# Epidemiology, Risk Factors, and Comorbidities Associated With MRSA Infections

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Brussels, Belgium
http://www.facm.ucl.ac.be

**ECCMID MSD Integrated Symposium**

**Walking a fine line to meet the clinical realities**

**Monday 15 April 2019 – 16:00 – 18:00**

29th ECCMID Amsterdam, Netherlands 13–16 April 2019 | ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

# Disclosures

Research grants and Speaker's honoraria from

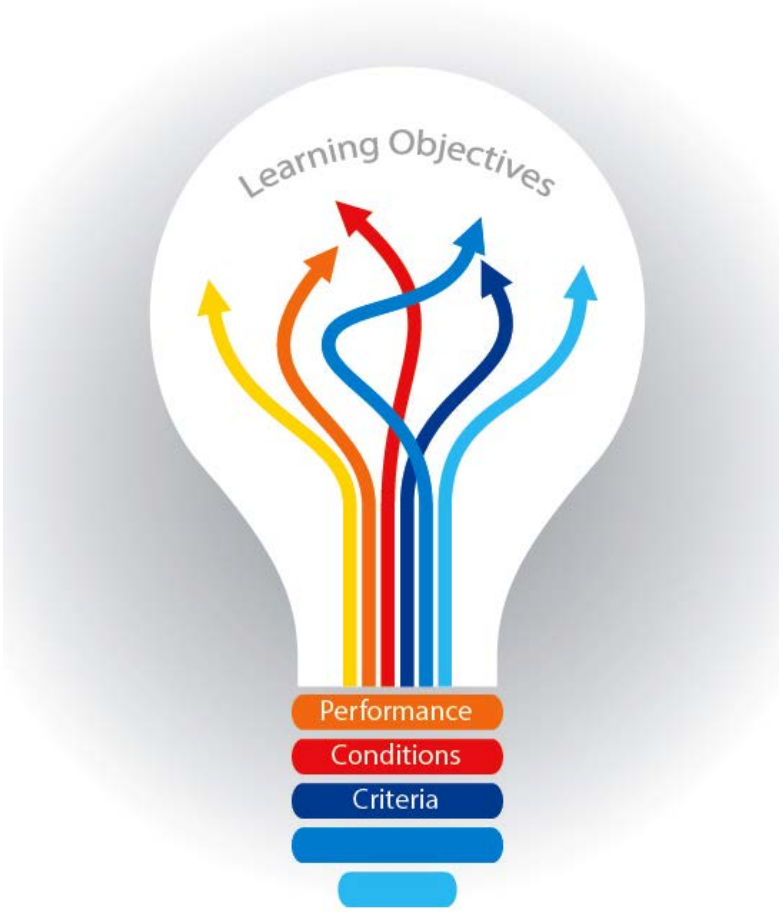
- Cempra Pharmaceuticals [1]
- Cerexa
- GSK
- Melinta Therapeutics [2]
- MerLion Pharmaceuticals
- Theravance
- Trius Therapeutics [3]
- Merck
- Bayer [4]
- Menarini

Influenced by my participation to the

- Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
- EUCAST steering committee (2008-2010) and General Assembly (current)
- the Governance Body of DRIVE-AB (2014-2017)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

[1] merged in 2017 with and renamed as Melinta Therapeutics
[2] formerly RibX Pharmaceuticals
[3] acquired by Cubist (2014), which was then acquired by Merck (2016)
[4] discontinued antibiotic R&D in 2018

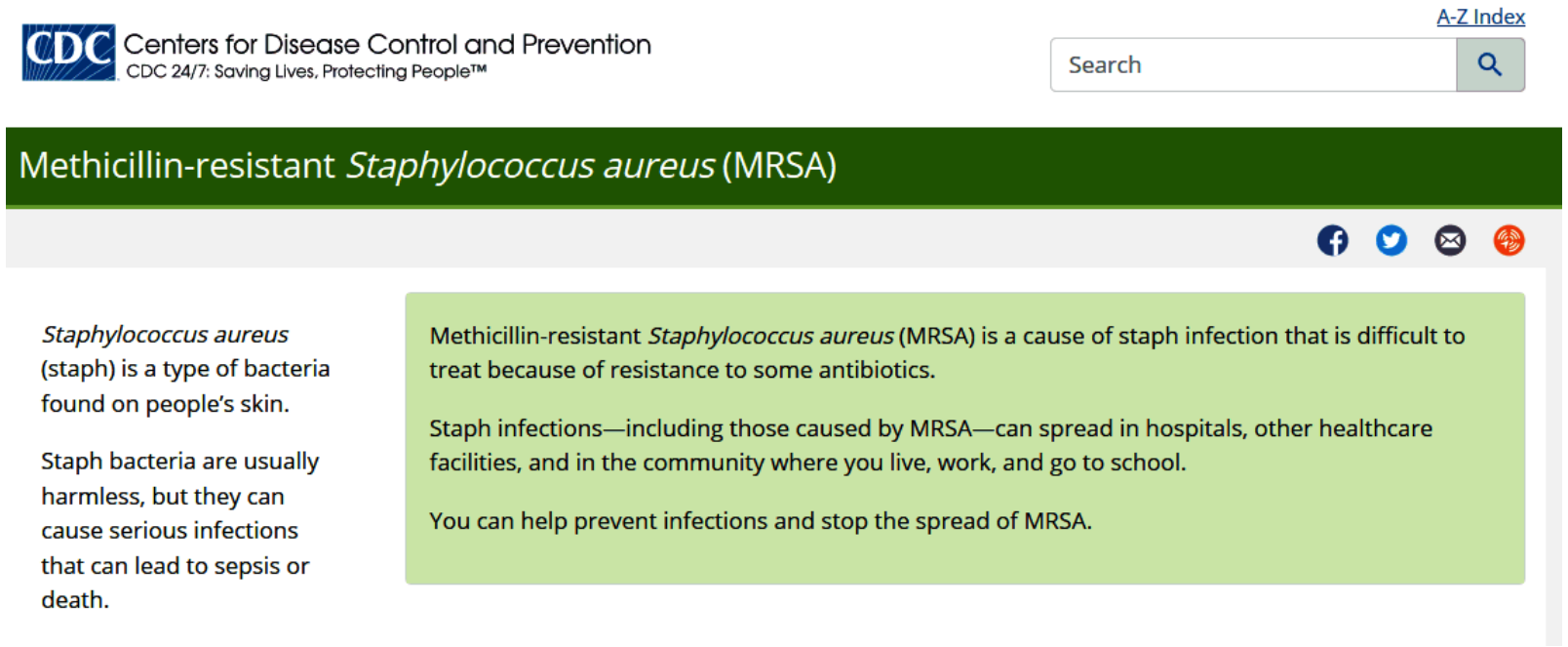
# Learning objectives




- Understanding the current epidemiological situation …
- Defining which are the risks for your patients …
- Should we pay attention to comorbidities ?

https://novaonline.nvcc.edu/TOTAL_Workshops/LearningObjectives_v4/LearningObjectives_v4_print.html
Last visited: 1 Apr 2019

# Do we need to pay attention to MRSA ?



CDC Centers for Disease Control and Prevention
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A-Z Index

Search

## Methicillin-resistant *Staphylococcus aureus* (MRSA)

*Staphylococcus aureus* (staph) is a type of bacteria found on people's skin.

Staph bacteria are usually harmless, but they can cause serious infections that can lead to sepsis or death.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a cause of staph infection that is difficult to treat because of resistance to some antibiotics.

Staph infections—including those caused by MRSA—can spread in hospitals, other healthcare facilities, and in the community where you live, work, and go to school.

You can help prevent infections and stop the spread of MRSA.

https://www.cdc.gov/mrsa/ - Last visited: 1 Apr 2019

The US CDC warns us !

# Do we need to pay attention to MRSA ?

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https://www.cdc.gov/mrsa/ - Last visited: 1 Apr 2019

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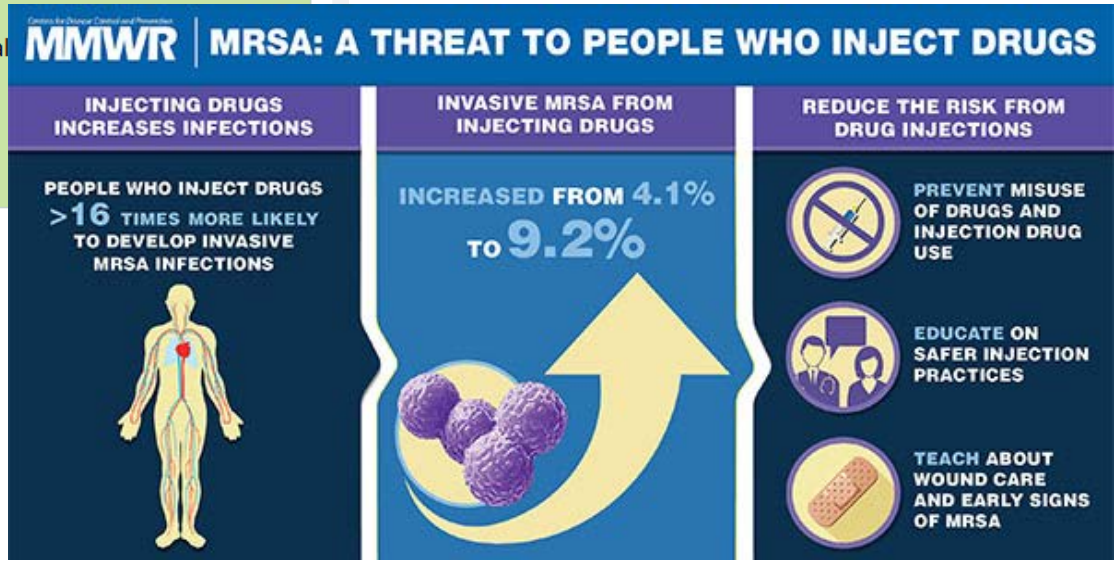
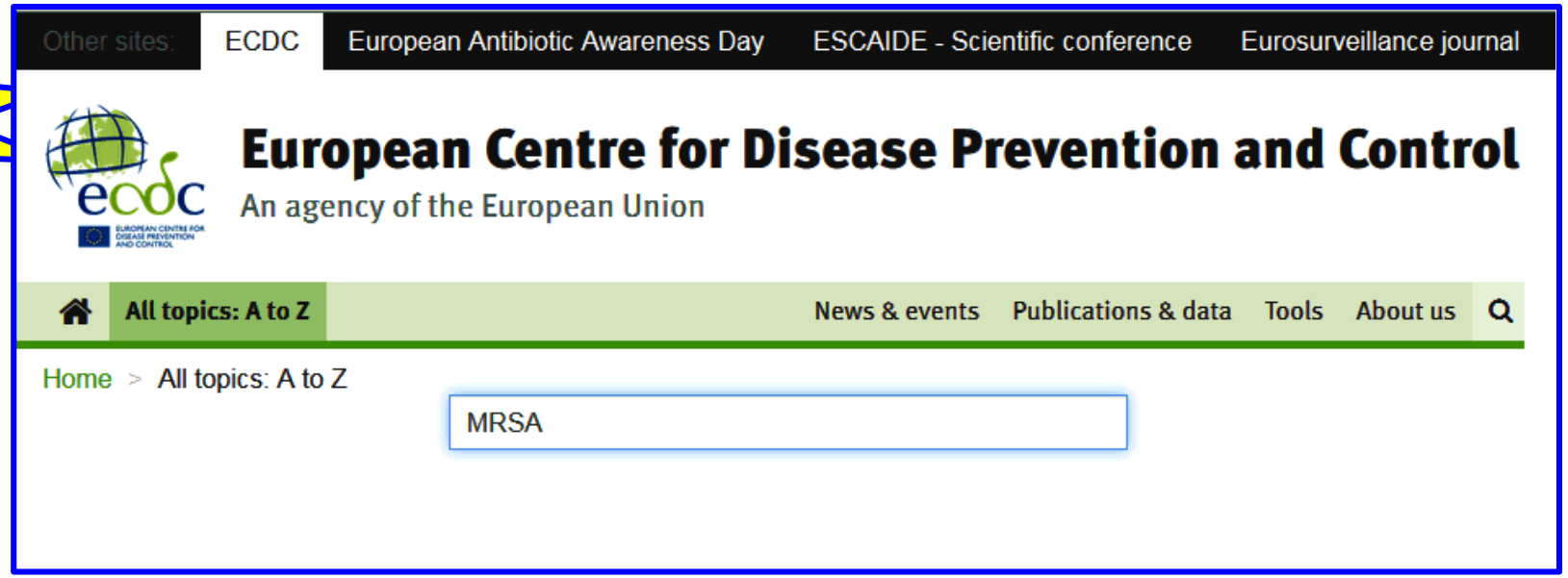
and here is why …




Morbidity and Mortality Weekly Report (MMWR) 2018;67:625-28
https://www.cdc.gov/mmwr/volumes/67/wr/mm6722a2.htm
Last visited: 1 Apr 2019

# Do we need to pay attention to MRSA ?

but what in Europe ?




https://www.ecdc.europa.eu/en/all-topics - Last visited: 1 Apr 2019

# Do we need to pay attention to MRSA ?

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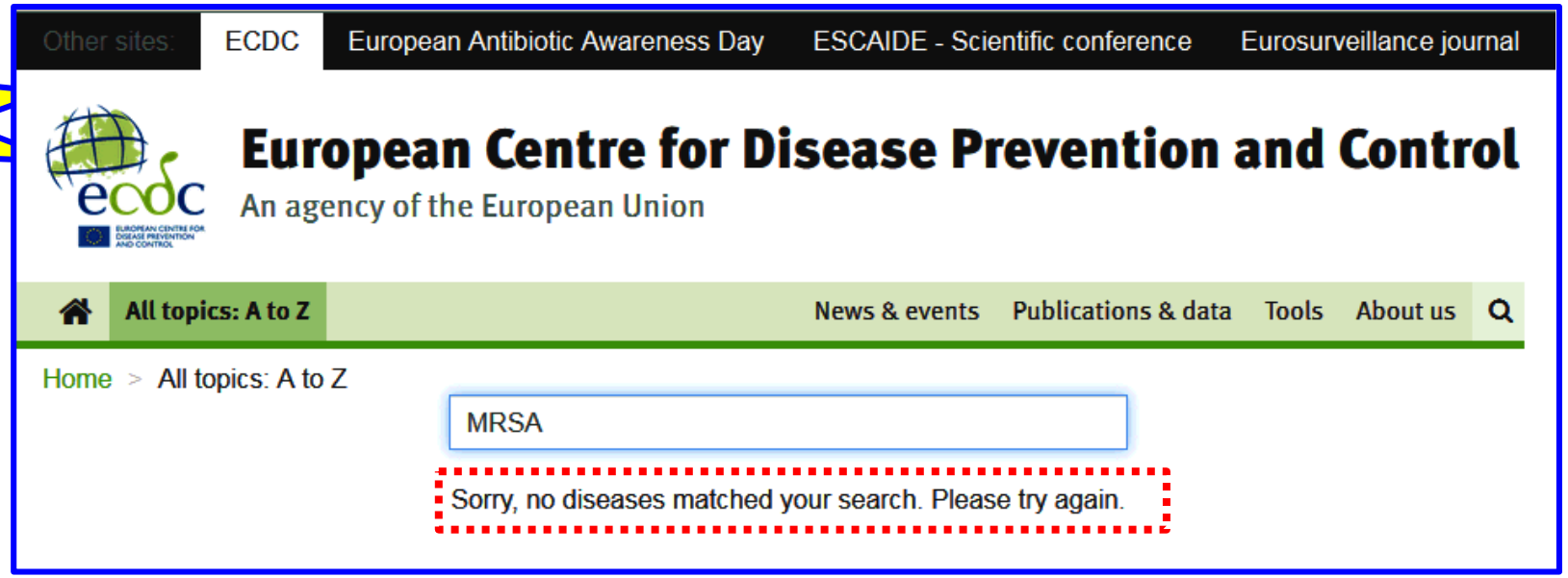
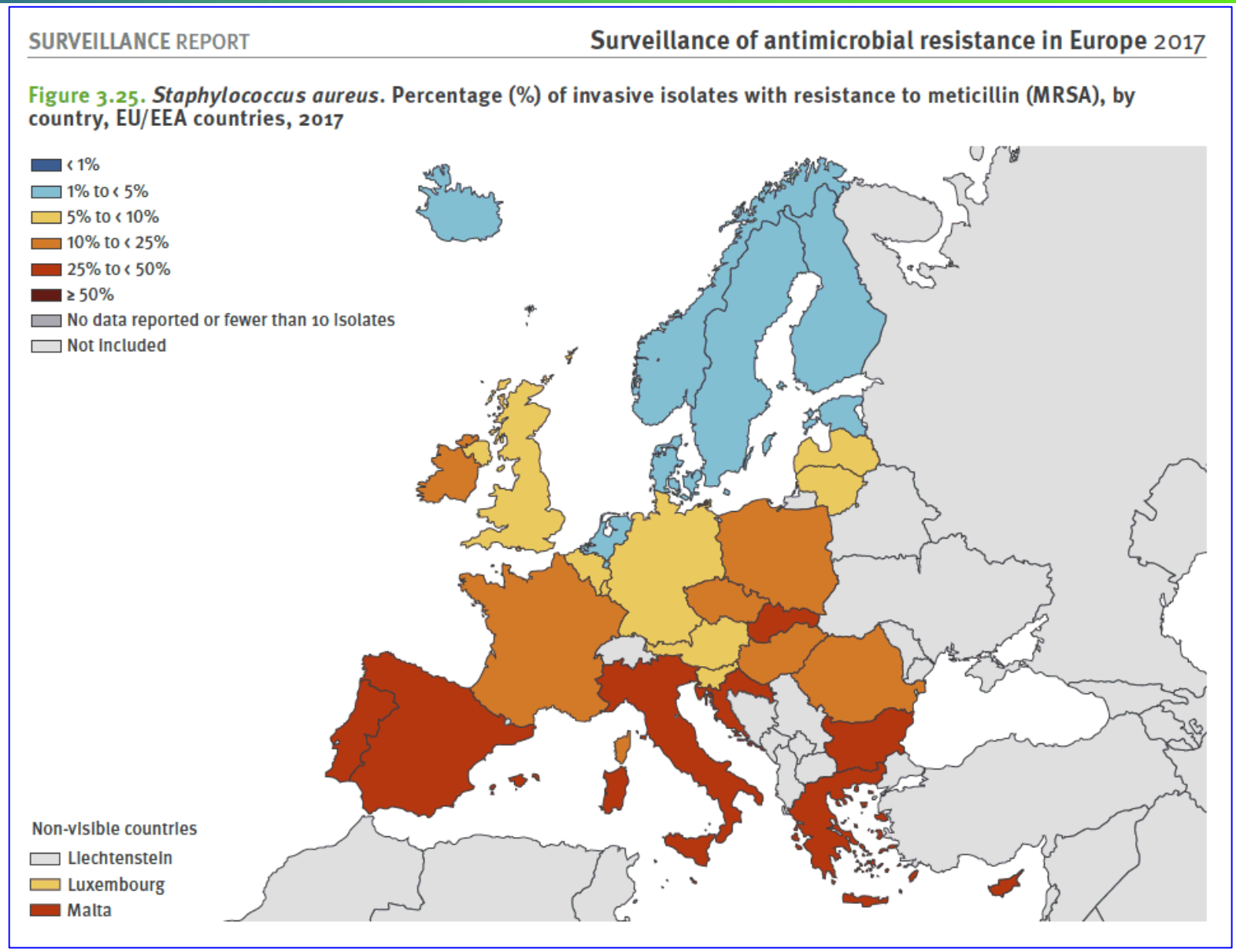



https://www.ecdc.europa.eu/en/all-topics - Last visited: 1 Apr 2019

# But here is a reason to worry in Europe …


European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe
Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017. Stockholm: ECDC; 2018.
http://ecdc.europa.eu/sites/portal/files/documents/EARS-Net-report-2017-update-jan-2019.pdf
Last visited: 1 Apr 2019



# And in the world ?

World Health Organization

## GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

**Chair:** E. Tacconelli (Infectious Diseases, DZIF Center, Tübingen University, Germany) and N. Magrini (WHO, EMP Department)

**Coordinating group:** Y. Carmeli, Tel Aviv University, Israel; S. Harbarth, University of Geneva, Switzerland; G. Kahlmeter, University of Uppsala, Sweden; J. Kluytmans, University Medical Center Utrecht, Netherlands; M. Mendelson, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa; C. Pulcini, University of Lorraine and Nancy University Hospital, France; N. Singh, George Washington University, USA; U. Theuretzbacher, Center for Anti-infective Agents, Austria

http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
Published: 27 Feb 2017; Last accessed: 1 Apr 2019

# The WHO Global Priority List…

## Priority 1: CRITICAL[#]

***Acinetobacter baumannii***, carbapenem-resistant

***Pseudomonas aeruginosa***, carbapenem-resistant

***Enterobacteriaceae****, carbapenem-cephalosporin-resistant

## Priority 2: HIGH

***Enterococcus faecium***, vancomycin-resistant

***Staphylococcus aureus***, methicillin-resistant, vancomycin intermediate and resistant

***Helicobacter pylori***, clarithromycin-resistant

***Campylobacter***, fluoroquinolone-resistant

***Salmonella*** *spp.*, fluoroquinolone-resistant

***Neisseria gonorrhoeae***, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

## Priority 3: MEDIUM

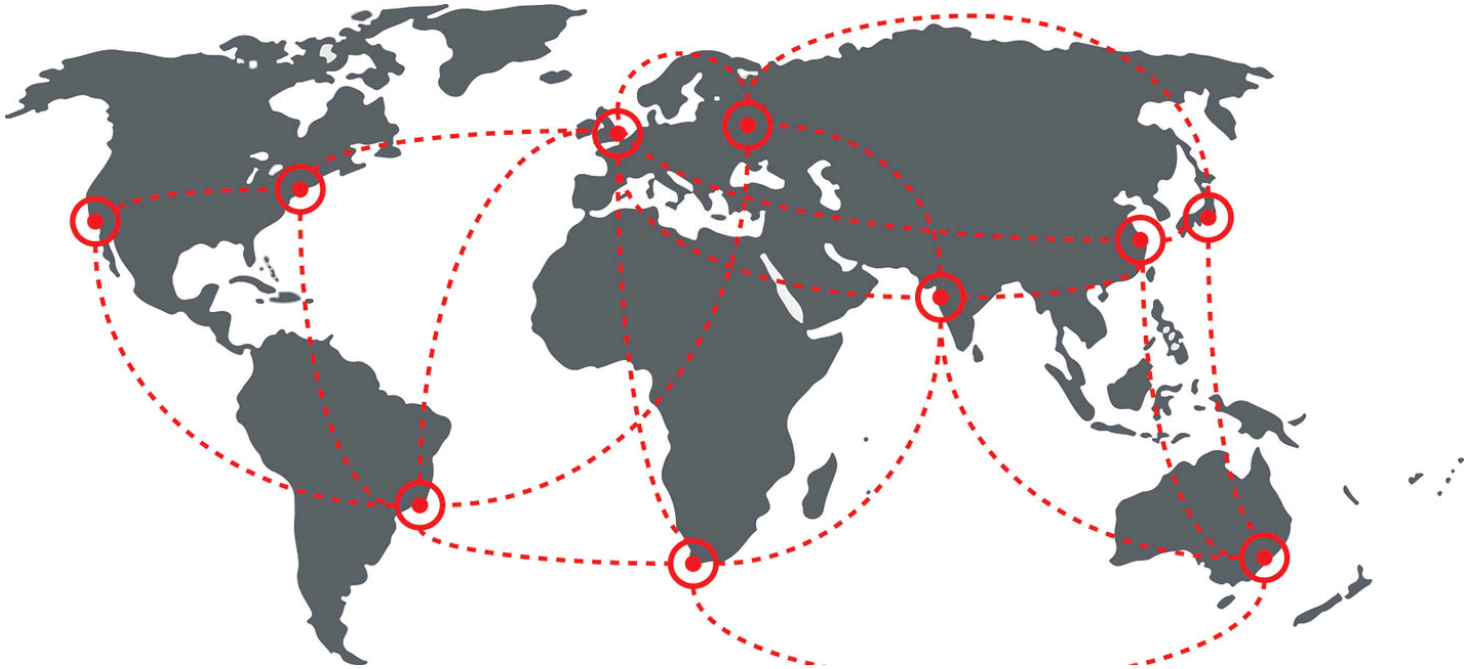
***Streptococcus pneumoniae***, penicillin-non-susceptible

***Haemophilus influenzae***, ampicillin-resistant

***Shigella*** *spp.*, fluoroquinolone-resistant

http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
Published: 27 Feb 2017; Last accessed: 1 Apr 2019

# 1. Epidemiology



https://publichealth.gwu.edu/sites/default/files/world_map.jpg
Last visited: 6 Apr 2019

# The current epidemiological situation… World and longitudinal view

*Open Forum Infectious Diseases*

SUPPLEMENT ARTICLE

## Twenty-Year Trends in Antimicrobial Susceptibilities Among *Staphylococcus aureus* From the SENTRY Antimicrobial Surveillance Program

**Daniel J. Diekema,[1] Michael A. Pfaller,[1,2] Dee Shortridge,[2] Marcos Zervos,[3,4] and Ronald N. Jones[2]**

[1]University of Iowa Carver College of Medicine, Iowa City, Iowa; [2]JMI Laboratories, North Liberty, Iowa; [3]Henry Ford Hospital, Detroit, Michigan; [4]Wayne State University School of Medicine, Detroit, Michigan

Diekema et al. Open Forum Infect Dis. 2019;6(Suppl 1):S47-S53 - PMID: 30895214

- 191 460 clinical *S. aureus* isolates
- 427 centers in 45 countries
- from 1997 to 2016 …
- bacteremia, pneumonia in hospitalized patients, urinary tract infection, and skin and skin structure infection….
- MRSA affect all ages but elderly are at higher risk…

**Table 1. Methicillin Resistance by Specimen Source, Health Care Association, and Age (SENTRY Program, 1997–2016)**

| Variable | No. Tested | % MRSA |
|---|---|---|
| Specimen source | | |
| BSI | 68 564 | 37.1 |
| PIHP | 34 029 | 45.6 |
| SSSI | 70 757 | 41.0 |
| UTI | 2916 | 51.9 |
| Health care association | | |
| Community onset | 86 366 | 36.8 |
| Nosocomial | 46 086 | 47.0 |
| Age, y | | |
| ≤10 | 19 109 | 37.2 |
| 11–20 | 10 425 | 33.9 |
| 21–30 | 13 048 | 37.7 |
| 31–40 | 15 428 | 38.1 |
| 41–50 | 21 690 | 38.7 |
| 51–60 | 27 120 | 40.2 |
| 61–70 | 27 174 | 41.5 |
| 71–80 | 24 502 | 45.1 |
| >80 | 17 371 | 48.0 |

Abbreviations: BSI, bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus;* PIHP, pneumonia in hospitalized patients; SSSI, skin and skin structure infection; UTI, urinary tract infection; y, years.

# The current epidemiological situation… World view

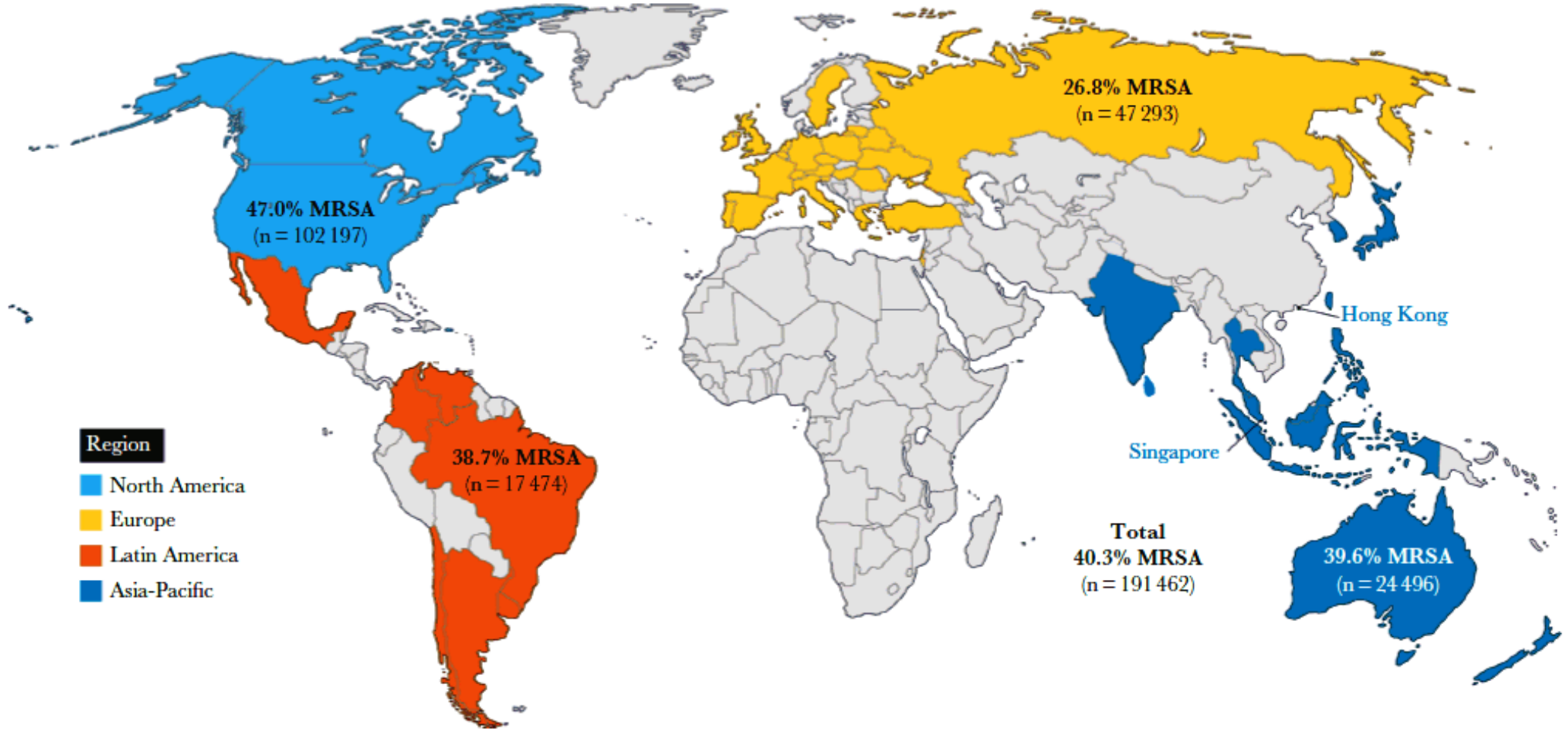
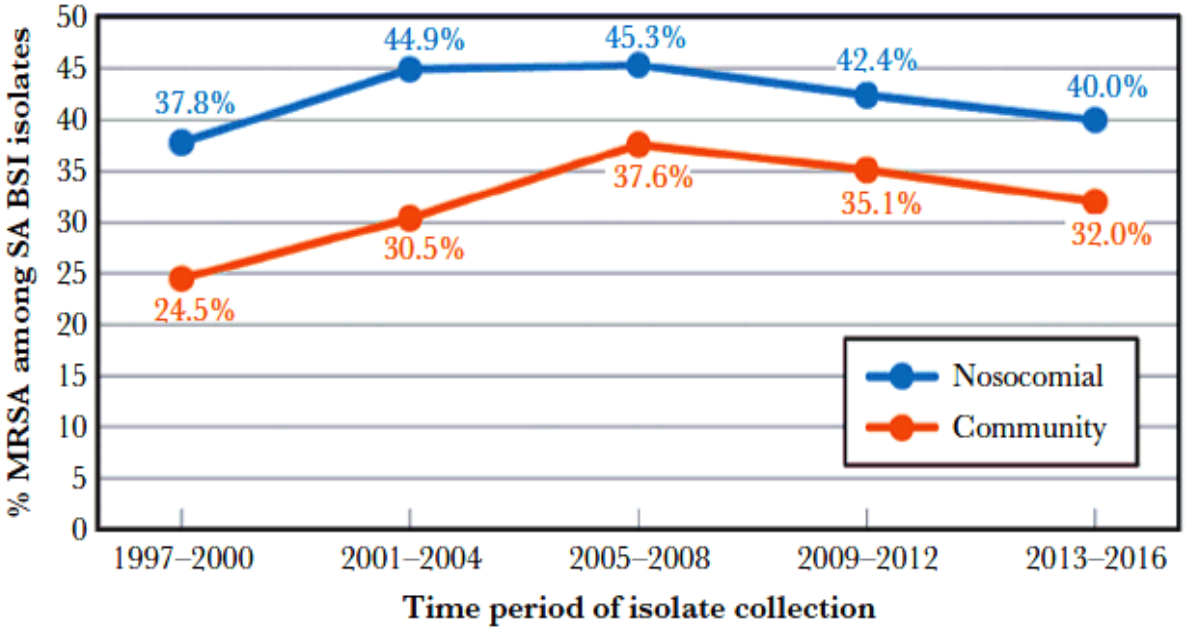



**Figure 1.** Percent MRSA by region. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Diekema et al. Open Forum Infect Dis. 2019;6(Suppl 1):S47-S53 - PMID: 30895214

# The current epidemiological situation… time effect and MIC ranges

**Not so nice an evolution …**




SENTRY Program 20-year trends in percentage of *Staphylococcus aureus* BSI isolates that are MRSA.

Abbreviations: BSI, bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*.

Diekema et al. Open Forum Infect Dis. 2019;6(Suppl 1):S47-S53 - PMID: 30895214

**And we start seeing vancomycin reduced susceptibility (MIC ≥ 2 mg/L / n=5375)**

| Antimicrobial Agent | No. of Isolates | $MIC_{90}$ | MIC Range | EUCAST R breakpoint |
|---|---|---|---|---|
| Ceftaroline | 1332 | 2 | 0.015–2 | >2 |
| Dalbavancin | 3318 | 0.12 | ≤0.03–>0.25 | >0.125 |
| Daptomycin | 3479 | 1 | ≤0.12–4 | >1 |
| Delafloxacin | 103 | 1 | ≤0.004–>1 | -- |
| Levofloxacin | 4549 | >4 | ≤0.5–>4 | >1 |
| Linezolid | 5093 | 2 | ≤0.25–>8 | >4 |
| Oritavancin | 1024 | 0.12 | ≤0.008–0.5 | >0.125 |
| Quinupristin-dalfopristin | 4506 | 1 | ≤0.5–>2 | >2 |
| Tedizolid | 190 | 0.25 | 0.03–0.25 | >0.5 |
| Teicoplanin | 5374 | 4 | 2–>16 | >2 |
| Telavancin | 867 | 0.06 | ≤0.015–0.12 | >0.125 |
| Tigecycline | 3497 | 0.5 | ≤0.12–1 | >0.5 |

# The current epidemiological situation… Some hope from the US ?


Morbidity and Mortality Weekly Report (*MMWR*)

*Vital Signs:* Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections — United States

Kourtis et al. MMWR Morb Mortal Wkly Rep. 2019;68:214-9 - PMID: 30845118

# The current epidemiological situation… Some hope from the US ?

CDC Centers for Disease Control an
CDC 24/7: Saving Lives, Protecting People™

Morbidity and Mortality Weekly

*Vital Signs:* Epidemiology and Recent
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Kourtis et al. MMWR Morb Mortal Wkly Rep. 2019;68:214-9
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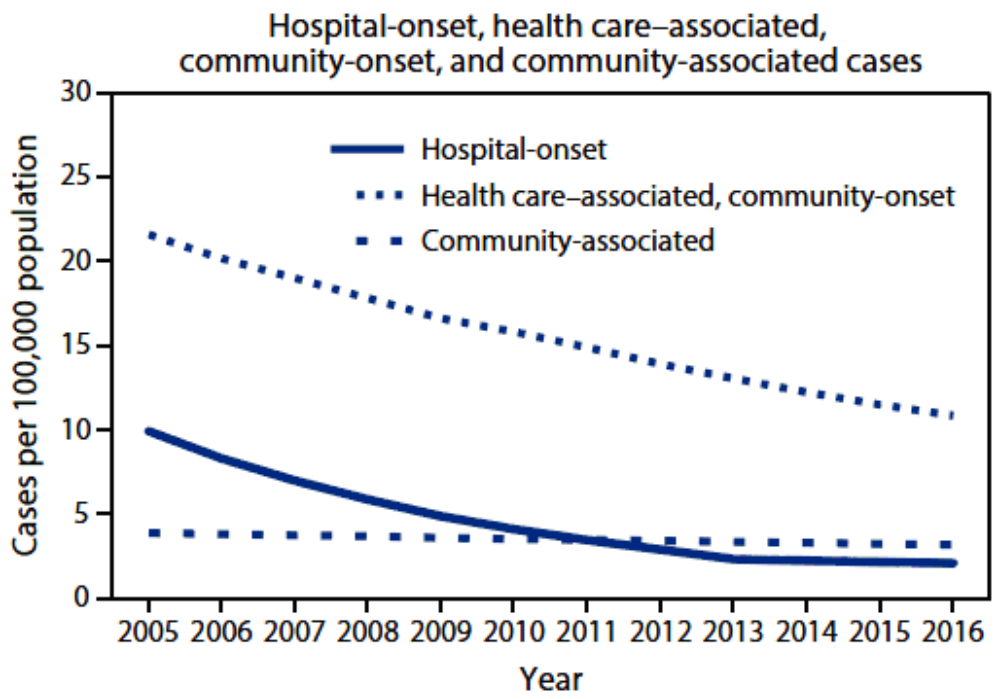
**Adjusted* methicillin-resistant *Staphylococcus aureus* bloodstream infection rates from population based surveillance six U.S. Emerging Infections Program sites,† 2005–2016**




Reasons for decline in hospital-onset MRSA bloodstream infections:

- enhanced infection control efforts,
- improved prevention of device- and procedure-associated infections
- interrupts in MRSA transmission

* Adjusted for year and distribution of age, sex, and race among overall and dialysis population. Community-onset infections comprise health care–associated community-onset and community-associated infections.

† California (three counties), Connecticut (statewide), Georgia (eight counties), Minnesota (one county), New York (one county), and Tennessee (one county).

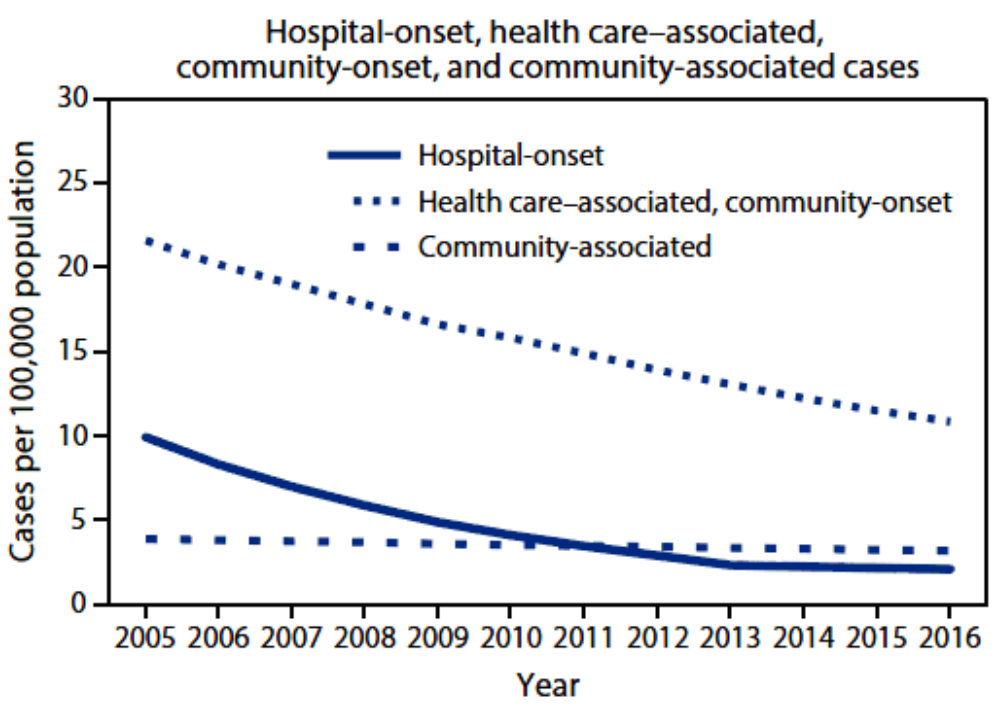
# The current epidemiological situation… Some hope from the US ?

**Conclusions and Implications for Public Health Practice:**

Despite reductions in incidence of MRSA bloodstream infections since 2005, *S. aureus* infections account for significant morbidity and mortality in the United States.

Ring still the bell !


**…sted* methicillin-resistant *Staphylococcus aureus* bloodstream infection**
**…s from population based surveillance**
**…U.S. Emerging Infections Program sites,† 2005–2016**

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# The current epidemiological situation… Hope also in Europe ?

Accepted Manuscript

Decrease of methicillin resistance in Staphylococcus aureus in nosocomial infections in Germany – a prospective analysis over 10 years

T.S. Kramer , C. Schröder , M. Behnke , S.J. Aghdassi , C. Geffers , P. Gastmeier , C. Remschmidt


Kramer et al. J Infect 2019;78:215-219 - Epub 2019 Jan 15 - PMID: 30658080

**Figure 1**. Time trend for percentage of nosocomial methicillin resistant *Staphylococcus aureus* (MRSA) infections. Data from the German national nosocomial infection surveillance system (KISS), 2007-2016.

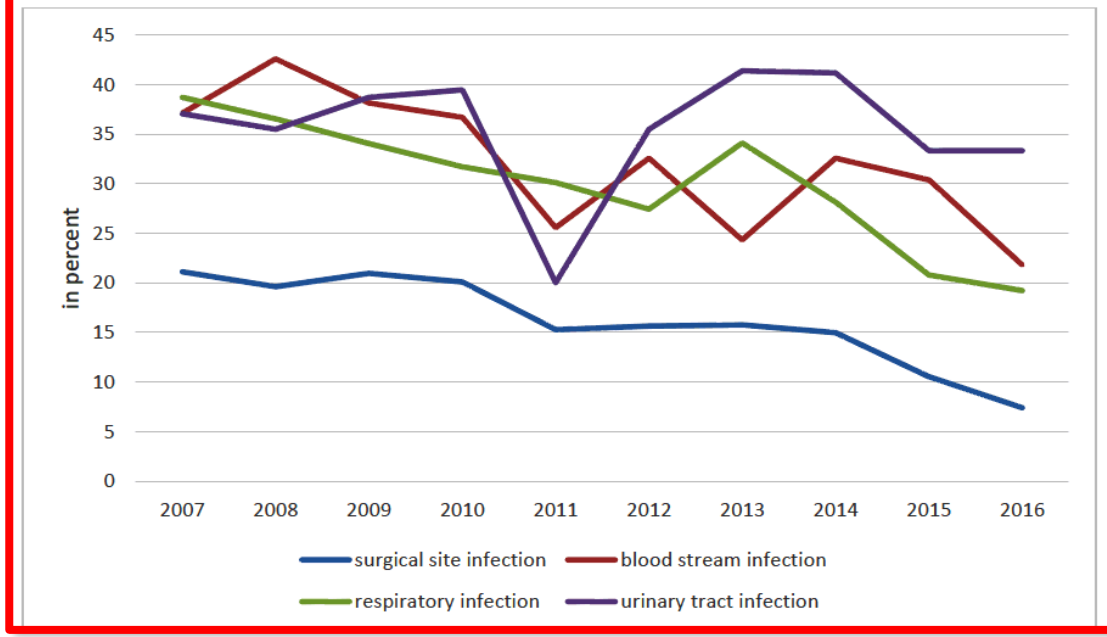
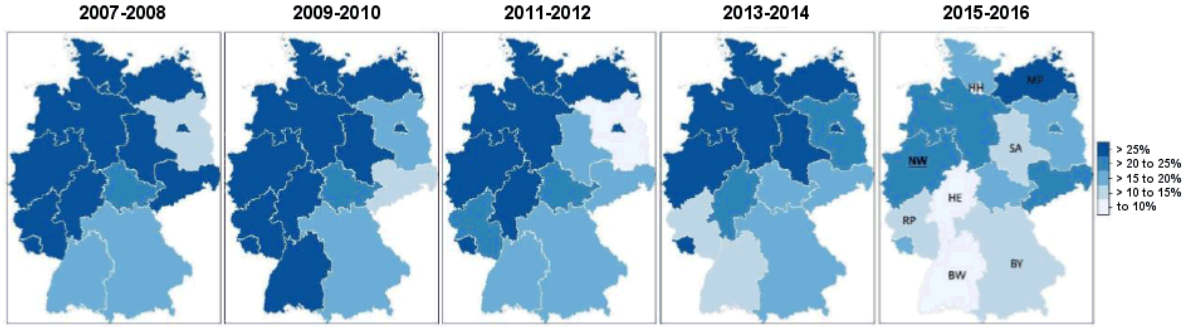



**Figure 3**. Distribution of the proportion of methicillin resistant *Staphylococcus aureus* (MRSA) infections among German federal states according to data from the German national nosocomial infection surveillance system (KISS) 2007-2016. (NW = North Rhine Westphalia, reference, RP = Rhineland Palatinate, BW = Baden Württemberg, BY = Bavaria, HE = Hesse, SA = Saxony Anhalt, HH = Hamburg, MP = Mecklenburg Western Pomerania)




## Conclusions

- **MRSA still remain a relevant part of healthcare associated infections**
- **A significant decrease of its proportion occurred over the past 10 years**
- **Reasons: changes in legislation, surveillance and implementation of infection prevention measures, and biological changes.**

# The current epidemiological situation… Blurring situation in Europe ?

PLOS | MEDICINE

RESEARCH ARTICLE

## Evidence for Community Transmission of Community-Associated but Not Health-Care-Associated Methicillin-Resistant *Staphylococcus Aureus* Strains Linked to Social and Material Deprivation: Spatial Analysis of Cross-sectional Data

**Olga Tosas Auguet[1,2]*, Jason R. Betley[3], Richard A. Stabler[4], Amita Patel[1], Avgousta Ioannou[3], Helene Marbach[1], Pasco Hearn[1], Anna Aryee[1], Simon D. Goldenberg[1], Jonathan A. Otter[1], Nergish Desai[5], Tacim Karadag[6], Chris Grundy[7], Michael W. Gaunt[4], Ben S. Cooper[2,8], Jonathan D. Edgeworth[1], Theodore Kypraios[9]**

Tosas Auguet et al. PLoS Med. 2016;13:e1001944 - PMID: 26812054

Map of London boroughs showing catchment areas for the hospital cohort. Shown in red from left to right, catchment areas for the hospital cohort were south of the river Thames and included the Southwark, Lambeth, and Lewisham boroughs.

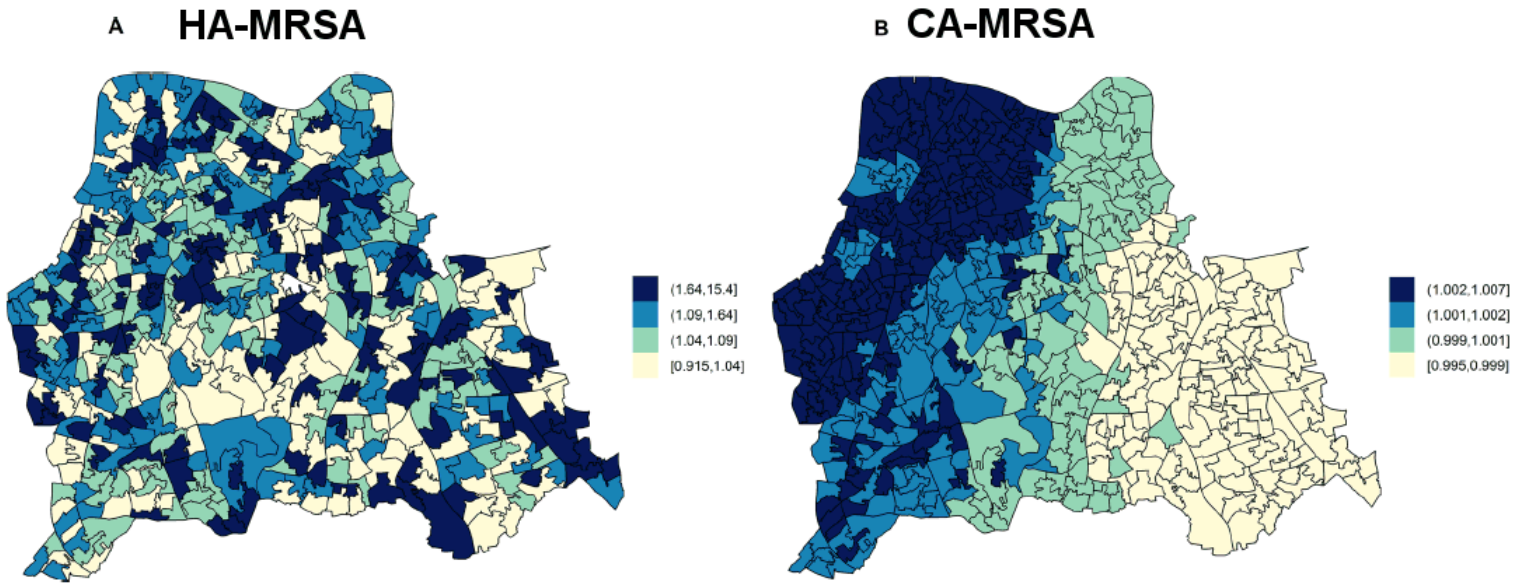



**Fig 2. Maps for RR of HA- and CA-MRSA in LSOAs compared to the whole catchment area in disease mapping (unadjusted) models.** Disease mapping models do not take into consideration the distribution and effect of risk factors for MRSA. These account for the observed and expected counts of HA- or CA-MRSA given the standardised age and gender population structure in each LSOA. HA-MRSA (A) was modelled considering unstructured random effects only (iid model). CA-MRSA (B) was modelled considering both unstructured and structured (spatial) random effects (BYM model). Cut-off values in figure legends correspond to quantiles for area-specific RRs of HA- and CA-MRSA, respectively.

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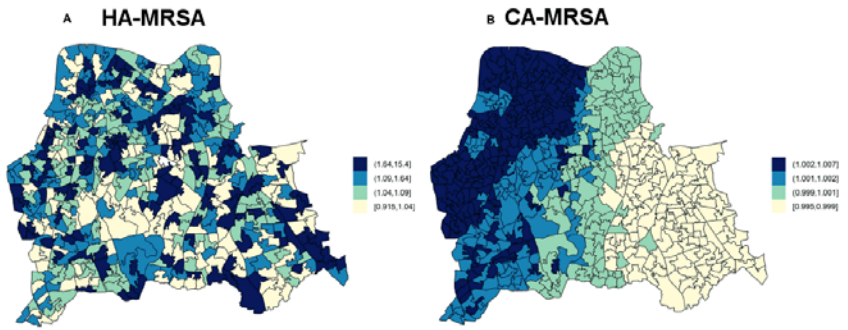


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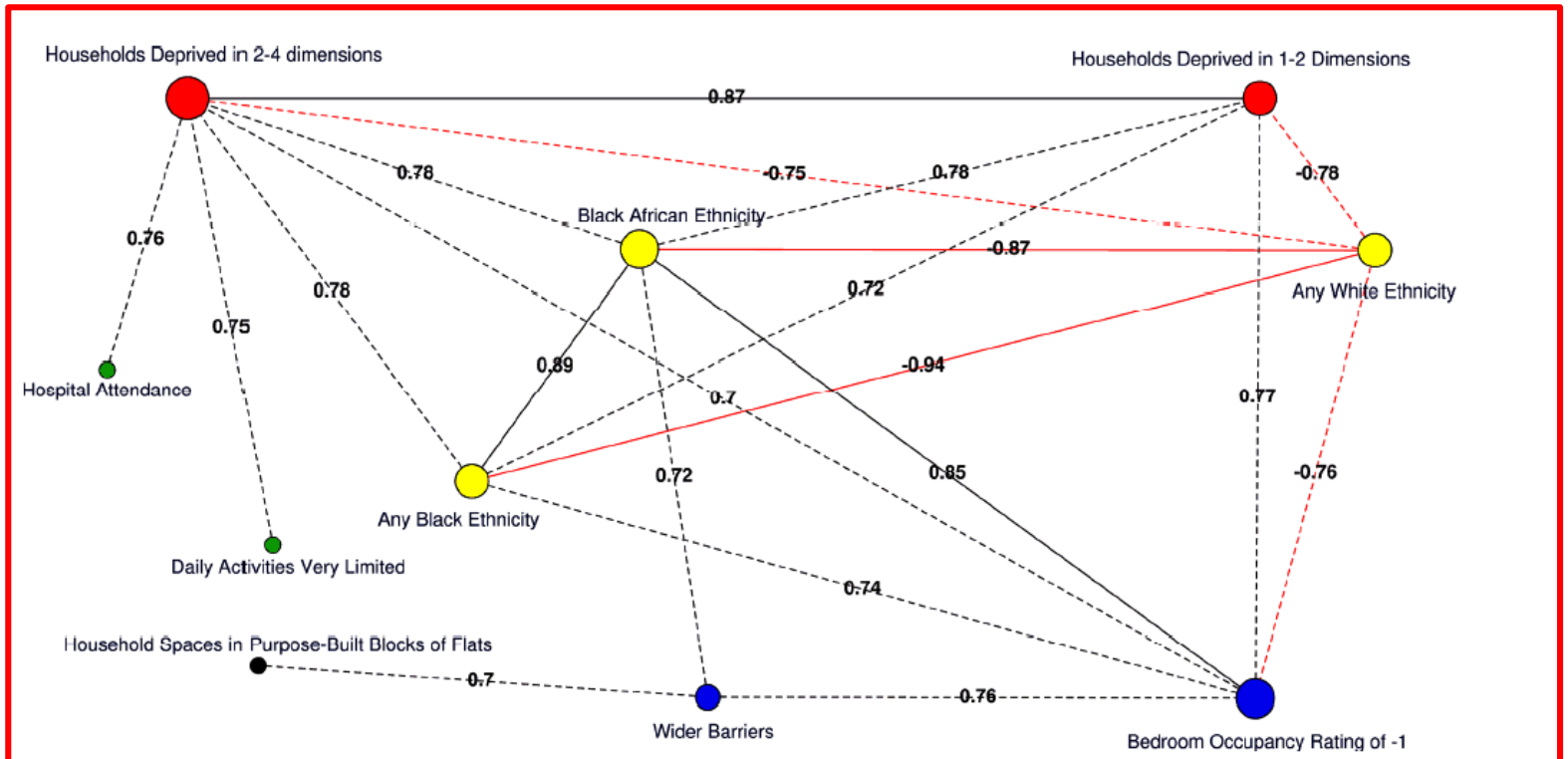


**Fig 4. Correlation network of area-level significant predictors of MRSA infection or colonisation in catchment areas of the London hospital cohort.** Moderate positive PCCs are shown by black dashed edges (≥0.70 and ≤0.80) and strong PCCs by continuous black edges (>0.80)

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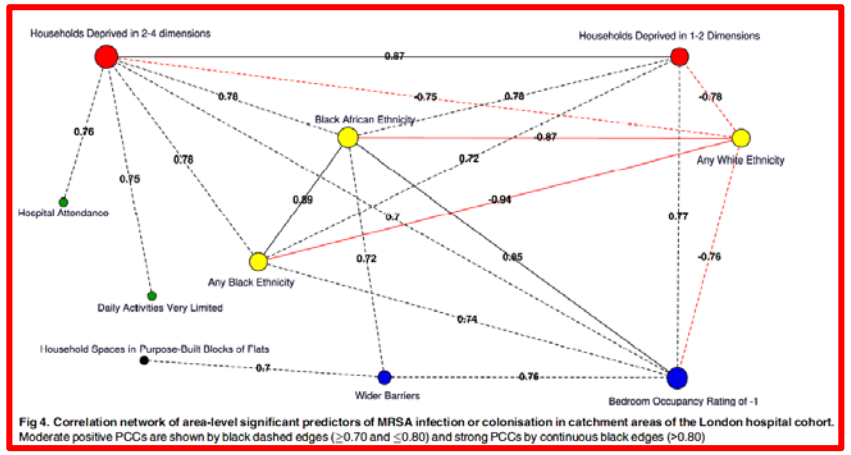


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**Main messages:**

- the predominant transmission niches for HA- and CA-MRSA are specific to each genetic classification.
  - ➢ HA-MRSA lineages originate from hospitals
  - ➢ CA-MRSA strains are spreading in the community (from the most deprived areas)

- The extent to which CA-MRSA is transmitting within health care premises is unknown [*from this study*],
  **BUT**
  in some countries, CA-MRSA is increasingly implicated in nosocomial infections,[1,2] has begun to spread within hospitals[1] due to repeated community admissions.[3]

Future reviews of UK hospital admission screening policies for MRSA should consider the growing threat of importation of CA-MRSA lineages into hospitals.

1. Egea et al. Int J Med Microbiol2014;304:1086–99 - PMID: 25240872
2. Otter & French. J Hosp Infect. 2011;79:189–93 - PMID: 21741111
3. Harris et al. Lancet Infec Dis 2013;13:130–6 - PMID: 23158674

# The current epidemiological situation… Imported cases in Europe ?

ARTICLE IN PRESS

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

## Import of community-associated, methicillin-resistant *Staphylococcus aureus* to Europe through skin and soft-tissue infection in intercontinental travellers, 2011–2016☆

D. Nurjadi [1], R. Fleck [2], A. Lindner [3], J. Schäfer [2], M. Gertler [3], A. Mueller [4], H. Lagler [5,6], P.J.J. Van Genderen [7], E. Caumes [8], S. Boutin [1], E. Kuenzli [9,10], J. Gascon [11], A. Kantele [12], M.P. Grobusch [13], K. Heeg [1], P. Zanger [1,14,*] on behalf of the StaphTrav Network

Nurjadi et al. Clin Microbiol Infect. 2018;S1198-743X(18)30663-3 - [Epub ahead of print] - PMID: 30315958.

# The current epidemiological situation… Imported cases in Europe ?

ARTICLE IN PRESS

ELSEVIER

journal

Original article

Import of community-a
*aureus* to Europe throug
intercontinental travelle

D. Nurjadi [1], R. Fleck [2], A. Lind
P.J.J. Van Genderen [7], E. Caume
M.P. Grobusch [13], K. Heeg [1], P.

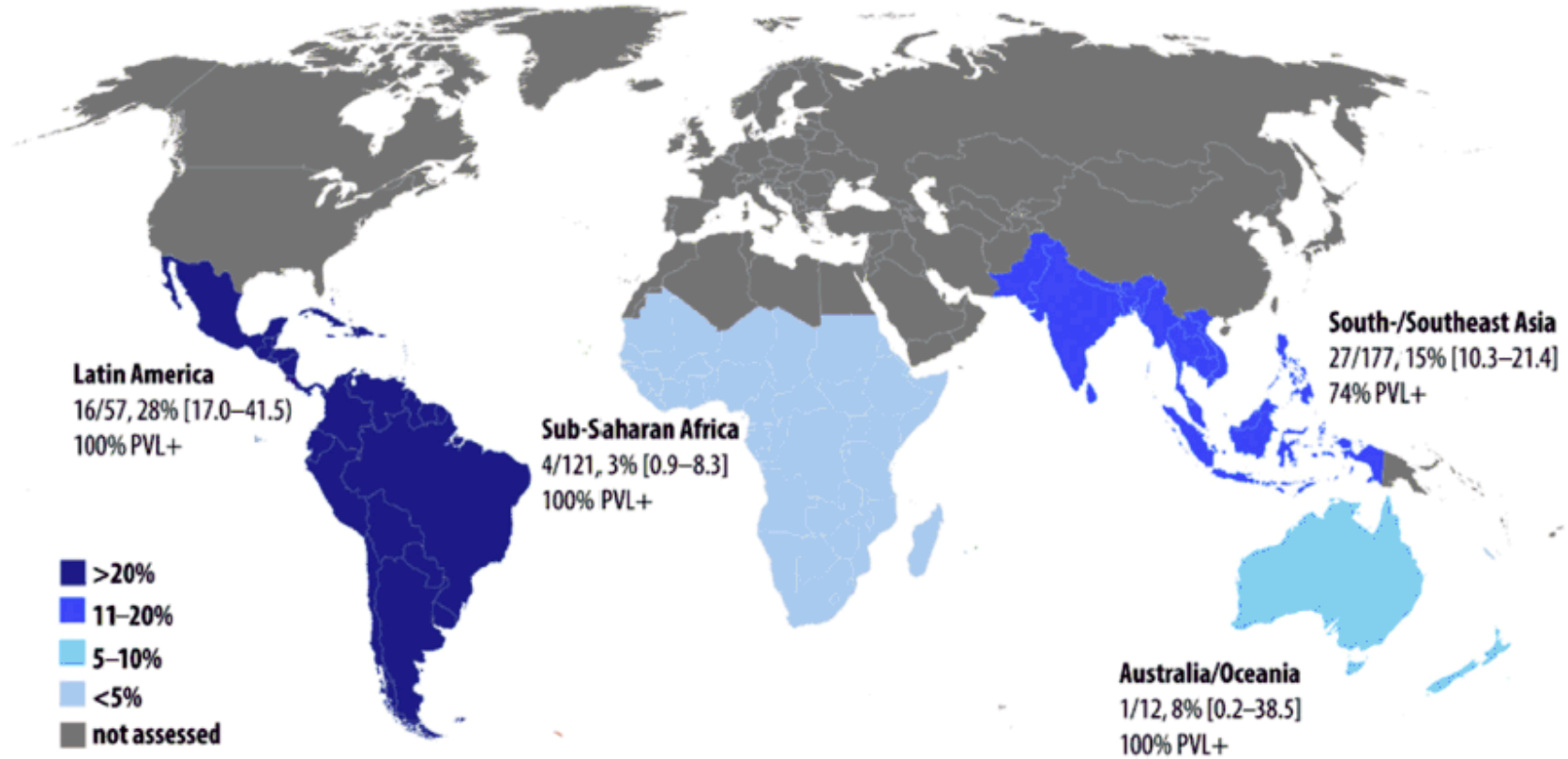


**Fig. 1.** Resistance to methicillin in *Staphylococcus aureus* imported to Europe, by region of travel destination, StaphTrav Network 2011–2016. Displayed and coded in blue are – for destinations with at least ten *S. aureus* submissions – prevalence estimates of methicillin-resistance (95% confidence interval) among *S. aureus* imported from a geographic region together with estimates of Panton–Valentine leucocidin (PVL) -positive isolates among methicillin-resistant *S. aureus*. Not displayed are estimates for regions with less than ten *S. aureus* submitted, i.e. West Asia (2/3, 67% (9.4–99.2), 100% PVL+) and North Africa (1/4, 25% (0.6–80.6), 100% PVL+). Chi-squared-test with five degrees of freedom for H0: 'The proportion of methicillin-resistant *S. aureus* is equally distributed over regions of travel destination.' gives p <0.001.

Nurjadi et al. Clin Microbiol Infect. 2018;S1198-743X(18)30663-3 - [Epub ahead of print] - PMID: 30315958.

# The current epidemiological situation… Imported cases in Europe ?

ARTICLE IN PRESS

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Import of community-associated, methicillin-resistant *Staphylococcus aureus* to Europe through skin and soft-tissue infection in intercontinental travellers, 2011–2016☆

D. Nurjadi [1], R. Fleck [2], A. Lindner [3], J. Schäfer [2], M. Gertler [3], A. Mueller [4], H. Lagler [5,6], P.J.J. Van Genderen [7], E. Caumes [8], S. Boutin [1], E. Kuenzli [9,10], J. Gascon [11], A. Kantele [12], M.P. Grobusch [13], K. Heeg [1], P. Zanger [1,14,*] on behalf of the StaphTrav Network

## Conclusions

- Long-distance travel is an important driver for the spread of epidemic CA-MRSA
- Implementation of infection control and prevention measures is important when travelers with skin infections have contact to the health-care system.
- Caution should be exerted for their household contacts, because these are commonly affected by secondary SSTI.

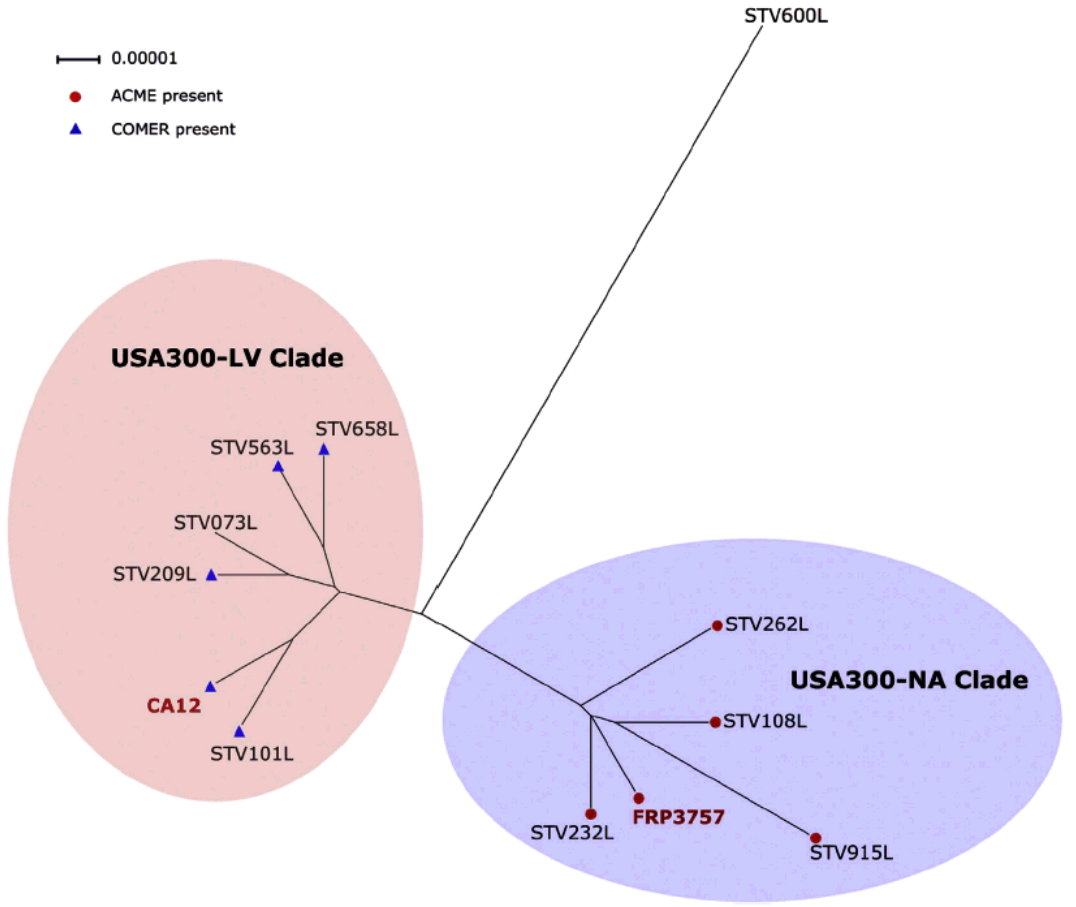


**Fig. 3.** Relatedness of methicillin-resistant *Staphylococcus aureus* (MRSA) multi-locus sequence type 8 imported to Europe, 2011–2016 ($n = 10$).Unrooted maximum likelihood tree based on allelic differences in the core genome (core genome multi-locus sequence typing). Imported isolates of community-associated MRSA MLST ST8/spa t008 belong to two major clades: USA300-North American Clade (USA300-NA), shaded in blue, and USA300-Latin-American Variant (USA300-LV), shaded in red. Reference sequences for North and South American ST8-USA300 MRSA are FRP3757 [18] and CA12 [19], respectively, and marked in red and bold. Presence of the copper and mercury resistance (COMER) mobile element typically found in USA300 of the Latin-American Variant [20] is marked by blue triangles. Presence of the arginine catabolic mobile element (ACME), which is the hallmark of the North American USA300 [20], is marked by red circles. The STV073L isolate, lacking both, COMER and ACME, was acquired in South Sudan, whereas the remaining isolates in the USA300-LV clade were imported from Cuba ($n = 2$) and Colombia ($n = 2$).

Nurjadi et al. Clin Microbiol Infect. 2018;S1198-743X(18)30663-3 - [Epub ahead of print] - PMID: 30315958.

# The current epidemiological situation… Europe … and the animals …

Contents lists available at ScienceDirect
Veterinary Microbiology 200 (2017) 6–12
Veterinary Microbiology
journal homepage: www.elsevier.com/locate/vetmic

## MRSA colonization and infection among persons with occupational livestock exposure in Europe: Prevalence, preventive options and evidence

Tobias Goerge[a], Marthe Barbara Lorenz[a], Sarah van Alen[b], Nils-Olaf Hübner[c], Karsten Becker[b], Robin Köck[b,*]

[a] University Hospital Münster, Department of Dermatology, Von-Esmarch-Str. 58, 48149 Münster, Germany
[b] University Hospital Münster, Institute of Medical Microbiology, Domagkstr. 10, 48149 Münster, Germany,
[c] Institute of Medical Diagnostics (IMD), Vitus-Bering-Straße 27a, 17493 Greifswald, Germany

Goerge et al. Vet Microbiol. 2017;200:6-12 - PMID: 26658156

# The current epidemiological situation… Europe … and the animals …

## 1. How frequent are LA-MRSA infections among persons with livestock contact ?

**Table 1**
Prevalence of nasal colonization with MRSA among personnel with livestock contact in European countries.

| Study | Country | Exposed to | Occupation | No. of MRSA carriers/participants (%) |
|---|---|---|---|---|
| Gilbert et al. (2012) | Netherlands | Pigs | Slaughterhouse personnel | 11/341 (3.2%) |
| Van Cleef et al. (2010a) | Netherlands | Pigs | Slaughterhouse personnel | 14/249 (5.6%) |
| Morcillo et al. (2011) | Spain | Pigs | Slaughterhouse personnel | 2/25 (8%) |
| Mulders et al. (2010) | Netherlands | Poultry | Slaughterhouse personnel | 46/466 (5.6%) |
| Bisdorff et al. (2012) | Germany | Diverse | "Livestock contact" | 46/190 (24.2%) |
| Vandendriessche et al. (2013) | Belgium | Diverse | Farmer | 36/138 (26.1%) |
| Van Cleef et al. (2010b) | Netherlands | Diverse | Farmer | 13/49 (26.5%) |
| Van Den Broek et al. (2009) | Netherlands | Pigs | Farmer[a] | 33/139 (23.7%) |
| Cuny et al. (2009) | Germany | Pigs | Farmer | 97/113 (85.8%) |
| Köck et al. (2012) | Germany | Pigs | Farmer | 27/35 (77%) |
| Dahms et al. (2014) | Germany | Pigs | Farmer | 20/36 (56%) |
| Van Cleef et al. (2014) | Netherlands | Pigs | Farmer | 42/110 (38.2%) |
| Graveland et al. (2011) | Netherlands | Cattle | Farmer | 19/51 (37.3%) |
| Antoci et al. (2013) | Italy | Cattle | Farmer | 40/113 (35.4%) |
| Dahms et al. (2014) | Germany | Cattle | Farmer | 0/25 (0%) |
| Graveland et al. (2010) | Netherlands | Veal calves | Farmer | 41/131 (31.3%) |
| Geenen et al. (2013) | Netherlands | Poultry | Farmer | 5/56 (8.9%) |
| Dahms et al. (2014) | Germany | Poultry | Farmer | 0/17 (0%) |
| Richter et al. (2012) | Germany | Turkeys | Farmer | 22/59 (37.3%) |
| Wulf et al. (2006) | Netherlands | Diverse | Veterinarian | 7/179 (3.9%) |
| Wulf et al. (2008b) | Denmark | Diverse | Veterinarian | 34/272 (12.5%) |
| Garcia-Graells et al. (2012) | Belgium and Denmark | Diverse | Veterinarian | 16/289 (5.5%) |
| Paterson et al. (2013) | UK | Cattle | Veterinarian | 8/307 (2.6%) |
| Verkade et al. (2013) | Netherlands | Pigs, cattle | Veterinarian | 60/137 (43.8%) |
| Cuny et al. (2009) | Germany | Pigs | Veterinarian | 22/49 (45%) |

[a] from MRSA positive farms.

Could be…

as low as 3.2 % … in the Netherlands …

but as high as 86% … in Germany …

UK is also quite low … but they are different, are they not ?

Goerge et al. Vet Microbiol. 2017;200:6-12 - PMID: 26658156

# The current epidemiological situation… Europe … and the animals …

## 2. But do they get infections ?

**Table 2**
Reports on infections associated with LA-MRSA among persons with livestock contact.

| Publication | Type of infection (clonal information) | Country | Type of livestock exposure | Treatment (outcome) |
|---|---|---|---|---|
| Huijsdens et al. (2006) | Mastitis (CC398, t108) | Netherlands | Wife of pig farmer | Teicoplanin (recovered) |
| Declercq et al. (2008) | Complicated wound infection after pig bite (CC398, t011/t108) | Belgium | Pork keeper | Local treatment plus vancomycin and linezolid (recovered) |
| Ruhlmann et al. (2008) | Wound infection/septic arthritis after knee surgery complicated by renal micro-abscesses; ear lobe infection (CC398, t034) | Denmark | Pig farm workers | Vancomycin/penicillin (later linezolid, ciprofloxacin, penicillin) for wound infection (recovered); local treatment for ear lobe (recovered) |
| Pan et al. (2009) | Cellulitis, pyomyositis, pelvic abscesses (CC398, t899) | Italy | Pig farmer | Vancomycin + rifampicin (improved) |
| Aspiroz et al. (2010) | Skin lesion (CC398, t011) | Spain | Girl living close to pig farm, where parents worked | Topical treatment with mupirocin ointment (recovered) |
| Hartmeyer et al. (2010) | Pressure ulcer and pneumonia of newborn (CC398, t034) | Denmark | Pig farmer and newborn within same family | Vancomycin to treat pneumonia (recovered) |
| Soavi et al. (2010) | Necrotizing fasciitis (CC398, t899) | Italy | 52-year old dairy cattle farmer | Teicoplanin, clindamycin, linezolid (recovered) |
| Lozano et al. (2011a) | Skin lesion, psoriasis superinfection (CC398, t011, t108) | Spain | Pig farmer | Antiseptic, metilprednisole solution and betametasone cream, fusidic acid for cutaneous lesions, mupirocin nasal ointment (improved) |
| Lozano et al. (2011c) | Thoracic empyema (CC398, t011) | Spain | 79-year old man with COPD living close to pig farm and working there part-time | Linezolid (fatal) |
| Lozano et al. (2011b) | Skin lesions (CC398, t1451) | Spain | Pig farmer | Fusidic acid and mupirocin nasal ointment (improved) |
| Omland and Hoffmann (2012) | Impetigo and tonsillitis (CC398) | Denmark | Farmers | Information not provided |
| Berning et al. (2015) | Joint infection followed by endocarditis and bacteremia, pneumonia (CC398, t011/t2576) | Germany | Immunocompromised patients from pig farming families | Daptomycin/fosfomycin, Linezolid (both fatal) |

Yes, they got infections,…

and most were successfully treated, …

but for 2 cases…

# The current epidemiological situation… animals again …

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RESEARCH ARTICLE
Clinical Science and Epidemiology

## Drivers and Dynamics of Methicillin-Resistant Livestock-Associated *Staphylococcus aureus* CC398 in Pigs and Humans in Denmark

Raphael N. Sieber,[a] Robert L. Skov,[a]* Jens Nielsen,[a] Jana Schulz,[b] Lance B. Price,[c,d] Frank M. Aarestrup,[e] Anders R. Larsen,[a] Marc Stegger,[a,c] Jesper Larsen[a]

[a]Statens Serum Institut, Copenhagen, Denmark
[b]National Veterinary Institute, Technical University of Denmark, Kgs. Lyngby, Denmark
[c]Translational Genomics Research Institute, Flagstaff, Arizona, USA
[d]George Washington University, Washington, DC, USA
[e]National Food Institute, Technical University of Denmark, Kgs. Lyngby, Denmark

Sieber et al. MBio. 2018;9:e02142-18 - PMID: 30425152

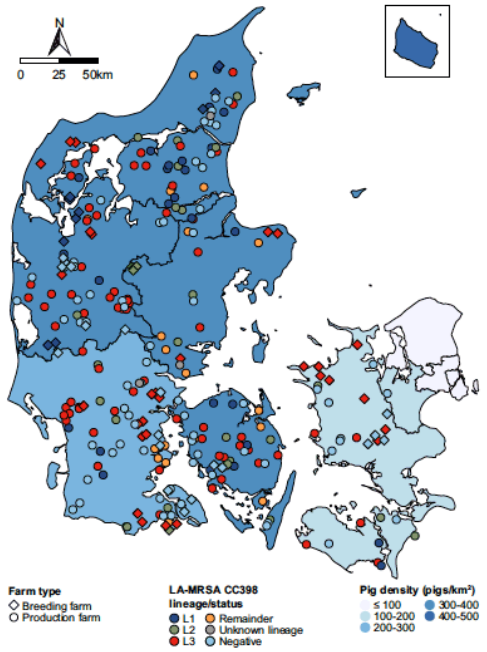


FIG 4 Spatial distribution of pig farms from the 2014 survey. Each farm was placed randomly within a 5-km radius of the exact CHR address to protect anonymity. The pig density per km² is shown for each province. Abbreviations: LA-MRSA, livestock-associated methicillin-resistant *Staphylococcus aureus*; CC, clonal complex; L1, lineage 1; L2, lineage 2; L3, lineage 3. The administrative boundaries are from EuroGeographics.

**Key messages:**

- LA-MRSA CC398 is resistant to nearly all β-lactams and several non-β-lactam antimicrobials.
- An important cause of human infections in countries with previously low levels of MRSA, (Netherlands, Denmark).
- important drivers for rapid spread:
  - ➢ pig movements between farms
  - ➢ resistance to specific antibiotics (aminoglycosides [*aadD* and *aadE*; *str*], lincosamides [*lnu*(B)],, quinolones [*gyr*A], tetracyclines [*tet*M]), and heavy metals (cadmium/zinc [*czrC*])

# The current epidemiological situation… Still Europe but beyond…

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

Infection, Genetics and Evolution 53 (2017) 189–194

journal homepage: www.elsevier.com/locate/meegid

Research paper

## Molecular epidemiology and antibiotic resistance of methicillin-resistant *Staphylococcus aureus* circulating in the Russian Federation

Vladimir Gostev [a], Alexander Kruglov [b], Olga Kalinogorskaya [a], Olga Dmitrenko [c], Olga Khokhlova [d], Tatsuo Yamamoto [e,f], Yuri Lobzin [a,g], Irina Ryabchenko [b], Sergey Sidorenko [a,g,*]

[a] Scientific Research Institute of Children's Infections, Saint Petersburg, Russia
[b] National Agency for Clinical Pharmacology and Pharmacy, Moscow, Russia
[c] N. F. Gamaleya Federal Research Centre of Epidemiology and Microbiology, Moscow, Russia
[d] State Medical University named after Professor V.F. Vojno-Yasenetsky, Krasnoyarsk, Russia
[e] Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[f] International Medical Education and Research Centre, Niigata, Japan
[g] North-western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

Gostev et al. Infect Genet Evol. 2017;53:189-94 - PMID: 28600216


**Hospital acquired MRSA**

- 83.1% CC8 isolates (ST8 + ST239) (CC5: 12.2%; CC22: 1.2%)
- livestock-associated MRSA (clusters CC398 and CC97) detected in humans !
- high resistance: ciprofloxacin, gentamicin, and chloramphenicol (76%–92%),
- moderate resistance: tetracycline, erythromycin, clindamycin, and rifampicin (38%–54%)
- low resistance: fusidic acid, co-trimoxazole, mupirocin, and daptomycin (2%–7%)
- **26% with vancomycin MIC= 2 mg/L !**
- **CC5 isolates show ceftaroline MIC=2 mg/L !**
- all isolates susceptible to linezolid and tigecycline.

- 2053 healthy persons screened (nasal carriage): **21% positive !** 13 cases CA-MRSA (ST22 - SCCmec types IVa and IVc, agr type I, tst-positive) - similar to the EMRSA-15/Middle Eastern variant (Gaza strain).

# The current epidemiological situation… South America …

frontiers in Microbiology

ORIGINAL RESEARCH
published: 27 February 2019
doi: 10.3389/fmicb.2019.00082

## Local Diversification of Methicillin-Resistant *Staphylococcus aureus* ST239 in South America After Its Rapid Worldwide Dissemination

*Ana Maria Nunes Botelho[1], Maiana Oliveira Cerqueira e Costa[2], Ahmed M. Moustafa[3], Cristiana Ossaille Beltrame[1], Fabienne Antunes Ferreira[1], Marina Farrel Côrtes[1], Bruno Souza Scramignon Costa[1], Deborah Nascimento Santos Silva[1], Paula Terra Bandeira[1], Nicholas Costa Barroso Lima[2], Rangel Celso Souza[2], Luiz Gonzaga Paula de Almeida[2], Ana Tereza Ribeiro Vasconcelos[2], Apurva Narechania[4], Chanelle Ryan[3], Kelsey O'Brien[3], Sergios-Orestis Kolokotronis[4,5], Paul J. Planet[3,4]*, Marisa Fabiana Nicolás[2]* and Agnes Marie Sá Figueiredo[1]**

Botelho et al. Front Microbiol. 2019;10:82 - PMID: 30873127


**Background:**

- Multilocus sequence type ST 239 (cassette chromosome type III [SCCmecIII]) is one of the most successful HA-MRSA lineages.
- ST239 lineage has long been an emerging clone in Europe and Asia…
- Heteroresistance to vancomycin (hVISA) has recently been detected in ST239 isolates…

**What was seen:**

- ST239 began to spread in South America and Brazil in approximately 1988.
- Phylogenomic analyses suggest rapid initial global radiation, with subsequent local spread and adaptation in multiple different geographic locations….

**What is the risk …**

- Most ST239 isolates harbor the *ardA* gene, … which may have improved its ability to acquire multiple resistance genes and distinct virulence-associated genes in each local context.

# The current epidemiological situation… Asia … and CA-MRSA

Clinical Epidemiology

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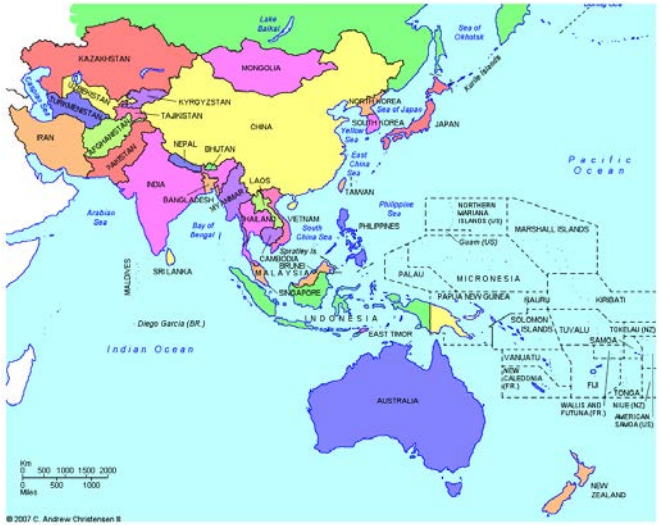
REVIEW

## Prevalence and risk factors of community-associated methicillin-resistant *Staphylococcus aureus* carriage in Asia-Pacific region from 2000 to 2016: a systematic review and meta-analysis

Jonathan WH Wong,[1] Margaret Ip,[2] Arthur Tang,[3] Vivian WI Wei,[1] Samuel YS Wong,[1] Steven Riley,[4] Jonathan M Read,[5,6,*] Kin On Kwok[1,7,8,*]

Wong et al. Clin Epidemiol. 2018;10:1489-1501 - PMID: 30349396



# The current epidemiological situation… Asia … and CA-MRSA

Clinical Epidemiology

Open Access Full Text Article

## Prevalence and risk factors of cor… associated methicillin-resistant *Sta… aureus* carriage in Asia-Pacific regi… to 2016: a systematic review and …

Jonathan WH Wong,[1] Margaret Ip,[2] Arthur Tang,[3] Vivian WI Wei,[1] Samuel … Jonathan M Read,[5,6,*] Kin On Kwok[1,7,8,*]

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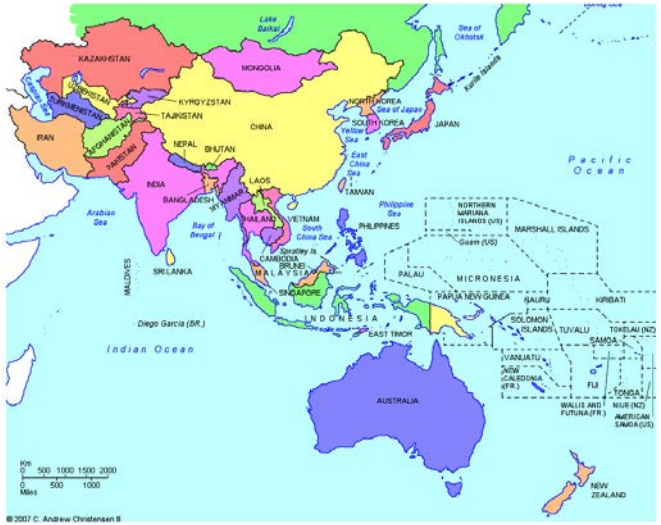


**Table 1** Country-specific CA-MRSA carriage prevalence

| Community settings | | | | | Hospital settings | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Studies** | **Study number[a]** | **Study start year** | **Prevalence (%)** | **Binomial 95% CI[b]** | **Studies** | **Study number[a]** | **Study start year** | **Prevalence (%)** | **Binomial 95% CI[b]** |
| Australia | | | | | | | | | |
| Munckhof et al 2009[50] | 95 | 2005 | 0.3 | 0.0, 1.0 | Brennan et al 2013[66] | 6 | 2009 | 0.9 | 0.1, 3.2 |
| | | | | | Brennan et al 2013[66] | 7 | 2010 | 10.4 | 6.6, 15.5 |
| | | | | | Verwer et al 2012[58] | 132 | 2007 | 2.8 | 2.0, 3.7 |
| China | | | | | | | | | |
| Chen et al 2015[51] | 21 | 2013 | 0.3 | 0.0, 1.9 | | | | | |
| India | | | | | | | | | |
| Goud et al 2011[52] | 32 | 2003 | 16.5 | 13.9, 19.4 | George et al 2016[59] | 30 | 2012 | 2.3 | 1.3, 3.8 |
| Jain et al 2014[53] | 56 | 2006 | 23.5 | 17.8, 30.0 | | | | | |
| Taiwan | | | | | | | | | |
| Lu et al 2005[54] | 88 | 2001 | 3.5 | 2.7, 4.4 | Chang et al 2015[60] | 10 | 2014 | 3.6 | 1.0, 9.0 |
| Wang et al 2009[55] | 136 | 2007 | 3.8 | 3.2, 4.6 | Chen et al 2010[61] | 17 | 2008 | 3.4 | 1.3, 7.2 |
| | | | | | Wang et al 2010[62] | 141 | 2008 | 1.8 | 1.2, 2.6 |
| South Korea | | | | | | | | | |
| Ro et al 2012[56] | 114 | 2007 | 1.1 | 1.0, 1.1 | Park et al 2016[63] | 107 | 2007 | 2.6 | 2.4, 2.8 |
| Vietnam | | | | | | | | | |
| Van Nguyen et al 2014[57] | 131 | 2012 | 7.9 | 6.3, 9.7 | | | | | |
| Nepal | | | | | | | | | |
| | | | | | Joshi et al 2017[64] | 62 | 2014 | 0.7 | 0.2, 1.9 |
| New Zealand | | | | | | | | | |
| Williamson et al 2013[65] | 144 | 2005 | 0.0[c] | 0.0, 0.0 | | | | | |
| Range (%) | | | 0.0–23.5 | | | | | 0.7–10.4 | |

**Notes:** [a]Refer to Appendix VIII for study details; [b]Clopper–Pearson exact transformation; [c]The precise value is 0.009%.
**Abbreviation:** CA-MRSA, community associated methicillin-resistant *Staphylococcus aureus*.

# The current epidemiological situation… Asia … and CA-MRSA

Clinical Epidemiology

Open Access Full Text Article

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Jonathan WH Wong,[1] Margaret Ip,[2] Arthur Tang,[3] Vivian WI Wei,[1] Samuel … Jonathan M Read,[5,6,*] Kin On Kwok[1,7,8,*]

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| Range (%) | | | 0.0–23.5 | | | | | 0.7–10.4 | |

**Notes:** [a]Refer to Appendix VIII for study details; [b]Clopper–Pearson exact transformation; [c]The precise value is 0.009%.
**Abbreviation:** CA-MRSA, community associated methicillin-resistant *Staphylococcus aureus*.

### Conclusions

- CA-MRSA carriage is widespread in the Asia-Pacific region and poses a clear health threat with a potentially large health care cost.
- We urge health authorities, especially those from developing countries, to prioritize the control of CA-MRSA through community action plans and multilevel antibiotic stewardship

# The current epidemiological situation… Asia … a broader view

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

Journal of Global Antimicrobial Resistance 16 (2019) 17–27

journal homepage: www.elsevier.com/locate/jgar

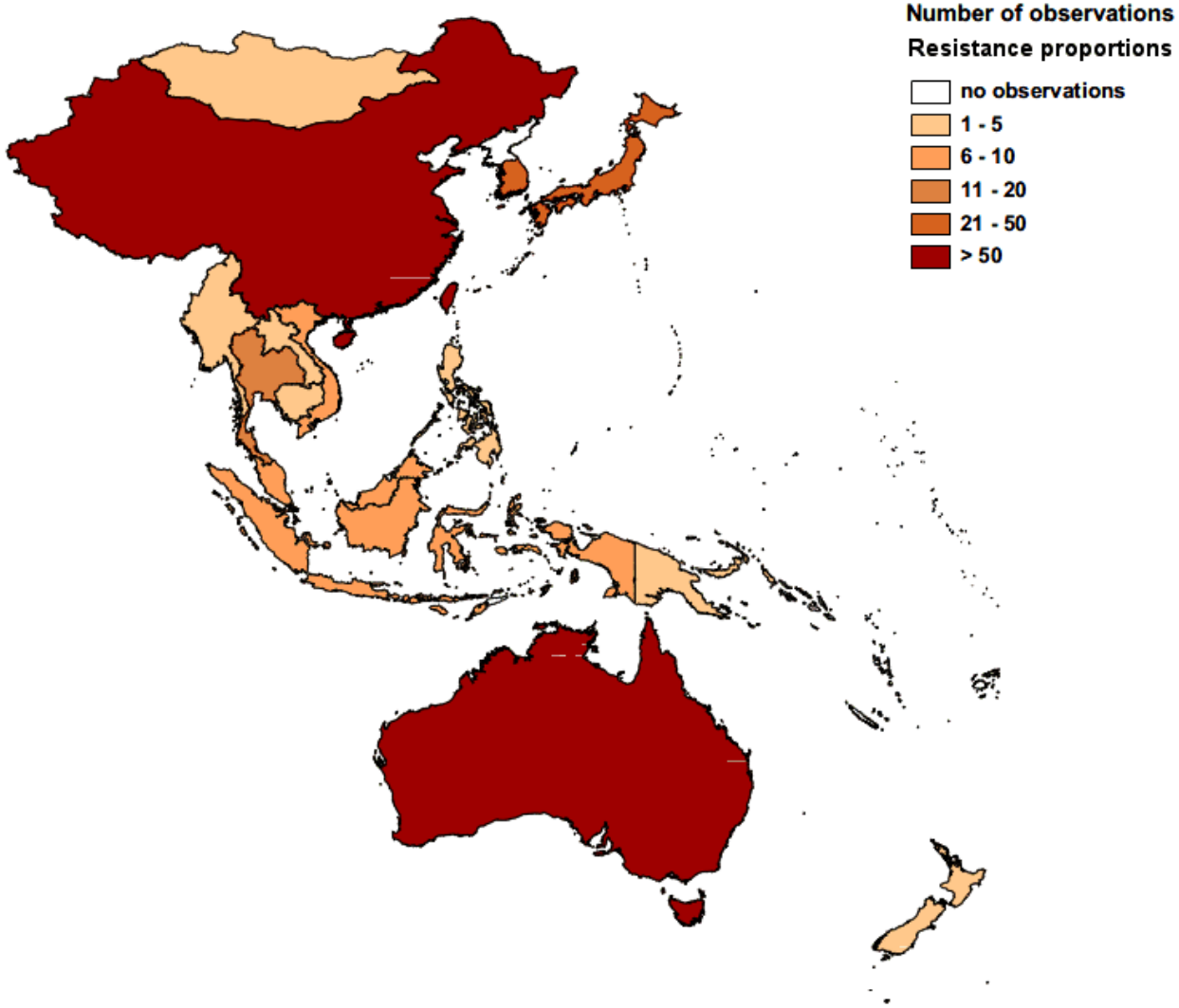
Review

## Determinants of methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence in the Asia-Pacific region: A systematic review and meta-analysis

Wey Wen Lim[a], Peng Wu[a,*], Helen S. Bond[a], Jessica Y. Wong[a], Kaiwen Ni[a], Wing Hong Seto[a], Mark Jit[a,b,c], Benjamin J. Cowling[a]

[a] *World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[b] *Modelling and Economics Unit, Public Health England, London, UK*
[c] *Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK*

Lim et al. J Glob Antimicrob Resist. 2019;16:17-27 - PubMed PMID: 30145271




Number of observations reported for methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence and resistance proportions in selected locations in the Asia-Pacific region (2000–2016).

# The current epidemiological situation… Asia … a broader view

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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[a] World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
[b] Modelling and Economics Unit, Public Health England, London, UK
[c] Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

Lim et al. J Glob Antimicrob Resist. 2019;16:17-27 - PubMed PMID: 30145271

Conclusions:

- Prevalence of MRSA infections in the Asia-Pacific region is comparable with what is reported in other regions.
- Greater influence of country income status and the sample population characteristics…
- MRSA prevalence and resistance must be analyzed separately as these are two distinct metrics.

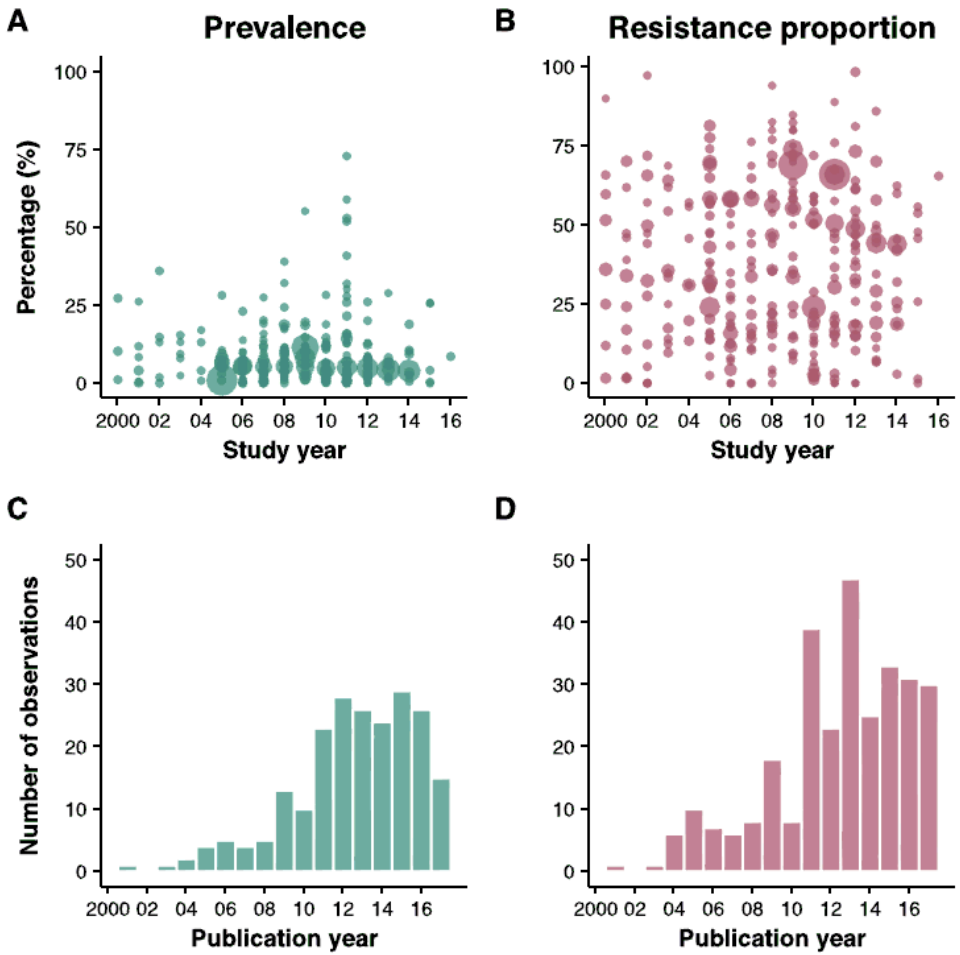


**Fig. 3.** Methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence and resistance proportions reported in Asia-Pacific by year of study and the number of observations or data points by year of publication. (A) MRSA prevalence, defined as the proportion of MRSA among all tested samples, reported in selected countries between the years 2000 and 2016. For studies that report prevalence for more than one year, the midpoint of the study is reported as the study year. Bubble sizes reflect the study sample size for each observation. (B) MRSA resistance proportion, defined as the proportion of MRSA among all *S. aureus* isolates, reported in selected countries between the years 2000 and 2016. For studies that report the proportion for more than one year, the midpoint of the study is reported as the study year. Bubble sizes reflect the study sample size for each observation. (C) Number of observations or data points of MRSA prevalence in selected countries in 2000–2017. (D) Number of observations or data points of MRSA resistance proportions in selected countries in 2000–2017.

# 2. Risks

http://www.bbc.co.uk/learningenglish/english/features/6-minute-english/ep-151217
Last visited: 6 Apr 2019

# But what are the risks … for all invasive infections in early evaluations

MAJOR ARTICLE

## Population-Based Study of the Epidemiology of and the Risk Factors for Invasive *Staphylococcus aureus* Infections

**Kevin B. Laupland,[1,2,3] Deirdre L. Church,[1,3,6] Melissa Mucenski,[4] Lloyd R. Sutherland,[1,5] and H. Dele Davies[4,5,6]**

Departments of [1]Medicine, [2]Critical Care Medicine, [3]Pathology and Laboratory Medicine, [4]Pediatrics, [5]Community Health Sciences, and [6]Microbiology and Infectious Diseases, University of Calgary, Calgary Health Region, and Calgary Laboratory Services, Calgary, Canada

Laupland et al. J Infect Dis. 2003;187:1452-9 - PMID: 12717627

### 1. age

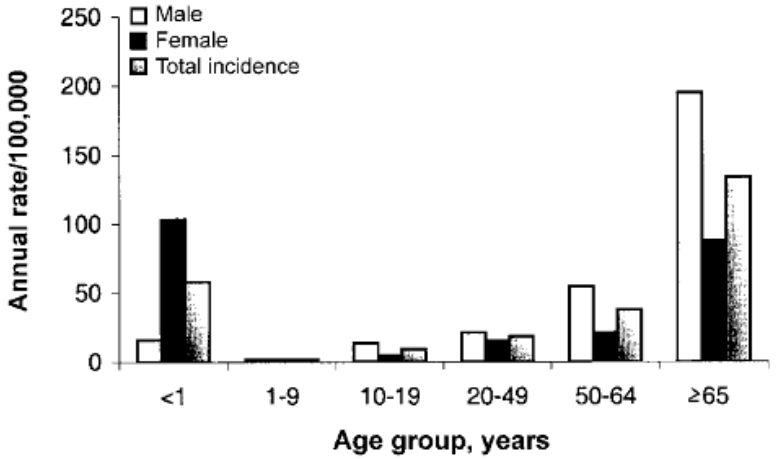


**Figure 2.** Age-specific incidence of invasive *Staphylococcus aureus* infections in Calgary, Canada (May 1999 to April 2000). Data are annual incidence per 100,000 population

### 2. underlying conditions

**Table 1. Risk of invasive *Staphylococcus aureus* infection, associated with selected underlying conditions, in adults ⩾20 years old.**

| Underlying condition | No. of patients with ISA infection ($n$ = 226) | Annual incidence, per 100,000 | Relative risk (95% confidence interval) | $P$ |
|---|---|---|---|---|
| Hemodialysis | 24 | 7692 | 257.2 (161.0–393.6) | <.001 |
| Peritoneal dialysis | 3 | 4918 | 150.0 (30.5–441.1) | <.001 |
| Human-immunodeficiency-virus infection | 4 | 778 | 23.7 (6.4–61.4) | <.001 |
| Solid organ transplantation | 3 | 683 | 20.7 (4.2–61.3) | <.001 |
| Heart disease | 114 | 362 | 20.6 (15.8–27.0) | <.001 |
| Cancer | 47 | 348 | 12.9 (9.1–17.8) | <.001 |
| Illicit intravenous drug use | 13 | 321 | 10.1 (5.3–17.7) | <.001 |
| Alcohol abuse | 31 | 241 | 8.2 (5.4–12.0) | <.001 |
| Diabetes mellitus | 48 | 192 | 7.0 (5.0–9.7) | <.001 |
| Stroke | 16 | 200 | 6.4 (3.6–10.6) | <.001 |
| Chronic obstructive pulmonary disease | 26 | 120 | 3.9 (2.5–5.9) | <.001 |
| Systemic lupus erythematosus | 2 | 80 | 2.4 (0.3–8.7) | .3 |
| Rheumatoid arthritis | 5 | 74 | 2.2 (0.7–5.3) | .1 |

**NOTE.** ISA, invasive *Staphylococcus aureus*.

# But what are the risks as seen today at the Mayo Clinic

MAYO CLINIC

Patient Care & Health Information › Diseases & Conditions

## MRSA infection

https://www.mayoclinic.org/diseases-conditions/mrsa/symptoms-causes/syc-20375336
Last visited: 3 Apr 2019

**Risk factors**

Because hospital and community strains of MRSA generally occur in different settings, the risk factors for the two strains differ.

**Risk factors for HA-MRSA**

- **Being hospitalized.** MRSA remains a concern in hospitals, where it can attack those most vulnerable — older adults and people with weakened immune systems.
- **Having an invasive medical device.** Medical tubing — such as intravenous lines or urinary catheters — can provide a pathway for MRSA to travel into your body.
- **Residing in a long-term care facility.** MRSA is prevalent in nursing homes. Carriers of MRSA have the ability to spread it, even if they're not sick themselves.

**Risk factors for CA-MRSA**

- **Participating in contact sports.** MRSA can spread easily through cuts and abrasions and skin-to-skin contact.
- **Living in crowded or unsanitary conditions.** Outbreaks of MRSA have occurred in military training camps, child care centers and jails.
- **Men having sex with men.** Homosexual men have a higher risk of developing MRSA infections.
- **Using intravenous drugs.** People who inject drugs are an estimated 16.3 times more likely to develop invasive MRSA infections than others.

# A recent European view on the risk of MRSA pneumonia

## Accepted Manuscript


Healthcare-asociated pneumonia:Any reasons to still utilize this label in 2019?

Santiago Ewig, Martin Kolditz, Mathias W. Pletz, James Chalmers

To appear in: *Clinical Microbiology and Infection*

Ewig et al. Clin Microbiol Infect. 2019; Feb 27: S1198-743X(19)30090-4 [Epub ahead of print] PMID: 30825674

**Table 3**

Predictors of MRSA and P.aeruginosa pneumonia (45)

| **MRSA pneumonia** |
|---|
| *Positive association* |
| Male gender |
| Age > 74 |
| Diabetes mellitus |
| COPD |
| Recent nursing home or hospital stay |
| Recent exposure to fluoroquinolones or antibiotics treating Gram-positive pathogens |
| Severe pneumonia |
| *Negative association* |
| Complicated diabetes mellitus |

# Development of a scoring system for Community-Onset MRSA

MICROBIAL DRUG RESISTANCE
Volume 24, Number 5, 2018

DOI: 10.1089/mdr.2017.0236

## A Risk-Scoring System for Predicting Methicillin Resistance in Community-Onset *Staphylococcus aureus* Bacteremia in Korea

Hyeon Jeong Suh,[1,*] Wan Beom Park,[2,*] Sook-In Jung,[3] Kyoung-Ho Song,[1] Yee Gyung Kwa
Kye-Hyung Kim,[5] Jeong-Hwan Hwang,[6] Na Ra Yun,[7] Hee-Chang Jang,[8] Young Keun Kim,
Nak-Hyun Kim,[1] Kyung-Hwa Park,[3] Seung Ji Kang,[8] Shinwon Lee,[5] Eu Suk Kim,[1]
Hong Bin Kim[1]; and the Korea Infectious Diseases (KIND) Study Group**

Suh et al. Microb Drug Resist 2018;24:556-62 - PMID: 29863981

**THE METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* -PREDICTIVE SCORING SYSTEM FOR COMMUNITY-ONSET *STAPHYLOCOCCUS AUREUS* BACTEREMIA**

| | *Beta* | *aOR (95% CI)* | p | *Points* | |
|---|---|---|---|---|---|
| Age ≥65 years | 0.456 | 1.577 (1.263–1.970) | <0.001 | | |
| Underlying illness | | | | | |
| Hematologic disease | –0.809 | 0.445 (0.234–0.847) | 0.014 | √ | –1.0 |
| Primary site of infection | | | | | |
| BJI | –0.431 | 0.650 (0.481–0.878) | 0.005 | | |
| SSTI | –0.562 | 0.570 (0.410–0.793) | 0.001 | | |
| Endovascular | –0.786 | 0.456 (0.263–0.790) | 0.005 | √ | –1.0 |
| Epidemiological characteristics | | | | | |
| Hospitalization or surgery[a] | 0.718 | 2.050 (1.640–2.563) | <0.001 | √ | +0.5 |
| Long-term facility[a] | 0.518 | 1.679 (1.297–2.173) | <0.001 | | |
| Dialysis[a] | 0.389 | 1.475 (1.075–2.024) | 0.016 | | |
| Previous isolation of MRSA[b] | 1.494 | 4.456 (2.974–6.677) | <0.001 | √ | +1.5 |

[a]Within past 1 year.
[b]Within 6 months.
√, factors included in the scoring system; aOR, adjusted odds ratio; CI, confidence interval.

# Development of a scoring system for Community-Onset of MRSA

MICROBIAL DRUG RESISTANCE
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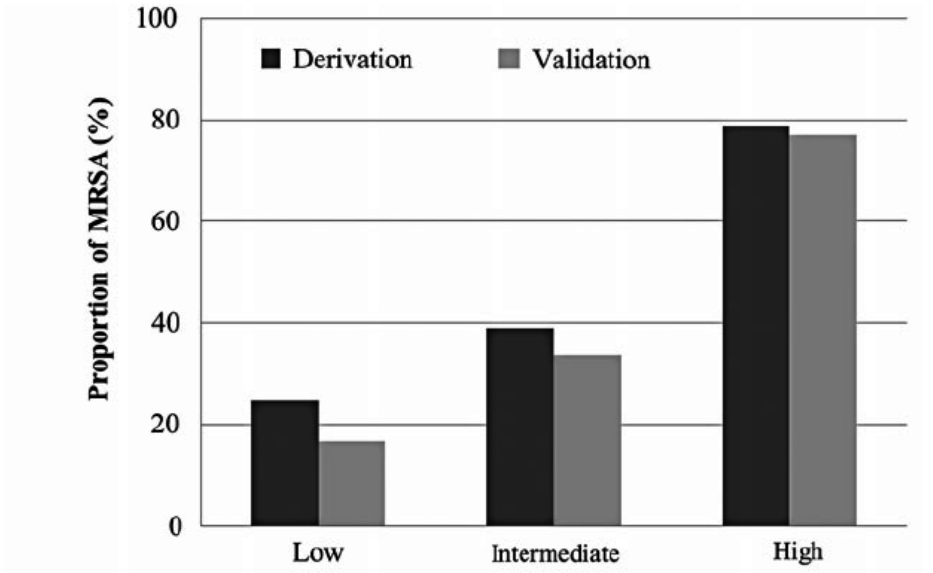



| | Low (score*<-0.5) | Intermediate (-0.5≤score*<1.5) | High (score*≥1.5) |
|---|---|---|---|
| Derivation, n (%) | 22/89 (24.7) | 607/1557 (39.0) | 123/156 (78.8) |
| Validation, n (%) | 1/6 (16.7) | 112/331 (33.8) | 10/13 (76.9) |

**FIG. 1.** The proportion of MRSA among community-onset *Staphylococcus aureus* bacteremia patients in each risk group. *The score ranged from −2 to +2 points. MRSA, methicillin-resistant *S. aureus*.

# The risks seen in (some of the ) recent literature

- **Children:**
  ↗ ↗ : dialysis or plasmapheresis, organ transplantation, cancer,
  ↗ : chromosomal anomalies, atopic dermatitis, congenital heart disease and surgery
  (Bruun Oestergaard *et al.*)

- **HIV patients:**
  ↗ previous MRSA infection, hospitalization in the past year, use of antibiotics
  (Sabbagh *et al*.)

- **Prisonners:**
  MRSA colonization, previous skin infection, sharing soap or personal items, SSTI presenting as an abscess or furuncle, younger age, non-Caucasian, overweight, communal laundering, infrequent handwashing, lower hygiene score
  (Haysom *et al*.)

- **MRSA skin and soft tissue infections for MRSA-colonized patients on discharge**:
  prior hospital admission within 12 months, prior MRSA infection, previous myocardial infarction
  (Cadena *et al*.)

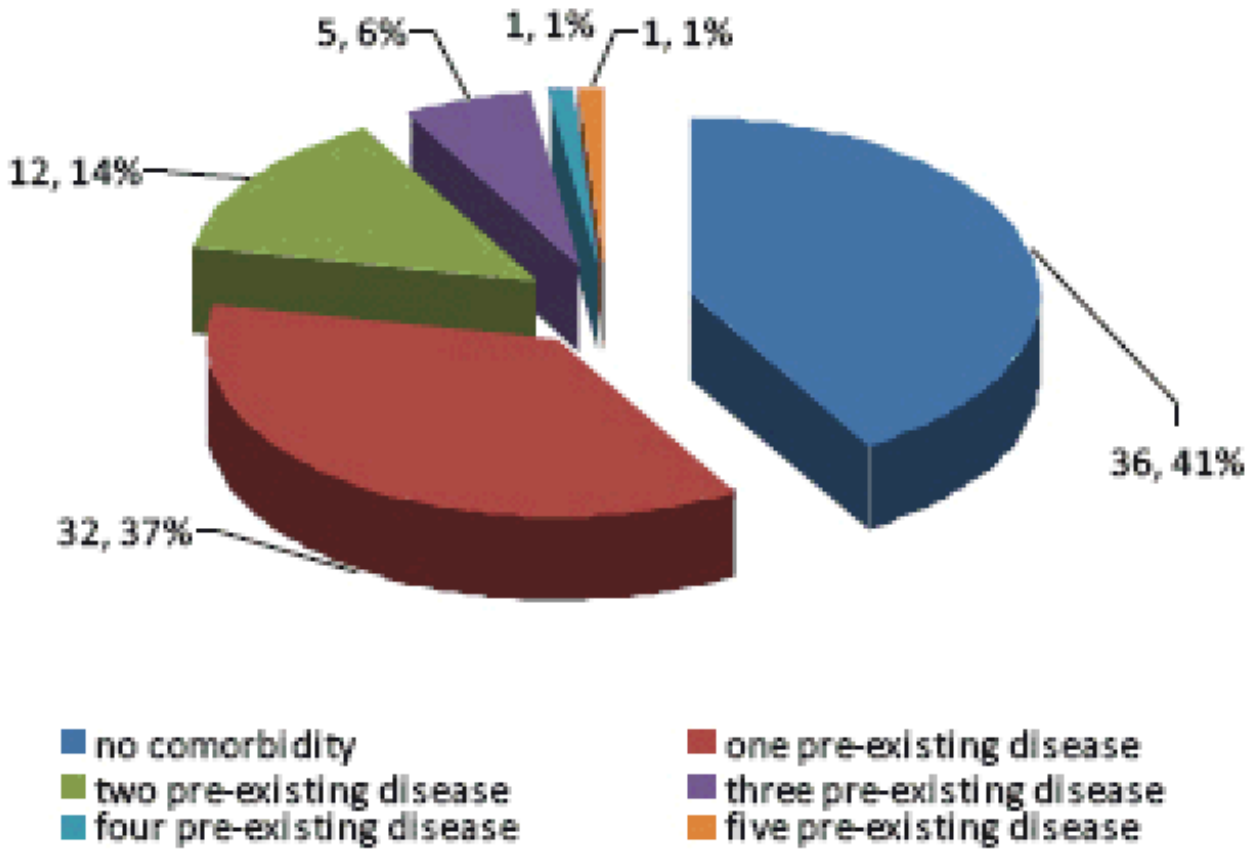

Bruun Oestergaard et al. J Pediatr. 2018;203:108-15.e3 - PMID: 30244992
Sabbagh et al. Am J Infect Control 2019;47:323-333 - PMID: 30170767
Haysom et al. J Correct Health Care. 2018;24:197-213 - PMID: 29661109
Cadena et al. Epidemiol Infect. 2016;144:647-51 - PMID: 26194247

# The risks seen in recent literature: some (selected) points of discussion …

- **Can you predict/distinguish MSSA and MRSA ?**
  - "*no definitive clinical or epidemiological risk factors which could distinguish MRSA from MSSA in bacteraemic patients with the exception of the previous use of antibiotics*"
    (Wi *et al.* )
- **Predictors of MRSA infection ?**
  - "*colonization status appears to be the only independent and reliable predictor of MRSA infection in cases of S. aureus bacteremia. A clinical approach based on a patient's known MRSA colonization status and on local susceptibility patterns may be appropriate*"
    (Butler-Laporte et al.)
- **Are Health Care workers a risk ?**
  - "*579 employees from 39 outpatient services: MRSA prevalence was 1.2% in all and 1.7% in nursing staff*"
    (Peters *et al.*)
- **What happens in ICU ?**
  - "*APACHE-II score >15 and hospital stay of >4 days with MRSA increase the risk of developing a second multidrug-resistant colonization/infection …*"
    (Ochotorena *et al*.)


Wi et al. Epidemiol Infect. 2018;146:1326-36 - PMID: 29781425
Butler-Laporte et al. BMC Infect Dis 2018;18:270 - PMID: 29890954
Peters et al. BMJ Open 2018;8:e021204 - PMID: 30012786
Ochotorena et al. Biol Res Nurs 2019;21:190-7 - PMID: 30537857

# Co-morbidities




Lukovac et al. Mater Sociomed 2012;24(Suppl 1):13-5 - PMID: 24493989

# Co-morbidities or risks ?

## 2. underlying conditions

Renal failure

Immunosuppression

Unsafe injections
Low hygiene

Vascular insufficiency

Colonization
Antibiotics

**Table 1. Risk of invasive *Staphylococcus aureus* infection, associated with selected underlying conditions, in adults ≥20 years old.**

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**NOTE.** ISA, invasive *Staphylococcus aureus*.

Laupland et al. J Infect Dis. 2003;187:1452-9 - PMID: 12717627

# Do we need to take care of co-morbidities ?

## in 2002

*Journal of Antimicrobial Chemotherapy* (2002) **49**, 999–1005
DOI: 10.1093/jac/dkf009

JAC

### Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials

Eileen M. Graffunder* and Richard A. Venezia

*Department of Epidemiology MC-45, Albany Medical Center Hospital, 43 New Scotland Avenue, Albany, NY 12208, USA*

Graffunder et al. J Antimicrob Chemother 2002;49:999-1005 - PMID: 12039892

"*Patients infected with MRSA tended to have **more co-morbidities**, longer lengths of stay and greater exposure to antibiotics than MSSA-infected patients… but these factors **failed to achieve statistical significance** in multivariate analysis.*"

## in 2019

Accepted Manuscript

Healthcare-asociated pneumonia:Any reasons to still utilize this label in 2019?

Santiago Ewig, Martin Kolditz, Mathias W. Pletz, James Chalmers

To appear in: *Clinical Microbiology and Infection*


Ewig et al. Clin Microbiol Infect. 2019; Feb 27: S1198-743X(19)30090-4 [Epub ahead of print] PMID: 30825674

"*The use of validated predictive scores along with implementation of deescalation strategies and **careful individual assessment of comorbidity** and functional status seem superior strategies for the clinical management*"

# But do we have good predictive scores ?

American Journal of Epidemiology
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Vol. 161, No. 5
*Printed in U.S.A.*
DOI: 10.1093/aje/kwi068

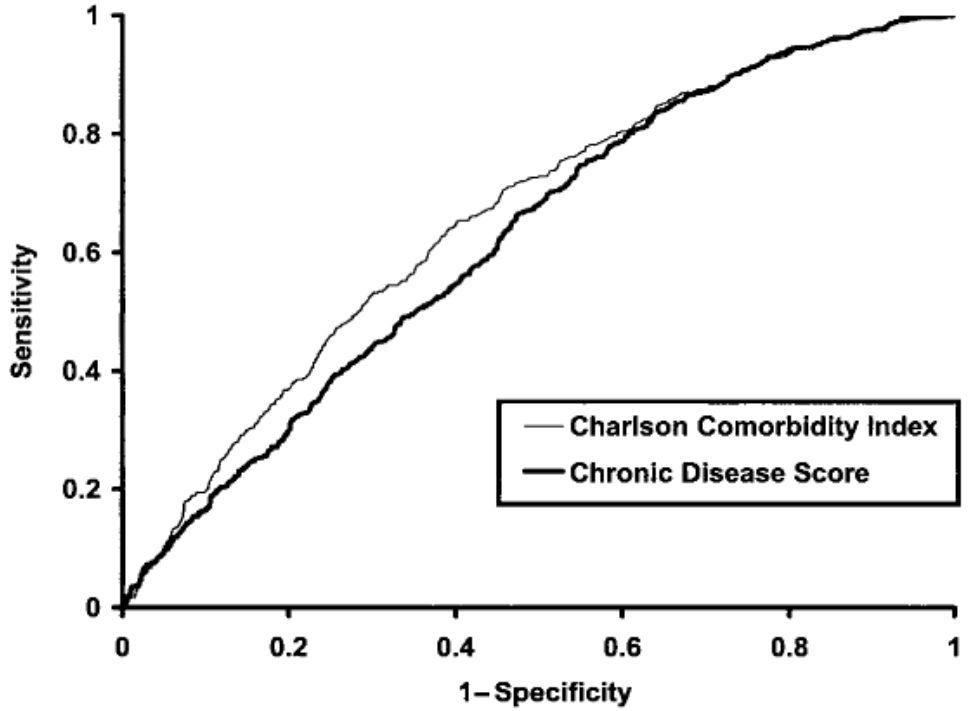
**PRACTICE OF EPIDEMIOLOGY**

## Utility of the Chronic Disease Score and Charlson Comorbidity Index as Comorbidity Measures for Use in Epidemiologic Studies of Antibiotic-resistant Organisms

**Jessina C. McGregor[1], Peter W. Kim[2], Eli N. Perencevich[1,3], Douglas D. Bradham[1,3], Jon P. Furuno[1], Keith S. Kaye[4], Jeffrey C. Fink[1,5], Patricia Langenberg[1], Mary-Claire Roghmann[1,3], and Anthony D. Harris[1,3]**

[1] Department of Epidemiology and Preventive Medicine, School of Medicine, University of Maryland, Baltimore, MD.
[2] Division of Anti-Infective Drug Products, Office of Drug Evaluation IV, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD.
[3] VA MD Health Care System, Baltimore, MD.
[4] Department of Medicine, Duke University Medical Center, Durham, NC.
[5] Division of Nephrology, Department of Medicine, University of Maryland Medical Center, Baltimore, MD.

McGregor at al. Am J Epidemiol 2005;161:483-93 - PMID: 15718484




Receiver operator characteristic curves for the Chronic Disease Score and Charlson Comorbidity Index as predictors of methicillin-resistant *Staphylococcus aureus* clinical culture positivity with age (years) and sex included in the model

**Note:**
The closer the ROC curve is to the **upper left corner**, the higher the overall accuracy of the test …
(Zweig & Campbell. Clin Chem 1993;39:561-77 - PMID: 8472349 )

# But do we have good predictive scores ?

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[3] VA MD Health Care System, Baltimore, MD.
[4] Department of Medicine, Duke University Medical Center, Durham, NC.
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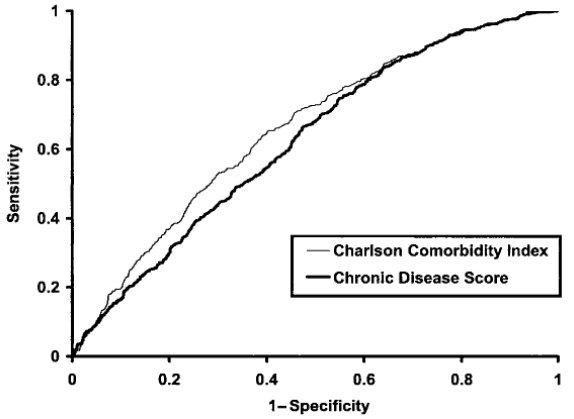
McGregor at al. Am J Epidemiol 2005;161:483-93 - PMID: 15718484




Receiver operator characteristic curves for the Chronic Disease Score and Charlson Comorbidity Index as predictors of methicillin-resistant *Staphylococcus aureus* clinical culture positivity with age (years) and sex included in the model

"*The **Charlson Comorbidity Index** was not originally designed for use as predictor of nosocomial infections with antibiotic-resistant bacteria …*"

The authors have proposed a more dedicated score but its discrimination ability remains low (c statistic < 0.7)…
(McGregor et al. J Clin Epidemiol 2006;59:1266-73 – 17098569)

**Comparison of the discriminating abilities of the CDS* and the CCI* in the methicillin-resistant *Staphylococcus aureus* study**

| | *c* statistic | 95% CI* | Chi-square *p* value |
|---|---|---|---|
| CDS, unadjusted | 0.6076 | 0.5801, 0.6342 | <0.01 |
| CCI, unadjusted | 0.6528 | 0.6272, 0.6784 | |
| CDS, adjusted† | 0.6252 | 0.5994, 0.6509 | 0.01 |
| CCI, adjusted† | 0.6586 | 0.6330, 0.6842 | |

* CDS, Chronic Disease Score; CCI, Charlson Comorbidity Index; CI, confidence interval.
† Adjusted for age and sex.

"*It is typically desirable that model discrimination (the c statistic) be greater than 0.70.*"

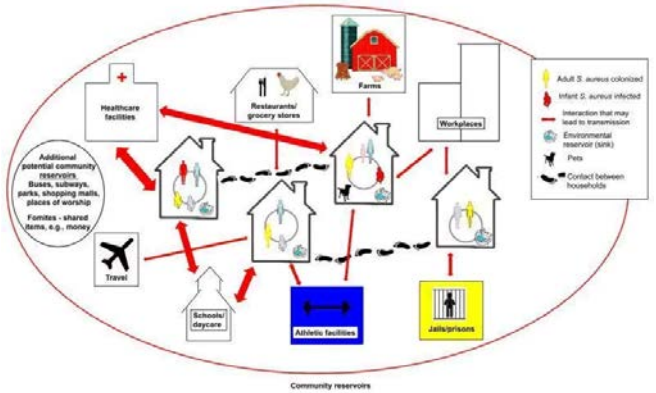
# A few more comments …

- **Paying attention ?**

*"Here's your problem—it looks like you're paying attention to what's going on."*

https://condenaststore.com/featured/paying-attention-pia-guerra.html
Last visited: 6 Apr 2019

- **Preventing transmission ?**




https://drewsmithblog.com/2018/01/my-roommate-is-colonized-with-mrsa-how-contagious-is-he-and-what-should-i-do-to-ensure-that-i-do-not-get-it/
Last visited: 6 Apr 2019

- **Do we need new drugs**


https://www.youtube.com/watch?v=hu6DqeaOFXk
Last visited: 6 Apr 2019

# Why do we need to pay attention to MRSA ?

*European Journal of Public Health*, Vol. 0, No. 0, 1–6

doi:10.1093/eurpub/cky262

## Risk of hospital readmission and associated factors after a positive sample for a multidrug-resistant microorganism

Alexis Sentís[1,2,3], Cristina González[1], Maria Montero[4,5,6], Milagros Herranz[1], Carlota Hidalgo[1], Cristina Campà[1], Maria Sala[1,6,7,8], Francesc Macià[1,2,6,7], Marta Román[1,6,7], Albert Prats-Uribe[1,2], Juan Pablo Horcajada[4,5,6,8], Xavier Castells[1,6,7,8]

1 Department of Epidemiology and Evaluation, Hospital del Mar, Barcelona, Spain
2 Preventive Medicine and Public Health Training Unit, Hospital del Mar-UPF-ASPB, Barcelona, Spain
3 Universitat Pompeu Fabra, Barcelona, Spain
4 Department of Infectious Diseases, Hospital del Mar, Barcelona, Spain
5 (REIPI) Spanish Network for Research Infectious Diseases, Sevilla, Spain
6 (IMIM) Hospital del Mar Research Institute, Hospital del Mar Research Institute (IMIM), Barcelona, Spain
7 REDISSEC (Health Services Research on Chronic Patients Network), Barcelona, Spain
8 Universitat Autònoma de Barcelona, Barcelona, Spain

Sentís et al. Eur J Public Health 2018; Dec 24 [Epub ahead of print] - PMID: 30590519

**Readmission risk at 30 days**

| | ORa (95% CI) (*N*=40 306) |
|---|---|
| **MRM-positive sample *** | |
| No | 1.00 |
| Yes | 1.41 (1.17–1.69) |
| **Sex** | |
| Women | 1.00 |
| Men | 1.19 (1.11–1.27) |
| **Age** | |
| 18–40 years | 1.00 |
| 41–64 years | 1.45 (1.26–1.66) |
| ≥65 years | 1.71 (1.50–1.96) |
| **Grouped Charlson index** | |
| 0. No comorbidities | 1.00 |
| 1. Low comorbidity | 1.30 (1.18–1.42) |
| 2. High comorbidity | 2.14 (1.97–2.33) |
| **Admission type** | |
| Elective | 1.00 |
| Urgent | 1.25 (1.16–1.34) |

Three logistic regression models

*** MRM: multidrug-resistant microorganisms**

# Why do we need to pay attention to MRSA ?

*European Journal of Public Health*, Vol. 0, No. 0, 1–6

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Sentís et al. Eur J Public Health 2018; Dec 24 [Epub ahead of print] - PMID: 30590519

### Readmission risk at 30 days

**Patients with an MRM-positive sample**

| | ORa (95% CI) (*N*=983) |
|---|---|
| **Microorganism type** | |
| ESBL-KP | 1.00 |
| ESBL-EC | 1.30 (0.73–2.30) |
| MRSA | 2.03 (1.10–3.75) |
| PAMR | 1.65 (0.87–3.13) |
| MREC | 1.10 (0.45–2.69) |
| Others | 0.37 (0.05–2.93) |

Three logistic regression models

ESBL, producing extended-spectrum β-lactamase;
EC, *E. coli*;
KP, *K. pneumoniae*;
MRSA, methicillin-resistant *S. aureus*;
PAMR, multi-resistant *P. aeruginosa*.
MREC, multi-resistant *E. cloacae*;

# Why do we need to pay even more attention (in €…) to MRSA ?

RESEARCH ARTICLE

## The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and *Staphylococcus aureus* in European hospitals, 2010 and 2011: a multicentre retrospective cohort study

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Stewardson et al. Euro Surveill. 2016;21:pii=30319 - PMID: 27562950

# Why do we need to pay even more attention (in €…) to MRSA ?

RESEARCH ARTICLE

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Monte Carlo simulation results using economic and accounting bed-day values to estimate the cost of bloodstream infections, 10 European hospitals, 2010–2011 (n = 606,649)

| Exposure | Population | Excess LOS per BSI days (95% CrI) [a] | Expected annual cumulative incidence per hospital [b] | Estimated cost per infection EUR (95% CrI) | |
|---|---|---|---|---|---|
| | | | | Economic costing [c] | Accounting costing [d] |
| MSSA BSI | Hospitalised patients | 10.3 (9.3–11.5) | 102 | 760 (190–3,000) | 9,500 (5,800–16,000) |
| MRSA BSI | Hospitalised patients | 12.2 (9.9–14.7) | 19 | 890 (220–3,600) | 11,000 (6,600–19,000) |
| Meticillin resistance | Patients with *S. aureus* BSI | 1.9 (–0.7 TO 4.6) | NA | 120 (–60 TO 740) | 1,600 (–700 TO 5,000) |

BSI: bloodstream infection;
LOS: length of stay;
MRSA/MSSA: meticillin-resistant/susceptible *Staphylococcus aureus*;

[a] Output from probabilistic sensitivity analysis
[b] Estimated for a hospital with 450,000 bed-days annually
[c d] Employs the bed-day valuation

# Lastly… Can we prevent MRSA spread ?

eLIFE elifesciences.org RESEARCH ARTICLE

## Inference and control of the nosocomial transmission of methicillin-resistant *Staphylococcus aureus*

**Sen Pei[1]*, Flaviano Morone[2], Fredrik Liljeros[3], Hernán Makse[2], Jeffrey L Shaman[1]***

[1]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, United States; [2]Levich Institute and Physics Department, City College of New York, New York, United States; [3]Department of Sociology, Stockholm University, Stockholm, Sweden

Pei et al. Elife 2018;7:e40977 - PMID: 30560786

**Background:**

- MRSA are moving between hospitals and community,[1] obscuring our understanding of their dynamics and persistence.
- MRSA often colonize silently ... and can be transmitted stealthily [2]...
- Sweden has a low prevalence of MRSA (mostly imported) making outbreak studies quite interesting (importation → nosocomial transmission)

**Approach:**

- Agent-based network model-Bayesian inference system for estimating unobserved colonization and importation rates from simple incidence records.

**Key observations:**

- a small number of patients have a disproportionately high risk of colonization…
- the inference-based intervention can identify and treat the pivotal individuals, or superspreaders…

1. Tosas et al. PLoS Med. 2016;13:e1001944 - PMID: 26812054
2. Cooper et al. Proc Natl Acad Sci USA 2004;101:10223-8 - PMID: 15220470

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**Message:**

Cost-effective int (should ?) be pra targeted screen a of **identified high-risk patients**.

# Why do we need to pay even still more attention to MRSA ?

MIT Technology Review

Rewriting Life

## A New MRSA Defense

Marijuana extracts kill antibiotic-resistant MRSA

by Nora Schultz September 12, 2008

Scientists from Italy and the United Kingdom, who published their research in the *Journal of Natural Products* last month, say that cannabis-based creams could also be developed to treat persistent skin infections.


**We may need effective drugs…**

http://www.mrsaidblog.com/2012/09/13/can-honey-really-cure-mrsa/
Last visited: 1 Apr 2019

# What will be our future ?


Anatomy Lesson of Dr. Nicolaes Tulp – 1632 Mauritshuis Museum - The Hague , The Netherlands - https://favourite-paintings.blogspot.com/2011/06/rembrandt-van-rijn-anatomy-lesson-of-dr.html - Last visited: 2 Apr 2019