Summary

Swine influenza is a highly contagious acute viral disease of the respiratory tract in pigs, which is prevalent worldwide. The disease causes considerable economic damage primarily due to reduced weight gain in finishing pigs and reduced reproductive performance of sows [9]. A field survey performed in the winter of 1995-96 in the Netherlands revealed that swine influenza virus is a major cause of outbreaks of acute respiratory disease in finishing pigs [27]. This finding indicated that influenza is a bigger problem amongst pigs than was commonly thought. In addition, influenza is a zoonotic disease, because swine influenza viruses can transmit to, and cause disease in people, and pigs can be a source of new human influenza strains. Moreover, antigenic drift of the swine influenza A H3N2 viruses was demonstrated in the Netherlands and Belgium. This drift has led to a loss of cross-reactivity of recent field isolates with the human A/Port Chalmers/1/73 (H3N2), which is the current strain in the swine influenza vaccine. Therefore, replacement of this strain by a more recent swine H3N2 isolate has been recommended [16]. The increasing economic impact of swine influenza infections, its zoonotic risk, and the unexpected antigenic drift observed, prompted us to intensify research on swine influenza virus infections in the field, and on vaccine development. The studies described in this thesis deal with factors that are relevant to the development of swine influenza vaccines, and hence, may be relevant to the development of human influenza vaccines.

In contrast to swine H3N2 viruses, no significant antigenic drift was observed in swine H1N1 viruses isolated from the late 1980s to 1996. However, a marked antigenic and genetic heterogeneity was detected, which might hamper the control of swine influenza by vaccination. Nevertheless, a current commercial split virus in oil adjuvant vaccine was shown to be significantly efficacious in protecting pigs against a drift variant of H3N2 in a vaccination-challenge experiment. Therefore, there does not yet seem to be an urgent need for the A/Port Chalmers/1/73 (H3N2) strain to be replaced by a more recent strain, in order to protect fattening pigs from clinical signs during their short life span. Maternal immunity of the piglets however, will inhibit the immune response to vaccination and will further jeopardise protection in the field. Replacing the vaccine strains for strains that better match the current field strains would result in higher antibody titres to the field strains, which would further improve and prolong protection. Higher antibody titres would reduce the likelihood of viral replication and transmission in the population, and thus also of further antigenic drift. Therefore, a regular influenza surveillance among pigs is recommendable to ensure that the field strains are not too different from the vaccine strain, be it the result of antigenic drift or of new introductions. The swine vaccine may confer a broader protection than human sub-unit vaccines possibly because of the presence of the other viral proteins in addition to the HA and NA. Current vaccines are administered intramuscularly and protection may
strongly depend on the induction of sufficiently high IgG antibody levels. Theoretically, intranasal vaccination would be extremely attractive, as it would induce mucosal IgA, IgG, and cellular immune responses. These responses could provide protection against a broader spectrum of influenza viruses. Moreover, intranasal vaccination would probably be less hampered by maternal immunity than intramuscular vaccination. Unfortunately, intranasal vaccination is not practical in pig farming. One aspect of the vaccine that could be improved however, is its ability to protect against a broader spectrum of influenza viruses. Antibodies to the highly conserved extracellular domain of M2 and CTLs to the NP seemed to be involved in broad-spectrum protection in pigs, but are not induced by current vaccines. However, an experimental vaccine that induced those effectors, and no antibodies to the HA and NA, enhanced instead of prevented clinical signs after challenge. This indicates that those effectors can even exacerbate disease, when induced parenterally and/or if other effectors are absent. Nevertheless, including conserved antigens in vaccines and enhancing the response against them could improve protection. However, caution must be exercised and special attention given to non-neutralising cell-targeting antibodies, to make sure they do not enhance disease after vaccination with novel generations of vaccines. Successive intranasal vaccination with an attenuated H1N1 strain and an H3N2 strain will specifically induce mucosal subtype cross-reactive IgA and IgG antibodies, as well as CTLs. Although such drastic vaccination strategies are not applicable to pigs they might be applied as a strategy of immunisation in case of a next human pandemic. Improvement of the current swine influenza vaccine nor of the human influenza vaccines will be easy, and will remain an exciting challenge.

References


36 Mozdzanowska, K., Maiese, K., Furchner, M. & Gerhard, W. Treatment of influenza virus-infected SCID mice with nonneutralizing antibodies specific for the transmembrane proteins matrix 2 and neuraminidase reduces the pulmonary virus titer but fails to clear the infection. Virology 1999, 254(1), 138-146.


