Preventive Veterinary Medicine 153 (2018) 71–76

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Meta-analysis of the efficacy of *Leptospira* serovar Hardjo vaccines to prevent urinary shedding in cattle

J.M. Sanhueza[a,*], P.R. Wilson[b], J. Benschop[c], J.M. Collins-Emerson[c], C. Heuer[b]

[a] Veterinary Population Medicine Department, College of Veterinary Medicine, University of Minnesota, Saint Paul, MN, USA
[b] EpiCentre, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North, New Zealand
[c] mEpiLab, Infectious Disease Research Centre (IDReC), Hopkirk Research Institute, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North, New Zealand

ARTICLE INFO

Keywords:
Leptospira
Hardjo
Vaccine efficacy
Urinary
Shedding
Meta-analysis
Bayesian analysis

ABSTRACT

Leptospirosis is a zoonosis often associated with occupational exposure from livestock that can be prevented by animal vaccination. Several trials have assessed vaccine efficacy in livestock but there have been no attempts to evaluate these trials jointly. This systematic review and meta-analysis aimed to estimate vaccine efficacy to prevent urinary shedding of *Leptospira* serovar Hardjo (Hardjo) in cattle. Three databases were used to search for relevant papers published from 1980 to 2015 evaluating commercial vaccines to prevent urinary shedding of leptospires after artificial conjunctival or natural challenge. A total of 1237 articles were initially identified. Eight articles containing information from nine trials that assessed vaccine efficacy to prevent Hardjo urinary shedding, as per bacteriological culture, were included in the meta-analysis. Fixed effects Mantel-Haenszel (MH) and a Bayesian random effects meta-analyses were used to estimate the efficacy of vaccination to prevent Hardjo shedding in urine. Vaccine efficacy against Hardjo challenge was 88.7% (95% CI 81.0%–93.2%) in the MH meta-analysis and 89.9% (95% probability interval 80.6%–94.9%) in the Bayesian random effects meta-analysis. There was no evidence of heterogeneity of study results ($p = 0.17$). The estimated vaccine efficacy to prevent urinary shedding of Hardjo in cattle may be sufficient to reduce disease incidence in animals and exposure risk of people working in close contact with cattle.

1. Introduction

Leptospirosis is a zoonosis of world-wide distribution that in humans can result in a severe life threatening infection or a subclinical or mild self-limited illness (Haake and Levett, 2015). Occupational exposure to livestock is a risk factor for human leptospirosis worldwide (Waitkins, 1986; Thornley et al., 2002; Adler and de la Peña Moctezuma, 2010). Evidence suggests that a vaccination programme comprising annual vaccination of animals is an effective way to reduce the risk of infection in livestock and consequentially, transmission to humans. In New Zealand for example, a reduction in the number of human notified cases coincided with implementation of vaccination in dairy cattle (Marshall, 1987).

Several studies have been conducted to evaluate urinary shedding of leptospires after artificial or natural challenge in vaccinated animals compared with unvaccinated controls. Early vaccination trials mostly evaluated the effect of experimental *Leptospira interrogans* serovar Pomona vaccines to prevent infection in cattle after artificial challenge. In those trials, urinary shedding was measured by culture or dark field microscopy (DFM) and 100% vaccine efficacy was observed in some (Hoag and Bell, 1955; Webster and Reynolds, 1955; Rhodes, 1960). However, lower vaccine efficacy was reported by others (Gillespie and Kenzy, 1958b, a; Kiesel and Dacres, 1959). In the 1970s, attention changed to evaluating the efficacy of Hardjo vaccines, with results ranging from 0%–100% efficacy in prevention of renal colonisation or shedding of leptospires in urine of cattle challenged with Hardjo (Strother, 1974; Tripathy et al., 1976; Bolin et al., 1991).

Urinary shedding of leptospires can be assessed by different methods that vary in their ability to detect the organism. Bacteriological culture has been widely used in the past but whereas its specificity for detecting leptospires may be 100%, its sensitivity appears to be low compared with fluorescent antibody (FA) and polymerase chain reaction (PCR) techniques (Bolin et al., 1989a; Zuerner et al., 2011; Ellis, 2015). Nevertheless, bacteriological culture is still commonly used in vaccination trials, although not without controversy when it is the only method used for assessing shedding of leptospires in urine since its lower sensitivity may overestimate vaccine efficacy compared for example with PCR (Alt et al., 2012; Rinehart et al.,

* Corresponding author.
E-mail address: jsanhuez@umn.edu (J.M. Sanhueza).

https://doi.org/10.1016/j.prevetmed.2018.02.015
Received 3 October 2017; Received in revised form 11 February 2018; Accepted 26 February 2018

2012a).

Many factors may influence the efficacy of vaccination to prevent shedding of leptospires in urine. For example, age at first vaccination may be important, especially under farming conditions, since vaccination is less efficacious for reducing urinary shedding in already infected than naïve animals (Hancock et al., 1984). Also, vaccine composition may influence efficacy since it has recently been suggested that monovalent vaccines have a higher efficacy than multivalent vaccines in activation of the immune system and prevention of shedding of leptospires in urine (Brown et al., 2003; Ellis, 2015).

No formal comprehensive literature review or meta-analysis assessment has reported of the efficacy of *Leptospira* vaccines to prevent shedding of leptospires in urine. This systematic review and meta-analysis aims to estimate the efficacy of commercial Hardjo vaccines to prevent urinary shedding of leptospires in cattle.

2. Materials and methods

The review process and reporting of results were guided by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009).

2.1. Research question

The meta-analysis aimed to estimate vaccine efficacy of Hardjo commercial vaccines in cattle to prevent shedding of leptospires in urine. Although the scope of the literature search also included articles assessing the effect of vaccination on cattle, sheep and deer challenged with Hardjo or Pomona; few articles evaluated the effect of vaccination on any of these species after Pomona challenge, or on sheep or deer after Hardjo challenge.

2.2. Literature search

An electronic literature search was conducted to include articles published up to February, 2015. Article databases searched were the Web of Science (including Science Citation Index Expanded and Conference Proceedings Citation Index- Science, Biological Abstracts, CABI: CAB Abstracts, Current Contents Connect, PubMed (MEDLINE), SciELO citation index), Scopus and PubMed. Key-words used in the search to select relevant studies were: [Lepto* OR Weil] AND [cattle OR bovine OR cow OR calves OR deer OR cervine OR fawn OR sheep OR ovine OR ewe OR lamb] AND [Vacc* or Immun*] AND [efficacy OR effect* OR protect* OR shed*]. The asterisk is used to extend the search to related words with similar meaning, e.g. Vacc* searches for vaccine, vaccination and vaccinate. Secondary sources of potentially useful studies were PhD theses available from the Massey University library and the book "*Leptospira* and leptospirosis" (Adler, 2015).

2.3. Screening of records

Article titles and abstracts were screened to select those that evaluated the effects of *Leptospira* vaccination in cattle only, since data for the other livestock species included in the search were limited. This selection included studies that evaluated antibody response with or without leptospiral challenge and with, or without urinary shedding assessment. Whenever a title/abstract was inconclusive for the decision to exclude a publication, the article was considered for full-text evaluation.

2.4. Eligibility criteria

Full-text articles were reviewed for eligibility. Inclusion criteria were: original articles (i.e. not reviews); articles evaluating vaccine efficacy in a vaccination trial, under either natural exposure or artificial conjunctival challenge; articles evaluating shedding of leptospires in urine as an outcome measured by culture; and articles using commercially available vaccines published from 1980 to 2015. No language restriction was applied.

2.5. Data extraction

Information extracted for each article was title, authors, study type (controlled trial or field trial), species used, vaccine information, age at vaccination, time from vaccination to challenge, challenge source (artificial or natural), serovar, challenge dose, route used when challenge was artificial, number of shedders in vaccinated and control groups, and total number in vaccinated and control groups. Relevant information from each article was summarised in an Excel spreadsheet. If required, authors were contacted for additional information.

2.6. Bias assessment for individual studies

Eligible articles were reviewed for evidence of bias using the tool for assessing the risk of bias in randomised trials described by Higgins et al. (2011). Bias domains assessed in the included articles were: random sequence generation; allocation concealment; blinding of outcome assessment; incomplete outcome data; and selective reporting. Each of these domains were categorised into "low", "high", or "unclear" evidence of bias (Table 1).

2.7. Meta-analysis

Two approaches were used to estimate the combined vaccine efficacy: a fixed effects Mantel-Haenszel meta-analysis which used a continuity correction of 0.5 that was added to treatment arms with zero cell frequencies in the 2 by 2 contingency table and: a Bayesian random effects meta-analysis that used the data without adding a continuity correction factor. Two approaches were used for comparative purposes

Table 1
Systematic bias assessment of 12 articles according to the guideline for randomised trials (Higgins et al., 2011).

Author	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Cortese et al. (2014)	Unclear	Unclear	Low	Low	Low
Zimmerman et al. (2013)	Unclear	Unclear	Low	Low	Low
Rinehart et al. (2012b)	Low	Unclear	Low	Low	Low
Zuerner et al. (2011)	Unclear	Unclear	Unclear	Low	Low
Bolin and Alt (2001)	Unclear	Unclear	Unclear	Unclear	Low
Ellis et al. (2000)	Unclear	Unclear	Unclear	Low	Low
Bolin et al. (1989a)	Unclear	Unclear	Unclear	Low	Low
Goddard et al. (1986)	Unclear	Unclear	Unclear	Low	Low
Broughton et al. (1984)	Unclear	Unclear	Unclear	Low	Low
Hancock et al. (1984)	Unclear	Unclear	Low	Low	Low
Allen et al. (1982)	Unclear	Unclear	Low	Low	Low
Mackintosh et al. (1980)	Unclear	Unclear	Unclear	Unclear	Low