The Epidemiology of Methicillin-Resistant Staphylococcus aureus (MRSA) in Germany

Robin Köck, Alexander Mellmann, Frieder Schaumburg, Alexander W. Friedrich, Frank Kipp, Karsten Becker

SUMMARY
Background: For decades, methicillin-resistant Staphylococcus aureus (MRSA) has been a major cause of infection in hospitals and nursing homes (health care-associated MRSA, HA-MRSA). Beginning in the late 1990s, many countries have also experienced a rising incidence of MRSA infection outside of the health care setting (community-associated MRSA, CA-MRSA). Moreover, animal reservoirs are increasingly considered to represent an important source of human MRSA acquisition. In this review article the authors describe the current epidemiological situation of MRSA in Germany.

Methods: This review is based on pertinent articles published up to 2010 that were retrieved by a selective PubMed search, as well as on publications issued by national reference institutions up to 2010.

Results: There are about 132 000 cases of MRSA in German hospitals each year. MRSA is found in about 18% to 20% of all inpatient-derived culture specimens that are positive for S. aureus. CA-MRSA is not yet endemic in Germany; important risk factors for its acquisition include travel to high-prevalence areas and household contact with persons that harbor a CA-MRSA infection. Agricultural livestock is the main animal reservoir for MRSA, which is often zoonotically transmitted from animals to human beings by direct contact. However, both CA-MRSA and MRSA from animal reservoirs can be imported into hospitals and cause nosocomial infections.

Conclusion: Hospitals and nursing homes were once the main reservoirs of MRSA, but new ones have now emerged outside of the healthcare setting. Efforts to prevent MRSA and limit its spread must rise to this new challenge.

Cite this as:

Methicillin-resistant Staphylococcus aureus (MRSA) is the most common multidrug-resistant pathogen causing nosocomial infections in Europe (1). Estimates indicate that there are approximately 170 000 MRSA infections in European healthcare systems each year, causing more than 5000 fatalities, more than 1 million additional inpatient days, and additional costs of approximately €380 million (1). However, for a number of years several countries have also been reporting successes in the prevention and control of health care-associated MRSA (HA-MRSA) infections. At the same time, new MRSA reservoirs outside hospitals have also been identified. In addition to community-associated MRSA (CA-MRSA) infections among the general population, these new reservoirs also include companion animals and agricultural livestock (hence the term livestock-associated MRSA, or LA-MRSA) and humans who come into contact with them.

Aims
The aim of this review article is to describe the current epidemiological status of methicillin-resistant S. aureus strains in Germany. In addition to the situation in healthcare facilities, the incidence of MRSA in the general population and in animal reservoirs will be highlighted, and the issues that arise from this and the conclusions for prevention will be discussed.

Methods
Epidemiological parameters are summarized on the basis of a selective review of the literature in PubMed (search term “MRSA AND Germany”) and publications issued by national reference institutions (the Robert Koch Institute, the German National Reference Center for the Surveillance of Nosocomial Infections [Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen], and the Federal Institute for Risk Assessment [Bundesinstitut für Risikobewertung]). This includes literature published up to and including 2010, not limited to a specific study type.
MEDICINE

MRSA in hospitals, homes for the elderly, and care homes

Hospitals and other healthcare facilities (e.g. homes for the elderly and care homes) have been the traditional locations for MRSA infections for many decades. In terms of its incidence rate (the number of cases per 1000 patient days), MRSA remains the most common multidrug-resistant pathogen causing nosocomial infections in Germany (e1). Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) (e2) indicate that the proportion of MRSA among all S. aureus isolates from blood cultures in Germany has substantially increased in the 1990s and has now remained stable at 16–20% for several years. This trend is confirmed by data from the National Resistance Study of the Paul Ehrlich Society (PEG, Paul-Ehrlich-Gesellschaft) (e3). In that study, the proportion of MRSA among S. aureus isolates from clinical examination materials was 1.1% in 1990, had increased to 17.5% by 2001, and finally reached 20.3% in 2007. Current data from the Robert Koch Institute’s (RKI) interactive Antibiotics Resistance Surveillance Database also indicate a relatively stable percentage of MRSA cases (all S. aureus isolates obtained from inpatients) for 2008 and 2009: 19.2% (2008) and 21.9% (2009) (RKI: https://ars.rki.de, last accessed on 30 November, 2010). In individual at-risk areas (e.g. intensive care units) in particular, however, higher MRSA rates (>37%) are reported (e4).

A new data source on the number of invasive infections appeared in 2009, with the introduction of compulsory reporting by laboratories (according to Article 7 of the German Infection Protection Act) of MRSA detected in blood cultures and cerebrospinal fluid (CSF). More than 3000 cases have been reported in Germany via this system since it was introduced, corresponding to an incidence of 1.94/100 000 inhabitants (RKI: SurvStat, http://www3.rki.de/SurvStat, data as of December 15, 2011).

<table>
<thead>
<tr>
<th>Study (year of investigation, type)</th>
<th>Region</th>
<th>Area</th>
<th>No. of facilities</th>
<th>No. of examined patients</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA KISS reference data (2009, A)</td>
<td>Germany</td>
<td>All patients</td>
<td>199</td>
<td>–*4</td>
<td>0.66%</td>
</tr>
<tr>
<td>Reich-Schupke et al. (2008, A)</td>
<td>Bochum</td>
<td>Dermatology</td>
<td>1</td>
<td>384</td>
<td>3.1%</td>
</tr>
<tr>
<td>Grabe et al. (2008, A)</td>
<td>Siegen-Wittgenstein</td>
<td>All patients</td>
<td>14</td>
<td>6985</td>
<td>1.4%</td>
</tr>
<tr>
<td>Woltering et al. (2006) ()</td>
<td>Höxter</td>
<td>All patients</td>
<td>5</td>
<td>494</td>
<td>3.4%</td>
</tr>
<tr>
<td>Schulz et al. (2006/7, A)</td>
<td>Marburg</td>
<td>Surgery</td>
<td>1</td>
<td>442</td>
<td>3.9%</td>
</tr>
<tr>
<td>Kock et al. (2006, A)</td>
<td>Münsterland</td>
<td>All patients</td>
<td>39</td>
<td>25 540</td>
<td>1.6%</td>
</tr>
<tr>
<td>Chaberny et al. (2005)</td>
<td>Hannover</td>
<td>All patients</td>
<td>1</td>
<td>509</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

| Hospitals |
|-----------------------------------|--------|------|------------------|-------------------------|----------|
| MRSA KISS reference data (2009, A) | Germany | All patients | 199 | –*4 | 0.66% |
| Reich-Schupke et al. (2008, A) | Bochum | Dermatology | 1 | 384 | 3.1% |
| Grabe et al. (2008, A) | Siegen-Wittgenstein | All patients | 14 | 6985 | 1.4% |
| Woltering et al. (2006) () | Höxter | All patients | 5 | 494 | 3.4% |
| Schulz et al. (2006/7, A) | Marburg | Surgery | 1 | 442 | 3.9% |
| Kock et al. (2006, A) | Münsterland | All patients | 39 | 25 540 | 1.6% |
| Chaberny et al. (2005) | Hannover | All patients | 1 | 509 | 5.3% |

| Homes for the elderly, care homes |
|-----------------------------------|--------|------|------------------|-------------------------|----------|
| Woltering et al. (2006) () | Höxter | Home for the elderly/ care home | 6 | 265 | 2.3% |
| Martin et al. (2004) () | Duisburg | Home for the elderly/ care home | 3 | 65 | 9% |
| Daeschlein et al. (2003) | Chemnitz | Home for the elderly/ care home | 3 | 500 | 0% |
| Neuhaus et al. (2000/2001) | North Rhine-Westphalia (NRW) | Home for the elderly/ care home | 61 | 1057 | 3.1% |
| Robert Koch Institute (1999/2000) | Brandenburg, Berlin, NRW, Hessen | Home for the elderly/ care home | 32 | 1342 | 2.4% |
| von Baum et al. (1999/2000) | Rhine-Neckar region, Heidelberg | Home for the elderly/ care home | 47 | 3 236 | 1.1% |
| Höpken et al. (1999/2000) | Lower Saxony | Home for the elderly/ care home | 1 | 33/346 | 21/26%*6 |
| Heudorf et al. (1999) | Frankfurt | Home for the elderly/ care home | 7 | 359 | 2.2% |

*1 Classified by year of investigation, type of investigation: if prevalence was ascertained on admission, this is indicated by the letter A (admission); data from sources [10, 13–24] and www.nrz-hygiene.de/surveillance/kiss/mrsa-kiss/; *2 Area of investigation; *3 Number of participating facilities; *4 Data not available; *5 Date added following personal correspondence with the authors; *6 Investigated at two separate points in time.
TABLE 2

Differences between MRSA subtypes

<table>
<thead>
<tr>
<th>PVL formation</th>
<th>HA-MRSA</th>
<th>CA-MRSA</th>
<th>LA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant clinical manifestation</td>
<td>Rare</td>
<td>Frequent</td>
<td>Single cases</td>
</tr>
<tr>
<td>Indicators of frequency of infection in Germany</td>
<td>Approx. 14 000 healthcare-associated MRSA infections/year (&lt;5% of all nosocomial infections) (25)</td>
<td>2 to 3% of MRSA cases in Germany are PVL-positive (e11); overall incidence of CA-MRSA infections unknown</td>
<td>&lt;1% of health care-associated MRSA infections; number of infections in outpatients unknown (11)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Hospital stays, residents of homes for the elderly/care homes, catheters, chronic wounds, antibiotic treatment</td>
<td>Travel to high-risk areas, contact with individuals infected with CA-MRSA</td>
<td>Direct contact with agricultural livestock (e.g. farmers, veterinarians, abattoir employees)</td>
</tr>
<tr>
<td>Prevention</td>
<td>Screening on or before hospital admission, measures to cure colonization, particular hygiene measures in healthcare facilities according to RKI recommendations</td>
<td>Washing clothes, bedclothes, and towels at temperatures above 60 °C whenever possible; measures to cure colonization where appropriate</td>
<td>Careful cleanliness of animal enclosures, measures to cure colonization before elective surgery</td>
</tr>
</tbody>
</table>


2010) with data from some German federal states not yet examined. By way of comparison, the incidence of hospital-associated MRSA bacteremia in England and the USA in 2006 and 2007 was between 7.2 and 7.8/100 000 inhabitants (e5). On the basis of the results of the MRSA module of Germany’s Hospital Infection Surveillance System (KISS, Krankenhaus-Infektions-Surveillance-System) (http://www.nrz-hygiene.de), the annual number of MRSA cases in German hospitals (2008) is estimated at approximately 132 000 (including both colonizations and infections), and the number of nosocomially-acquired infections at 34 000 (2). In 2009, the mean MRSA incidence rate (both colonizations and infections) in the 199 hospitals that take part in KISS was 1.14/1000 patient days. Most patients had already been colonized at the time of admission to hospital (79.5% imported cases); 20.5% of cases were classified as “nosocomially-acquired” (e6). One marker of the entry of MRSA into hospitals is the prevalence on admission (Table 1). Residents of care homes and homes for the elderly are high-risk groups for MRSA acquisition. Overall, several studies, most of them old, indicate an MRSA prevalence rate (including colonizations) of approximately 1 to 3% (Table 1), with high levels of local variability (17, 22).

MRSA in the general population

Until the 1990s, MRSA infections were only sporadically described outside the health care setting. Since then, in some countries an increasing number of CA-MRSA infections has been documented. CA-MRSA is defined as MRSA detected in outpatients or in patients in the first 48 to 72 hours after hospital admission, provided patients have no traditional risk factors for healthcare-associated MRSA (history of MRSA, contact with MRSA, previous hospital or care home stay, dialysis) (3).

A particularly high number of CA-MRSA infections is described in the USA, where CA-MRSA is now the most common pathogen (>50%) causing skin and soft tissue infections (particularly abscesses) acquired by outpatients, the number of these infections has nearly doubled in six years, and the main burden of MRSA infections, measured as the incidence per 100 000 inhabitants, now falls on the general population (3). In addition, CA-MRSA is imported into hospitals and causes nosocomial infections (3), so the above-mentioned epidemiological definition of CA-MRSA is becoming increasingly inaccurate. However, CA-MRSA is also molecularly different from HA-MRSA: the increase of MRSA outside hospitals in the USA is caused mainly by the epidemic spread of two clonal lines of MRSA (USA300/ST8 and USA400/ST1), which can usually form the toxin Panton-Valentine leukocidin (PVL) (3, 4) (Table 2). Due to cytotoxic effects, particularly on neutrophil granulocytes, PVL contributes to the virulence of S. aureus (4). In contrast to the USA, the CA-MRSA clones detected in Germany to date are heterogeneous (Table 3). Cases of necrotizing pneumonia (e7, e8) and fasciitis/myositis (e9) caused by these strains of S. aureus are much rarer than PVL-associated skin manifestations, but often peracute and associated with high mortality rates (>30%).

The illness burden caused by CA-MRSA in Germany is currently significantly smaller than in the USA. In the 1990s, a multicenter study detected PVL-encoding genes in 0.9% (blood culture isolates) and 1.4% (nasal swab isolates) of S. aureus (e10). A prospective study of 248 patients with skin infections in
The currently low burden of CA-MRSA illness in Germany makes it difficult to provide precise definitions of high-risk groups for such infection. In the USA, high numbers of CA-MRSA infections have been observed where people live in close proximity to one another (barracks, prisons, households), engage in sports in which skin abrasions are common (soccer, rugby), or share items of personal hygiene (e.g. towels). HIV-positive individuals and men who have sex with men have also been stated to be high-risk populations (3). In the context of the current epidemiological status of CA-MRSA in Germany, these groups do not constitute high-risk groups per se (although single cases have been described [e16]). Various European studies have found a high risk of CA-MRSA acquisition among those who travel to high-prevalence areas (e17–e19). This is confirmed by a study conducted in Bavaria, in which 14 of 39 cases of CA-MRSA were either associated with travel or occurred in individuals living in Germany but of Mediterranean (particularly Greek, Turkish, or Italian) family origin (e20). In fact, Greece in particular seems to be a European hotspot for CA-MRSA, as infection rates there are similar to those in the USA. In addition, CA-MRSA infections are detected more frequently in those returning from travel to East Asia, Oceania, Africa, and the Middle East. A further risk factor for CA-MRSA in Germany is close contact (the same household) with persons infected with CA-MRSA, as studies of CA-MRSA index cases have shown that the pathogen was transmitted to other members of the same household in 43 to 47% of cases (e21, e22), with 67% of all household contacts testing positive for MRSA (e21).

**MRSA in animals**

MRSA colonizations and infections have been described in a range of animal species. In recent years, studies have concentrated on livestock (swine, cattle, poultry). As a result, the term “livestock-associated” MRSA (LA-MRSA) is often used to describe these isolates. It has been established that LA-MRSA strains can be detected in 43 to 70% of pig farms in Germany (e23, e24), and that up to 71% of individual animals in abattoirs have been colonized (6). In addition to swine, MRSA has also been detected in cattle (7, 8), poultry flocks, and samples of chicken meat (7). Although there have been individual reports of livestock infected with LA-MRSA (e25, e26), most colonized animals are asymptomatic. Molecular analysis of MRSA isolates from livestock shows that most cases (>90% in swine) are caused by one specific clonal complex of MRSA (CC398). These cases of MRSA from animal reservoirs are therefore different from human HA- and CA-MRSA (Table 2). In addition to livestock, MRSA has also been detected in companion animals. For example, outbreaks of nosocomial MRSA infection in Germany have been detected in horses at veterinary hospitals (8, e27, e28), and MRSA has been described in dogs, cats, pigeons, and guinea pigs (e29–e31). In contrast to livestock, where the clonal line CC398 is predominant,
MRSA clones found among companion animals are often typical human molecular lines indicating a transmission from human to pets rather than vice versa. (e32).

**MRSA from zoonotic reservoirs in humans**
Numerous studies show that clonal line CC398 MRSA can be transmitted from animals to humans. In connection with this it has been shown that 86% of pig farmers in Germany are carriers of nasal MRSA (9). Veterinarians (12 to 45%) (9) and relatives of pig farmers who do not themselves come into regular direct contact with animals (4%) were also frequently colonized in these studies (9). In regions with high numbers of livestock (e.g. Lower Saxony or Westphalia in Germany), CC398 isolates are often imported into healthcare facilities. For example, amongst MRSA from screenings in the Münsterland region (hospitals belonging to the quality network EUERGEO MRSA-net), this particular MRSA clone accounted for 17% of all MRSA cases in 2006 (10). In this region, contact with swine and cattle represented independent risk factors for MRSA CC398 colonization on hospital admission (e24).

Although many publications have documented MRSA CC398’s potential for causing infections (endocarditis, pneumonia, wound infections) in humans (1), as yet there is no systematic summary of the incidence of MRSA infections in the high-risk groups mentioned above. It is therefore currently impossible to estimate whether farmers or other exposed persons suffer from MRSA infections more frequently than the general population. MRSA CC398 represents a total of approximately 0.6% of all human (mostly nosocomial) MRSA isolates examined at the national reference center for staphylococci between 2006 and 2008 (11). A Europe-wide study of MRSA blood culture isolates also concluded that MRSA CC398 accounted for less than 1% of all MRSA cases (e33). This indicates that the numbers of hospital infections caused by MRSA CC398 are as yet low, despite the higher colonization rates for particular high-risk groups and the importation of these strains into hospitals. However, there are substantial regional variations. In the Münsterland region, MRSA CC398 accounted for 4.3% of all MRSA cases from clinical materials between 2006 and 2008 (e34).

The risk of foodborne infections due to MRSA is currently judged by the monitoring authorities to be low (e35, e36). Although MRSA (mostly CC398) has been detected in beef, veal, lamb, pork, chicken, turkey, other poultry, and game on the retail market (7), quantitative investigation indicates low-grade contamination. There is no evidence of infection associated with contact with or consumption of food contaminated with MRSA (7).

**Discussion and conclusions for prevention and control**

**Hospitals, homes for the elderly, and care homes**
The number of MRSA infections in German hospitals seems to have stabilized. Despite several reports of success (e37, e38), as yet no significant impact has been achieved in Germany as a whole on the overall incidence of health care-associated MRSA infections as it has in other European countries (e.g. Britain, France, Belgium) (1). This explains the need for further improvement of the implementation of control measures locally, and within the regional networks for MRSA prevention that are currently established in most German federal states (e39–e41). Detailed recommendations on handling MRSA patients in homes for the elderly and care homes exist; there are national recommendations for defining which patients belong to high-risk groups and should therefore be tested for MRSA colonization when admitted to the hospital (e42). However, structural shortcomings still make it difficult to take measures to cure MRSA colonization and to control it in this area of health care.

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**TABLE 4**

<table>
<thead>
<tr>
<th>MRSA in Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population 82 000 000</td>
</tr>
<tr>
<td>More than 160 000 000 heads of livestock</td>
</tr>
<tr>
<td><strong>No. of animals</strong></td>
</tr>
<tr>
<td>Horses</td>
</tr>
<tr>
<td>Cattle</td>
</tr>
<tr>
<td>Dairy cows</td>
</tr>
<tr>
<td>Sheep</td>
</tr>
<tr>
<td>Swine</td>
</tr>
<tr>
<td>Poultry</td>
</tr>
<tr>
<td><strong>Approx. 27 000 000 companion animals</strong></td>
</tr>
<tr>
<td>Individual cases of MRSA described, no data available on prevalence</td>
</tr>
</tbody>
</table>

*1 n/a: No data available but detected cases described; *2 In milk samples
time in Germany, as part of the projects EUREGIO MRSA-net (e43) and EurSafety Health-net (www.mrsa-net.eu; http://www.eursafety.eu/index.html), in the territory covered by the Westphalia–Lippe Association of Statutory Health Physicians (KVWL, Kassenärztliche Vereinigung Westfalen-Lippe) icon numbers have been created so that the number of MRSA patients being treated on an outpatient basis can be determined. Treatment costs can also be measured, particularly costs associated with laboratory tests. There is also the possibility that drugs needed to eradicate MRSA (e.g. mupirocin nasal ointment) might be removed from the medication budget of practicing physicians, if there is a test of cost-effectiveness. Swab tests that are part of the monitoring of curative treatment do not conflict with cost-effectiveness incentives. However, as yet, these regulations apply only in the territory covered by the KVWL, not in the rest of Germany.

**The general population**

There are no indications as yet that CA-MRSA is spreading to the German population. However, the fact that individual areas with higher prevalences of CA-MRSA have been identified even in Europe does make CA-MRSA infection increasingly likely. CA-MRSA should therefore be one of the possibilities considered in patients with compatible travel history and/or clinical symptoms, particularly patients with recurrent abscess-type skin inflammation. Because infection is frequently transmitted to other members of the same household, such persons should also be considered for diagnosis and treatment, particularly in cases in which multiple curative treatment attempts have failed. Appropriate classification by means of molecular typing should be arranged for suspected CA-MRSA isolates. Antibiotic treatment of CA-MRSA infections in outpatients is usually uncomplicated, because several antibiotics that can be taken orally are available (*Table 3*). There are recommendations on handling CA-MRSA in the home environment available in German (12).

**Animal reservoirs**

The significance of zoonotic transmission of multidrug-resistant bacterial pathogens is becoming increasingly clear (*Table 4*). This also reflects the number of projects currently being conducted by German research associations on the subject (http://www.zoonos.net/). For example, the German Federal Ministry of Food, Agriculture and Consumer Protection (BMELV, Bundesministerium für Ernährung, Landwirtschaft und Verbraucherschutz) is currently sponsoring five projects on MRSA in livestock rearing, while the Federal Ministry of Education and Research (BMBF, Bundesministerium für Bildung und Forschung) is sponsoring a research association (Med-Vet-Staph) to determine the virulence, pathogenicity, transmissibility, and epidemiology of S. aureus/MRSA in animal reservoirs.


Corresponding author
Dr. med. Robin Köck
Universitätsklinikum Münster
Institut für Hygiene
Institut für Medizinische Mikrobiologie
Robert-Koch-Str. 41
48149 Münster, Germany
robin.koeck@ukmuenster.de

For eReferences please refer to:
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