Vaccines for Bovine Mycoplasmoses

Subjects: Infectious Diseases
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Two of the most important diseases of cattle are caused by mycoplasmas. *Mycoplasma bovis* is a world-wide bovine pathogen that can cause pneumonia, mastitis and arthritis. Due to its increasing resistance to antimicrobial therapy, vaccination is the principal focus of the control of infection, but effective vaccines are currently lacking. Despite being eradicated from most parts of the world, *Mycoplasma mycoides* subsp. *mycoides*, the cause of contagious bovine pleuropneumonia (CBPP), continues to plague sub-Saharan Africa. Numerous new experimental vaccines have been developed over the last 20 years to improve on protection afforded by the T1/44, a live vaccine in continuous use in Africa for over 60 years, but none so far have succeeded; indeed, many have exacerbated the disease.

Keywords: vaccine ; cattle ; Mycoplasma bovis ; Mycoplasma mycoides subsp. mycoides

1. Overview

Two of the most important diseases of cattle are caused by mycoplasmas. *Mycoplasma bovis* is a world-wide bovine pathogen that can cause pneumonia, mastitis and arthritis. It has now spread to most, if not all, cattle-rearing countries. Due to its increasing resistance to antimicrobial therapy, vaccination is the principal focus of the control of infection, but effective vaccines are currently lacking. Despite being eradicated from most parts of the world, *Mycoplasma mycoides* subsp. *mycoides*, the cause of contagious bovine pleuropneumonia (CBPP), continues to plague sub-Saharan Africa, affecting at least 25 countries. Numerous new experimental vaccines have been developed over the last 20 years to improve on protection afforded by the T1/44, a live vaccine in continuous use in Africa for over 60 years, but none so far have succeeded; indeed, many have exacerbated the disease. Tools for diagnosis and control are adequate for eradication but what is necessary are resources to improve vaccine coverage to levels last seen in the 1970s, when CBPP was restricted to a few countries in Africa. This paper summarizes the results of the main studies in the field of experimental mycoplasma vaccines, reviews data on commercially available bacterin vaccines and addresses issues relating to the search for new candidates for effective vaccines to reduce economic losses in the cattle industry caused by these two mycoplasmas.

2. Background

Mycoplasmas are the smallest self-replicating bacteria and are pleomorphic, have a low GC content and are devoid of a cell wall[1]. Out of over 200 recognized mycoplasma species, 13 have been identified in cattle, with *Mycoplasma bovis* and *Mycoplasma mycoides* subsp. *mycoides* being the most pathogenic and responsible for significant economic losses[2].

M. bovis is the etiological agent of many disorders in cattle with different clinical manifestations, such as pneumonia, mastitis, arthritis, otitis, keratoconjunctivitis, endocarditis and brain disorders [3]. *M. bovis* has the ability to form an adherent biofilm, which facilitates its survival in the host and aids the chronic course of the disease [1][4][5]. It is known that *M. bovis* is able to evade the host immune system most of all due to high antigenic variability of the strains, its intracellular persistence in both phagocytic and non-phagocytic cells and the immune response modulation by the bacteria[6][7][8][9]. Due to the increasing resistance of European field strains to most antimicrobials with the exception, so far, of the fluoroquinolones, and overall difficulties in *M. bovis* therapy, the only principal strategy for control of these infections is the use of effective vaccines[10][11]. Many studies have been done using experimental vaccines but, to date, commercially available vaccines are available only in the United States, and their efficacy is not fully satisfactory[12].

Contagious bovine pleuropneumonia (CBPP), one the great historic plagues of cattle alongside the now eradicated rinderpest, continues to inflict serious losses on livestock in many parts of sub-Saharan Africa[13]. But why is CBPP continuing to cause problems when it has been eradicated from Europe, Australia, Asia and North America? Sadly, because of economic hardships, civil wars and droughts affecting the countries where the disease is endemic and the inability to prevent transboundary movement of livestock, control in Africa seems further away than ever. CBPP is a severe pneumonia of cattle caused by the wall-less bacterium *Mycoplasma mycoides* subsp. *mycoides*. The disease is

localized in the lungs, where it causes a highly characteristic “marbling” of the lungs in the acute stages and lesions known as a “sequestra” in the chronic form of the disease[14]. Clinical signs include rapid breathing, fever, nasal discharge, anorexia, cough on exertion and sudden death. Mortality rates can exceed 50% when the disease appears for the first time in herds. The mycoplasma is transmitted by close and repeated contact with aerial and environmental infection playing little or no role in its epidemiology. Consequently, it was recognized very early on that the slaughter of affected and contact animals with strict movement restrictions could effectively control the disease[15]. The difficulty, however, is identifying affected animals quickly enough to prevent the disease spreading because, though the lung may be very severely damaged, clinical signs are often lacking[16]; this was particularly true in outbreaks in European herds where cattle remain housed throughout the year. The disease is more obvious in the nomadic herds of sub-Saharan Africa where animals endure a much more hostile environment, leading to higher morbidity and mortality rates than in European cattle.

3. The Future

The successful development of protective *M. bovis* vaccines is still a long way off and much research is still needed in this area, especially on developing an animal challenge model. Data on the present commercial vaccines in use today are modest at best, with one showing an efficacy of 1%. Clearly, improvements need to be made before control of this fast-emerging disease is possible. What is clear, however, is that any *M. bovis* vaccine needs to be part of a wider vaccination program involving other respiratory pathogens, including BVD, PI3V, *Mannheimia*, *Pasteurella* and possibly others. Hopefully, the use of bioinformatics tools will allow the proteomics analysis of the *M. bovis* secretome and consequently the detection of novel secreted proteins that can be used not only as diagnostic biomarkers, but also in the development of a potent vaccine for effective control of *M. bovis* infections.

With little immediate prospect of an improved vaccine, the CBPP community does what it has done many times and produces a report providing recommendations for better vaccines[17]. While many of the proposals in the report have been recorded before, the group has also identified development of a robust challenge model as a research priority, as adult cattle are expensive, raise ethical issues and are variable in their response to *M. mycoides subsp. mycoides*, making experiments unreproducible. However, apart from the use of highly speculative tissue explants, there are few other surprises. It is encouraging, however, that the Global Alliance for Livestock Veterinary Medicine (GALVmed) has written: *work is now proceeding to improve the performance and production processes of the existing vaccine*[18]. While this will certainly help, it is annual vaccination with high coverage that remains the key to successful CBPP eradication.

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