Am. J. Trop. Med. Hyg., 96(3), 2017, pp. 749–757
doi:10.4269/ajtmh.16-0573

Estimating Burdens of Neglected Tropical Zoonotic Diseases on Islands with Introduced Mammals

Luz A. de Wit,[1]* Donald A. Croll,[1] Bernie Tershy,[1] Kelly M. Newton,[1] Dena R. Spatz,[1,2] Nick D. Holmes,[2] and A. Marm Kilpatrick[1]

[1]*Department of Ecology and Evolutionary Biology, University of California, Santa Cruz, California;* [2]*Island Conservation, Santa Cruz, California*

Abstract. Many neglected tropical zoonotic pathogens are maintained by introduced mammals, and on islands the most common introduced species are rodents, cats, and dogs. Management of introduced mammals, including control or eradication of feral populations, which is frequently done for ecological restoration, could also reduce or eliminate the pathogens these animals carry. Understanding the burden of these zoonotic diseases is crucial for quantifying the potential public health benefits of introduced mammal management. However, epidemiological data are only available from a small subset of islands where these introduced mammals co-occur with people. We examined socioeconomic and climatic variables as predictors for disease burdens of angiostrongyliasis, leptospirosis, toxoplasmosis, toxocariasis, and rabies from 57 islands or island countries. We found strong correlates of disease burden for leptospirosis, *Toxoplasma gondii* infection, angiostrongyliasis, and toxocariasis with more than 50% of the variance explained, and an average of 57% (range = 32–95%) predictive accuracy on out-of-sample data. We used these relationships to provide estimates of leptospirosis incidence and *T. gondii* seroprevalence infection on islands where nonnative rodents and cats are present. These predicted estimates of disease burden could be used in an initial assessment of whether the costs of managing introduced mammal reservoirs might be less than the costs of perpetual treatment of these diseases on islands.

INTRODUCTION

Introduced mammals are reservoirs of zoonotic pathogens and are also well-known drivers of decline and extinction of native species and changes to ecosystems on islands.[1–4] Rodents (*Mus* spp., *Rattus* spp.), cats (*Felis catus*), and dogs (*Canis familiaris*) are the most common introduced mammals.[5,6] These introduced mammals co-occur with over 470 million people on at least 560 islands that also harbor Critically Endangered and Endangered vertebrates as defined by the International Union for Conservation of Nature (IUCN).[7,8] Peri-domestic rodents and domestic, stray, and feral cats and dogs are reservoirs for many neglected zoonotic diseases, including angiostrongyliasis, some strains of leptospirosis and rabies, as well as toxoplasmosis, toxocariasis, and echinococcosis (Supplemental Table 1).[9,10] Although these diseases have a worldwide distribution, they have disproportionate impacts on marginalized human populations with limited access to health-care services.[11–13] Treatment of these diseases includes antibiotics, antiprotozoals, and vaccinations, but treatment is challenging to administer to remote populations. In mainland areas, controlling the reservoir host populations can reduce the source of infection,[14–16] but the ongoing costs for control can be prohibitively expensive.[17–19] In contrast, on islands where immigration of introduced mammals is low and potentially preventable, management actions to control (reduce populations) or eradicate (completely remove) introduced mammals represent significant public health opportunities to reduce or potentially eliminate these diseases.

Management of introduced mammals on islands is a common practice to protect native biodiversity. For many islands, complete eradication of introduced rodents, and feral cats and dogs is possible, with island size and human population size being key limiting factors on where that can occur.[6,20,21] Where this is not currently feasible, controlling rodents, and feral dogs and cats on islands utilizes techniques to reduce populations of these introduced mammals to a desired state, ideally an outcome state for a native species.[22,23]

Islands represent a potential opportunity for reducing zoonotic disease burden because control or eradication of introduced mammal populations could result in disease alleviation or disease elimination, particularly if reintroductions of reservoirs can be prevented. Determining whether control or eradications are a cost-effective approach to controlling zoonotic diseases requires weighing the potential ecological, economic, and social costs of management against the human health and ecological benefits. The costs include the economic cost of control or eradication, economic and cultural benefits of the introduced mammal, and nontarget ecological impacts of removal.[6,20] The benefits potentially include reduction of zoonotic disease in human populations, enhanced economic growth due to alleviation of economic costs of zoonotic disease on human livelihoods and local economies,[24] reduced costs of disease control, and recovery of impacted native diversity.[25] A first step in quantifying the potential benefits of management of introduced mammals is an assessment of the burden of zoonotic diseases on island communities.

Although there has been a considerable effort to estimate the global burden of neglected zoonotic diseases such as rabies,[26] congenital toxoplasmosis,[13] and leptospirosis,[27] very little is known about the burden of zoonotic diseases transmitted by introduced mammals on islands. Only a fraction of the 560 islands where people co-occur with introduced mammal host populations[7] has information on disease burdens for any zoonotic disease. However, if disease burdens could be estimated using other readily available ecological and socioeconomic data, these estimates could then be used to inform preliminary cost-effectiveness analyses for management of introduced mammal populations on islands, and identify where local disease burden assessments could then be conducted.

*Address correspondence to Luz A. de Wit, Department of Ecology and Evolutionary Biology, University of California Santa Cruz, 100 Shaffer Road, Santa Cruz, CA 95060. E-mail: ldewit@ucsc.edu

The goals of our study were to examine whether a suite of climatic and socioeconomic factors can be predictive of burden of zoonotic pathogens transmitted by introduced mammals on islands, and thereby to provide a tool that can be used in cost-effectiveness analyses to identify where control of introduced mammals could be applied as a public health mitigation tool. Several readily available socioeconomic and climatic variables could serve as useful predictors of disease burdens through direct, indirect, or correlated influences on pathogen transmission.

Socioeconomic factors such as gross domestic product (GDP) per capita and population size are often correlated with zoonotic disease burden possibly due to their inherent connection to public health-care services and infrastructure. Infrastructure in public services is predicted to scale exponentially with increasing population size through economies of scale.[28] In particular, efficiency in public services such as solid waste management and access to waste disposal centers lead to decreased rodent population sizes, and decreased contact with commensal rodents and rodent-borne pathogens.[29–31] This in turn may have a cascading effect on cat abundance through bottom-up processes,[32] and in consequence affect the environmental load of parasites like *Toxoplasma gondii*.[33,34] However, this pattern has only been studied in large metropolitan areas, and whether it persists at smaller population sizes is currently unknown. Climate can influence disease dynamics by affecting host and pathogen population fluctuations via availability of resources in the form of vegetation or prey, or by creating suitable environmental conditions for free-living stages of pathogens.[35]

We searched the literature and other sources for data on population size, economic development, and climatic variables. We correlated these variables with disease burden data for five important zoonotic diseases: angiostrongyliasis, leptospirosis, toxoplasmosis, toxocariasis, and rabies. We focused on these diseases because of their public health importance and neglected status,[11,13,36–38] as well as on the availability of epidemiological information.

METHODS

We collected disease data for angiostrongyliasis, leptospirosis, toxoplasmosis, toxocariasis, rabies, and echinococcosis from the Global Infectious Disease and Epidemiology Network (GIDEON) online database[39] and by searching Google Scholar and PubMed for published epidemiological studies from islands, island countries, or countries within islands. We found incidence data for cystic echinococcosis and alveolar echinococcosis for only eight islands and one island, respectively (Supplemental Table 2). Given the limited availability of incidence data for these diseases, we did not pursue further analysis.

For islands that do not harbor native felids, *T. gondii* can be exclusively maintained by introduced cats,[40] and both introduced cats and dogs can maintain *Toxocara* spp.[41] However, some species and serotypes of *Leptospira* and rabies can be maintained by native mammal species in islands.[42,43] For these two diseases, we only included cases of species or serotypes associated with rodents or dogs, respectively.

We obtained the majority of disease information for leptospirosis and rabies from the GIDEON online database (Supplemental Table 2), which reports number of cases per year. We calculated incidence using the average number of cases reported between 2005 and 2015 to account for variability between years. We calculated the average yearly incidence of these diseases by dividing the number of cases by the island's population. We estimated countrywide incidence for archipelagos when cases were not reported for a specific island. We obtained the majority of information for angiostrongyliasis from epidemiological studies (Supplemental Table 2). To meet assumptions of normality, we log-transformed leptospirosis and rabies incidence data after adding one to account for islands that reported zero cases, and log-transformed angiostrongyliasis incidence data.

Reporting of cases is thought to be heterogeneous, with underreporting being higher in rural populations. As a result, we performed analyses on estimates of incidence, one using total population size, and another using urban population size to account for underreporting in rural areas. We primarily used The World Bank Group (World Bank)[44] and Central Intelligence Agency (CIA) World Factbook[45] to obtain information on total and urban population size. However, when data were not available in these databases, we searched the country profiles of the UNdata,[46] United Nations Children's Emigration Fund Migration Profiles,[47] and the Insee (Institut national de la statistique et des etudes économiques).[48]

We obtained data for prevalence of *T. gondii* infection and toxocariasis from epidemiological studies (Supplemental Tables 3 and 4). These diseases were reported as seroprevalence, and for both diseases the age classes for which data were collected for each island differed. To compare seroprevalence between islands, we only included data from islands with disease information stratified by age classes. For seroprevalence of *T. gondii* infection, we imputed missing values using pairwise multivariate correlations.[49] We analyzed adjusted estimates for the 31- to 40-year age class for seroprevalence of *T. gondii* infection, and the 5- to 15-year age class for toxocariasis, which were the most commonly reported age classes in the epidemiological studies (Supplemental Tables 3 and 4). Seroprevalence was arcsine square-root transformed to normalize the data.

For islands with disease information, we obtained data on climate, population size, and per capita GDP. We obtained climatic data from Bioclim World Climate,[50] and focused on mean annual temperature, temperature variability, annual precipitation, and precipitation variability. This database reports temperature variability as the standard deviation of the monthly values of temperature, and precipitation variability as the coefficient of variation in monthly precipitation. We used ESRI ArcMap version 10.2[51] to obtain the climate values for each island by extracting the corresponding BioClim layers using the 30 arc-seconds spatial resolution. We primarily used the World Bank and CIA World Factbook to obtain information on per capita GDP and population size that corresponded to the year the epidemiological study was done. We log-transformed population size as well as per capita GDP to equalize leverage in the analyses.

We used R version 3.2.1[52] to perform regression analyses. We performed stepwise backward regression for leptospirosis and *T. gondii* infection, starting with six predictor variables (annual temperature, temperature variability, annual precipitation, precipitation variability, population

size, and per capita GDP), until only significant ($P < 0.05$) predictors remained in the model. Models obtained through stepwise regression have been shown to have higher predictive power than regression trees and similar predictive power to models obtained through exhaustive subset search and stepwise elimination using Akaike information criterion.[53] Although stepwise regression can lead to bias in coefficients when predictor variables are correlated, the alternative, including nonsignificant and possibly spurious variables can lead to overfitting. In our analyses, coefficients of predictors in reduced models were very similar to those estimated for the full models, suggesting that bias in coefficients due to variable selection was minor. Sample sizes of islands for rabies, angiostrongyliasis, and toxocariasis were too small to examine in multiple regression analyses. Thus, we performed univariate regression analyses for these diseases. We included population size as a predictor variable in our analyses, and although very low incidence can result in spurious negative relationships with population, analyses in which we excluded islands that reported zero and one cases were qualitatively identical to the results reported below. The residuals of all analyses did not significantly deviate from normality (Shapiro–Wilks tests, $P > 0.05$) and inspection of residual plots did not reveal any clear nonlinearities.

For seroprevalence of *T. gondii* infection and toxocariasis, we also fit the nontransformed seroprevalence data with a generalized linear model with a binomial distribution and logit link. This analysis weights each seroprevalence estimate by the sample size in the study, rather than giving each data point equal weight, as in the Gaussian regression.

We tested the prediction accuracy of the Gaussian models by using leave-one-out cross-validation (LOOCV). We used prediction accuracy to determine whether total population or urban population was more appropriate for estimating incidence. In addition, we calculated the correlation coefficients of the socioeconomic predictors with the residuals of the final model of each disease to test for potential reverse causation between disease data and the socioeconomic variables, which would indicate a need to add instrumental variables to our models.[54] For all models, we did not find any correlation between residuals and the socioeconomic predictor variables, suggesting that there was no need to use instrumental variables.

We used the Gaussian regression models for leptospirosis and *T. gondii* infection, which were cross-validated, and were based on the largest sample size of islands, to predict disease burdens on a subset of islands lacking local disease data to illustrate the potential use of the fitted models. We used the Threatened Island Biodiversity database, which is a global dataset of islands based on the presence of breeding populations of IUCN Critically Endangered and Endangered vertebrates to identify islands with human population, and introduced rodents and/or cats.[7,8] We used the Threatened Island Biodiversity database to obtain population size, and the sources described above to obtain climate data and per capita GDP. We primarily focused on islands with known per capita GDP, or that form part of an island country or state with known per capita GDP. However, when GDP per capita was not available for the island or island country, we assigned the GDP per capita value of the sovereign country of the island.

To predict estimates of leptospirosis and *T. gondii* infection we used the "sp" package in R[52] to create bivariate polygon regions to identify islands with values that fell within the range of the predictor values that were used to fit the models (Supplemental Figures 1 and 2). We expect the average prediction accuracy for these estimates to be close to that reported in our analyses. We did not predict disease for islands with values that fell outside the range of these predictors, except for population size. We extrapolated disease estimates for islands with small population sizes (and clearly identify them as extrapolations) because population size is a limiting factor for management of introduced mammals. Specifically eradications are currently feasible on islands with population sizes less than approximately 1,000 people.[55] A substantial fraction of the islands that are therefore suitable for management were less populous than the range of islands in the dataset we used to fit the models. As a result, these extrapolated predictions should be used in planning with extreme caution and, as with all our predicted estimates, should be verified by on-the-ground measurement before any rigorous cost-benefit analyses are undertaken.

RESULTS

Data existed for at least one disease on 57 populated islands (including island countries or countries within islands) that were also inhabited by introduced rodents, cats, and/or dogs.[7] We found significant associations for four of the five diseases with 53–95% of the variance explained. Based on the average predictive accuracy values of the regression models, incidence of leptospirosis and angiostrongyliasis were better described when estimated using total population size than urban population size (Supplemental Tables 5 and 6, respectively).

The best fitting model for incidence of leptospirosis was the full model. Leptospirosis decreased with increasing values of population size, GDP per capita, temperature variability, and annual temperature, and decreasing values of annual precipitation and precipitation variability, explaining 57% of the variability with 35% out-of-sample average predictive accuracy (Figure 1, Supplemental Table 5). When incidence was estimated using the most recent (2013–2015) reported number of cases, the same model showed an even better fit with higher predictive accuracy ($R^2 = 0.64$, $P < 0.0001$, LOOCV = 0.44). Island population size and per capita GDP were not correlated with the residuals in the models.

Incidence of angiostrongyliasis decreased significantly with population size, explaining 95% of the variability with 94% out-of-sample average predictive accuracy (Figure 2, Supplemental Table 6). Island population was not correlated with the residuals in the models.

Seroprevalence of *T. gondii* infection decreased with increasing per capita GDP and increasing population size in both Gaussian and binomial regression models (Supplemental Table 7). The predictors in the Gaussian model explained 53% of the variability with 32% average out-of-sample predictive accuracy (Figure 3, Supplemental Table 7). Island population and per capita GDP were not correlated with the residuals in the Gaussian model.

Seroprevalence of toxocariasis was significantly and positively correlated with annual precipitation in both the

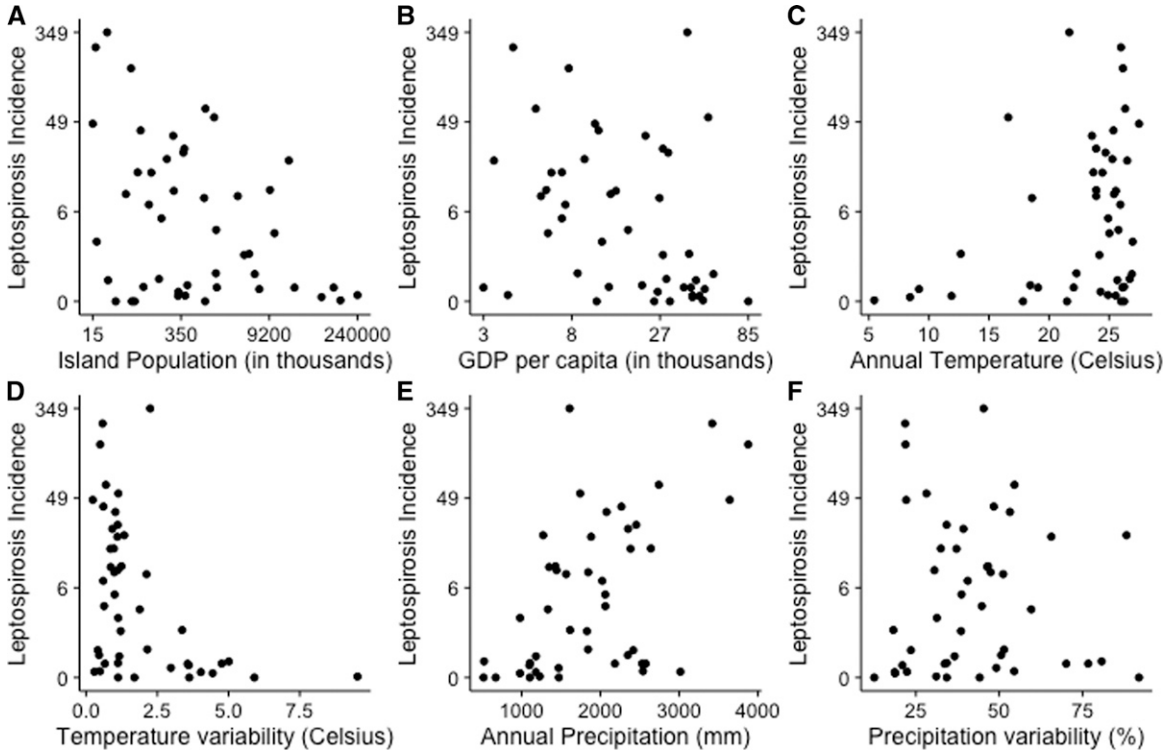

FIGURE 1. Univariate plots of leptospirosis incidence vs. six predictor variables: (**A**) Total population, (**B**) gross domestic product (GDP) per capita, (**C**) annual temperature, (**D**) temperature variability, (**E**) annual precipitation, and (**F**) precipitation variability. Leptospirosis is in per 100,000 individuals and is on a log (x + 1) scale in all plots, population and per capita GDP are shown on a log scale, temperature variability is the standard deviation of the monthly values of temperature, and precipitation variability is the coefficient of variation in monthly precipitation. Although not all of these univariate plots reveal strong relationships, all six predictors were significant in a multiple regression (leptospirosis incidence = 6.96–0.38 (log population size) – 0.57 (log GDP per capita) – 0.11 (annual temperature) – 0.23 (temperature variability) + 0.0004 (annual precipitation) + 0.01 (precipitation variability); $R^2 = 0.57$, $N = 46$, $P < 0.0001$, leave-one-out cross-validation [LOOCV] = 0.35).

Gaussian and binomial regression models (Supplemental Table 8). Annual precipitation explained 77% of the variability with 67% out-of-sample average predictive accuracy (Figure 4, Supplemental Table 8).

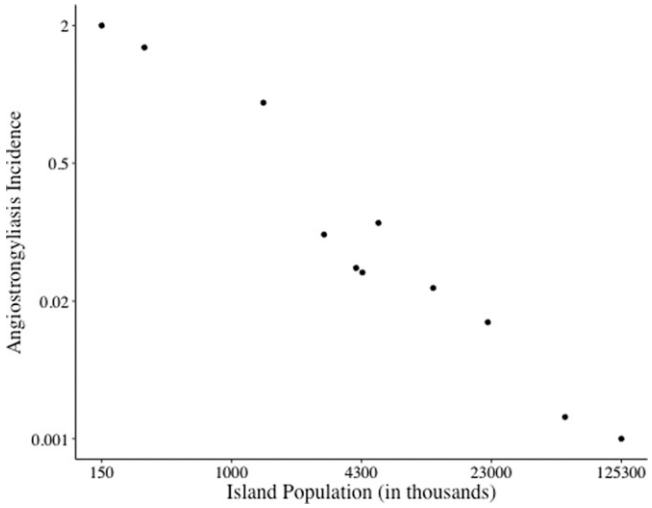

FIGURE 2. Univariate plot of angiostrongyliasis incidence vs. population. Angiostrongyliasis is in per 100,000 individuals and on a log scale, and population size is log-transformed. The model was highly significant (angiostrongyliasis incidence = 6.36–1.16 (log population size); $R^2 = 0.96$, $N = 11$, $P < 0.0001$, leave-one-out cross-validation [LOOCV] = 0.94).

Rabies incidence was not significantly correlated with any of the predictor variables (Supplemental Table 9).

We used the fitted models for leptospirosis and *T. gondii* infection to generate preliminary estimates of disease burdens on islands lacking local information. Preliminary estimates included seven and 32 islands with values within the bivariate polygon regions of predictors of our fitted models for leptospirosis (Figure 5; Supplemental Table 10) and *T. gondii* infection (Figure 6; Supplemental Table 11), respectively, and 30 and 61 additional islands for which we extrapolated outside the range of population size.

DISCUSSION

Introductions of nonnative mammals have facilitated the establishment and persistence of several important zoonotic diseases.[56] Efforts to reduce or eradicate introduced mammal hosts from islands could result in elimination or reduction of the zoonotic pathogens they transmit, particularly if they are the sole pathogen reservoirs on the island (i.e., cats for *T. gondii*, dogs and cats for *Toxocara* spp.). However, the costs of controlling or eradicating introduced mammals from islands is nontrivial and cost-effectiveness analyses are needed to assess whether management is worthwhile to attempt as a public health mitigation tool.[20,57,58] Cost-effectiveness analyses require estimates of disease incidence or prevalence, which are lacking for most islands globally.

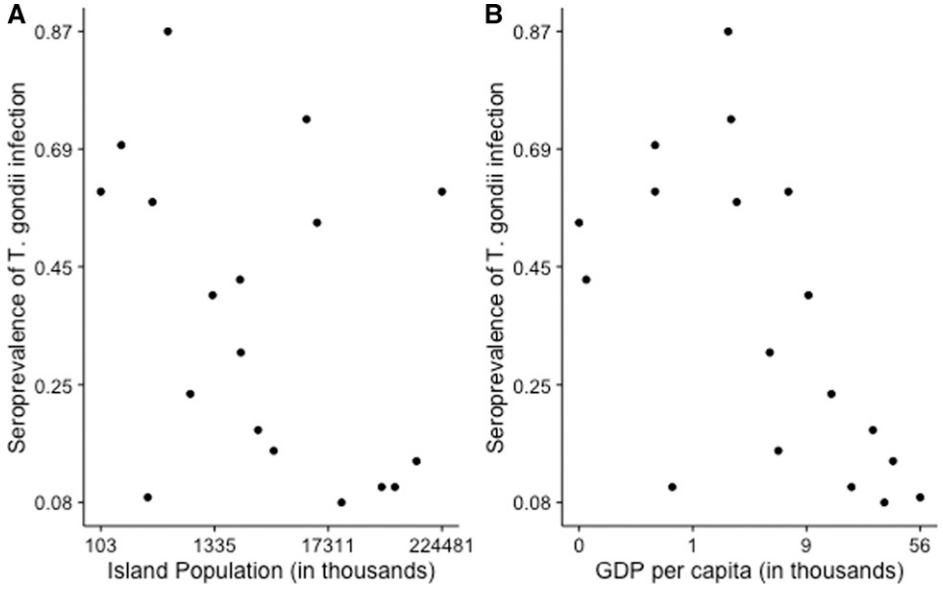

FIGURE 3. Univariate plots of seroprevalence of *Toxoplasma gondii* infection vs. (**A**) total population and (**B**) gross domestic product (GDP) per capita. Seroprevalence is shown on an arcsine square root scale, and GDP per capita and total population are shown on a log scale. Both predictors were significant in a multiple regression model (seroprevalence of *T. gondii* infection = 2.32–0.25 (log per capita GDP) – 0.11 (log population size); $R^2 = 0.53$, $N = 18$, $P = 0.003$, leave-one-out cross-validation [LOOCV] = 0.32).

We developed models to provide initial estimates of incidence or seroprevalence on islands where diseases transmitted by rodents, cats, or dogs are present. We found that widely available island attributes explained most of the variation in incidence and seroprevalence for four zoonotic diseases. Although the socioeconomic and ecologic variables rarely directly influence the incidence of zoonotic disease, they appear to be useful correlates in providing an estimate of incidence when local data are lacking. Due to the correlative nature of our analyses, our estimates should be used in the initial identification stage. After prospective islands for management of introduced mammals are identified, local incidence estimates should be obtained before formal cost-effectiveness analyses are undertaken.

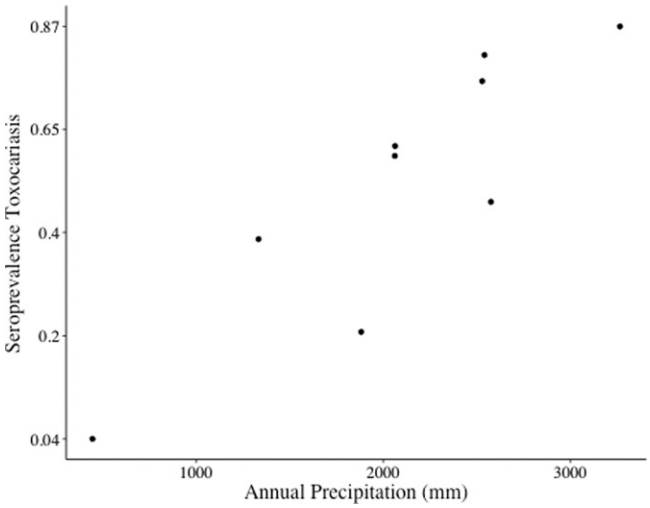

FIGURE 4. Univariate plot of toxocariasis seroprevalence and annual precipitation. Toxocariasis is arcsine square root transformed. The model was highly significant (toxocariasis seroprevalence = 0.09 + 0.0003 (annual precipitation); $R^2 = 0.77$, $N = 9$, $P = 0.002$, leave-one-out cross-validation [LOOCV] = 0.67).

Determining whether management of introduced mammal populations offers a conclusive benefit to public health requires an assessment of the disease burden and a cost-effectiveness analysis of the proposed management action at an island scale.[59] Disability-adjusted life years (DALYs) are commonly integrated into cost-effectiveness analyses as a value for healthy years of life lost through premature mortality or disability.[60] The monetary value of DALYs can be estimated based on the region's income, the funds allocated toward disease alleviation, and the DALY value of the disease.[61] The fitted models above could be used to provide an initial estimate of disease incidence or seroprevalence on islands, island countries, or countries within islands where this information is missing to identify prospective islands in which local data should be collected. Ultimately, these results could be converted into DALYs.[60] The results can be used to estimate the number of DALYs potentially saved through management of introduced mammal populations on a particular island, and then be assigned a monetary value to be compared with the monetary costs of the management action.[61]

Management of introduced mammals on inhabited islands implies social, cultural, and economic challenges that should be considered when assessing the feasibility of management actions.[58,62,63] For example, costs of eradication vary greatly, mostly as a function of population size, island area (e.g., US $3 to $20,000 per hectare), the type of eradication method (target species dependent), and other variable costs such as capacity building, environmental compliance, and mitigation of nontarget species.[20,57,58] Incorporating disease burden estimates into feasibility assessments for introduced mammal eradications can potentially expand the rationale and utility of these actions.

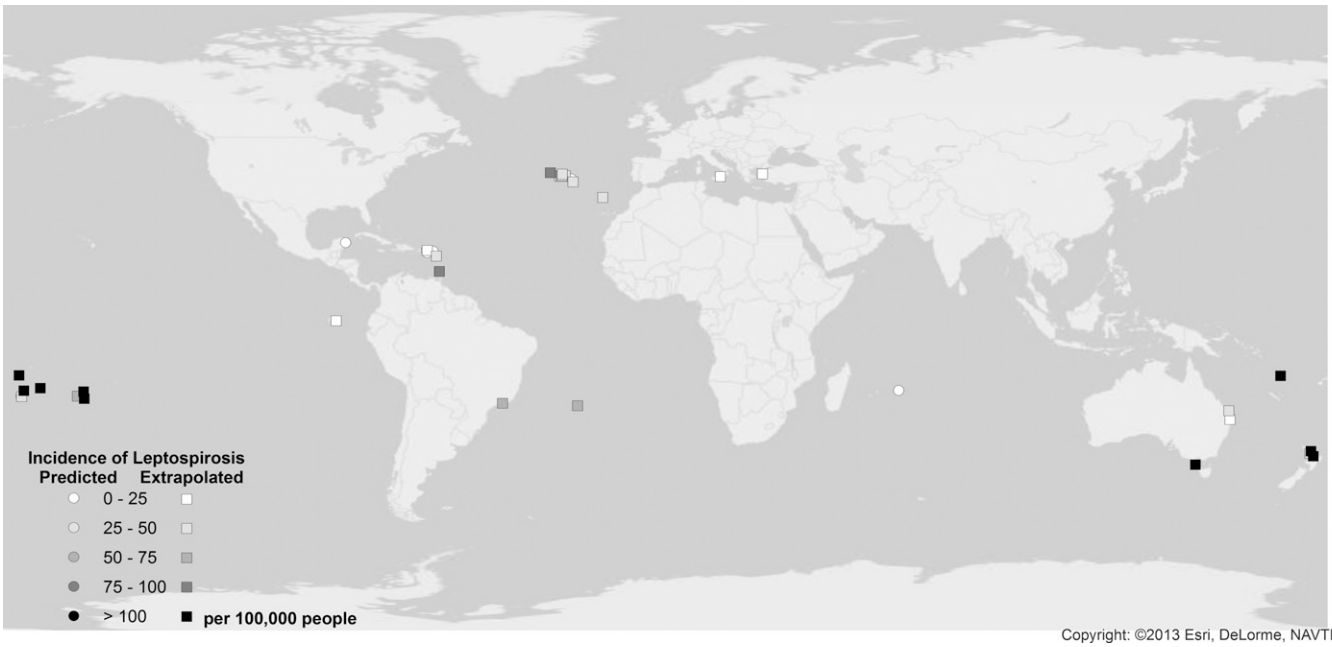

FIGURE 5. Predicted incidence of leptospirosis. Circles show predicted values and squares show extrapolated values. Leptospirosis is reported as incidence per 100,000 people.

We validated our Gaussian models using the LOOCV technique. For leptospirosis and *T. gondii* infection, prediction accuracy was 35% and 32%, respectively, and thus, for islands whose traits fall within the bivariate polygon regions of predictors, the predicted values should offer a useful initial estimate of disease burdens. However, disease data were particularly limited for islands with small populations and low GDP per capita (Supplemental Figures 1 and 2). The paucity of epidemiological information from islands with these traits limits the extent of our predictions, yet highlights islands where disease sur veillance could be relevant based on our model results. Furthermore, given that population size is currently a limiting factor for management of introduced mammals on islands, we extrapolated burden estimates of leptospirosis and *T. gondii* infection on islands in which eradication might be feasible, yet based on information from islands with larger population sizes. This may lead to less accurate predicted estimates of disease burden. Obtaining local data from the prospective islands for formal cost-effectiveness analyses is

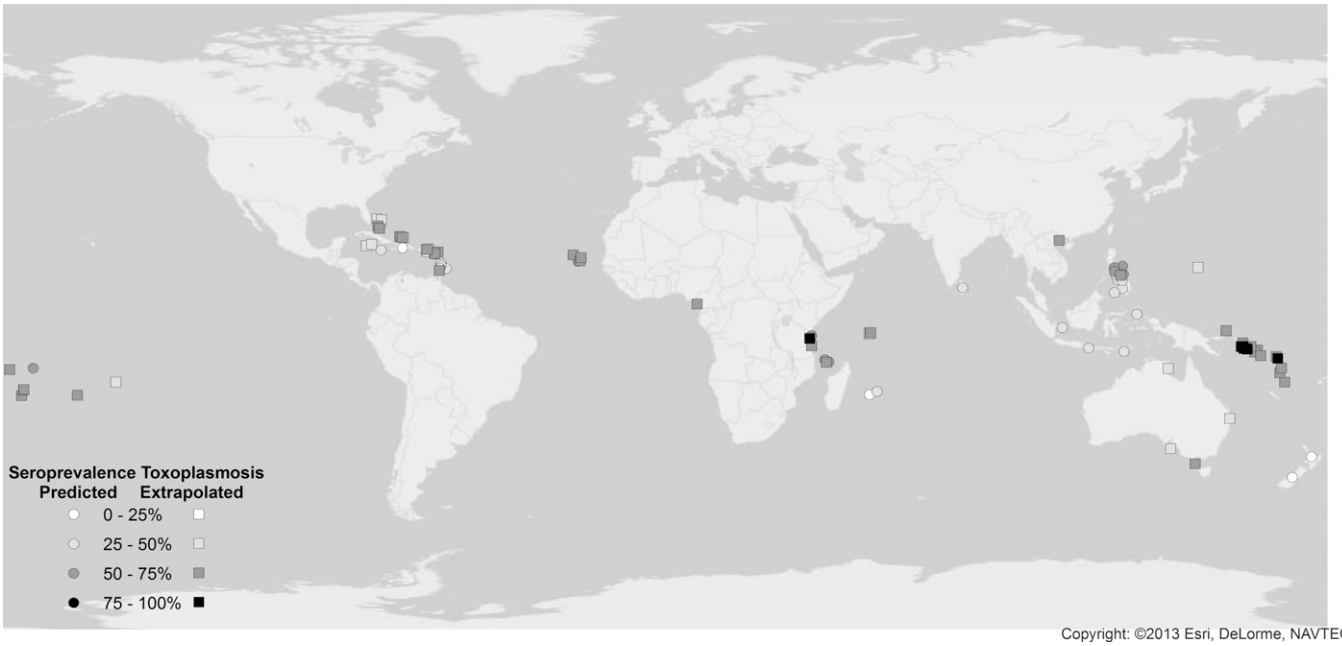

FIGURE 6. Predicted seroprevalence of *Toxoplasma gondii* infection. Circles show predicted values and squares show extrapolated values. Seroprevalence of *T. gondii* infection is reported as a percentage.

thus especially important for islands with population values outside those used to build the models described above.

Three recent studies have developed estimates of countrywide incidence for rabies,[26] congenital toxoplasmosis,[13] and leptospirosis,[27] to guide surveillance, vaccination, and reservoir control programs. These studies include incidence estimates for some islands, the majority of which have large populations. Our estimates for predicted and extrapolated incidence of leptospirosis were similar to some of those developed by Costa and others[27] (Supplemental Table 12). Unfortunately, we could not compare our estimates of *T. gondii* burden because we calculated seroprevalence estimates for the 31- to 40-year old age-group, whereas Torgerson and Mastroiacovo[13] examined incidence of congenital toxoplasmosis. We did not develop estimates for rabies incidence that could be compared with Hampson and others,[26] because none of our predictors reached statistical significance. However, as more data become available, all our models should be updated and estimated values should be compared with other estimates, and if possible, merged into a single dataset to identify islands for potential eradications of introduced mammals.

Improving public health and reducing threats from introduced species are recognized in global targets for sustainable development and biodiversity conservation.[64,65] There has been substantial recent attention investigating the relationship between biodiversity and human health,[26,66] but there are few concrete examples of the potential for synergistic interventions that benefit both.[67,68] However, the biodiversity benefits of eradicating introduced mammals from islands has been well documented,[55,69] and our study enables a way to connect these biodiversity benefits to improve public health.

Received July 13, 2016. Accepted for publication October 27, 2016.

Published online January 30, 2017.

Note: Supplemental tables and figures appear at www.ajtmh.org.

Acknowledgments: We are very grateful to Erin McCreless for sharing climatic data from inhabited islands.

Financial support: This research was supported by a joint scholarship for LDW from the National Council of Science and Technology of Mexico (CONACyT) and UC MEXUS, and the Complementary Scholarship from the Ministry of Education (SEP) of Mexico. This research was also supported by the National Science Foundation (grant number DEB-1115895) for AMK, and grants from the David and Lucile Packard Foundation.

Authors' addresses: Luz A. de Wit, Donald A. Croll, Bernie Tershy, Kelly M. Newton, and A. Marm Kilpatrick, Department of Ecology and Evolutionary Biology, University of California Santa Cruz, Santa Cruz, CA, E-mails: ldewit@ucsc.edu, dcroll@ucsc.edu, tershy@ucsc.edu, newton@ucsc.edu, and akilpatr@ucsc.edu. Dena Spatz, Department of Ecology and Evolutionary Biology, University of California Santa Cruz, Santa Cruz, CA, and Island Conservation, Santa Cruz, CA, E-mail: dspatz@ucsc.edu. Nick D. Holmes, Island Conservation, Santa Cruz, CA, E-mail: nick.holmes@islandconservation.org.

REFERENCES

1. Aguirre-Muñoz A, Croll D, Donlan CJ, Henry RW, Hermosillo MA, Howald GR, Keitt BS, Luna-Mendoza L, Rodríguez-Malagón M, Salas-Flores LM, Samaniego-Herrera A, Sanchez-Pacheco JA, Sheppard J, Tershy BR, Toro-Benito J, Wolf S, Wood B, 2008. High-impact conservation: invasive mammal eradications from the islands of western México. *Ambio 37:* 101–107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18488552. Accessed August 22, 2013.
2. Chanteau S, Ratsifasoamanana L, Rasoamanana B, Rahalison L, Randriambelosoa J, Roux J, Rabeson D, 1998. Plague, a reemerging disease in Madagascar. *Emerg Infect Dis 4:* 101–104.
3. Reaser JK, Meyerson LA, Cronk Q, De Poorter M, Eldrege LG, Green E, Kairo M, Latasi P, Mack RN, Mauremootoo J, O'Dowd D, Orapa W, Sastroutomo S, Saunders A, Shine C, Thrainsson S, Vaiutu L, 2007. Ecological and socioeconomic impacts of invasive alien species in island ecosystems. *Environ Conserv 34:* 98.
4. Levy JK, Crawford PC, Lappin MR, Dubovi EJ, Levy MG, Alleman R, Tucker SJ, Clifford EL, 2008. Infectious diseases of dogs and cats on Isabela Island, Galapagos. *J Vet Intern Med 22:* 60–65.
5. Atkinson IAE, 1985. The spread of commensal species of *Rattus* to oceanic islands and their effects on island avifaunas. Moors PJ, ed. *Conservation of Island Birds*. Bristol, United Kingdom: International Council for Bird Preservation, 35–81.
6. Oppel S, Beaven BM, Bolton M, Vickery J, Bodey TW, 2011. Eradication of invasive mammals on islands inhabited by humans and domestic animals. *Conserv Biol 25:* 232–240.
7. Threatened Island Biodiversity Database Partners, 2014. *The Threatened Island Biodiversity Database* (developed by Island Conservation,University of California Santa Cruz Coastal Conservation Action Lab, BirdLife International and IUCN Invasive Species Specialist Group). Available at: http://tib.islandconservation.org/. Accessed February 1, 2014.
8. IUCN, 2015. *The IUCN Red List of Threatened Species*. Available at: http://www.iucnredlist.org. Accessed April 27, 2015.
9. World Health Organization, 2016. *Zoonoses and Veterinary Public Health*. Available at: http://www.who.int/zoonoses/en/. Accessed February 1, 2015.
10. Centers for Disease Control and Prevention (CDC), 2015. *Diseases That Can Be Spread From Pets to People*. Atlanta, GA: CDC.
11. King L, 2011. Neglected zoonotic diseases. Choffnes ER, Relman DA, eds. *The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Opportunities for Integrated Intervention Strategies*. Washington, DC: The National Academies Press, 342–346.
12. Molyneux D, Hallaj Z, Keusch GT, Mcmanus DP, Ngowi H, Cleaveland S, Ramos-jimenez P, Gotuzzo E, Kar K, Sanchez A, Garba A, Carabin H, 2011. Zoonoses and marginalised infectious diseases of poverty: where do we stand? *Parasit Vectors 4:* 106.
13. Torgerson PR, Mastroiacovo P, 2013. The global burden of congenital toxoplasmosis: a systematic review. *Bull World Health Organ 91:* 501–508.
14. Hampson K, Dushoff J, Cleaveland S, Haydon DT, Kaare M, Packer C, Dobson A, 2009. Transmission dynamics and prospects for the elimination of canine rabies. *PLoS Biol 7:* e53.
15. Victoriano AFB, Smythe LD, Gloriani-Barzaga N, Cavinta LL, Kasai T, Limpakarnjanarat K, Ong BL, Gongal G, Hall J, Coulombe CA, Yanagihara Y, Yoshida S-I, Adler B, 2009. Leptospirosis in the Asia Pacific region. *BMC Infect Dis 9:* 147.
16. Dabritz HA, Conrad PA, 2010. Cats and *Toxoplasma*: implications for public health. *Zoonoses Public Health 57:* 34–52.
17. Patronek GJ, Beck AM, Glickman LT, 1997. Dynamics of dog and cat populations in a community. *J Am Vet Med Assoc 210:* 637–642. Available at: http://europepmc.org/abstract/MED/9054991. Accessed May 27, 2013.
18. Easterbrook JD, Shields T, Klein SL, Glass GE, 2005. Norway rat population in Baltimore, Maryland, 2004. *Vector Borne Zoonotic Dis 5:* 296–299.
19. Flores-Ibarra M, Estrella-Valenzuela G, 2004. Canine ecology and socioeconomic factors associated with dogs unvaccinated against rabies in a Mexican city across the US–Mexico border. *Prev Vet Med 62:* 79–87.
20. Howald G, Donlan CJ, Galván JP, Russell JC, Parkes J, Samaniego A, Wang Y, Veitch D, Genovesi P, Pascal M, Saunders A, Tershy B, 2007. Invasive rodent eradication on islands. *Conserv Biol 21:* 1258–1268.

21. Phillips RA, 2010. Eradications of invasive mammals from islands: why, where, how and what next? *Emu 110:* 1–8.
22. Reardon JT, Whitmore N, Homes KM, Judd LM, Hutcheon AD, Norbury G, Mackenzie DI, 2012. Predator control allows critically endangered lizards to recover on mainland New Zealand. *N Z J Ecol 36:* 141–150.
23. Pender RJ, Shiels AB, Bialic-Murphy L, Mosher SM, 2013. Large-scale rodent control reduces pre- and post-dispersal seed predation of the endangered Hawaiian lobeliad, *Cyanea superba* subsp *superba* (Campanulaceae). *Biol Invasions 15:* 213–223.
24. Bonds MH, Dobson AP, Keenan DC, 2012. Disease ecology, biodiversity, and the latitudinal gradient in income. *PLoS Biol 10:* e1001456.
25. Beltran RS, Kreidler N, Van Vuren DH, Morrison SA, Zavaleta ES, Newton K, Tershy BR, Croll DA, 2014. Passive recovery of vegetation after herbivore eradication on Santa Cruz Island, California. *Restor Ecol 22:* 790–797.
26. Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, Barrat J, Blanton JD, Briggs DJ, Cleaveland S, Costa P, Freuling CM, Hiby E, Knopf L, Leanes F, Meslin FX, Metlin A, Miranda ME, Müller T, Nel LH, Recuenco S, Rupprecht CE, Schumacher C, Taylor L, Vigilato MAN, Zinsstag J, Dushoff J, 2015. Estimating the global burden of endemic canine rabies. *PLoS Negl Trop Dis 9:* 1–20.
27. Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-Silveira MS, Stein C, Abela-Ridder B, Ko AI, 2015. Global morbidity and mortality of leptospirosis: a systematic review. *PLoS Negl Trop Dis 9:* 0–1.
28. Bettencourt LMA, Lobo J, Helbing D, Kühnert C, West GB, 2007. Growth, innovation, scaling, and the pace of life in cities. *Proc Natl Acad Sci U S A 104:* 7301–7306.
29. Traweger D, Travnitzky R, Moser C, Walzer C, Bernatzky G, 2006. Habitat preferences and distribution of the brown rat (*Rattus norvegicus* Berk.) in the city of Salzburg (Austria): implications for an urban rat management. *J Pest Sci 79:* 113–125.
30. Barcellos C, Sabroza PC, 2000. Socio-environmental determinants of the leptospirosis outbreak of 1996 in western Rio de Janeiro: a geographical approach. *Int J Environ Health Res 10:* 301–313.
31. Reis RB, Ribeiro GS, Felzemburgh RDM, Santana FS, Mohr S, Melendez AXTO, Queiroz A, Santos AC, Ravines RR, Tassinari WS, Carvalho MS, Reis MG, Ko AI, 2008. Impact of environment and social gradient on *Leptospira* infection in urban slums. *PLoS Negl Trop Dis 2:* 11–18.
32. Ringler D, Russell J, Le Corre M, 2015. Trophic roles of black rats and seabird impacts on tropical islands: mesopredator release or hyperpredation? *Biol Conserv 185:* 75–84.
33. Dabritz HA, Miller MA, Atwill ER, Gardner IA, Leutenegger CM, Melli AC, Conrad PA, 2007. Detection of *Toxoplasma gondii*-like oocysts in cat feces and estimates of the environmental oocyst burden. *J Am Vet Med Assoc 231:* 1676–1684.
34. Gotteland C, Gilot-Fromont E, Aubert D, Poulle M-L, Dupuis E, Darde M-L, Forin-Wiart M-A, Rabilloud M, Riche B, Villena I, 2014. Spatial distribution of *Toxoplasma gondii* oocysts in soil in a rural area: influence of cats and land use. *Vet Parasitol 205:* 629–637.
35. Altizer S, Dobson A, Hosseini P, Hudson P, Pascual M, Rohani P, 2006. Seasonality and the dynamics of infectious diseases. *Ecol Lett 9:* 467–484.
36. Wang Q-PP, Lai D-HH, Zhu X-QQ, Chen X-GG, Lun Z-RR, 2008. Human angiostrongyliasis. *Lancet Infect Dis 8:* 621–630.
37. World Health Organization, 2006. *Informal Consultation on Global Burden of Leptospirosis: Methods of Assessment*. Geneva, Switzerland: World Health Organization.
38. Torgerson PR, Budke CM, 2003. Echinococcosis: an international public health challenge. *Res Vet Sci 74:* 191–202.
39. Gideon, 2016. Gideon infectious diseases database. Available at: www.gideononline.com. Accessed August 2, 2016.
40. Dubey JP, 1998. Advances in the life cycle of *Toxoplasma gondii*. *Int J Parasitol 28:* 1019–1024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9724872. Accessed May 15, 2011.
41. Overgaauw PAM, van Knapen F, 2013. Veterinary and public health aspects of *Toxocara* spp. *Vet Parasitol 193:* 398–403.
42. Desvars A, Cardinale E, Michault A, 2011. Animal leptospirosis in small tropical areas. *Epidemiol Infect 139:* 167–188.
43. Cleaveland S, Kaare M, Knobel D, Laurenson MK, 2006. Canine vaccination: providing broader benefits for disease control. *Vet Microbiol 117:* 43–50.
44. World Bank Group, 2016. *World Bank Open Data*. Available at: http://data.worldbank.org. Accessed February 1, 2016.
45. The CIA World Factbook, 2016. *The CIA World Factbook Library*. Available at: https://www.cia.gov/library/publications/the-world-factbook/. Accessed February 26, 2015.
46. UNdata, 2015. *UNdata Country Profiles*. Available at: http://data.un.org. Accessed February 27, 2015.
47. United Nations Children's Emergency Fund, 2014. *Migration Profiles: Common Set of Indicators*. New York, NY: DESA-Population Division and UNICEF.
48. INSEE, 2015. *Économie: Produits intérieurs bruts régionaux et valeurs ajoutées régionales de 1990 à 2012*. Institut national de la statistique et des études économiques. Available at: http://www.insee.fr/fr/themes/detail.asp?reg_id=99&ref_id=pib-va-reg-base-2005. Accessed January 15, 2015.
49. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR, 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ 338:* b2393.
50. Hijmans R, Cameron S, Parra J, Jones P, Jarvis A, Richardson K, 2015. *WorldClim: Global Climate Data*. Available at: http://www.worldclim.org/. Accessed August 21, 2014.
51. Environmental Systems Resource Institute (ESRI), 2015. *ArcGIS*. Available at: http://www.esri.com/software/arcgis/arcgis-for-desktop. Accessed August 27, 2014.
52. R-Core-Team, 2014. *R: A Language and Environment for Statistical Computing*. Available at: http://www.r-project.org/.
53. Murtaugh PA, 2009. Performance of several variable-selection methods applied to real ecological data. *Ecol Lett 12:* 1061–1068.
54. Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH, 2006. Instrumental variables application and limitations. *Epidemiology 17:* 260–267.
55. Jones HP, Holmes ND, Butchart SHM, Tershy BR, Kappes PJ, Corkery I, Aguirre-muñoz A, Armstrong DP, Bonnaud E, Burbidge AA, Campbell K, 2016. Invasive mammal eradication on islands results in substantial conservation gains. *Proc Natl Acad Sci USA 113:* 4033–4038.
56. Torchin ME, Lafferty KD, Dobson AP, Mckenzie VJ, Kuris AM, 2003. Introduced species and their missing parasites. *Nature 421:* 628–630.
57. Martins TLF, Brooke MDL, Hilton GM, Farnsworth S, Gould J, Pain DJ, 2006. Costing eradications of alien mammals from islands. *Anim Conserv 9:* 439–444.
58. Donlan CJ, Wilcox C, 2007. Complexities of costing eradications. *Anim Conserv 10:* 154–156.
59. Fox-Rushby JA, Hanson K, 2001. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy Plan 16:* 326–331.
60. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N,

Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gonzalez-Medina D, Gosselin R, Grainger R, Grant B, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Laden F, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Levinson D, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mock C, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leòn FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiebe N, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, AlMazroa MA, Memish ZA, 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet 380:* 2197–2223.

61. Brent RJ, 2015. An implicit price of a DALY for use in a cost-benefit analysis of ARVs. *Appl Econ 2011:* 1413–1421.
62. Nogales M, Martin A, Tershy BR, Donlan CJ, Veitch D, Puerta N, Wood B, Alonso J, 2004. A review of feral cat eradication on islands. *Conserv Biol 18:* 310–319.
63. Townsend SE, Sumantra IP, Pudjiatmoko, Bagus GN, Brum E, Cleaveland S, Crafter S, Dewi APM, Dharma DMN, Dushoff J, Girardi J, Gunata IK, Hiby EF, Kalalo C, Knobel DL, Mardiana IW, Putra AAG, Schoonman L, Scott-Orr H, Shand M, Sukanadi IW, Suseno PP, Haydon DT, Hampson K, 2013. Designing programs for eliminating canine rabies from islands: Bali, Indonesia as a case study. *PLoS Negl Trop Dis 7:* e2372.
64. United Nations, 2015. *Resolution Adopted by the General Assembly on 25 September 2015. Transforming Our World: The 2030 Agenda for Sustainable Development*. Available at: http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E. Accessed June 6, 2016.
65. Convention on Biological Diversity, 2011. *Conference of the Parties Decision X/2: Strategic Plan for Biodiversity 2011–2020*. Available at: www.cbd.int/decision/cop/?id=12268. Accessed June 6, 2016.
66. Morand S, Jittapalapong S, Suputtamongkol Y, Abdullah MT, Huan TB, 2014. Infectious diseases and their outbreaks in Asia-Pacific: biodiversity and its regulation loss matter. *PLoS One 9:* e90032.
67. Ostfeld RS, Keesing F, 2000. Biodiversity and disease risk: the case of Lyme disease. *Conserv Biol 14:* 722–728.
68. Wolfe ND, Daszak P, Kilpatrick AM, Burke DS, 2005. Bushmeat hunting, deforestation, and prediction of zoonotic disease emergence. *Emerg Infect Dis 11:* 1822–1827.
69. Lavers JL, Wilcox C, Donlan CJ, 2010. Bird demographic responses to predator removal programs. *Biol Invasions 12:* 3839–3859.