Summary
Introduction

*Staphylococcus aureus* (*S. aureus*) is a commensal bacterium for humans, and generally resides on skin and mucous membranes, like nares, pharynx, and perineum. About one in three persons carry *S. aureus* in their nose. Next to being a commensal bacterium, *S. aureus* is also known for its pathogenic potential, with a range of harmless skin infections like impetigo and furuncles to severe infections like sepsis, osteomyelitis and pneumonia.

Shortly after the introduction of methicillin for the treatment of *S. aureus* infections, the first methicillin-resistant *S. aureus* (MRSA) was reported. At first the problems centred in hospitals (hospital-associated MRSA: HA-MRSA), however, in the last decades MRSA causes infections in the community in previously healthy persons as well (community-associated MRSA: CA-MRSA). Due to a strict search and destroy strategy in the Netherlands, prevalence of MRSA in hospitals has remained low, compared to other countries.

In 2003 the association of MRSA with livestock was first reported in the Netherlands. Subsequent investigations revealed a huge reservoir of MRSA in livestock, which consisted of a highly clonal population of MRSA, designated livestock-associated MRSA (LA-MRSA). Pig farmers and pig veterinarians were frequently carrying these strains, with an initially reported prevalence of approximately 25%.

Aim of this thesis

The initial studies described in this thesis aim to estimate prevalence of and find determinants for LA-MRSA carriage in multiple populations: pig farmers (Chapter 2.1), their household members (Chapter 2.1), slaughterhouse workers (Chapter 2.2), persons living in pig-dense municipalities (Chapter 2.3), and field workers with intense pig contact for a short duration (Chapter 2.4). In addition, the presence of LA-MRSA in European countries was described in Chapter 2.5. The public health threat of MRSA in general and LA-MRSA in specific was studied in Chapters 3.1, 3.2 and 3.3. Lastly, dynamics of carriage in pig farmers and household members are presented in Chapters 4.1, 4.3 and 4.4.
Prevalence of LA-MRSA carriage

Persons in direct contact with pigs or veal calves had the highest risk of nasal LA-MRSA carriage. Chapter 2.1 shows that in 2007 29% of pig farmers were LA-MRSA positive, by 2010 this cross-sectional prevalence rose to 63%. During follow up it was found that 38% of the pig farmers carried LA-MRSA persistently (Chapter 4.3). Studies in other professional groups with pig contact show comparable results. In pig slaughterhouse personnel in contact with live pigs LA-MRSA prevalence was 15% (Chapter 2.2). Field workers temporarily taking samples from pigs and stables acquired LA-MRSA at rates as high as 48%. Of these persons, 94% were LA-MRSA negative after 24 hours, indicating that short and intense pig contact can result in LA-MRSA acquisition but carriage usually lasts for very short periods (Chapter 2.4). Four percent of household members of pig farmers were LA-MRSA positive in 2007 (Chapter 2.1), in 2010 the cross-sectional prevalence was 10%, and 4% of household members were persistently carrying LA-MRSA in their nose (Chapter 4.4). Household members of pig farmers had LA-MRSA carriage percentages much lower than those of the livestock farmers themselves, but were still more often MRSA positive than community dwelling individuals in the Netherlands.

Persons living in the most pig-dense municipalities in the Netherlands, but without pig contact were MRSA positive in 0.2% (Chapter 2.3), which is in accordance with the general Dutch MRSA carriage percentage, estimated at 0.11%. These findings result in the conclusion that LA-MRSA has not yet spread from the farms into the community on a measurable scale.

LA-MRSA internationally

Chapter 2.5 illustrates that in several European countries LA-MRSA could be found, but mostly in low proportions of MRSA clinical isolates. Countries with higher densities of pigs and veal calves, and higher human population densities had higher proportions of LA-MRSA. Apparently, both livestock animals and humans need to be in close relation to each other in order to spread the bacterium.

Potential for public health threat

The Dutch rate of MRSA bacteraemia (including those caused by LA-MRSA) was lower than in other countries (Chapters 3.1 and 3.2), and an association between LA-MRSA and infections or quality of life could not be proven (Chapter 3.3). Next to differences in
healthcare structure and human antimicrobial use, the active search and destroy strategy in the Netherlands appeared to be effective in preventing many serious MRSA infections (Chapter 3.1). In addition, the population affected by LA-MRSA is healthier compared to the average MRSA infected patient, contributing to a lower infection rate for LA-MRSA as well. Finally, reduced virulence of the livestock-associated strains for humans may have played a role (Chapter 3.2). At the moment, in humans both MRSA at large and LA-MRSA specifically in the Netherlands appears to be under control.

Dynamics of LA-MRSA carriage

Nasal carriage of a methicillin-sensitive S. aureus (MSSA) was associated with less LA-MRSA carriage for both pig farmers and their household members, as described in Chapters 4.3 and 4.4. This might have been the result of a phenomenon known as bacterial interference, or competition for colonization space. Whether LA-MRSA replaced MSSA in previous MSSA carriers, or came on top of MSSA carriage numbers, is not completely clear.

The high prevalence found in pig farmers was likely the result of true colonization; repeated contamination of the nose by inhalation of LA-MRSA contaminated dust appeared to be less obvious (Chapter 4.3). Indeed, contamination of the environment in the stables was extreme, with high amounts of LA-MRSA found. On the contrary, persistently LA-MRSA carrying pig farmers had higher nasal loads of LA-MRSA, and were more often throat carriers, compared with pig farmers who intermittently or never carried MRSA.

Like for the farmers, pig contact was the most important determinant for LA-MRSA carriage in household members (Chapter 4.4). Human-to-human transmission from pig farmers to household members seemed to play a role as well, but needs to be studied further in other settings.

Possible interventions

Chapters 4.3 and 4.4 report that continuously wearing a mouth mask while working in the stables was associated with a lower risk for LA-MRSA carriage for both pig farmers and their household members. This and other infection control measures can be verified in future intervention studies, where the existing cohort can be utilized and further studied.

The huge reservoir of resistance in livestock is potential treat for the future. Follow up of the existing cohorts results in a useful inside view of LA-MRSA. Molecular evolution,
human-to-human transmission, illnesses, prevalence and possible interventions can be studied in these fully recorded groups of pig and veal farmers, livestock veterinarians, and their household members. Livestock animals remain the primary source of LA-MRSA. Attempts are already made to eliminate LA-MRSA from pig farms by minimizing antimicrobial use in animals and by exploring cleaning methods of stables. Since elimination of this bacterial strain from the animals and stable environment will probably not be feasible, following up the created cohorts, and testing interventions is needed in order to gain control of the situation.