Molecular Epidemiology of MRSA in Europe

Alex W. Friedrich, University of Muenster, Germany
State of North Rhein-Westfalia
18 Mio inhabitants
2nd largest university in Germany

Townhall of the Westfalian Peace Treaty
City of Münster
Münsterland
MRSA prevalence in *S. aureus* bacteriaemia worldwide
MRSA in Europe

- Affects **150,000 patients** per year in Europe

- **MRSA-infection:**
  Up to 2.4 times significantly higher Mortality

- **Issue of patient safety**

- **Reason for emerging MRSA**
  - insufficient hygiene in hospitals
  - too many antibiotics given
  - lack of trans-mural case management

- **Nasal carriage** origin of infection
  -> Finding and treating carriers avoids infection!

- **MRSA additional costs:** Per patient: 5,000 € to 20,000 €
  EU healthcare system: 380 Mio € per year

- **Differences in MRSA-Prevalence** between countries

  Koeck et al. 2010. Eurosurreillance
Methicillin-resistant *Staphylococcus aureus* (MRSA): burden of disease and control challenges in Europe

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14. National Reference Centre for MRSA, University Hospital Zurich, Zurich, Switzerland

<table>
<thead>
<tr>
<th>Type, place and period of study</th>
<th>Odds ratio/hazard ratio for MRSA-associated mortality (95% CI)</th>
<th>Percentage mortality in MRSA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-centre, university hospital, Taiwan, 1990–2004</td>
<td>1.78 (1.3–2.44)</td>
<td>50%</td>
</tr>
<tr>
<td>Single-centre, university hospital, Belgium, 1992–1998</td>
<td>1.93 (1.18–3.18)</td>
<td>64%</td>
</tr>
<tr>
<td>Single-centre, teaching hospital, UK, 1995–2000</td>
<td>1.72 (0.92–3.20)</td>
<td>12%</td>
</tr>
<tr>
<td>Veterans affairs healthcare system, USA, 1995–2003</td>
<td>1.8 (1.2–3.0)</td>
<td>34%</td>
</tr>
<tr>
<td>Single-centre, university hospital, USA, 1996–2001</td>
<td>5.4 (1.5–18.7)</td>
<td>35%</td>
</tr>
<tr>
<td>Single-centre, university hospital, France, 1997–1998</td>
<td>2.97 (1.12–7.88)</td>
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<tr>
<td>Single-centre, tertiary-care teaching hospital, USA, 1997–2000</td>
<td>1.2 (0.68–2.12)</td>
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<tr>
<td>Multi-centre, Germany, 1997–2002</td>
<td>3.84 (1.51–10.2)</td>
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<td>Two centres, teaching hospital UK, 1997–2004</td>
<td>1.49 (0.99–2.26)</td>
<td>34%</td>
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<tr>
<td>Single-centre, teaching hospital, USA, 1999–2001</td>
<td>1.4 (0.7–3.0)</td>
<td>31%</td>
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<tr>
<td>Single-centre, university hospital, Brazil, 2000–2001</td>
<td>2.52 (0.96–6.6)</td>
<td>55%</td>
</tr>
<tr>
<td>Single-centre, university hospital, Taiwan, 2001–2006</td>
<td>0.73 (0.21–2.60)</td>
<td>10%</td>
</tr>
<tr>
<td>Single-centre, university hospital, Belgium, 2002–2004</td>
<td>3.04 (1.15–8.04)</td>
<td>42%</td>
</tr>
<tr>
<td>Single-centre, university hospital, Germany, 2002–2007</td>
<td>2.6 (1.4–4.9)</td>
<td>42%</td>
</tr>
<tr>
<td>Single-centre, tertiary care, USA, 2004–2005</td>
<td>5.1 (1.1–22.9)</td>
<td>47%</td>
</tr>
</tbody>
</table>

*Percentage mortality in MRSA patients*
The question is: Which MRSA are rising, which are falling?
National guideline on MRSA

<table>
<thead>
<tr>
<th>Country</th>
<th>Available</th>
<th>YES/NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>35%</td>
</tr>
</tbody>
</table>
First edition of national MRSA guidelines

First national MRSA guidelines were released in the following countries:

- Denmark (1988)
- Netherlands (1991)
- Belgium (1993)
- Germany (1999)
- France (1995)
- Finland (1994)
- Malta (2001)
- Hungary (2001)
- Bulgaria (2000)
- Slovenia & UK/Scotland (2003)
- Luxembourg (2002)
- Norway (2004)
- Latvia (2005)
- Ireland (2005)
- Czech Republic & Macedonia (2006)
- Turkey (2009)
- Croatia (2008)
- Spain (2007)
- Italy (2011)

First national Nosocomial infection control programme:

**Preventive Microbiology = infection control**

**Cholera-infection control measures (1908):**

„Everything depends on the fact that we have valid detection methods for the microorganisms. This counts especially for the human carriers who contribute most for the spread of the disease“

Speech of Robert Koch on 11.2.1908 in front of the Medical order of Berlin. Deutsche Medizinische Wochenschrift, 1908, Nr. 8

**MRSA „search&follow-Strategy“ (2010)**

Colonisation comes before infection

A: Rapid identification of MRSA-carriers
B: Decolonization of MRSA-carriers,

In order to:

a.) prevent infection in the patient
b.) prevent spread to other patients

c.) start early an optimal antibiotic therapy
Health-care settings covered by MRSA national guideline

**Acute care**
- Guideline available (n=19)?
  - 19 100% YES
  - 0 0% NO

**Long-term**
- Guideline available?
  - 12 63% YES
  - 7 37% NO

**Primary care**
- Guideline available?
  - 6 32% YES
  - 13 68% NO
SeqNet.org does...

A. Capacity building for sequence based typing in European laboratories
   - International workshops since 2004, next 5-8 of October 2010
     Münster, Zagreb, Sophia

B. Internal quality control
   - SOP for internal quality control

C. External quality control
   - SeqNet.org certification
   - Annual proficiency testing
   - Continuous quality control

D. Curatorship for spa server
   - Synchronization of typing data
   - Access via StaphType and Bionumerics
   - Study groups within spa server
     (Euregio study area, SRL-study group)

Friedrich A.W. et al. 2006. Euro Surveill;
Ensuring a common typing language...

Advisory board: H. Westh [DK], J. Scheres [NL], W. Hryniewicz [PL] & H. de Lencastre [USA]

Friedrich A.W. et al. 2006. Euro Surveill; 11
de Sousa et al. 2006. J Clin Microbiol; 44
Friedrich A. W. et al. 2008 Euro Surveill; 13
Harmsen et al., J Clin Microbiol 2003
Strommenger et al J Clin Microbiol 2006
SeqNet.org Network
Laboratory-Esperanto for *S. aureus*

**Coordinators:** A.W. Friedrich [Münster] & W. Witte [Robert Koch Institut]
**Advisory board:** H. Westh [DK], J. Scheres [NL], W. Hryniewicz [PL] & H. de Lencastre [USA]

- Spa-types: 7425
- Repeats: 426
- Total strains: 147086
- Strain records: 94505
- Strain countries: 76
- Registered users: 367
- User countries: 37

n = 118,397

- no data
- < 1% of all data
- 1% to 4%
- 5% to 10%
- > 10%

Friedrich A. W. et al. Euro Surveill; 2008
Harmsen et al., J Clin Microbiol 2003
Strommenger et al J Clin Microbiol 2006
Grundmann et al. PloS Med. 2010

12.10.2010
Geographic Distribution of *Staphylococcus aureus* Causing Invasive Infections in Europe: A Molecular-Epidemiological Analysis

Hajo Grundmann¹, David M. Aanensen³, Cees C. van den Wijngaard¹, Brian G. Spratt³, Dag Harmsen⁴, Alexander W. Friedrich⁵, the European Staphylococcal Reference Laboratory Working Group⁶

¹ National Institute for Public Health and the Environment, Bilthoven, The Netherlands, ² Department of Medical Microbiology, University Medical Centre, Groningen, The Netherlands, ³ Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom, ⁴ Department of Periodontology, University Hospital Münster, Germany, ⁵ Institute of Hygiene, University Hospital Münster, Germany

Abstract

**Background:** *Staphylococcus aureus* is one of the most important human pathogens and methicillin-resistant *S. aureus* (MRSA) is a major cause of hospital and community-acquired infections. MRSA is the dominant clones that cause invasive infections in Europe.

**Methods and Findings:** In each country, staphylococcal reference laboratories recruited a number of hospital laboratories to achieve national geo-demographic representation of MRSA and successive methicillin-susceptible (MSSA) and MRSA isolates from patients. Relevant genetic and phenotypic information was assembled into a Web-based mapping application. Between September 2006 and February 2007, five countries collected 2890 MSSA and MRSA isolates from patients with invasive infections. The distribution of spa types was found with some prevalent in all European countries. Genetic diversity of MRSA differed considerably between countries with and without geographical clusters. We provide evidence that a network approach consisting of aggregated data using an interactive mapping tool can provide important information for populations such as early signalling of emerging strains, cross border spread.

**Conclusions:** In contrast to MSSA, MRSA spa types have a predominantly restricted distribution indicating the selection and spread of a limited number of clones within health care institutions. These efforts aimed at interrupting the spread within and between health care institutions have been successful and should therefore be strongly encouraged.
# General results

<table>
<thead>
<tr>
<th>Statistics</th>
<th>n(^a)</th>
<th>MSSA (%)</th>
<th>MRSA (%)</th>
<th>Total/Overall (%)</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>2,890</td>
<td>1,923 (66.5)</td>
<td>967 (33.5)</td>
<td>2,890 (100%)</td>
<td>—</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>2,836</td>
<td>63 (46–75)</td>
<td>69 (55–78)</td>
<td>66 (49–76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>2,862</td>
<td>1,159 (60.8)</td>
<td>606 (63.3)</td>
<td>1,765 (61.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>All-cause mortality after 14 d (%)</td>
<td>1,838</td>
<td>153 (13.2)</td>
<td>141 (20.8)</td>
<td>294 (16.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital acquisition (%)</td>
<td>2,322</td>
<td>777 (51.6)</td>
<td>585 (71.7)</td>
<td>1,362 (58.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>N spa types</td>
<td>2,850</td>
<td>565</td>
<td>155</td>
<td>660(^b)</td>
<td>—</td>
</tr>
<tr>
<td>N not typeable</td>
<td>2,850</td>
<td>27 (1.4)</td>
<td>13 (1.3)</td>
<td>40 (1.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Index of diversity (95% CI)</td>
<td>2,850</td>
<td>0.985 (0.983–0.987)</td>
<td>0.940 (0.933–0.947)</td>
<td>0.983 (0.982–0.984)</td>
<td>&lt;0.05(^c)</td>
</tr>
<tr>
<td>Mean distance in kilometres between laboratories that isolated identical spa types (95% CI)</td>
<td>1,614(^d)</td>
<td>1,046.2 (1109.5–983.0)</td>
<td>786.8 (975.7–597.9)</td>
<td>—</td>
<td>0.03(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Number of isolates for which data were available.
\(^b\) Total number of spa types includes 60 spa types that contain both MSSA and MRSA.
\(^c\) Deduced from non-overlapping 95% confidence intervals.
\(^d\) Includes only MRSA and MSSA with more than ten isolates per spa type.

DOI: 10.1371/journal.pmed.1000215.t002
MRSA vs. MSSA

Diversity indices & confidence intervals

MRSA

MSSA

Countries: Austria (119, 54), Belgium (107, 87), Bulgaria (23, 25), Croatia (47, 35), Czech (94, 51), France (114, 111), Germany (98, 81), Greece (15, 14), Hungary (64, 44), Ireland (65, 84), Italy (60, 67), Malta (2, 10), Poland (132, 47), Portugal (48, 40), Romania (25, 11), Spain (112, 91), United Kingdom (68, 96)
### S. aureus blood culture isolates in Europe

<table>
<thead>
<tr>
<th>Rank</th>
<th>MSSA spa Type</th>
<th>MLST</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Percent</th>
<th>Rank</th>
<th>MRSA spa Type</th>
<th>MLST</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t002</td>
<td>ST-5*, S-231a</td>
<td>93</td>
<td>4.8</td>
<td>4.8</td>
<td>1</td>
<td>t032</td>
<td>ST-22*</td>
<td>140</td>
<td>14.5</td>
<td>14.4</td>
</tr>
<tr>
<td>2</td>
<td>t084</td>
<td>ST-15* (ST-18)</td>
<td>89</td>
<td>4.6</td>
<td>9.5</td>
<td>2</td>
<td>t008</td>
<td>ST-8* (ST-247, ST-250, ST-254)</td>
<td>120</td>
<td>12.4</td>
<td>26.8</td>
</tr>
<tr>
<td>3</td>
<td>t015</td>
<td>ST-45*</td>
<td>84</td>
<td>4.4</td>
<td>13.8</td>
<td>3</td>
<td>t041</td>
<td>ST-111*, ST-228*</td>
<td>72</td>
<td>7.4</td>
<td>34.2</td>
</tr>
<tr>
<td>4</td>
<td>t091</td>
<td>ST-7*</td>
<td>82</td>
<td>4.3</td>
<td>18.1</td>
<td>4</td>
<td>t003</td>
<td>(ST-5) ST-225*</td>
<td>71</td>
<td>7.3</td>
<td>41.6</td>
</tr>
<tr>
<td>5</td>
<td>t012</td>
<td>ST-30*</td>
<td>77</td>
<td>4.0</td>
<td>22.1</td>
<td>5</td>
<td>t002</td>
<td>ST-5*, ST-231*</td>
<td>62</td>
<td>6.4</td>
<td>48.1</td>
</tr>
<tr>
<td>6</td>
<td>t127</td>
<td>ST-1*</td>
<td>57</td>
<td>3.0</td>
<td>25.1</td>
<td>6</td>
<td>t067</td>
<td>ST-5*, ST-125*</td>
<td>50</td>
<td>5.2</td>
<td>53.3</td>
</tr>
<tr>
<td>7</td>
<td>t008</td>
<td>ST-8* (ST-247, ST-250, ST-254)</td>
<td>55</td>
<td>2.9</td>
<td>27.9</td>
<td>7</td>
<td>t001</td>
<td>(ST-5, ST-222) ST-228*</td>
<td>30</td>
<td>3.1</td>
<td>56.4</td>
</tr>
<tr>
<td>8</td>
<td>t021</td>
<td>ST-30* (ST-33, ST-55)</td>
<td>49</td>
<td>2.5</td>
<td>30.5</td>
<td>8</td>
<td>t037</td>
<td>ST-239* (ST-240, ST-241*)</td>
<td>27</td>
<td>2.8</td>
<td>59.2</td>
</tr>
<tr>
<td>9</td>
<td>t005</td>
<td>ST-22* (ST-23, ST-60)</td>
<td>42</td>
<td>2.2</td>
<td>32.7</td>
<td>9</td>
<td>t030</td>
<td>ST-239* (ST-246)</td>
<td>20</td>
<td>2.1</td>
<td>61.2</td>
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<tr>
<td>10</td>
<td>t026</td>
<td>(ST-45, ST-47)</td>
<td>27</td>
<td>1.4</td>
<td>34.1</td>
<td>10</td>
<td>t024</td>
<td>ST-8*</td>
<td>14</td>
<td>1.4</td>
<td>62.7</td>
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<tr>
<td>11</td>
<td>t065</td>
<td>(ST-45, ST-46)</td>
<td>26</td>
<td>1.4</td>
<td>35.4</td>
<td>11</td>
<td>t190</td>
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<td>64.1</td>
</tr>
<tr>
<td>12</td>
<td>t160</td>
<td>(ST-12, ST-13)</td>
<td>26</td>
<td>1.4</td>
<td>36.8</td>
<td>12</td>
<td>t515</td>
<td>ST-22*</td>
<td>12</td>
<td>1.3</td>
<td>65.5</td>
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<tr>
<td>13</td>
<td>t056</td>
<td>(ST-101)</td>
<td>25</td>
<td>1.3</td>
<td>38.1</td>
<td>13</td>
<td>t038</td>
<td>ST-45*</td>
<td>12</td>
<td>1.2</td>
<td>66.7</td>
</tr>
<tr>
<td>14</td>
<td>t050</td>
<td>ST-45*</td>
<td>21</td>
<td>1.1</td>
<td>39.2</td>
<td>14</td>
<td>t022</td>
<td>ST-22*</td>
<td>11</td>
<td>1.1</td>
<td>67.8</td>
</tr>
<tr>
<td>15</td>
<td>t078</td>
<td>(ST-26)</td>
<td>21</td>
<td>1.1</td>
<td>40.2</td>
<td>15</td>
<td>t740</td>
<td>ST-45*</td>
<td>11</td>
<td>1.1</td>
<td>69.0</td>
</tr>
<tr>
<td>16</td>
<td>t164</td>
<td>(ST-20)</td>
<td>19</td>
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<td>16</td>
<td>t012</td>
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<td>0.9</td>
<td>69.9</td>
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<tr>
<td>17</td>
<td>t346</td>
<td>(ST-15, ST-620)</td>
<td>18</td>
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<td>17</td>
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<td>9</td>
<td>0.9</td>
<td>70.8</td>
</tr>
<tr>
<td>18</td>
<td>t024</td>
<td>ST-8*</td>
<td>17</td>
<td>0.9</td>
<td>43.1</td>
<td>18</td>
<td>t044</td>
<td>ST-80*</td>
<td>9</td>
<td>0.9</td>
<td>71.8</td>
</tr>
<tr>
<td>19</td>
<td>t230</td>
<td>ST-45*</td>
<td>17</td>
<td>0.9</td>
<td>43.9</td>
<td>19</td>
<td>t045</td>
<td>ST-5*, ST-225</td>
<td>8</td>
<td>0.8</td>
<td>72.6</td>
</tr>
<tr>
<td>20</td>
<td>t166</td>
<td>(ST-34)</td>
<td>16</td>
<td>0.8</td>
<td>44.8</td>
<td>20</td>
<td>t127</td>
<td>ST-1*</td>
<td>8</td>
<td>0.8</td>
<td>73.4</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>—</td>
<td>1,062</td>
<td>55.2</td>
<td>100.0</td>
<td></td>
<td>Other</td>
<td>—</td>
<td>258</td>
<td>26.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>—</td>
<td>1,923</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>967</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

STs in parentheses are those associated with the spa type in the SeqNet.org Spa typing data base.

*MLST as determined by SRLs.

doi:10.1371/journal.pmed.1000215.t003
MRSAB spa types?

[Map of Europe with various countries highlighted in different colors, each labeled with a code (e.g., t008, t032, t037).]
MRSA spa types on the spa server

- t037
- t001
- t190
- t010
- t008
- t041
- t030
- t012
- t030
- t003
- t024
- t044
- t044
- t002
- t003
- t032
- t032
- t008
- t041
- t041
- t030
- t127
- t008
- t030
- t190
- t030
- Lebanon

- t030
- t190
- ST239
- ST8
- CC8
- CC8
TOP 30 MRSA in Europe

MRSA on the *spa* server

MRSAB from SRL-study

n= 25995

n= 960
PVL-positive CA-MRSA

194 different spa types

75 different spa types
Change over time
PVL+ MRSA (n= 2035)
Most frequent PVL-positive MRSA-spa type

spa server 2008-2010
## Regional Cluster

<table>
<thead>
<tr>
<th>Regional Cluster Number</th>
<th>spa Type</th>
<th>spa Complex*</th>
<th>STb</th>
<th>Window Centre</th>
<th>Window Radius (km)</th>
<th>Countries reporting Clustered spa Type within Window</th>
<th>n Isolates Observed</th>
<th>n Isolates Expected</th>
<th>Log Likelihood Ratio</th>
<th>n MRSA among Observed Isolates</th>
<th>Percent MRSA among Observed Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  t067</td>
<td>2</td>
<td>5 &amp; 125</td>
<td></td>
<td>Alicante, Spain</td>
<td>716</td>
<td>ES, FR</td>
<td>55</td>
<td>4.7</td>
<td>126.9</td>
<td>46</td>
<td>84</td>
</tr>
<tr>
<td>2  t041</td>
<td>1</td>
<td>228</td>
<td></td>
<td>Split, Croatia</td>
<td>522</td>
<td>AT, HR, HU, SI, IT</td>
<td>59</td>
<td>10.6</td>
<td>84.76</td>
<td>59</td>
<td>100</td>
</tr>
<tr>
<td>3  t032</td>
<td>32</td>
<td>22</td>
<td></td>
<td>Belfast, Northern Ireland (UK)</td>
<td>596</td>
<td>IE, UK</td>
<td>77</td>
<td>15.9</td>
<td>84.74</td>
<td>75</td>
<td>97</td>
</tr>
<tr>
<td>4  t003</td>
<td>45</td>
<td>225</td>
<td></td>
<td>Leipzig, Germany</td>
<td>386</td>
<td>CZ, DE, PL</td>
<td>58</td>
<td>10.0</td>
<td>82.26</td>
<td>54</td>
<td>93</td>
</tr>
<tr>
<td>5  t008</td>
<td>8</td>
<td>8</td>
<td></td>
<td>Perpignan, France</td>
<td>931</td>
<td>AT, BE, DE, ES, FR, HR, PT, SI</td>
<td>119</td>
<td>45.5</td>
<td>72.96</td>
<td>105</td>
<td>88</td>
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<tr>
<td>6  t740</td>
<td>740</td>
<td>45</td>
<td></td>
<td>Goes, Netherlands</td>
<td>81</td>
<td>BE, NL</td>
<td>15</td>
<td>0.6</td>
<td>50.36</td>
<td>11</td>
<td>73</td>
</tr>
<tr>
<td>7  t030</td>
<td>12</td>
<td>239</td>
<td></td>
<td>Pleven, Bulgaria</td>
<td>331</td>
<td>BG, RO</td>
<td>16</td>
<td>0.7</td>
<td>45.24</td>
<td>15</td>
<td>94</td>
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<tr>
<td>8  t037</td>
<td>12</td>
<td>239</td>
<td></td>
<td>Plock, Poland</td>
<td>330</td>
<td>PL</td>
<td>21</td>
<td>2.2</td>
<td>36.02</td>
<td>18</td>
<td>86</td>
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<tr>
<td>9  t038</td>
<td>45</td>
<td>8</td>
<td></td>
<td>Wilrijk, Belgium</td>
<td>92</td>
<td>BE</td>
<td>12</td>
<td>0.8</td>
<td>32.71</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>10 t190</td>
<td>190</td>
<td>8</td>
<td></td>
<td>St Pölten, Austria</td>
<td>56</td>
<td>AT</td>
<td>10</td>
<td>0.3</td>
<td>29.63</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>11 t001</td>
<td>1</td>
<td>228</td>
<td></td>
<td>Sibenik, Croatia</td>
<td>885</td>
<td>AT, DE, HU, IT, MT</td>
<td>29</td>
<td>10.2</td>
<td>27.55</td>
<td>29</td>
<td>100</td>
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<tr>
<td>12 t435</td>
<td>435</td>
<td>427</td>
<td></td>
<td>Daugavpils, Latvia</td>
<td>189</td>
<td>LV</td>
<td>8</td>
<td>0.2</td>
<td>25.82</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13 t425</td>
<td>239</td>
<td>368</td>
<td></td>
<td>Riga, Latvia</td>
<td>0</td>
<td>LV</td>
<td>5</td>
<td>0.1</td>
<td>22.76</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>14 t127</td>
<td>127</td>
<td>1</td>
<td></td>
<td>Inowroclaw, Poland</td>
<td>131</td>
<td>PL</td>
<td>12</td>
<td>0.9</td>
<td>22.65</td>
<td>0</td>
<td>0</td>
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<tr>
<td>15 t032</td>
<td>32</td>
<td>22</td>
<td></td>
<td>Berlin, Germany</td>
<td>178</td>
<td>DE</td>
<td>19</td>
<td>3.2</td>
<td>22.2</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>16 t015</td>
<td>15</td>
<td>45</td>
<td></td>
<td>Lomza, Poland</td>
<td>558</td>
<td>CZ, LV, PL</td>
<td>35</td>
<td>11</td>
<td>20.72</td>
<td>7</td>
<td>20</td>
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<tr>
<td>17 t091</td>
<td>91</td>
<td>5</td>
<td></td>
<td>Ried, Austria</td>
<td>771</td>
<td>AT, BE, CZ, DE, FR, HR, HU, IT, NL, PL, SI</td>
<td>71</td>
<td>42.8</td>
<td>20.68</td>
<td>4</td>
<td>6</td>
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<td>18 t777</td>
<td>777</td>
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<td>277</td>
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<td>20.61</td>
<td>7</td>
<td>100</td>
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<tr>
<td>19 t081</td>
<td>78</td>
<td>25</td>
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<td>Maków Mazowiecki, Poland</td>
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<td>PL</td>
<td>4</td>
<td>0.0</td>
<td>19.37</td>
<td>3</td>
<td>75</td>
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<td>20 t515</td>
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<td>22</td>
<td></td>
<td>Mullingar, Ireland (UK)</td>
<td>196</td>
<td>IE, Northern Ireland (UK)</td>
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<td>0.7</td>
<td>18.94</td>
<td>9</td>
<td>100</td>
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<td>21 t002</td>
<td>2</td>
<td>5, 231</td>
<td></td>
<td>Coimbra, Portugal</td>
<td>484</td>
<td>ES, PT</td>
<td>33</td>
<td>10.6</td>
<td>18.37</td>
<td>20</td>
<td>61</td>
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<tr>
<td>22 t230</td>
<td>728</td>
<td>45</td>
<td></td>
<td>Hillerød, Denmark</td>
<td>235</td>
<td>DE, DK, SE</td>
<td>11</td>
<td>1.4</td>
<td>17.19</td>
<td>0</td>
<td>0</td>
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<tr>
<td>23 t044</td>
<td>4</td>
<td>80</td>
<td></td>
<td>Nicosia, Cyprus</td>
<td>916</td>
<td>GR, CY</td>
<td>6</td>
<td>0.2</td>
<td>17.09</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>24 t2054</td>
<td>8</td>
<td>8</td>
<td></td>
<td>St Mande, France</td>
<td>226</td>
<td>BE, FR4</td>
<td>5</td>
<td>0.2</td>
<td>16.64</td>
<td>3</td>
<td>60</td>
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<tr>
<td>25 t062</td>
<td>5</td>
<td>singleton</td>
<td></td>
<td>Szolnok, Hungary</td>
<td>145</td>
<td>HU</td>
<td>6</td>
<td>0.3</td>
<td>15.24</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>368 (mean)</td>
<td>339</td>
<td>702</td>
<td>173.1</td>
<td></td>
<td>522</td>
<td>74</td>
</tr>
</tbody>
</table>
SatScan Analysis for border independent cluster
22% of European population lives close borders

**Dutch-German Euregios**
Since 1958
12.4 Mio inhabitants
12,000 crossborder commuters/day
500 to 30,000 crossborder patient per year
Euregionale Netzwerk für Patientensicherheit und Infektionsprävention

www.eursafety.eu
www.mrsa-net.eu
EUREGIO MRSA-net (2009)

- Crossborder network of 44 German and Dutch hospitals
- Integrated network with GPs
- Common quality standards (search&follow)

- Prevalence screening of 23566 (D) and 3544 (NL) patients
- Each new MRSA isolate from all patients is *spa* typed by hospitals
- Hospital and laboratory data collected on EUREGIO server

**Twente/Achterhoek**

Inhab. 990,000
2,5 beds/1000 inhab
36 GPs/100,000 inhab
Microbiologists: 2,9 per 1000 patients
MRSA: 78 (7,8/100,000 inhab)
0,1 per 100 admissions
MRSA/ S. aureus: 1%
MRSAB: 1 (0,1/100,000)

**Münsterland**

Inhab. 1,566,000
6,9 beds/1000 Einw.
146 GPs+Specialists/100,000 inhab
Microbiologists: 1,0 per 1000 patients
MRSA: 2953 (189/100,000 inhab)
1,6/100 admissions
MRSA/ S. aureus: 3%-30%
MRSAB: 41 (2,6/100,000)

Friedrich et al. 2008. Eurosurveillance
Köck et al. 2009, JHI
Böcher et al. JAC 2010
EUREGIO mrsa-net
Twente/Münsterland

Friedrich et al. 2008. Eurosurveillance
Dreiländereck: NL, NRW, Nds
Real-time Surveillance of human MRSA isolates in the EUREGIO

Healthcare-associated (HA-) MRSA

- HA-MRSA respect the borders
- Patients coming from German hospitals are put into isolation
- HA-MRSA not transmitted via social contacts

Livestock-associated (LA-)MRSA

Incidence of spa types indicative for MLST CC398 (t011, t034, t108, t567, t571, t588, t753, t898, t899, t1184, t125, t1451, t1456, t1457, t2123, t2330, t2383, t2582, t3013):
Equal incidence of LA-MRSA genotypes on both sides of the border

Friedrich et al. 2008, Eurosurveillance
Data from EUREGIO MRSA-GIS, 2010, date of data retrieval June, 21st 2010
# Prevalence screening in the EUREGIO (n= 23,566)

- Admission screening and risk factor analysis of all patients in all 44 hospitals in the EUREGIO
- All MRSA spa typed
- 1,6 / 100 patients colonized at admission
- 33% of all patients with MRSA risk factor
- 89% of patients with MRSA show up with classical HA risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>MRSA (n=354)</th>
<th>No MRSA (n=20836)</th>
<th>Beta Coefficient</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive MRSA history</td>
<td>27</td>
<td>232</td>
<td>4.20</td>
<td>25.5</td>
<td>95% CI</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contact to MRSA carrier</td>
<td>9</td>
<td>177</td>
<td>1.64</td>
<td>15.9</td>
<td>95% CI</td>
<td>0.0044</td>
</tr>
<tr>
<td>History of hospital admission &lt; 6 months</td>
<td>173</td>
<td>4806</td>
<td>0.91</td>
<td>3.2</td>
<td>95% CI</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Direct transfer from other hospital</td>
<td>32</td>
<td>651</td>
<td>1.02</td>
<td>5.1</td>
<td>95% CI</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfer from nursing home</td>
<td>58</td>
<td>558</td>
<td>3.64</td>
<td>34.2</td>
<td>95% CI</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>89</td>
<td>2742</td>
<td>0.29</td>
<td>1.3</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>3</td>
<td>179</td>
<td>-§</td>
<td>-§</td>
<td>-§</td>
<td>-§</td>
</tr>
<tr>
<td>Burning trauma</td>
<td>0</td>
<td>39</td>
<td>-§</td>
<td>-§</td>
<td>-§</td>
<td>-§</td>
</tr>
<tr>
<td>Chron. wounds</td>
<td>48</td>
<td>415</td>
<td>4.0</td>
<td>54.5</td>
<td>26.2</td>
<td>113.6</td>
</tr>
<tr>
<td>Katheter</td>
<td>49</td>
<td>541</td>
<td>2.09</td>
<td>8.1</td>
<td>4.1</td>
<td>15.9</td>
</tr>
<tr>
<td>Chron. nursing</td>
<td>55</td>
<td>662</td>
<td>1.22</td>
<td>3.4</td>
<td>1.8</td>
<td>6.4</td>
</tr>
</tbody>
</table>

22% of MRSA carriers without classical risk factors

Real-time Surveillance of human MRSA isolates in the EUREGIO

Healthcare-associated (HA-) MRSA

Incidence of all MRSA cases per 100,000 inhabitants:
HA-MRSA respect the borders

Livestock-associated (LA-) MRSA

Incidence of spa types indicative for MLST CC398 (t011, t034, t108, t567, t571, t588, t753, t898, t899, t1184, t125, t1451, t1456, t1457, t2123, t2330, t2383, t2582, t3013):
Equal incidence of LA-MRSA genotypes on both sides of the border

Friedrich et al. 2008. Eurosurveillance
Data from EUREGIO MRSA-GIS, 2010, date of data retrieval June, 21st 2010
LA-MRSA in human MRSA-isolates of the EUREGIO

n = 283

EUREGIO (NL)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>8/65</td>
</tr>
<tr>
<td>2007</td>
<td>20/95</td>
</tr>
<tr>
<td>2008</td>
<td>56/123</td>
</tr>
</tbody>
</table>

n = 7191

EUREGIO (DE)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>180/1790</td>
</tr>
<tr>
<td>2007</td>
<td>223/2501</td>
</tr>
<tr>
<td>2008</td>
<td>295/2900</td>
</tr>
</tbody>
</table>
### Pig density in the Dutch-German border region

#### Study region

<table>
<thead>
<tr>
<th>Pigs / 100 ha or 1 km²</th>
<th>NL</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 500</td>
<td><strong>Blue</strong></td>
<td><strong>Pink</strong></td>
</tr>
<tr>
<td>300 – 500</td>
<td><strong>Teal</strong></td>
<td><strong>Orange</strong></td>
</tr>
<tr>
<td>100 – 300</td>
<td><strong>Light Blue</strong></td>
<td><strong>Yellow</strong></td>
</tr>
<tr>
<td>0 – 100</td>
<td><strong>Light Blue</strong></td>
<td><strong>White</strong></td>
</tr>
</tbody>
</table>

---

**Legend:**
- **Blue** for > 500 pigs/ha or 1 km²
- **Teal** for 300 – 500 pigs/ha or 1 km²
- **Orange** for 250 – 500 pigs/ha or 1 km²
- **Yellow** for 100 – 250 pigs/ha or 1 km²
- **White** for 0 – 100 pigs/ha or 1 km²

---

**Map:**
- **Netherlands**
- **Germany**
Trading networks are important for spreading
# Case-control study:
## Risk factors for the acquisition of LA-MRSA

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number of patients</th>
<th>Univariate analysis</th>
<th>Final logistic regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case group</td>
<td>Control group</td>
<td>$P$ value$^a$</td>
</tr>
<tr>
<td>Residence in a nursing home</td>
<td>Yes: 0 No: 100</td>
<td>Yes: 2 No: 98</td>
<td>0.497</td>
</tr>
<tr>
<td>Prescribing of antibiotics$^c$</td>
<td>Yes: 35 No: 65</td>
<td>Yes: 39 No: 61</td>
<td>0.7</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>Yes: 0 No: 100</td>
<td>Yes: 2 No: 98</td>
<td>0.3</td>
</tr>
<tr>
<td>Male gender</td>
<td>Yes: 77 No: 23</td>
<td>Yes: 62 No: 38</td>
<td>0.03</td>
</tr>
<tr>
<td>Age 0–2 years</td>
<td>Yes: 3 No: 97</td>
<td>Yes: 2 No: 98</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Age 3–18 years</strong></td>
<td>Yes: 9 No: 91</td>
<td>Yes: 2 No: 98</td>
<td><strong>0.0588</strong></td>
</tr>
<tr>
<td>Age 19–65 years</td>
<td>Yes: 61 No: 39</td>
<td>Yes: 60 No: 40</td>
<td>0.885</td>
</tr>
<tr>
<td>Age 66–80 years</td>
<td>Yes: 24 No: 76</td>
<td>Yes: 33 No: 67</td>
<td>0.159</td>
</tr>
<tr>
<td>Age &gt;81 years</td>
<td>Yes: 3 No: 97</td>
<td>Yes: 3 No: 97</td>
<td>1.0</td>
</tr>
<tr>
<td>Indwelling devices</td>
<td>Yes: 12 No: 88</td>
<td>Yes: 28 No: 72</td>
<td>0.008</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Yes: 46 No: 54</td>
<td>Yes: 70 No: 30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contact with human MRSA carriers</td>
<td>Yes: 8 No: 92</td>
<td>Yes: 13 No: 87</td>
<td>0.356</td>
</tr>
<tr>
<td>Chronic need for nursing care</td>
<td>Yes: 3 No: 97</td>
<td>Yes: 23 No: 77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Yes: 5 No: 95</td>
<td>Yes: 23 No: 77</td>
<td>0.001</td>
</tr>
<tr>
<td>Contact with pets</td>
<td>Yes: 78 No: 22</td>
<td>Yes: 48 No: 52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contact with horses</td>
<td>Yes: 19 No: 81</td>
<td>Yes: 5 No: 95</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Contact with cattle</strong></td>
<td>Yes: 25 No: 75</td>
<td>Yes: 3 No: 97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Contact with pigs</strong></td>
<td>Yes: 62 No: 38</td>
<td>Yes: 6 No: 94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contact with sheep</td>
<td>Yes: 2 No: 98</td>
<td>Yes: 2 No: 98</td>
<td>0.689</td>
</tr>
</tbody>
</table>

$^a$P value resulting from univariate (Chi-square or Fisher Exact test) analysis; all factors with $P$<0.2 were included in the initial regression model

$^b$Odds ratio (95% confidence interval, CI) and $P$ value of variables included in the final logistic regression model

$^c$During the previous 6 months

AFLP-analysis of clinical MSSA/MRSA-isolates

Blue, carriage isolates (n = 829);
black, bacteremia isolates (n = 146);
yellow, animal isolates (n = 77);
red, ST398 MRSA isolates (n = 46);
pink, reference strains (Mu50/N315).

Other reservoirs for MRSA?

- MRSA in horses, cattle
- MRSA in cats and dogs
- MRSA in rabbits
- MRSA in rats

Walther et al. Berl Munch Tierarztl Wochenschr 2006
MRSA is not the same as MRSA

PVL –negative (2 exceptions in SE, NL)
Livestock-associated (LA)-MRSA

PVL –positive
Community-acquired (CA)-MRSA

Hospital-acquired (HA)-MRSA

Community-MRSA

Hospital-MRSA
Extended MRSA-Epidemiology
Conclusions

1. MRSA spread different from MSSA

2. Resistances diffuse locally und regionally across the border
   Transmission of HA- MRSA via health care networks
   of LA-MRSA via production ways
   of CA-MRSA via social networks

3. MRSA-prevention needs to be implemented at the critical points

4. Preventive Microbiology, infection control and antibiotic stewardship is the future

5. Molecular typing is of epidemiological and clinical interest

6. Collaboration between human medicine and veterinary medicine necessary (One-health)
Thanks to

- Dag Harmsen
- Alex Mellmann
- Robin Köck
- Hajo Grundmann
- Lothar Wieler
- Helge Karch
- Wolfgang Witte
- All SeqNet.org participants
  and the SRL study group