Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Rabies vaccine is associated with decreased all-cause mortality in dogs

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ARTICLE INFO

Article history:
Received 14 April 2017
Received in revised form 25 May 2017
Accepted 26 May 2017
Available online xxxx

Keywords:
Non-specific effects
Rabies
Mortality
Survival
Vaccine
Veterinary

ABSTRACT

Evidence suggests that rabies vaccine may have non-specific protective effects in animals and children. We analyzed four years of data (2012–2015) from an observational study of the health and demographics of a population of owned, free-roaming dogs in a low-income community in South Africa. The objective of this analysis was to assess the association between rabies vaccine and all-cause mortality in dogs, stratified by age group (0–3 months, 4–11 months, and 12 months and older), and controlling for the effects of sex and number of dogs in the residence. Rabies vaccination reduced the risk of death from any cause by 56% (95% CI = 16–77%) in dogs aged 0–3 months, by 44% (95% CI = 21–60%) in dogs aged 4–11 months and by 16% (95% CI = 0–29%) in dogs aged 12 months and older. We hypothesize that the protective association between rabies vaccination status and all-cause mortality is due to a protective effect of rabies vaccine against diseases other than rabies. Existence of a strong non-specific protective effect of rabies vaccine on mortality in dogs would have implications for the design of dog rabies control programs that aim to eliminate dog-mediated human rabies cases. Further, we propose that owned domestic dogs in high mortality settings provide a useful animal model to better understand any non-specific protective effect of rabies vaccine in children, due to dogs' high numbers, high morbidity and mortality rates, relatively short lifespan, exposure to a variety of infectious and parasitic diseases, and shared environment with people.

1. Introduction

Non-specific effects (NSEs) of vaccines are defined as those effects on the immune system of the recipient that alter the risk of illness or death from conditions other than the specific infectious disease the vaccine is designed to prevent [1,2]. Evidence for NSEs of Bacillus Calmette–Guérin (BCG), diphtheria, tetanus, and pertussis (DTP) and measles-containing vaccines (MCV) on mortality in children under five years old was recently reviewed [3]. The results suggest that BCG and MCV have substantial protective NSEs on infant mortality with some evidence of differences in effect sizes between girls and boys; however, the authors of the review stress that much of the evidence came from observational studies with a high risk of bias [3].

Other vaccines may also have protective NSEs. Gessner et al. [4] recently proposed that the meningitis and cerebral malaria safety signals in the RTS,S malaria vaccine clinical trial in children [5] were due to a protective NSE of rabies vaccine used as a comparator vaccine in the control group. In this randomized controlled trial, the 5–17 month old age group control arm had unexpectedly low incidences of both meningitis and cerebral malaria, while other arms in both age groups (5–17 month old and 6–12 week old) had incidences similar to background rates. Only the 5–17 month old age group control arm received rabies vaccine. In their systematic review, Gessner et al. [4] found additional evidence for protective NSEs of rabies vaccine in two different experimental studies: mice vaccinated against rabies had significantly lower mortality rates when challenged with *Klebsiella pneumoniae* sepsis [6] and with intracerebral injection of a neurotropic strain of herpes virus [7].

Abbreviations: DSA, Demographic surveillance area; HAC, Hluvukani Animal Clinic; HDSS-Dogs, Health and demographic surveillance system in dogs; MRR, Mortality rate ratio; MVS, Mpumalanga Veterinary Services; NSE, Non-specific effect.

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http://dx.doi.org/10.1016/j.vaccine.2017.05.095
0264-410X/

Rabies vaccine is widely used in dogs, which are the main reservoir hosts for rabies virus in many parts of the world [8]. Previously, in a paper on the demographics of a population of owned, free-roaming dogs in a low-income community in South Africa [9], we reported our observation that dogs 0–3 months old that received rabies vaccine had a greatly reduced risk of death compared to their unvaccinated counterparts over a two-year period (all-cause mortality rate ratio among 0–3 month old dogs was 0.11 (95% CI, 0.05–0.21) during 2012 and 0.31 (95% CI, 0.11–0.69) during 2013). This paper was also covered in the review by Gessner et al. [4]. Rabies control regulations in South Africa make allowance for vaccination of dogs younger than 3 months old, and dogs in this age group are included in annual rabies vaccination campaigns conducted free of charge by the local veterinary services in the study area.

To better estimate the effect of rabies vaccine on all-cause mortality, in the current study we analyzed four years of data (2012 through 2015) from the same population, controlling for the effects of age, sex, number of dogs in the residence and non-independence of observations within the same residence.

2. Material and methods

In 2011, we established a health and demographic surveillance system (HDSS-Dogs) in a population of owned, largely free-roaming dogs in a low-income community in the village of Hluvukani, Mpumalanga Province, South Africa. We defined a demographic surveillance area (DSA) using natural and artificial boundaries (Fig. 1), and monitored all of the approximately 2500 households in the DSA through regular visits, every five to six months. In each household, we collected data on entry and exit events of owned dogs (birth, death, in- and out-migration). Dogs that entered this population were uniquely and permanently identified by subcutaneous implantation of a radio frequency identification microchip, or through photo identification if they could not be handled. Dog name, sex and age were also used by the field team to identify dogs with the owner. Dates of events were estimated by owners, with uncertainty reflected by a lower and upper estimate of the time since the event. We considered the midpoint between the estimates to be the estimated event date. At each visit, we recorded the rabies vaccination status of new dogs, and updated the vaccination history of dogs resident in the household since the previous visit. We relied on owners for reports of vaccination and for estimates of vaccination date. Rabies vaccination campaigns are carried out regularly by the Mpumalanga Veterinary Services (MVS). Although issued to every animal at vaccination, certificates were not sought during visits, as a previous study had shown that fewer than half of owners of vaccinated dogs were able to produce certificates from recent vaccinations [10]. Prior to 2014, the date of vaccination was recorded as a categorical variable representing the time in one-year increments since last vaccination (0–12 months, 13–24 months, etc.). From 2014 we increased precision by estimating month and year of last vaccination. The dates of the visit and of the entry or exit of the dog in the household are also taken into account to enhance the accuracy of the estimated date of vaccination. Additional details on the HDSS-Dogs methodology are provided elsewhere [9]. Here, we present data from the HDSS-Dogs collected from 1st January 2012 through 31st December 2015.

Data were entered in a relational database. Tables include the list of dogs and their individual characteristics (date of birth, sex, breed); residence episodes in households (with a residence episode beginning at the start of the study period, or when a dog enters a household through birth or in-migration e.g. as a gift or purchase, and ending at the end of the study period, or through death or out-migration); and a table of vaccination episodes. In the latter, each row represents a continuous period during which the dog is considered immunized against rabies. A dog is considered immunized for 3 years after a single vaccination [11,12]. If a booster dose is administered before the end of the 3 years, the vaccination episode is extended for 3 more years after the booster. If the booster is administered more than 3 years after the initial vaccination, a second vaccination episode is created.

Survival analysis was performed following the description of the model given in Conan et al. [9]. One model for each age class was built, with age classes defined as 0–3 months, 4–11 months, and 12 months and over. We assumed that the hazard of death was constant within each age group. We fitted a piecewise exponential survival model by age group, using the equivalent Poisson regression model [13]. To account for cluster (residence) effects, including possible confounding by cluster, we used a generalized estimating equation approach with an independence working correlation structure [14]. The exposure variable was vaccination status (immunized vs. non-immunized) and the outcome variable was death from any cause. The residence episode represented the risk period of death for each dog in a residence. For each age stratum, we created a Poisson regression model with sex as a forced variable in the model, as we wished to control for its effect across all age strata [15]. We also included cluster size (number of dogs) as a covariate in the regression models. Number of dogs was taken as the median of the daily number of dogs in the household during the residence episode of the focal dog. We included all interaction terms in the initial models. We used backward stepwise selection to evaluate the interaction terms in each model (Wald test with p-value >0.05). Dogs without recorded sex or date of birth were excluded from the analysis (n = 55).

Dog rabies vaccines are labeled for either a 3-year or 1-year duration of effect. To test the effect of our assumption of a 3-year duration of immunity, we performed a sensitivity analysis in which we adjusted the vaccination episodes assuming a 1-year duration of immunity only. We also performed two separate subset analyses, restricted to (i) data from 2014 to 2015, or (ii) only dogs that entered the study population by birth from the 1st January 2012. All analyses were performed with R software [16], using packages *RODBC* [17], *geepack* [18] and *survival* [19].

The HDSS-Dogs study was approved by the University of Pretoria Animal Ethics Committee (protocol No. V033-11) and the RUSVM Institutional Animal Care and Use Committee (IACUC number 15–3-011). Written informed consent was obtained from dog owners to participate in the study.

3. Results

From 1st January 2012 through 31st December 2015, 2903 residence episodes were recorded for dogs in the DSA. Of these, 1263 episodes started at birth. By sex, 1589 episodes (55%) were of male dogs and 1259 (43%) were of female dogs; sex was not recorded for 55 dogs. The population fluctuated seasonally, between a minimum of 737 (observed on 18th-20th March 2015) and a maximum of 1083 (observed on the 9th November 2012), with an overall daily median of 820 and interquartile range of 126. The number of households visited at least once since the start of the study was 2503, of which 653 (26%) reported at least one residence episode of a dog. The median cluster size (median daily number of dogs in household for each residence episode within a particular age category) was 6 (range 1–19) for dogs aged 0–3 months, 3 (range 1–20) for dogs aged 4–11 months and 2 (range 1–18) for dogs 12 months and older. Exposure data (rabies vaccination) for the population is presented in Table 1.

Over the 4-year period, 1335 deaths were recorded in 3371 dog-years of observation (crude mortality rate of 396 deaths per 1000

Please cite this article in press as: Knobel DL et al. Rabies vaccine is associated with decreased all-cause mortality in dogs. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.05.095