

CA-MRSA

why such a failure in Europe ?

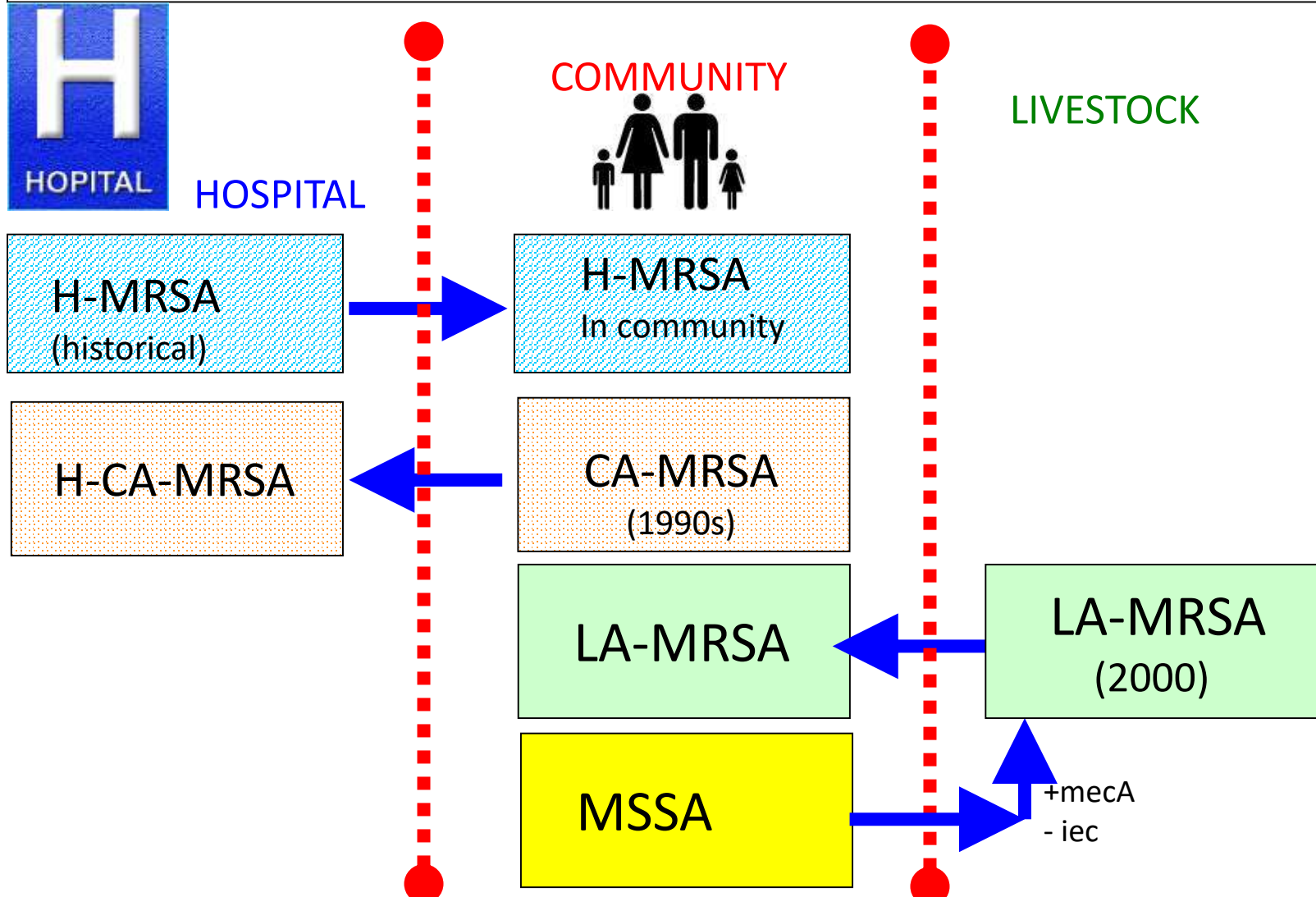
F. Vandenesch, MD, PhD

J.P. Rasigade, MD, PhD

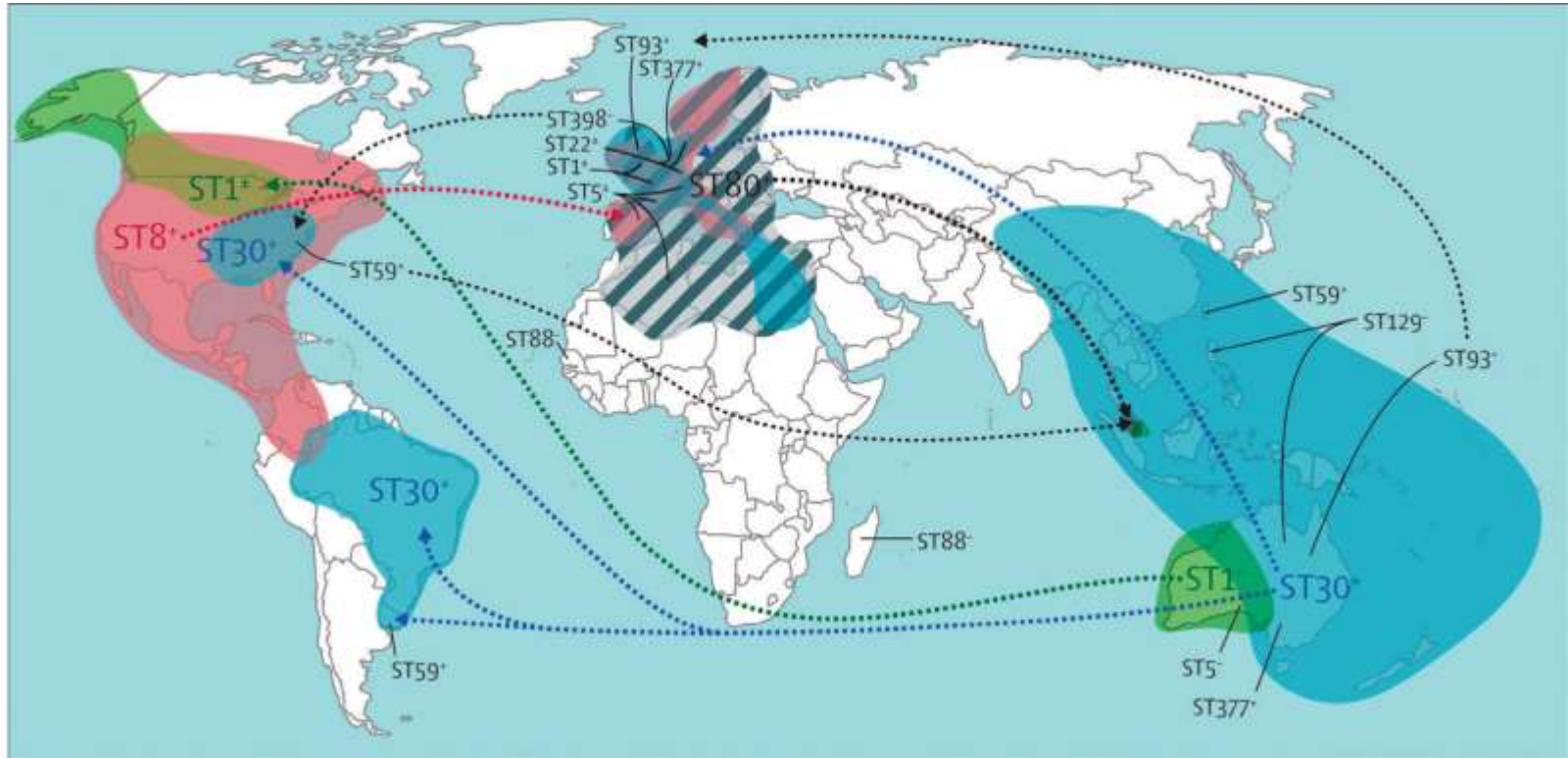
INSERM U1111, University of Lyon, National Reference Center for Staphylococci

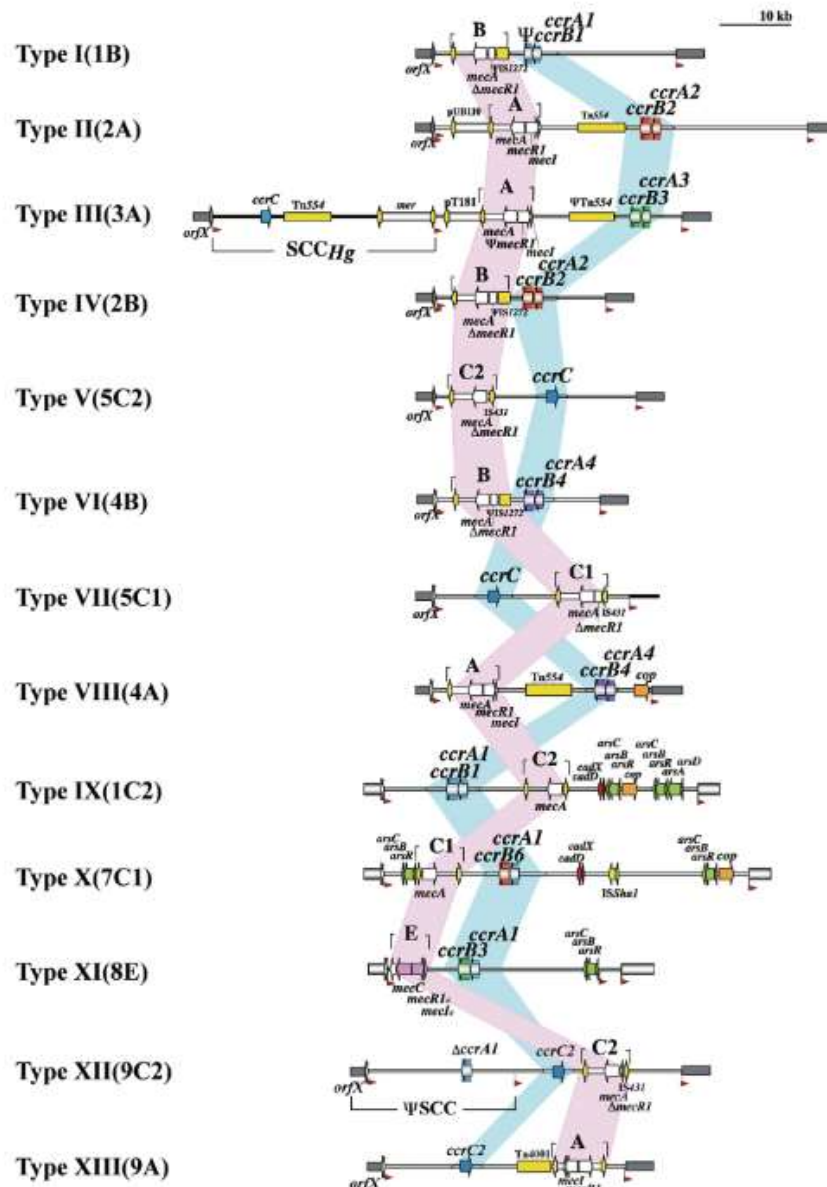


Three categories of MRSA



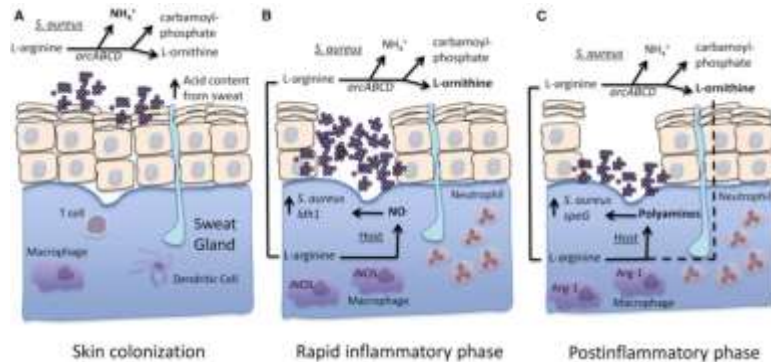
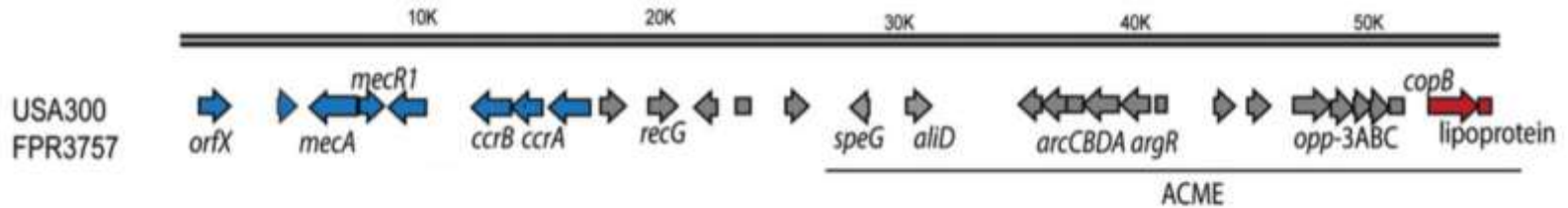
CA-MRSA distribution





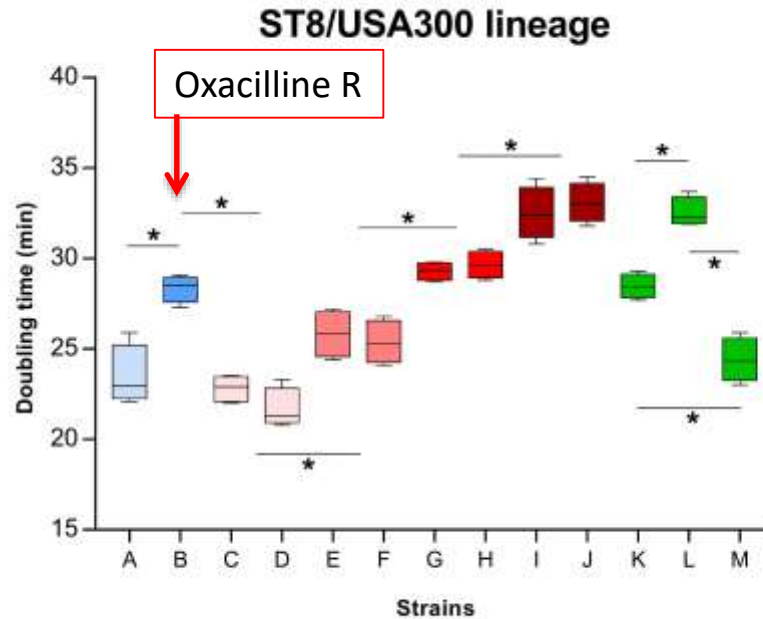
SCCmec classification

SCCmec: a convenient vehicle for virulence genes



ACME contributes to *S. aureus* survival on and within human skin

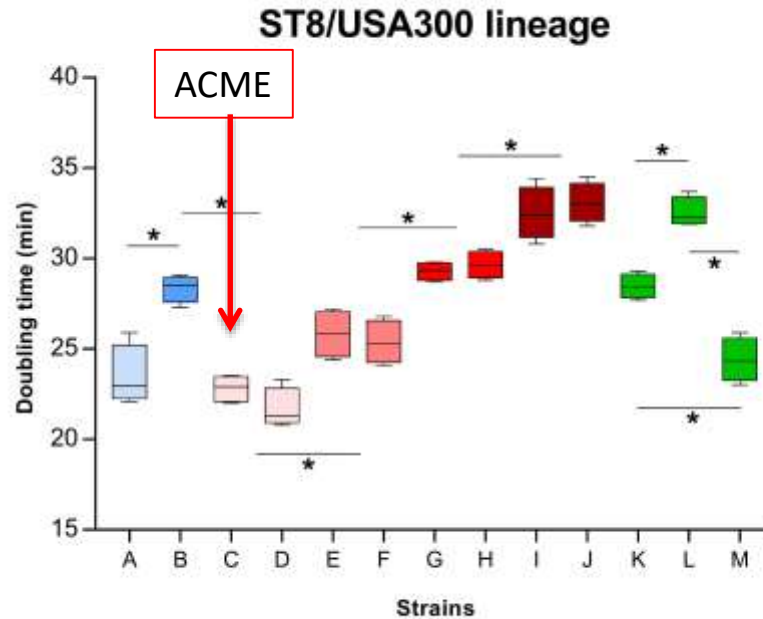
Doubling time



Strain ID	SCCmec	ACME	Antibiotic resistance	Clade
A	Neg	Neg	P, F	Ancestral ST8
B	POS	Neg	P, Oxa	Basal USA300
C	POS	POS	P, Oxa	Derived USA300
D	POS	POS	P, Oxa	Derived USA300
E	POS	POS	P, Oxa, K, E	Derived USA300
F	POS	POS	P, Oxa, K, E	Derived USA300
G	POS	POS	P, Oxa, K, E, O	Derived USA300
H	POS	POS	P, Oxa, K, E, O	Derived USA300
I	POS	POS	P, Oxa, K, E, O, T	Derived USA300
J	POS	POS	P, Oxa, K, E, O, T	Derived USA300
K	Neg	Neg	P, E, C, T, Cip, Mup	Ref. strain mutant
L	POS	Neg	P, Oxa, E, C, T, Cip, Mup	Ref. strain mutant
M	POS	POS	P, Oxa, E, C, T, Cip, Mup	USA300 ref. strain

-> mecA increases doubling time

Doubling time

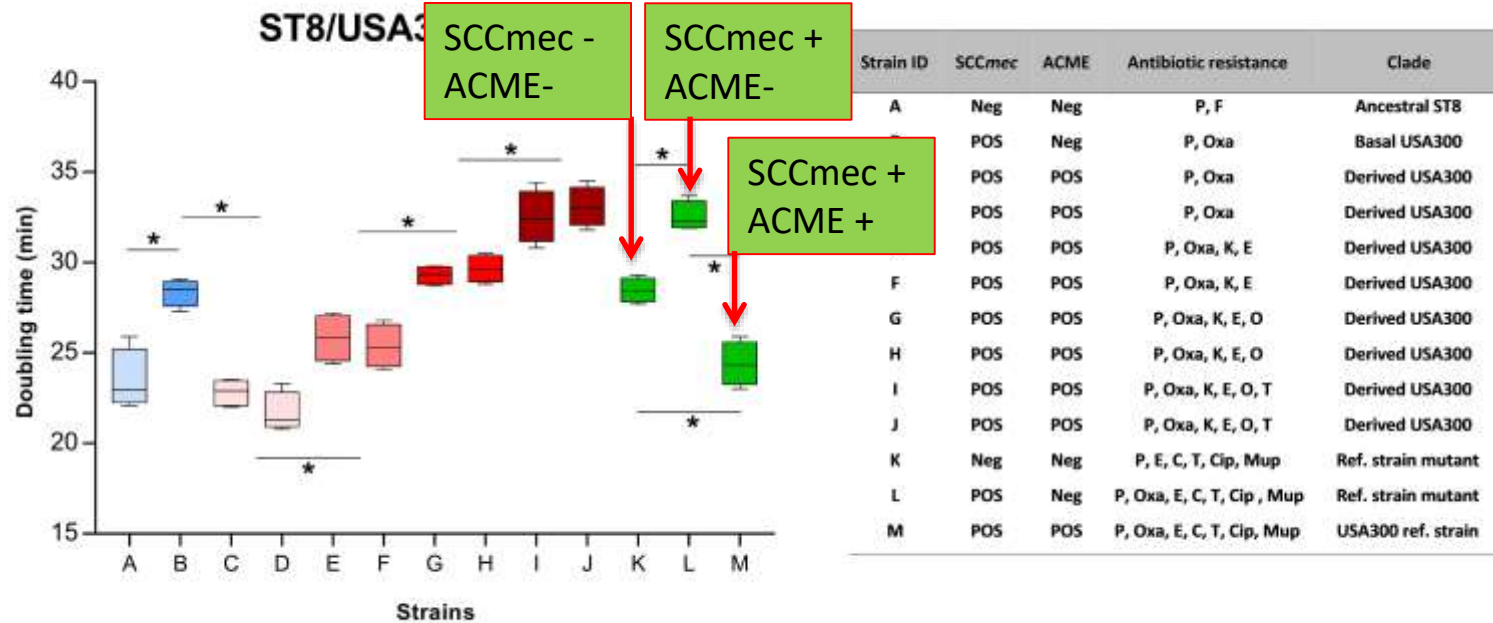


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-> mecA increases doubling time

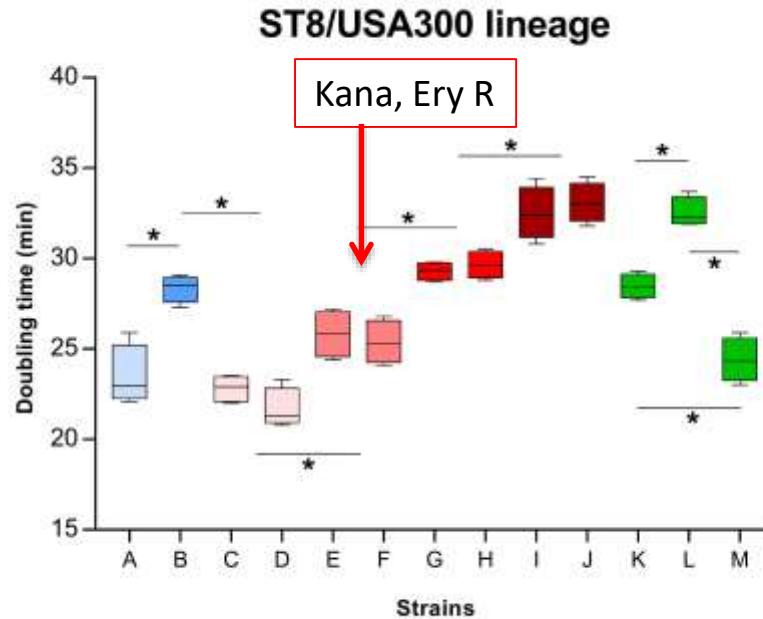
-> ACME is associated with reduced doubling time

Doubling time



-> Isogenic strains confirm the opposite effect of ACME and SCCmec on doubling time

Doubling time

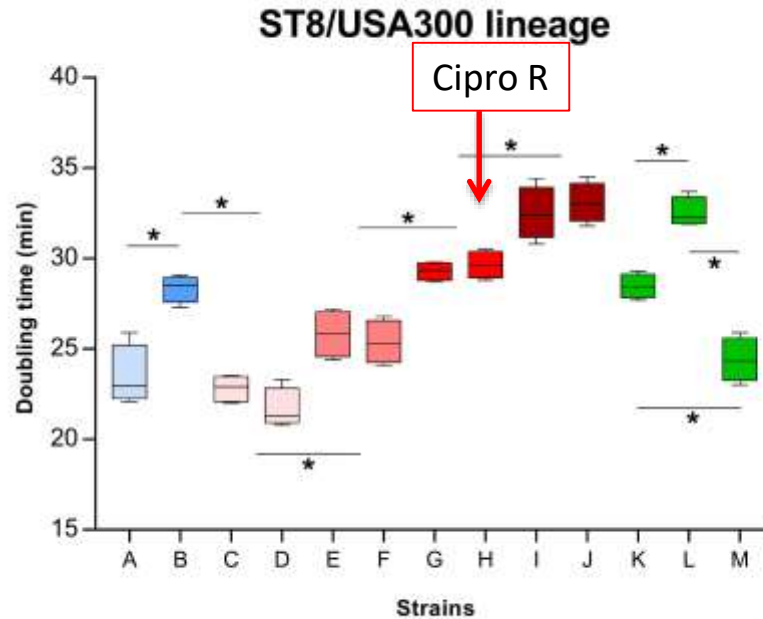


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-> ATB resistances (Oxacilline, aminoglycosides, macrolides, fluroquinolones, tetraccylcine) increased doubling time

-> ACME is associated with reduced doubling time

Doubling time

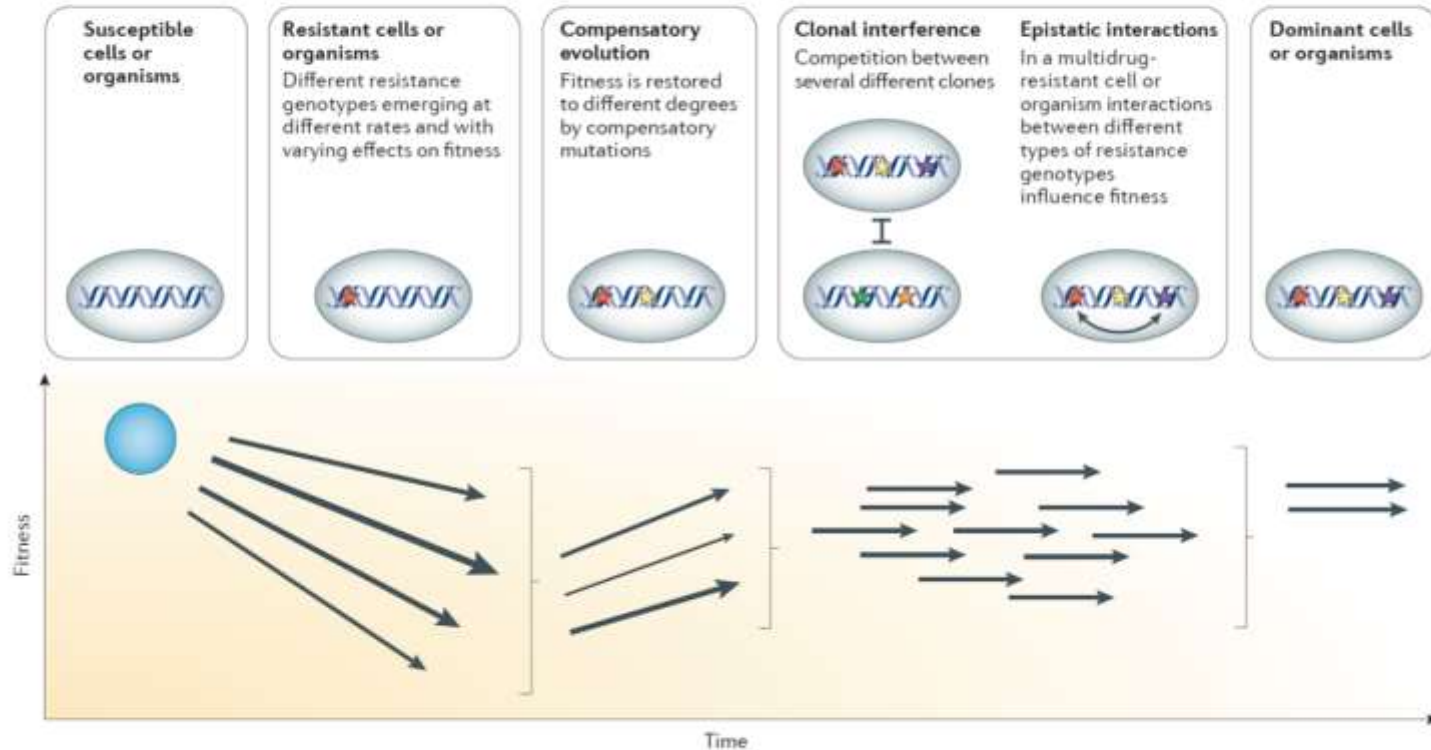


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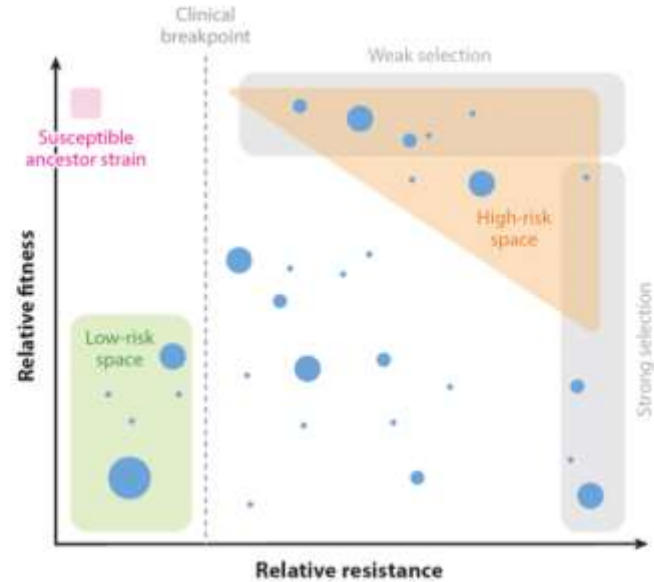
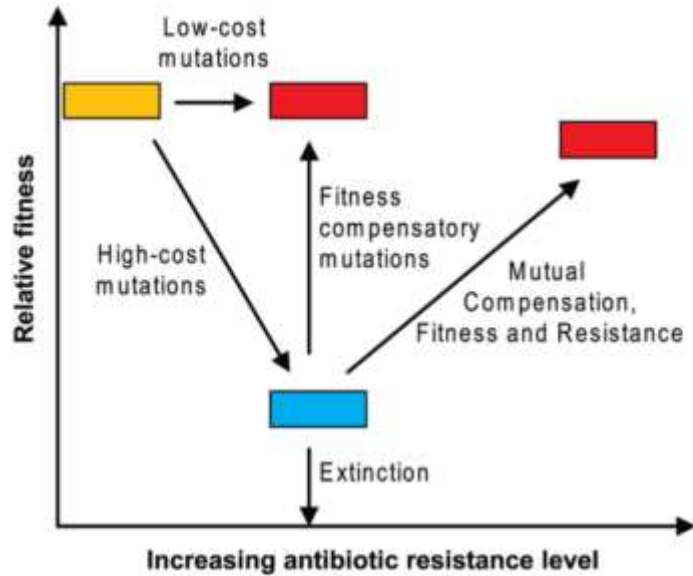
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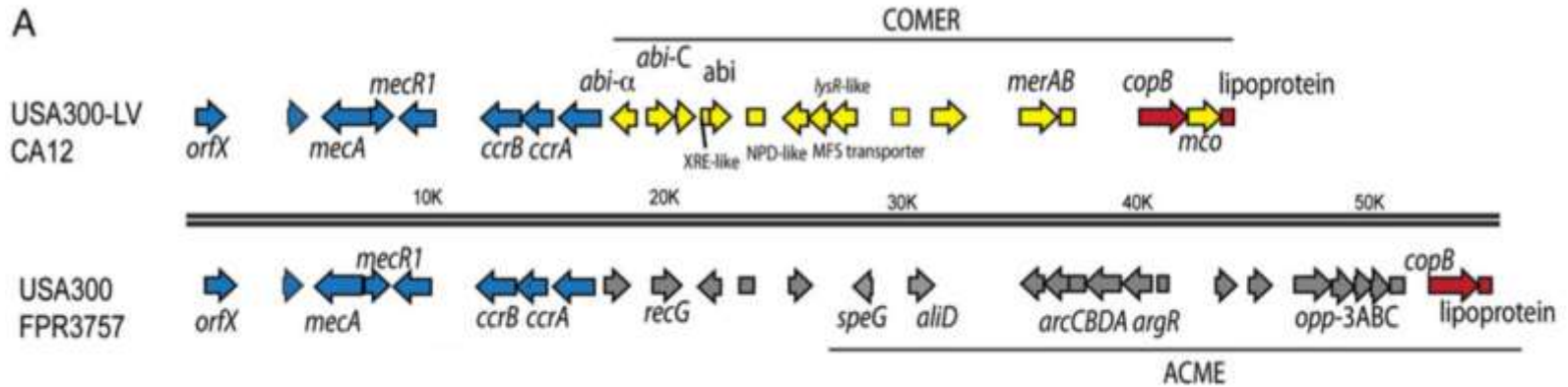
Evolutionary trajectories



AMR mutational space

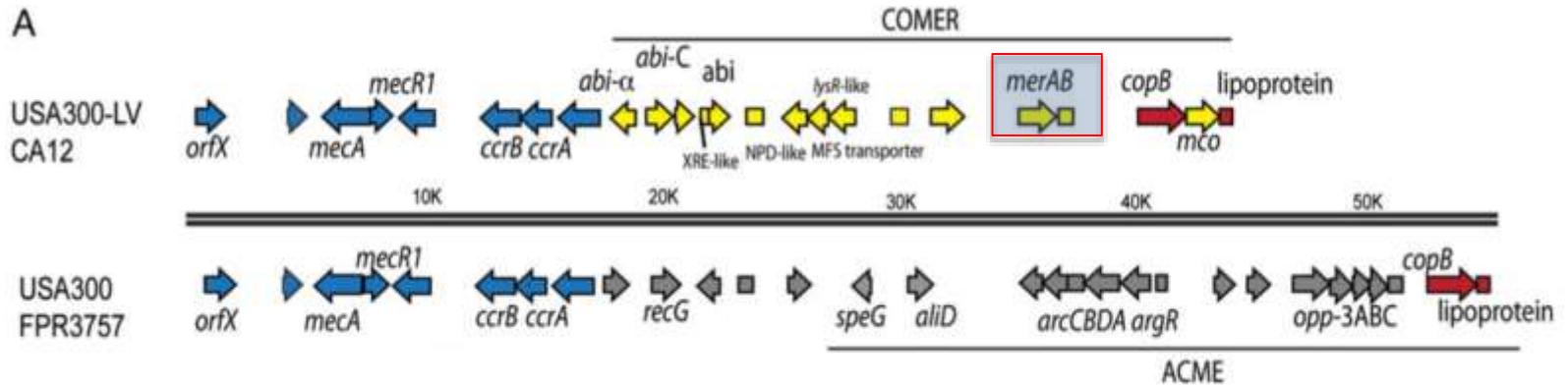


SCC*mec*: a convenient vehicle for other resistance genes



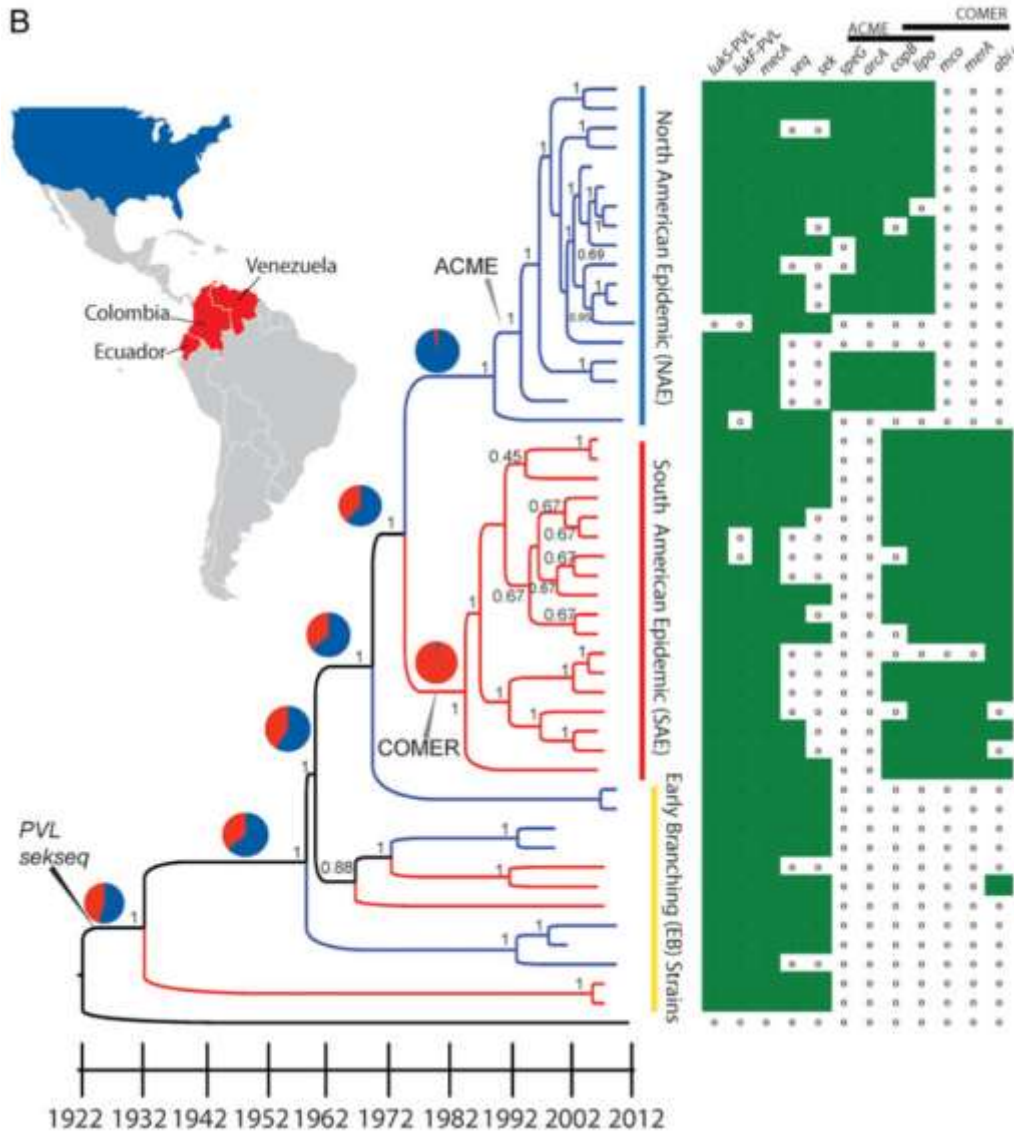
USA300 NA and LV SCC*mec* share an hyperresistance locus to copper

SCC*mec*: a convenient vehicle for other resistance genes



USA300 NA and LV SCC*mec* share an hyperresistance locus to copper
 USA300 LV SCC*mec* encodes a mercury resistance gene

B



2 distinct clades (South America and North America) that segregate by geographical region

ACME in NA clade
COMER in SA (or LV) clade

SA and NA clades diverged before the emergence of the USA300 epidemic in NA

USA300 LV in Latin America

- USA300-LV is the dominant CA-MRSA clone in Colombia, Ecuador, Peru, Trinidad and Venezuela



Reyes, Clin Infect Dis 2009

Alvarez, Am J Infect Control 2010

Garcia, J Infect 2011

Monecke, Eur J Clin Microbiol Infect Dis 2011

Sola, Plos One 2012

Nimmo, Clin Microbiol Infect 2012

Arias, AAC 2017

USA300 LV in Latin America

- USA300-LV is the dominant CA-MRSA clone in Colombia, Ecuador, Peru, Trinidad and Venezuela
- -> Why such success in these countries ?



Reyes, Clin Infect Dis 2009

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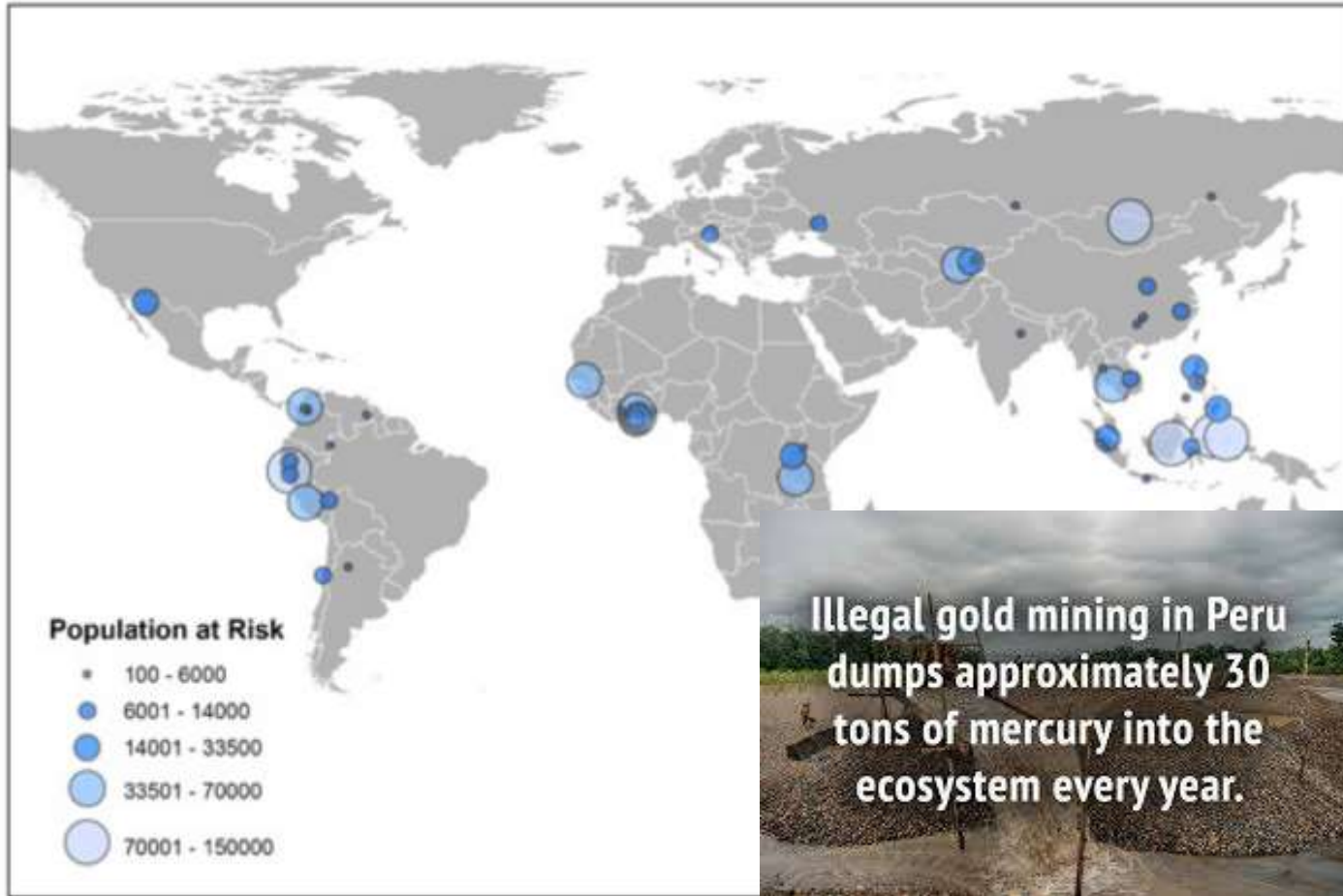
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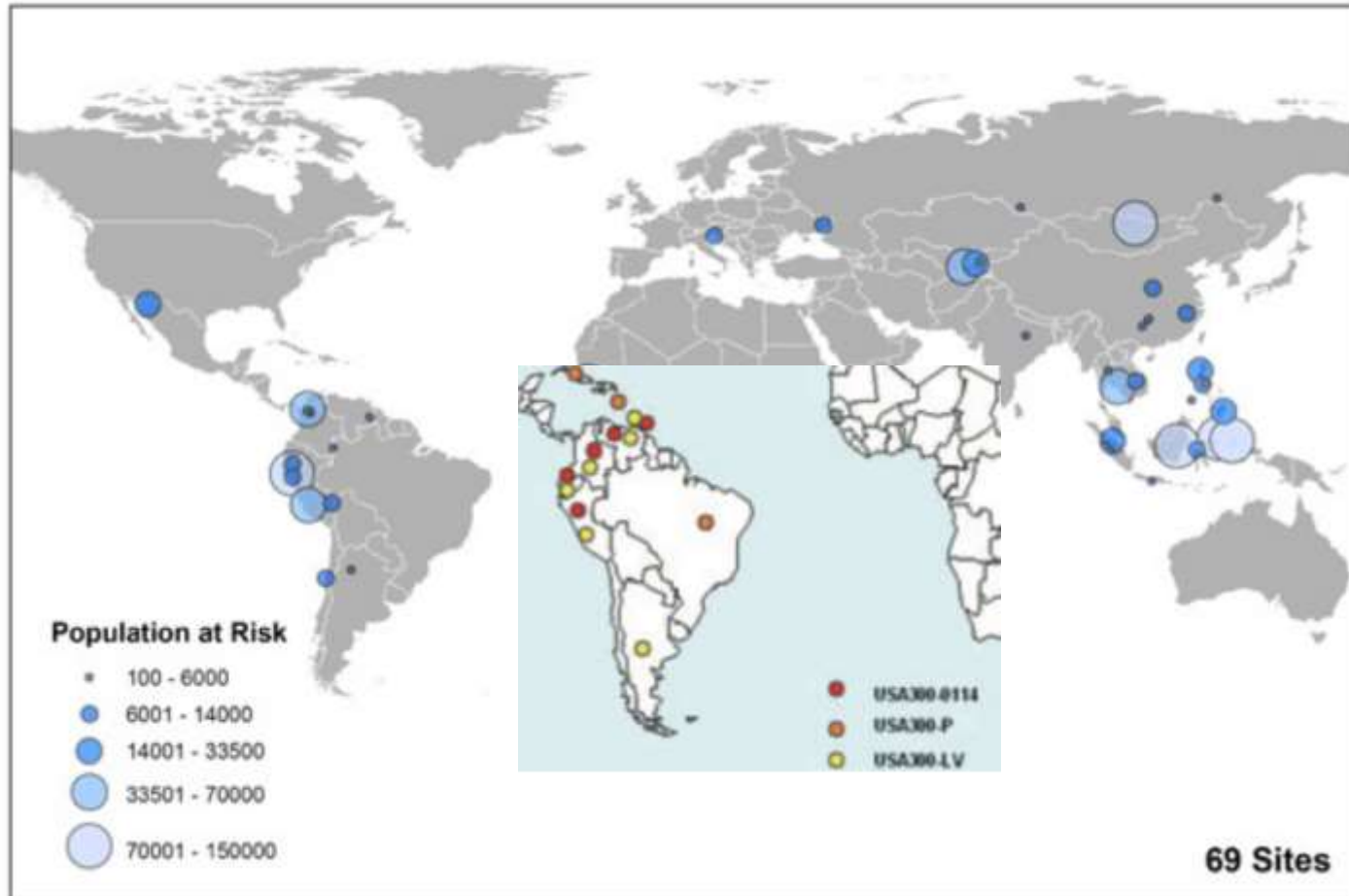
Nimmo, Clin Microbiol Infect 2012

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Mercury Pollution from Mining and Ore Processing



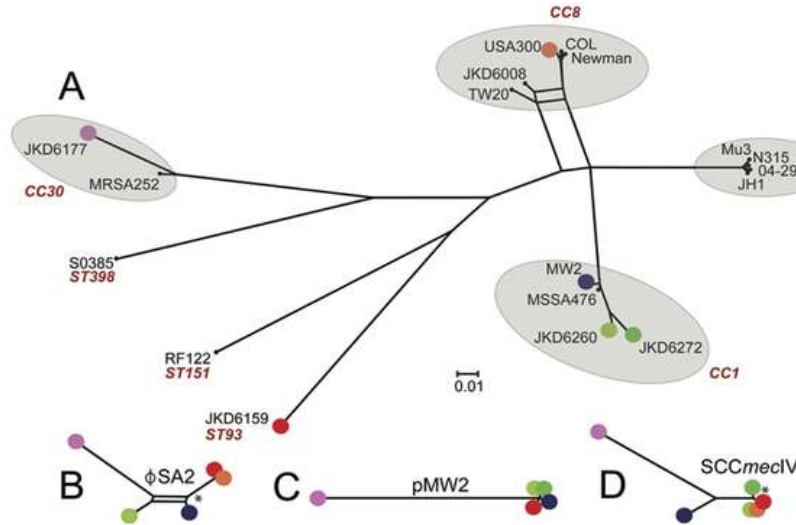
Mercury Pollution from Mining and Ore Processing



Human exposure to Mercury in Golden mines !



(historical) CA MRSA build up at genomic level



- Genetically distinct lineages
- conserved repertoire of accessory elements
 - PVL harbouring phage
 - SCCmec type IV or V
 - pMW2

Vandenesch et al. Emerging Infect Dis (2003)

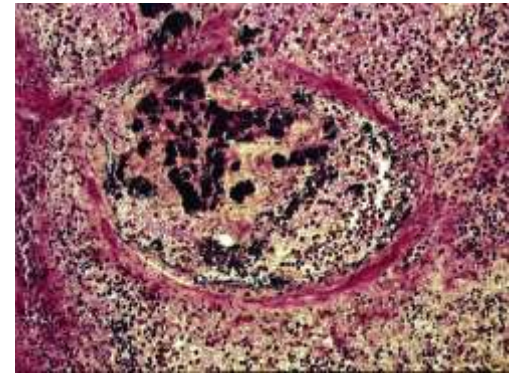
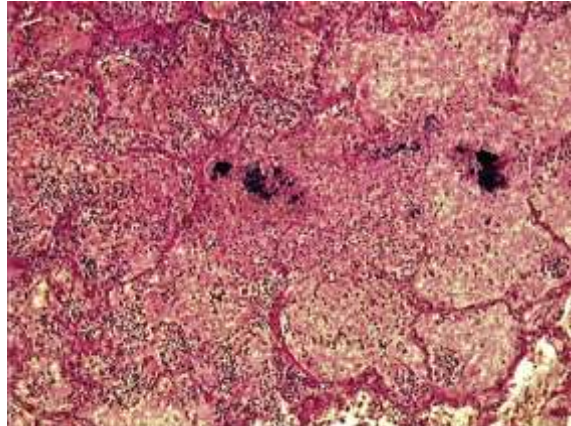
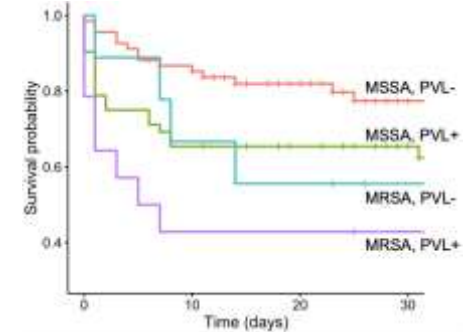
Li et al. J Infect Dis (2010)

Chua KYL et al. PLoS ONE (2011)

Carpaiz et al. PLoS One (2011)

Diseases associated with PVL

- Severe CA-pneumonia occurring in healthy adolescent and adults, leucopenia, hemoptysis, rash
 - Gillet et al. Lancet 2002; Gillet et al Clin Infect Dis. 2007; Gillet et al ERJ 2021 (prospective study, 163 patient cohort)
- Severe and chronic primary bone and joint infections: extraosseous involvement, myositis
 - Pantou NP, Valentine FCO. Lancet 1932; Martinez-Aguilar G, Pediatr Infect Dis J. 2004; Bocchini CE, Pediatrics. 2006; Dohin, Pediatr Infect Dis J. 2007
- Primary cutaneous infections, pyomyositis



Cutaneous infections and PVL

Table 1. Type and number of skin and soft tissue infections and rate of PVL-positive strains for each clinical diagnosis

Clinical diagnosis	Total	PVL-positive isolates
Follicular infections	53	39 (74)
Folliculitis	17	8 (47)
Furuncle	35	30 (85.5)
Carbuncle	1	1 (100)
Nonfollicular infections	131	16 (12)
Impetigo	35	3 (8.5)
Ecthyma	3	1 (33)
Lymphangitis	2	0 (0)
Cellulitis	37	7 (19)
Necrotizing cellulitis	5	1 (20)
Secondary abscesses	18	2 (11)
Felon/paronychia	9	1 (11)
Secondary pyodermas	12	1 (8.5)
SSSS	5	0 (0)
Scarlet fever	3	0 (0)
Rash secondary to TSS	2	0 (0)
Primary abscesses	45	42 (93.5)
Total	229	97 (42.5)

Cutaneous infections and PVL

- Folliculitis, furuncles, primary abscesses
- Severity: larger, more erythematous and more painful furuncles
- Recurrence of furunculosis:
 - 63% of patients with PVL-positive furunculosis
 - 17% of PVL-negative (Yamasaki CID 2005)

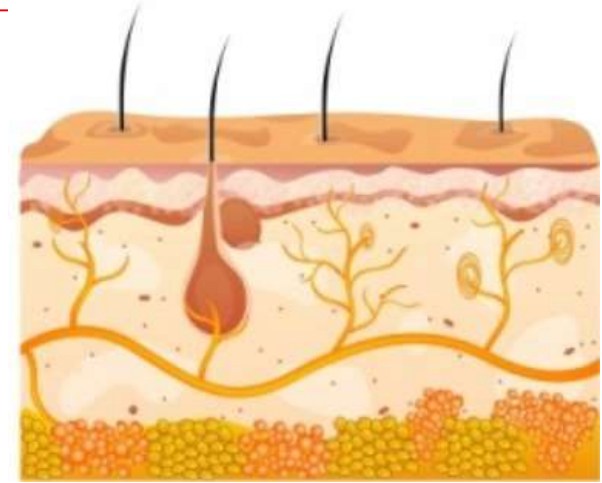


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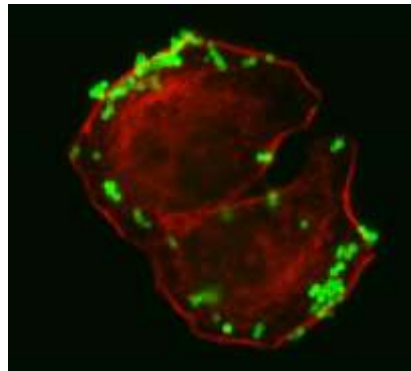
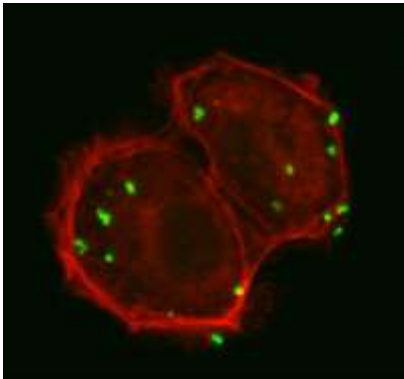
Pathogenesis mechanism ?

- PVL may -> *S.aureus* penetration of the hair follicles and progress from folliculitis, to furunculosis.
- Mechanism unknown but might be secondary to moonlighting function of PVL signal peptide



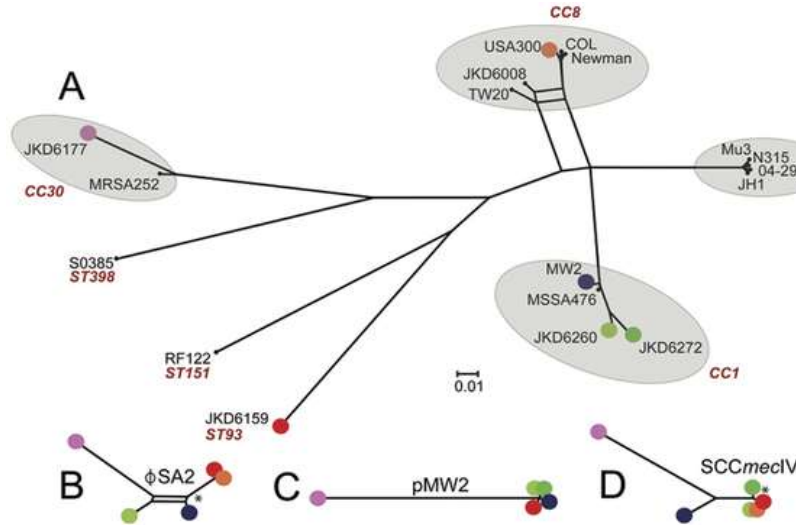
<http://healthmd.blogspot.fr/2011/10/infected-hair-follicle-symptoms-and.html>

RN6390 Δ *spa*
on HaCat
Keratinocytes

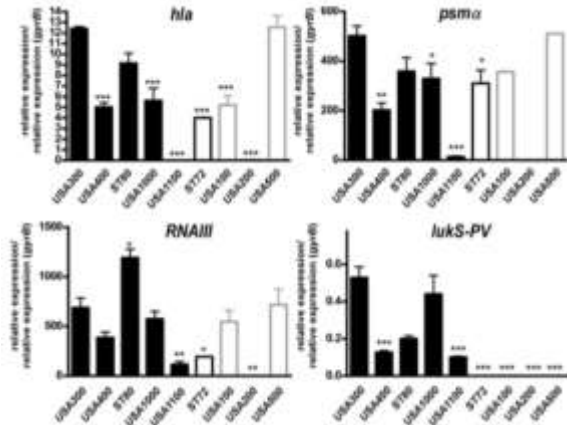


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
(historical) CA MRSA build up at genomic level



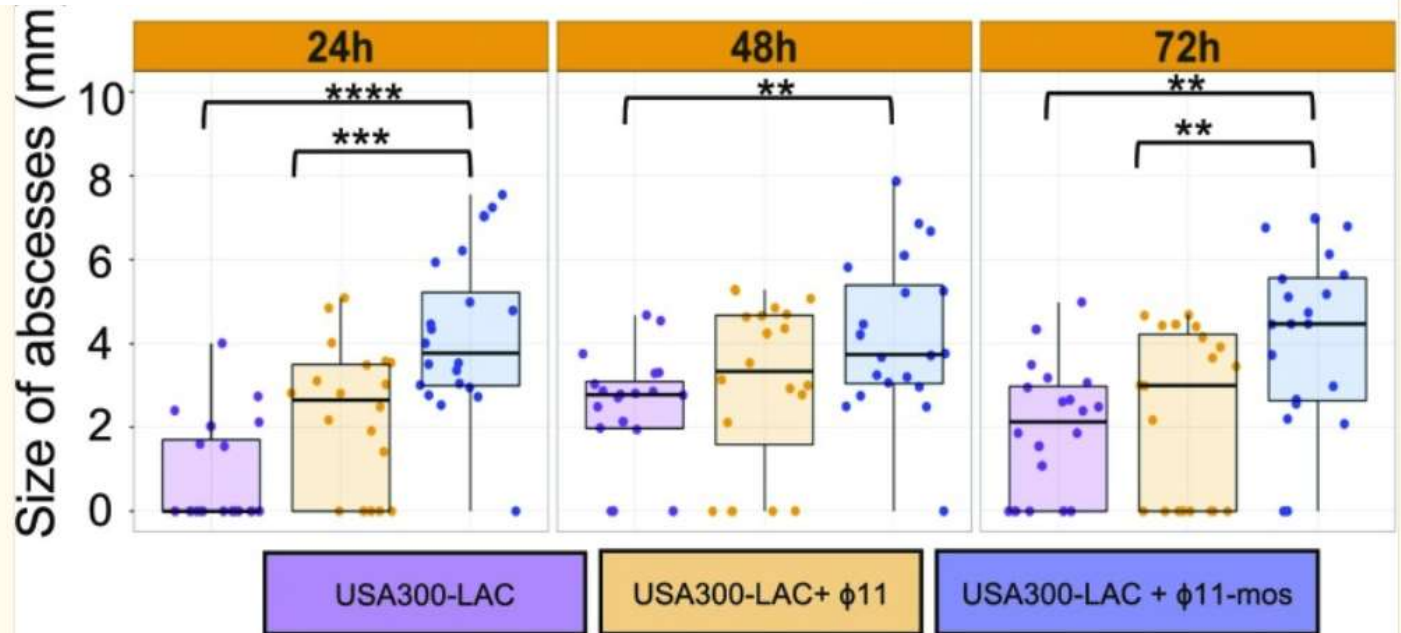
- Genetically distinct lineages
- conserved repertoire of accessory elements
 - PVL harbouring phage
 - SCCmec type IV or V
 - pMW2
- Increased expression of core-genome-encoded virulence factors



Sequential evolution of virulence and resistance during clonal spread of community-acquired methicillin-resistant *Staphylococcus aureus*

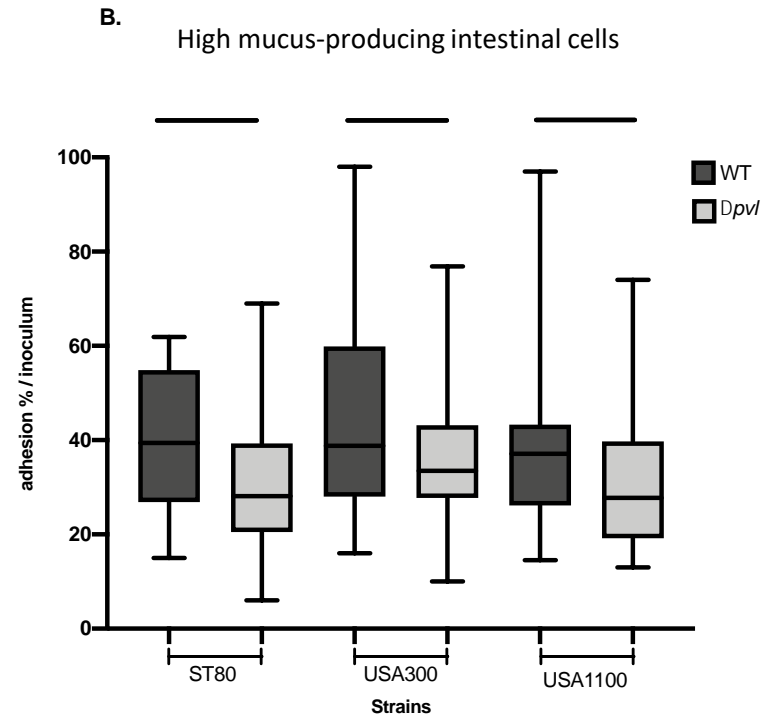
Richard Copin ^{a,1}, William E. Sause ^{b,1}, Yi Fulmer ^a, Divya Balasubramanian ^b, Sophie Dyzenhaus ^b, Jamil M. Ahmed ^a, Krishan Kumar ^a, John Lees ^b, Anna Stachel ^a, Jason C. Fisher ^c, Karl Drlica ^{d,e}, Michael Phillips ^a, Jeffrey N. Weiser ^b, Paul J. Planet ^f, Anne-Catrin Uhlemann ^g, Deena R. Altman ^{h,1}, Robert Sebra ¹, Harm van Bakel ¹, Jennifer Lighter ^{1,2}, Victor J. Torres ^{b,2} and Bo Shoppin ^{a, b, 2}

USA300 strain cluster within an enclosed Brooklyn community



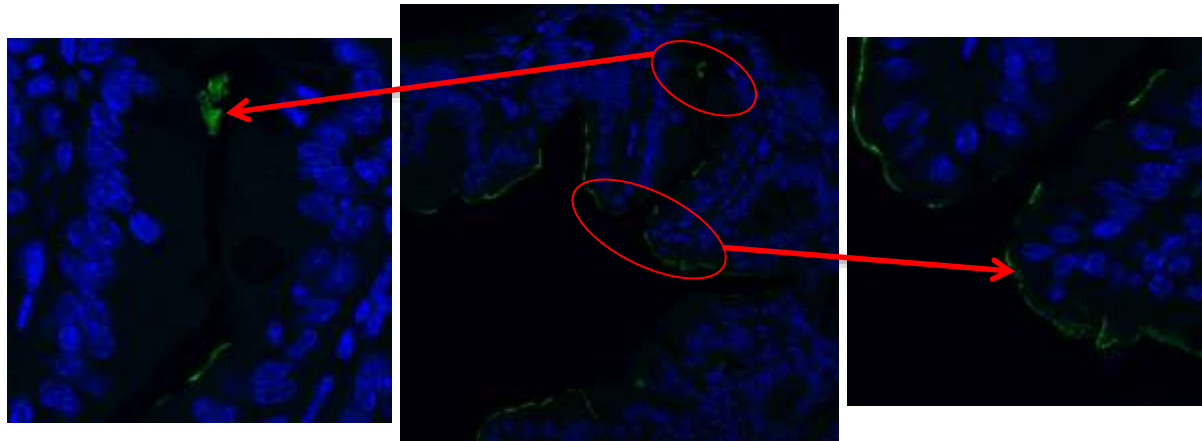
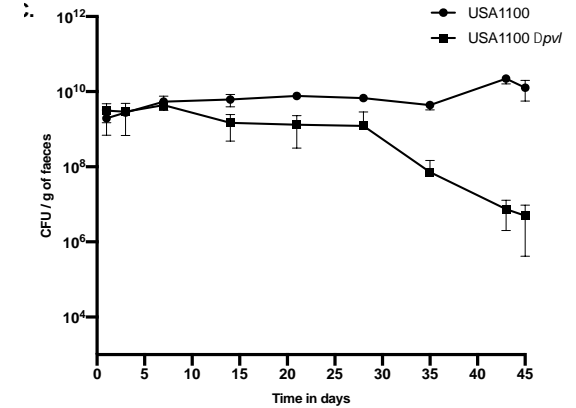
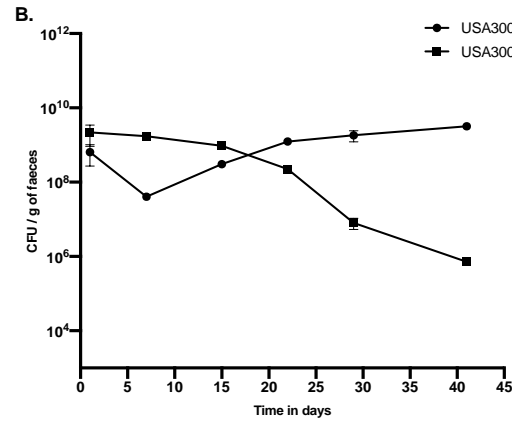
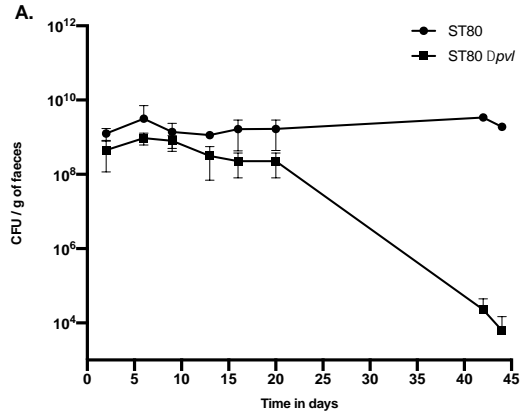
PVL and carriage ?

- pelvic sites and gut carriage have been associated with **CA-MRSA** (Faden H, Pediatrics. 2010, Miko BA, Microbes Infect. 2012)
- PVL-positive adhere more strongly than PVL-mutant to mucus-producing intestinal cells (Couzon F, bioRxiv 2020)



(Couzon F, bioRxiv 2020)

WT PVL-positive outcompete Delta-PVL mutant in a gut colonization model in mice



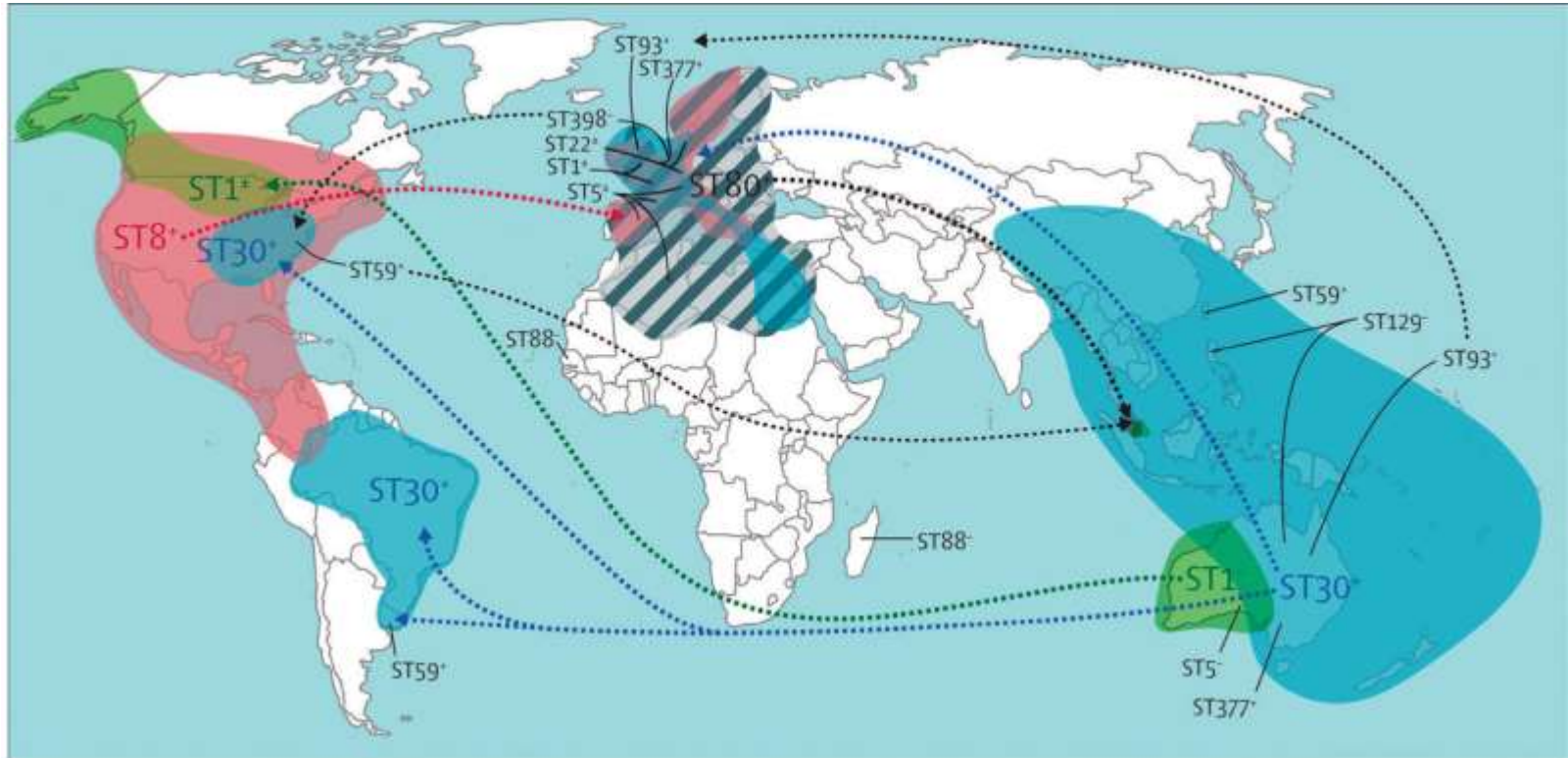
(Couzon F, bioRxiv 2020)

Why should have CA-MRSA succeeded?

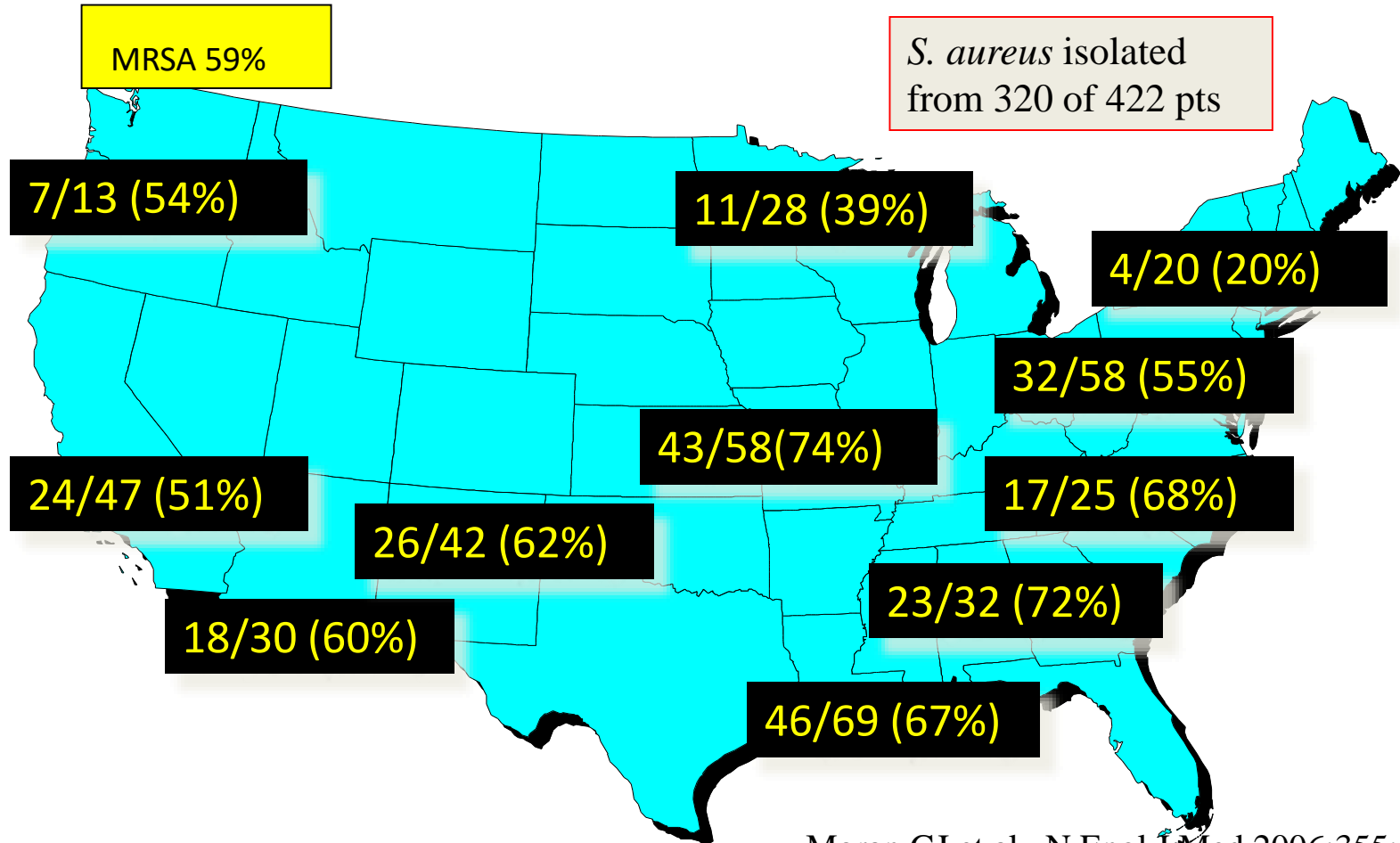
- Short SCCmec -> potentially lower fitness cost
- ACME in USA300
 - Contributes to cutaneous infections
 - Compensates fitness cost of mecA
- PVL
 - Increases severity of cutaneous infection -> increases CFU → increases transmission
 - Favor extra-nasal carriage -> lower efficiency of decolonisation
- Increased expression of virulence factors
- -> Expected Natural evolution of resistant strains

Epidemiological evidences of sucess ... in the US

CA-MRSA distribution



High Prevalence of MRSA USA300 among 422 Emergency Department Patients with SSTI



USA300 (ST8) has become prevalent in hospitals

- Atlanta Grady Memorial hospital 2004
 - 116 MRSA from bloodstream infection: 34% = USA300
 - 28% of nosocomial bacteremia are caused by USA300
- Detroit, MI, hospital - 2005 to 2007
 - 20% of nosocomial bacteremia are caused by USA300
- San Francisco long-term care facility 2002-2006
 - USA300 increased among MRSA isolates from 11.3% in 2002 to 64% in 2006

Seybold U et al CID 2006;42:647-56

Chua T et al. J. Clin. Microbiol. 2008;46:2345–2352

Tattevin et al. Emerg. Infect. Dis. 2009;15:953–955

Epidemiological evidences of sucess
... in the US

.... but not in Europe

Methicillin-resistant *Staphylococcus aureus* (MRSA): burden of disease and control challenges in Europe

R Köck^{1,2}, K Becker², B Cookson³, J E van Gemert-Pijnen⁴, S Harbarth^{5,6}, J Kluytmans^{7,8}, M Mielke⁹, G Peters², R L Skov¹⁰,
M J Struelens^{11,12}, E Tacconelli¹³, A Navarro Torné¹², W Witte¹⁴, A W Friedrich (alexander.friedrich@ukmuenster.de)²

- overall burden of CA-MRSA in European countries is hindered by differences in the definitions used
- The proportion of CA-MRSA / total MRSA range
 - between 1% and 2% in Spain and Germany
 - 29–56% in Denmark and Sweden, partly reflecting the low prevalence of HA-MRSA in these Scandinavian countries
- Among outpatients with *S. aureus* infections, MRSA accounted for 6% in the Ligurian region in Italy, 14% in Germany, 18% in France and 30% in Greece

MRSA infections among patients in the emergency department: a European multicentre study

C. Bouchiat^{1*}, S. Curtis², I. Spiliopoulou³, M. Bes¹, C. Cocuzza⁴, I. Codita⁵, C. Dupieux¹, N. Giormezis³, A. Kearns², F. Laurent¹, S. Molinos^{6,7}, R. Musumeci⁴, C. Prat^{6,7}, M. Saadatian-Elahi⁸, E. Tacconelli⁹, A. Tristan¹, B. Schulte¹⁰ and F. Vandenesch¹ on behalf of the ESCMID Study Group on Staphylococci and Staphylococcal Infections (ESGS)

- Methodology = Moran' like: Patients admitted to emergency room with *S.aureus* SSTI
- 8 centers-countries
- 205 cases of *S. aureus*-associated CA-SSTIs
- 34 MRSA: prevalence 15.1% with a north (UK 0%) to south (Greece 29%) gradient
- 51 PVL-positive including 19 MRSA strains: 10 CC80, 3 CC5, 1 USA300..

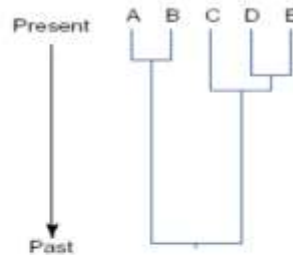
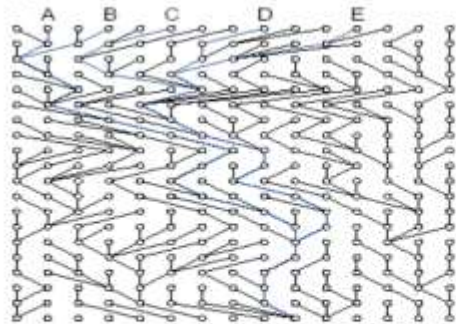
Country with higher prevalence: Algeria

- 1800 bed-Mustapha Pacha Hospital
- 221 *S.aureus* infections collected in 2007
- 84 CA infection
 - MRSA 40.5% : ST80 PVL+
- 137 HA infection
 - MRSA 47.4% = 3/4 of ST80 PVL+



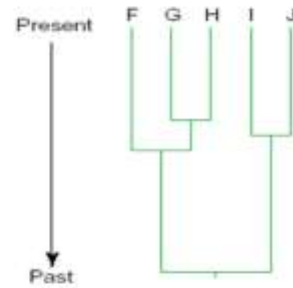
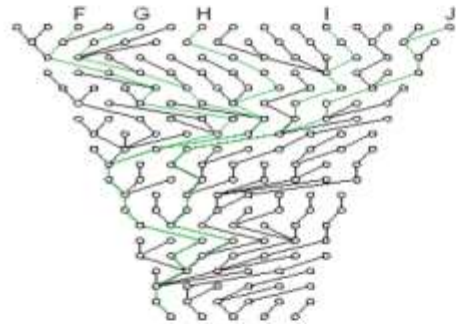
Genomic evidences of sucesess (and decline)

(a)

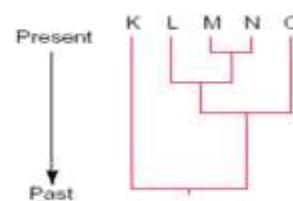
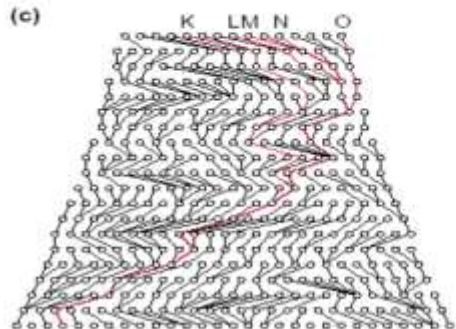


**Demographic changes
leave signatures on
gene genealogies**

(b)

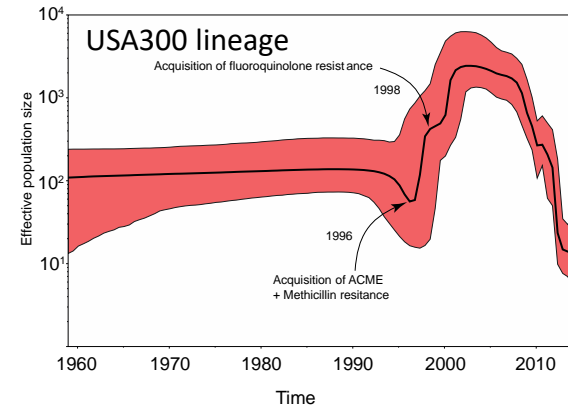
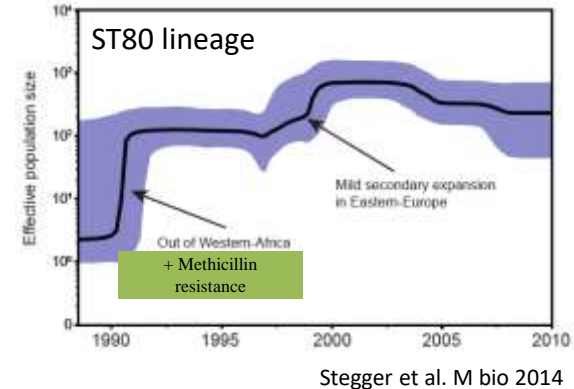


(c)

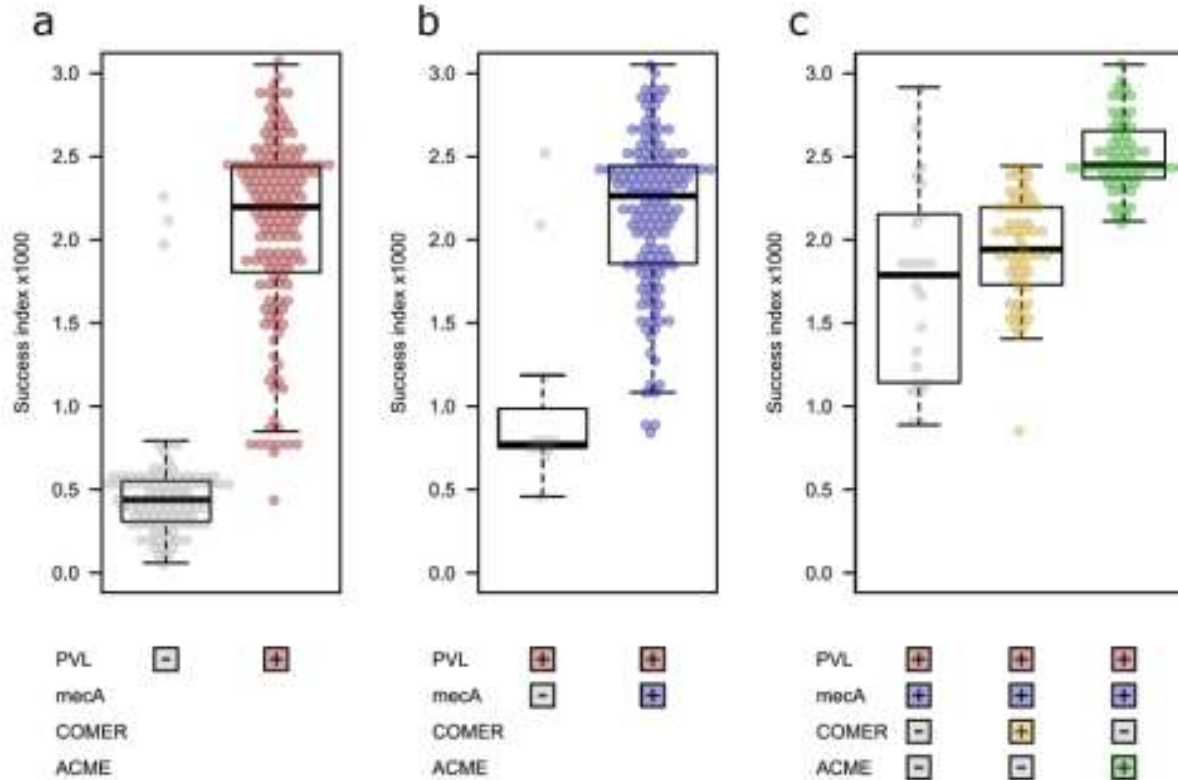


Genomic evidences of success (and decline)

- CA-MRSA emerged independently on different continent outside hospitals
- Bayesian approaches on large genomic datasets: antibiotic resistance is concomitant to strong demographic expansion



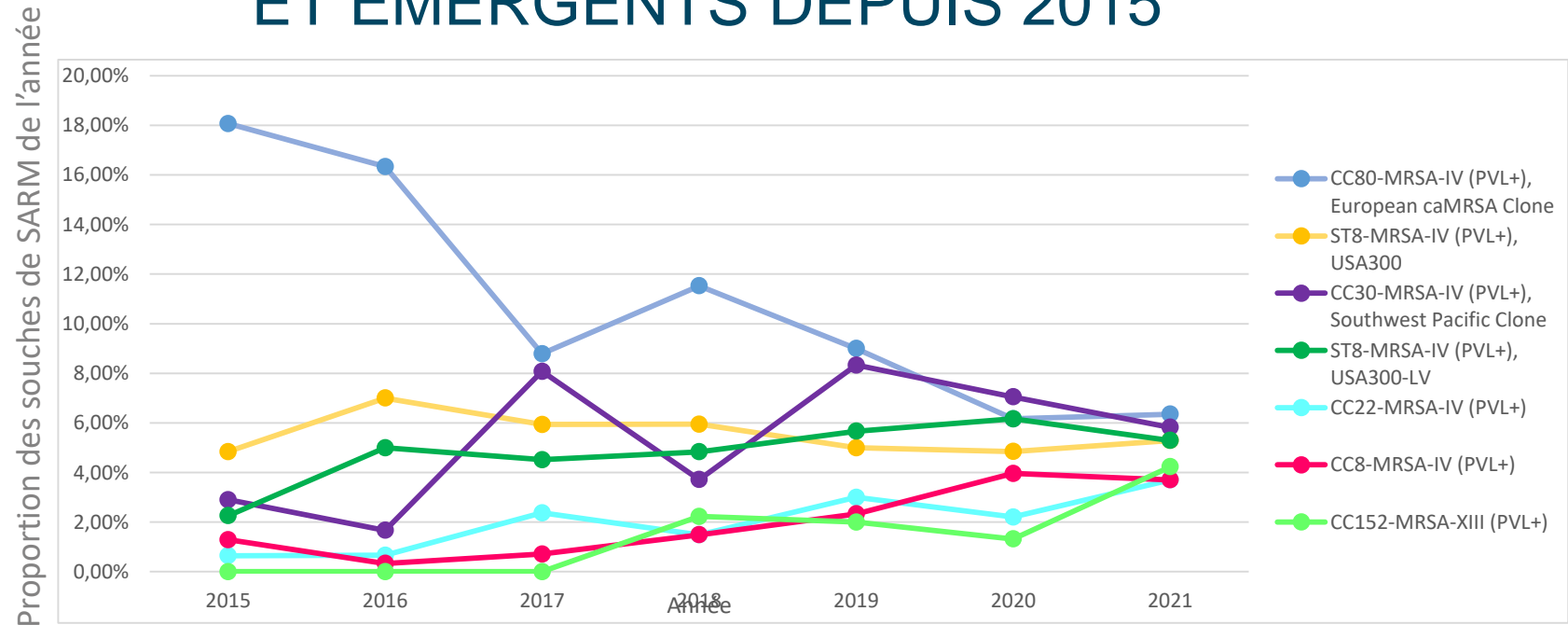
Transmission index of the ST8 ancestor and USA300 subclades



Sequential acquisition of PVL, mecA, ACME and COMER increases epidemic success

Evolution des clones de SARM-Co en France ? Données du CNR

CLONES SARM PVL+ MAJORITAIRES ET ÉMERGENTS DEPUIS 2015



- Baisse de la prévalence de European caMRSA Clone
- Hausse de la prévalence du Southwest Pacific Clone, du CC8-MRSA-IV (PVL+) et du CC22-MRSA-IV (PVL+)
- Emergence du CC152-MRSA-XIII (PVL+) depuis 2018

Why it did not work in Europe?

- Neither USA300, nor ST80 or the other lineages really succeeded in Europe
- Health care system?
- Prison and jails?
- MSM?
- Antibiotic consumption in the community: oral 3rdG cephalosporin?

CA-MRSA

why such a failure in Europe ?

We do not know!

CA-MRSA

why such a failure in Europe ?

The Journal of Infectious Diseases

SUPPLEMENT ARTICLE



Life After USA300: The Rise and Fall of a Superbug

Paul J. Planet^{1,2,3}

¹Sackler Institute for Comparative Genomics, American Museum of Natural History, New York ²Pediatric Infectious Disease Division, Children's Hospital of Philadelphia ³Perelman School of Medicine, University of Pennsylvania, Philadelphia

- -> science is not all powerful!
- -> a lesson in humility and modesty



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Review

Fluoroquinolone antibiotics: An emerging class of environmental micropollutants



Xander Van Doorslaer, Jo Dewulf, Herman Van Langenhove, Kristof Demeestere *

Research Group EnVOC, Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

CLEAN

Soil Air Water

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Ritu Gothwal
Thhatikkonda Shashidhar

Department of Civil Engineering,
Indian Institute of Technology
Hyderabad, Ordnance Factory Estate,
Yeddumailaram, Andhra Pradesh,
India

Review

Antibiotic Pollution in the Environment: A Review

Antibiotics have been extensively and effectively used in human and veterinary medicines. Their benefits have been recognized in agriculture, aquaculture, bee-keeping, and livestock as growth promoters. This paper collects information from

Proc. R. Soc. B (2009) **276**, 2521–2530
doi:10.1098/rspb.2009.0320
Published online 8 April 2009

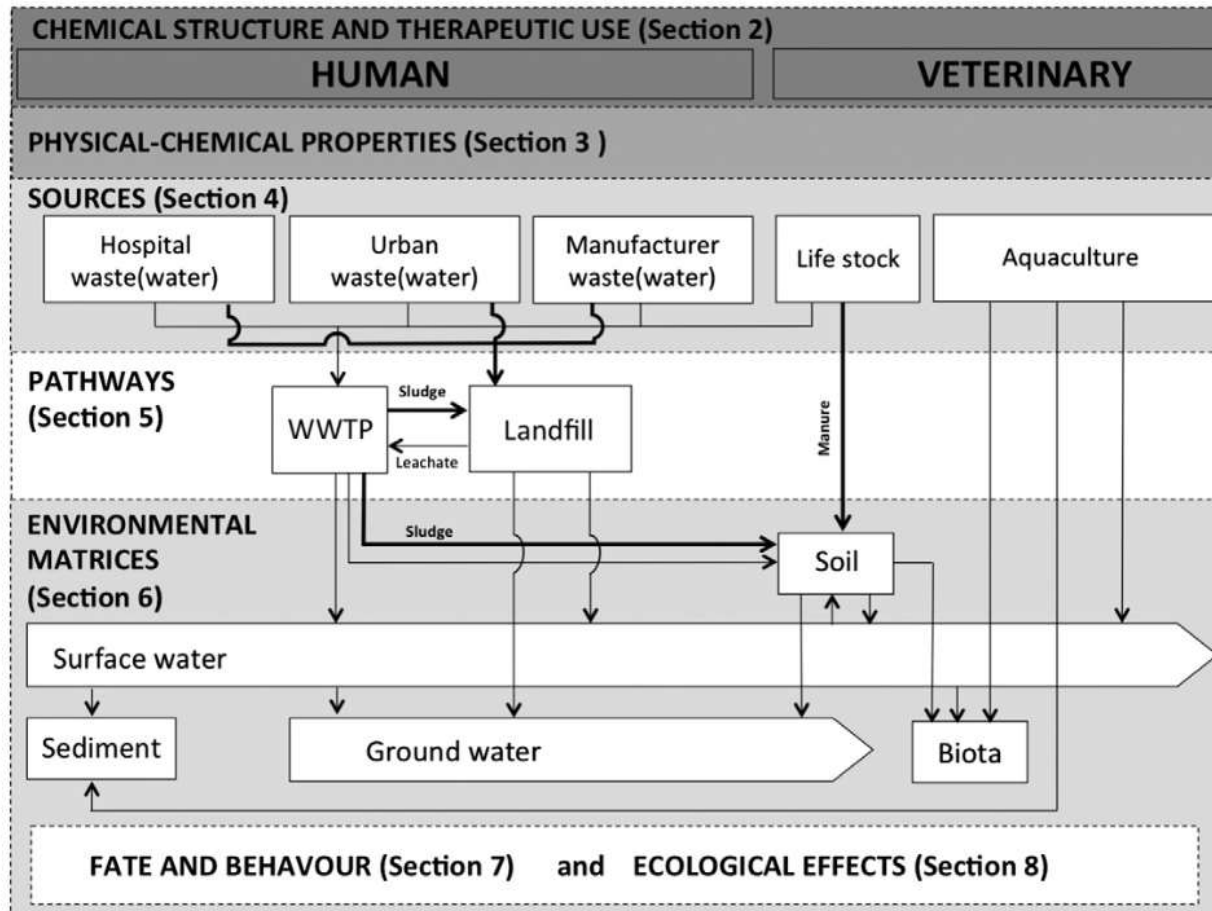
PROCEEDINGS
OF
THE ROYAL
SOCIETY **B**

Review

The role of natural environments in the evolution of resistance traits in pathogenic bacteria

Jose L. Martinez^{*}

Departamento de Biotecnología Microbiana, Centro Nacional de Biotecnología,
Consejo Superior de Investigaciones Científicas, Darwin 3, Cantoblanco, 28049 Madrid, Spain

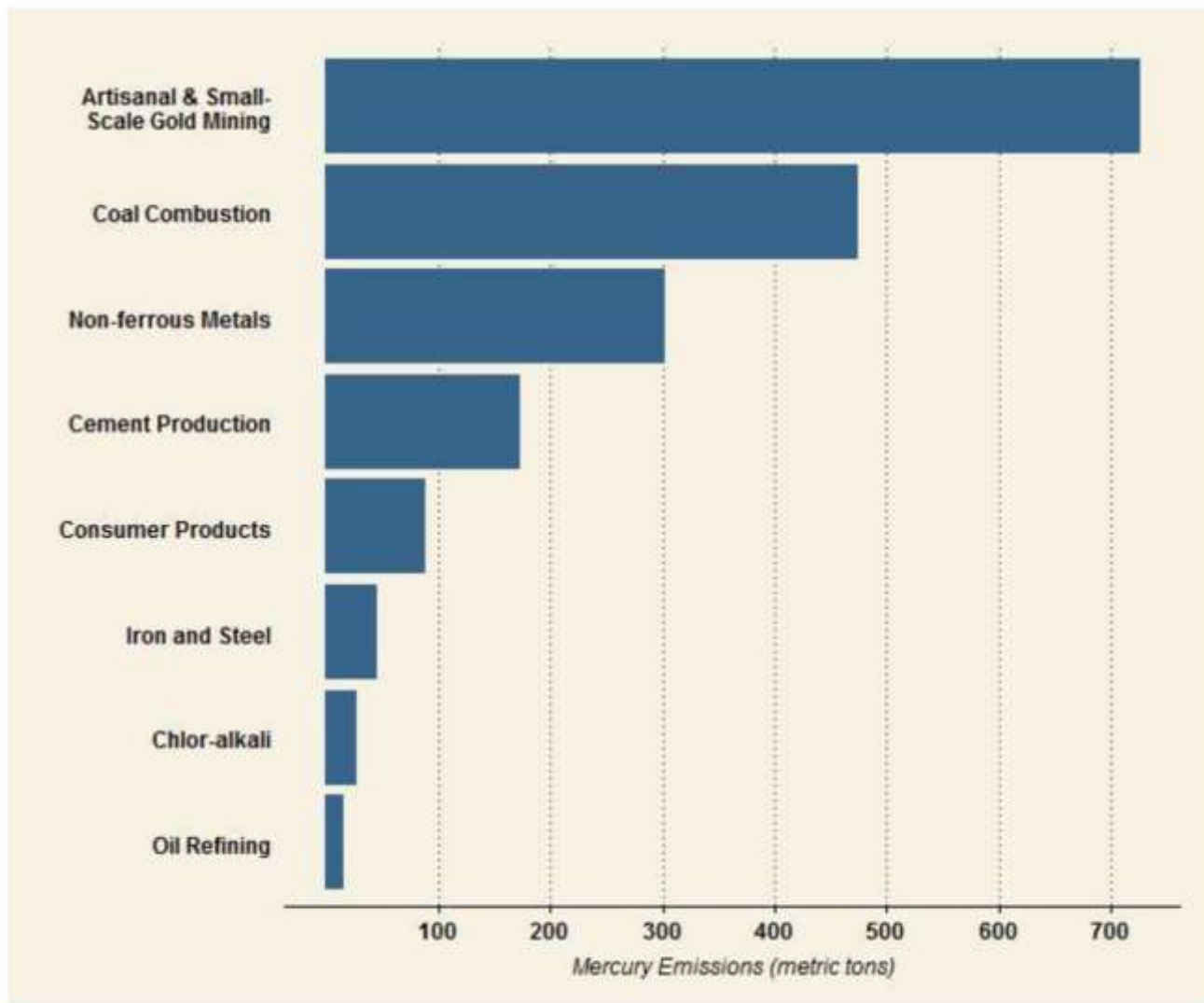


-> e.g. FQ concentration can be as high as 240 ug/L in HWW and 5.7 ug/L in surface water

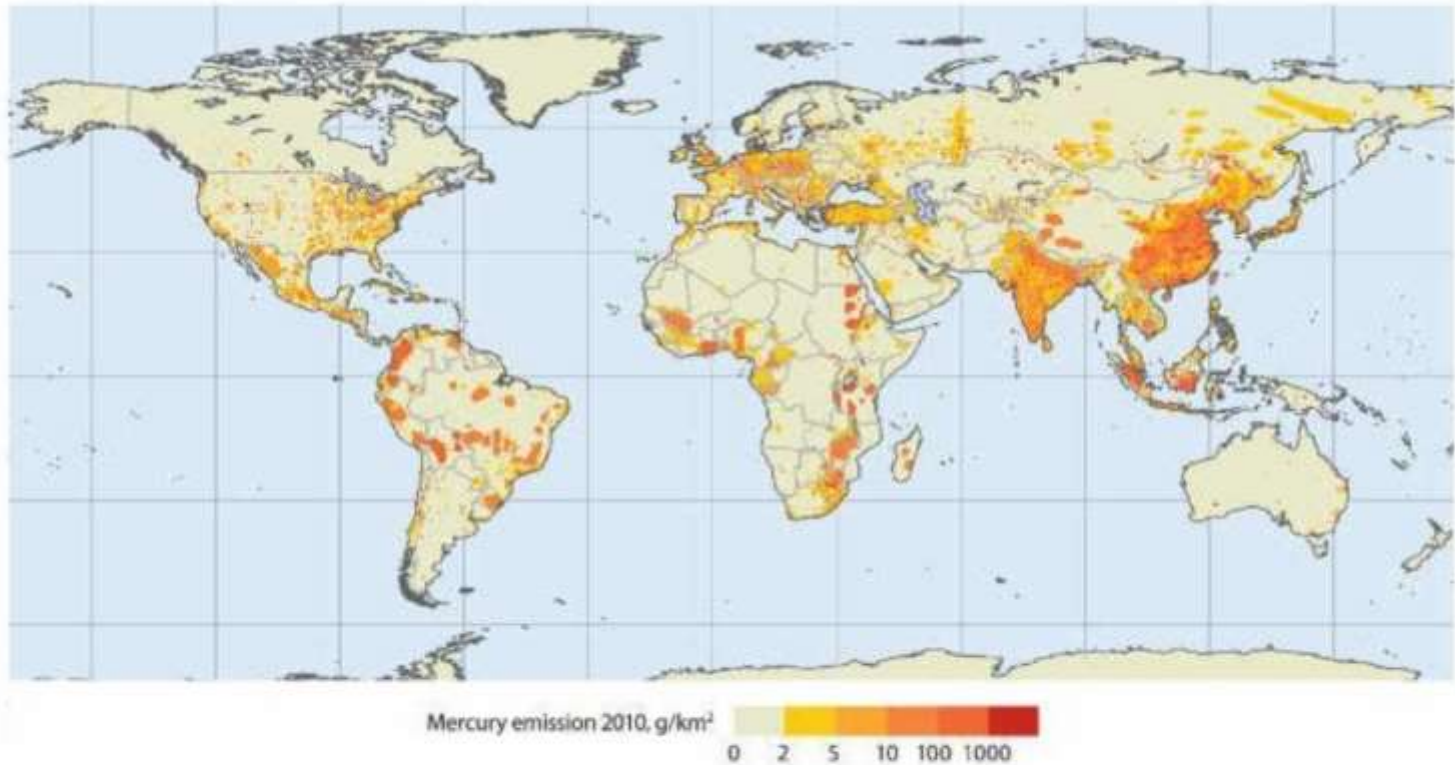
-> Favour AB entry AND accumulation into biota: vegetables, crops, aquatic plants, and animals

A trivial scenario

- ACME acquisition (USA300) and slight increased expression of virulence factors may have contributed to the success via enhanced inter-human transmission
- The most striking event is the acquisition of resistance genes
 - > biological cost of antibiotic resistance genes is totally reversed in the presence of trace amount of antibiotics
 - > Inappropriate antibiotic use / antibiotic in the environment may have driven the expansion
- A novel link between effective population size and a selective advantage conferred by antibiotic resistance



Mercury emissions from the eight highest emitting industry sectors. Data for 2010 from the 2013 UNEP Global Mercury Assessment. Total estimated global anthropogenic mercury emissions are 1960 metric tons.



Global distribution of anthropogenic mercury emissions to air in 2010.

Source: [United Nations Environment Programme \(UNEP\), Global Mercury Assessment, 2013](#)

EXIT