Spora: A Journal of Biomathematics

Volume 6 Article 7

2020

Impulse Vaccination Model for the Control of Devil Facial Tumor Disease

Zachary Bobbitt
University of North Carolina Asheville, zbobbitt@unca.edu

Timothy Comar
Benedictine University, tcomar@ben.edu

Megan O. Powell
University of North Carolina at Asheville, mpowell4@unca.edu

Catherine Roberts
University of North Carolina Asheville, crobert9@unca.edu

Nicholas Schneider
University of North Carolina Asheville, nschneid@unca.edu

See next page for additional authors

Impulse Vaccination Model for the Control of Devil Facial Tumor Disease

Cover Page Footnote

We acknowledge the support of the Intercollegiate Biomathematics Alliance in the creation of this manuscript.

Authors

Zachary Bobbitt, Timothy Comar, Megan O. Powell, Catherine Roberts, Nicholas Schneider, and Teagen Smith

Intercollegiate Biomathematics Alliance

SPORA
A Journal of Biomathematics

ISSN 2473-3067 (Print)
ISSN 2473-5493 (Online)

Impulse Vaccination Model for the Control of Devil Facial Tumor Disease

Zachary Bobbitt[1], Timothy Comar[2], Megan O. Powell[1,*], Catherine Roberts[1], Nicholas Schneider[1], Teagen Smith[3]

*Correspondence:
Dr. Megan Powell,
Mathematics Department,
University of North Carolina Asheville, 1 University Heights, Asheville, NC 28804, USA
mpowell4@unca.edu

Abstract

Devil facial tumor disease (DFTD) is a cancer that affects Tasmanian devils and that has caused the devil population to grossly decline since 1996. We present an SEIVR model to explore if recent advances in DFTD vaccines can help the wild population recover. Considering both and bi-annual impulse of vaccinating wild devils through food drops and introducing vaccinated captive-bred devils into the population, we explore the vaccine efficacy, percent of healthy devils receiving the vaccine, and years of campaign necessary for the devil population to have a long-term recovery. Based on our initial parameter estimations, we find a stable population can be reached after 8 years of bi-annual bait drop vaccine campaigns and introduction of 2 captive-bred vaccinated devils into the wild population. Additionally, we find a 14% maximum vaccine failure rate and 60% minimum vaccine bait ingestion by wild devils is necessary for a successful 10-year campaign.

Keywords: Tasmanian devil, devil facial tumor disease, wildlife vaccine, oral bait vaccine, impulse vaccination

1 Introduction

The Tasmanian devil (*Sarcophilus harrisii*) is the largest carnivorous marsupial in the world. Originally driven to extinction by dingoes on the Australian mainland, devils currently live exclusively on the island of Tasmania just south of Australia [11]. Today the Tasmanian devil is officially endangered due to the outbreak of Devil Facial Tumor Disease (DFTD). DFTD was first discovered in 1996 in the north-east region of Tasmania. It is a transmissible cancer transferred via bite. It causes large tumors around the face that eventually lead to death by inability to feed or by metastasising to vital organs. The cancer has a nearly 100% mortality rate [12]. Since its initial discovery, DFTD has destroyed roughly 90% of the devil population leaving only a small unaffected population remaining in the south-eastern corner of the island [14]. Though it is debated whether this disease could lead to complete extinction of the population, it is likely that this infection will persist until human intervention or the devil's total extinction [2]. In this paper we discuss current and potential efforts to conserve the devil population including potential vaccine use in captive or wild populations. We provide an analysis of an impulsive differential equation model that could be used for an oral bait-drop vaccine strategy combined with the release of captive-bred vaccinated devils into the wild.

2 Current Conservation Efforts

In response to the decreasing devil population, Tasmania has employed multiple strategies to combat the rapid spread of the disease. Researchers have created an insurance population on Maria Island, a previously devil-free island off the eastern shore of Tasmania, that serves to maintain a healthy population of devils unaffected by DFTD. In 2012, the Save the Tasmanian Devil Program (STDP) introduced 15 captive-bred devils onto the island [25]. They introduced 13 more in 2013 and then 6 more in 2017, for a total of 34 captive-bred released devils on Maria Island [21]. Their aim was to cultivate a healthy population that required minimal post-release management and to see if their offspring would be a good source of devils to reintroduce to Tasmania [25], to increase both the population numbers and genetic diversity of individuals. Maria Island devils can also be used to re-populate the mainland should DFTD lead to extinction. Maria Island was chosen both due to lack of exposure to DFTD and decreased chance of vehicular strike. On mainland Tasmania, after DFTD, vehicle strike is the largest threat to the devil population [22].

[1]Mathemaics Department, University of North Carolina Asheville, Asheville, NC, [2]Mathematics Department, Benedictine University, Lisle, IL, [3]Department of Mathematics, Illinois State University, Normal, IL

The results of this program have been fruitful. As of the beginning of 2018, the population had grown to about 103 devils, after 5 years and 5 breeding seasons [25]. The devils were born and raised in captivity, either in free range enclosures (FRE) or intensively managed captive (IC) facilities. The results of the experiment showed that where the devils were raised did not affect their survival post-release; thus, in the future, the most cost-effective facilities can be used. After 12 months of care, the devils were released onto Maria Island with GPS collars to track their progress [18]. To increase the effectiveness of these strategies and general understanding of the disease, the devils are also being annually monitored.

In addition to the Maria Island release, devils are being bred in facilities throughout the world, although many captive devils may not be suitable for eventual release due to a lack of natural instincts such as they are not naturally fearful of humans. In the next section, we discuss vaccine development and possible vaccination strategies that may be implemented once a viable vaccine is fully developed to complement the breeding and release programs currently in place.

3 Vaccine Development and Strategies

If a complete vaccine to DFTD is to be developed, researchers must first have a better understating of a few traits of DFTD and why devils are unable to recover from it. Recently, there have been a few cases of devils displaying natural tumor regression, with a few even having the tumors disappear completely and the devils recovering from DFTD [10, 16], but the vast majority of devils never recover and eventually die from it or starvation because of devils inhibiting food intake. We include a recovered class in our model for demonstrative purposes should there be additional research on DFTD recovery in the future, but due to the limited number of studies showing devil recovery through natural means or immunotherapy intervention, we set the parameters dictating recovery of devils from DFTD to zero.

3.1 Current State of Vaccine Development

A full understanding the cellular origins of the tumor cells in order to identify tumor-cell specific and tumor-cell associated antigens is imperative to finding a successful vaccine for both DFTD and DFT2 (a mutated form of DFTD). It is currently known that DFTD emerged from a devil Schwann cell, but research into such cells is currently scarce [26]. There is also insufficient understanding of the devils histocompatibility complex (MHC) molecules that could be inhibiting the path to a vaccine. Due to the downregulating MHC expression by DFTD, where MHC would typically prevent cancer cells, they are not in devils who are exposed to DFTD [15].

Despite an incomplete understanding of the origins of DFTD, research into immunotherapy is promising. Immunotherapy for Tasmanian devils typically consists of a series of vaccinations starting with the original vaccination and followed by boosters in regular intervals [24]. Generally the vaccines that are being developed for Tasmanian devils include killed DFTD cells as well as the adjuvant IFN-γ although those doing research for the immunotherapy of Tasmanian devils are still testing different methods to find one that works best. In a study of 9 healthy devils conducted over the course of five years, seven of these devils were immunized using varying techniques and all were then exposed to DFTD cells. If cancer cells developed the devils would then undergo immunotherapy. Anti-body production and tumor regression did occur for 3 devils showing such a method is viable for injection based vaccines [24]. Additional research is needed to develop a vaccine suitable to the multiple strategies discussed next, but there is promise that this is possible.

3.2 Captive Breeding Vaccination

A captive breeding and vaccination program (CBV) would involve raising devils in either FRE or IC facilities, releasing them onto Maria Island (or other similar controlled areas), vaccinating their offspring, releasing them onto mainland Tasmania, and monitoring them post-release (a program similar to what is currently in operation). The purpose of such a strategy is to increase the number of healthy animals in the population. This new class of vaccinated devils is less likely to receive or spread the disease [17].

There have been programs that have utilized CBV in the past that were not effective and have had logistical difficulties—such as the behavioral problems that occurred with the reintroduction of the captive-bred swift fox in the late '90s [3]. The successful Maria Island experiment, however, has proven that Tasmanian devils cope well with captive-breeding management. STDP routinely trapped the devils on Maria Island to check on their welfare, collected samples of their stool to observe their diet, and set up feeding stations with cameras [18]. Over their study period, they observed that the devils increased their body mass [18], a measure of how well they were doing over time. They were breeding at the usual times of the year and at the appropriate rate. This study demonstrated that it is possible for a successful vaccinated, captive-bred devil release onto Tasmania.

3.3 Oral Vaccination and Trap, Vaccinate, Release

Oral vaccination (OV) programs originated in Switzerland in 1978 to eliminate fox rabies, and was soon adopted by most European countries. Oral vaccination (OV) programs use aerial or ground distribution of orally ingestable vaccines. Most OV programs were typically able to bring the infected fox population to below 10 percent within ten years [8]. Since its conception, OV has been used in many other instances of a rabid population spread out over a wide area. In the spread of raccoon rabies in Ohio, this method of ground and aerial distribution was used with a mean cost of \$153/km^2 per trial [7]. An alternative to manual dispersion of such baits is automated bait dispensers that would also allow for collection of data via remote cameras [6].

An alternative method to OV is trap, vaccinate, release (TVR) programs which consist of capturing susceptible animals via baited traps, administering vaccine, and releasing them back into the wild. As this method requires dispersing and maintaining traps, it is labor intensive, expensive, and mostly employed in small pockets of infected populations in urban environments. TVR was used in the late 1980s to early 1990s to control fox, raccoon, and skunk rabies in Ontario, Canada with an average cost of \$548/km^2 [23] making them much more costly than the alternative OV method.

3.4 Strategies Modeled

We choose to model a vaccination strategy that includes both an OV and CBV consistent with the Maria Island project [21] and suggestions by Flies et al. [6]. We choose an OV strategy due to its economic viability over TVR and common use in rural areas. As a captive breeding infrastructure is already in place on Maria Island, we are assuming it could be modified to include a vaccine; thus, we also include a CBV strategy where small number of devils are released into the wild at regular intervals.

4 Model of Vaccination Strategies

We develop a Susceptible-Exposed-Infected-Vaccinated-Recovered model to determine the potential effectiveness of OV and CBV strategies in eradicating DFTD or protecting the uninfected population. Devils enter and exit age and disease classes through birth, death, age, disease transmission, or vaccine failure. We denote age classes by $i = 0, 1, 2, 3, 4$, where $i = 0$ represents devils less than 1 year old, $i = 1, 2, 3$ represents devils between i years old and $i + 1$ years old, and $i = 4$ represents devils that are at least four years old. The disease states in our model are Susceptible, S; Exposed, E; Infected, I; captive-bred Vaccinated, V; Wild vaccinated, W; and Recovered, R.

Pre-DFTD, the average lifespan of devils was six, but in recent years devils over the age of three have not been found in the wild [9, 12]. Therefore, it is unlikely for devils to naturally age up into the S_4 class; however, we allow for vaccinated devils in the V_4 and W_4 classes to reenter the Susceptible class S_4. We let $N_m = S_m + E_m + I_m + V_m + W_m + R_m$, $P = \sum_{m=1}^{4} N_m$ and $I = \sum_{n=1}^{4} I_i$.

4.1 Continuous Population Equations Description

As there is no evidence that DFTD transmits vertically [19], each devil is born into the Susceptible class, S_0. Devil births are modeled using a logistic-type birth rate of

$$\left(\sum_{i=1}^{4} \alpha_i N_i\right)\left(1 - \frac{P}{K}\right),$$

where α_i is the reproductive rate of devils in age class i and K is the carrying capacity. Because devils under the age of one year have minimal contact with other devils, our model assume that devils leave the S_0 class by natural death, $d_0 S_0$ or by aging out, S_0. Hence the dynamics of S_0 is given by

$$\frac{dS_0}{dt} = \left(\sum_{i=1}^{4} \alpha_i N_i\right)\left(1 - \frac{P}{K}\right) - d_0 S_0 - S_0.$$

For each Susceptible class, S_i, $i = 1, 2, 3$, devils enter from the the Susceptible class S_{i-1} by aging up. Devils in the S_i class become exposed (and enter the class E_i) at rate of $kS_i\frac{I}{P}$ for $i - 2, 3$ or $b_1 kS_1\frac{I}{P}$, where k is the transmission rate and b_1 is a reduction in the transmission rate seen in 1-year-olds. We use a frequency-dependent transmission rate following the model in [1]. Devils also can leave S_i by natural death, $d_i S_i$, or, if $i = 1, 2$, by aging up. The model equations for the other susceptible classes are hence given by

$$\begin{aligned}
\frac{dS_1}{dt} &= S_0 - b_1 kS_1\frac{I}{P} - d_1 S_1 - S_1\\
\frac{dS_2}{dt} &= S_1 - kS_2\frac{I}{P} - d_2 S_2 - S_2\\
\frac{dS_3}{dt} &= S_2 - kS_3\frac{I}{P} - d_3 S_3 - S_3\\
\frac{dS_4}{dt} &= S_4 - kS_4\frac{I}{P} - d_4 S_4.
\end{aligned}$$

Devils enter the Exposed class E_j, $j = 1, 2, 3, 4$, from of the corresponding Susceptible class, S_j, (only for $j = 1, 2$, 3), captive-bred Vaccinated, V_j, or Wild vaccinated, W_j classes. The vaccine failure rates are σ_{1j} for V_j and σ_{2j} for W_j. Devils leave the E_j class by showing symptoms

after a latency period of $1/L$ or by natural death $d_j E_j$. As Exposed devils show tumors within one year, they do not age up into the subsequent Exposed class. We also represent the possibility of devils naturally recovering from the disease by η_{E_j}, even though this is currently extremely uncommon. It is possible that devils will further adapt to the disease in the future, and we want to be able to represent recovery in future work. Currently, we set $\eta_{E_j} = 0$. The Exposed model equations are

$$\begin{aligned}
\frac{dE_1}{dt} &= b_1 k \left(S_1 + \sigma_{11} V_1 + \sigma_{21} W_1\right) \frac{I}{P} \\
&\quad - \left(\frac{1}{L} + \eta_{E_1} + d_1\right) E_1 \\
\frac{dE_2}{dt} &= k \left(S_2 + \sigma_{12} V_2 + \sigma_{22} W_2\right) \frac{I}{P} \\
&\quad - \left(\frac{1}{L} + \eta_{E_2} + d_2\right) E_2 \\
\frac{dE_3}{dt} &= k \left(S_3 + \sigma_{13} V_3 + \sigma_{23} W_3\right) \frac{I}{P} \\
&\quad - \left(\frac{1}{L} + \eta_{E_3} + d_3\right) E_3 \\
\frac{dE_4}{dt} &= k \left(S_4 + \sigma_{14} V_4 + \sigma_{24} W_4\right) \frac{I}{P} \\
&\quad - \left(\frac{1}{L} + \eta_{E_4} + d_4\right) E_4.
\end{aligned}$$

Devils join the Infected class, I_j, $j = 1, 2, 3, 4$ from the Exposed class E_j after symptoms begin to show after the latency period. They exit the infected class by death at a rate of $d_I I_i$ or by natural recovery, η_{I_j}. The parameter d_I encompasses both death due to DFTD and natural death. As above $\eta_{I_j} = 0$ for this current study. Infected devils generally die within 1 year and therefore do not age up into a subsequent Infected class. The Infected model equations are

$$\begin{aligned}
\frac{dI_1}{dt} &= \frac{1}{L} E_1 - \eta_{I_1} I_1 - d_I I_1 \\
\frac{dI_2}{dt} &= \frac{1}{L} E_2 - \eta_{I_2} I_2 - d_I I_2 \\
\frac{dI_3}{dt} &= \frac{1}{L} E_3 - \eta_{I_3} I_3 - d_I I_3 \\
\frac{dI_4}{dt} &= \frac{1}{L} E_4 - \eta_{I_4} I_4 - d_I I_4.
\end{aligned}$$

Devils enter the captive-bred Vaccinated, V_j and Wild vaccinated, W_j, $j = 1, 2, 3, 4$, classes by impulsive events described below or by aging up from a previous age class. Devils leave the V_j and W_j classes by natural death at the rate d_j, by infection due to vaccine failure, or, if $j = 1, 2, 3$, by aging up. The continuous model equations for the vaccinated classes are given by

$$\begin{aligned}
\frac{dV_1}{dt} &= -b_1 k \sigma_{11} V_1 \frac{I}{P} - d_1 V_1 - V_1 \\
\frac{dV_2}{dt} &= V_1 - k \sigma_{12} V_2 \frac{I}{P} - d_2 V_2 - V_2 \\
\frac{dV_3}{dt} &= V_2 - k \sigma_{13} V_3 \frac{I}{P} - d_3 V_3 - V_3 \\
\frac{dV_4}{dt} &= V_3 - k \sigma_{14} V_4 \frac{I}{P} - d_4 V_4 \\
\frac{dW_1}{dt} &= -b_1 k \sigma_{21} W_1 \frac{I}{P} - d_1 W_1 - W_1 \\
\frac{dW_2}{dt} &= W_1 - k \sigma_{22} W_2 \frac{I}{P} - d_2 W_2 - W_2 \\
\frac{dW_3}{dt} &= W_2 - k \sigma_{23} W_3 \frac{I}{P} - d_3 W_3 - W_3 \\
\frac{dW_4}{dt} &= W_3 - k \sigma_{24} W_4 \frac{I}{P} - d_4 W_4.
\end{aligned}$$

Finally devils can enter the Recovered class by natural recovery from either the Exposed or Infected class at rates of η_{Ej} and η_{Ij}, respectively, and leave the Recovered class by natural death d_j or, if $j = 1, 2, 3$, by aging up. The Recovered model equations are

$$\begin{aligned}
\frac{dR_1}{dt} &= \eta_{E_1} E_1 + \eta_{I_1} I_1 - d_1 R_1 - R_1 \\
\frac{dR_2}{dt} &= R_1 + \eta_{E_2} E_2 + \eta_{I_2} I_2 - d_2 R_2 - R_2 \\
\frac{dR_3}{dt} &= R_2 + \eta_{E_3} E_3 + \eta_{I_3} I_3 - d_3 R_3 - R_3 \\
\frac{dR_4}{dt} &= R_3 + \eta_{E_4} E_4 + \eta_{I_4} I_4 - d_4 R_4.
\end{aligned}$$

Note that the domain for all of the continuous model equations above is $\{\, t \mid t \neq nT,\, n \in \mathbb{Z}_+,\, T = 1/2 \,\}$.

4.2 Impulse Equations Description

The impulse equations model the increase in captive-bred Vaccinated, V_j and Wild vaccinated W_j devils by the periodic release of captive-bred vaccinated devils and by oral vaccination through food bait drops. For our model, we assume these impulsive events occur on a biannual bases, which is the most common strategy employed in rabies vaccine distribution strategies [8]. We denote the new susceptible population of age class i after the impulsive event as $S_i(t^+)$ and similarly for all other classes. We note that devils in the S_0 class would not leave the den and eat the vaccinated bait and while captive-bred Vaccinated devils, V, and Wild vaccinated devils, W, are represented up to age 4 and up in the continuous equations, devils enter the 4 and up age group only by aging up, not by an impulsive event, therefore $i = 1, 2, 3$ in the impulsive equations.

After each bait drop, the susceptible population will lose a certain percentage of its population to the corresponding W class, due to susceptible devils eating the bait drop vaccine. We denote the fraction of devils who eat the vaccine and become immunized as p_{S_i}; thus, $1-p_{S_i}$ is the fraction of devils who remain susceptible and $p_{S_i}S_i(t)$ is the amount by which the W class increases by each impulse. We assume a fixed number, β_2, of two-year old captive-bred Vaccinated devils is added to the population during each impulsive event. For this study, we set $\beta_2 = 2$. As we are only adding two-year old captive bred Vaccinated devils, we only provide an impulsive equation for the V_2 class.

While we currently assume eating the bait dropped vaccine has no effect on exposed or infected devils, we show a potential way to represent the recovery of wild devils through immunotherapy delivered through bait drops, should this become feasible. We consider exposed and infected devils who both eat the vaccine and recover in proportions $p_{E_i}r_{E_i}$ and $p_{I_i}r_{I_i}$ to then enter the recovered class R_i. The impulsive equations are given by

$$\begin{aligned}
S_i(nT^+) &= S_i(nT)(1-p_{S_i})\\
W_i(nT^+) &= W_i(nT) + p_{S_i}S_i(nT)\\
V_2(nT^+) &= V_2(nT) + \beta_2\\
E_i(nT^+) &= E_i(nT)(1-p_{E_i}r_{E_i})\\
I_i(nT^+) &= I_i(nT)(1-p_{I_i}r_{I_i})\\
R_i(nT^+) &= R_i(nT) + p_{E_i}r_{E_i} + p_{I_i}r_{I_i},
\end{aligned}$$

for $i = 1, 2, 3$, and $n \in \mathbb{Z}_+$, $T = 1/2$.

5 Parameter Values

Birth(α_i), death (d_I), carrying capacity (K), transmission rates (b_ik) and latency period (L) for the different age groups are based on a previous study with a similar age-based model for Tasmanian devils [4]. Information on vaccine failure rates for a potential DFTD vaccine is unavailable at this time so we base vaccine failure rates (σ_{1i} and σ_{2i}) on a study of rabies vaccination failure in dogs based on age, converted to approximately correspond to devil age classes 1,2,3 and over 4 [13]. We note that younger devils are assumed to have a lower vaccine failure rate than the older devils. We do not have evidence that vaccine failure rates between vaccines administered to captive-bred devils before release, presumably through injection similar to the dog rabies vaccines study [13], would be different than vaccines administered to wild devils through bait drops, therefore we assume the failure rates are the same for both the V and W corresponding age classes. We assume no natural or immunotherapy recovery of Exposed and Infected devils, thus η, r_{E_i}, and r_{I_i} are all set to zero. With the nature of competition for food in devil social structures, it is hard to estimate what proportion of Susceptible devils would consume the vaccine in a single bait drop, we initially estimate p_{S_i} to be 0.80 across all age classes [20] but consider other values in our analysis. We assume captive-bred vaccinated devils are introduced at age two.

6 Results

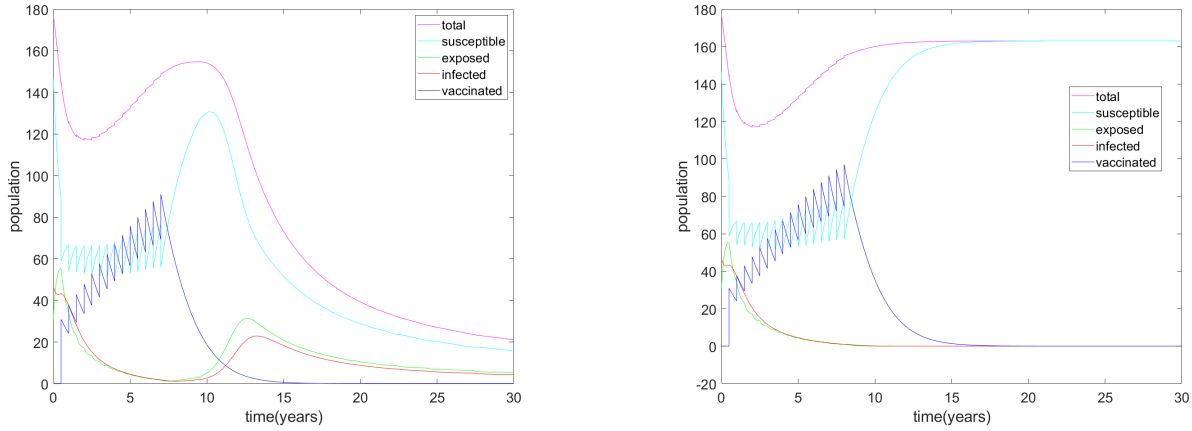
We analyze the model using two impulses a year to determine how long an impulse campaign would need to last in order to be successful, with success determined by a continued increase in devil population after the campaign ends. We consider how results are affected by a variation in the proportion of Susceptible devils who eat the vaccine, p_{s_i}, the vaccine failure rate of wild devils, σ_2, and the number of captive-bred vaccinated devils added to the population, β, and the number of years of impulse campaigns.

Firstly, we determine the number of years of impulse campaigns needed for the population to continue growing after the campaign ends. With the variable vaccine failure rates listed in Table 1, two devils added to the population annually ($\beta = 2$) and the proportion of Susceptible devils eating the vaccine (p_{S_i}) of 0.80 across all age groups, if the campaigns are conducted bi-annually for 7 years, the population will die off after the impulses end (Figure 1a), but if they are continued for at least 8 years, then the population will recover after the vaccination campaign has ended (Figure 1b). Based on the comprehensive overview of OV trials performed in Europe against rabies [8], we consider a 10 year campaign of bi-annual vaccine bait drops to have a sufficient factor of safety for use in our analysis of σ_2 and p_{s_i}.

Next, we consider what proportion of the Susceptible devil population would have to successfully eat the vaccine (p_{S_i}) and enter the corresponding Wild Vaccinated class (W_i). Since devils can be very competitive during feeding, we wanted to find the lowest proportion that would need exposure to the vaccine in order for a 10-year campaign to be successful. We find that if $p_{s_i} = 0.6$, the population quickly decreases again after the trials end (Figure 2a), but if we increase p_{s_i} to 0.7, the population is able to recover (Figure 2b). This suggests a minimum proportion of devils consuming the vaccine in each drop is 0.7, thus, any p_{s_i} with value greater or equal to 0.7 will achieve a stable population after the impulse campaigns end. In a fox rabies control program in Britain, it was found that in rural areas pick-up rates fell around 80% [20], suggesting that this minimum for p_{s_i} is achievable. For our remaining models we will be assuming an 80% pick up rate per trial. It is possible the proportion of

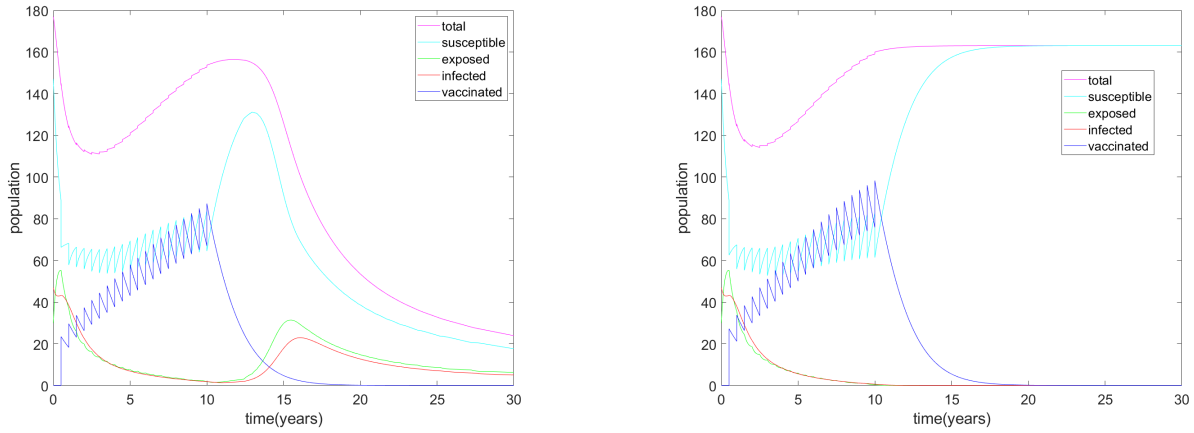
Table 1: Starting parameter values.

Parameter	Value	Description	Reference
K	217	Carrying capacity	[4]
$\frac{1}{L}$	0.75	Latency period (years)	[4]
η	0	Fraction of devils who recover naturally	
k	10	Transmission contact per year per devil	[4]
$\sigma_{11} = \sigma_{21}$	0.02	Vaccine failure rate for 1-year-olds	[13]
$\sigma_{12} = \sigma_{22}$	0.03	Vaccine failure rate for 2-year-olds	[13]
$\sigma_{13} = \sigma_{23}$	0.04	Vaccine failure rate for 3-year-olds	[13]
$\sigma_{14} = \sigma_{24}$	0.12	Vaccine failure rate for 4-year-olds and up	[13]
d_0	0.22	Death rate for baby devils	[4]
d_1	0.49	Death rate for 1-year-olds	[4]
d_2	0.30	Death rate for 2-year-olds	[4]
d_3	0.33	Death rate for 3-year-olds	[4]
d_4	0.73	Death rate for 4-year-olds and up	[4]
d_I	1.28	Death rate for infected devils	[4]
b_1	0.602	Transmission rate reduction for 1-year-olds	[4]
α_1	0.68	Birth rate for 1-year-olds	[4]
α_2	1.54	Birth rate for 2-year-olds	[4]
α_3	1.54	Birth rate for 3-year-olds	[4]
α_4	1.2	Birth rate for 4-year-olds and up	[4]
p_{S_i}	0.80	Percent of Susceptibles who eat vaccine	[20]
p_{E_i}	0	Percent of Exposed who eat vaccine	
$r_{E_i} = r_{I_i}$	0	Percent of Exposed devils who eat vaccine and recover	
β_2	2	Number of 2-year-old captive-bred devils who are released into the wild	



(a) Pop. fails to recover after 7 years of impulse campaigns. (b) Population recovers after 8 years of impulse campaigns.

Figure 1: Devil population over time with a bi-annual 7-year and 8-year impulse vaccine campaigns with the vaccine failure rates found in Table 1 and 2 captive-bred vaccinated devils added to population annually (β=2).



(a) Population declines after campaign ends at $p_{s_i} = 0.6$.

(b) Population recovers after campaign end at $p_{s_i} = 0.7$.

Figure 2: Devil population over time with a bi-annual 10-year impulse vaccine campaign with proportion of devils consuming vaccine $p_{s_i} = 0.6$ and $p_{s_i} = 0.7$.

devils consuming the bait dropped vaccine may vary by age class, but there is currently not sufficient evidence to support varying by age, but should be considered in further study.

After considering what proportion of the population who need to eat the vaccine (p_{s_i}) for a successful campaign, we consider how high the vaccine failure rate for wild devils (σ_2) can be in order for the campaign to still be successful. The initial values were extrapolated from a study of rabies vaccine failure rate from vet administered vaccine injections to domestic dogs show in Table 1. We acknowledge that these values may be considerably different for a vaccine administered to a wild devils population through oral bait. Therefore we focus our analysis on variations in the vaccine failure rate of wild devils (σ_{2_i}) and do not vary the vaccine failure rate of vaccines administered to captive-bred devils before release (σ_{1_i}).

We consider the highest vaccine failure for the oldest group of devils, initially set at 0.12 and consider if that value were true for all devils, what is the highest it could be and still have the population recover after the campaign ends. We find that if no additional captive-bred vaccinated devils are added to the population ($\beta = 0$), then at $\sigma_2 = 0.10$ across all age groups, the population declines after the campaign ends (Figure 3a), but at $\sigma_2 = 0.09$, the population will recover following the end of the campaign (Figure 3b). Thus, we conclude that as long as all of the σ_2 values are less than or equal to 0.09, the population will survive past the end of the campaign. We find that with only 2 devils added to the population yearly ($\beta = 2$), the maximum wild vaccine failure rate increases to 0.10 (Figure 4b).

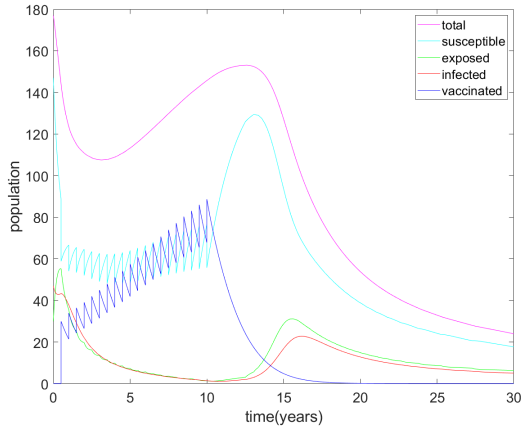
As this model is highly sensitive to both the vaccine failure rate σ_2 and the proportion of population receiving the vaccine p_{S_i}, we lastly consider the effects of varying both of them. This provides us with a range of values for both σ_2 and p_{S_i} which, together, could yield a successful vaccination campaign.

With a bi-annual, 10-year impulse vaccine campaign we find that only a small number of p_{S_i} and σ_2 combinations could yield a successful campaign after 30 years (Figure 5a). For a vaccine with an exceptionally low failure rate $\sigma_2 \leq 0.01$, as little as 55% of the population would need to receive the vaccine for the campaign to succeed. Similarly if nearly 100% of the population could be vaccinated then the failure rate could be as high as $\sigma_2 = 0.14$.

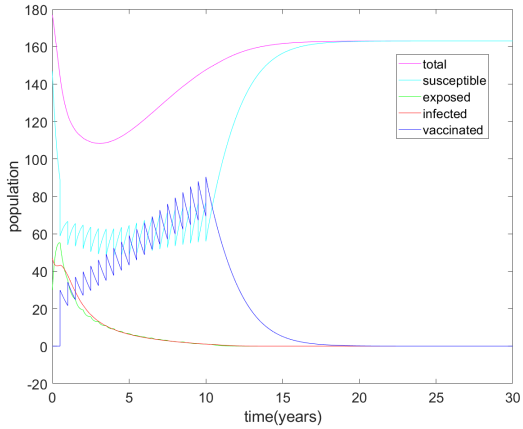
It is important to note, however, that it is possible the vaccine failure rate may be much higher, in which case, a longer campaign, or more impulses per year may be necessary. A study of wild brushtail possums infected with bovine tuberculosis found a vaccine failure rate of 31% [5]. Thus, it is possible a potential DFTD vaccine to have a failure rate higher than assumed in this study.

7 Conclusion

Since its conception in Switzerland, oral vaccination has become the primary method of assisting diseased animal populations from foxes in Switzerland [8] and is now used all around the world. With the possibility of a bait vaccine on the horizon, an OV campaign might be the most effective defense against DFTD's spread. Moreover, given that infrastructure to supplement the mainland population with wild-bred devils to increase genetic diversity (specifically in MHC cells) is already in place, it is logical that vaccinating the devils before release would only

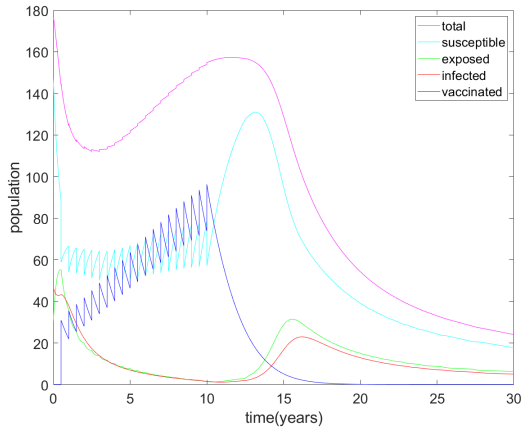


(a) Population declines after campaign end at $\sigma_2 = 0.10$.

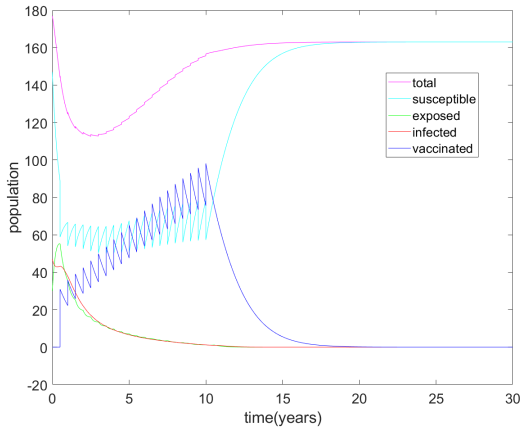


(b) Population recovers after campaign ends at $\sigma_2 = 0.09$.

Figure 3: Devil population over time with a bi-annual 10-year impulse vaccine campaign with wild vaccine failure rates σ_2=0.09 and σ_2=0.10, with no captive-bred vaccinated devils added to population (β=0).

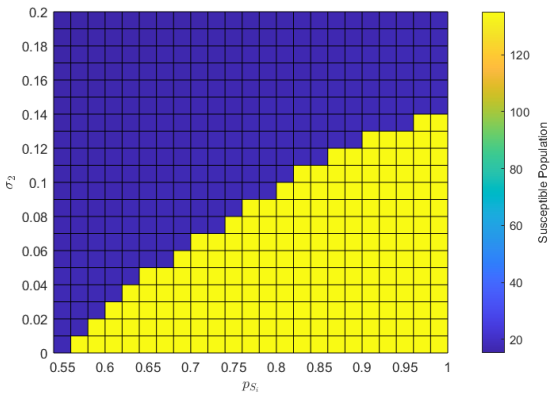


(a) Population declines after campaign end at $\sigma_2 = 0.11$.

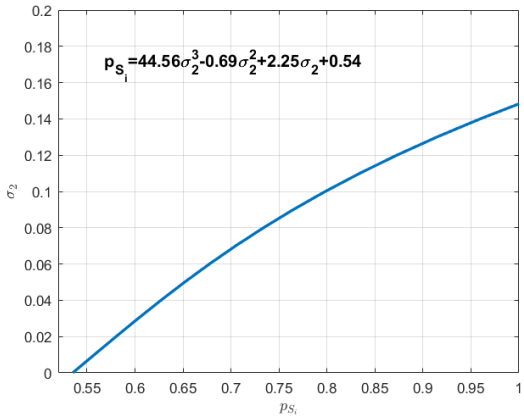


(b) Population recovers after campaign end at $\sigma_2 = 0.10$.

Figure 4: Devil population over time with a bi-annual 10-year impulse vaccine campaign with wild vaccine failure rates σ_2=0.10 and σ_2=0.11, with 2 captive-bred vaccinated devils added to population yearly (β=2).



(a) Susceptible population (shown in color) after campaign ends for a range of combinations of σ_2 and p_{S_i}.



(b) Approximate polynomial representation of the transition points in part 5a.

Figure 5: Susceptible population after 30 years where both the vaccine failure rate σ_2 and the proportion of population receiving vaccine p_{S_i} are varied.

increase the chances of reaching reproduction thus increasing genetic diversity as well as simply increasing the healthy population. Of course, the possibility of either of these strategies relies on the development of a DFTD vaccine, both for injection and bait. If such vaccines are created, our model shows they could be used to eliminate DFTD in a time frame comparable with other OV campaigns, though this will vary with the vaccine failure rate. Once a bait drop vaccine is fully developed, parameters may be able to be more accurately estimated to inform researchers on how often and how long an oral vaccine would need to last to successfully help the devils recover from near extinction. With our current parameters, our model demonstrates that with 8 years of bi-annual impulse campaigns, including the insertion of 2 vaccinated captive bred devils every six months, the Tasmanian devil can be saved from extinction. When we consider a bi-annual 10-year campaign, the standard for oral rabies vaccine programs [8], we find a minimum of 70% of wild healthy devils must ingest the vaccine at each drop with an age-based vaccine failure rate based on failure of the rabies vaccine in dogs ranging from 2% to 12% [13]. Additionally, with a 10-year campaign, the vaccine failure rate can be as high as 9% amongst all age groups if a minimum of 80% of wild healthy devils consume the vaccine bait, a value consistent with oral rabies vaccine campaigns [20]. Overall, there is high hope the devils will recover in the coming years. Continued progress towards a vaccine [24] with the potential for oral vaccine campaigns [6], as well as promise that devils may be able to develop a recovery mechanism naturally [10, 16] indicates the endangered devils may soon be on a road to population recovery.

Author Contributions

T.C. conceived of the project and helped create the model. N.S. created and analyzed the model including the numerical and graphical output found in the paper. C.R., Z.B., and T.S. reviewed the literature on vaccines and recovery. M.P. directed the project, helped create the model, and assisted in the organization of the manuscript. All authors contributed to the writing of the manuscript.

References

[1] Beeton, N. and McCallum, H. (2011). Models predict that culling is not a feasible strategy to prevent extinction of Tasmanian devils from facial tumour disease. *Journal of Applied Ecology*, 48(6):1315–1323.

[2] Bradshaw, C. J. and Brook, B. W. (2005). Disease and the devil: Density-dependent epidemiological processes explain historical population fluctuations in the Tasmanian devil. *Ecography*, 28(2):181–190.

[3] Bremner-Harrison, S., Prodohl, P. A., and Elwood, R. W. (2004). Behavioural trait assessment as a release criterion: Boldness predicts early death in a reintroduction programme of captive-bred swift fox (Vulpes velox). *Animal Conservation*, 7(3):313–320.

[4] Bruno, C. D., Comar, T., Powell, M. O., and Tameklo, A. (2017). Age-Structured and Vaccination Models of Devil Facial Tumor Disease. *SPORA: A Journal of Biomathematics*, 3(1).

[5] Corner, L. A., Norton, S., Buddle, B. M., and Morris, R. S. (2002). The efficacy of bacille Calmette-Guérin

vaccine in wild brushtail possums (Trichosurus vulpecula). *Research in Veterinary Science*, 73(2):145–152.

[6] Flies, A. S., Flies, E. J., Fox, S., Gilbert, A., Johnson, S. R., Liu, G. S., Lyons, A. B., Patchett, A. L., Pemberton, D., and Pye, R. J. (2020). An oral bait vaccination approach for the Tasmanian devil facial tumor diseases. *Expert Review of Vaccines*, 19(1):1–10.

[7] Foroutan, P., Meltzer, M. I., and Smith, K. A. (2002). Cost of distributing oral raccoon-variant rabies vaccine in Ohio: 1997-2000. *Journal of the American Veterinary Medical Association*, 220(1):27–32.

[8] Freuling, C. M., Hampson, K., Selhorst, T., Schröder, R., Meslin, F. X., Mettenleiter, T. C., and Müller, T. (2013). The elimination of fox rabies from Europe: Determinants of success and lessons for the future. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1623).

[9] Guiler, E. (1978). The Tasmanian Devil at Granville Harbour , 1966-1975. *Papers and Proceedings of the Royal Society of Tasmania*, 112:161–188.

[10] Hohenlohe, P. A., McCallum, H. I., Jones, M. E., Lawrance, M. F., Hamede, R. K., and Storfer, A. (2019). Conserving adaptive potential: lessons from Tasmanian devils and their transmissible cancer. *Conservation Genetics*, 20(1):81–87.

[11] Jones, J. H. (2007). Notes on R_0. *Notes*, pages 1–19.

[12] Jones, M. E., Cockburn, A., Hamede, R., Hawkins, C., Hesterman, H., Lachish, S., Mann, D., McCallum, H., and Pemberton, D. (2008). Life-history change in disease-ravaged Tasmanian devil populations. *Proceedings of the National Academy of Sciences of the United States of America*, 105(29):10023–7.

[13] Kennedy, L. J., Lunt, M., Barnes, A., McElhinney, L., Fooks, A. R., Baxter, D. N., and Ollier, W. E. (2007). Factors influencing the antibody response of dogs vaccinated against rabies. *Vaccine*, 25(51):8500–8507.

[14] Lachish, S., Jones, M., and McCallum, H. (2007). The impact of disease on the survival and population growth rate of the Tasmanian devil. *The Journal of Animal Ecology*, 76(5):926–36.

[15] Owen, R. S. and Siddle, H. V. (2019). Devil Facial Tumours: Towards a Vaccine. *Immunological Investigations*, 48(7):719–736.

[16] Pye, R. J., Pemberton, D., Tovar, C., Tubio, J. M., Dun, K. A., Fox, S., Darby, J., Hayes, D., Knowles, G. W., Kreiss, A., Siddle, H. V., Swift, K., Lyons, A. B., Murchison, E. P., and Woods, G. M. (2016). A second transmissible cancer in Tasmanian devils. *Proceedings of the National Academy of Sciences of the United States of America*, 113(2):374–379.

[17] Robert, A. (2009). Captive breeding genetics and reintroduction success. *Biological Conservation*, 142(12):2915–2922.

[18] Rogers, T., Fox, S., Pemberton, D., and Wise, P. (2016). Sympathy for the devil : captive-management style did not in fl uence survival , body-mass change or diet of Tasmanian devils 1 year after wild release. *Wildlife Research*, 43:544–552.

[19] Siddle, H. V. and Kaufman, J. (2015). Immunology of naturally transmissible tumours. *Immunology*, 144(1):11–20.

[20] Smith, G. C. and Wilkinson, D. (2003). Modeling control of rabies outbreaks in red fox populations to evaluate culling, vaccination, and vaccination combined with fertility control. *Journal of Wildlife Diseases*, 39(2):278–286.

[21] STDP. Maria Island Translocation Project — Department of Primary Industries, Parks, Water and Environment, Tasmania.

[22] STDP. Roadkill Project — Department of Primary Industries, Parks, Water and Environment, Tasmania.

[23] Sterner, R. T., Meltzer, M. I., Shwiff, S. A., and Slate, D. (2009). Tactics and Economics of Wildlife Oral Rabies Vaccination , Canada and the United States. *Emerging Infectious Diseases*, 15(8).

[24] Tovar, C., Pye, R. J., Kreiss, A., Cheng, Y., Brown, G. K., Darby, J., Malley, R. C., Siddle, H. V. T., Skjødt, K., Kaufman, J., Silva, A., Morelli, A. B., Papenfuss, A. T., Corcoran, L. M., Murphy, J. M., Pearse, M. J., Belov, K., Lyons, A. B., and Woods, G. M. (2017). Regression of devil facial tumour disease following immunotherapy in immunised Tasmanian devils. *Scientific Reports*, 7(February):43827.

[25] Wise, P., Lee, D., Peck, S., Clake, J., Thalmann, S., Hockley, J., Schaap, D., and Pemberton, D. (2016). *The conservation introduction of Tasmanian Devils to Maria Island National Park: A response to Devil Facial Tumor Disease (DFTD).*

[26] Woods, G. M., Howson, L. J., Brown, G. K., Tovar, C., Kreiss, A., Corcoran, L. M., and Lyons, A. B. (2015). Immunology of a Transmissible Cancer Spreading among Tasmanian Devils. *The Journal of Immunology*, 195(1):23–29.