

ULB

HOPITAL ERASME

# Resistance: an update on Belgian and European data

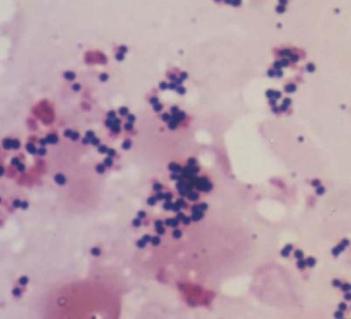
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***Staphylococcus aureus* from basic science to clinical applications**

Friday 5 October 2012

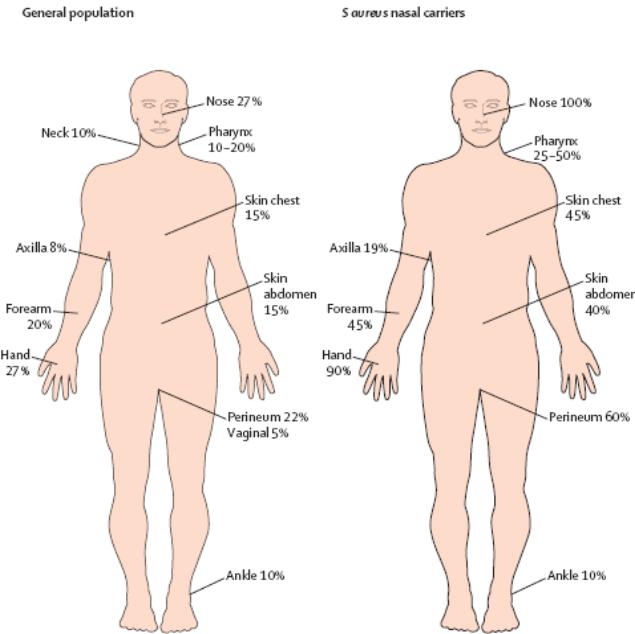
Université Catholique de Louvain



# *Staphylococcus aureus*



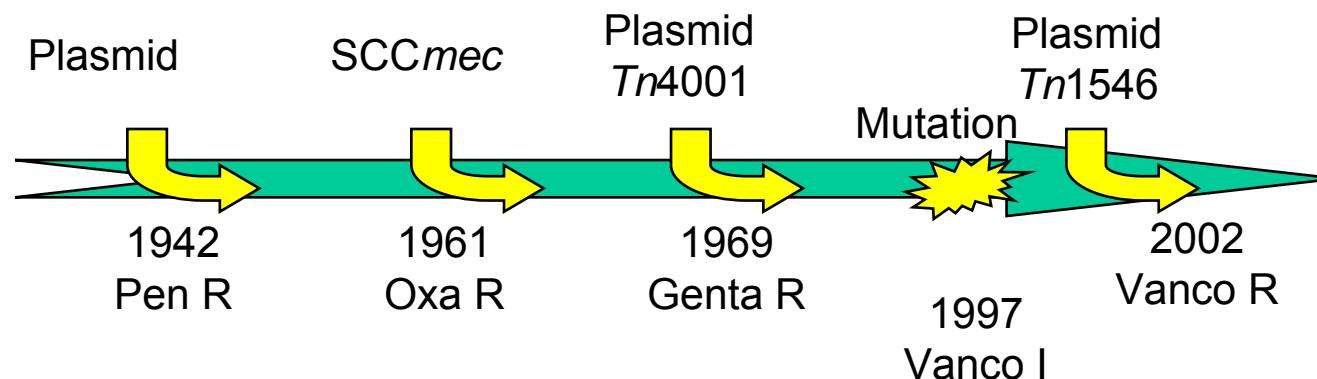
- Gram-positive cocci in clusters
  - 1<sup>st</sup> description in 1882 by Sir Alexander Ogston
- Natural part of flora of skin and mucosa
  - Animals including mammals and birds
  - Humans :
    - Non-carriers, persistent and transient carriers
    - Nose, tonsils, skin, perineum





# *Staphylococcus aureus*

- Major opportunistic pathogen responsible for infections both in hospitals and in the community
- Clinical manifestations
  - Pyogenic infections : Skin and soft tissue infections to endocarditis
  - Toxin mediated diseases : SSSS, SFP, TSS
- Master of creating/picking up resistance determinants



# Methicillin-resistant *S. aureus* (MRSA)

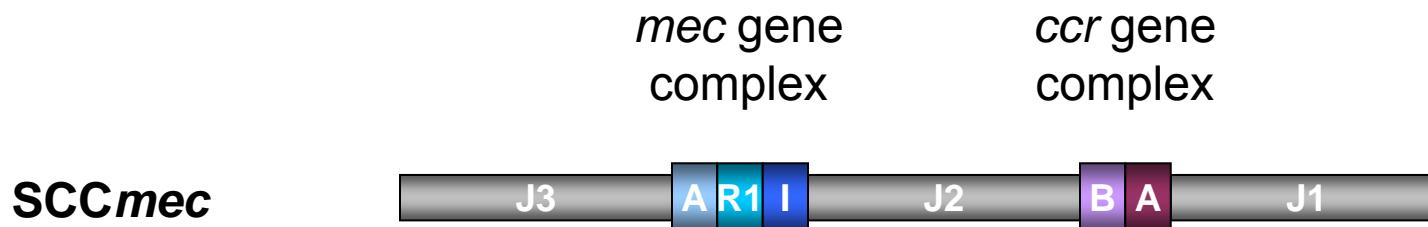
- Acquisition of *mecA* (or homologue) gene encoding PBP2a
  - PBP2a shows low affinity to β-lactams
  - Cross-resistance to all β-lactams, except for the novel anti-MRSA cephalosporins
  - Three different types described: *mecA*, *mecB*, *mecC*
    - A *mec* gene type encompasses *mec* genes sharing ≥70% nucleotide sequence identity with their respective prototype.
    - Found in *Staphylococci* and *Marcococcus*

Strain	Reported gene name	Proposed new name	Size (bp)	% identity with the <i>mecA</i> gene in <i>S. aureus</i> N315
<i>S. aureus</i> N315 <sup>a</sup>	<i>mecA</i>	<i>mecA</i>	2,007	100
Staphylococcal strains that carry <i>mecA</i>	<i>mecA</i>	<i>mecA</i>	2,007	98.3–100
<i>S. sciuri</i> K11 <sup>a</sup>	<i>mecA</i> ( <i>mecA1</i> )	<i>mecA1</i>	2,001	79.1
<i>S. sciuri</i> ATCC 700061	<i>mecAs</i>	<i>mecA1</i>	2,001	80.2
<i>S. vitulinus</i> CSBO8 <sup>a</sup>	<i>mecA</i>	<i>mecA2</i>	2,007	91
<i>M. caseolyticus</i> JCSC5402 <sup>a</sup>	<i>mecAm</i>	<i>mecB</i>	2,025	61.6
<i>S. aureus</i> LGA251 <sup>a</sup>	<i>mecA</i> <sub>LGA251</sub>	<i>mecC</i>	1,998	68.7

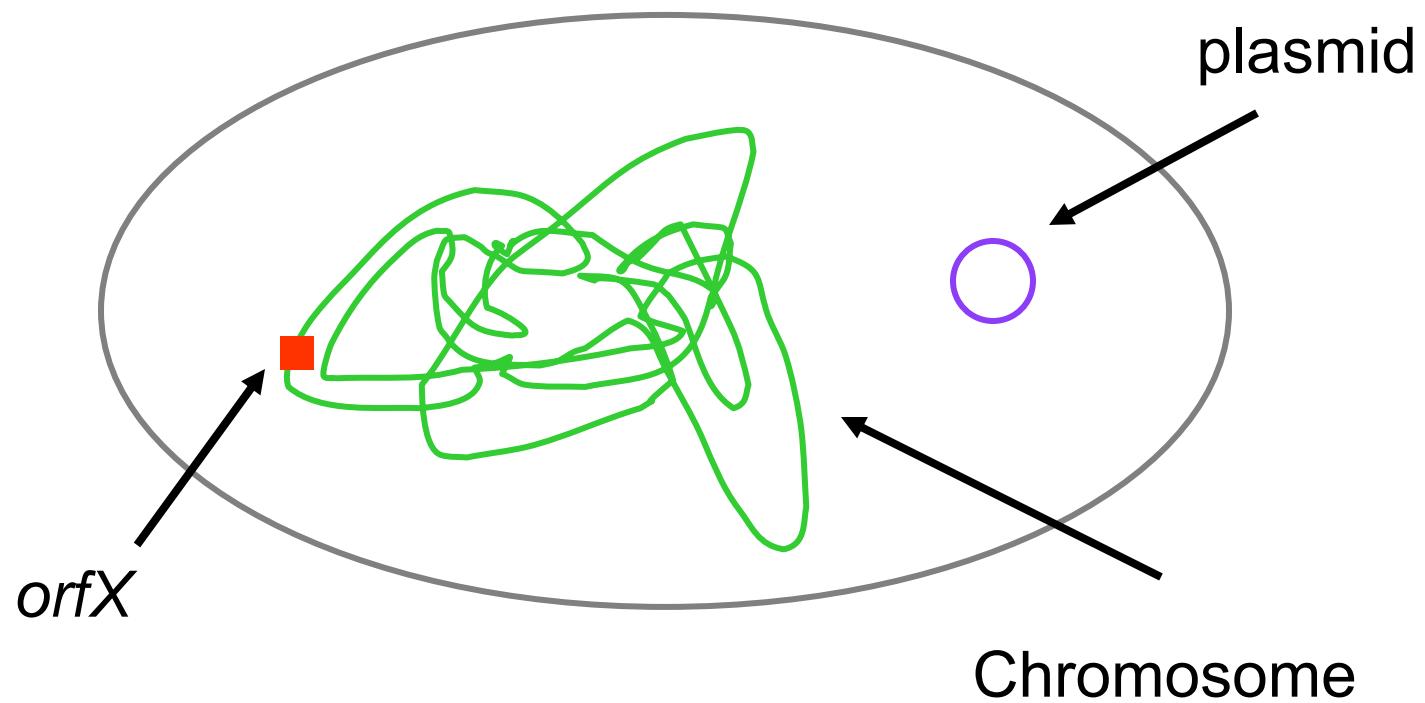
<sup>a</sup> Prototype strains representing each *mec* gene: *S. aureus* N315 for *mecA*, *S. sciuri* K11 for *mecA1*, *S. vitulinus* CSBO8 for *mecA2*, *M. caseolyticus* JCSC5402 for *mecB*, and *S. aureus* LGA251 for *mecC*.

# *Staphylococcal cassette chromosome mec*

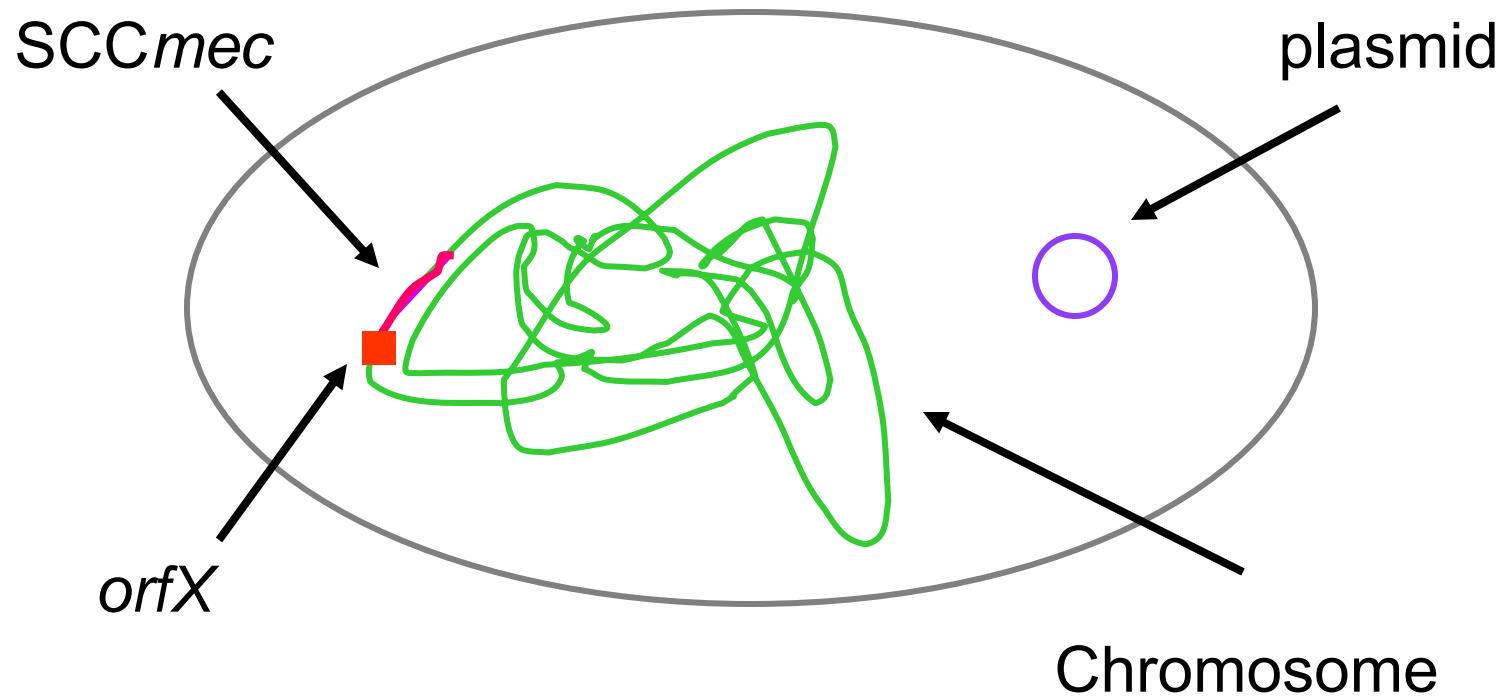
- The *mec* gene is integrated into mobile genetic element
  - Staphylococcal cassette chromosome *mec* (SCC*mec*)
  - Chromosomal insertion at the  $\text{attB}_{\text{SCC}}$  at the end of *orfX*
  - Often contain plasmids or transposons carrying resistance genes
- Subdivided into types I to XI
  - *mec* gene complex (*mecA* (homologue) gene → PBP2a)
  - *ccr* gene complex : Responsible for the movement (excision and integration) from and into the bacterial chromosome



# MSSA genome



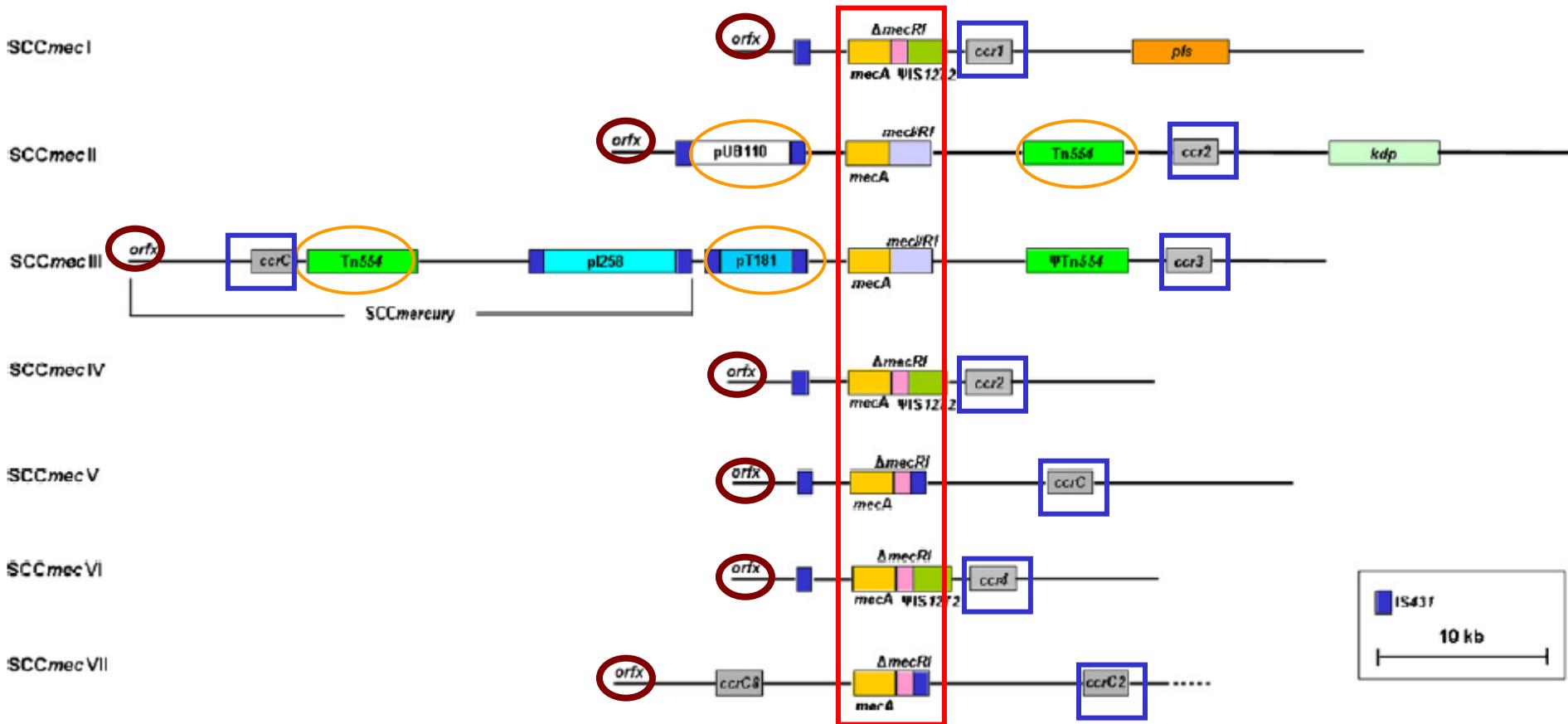
# MRSA genome



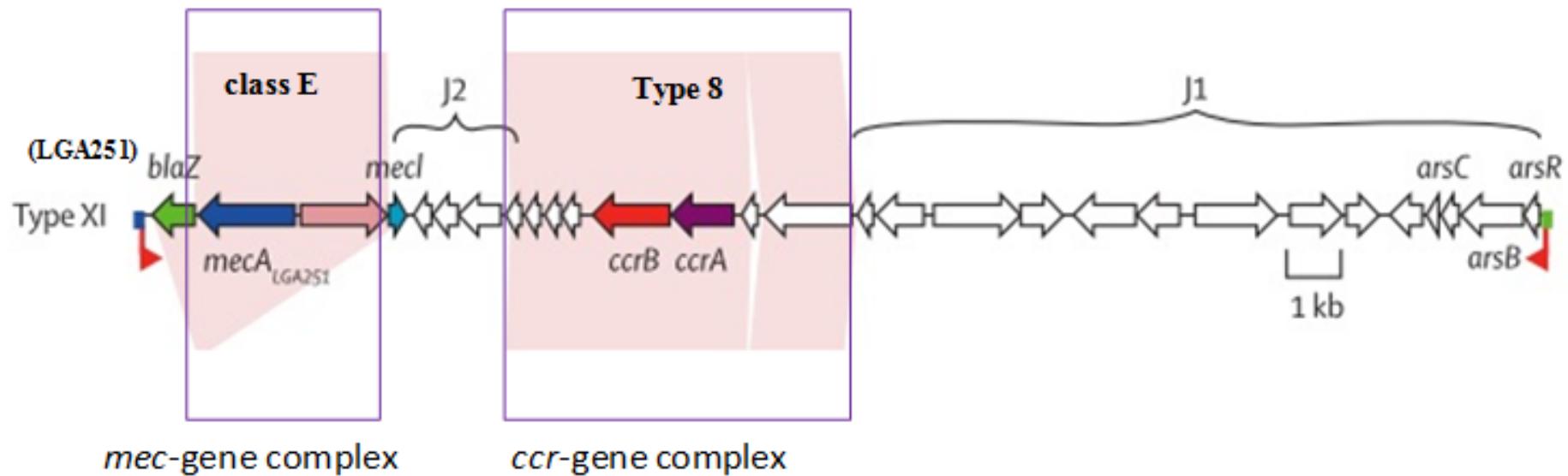
# The SCCmec elements identified in *S. aureus*

SCCmec-type	ccr-gene complex	mec-gene complex	Representative strain	Size of SCCmec
I (1B)	1	B	NCTC10442	34.4kb
II (2A)	2	A	N315	52kb
III (3A)	3	A	85/2082	66.9kb
IV (2B)	2	B	CA05	24.2kb
			8/6-3P	20.9kb
IV (2B&5)	2 & 5	B	ZH47	33.7kb
V (5C2)	5	C2	WIS	27.6kb
V (5C2&5)	5 & 5	C2	PM1*	41.8kb
			JCSC6944 <sup>a</sup>	43.4kb
VI (4B)	4	B	HDE288*	23.3kb
VII (5C1)	5	C1	JCSC6082	26.7kb
VIII (4A)	4	A	C10682	32.2kb
IX (1C2)	1	C2	JCSC6943 <sup>a</sup>	43.7kb
X (7C1)	7	C1	JCSC6945 <sup>a</sup>	50.8kb
XI (8E)	8	E	LGA251 <sup>a</sup>	29.4kb

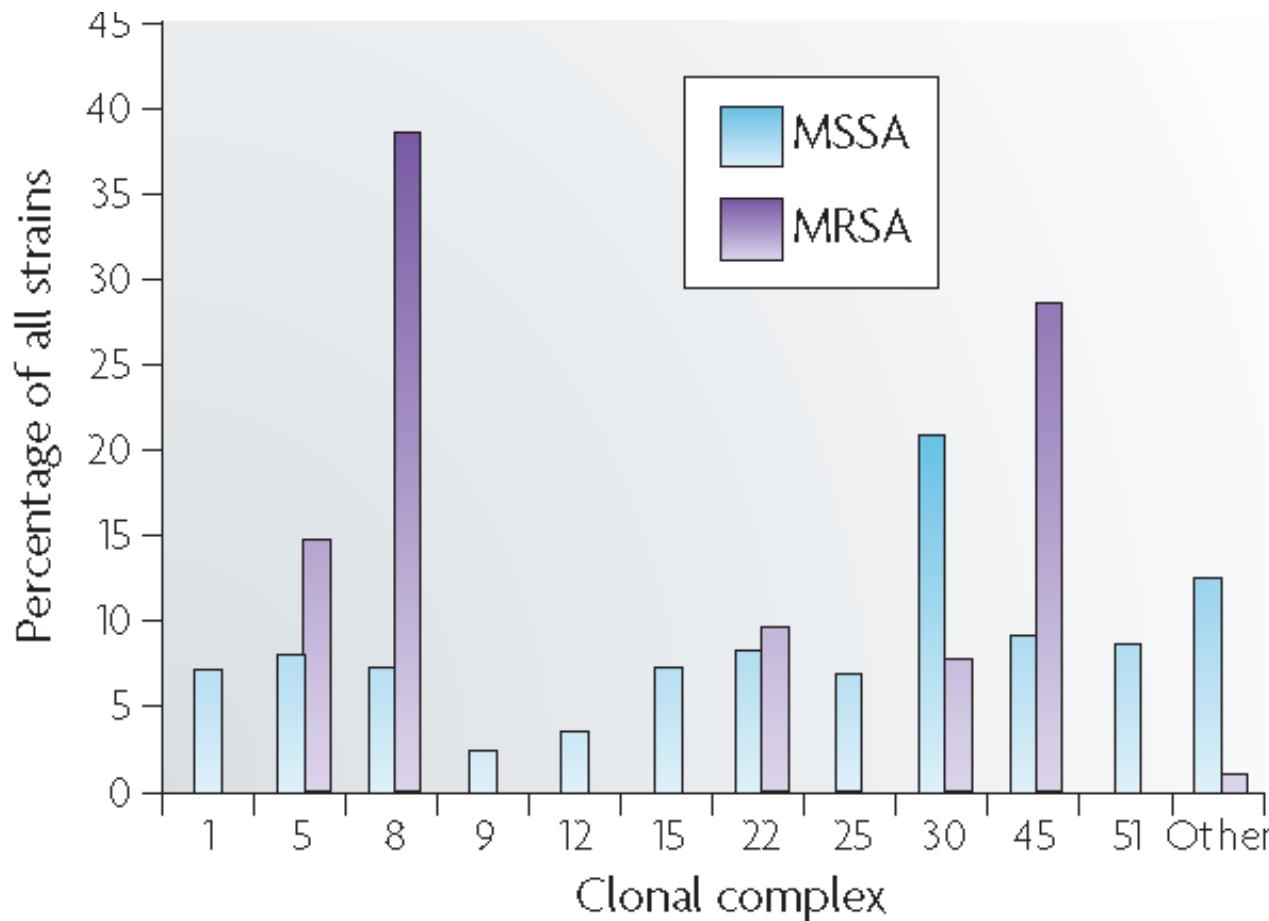
# SCCmec types I to VII



# Structural representation of *SCCmec* element type XI



# The distribution of MSSA and MRSA among the various clonal complexes



- Acquisition of *SCCmec* is a very rare event
- Evidence that the *SCCmec* elements are distributed within certain lineages at higher frequency

# Epidemic waves of Hospital-associated MRSA

## First HA-MRSA "wave" (1960- mid 1970s)

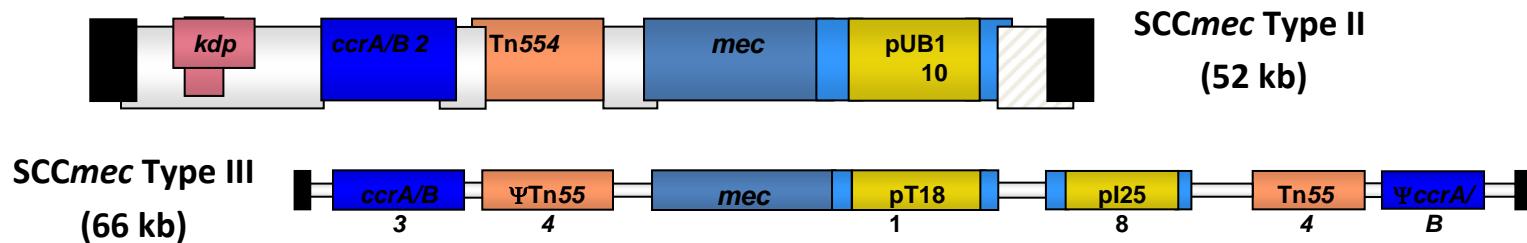
- Almost monoclonal belonging to CC8
  - Archaic clone ST250-SCCmec I
  - Especially in Europe (Denmark, France, Switzerland, UK) and USA
  - By the 1980s, archaic clone disappeared and was replaced by descendants or new emerging clones
  - Descendants of archaic clone : Iberian clone



# Epidemic waves of Hospital-associated MRSA

## Second HA-MRSA "wave" (mid-1970s – 1980s)

- Acquisition of the *mecA* gene both in new cassettes and in new MSSA strains (rare event)
  - Initially belonging to CC5, CC8 and CC30
  - SCC*mec* II + III
- Clones : New-York/Japan, Brazilian/Hungarian, UK-EMRSA 16

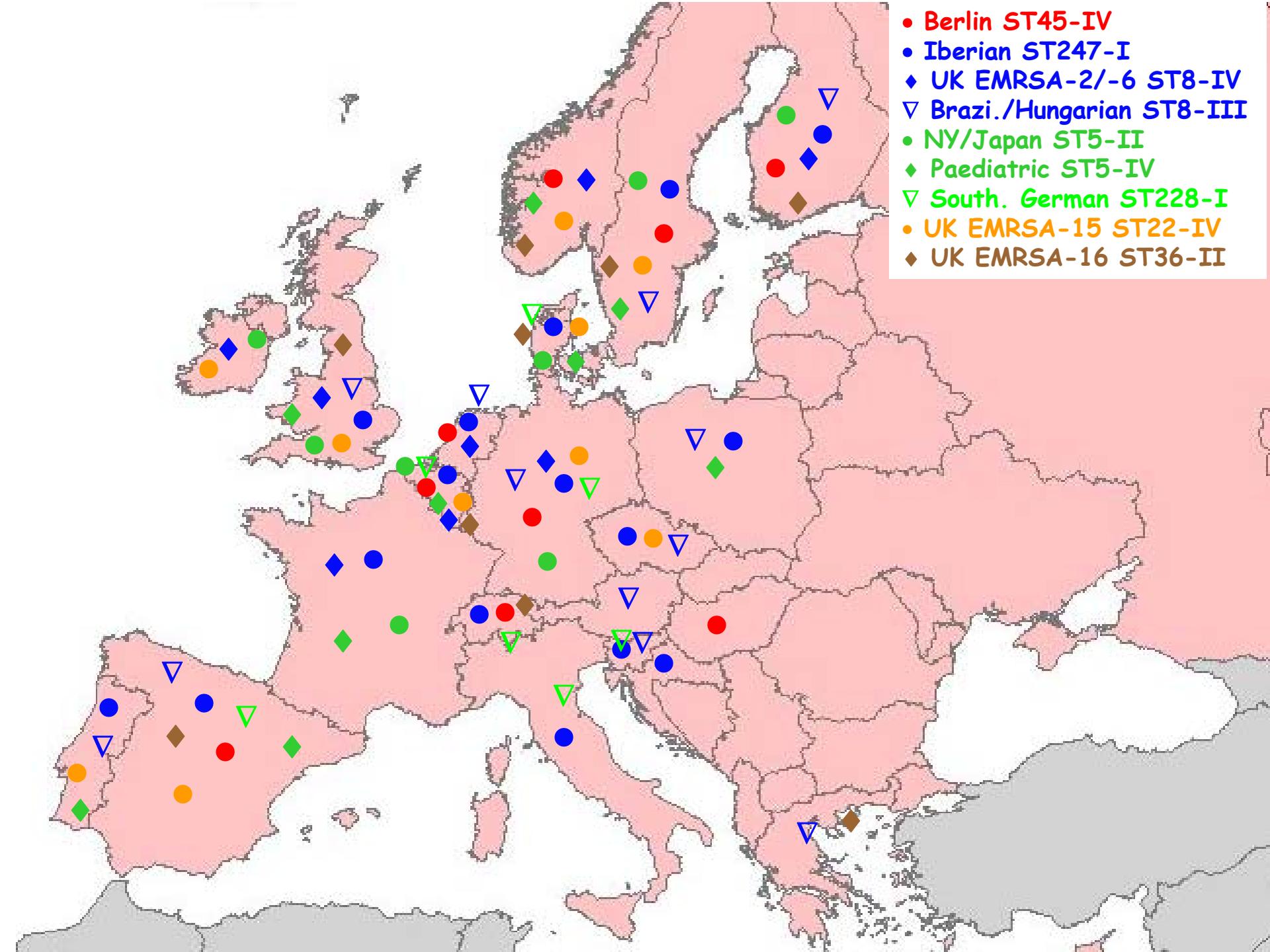


# Epidemic waves of Hospital-associated MRSA

## Third HA-MRSA "wave" (late 1980s-)

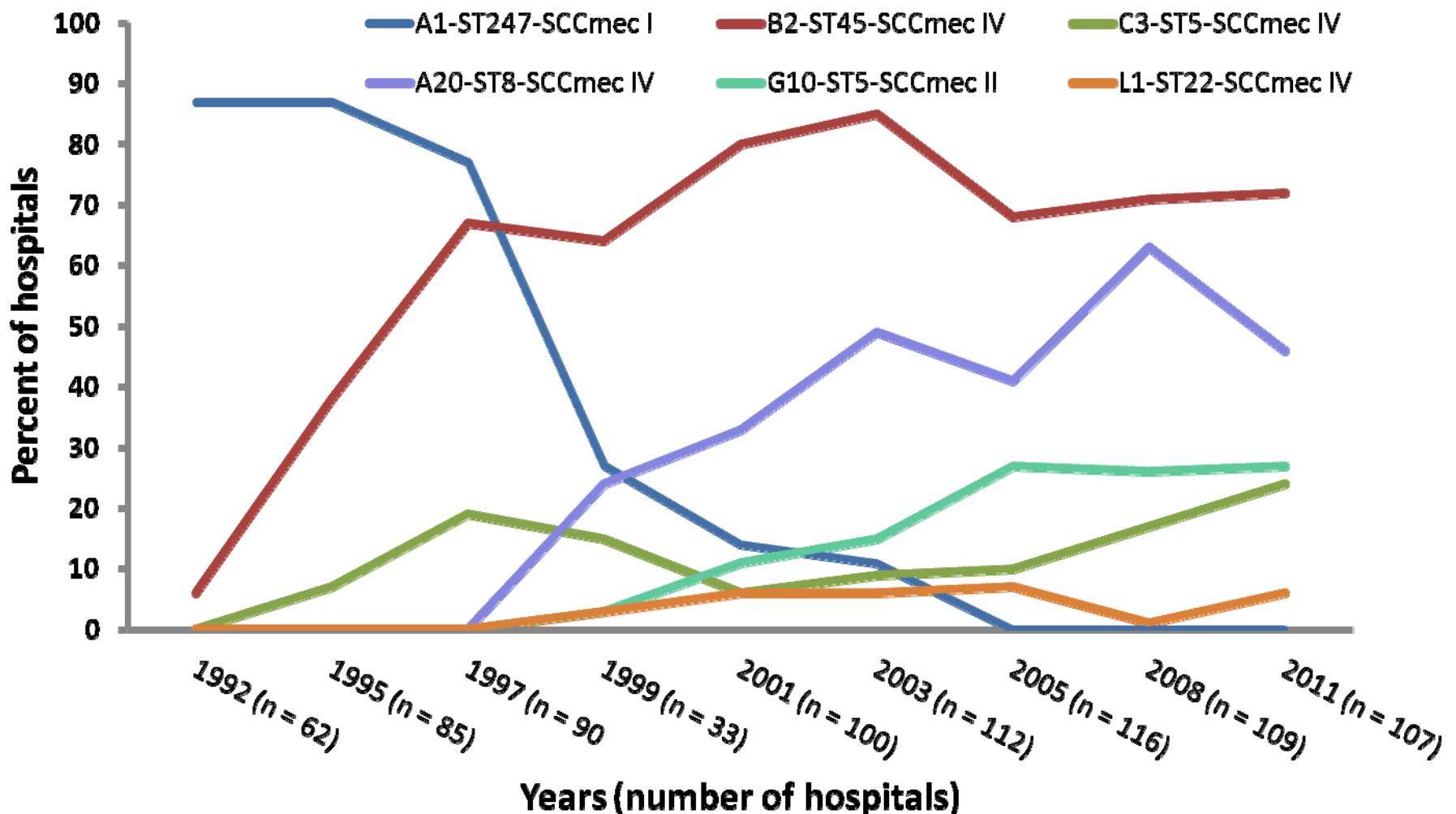
- Acquisition of the new smaller *SCCmec* IV
  - New HA-MRSA clones (i.e. CC 22, CC 45)
  - Transfer of *SCCmec* IV to CC 5 and CC8
  - Accounts for more than 90% of HA-MRSA in the world
- Clones : UK-EMRSA 15, Berlin, Pediatric, Lyon



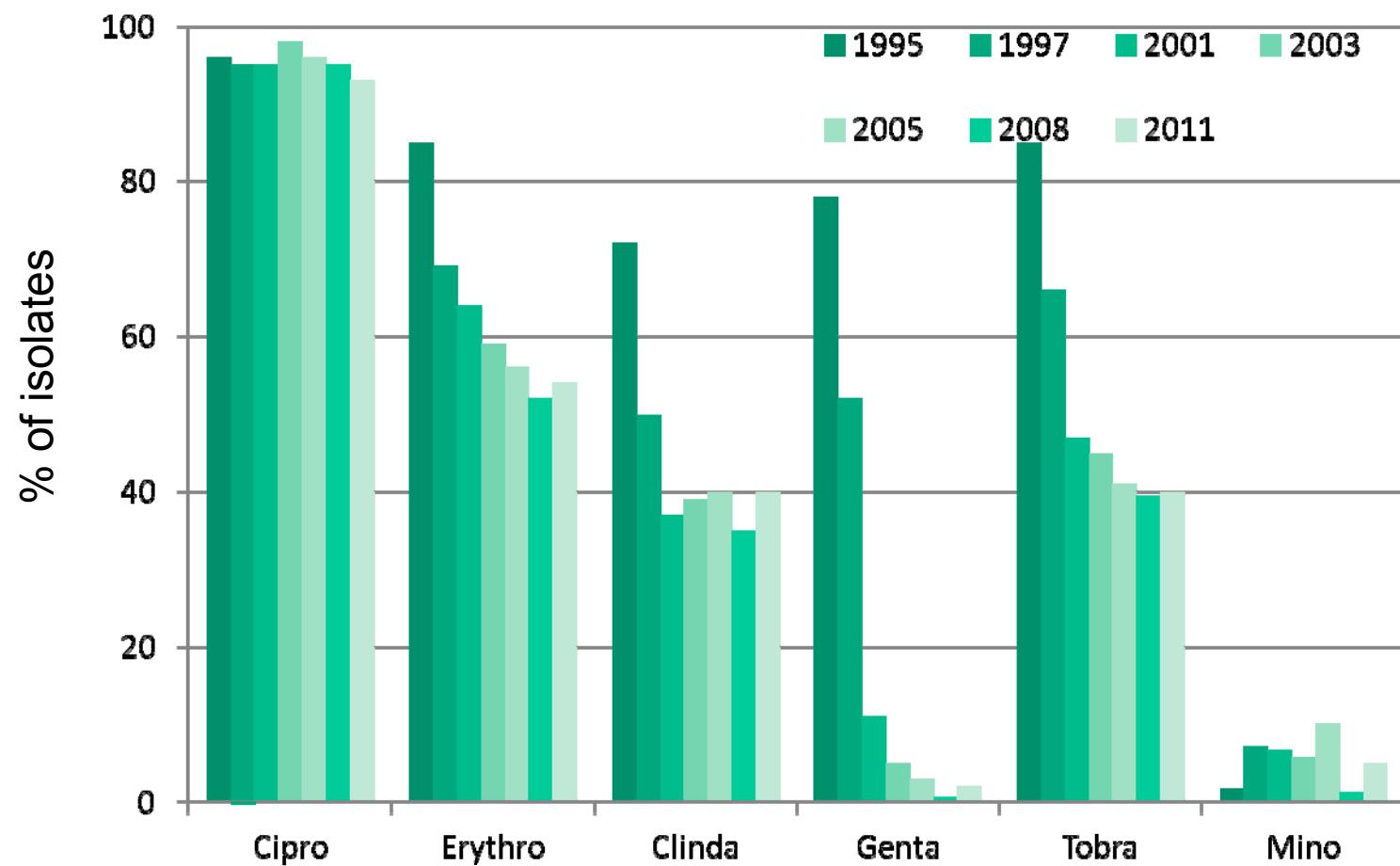


# Secular trends of MRSA clonal distribution

## National Surveillance, hospitals, Belgium 1992-2011



# Proportion of HA-MRSA strains resistant to selected antimicrobials, Belgium, 1995-2011



MGEs including toxin genes and resistance determinants are closely linked to certain clonal lineages

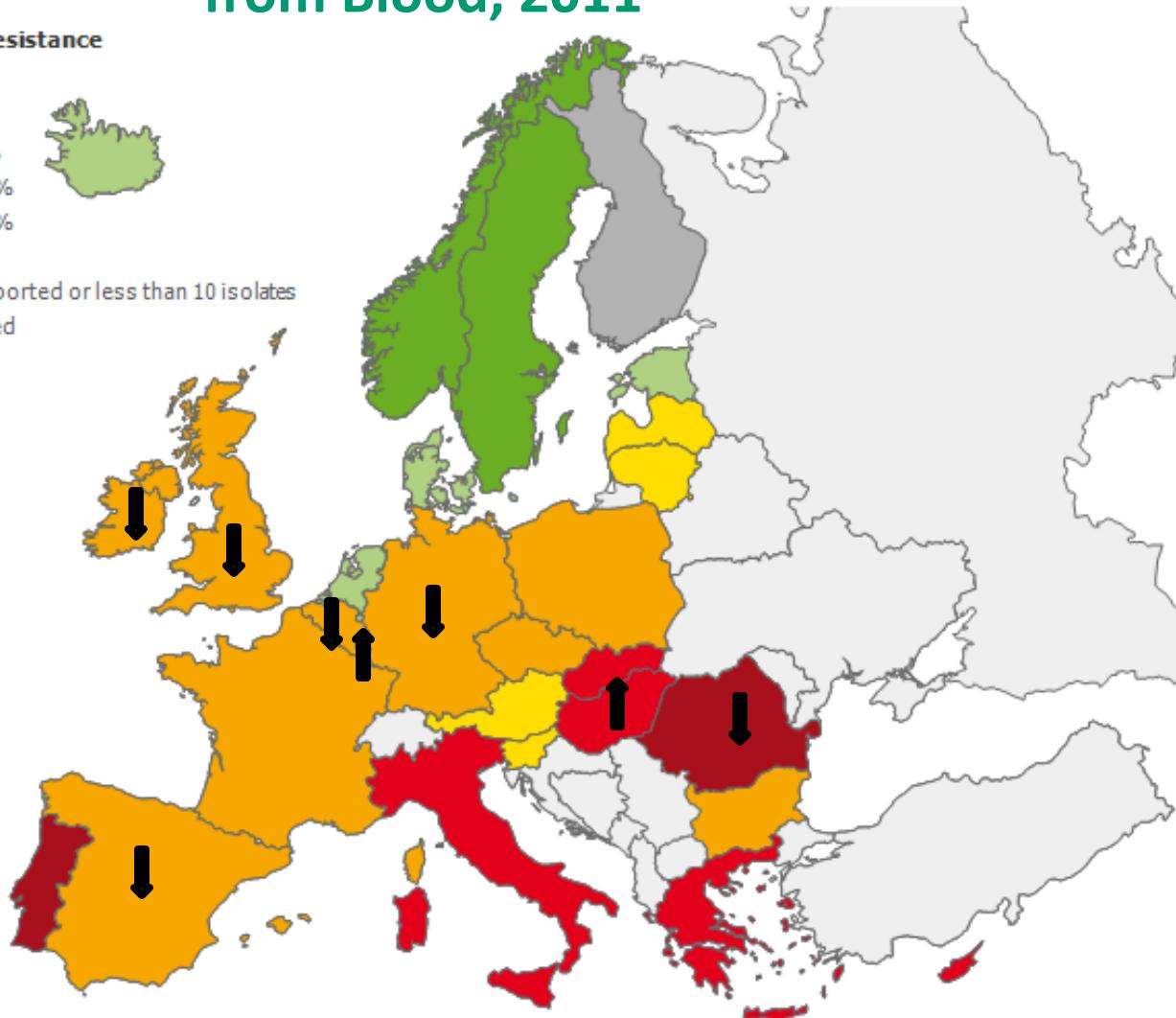
# % Methicillin-Resistant *Staphylococcus aureus* (MRSA) from Blood, 2011

## Percentage resistance

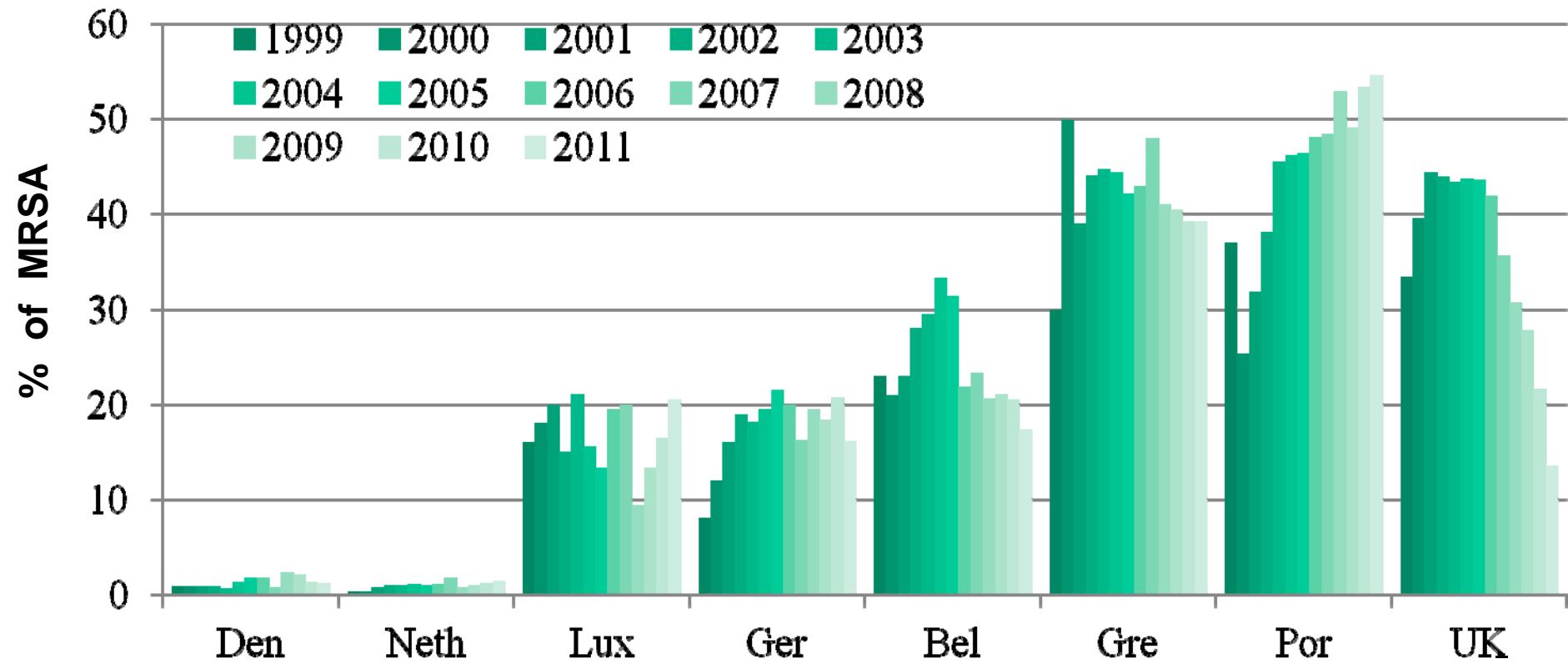
- < 1%
- 1 to < 5%
- 5 to < 10%
- 10 to < 25%
- 25 to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

Country with:

- ↑ Significant increase  
(2008-11)
- ↓ Significant decrease  
(2008-11)



# Trends of MRSA proportion from *S. aureus* bacteremia, EARSS, 1999 to 2011



# Changes in MRSA rate, France, 1993-2007

## Implementation of MRSA control program

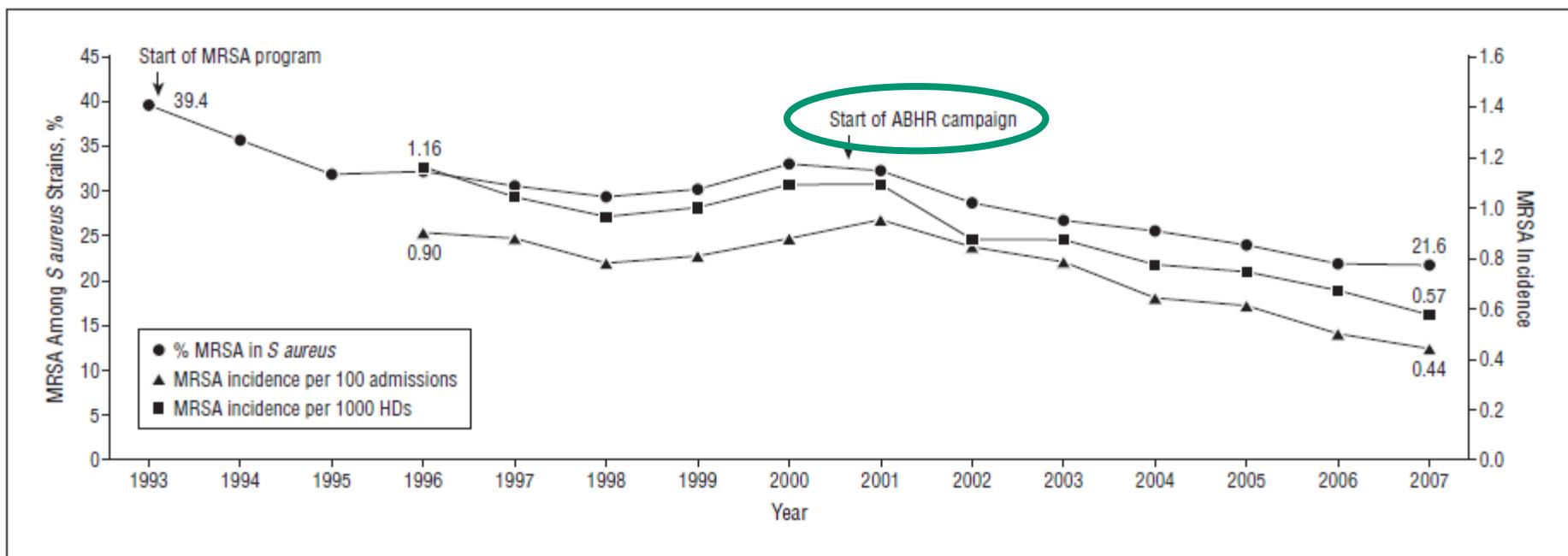
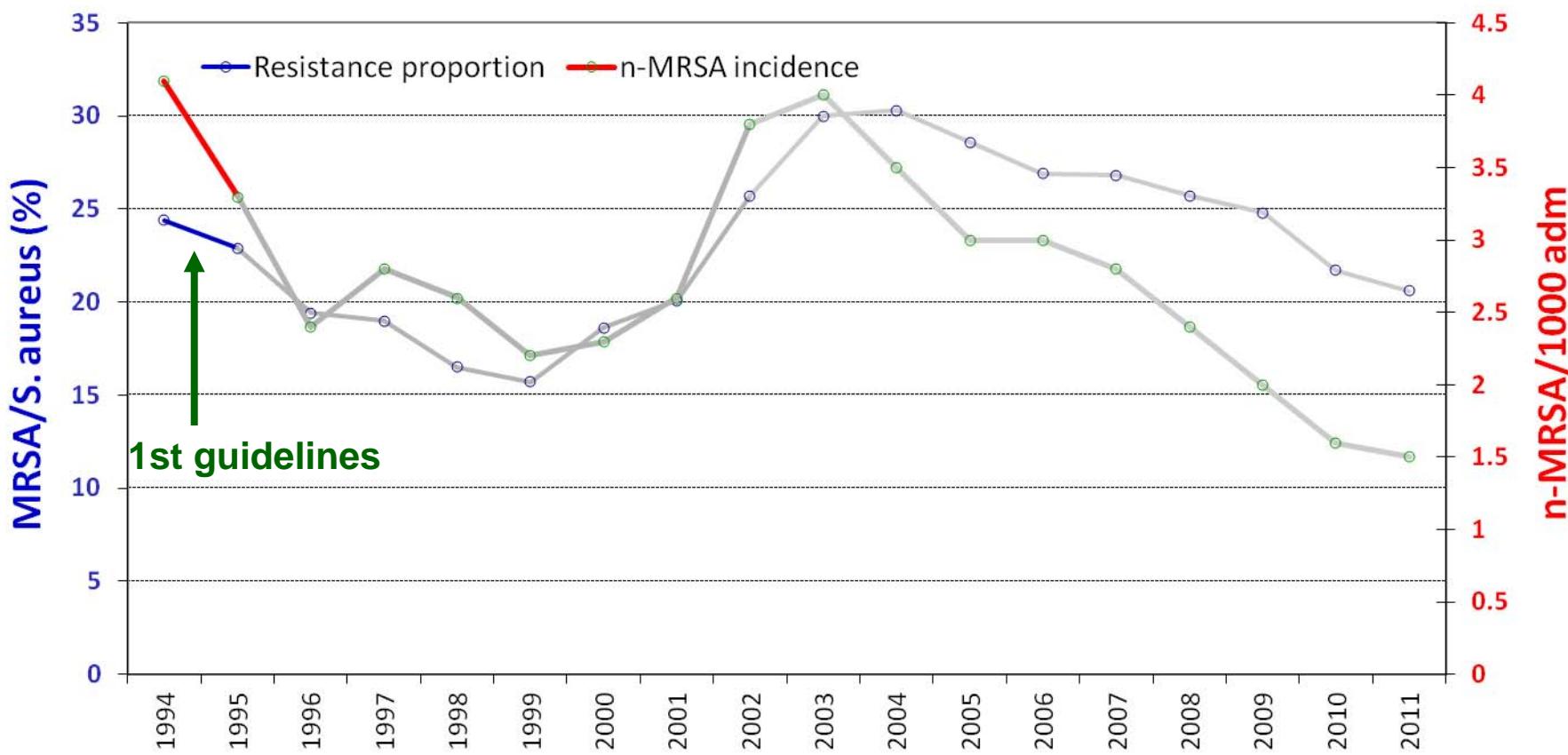


Figure 2. Change in methicillin-resistant *Staphylococcus aureus* (MRSA) rates from 1993 to 2007. Data are given as proportion (percentage) of MRSA in *S. aureus*, MRSA incidence per 1000 hospital days, and MRSA rate per 100 admissions.

Identification of carriers + Isolation interventions  
+ Hand hygiene & Feedback

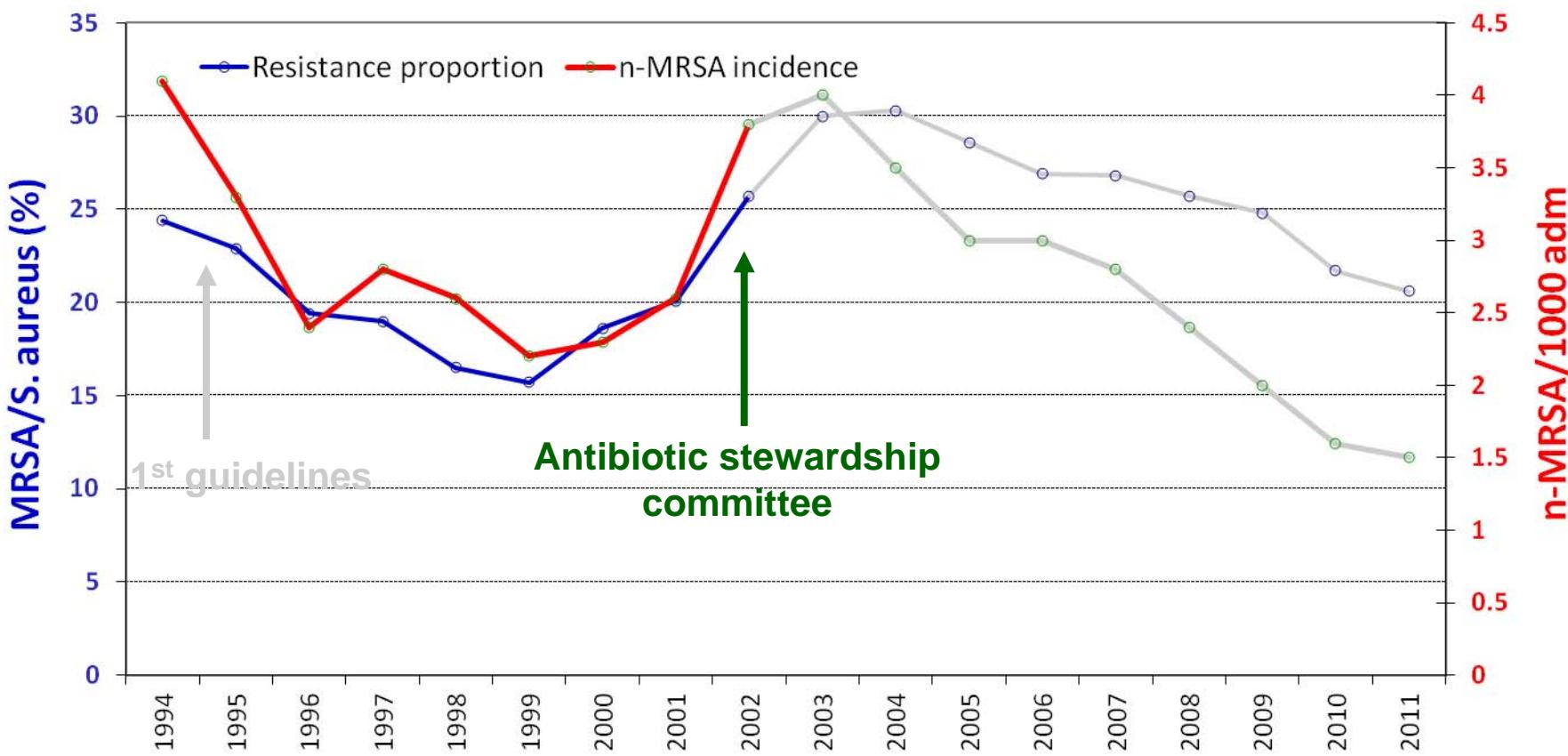
# MRSA in Belgian acute care hospitals

Proportion of *S. aureus* clinical isolates and incidence of nosocomial acquisition, 1994-2011



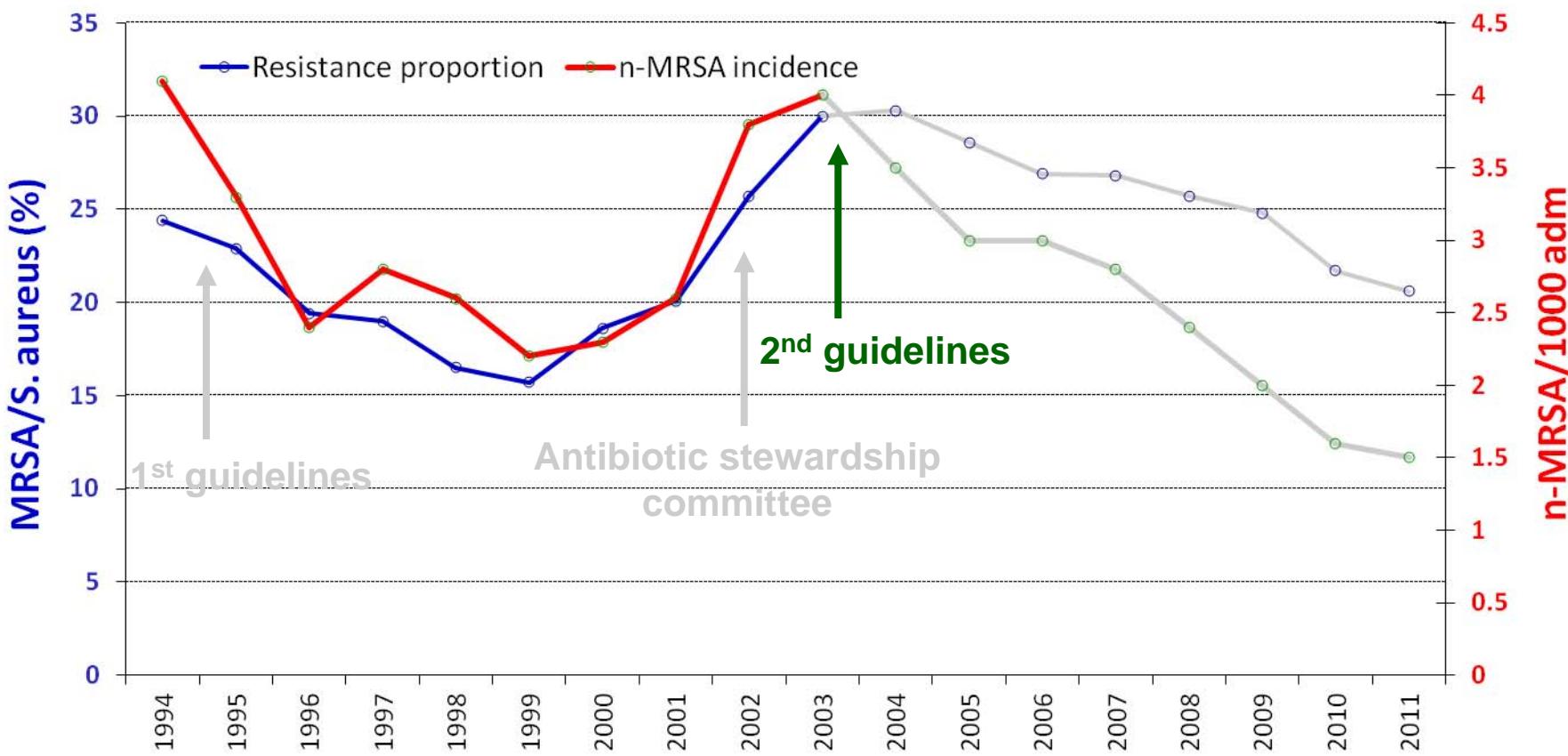
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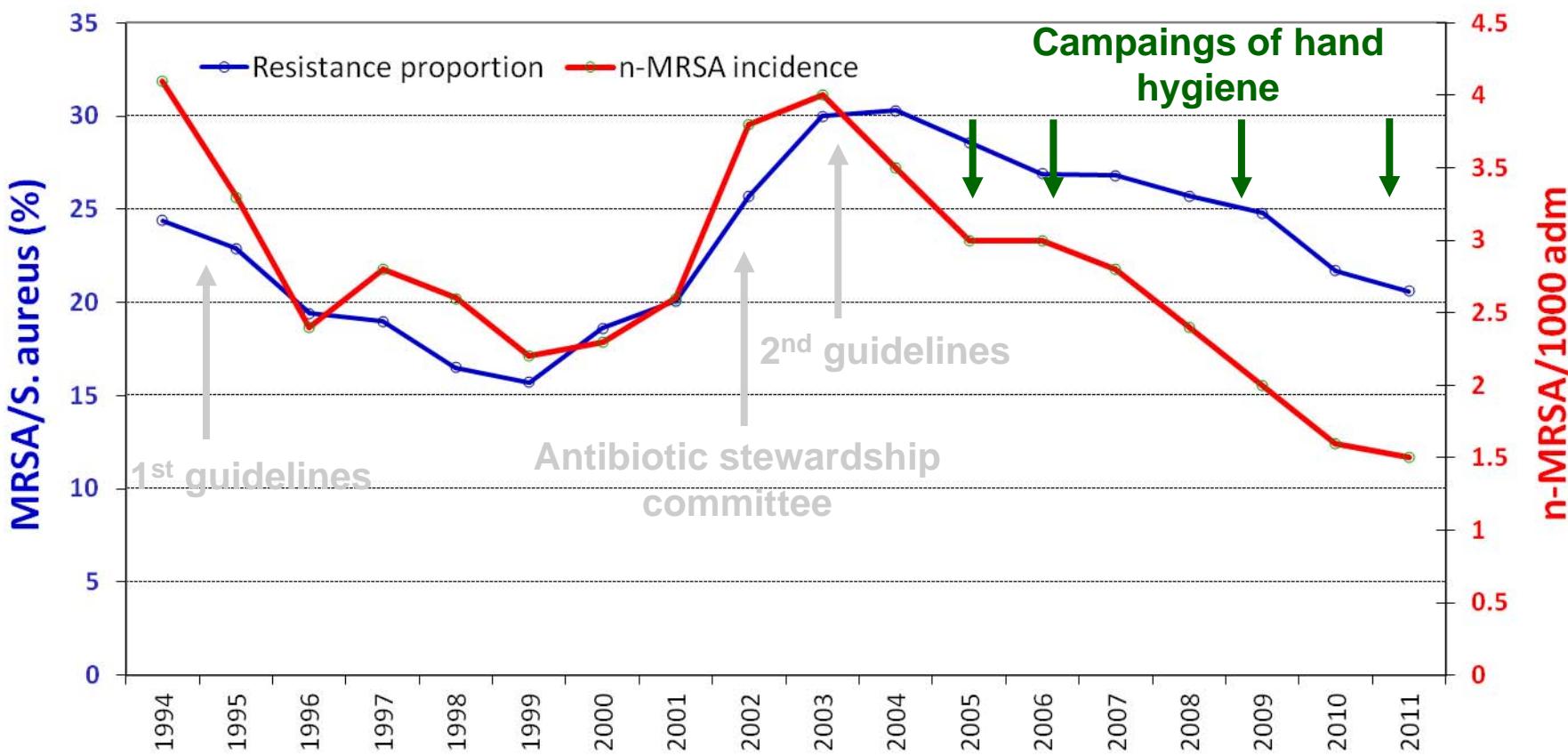
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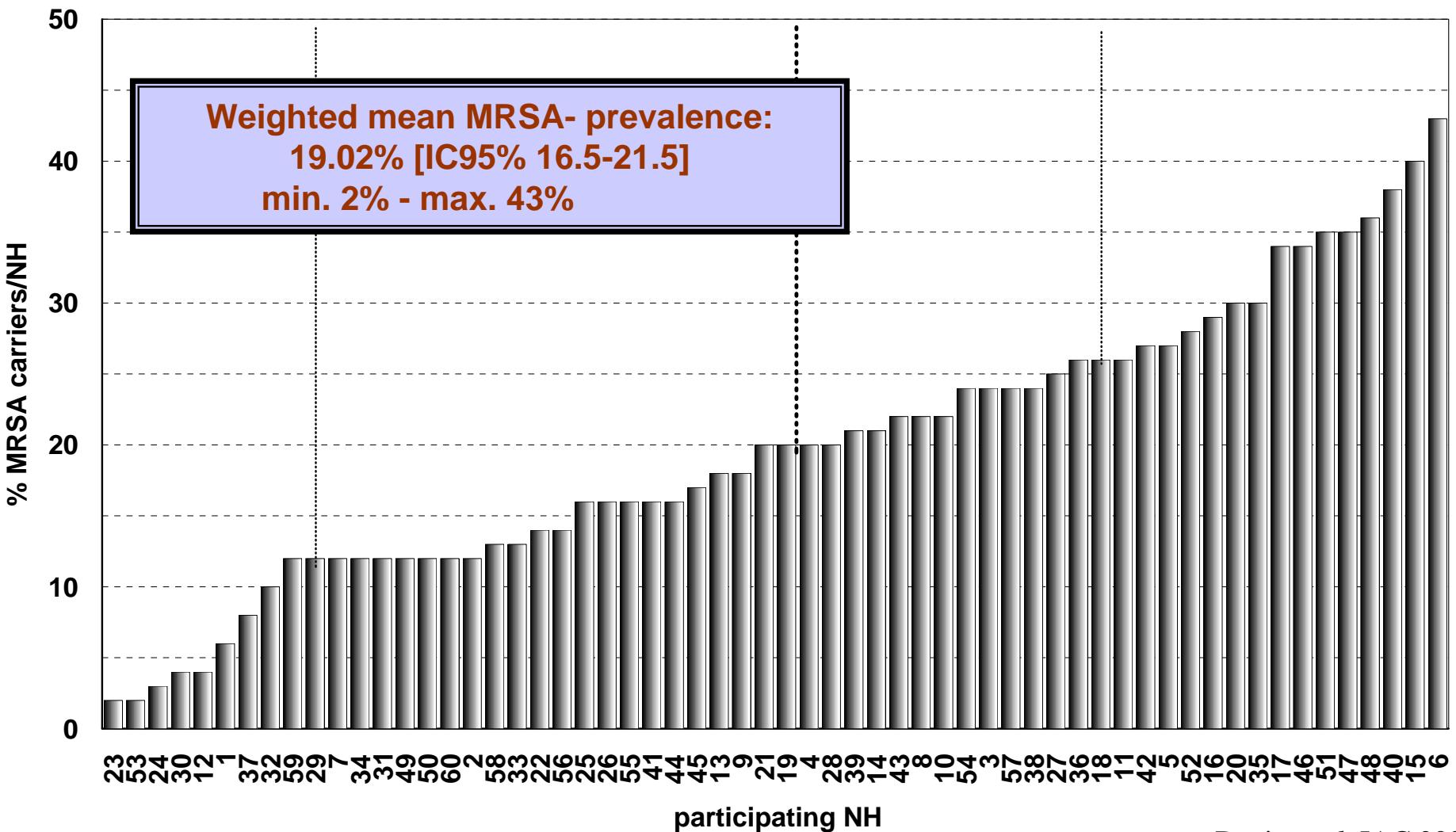


# MRSA in Belgian acute care hospitals

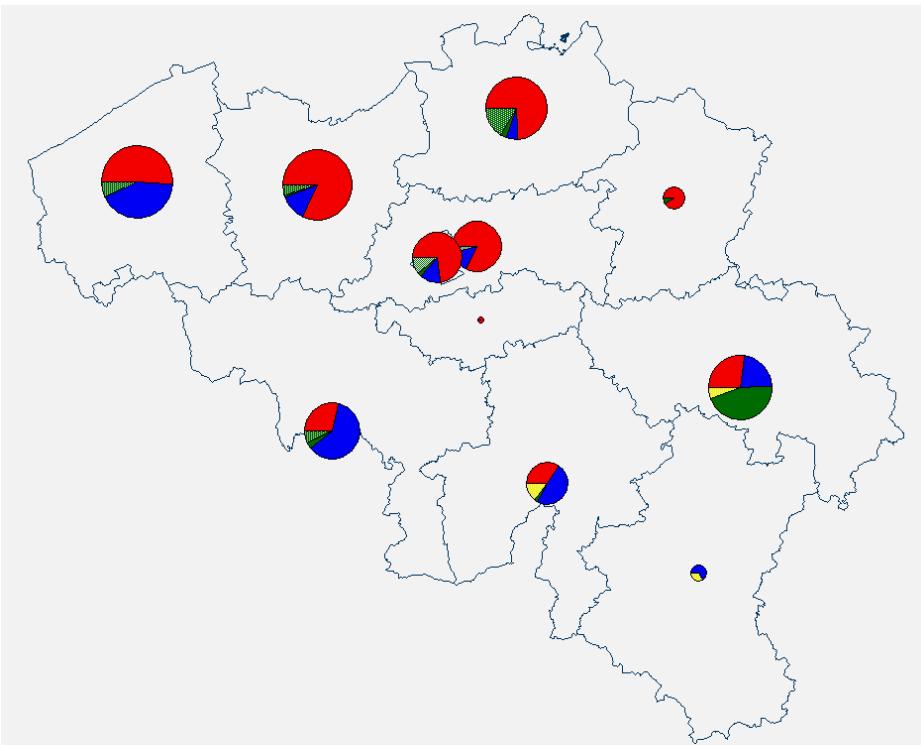
Proportion of *S. aureus* clinical isolates and incidence of nosocomial acquisition, 1994-2011



# Prevalence of MRSA carriage in 2953 residents of 60 NHs. Belgium.

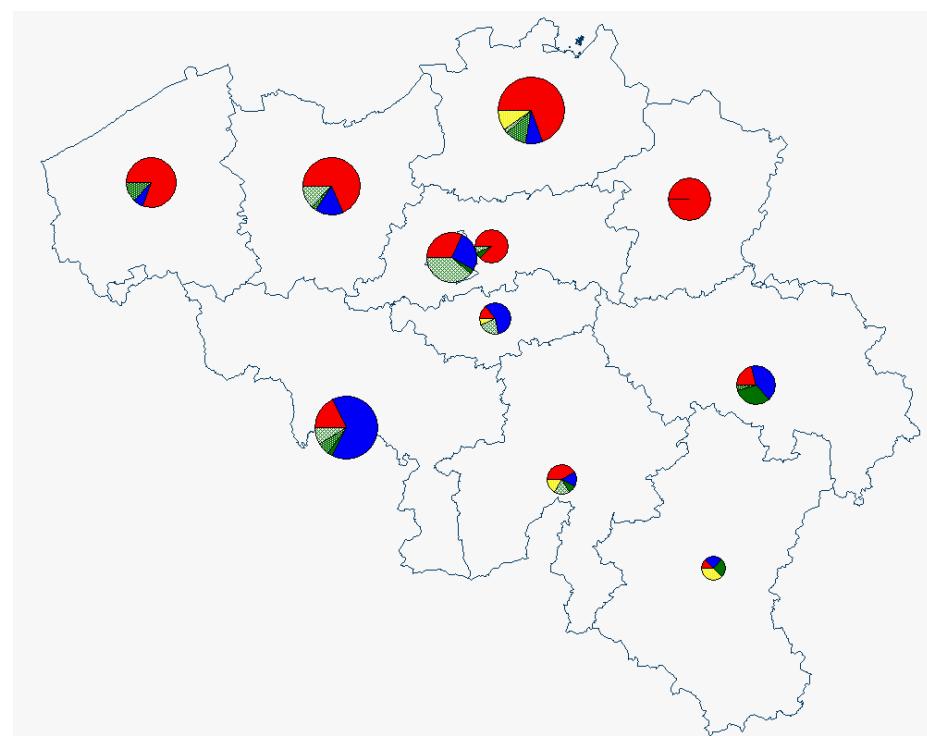


# Distribution of epidemic MRSA by genotype Nursing Homes versus Hospitals, 2005



Nursing Homes  
(n = 587 strains)

- ST45-IV
- ST8- IV
- ST225- II
- ST5-IV
- ST5- II
- ST22-IV



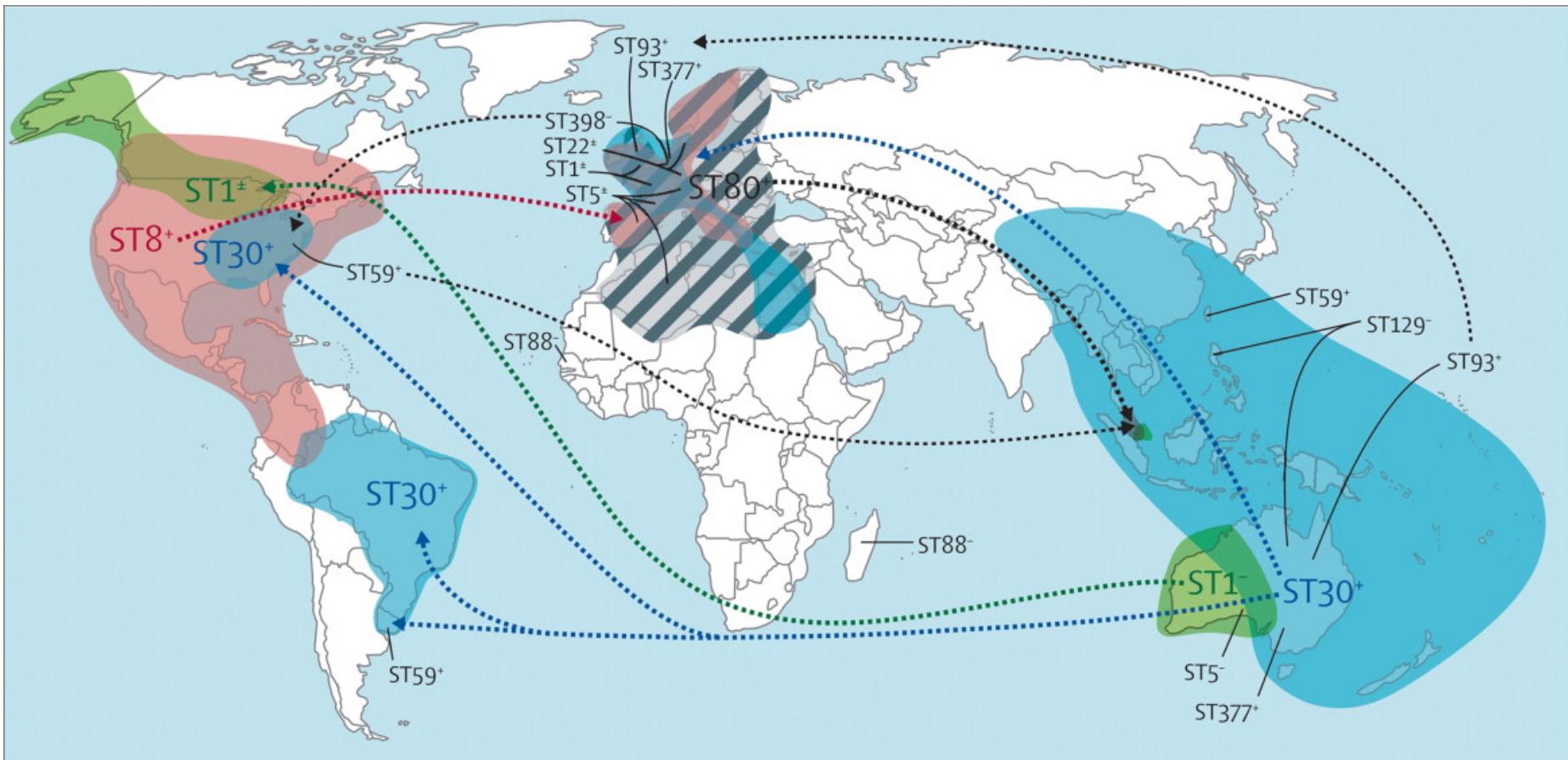
Hospitals  
(n = 326 strains)

# Spread outside the hospital environment

## 1<sup>st</sup> wave : Community-associated MRSA (late 1990s)

- Acquisition of the *SCCmec* IV and other small *SCCmec* into completely different lineages - not just descendants of HA-MRSA strains
  - Solitary reports of CA-MRSA goes back to the 1980s (US, Australia, Europe)
  - *SCCmec* type IV
  - Type V, VII and VIII, NT (i.e. probably several new types / subtypes)
  - Described as being less multi-resistant
    - Highly dependant on clonal background
    - ST59 and ST80 are often multi-resistant
  - Most of the dominant CA-MRSA strains produce the PVL

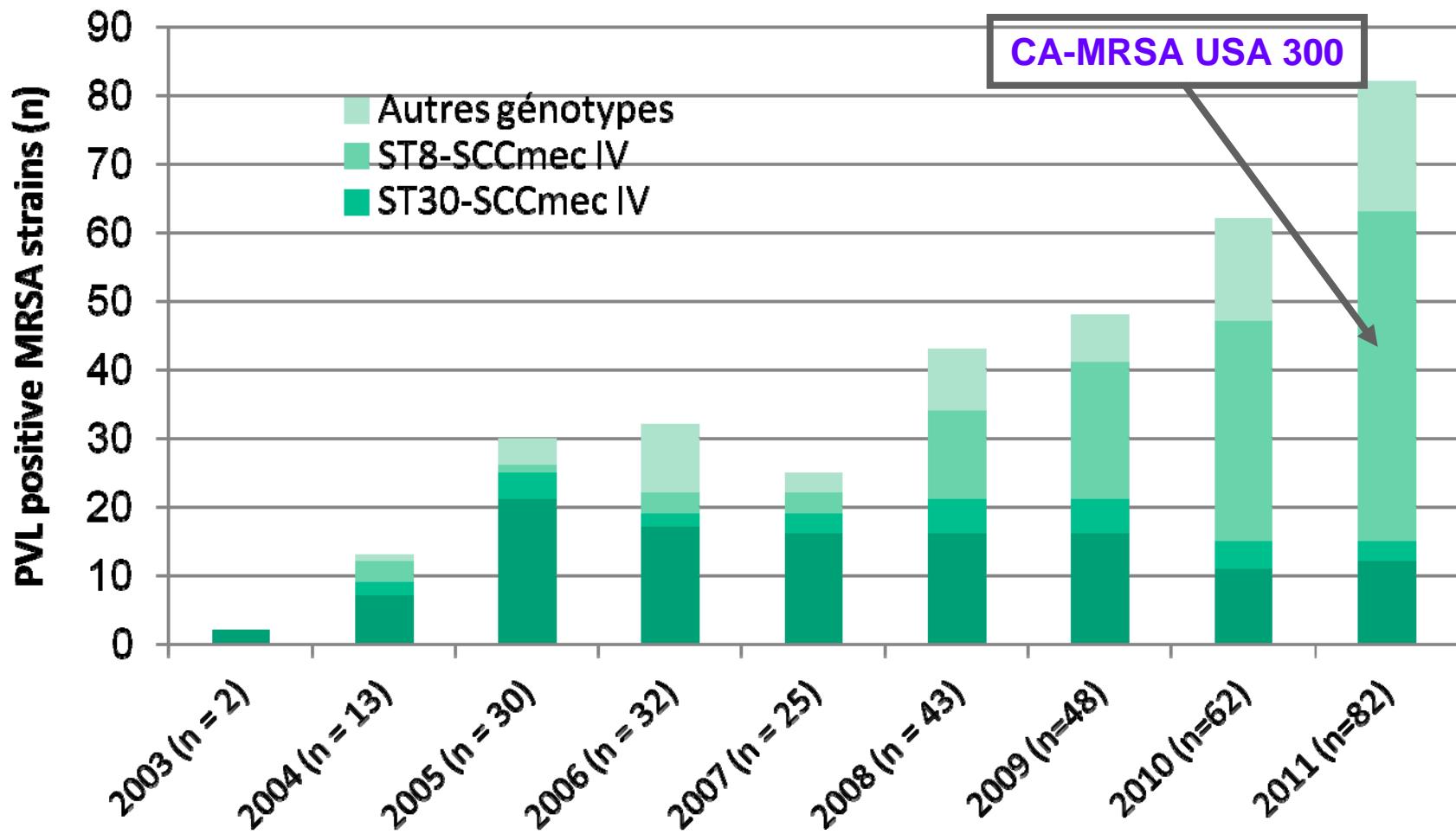
# World distribution of PVL positive CA-MRSA clones



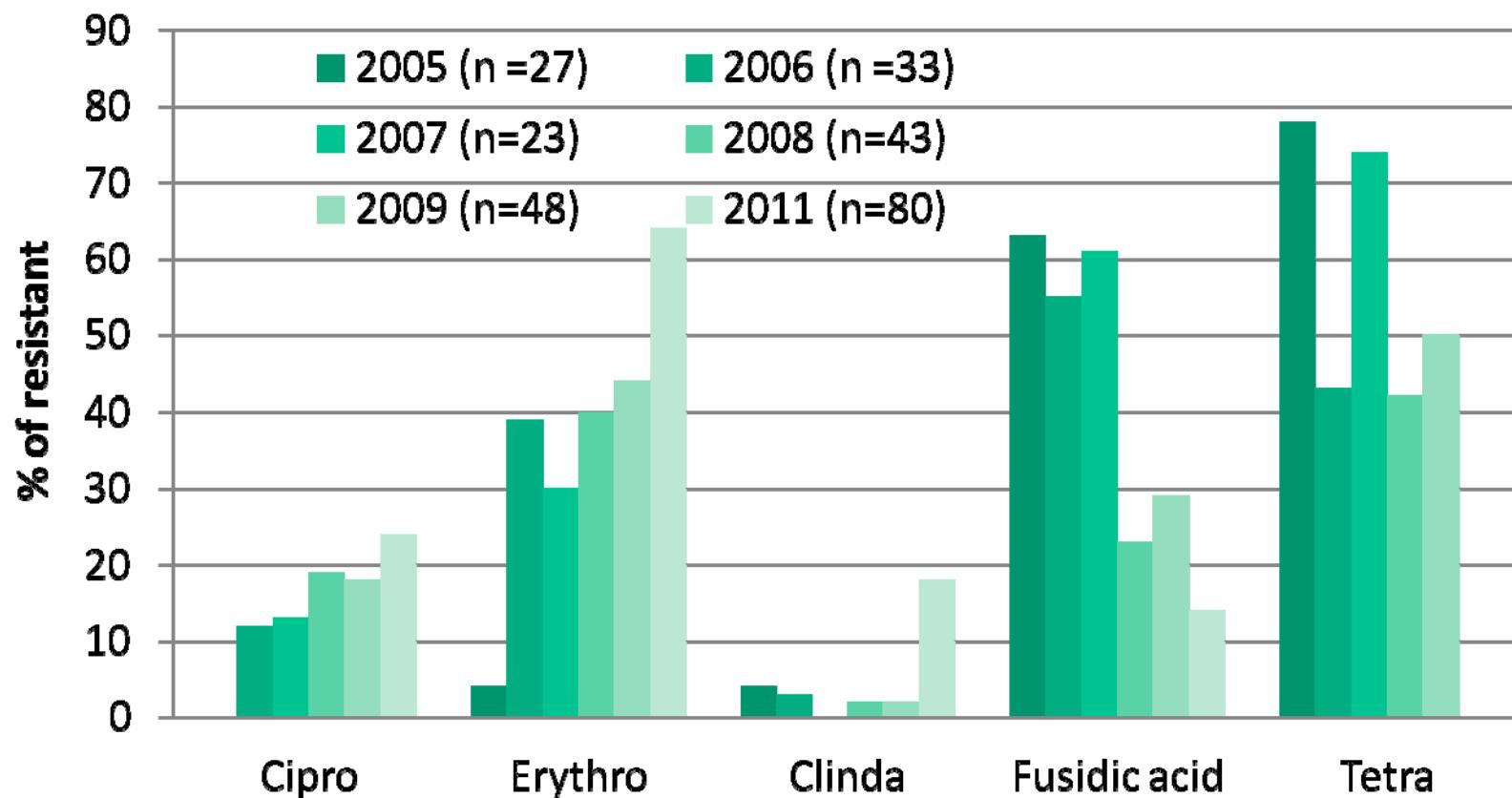
Five lineages dominate:

ST80-IV (European), ST8-IV (USA300), ST30-IV (Pacific/Oceania), ST59-IV/V (Taiwan), ST1-IV (USA400)

# Molecular typing of CA-MRSA PVL positive in Belgium from 2003 to 2011



# Proportion of PVL-positive MRSA strains resistant to antimicrobials, Belgium, 2005-2011



# Common risk factors for CA-MRSA infection

- One or more of the following are characteristic of the populations at highest risk
  - frequent Antibiotic use and overuse
  - Poor hygiene / **Cleanliness**
  - **Compromised skin**
  - Frequent skin **Contact**
  - **Contaminated surfaces and shared items**
  - **Crowding (up to 7.5 persons per bedroom)**
- **These groups amplify MRSA!**
  - MRSA is likely to disseminate from these communities to the population in general

# Evidence of CA-MRSA as cause of HAI

- Increasing introduction of MRSA into hospitals
- Europe
  - Greece, ST80 caused 25% of hospital-acquired infections in 2004

Chini V et al. *Scand J Infect Dis* 2008;368

- But still low prevalent (<2%) in Germany and Belgium

Vandendriessche et al. *Eur J Clin Microbiol Infect Dis* 2012;2283  
Schaumburg F et al. *J Clin Microbiol* 2012;3186

- USA the epidemiology both in the community but also increasingly in hospitals is dominated by ST8-IV, spa t008 (USA300)

Seybold, CID, 2006; 42:647–56 Klevens, CID, 2006; 389;  
Miller, Emerg Inf Dis 2007;236;

- Taiwan, ST59 V<sub>T</sub> caused 13% of HA-MRSA and 47% of HACO infections

Huang, CMI,2008;14:1167-72

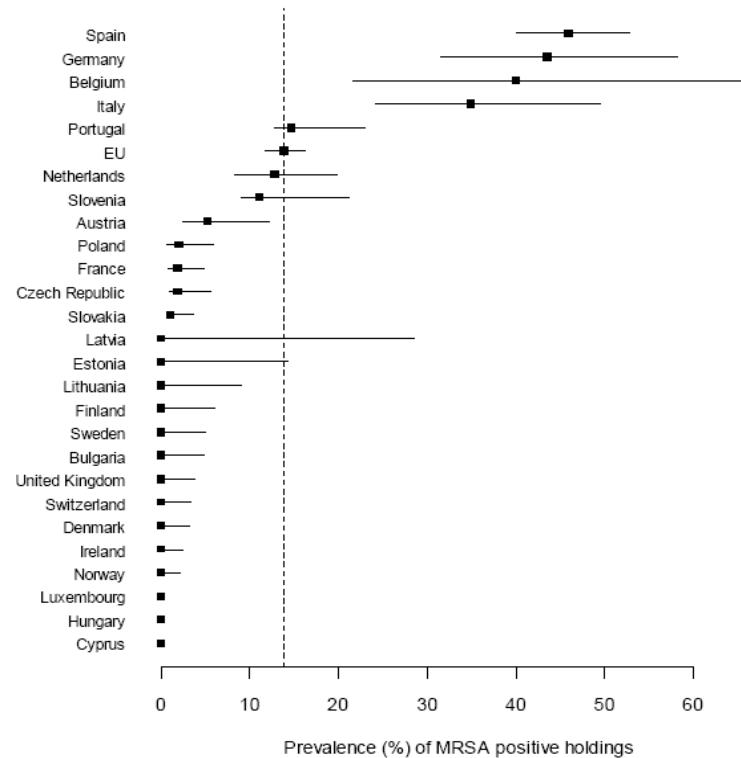
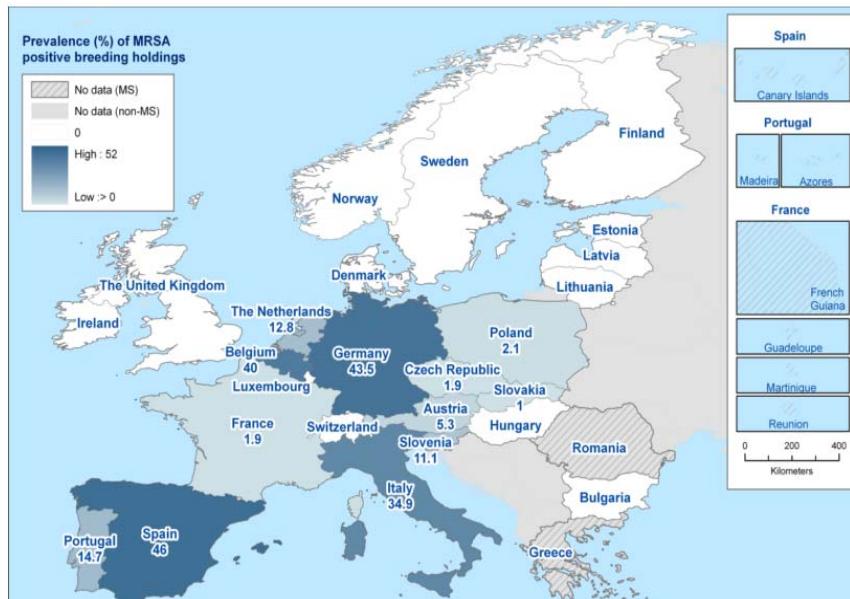
# Spread outside the hospital environment

## 2<sup>nd</sup> wave : Livestock-associated MRSA (2000s)

- Almost monoclonal belonging to CC398
  - Highly frequent in Europe but also in the USA
  - In Asia ST9
  - Acquisition of the SCCmec V but also IV, "VII" new variants (IX, X)
- Often multi-resistant
  - To antibiotics (including tetracyclines, aminoglycosides, MLS...)
  - To heavy metals (Zn,..)
  - High diversity of resistance genes
    - Tetracycline: tetM, tetK, tetL,...
    - MLS: ermA, ermC, ermT,..
    - Linezolid: cfr
- PVL negative, staphylococcal enterotoxine negative

# MRSA ST398 in Europe

EFSA baseline survey on MRSA prevalence in holdings with breeding pigs (Pigs sampled in 2008)



- Prevalence varies between countries<sup>1</sup>
- Belgium: High MRSA prevalence (3rd place)
- Also detected in USA, Canada, China, Malaysia, ...



# Risk factors for LA-acquisition

- Exposure to pigs and calves were significantly associated with risk of LA-MRSA
- Risk for being colonized is closely linked to direct contact and to living animals with MRSA
- Human populations at high risk
  - Belgium
    - Veal farmers (58%), pig farmers (38%)
    - Veterinarians (7.5%)
- Food borne route of transmission of MRSA CC398 seems negligible
- Elimination of carriage in persons with daily animal contact is futile
- Worries
  - Transmission of SCCmec to hitherto susceptible lineages
  - Adaptation to humans leading to human to human transmission

# **Meticillin-resistant *Staphylococcus aureus* with a novel *mecA* homologue in human and bovine populations in the UK and Denmark: a descriptive study**

Laura García-Alvarez, Matthew T G Holden, Heather Lindsay, Cerian R Webb, Derek F J Brown, Martin D Curran, Enid Watpole, Karen Brooks, Derek J Pickard, Christopher Teale, Julian Parkhill, Stephen D Bentley, Giles F Edwards, E Kirsty Girvan, Angela M Kearns, Bruno Pichon, Robert L R Hill, Anders Rhod Larsen, Robert L Skov, Sharon J Peacock, Duncan J Maskell, Mark A Holmes

- Unusual MRSA clones harboring *mecC* gene
- Belonging to clone CC130, CC705, ST425
- Reported in the UK, Denmark, Ireland, Germany, France... and Belgium
- Isolated from various animals
  - Bovine but also dog, rabbit, rat, seal, sheep, chaffinch
  - Causing mastitis
- Isolated from humans causing SSTI, arthritis, bacteremia or asymptomatic carriage
- Problems of detection
  - Low level resistance to oxacillin and cefoxitin
  - Not detected by automated system
  - No detection by usual PCR including Xpert MRSA

# Conclusions

- Whereas HA-MRSA seems to be in control in many parts of Europe
- CA-MRSA and LA-MRSA are increasing
  - Increasing prevalence of MRSA in the general population may jeopardize efforts to control HA-MRSA in the future
- Emergence of MRSA harboring the novel *mecC* gene
  - Problem of detection using routine methods

# Acknowledgements

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