Jordan Midway

UFR de Médecine

UNIVERSITÉ Grenoble Alpes

CHU GRENOBLE ALPES

Les antibiotiques : une pré-nécrologie

O. Epaulard
Infectiologie, CHU de Grenoble

2 avril 2019

DES(C) de Maladies Infectieuses et Tropicales
2018-2019

ibs Institut de Biologie Structurale

Au commencement était la sensibilité

- *Streptococcus pneumoniae* :
  - 100% de sensibilité à la pénicilline G
- *Neisseria meningitidis* :
  - 100% de sensibilité à la pénicilline G
- *Staphylococcus aureus* :
  - 100% de sensibilité aux pénicillines M
- *Salmonella typhi* :
  - 100% de sensibilité aux pénicillines A, aux quinolones, aux sulfamides …
- *E. coli* :
  - 100% de sensibilité aux pénicillines A, aux quinolones, aux sulfamides …

Sensibilité, certes, inégale …

- Presque tous les staphylocoques résistent aux pénicillines non A …
- Tous les *Pseudomonas aeruginosa* résistent aux sulfamides, aux quinolones non F, aux pénicillines A, aux C3G …
- Tous les *Enterobacter* résistent aux C1G, aux pénicillines A …
- Tous les entérocoques résistent aux C3G
- Toutes les *Klebsiella* résistent aux pénicillines A

OPEN ACCESS Freely available online

PLoS one

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

Kirandeep Bhullar[1], Nicholas Waglechner[1], Andrew Pawlowski[1], Kalinka Koteva[1], Eric D. Banks[2], Michael D. Johnston[2], Hazel A. Barton[2], Gerard D. Wright[1]*

1 M.G. DeGroote Institute for Infectious Disease Research, Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada, 2 Department of Biology, University of Akron, Akron, Ohio, United States of America

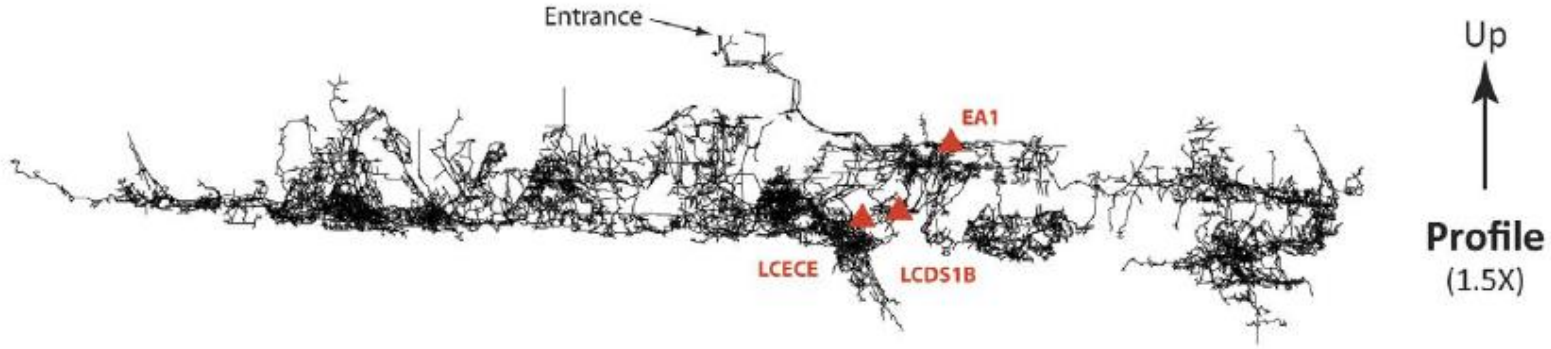
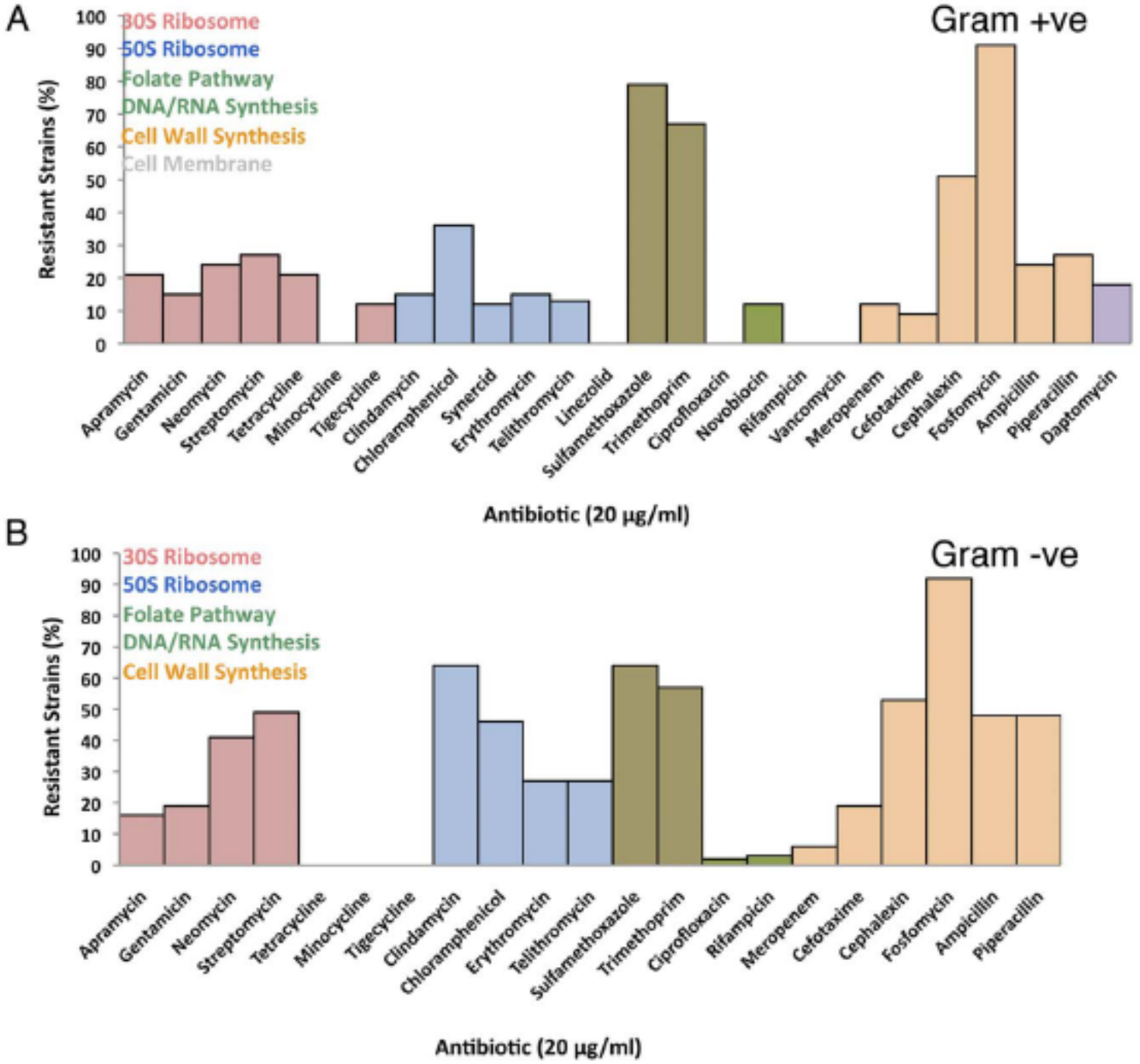


Figure 1. Plan and profile maps of Lechuguilla Cave, Carlsbad Caverns National Park, New Mexico. The sites where microbial strains were collected (LCECE, LCDS1 and LCEA1) are shown relative to the entrance and depth. tN represents true North on the plan, while the profile has an exaggerated vertical profile of 1.5×.
doi:10.1371/journal.pone.0034953.g001


A
Gram +ve
30S Ribosome
50S Ribosome
Folate Pathway
DNA/RNA Synthesis
Cell Wall Synthesis
Cell Membrane
Resistant Strains (%)
100
90
80
70
60
50
40
30
20
10
0
Apramycin
Gentamicin
Neomycin
Streptomycin
Tetracycline
Minocycline
Tigecycline
Clindamycin
Chloramphenicol
Synercid
Erythromycin
Telithromycin
Linezolid
Sulfamethoxazole
Trimethoprim
Ciprofloxacin
Novobiocin
Rifampicin
Vancomycin
Meropenem
Cefotaxime
Cephalexin
Fosfomycin
Ampicillin
Piperacillin
Daptomycin
Antibiotic (20 µg/ml)
B
Gram -ve
30S Ribosome
50S Ribosome
Folate Pathway
DNA/RNA Synthesis
Cell Wall Synthesis
Resistant Strains (%)
100
90
80
70
60
50
40
30
20
10
0
Apramycin
Gentamicin
Neomycin
Streptomycin
Tetracycline
Minocycline
Tigecycline
Clindamycin
Chloramphenicol
Erythromycin
Telithromycin
Sulfamethoxazole
Trimethoprim
Ciprofloxacin
Rifampicin
Meropenem
Cefotaxime
Cephalexin
Fosfomycin
Ampicillin
Piperacillin
Antibiotic (20 µg/ml)

Paradigme

- Haute virulence, réservoir humain, faible résistance initiale
  - *Salmonella typhi*
  - *Neisseria meningitidis*
  - *Treponema pallidum*
  - *Streptococcus pneumoniae*

- Faible virulence, réservoir environnemental, haute résistance initiale
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumanii*
  - *Stenotrophomonas maltophila*

- Les exceptions: réservoir environnemental, faible résistance, virulence importante
  - *Clostridium* toxinogènes
  - *Listeria monocytogenes*

Puis l’homme a mis la main sur les ATB

À l'aube des antibiotiques

Travaux de Vincenzo Tiberio, publiés en 1895 :

1ère extraction d'un composé fungique microbicide

- « L'auteur a observé l'action d'extraits aqueux du *Mucor mucedo*, du *Penicillium glaucum* et de l'*Aspergillus flavescens* sur quelques schizomycètes pathogènes et sur quelques saprophytes, les constatant doués, en particulier celui tiré de l'*Aspergillus*, d'un notable pouvoir **bactéricide**. »

Sugli estratti di alcune muffe. Ann Ig Sperim 1895;1:91-102

À l'aube des antibiotiques

- 1897 : thèse d'Ernest Duchesne (Lyon) :
  - Les moisissures éliminent les bactéries d'une culture
  - Guérison d'animaux infectés

FACULTÉ DE MÉDECINE ET DE PHARMACIE DE LYON
Année scolaire 1897-98. — N° 59.

CONTRIBUTION A L'ÉTUDE

DE LA

CONCURRENCE VITALE

CHEZ LES MICROORGANISMES

Antagonisme entre les Moisissures et les Microbes

THESE

PRÉSENTÉE

A LA FACULTÉ DE MÉDECINE ET DE PHARMACIE DE LYON

Et soutenue publiquement le 17 Décembre 1897

POUR OBTENIR LE GRADE DE DOCTEUR EN MÉDECINE

PAR

Ernest DUCHESNE

Né le 30 mai 1874, à Paris (Seine),

Elève de l'École du Service de Santé Militaire.

LYON

ALEXANDRE REY, IMPRIMEUR DE LA FACULTÉ DE MÉDECINE

4, RUE GENTIL, 4

Décembre 1897

À l'aube des antibiotiques

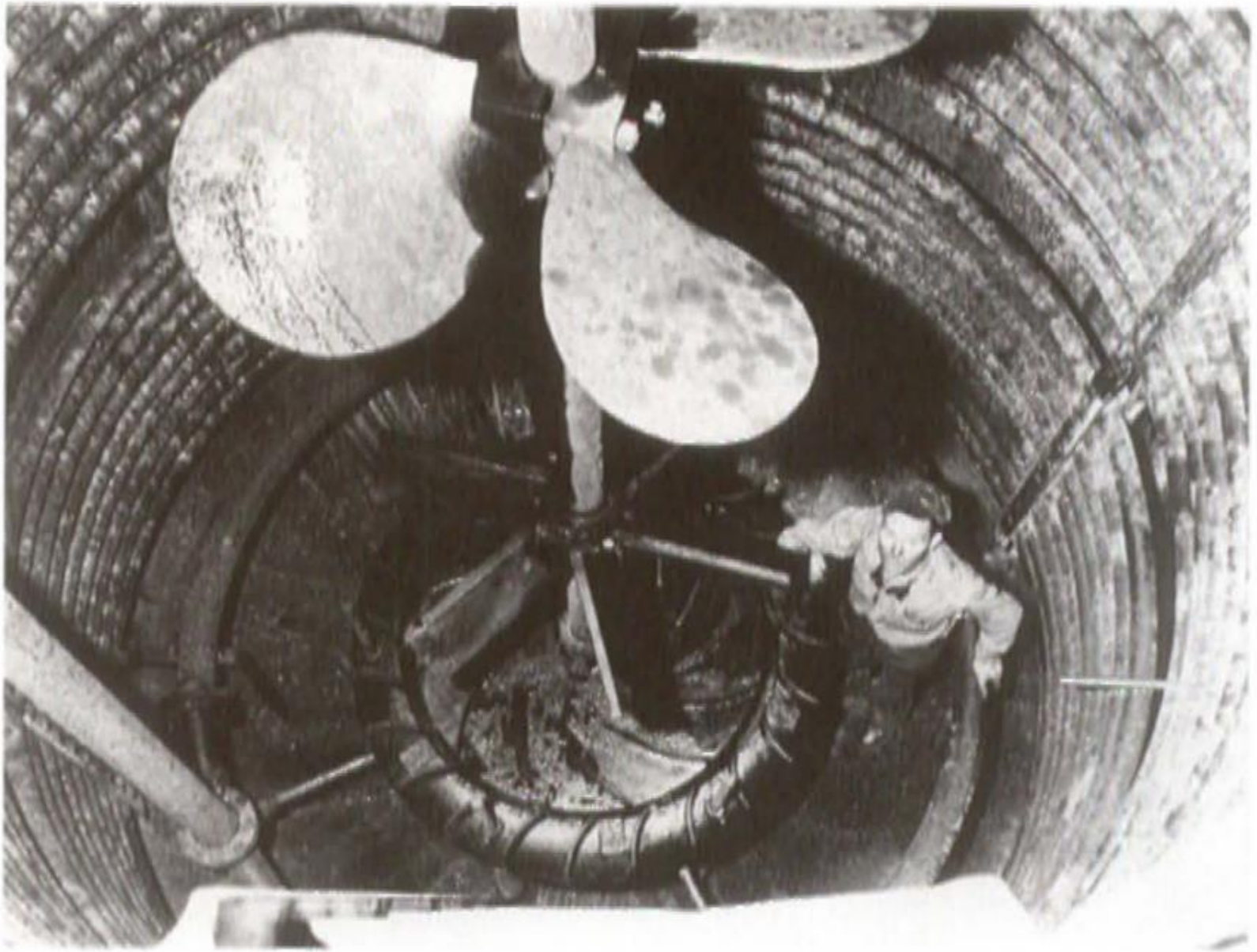
- 1928 : expériences de Fleming (Londres)
  - Contamination accidentelle d'une culture bactérienne

Howard Florey

Ernst Chain

- 1940 : conflit mondial
- Florey, Chain & Heathley parviennent à purifier la pénicilline et à traiter des souris
  - Mais il faut 2000 litres de culture fungique pour traiter un humain …
- 1943 : production d'assez de pénicilline pour traiter les humains
  - Grace à une souche de *Penicillium chrysogenum*
    - Constatée sur un melon et menée au laboratoire par Mary Hunt
  - Utilisation à grande échelle chez les blessés britanniques et américains

Penicillin manufacture at Oxford University, early 1940s



Fermentation vat at Merck c.1945 (courtesy of Merck Inc.)

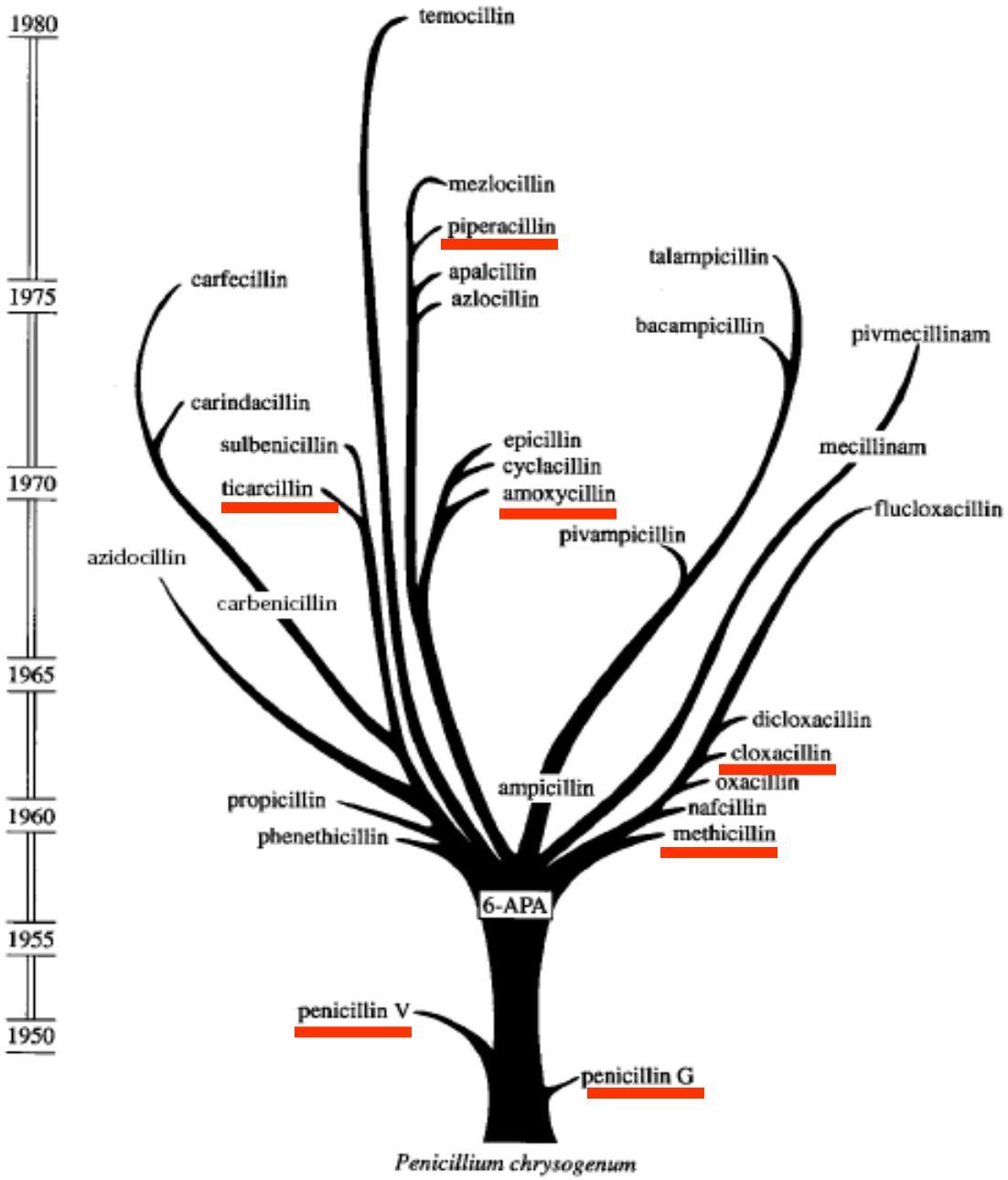

Thanks to PENICILLIN
...He Will Come Home!
FROM ORDINARY MOLD—
the Greatest Healing Agent of this War!
SCHENLEY LABORATORIES, INC.
Producers of PENICILLIN-Schenley

Aout 1944

Origine fungique des antibiotiques …

- *Streptomyces erythreus* : érythromycine
- *Streptomyces orientalis* : vancomycine
- *Streptomyces chrysogenum* : pénicilline
- *Cephalosporum acremonium*: céphalosporine
- *Streptomyces cattleya* : thiénamycine puis imipénème
- *Micromonospora purpurea* : gentamicine
- *Streptomyces griseus* : streptomycine
- *Streptomyces rimosus* : tétracycline
- *Streptomyces mediterranei* : rifampicine
- Etc …

G. N. Rolinson

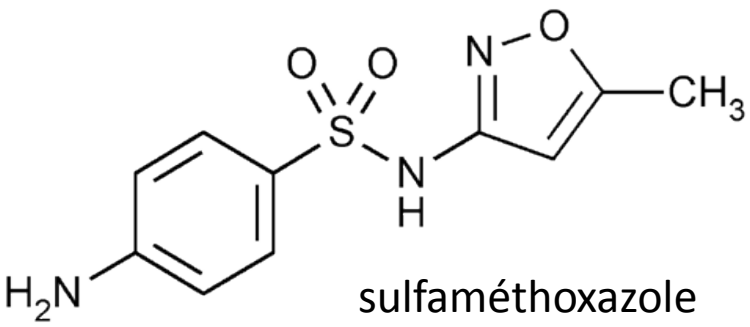

1980
1975
1970
1965
1960
1955
1950
temocillin
mezlocillin
piperacillin
apalcillin
azlocillin
carfecillin
talampicillin
bacampicillin
pivmecillinam
carindacillin
sulbenicillin
epicillin
cyclacillin
amoxycillin
mecillinam
ticarcillin
pivampicillin
flucloxacillin
azidocillin
carbenicillin
dicloxacillin
cloxacillin
oxacillin
ampicillin
propicillin
nafcillin
phenethicillin
methicillin
6-APA
penicillin V
penicillin G
Penicillium chrysogenum

Les sulfamides

- Découverts par les chimistes d'un teinturier allemand, I.G. Farben

Fig. 1. Gerhard Johannes Paul Domagk examining microscopic preparations in the laboratory of I. G. Farben, Wuppertal-Elberfeld, Germany.

Les sulfamides



sulfaméthoxazole

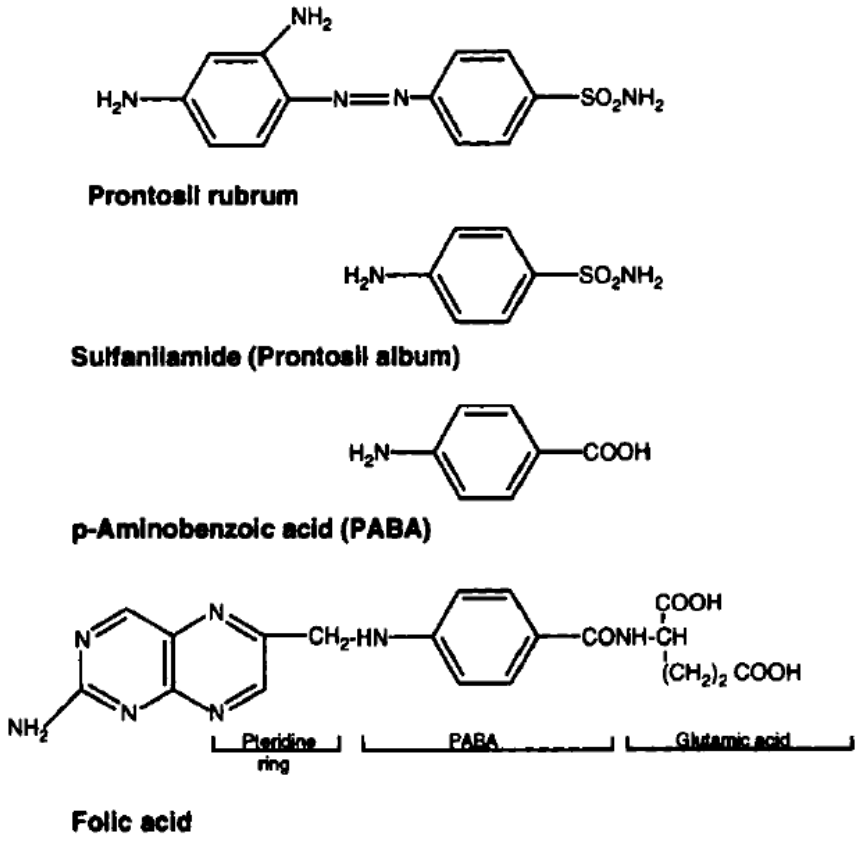


Fig. 2. Structural formulas of protosil rubrum, sulfanilamide, para-aminobenzoic acid and folic acid.

- Effet antibactérien en modèle murin
  - Démontré par GJP Domagk (1895-1964), Nobel 1939

COMMUNICATION TO THE EDITOR

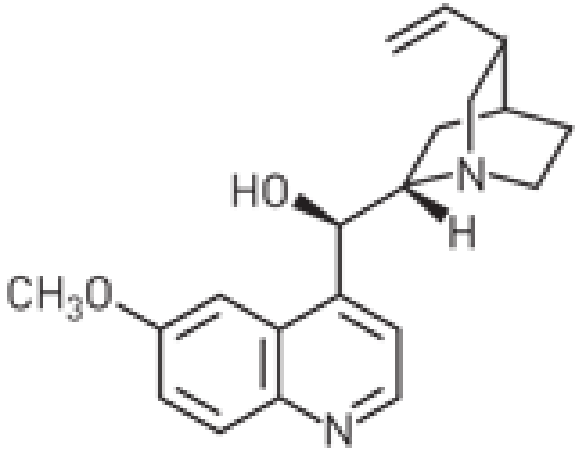
1,8-Naphthyridine Derivatives. A New Class of Chemotherapeutic Agents

GEORGE Y. LESHER, ERNEST J. FROELICH, MONTE D. GRUETT, JOHN HAYS BAILEY AND R. PAULINE BRUNDAGE

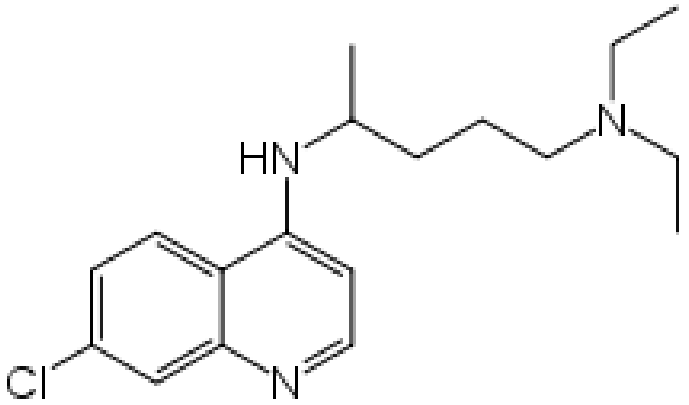
Sterling-Winthrop Research Institute, Division of Sterling Drug Inc., Rensselaer, New York

Received June 15, 1962

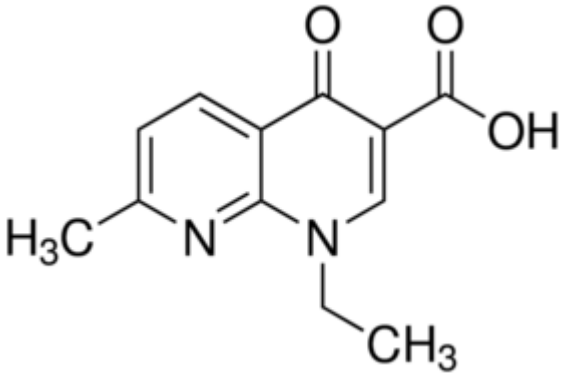
As part of a general investigation of new antibacterial agents,[1] we have prepared a series of 1-alkyl-1,8-naphthyridin-4-one-3-carboxylic acid derivatives. Several members of the series, listed in Table I, were found to be highly effective antibacterial agents both *in vitro* and *in vivo*.



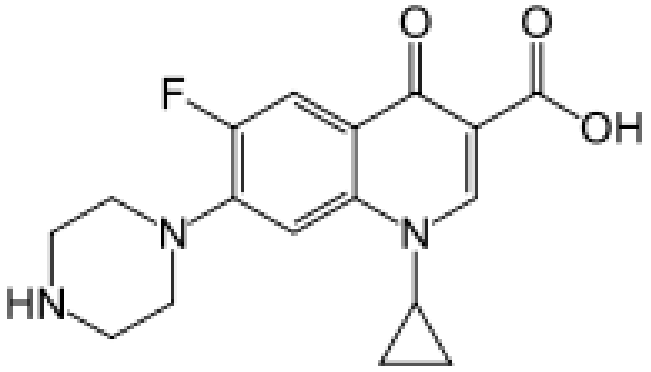
Quinine



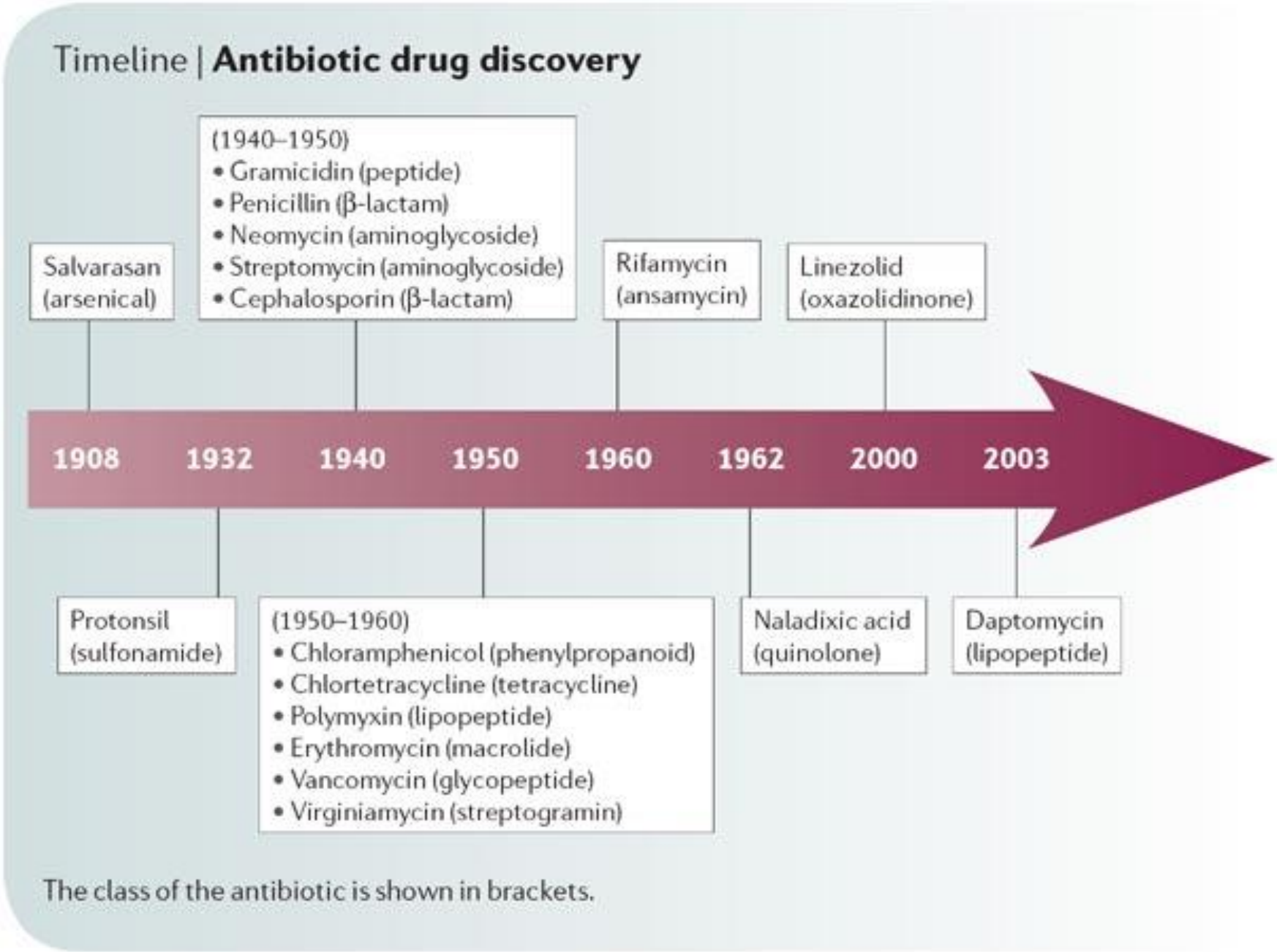
Chloroquine



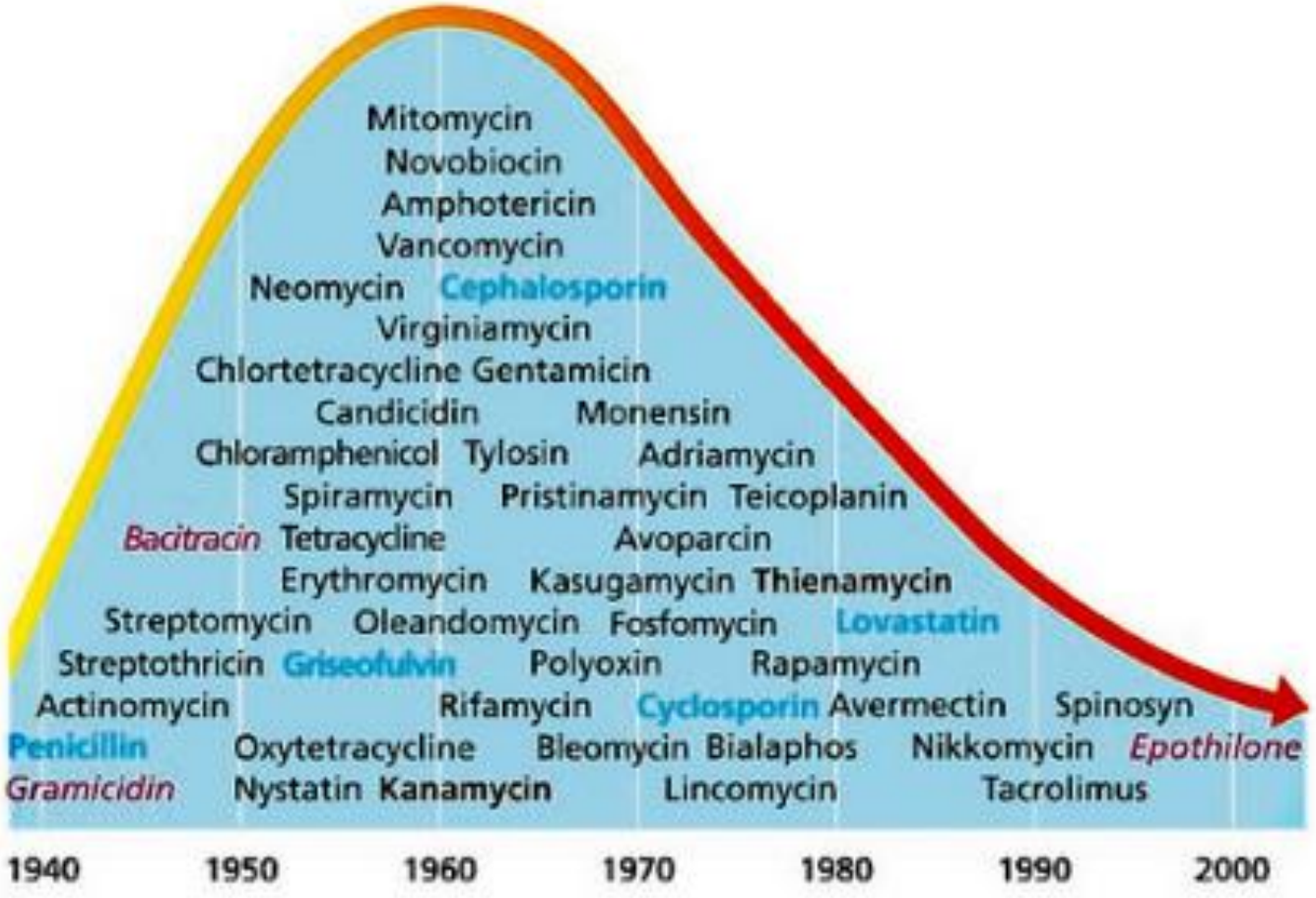
Acide nalidixique



Ciprofloxacine

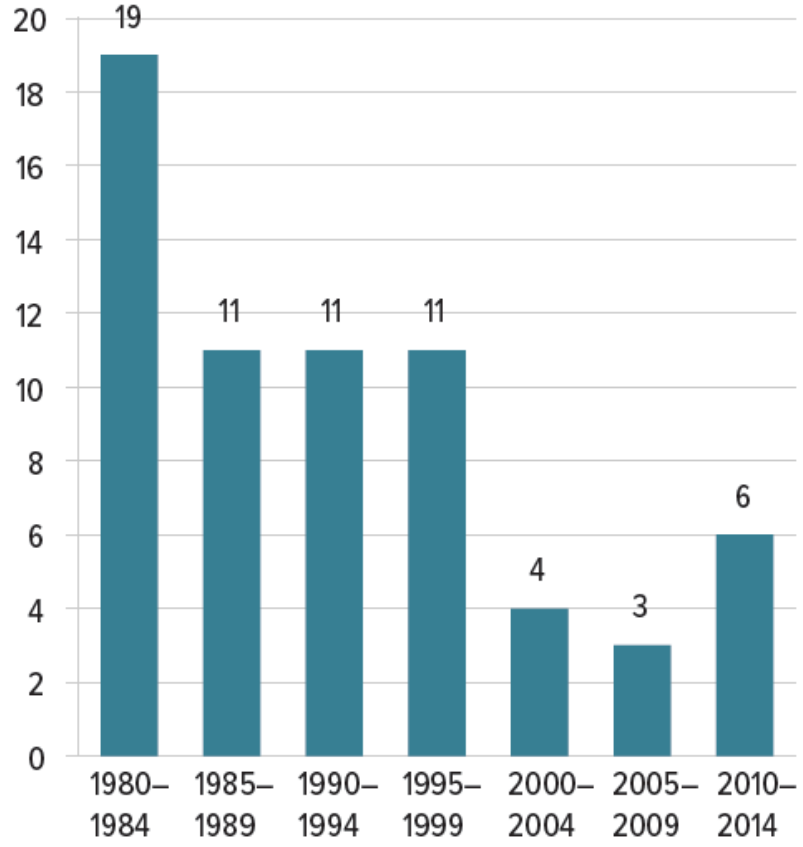

Timeline | Antibiotic drug discovery
(1940–1950)
• Gramicidin (peptide)
• Penicillin (β-lactam)
• Neomycin (aminoglycoside)
• Streptomycin (aminoglycoside)
• Cephalosporin (β-lactam)
Salvarasan (arsenical)
Rifamycin (ansamycin)
Linezolid (oxazolidinone)
1908
1932
1940
1950
1960
1962
2000
2003
Protonsil (sulfonamide)
(1950–1960)
• Chloramphenicol (phenylpropanoid)
• Chlortetracycline (tetracycline)
• Polymyxin (lipopeptide)
• Erythromycin (macrolide)
• Vancomycin (glycopeptide)
• Virginiamycin (streptogramin)
Naladixic acid (quinolone)
Daptomycin (lipopeptide)
The class of the antibiotic is shown in brackets.

Wright 2007


Mitomycin
Novobiocin
Amphotericin
Vancomycin
Neomycin
Cephalosporin
Virginiamycin
Chlortetracycline
Gentamicin
Candicidin
Monensin
Chloramphenicol
Tylosin
Adriamycin
Spiramycin
Pristinamycin
Teicoplanin
Bacitracin
Tetracycline
Avoparcin
Erythromycin
Kasugamycin
Thienamycin
Streptomycin
Oleandomycin
Fosfomycin
Lovastatin
Streptothricin
Griseofulvin
Polyoxin
Rapamycin
Actinomycin
Rifamycin
Cyclosporin
Avermectin
Spinosyn
Penicillin
Oxytetracycline
Bleomycin
Bialaphos
Nikkomycin
Epothilone
Gramicidin
Nystatin
Kanamycin
Lincomycin
Tacrolimus
1940
1950
1960
1970
1980
1990
2000

Lee Ventola, 2015

Figure 3 Number of Antibacterial New Drug Application Approvals Versus Year Intervals



The number of new antibiotics developed and approved has decreased steadily over the past three decades (although four new drugs were approved in 2014), leaving fewer options to treat resistant bacteria.

* Drugs are limited to systemic agents. Data courtesy of the CDC[5] and the FDA Center for Drug Evaluation and Research.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

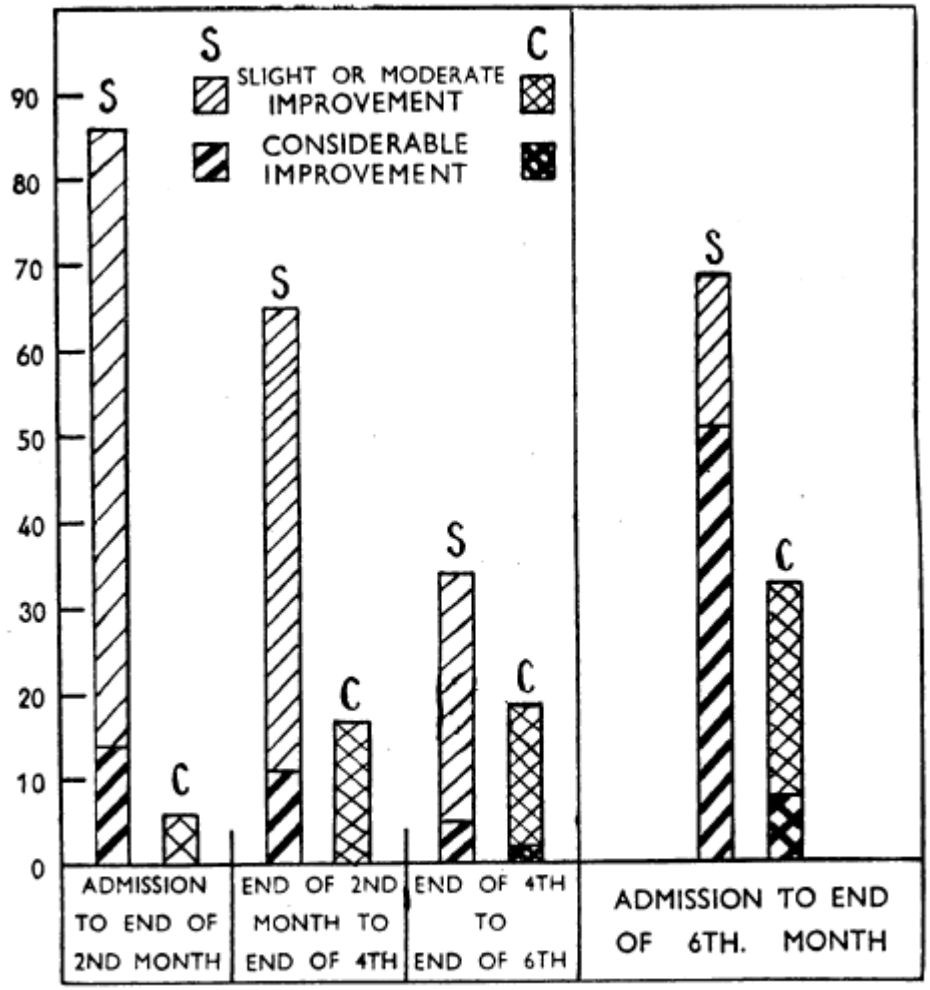


CHART IV.—Percentage of total patients admitted (*not* of survivors at beginning of each period) showing improvement in radiological picture in succeeding two-monthly periods and in six months.

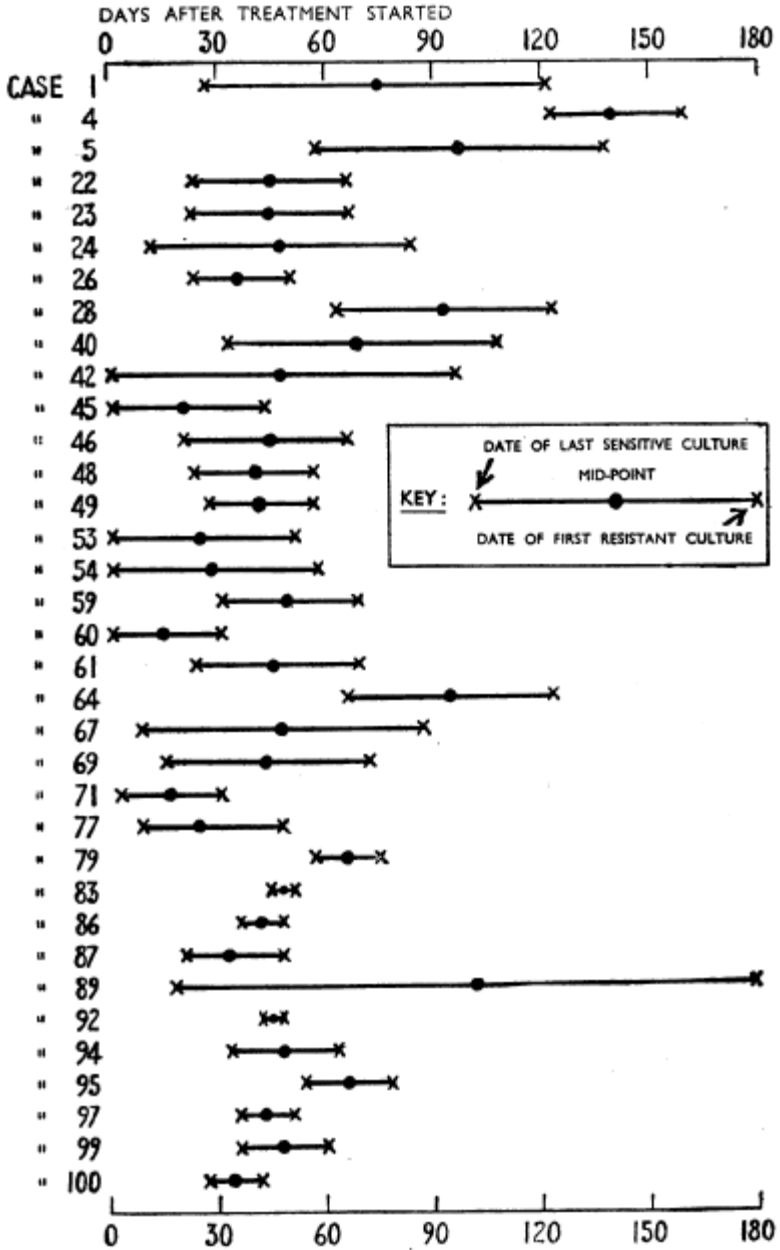
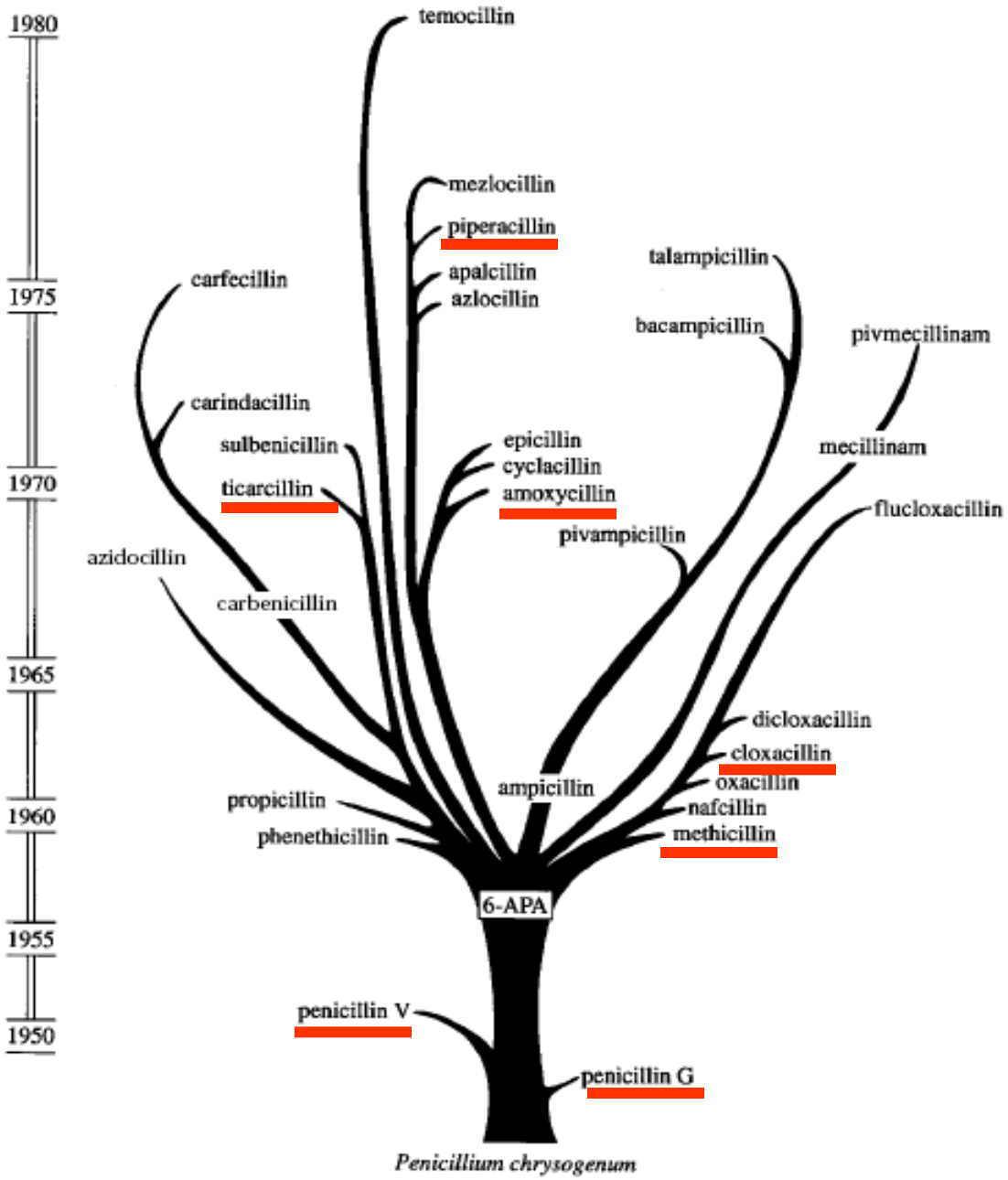
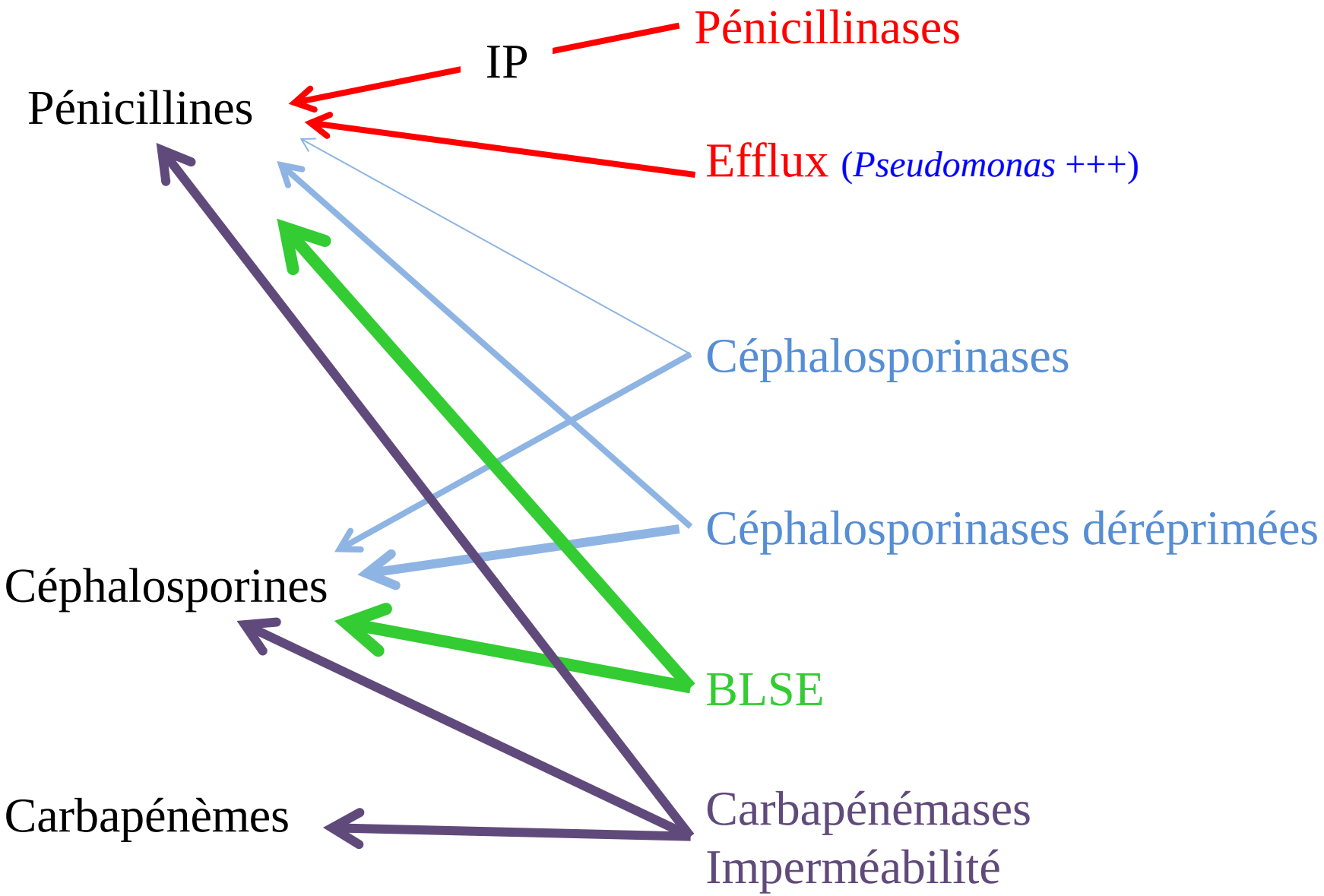


CHART V.—Showing date of emergence of streptomycin resistance (over 10 times that of H37Rv)

G. N. Rolinson


1980
1975
1970
1965
1960
1955
1950
temocillin
mezlocillin
piperacillin
apalcillin
azlocillin
carfecillin
talampicillin
bacampicillin
pivmecillinam
carindacillin
sulbenicillin
epicillin
cyclacillin
amoxycillin
mecillinam
ticarcillin
pivampicillin
flucloxacillin
azidocillin
carbenicillin
dicloxacillin
cloxacillin
oxacillin
ampicillin
propicillin
nafcillin
phenethicillin
methicillin
6-APA
penicillin V
penicillin G
Penicillium chrysogenum


Pénicillinases
IP
Pénicillines
Efflux (*Pseudomonas* +++)
Céphalosporinases
Céphalosporinases déréprimées
Céphalosporines
BLSE
Carbapénèmes
Carbapénémases
Imperméabilité

ELSEVIER

2006

The CTX-M β-lactamase pandemic

Rafael Cantón and Teresa M Coque

Table 1

Different CTX-M clusters and origin of *bla*$_{CTX-M}$.

	CTX-M cluster				
	CTX-M-1	CTX-M-2	CTX-M-8	CTX-M-9	CTX-M-25
Year (enzyme, country)[a]	1989 (CTX-M-1, Germany)	1986 (FEC-1, Japan)	1996 (CTX-M-8, Brazil)	1994 (CTX-M-9, Spain)	2000 (CTX-M-25, Canada)
Enzymes	CTX-M-1, -3, -10, -11, -12, -15, -22, -23 -29, -30, -32, -33, -28, -36, -54, UOE-1	CTX-M-2, -4, -6, -7, -20, -31, -44 (previously TOHO-1), FEC-1	CTX-M-40	CTX-M-9, -13, -14, -16, -17, -18, -19, -24, -27, -45 (previously TOHO-2), -46, -47, -48, -49, -50,	CTX-M, -26, -25, -39, -41
Origin	*K. ascorbata*	*K. ascorbata*	*K. georgiana*	*K. georgiana*	ND

[a] Year of first isolation or description (first enzyme described and country of isolation); CTX-M-14 and CTX-M-18 are identical; ND: not defined.

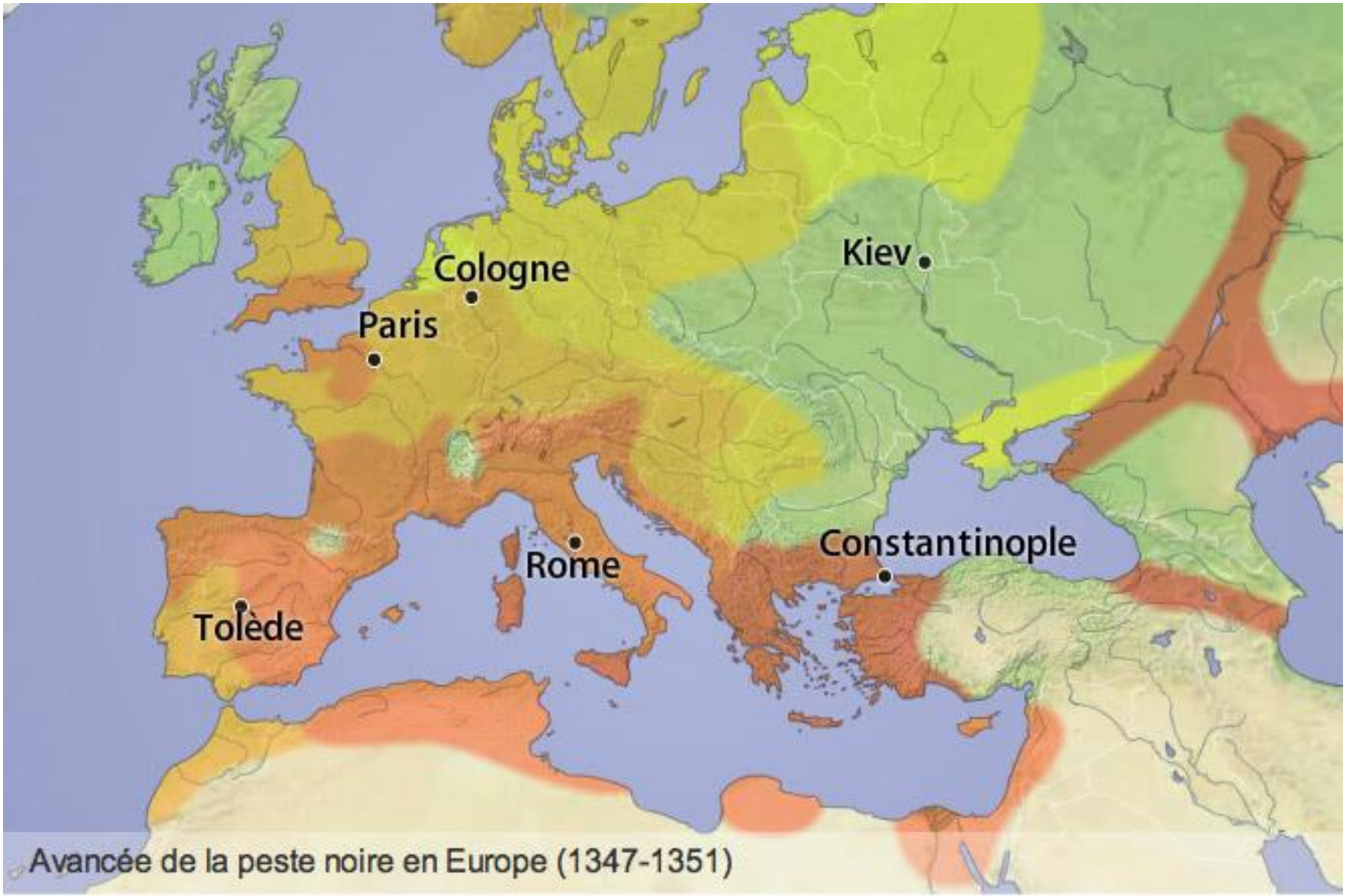
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2006, p. 1282–1286 Vol. 50, No. 4
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.4.1282–1286.2006

In Vitro Analysis of IS*Ecp1B*-Mediated Mobilization of Naturally Occurring β-Lactamase Gene *bla*$_{CTX-M}$ of *Kluyvera ascorbata*

Marie-Frédérique Lartigue, Laurent Poirel, Daniel Aubert, and Patrice Nordmann*

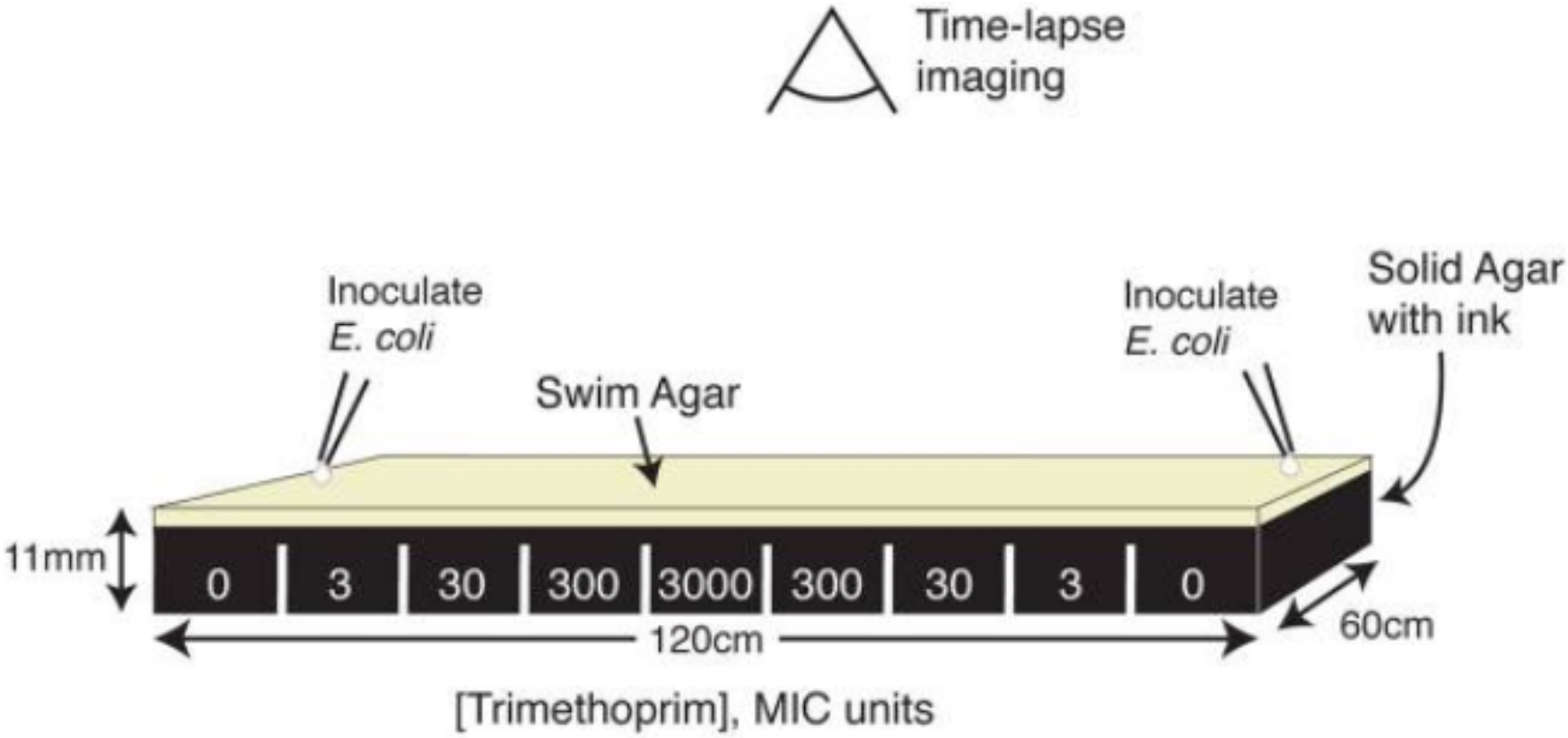
Service de Bactériologie-Virologie, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris-Sud, Université Paris XI, 94275 K-Bicêtre, France

Received 14 November 2005/Returned for modification 13 December 2005/Accepted 11 January 2006



Avancée de la peste noire en Europe (1347-1351)

Migration … évolution … résistance …



Baym *Science*. 2016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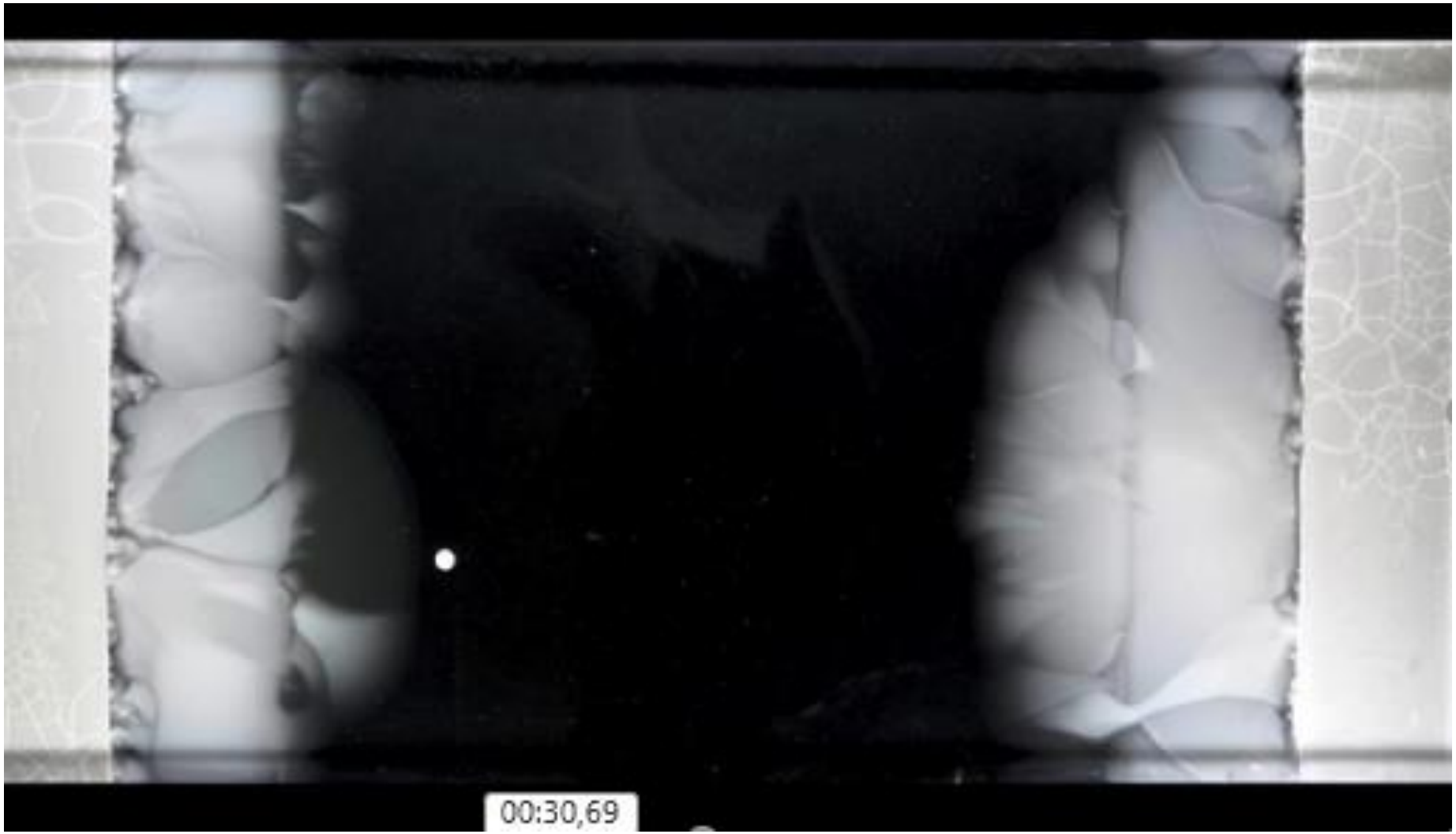
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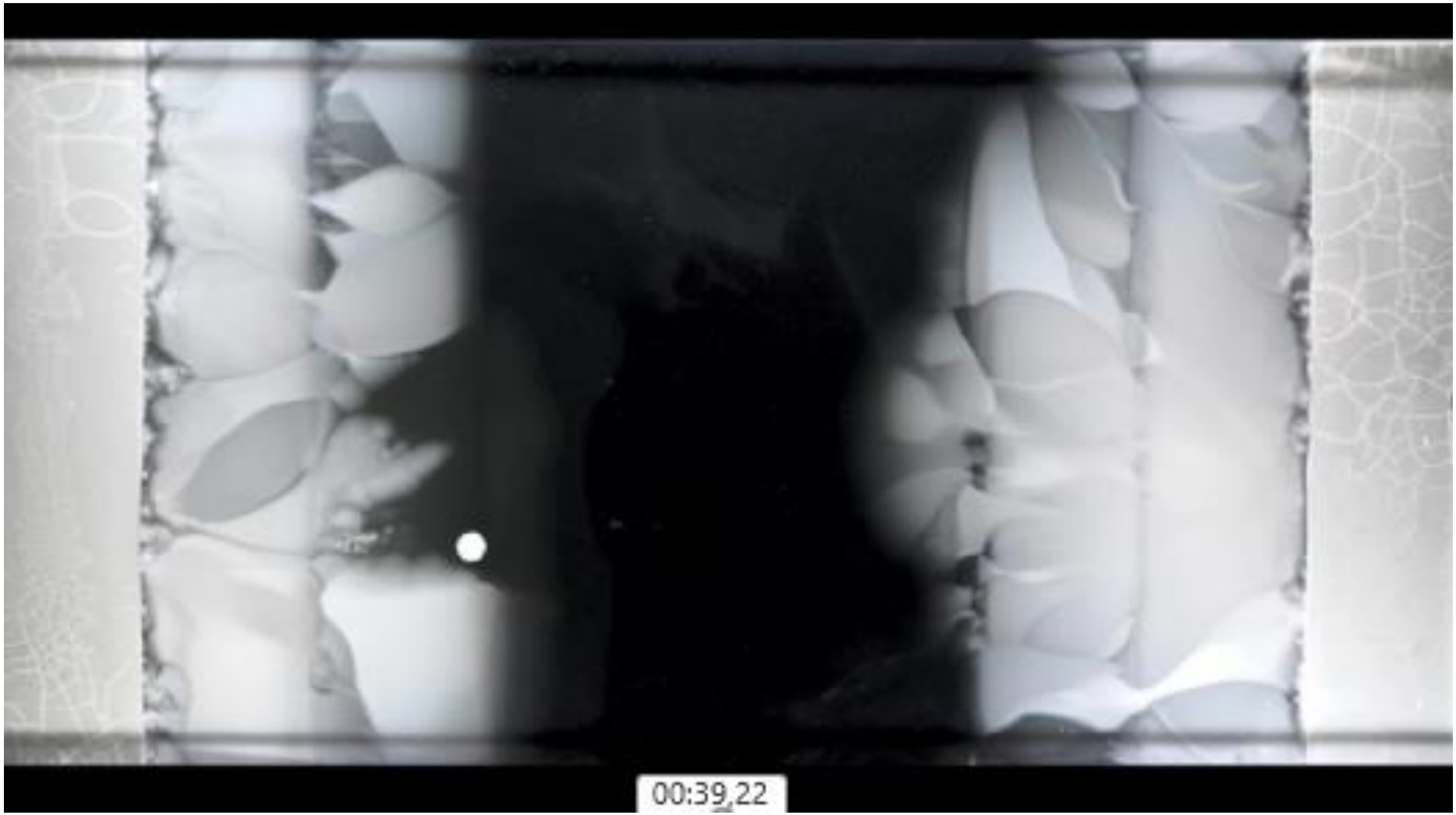

00:39,22

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

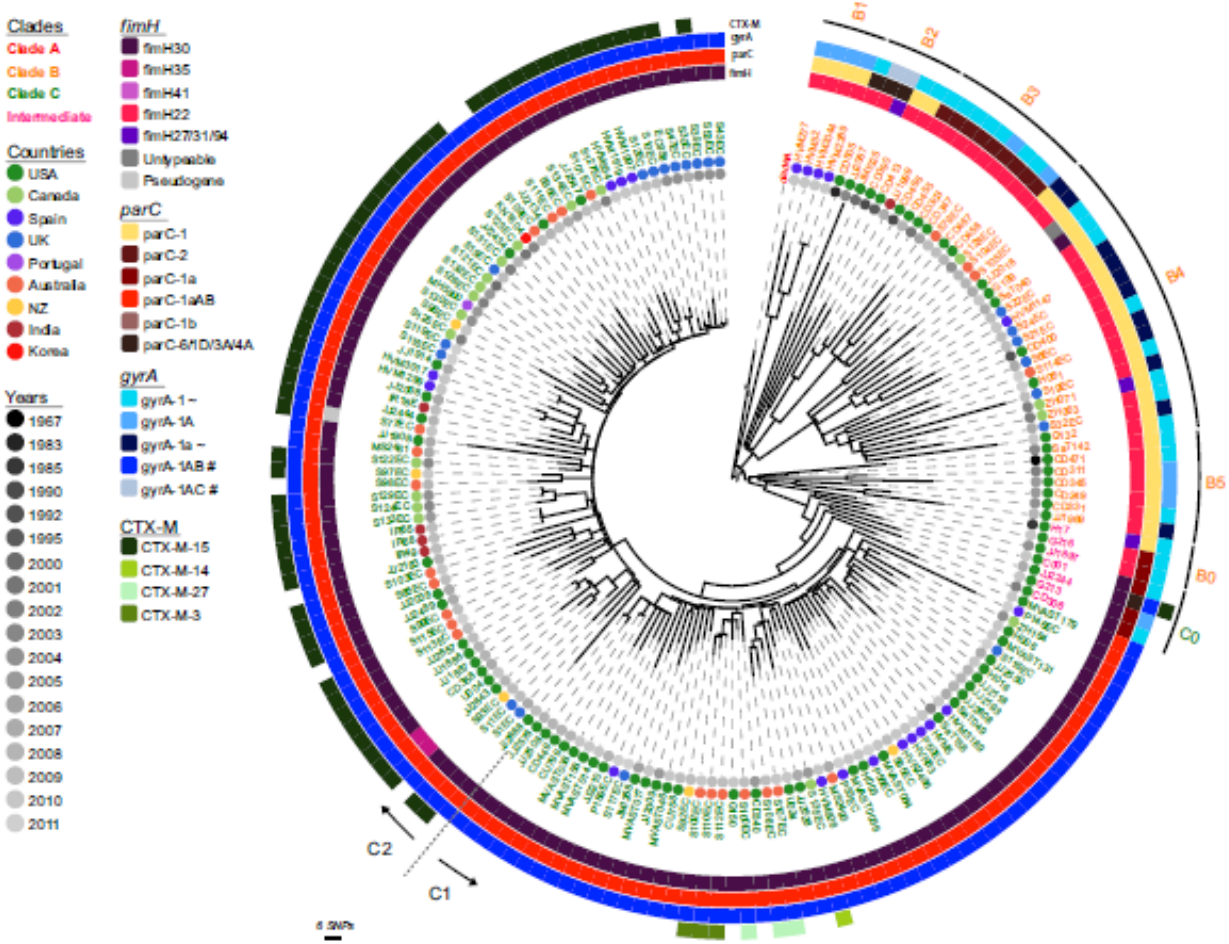
RESEARCH ARTICLE

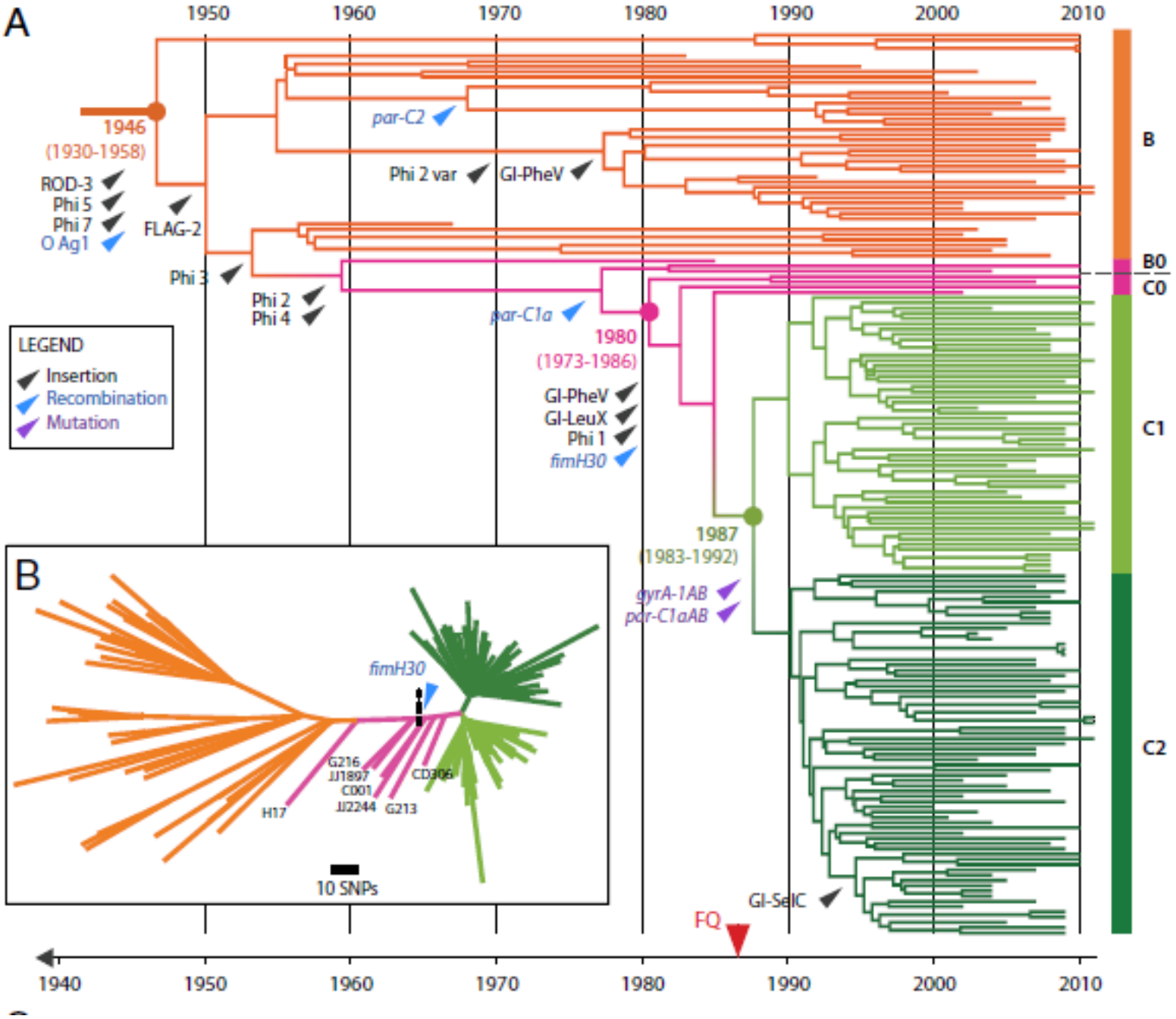
Sequential Acquisition of Virulence and Fluoroquinolone Resistance Has Shaped the Evolution of *Escherichia coli* ST131

Nouri L. Ben Zakour,[a,b] Areej S. Alsheikh-Hussain,[a,b] Melinda M. Ashcroft,[a,b] Nguyen Thi Khanh Nhu,[a,b] Leah W. Roberts,[a,b] Mitchell Stanton-Cook,[a,b] Mark A. Schembri,[a] Scott A. Beatson[a,b]

Australian Infectious Diseases Research Centre[a] and Australian Centre for Ecogenomics,[b] School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Australia

A.S.A.-H., M.M.A., and N.T.K.N. contributed equally to this article.




A
1950
1960
1970
1980
1990
2000
2010
1946
(1930-1958)
ROD-3
Phi 5
Phi 7
O Ag1
FLAG-2
Phi 3
Phi 2
Phi 4
par-C2
Phi 2 var
GI-PheV
par-C1a
1980
(1973-1986)
GI-PheV
GI-LeuX
Phi 1
fimH30
1987
(1983-1992)
gyrA-1AB
par-C1aAB
GI-SelC
FQ
LEGEND
Insertion
Recombination
Mutation
B
B0
C0
C1
C2
1940
1950
1960
1970
1980
1990
2000
2010
B
fimH30
G216
JJ1897
C001
JJ2244
G213
CD306
H17
10 SNPs

PLOS ONE

RESEARCH ARTICLE

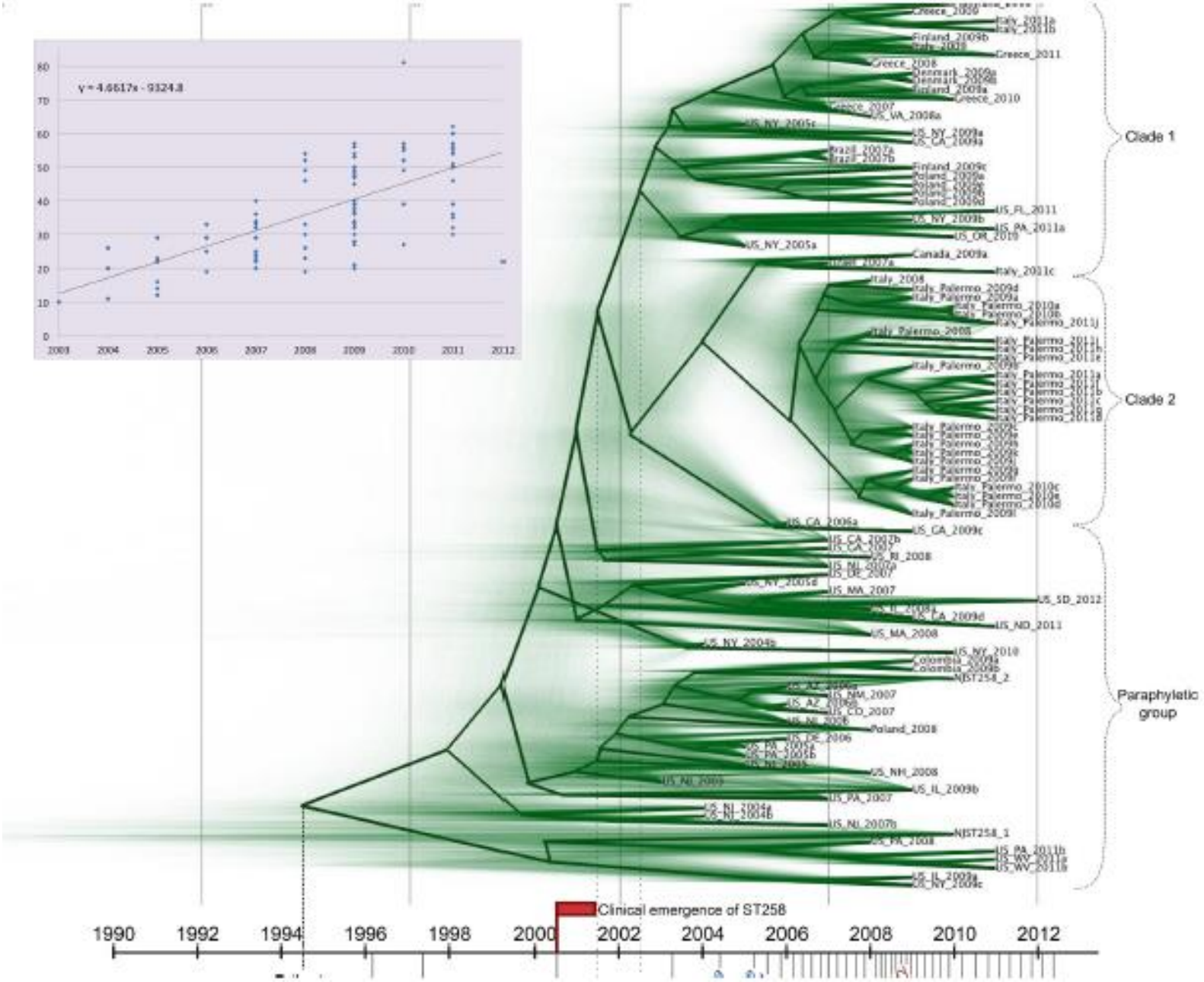
Genomic Analysis of the Emergence and Rapid Global Dissemination of the Clonal Group 258 *Klebsiella pneumoniae* Pandemic

Jolene R. Bowers[1☯]*, Brandon Kitchel[2☯], Elizabeth M. Driebe[1], Duncan R. MacCannell[2], Chandler Roe[1], Darrin Lemmer[1], Tom de Man[2], J. Kamile Rasheed[2], David M. Engelthaler[1], Paul Keim[1‡], Brandi M. Limbago[2‡]

1 Translational Genomics Research Institute, Flagstaff, Arizona, United States of America, **2** Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

☯ These authors contributed equally to this work.
‡ PK is joint senior author for genomics and BL is joint senior author for microbiology and epidemiology on this work.
* jbowers@tgen.org

Clone producteur de carbapénémase

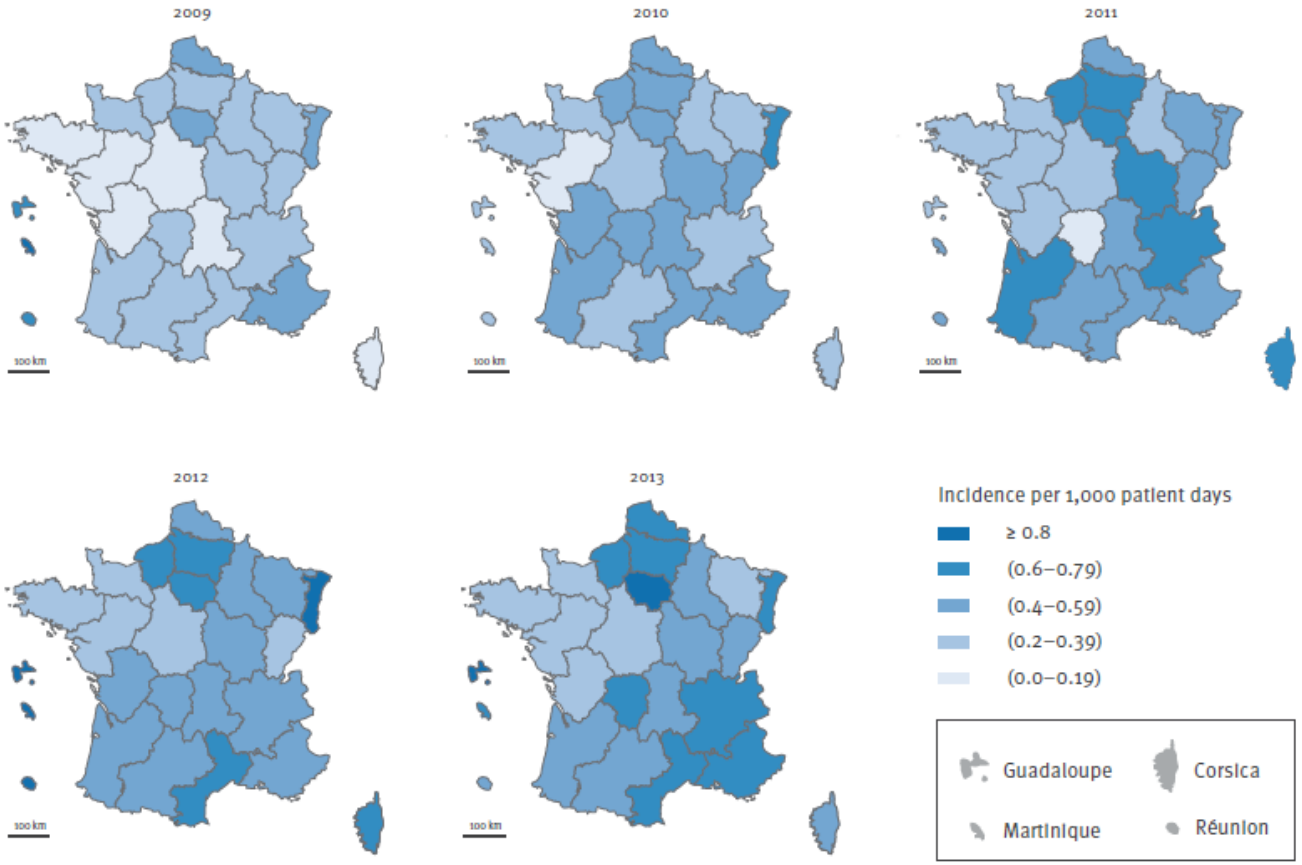

y = 4.6617x - 9324.8
Clade 1
Clade 2
Paraphyletic group
Clinical emergence of ST258
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012

Ongoing increasing temporal and geographical trends of the incidence of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* infections in France, 2009 to 2013

I Arnaud [1], S Maugat [2], V Jarlier [3], P Astagneau [1,4], for the National Early Warning, Investigation and Surveillance of Healthcare-Associated Infections Network (RAISIN)/multidrug resistance study group [5]

1. Regional Coordinating Centre for Healthcare-Associated Infections Control (CClin Paris – Nord), Paris, France
2. French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS), Saint Maurice, France
3. AP-HP (Assistance Publique - Hôpitaux de Paris), Paris, France
4. École des hautes études en santé publique (EHESP) Sorbonne Paris Cité University, Paris, France
5. Members of the group are listed at the end of the article.

Correspondence: Isabelle Arnaud (isabelle.arnaud@aphp.fr)

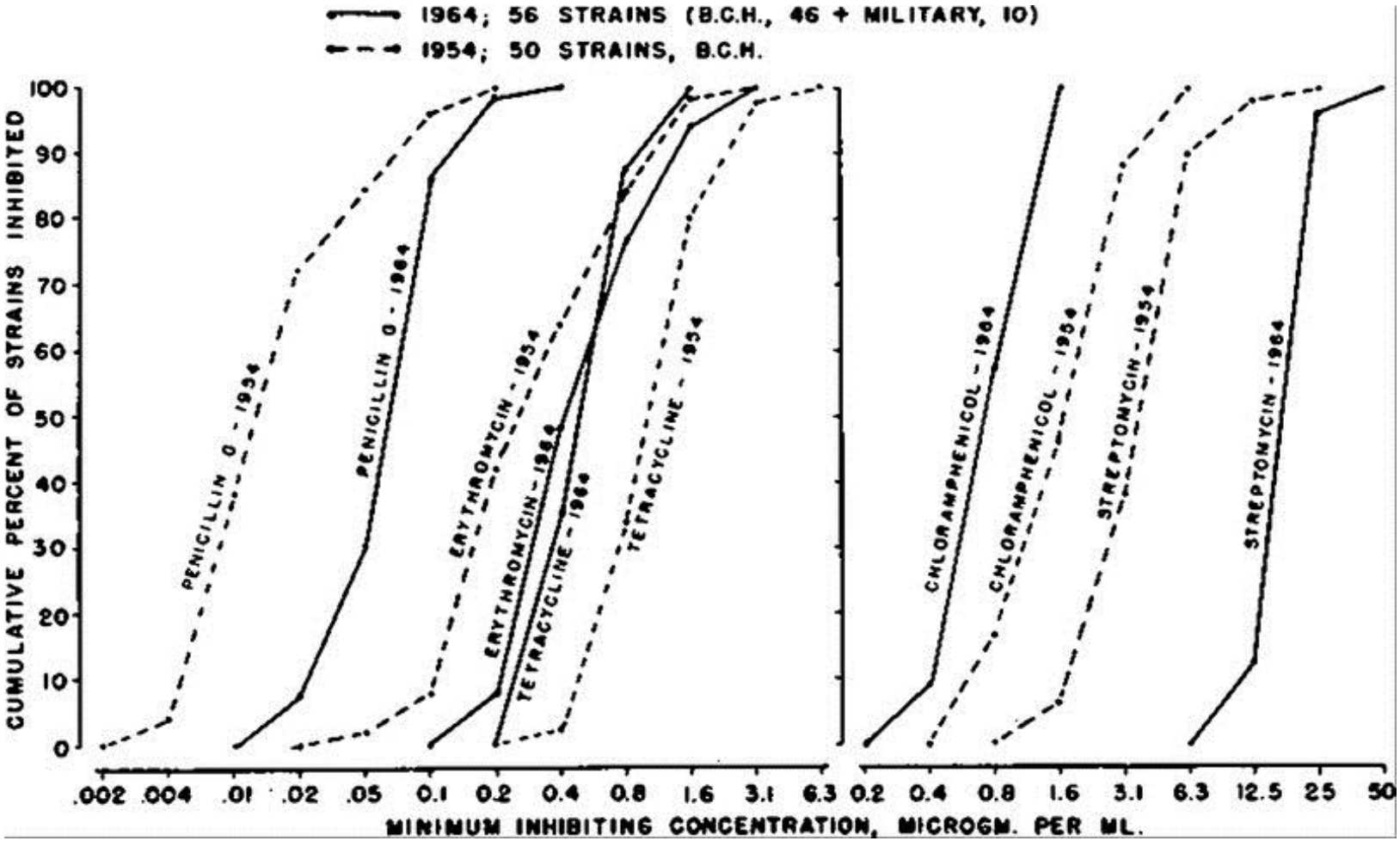


The NEW ENGLAND JOURNAL of MEDICINE

1965

Changing Susceptibility of Meningococci to Antimicrobial Agents

Theodore C. Eickhoff, M.D.†, Maxwell Finland, M.D.‡, and Clare Wilcox

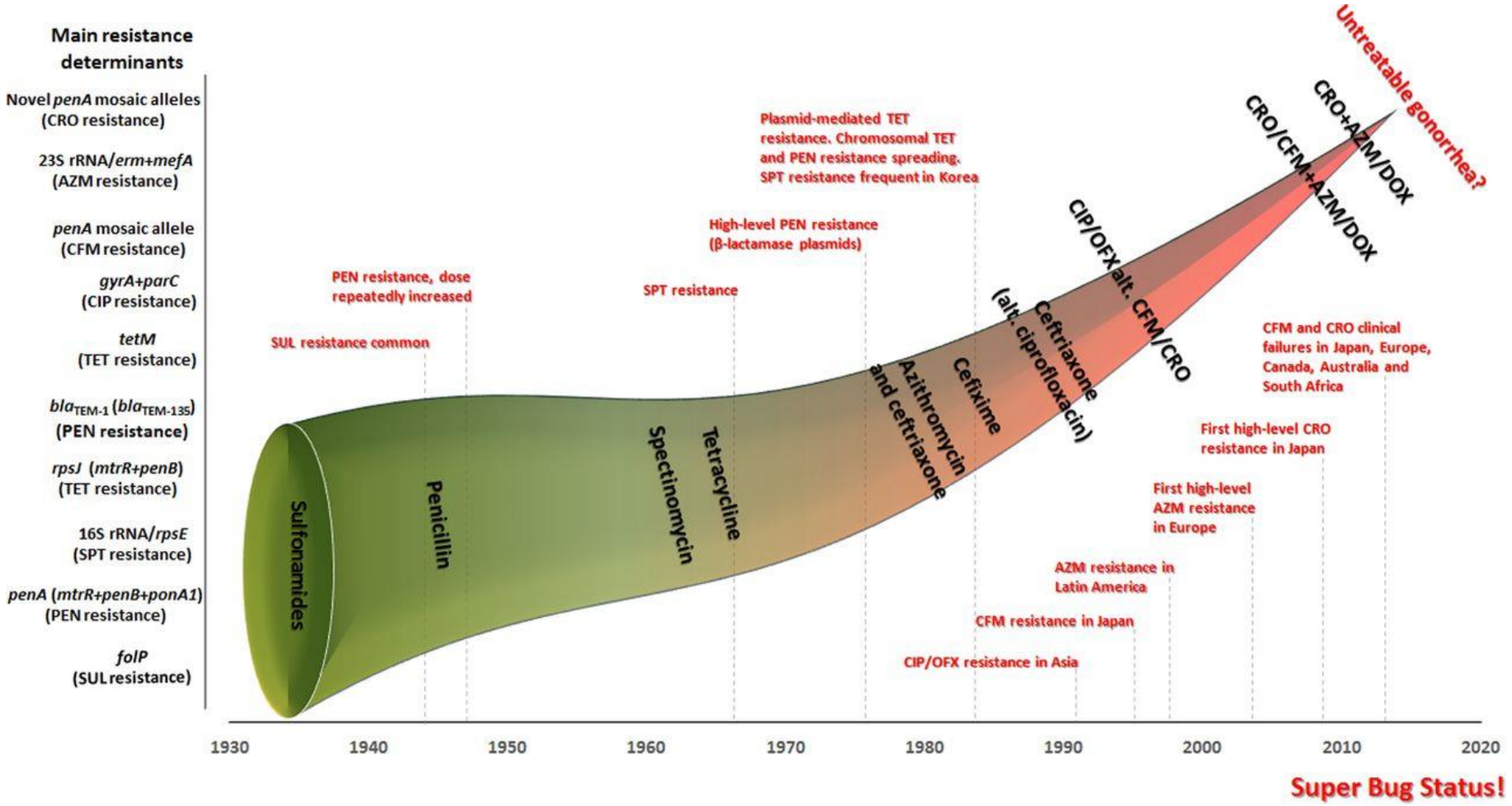



BUY BONDS
PENICILLIN
CURES
GONORRHEA
IN 4 HOURS
SEE YOUR DOCTOR TODAY

Antimicrobial Resistance in *Neisseria gonorrhoeae* in the 21st Century: Past, Evolution, and Future

Magnus Unemo,[a] William M. Shafer[b,c]

WHO Collaborating Centre for Gonorrhoea and Other Sexually Transmitted Infections, National Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden[a]; Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, Georgia, USA[b]; Laboratories of Bacterial Pathogenesis, Veterans Affairs Medical Center, Decatur, Georgia, USA[c]

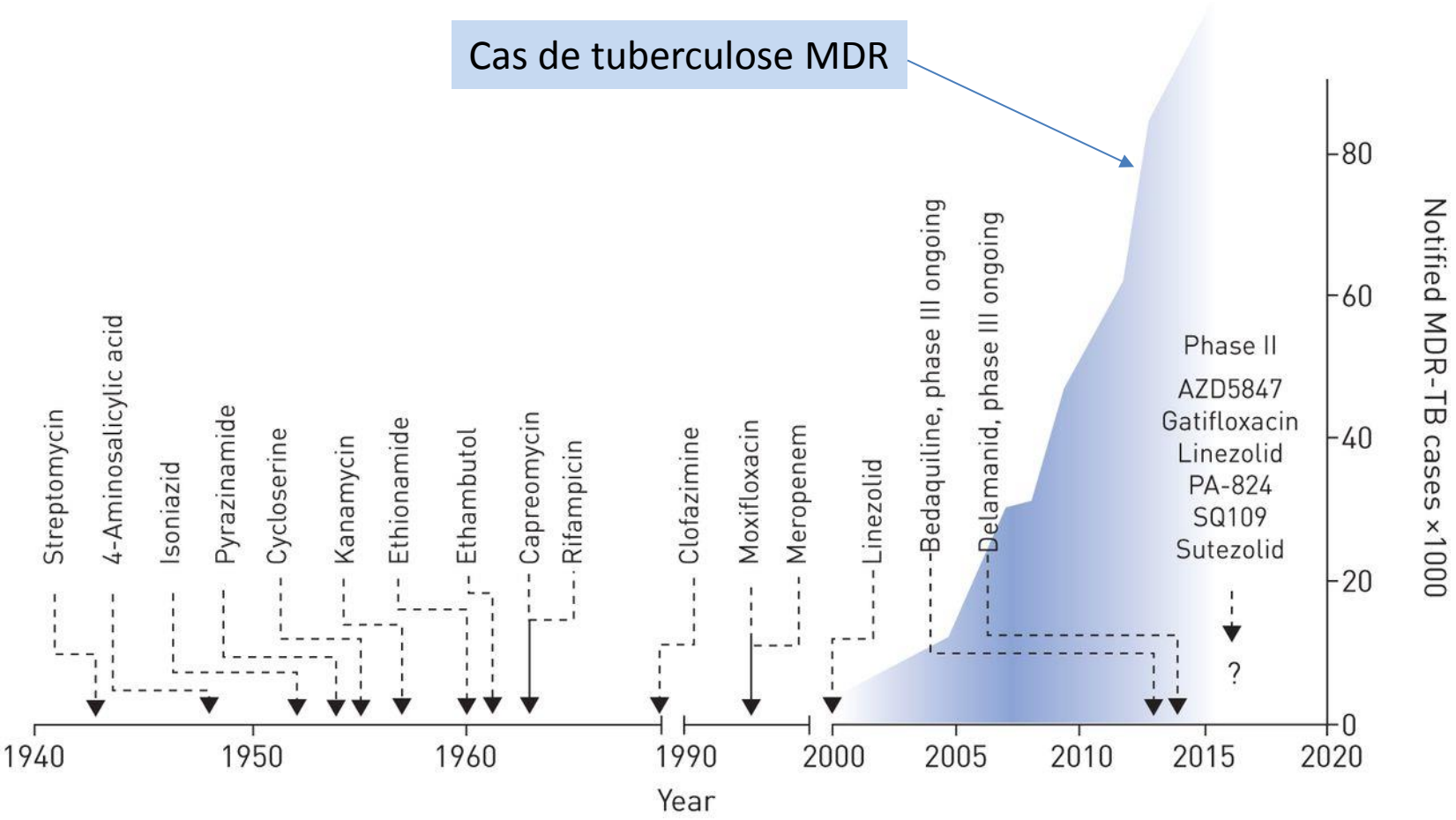


2014

2015

Novel drugs against tuberculosis: a clinician's perspective

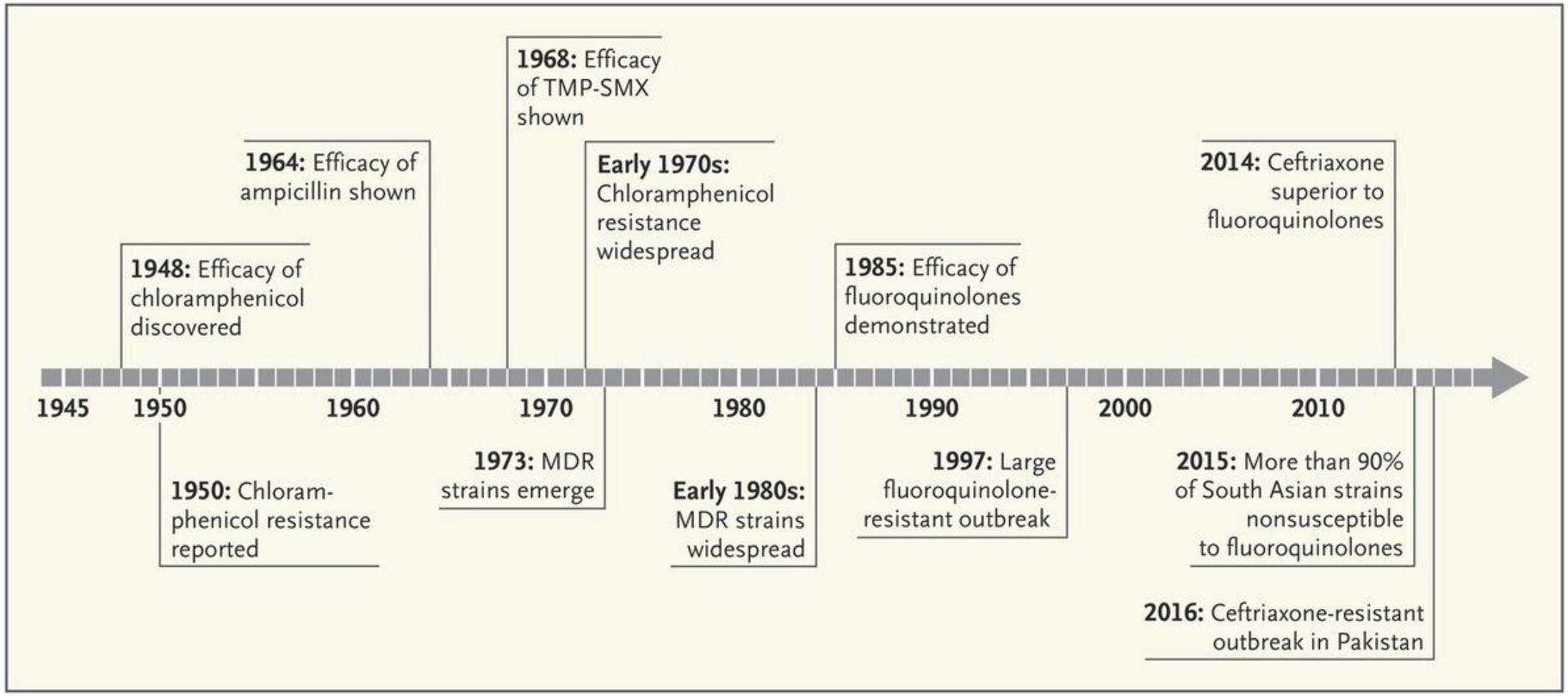
Ioana Diana Olaru[1], Florian von Groote-Bidlingmaier[2], Jan Heyckendorf[1], Wing Wai Yew[3], Christoph Lange[1,4,5,6] and Kwok Chiu Chang[7]



Extensively Drug-Resistant Typhoid — Are Conjugate Vaccines Arriving Just in Time?

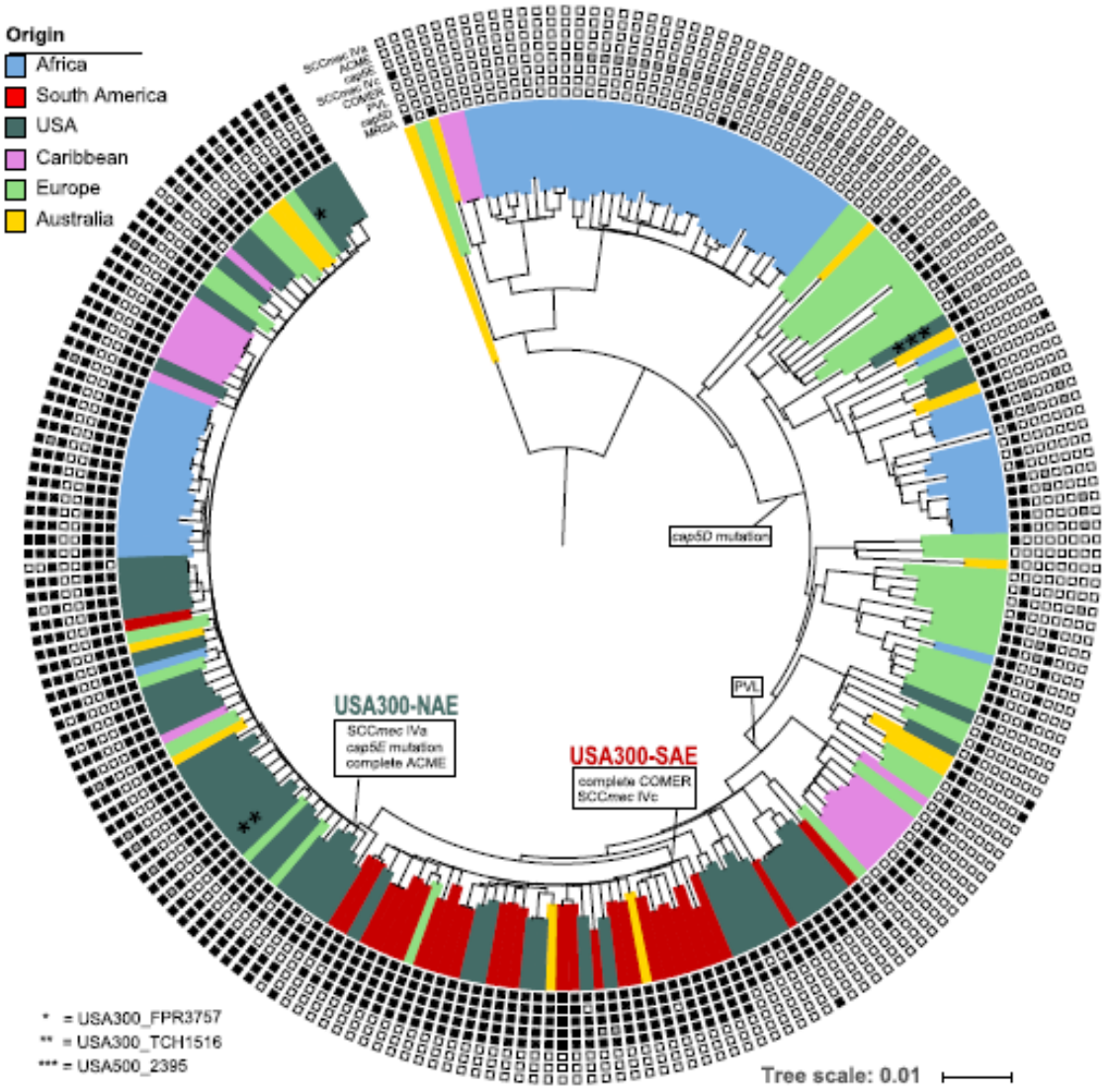
Jason R. Andrews, M.D., Farah N. Qamar, F.C.P.S., Richelle C. Charles, M.D., and Edward T. Ryan, M.D.

2018



Origin, evolution, and global transmission of community-acquired *Staphylococcus aureus* ST8

Lena Strauß[a], Marc Stegger[b,c], Patrick Eberechi Akpaka[d], Abraham Alabi[e,f], Sebastien Breurec[g,h], Geoffrey Coombs[i,j], Beverly Egyir[k], Anders Rhod Larsen[b], Frederic Laurent[l], Stefan Monecke[m,n], Georg Peters[o], Robert Skov[b,p], Birgit Strommenger[q], François Vandenesch[l], Frieder Schaumburg[o], and Alexander Mellmann[a,1]



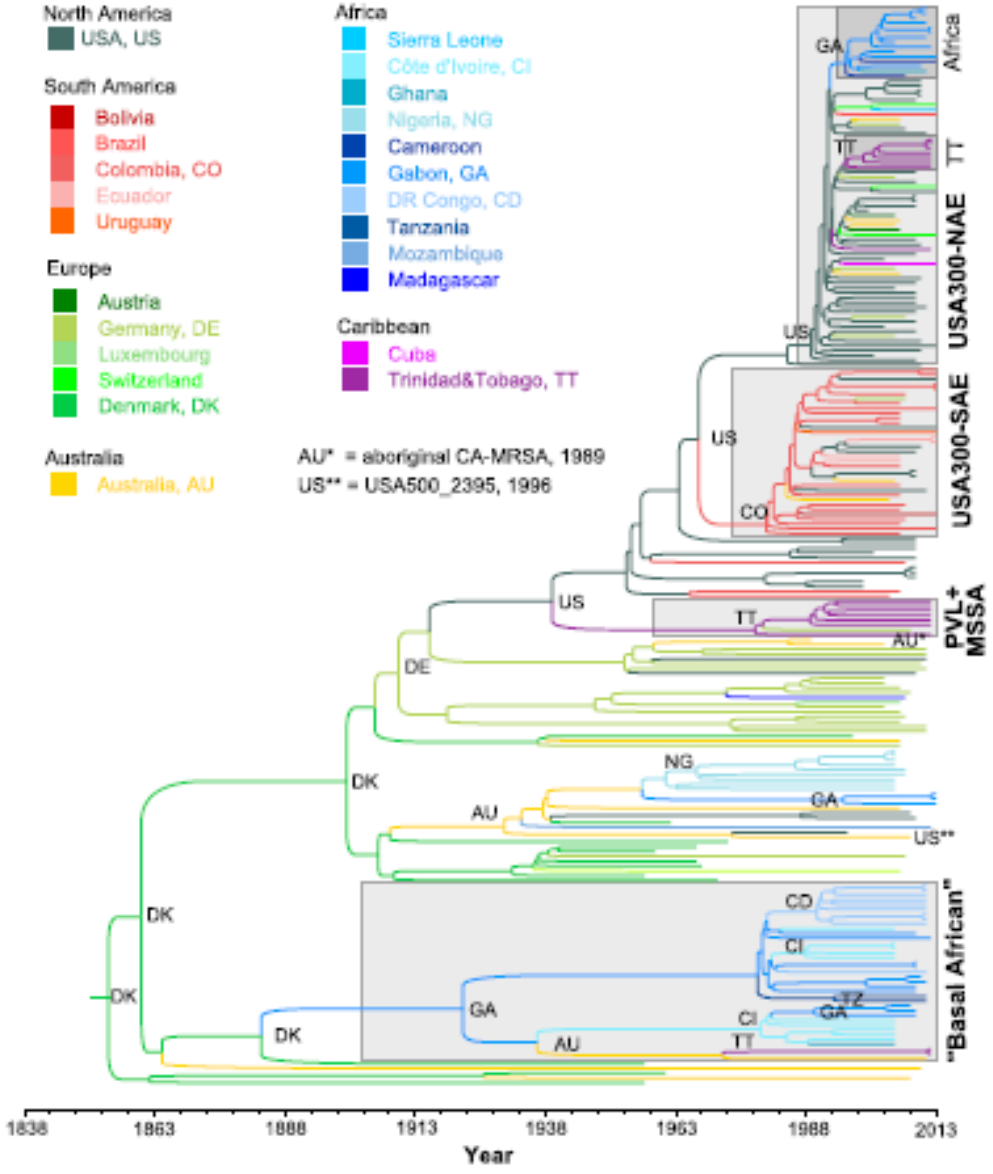


Fig. 2. Bayesian maximum clade credibility tree calculated from 10,801 sampled trees. Branch colors represent the country of origin of each sample and their most recent common ancestor (MRCA), respectively. Major clade's MRCA origins are verbalized using international country codes. Important groups like USA300 or the "Basal African" clade are highlighted with gray squares (annotation in bold). Time periods and age of clades can be inferred using the timeline at the bottom. The most recent isolate was collected in 2013; the MRCA of all isolates was dated to 1854 (HPD 95%, 1846 to 1865). MSSA, methicillin-susceptible *S. aureus*; PVL^{+}, Panton–Valentine leukocidin positive; USA300-NAE, North American Epidemic USA300 clone; USA300-SAE, South American Epidemic USA300 clone. Detailed divergence timings and countries for each node are displayed in Fig. S1.

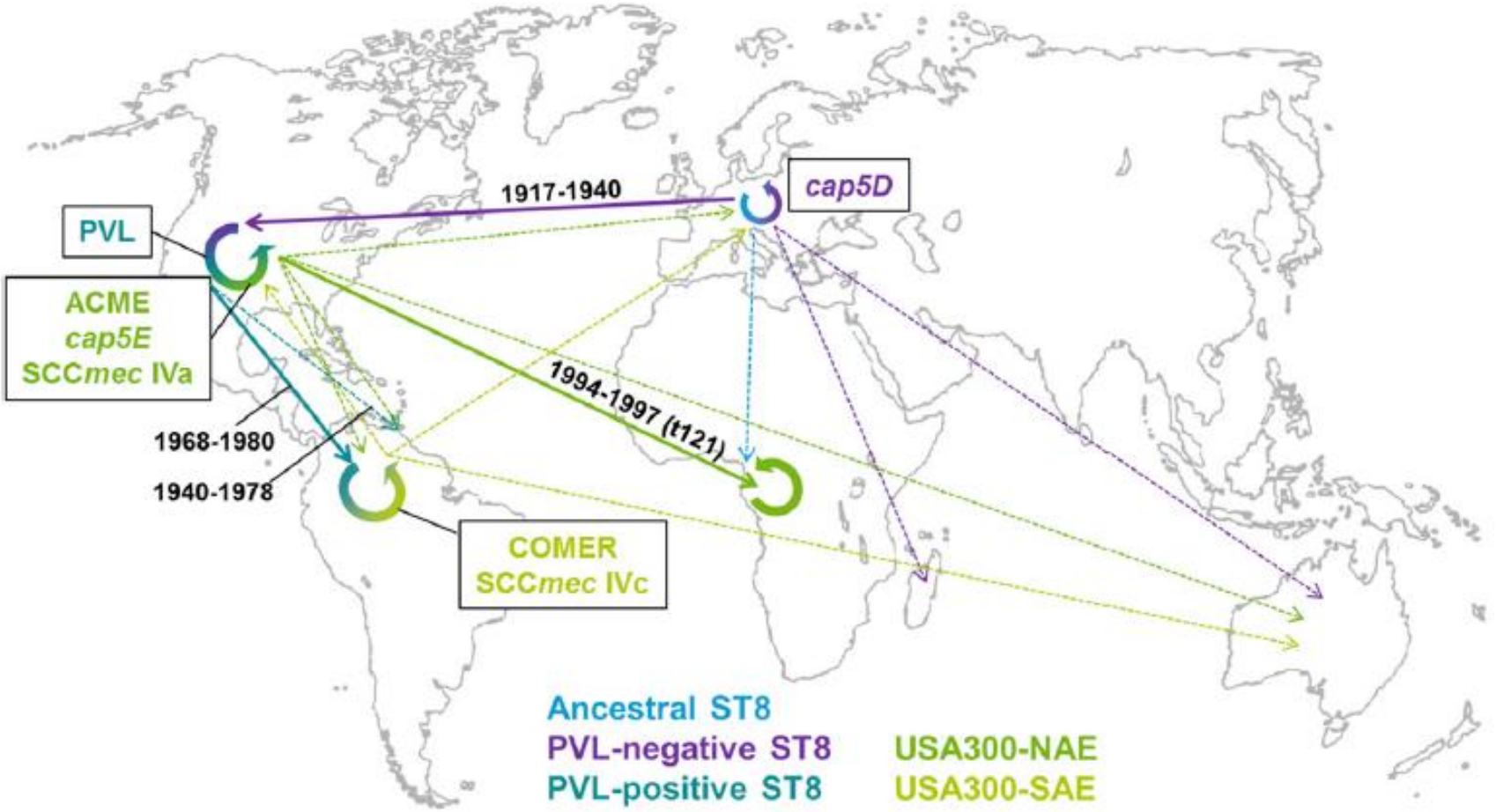
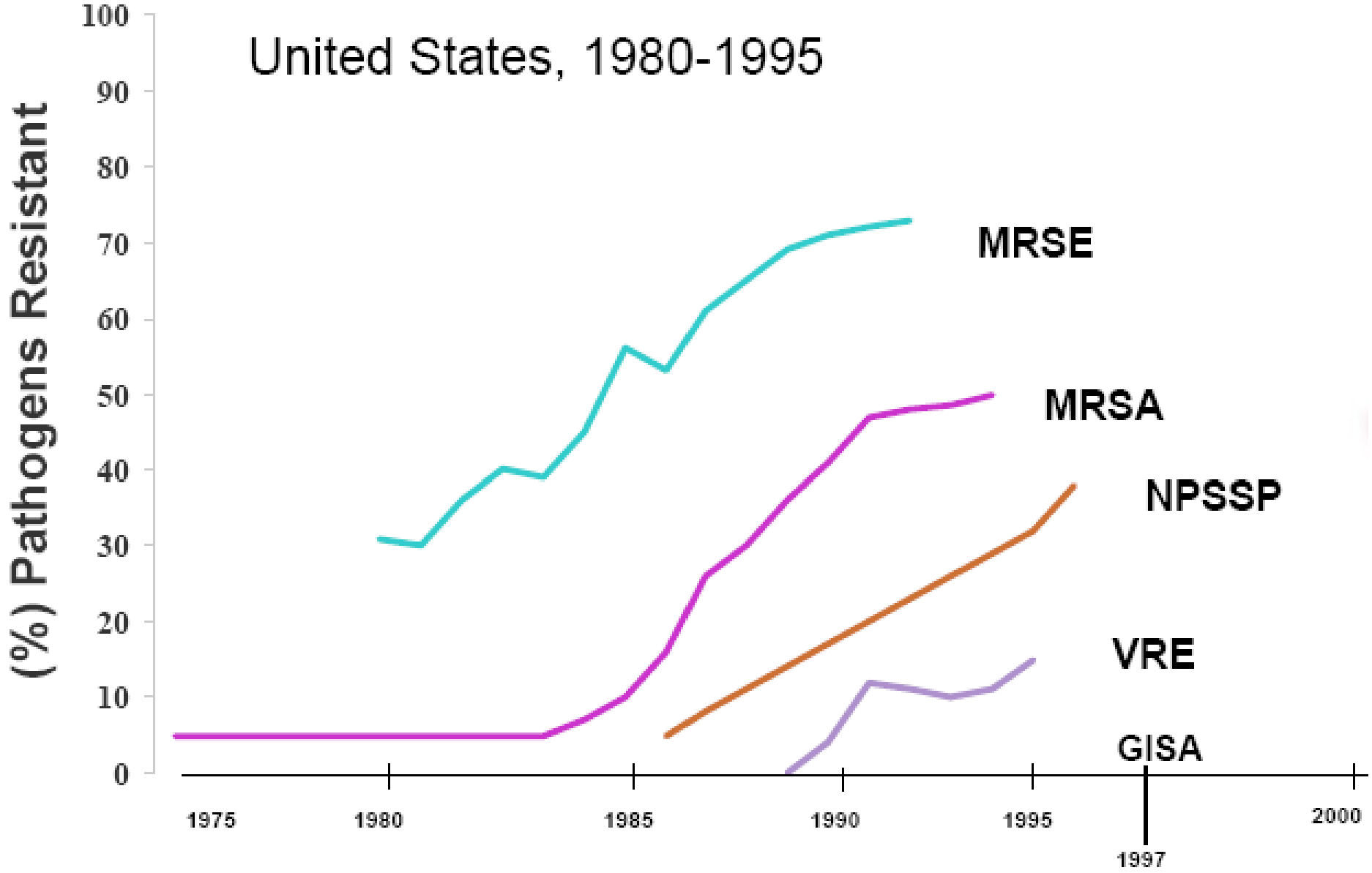


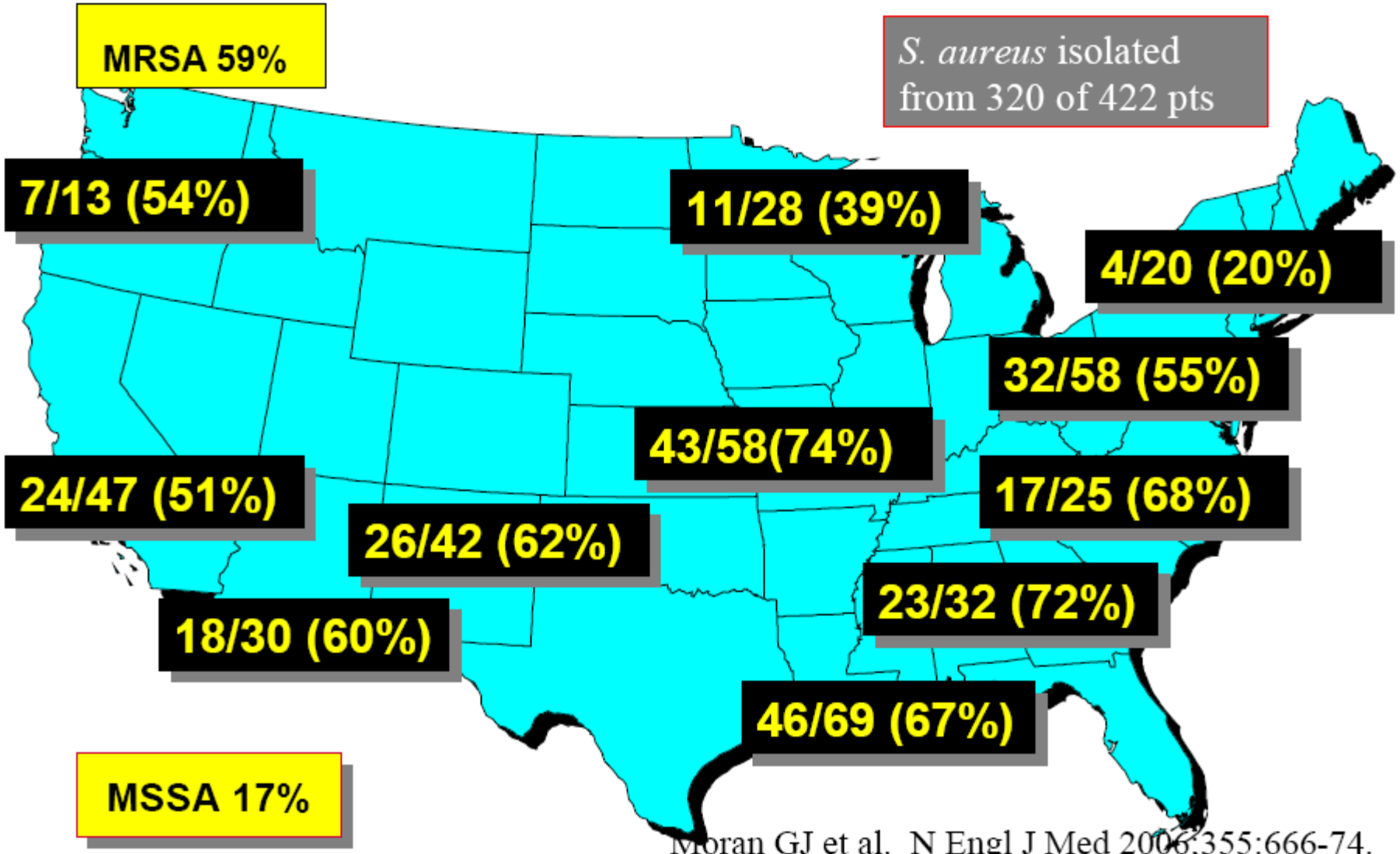
Fig. 3. Phylogeographic evolution of *S. aureus* USA300. The figure shows a subset of the global transmission routes of different ST8 lineages, including USA300. Different lineages are highlighted in different colors; thick lines represent major transmission events during the evolution of USA300; dotted lines represent other transmissions. Transmission times are indicated on major routes. For a comprehensive view of all transmission routes, including single isolates, view Dataset S6 using Google Earth.



Hiramatsu K, *MMWR*, July 11, 1997; 46(7):624-636.
Thornsberry C NNIS 38th ICAAC 1998; San Diego, CA; Abstract E22.

about *Penicillium notatum*

Prevalence of MRSA among 422 Emergency Department Patients with SSTI



Moran GJ et al. N Engl J Med 2006;355:666-74.

J Antimicrob Chemother 2018; **73**: 41–51
doi:10.1093/jac/dkx370 Advance Access publication 30 October 2017

Journal of Antimicrobial Chemotherapy

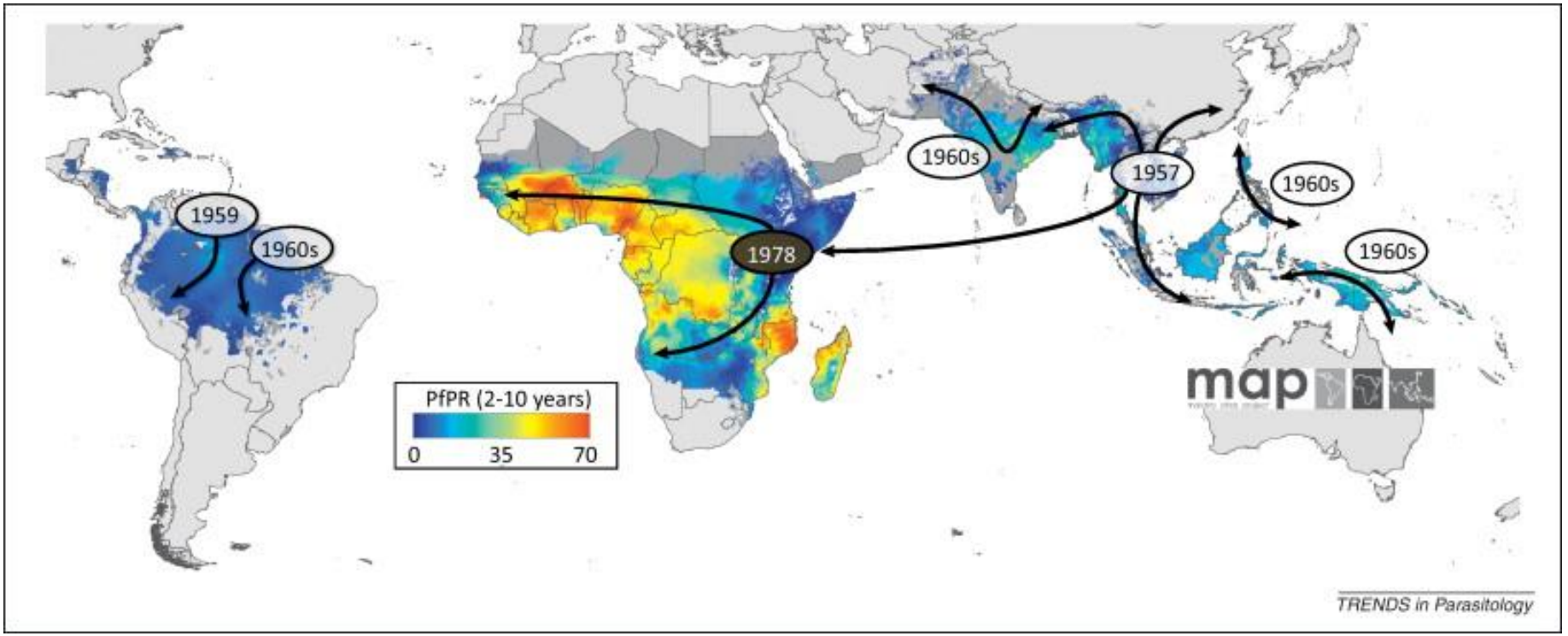
Long-lasting successful dissemination of resistance to oxazolidinones in MDR *Staphylococcus epidermidis* clinical isolates in a tertiary care hospital in France

Laurent Dortet[1–4]*†, Philippe Glaser[4,5]†, Najiby Kassis-Chikhani[6], Delphine Girlich[2–4], Philippe Ichai[7], Marc Boudon[7], Didier Samuel[7], Elodie Creton[2–4], Dilek Imanci[8], Rémy Bonnin[2–4], Nicolas Fortineau[1–4] and Thierry Naas[1–4]

High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

A. Capone[1], M. Giannella[1], D. Fortini[2], A. Giordano[3], M. Meledandri[4], M. Ballardini[4], M. Venditti[5], E. Bordi[6], D. Capozzi[7], M. P. Balice[8], A. Tarasi[9], G. Parisi[10], A. Lappa[10], A. Carattoli[2], N. Petrosillo[1] and on behalf of the SEERBIO-GRAB network[†]

Diffusion de la chloroquinorésistance chez *Plasmodium falciparum*



Ecker 2012

Prescription vs sens. diminuée : pénicilline

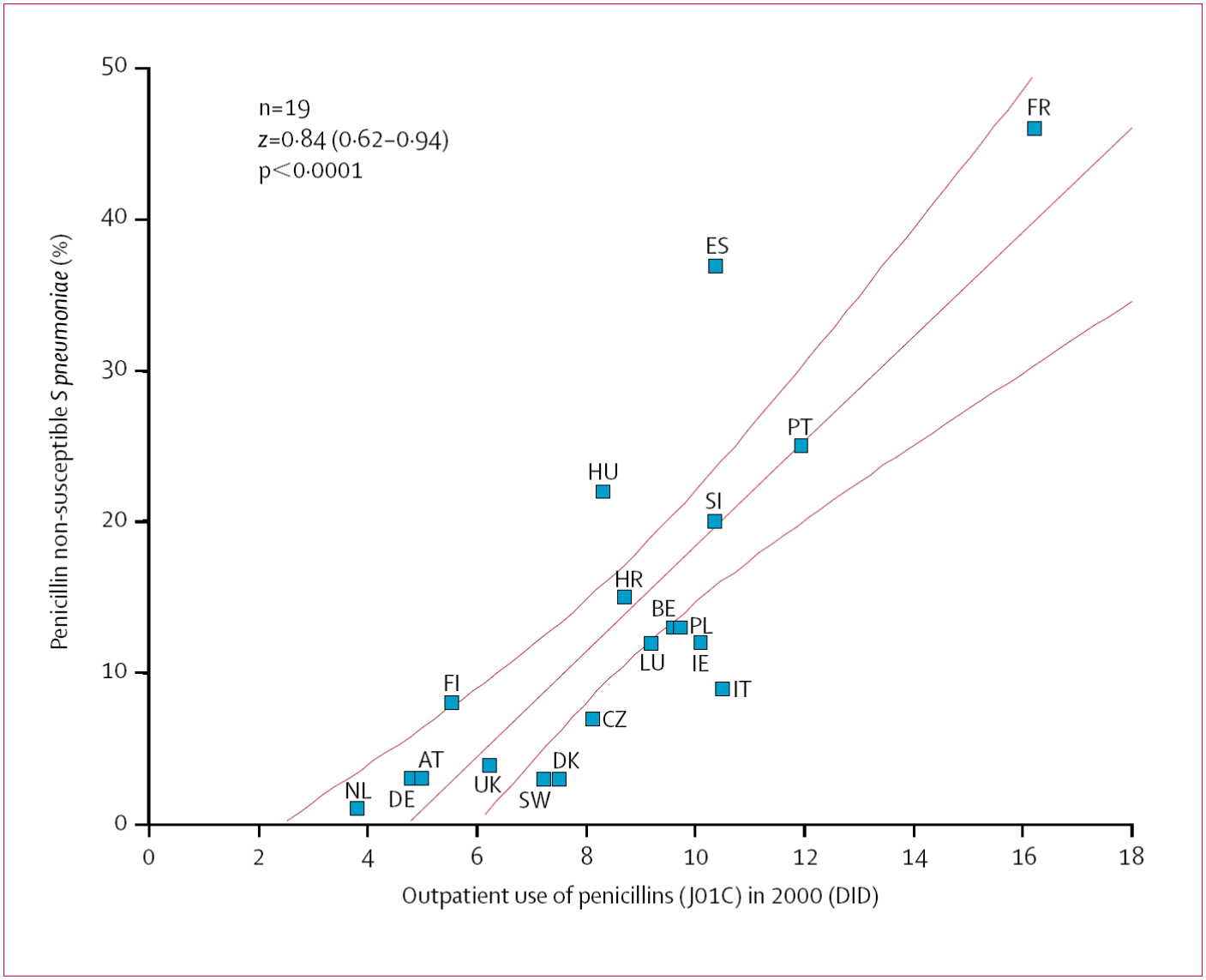
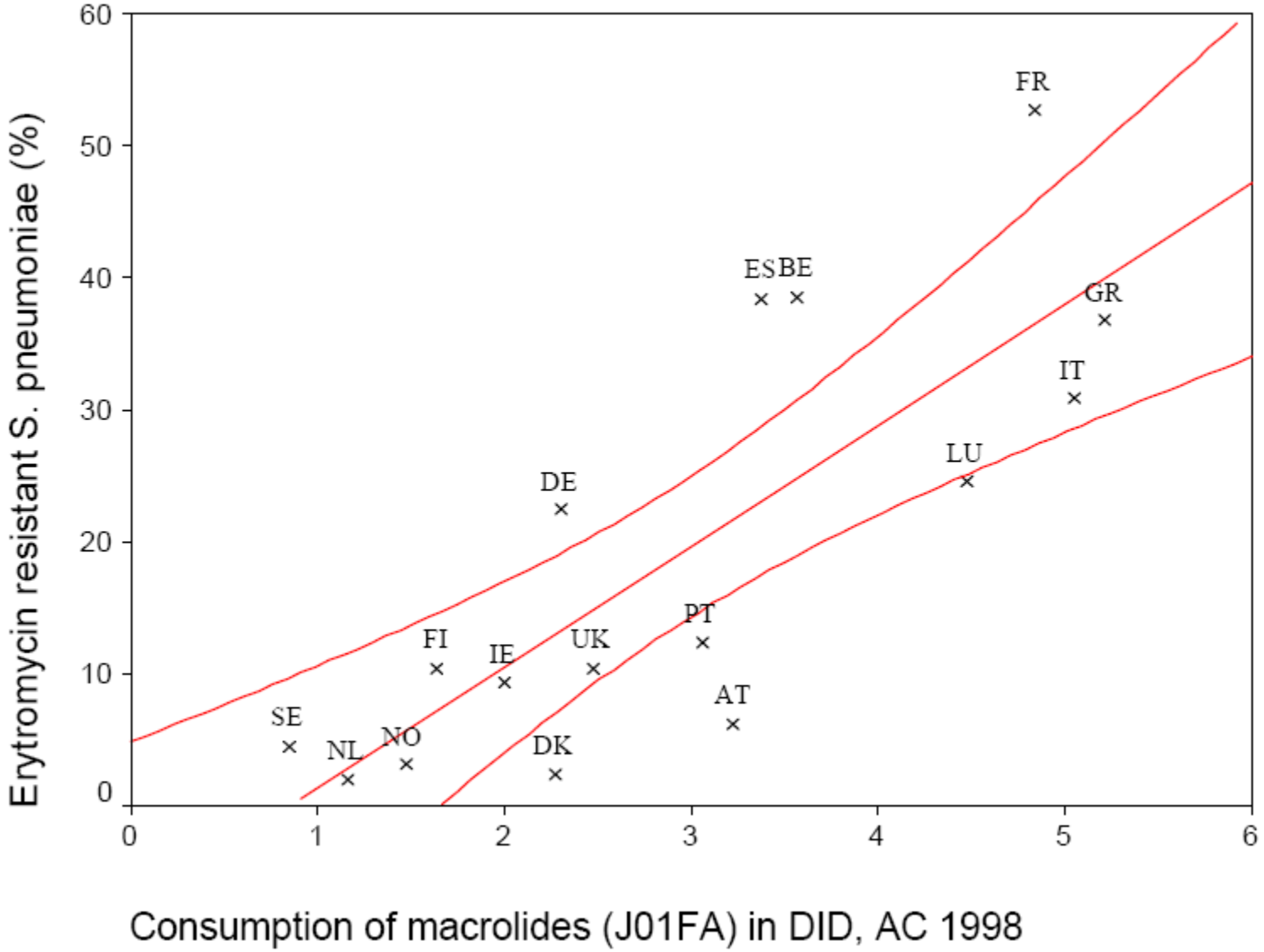


Figure 6: Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae*

Prescription vs résistance : macrolides



Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

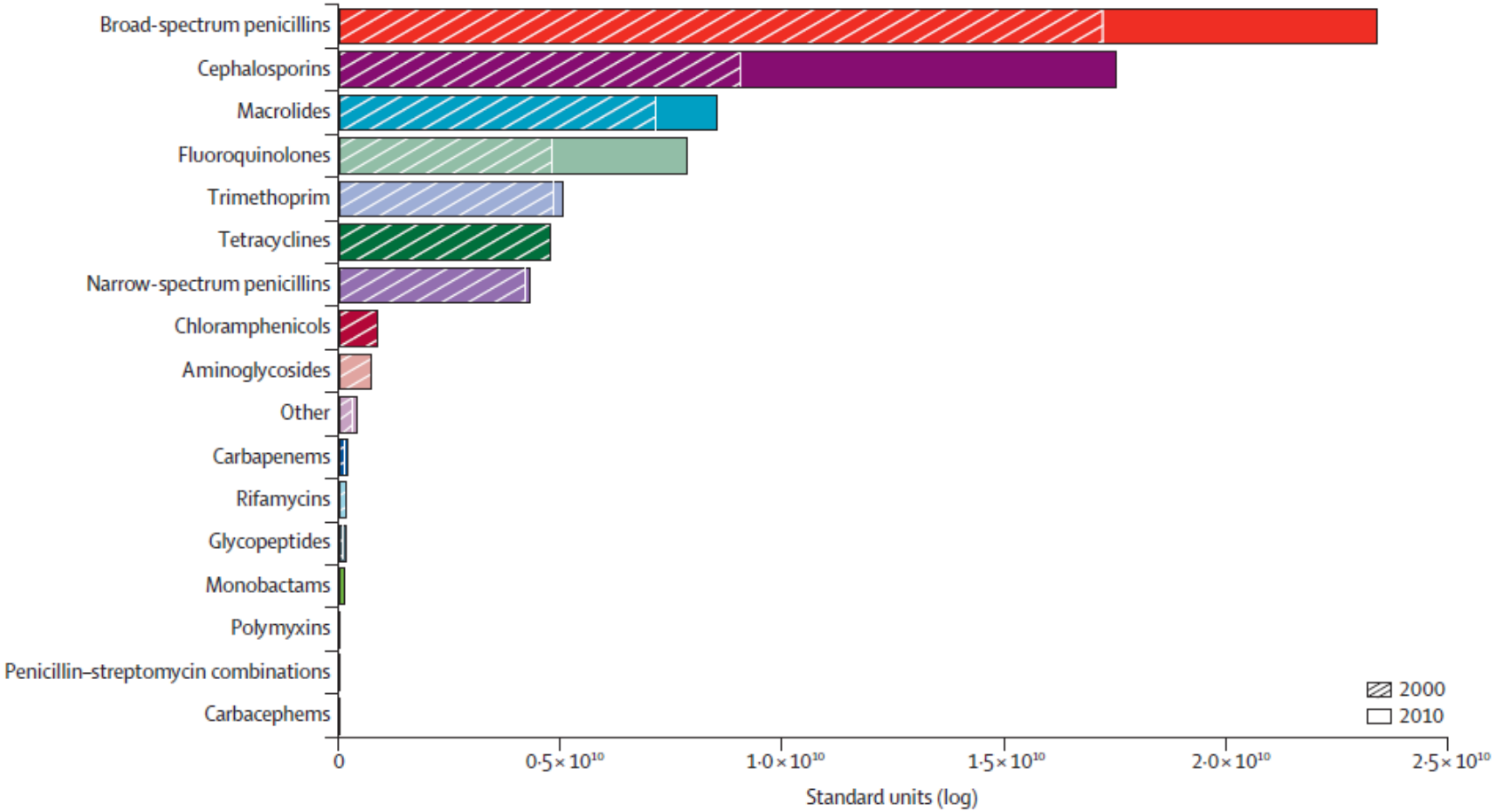
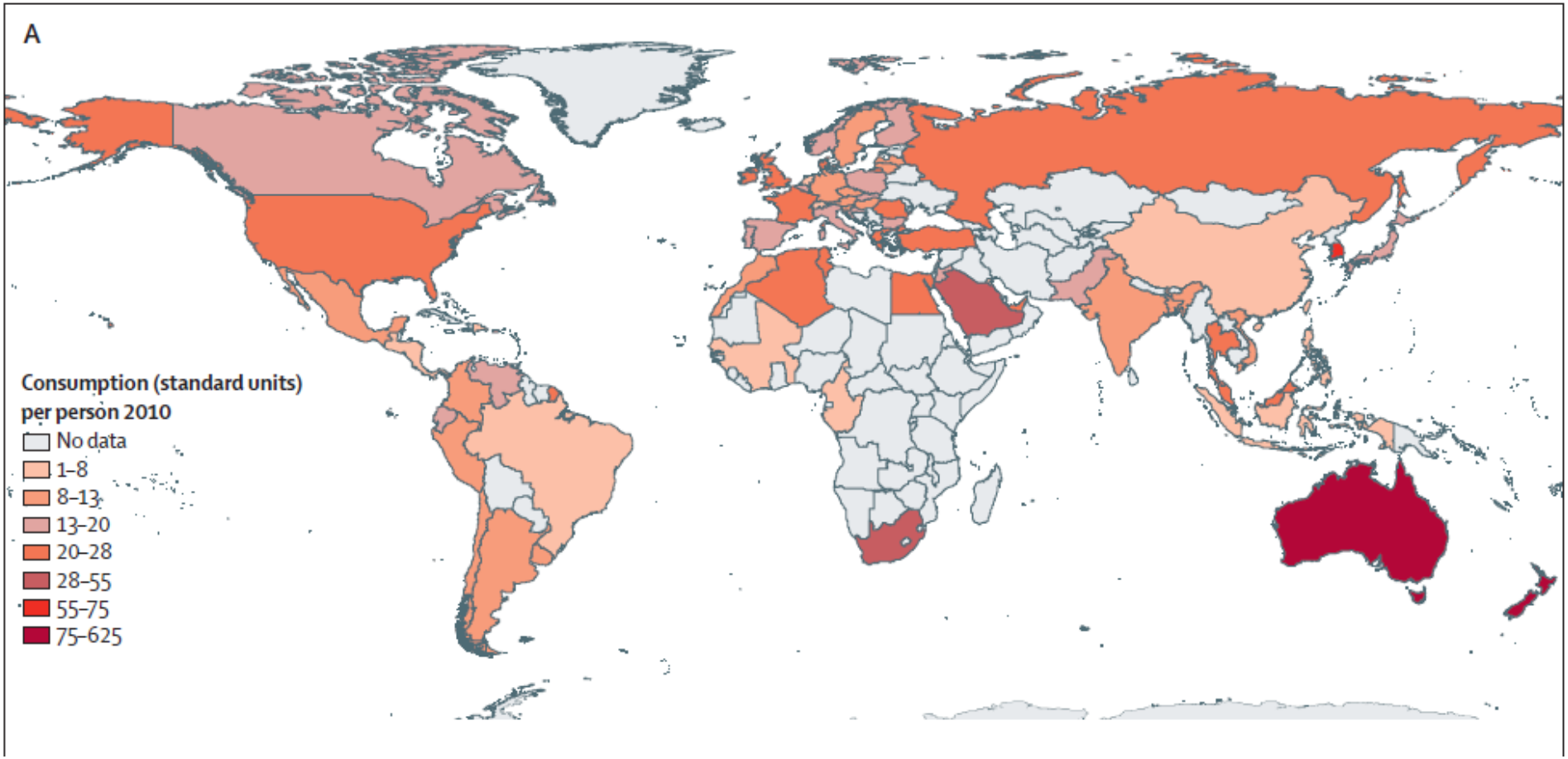


***Figure* 1: Global antibiotic consumption by class in 2000 and 2010**
Standard units are defined as a single dose unit (ie, pill, capsule, or ampoule).

Consommation d'ATB



Évolution de la consommation

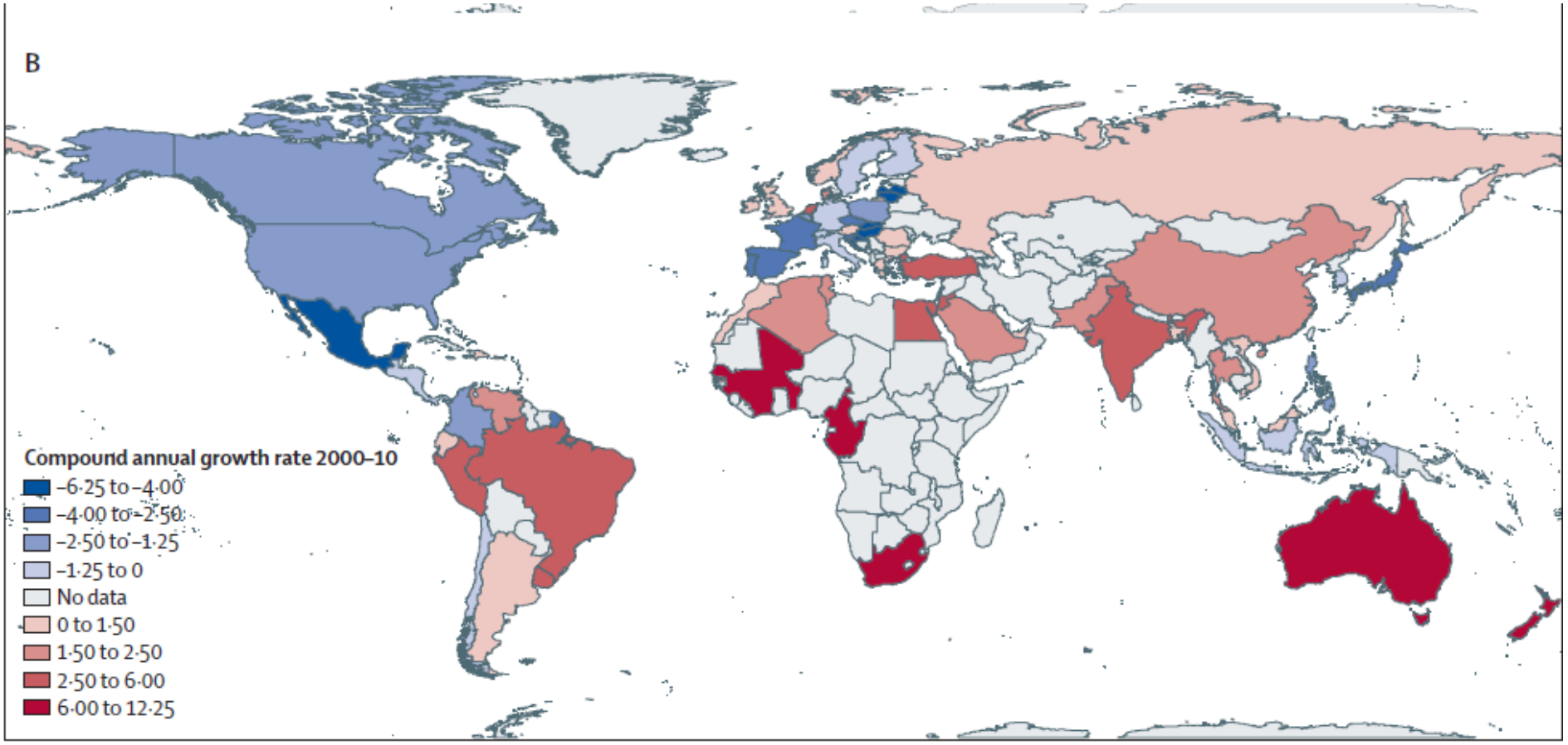
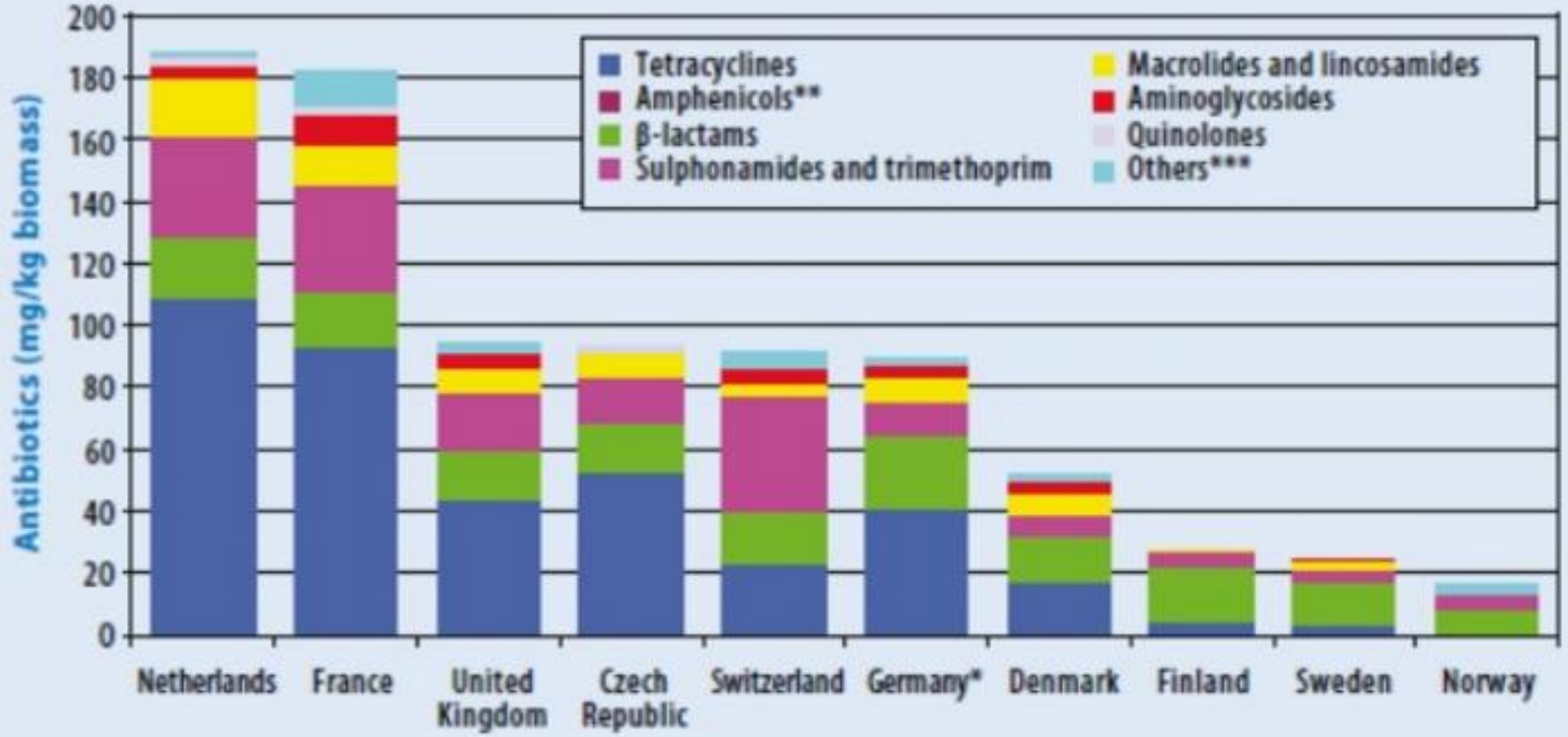
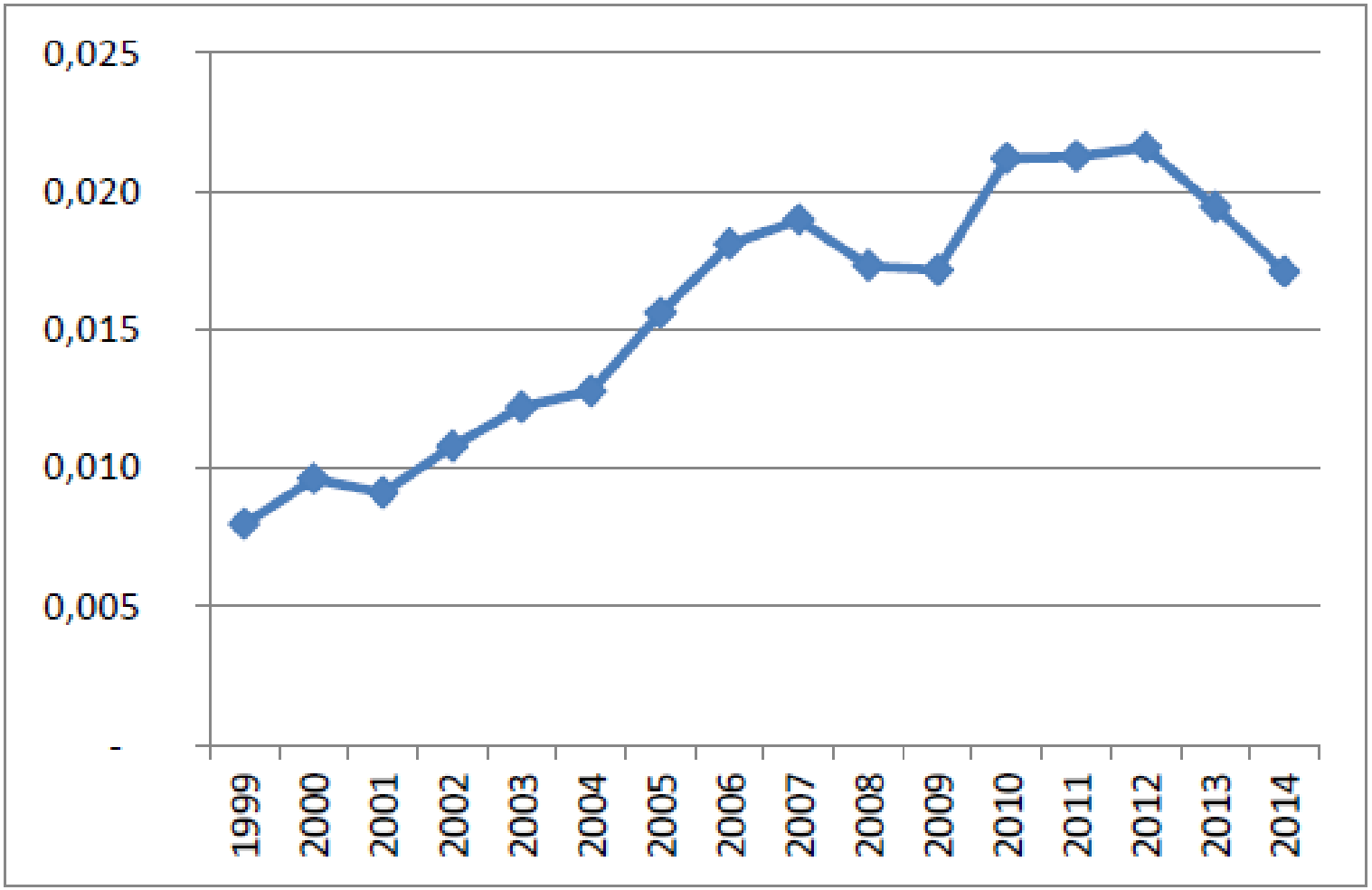


Fig. 3. Amounts of veterinary antibiotics sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced, plus estimated live weight of dairy cattle



* 2005 data.
** Amounts are so small as to be invisible in this figure.
*** The substances included in this category vary between countries.
Source: Grave, Torren-Edo & Mackay *(19)*.

Figure 2. Evolution de l'exposition aux Céphalosporines par voie parentérale (ALEA)

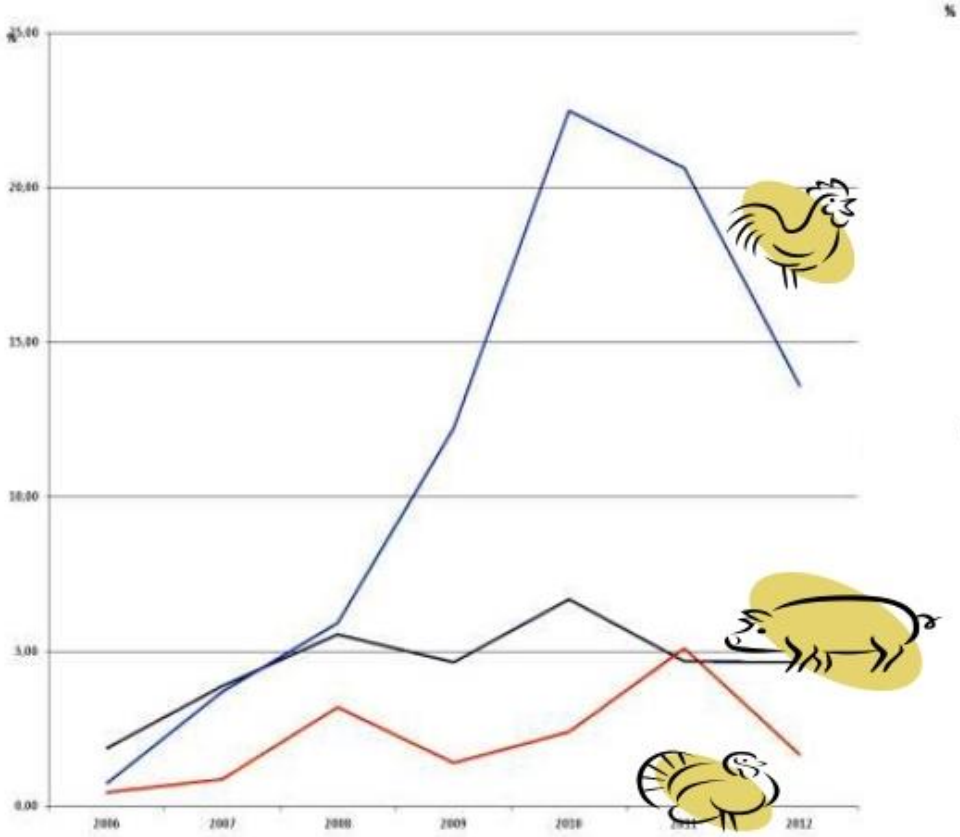


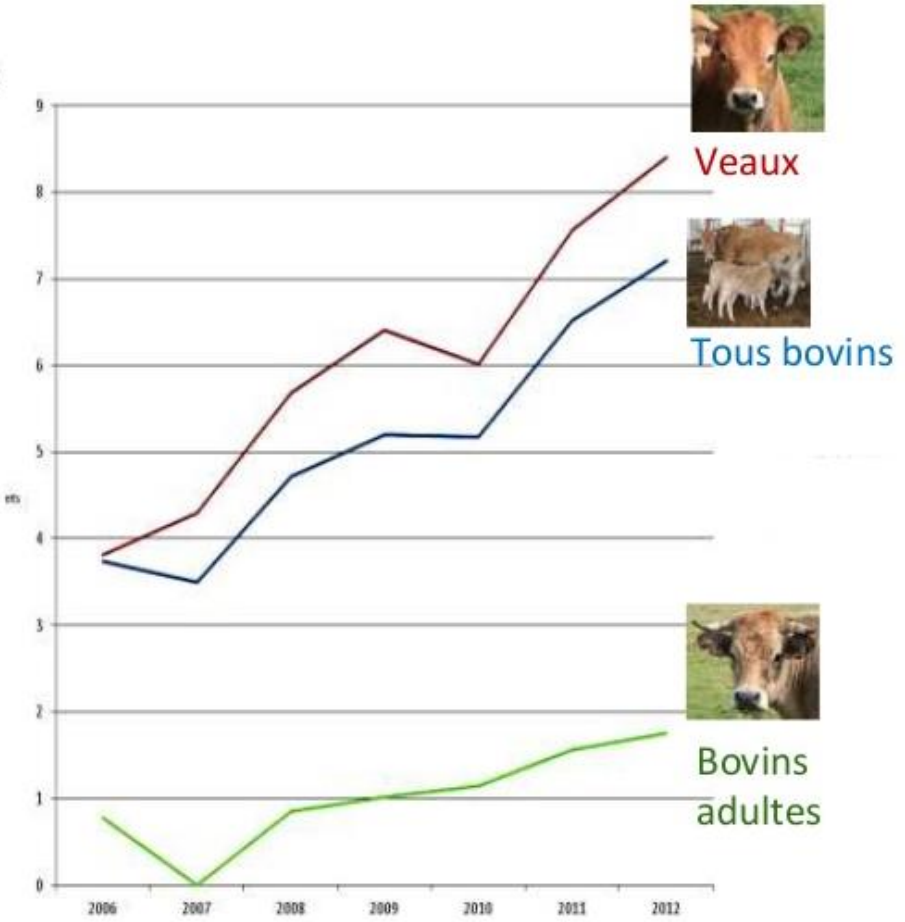
Consommation animale

ANMV

Sensibilité *d'E. coli* aux céphalosporines

Evolution des proportions de souches d'E. coli <u>non-sensibles</u> au ceftiofur entre 2006 et 2012

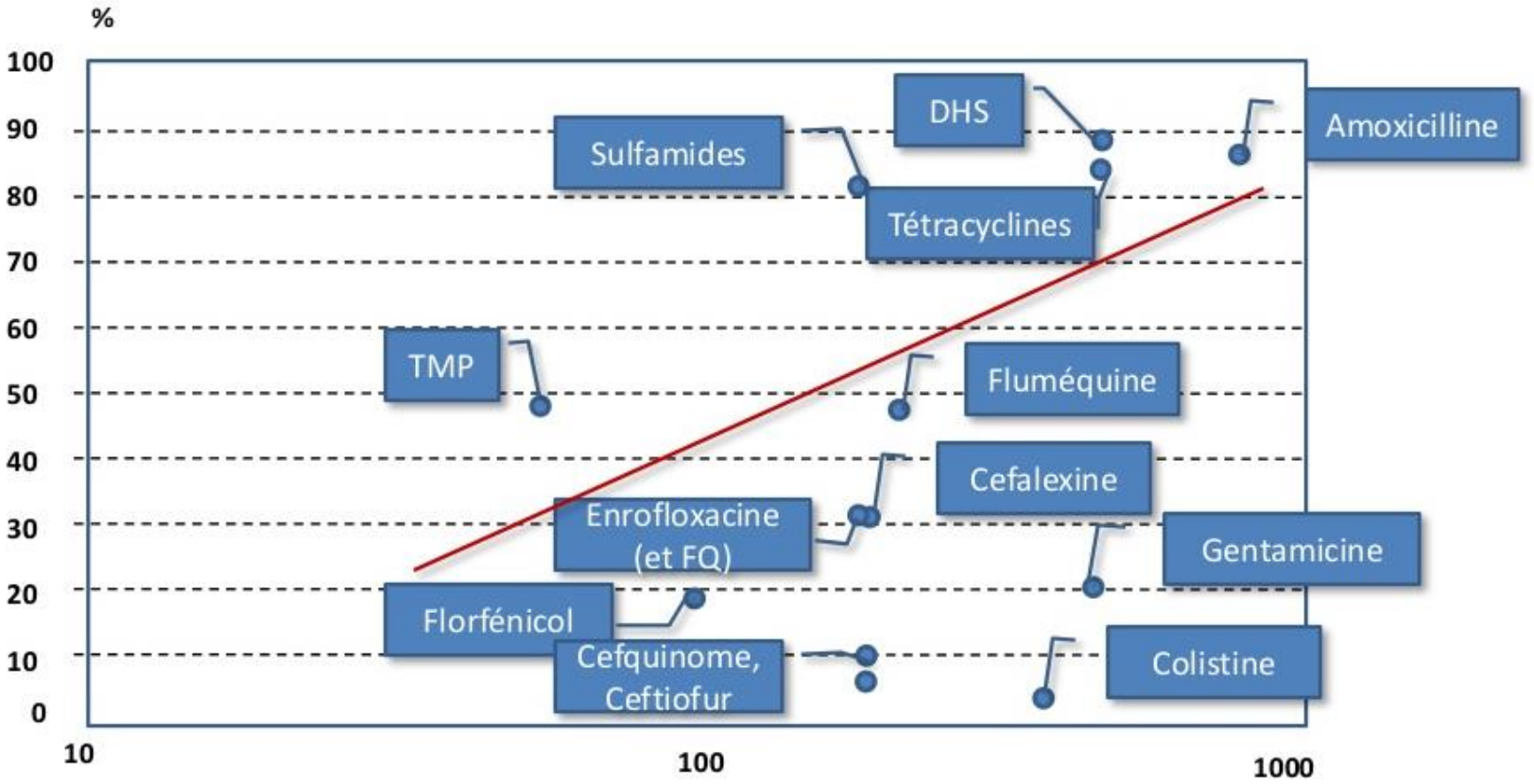




Source : Résapath 2012

Corrélation entre niveau d'exposition et résistance

Exemple d'*E. coli* chez les bovins

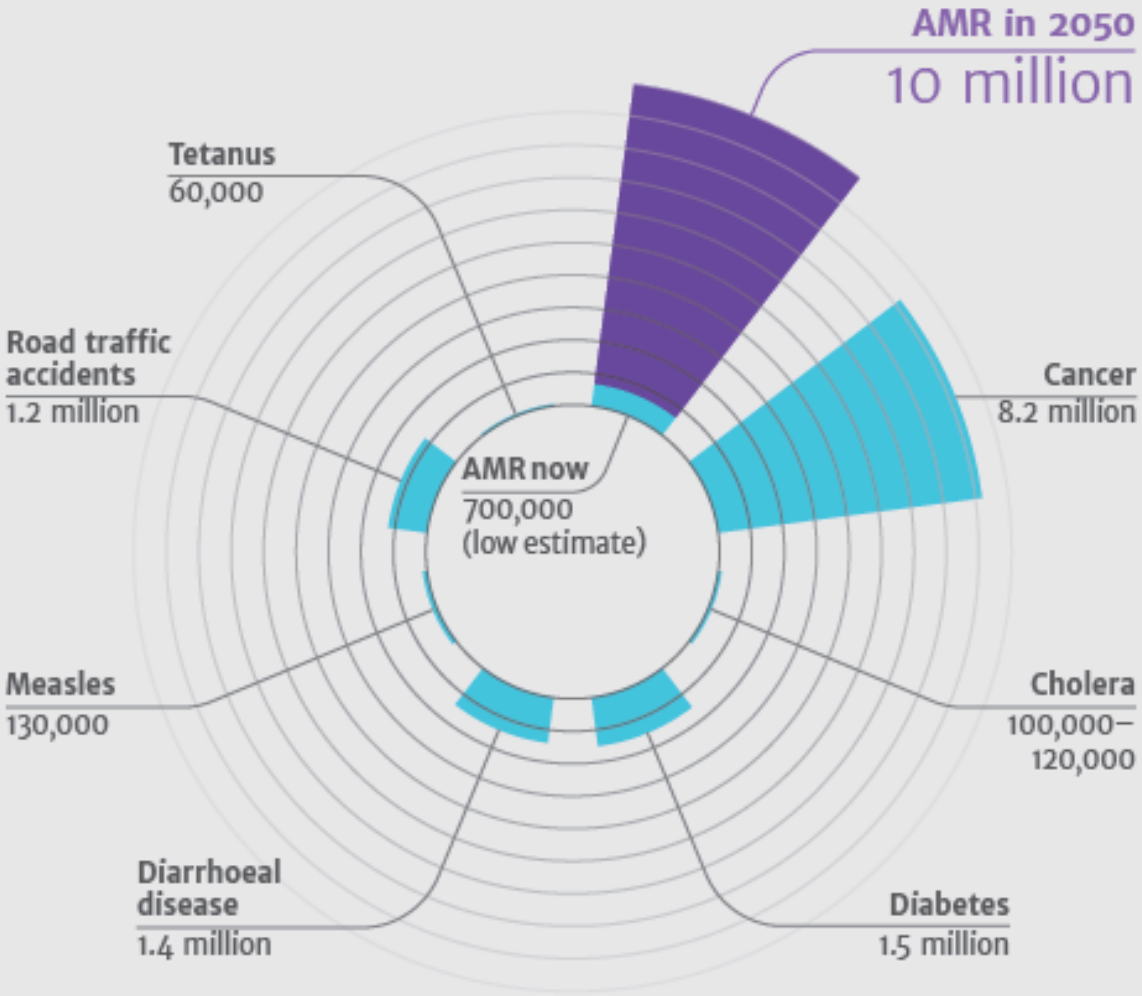


Corrélation marquée entre niveau d'utilisation et antibiorésistance, sauf pour la colistine. Source: Le point vétérinaire

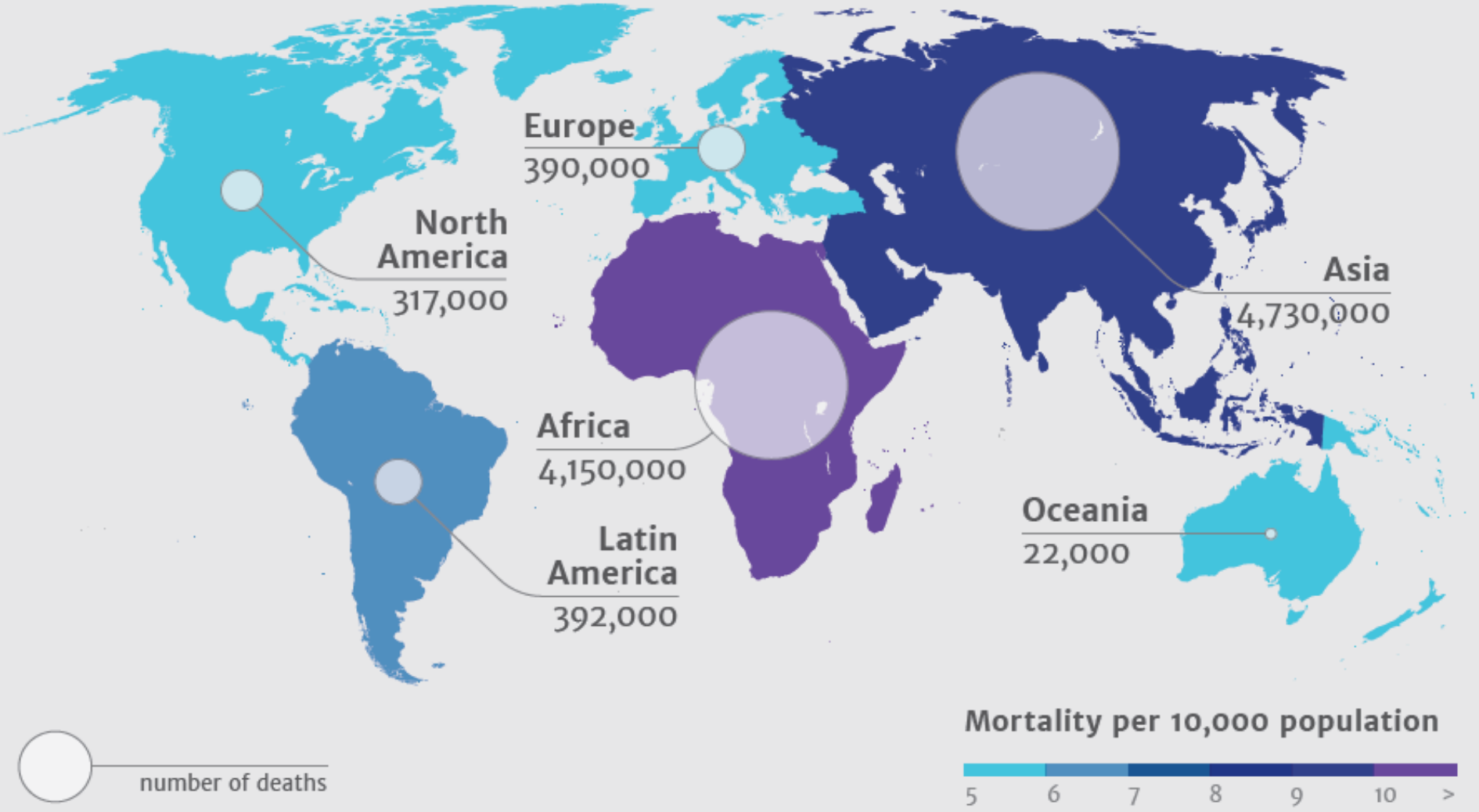
Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations

The Review on Antimicrobial Resistance
Chaired by Jim O'Neill
December 2014

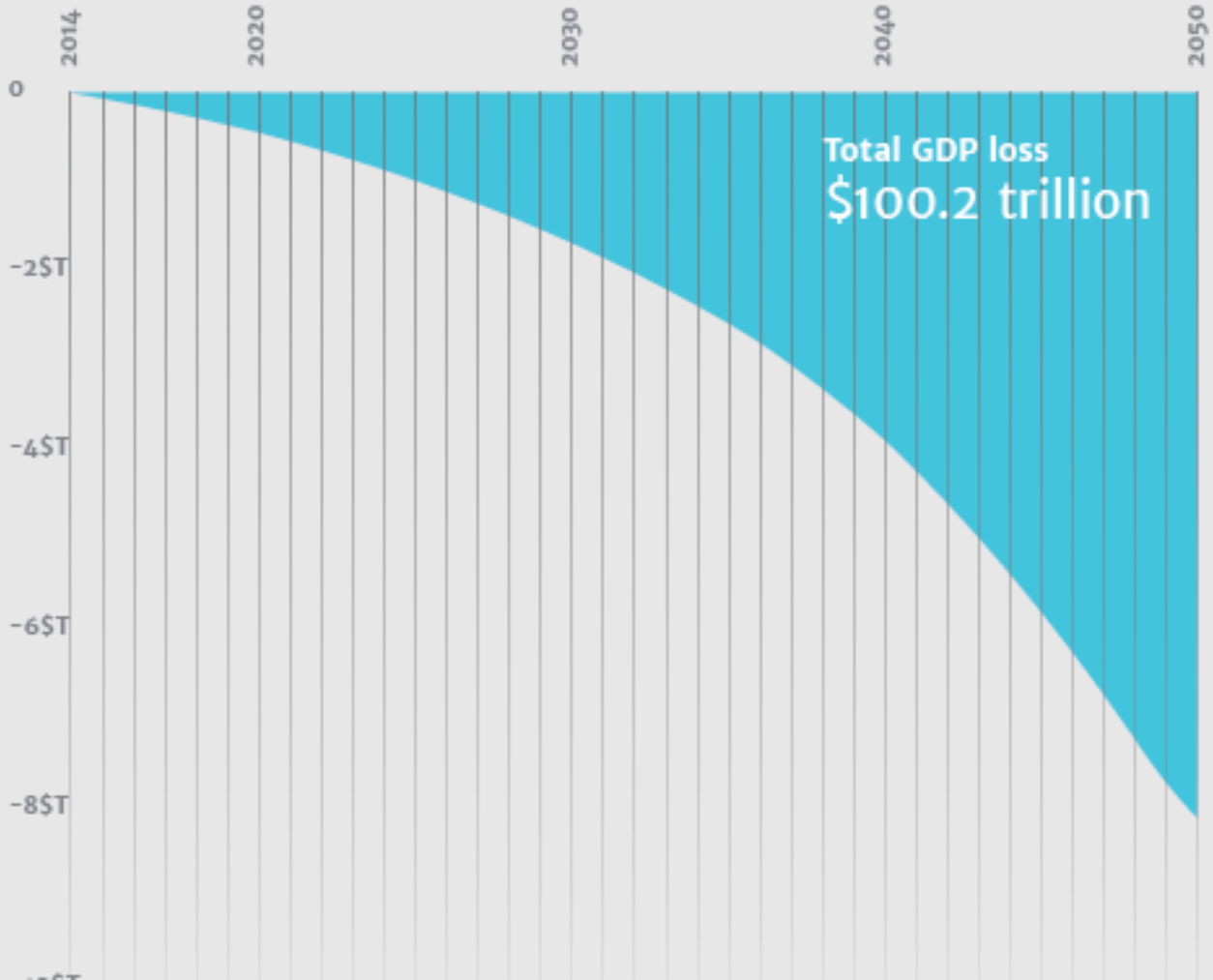
Deaths attributable to AMR every year
compared to other major causes of death



Deaths attributable to AMR every year
by 2050



AMR's impact on World GDP
in trillions of USD



Colomb-Cotinat *et al. Antimicrobial Resistance and Infection Control* (2016) 5:56
DOI 10.1186/s13756-016-0154-z

Antimicrobial Resistance
and Infection Control

RESEARCH Open Access

Estimating the morbidity and mortality associated with infections due to multidrug-resistant bacteria (MDRB), France, 2012

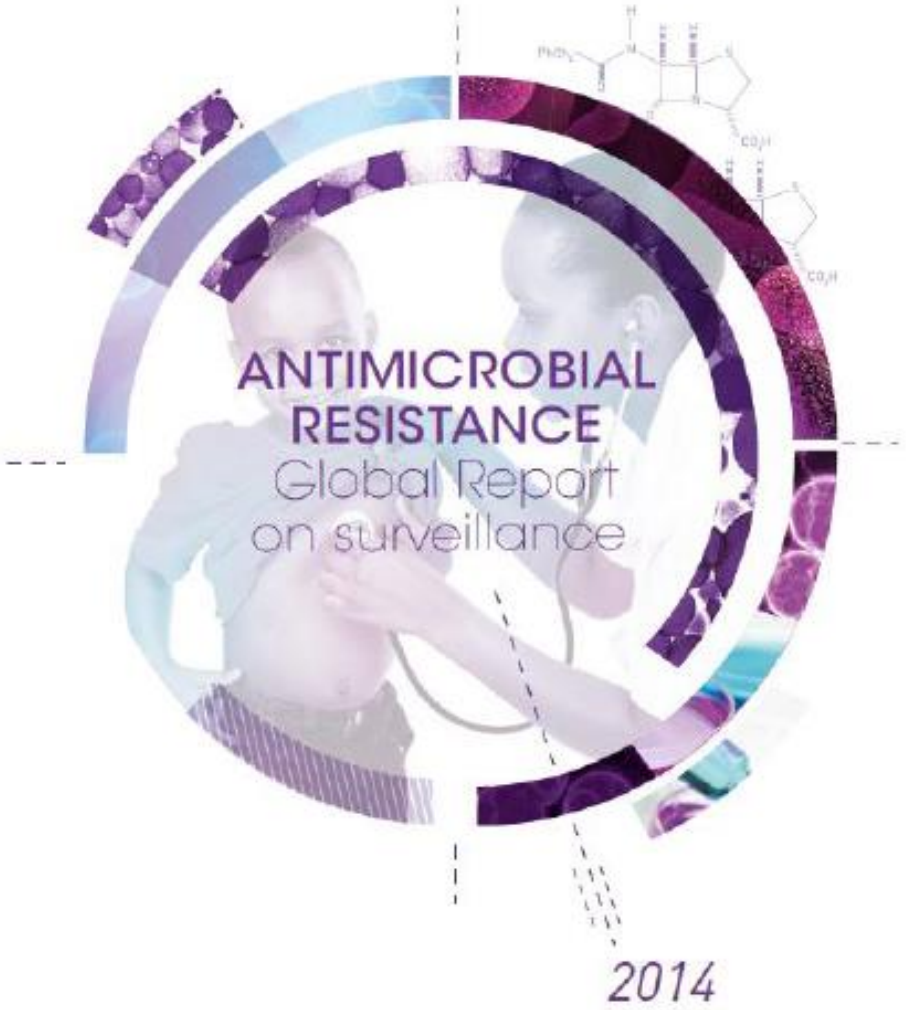
M. Colomb-Cotinat[1*], J. Lacoste[1], C. Brun-Buisson[2], V. Jarlier[3], B. Coignard[1] and S. Vaux[1]

- 158 000 infections
- 12 500 décès en 2012

Morbidité et mortalité des infections à bactéries multi-résistantes aux antibiotiques en France en 2012

Étude Burden BMR, rapport - Juin 2015

- *Staphylococcus aureus* resistant to methicillin (MRSA);
- *Enterococcus faecium* and *E. faecalis* resistant to glycopeptides (GRE);
- *Escherichia coli* resistant to third-generation cephalosporins (3GC-R *E. Coli*);
- *Klebsiella pneumoniae* resistant to third-generation cephalosporins (3GC-R *K. pneumoniae*);
- *Pseudomonas aeruginosa* resistant to carbapenems (CR *P. aeruginosa*);
- *Klebsiella pneumoniae* resistant to carbapenems (CR *K. pneumoniae*);
- *Acinetobacter spp.* resistant to carbapenems (CR *Acinetobacter spp*).



World Health Organization

PLAN D'ACTION MONDIAL

POUR COMBATTRE LA RÉSISTANCE AUX ANTIMICROBIENS

Organisation mondiale de la Santé

Objectif 1. Mieux faire connaître et comprendre le problème de la résistance aux antimicrobiens grâce à une communication, une éducation et une formation efficaces

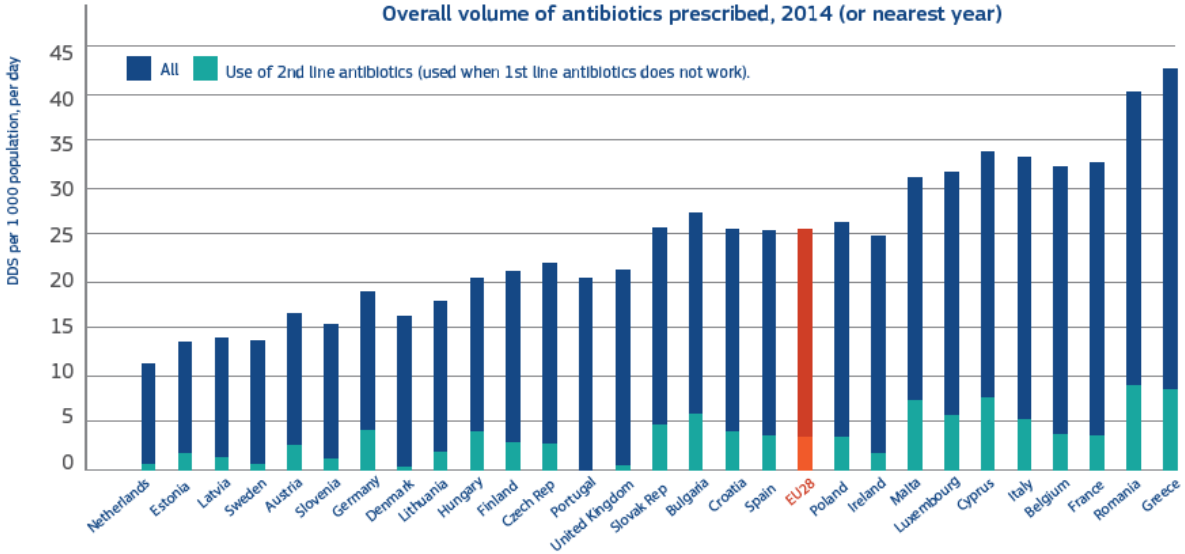
Objectif 2. Renforcer les connaissances et les bases factuelles par la surveillance et la recherche

Objectif 3. Réduire l'incidence des infections par des mesures efficaces d'assainissement, d'hygiène et de prévention des infections

Objectif 4. Optimiser l'usage des médicaments antimicrobiens en santé humaine et animale

Objectif 5. Dégager les arguments économiques en faveur d'investissements durables qui tiennent compte des besoins de tous les pays et accroître les investissements dans la mise au point de nouveaux médicaments, outils diagnostiques, vaccins et autres interventions

A European One Health Action Plan against Antimicrobial Resistance (AMR)



What is the EU doing?

The **key objectives** of this new plan are built on three main pillars:

Making the EU a best practice region

Boosting research, development and innovation

Shaping the global agenda

ansm
Agence nationale de sécurité du médicament et des produits de santé

Rapport

Liste des antibiotiques critiques

Actualisation 2015

Publication Février 2016

Antibiotiques particulièrement générateurs de résistances bactériennes

- association amoxicilline-acide clavulanique
- céphalosporines : plus grande préoccupation pour les spécialités administrées par voie orale que par voie injectable ; plus grande préoccupation pour les céphalosporines de troisième et quatrième générations, et pour la catégorie « autres céphalosporines » ; préoccupation pour la ceftriaxone
- fluoroquinolones
- témocilline*

** Pression de sélection en lien avec la problématique d'une dose optimale non établie*

Antibiotiques de dernier recours

Vis à vis des *cocci* à Gram positif

- daptomycine
- glycopeptides**
- linézolide, tédizolide

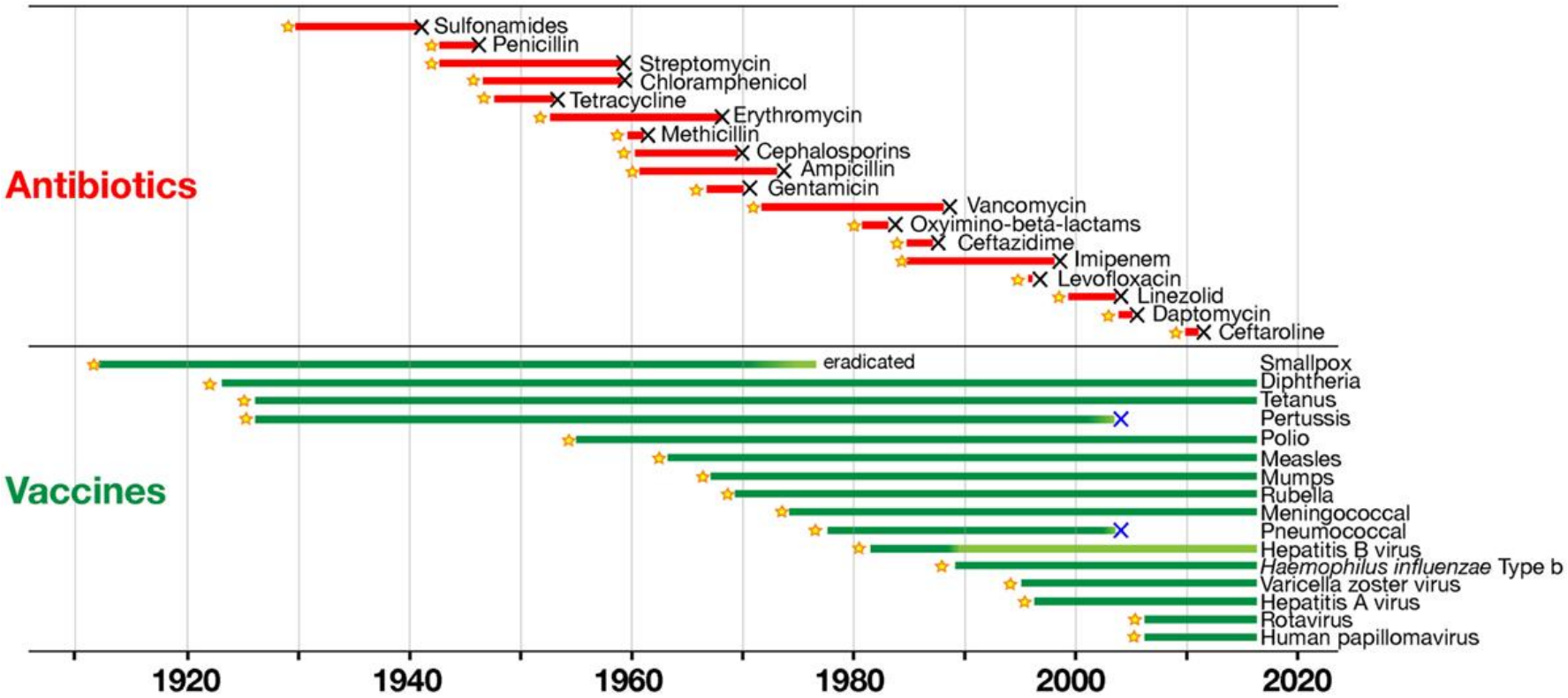
Vis à vis des bactéries à Gram négatif

- colistine injectable
- pénèmes**
- phénicolés
- tigécycline

Vis à vis des bactéries à Gram positif et à Gram négatif

- fosfomycine injectable

***Particulièrement générateurs de résistances bactériennes*



Tagliabue 2018

Vous êtes la génération d'après

- Après le *peak oil*
- Après l'apparition du continent de plastique
- Après l'établissement du réchauffement climatique
  - Et les lobbies qui le nient
- Après le trou dans la couche d'ozone
- Après l'établissement de la multirésistance bactérienne

Deux destins possibles

- Poursuite de l'irresponsabilité
  - Poursuite du mésusage humain
    - Indication, dose, durée, molécule …
  - Poursuite du manuportage en soin
  - Poursuite du mésusage animal
  - Sans développement de nouveaux ATB …
- Redressement de la situation
  - Cultiver le bon usage
  - Volonté politique à tous les niveaux