# Proceedings

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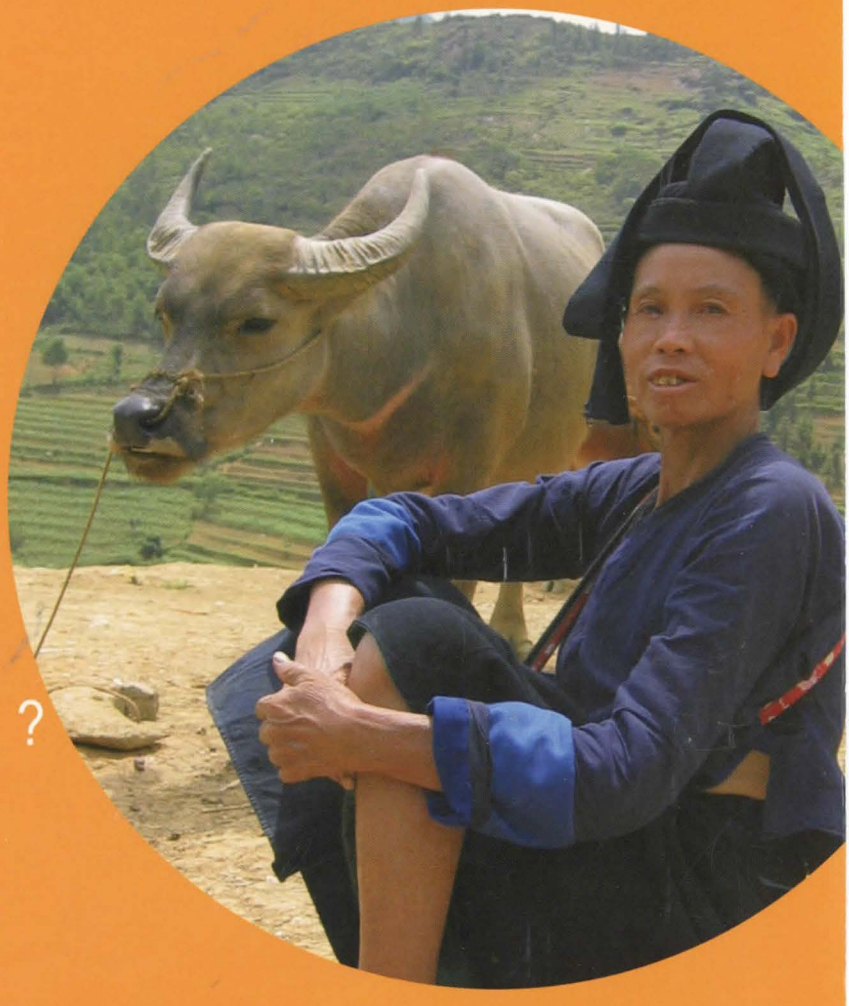

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# CONTAGIOUS BOVINE PLEUROPNEUMONIA: TOWARDS THE DEVELOPMENT OF NEW VACCINE STRATEGIES

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## ABSTRACT

Contagious bovine pleuropneumonia (CBPP), caused by *Mycoplasma mycoides* subsp. *mycoides* biotype Small Colony *(Mmm*SC*),* is one of the most serious cattle diseases in Africa. Its eradication still requires the development of efficient long term protective vaccines. To this aim, current researches are dedicated to: 1) the characterization of the protective immune parameters and the understanding of the immunopathological mechanisms and 2) the development of improved vaccine strategies either relying on the identification of potential *Mmm*SC vaccine antigens and relevant delivery systems for the development of sub unit vaccines or based on recombinant *Mmm*SC vaccines by inactivation of selected virulent factors. A review of the scientific results and vaccinal strategies will be presented.

## INTRODUCTION AND RATIONALE

Contagious bovine pleuropneumonia (CBPP), caused by *Mycoplasma mycoides* subsp. *mycoides* SC *(Mmm*SC*),* remains one of the major cattle diseases in Africa. It is responsible for heavy economic losses and is included in the OIE list of pathologies requiring official declaration. Infected countries are thus excluded from international trade. Improved vaccines are the only realistic prophylaxis to eradicate it from Africa, since 1) live attenuated T1 vaccines currently in use are of low efficacy requiring annual, costly, vaccination campaigns and 2) the combination of stamping-out, cattle movement control and quarantine used in other continents to eradicate CBPP is impracticable in Africa where cattle raising relies on nomadism and transhumance. Development of optimised long-term protective vaccines against CBPP is thus a necessity.

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## VACCINE STRATEGY AGAINST CBPP

The vaccinal strategy is determined by 1) the protective immune parameters to trigger, 2) the *Mmm*SC components to include and 3) the immunopathological mechanisms to control.

### Protective immune parameters

The feasibility of triggering a protective immune response by vaccination is sustained by the fact that cattle recovering from an *Mmm*SC infection are then protected against any new *Mmm*SC contact. Recovered cattle, therefore, not only succeed in controlling the infection by mounting a relevant immune response, but also retained in their lymph nodes, an *Mmm*SC-specific memory immune response. The characterisation of the underlying immune parameters can thus allow defining the main actors in protection against *Mmm*SC. To this aim, several studies were implemented in CIRAD in collaboration with African partners (LANAVET in Cameroon, CVL in Mali, OVI in South Africa). Experimental *Mmm*SC infections were done locally, as described by Niang et al. (2004) and comparative analysis were performed between animals recovering or dying from the infection. The *Mmm*SC-specific humoral and cellular response was evaluated. The results revealed that recovered animals were characterised by 1) a stronger and persisting local IgA response (Niang et al, 2006) and 2) a higher *Mmm*SC-specific CD4 T-cell-mediated response with IFNγ production (Dedieu et al, 2005, 2006). Therefore, both arms of the immune system play a role in protection against CBPP, the local humoral response relying on IgAs and the cellular response based on Th1-like CD4 T-cells. Both represent thus the main targets of an optimised vaccine against CBPP.

### Immunopathological aspect of CBPP

Understanding the immunopathological aspects of CBPP is also an important step for a rational design of the vaccine. Indeed, stimulating a vaccine-induced immune response against *Mmm*SC implies that the host still maintains its ability to mount an efficient response when in contact with *Mmm*SC. However, *Mmm*SC possess immunosuppressive properties (ability to survive in lung lesions and lymph nodes of infected cattle (Bashiruddin et al., 2005; Scanziani et al., 1997). To characterise this effect, the interaction between *Mmm*SC and bovine immune cells was analysed. The results demonstrated that 1) viable *Mmm*SC can trigger

apoptosis of the bovine leukocytes, 2) *Mmm*SC-secreted components appears to be responsible (Dedieu *et al.,* 2005b) and 3) viable *Mmm*SC depress the ConA T-cell mitogenic activity (Dedieu *et al.,* 2006b). These data confirm that *Mmm*SC had evolved an efficient way to escape the bovine immune response which might hamper vaccine efficacy. Blocking the *Mmm*SC component(s) involved can thus also represent an important vaccinal target.

### Potential MmmSC vaccine candidates

Considering the need to elicit an antibody as well as a cellular immune response, *Mmm*SC vaccine candidates have to be selected on these two criteria. Selection thus relies on 1) screening *Mmm*SC libraries with relevant sera to detect proteins with B-cell epitopes (IgA, IgG2) and 2) screening of *Mmm*SC components by *in vitro* T-cell assays. Using antibody screening, a panel of *Mmm*SC components has already been selected for which T-cell screening is underway. Indeed, several proteins did contain B- and T-cell epitopes. This approach is the most rationale for sub-unit or recombinant CBPP vaccines. Other approaches such as attenuated CBPP vaccines relying on inactivation of selected virulent factors also exist.

### Identification of a relevant vaccinal delivery system and route of delivery

The trend in vaccine development now focuses on sub-unit vaccines. However, purified proteins are often of low immunogenicity. Vaccine efficacy thus requires the addition of relevant immunostimulating molecule and delivery system to enhance the immune response. Their choice depends mainly on the type of immune response to be triggered, which, for CBPP, relies on CD4 IFNγ-secreting T-cells and local IgAs. This determines that, for the development of an efficient CBPP vaccine, 1) Th1-inducing adjuvant and delivery system should be used and 2) the most efficient route of delivery is mucosal (oral or intra-nasal).

## CONCLUSION

The scientific results obtained allow defining the best immune strategy for the development of a CBPP vaccine with optimal efficacy. Indeed, they determine i) the type of *Mmm*SC vaccinal antigens to be selected, ii)

the immune mechanisms to be stimulated by the vaccine and iii) the most appropriate route and delivery system for optimal efficacy.

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