Due to the fast transmission from infected to uninfected animals, *S. aureus* intramammary infections are apparently not easy to control and many components of mastitis control programs are necessary to fully control *S. aureus* on dairy farms (Barkema et al., 2006). Such control programs include management procedures such as optimal milking routine, past milking teat disinfection, a well-functioning milking machine, and segregation of known infected animals, culling of long-term affected animals, treatment of infected quarters and the use of dry cow therapy. More recently, the use of vaccines has become an additional tool in the control of *S. aureus* intramammary infections as well (Schubken et al., 2014).

This paper gives an overview of vaccination against mastitis with a focus on the efficacy of vaccination against *S. aureus*.

### What is vaccination?

In essence, vaccination is a form of active immunization entailing the introduction of a foreign molecule, e.g. bacteria or parts of the bacteria into the cow itself to generate immunity via the production of antibodies specifically oriented against the target. Using this binding mechanism, an antibody can "tag" the bacteria for attack by other parts of the cow’s immune system such as macrophages and neutrophils ("opsonization") or can neutralize its target directly, e.g., by blocking a part of the molecule that is essential for either its invasion or survival.

Each vaccine contains a killed or weakened form of the specific organism (e.g. *S. aureus*, E. coli, ...) that causes a disease such as mastitis. Even though the organism in the vaccine has been altered so that it won’t cause sickness, the part of the organism that stimulates the immune system to respond ("antigen") is still present. Vaccines against E. coli primarily contain the inactive J5 E. coli strain, resulting in the formation of antibodies against the uniform component lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria causing the severe symptoms associated with hyperacute clinical mastitis. Vaccines against *S. aureus* consist of either bacterins or exopolysaccharides (= sugar residues secreted by bacteria in the surrounding environment). One of those exopolysaccharides is poly-N-acetylglucosamine (PNAG), a surface polymer produced by a variety of bacterial species, including *S. aureus* and *Staphylococcus epidermidis*.

### What is vaccine efficacy and effectiveness?

Effectiveness of a vaccine refers to the reduction in disease measured in a carefully monitored, randomized, controlled clinical trial conducted in a homogenous population according to a defined protocol. In essence, the vaccine efficacy is determined by 4 parameters. The first parameter is the impact of vaccinations on the rate of new infections. This represents the classic vaccine effect, whereby the vaccine reduces the susceptibility of non-infected individuals such that no or fewer infections take place. The second parameter is the impact of vaccination on the infectiousness of an infected individual. The vaccine reduces the amount of shedding of infected but vaccinated individuals compared to nonvaccinated infected individuals. As *S. aureus* is a mammary pathogen that may be transmitted from cow-to-cow, a reduction in the infectiousness of a vaccinated individual would be valuable. This reduction in infectiousness was also observed in the reported challenge trials (Pérez et al., 2003). The third parameter is the impact of vaccination on the cure of infection. Vaccinations may result in a shorter duration of infection. The duration is essentially the inverse of cure, so a higher cure will result in a shorter duration. The fourth and final parameter of vaccine impact is the reduction in progression of infection from subclinical to clinical mastitis. As clinical mastitis results in milk discard, treatment and animal sickness, a reduction in progression of infection would be of value to the dairy industry. Even though challenge and controlled clinical trials might have shown a certain degree of protection against *E. coli* mastitis, the ultimate value, the so-called effectiveness, of the vaccine will always need to be shown under commercial farm conditions. Effectiveness refers to the reduction in disease measured under conditions of use of the vaccine in ordinary clinical practice. The effectiveness is in general somewhat lower than the efficacy.

### Vaccines against mastitis

Commercial mastitis vaccines are currently available for immunization against mastitis caused by *S. aureus* and *E. coli*. In the US, there are two *S. aureus* bacterins available. The vaccines are marketed as Somato-Staph® and Lysynth® and are labeled as somatic antigen containing phage types I, II, III, IV and miscellaneous groups of *S. aureus*. There are also 3 *coliform* mastitis vaccines available. Two of them are identical and marketed as JS Bacterin® and Mastiguard®. A separate bacterin-toxin (J5V®) is also available. The 4th Gram-negative mastitis vaccine contains a 17-mutant Salmonella typhimurium bacterin-toxin. On the European market, there is only one labeled vaccine against *mastitis* available (Sterilac®). The vaccine contains inactivated E. coli (J5), inactivated S. aureus (CP8) SP 140 strain expressing Slime Associated Antigenic Complex (SAAC) and adjuvant. The vaccine has a label claim for reducing the incidence of subclinical mastitis and the incidence and severity of clinical symptoms.

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The mechanism behind vaccination fully relies on the acquired immune response. Vaccination essentially evokes a primary response in which the CD4+ T lymphocytes and B-lymphocytes play a crucial role. After vaccination, the B-lymphocytes start reacting as if the real infectious organism is invading the body. They start multiplying to form a clone of identical cells that are able to respond to the specific antigen the vaccine contains. The cloned cells subsequently evolve into either plasma cells or memory B-cells. The plasma cells produce antibodies which are trained specifically to attach to and inactivate the organism one is vaccinated against. Over time, the antibody concentration will gradually disappear; but the memory B-cells will remain dormant in the body for a while. The memory B-cells keep a memory of the organism that one was vaccinated against. If one is ever re-exposed again to the identical organism, the dormant memory cells will recognize it straight away and rapidly start multiplying and developing into plasma cells. As the plasma cells are already trained to produce antibodies against the organism, they are able to produce large numbers of antibodies in a short time period. As the antibodies are produced so quickly, they are able to fight the disease even before sickness can occur.

Still, one should keep in mind that the first line cellular immune defense of the mammary gland is determined by the nonspecific immunity including the neutrophils and macrophages rather than by the acquired immunity. Lymphocytes, in particular CD4+ and B-lymphocytes seem to be primarily involved in the subacute and chronic phases of mastitis and not in the very early stages of the infection (Sordillo and Streicher, 2002; Grönlund et al., 2006). A long-lasting immunological memory against mastitis causing pathogens as described above could yet be induced, neither by the cow nor by vaccination.

### Conclusion

Vaccination against mastitis has resulted in a number of yet unsuccessful attempts to produce vaccines against these pathogens. The wide spectrum of pathogens with the strain-specific protection in particular slows down the development of vaccines specifically oriented against mastitis causing pathogens (Dennis et al., 2009).
The higher anti-SAAC blood concentrations suggested a more pronounced humoral specific immune response which might explain the shorter duration of the S. aureus infections as was found in the study of Schukken et al. (2014). Also, the higher anti-SAAC concentrations in milk might potentially trigger the opsonization of the inoculated S. aureus bacteria and partly explain why vaccinated animals suffered from a less severe inflammatory reaction than the non-vaccinated animals. In this regard, Camussone et al. (2014) immunized 17 pregnant heifers with one of two vaccine formulations comprised by either S. aureus whole or lysed cells formulated with BCGOM. Both immunogens induced a strong humoral immune response in blood and milk characterized by a substantial increase in antibody concentration. Neutrophil phagolysosomes were much more pronounced in the vaccinated animals than in the non-vaccinated ones, suggesting an increased opsonization of the S. aureus bacteria in case of increased antibody concentrations.

Conclusions

The efficacy of vaccination against S. aureus is dependent upon the vaccine formulation that is used, the cow’s parity, the prevalence of S. aureus mastitis at the herd level and the farm management practices that are applied. As concluded by Schukken et al. (2014), it seems that on farms with good management practices including excellent milking procedures, antibiotic therapies, and segregation and culling of known persistently infected animals, vaccination will most probably result in a relatively low reduction in infection rate and a moderate shorter duration of intramammary infections caused by S. aureus which might eventually result in an elimination of S. aureus. Farms with a poor management, S. aureus will most likely show a reduced prevalence but remain endemic despite vaccination. The protection against S. aureus is most likely the result of an increased opsonization via a vaccine-induced increase in antibody concentrations in blood and milk, facilitating the clearance of S. aureus from the mammary gland.

References