



Invited lecture/Review

Vaccine Development against Paratuberculosis

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Abstract:

Paratuberculosis or Johne's disease (JD) is a chronic granulomatous enteritis affecting ruminants worldwide. It is caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP) and the rate of prevalence is increasing. Based on high economic impacts and public health concern, vaccine development against paratuberculosis is very essential. There is a lot of research articles about finding the best management approach for eradicating MAP, and also finding an ideal vaccine against the disease. But unfortunately, until now, there is no ideal management approach against the disease because we don't have any ideal vaccine against it. This mini review discusses about management strategies with the focus on researches about various types of vaccines against JD.

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1. Spread status of JD

1.1. Transmission

The bacteria infecting animals via faeco-oral route and also by bioaerosols. The infected animals with no clinical signs, even in early stages of paratuberculosis, shed MAP in their faeces and spread JD in the field silently (Scanu et al., 2007; Faisal et al., 2013; Gurung et al., 2012; More S. et al., 2017).

The pathogenesis of JD is similar to other mycobacterial infections and the clinical signs of infected animals in the end stage of paratuberculosis are including weight loss, decreasing milk production, diarrhoea, and death.

1.2. Epidemiology

MAP can infect all domestic and wild ruminants worldwide, even some infected monogastric species are reported (Hutchings et al., 2010; More et al., 2017). The disease is not eradicated in any country until now; but Sweden and Norway claim that they did not observe any infected animals by MAP until 2008 and 2015, respectively (Whittington et al., 2019).

2. MAP characteristics

Mycobacterium avium subsp. *paratuberculosis* is an intracellular pathogen and it uses macrophages inside the body as a shelter for surviving and multiplying (Arteche-Villasol et al., 2022). There are some evidences about the potential role of neutrophils in preventing development of MAP and protection against paratuberculosis (Khare et al., 2009; Dotta et al., 1991; Ladero-Auñon et al., 2021; Martineau et al., 2007). The bacteria are very persistent to acidic soils, sunlight, low temperature like freezing, heat like pasteurization and dry climate. Then it can survive in the environment for a long time (Whittington et al., 2004; Eppleston et al., 2014).

3. Treatment and Diagnosis

Because the disease is asymptomatic until the end stage, there is no treatment for JD. As a routine strategy for control of JD, it needs to be diagnosed and all infected animals should be culled (Park and Yoo, 2016). Culturing of bacteria from faecal samples, detection of MAP DNA from faecal and intestine samples, and detection of antibodies from serum and milk samples are routine ways for diagnosis of paratuberculosis.

4. Control

The global spread of MAP is high and based on its high economic impacts and public health concern, paratuberculosis should be controlled worldwide. There are some strategies for decreasing of MAP prevalence like testing and culling, preventing the exposure of calves to adult faeces, and vaccination. Seven countries are using vaccination as a control strategy including Iceland, Spain, New Zealand, Australia, India, Netherlands, and Canada (Table 1). The other countries are using test and cull strategy.

**Table 1.** Countries using vaccination as a part of control strategies

Country name	Control Strategy	Vaccine type	Output of control strategy	Reference
Australia	Testing and Culling; Testing of environmental faecal samples; Vaccination	Killed vaccine	Significantly reduced JD incidence; Reduced risk of MAP infection entering the human food chain	Whittington et al., 2019; Windsor et al., 2020.
New Zealand	Testing and Culling; Testing of environmental faecal samples; Vaccination	Killed vaccine	Significantly reduced JD incidence	Gautam et al., 2018
Spain	Testing the animals; Culling; Vaccination	LAV and killed vaccines	Significantly reduced JD incidence	Juste et al., 2011
Iceland	Testing the animals; Culling; Vaccination	Killed vaccine	Significantly reduced JD incidence	Sigurdsson., 1960; Whittington et al., 2019
Canada	Testing and Culling; Testing of environmental faecal samples; Vaccination	Killed vaccine	Significantly reduced JD incidence	Whittington et al., 2019
India	Testing the animals; Culling; Vaccination	LAV and killed vaccines	Significantly reduced JD incidence	Singh et al., 2009
Netherlands	Testing the animals; Culling; Vaccination	Killed vaccine	Significantly reduced JD incidence	Groenendaal et al., 2003

5. Vaccination

There are some commercially available vaccines against paratuberculosis, but all of them can interfere with tuberculosis or paratuberculosis test. A lot of researchers are working on finding an ideal vaccine against JD especially in the field of Live Attenuated Vaccine (LAV), and inactivated vaccines including vector-based vaccines, and subunit vaccines.

4.1. LAV

Knock-out and deletion of known virulence genes of MAP and creating mutant, is a strategy to create LAV against paratuberculosis (Phanse et al., 2020; Shanmugasundaram et al., 2018; Ghosh et al., 2014; Ghosh et al., 2015; Rathnaiah et al., 2014). This kind of vaccine, unfortunately, can not eradicate the disease and also, it can interfere with the test of paratuberculosis.

4.2. Inactivated vaccines

Researchers used Viruses, Bacteria and Nanoparticles as vectors to create vector-based vaccines against MAP. Using nanoparticles is quiet new strategy with promising results (Abdellrazeq et al., 2019; Thukral et al., 2020). As a virally vectored vaccine against JD, Lentivirus (Franceschi et al., 2019) and Adenoviruses (Bull et al., 2007; Bull et al., 2014) were used until now. Bacterial vectors like *Escherichia coli* (Qiu Xu et al., 2021) and *Salmonella* (Faisal et al., 2013; Motamedi boroojeni et al., 2019) were used in some researchs and based on their results, the protective immunity against paratuberculosis was reported by using *E. coli*. The most of researches about creating vaccine against paratuberculosis are in the field of subunit vaccines. There are a lot of research on engineered plasmids that can produce antigens in bacterial and mammalian hosts (Eraghi et al., 2017; Monreal-Escalante et al., 2021). Also, several purified proteins were investigated as vaccine candidates against MAP (Gupta et al., 2021; Eraghi et al., 2019; Fernández et al., 2022).

6. Conclusion

Regarding huge spread of paratuberculosis worldwide, public health concern, the outcome of using control strategy including vaccination, also, the need to ideal vaccines against MAP, doing research in the field of finding new control strategies and vaccine development are very important and helpful.



Conflicts of Interest: The author declares no conflict of interest.

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