Staphylococcus aureus epidemiology and control:

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Chapter 5

General Discussion

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Up till now, by the application of the MRSA Search and Destroy (S&D) policy, the Netherlands and Scandinavian Countries have managed to keep their MRSA rates low.[1,2] The percentage of *S. aureus* bacteraemia caused by MRSA in these countries is very low (<1%), contrary to other European countries that have reached percentages of up to 50%. The S&D policy focuses on isolation of MRSA positive and patients at increased risk for MRSA, wearing of personal protective equipment (PPE) by HCW, and cleaning/ disinfection of the room after discharge of these patients. Furthermore, screening of patients at increased risk and of HCW that had been in contact with MRSA positive patients is an important aspect. We showed that the S&D policy resulted in control of nosocomial transmission if adequate measures outlined in the S&D policy were taken **(Chapter 2.1)**. The outbreaks described were due to an omission in the procedure; the index patient had been admitted to a hospital in Turkey a month before the admission to our hospital. However, this risk had not been recognised and therefore he was not treated with adequate isolation precautions for several days, resulting in transmission to both HCW and patients. We calculated that the S&D policy saves costs for the hospital and it also saves lives **(Chapter 2.2)**.

This controlled situation by the application of the S&D policy is threatened by the emergence of two new variants of MRSA. First, the emergence of livestock-associated MRSA (LA-MRSA). This LA-MRSA was found to be associated with professional contact with pigs and veal calves.[3,4] After the introduction of this new risk group in the national and hospital guidelines in 2006, hospitals in pig- and veal calf dense areas experienced logistic problems by treating the numerous patients of this new risk group in isolation **(Chapter 3.1)**. However, the transmission of LA-MRSA in healthcare is also under control, even with modifications of the policy in the out-patient setting **(Chapter 3.2)**. A second threat is the emergence of the so-called MRSA of unknown origin (**Chapter 2.1**).[5-7] This is a threat because of the lack of known risk factors in this patient group, resulting in admission without adequate isolation precautions, which may result in transmission of MRSA to HCW and/or other patients. About a quarter of all newly identified MRSA positive patients don't belong to any of the known risk groups (**Chapters 2.1 and 3.5**).[5] These patients are usually not admitted for their MRSA but for other reasons and their MRSA can only found by coincidence. Therefore the estimated quarter is even an underestimation of the real proportion. Because of this threat we performed an exploratory case-control study to identify community-associated risk factors for MRSA-carriage **(Chapter 3.4)**. Regular consumption of poultry, cattle density per municipality, and sharing of scuba diving equipment were found to be associated with CA-MRSA carriage. The finding that the regular consumption of poultry is associated with CA-MRSA carriage may be explained by the abundant presence of MRSA in meat.[8,9] A Dutch study

demonstrated that a substantial part of the meat pieces obtained from retail stores in the Netherlands were harbouring MRSA, including both LA-MRSA and non LA-MRSA strain types. Colonisation rates varied from 10.6% for beef, 10.7% for pork, up to 16.0% for chicken and 35.3% for turkey.[10] To the best of our knowledge we are the first to identify an association between the consumption of poultry and MRSA carriage in humans, which suggests that MRSA in the food chain may be a source for MRSA carriage in humans. The observed association may be explained by the incomplete cooking of the meat, but also by the consumption of simultaneously prepared food products, such as salads, using contaminated kitchen equipment. Furthermore, we showed that sharing of scuba diving equipment was independently associated with CA-MRSA carriage **(Chapter 3.4)**. This finding corresponds with previous publications of outbreaks of CA-MRSA infections in divers, and the role of sharing of scuba diving equipment as a possible mode of transmission of CA-MRSA.[11,12] Whether the presence of skin abrasions in divers, the lack of decontamination of diving suites and other diving materials after use, or the favourable high salt content of sea water play a role in the observed association remains to be elucidated.

Based on the first studies that identified an association between the presence of MRSA in livestock and the occurrence of MRSA in humans, it was assumed that the risk for acquisition of LA-MRSA was confined to persons with direct contact with livestock.[4] However, several outbreaks with LA-MRSA in healthcare facilities have been reported since then, indicating that human-to-human transmission occurs, although it has been estimated that LA-MRSA is 5.9 times less transmissible than other MRSA.[13,14] In addition, a recently published case-control study identified pig-, cattle- and veal calf densities per municipality as independent risk factors for carriage of LA-MRSA as compared to non LA-MRSA.[15] These latter findings are supported by the results of our study showing that persons without direct contact with livestock but living in areas with a high cattle density area are at higher risk for LA-MRSA carriage **(Chapter 3.4)**. Furthermore, we found that 20.7% of individuals with CA-MRSA carried LA-MRSA **(Chapter 3.5)**. Although it cannot be excluded that human-to-human transmission occurs in areas with a high LA-MRSA density, environmental contamination with LA-MRSA may play a role as well. MRSA has been shown to be present in air and soil samples collected downwind of pig and swine barns.[16]

Further studies are warranted to confirm our findings and to determine the absolute risks of MRSA acquisition. However, it is not feasible to implement these risk factors in the S&D policy. If all people that consume poultry at least once a week and all people living in a cattle-dense areas must be screened, almost all patients need to be screened. If the number of MRSA without known risk factor continues to rise, application of the S&D policy will probably not be sufficient anymore to prevent MRSA transmission in hospitals. For countries with frequent transmission of the CA-MRSA strain USA300 in

the community it has also been questioned whether implementation of such a stringent preventive policy would be effective.[17]

Sometimes, it is wondered whether all these precautions are worth the time and effort. It has been questioned whether people are getting ill from these LA-MRSA and CA-MRSA. For LA-MRSA, there are indeed reports showing serious infections caused by this variant, e.g. endocarditis.[18] CA-MRSA has been isolated predominantly from skin and soft tissue infections (SSTI), such as abscesses, cellulitis, folliculitis and impetigo **(chapter 3.3)**.[6,7] In our case-control study we also found that participants with CA-MRSA more often suffered from abscesses, boils and open wounds than participants without MRSA (unpublished data). Although CA-MRSA infections are usually mild, they may also be severe, and can result in hospitalisation and even death.[19-21] So, prevention of transmission can save infections and deaths. Therefore, it is important to apply preventive precautions for these variants also. In a pooled analysis of primary data from three studies across international settings, we showed that the index being colonised with the clinical isolate and the percent of household members <18 years were independently associated with CA-MRSA transmission in the household **(Chapter 3.6)**. Therefore, household members and other close contacts with complaints matching a *S. aureus* infection must be involved in any MRSA eradication procedure **(Chapters 3.3 and 3.6)**.

Because of the emergence of the meticillin-resistant *S. aureus* variant (MRSA) in the eighties and the lack of development of new antibiotics during the last decades, much attention is paid globally to prevention of MRSA transmission and MRSA eradication therapy while there is less focus on control and eradication of the sensitive variant (MSSA). Because *S. aureus* is the leading pathogen in hospitals world-wide it is important to focus on infections caused by *S. aureus* in general (both MRSA and MSSA). The pathogenicity and virulence of the strain is dependent on the presence of virulence markers and not on the presence of the mec-A gene. For example, recently it was shown that the prevalence of Panton Valentine Leucocidin (PVL) in community-onset *S. aureus* SSTI in children in Spain was associated with more abscess formation, regardless of meticillin-resistance.[22] The only difference between MRSA and MSSA are the limited treatment options for MRSA. This is the reason the strict S&D policy was introduced for MRSA and not for MSSA. To prevent transmission of MSSA, the guidelines prescribe general precautions to be sufficient, meaning that HCW have to apply hand hygiene and wear PPE during the inspection and treatment of an infected wound. No separate room is required for these patients unless the infected wound cannot be covered with a wound dressing. Both MRSA and MSSA are known to cause outbreaks in hospitals.[23-25] For example, in our hospital we had two outbreaks of MSSA proven to be initiated by HCW with nasal carriage, which resulted in infections with the identical MSSA strain in patients undergoing thoracoscopy or having a thorax drain (unpublished data).

After MSSA eradication therapy for the HCW no new patients developed *S. aureus* infections with the original strains of the HCW. In another hospital in the Netherlands an outbreak of Bullous Impetigo caused by MSSA affected nine neonates and three HCW.[26] These are all examples of cross-transmission, but there is another area that needs to be addressed. A large proportion (±80%) of nosocomial *S. aureus* infections originate from the patients' own flora.[27-30] Approximately 30% of the population carries *S. aureus* at a given moment in time, which has limited consequences in the extramural setting. However, nasal carriage of *S. aureus* is a well-known risk factor for subsequent infection in patients undergoing surgery, in patients on dialysis or with intravascular devices, and those with cirrhosis of the liver or intensive care.[31-33] In a systematic review, we showed that prophylactic intranasal mupirocin reduced the rate of post-operative *S. aureus* infections by 52% among surgical patients who were *S. aureus* nasal carriers **(Chapter 4.1)**. This was also shown in a multicentre double-blind randomised controlled trial in which carriers of *S. aureus* were randomised to receive treatment with mupirocin and chlorhexidine gluconated soap.[30] By this screen-and-treat strategy a 56% reduction in the rate of *S. aureus* SSI was achieved. This advocates a screen-and-treat strategy for *S. aureus* in general, instead of MRSA only which was done in some other studies.[34,35] A calculation of the hospital costs showed that costs of care in the treatment arm were on average €1911 lower per carrier than costs of care in the placebo arm (p=0.01) **(Chapter 4.4)**. Based on the *S. aureus* nasal carriage rate of 20% found in the multicentre trial, per thousand surgical patients ± €400,000 could be saved. Furthermore, one-year mortality in surgical patients who underwent clean procedures, was significantly reduced after screening and treatment of carriers **(Chapter 4.5)**. We also found that readmissions were 57% lower in the treated group (unpublished data).

A recent study concluded that in routine ICU practice, universal decolonisation was more effective than targeted screening and subsequent decolonisation in reducing MRSA clinical isolates.[34] Also, Wassenburg et al showed that treating all patients without screening would result in a saving of €7339 per life year gained, as compared to €3330 if only identified carriers were treated.[36] The easy implementation of a treat-all strategy and the low price and safety of mupirocin will easily lead to non-prudent use of this important antimicrobial agent. However, this treat-all strategy is associated with a high rate of unnecessary and thus unethical treatments that increase the likelihood of the development of resistance.[37] Mupirocin resistance will obviously lead to failure of *S. aureus* decolonisation strategies.[38] Cautious use of mupirocin is likely to maintain the mupirocin resistance at a low level, thus preserving its efficacy. The aim of the prophylactic treatment is not to eradicate *S. aureus* forever but to result in short-term *S. aureus* eradication of approximately a month to prevent postoperative *S. aureus* wound infections. In the systematic review it was also shown that mupirocin treatment in the nose reduced *S. aureus* infections in dialysis patients **(Chapter 4.1)**. However, because

of its long-term use, this has not become standard procedure until now. The US Centres for Disease Control have now included the screen-and-treat strategy for surgical patients as a consideration in their top recommendations for safer health care.[39]

Conclusions

By application of the S&D policy the nosocomial transmission of HA-MRSA is under control. This S&D policy is cost-saving for the hospital. The emerging LA-MRSA was a new challenge but after some adjustments of the policy for outpatients this new variant can be handled well in hospitals. A more concerning development is the emerging of the CA-MRSA. Individuals carrying this CA-MRSA have no established risk factors and can therefore not be treated with adequate precautions, which may result in transmission to HCW and other patients. It is assumed that the MRSA incidence in the community will increase due to this strain and it can be questioned whether the S&D policy can be maintained in the current way.

Together with a focus on cross-transmission, we must focus on infections caused by the patients' own flora. Treatment of *S. aureus* nasal carriers with mupirocin nasal ointment in combination with chlorhexidine gluconated soap results in a reduction of *S. aureus* infections after surgery, less re-admissions, a reduction in hospital costs and also a significant decrease in one-year mortality in surgical patients who undergo clean procedures.

The results of the studies presented in this thesis have contributed to or are taken into consideration at this moment for changes in national MRSA guidelines and are used in the development of an international guideline of the World Health Organisation for the prevention of surgical site infections.[1,40]

Considerations for the future

The emergence of CA-MRSA is a threat for the successful S&D policy. Up till now we have managed to keep the MRSA incidence low, but individuals without established risk factors can carry MRSA for a long time without complaints. Meanwhile, their MRSA can be spread into the community by transmission to household members and other contacts **(Chapters 3.3 and 3.6)**. In the future, the current S&D policy will probably not be sufficient any more to prevent transmission in the hospital. Alternatives strategies have to be developed. For this we have to focus on high-risk patients and procedures. Implementation of a screen-and-treat strategy for all high-risk patients and patients undergoing high-risk procedures will probably be sufficient to prevent the

most important morbidity and mortality caused by *S. aureus* (MRSA and MSSA). At the moment, a screen-and-treat strategy for cardiothoracic, cardiovascular, orthopaedic and neurosurgical procedures with implants has been implemented. Probably, we have to expand this to other areas like patients undergoing a thoracoscopy or receiving a central venous catheter.

For eradication, it is an option to eradicate only the virulent and easily transmitted MRSA and MSSA strains. Further research is required to identify the strains that possess these properties.

In summary, the current successful MRSA 'Search and Destroy' strategy applied in healthcare settings in the Netherlands is threatened by the emergence of LA-MRSA and CA-MRSA in the Dutch community. New strategies must be developed for 1. the prevention of spread of LA-MRSA from animals to humans and for short-term eradication of LA-MRSA positive individuals and 2. the prevention of spread of CA-MRSA in health care settings and in the community.

For LA-MRSA the 'destroy' part of the policy cannot be applied because permanent eradication of LA-MRSA in humans is not feasible because of their return to the MRSA positive animals in the stables. Therefore, an alternative is giving eradication treatment to LA-MRSA positive farmers and their household members peri-operatively to prevent endogenous MRSA infections. It has been shown that short-term eradication is feasible when the farmer is willing to transfer work to a colleague during therapy. A positive development is the drop of total sales of antibiotics in industrial farming by 51%, during the period 2009-2012 (495 tonnes in 2009 to an estimated 244 tonnes in 2012), which hopefully will result in a reduction of LA-MRSA positive animals.[41] Furthermore, general precautions (e.g. wearing mouth masks (unpublished data)) in the stables must be taken into consideration to prevent farmers to become MRSA positive.

CA-MRSA cannot be recognised on admission because of the lack of known risk factors. Therefore, both the 'search and destroy' parts of the 'Search and Destroy' policy are threatened. It is not clear which patients are at risk for this CA-MRSA, so it is unknown who are the individuals to search for and therefore it is not feasible to destroy all this CA-MRSA in the community. Therefore, the focus must be on treatment of all individuals suffering from infections.

In conclusion, both for MRSA and MSSA we have to apply a 'Search and Control' policy with a focus on vulnerable patients in healthcare settings, undergoing high-risk procedures in which the skin is disrupted. This will improve patient safety in a population that becomes more vulnerable to nosocomial infections in the future. This shows that Florence Nightingale's statement is still valid: A hospital should do the sick no harm.

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