Interaction of *E. coli* with the intestinal immune system of the pig in the post-weaning period

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Intestinal infections with enterotoxigenic *Escherichia coli* (ETEC) are prevalent in humans, pigs, calves and sheep. In neonatal and recently weaned piglets, ETEC-associated diarrhoea results in morbidity and mortality (Gyles, 1994) and is considered as one of the economically most important diseases in swine husbandry (Van den Broeck et al., 1999a). Fimbriae associated with ETEC strains involved in diarrhoea in pigs are F4 (K88), F5 (K99), F6 (987P), F7 (F41) and F18 (Wilson and Francis, 1986; Casey et al., 1992; Nagy and Fekete, 1999). F4 fimbriae producing strains are most frequently found in ETEC causing diarrhea and mortality in newborn, suckling and newly weaned piglets, whereas F5, F6 and F41 are associated with neonatal diarrhea and F18 fimbriae are typically associated with postweaning diarrhea. F4 fimbriae occur as F4ab, F4ac and F4ad (Orskov et al., 1964; Guinée and Jansen, 1979). For F18, 2 antigenic variants were discovered, namely F18ab and F18ac (Rippinger et al., 1995). In general, postweaning diarrhoea is caused by the F18ac variant whereas F18ab is more related to edema disease caused by shiga toxin Stx2e producing *E. coli* strains (VTEC or STEC) (Hide et al., 1995, Rippinger et al., 1995). After colonization, ETEC produce enterotoxins inducing a severe watery diarrhea by disrupting the water and electrolyte balance in the intestine. These enterotoxins include heat-labile toxin (LT), porcine heat-stable toxin a (StaP), heat-stable toxin b (STb), and enteroaggregative heat-stable toxin 1 (EAST1).

In general, most neonatal infections can be prevented by passive colostral and lactogenic immunity obtained following infection of vaccination of dams (Rutter and Jones, 1973). Commercial vaccines for sows contain F4, F5, F6 and/or F41 fimbriae, either purified or as inactivated *E. coli* expressing these fimbriae with or without the LT toxoid. The aging pig remains susceptible to infection with F4+ ETEC and also becomes susceptible to F18+ E. coli infections at two to three weeks of age (Coddens et al., 2007). However, passive protection decreases with aging and lactogenic immunity suddenly stops by weaning. Weaning itself and the change in food and environment are important stressors decreasing food uptake and gastrointestinal transit time. Enterotoxigenic *E. coli* use the short window after weaning that lactogenic immunity is ceased and active immunity still has to build up to colonize the gut mucosa. (Hampson, 1994). The ETEC infections that most often occur the first week after weaning are carrying F4+ ETEC. The F4 fimbriae allow them to colonize the gut rapidly. Furthermore, these F4+ETEC very often produce the 3 major enterotoxins LT, STaP and STb enterotoxins. Loos et al. (2012) demonstrated that STb can induce important fluid loss within 4 hours after colonization and also activates inflammation in the small intestine. So diarrhoea can occur rapidly following colonization, which will enhance the dissemination of the bacteria in the environment, so increasing the infection pressure for other piglets. StaP had less effect on fluid loss in the weaned piglet during the first 4 hours after colonization than STb and is probably more important in the neonatal piglet. The LT enterotoxin exerts

its effect later, probably starting around 12 hours after infection. It is not onlogic that many strains carry all 3 enterotoxins since F4+ E. coli are very immunogenic pathogens. Indeed we demonstrated that F4 is a very potent oral immunogen; oral administration of F4 can induce an anti-F4 IgA response in the gut within 7 to 11 days (Van de Broeck et al., 1999). Furthermore, LT enterotoxin, not only induces fluid secretion but is a very potent intestinal mucosal adjuvant (Cox et al., 2006). Infection with F4+ ETEC results in a very high faecal excretion of bacteria the first days after infection whereafter faecal shedding very rapidly decreases and 6 to 7 days after infection most pigs stop excreting the pathogen. The decrease in excretion coincides with the appearance of the intestinal mucosal immune response against the pathogen (Verdonck et al., 2002).

Infections with F18+ STEC are less potent inducers of immune responses. This is partly due to the lower immunogenicity of F18 fimbriae. Oral immunisation with low to high amounts of these fimbriae does not induce an intestinal IgA response are only weakly primes the intestinal mucosal immune system (Verdonck et al., 2007). Piglets infected with F18+STEC have a more constant faecal excretion of the bacteria during 6 to 8 days, whereafter the shedding decreases. Bacteria can be still isolated from the faeces 10 to 11 days after infection. This significantly longer period of excretion coincides with a slow and gradual appearance of the intestinal mucosal immune response (Verdonck et al., 2002) and partly explains the appearance of the infection the 2nd weak after weaning.

To protect newly weaned piglets, an active intestinal mucosal immunity is required, in which the production of antigen-specific secretory IgA against fimbriae and toxins plays an important role. However, since these ETEC infections occur immediately postweaning. The major challenge remains to induce a protective intestinal immunity at weaning. The colonization immediately post-weaning has the consequence that there is only a small window in which animals can be efficiently immunized. Potential strategies have to be based on good insights in the interaction of the bacteria with the intestinal mucosa.