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Dynamics of leprosy in nine-banded armadillos: Net reproductive number and effects on host population dynamics

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ABSTRACT

Leprosy (or Hansen's disease) remains an important public health challenge globally, with an estimated 5.5 million total number of cases and 200,000–300,000 new cases reported annually. The nine-banded armadillo (*Dasypus novemcinctus*) is the only known natural non-human vertebrate host of *Mycobacterium leprae*, the causative agent of leprosy, in the Americas, yet gaps in knowledge remain regarding the dynamics of leprosy in wild populations. Here, we used data from a six-year study of a population of armadillos in Mississippi, USA to quantify the influence of leprosy on armadillo population dynamics, and to investigate leprosy dynamics within the host population. Leprosy reduced annual survival of adult armadillos by ~15%, and growth rate of the population by ~13%. The annual infection rate for adult armadillos (i.e., probability that a non-leprous adult armadillo seroconverts, conditional on survival) was 0.18, with no possibility of recovery. Assuming frequency-dependent transmission of leprosy, 18% to 25% of the adult armadillos will acquire leprosy infection in the long run. Finally, the basic reproductive ratio (R_0) was 1.36, suggesting 36% increase in seroprevalence per leprosy generation. Assuming that leprosy generation time is 3–5 years, *M. leprae* will spread within the armadillo population at the rate of 7–12% per year. Our results are consistent with recent evidence that leprosy infection in armadillos in the USA is spreading rapidly with a concomitant increase in risk for zoonotic transmissions.

1. Introduction

Leprosy, or Hansen's disease, is a chronic infectious disease of humans that has been reported from 115 countries, with an estimated 5.5 million cases living worldwide, and 200,000–300,000 new cases reported annually (CDC, 2014; Noorden et al., 1992; WHO, 2013). Nine-banded armadillos (*Dasypus novemcinctus*) are the only non-human vertebrates found in the Americas known to be naturally infected by *Mycobacterium leprae*, the causative agent of leprosy (Loughry et al., 2009; Truman, 2005; but see Avanzi et al., 2016). In the United States, some of the highest prevalence of leprosy infection in armadillos occurs in the coastal counties of Louisiana and Texas (Loughry and McDonough, 2013; Loughry et al., 2009; Truman, 2005). Interestingly, the central Gulf Coast counties also have some of the largest number of reported human leprosy cases in the US, many of them autochthonous in origin. Truman et al. (2011) showed that the *M. leprae* genotype isolated from nine-banded armadillos and leprosy-infected native-born Americans in the central Gulf Coast counties is unique and has not been reported elsewhere, providing strong support for zoonotic transmission of the disease (see also Sharma et al., 2015). Consistent with this evidence, new cases of leprosy with possible ties to infected armadillos have recently been reported from Florida (http://www.cbsnews.com/news/three-leprosy-cases-confirmed-in-florida/) and Georgia (Lane et al., 2006). However, there remain gaps in knowledge regarding mechanisms underlying zoonotic as well as intraspecific transmission in wildlife host populations (but see Perez-Heydrich et al., 2016).

Wildlife diseases can have substantial ecological, economic and public health implications (e.g., Daszak et al., 2000; McCallum, 2012), but the potential influence of leprosy on armadillo demography and population dynamics remains unknown. Our goal was

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to fill this knowledge gap by addressing the following questions: (1) does leprosy influence demographic parameters in armadillos? If so, how are these demographic effects translated into armadillo population dynamics? (2) What are the transmission and recovery rates of the disease, and what factors influence these rates? (3) Given empirical estimates of demographic and disease parameters, what can be said about the dynamics of the disease within the host population? We applied multistate capture-mark-recapture CMR models to six years of and serological data obtained from a population of armadillos in western Mississippi. Using empirically estimated parameters, we constructed a time-invariant stage-structured matrix population model to explore population and disease dynamics, and to quantify the potential influence of the disease on armadillo population dynamics. Because many diseases exhibit non-linear transmission dynamics (e.g., Begon et al., 2002; Hobbs et al., 2015; Klepac and Caswell, 2011; McCallum et al., 2001), we also analyzed a non-linear model assuming frequency-dependent (or proportional mixing) disease transmission. The non-linear model provided insights into the dynamics of the disease itself, and allowed us to calculate both the net reproductive number of leprosy and endemic equilibrium proportion of leprous armadillos, and to perform sensitivity analyses to quantify the relative importance of the demographic and disease parameters on leprosy dynamics. Our study is the first attempt to quantify the dynamics of leprosy in armadillos, and to assess its impact on the population dynamics of this important wildlife host.

2. Materials and methods

2.1. Study area and methods

Data were collected from 2005 to 2010 at the Yazoo National Wildlife Refuge in western Mississippi, USA (33°05′/90°59′), primarily within an approximately 750 ha area in the central part of the refuge that contained an extensive network of roads and trails that facilitated capture and observation of armadillos (Loughry and McDonough, 2013; Perez-Heydrich et al., 2016). Sampling in 2005 and 2006 was limited to 2–3 weeks in May, but in subsequent years extended from mid-May until late July (50–55 days in the field per year).

We attempted to capture or, in the case of animals that were already marked, to identify, all armadillos encountered during nightly censuses of the refuge (for details, see Loughry and McDonough, 2013; Morgan and Loughry, 2009; Williams and Loughry, 2012). Unmarked armadillos were live-caught in dip nets. At first capture each animal was permanently marked by injecting a passive induced transponder (PIT) tag under the dorsal, front edge of the front carapace, at its junction with the neck. Armadillos were also marked for temporary, long-range identification by gluing various shapes and colors of reflective tape to the carapace. After marking, animals were weighed and measured. Body mass was used to assign each individual to one of three broad age categories: juveniles = <2 kg, yearlings = 2–3 kg, and adults = >3 kg (Loughry and McDonough, 1996, 2013).

The lactation status of adult females was classified as definitely lactating, possibly lactating or definitely not lactating by inspection of nipple size. As in previous studies (Loughry et al., 2013a), we considered females classified as lactating and possibly lactating to represent the reproductive individuals in the population, while females that were not lactating were categorized as non-reproductive (note that the reproductive status of males could not be determined).

As part of the marking procedures a blood sample was obtained in order to test for exposure to *M. leprae*. Blood was collected onto Nobuto blood strips (Advantec, Dublin, California, USA) by clipping the end of one toenail from one of the forefeet. During the course of a field season animals were often recaptured frequently in order to reapply reflective tape but blood samples were only collected upon first capture each year. Blood samples were screened for exposure to *M. leprae* at the Hansen's Disease Center, Baton Rouge, LA, USA, using an enzyme-linked immunosorbent assay (ELISA) to detect antibodies against the *M. leprae*-specific PGL-1 antigen (Truman et al., 1986). All samples were run at least twice to confirm consistency. An antibody titer of 0.70 optical density was the threshold for designating an animal as seropositive. Note that, because we defined disease states on the basis of serology, the mention of leprous and non-leprous states hereafter corresponds to seropositive and seronegative ELISA results, respectively.

2.2. Estimation of population and disease parameters

We used a multistate capture-mark-recapture modeling framework to estimate and model annual state-specific capture probabilities, apparent survival and disease parameters (Cooch et al., 2012; Oli et al., 2006; Ozgul et al., 2009; Williams et al., 2001). We considered three age classes: 0–1 yr: juveniles; 1–2 yrs: yearlings; and ≥2 yrs: adults. Adult armadillos were further classified as leprous (seropositive) or non-leprous (seronegative) as discussed previously. We then estimated annual apparent survival of juveniles (S_j), yearlings (S_y), non-leprous adults (S_n) and leprous adults (S_l), and the probability of non-leprous adults acquiring leprosy infection conditional on survival (ψ) using the multistate CMR model. Because the three demographic states were based on estimated age, transition from juvenile to yearling, and from yearling to adult states were automatic, conditional on survival. None of the juvenile and yearling armadillos we sampled were seropositive to *M. leprae* (Perez-Heydrich et al., 2016) and were thus considered disease-free. Furthermore, none of the surviving yearlings ever tested seropositive. Consequently, we set the probability of transition from yearling to leprous adult state (conditional on survival) to zero. Transitions from both leprous and non-leprous adult states to yearling or juvenile stages, from yearling to juvenile stage, and from juvenile to leprous adult states were fixed to zero because these transitions are not biologically feasible. Finally, we set the recovery probability (i.e., probability of seropositive adult armadillos becoming seronegative, conditional on survival), to zero because no such transition was observed in this population. We allowed S to be affected by sex, demographic and disease state (juveniles, yearlings, non-leprous adults and leprous adults) and an additive effect of the two; capture probability by time, stratum, sex, and additive effects of two variables at a time; and ψ by stratum. Our data were not sufficient to support more complex models. We estimated the probability of reproduction using a multistate CMR analysis, using data only for adult females, and reproductive status (reproductive or not reproductive) as states (Appendix A in Supplementary material).

The multistate CMR models were implemented in program MARK (White and Burnham, 1999) version 6.2 using the RMark package (Laake, 2013) version 2.2.0 for the R computing environment (R Core Team, 2014). We used an information-theoretic approach for model selection, with Akaike's information criterion corrected for small sample size (AIC_c) as a measure of model parsimony (Burnham and Anderson, 2002; Williams et al., 2001).

2.3. Population and leprosy dynamics

Epidemiological models are used to describe transmission and recovery processes, and attempt to track changes in the number (or proportion) of hosts that acquire (or recover from) infection over time (Anderson and May, 1991; Diekmann and Heesterbeek, 2000). Models of disease dynamics can be formulated as stage-structured population models, with stages being comprised of a combination

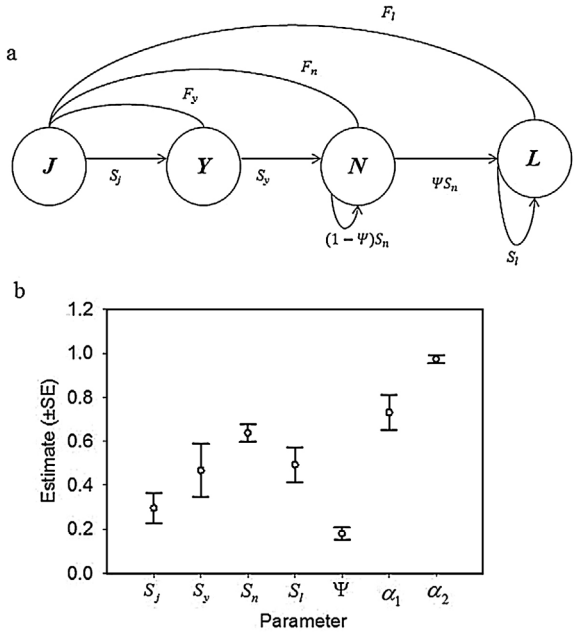

Fig. 1. (a) Stage-specific life cycle graph based on demographic and disease (leprosy) states for the nine-banded armadillo population at Yazoo National Wildlife Refuge, Mississippi, USA. Stages are: juveniles (*J*), yearlings (*Y*), non-leprous adults (*N*) and leprous adults (*L*). Symbols are: F_y, F_n, F_l = fertility rates of yearlings, non-leprous adults and leprous adults; S_y, S_n, S_l = survival of yearling, non-leprous adults, and leprous adults, respectively, and ψ is the probability of transition from non-leprous adult stage to leprous adult stage (conditional on survival). (b) Estimates (±SE) of demographic and disease parameters using the multistate capture-mark-recapture method. α_1 and α_2 represent the probability of reproduction for primiparous and multiparous females, respectively; other parameters are defined in Fig. 1a.

of disease status and age and/or demographic stages (Hobbs et al., 2015; Klepac and Caswell, 2011; Perez-Heydrich et al., 2012). Thus, we used a matrix population model to study the population dynamics of armadillos and the dynamics of leprosy within the armadillo population (Caswell, 2001; Oli et al., 2006). As described previously, we considered four stages based on age and leprosy infection status: juveniles, yearlings, non-leprous adults, and leprous adults. Juveniles survive with annual survival probability S_j and all survivors become yearlings the following year. Yearlings survive with annual survival rate S_y and all surviving yearlings become non-leprous adults the following year. As mentioned previously, none of the surviving yearling armadillos seroconverted; consequently, we set the probability of transitioning from yearling to leprous adult stage to zero. Non-leprous and leprous adults survive the year with annual survival probability S_n and S_l, respectively. Additionally, non-leprous adults that survive the year become leprous the following year with probability ψ, and remain non-leprous adults with probability $(1-\psi)$. We set the recovery probability to zero because none of the leprous adult armadillos ever tested seronegative against *M. leprae* subsequently. The stage-structured population and leprosy projection matrix was of the form:

$$\mathbf{A} = \begin{pmatrix} 0 & F_y & F_n & F_l \\ S_j & 0 & 0 & 0 \\ 0 & S_y & (1-\Psi)S_n & 0 \\ 0 & 0 & \Psi S_n & S_l \end{pmatrix}, \quad (1)$$

where F_n and F_l are fertility rates for non-reproductive and reproductive adults (Fig. 1a). Following Loughry et al. (2013a), we estimated fertility rates as $F_y = (0.5\alpha_1 LS\gamma S_y)$, which reduces to $F_n = 0.5\alpha_2 LS\,\gamma\, S_n$, and $F_l = 0.5\alpha_2\, LS\,\gamma\, S_l$, where *LS* is litter size, α_1 and α_2 are the probabilities that non-reproductive and reproductive adult females reproduce the following year conditional on survival, γ is the probability of survival from birth until the trappable age, ψ is the probability of transition from non-leprous adult stage to leprous adult stage (conditional on survival), and S_y, S_n, S_l, are the survival of yearling, non-leprous adults, and leprous adults, respectively. Notice that ψ = 0 implies a disease-free population, whereas ψ = 1 implies that all adult armadillos become leprous if they survive the first year as adults. *LS* is fixed at 4 because females exhibit obligate polyembryony whereby they invariably produce a single litter of genetically identical quadruplets from a single fertilized egg in the years in which they reproduce (Loughry et al., 1998). Because we did not have an empirical estimate of γ, we analyzed the model for three values (0.5, 0.8, and 1.0 to represent low, medium and high survival from birth until trappable age) for this parameter. We tested for the effect of leprosy on the probability of reproduction using multistate CMR analyses and found no evidence that leprosy reduced probability of reproduction (Appendix A in Supplementary material). Also, we found no evidence that leprosy affects litter size or survival of neonates. Thus, we assumed that *LS* and γ did not differ between non-leprous and leprous adults. All parameters except *LS* and γ were estimated using multistate capture-mark-recapture (CMR) models, as described previously.

We analyzed the matrix population models to calculate deterministic finite population growth rate (λ), stable stage distribution, reproductive values, and elasticity of λ to changes in entries of the population projection matrix, as well as lower-level vital rates, following Caswell (2001). We used the delta method to estimate variance and confidence intervals of λ (Caswell, 2001; Williams et al., 2001):

$$var\,(\lambda) = \sum_j \sum_i Cov\,(x_i, x_j)\,\frac{\partial\lambda}{\partial x_i}\,\frac{\partial\lambda}{\partial x_j}, \quad (2)$$

where $Cov(x_i, x_j)$ is the covariance between parameters x_i, and x_j, and $\frac{\partial\lambda}{\partial x_i}$ and $\frac{\partial\lambda}{\partial x_j}$ are the sensitivity of λ with respect to x_i, and x_j, respectively. The variance-covariance matrix for S_j, S_y, S_n, S_l, and ψ, and that for α_1 and α_2, were estimated using multi-state CMR models as described previously. We did not have variance estimates for *LS* and γ so we assumed their variances (and covariance between these and other parameters) to be zero.

2.4. Population and leprosy dynamics: frequency-dependent transmission

Transmission of infectious diseases often depends on the proportion of infectious individuals in the host population. Such a transmission process, called "frequency-dependent" (or proportional mixing) transmission, is thought to underlie the dynamics of many infectious diseases (Begon et al., 2002; McCallum et al., 2001). In our study system, only adult armadillos were capable of seroconverting, so we considered a function of the form:

$$\psi_{\mathbf{n}} = 1 - e^{-\beta\left(\frac{n_4}{n_3+n_4}\right)}, \quad (3)$$

where n_3 and n_4 represent the number of susceptible and infectious adult armadillos, respectively, and β is the frequency-dependent leprosy transmission (or mixing) parameter. We estimated β = 1.079 because this value led to an estimate of ψ_n that matched the empirically-estimated value of ψ = 0.18. The

population projection matrix with frequency-dependent leprosy transmission is:

$$\mathbf{A_n} = \begin{pmatrix} 0 & F_y & F_n & F_l \\ S_j & 0 & 0 & 0 \\ 0 & S_j & (1-\Psi_{\mathbf{n}})S_n & 0 \\ 0 & 0 & \Psi_{\mathbf{n}} S_n & S_l \end{pmatrix} \quad (4)$$

The population projection equation is:

$$\mathbf{n}(t+1) = \mathbf{A_n}\mathbf{n}(t). \quad (5)$$

The vector-valued subscript $\boldsymbol{n}$ indicates frequency-dependence. The dynamics of frequency-dependent matrix models are similar to the dynamics of two-sex demographic models with frequency-dependent reproduction, and are described in detail by Caswell (2001). Briefly, Eq. (5) is a homogeneous equation of degree zero and converges to an equilibrium proportional stage structure such that:

$$\mathbf{p}(t) = \hat{\mathbf{p}}\lambda^t, \quad (6)$$

with $\hat{p}_i \geq 0$ and $\sum \hat{p}_i = 1$ (Caswell, 2001, 2008), and λ is the dominant eigenvalue of $\mathbf{A}_n$ at equilibrium. The equilibrium proportional stage structure is obtained by iterating Eq. (6).

It is of interest to know how various demographic and disease parameters influence $\hat{\boldsymbol{p}}$. Thus, we calculated the sensitivity of $\hat{\boldsymbol{p}}$with respect to a vector of parameters θ following Caswell (2008):

$$\frac{d\hat{\boldsymbol{p}}}{d\boldsymbol{\theta}^T} = \left[\lambda \mathbf{I}_s - \boldsymbol{A_n} + \hat{\boldsymbol{p}}\boldsymbol{e}^T\boldsymbol{A_n} - \left(\hat{\boldsymbol{p}}^T \otimes \left[\mathbf{I}_s - \hat{\boldsymbol{p}}\boldsymbol{e}^T\right]\right)\frac{\partial v\mathbf{e}c\ \mathbf{A_n}}{\partial \hat{\boldsymbol{p}}^T}\right]^{-1} \times \left(\hat{\boldsymbol{p}}^T \otimes \left[\mathbf{I}_s - \hat{\boldsymbol{p}}\boldsymbol{e}^T\right]\right)\frac{\partial v\mathbf{e}c\ \mathbf{A_n}}{\partial \boldsymbol{\theta}^T}, \quad (7)$$

where $\mathbf{I}_s$ is an identity matrix of size s (with s = number of stages = 4), $\mathbf{e}$ is a vector of 1′s of length s, $vec\mathbf{A}_n$ is the vectorized matrix $\mathbf{A}_n$, superscript ^{T} represents a matrix (or a vector) transpose, and ⊗ is the Kronocker (or tensor) product. Elasticities were calculated as:

$$diag\left(\theta\right)^{-1}\frac{d\hat{\boldsymbol{p}}}{d\theta^T}diag\left(\theta\right). \quad (8)$$

Sensitivities of λ with respect to θ were calculated as:

$$\frac{d\lambda}{d\boldsymbol{\theta}^T} = \left(\hat{\mathbf{p}}^T \otimes \mathbf{v}^T\right)\left[\frac{\partial vec\ \mathbf{A}}{\partial \boldsymbol{\theta}^T} + \frac{\partial vec\ \mathbf{A}}{\partial \hat{\boldsymbol{p}}^T}\frac{d\hat{\boldsymbol{p}}}{d\boldsymbol{\theta}^T}\right], \quad (9)$$

with elasticities given by $\frac{d\lambda}{d\theta}\frac{\theta}{\lambda}$, where $\mathbf{v}$ is the right eigenvector corresponding to the dominant eigenvalue of $\mathbf{A}_n$. Derivatives were evaluated at the equilibrium (Caswell, 2008). All analyses were performed for three values of γ (0.5, 0.8 and 1.0), the probability of survival from birth until trappable age.

2.5. Calculation of the basic reproductive ratio

The net reproductive number R_0 of an epidemic measures the mean number of new cases produced by introducing a single infected individual into an uninfected population (Anderson and May 1991; Heesterbeek 2002). If $R_0 < 1$ the infection will die out, whereas if $R_0 > 1$ the infection will spread. Methods for calculating R_0 exist for many diseases and patterns of infection (Bani-Yaghoub et al., 2012; Heesterbeek, 2002; Klepac and Caswell, 2011; Oli et al., 2006). These all involve calculating a "next-generation" matrix that projects over the generation of the infection, the linearization of the model in the neighborhood of a disease-free state if disease transmission is non-linear, and calculating R_0 as the dominant eigenvalue of that matrix. The process becomes more complicated when individuals are classified by demographic stages as well as infection status. Klepac and Caswell (2011) derived a general approach applicable to all age- or stage-structured epidemic models. In our case, only adult armadillos can acquire infection or infect other susceptible adults, and leprosy can be transmitted only horizontally. The matrices **X(n)**, **Y(n)**, and **Z(n)** that appear in Eq. (22) of Klepac and Caswell (2011) simplify to:

$$\mathbf{X}(\mathbf{n}) = \psi_n S_n$$
$$\mathbf{Y}(\mathbf{n}) = S_l \quad (10)$$
$$\mathbf{Z}(\mathbf{n}) = \begin{pmatrix} 0 & 0 \end{pmatrix}.$$

Klepac and Caswell (2011) show that the Jacobian matrix for a general case where individuals are classified based on demographic stages as well as infection status is given by (assuming $\mathbf{Z}(\mathbf{n}) = \mathbf{0}$):

$$\mathbf{J} = \mathbf{Y}(\mathbf{n}) + (\mathbf{n}_S \otimes \mathrm{I})\frac{d\mathrm{vec}\ \mathbf{X}}{d\mathbf{n}_I^T}, \quad (11)$$

where $\mathbf{I}$ is an identity matrix, $\mathbf{n}_S$ and $\mathbf{n}_I$ are vectors containing the number of individuals of susceptible and infectious stages, respectively. Recalling that there is only one susceptible (n_3) and one infectious stage (n_4), linearization about any population with $n_4 = 0$ (i.e., no infection) and $n_3 > 0$ (i.e., some susceptible individuals available), Eq. (12) simplifies to $\mathbf{J} = S_I + \beta S_n$ (a scalar in this case), and R_0 is given by (Eqs. (27)–(29) of Klepac and Caswell 2011):

$$R_0 = \frac{\beta S_n}{1 - S_I}. \quad (12)$$

The value of R_0 is independent of n_3 (provided that $n_3 > 0$) and thus the linearization applies to the disease-free equilibrium stage distribution with $n_4 = 0$. Using the standard methods (e.g., Caswell, 2001; Klepac and Caswell, 2011), elasticity (or proportional sensitivity) of R_0 to demographic and disease parameters are given by:

$$\frac{\partial R_0}{\partial S_n}\frac{S_n}{R_0} = 1$$
$$\frac{\partial R_0}{\partial \beta}\frac{\beta}{R_0} = 1 \quad (13)$$
$$\frac{\partial R_0}{\partial S_I}\frac{S_I}{R_0} = \frac{S_I}{1 - S_I}.$$

All matrix model calculations were performed in MATLAB Version 14a (MathWorks, 2014).

3. Results

3.1. Demographic and disease parameters

During the study period (2005–2010), we captured 640 (297 females, 343 males) individual armadillos 855 times. Of these, 160 were first marked as juveniles, 26 as yearlings, and 454 as adults. Across all years, no juveniles or yearling armadillos tested seropositive for the presence of antibodies for *M. leprae* at first capture, but 8.67% of adult females (n = 219) and 8.93% of males (n = 235) did. In addition, 36 armadillos that were initially captured as disease-free subsequently acquired leprosy infection during this study.

The most parsimonious multistate CMR model revealed that capture probability (p) varied over time, with lowest and highest values being observed in 2006 and 2010, respectively. There was no evidence that annual apparent survival probability differed between sexes (Appendix A in Supplementary material). Estimates of demographic and disease parameters are presented in Fig. 1b. Annual apparent survival probability was the lowest for juveniles (0.30 ± 0.06 [SE]), and highest for non-leprous adults (0.64 ± 0.029) The annual probability of a non-leprous adult armadillo seroconverting was 0.18 ± 0.027 (Fig. 1b).

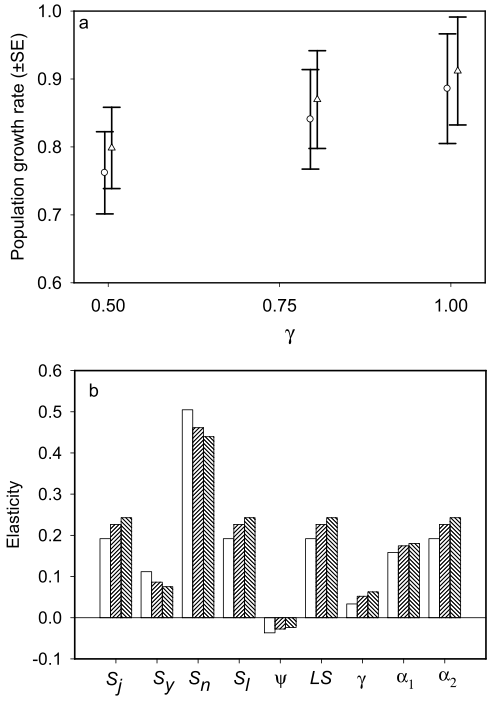

Fig. 2. (a) Annual asymptotic population growth (λ) rate for the nine-banded armadillo population at Yazoo National Wildlife Refuge, Mississippi, USA using estimated parameters (circles), and assuming ψ = 0 (which eliminates adult leprous stage; triangles). (b) Elasticity (proportional sensitivity) of λ to changes in demographic and disease parameters for the nine-banded armadillo population at Yazoo National Wildlife Refuge, Mississippi, USA. Population growth rates and elasticity were calculated for γ = 0.5 (left most bar in each group), γ = 0.8 (middle bar) γ = 1.0 (right most bar in each group). Parameters are: *LS* = litter size, and γ = probability of surviving from birth until trappable age; other parameters are defined in Fig. 1.

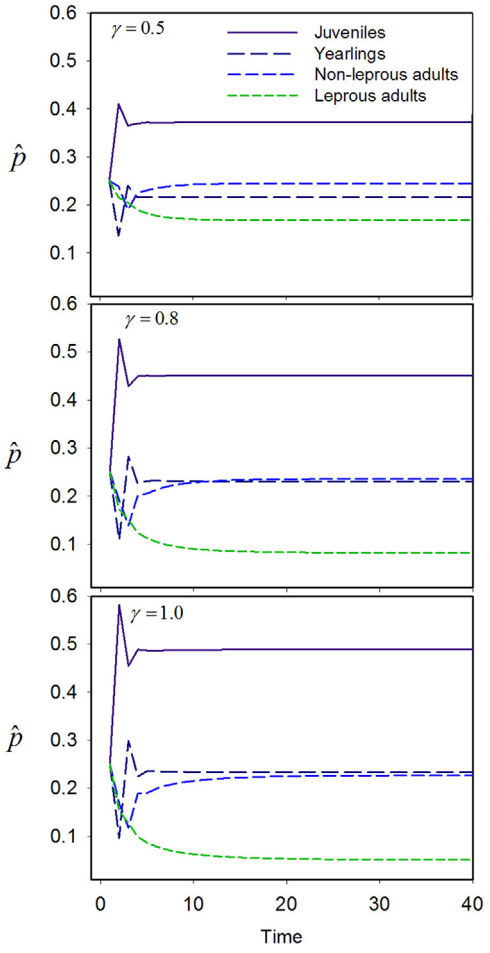

Fig. 3. Equilibrium proportion ($\hat{p}$) of juvenile, yearling, non-leprous adult and leprous adult armadillos for three values of γ (probability of surviving from birth until trappable age) under the assumption of frequency-dependent leprosy transmission.

3.2. Population and disease dynamics

The overall annual asymptotic population growth rate (λ) ranged from 0.76 to 0.89, depending on the value of γ (Fig. 2a). The mean life expectancy for juvenile, yearling, non-leprous adults and leprous adults was 1.65, 2.20, 2.57 and 1.97 years, respectively. Across all values of γ, survival of non-leprous adults was proportionately the most influential vital rate affecting λ, followed by survival of juveniles and yearlings, litter size and γ, all of which were equally influential (Fig. 2b). All demographic parameters positively influenced λ except the disease transmission rate, which negatively influenced it (Fig. 2b).

3.3. Population and disease dynamics: frequency-dependent disease transmission

The proportional stage structure at equilibrium varied depending on the value of γ, with a lower proportion of leprous adults for higher values of γ (Fig. 3). The proportion of adults that were leprous at the equilibrium (calculated as $\hat{n}_4/(\hat{n}_3 + \hat{n}_4)$) was 40.7%, 25.9%, and 18.4% for γ = 0.5, 0.8 and 1.0, respectively.

Elasticity analysis revealed that the influence of vital rates on the equilibrium proportional stage structure varied among stages (Table 1). Increasing S_j increased $\hat{p}_2$ and $\hat{p}_3$, but reduced $\hat{p}_1$and $\hat{p}_4$. Increasing S_y increased $\hat{p}_3$ but reduced $\hat{p}_2$ and $\hat{p}_4$; it had little influence on $\hat{p}_1$. S_n and S_l negatively influenced $\hat{p}_2$ and $\hat{p}_3$, but positively affected $\hat{p}_1$ and $\hat{p}_4$. All components of fertility (*LS*, α_1, α_2, and γ) had positive influence on $\hat{p}_1$ and $\hat{p}_2$ but negative influence on $\hat{p}_3$ and $\hat{p}_4$. The frequency-dependent disease transmission parameter β positively influenced $\hat{p}_4$ and negatively influenced $\hat{p}_3$; it had little influence on $\hat{p}_1$ and $\hat{p}_2$. Values of γ did not alter the relative magnitudes of elasticities; however, they appeared to have larger impact on the elasticity of $\hat{p}_4$ to all parameters (Table 1).

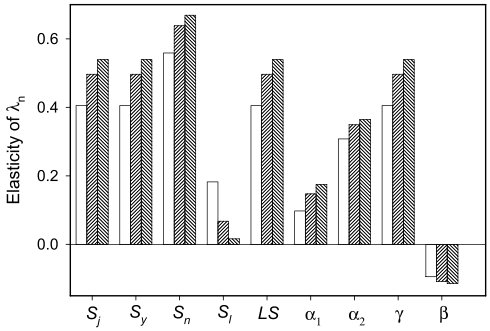

Fig. 4. Elasticity (proportional sensitivity) of frequency-dependent population growth rate (λ_n) to changes in demographic and disease parameters for the nine-banded armadillo population at the Yazoo National Wildlife Refuge, Mississippi, USA. Elasticities were calculated for three values of γ (the probability of survival from birth until trappable age), γ = 0.5 (left-most bar); γ = 0.8 (middle bar), and γ = 1.0 (right most bar). Parameters are defined in Table 1.

The population growth rate at the equilibrium proportional stage distribution was 0.824, 0.938, and 1.003 for γ = 0.5, 0.8 and 1.0, respectively. Elasticity analysis of the growth rate of the frequency-dependent model (Caswell 2008) revealed that the elasticity pattern (Fig. 4) was almost identical to that obtained from the linear model (Fig. 2b), except that the disease transmission param-

Table 1
Elasticity (proportional sensitivity) of equilibrium proportional stage distribution $(\hat{\boldsymbol{p}})$ to changes in demographic and disease parameters for the nine-banded armadillo population at the Yazoo National Wildlife Refuge, Mississippi, USA. Elasticities were calculated for three values of γ (the probability of survival from birth until trappable age). Parameters are: S_y, S_n, S_l = survival of yearling, non-leprous adults, and leprous adults, respectively; LS = litter size; α_1, α_2 = probability of reproduction for primiparous and multiparous females; and β = frequency-dependent leprosy transmission parameter.

		Elasticity of:			
	Parameter	$\hat{p}_1$	$\hat{p}_2$	$\hat{p}_3$	$\hat{p}_4$
a) γ = 0.5	S_j	−0.174	0.565	0.364	−0.870
	S_y	0.042	−0.219	0.579	−0.655
	S_n	0.100	−0.260	−0.033	0.161
	S_l	0.033	−0.085	−0.910	1.364
	LS	0.454	0.193	−0.008	−1.242
	α_1	0.109	0.046	−0.002	−0.299
	α_2	0.345	0.147	−0.006	−0.943
	γ	0.454	0.193	−0.008	−1.242
	β	−0.017	0.044	−0.739	1.058
a) γ = 0.8	S_j	−0.175	0.533	0.309	−1.414
	S_y	0.055	−0.237	0.539	−1.184
	S_n	0.108	−0.268	−0.110	0.471
	S_l	0.011	−0.028	−0.738	2.127
	LS	0.374	0.082	−0.143	−1.865
	α_1	0.111	0.024	−0.042	−0.553
	α_2	0.263	0.057	−0.100	−1.312
	γ	0.374	0.082	−0.143	−1.865
	β	−0.018	0.046	−0.732	2.067
a) γ = 1.0	S_j	−0.172	0.522	0.288	−2.010
	S_y	0.061	−0.245	0.521	−1.777
	S_n	0.109	−0.270	−0.143	0.826
	S_l	0.003	−0.007	−0.666	2.961
	LS	0.339	0.033	−0.201	−2.499
	α_1	0.110	0.011	−0.065	−0.811
	α_2	0.229	0.022	−0.136	−1.688
	γ	0.339	0.033	−0.201	−2.499
	β	−0.019	0.046	−0.730	3.208

eter ψ (which was assumed to be constant in the linear model) is replaced with the mixing parameter β.

With the empirically estimated parameters and using β = 1.079, we find that R_0 = 1.36. Elasticity of R_0 to S_n and β was 1, whereas the elasticity of R_0 to S_l was 0.97.

4. Discussion

Until recently, there were few reports of leprosy in armadillos outside of Texas and Louisiana (Loughry and McDonough, 2013; Loughry et al., 2009; Perez-Heydrich et al., 2016). However, a recent study has shown that the disease has spread throughout the southeastern USA (including Alabama, Georgia and Florida), with ∼16% of armadillos being infected in sampled locations (Sharma et al., 2015). Concomitant with ongoing armadillo range expansion and spread of leprosy within armadillo populations, the number of leprosy cases in humans may also be increasing (Sharma et al., 2015), as evidenced by new cases of leprosy with possible links to leprous armadillos reported from Florida (http://www.who.int/mediacentre/factsheets/fs101/en/;http://www.techtimes.com/articles/36252/20150228/leprosy-cases-confirmed-in-florida-are-armadillos-to-blame.htm) and Georgia (Lane et al., 2006). In fact, three cases of human leprosy were reported from areas in Mississippi near our Yazoo study population (Abide et al., 2008). About 200 new cases of leprosy are reported in the United States annually, many of which are within the geographic range of armadillos (Wheat et al., 2014). Thus, understanding demographic effects of leprosy and dynamics of the disease within armadillo populations is important from ecological as well as public health perspectives.

Contrary to our expectation, there was no evidence that leprosy reduced the probability of reproduction in adult females, suggesting that the physiological costs associated with *M. leprae* infection do not negatively impact reproductive success. We note, however, that association between serological status and lactation status is confounded by age because older females are more likely to acquire *M. leprae* infection, and they are also more likely to reproduce (Loughry et al., 2013a; Perez-Heydrich et al., 2016; Williams and Loughry, 2012).

The absence of observed seroconversion in juveniles and yearlings suggests that vertical transmission of leprosy does not occur (Morgan and Loughry, 2009). Even among adults, a detectable immune response against *M. leprae* is more likely among older animals, probably because leprosy is a slow-acting disease with a long incubation period (Williams and Loughry, 2012). Based on experimental transmission studies, a detectable immune response can take between 10 and 12 months to develop (Duthie et al., 2011). Consequently, the ELISA used to define *M. leprae* infection in this study would not have detected exposure at the early stages of infection. Although the diagnostic tool used in this study had low sensitivity for early detection, none of the surviving yearlings acquired infection the following year. Only adult armadillos (≥2 years of age) had a non-zero probability of becoming exposed to *M. leprae*. In our study population, a disease-free adult armadillo had 18% probability of seroconverting. Our result that there is no possibility of recovery from leprosy is consistent with laboratory studies showing that armadillos do not recover from leprosy infection (Truman, 2005). Thus, although it may take years, infection ultimately leads to disease and eventual mortality as more and more of the body's systems become compromised. With this study we addressed how such disease-induced mortality affected the long-term growth rate of an exposed armadillo population.

Given the features of the disease, the conventional wisdom for years has been that leprosy must lead to negative impacts on both individuals and populations of armadillos. However, data showing population level effects have heretofore been lacking. In our study population leprosy reduced survival of adult armadillos by 14.5%, suggesting that leprosy-induced mortality is most likely additive to natural mortality. Not surprisingly, the disease reduced growth rate of the armadillo population by ∼0.13, showing a rather substantial population-level effect. The finite population growth rate λ was <1. This was most likely a consequence of the fact that we estimated survival using the multi-state CMR method. Using this method, it is not possible to distinguish between death and dispersal, which leads to underestimation of survival as well as population growth rate. This issue, however, is unlikely to have influenced our results because survival of both leprous and non-leprous adults was estimated using the same method. Elasticity analyses revealed that λ was proportionately most sensitive to changes in survival of non-leprous adults across all values of γ, suggesting the importance of the survival of healthy adults to armadillo population dynamics. The negative elasticity of λ to the disease transmission probability was as expected because leprosy infection reduces survival, and an increase in the infection rate will lower population growth rate (Fig. 2b).

Because there is no possibility of recovery from the disease, dynamics of *M. leprae* in host populations is determined solely by the transmission process. Unfortunately, we know little about factors and processes that drive infection in armadillo populations. A recent analysis failed to find spatial structure in the distribution of leprous armadillos in our study population (Perez-Heydrich et al., 2016). *M. leprae* is an intracellular obligate pathogen, and is thought to be viable only for a short period of time once released to the environment. However, a recent study showed that the bacillus can remain viable for ≤8 months within amoebic cysts (Wheat et al., 2014). Thus, a leprous armadillo can potentially infect other

armadillos or humans long after its death. These findings have been offered as an explanation for the fact that leprosy cases in humans have not substantially decreased despite the success of multi-drug therapy to cure leprosy (Wheat et al., 2014).

Under the assumption of frequency-dependent leprosy transmission, the armadillo population quickly converged to a stable stage distribution, with juveniles and non-leprous adults dominating the population. The proportion of juveniles at equilibrium increased from 36.2% for $\gamma = 0.5$ to 48.9% for $\gamma = 1.0$, with a corresponding decline in the proportion of leprous adults from 16.8% to 5.1%. An increase in γ would mean that a greater proportion of newborns survive to trappable age, thereby increasing the proportion of juveniles in the population, with a corresponding decline in the proportion of other age classes.

Elasticity analysis of the frequency-dependent model revealed that the proportion of adults that are leprous ($\hat{p}_4$) at equilibrium was negatively influenced by all reproductive parameters and early survival, and positively influenced by the mixing parameter (β) and survival of leprous and non-leprous adults. These results make intuitive sense because an increase in reproductive output and early survival would necessarily cause an increase in the proportion of younger animals, with a corresponding decline in the proportion of older ones. Furthermore, an increase in the survival of leprous animals would increase the number of new infections they could cause, and at an increasingly higher rate as the value of β increases. Values of γ changed the elasticities to various extents (with elasticity of $\hat{p}_4$ being the most strongly affected); however, they did not change the relative magnitude of elasticities. It would be instructive to test the generality of these patterns; unfortunately, however, we are not aware of other data-based studies that have performed sensitivity analysis of stage-structured epidemic models with frequency dependent disease transmission (but see Klepac and Caswell, 2011 for theoretical explorations).

Attempts have been made to model leprosy dynamics in both humans (Chiyaka et al., 2013) and armadillos (Scholl et al., 1995) but these were primarily theoretical analyses of hypothetical scenarios. R_0 estimated using the frequency-dependent model was 1.36, suggesting 36% increase in adult seroprevalence per leprosy generation time. If one assumes a leprosy generation time of 3–5 years, leprosy can be expected to spread within our study population by ca. 7%-12% annually. Substantial variation in individual-level immune responses to *M. leprae* has been noted in previous experimental transmission studies involving armadillos, with up to 20% of animals resisting challenge to experimental infection (see review in Truman et al., 2013). Hypothetically, based on our estimate of R_0, at least 56% ($1 - 1/R_0 = 1 - 1/1.36 = 0.56$) of armadillos would have to be immune to prevent leprosy from spreading. Our study is the first to provide data-based estimates of infection rate and the net reproductive number R_0 of leprosy for any population (human or armadillo).

Unfortunately, there are no other estimates of R_0 for leprosy in armadillos or in humans so we cannot compare our results with other published reports. For comparative purposes we calculated this quantity using an alternative approach. Anderson and May (1991) suggested that R_0 can be approximated as $R'_0 \approx L/A$, where L is life expectancy and A is the average age at infection. Based on our data, armadillos do not seroconvert until two (and possibly three) years of age, and that older armadillos have a higher probability of being infected. We have shown that, once infected, leprous adults are expected to survive 1.97 additional years; the life expectancy at birth of armadillos that survive long enough to acquire infection (L) is then the sum of the average age at infection and life expectancy of leprous armadillos. Because exact average age at infection is unknown, we calculated approximate R'_0 for a range of values of A (Fig. 5), assuming $L = A + 1.97$ years. The results showed that our estimate of R_0 was consistent with values of R'_0 for average age at infection of 5–6 years. Thus, Anderson-May approximation of the net reproductive number is consistent with our conclusion that leprosy is spreading in our study population.

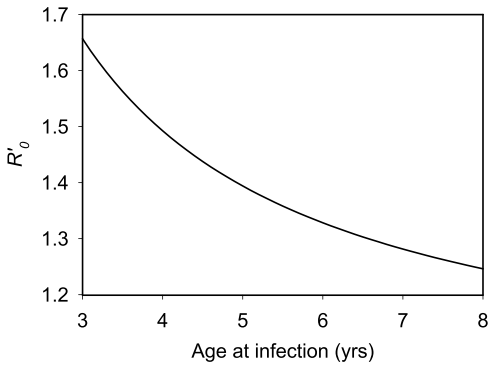

Fig. 5. Approximate basic reproductive number (R'_0) as a function of average age at infection (A), calculated as: $R'_0 \approx L/A$ (Anderson and May, 1991), where $L = A + 1.97$ is the armadillo life expectancy.

The analytical result for R_0 and elasticity of R_0 to model parameters suggest that the ability of leprosy infection to spread is positively related to the mixing parameter β and the survival probability S_n of the susceptible adult stage, and inversely related to the mean lifetime of an infected individual, which is given by $(1 - S_l)^{-1}$. A proportional change in S_l will have a greater effect on R_0 than the same change in S_n whenever $S_l > 0.5$. In our case, these effects were almost equal, albeit S_n and β were marginally more influential. *M. leprae* infections have long incubation periods, and chronically infected hosts do not recover from infection. Thus, the ability of infected hosts to transmit the disease seems to be limited by the availability of susceptible hosts.

Historically, diseases have been a powerful force in driving wildlife population dynamics and persistence (Cleaveland et al., 2001; de Castro and Bolker, 2005; Gulland, 1995). Recent reports include facial tumors that threaten the persistence of Tasmanian devils (*Sacrophilus harrissi*) (McCallum, 2008; McCallum et al., 2009), chytrid fungus as a major threat to amphibian populations (Pounds et al., 2006), and white-nose syndrome as a cause of large-scale population collapse of North American bats. These high-profile examples highlight that diseases will remain an important conservation challenge (Frick et al., 2010; Langwig et al., 2012). Additionally, because many wildlife species serve as primary, secondary or intermediate hosts for a number of zoonotic diseases, an ever-shrinking wildlife-domestic livestock-human interface will continue to pose important ecological, economic and public health challenges (e.g., Hilbert et al., 2012; Jones et al., 1998; Miller et al., 2013; Ostfeld and Brunner, 2015). In the United States, nine-banded armadillos are well-adapted to the rapidly urbanizing landscape, and their geographic range continues to expand northward (Loughry and McDonough, 2013; Loughry et al., 2013b). It is therefore possible that both the frequency and geographic distribution of zoonotic transmission of leprosy can potentially increase. Consistent with this view, until very recently armadillos in Alabama, Georgia and Florida were thought to be free of leprosy infection (Loughry and McDonough, 2013), and there had been no known cases of armadillo to human transmission of the disease there. However, leprosy in armadillos as well as zoonotic infection have been increasing drastically in the south-central and south-eastern United States (Abide et al., 2008; Lane et al., 2006; Perez-Heydrich et al., 2016; Sharma et al., 2015; Truman et al., 2011), and possibly elsewhere within the armadillo's distributional range. Thus, understanding leprosy dynamics within armadillo populations is important from ecological as well as public health perspectives as the wildlife-human interface shrinks and the geo-

graphic range of armadillos continues to expand (Loughry et al., 2013b; Loughry and McDonough, 2013b). Our study provides the first data-based estimate of leprosy R_0 and empirical assessment of disease impact on host population dynamics. Additional long-term studies of leprosy dynamics elsewhere within the nine-banded armadillo's distributional range will be important in assessing the generality of our findings.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ecolmodel.2017.02.001.

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