Analyse pharmaco-épidémiologique de l'impact de l'exposition des populations aux antibiotiques sur le risque de résistance bactérienne

Didier Guillemot

CeRBEP, IP / U657, INSERM

Qu’est ce que la Pharmaco-epidemiologie ?

Pharmacologie clinique :

Etude de l’effet des médicaments sur les individus

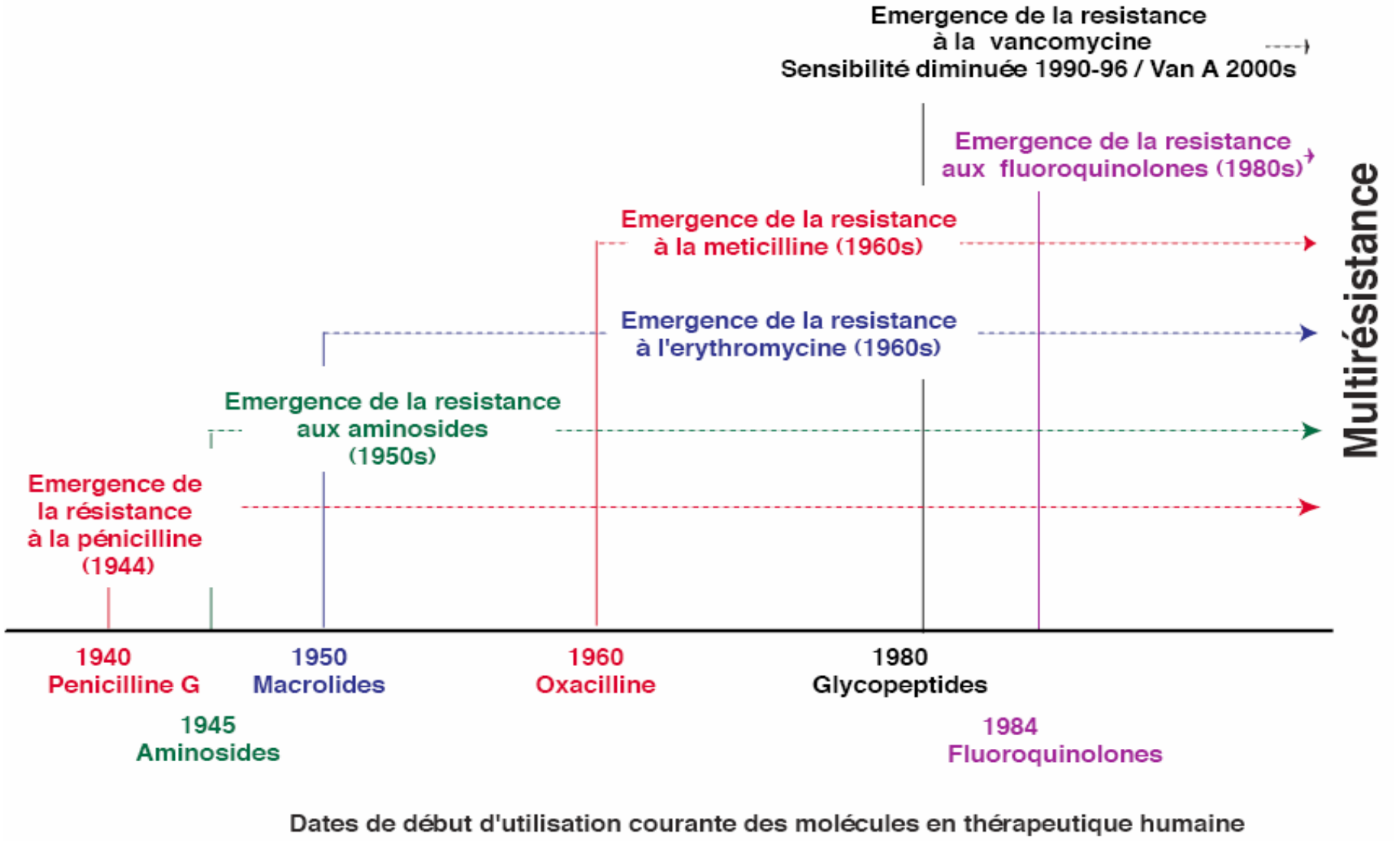
Épidémiologie :

Etude des déterminants de l’état de santé des populations

Pharmaco-épidémiologie :

Etudes de l’effet des médicaments sur l’état de santé des populations

Emergence de la résistance : *S. aureus*



Dates de début d'utilisation courante des molécules en thérapeutique humaine

Impact of antimicrobials on bacterial resistance (basic model)

Gene level	Mutation Gene transfer	**Emergence of a new mechanism**
Bacteria	Survival of resistant strains / Death of susceptible strains	**Selection in individuals**
Individual	Colonisation of individual ecosystems (gut, skin, naso- and oro-pharynx)	
Population	Cross transmission • Between humans • Animals ⟺ humans Environment	**Selection in population and spread**

Antibiotique et mutation ?

Les antibiotiques ne sont pas des « mutagènes » aux concentrations thérapeutiques, mais ils pourraient dans certaines conditions favoriser la survenue des mutations chez les bactéries

Stress-Induced Mutagenesis in Bacteria

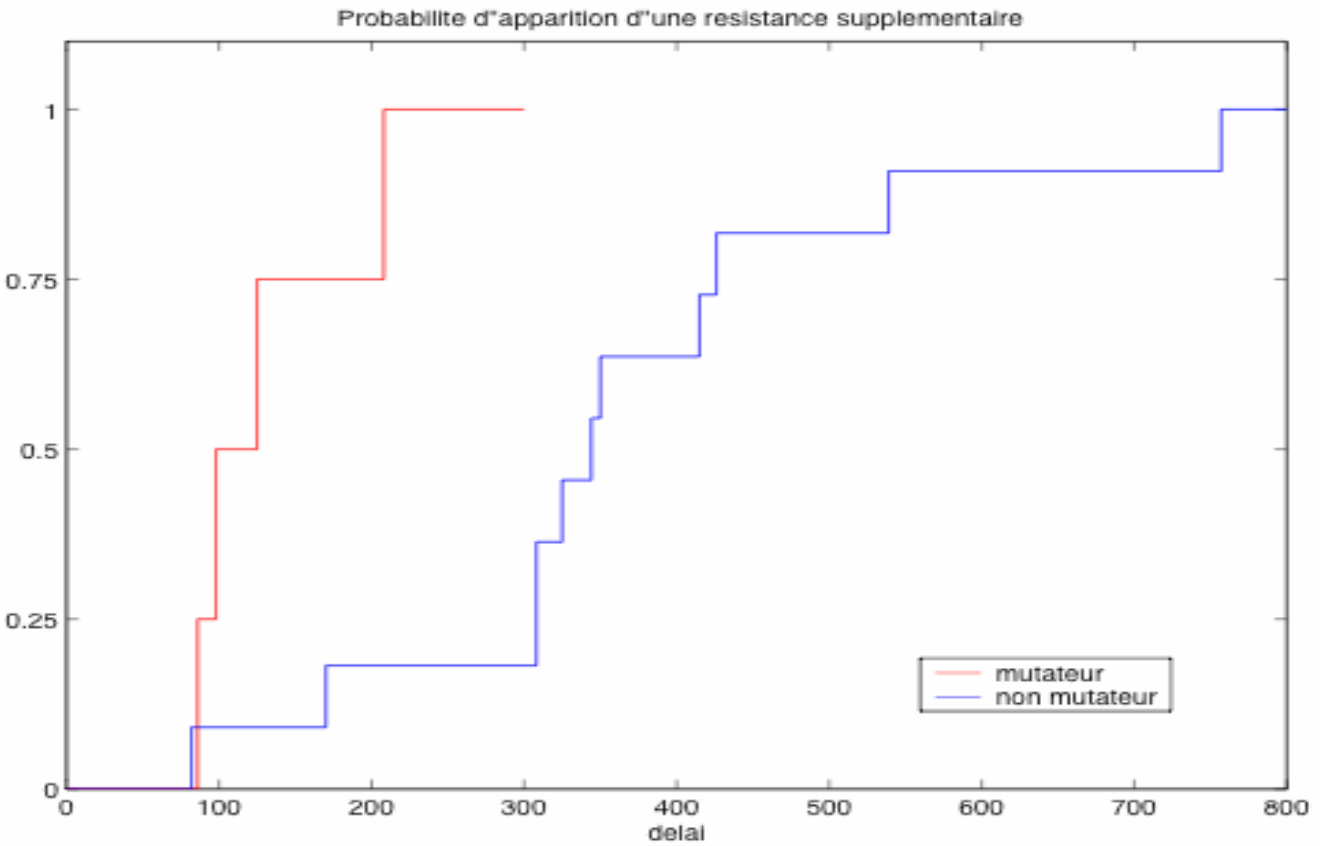
Ivana Bjedov,[1]* Olivier Tenaillon,[2]* Bénédicte Gérard,[2]* Valeria Souza,[3] Erick Denamur,[2] Miroslav Radman,[1] François Taddei,[1] Ivan Matic[1]†

30 MAY 2003 VOL 300 SCIENCE www.sciencemag.org

QuickTime™ et un
décompresseur TIFF (non compressé)
sont requis pour visionner cette image.

Phénotype mutateur chez *E. coli* (résistance à la rifampicine) sous l'influence du stress

Mutator phenotype of *P. aeruginosa* and emergence of antibiotic resistance, in cystic fibrosis children



P < 0.02

Next step : interaction between antibiotic exposure and mutator phenotype

In collaboration with F. Taddei (INSERM U571), A Ferronni (department of microbiology, CHU Necker Enfants Malades)

Impact of antimicrobials on bacterial resistance (basic model)

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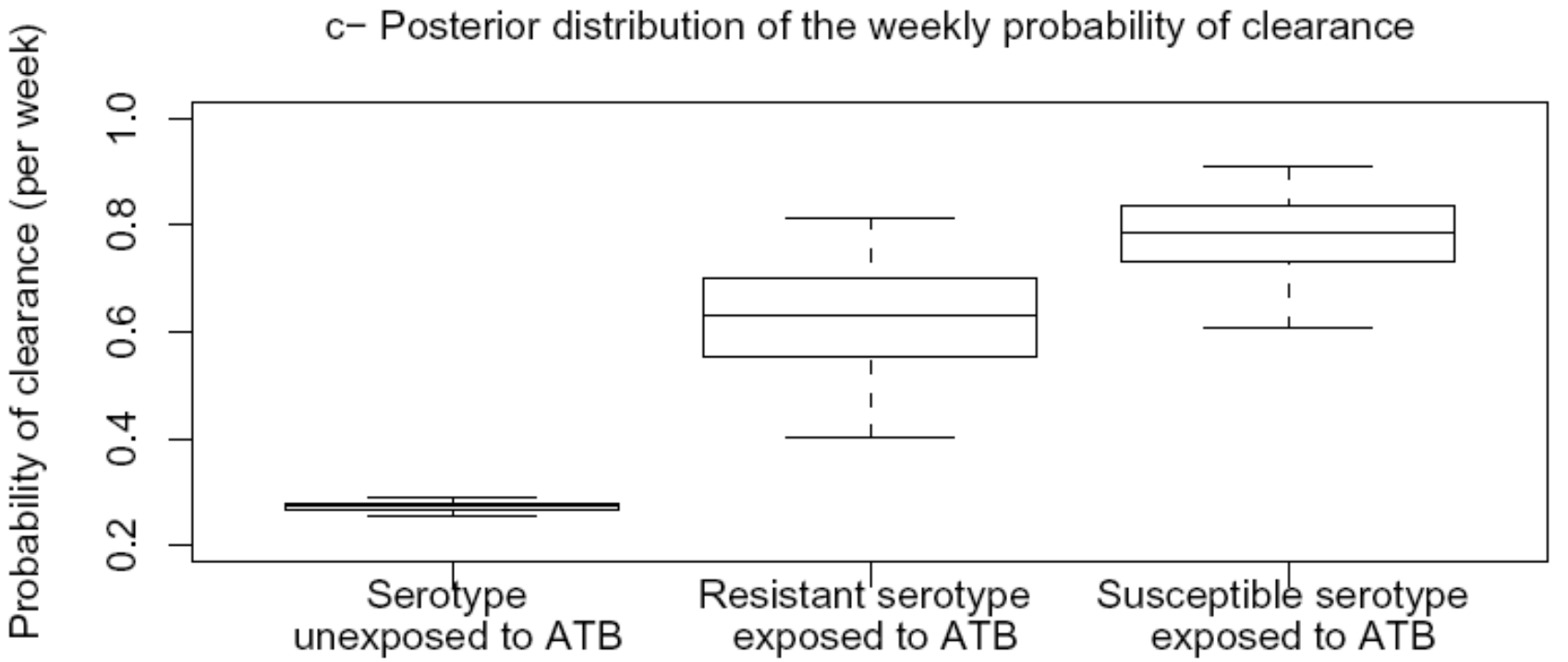
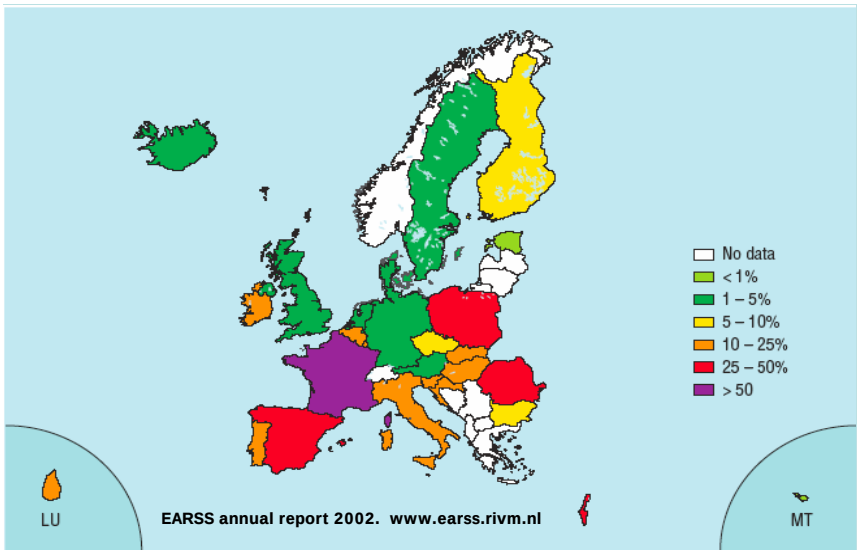
Population	Cross transmission • Between humans • Animals ⟺ humans Environment	**Selection in population and spread**

Impact of antibiotic use on selection of penicillin G resistant *S. pneumoniae*



In collaboration with PY Boelle (INSERM U444), E. Varon (Nationa Reference Center of Pneumococcus))

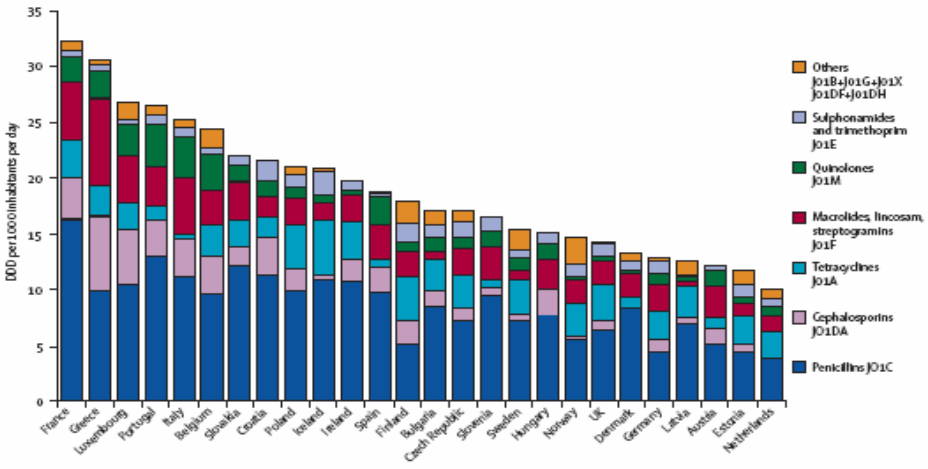
Penicillin G Decreased Susceptibility . Pneumoniae and antibiotic use, in EU



Outpatient antibiotic use in Europe and association with resistance: a cross-national database study

Herman Goossens, Matus Ferech, Robert Vander Stichele, Monique Elseviers, for the ESAC Project Group*

Lancet 2005; 365: 579–87



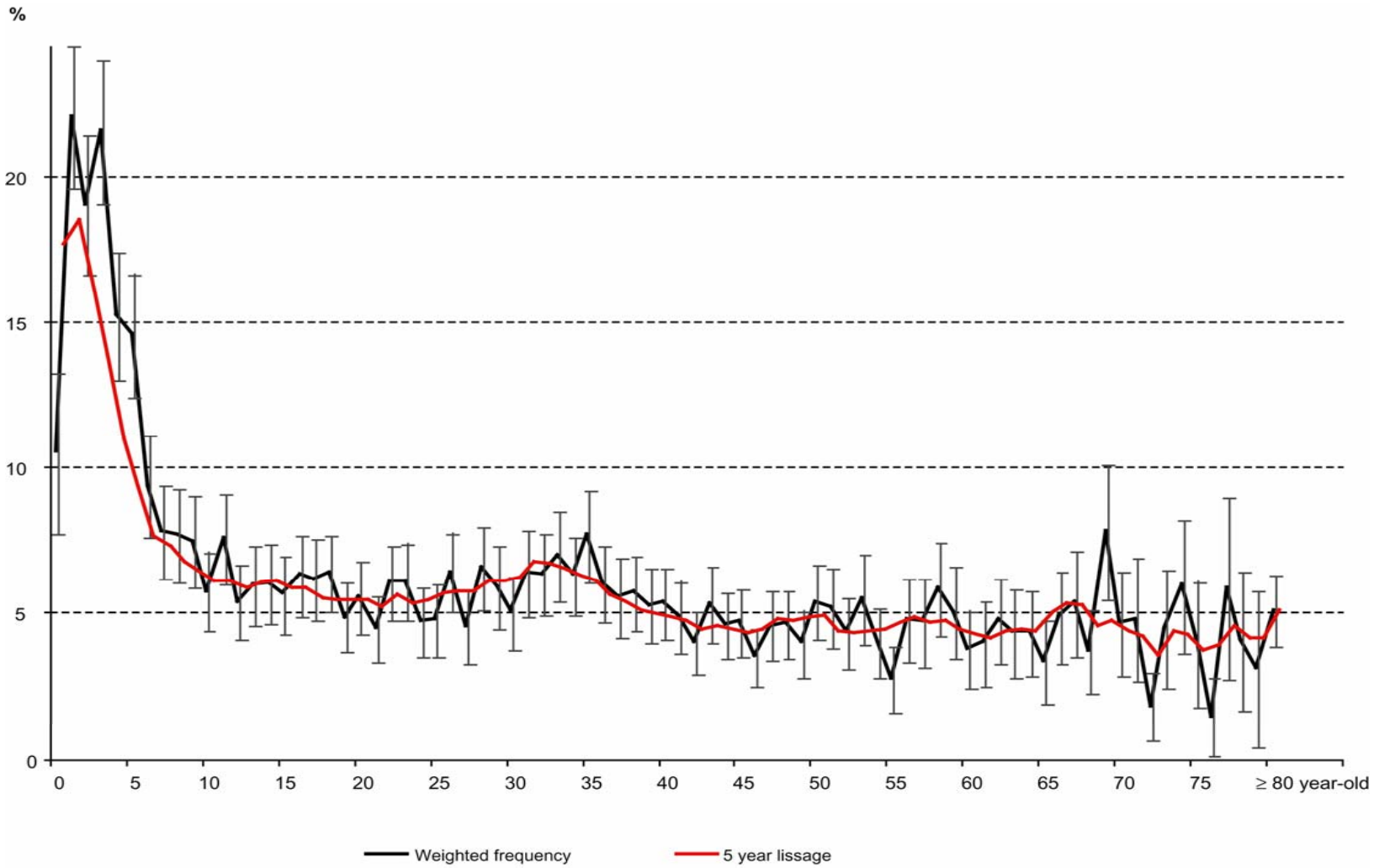
The ESAC project group
Helmut Mittermayer, Sigrid Metz (Austria); Herman Goossens (Belgium); Boyka Markova, (Bulgaria); Arjana Andrasevic, Igor Francetic (Croatia); Ludvik Stika (deceased Sept 9, 2004), Petr Dvorak (Czech Republic); Dominique L Monnet, Annemette Anker Nielsen (Denmark); Pentti Huovinen, Pirkko Paakkari (Finland); Philippe Maugendre, Didier Guillemot (France); Winfried Kern, Helmut Schroeder (Germany); Helen Giamarellou, Anastasia Antoniadou (Greece); Gabor Ternak (Hungary); Karl Kristinsson (Iceland); Edmond Smyth, Robert Cunney (Ireland); Giuseppe Cornaglia (Italy); Sandra Berzina (Latvia); Rolanda Valenteliene (Lithuania); Robert Hemmer, Marcel Bruch (Luxembourg); Michael Borg, Peter Zarb (Malta); Robert Janknegt, Margreet Filius (the Netherlands); Hege Salvesen Blix (Norway); Waleria Hryniewicz, Pawel Grzesiowski (Poland); Luis Caldeira (Portugal); Irina Codita (Romania); Viliam Foltan, Tomas Tesar (Slovak Republic); Milan Cizman (Slovenia); José Campos (Spain); Otto Cars, Gunilla Skoog (Sweden); Serhat Unal (Turkey); Peter Davey (UK).

No significant decrease in antibiotic use from 1992 to 2000, in the French community

Agnès Sommet[1], Catherine Sermet[2], Pierre Yves Boëlle[3], Muriel Tafflet[2], Claire Bernède[1] and Didier Guillemot[1]*

[1]Institut Pasteur, 25–28 rue du Dr Roux, 75724 Paris Cedex 15, France; [2]Centre de Recherche et de Documentation en Economie de la Santé, Paris, France; [3]INSERM U444, Paris, France

Journal of Antimicrobial Chemotherapy

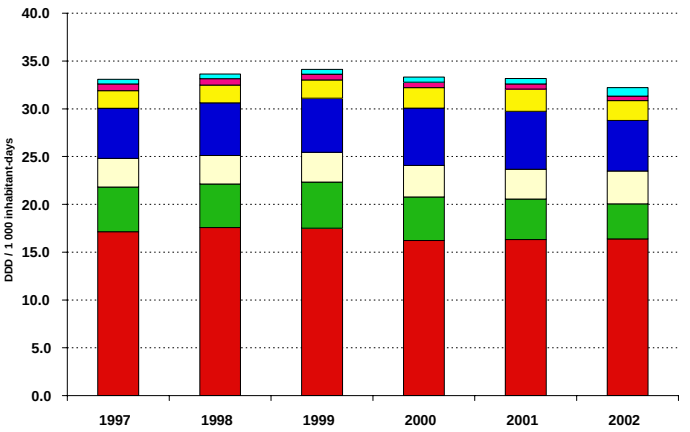


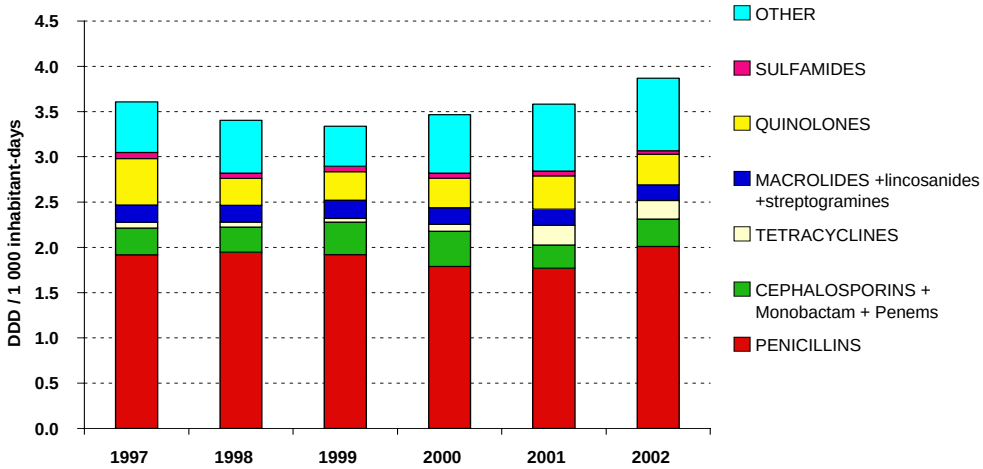
Consommation des antibiotiques en France

Didier Guillemot[1], Philippe Maugendre[2], Claire Chauvin[3], Catherine Sermet[4]

[1]Centre de ressource en biostatistiques, épidémiologie et pharmacoépidémiologie appliquées aux maladies infectieuses, Institut Pasteur, Paris
[2]Secrétariat général de la commission de la transparence, Agence française de sécurité sanitaire des produits de santé, Saint-Denis
[3]Agence française de sécurité sanitaire des aliments, Maisons-Alfort
[4]Institut de recherche et de documentation en économie de la santé, Paris

BEH Numéro thématique : Résistance aux antibiotiques p. 141
N° 32-33/2004
13 juillet 2004

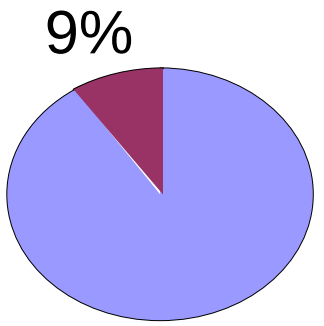




Pattern in 2000

Community (DDD/1 000 inhab-days)

Hospital (DDD/1 000 inhab-days)

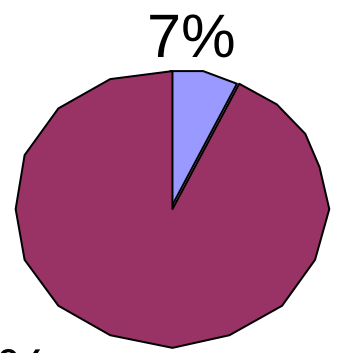


Hospital

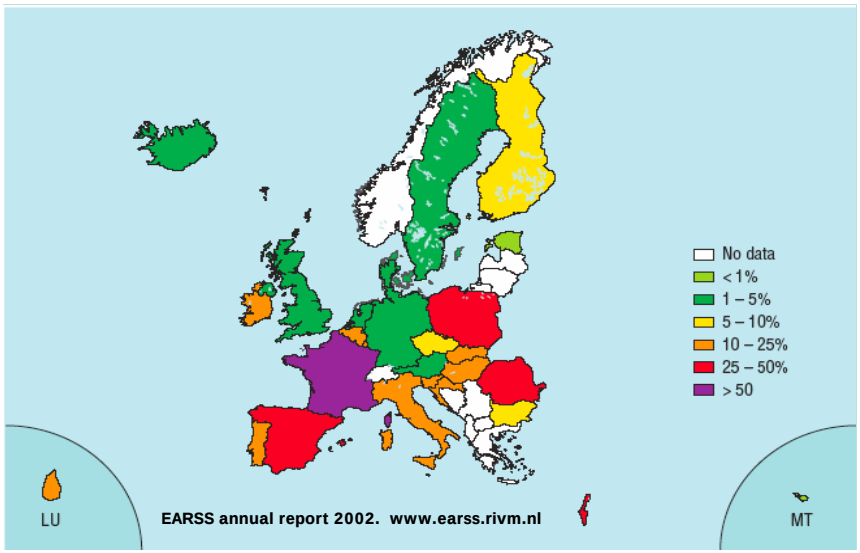
Community

Community (DDD/1 000 inhab-days)

Hôpital (DDD/1 000 hospitalization days)



Penicillin G Decreased Susceptibility . Pneumoniae and antibiotic use, in EU



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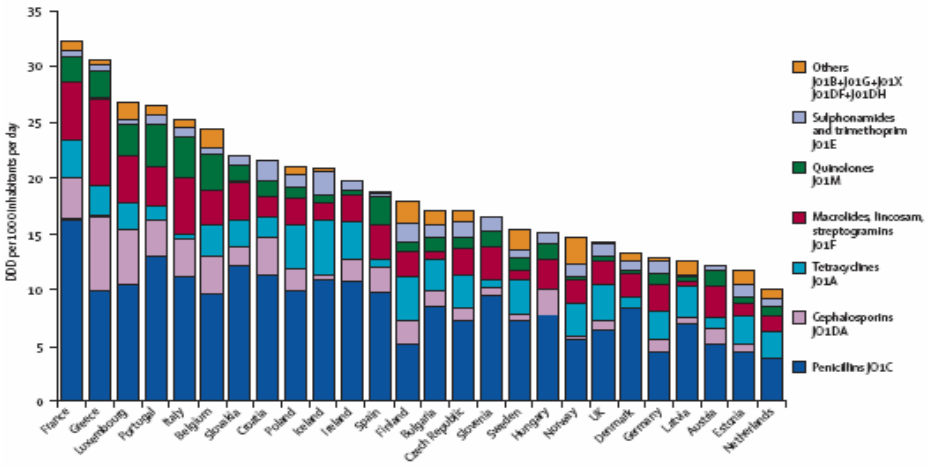

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Antibiotic Selection Pressure and Resistance in *S. pneumoniae* and *S. pyogenes*

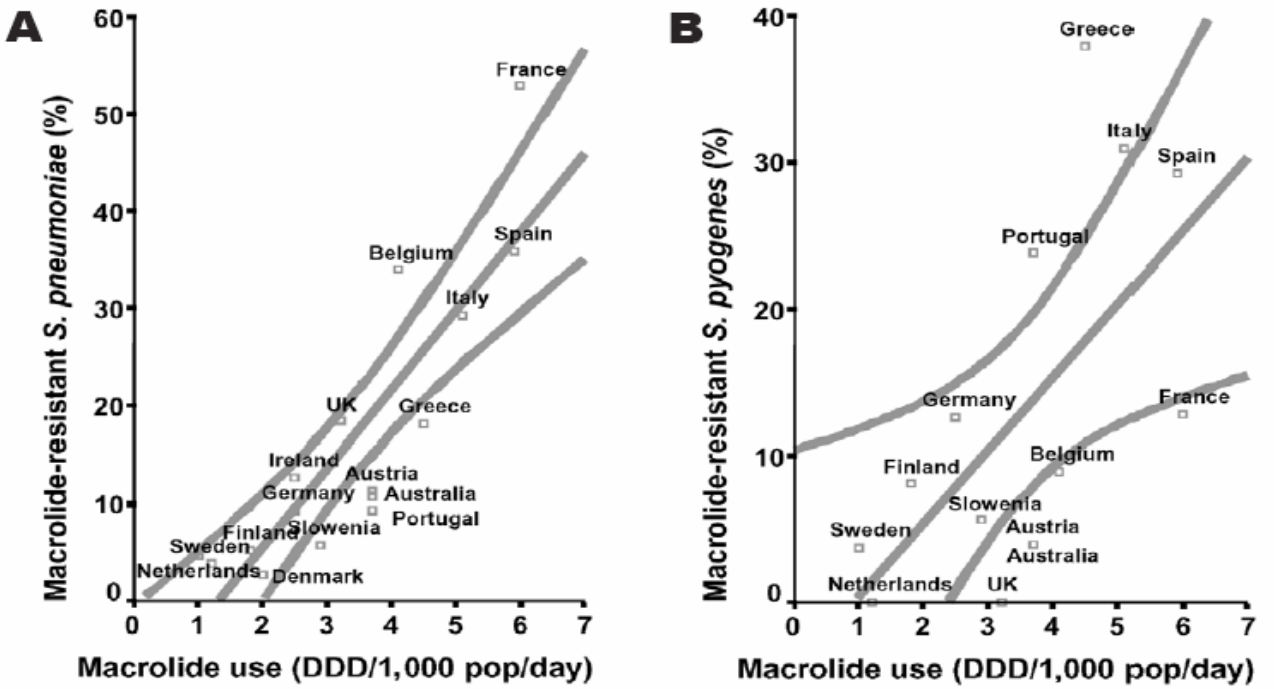
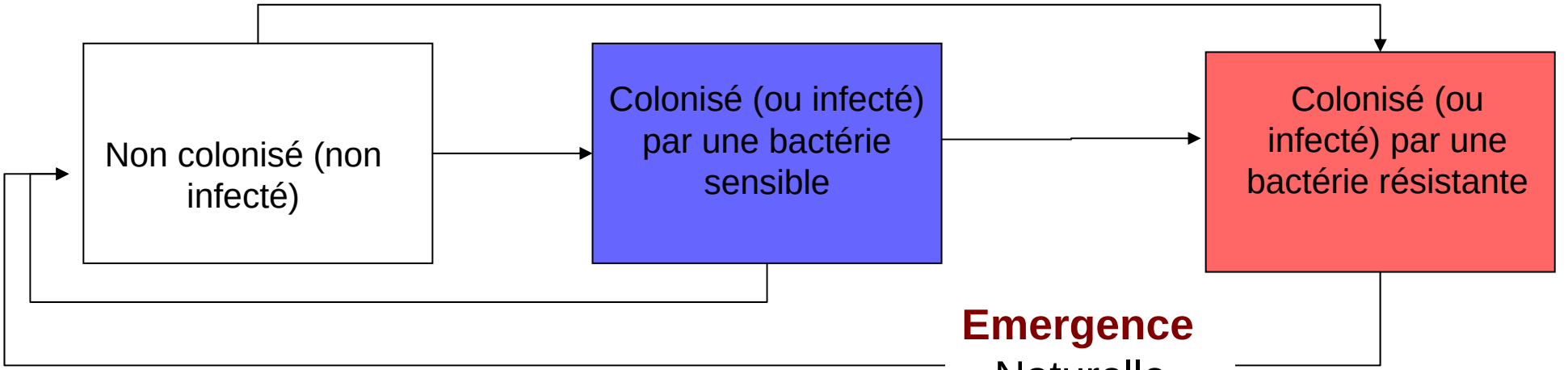


Figure 2. A. Relationship between macrolide use in the outpatient setting (horizontal axis) and prevalence of macrolide-resistant *Streptococcus pneumoniae* (vertical axis) in 16 industrialized countries. A regression line was fitted with 95% confidence bands ($r = 0.88$; $p < 0.001$). B. Relationship between macrolide use in the outpatient setting (horizontal axis) and prevalence of macrolide-resistant *S. pyogenes* (vertical axis) in 14 industrialized countries. A regression line was fitted with 95% confidence bands ($r = 0.71$; $p = 0.004$).

Albrich WC et al. Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 10, No. 3, March 2004

Transmission inter-individuelle

- Contacts directs ou indirects + hygiène
- Antibiotique ?



Emergence

- Naturelle
- Antibiotique

Décolonisation

- Naturelle (immunité ?)
- Antibiotique

Que doit on considérer ?

	Non colonisé (ou non infectés)	Colonisés (ou infectés)		Total
		AtbS	AtbR	
Non exposés	X_u	S_u	R_u	N_u
Exposés	X_t	S_t	R_t	N_t

- Taux de résistance dans l'espèce ? : = $(R_u + R_t) / [(S_u + S_t) + (R_u + R_t)]$
  - Le dénominateur est le nombre de souches isolées (ou un nombre d'individus colonisés)
  - Pertinent pour le prescripteur (décision individuelle)

- Taux d'incidence (ou de prévalence) d'infection à bactérie résistante (ou d'individus colonisés) = $(R_u + R_t) / [(S_u + S_t) + (R_u + R_t) + (X_u + X_t)]$
  - Le dénominateur est un nombre d'individus
  - Pertinent pour la santé publique (décision collective)

	Non colonisé (ou non infectés)	Colonisés (ou infectés)		Total
		AtbS	AtbR	
Non exposés	X_u	S_u	R_u	N_u
Exposés	X_t	S_t	R_t	N_t

- ORc : = $S_u .R_t / (R_u . S_t)$
  - mesure l'effet de pression de sélection si l'impact sur l'émergence peut être considéré comme marginal

- ORs= $(X_u + S_u) .R_t / [R_u . (S_t + X_t)]$
  - Mesure l'impact global sur la population

Measuring and Interpreting Associations between Antibiotic Use and Penicillin Resistance in *Streptococcus pneumoniae*

Marc Lipsitch
Department of Epidemiology, Harvard School of Public Health, Boston

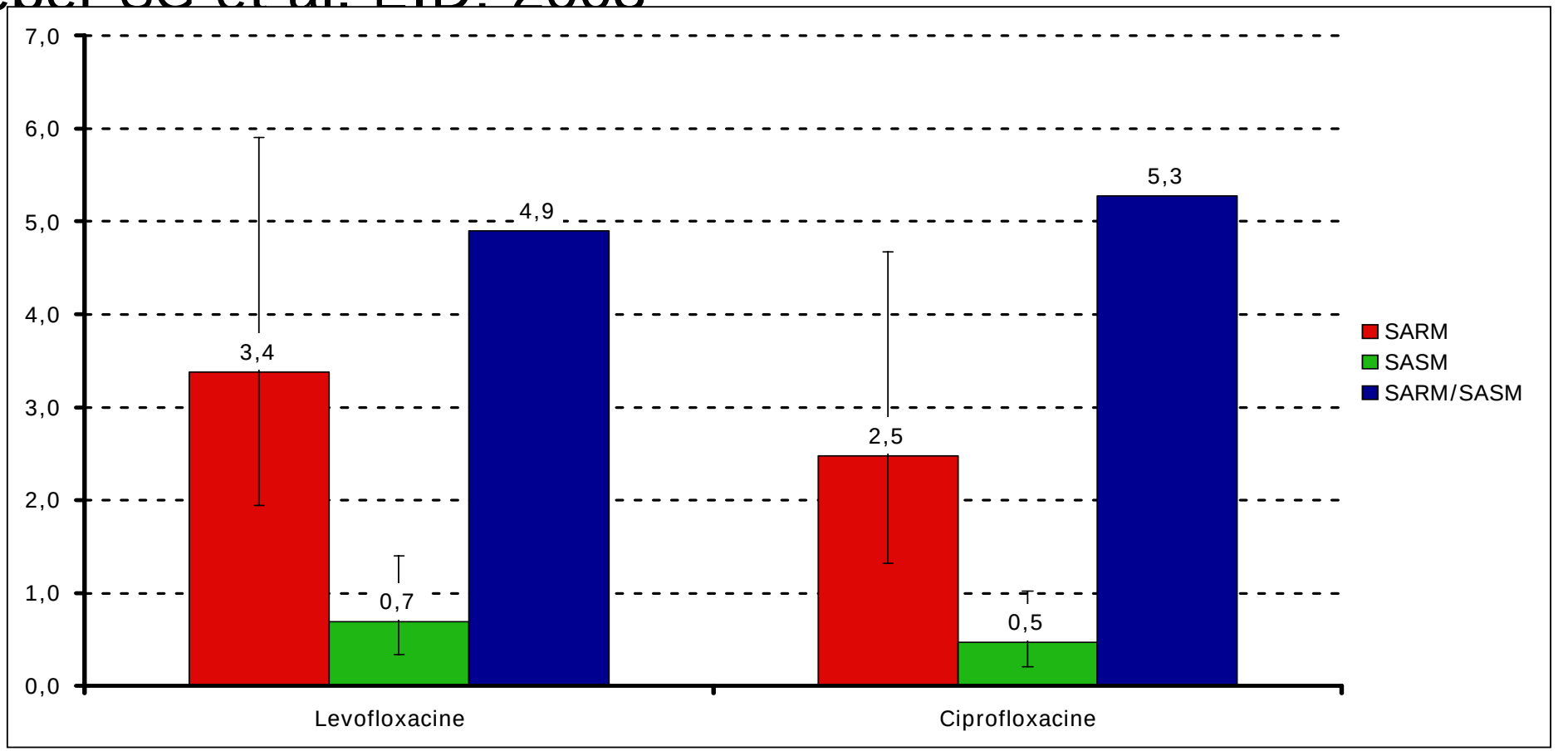
CID 2001:32 (1 April)

Auteur, ann ée	Pays	OR c	OR s
Dagan R et al., 1998	Israel	5.5	0.7
Arason VA et al., 1996	Iceland	min:6 * max:13.1*	
Boken DJ et al. 1996	Etats Unis	2.1	
Robins-Browne RM et al., 1984	South Africa	4.2	
Melander E et al., 1998	Sweden		1.4
Kellner JD et al., 1999	Canada	2.5*	
Cohen R et al., 1999	France	4.3*	0.36*
Dabernat H et al., 1998	France	6.7*	0.3*
Tsolia M et al., 1999	Greece	5.6*	3.2
Arnold KE et al., 1996	Memphis	2.7*	
Radestky MS et al., 1981	Etats Unis		7.3*
Cojen et al., 1997	France	4.1*	0.36*
Yagupsky et al., 1998	Israel		3.35*
Reichler MR et al., 1992	Etats Unis		7.3*

* : $p < 0.05$

Fluoroquinolones et risque de SARM et SASM chez les patients hospitalisés

Weber SG et al. EID. 2003



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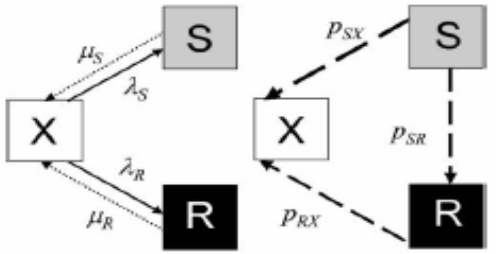


Figure 1. Structure of a simple model for analysis of an antibiotic treatment trial in a population exposed to colonization by both resistant and susceptible pneumococci. *Left,* Before treatment, susceptible patients *(X)* are colonized by penicillin-susceptible and penicillin-resistant pneumococci at rates of λ_S and λ_R, respectively. Colonization is lost at rates of μ_S and μ_R, respectively. These processes are described by equation [1] in the text. *Right,* Treatment clears carriage of susceptible bacteria with probability p_{SX}, clears carriage of resistant bacteria with probability p_{RX}, and transfers patients from primarily carrying susceptible bacteria to primarily carrying resistant bacteria with probability p_{SR}. These processes are described by equation [2] in the text. At the end of treatment, patients are again exposed to the processes of colonization and loss at their pretreatment rates. *X,* noncarriers of *Streptococcus pneumoniae; S,* carriers of penicillin-susceptible pneumococci; *R,* carriers of penicillin-resistant pneumococci; arrows, transitions between categories. See table 2 for a list of parameter values for this illustrative model.

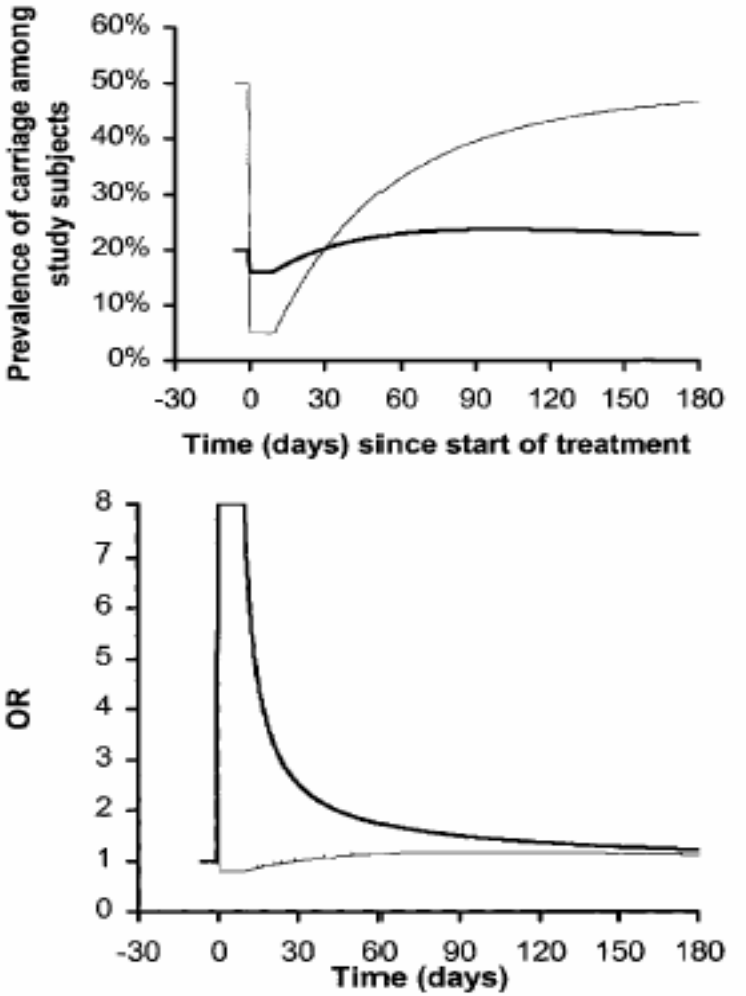
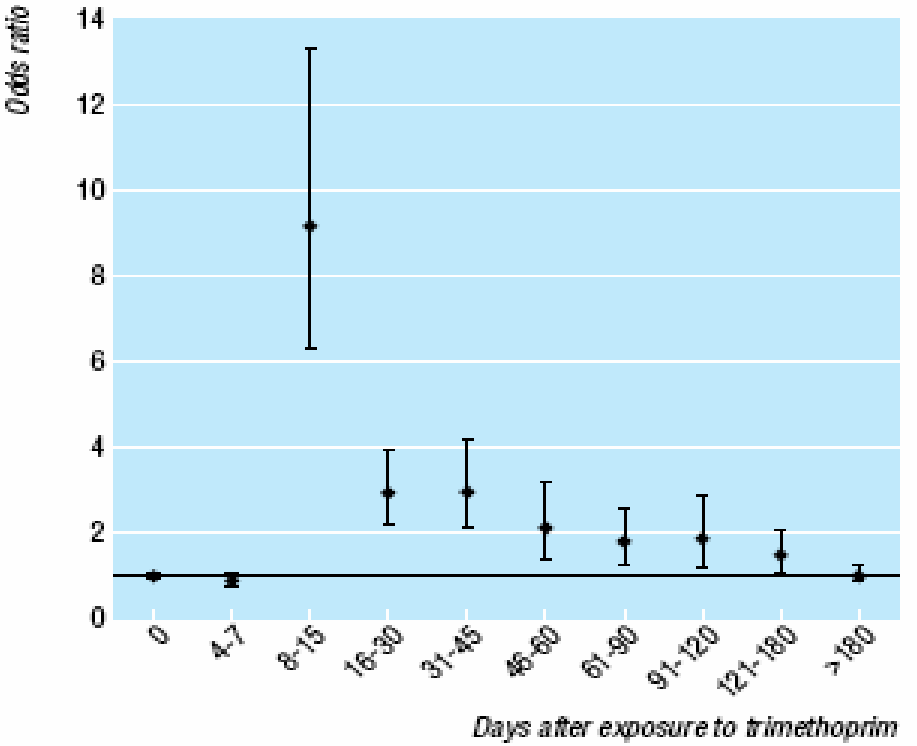


Figure 2. Time course of a hypothetical study of the effect of an antibiotic treatment on carriage. *Top,* Proportions of the subjects in the trial who had carriage of resistant *(thick line)* or susceptible *(thin line)* pneumococci. *Bottom,* The 2 measures of association between treatment and resistance—simple OR *(thick line)* and conditional OR *(thin line)*—at various times after treatment. Parameters are the same as those shown in table 2.

Presence of bacteriuria caused by trimethoprim resistant bacteria in patients prescribed antibiotics: multilevel model with practice and individual patient data

P T Donnan, L Wei, D T Steinke, G Phillips, R Clarke, A Noone, F M Sullivan, T M MacDonald, P G Davey

BMJ VOLUME 328 29 MAY 2004 bmj.com

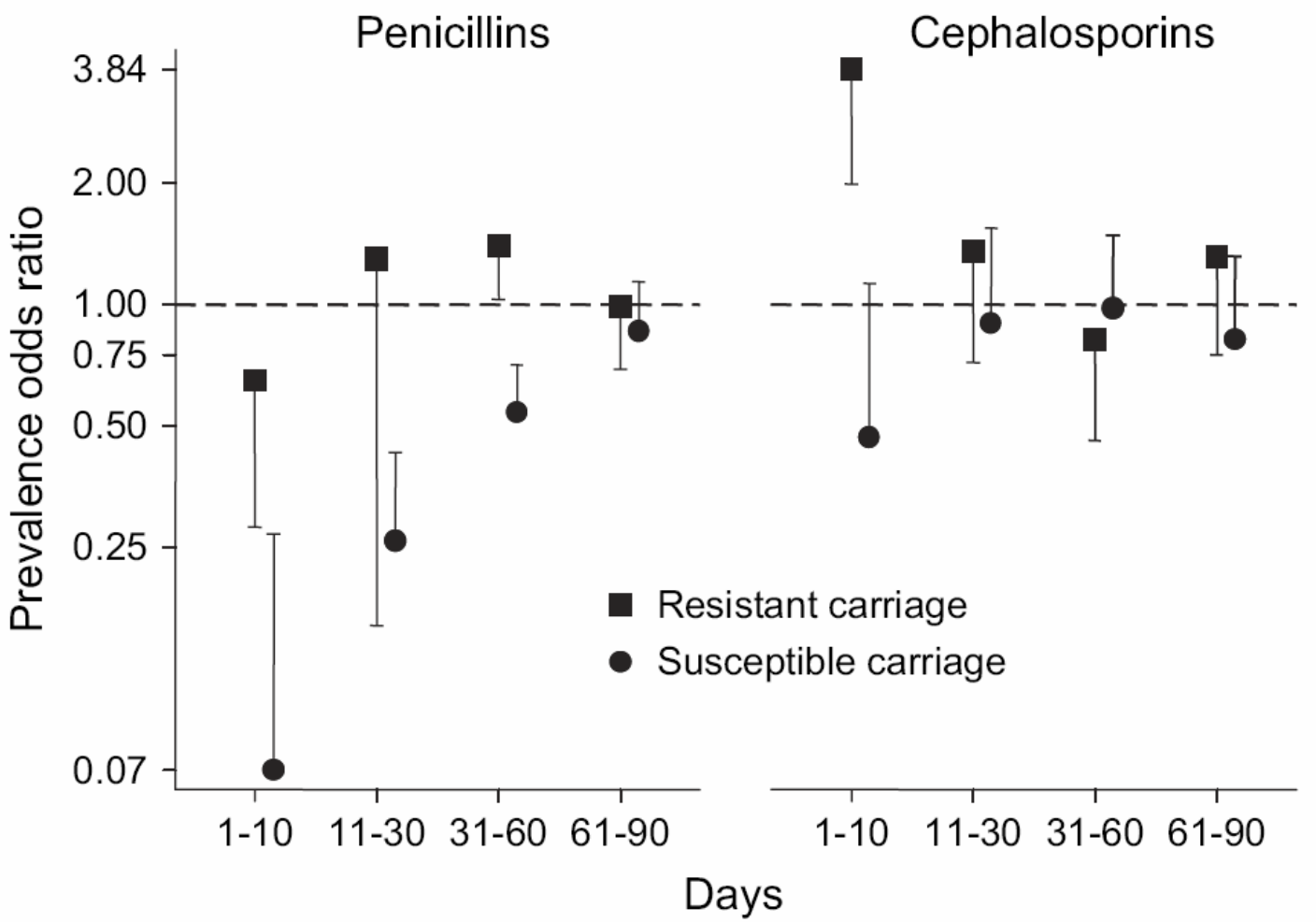


Odds ratio (95% confidence interval) of trimethoprim exposure in patients with trimethoprim resistant bacteria in urine versus those with sensitive bacteria by days after exposure to trimethoprim

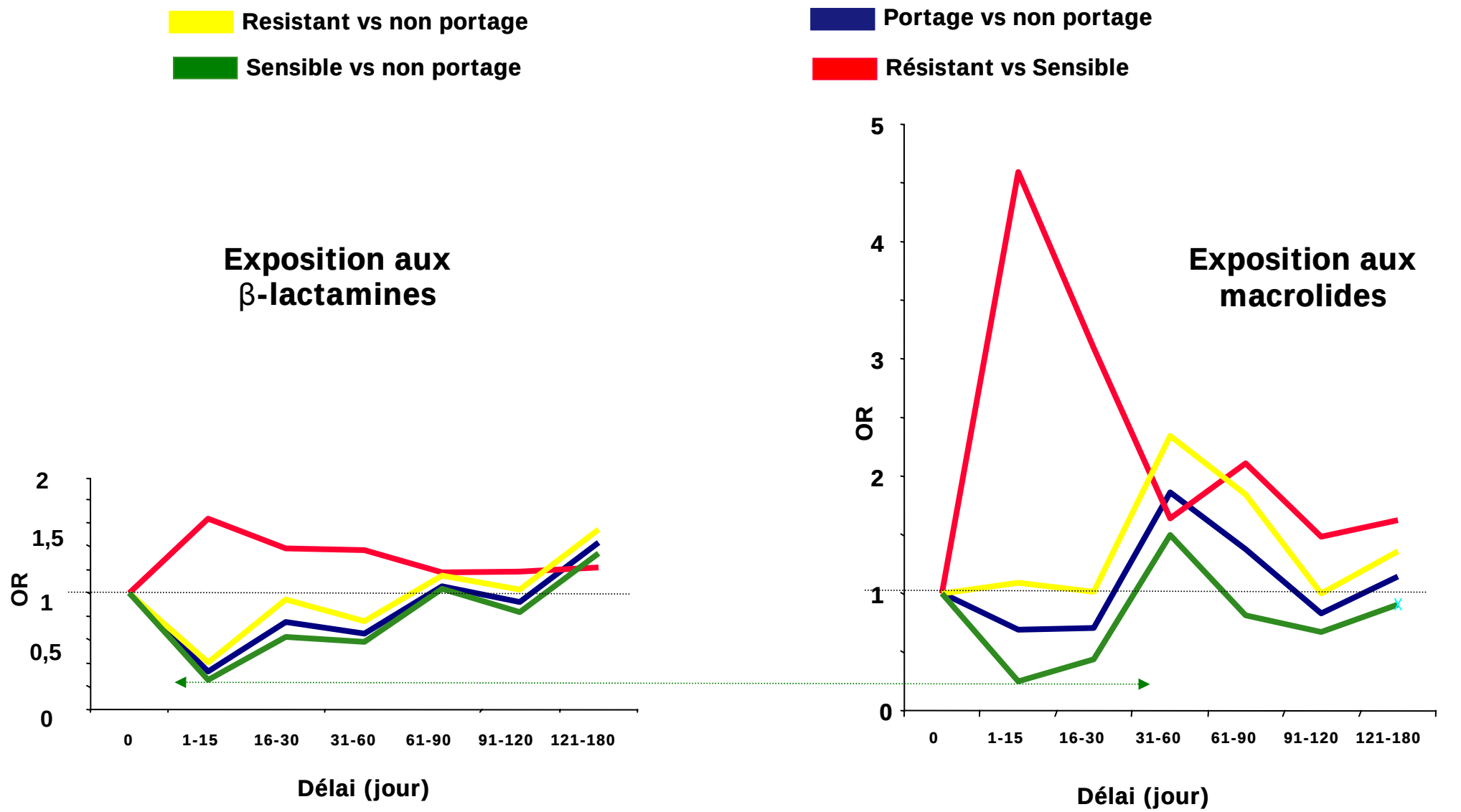
Mechanisms by Which Antibiotics Promote Dissemination of Resistant Pneumococci in Human Populations

Matthew H. Samore[1], Marc Lipsitch[2,3], Stephen C. Alder[1], Bassam Haddadin[1], Greg Stoddard[1], Jacquelyn Williamson[1], Katherine Sebastian[1], Karen Carroll[4], Onder Ergonul[2,3], Yehuda Carmeli[1], and Merle A. Sande[5]

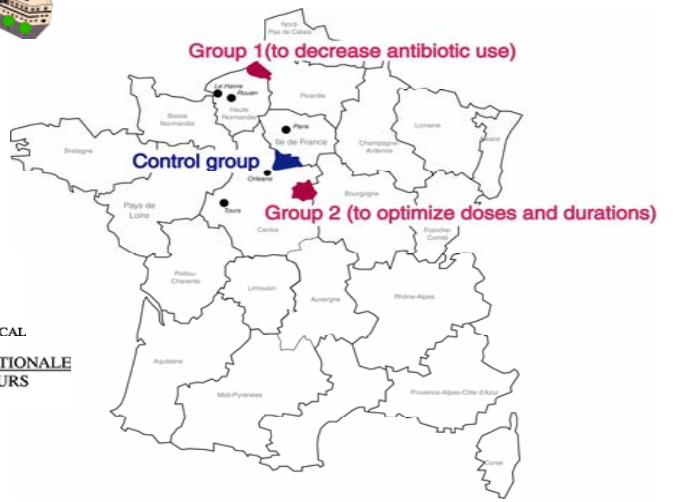
American Journal of Epidemiology



Sensibilité à l'érythromycine de *S. pneumoniae* en fonction des antibiotiques utilisés



Essai d'INtervention (AUBEPPIN)



Service S P S E L de promotion de la santé en faveur des élèves du LOIRET - SERVICE MEDICAL

MINISTERE DE L'EDUCATION NATIONALE
ACADEMIE D'ORLEANS-TOURS
INSPECTION ACADEMIQUE DU LOIRET

Prospective population based epidemiological trial : january to May 2000

3 areas : 1500 children 3 to 6 years old / area

=> 30.000 - 40.000 inhabitants

=> 35-45 GPs

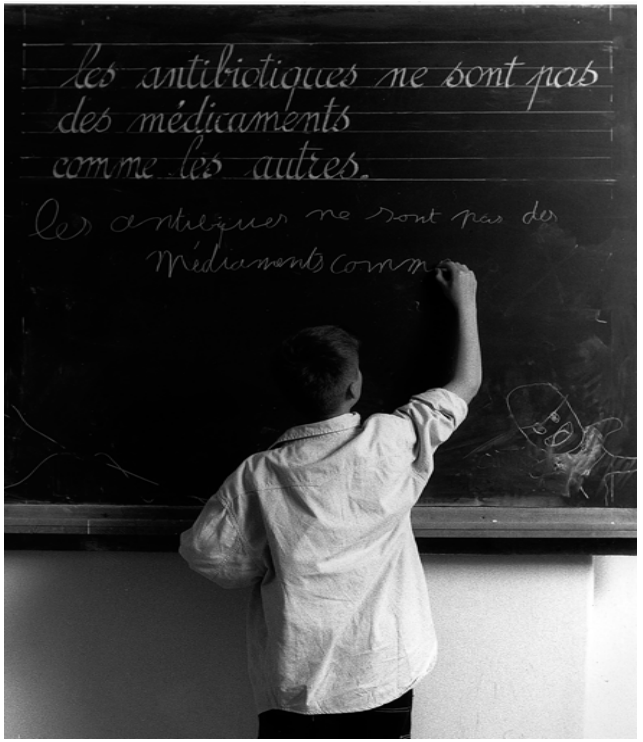
Optimal use of antibiotic during 5 months

Group 1 (North Seine Maritime)	Group 2 (South Loiret)	Group 3- Control group (North Loiret)
1 - to not prescribe antibiotic in Presumed Viral Respiratory Tract Infection	1 - Daily dosage have to be ≥ clinical recommandations	No intervention
2 - To use rapid diagnostic test in pharyngitis	2 - Duration of treatment ≤ 5 days	

Méthode et outils de communication

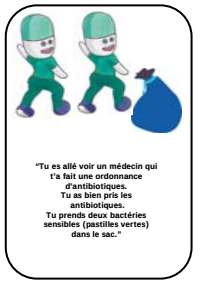
Sensibilisation globale

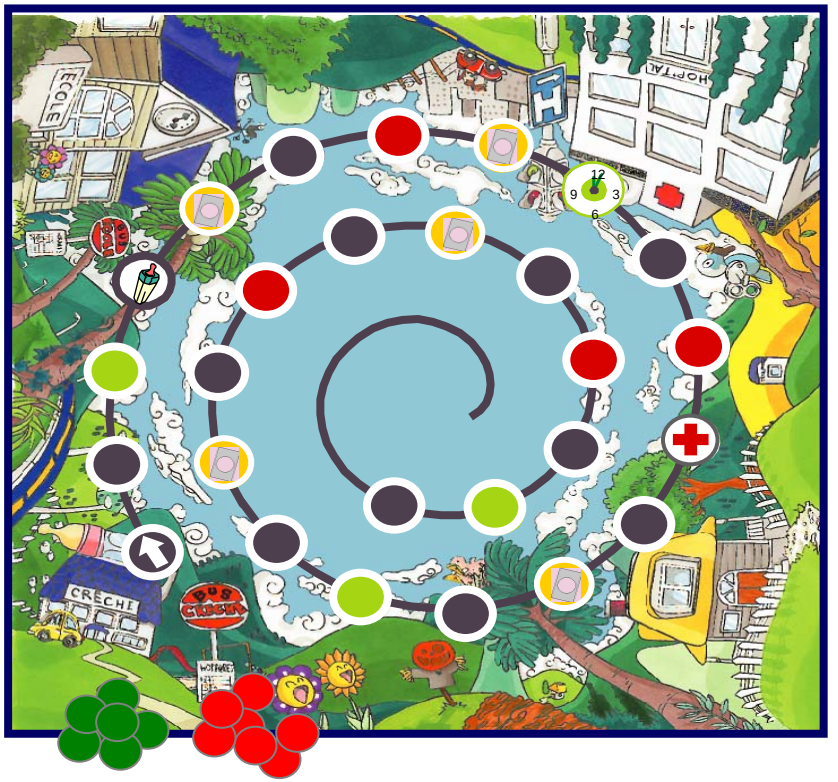
Affiches : écoles, cabinet médicaux, pharmacies…



Auprès des enfants

Jeu éducatif « A la recherche de la bactérie perdue »





Auprès des prescripteurs

Entretiens confraternels

Réunions collectives

Courrier de rappel tous les mois

Auprès des parents

Réunions collectives (écoles, communes)

Courrier d'information tous les mois

Recorded data

- Questionnaire (monthly during 6 months):
  - physician consultations & hospitalisations,
  - diagnosis as stated by the practitioners,
  - drug use.
- Antibiotic delivered to children by pharmacists
- Pharyngeal carriage of *S. pneumoniae* + body weight
  - J0 and 180
  - *S. pneumoniae* carriers: 1x / 30 days
- Quality assesment:
  - screening, identification,
  - antibiotic susceptibility
  - INSERM audit

Antibiotic use (data provided by questionnaire

	Prescription–reduction N=601	Dose/duration N=483	Control N=405	Prescription–reduction vs Control Difference	P	Dose/duration vs Control Difference	P
January							
All antibiotics -%	33.0	23.4	22.8	**10.2**	**0.001**	**0.6**	**0.9**
Aminopenicillins - %	13.6	11.1	8.9	4.7	0.02	2.2	-
Cephalosporins - %	10.6	6.3	6.2	4.4	0.01	0.1	-
Macrolides - %	8.0	5.7	7.7	0.3	0.8	-2.0	-
May							
All antibiotics -%	14.2	6.3	19.0	**–4.8**	**0.04**	**–12.7**	**<0.001**
Aminopenicillins - %	7.8	1.9	6.6	1.2	0.5	–4.6	<0.001
Cephalosporins - %	4.0	2.3	2.6	1.5	0.2	–0.3	0.9
Macrolides - %	2.3	1.9	9.9	–7.7	<0.001	–8.1	<0.001
Difference between January and May 2000							
All antibiotics - % (P value)	**–18.8 (<0.001)**	**–17.1 (<0.001)**	**–3.8 (0.2)**				
Aminopenicillins - % (P value)	–5.8 (0.001)	–9.1 (<0.001)	–2.3				
Cephalosporins - % (P value)	–6.5 (<0.001)	–4.0 (0.002)	–3.6				
Macrolides - % (P value)	–5.7 (<0.001)	–3.8 (0.001)	2.3				

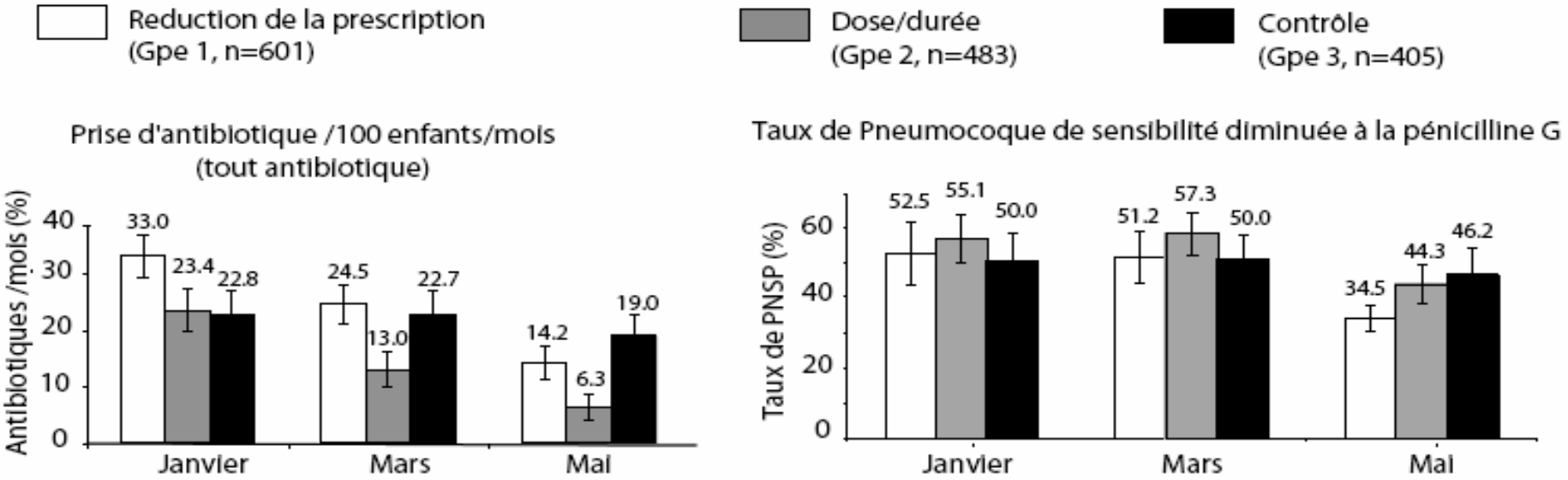
Penicillin susceptibility of *S. pneumoniae* strains

	Prescription-reduction N=601	Dose/duration N=483	Control N=405	Prescription-reduction vs Control Difference	P	Dose/duration vs Control Difference	P
January							
S. pneumoniae colonization - %	13.3	28.2	21.7	-8.4	<0.001	6.4	0.03
PNSP* Rate - %	52.5	55.1	50.0	2.5	0.7	5.1	0.5
May							
S pneumoniae colonization - %	41.4	36.4	22.5	**19.0**	**<0.001**	**14.0**	**<0.001**
PNSP* Rate - %	34.5	44.3	46.2	**-11.6**	**0.05**	**-1.8**	**0.8**
Difference between January and May bacterial screenings							
S. pneumoniae colonization - % (P value)	**28.1 (<0.001)**	**8.3 (0.006)**	**0.7 (0.8)**				
PNSP* Rate - % (P value)	**-18.0 (0.004)**	**-10.8 (0.06)**	**-3.8 (0.6)**				

* PNSP : penicillin G non-susceptible pneumococcus (MIC 0.1 µg/ml).

Optimization of Antibiotic Prescribing Practices in the Community Reduces the Rate of Penicillin G Non-Susceptible *Streptococcus pneumoniae* in Children 3 to 6 Years Old

Didier Guillemot (M.D., Ph.D.), Emmanuelle Varon (M.D.), Claire Bern¸ de (M.Sc.A.), Philippe Weber (Pharm D.), Laurence Henriet (M.D.), Sylvie Simon (M.Sc.), C˘ cile Laurent (M.Sc.A.), Herv˘ Lecoeur (M.D.) and Claude Carbon (M.D)

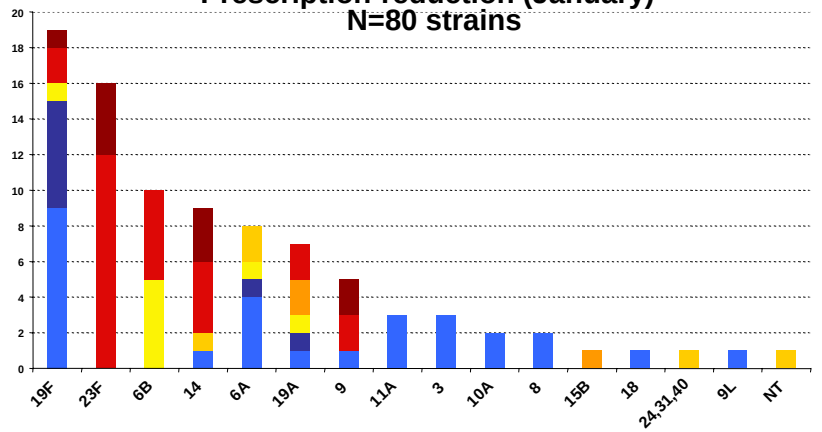


Additional slides ...

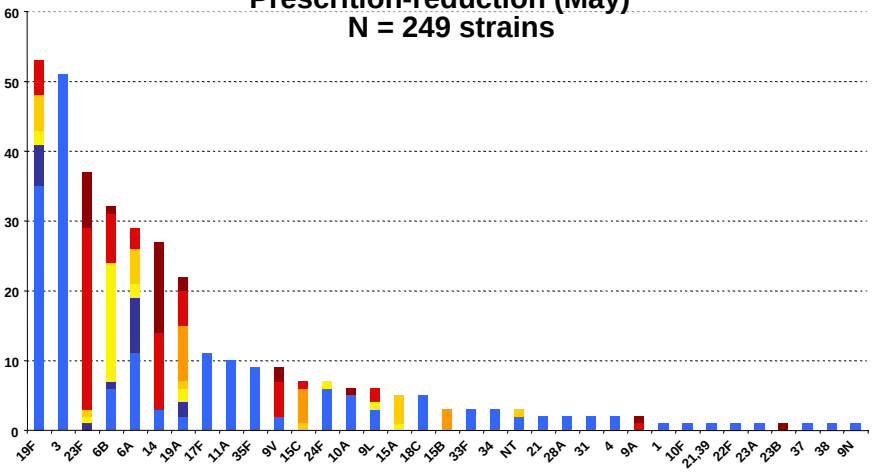
Penicillin G minimal inhibitory concentrations

≤ 0.03 µg/ml | 0.06 µg/ml | 0.125 µg/ml | 0.25 µg/ml | 0.5 µg/ml | 1 µg/ml | ≥ 2 µg/ml

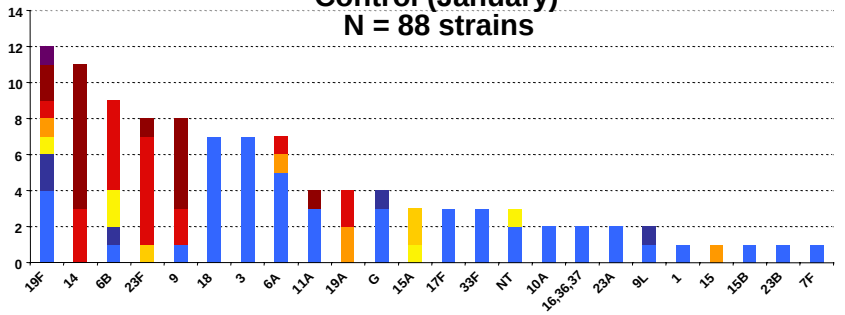
Prescription-reduction (January)
N=80 strains



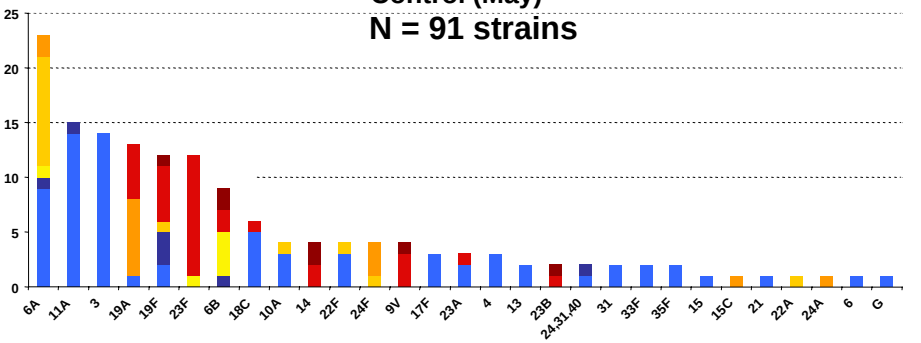
Prescrition-reduction (May)
N = 249 strains



Control (January)
N = 88 strains



Control (May)
N = 91 strains



Bacterial Resistance to Penicillin G by Decreased Affinity of Penicillin-Binding Proteins: A Mathematical Model

L. Temime,* P.Y. Boëlle,* P. Courvalin,† and D. Guillemot†

Emerging Infectious Diseases • Vol. 9, No. 4, April 2003

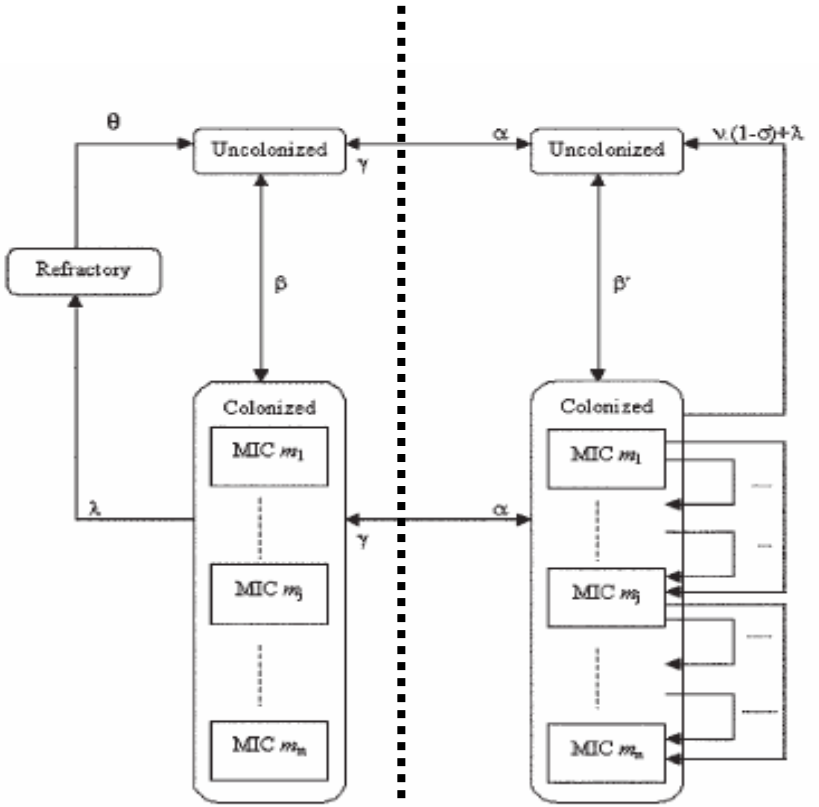
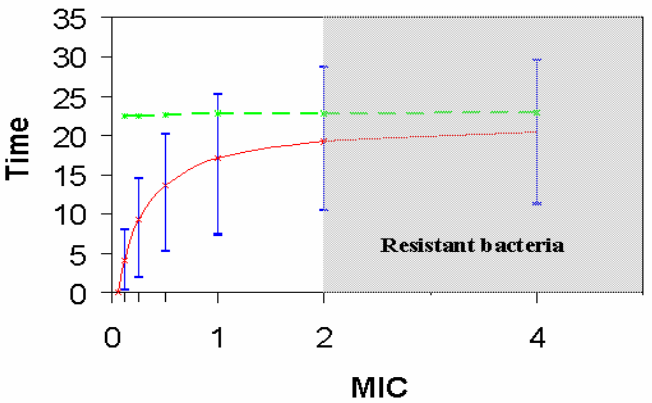


Figure 1. Structure of the model emergence and transmission of penicillin G resistance in *Streptococcus pneumoniae* and *Neisseria meningitidis*.



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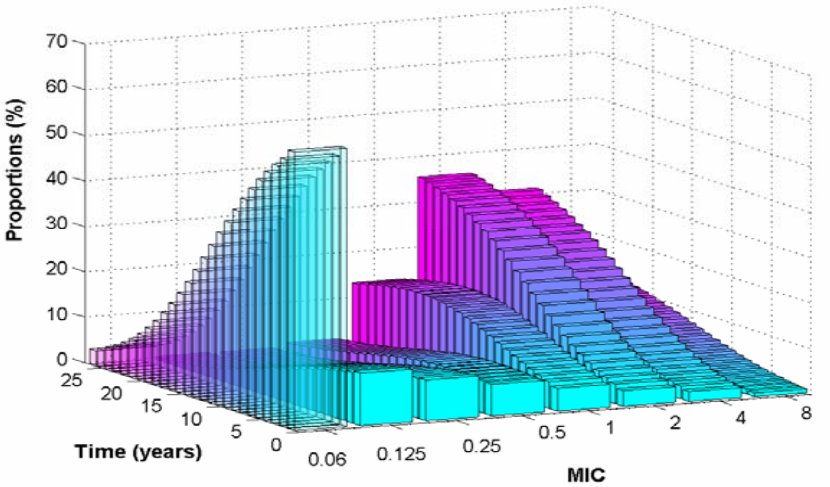
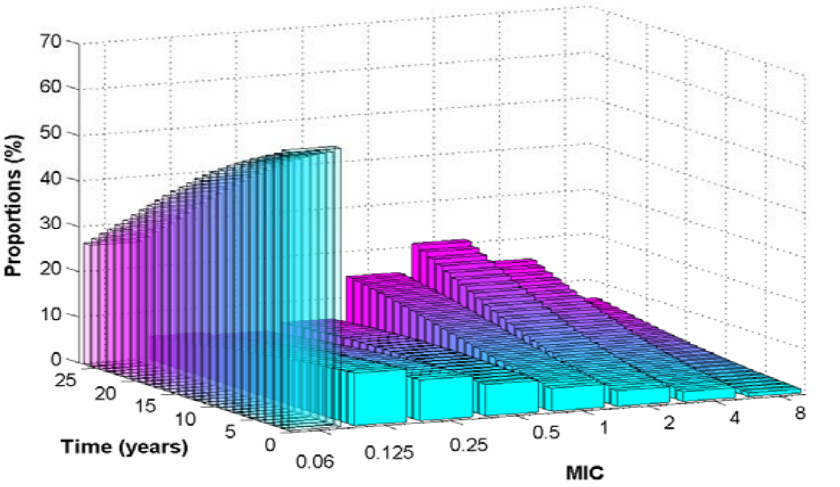
Sélection de la résistance de *N. meningitidis*

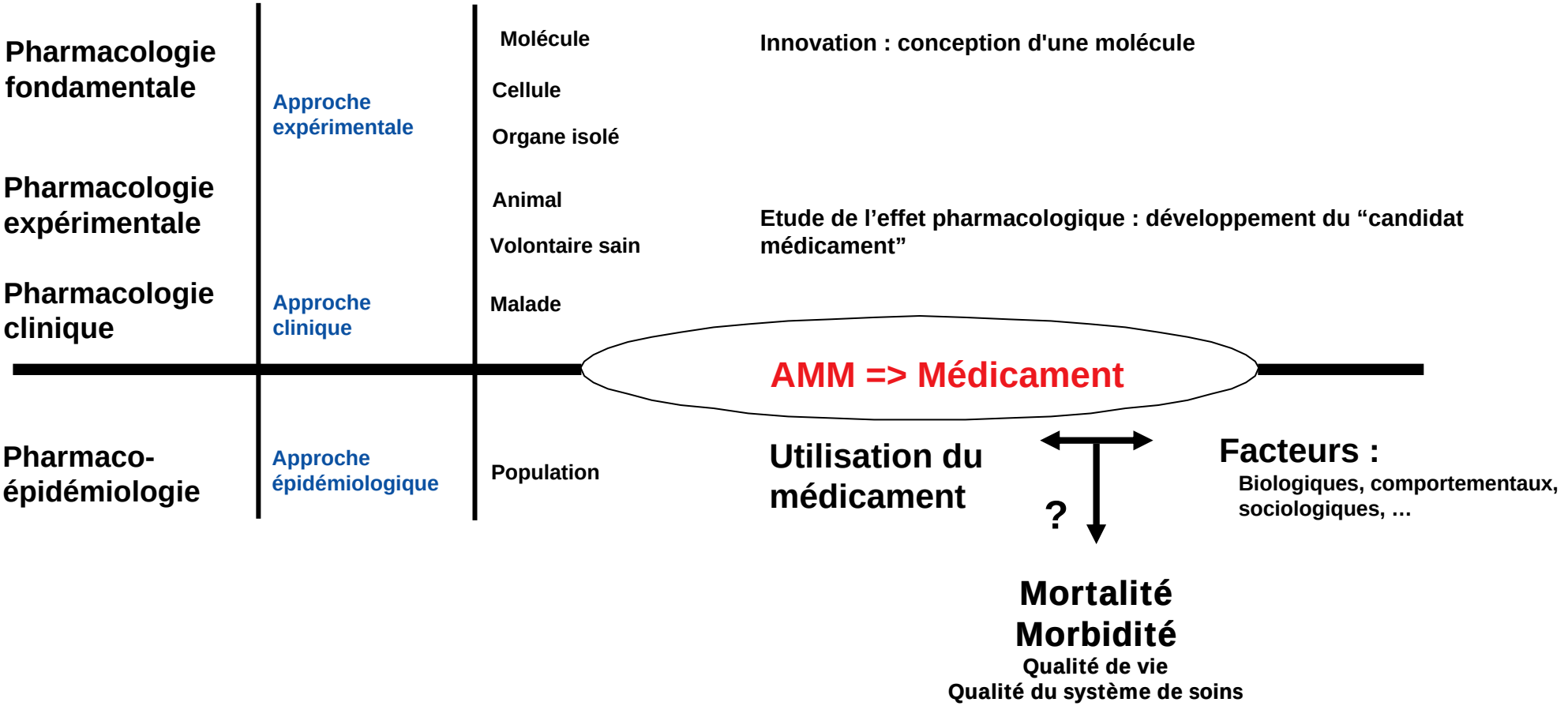


Conditions de traitement actuelles

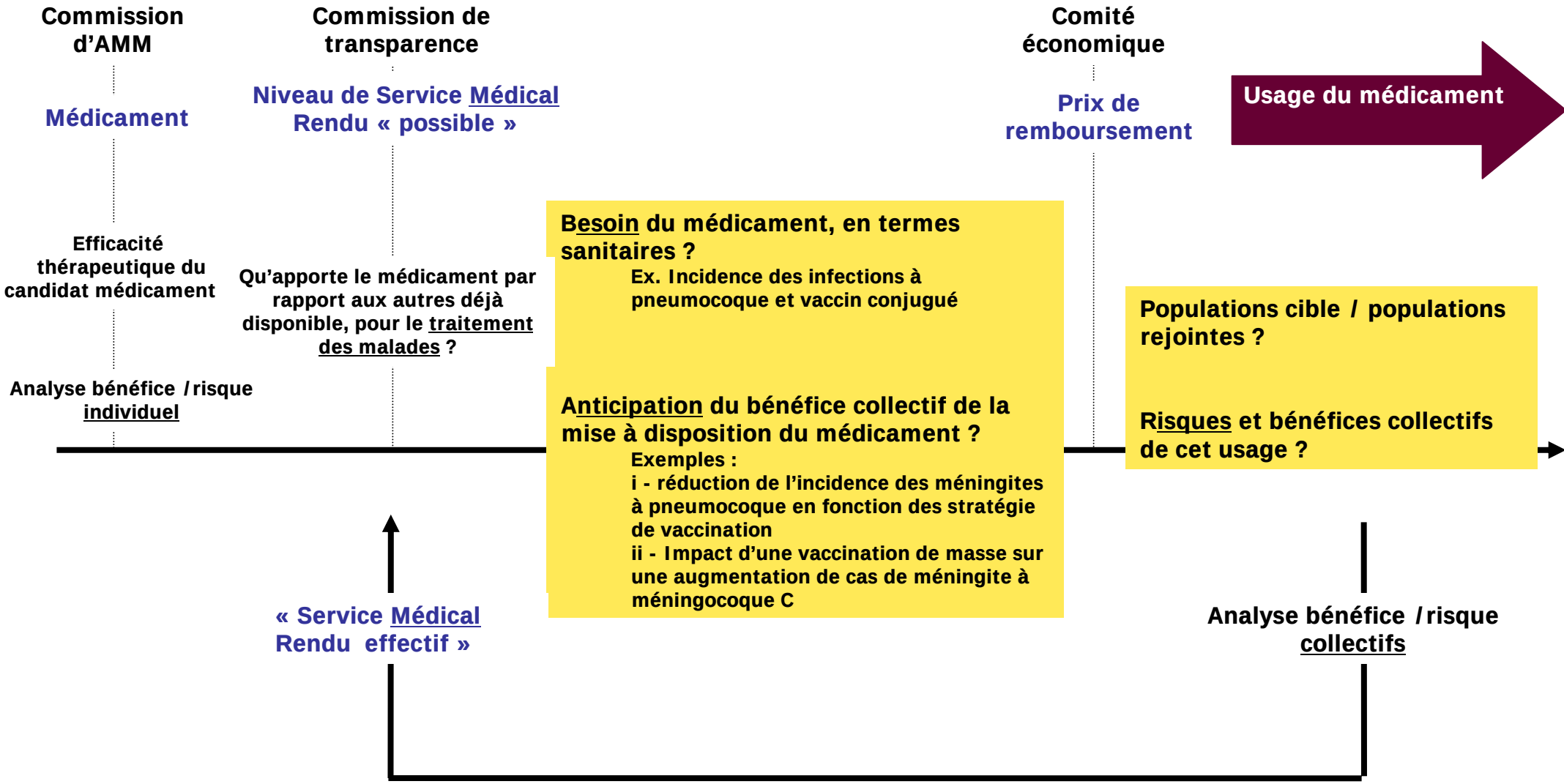


Fréquence de traitement divisée par 2

Les étapes de la « vie » d'un médicament



Pharmacoépidémiologie et décision sanitaire



Les déterminants de l'état de santé d'une population