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

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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.

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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].

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
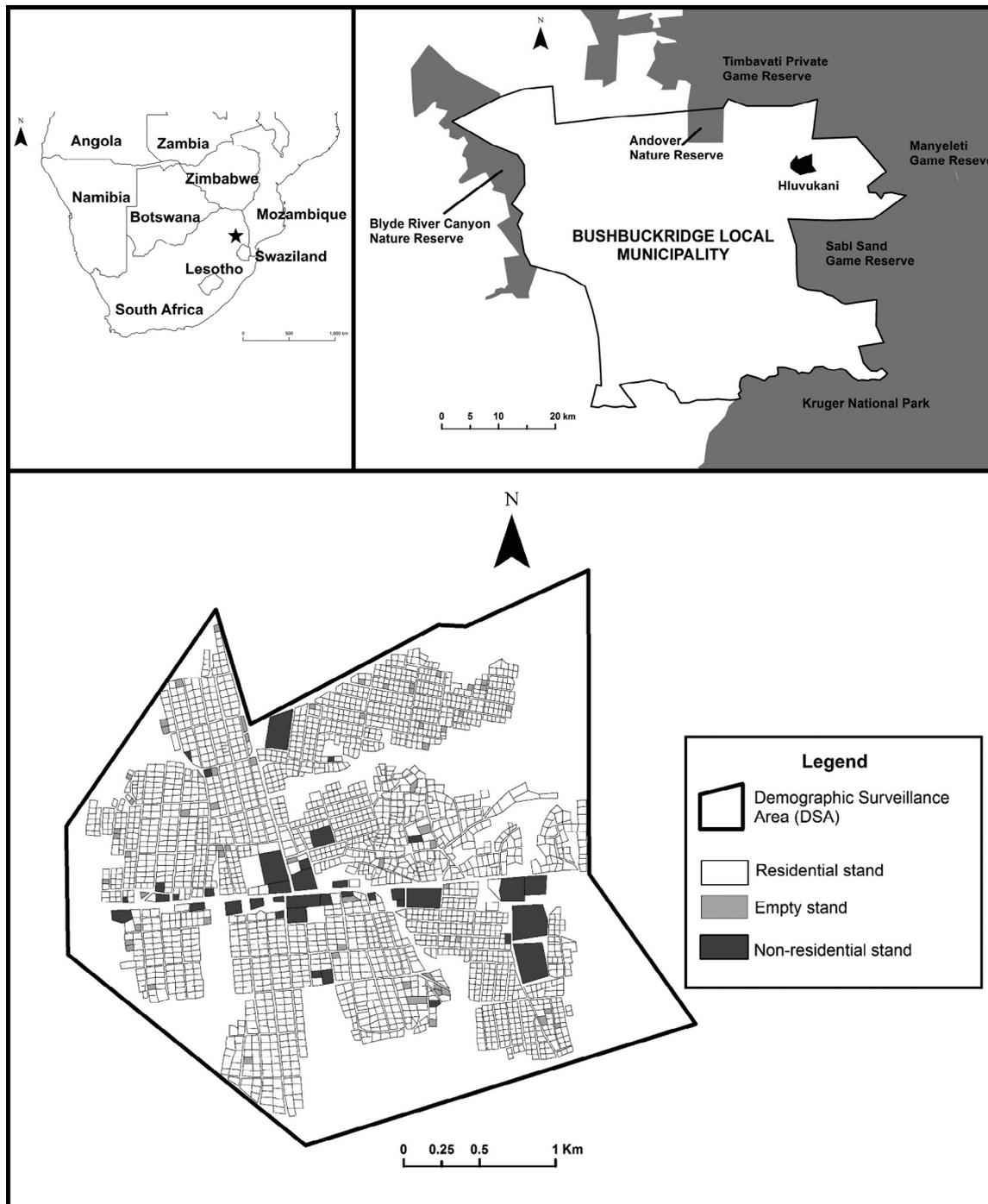
Fig. 1. Location and map of the study area.

Table 1
Rabies vaccination information reported by owners for dogs resident in the demographic surveillance area, from 1st January 2012 through 31st December 2015.

	Number of residence episodes	Number (%) vaccinated for any period of residence episode	Median age (interquartile range) at first vaccination (in days)
All	2903	1209 (41.6%)	367 (134–913)
Males	1589	725 (45.6%)	366 (124–896)
Females	1259	484 (38.4%)	391 (140–913)

dog-years). Estimates of the effect of vaccination on all-cause mortality by age group are presented in Table 2. Controlling for sex and cluster size, vaccination reduced the risk of all-cause mortality 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. Results of the sensitivity and subset analyses (Table 3) continued to show a protective effect of vaccination, although in the subset analyses the 95% confidence intervals tend to be wider and in some cases span the null value; this may be expected due to the smaller number of events in the subsets.

Table 2
Estimated effects of vaccination on all-cause mortality rates, stratified by age group, for the owned dog population present in the DSA from 1st January 2012 through 31st December 2015. MRR = Mortality rate ratio.

	Dog-Years	Deaths	Mortality rate per 1000 dog-years	Unadjusted MRR (95% CI)	Adjusted MRR[*] (95% CI)
0–3 months					
Unvaccinated	329	386	1174		
Vaccinated	31	10	323	0.28 (0.15–0.52)	0.44 (0.23–0.84)
4–11 months					
Unvaccinated	359	205	571		
Vaccinated	212	59	278	0.49 (0.35–0.68)	0.56 (0.40–0.79)
12 + months					
Unvaccinated	628	203	323		
Vaccinated	1811	472	261	0.81 (0.68–0.96)	0.84 (0.71–1.00)

[*] Adjusted for the effects of sex and cluster size (number of dogs in the stand).

Table 3
Results of sensitivity and subset analyses, showing mortality rate ratios (with 95% confidence intervals) for vaccinated compared with unvaccinated dogs in three age groups, adjusted for sex and cluster size.

	Model	Sensitivity analysis	Subset analyses	
		1-year duration of immunity	Data from 2014–2015 only	Data from dogs born into the population after 1st Jan 2012 only
0–3 months	0.44 (0.23–0.84)	0.58 (0.44–0.76)[*]	0.68 (0.25–1.82)	0.41 (0.16–1.04)
4–11 months	0.56 (0.40–0.79)	0.53 (0.38–0.74)	0.84 (0.39–1.83)[*]	0.58 (0.31–1.09)
12 + months	0.84 (0.70–1.00)	0.54 (0.44–0.66)	0.76 (0.58–0.99)	0.84 (0.41–1.73)

[*] Includes interaction term between vaccination and cluster size.

4. Discussion

We found a strong association between rabies vaccination status and decreased all-cause mortality in a population of owned, free-roaming dogs in a low-income community in South Africa over a four-year period. These results are consistent with the previous analysis [9], showing the association is still present after controlling for the effects of age, sex and cluster (residence), including confounding by cluster and informative cluster size [14]. The effect was present across the three age groups analyzed, but weakened with increasing age. Strength of the association was greatest in the age group with the highest mortality rate (0–3 months).

In this low-income community, veterinary services for companion animals are not regularly utilised, and infectious and parasitic diseases are common in the dog population, particularly among young dogs. These are caused by viruses (e.g. canine distemper virus, canine parvovirus), tick-transmitted hemoparasites (e.g. *Babesia rossi*, *Ehrlichia canis*) and helminths (e.g. *Dipylidium caninum*, *Toxocara canis*, *Ancylostoma* spp.), among others [20]. The cause of death most frequently reported by owners is infectious/parasitic disease [9,21], but conditions in the field prevent definitive identification of cause of death through post-mortem examination in the vast majority of cases [21].

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. This hypothesis requires further investigation through randomized controlled trials. The potential biological mechanisms responsible for NSEs of vaccines have been reviewed [1,22]. These include cross-reactivity of T-lymphocytes ("heterologous immunity") [23] and epigenetic reprogramming of innate immune cells ("trained innate immunity") [24]. A plausible mechanism by which rabies vaccine could exert a non-specific protective effect is through the superantigenic properties of the rabies nucleocapsid protein [25,26]. Superantigens are capable of eliciting strong primary T cell proliferation without priming, through their capacity to bind to $V\beta$ chains of T cell receptors without prior processing [27]. Further immunological studies are needed to understand the role of the superantigenic properties of rabies virus and its possible underpin-

ning of any non-specific effects in important vaccine target species, including humans and dogs.

The observational nature of our study presents several limitations. Foremost is the potential for owner behavior and provision of veterinary care to confound the relationship between vaccination and mortality. It is plausible that owners who have their dogs vaccinated against rabies may also provide higher levels of care in other respects, such as nutrition or veterinary intervention, which would improve survival rates in these dogs. These variables were not measured in our study. In general, the level of care provided to dogs in this resource-poor community is not high, in part due to the lack of accessibility and affordability of veterinary care. Because of the public health importance of controlling the disease, vaccination of dogs against rabies is a legal requirement and mass rabies vaccination campaigns of dogs are systematically conducted by mobile vaccination teams of the MVS, who proceed door-to-door and administer rabies vaccine to dogs free of charge. By contrast, other vaccines or treatments are not administered by the state, and have to be purchased by owners from the only other veterinary health service provider in the area, the Hluvukani Animal Clinic (HAC) run by the University of Pretoria. Thus, owner behavior may not be a strong confounding factor. Furthermore, our method of analysis (generalized estimating equation with independence working correlation structure) can account to some degree for unmeasured confounding by cluster (owner or residence) [14].

We rely entirely on owner reports of dog vaccination status, which could introduce bias in the classification of exposures. In addition to possible recall bias, failure to verify vaccination status through inspection of certificates raises the possibility that dogs reported as vaccinated may have been vaccinated against diseases other than rabies, alone (introducing misclassification bias) or in combination with rabies vaccine (introducing confounding). We have reason to expect that this would have been an uncommon occurrence in the study area, for the reasons explained above (lack of affordability and accessibility of veterinary health care other than rabies vaccination). From 2013 through 2015, the MVS administered 783 doses of rabies vaccine to dogs in the study village, mostly during regular annual mass vaccination campaigns, with additional doses administered by the HAC. By contrast, over

the same period very few doses of other vaccines were administered in the study village (Dr. Louise Biggs, HAC veterinarian, personal communication). Although costly, titres of rabies virus neutralizing antibodies could also have been used to verify rabies vaccination status; however, experience in similar field settings show that while the vast majority of dogs seroconvert following vaccination, titres decline rapidly and may therefore not be a particularly sensitive indicator of past vaccination [28].

A further limitation of our study is that we did not rule rabies in or out as a cause in all cases of death, leaving open the possibility that the protective effect of vaccination was specific to rabies (or closely-related lyssaviruses). We can use the attributable fraction to estimate the proportion of deaths over the 4-year period that would have been due to rabies, if this hypothesis were correct. Applying formula 4 in Table 1 of Rockhill et al. [29], and using the overall unadjusted mortality rate ratio of 2.29, we estimate that one third of all deaths during the study period should have been due to rabies for this hypothesis to hold, amounting to 447 dog rabies cases. In our study area, 3 cases of rabies in dogs were officially reported over the four years, which would be equivalent to a case detection proportion of less than 1% if the hypothesis of a specific protective effect were correct. Mollentze et al. [30] estimated a case detection proportion of more than 50% by the veterinary services in another province of South Africa in which dog rabies is endemic, which we believe to be a reasonably accurate reflection of the rabies surveillance system operating in our study area, given the relatively high presence on the ground of the local veterinary services, as well as additional primary health care services by the HAC. A nested study within our population interviewed owners of a cohort of 200 adult dogs and 200 puppies in the event of a death. These data are being prepared for a separate publication, but any clinical signs consistent with rabies were reported to the State Veterinarian for follow up, representing an enhanced, active surveillance system for rabies for a proportion of the population. Our expectation of a low number of dog rabies cases is also derived from our observation that the reported vaccination coverage remained above the critical threshold for herd immunity during the study period [9]. Less plausibly, the protective effect of rabies vaccine could be due to cross-protection against rabies-related lyssaviruses. Rabies vaccine only provides cross-protection against lyssaviruses in phylogroup I [31], of which only Duvenhage virus is reported to occur in southern Africa, maintained in insectivorous bats. This produces a disease indistinguishable from that caused by rabies virus itself in the mammalian host [32]; therefore, the preceding argument based on the attributable fraction and case detection proportion would still apply.

While we do not think that the limitations of the observational nature of our study affect our conclusion of a non-specific protective effect of rabies vaccine, we recognize that a more rigorous study design is needed to further test the hypothesis. Specifically, we think the next step is a randomized controlled field trial, in which puppies are randomly allocated within litters to receive either an injection of rabies vaccine or of a placebo, with owners blind to the exposure allocation; this study could have a nested assessment of immunological differences between vaccinated and unvaccinated dogs. Existence of a strong non-specific protective effect of rabies vaccine on mortality in dogs will have implications for the design of dog rabies control programs that aim to eliminate dog-mediated human rabies cases [33]. Reduced mortality in vaccinated subgroups following mass vaccination campaigns in dogs will have the beneficial effect of extending the period during which population immunity remains above the critical threshold needed to prevent outbreaks of rabies. Finally, 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 as proposed by Gessner et al.

[4], 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.

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