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Impact of imperfect *Mycobacterium avium* subsp. *paratuberculosis* vaccines in dairy herds: A mathematical modeling approach

Zhao Lu*, Ynte H. Schukken, Rebecca L. Smith, Rebecca M. Mitchell, Yrjö T. Gröhn

Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA

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ABSTRACT

The objective of this study was to investigate the potential impacts of imperfect *Mycobacterium avium* subsp. *paratuberculosis* (MAP) vaccines on the dynamics of MAP infection in US dairy herds using a mathematical modeling approach. Vaccine-based control programs have been implemented to reduce the prevalence of MAP infection in some dairy herds; however, MAP vaccines are imperfect. Vaccines can provide partial protection for susceptible calves, reduce the infectiousness of animals shedding MAP, lengthen the latent period of infected animals, slow the progression from low shedding to high shedding in infectious animals, and reduce clinical disease. To quantitatively study the impacts of imperfect MAP vaccines, we developed a deterministic multi-group vaccination model and performed global sensitivity analyses. Our results explain why MAP vaccination might have a beneficial, negligible, or detrimental effect in the reduction of prevalence and show that vaccines that are beneficial to individual animals may not be useful for a herd-level control plan. The study suggests that high efficacy vaccines that are aimed at reducing the susceptibility of the host are the most effective in controlling MAP transmission. This work indicates that MAP vaccination should be integrated into a comprehensive control program that includes test-and-cull intervention and improved calf rearing management.

1. Introduction

Johne's disease (JD), or paratuberculosis, is a chronic enteric disease of cattle and other ruminants infected by *Mycobacterium avium* subsp. *paratuberculosis* (MAP) (Behr and Collins, 2010). As one of the most important infectious diseases in dairy cattle, JD causes considerable financial losses due to a decreased milk production, premature culling, low fertility, and reduced slaughter value. The cost to dairy producers was estimated to be more than $200 million per year (Ott et al., 1999). JD may also pose a potential threat to public health through a putative association between MAP and Crohn's disease in humans (Behr and Kapur, 2008).

Control programs such as test-and-cull of adult animals and improved calf rearing management have been recommended to reduce MAP infections in dairy herds (NRC, 2003; Dorshorst et al., 2006; Kudahl et al., 2008; Collins et al., 2010; Ridge et al., 2010). Culling of test-positive shedding animals is usually implemented as a control program in MAP-infected herds. Due to infrequent testing and low diagnostic test sensitivity for animals shedding low loads of MAP, the test-and-cull strategy alone may not be effective in controlling MAP transmission (Lu et al., 2008; Behr and Collins, 2010). To protect susceptible calves from MAP infection, improved calf rearing management aimed at blocking MAP transmission routes in young susceptible calves has been suggested (Dorshorst et al., 2006; Kudahl et al., 2008; Ridge et al., 2010). Although combining test-and-cull and improved calf rearing management has been reported to be effective in reducing the incidence of MAP

* Corresponding author at: S2-064 Schurman Hall, Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA. Tel.: +1 607 253 4086; fax: +1 607 253 3440.
E-mail address: ZL73@cornell.edu (Z. Lu).

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infection, changes in herd management to reduce MAP prevalence require substantial effort by the dairy producer (Collins et al., 2010; Ridge et al., 2010).

Vaccination against JD as a control measure has been used in a limited number of MAP-infected herds. In the United States, the only vaccine approved for the reduction of MAP infection is a killed, whole organism-based vaccine with an oil adjuvant (*Mycopar*®) (Whitlock, 2010). The vaccine is administered to calves less than 1 month of age. Because vaccinated animals are more likely to be false-positive on the standard bovine tuberculosis (TB) test, use of this vaccine is currently limited and typically under strict control of the local veterinary authorities. Attenuated live vaccines have also been developed and were reported to be more effective, but due to the potential risk of spreading viable MAP the attenuated live vaccine is not available for use in the US at this time (Lei et al., 2008; Scandurra et al., 2010). To overcome the cross-reactivity to the bovine TB test, second generation MAP vaccines (subunit-based, DNA-based, and recombinant) have been developed and these vaccine candidates are now under evaluation (Behr and Collins, 2010; Hines and Kapur, 2010).

Studies on MAP vaccine efficacy, including studies of experimental infection challenge on individual animals and field trials, have shown that MAP vaccines do not fully protect susceptible calves from MAP infection, and imperfect vaccine efficacies have been reported. Vaccines may partially reduce the infectiousness or shedding load of animals shedding MAP, prolong the latent period of infected animals, slow the progression of infectious animals from low to high shedding states, or decrease the cumulative incidence of clinical JD cases (Kormendy, 1992, 1994; Wentink et al., 1994; van Schaik et al., 1996; Harris and Barletta, 2001; Kalis et al., 2001; Koets et al., 2006; Rosseels et al., 2006; Kathaperumal et al., 2008, 2009; Rosseels and Huygen, 2008; Keeble and Walker, 2009; Romano and Huygen, 2009; Santema et al., 2009; Behr and Collins, 2010; Alonso-Hearn et al., 2012).

The objective of this study was to investigate the potential impact of imperfect MAP vaccines on the dynamics of MAP infection in dairy herds using a mathematical modeling approach. Specifically, we studied how different MAP control options, including vaccination, influenced MAP prevalence over time, and the overall effects at population level. This study may help researchers interpret various outcomes from field trials of MAP vaccines and can be used as a tool to evaluate the overall effectiveness of MAP control programs using vaccination, test-and-cull, and improved calf rearing management.

2. Materials and methods

2.1. Flow chart of MAP vaccination model

Mathematical models for JD in dairy cattle have been developed to understand MAP transmission dynamics and to evaluate the effectiveness of recommended control programs (Collins and Morgan, 1992; Beyerbach et al., 2001; Groenendaal et al., 2002, 2003; Pouillot et al., 2004; Kudahl et al., 2007a,b, 2008; Lu et al., 2008, 2010; Mitchell et al., 2008; Marce et al., 2010). However, models of MAP vaccination and its impact in dairy herds have not been explored. The conceptual flow chart of a MAP vaccination model (Fig. 1 with the description of state variables given in Table 1) in dairy herds was constructed from our previous multi-group MAP transmission model (Lu et al., 2008, 2010; Mitchell et al., 2008).

Table 1
Variable names used in the compartmental model of *Mycobacterium avium* subs. *paratuberculosis* (MAP) vaccination.

Symbol	Description
X_1	Susceptible calves
X_2	Resistant heifers
X_3	Resistant adult cows
Tr_1	Transiently shedding calves
Tr_2	Transiently shedding heifers
H_2	Latently infected heifers
H_3	Latently infected adult cows
Y_1	Low shedding adult cows
Y_2	High shedding adult cows
V_{X_1}	Vaccinated susceptible calves
V_{X_2}	Vaccinated resistant heifers
V_{X_3}	Vaccinated resistant adult cows
V_{Tr_1}	Vaccinated transiently shedding calves
V_{Tr_2}	Vaccinated transiently shedding heifers
V_{H_2}	Vaccinated latently infected heifers
V_{H_3}	Vaccinated latently infected adult cows
V_{Y_1}	Vaccinated low shedding adult cows
V_{Y_2}	Vaccinated high shedding adult cows

Imperfect MAP vaccines in this study were assumed to fall into five modes of action of vaccine efficacy: (1) reduction of susceptibility, e_λ, (2) reduction of infectiousness/shedding load of MAP, e_β, with the assumption that the infectiousness was proportional to the shedding load, (3) prolongation of latency, e_σ, (4) slowed progression from low to high shedding, e_ν, and (5) reduction in the cumulative incidence of clinical JD cases, e_α. Vaccine efficacy in this study was defined as one minus some measure of relative risk (RR), $VE = 1 - RR$ (Halloran et al., 1997, 2010). The five modes of vaccine efficacy for imperfect MAP vaccines coincide with the vaccine efficacies defined by Halloran et al. where the components of vaccine efficacy are referred to as vaccine efficacy for susceptibility (e_λ), infectiousness (e_β), colonization (e_σ) progression (e_ν) and pathogenicity (e_α). We assumed that MAP vaccines were either ineffective or beneficial to vaccinated animals (though vaccines could theoretically be harmful); therefore vaccine efficacy ranged from 0 to 1. A vaccine efficacy of 0 indicates that the vaccine is not effective; and a vaccine efficacy of 1 indicates that it is fully efficacious. Values of vaccine efficacy in the range of 0.3–0.7 are generally considered 'reasonable', while vaccine efficacies above 0.7 are considered 'good' (Halloran et al., 2010).

An imperfect MAP vaccine does not necessarily have all five types of vaccine efficacy, but multiple vaccine efficacies are possible with a single MAP vaccine. The vaccine-induced immune response in vaccinated animals was plausibly assumed not to wane over the average lifetime of vaccinated animals. Booster vaccination (repeat vaccination of vaccinated animals) was not considered, because studies have shown that revaccination does not significantly improve the ability of an animal to resist MAP