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Prevention of ETEC and STEC infections using recombinant *Lactococcus lactis* expressing surface nanobodies against F4 and F18 fimbriae

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Post-weaning diarrhea and edema disease, caused by enterotoxigenic and Shiga toxin producing *Escherichia coli* (ETEC and STEC) strains, are important diseases of newly weaned piglets worldwide. We recently demonstrated that ETEC infections were wide spread among piggeries in Uganda, but the management practices such as extensive antibiotic prophylaxis and late weaning masked clinical disease outbreaks. The isolates from clinical cases showed extensive resistance to commonly used antibiotics. To prevent post-weaning diarrhea and edema disease, passive immunisation of weaning piglets with recombinant *Lactococcus lactis* as a probiotic was evaluated as an alternative to antibiotic prophylaxis. The variable domain of the llama heavy-chain antibodies, named VHHs or nanobodies (Nb), directed against fimbrial adhesions FaeG (F4) and FedF (F18) were cloned and expressed on the surface of *L. lactis*. *In vitro*, the recombinant Nb-expressing *L. lactis* strains agglutinated and inhibited adhesion of cognate F4 or F18 *E. coli* to pig villous preparation. *In vivo*, the anti-F4 Nb-expressing *L. lactis* were protective to weaned piglets against a challenge with an F4-positive ETEC strain. We found that the piglets receiving the anti-F4 Nb-expressing *L. lactis* showed a reduced faecal bacterial shedding and an increased immune response against F4 fimbriae. We concluded that the surface nanobodies on *L. lactis* strains effectively neutralised and abrogated gut colonisation by *E. coli*, the first step in disease pathogenesis. The protectiveness of the recombinant *L. lactis* tested provides a real potential for passive immunisation that should be explored further.

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