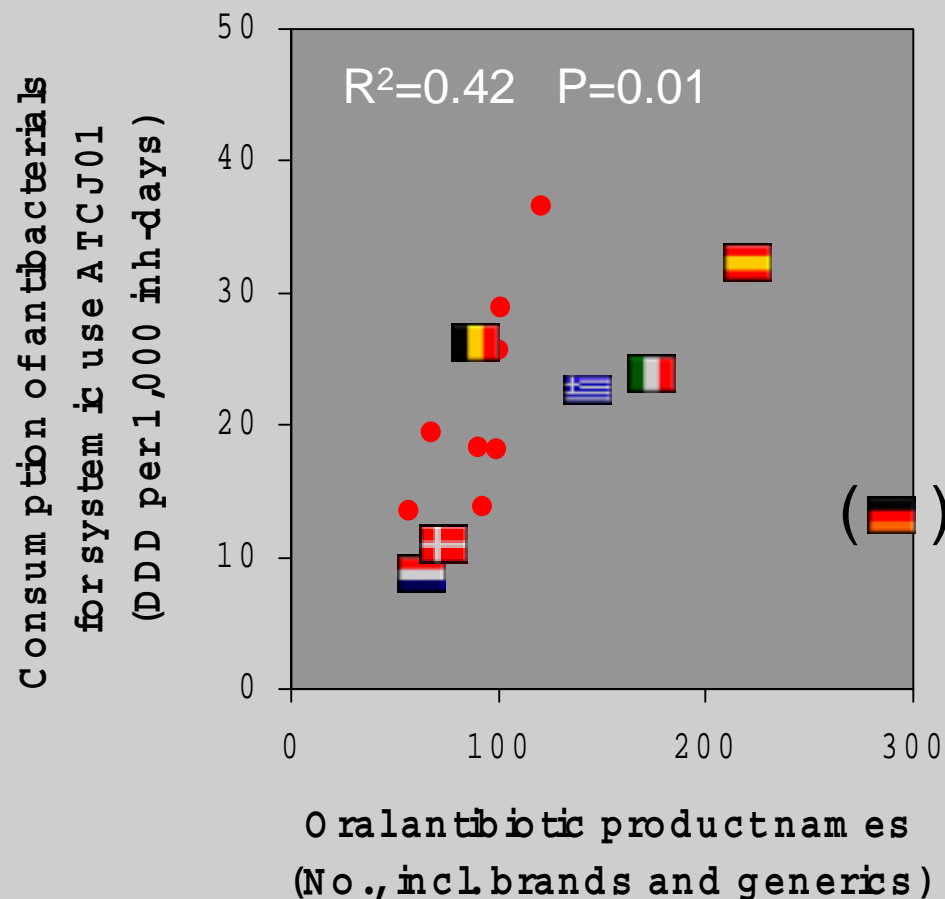
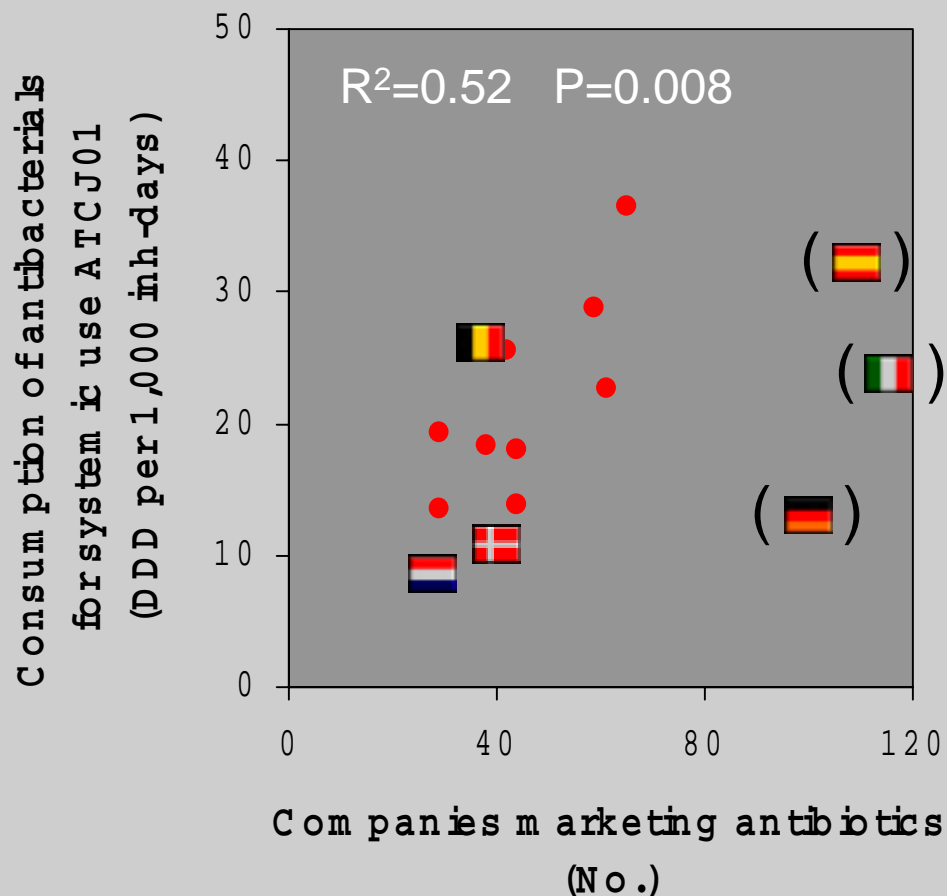


Overall Consumption of Fluoroquinolones (ATC J01MA) in Primary Health Care, Companies and Brands of Antibiotics, EU Member States, 1997



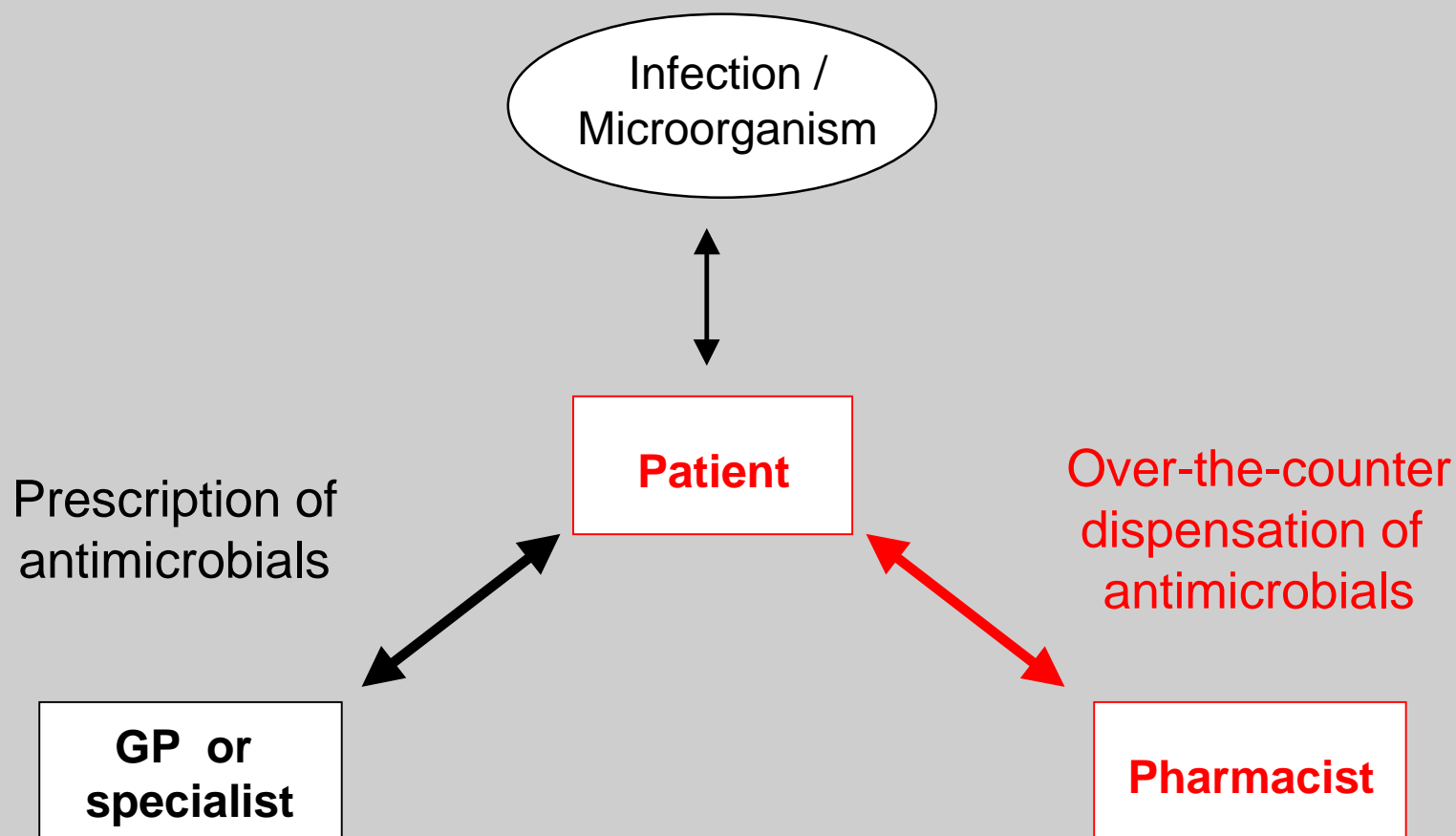


Overall Consumption of Systemic Antibacterials (ATC J01) in Primary Health Care, Companies and Brands of Antibiotics, EU Member States, 1997





Pathways of Antimicrobial Use in Primary Health Care (3)



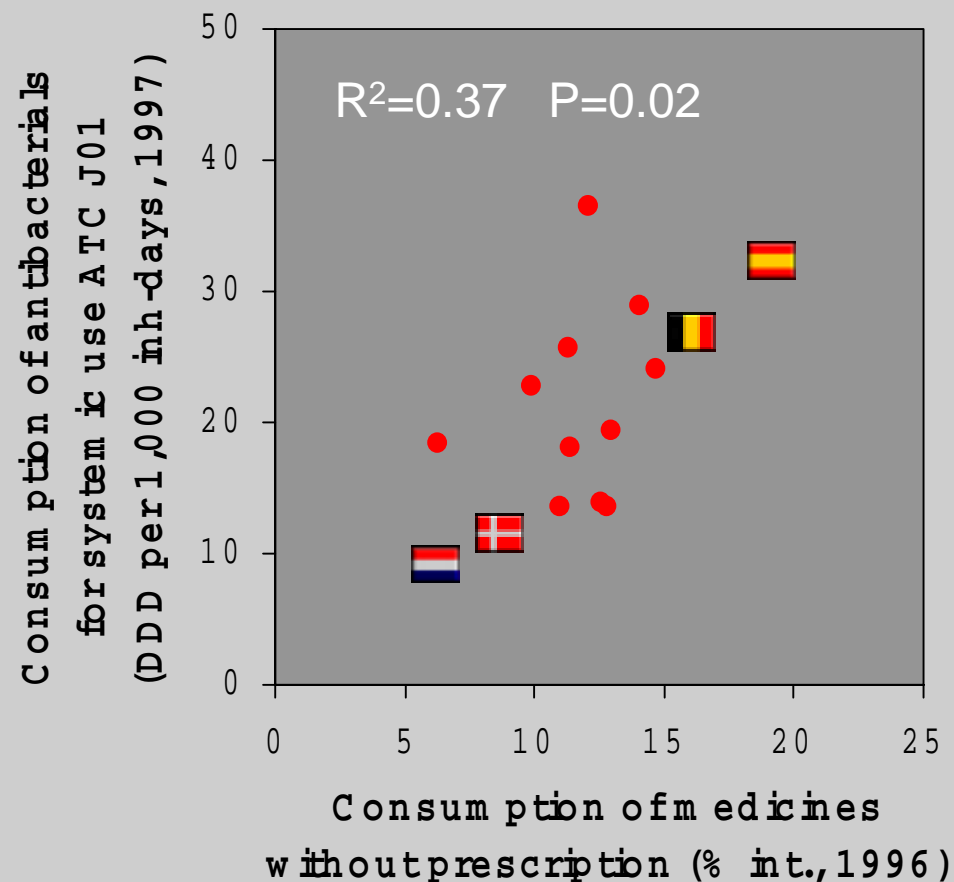
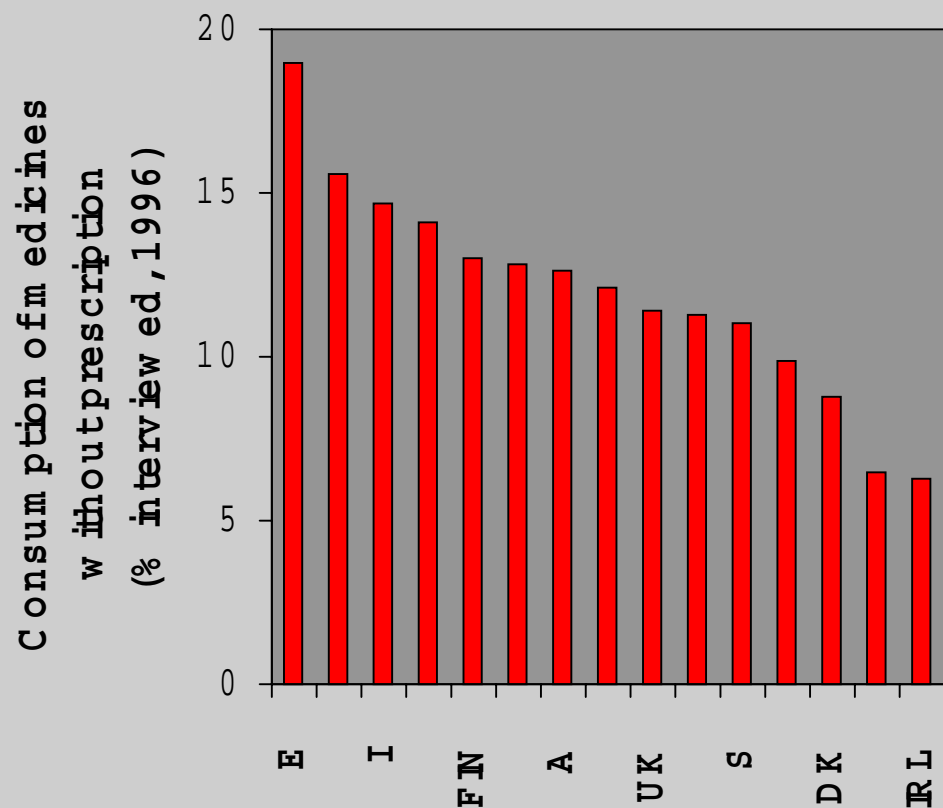


Over-The-Counter (OTC) Dispensation of Antimicrobials in Europe

- Anecdotal evidence from colleagues...
- Spain: 42% of 1,000 households reported having antimicrobial packages at home. Only 2/3 of these packages were the result of a physician's prescription
Orero A, et al. Med Clin (Barc) 1997; 109: 782-785.
- Greece: 69% and 86% of pharmacists offered antibiotics when presented with a high-fever and a low-fever rhinosinusitis scenario, respectively
Contopoulos-Ioannidis DG, et al. Clin Infect Dis 2001; 33: 76-82.
- EC-funded project "Self-medication with Antibiotics" started on 1st October, 2002

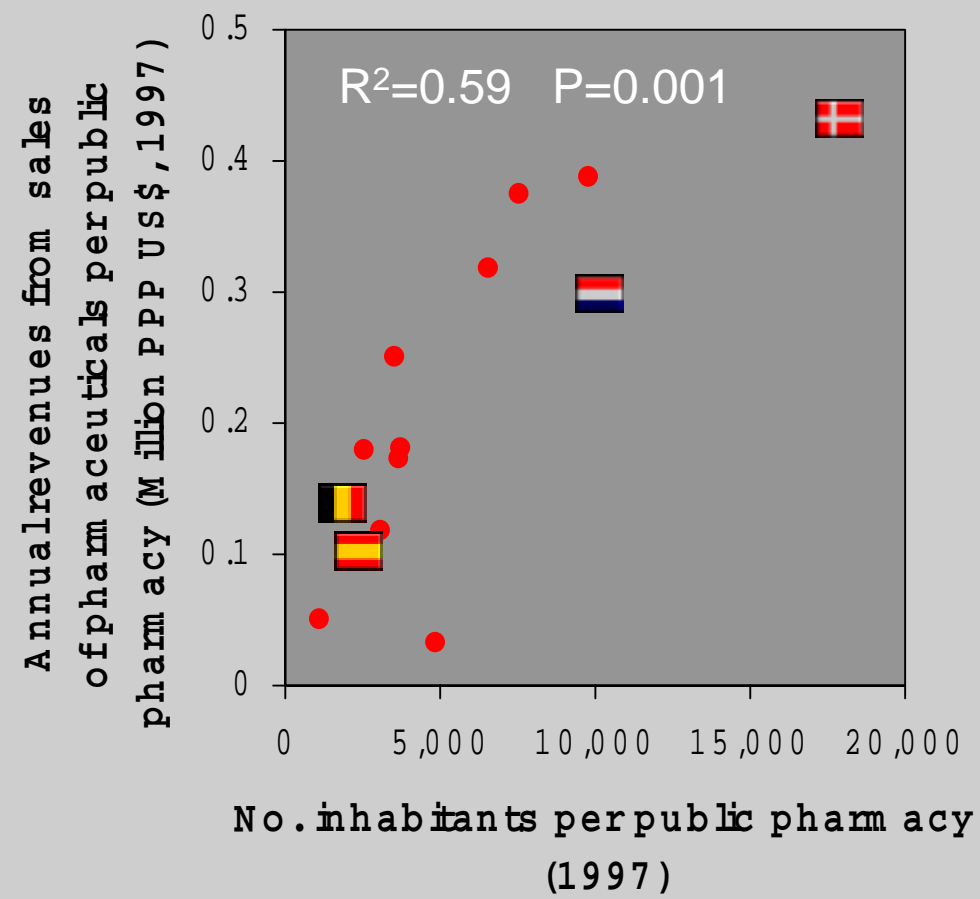
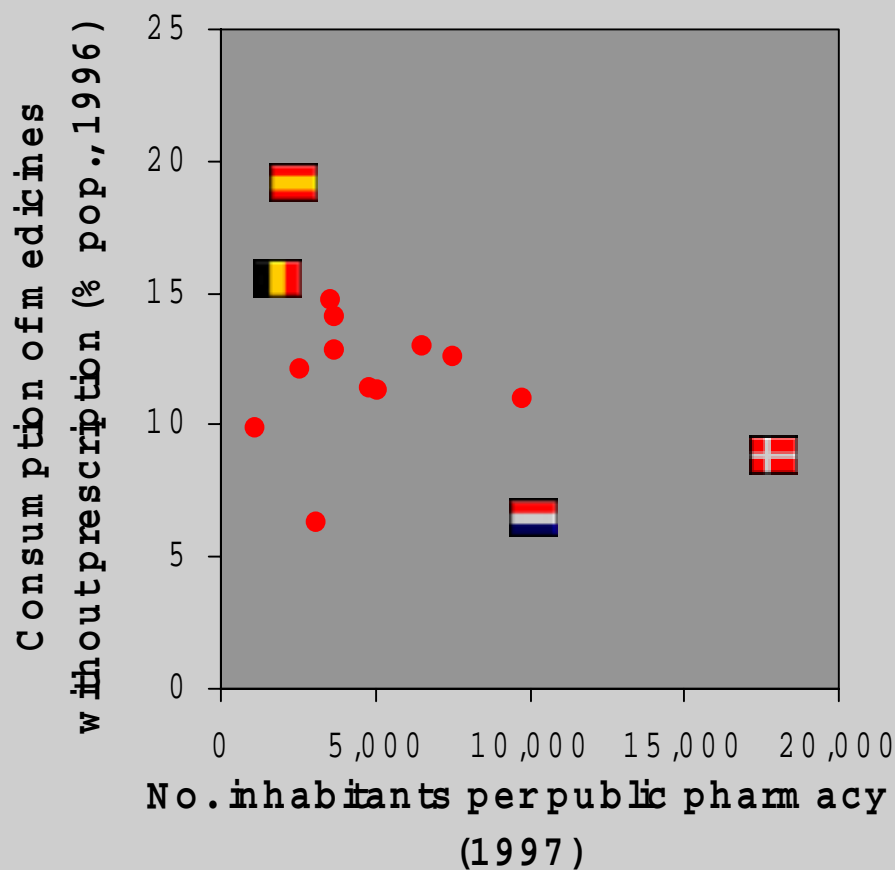


Overall Consumption of Systemic Antibacterials (ATC J01) in Primary Health Care and Consumption of Medicines Without Prescription, EU, 1996-1997





Consumption of Medicines Without Prescription, No. Inhabitants per Pharmacy, and Annual Revenues from Sales of Pharmaceuticals per Pharmacy, EU, 1996-1997



Sources: Eurobarometer 44.3, European Commission in Key Data on Health 2000, Eurostat; and GIRP and IMS Health.



Conclusions

- Food for thought...
- A "substantial" part of the observed differences in resistance are certainly due to different levels and patterns antimicrobial use
- Better understand determinants of antimicrobial use in Europe and generate hypotheses for interventions
- Study the possible adverse effects of restrictive and conservative antimicrobial use!
- Some missing data should soon be provided by European collaborative projects, e.g. ESAC (primary health care and hospitals), ARPAC (mainly hospitals), SAR (self-medication with antibiotics)