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A game-theoretic approach to valuating toxoplasmosis vaccination strategies

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ABSTRACT

The protozoan *Toxoplasma gondii* is a parasite often found in wild and domestic cats, and it is the cause of the disease toxoplasmosis. More than 60 million people in the United States carry the parasite, and the Centers for Disease Control have placed toxoplasmosis in their disease classification group Neglected Parasitic Infections as one of five parasitic diseases targeted as priorities for public health action. In recent years, there has been significant progress toward the development of a practical vaccine, so vaccination programs may soon be a viable approach to controlling the disease. Anticipating the availability of a toxoplasmosis vaccine, we are interested in determining when cat owners should vaccinate their own pets. We have created a mathematical model describing the conditions under which vaccination is advantageous. Our model can be used to predict the average vaccination level in the population. We find that there is a critical vaccine cost threshold above which no one will use the vaccine. A vaccine cost slightly below this threshold, however, results in high usage of the vaccine, and consequently in a significant reduction in population seroprevalence. Not surprisingly, we find that populations may achieve herd immunity only if the cost of vaccine is zero.

1. Introduction

The protozoan *Toxoplasma gondii*, discovered in 1908, is among the world's most widespread zoonotic pathogens (Dubey, 2010; Turner et al., 2013). *T. gondii* is found in a wide variety of warm blooded animals, including sheep, cows, pigs, dogs, pigeons and humans. Cats serve as the parasite's definitive host and are the only animal that sheds oocysts when infected (Dubey, 2010). Cats can shed over 100 million oocysts and as few as 200 oocysts can cause congenital disease in large mammals (Innes et al., 2009). Oocysts can remain infective for upwards of 200 days and will survive exposure to a wide range of temperatures and most common household cleaning products (Dumètre et al., 2013).

Serological surveys conducted in the United States with large sample sizes find that from 9.5% to 22.5% of subjects test positive for toxoplasmosis and an estimated 2.5 billion people worldwide carry the parasite (Dubey and Jones, 2008; Ling et al., 2011; Flegr et al., 2014b). The parasite is known to cause encephalitis, several congenital diseases and stillbirth (Zygmunt, 1990). Toxoplasmosis can damage the central nervous system and researchers hypothesize the parasite could be a factor in the etiology of many central nervous system conditions (Novotná et al., 2008; Miman et al., 2010; Holub et al., 2013; Flegr, 2013). The Centers for Disease Control have placed toxoplasmosis in their disease classification group Neglected Parasitic Infections in which there are five parasitic diseases targeted as priorities for public health action.

Vaccination programs may soon be a viable approach to controlling the disease. A commercial vaccine for sheep, Toxovax®, represents a milestone in the development of toxoplasmosis vaccines (Buxton, 1993). A promising finding is that injecting cats with the T-263 strain of *T. gondii* significantly reduces oocyst shedding by infected cats, rendering the treated cats practically non-infective (Freyre et al., 1993). As the development of a vaccine for cats comes to fruition (Innes et al., 2011), the importance of weighing the costs of vaccination against the costs of toxoplasmosis infection grows.

Game theory has been applied to major public health initiatives for promoting the vaccination coverage of infectious diseases, including smallpox (Bauch et al., 2003), measles (Shim et al., 2012b), rubella (Shim et al., 2009), childhood diseases (Bauch, 2005), influenza (Galvani et al., 2007) and many others. From the game-theoretic perspective, without any outer intervention, an individual adopts a vaccination strategy that will maximize personal payoff, taking into account the disease incidence and risk of infection, which is determined by vaccination decisions made by the rest of the population (Shim et al., 2012a). The theory assumes

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Table 1
Symbols and notation.

Symbol	Meaning	Value
S	Density of susceptible cat population	
I	Density of infective cat population	
R	Density of immune cat population	
O	Density of oocysts in environment	
$\mathcal{R}_0$	Basic reproductive rate of toxoplasmosis	
$\overline{\gamma}$	Population vaccination level, *PVL* (i.e. rate at which susceptible cats are vaccinated)	
γ	Vaccination strategy of an individual	
γ_{opt}	Optimal vaccination strategy for an individual	
$\overline{\gamma}_{\text{critical}}$	Least upper bound of $\overline{\gamma}$ for which $\gamma_{\text{opt}} = 1$	
$\overline{\gamma}_{\text{stable}}$	Stable population vaccination level	
$\pi_{S\to I}$	Probability that a susceptible cat becomes infective	
$\pi(\gamma, \overline{\gamma})$	Probability that a cat owner implementing γ in population with PVL $= \overline{\gamma}$ gets infected	
$E(\gamma, \overline{\gamma})$	Expected payoff for a cat owner implementing γ in population with PVL $= \overline{\gamma}$	
c_{vac}	Cost of vaccine	variable
c_I	Cost of infection	variable
c	Relative cost of vaccine	c_{vac}/c_I
p	Probability that a cat owner gets infected by his or her household cat given that the cat is infective	unknown
β	Contact rate	unknown[a]
α	Recovery rate of infective cats	0.5 weeks^{-1}[a]
k	Rate at which infective cats produce oocysts	10^7 weeks^{-1}[a]
μ_v	Mortality rate of domestic cats	730^{-1} weeks^{-1}[b]
μ_O	Oocyst mortality rate	29^{-1} weeks^{-1}[c]

[a] González-Parra et al. (2009).
[b] Taylor et al. (1995).
[c] Dubey (1998).

that individuals are driven by self-interests which can often differ from the interest of the group (Shim et al., 2011). The difference is generated by a fact that as the vaccination coverage increases, the incentive to vaccinate decreases due to indirect protection by other vaccinated individuals (Bauch and Earn, 2004). This makes the eradication of disease very difficult, even when the cost of vaccination is very low (Geoffard and Philipson, 1997).

The game theoretical models of vaccination consider a situation where individuals face a decision to either do a potentially costly preventive action (to vaccinate themselves or their children) or to skip the vaccination and risk that they (or their children) contract the disease. In this paper we follow the general approach of previous models such as Bauch and Earn (2004) and apply the approach to a situation where individuals choose to vaccinate their cat against toxoplasmosis or to skip the vaccination and risk that the cat and eventually also the cat owner get the toxoplasmosis infection. We propose conditions under which vaccination against toxoplasmosis is advisable for individuals and apply our findings to predict changes in Population Vaccination Level (PVL).

The organization of this paper is as follows. In Section 2.1, we describe the toxoplasmosis transmission dynamics model by Arenas et al. (2010). In Section 2.2 we apply a general vaccination game theory model (Bauch and Earn, 2004) to evaluate benefits of individual vaccination decisions. In Section 3.1 we determine the conditions under which the risks of inaction are more prohibitive than the cost of vaccination. In Section 3.2 we establish that the PVL will stabilize and we find an expression for the stable PVL. We determine that the cost of vaccination must be zero for the PVL to meet the threshold needed to confer herd immunity. We are also able to determine a cost threshold above which no rational individual will use the vaccine. However, when the cost is only slightly below this threshold, a sizable portion of the population will use the vaccine, which will significantly reduce seroprevalence.

2. The model

2.1. Transmission dynamics

The transmission dynamics model by Arenas et al. (2010) provides a representation of the population levels of susceptible, infective and immune cats, which we employ in Section 2.2. A schematic diagram of their model can be found in Fig. 1. The symbols and notation are summarized in Table 1. The compartment S represents the population of susceptible cats, I represents infective cats, R represents immune cats and O represents oocysts in the system. The growth rates are given by

$$\begin{cases} \dot{S}(t) = \mu_v R(t) - \beta S(t)O(t) - \overline{\gamma} S(t) \\ \dot{I}(t) = \beta S(t)O(t) - \alpha I(t) \\ \dot{R}(t) = \alpha I(t) + \overline{\gamma} S(t) - \mu_v R(t) \\ \dot{O}(t) = kI(t) - \mu_O O(t). \end{cases} \tag{1}$$

This system of differential equations resembles an SIR compartmental model, a mainstay of many epidemiological studies (Hethcote, 1989). Inherent in (1) is the assumption that the population birth rate is equal to the death rate. Arenas et al. (2010) show that (1) has a disease-free equilibrium point at

$$(S, I, O) = \left(\frac{\mu_v}{\mu_v + \overline{\gamma}}, 0, 0 \right), \tag{2}$$

and the point is locally asymptotically stable when

$$\overline{\gamma} > \frac{k\beta\mu_v}{\alpha\mu_O} - \mu_v. \tag{3}$$

On the other hand, if (3) does not hold, then the system stabilizes at the endemic equilibrium

$$(S, I, O) = \left(\frac{\alpha\mu_O}{k\beta}, \frac{\mu_v}{\mu_v + \alpha}\left(1 - \frac{1}{\mathcal{R}_0}\right), \frac{k\mu_v}{\mu_O(\mu_v + \alpha)}\left(1 - \frac{1}{\mathcal{R}_0}\right) \right), \tag{4}$$

where $\mathcal{R}_0$ is the basic reproductive rate (Anderson et al., 1992; Inaba and Nishiura, 2008) of toxoplasmosis given by

$$\mathcal{R}_0 = \frac{k\beta\mu_v}{\alpha\mu_O(\mu_v + \overline{\gamma})}. \tag{5}$$

Note that $\mathcal{R}_0 < 1$ if and only if (3) holds.

2.2. Individual's vaccination strategies

To valuate a vaccination strategy, we assign expected payoff values to each strategy. In general, a payoff associated with a strategy is the benefit that an individual derives from implementing the