Enterohaemorrhagic *Escherichia coli* O157:H7 are zoonotic pathogens associated with haemorrhagic colitis (HC) and the haemolytic uremic syndrome (HUS). Ruminants are the main reservoir of this organism and most outbreaks of *E. coli* O157:H7 infections are food borne. Food contamination by ruminant manure has been reported as the primary source of human infection, therefore inhibition of *E. coli* O157:H7 colonization and shedding in ruminants could control the risk of human exposure to this pathogen. In the present study a vaccine based on the translocon proteins EspA and EspB and the outer membrane adhesion factor intimin significantly reduced faecal shedding of *E. coli* O157:H7 by orally infected sheep. Protection correlates with serum antibody responses to the defined antigens and validates the targeting of these colonization factors. Preliminary studies on the mechanism of this immune response shows presence of antigen-specific IgG antibody secreting cells in the mucosae of the small intestine. Whereas vaccination has already been described in cattle, this is the first study describing a significant decrease in faecal shedding following systemic immunization of sheep.