

Paratuberculosis Vaccination

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Although the earliest record of vaccination for Johne's disease (JD) dates back to 1926, it has not been widely used in the United States.¹ Currently, there is only one approved vaccine for JD in the United States, Mycopar (Boehringer Ingelheim, Ridgefield, CT, USA). It is a whole-cell bacterin consisting of inactivated *Mycobacterium avium* subsp. *paratuberculosis* (also known as MAP) mixed with an oil adjuvant. Although multiple studies on the efficacy of Johne's vaccine have been published, differences in study design and outcome measures have made direct comparisons challenging. The vast majority of such studies, however, have shown a protective effect of vaccination on MAP infection and clinical disease.^{2,3}

REQUIREMENTS FOR JOHNE'S DISEASE VACCINATION

Purchase and administration of Johne's vaccine in the United States is limited to veterinarians approved by state animal health officials. Participating states must follow regulations in USDA Veterinary Services Memo No. 553.4, *Mycobacterium Paratuberculosis Bacterin: Use in Johne's Disease Vaccination Programs in Participating States*. The memorandum requires that the herd owner and herd veterinarian enter into an agreement with the state animal health official regarding the use of the vaccine. Several prerequisites must be completed before the agreement can be approved by the state animal health official. These include (1) confirm premises is infected with MAP (i.e., at least 1 positive fecal culture or polymerase chain reaction for MAP on individual, pooled, or environmental fecal samples), (2) negative tuberculin test on all test-eligible animals as defined under herd accreditation test in the Bovine Tuberculosis Eradication Uniform Methods and Rules, (3) herd owner and State animal health agency sign agreement for vaccine use. In addition, there are TB testing requirements for purchased replacement stock that must be met prior to introduction of the animals into vaccinating herds.

SPECIFICS OF JOHNE'S DISEASE VACCINE ADMINISTRATION

In the United States, only replacement heifers and bull calves between 1 and 35 days of age are currently eligible to receive JD vaccine. It is administered subcutaneously in the dewlap approximately 1 inch proximal to the brisket. Vaccinated calves must be identified with an official identification, including external identification and a tattoo indicating the animal is a JD vaccinee, in the left ear, as specified by the USDA memorandum on JD vaccine use. A vaccination report must be submitted to the state animal health official by the veterinarian administering the vaccine.

NEGATIVE ASPECTS OF CURRENT JOHNE'S DISEASE VACCINES

There are several disadvantages to the currently available JD vaccines that include risk of granuloma at the injection site, human health risks from accidental inoculation, and interference with diagnostic testing for bovine tuberculosis (TB) and paratuberculosis.

Cattle may develop a granulomatous lesion at the site of JD vaccine injection (**Fig. 1**); however, approximately 80% of lesions are less than 10 cm in diameter and do not appear to cause discomfort.³ The vaccine is administered in the dewlap region in an effort to prevent trauma to the site, that might exacerbate the granuloma. In rare instances, granulomas may become abscessed and drain.³ A study using Gudair vaccine (Pfizer, NSW, Australia; not licensed for use in the United States) in sheep showed that 20–25% of vaccinees had a palpable injection site lesion after 12 months of age and no significant losses were noted at slaughter.⁴ There is a

clinical impression among veterinarians that when using the Mycopar vaccine, fewer vaccination reactions occur when smaller-gauge needles are used (18 gauge or smaller); however, the product is very viscous and must be warmed in order to flow through smaller-gauge needles (personal communication with various Wisconsin veterinarians).

Accidental inoculation of humans with JD vaccines may also cause a granulomatous lesion at the injection site.^{5,6} The severity of lesions may depend on the amount of vaccine injected and the amount of trauma to the injection site. In the event of an accidental inoculation, veterinarians are advised to contact their health care provider and state public health office immediately for specific treatment recommendations.



Fig. 1. Granuloma induced by a killed, oil-adjuvanted Johne's disease vaccine. (Courtesy of Michael T. Collins, DVM, PhD, Madison, WI.)

Current recommendations for initial treatment include removing the bacterin from the inoculated area by thorough washing and suction. The inoculation site should not be traumatized by squeezing. Reports on treatment of accidental inoculation suggest curettage or excision of the lesion may be the only effective treatment.⁶ Other oil-based vaccines have been reported to cause similar lesions.⁷ Use of smaller gauge needles may reduce the amount of trauma and vaccine injected in cases of accidental inoculation. Proper restraint of calves is important to reduce the risk of self-inoculation (**Fig. 2**).

Calves can be vaccinated either in a standing or recumbent position, with care taken to keep the handler's body clear of the area to be vaccinated. The veterinarian administering the vaccine should use a "one-handed" injection technique to reduce the chance of self-inoculation. Care must be taken in disposing of needles after vaccination. Ideally, needles should not be recapped but rather placed directly into a sharps disposal container. Use of shrouded needles has also been suggested as a potential precaution.

Cattle vaccinated with Mycopar develop a cell-mediated response which increases the likelihood of testing positive to the screening test for TB (caudal-fold skin test or CFT). Current bovine TB testing relies on cell mediated immune response to an intradermal injection of *Mycobacterium bovis* purified protein derivative (PPD) antigen. In the US, 2–3% of cattle are expected to have false-positive (FP) test results to the CFT (i.e., CFT specificity of 97–98%). Exposure to other mycobacterial organisms can contribute to these FP results. Although results were not statistically significant, a recent study showed that animals testing positive to a MAP



Safety measures for administration of Johne's disease vaccines. (A) Standing calf restraint with a portable headlock. (B) Recumbent calf restraint. (C) Use of 'one-handed' technique. (Courtesy of Jeffery Bohn, DVM, Amery, WI.).

ELISA or fecal culture showed a trend toward higher CFT positive rates than in MAP test-negative herd mates.⁸ In addition, an increased percentage of JD vaccinated cattle will have higher FP CFT rates as compared to nonvaccinated controls (23% vs. 6%, respectively).³ The effect of JD vaccine on bovine CFT for TB can be prolonged in some animals.⁹

When an animal tests positive to the screening CFT, a confirmatory comparative cervical test (CCT) must be conducted to determine the true infection status of the animal in accordance with federal regulations.¹⁰ The CCT compares the cell mediated immune response the animal mounts to side-by-side intradermal inoculations of *M bovis* PPD and *M avium* PPD. The CCT for bovine TB can be used as a secondary test to distinguish *M avium* (including MAP) from *M bovis* immune responses. It is performed by state animal health officials and must be completed within 10 days or more than 60 days after the CFT. JD vaccinates typically mount a much larger response to the *M avium* PPD than *M bovis* PPD as determined by skin thickness measurements.³

The cost of additional CCT tests in herds with a large number of JD vaccinated animals can become significant for state and federal agencies. Herds with animals testing positive to the CFT are placed under quarantine until the true TB status of the test-positive animal(s) has been resolved. Although herds can still ship milk, animals cannot be moved except under special permit direct to slaughter. These potential costs should be discussed with producers when deciding whether to use JD vaccine as a part of their herd paratuberculosis control program.

In addition to cell mediated responses, JD vaccination induces a humoral immune response in most vaccinated animals, causing animals to test positive on antibody based diagnostic tests for JD such as ELISA.⁹ Because of this, antibody-based JD tests are not reliable to diagnose JD in vaccinated animals. Some JD vaccinating herd owners choose not to test. Those who elect to include MAP testing in their control program have the option of using organism detection-based tests such as fecal culture or fecal polymerase chain reaction as these tests are unaffected by the animals JD vaccination status. While the cost of MAP detection-based tests on individual animals are significantly higher than antibody-based tests, fecal sample pooling may be an economical alternative to individual animal testing in some circumstances.^{11,12}

EFFICACY OF JOHNE'S DISEASE VACCINATION

JD vaccine does not prevent all new infections; efficacy may depend on age of exposure versus age of vaccination, environmental MAP burden on the farm, and MAP exposure opportunities based on herd management. Most producers and veterinarians that use vaccine find it beneficial in their control program. Further, a majority of studies report that use of the JD vaccine significantly reduces clinical disease, MAP fecal shedding, and MAP tissue burden compared to control animals.² It is reasonable to predict that vaccinating herds that integrate best management practices to reduce the risk of MAP transmission, as described in the USDA Johne's disease program standards,¹³ will see more significant reduction in disease than will herds using vaccine alone. As with any vaccination program, JD vaccination should be a part of a control program, not the entire program.

WHEN TO USE JOHNE'S DISEASE VACCINE

Restrictions on the use of the JD vaccine in the United States are largely due to the negative aspects of current JD vaccines, as discussed earlier. Many states do not allow JD vaccination and successful JD control has been demonstrated in dairy herds that have not used vaccine.¹⁴ JD vaccine is not necessary for every herd; however, it may help to speed the progress of a JD

control program. Indications for JD vaccine are (1) herds with a high MAP infection prevalence (likely to have a heavy environmental MAP burden) or (2) herds that have limited labor, financial, or facility resources and are unable to achieve the management changes needed to reduce the cycle of MAP transmission. Many factors, including cost and benefit of a vaccine program, should be discussed with your client before determining whether vaccine is indicated in a herd's JD control program.

JOHNE'S DISEASE VACCINES IN OTHER COUNTRIES

The use of JD vaccine in Australia's Ovine Johne's Disease Management Plan (OJDMP) is encouraged in all prevalence areas along with pasture and biosecurity planning.¹⁵ The OJDMP is an important part of Australia's National Johne's Disease Control Program (NJDCP). The NJDCP is a program developed with the input of industry and regulatory groups and funded through industry. The OJDMP's 5-year plan was based on aims identified by industry and focuses on reducing risks of purchased animals, use of vaccine, and on-farm best management practices.¹⁵ In 2002, Gudair, a killed JD vaccine, was registered in Australia and is now a central component of their OJDMP. Initial studies using Gudair vaccine demonstrated 90% reduction in clinical JD in sheep, reduced fecal shedding of MAP by 90%, and, in those that did shed, delayed fecal shedding by 1 year compared with nonvaccinated control animals.⁴ Additionally, modeling studies demonstrated that heavily MAP infected flocks, suffering from clinical JD, could expect a return on investment within 2 to 3 years.¹⁶ Gudair vaccine shares some of the same negative aspects as other current JD vaccines, including interference with immunologically based diagnostic tests for paratuberculosis and creation of granulomatous lesions in animals and humans following accidental inoculation.^{4,6} Although JD vaccination lesions were found at slaughter in 18% of adult sheep and 65% of lamb carcasses, no economic losses were incurred at slaughter due to these lesions.¹⁷ Gudair is also approved for use in the Australian Goat Johne's Disease Market Assurance Program (GoatMAP) in kids between 4 and 16 weeks of age.¹⁸ Silirum (Pfizer, NSW, Australia),¹⁹ a JD vaccine for cattle, is being evaluated in Australian cattle herds and has recently been shown to reduce fecal shedding and increase milk production compared to nonvaccinating control herds.²⁰

NEW VACCINES ON THE HORIZON

Researchers continue to look for new vaccine candidates with improved efficacy and reduced negative side effects.²¹ Candidates include subunit vaccines, some of which may have the advantage of not interfering with diagnostic tests for either bovine TB or paratuberculosis. Studies on an HSP70 subunit vaccine demonstrated reduced fecal shedding in an experimental infection model and a lack of interference with current immunodiagnostic assays for bovine tuberculosis and paratuberculosis.^{22,23} Injection site lesions using this subunit vaccine were reported to be small with subcutaneous administration and undetectable with intramuscular injection. A JD vaccine without the negative side effects of currently available vaccines would likely require less regulatory oversight and would have the potential to be broadly included in JD control programs.

SUMMARY

Vaccination can be a useful tool in controlling JD. It has been shown to significantly decrease not only clinical disease but also fecal shedding and tissue levels of MAP. However, currently available vaccines have some significant drawbacks that prevent widespread use of JD vaccine in the US JD control program. At present, each state must weigh JD vaccination benefits to herds against the risks of increased costs of bovine TB surveillance and confirmatory testing. In states that allow JD vaccination, practitioners must help herd owners understand and evaluate

the costs and benefits of vaccination. MAP infection prevalence, calf exposure rates, and ability to reduce MAP exposure to young stock by improved management are important considerations. In herds where the environmental MAP burden is high or the ability to reduce MAP exposure of young stock through management is limited, the addition of JD vaccine may be important in reducing the cycle of transmission. Ideally, JD vaccine should be used in conjunction with management changes to reduce MAP transmission. Results from Australia's broad use of Gudair vaccine in their sheep JD control program will be highly instructive over the next several years. Research on subunit vaccines appears promising and may provide the MAP infection protection without the negative side effects of current vaccines. Such advances would allow JD vaccination to be broadly incorporated into JD control programs around the globe.

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