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LETTERS

Low-coverage vaccination strategies for the conservation of endangered species

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The conventional objective of vaccination programmes is to eliminate infection by reducing the reproduction number of an infectious agent to less than one[1], which generally requires vaccination of the majority of individuals. In populations of endangered wildlife, the intervention required to deliver such coverage can be undesirable and impractical[2]; however, endangered populations are increasingly threatened by outbreaks of infectious disease for which effective vaccines exist[3,4]. As an alternative, wildlife epidemiologists could adopt a vaccination strategy that protects a population from the consequences of only the largest outbreaks of disease. Here we provide a successful example of this strategy in the Ethiopian wolf, the world's rarest canid[5], which persists in small subpopulations threatened by repeated outbreaks of rabies introduced by domestic dogs[6]. On the basis of data from past outbreaks, we propose an approach that controls the spread of disease through habitat corridors between subpopulations and that requires only low vaccination coverage. This approach reduces the extent of rabies outbreaks and should significantly enhance the long-term persistence of the population. Our study shows that vaccination used to enhance metapopulation persistence through elimination of the largest outbreaks of disease requires lower coverage than the conventional objective of reducing the reproduction number of an infectious agent to less than one[1].

The use of safe and effective vaccination can have a vital role in managing infectious disease in wildlife populations. For logistic, economic and ethical reasons, however, it will always be desirable to minimize the number of animals to be vaccinated. We distinguish between two different uses of vaccination: one focused on eliminating disease from a population, and another focused on protecting an endangered population from extinction. The design of vaccination programmes to eliminate infectious disease from populations has received much attention[1,7,8], and usually requires vaccinating a proportion of the population upward of $1–1/R_0$, where R_0 is the reproduction number of the infectious agent[1]. A conceptually distinct approach is to assume that wildlife populations can tolerate limited outbreaks of disease, but their viability is threatened by large outbreaks that could reduce their size to below a minimally viable threshold[9,10]. Targeted vaccination could be then used to curtail the largest and most damaging outbreaks, while reducing the proportion of individuals required to be vaccinated. Here we examine the effectiveness of such a strategy in conserving populations of Ethiopian wolves (*Canis simensis*) threatened by outbreaks of rabies, a fatal viral disease of mammals.

Ethiopian wolves in the Bale Mountains persist in several subpopulations connected by narrow corridors of habitat[11] (Fig. 1). Within these subpopulations, two large outbreaks of rabies were detected in 1992 and 2003 (ref. 12), and rabies was the suspected cause of a population crash in 1991 (refs 12–14); canine distemper was also suspected to have infected wolves in 1993 (ref. 15). These repeated introductions of infection into the wolf population from a domestic dog reservoir[6], together with permission to mount a reactive vaccination campaign in response to one such outbreak, have provided a rare opportunity to test experimentally a vaccination control strategy in an endangered species. Here we briefly review the

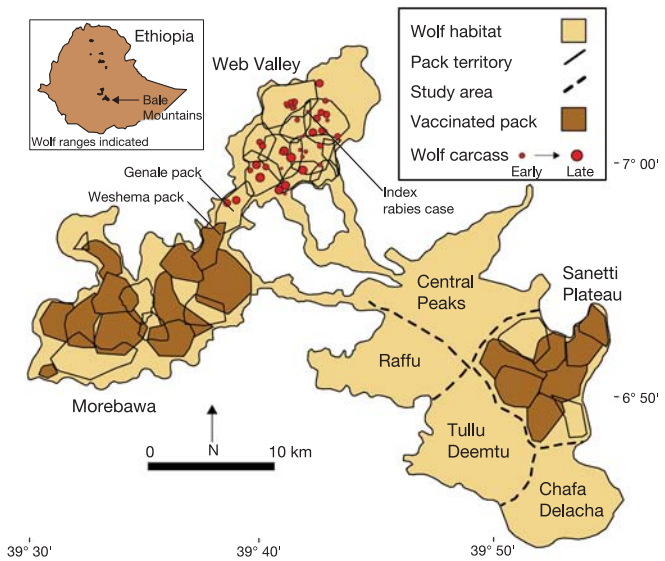

Figure 1 | Known distribution of Ethiopian wolf packs in three subpopulations in the Bale Mountains. Shown is the configuration of territories in the Web Valley, Sanetti Plateau and Morebawa, including the Genale and Weshema packs located in and immediately beyond the corridor linking the Web Valley with Morebawa. Packs are present in Central Peaks, Raffu, Chafa Delacha and Tullu Deemtu areas, but territory boundaries are not known with any precision. Filled red circles indicate the location of carcasses found in the 2003 outbreak; circle size indicates the relative timing of carcass recovery. Filled polygons indicate vaccinated packs. Inset shows the current distribution of the species throughout Ethiopia.

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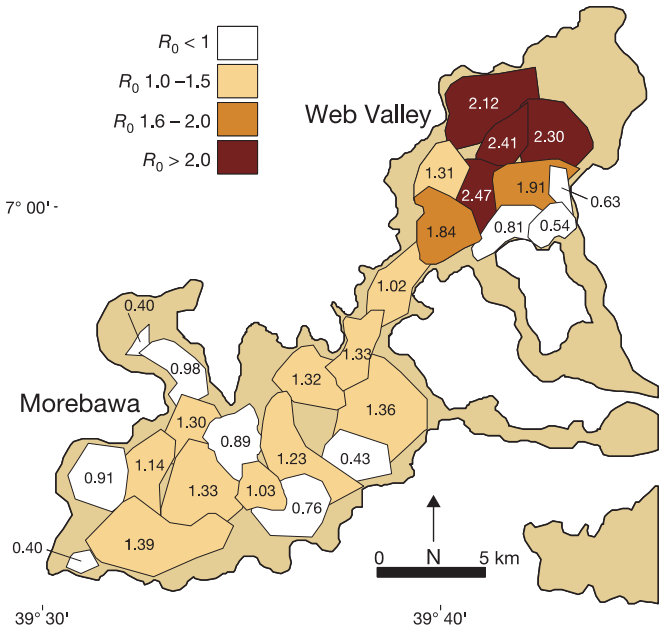

Figure 2 | R_0 map of the Web Valley and Morebawa subpopulations. Mixing is assumed to be intermediate (between pack transmission is 10% of within pack transmission). R_0 was predicted from the application of per capita transmission rates estimated from the fit of the SEIR model to data from the Web Valley, calculated by direct simulation assuming a single index case arose within each pack.

outbreak and the adopted vaccination strategy, and then describe and parameterize an epidemiological model that predicts the potential course of the outbreak without vaccination. Finally, we extend the model to explore the increase in population persistence times resulting from vaccinating in subpopulations as compared with vaccinating only in packs occupying corridor habitats between subpopulations. Additional data and analyses are given in the Supplementary Information.

In August 2003, the Bale wolf population comprised 200–250 individuals (aged >1 yr) in 36 packs associated with known territory locations. In the Web Valley, roughly 95 wolves resided in ten packs. Between August 2003 and January 2004, an outbreak of rabies resulted in the deaths of 72 (76%) of these wolves[12]. Disease spread outward from the putative index case, and a total of 38 carcasses were recovered from all territories in the Web Valley, suggesting a carcass detection probability of ~50% (38/72; Fig. 1). A parenteral reactive vaccination programme implemented in November was designed to prevent transmission between subpopulations, while limiting the number of wolves handled. The campaign initially targeted packs immediately beyond the corridor connecting the Web Valley and Morebawa subpopulations (Genale pack, Fig. 1) and then gradually moved to packs further away from the disease front (Fig. 1). Final coverage averaged over the whole Morebawa subpopulation was 37.5%. Subsequent monitoring suggested a maximum of seven deaths out of 105 wolves in the Morebawa subpopulation, all from a single front-line territory (Weshema pack; Fig. 1). Although carcasses continued to be recovered in the Web Valley, the epidemic made no further incursion into the vaccination zone.

To determine whether the vaccination programme itself limited the severity of the outbreak we developed a spatially explicit demographically stochastic susceptible–exposed–infectious–removed (SEIR) model[9]. The model was parameterized, taking into account pack and population age structure and the final epidemic size in the Web Valley (Supplementary Table S2 and Fig. S1). The maximum likelihood estimate of R_0 depended on the assumed ratio of between (β_b) to within (β_w) pack transmission (Supplementary Table S3). The results suggested, however, that the observed pattern of mortality across packs was most consistent with an intermediate to high ratio of β_b/β_w (see Supplementary Information), and here we present results assuming that $\beta_b = 0.1\beta_w$ (further results and genetic data in support of this choice are reported in the Supplementary Information). The maximum likelihood estimate of R_0 for the 2003 outbreak was 2.4 (95% confidence intervals: 1.7–3.4; Supplementary Table S3). A risk map constructed from predicted values for R_0 for epidemics starting in different packs reflects the importance of pack composition and configuration (Fig. 2). In Morebawa, pack size averaged 6.1 individuals, as compared with 8.8 in the Web Valley, and predicted R_0 values were correspondingly lower.

By repeatedly simulating outbreaks in subpopulations structured as in 2003, the model suggested that there was a 40% chance that

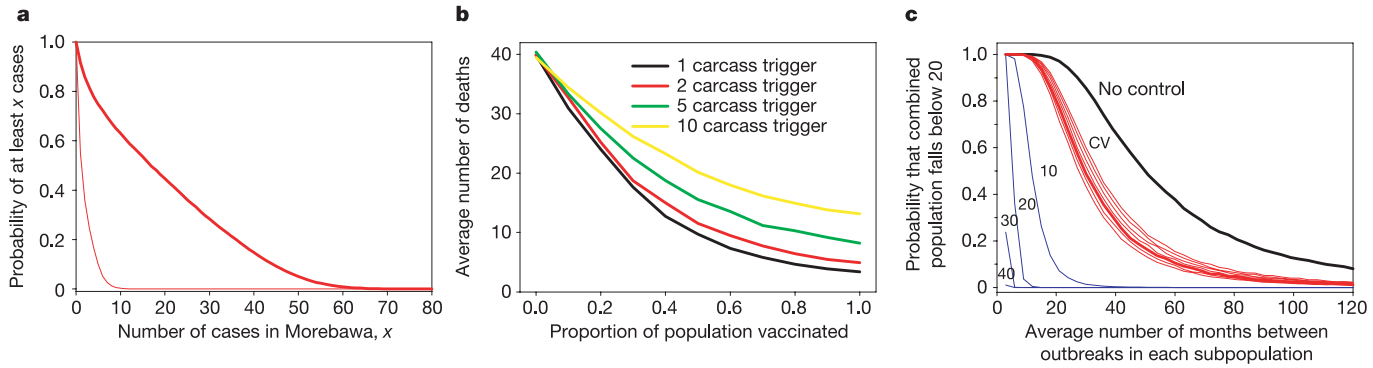

Figure 3 | Model projections. **a**, Probability that a rabies outbreak starting with a single index case in the central Web Valley goes on to cause a subsequent outbreak in the subpopulation in Morebawa, assuming the subpopulation to be fully susceptible and unvaccinated. Results are from an intermediately mixed model ($R_0 = 2.4$) in which per capita transmission rates between packs were 10% of within packs (thick red line). Thin red line indicates the outcome of an equivalent simulation that includes the effect of the vaccination programme as implemented during the outbreak. **b**, Effects of reactive vaccination in the Web Valley subpopulation on total epidemic size implemented after the deaths of different numbers of wolves. Vaccination was assumed to be instantaneously protective when administered to unexposed individuals (see Supplementary Information), but not effective when administered to incubating individuals. **c**, Probability of catastrophic metapopulation reduction occurring over a 20-yr period as a function of increasing rates of disease introduction into each subpopulation. The model assumes three subpopulations, linked by habitat and migration, that support a maximum of 100 individuals each. Black line, no control; red lines, corridor vaccination (CV) that reduces the probability of an epidemic in one subpopulation spreading to another from 0.25 to a range of possible values rising in increments of 0.02 from 0.04 to 0.16; blue lines, reactive vaccination implemented after the death of ten individuals with coverages of 10, 20, 30 and 40%, as indicated (see Supplementary information for further details of the model).

rabies epidemics arising from a single index case would fade out with less than ten (and usually less than four) individuals becoming infected. Once they exceeded this number, however, the epidemic would almost certainly go on to be large. Results from the model indicated that the probability of infection passing through the corridor into Morebawa increased from 0.08 with vaccination (as implemented during 2003) to 0.25 in the absence of vaccination (Supplementary Table S3). The upper ninety-fifth percentile interval estimates for final outbreak size in the Morebawa subpopulation started through this route increased from 8 wolves with vaccination to 41 without (Fig. 3a). Given how close the estimated R_0 values are to the unit threshold for packs in this subpopulation (Fig. 2), small increases in wolf density could result in sharp rises in the probability of even more damaging outbreaks.

Assuming a randomly located index case in the Web Valley, the model predicted an average time delay between the first death and an individual becoming infected in the Genale pack in the corridor to Morebawa at 74 d. The corresponding values for the second, fifth and tenth deaths were 66 d (lower eightieth percentile interval: 33 d), 51 d (21 d) and 38 d (10 d), respectively. This suggests that even if carcass detection rates fall as low as 20%, there would still be sufficient time in which to implement a reactive corridor vaccination campaign triggered by the detection of two carcasses.

By the time permission to vaccinate had been granted, the outbreak was considered too far advanced to protect the Web Valley subpopulation. Modification of the model to include reactive vaccination in an affected subpopulation triggered after the death of different numbers of individuals suggested, however, that vaccination would remain beneficial even after 10% of the subpopulation had died from rabies (Fig. 3b).

These analyses show that the extent of rabies outbreaks can be limited by low-coverage reactive vaccination strategies, but does such action mitigate the risk of extinction in the longer term? We used a population viability analysis[16] (PVA) to demonstrate the considerable risk posed by rabies outbreaks to these subpopulations and the substantial benefits of low-coverage reactive vaccination for the persistence of the metapopulation as a whole. The PVA assumed that habitat corridors between subpopulations act as conduits for disease transmission (see Supplementary Information) but also facilitate migration and recovery after epidemics[17]. The probability of catastrophic reduction of the metapopulation (defined here as the combined metapopulation falling below 20 individuals) at any time over a 20-yr period fell in response to implementation of reactive corridor vaccination, and even more quickly as reactive core vaccination strategies were adopted that targeted 40, 30, 20 and as little as 10% of the affected subpopulation (Fig. 3c). For example, the PVA predicted that, if rabies virus was introduced at an average rate of once every 5 yr into each subpopulation, corridor vaccination would reduce the probability of catastrophic metapopulation reduction almost fourfold from 0.38 to 0.10, and that reactive core vaccination of only 10% of individuals would reduce this probability to <0.001.

Aside from specific recommendations for this population (see Supplementary Information), our analyses underline the general importance of baseline ecological data, surveillance and detailed quantitative contingency planning in the management of epidemics[18–22]. High-quality demographic data enable interventions to be targeted, effective monitoring is essential for the early detection of suspected disease outbreaks, and appropriately calibrated trigger points minimize unnecessary interventions and facilitate the timing of decisive and effective action once an outbreak occurs. Taken together, these steps enable the threat of infectious disease to be managed through a programme of minimally invasive but demographically significant interventions.

Although preventative vaccination of reservoir hosts can reduce the frequency of stochastic spill-over infections into wildlife[4], the risk of outbreaks in unvaccinated wildlife populations cannot be eliminated, particularly when limited resources restrict the extent and coverage of reservoir vaccination programmes. Vaccination and handling of African canids has generated considerable controversy in the past[2,23], but our analysis provides strong evidence that targeted low-coverage and less-invasive reactive vaccination strategies can be effective in curtailing disease outbreaks and enhance the long-term persistence of endangered populations. However, progress is required in the development of protocols for more logistically feasible and cost-effective vaccine delivery methods such as oral vaccination[24–27], and policy-makers and conservation practitioners must be provided with epidemiologically sound, practical advice with which to develop contingency plans. Greater knowledge of the spatial ecology and social organization of other endangered species is likely to be fundamental to the development of practical and effective solutions to enduring threats to their persistence posed by infectious disease.

METHODS

Vaccination. Details of wolf monitoring and vaccination procedures are detailed in the Supplementary Information.

Models. We used a conventional SEIR model, which assumes demographically stochastic dynamics. The average infectious period was assumed to be 5 d (ref. 28), and an average incubation period of 12 d was fitted to match the duration of the outbreak. The model was fitted to data from the Web Valley, and then used to predict the probability of spread between subpopulations and the impact of such outbreaks in these subpopulations. Further details of the epidemiological model and its parameterization are supplied in the Supplementary Information.

The PVA model used demographic parameters from long-term monitoring studies, and probabilities of between subpopulation spread of infection and simulated distributions of outbreak sizes predicted by the model. Further details of this model are supplied in the Supplementary Information, together with a description of the genetic methods and analyses that indicated only limited movement of infected individuals.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions D.T.H. undertook much of the model formulation and analysis, and coordinated the synthesis of ideas and information. D.A.R. generated and compiled much of the empirical and all of the genetic data. L.M. assisted with formulation and interpretation of the analyses. D.L.K. managed the implementation of the vaccination programme. L.A.T. provided data and analysis for spatial distribution of the wolf population. M.B.G. assisted with early formulation of the modelling work and interpretation of later model output. S.D.W. coordinated fieldwork for much of the period over which this study applies. J.P.P. was instrumental in overseeing the genetic analyses. S.C. assisted in formulation of the vaccination strategy and in writing the manuscript. M.E.J.W. suggested analyses and assisted in writing the manuscript. C.S.-Z. was responsible for funding and coordinating Ethiopian wolf research and conservation work, and provided data on the 1992 outbreak. J.M. provided essential data on wolf demography for use in the PVA model. D.W.M. conceived and supervised several doctoral studies that have underpinned the project since its inception. M.K.L. was responsible for designing and implementing the disease control strategy.

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