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CHAPTER

# 9

# *STAPHYLOCOCCUS AUREUS* AND METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN WORKERS IN THE FOOD INDUSTRY

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## 1. INTRODUCTION

*Staphylococcus aureus* impresses with an enormous versatility. It is well known as part of the common flora on the skin and mucous membranes of mammals and approximately 20%–30% of humans are persistently colonized with *S. aureus*, mainly by mostly susceptible human-adapted isolates. In contrast, colonization with methicillin-resistant *S. aureus* (MRSA) is rare, predominantly transient and associated with prior contact to the health care system. Additionally, in recent years, community and livestock-associated *S. aureus* clones contributed to colonization in humans, latter especially in those working in close contact to farm animals.

On the other hand, *S. aureus* can cause a variety of different diseases leading from uncomplicated skin and soft tissue infections to life-threatening diseases such as septicemia. Additionally, toxin-mediated diseases such as toxic shock syndrome, staphylococcal scalded skin syndrome, and staphylococcal food poisoning (SFP) contribute to its burden of disease (Lowy, 1998).

SFP is a common foodborne disease, mediated by the ingestion of enterotoxins produced by enterotoxigenic strains of *S. aureus*. A considerable percentage of colonizing *S. aureus* isolates is equipped with enterotoxin genes. Humans carrying enterotoxigenic isolates represent a contamination source when handling food, thus generating a continuous risk of *S. aureus* food intoxication. While the majority of pathogens causing foodborne diseases infect humans (including workers in the food industry) and lead to symptomatic disease, staphylococci are resident skin inhabitants, putatively constituting a part of the skin microbiome. As such they largely remain unrecognized, until they become visible during the course of outbreak investigations related to epidemiologically linked cases of staphylococcal disease such as SFP (Todd et al., 2008).

Molecular characterization of isolates colonizing humans and obtained from food, respectively, enables the tracing of food-related outbreaks back to the source of food intoxication. However, because of the widespread occurrence of enterotoxigenic strains as human colonizers and the often transient nature of colonization the source of contamination cannot always be identified unambiguously. Therefore, compliance with hygiene measures is the most important requirement to prevent food contamination by both, human colonization and environmental *S. aureus* reservoirs.

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In this chapter we will summarize current knowledge about the *S. aureus* population colonizing humans, including those in close contact to animals and food, respectively. Additionally, we will review on the molecular characterization of *S. aureus* isolates related to staphylococcal foodborne disease and the elucidation of staphylococcal foodborne outbreaks.

## 2. *STAPHYLOCOCCUS AUREUS* AND METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* COLONIZATION IN HUMANS

As a commensal bacterium *S. aureus* colonizes the skin and the mucous membranes of humans worldwide (Williams, 1963; Wertheim et al., 2005; Verhoeven et al., 2014), and it is well established that colonization predisposes for *S. aureus* generalization and subsequent endogenous infection (von Eiff et al., 2001; Wertheim et al., 2005; Paling et al., 2016). The most common site of carriage is the nasal vestibule (Williams, 1963; Kaspar et al., 2016); additionally, *S. aureus* can be present at mucosa of the oropharynx, the skin, and the perineum but also the gastrointestinal tract (Acton et al., 2009), vagina (Guinan et al., 1982), and axillae are colonized in lower frequency (Williams, 1963). However, nasal carriage is regarded as the source of colonization of secondary body sites implicating that *S. aureus* transmission via colonized hands can be reduced by adherence to commonly recommended hand hygiene measures (see Chapter 12 for further details).

Historically, *S. aureus* carriage has been separated into three classes: persistent carriers, intermittent, and noncarriers based on the presence of *S. aureus* in nasal swab cultures of an individual over time (Nouwen et al., 2004). However, in a more recent study carriage states were reclassified based on staphylococcal antibody profiles and *S. aureus* elimination from the nose (van Belkum et al., 2009) leading to only two carriage types: persistent and "other" carriers. Approximately 20%–30% of humans are presumed to be persistent carriers, whereas the remainders of the population are potentially intermittent carriers. It can be considered that most individuals are exposed to the bacterium transiently throughout lifetime (Mulcahy and McLoughlin, 2016). A number of studies have shown that persistent carriage can be associated with clonally diverse *S. aureus* strains (VandenBergh et al., 1999; Cespedes et al., 2005; Bloemendaal et al., 2009; Miller et al., 2014). Persistent carriers are characterized by an elevated nasal bacterial load and shed a higher number of bacteria into the environment, thus increasing the risk of cross-transmission within households and consequently also into the food chain if workers in the food industry are affected (Davis et al., 2012).

### 2.1 *STAPHYLOCOCCUS AUREUS* CARRIAGE

As reflected by the growing number of studies on *S. aureus* carriage over the recent years, carriage decreased in the general population most probably because of improvements in personal hygiene and general living conditions (Verhoeven et al., 2014; Wertheim et al., 2005). These studies also indicated that prevalence rates of *S. aureus* nasal carriage and its antimicrobial drug resistance vary slightly from country to country and in dependence of the study population.

For Central Europe carriage rates reported from the general population were in the range of 20%–35% (Wertheim and Verbrugh, 2006; Sakwinska et al., 2009; Sangvik et al., 2011; den Heijer et al., 2013; Holtfreter et al., 2016). In the US prevalences around 30% were documented (Kuehnert

et al., 2006; Mainous et al., 2006; Gorwitz et al., 2008). Similar rates were found among the healthy Japanese population (Uemura et al., 2004), whereas the nasal carriage rate in a Chinese study was reported to be only 23% (Ma et al., 2011). For South and South East Asia quite variable carriage rates have been found, ranging from below 10% to more than 50% (Saxena and Panhotra, 2003; Anwar et al., 2004; Erdenizmenli et al., 2004; Lu et al., 2005; Choi et al., 2006; Severin et al., 2008; Chatterjee et al., 2009). For Australia a nasal colonization rate around 30% has been reported (Vlack et al., 2006; Munckhof et al., 2008). Recent reports from Africa also showed variable colonization rates ranging from around 10% to 30% (Adesida et al., 2007; Ben Slama et al., 2011; Ateba Ngoa et al., 2012; Omuse et al., 2012; Ouedraogo et al., 2016). In South America rather high carriage rates between 30% and 60% were reported (Hamdan-Partida et al., 2010; Ruimy et al., 2010). In several studies nasal carriage was associated with male sex and younger age (Skramm et al., 2011; Gorwitz et al., 2008; Holtfreter et al., 2016); however, in general, several different factors contribute to *S. aureus* carriage including those associated with the host, the pathogen itself, and the environment (Mulcahy and McLoughlin, 2016; Kluytmans et al., 1997).

## 2.2 METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN GENERAL AND HOSPITAL-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

MRSA colonizes the same body niches as *S. aureus*, however, in contrast to *S. aureus*, MRSA carriage, e.g., hospital-associated methicillin-resistant *S. aureus* (HA-MRSA) carriage in nonrisk populations remains rare. Depending on geographic region and study design 0%–35% of individuals are colonized with MRSA. For nine countries in Central Europe den Heijer et al. (2013) reported low MRSA prevalence in the healthy community from 0.0% (Sweden) to 2.1% (Belgium). Other studies from Europe showed similar colonization rates (Sakwinska et al., 2009; Lozano et al., 2011; Mehraj et al., 2014; Holtfreter et al., 2016). Similar or slightly elevated carriage rates were also reported in studies from Australia and several Asian countries (Munckhof et al., 2008; Chatterjee et al., 2009; Ma et al., 2011; Chen et al., 2013). Significantly higher rates were recorded in Southern European countries and the United States (up to 35%, Tavares et al., 2013; Champion et al., 2014). MRSA carriage rates are usually higher in children (Creech et al., 2005; Braga et al., 2014; Rodriguez et al., 2014); additionally, certain risk factors related to contact to health care institutions increase the probability of MRSA, particularly HA-MRSA carriage; these include contact to HA-MRSA positive patients, antibiotic therapy, hospitalization, or even contact with the health care system either as visitor or employee (Hardy et al., 2004; Coia et al., 2006). HA-MRSA, frequently exhibit multidrug-resistant phenotypes.

## 2.3 COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Since the 1990s colonization and infection with community-associated methicillin-resistant *S. aureus* (CA-MRSA) became increasingly prevalent in community settings worldwide (Mediavilla et al., 2012). CA-MRSA colonize individuals independent of risk factors mentioned before; they cause a growing number of uncomplicated to severe skin and soft tissue infections but can also lead to serious invasive infections such as necrotizing pneumonia or fasciitis. Although CA-MRSA are still rare in the general population in Europe (Sangvik et al., 2011; Lozano et al., 2011; Sakwinska et al., 2009; Monecke et al., 2009; Ruimy et al., 2009), they represent a major threat to human health in the United States, where they

became endemic by now (Seybold et al., 2006; Maree et al., 2007). However, elevated rates of CA-MRSA colonization were also reported from Southern Europe and the Middle East [11.4% (Tavares et al., 2013)]. The reason for the increased virulence potential of CA-MRSA is still controversially discussed; the frequent occurrence of Panton–Valentine leukocidin (PVL) in CA-MRSA strains is supposed to be a contributing factor but others are under discussion (Voyich et al., 2006; Labandeira-Rey et al., 2007; Wang et al., 2007). Most probably, the acquisition of new virulence and fitness determinants together with an altered gene expression of common virulence genes and alterations in protein sequence that increase fitness are involved (Thurlow et al., 2012). CA-MRSA are usually only resistant to few antibiotics.

### 2.4 LIVESTOCK-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

During the last decade livestock has been described as an additional reservoir of MRSA beyond the hospital environment and the newly described community reservoir. Livestock-associated methicillin-resistant *S. aureus* (LA-MRSA) have been found in several food producing animals and also frequently as colonizers in humans in close contact with these animals, such as farmers and veterinarians (Cuny et al., 2015). Thus, occupational contact to livestock became an important risk factor for carriage of MRSA, i.e., LA-MRSA.

LA-MRSA, such as HA-MRSA, frequently exhibit multidrug-resistant phenotypes. The spread of these *S. aureus* isolates outside hospitals poses a substantial risk to the community because it might lead to an increase in community-acquired infections, which are difficult to treat.

## 3. MOLECULAR EPIDEMIOLOGY OF COLONIZING *STAPHYLOCOCCUS AUREUS* ISOLATES

### 3.1 CLONALITY OF *STAPHYLOCOCCUS AUREUS*

Although the *S. aureus* population as such is rather clonal, *S. aureus* carriage isolates from community-based studies have been shown to be much more diverse than MRSA (Day et al., 2001; Feil et al., 2003; Kuehnert et al., 2006; Holtfreter et al., 2016). However, some clonal lineages, such as clonal complex (CC) CC30, 45, 15, 5, 121, and 8, are more common in carriage isolates and appear to be globally disseminated. Among these clonal lineages CC30 has been reported to be predominant in a variety of studies from all over the world (Melles et al., 2008; Ko et al., 2008; Sakwinska et al., 2009; Ruimy et al., 2009) suggesting its ecological success and overall transmissibility. Less pronounced than in MRSA, the composition of CCs representing the population of nasal colonizers can vary geographically, as demonstrated in studies investigating carriage isolates from several different continents (Ruimy et al., 2008, 2009; Schaumburg et al., 2011).

### 3.2 CLONALITY OF HOSPITAL-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Some of the lineages present as frequent methicillin-sensitive *S. aureus* (MSSA) nasal colonizers have acquired staphylococcal cassette chromosome *mec* (SCC*mec*), a mobile genetic element of staphylococci carrying the *mecA* gene and leading to the emergence of MRSA within the same clonal lineage; however, the global HA-MRSA population can be assigned to a limited number of CCs, which are distributed worldwide; these include CCs CC5, 8, 22, 30, and 45 (Enright et al., 2002).

Within these CCs several lineages evolved independently over time at different geographic locations. As mentioned above the composition of clonal lineages within the HA-MRSA population in a given geographic region varies considerably. For example, ST22 and ST36 dominate in the United Kingdom, ST22 and ST225 in Germany, ST239 in Asia and Australia, and ST5 in North America, Japan, and Korea (Deurenberg and Stobberingh, 2008; Grundmann et al., 2010; Chatterjee and Otto, 2013; Bal et al., 2016). However, the distribution of clones is subject to a constant dynamic resulting in a continuously changing epidemiology (Witte et al., 2001; Wyllie et al., 2011).

### 3.3 CLONALITY OF COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

CA-MRSA are phylogenetically distinct from traditional HA-MRSA clones. Although they share the same clonal lineage in some instances, they evolved independently from hospital-adapted strains. The most prevalent CCs in the community are CCs 1, 8, 30, 59, and 80. MRSA strains from CCs 8 and 30 are pandemic both in the hospitals and in the community and are a common cause of infections. Similar to HA-MRSA the distribution of predominant clones differs geographically: sequence type (ST)80 is most prevalent in Europe and Northern Africa, ST59 in the Far East, ST93 and ST1 in Australia, and ST1 and ST8 in the United States (Chatterjee and Otto, 2013; Bal et al., 2016). Finally, there are some regional clones, such as ST772, which is prevalent in Bangladesh and India, ST72 strains in South Korea and Portugal, ST152 in the Balkan States, and ST88 strains in Africa and Asia (Kim et al., 2007; Shambat et al., 2012; Tavares et al., 2014; Dermota et al., 2015; Abdulgader et al., 2015).

### 3.4 CLONALITY OF LIVESTOCK-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

As for CA-MRSA, LA-MRSA evolved independently from common HA- and CA-MRSA clones. LA-MRSA colonization in livestock and individuals in occupational contact in Europe is predominantly due to clonal lineage ST398 clone, whereas ST9 dominates in Asia. However, a substantial number of additional clonal lineages show apparent promiscuity presumably enabling both, long-term colonization in animals and colonization and infection of humans (Price et al., 2012). For example, MRSA isolates from poultry are often associated with ST5, which belongs to the most prevalent HA-MRSA lineages; additional MRSA lineages with supposed promiscuity are CC1, CC97, CC130, and ST425 (Fitzgerald, 2012).

## 4. COLONIZING *STAPHYLOCOCCUS AUREUS* AND METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*: THEIR ENTEROTOXIGENIC POTENTIAL AND INVOLVEMENT IN STAPHYLOCOCCAL FOODBORNE OUTBREAKS

### 4.1 ENTEROTOXIN GENE CONTENT OF COLONIZING *STAPHYLOCOCCUS AUREUS* AND METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

The majority of virulence and resistance genes are located on mobile genetic elements, thus constituting a major part of the so-called "accessory genome" (Lindsay et al., 2006). It has been shown previously that elements of the accessory genome, such as enterotoxin genes, are frequently associated with

particular clonal lineages (Melconian et al., 1983; Isigidi et al., 1992; Peacock et al., 2002; van Belkum et al., 2006; Lindsay et al., 2006). Several studies report on screening of *S. aureus* nasal carriage isolates for enterotoxin and enterotoxin-like genes (Becker et al., 2003; Omoe et al., 2005; Bania et al., 2006; Boerema et al., 2006; Nashev et al., 2007; Collery et al., 2008; Lozano et al., 2011). In these studies 75%–100% of investigated isolates carry enterotoxin (like) genes with 30%–67% of them being positive for the classical enterotoxin genes *sea* to *see*. The *egc* locus (complete or incomplete) was detected in 38%–84% of all isolates. Single toxin genes as well as combinations of different toxins were detected in all studies. The predominant classical enterotoxin gene varies considerably from country to country. Comparative investigation of MSSA and MRSA isolates or isolates from carriage and invasive infections revealed association of enterotoxin gene distribution with clonal lineage rather than with methicillin resistance or invasiveness.

The association between clonal lineage and toxin gene distribution was also described by Holtfreter et al. (2007) who investigated more than 200 *S. aureus* isolates from nasal colonization and from bacteremia cases for the presence of superantigen genes including enterotoxin genes in dependence of clonal lineage. Although they observed remarkably variable virulence profiles within each *S. aureus* CC, each lineage was characterized by a typical repertoire of superantigen toxin genes. For example, the *egc*-cluster enterotoxins, which cluster on the *S. aureus* genomic island vSAβ, were present in all CC5, CC22, and CC45 isolates but completely absent from CC8, CC12, CC15, and CC395. Moreover, an *egc* variant was almost exclusively linked to the CC30 background. Other enterotoxin genes with very strong linkage to certain CCs were *sec-sel*, and *sed-sej-ser*, they are colocalized on the pathogenicity island SaPI3 and were detected mainly in CC45 isolates, whereas the plasmid-borne enterotoxin genes *sed-sej-ser* were usually found in CC8. Enterotoxins with a broader distribution were the phage-borne *sea*, which was occasionally detected in CC8, -30, -45, and -395, and *seb*, on SaPI, which was infrequently found in CC5, -8, -12, -25, and -45. Similar gene distributions were also described by van Trijp et al. (2010) for strains from carriers with autologous invasive infection and by Monecke et al. (2011) for an *S. aureus* collection encompassing strains from a variety of different clonal lineages. Similar to MSSA and HA-MRSA lineages, common CA-MRSA harbor a lineage specific repertoire of enterotoxin genes; additionally, CA-MRSA lineages frequently harbor the genes for PVL (Diep et al., 2006; Tenover et al., 2006; El Garch et al., 2009; Shukla et al., 2010; Monecke et al., 2011; Portillo et al., 2013; Shore et al., 2014).

Although almost all human-associated MSSA and MRSA isolates carry enterotoxin and/or leukotoxin genes, several studies demonstrated that LA-MRSA ST398 rarely carry these genes (Köck et al., 2009; Gomez-Sanz et al., 2010; Huber et al., 2010; Hallin et al., 2011; Williamson et al., 2014; Moon et al., 2015; Normanno et al., 2015). However, only limited data are available for alternative LA-MRSA lineages. For LA-MRSA ST9 and ST5 from poultry the presence of the *egc*-cluster was demonstrated (Fessler et al., 2011; Wendlandt et al., 2013a; Monecke et al., 2013; Kraushaar et al., 2016) indicating that particular LA-MRSA lineages also might have enterotoxigenic properties (Johler et al., 2015). Beyond LA-MRSA, MSSA from different animal species have been shown to carry specific repertoires of enterotoxin genes (Fluit, 2012).

## 4.2 COLONIZING ENTEROTOXIGENIC *STAPHYLOCOCCUS AUREUS* AS CAUSE OF STAPHYLOCOCCAL FOODBORNE OUTBREAKS

Several studies compared isolates associated with SFPs to isolates from human carriage and/or human clinical infections to investigate the role of *S. aureus* colonizing and infecting humans as a

possible source of SFP. For example, Wattinger et al. (2012) found that SFP isolates could be assigned to the same common clonal lineages (mainly CC15, CC30, CC45) and showed highly similar virulence gene profiles as isolates from nasal colonization or invasive infection indicating that contamination of foodstuff with *S. aureus* colonizing and infecting food handlers represents a main source of SFP. Interestingly, the same group found no overlap in clonal lineages and virulence gene pattern for SFP isolates and isolates obtained from milk or pork, suggesting that pork or bovine mastitis milk do not represent the most common sources of SFP (Johler et al., 2011; Baumgartner et al., 2014). In contrast, several other studies identified enterotoxigenic *S. aureus* strains from animal sources, i.e., from bovine sources, as potential cause of primary contamination (Kerouanton et al., 2007; Bianchi et al., 2014).

Regarding the high prevalence of enterotoxigenic *S. aureus* as nasal colonizer in the population worldwide and the knowledge about human carriage as a major source of food contamination, the relatively low number of notified SFP outbreaks is striking. There might be different reasons for this discrepancy:

- Although there is no doubt that nasal and hand contamination is a major source of food contamination, mere carriage is not sufficient to initiate an outbreak if proper care is taken to prevent contamination of foods including the exclusion of workers with open wounds from preparing and handling food (al Bustan et al., 1996). Many of the studies cited previously in this chapter could link high carriage rates to a lack of personal and kitchen hygiene. Especially in developing countries training in food hygiene and safety often was shown to be insufficient.
- The real incidence of SFP is probably underestimated, which is due to several reasons, including unreported minor outbreaks, improper sample collection, and laboratory examination (Argudin et al., 2010).

Besides the low number of SFP outbreaks reported, only in a limited proportion of SFP outbreaks it is possible to trace back the causing strain to its source in the nose or on the hand of a food handler. In 2013, Johler et al. investigated an SFP outbreak caused by an enterotoxin A and *egc*-cluster positive strain of CC30 that was also found in the nose of a food handler. Another SFP outbreak reported recently was caused by an enterotoxin A and I producing strain, which was introduced most likely by a food handler (Gallina et al., 2013). Similarly, Wei et al. were able to trace back enterotoxigenic outbreak strains carrying *sea* and *seb*, respectively, to the hand lesion of a food handler in a cafeteria (Wei and Chiou, 2002). However, in a large percentage of outbreaks the initial source of contamination remains unknown. This might be due to the fact that carriage is often transient and might not be detected at the time of epidemiological investigations, which take place sometime after contamination of food.

## 5. ARE WORKERS IN THE FOOD INDUSTRY DIFFERENT?

Generally, workers in the food industry are colonized by *S. aureus* and MRSA with the same probability as the residual population. As such they mainly carry strains of those clonal lineages, which are common nasal colonizers in the respective geographic region.

However, because of their work environment and/or occupational behavior they might be at additional risk for acquisition of *S. aureus* or MRSA of specific clonal lineages as transient or persistent colonizer. The probability of acquisition, the strain type acquired, the risk of endogenous infection with multidrug

resistant *S. aureus* acquired but also the risk of transmission of enterotoxigenic *S. aureus* to food is associated with the stage of the food production chain (production, processing, distribution, or preparation, http://www.cdc.gov/foodsafety/outbreaks/investigating-outbreaks/production-chain.html) they are working at. To assess colonization rates and associated risks of infection and transmission of enterotoxigenic or multidrug-resistant isolates, a number of studies were conducted during recent years.

## 5.1 WORKERS EXPOSED TO LIVING ANIMALS AT SLAUGHTERHOUSES

A multitude of studies has investigated MRSA colonization in individuals in close contact with livestock, in especially farmers and veterinarians (van Cleef et al., 2014) as well as MRSA contamination of meat (de Boer et al., 2009; Kluytmans, 2010; Wendlandt et al., 2013b; Tenhagen et al., 2014; Kraushaar and Fetsch, 2014; Fetsch et al., 2017); however, although LA-MRSA from livestock can be easily transmitted to the abattoir environment and to abattoir workers, data on MRSA prevalence among abattoir workers are scarce.

Two Dutch studies documented an increased nasal MRSA carriage rate (3.2%–5.6%) in pig slaughterhouse workers in The Netherlands (Van Cleef et al., 2010; Gilbert et al., 2012). Colonization was predominantly due to LA-MRSA of CC398, which is the predominant LA-MRSA lineage among Dutch pigs. The colonization rates reported were significantly higher than the general population prevalence in The Netherlands (Wertheim et al., 2004), although they were much lower than reported from pig farmers or veterinarians with daily exposure to livestock (Cuny et al., 2009). Working with live pigs was shown to be the most important risk factor for colonization, although environmental contamination might also have played a role in the acquisition of MRSA. Mulders et al. (2010) found very similar results for the poultry food chain in The Netherlands. However, in contrast to the studies previously mentioned, LA-MRSA of the poultry-associated ST9 were frequently obtained from animals and workers in addition to CC398. LA-MRSA CC398 and ST9 were also isolated from broiler chickens and abattoir workers in Germany (Wendlandt et al., 2013a). Normanno et al. (2015) found nasal MRSA carriage in ~9% of abattoir workers screened in two industrial abattoirs in Southern Italy; MRSA strains isolated were more heterogeneous, but reflected the MRSA population isolated from slaughtered pigs during the same study, and included LA-MRSA isolates from CC398, CC1, and CC8.

Moon et al. (2015) collected data on MRSA carriage of workers in different slaughterhouses in Korea. The prevalence of MRSA in workers was 6.9% in chicken slaughterhouse workers, but no MRSA was detected in pig and cattle slaughterhouse workers. Besides LA-MRSA ST398 and ST692, isolates of Korean CA-MRSA lineage ST72 were identified in workers.

Finally, Leibler et al. (2016) recently investigated the *S. aureus* nasal carriage among beef-packing workers in Nebraska and did not find any indication of worker carriage with MRSA lineages previously associated with livestock. *S. aureus* carriage rates in general were concordant with data mentioned earlier in this chapter, and a slightly elevated MRSA carriage rate was due to human adapted isolates, mainly CA-MRSA lineage USA300.

## 5.2 BUTCHERS AND FOOD HANDLERS EXPOSED TO RAW MEAT

Gilbert et al. (2012) demonstrated that occupational exposure to MRSA decreased along the slaughter line, accompanied by a reduced risk of carriage for workers employed. However, on the other hand high MRSA contamination levels of retail meat were reported from several geographic regions

(de Boer et al., 2009; Kluytmans, 2010; Wendlandt et al., 2013b; Tenhagen et al., 2014; Kraushaar and Fetsch, 2014; Fetsch et al., 2017). To determine to what extent butchers and other food handlers exposed to raw meat are at increased risk of colonization with *S. aureus* and MRSA, several studies were conducted focusing on these individuals. Boost et al. (2013) investigated nasal colonization in 300 pork butchers at traditional "wet markets" throughout Hong Kong, dealing with fresh meat as well as carcasses, which may increase the risk of contamination, especially if protective clothing is not worn. They found an MRSA colonization rate of 5.6% in butchers, consisting of 2.3% of individuals colonized by non-LA-MRSA and 3.3% by LA-MRSA, which was considerably higher than in the general population in Hong Kong. The majority of LA-MRSA belonged to CC9, which was previously reported from pig carcasses in Hong Kong (Guardabassi et al., 2009; Ho et al., 2012), suggesting cross-contamination from carcasses to fresh meat and workers. In contrast, de Jonge et al. (2010) found no MRSA among 95 employees working in the Dutch cold meat processing industry and in institutional kitchens, although 31 participants (33%) were colonized with MSSA. Boost et al. attributed this difference to the higher level of automation associated with improved hygiene standards in the Dutch meat processing industry in comparison to the traditional butchering process at Hong Kong wet markets.

In a follow-up study the same group (Ho et al., 2014) investigated *S. aureus*/MRSA colonization in more than 400 food handlers from six large catering establishments in Hong Kong to determine whether individuals regularly in contact with raw meat exhibit an increased risk for carriage. Overall 22.8% of food handlers were colonized, but colonization rate was significantly higher in workers handling raw meat (30%), indicating an increased risk for colonization depending on regular exposition to raw meat. However, colonization rate was still in a range previously reported for the general public in Hong Kong and elsewhere (Zhang et al., 2011). A diverse range of clonal lineages was detected among MSSA isolates, also including clonal lineages previously associated with livestock (ST5, ST1, ST9, ST130, ST97, ST398); however, the majority of isolates belonged to clonal lineages common in human nasal colonization. Only five out of 99 *S. aureus* isolates were MRSA resulting in an MRSA colonization rate of 1.2%, which is comparable to the local MRSA colonization rate previously reported (Zhang et al., 2011); all MRSA isolates belonged to clonal lineage CC45, which represents the predominant HA-MRSA in Hong Kong (Ho et al., 2009; Gruteke et al., 2015) and was not previously associated with livestock indicating human rather than animal origin.

El Bayomi et al. (2016) recently investigated hand swaps from 30 raw chicken meat vendors in Egypt and found that 60% of food handlers were positive for *S. aureus* including 10% positive for MRSA. Within the study 31% of *S. aureus* isolates (and the majority of MRSA) harbored the PVL gene, whereas 10% were positive for the sea and *sed* genes each. Although most isolates were MSSA, they exhibited antibiotic resistance to several antibiotic compounds. Genotyping revealed relatedness between MRSA isolates of human and chicken meat origin, indicating cross-transmission.

In contrast to the previous studies Nnachi et al. (2014) reported an alarming MRSA carriage rate of 51% among raw meat handlers in Nigeria, which was most probably associated with insufficient hygiene measures during handling of raw meat.

## 5.3 FOOD HANDLERS NOT EXPOSED TO THE PREVIOUS RISK FACTORS

The studies mentioned above suggest that food handlers not exposed to living animals or carcasses likely do not have an increased risk to carry LA-MRSA. Similarly, they are only at low risk of

carrying HA-MRSA as long as they are not exposed to respective risk factors described earlier in this chapter. However, during the last decades food workers have been implicated in the occurrence of staphylococcal foodborne diseases in many different settings around the world mainly by contaminating food with methicillin sensitive, enterotoxin producing isolates originating from the handlers nose or hands. For example, Holmberg and Blake (1984) reviewed more than 100 SFP outbreaks in the United States and found the disease-causing strains in food handlers in a considerable proportion of cases. Wieneke et al. (1993) obtained similar results reviewing more than 300 outbreaks of SFP from 1969 to 1990 in the United Kingdom. To quantify the risk of food contamination by multidrug resistant or toxinogenic *S. aureus*, several studies have been conducted to determine the percentage of individuals colonized by multidrug resistant and toxin producing *S. aureus* isolates. Among these studies large variations in colonization rates, resistance rates, and in the proportions of toxinogenic *S. aureus* isolates occur. This variation may be attributed not only to geographical location of different studies, as mentioned earlier in this chapter, but also to methodological differences in study design, sampling, culturing (preenrichment vs. direct plating), typing (as far as conducted), and toxin or toxin gene detection. This immense variation makes objective comparison of presented results quite difficult. Because the problem of foodborne illness is more widespread and serious in developing countries, a great number of cross-sectional studies originate from these geographical regions (Akhtar et al., 2014).

In the following, an overview of *S. aureus* and MRSA carriage in humans in different geographical regions—Africa, Latin America, Asia, Middle East, Europe, North America and Oceania—is provided.

### 5.3.1 Africa

Oteri and Ekanem (1989) investigated nasal swabs from 160 food handlers in two hospital settings in Laos, Nigeria and found a carriage rate of 24% along with alarmingly poor adherence to personal hygiene measures. In a very recent study from Nigeria hand swaps from 60 food handlers at school cafeterias in Benin City revealed an *S. aureus* carriage rate of 38% (Okareh and Erhahon, 2015).

A carriage rate of 21.6% was reported for 259 food handlers, including restaurant workers, bakers, store keepers, milk distributors, butchers, and vegetable sellers, from Sudan (Saeed and Hamid, 2010); unexpectedly, carriage rates in this study varied substantially in dependence of food handler group with the highest abundance in store keepers (44.6%) and the lowest in vegetable sellers (3.6%). A similar carriage rate (20.5%) was reported from food handlers working at a university cafeteria in Ethiopia (Dagnew et al., 2012) and in 2% of the employees nasal MRSA carriage was detected; the remaining MSSA isolates were partially resistant to several antibiotics. At the same location Andargie et al. (2008) found *S. aureus* in 16.5% of 127 fingernail contents collected from food handlers.

In a study from Botswana, where 200 food handlers were sampled, also a high percentage of antibiotic resistant *S. aureus*, including MRSA, was found (Loeto et al., 2007). With a carriage rate of 57.7% a similarly high percentage of all employees were tested positive for *S. aureus* in nasal and/or skin swaps. Of the 204 *S. aureus* strains isolated, only 21% were enterotoxigenic and enterotoxin A was the most prevalent toxin. Resistance to methicillin was encountered in 33 isolates and, most alarming, for nine of the isolates elevated minimum inhibitory concentrations for vancomycin, one of the critically important antimicrobials for human medicine according to WHO (2016), was reported.

In 2012 and 2013 El-Shenawy et al. investigated the prevalence of *S. aureus* nasal and skin carriage, respectively, among 200 food handlers each, working in three different food processing plants in Egypt (milk, meat, and vegetable processing plants, respectively El-Shenawy et al., 2013, 2014). Colonization was quite similar in either of the studies (31% nasal colonization vs. 38% skin colonization), ranging from 27% to 34%, respectively, in workers in the vegetable processing plant to 36% and 45%, respectively, in workers in the milk and dairy processing plant. Although in the first study 34% of the isolates produced enterotoxins A–D or a combination thereof, in the second study only 14% of isolates tested positive for enterotoxin production. However, in both studies enterotoxins A and C were most predominant. In contrast to these results Zeinhom et al. (2015) investigated skin swaps from 75 milk and cheese handlers in Egypt and reported a carriage rate among individuals of only 17% with 5% of food handlers carrying enterotoxin B positive isolates.

### 5.3.2 Latin America

Cross-sectional studies from Latin America were reported predominantly from Brazil and Chile. In 1997, Soares et al. investigated *S. aureus* isolates obtained from nasal and skin swabs of 196 food handlers in community or hospital-located kitchens. 46% of employees were colonized, of which approximately two-third were colonized nasally, whereas 17% were colonized on their hands, and 18% were colonized at both locations. Pulsed field gel electrophoresis revealed a high diversity within the strain set. Of 91 carriers, 28.6% were colonized by enterotoxigenic strains. The majority of enterotoxigenic strains produced enterotoxin C, but toxins A, B, D, and E or combinations thereof were also found. Most isolates were resistant to Penicillin and Ampicillin but susceptible to other antimicrobials agents tested; however, three MRSA (1.5% of individuals) isolates were detected, which revealed multidrug resistant and were affiliated to a clonal lineage highly prevalent as HA-MRSA in Brazil; two of them likely had been acquired in the hospital environment by workers employed in the hospital-located kitchens.

Rall et al. (2010) collected samples from the hands and anterior nares of 82 food handlers in three industrial kitchens in a small town in Brazil and found 21.2% of the individuals to be colonized by *S. aureus*; 95% of *S. aureus* strains carried one of the enterotoxin genes *sea* to *sei* of which *sea* was the most frequent. However, they also found ~47% of commensal coagulase-negative staphylococci to be putatively enterotoxigenic. In a follow-up study the group analyzed 35 *S. aureus* isolates obtained by *spa*-typing and by polymerase chain reaction for the presence of the immune evasion cluster (IEC), which was present in only 10 (28.6%) strains (Baptistao et al., 2016). According to *spa*-typing the isolates were quite diverse with clonal lineages ST1, ST5, ST30, and ST45 being most prevalent. However, with respect to the high percentage of IEC-negative isolates the authors concluded that the food handlers in part might have been contaminated by IEC-negative *S. aureus* strains through food, which was also supported by the identification of *S. aureus* exhibiting *spa*-types associated with both, *S. aureus* from animals and from humans.

A much higher colonization rate was reported by da Silva Sdos et al. (2015) after investigating swabs from the anterior nostrils and hands of 30 food handlers at a university restaurant in Northeast Brazil. Forty percent of all food handlers investigated were tested positive for *S. aureus*, however, only two of them were colonized by staphylococci on their hands. Seventy five percent of these isolates carried enterotoxin genes (*sea* to *sei*), with *sei* being most prevalent. Most isolates showed sensitivity to the tested antibiotics, except for penicillin. Similar to the previous study the authors found a high percentage of commensal coagulase-negative staphylococci carrying enterotoxin genes indicating the potential to produce toxins and cause foodborne infections.

In another study conducted in Brazil, Ferreira et al. (2014) sampled 146 food handlers from 14 public hospitals in northeastern Brazil. The results indicated that 50% and 29% of them had coagulase-positive staphylococci on their hands and in their anterior nares, respectively. The majority of isolates were resistant to Penicillin, and 29% of the isolates were phenotypically identified as MRSA; additionally, resistances to other clinically important antibiotics, including vancomycin, were reported by the authors.

In a study conducted in Chile, Soto et al. (1996) screened 87 food handlers working at a metropolitan university in Chile for *S. aureus* carriage by swabbing several body sites. They found a carriage rate of 65.5%, with 41% of food handlers carrying enterotoxigenic strains. Enterotoxin B was the predominant toxin type detected. In contrast, Figueroa et al. (2002) found *S. aureus* colonization in only 34% of 102 food handlers from 19 restaurants in Santiago with 19% of them carrying enterotoxin producing isolates, predominantly of enterotoxin type A.

In a single study conducted in Argentina nasal swabs were obtained from 88 food handlers (Jorda et al., 2012). A total of 37.5% food handlers were positive for *S. aureus* with four (4.5%) of them carrying MRSA. Enterotoxin genes were found in 14.7% of food handlers. Enterotoxin gene *sea* was most frequently detected.

### 5.3.3 Asia

In Hong Kong, Ho et al. (2015b) conducted a longitudinal study of nasal colonization and hand contamination of food handlers with *S. aureus* starting in 2002 and lasting until 2011. Within this time frame hygiene measures were strictly implemented in 2003 in Hong Kong because of the outbreak of severe acute respiratory syndrome (SARS). The study started in 2002 with samples from 619 food handlers at 15 catering establishments, including supermarkets, canteens, and centralized kitchens serving hospitals and sporting facilities. Fourteen of these premises were revisited in 2003 and a further 527 samples were taken; 499 participants were sampled at both occasions. In 2011, 434 food handlers were sampled from six large catering establishments, similar to those mentioned above. In 2002 the authors found a nasal carriage rate of 35% and a hand contamination rate of 41%; in 2003 both, nasal and hand colonization rates were significantly reduced to 24% and 12%, respectively. In 2011 the nasal carriage rate remained stable (23%), whereas the hand contamination rate was further reduced to 4%. Most hand contamination was attributable to nasal isolates of persistently colonized (co-) workers who had presumably contaminated the environment (Ho et al., 2015c). Handling of cooked and raw meat was shown to increase the risk for colonization, as already previously anticipated (Ho et al., 2014). MRSA carriage was found in 1.2% in 2011 compared with 0.6% and 0.8% in 2002 and 2003, respectively. *Spa*-typing of isolates revealed a high diversity with isolates of clonal lineages ST188, CC15, and CC30 predominating and indicated a certain strain dynamic over time. Although MRSA isolates were diverse in 2002 and 2003, they were dominated by isolates of t1081/CC45, which was also the most common HA-MRSA in Hong Kong (Gruteke et al., 2015; Ho et al., 2009). Typing also enabled to estimate the rate of persistent carriers (18%). The considerable decrease in colonization rates, which was mainly due to a reduction of transient carriers, was attributed to the enhanced hygiene practices implemented during the SARS epidemic. These included, for example, the mandatory use of gloves and masks and the increased emphasis on hand hygiene in food handlers. Carriage rates were similar to those reported from the general population over the same time span (O'Donoghue and Boost, 2004; Zhang et al., 2011). Isolates originating from the study were subsequently analyzed for the presence of enterotoxin genes *sea* to *sej*, *sek* to *ser* and *selu*, *ses*, and *set* (Ho et al., 2015a). Enterotoxin and

enterotoxin-like genes were detected in 83%, 82%, and 80% of isolates, respectively. They were more often detected in isolates of persistent carriers, with *sea*, *seb*, and *sem* found to be statistically associated with persistent carriage. The most common enterotoxin genes were those associated with the *egc*-cluster; however, of the classical enterotoxin genes, *sea* and *see* were most prevalent. In contrast to other studies (Holtfreter et al., 2007) no association was found between clonal lineage and the presence of enterotoxin determinants.

Tan et al. (2014) investigated hand carriage rates in 85 food handlers at primary schools in Malaysia and found a mean carriage rate of 70%, depending on the time of sampling (before/during/after preparation of food). Of the *S. aureus* isolates obtained in this study 72% showed antibiotic resistance to at least one antibiotic tested, and a large proportion of isolates was resistant to ampicillin and penicillin; however, multidrug resistance was rare.

### 5.3.4 Middle East

In a cross-sectional study conducted in Anatolia and encompassing 299 food handlers Simsek et al. (2009) found 23.1% of individuals to be colonized with *S. aureus*. A second study performed in the same geographical area enrolled 30 food handlers who worked in catering services (Vatansever et al., 2016). Authors found that 36% of individuals showed nasal *S. aureus* carriage, whereas mouth and hand carriage were considerably lower (19% and 14%, respectively). Although no MRSA isolate was found, several isolates with resistance to critically important antimicrobials, including one multidrug-resistant isolate were found.

Al-Bustan et al. (1996) screened 500 restaurant workers in 100 restaurants of Kuwait City and found an *S. aureus* nasal carriage rate of 26.6%, which was low in comparison to the general public and the hospital population in the same region; they also looked for the strains ability of enterotoxin A–D production and found that 86.6% of isolates were able to produce either one or a combination of several toxins, with enterotoxin A and B being most prevalent. In a later study Udo et al. (2009) characterized 200 isolates obtained from nasal, skin, stool, and throat swaps from 250 food handlers working in 50 different restaurants in Kuwait City. Workers were sampled during mandatory screening or in context of outbreak associated epidemiological investigations. The authors found a much higher colonization rate (53.2%) than in the previous study; further (molecular) characterization revealed highly diverse strains and 92.5% of isolates expressing antibacterial resistance; two-third were unsusceptible to at least two different bacterial agents, and 23% were multidrug resistant, including one MRSA isolate. 71% of isolates were positive for enterotoxin genes (*sea* to *sei*), with *sei* being the most prevalent gene, and almost two-third of enterotoxigenic isolates carried more than one enterotoxin gene. Additionally, the authors found genes for PVL in 9% of the isolates, including the MRSA isolate indicating the presence of CA-MRSA.

In one of the most recent cross-sectional studies, conducted in Iran, 220 food handlers attending a public health center laboratory for annual checkup were examined by culturing nasal and fingernail content swaps. 65.4% and 46% of individuals were found to harbor *S. aureus* in their nostrils and in their fingernail content, respectively (Nasrolahei et al., 2016).

### 5.3.5 Europe, North America, and Oceania

Cross-sectional studies from Central Europe, North America, or Oceania focusing on *S. aureus* carriage in individuals working in the food industry are scarce. Screening of food handlers is conducted mostly regarding cases of SFP, as part of subsequent epidemiological investigations. In 2000, Finnish

researchers reported about hand and nasal samples of flight catering staff taken between 1995 and 1997 (Hatakka et al., 2000). 29% of the nasal samples and 9% of the hand samples were positive for *S. aureus*. 46% of the strains were enterotoxigenic, resulting in 12% and 6% of individuals carrying enterotoxigenic isolates in their nose and on their hands, respectively. Enterotoxin B was the most prevalent toxin within the highly diverse collection of isolates.

Uzunović et al. performed a laboratory-based study on all consecutive, nonduplicate *S. aureus* strains isolated from nasal swabs of food handlers in Bosnia-Herzegovina. Swabs were taken between 2007 and 2009 twice a year as part of regulatory mandatory surveillance for all persons dealing with food. Only 189 nonduplicate *S. aureus* isolates (including three MRSA) were recovered out of 13,690 nasal swabs resulting in an unexpectedly low average nasal carriage rate of 1.4%; however, all isolates were *spa*-typed, thus reflecting at least a snapshot of the clonal diversity of nasal carriage. *Spa*-typing revealed a high diversity of the population with the common clonal lineages, CC15, CC22, CC7, CC30, and CC5 being most prevalent (Uzunovic et al., 2013).

Castro et al. sampled nose and hands of 162 volunteers from a food processing company in Portugal. Nasal and hand carriage were found in 19.85% and 11.1%, respectively, with 6.2% of individuals being colonized at both sites. 82% of the isolates were resistant to at least one antibiotic tested, but no MRSA were detected and multidrug-resistant *S. aureus* were rare (Castro et al., 2016). The majority of isolates detected in this study (71.9% of nasal and 56% of hand isolates) were enterotoxigenic, with *egc*-located *seg* and *sei* being the most prevalent enterotoxin genes.

Recently, Caggiano et al. (2016) published a study on nasal screening of 323 healthy workers employed in the pasta and pork industry in Italy. *S. aureus* and MRSA carriage rate was 26.3% and 2.2%, respectively. Workers employed in the pasta industry had higher carriage rates than those employed in the pork industry (61.2% and 3.7% vs. 38.8% and 0.6%). Two MRSA isolates from pasta industry workers were assigned to CC398.

## 6. SUMMARY AND CONCLUSION

The impact of *S. aureus* and MRSA in workers in the food industry is not only manifold but also highly variable. For instance, employees working at the beginning of the food chain are at increased risk for carrying MRSA, especially if they are handling living animal. MRSA carriage in these individuals is mostly associated with LA-MRSA lineages present in the respective animal population. However, LA-MRSA carriage rate is significantly lower in food industry workers in comparison to farmers, veterinarians, etc. Nevertheless, it implies a certain risk for endogenous MRSA infections and for spreading LA-MRSA to the worker's household members. Data on MRSA and MSSA carriage in butchers are controversial. The probability of MRSA colonization seems to be associated with the degree of automation within the slaughter process as increased automation also implies improved hygiene standards. MRSA lineages found in these individuals mostly include LA-MRSA, however, colonization with CA-MRSA was also reported. Carriage is most probably associated with insufficient hygiene measures during handling of raw meat and in personal hygiene. Additionally, a few studies also report a slightly increased risk for MSSA colonization.

In general, occupational exposure to MRSA decreases along the slaughter line, accompanied by a reduced risk of MRSA carriage for workers employed. Food handlers without occupational contact to living animals and not exposed to "classical" risk factors for MRSA colonization (e.g., working in the

hospital environment) are not at increased risk for MRSA carriage, which is also reflected by the overall low MRSA carriage rates (mostly below 5%) reported in the studies summarized above.

As expected, MSSA colonization is common in workers in the food industry and MSSA carriage rates vary considerably (~20% to ~60%). This is in accordance to MSSA carriage in the general population, as outlined previously in this chapter. Also, the percentage of enterotoxigenic isolates (~20% to 90%) and the distribution of enterotoxin types (as far as investigated) is subject to an enormous variation, which is also seen in the general population. Although MRSA carriage is rare in most reports, the majority of isolates tested for their susceptibility exhibit antibiotic resistances to several antibiotics usually including penicillin.

Although controversially discussed in several studies, nasal colonization seems to be more common than contamination of hands. It is anticipated that persistently colonized individuals contaminate their hands as well as the environment and serve as the source for hand contamination of noncarriers. Unfortunately, most studies did not include comparable typing data for carriage isolates. However, existing typing data together with resistance and enterotoxin gene profiles indicate that MSSA carriage in food handling individuals is highly diverse and is due to the same clonal lineages as in the general population within a given geographic region. However, this implies that food handlers might also be colonized with CA-MRSA strains, which can be spread via the food chain because of improper personal and process hygiene. As a consequence, compliance with hygiene measures is the most important prerequisite to prevent food contamination by both, human and environmental *S. aureus* reservoirs.

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