An Immuno-Epidemiological Model of Paratuberculosis

Maia Martcheva

Department of Mathematics, University of Florida, Gainesville, FL 32611,USA

Abstract. The primary objective of this article is to introduce an immuno-epidemiological model of paratuberculosis (Johne's disease). To develop the immuno-epidemiological model, we first develop an immunological model and an epidemiological model. Then, we link the two models through time-since-infection structure and parameters of the epidemiological model. We use the nested approach to compose the immuno-epidemiological model. Our immunological model captures the switch between the T-cell immune response and the antibody response in Johne's disease. The epidemiological model is a time-since-infection model and captures the variability of transmission rate and the vertical transmission of the disease. We compute the immune-response-dependent epidemiological reproduction number. Our immuno-epidemiological model can be used for investigation of the impact of the immune response on the epidemiology of Johne's disease.

Keywords: paratuberculosis, Johne's disease, immunology, epidemiology, mathematical models, differential equations, reproduction number, mathematical immuno-epidemiology
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INTRODUCTION

Johne's disease, also called paratuberculosis, is a fatal gastrointestinal disease in animals. The disease is caused by a bacterium named *Mycobacterium avium ssp. paratuberculosis*, often abbreviated to **MAP**. The infection happens in the first few months of an animal's life but the animal may stay asymptomatic for a long time. Symptoms of disease may show many months to years later. Johne's disease primarily affects ruminant species (cattle, sheep, goats, deer, antelope, and bison) and occurs most frequently in domestic agricultural herds with the size of the herd playing an important role. It is particularly common in dairy cattle. Johne's disease causes reduction of milk production, weight loss, and early culling of clinically affected animals. In the U.S., Johne's disease has been found in 68% of dairy herds and causes an estimated annual loss of $220 million to the U.S. dairy industry.

MAP has some zoonotic potential, although the full extent of the ramifications that result of human exposure to MAP is still controversial. Humans can become exposed to MAP from (1) raw milk from MAP-infected dairy herds; (2) beef originating from MAP-infected cattle; (3) domestic water contaminated with MAP; (4) pasteurized milk. Studies [1, 2] suggest that MAP has infected humans although whether these infections subsequently were the direct cause of disease is an open question. In the cases when MAP could be isolated from humans, there is evidence that these infections were obtained from infected animals. MAP is found more often in people with Crohn's disease than in other humans. However, it is unknown if MAP causes Crohn's disease or not. Arguments both "for" and "against" exist [17].

The interplay of MAP with the immune systems has not this far been investigated through mathematical models. However, Johne's disease epidemiology has been addressed through mathematical models since the early 1990s. Mathematical models have been composed to investigate the dynamics of the disease in infected herds [12, 15] and to evaluate control strategies for Johne's disease [9, 10].

In this note our primary objective is to introduce an immuno-epidemiological model of Johne's disease. We build this model based on the nested approach which links immunological and epidemiological models through time-since-infection and parameters. We discuss the nested approach in the next section. In section 3 we introduce an immunological model of Johne's disease. In section 4 we introduce a time-since-infection epidemiological model of Johne's disease, and we link that model to the immunological model. In section 5 we summarize our results and the advantages and disadvantages of the nested approach to immuno-epidemiological modeling.

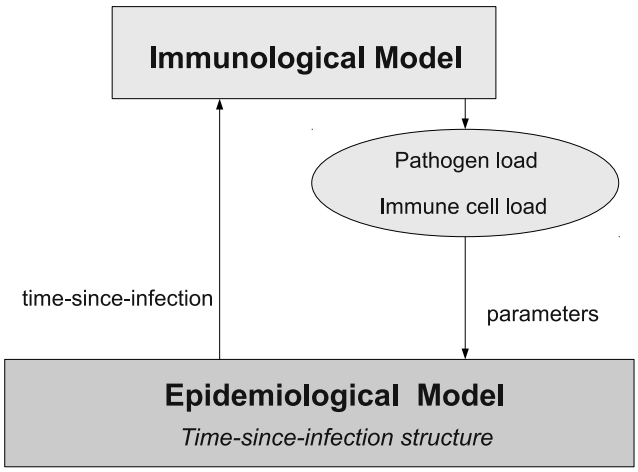

FIGURE 1. Diagram of the nested approach for immuno-epidemiological modeling.

NESTED APPROACH TO THE IMMUNO-EPIDEMIOLOGICAL MODELING

Immunology and epidemiology of a given disease are traditionally separate disciplines, studied by different scientists. Following this separation of disciplines in biology, mathematical modelers have also concentrated only on immunological modeling or epidemiological modeling. Immunological modeling is concerned with the within-host dynamics of the parasite. Typical components of the immunological model are the amount of pathogen, uninfected target cells, infected target cells, differentiated elements of the immune response: T-cells, B-cells, antibodies. Mathematical models of the within-host interaction of the pathogen with the immune system abound in the literature. Those models mostly target human diseases such as HIV [14], Hepatitis C [13], malaria [6], and human TB [16]. Immunological models within animal hosts are also widely used in the literature [4]. Most immunological models are self contained and do not incorporate links to the epidemiology of the disease. As focused units, these type of models ignore the amount of pathogen transmitted and the status of the immune system at infection.

Between host dynamical models, usually called epidemiological models, also abound in the literature. Epidemiological models target many more diseases, but a large proportion of them are also focused on human diseases or animal diseases with zoonotic potential. Epidemiological models are often structured in a way that captures at least at discrete level the immunological status of individuals. Epidemiological models often include compartments of susceptible (immunologically naive) individuals, latent individuals (infected but not showing symptoms), infectious individuals, recovered (immune) individuals. Models that include time-since-infection structure to account for variable infectivity during infection implicitly account for the pathogen load of the individuals [18]. Models, structured by time-since-recovery implicitly account for the gradual loss of immunity after recovery [19]. Yet, epidemiological models do not take into account the pathogen load of infected individuals and the detailed immune status during infection.

To overcome this division, scientists have started to bring together immunological and epidemiological models of a given disease. The resulting linked immunological and epidemiological models are called “immuno-epidemiological models”. Actually the term “immuno-epidemiology” is not new, but has traditionally been used in connection with macroparasitic (helminth) infections [20] and malaria [8]. Today, immuno-epidemiology is used in wider context, and immuno-epidemiological approach or modeling can be taken in connection to any disease. More specifically, immuno-epidemiology combines immunological and epidemiological approaches and bridges the gap between the two disciplines in empirical studies and mathematical and theoretical approaches [5]. Immuno-epidemiology:

- Investigates the influence of individuals’ immunological status on epidemiological patterns.
- Translates individual characteristics like immune status and pathogen load to population level and traces their epidemiological significance.
- Combines individual and population based approaches and links them based on their interdependence.

TABLE 1. *List of dependent variables in the immunological model*

Notation	Meaning
$B(\tau)$	number of bacteria at time-since-infection τ
$M(\tau)$	number of non-infected macrophages at time-since-infection τ
$M_i(\tau)$	number of infected macrophages at time-since-infection τ
$T(\tau)$	number of T-cells at time-since-infection τ
$A(\tau)$	number of antibodies at time-since-infection τ

Individual-based epidemiological modeling has a long history with the development of trait-structured (or size-structured) models in the 1980s. But until recently immunological and epidemiological models have not been linked in simple differential equations models. The nested approach, developed in [3], links an ODE immunological model to a time-since-infection epidemiological model. The two models are linked by two mechanisms (see Figure 1).

- **Link through a structural variable**. The epidemic model is structured through time-since-infection, denoted by τ. The time-since-infection is used as an independent variable in the immunological model which is valid only in the infected epidemiological class.
- **Link through parameters**. Parameters of the epidemiological model are expressed as functions of the dependent variables of the immunological model. For instance, the transmission rate is proportional to the within-host parasite load, disease-induced virulence depends on the parasite load and the immune response (cost to the individual).

The nested approach provides a simple framework for linking immunological and epidemiological models.

THE IMMUNOLOGICAL MODEL OF PARATUBERCULOSIS

Johne's disease is characterized by two phases: sub-clinical and clinical. In an entirely epidemiological model those two phases can be incorporated in different compartments; however, in an immuno-epidemiological model specifics of the immune response should be captured by the immunological model.

Johne's disease is one of the diseases for which immunological models have not been developed this far. We compose a simple immunological model to capture the main components of the within-host dynamics. The infection always starts with the sub-clinical phase.

Initially *M.paratuberculosis* (MAP) targets the lower part of the intestine, called the ileum. Later in the infection it spreads through the entire body. We will denote the number of bacteria in an individual by $B(\tau)$ where τ is the time since the start of the infection. The wall of the ileum contains pockets of tissue known as Peyer's patches. Peyer's patches are rich with macrophages. M cells, which cover the Peyer's patches, pass the bacteria through the wall to the macrophages of the Peyer's patch. In other words, M-cells present MAP to the macrophages. As a result, M.paratuberculosis is engulfed by the macrophages but for unknown reasons, the macrophages fail to destroy the bacteria. From the perspective of immunological modeling, in Johne's disease the target cells are the macrophages which could be uninfected or infected by the bacteria. We will denote the number of uninfected macrophages by $M(\tau)$ and the number of infected macrophages by $M_i(\tau)$. Infected macrophages then promote formation of microscopic granulomas, a characteristic feature of Johne's disease. During the sub-clinical stage of Johne's disease, which starts several months after MAP infection and lasts 2-5 years on average, various kinds of activated T cells attack MAP-infected macrophages and keep the infection under control. We will denote the integrated cell-immune response by $T(\tau)$ – the number of T-cells in the body. The list of dependent variables in the immunological model is given in Table 1.

However, the cell-mediated immune responses disappear at the subclinical stage of Johne's disease and during the clinical stage are replaced primarily by antibody-mediated immune responses. The number of the antibodies in the animal is denoted by $A(\tau)$. The switch between the cell-mediated immune response (Th1 response) and the antibody-mediated immune response (Th2 response) marks the beginning of the clinical stage. The trigger for transition to clinical stage is not known. Antibody immune response against MAP are not protective and cannot contain the infection. Surge and spread of the MAP occurs which triggers the influx of millions of macrophages. The wall of the lumen thickens and the animal shows visible signs of disease. Many of the diseased animals die [11].

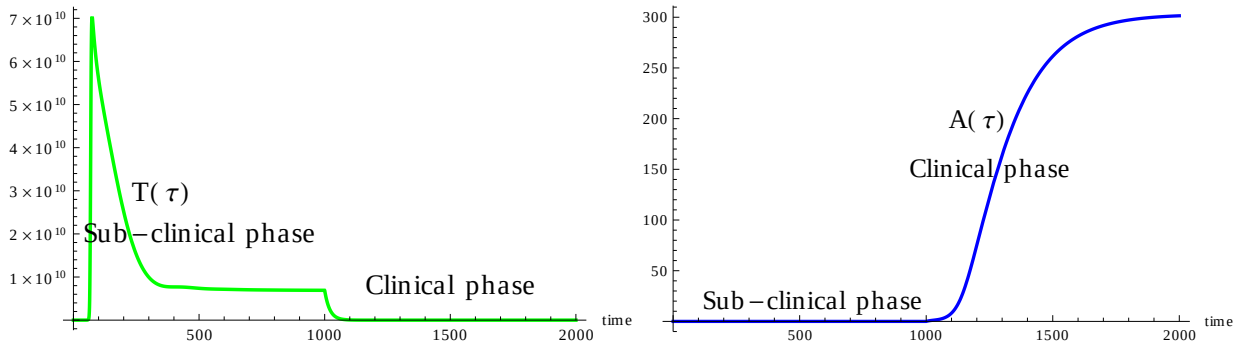

FIGURE 2. Left figure shows the T-Cell response within a host. During the subclinical phase the T-Cell load is high and it non-existent during the clinical phase. Right figure shows the antibodies response within a host. During the subclinical phase the antibody load is non-existent and it grows fast during the clinical phase

The T-cell/antibody switch that occurs in Johne's disease presents the main modeling difficulty. Th1/Th2 switches, which are responsible for the corresponding immune responses, have been considered by Yates *et al.* [21, 22]. We capture the switch by a much simpler model and incorporate Heaviside function $H(\tau)$ to "turn off" the T cell production, and "turn on" the antibody production (see Figure 2). That requires the moment when the switch occurs to be postulated. We call that moment τ_0. The immunological model of Johne's disease is introduced below.

$$\begin{aligned}
\frac{dM}{d\tau} &= \Lambda - \varepsilon BM - \mu M,\\
\frac{dM_i}{d\tau} &= \varepsilon BM - \alpha M_i T - \mu M_i,\\
\frac{dT}{d\tau} &= \rho(1 - H(\tau - \tau_0))M_i T - \delta_T T,\\
\frac{dA}{d\tau} &= \eta H(\tau - \tau_0)B - \delta_A A,\\
\frac{dB}{d\tau} &= rB(1 - B/K) - \varepsilon BM + p\mu M_i - qBA.
\end{aligned} \tag{1}$$

where Λ is the recruitment rate of healthy macrophages, μ is the natural death rate of macrophages (healthy or infected), ε is the rate of infection of healthy macrophages, α is the rate at which T-cells destroy infected macrophages, p is the number of bacteria produced by infected macrophages, q is the rate at which antibodies kill bacteria, ρ is the rate at which infected macrophages stimulate T-cell production, η is the rate at which bacteria stimulate antibody production, and δ_A and δ_T are the natural death rates of antibodies and T-cells. The parameters of the immune model are summarized in Table 2.

TABLE 2. *List of parameters for the immunological model*

Notation	Meaning
Λ	recruitment rate of healthy macrophages
μ	natural death rate of macrophages (healthy or infected)
ε	rate of infection of healthy macrophages by bacteria
α	rate at which T-cells destroy infected macrophages
p	number of bacteria produced by dying infected macrophages
q	rate at which antibodies kill bacteria
η	rate at bacteria stimulate antibody production
δ_A	natural death rates of antibodies
δ_T	natural death rates of antibodies and T-cells

We simulated with model (1) to confirm that it exhibits the switch between the T-cell immune response and the antibody immune response. Figure 3 shows that during the subclinical phase the bacterial load is low, while during

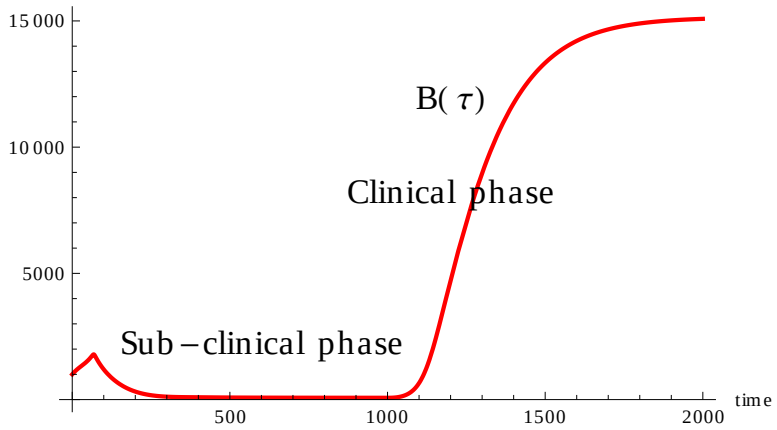

FIGURE 3. Figure shows the free bacteria within a host. During the subclinical phase the bacterial load is low and it grows rapidly during the clinical phase.

the clinical phase the bacterial load grows fast. The switch in the immune response is also captured and illustrated in Figure 2.

EPIDEMIOLOGICAL MODEL AND PARAMETER LINKING

MAP infects intestinal tissues usually of young animals. The disease progresses in two stages – latent, which lasts 2-10 years, and diseased stage. These correspond to the sub-clinical and clinical phases of the immune infection. During the long sub-clinical phase, when the infected animals are apparently healthy, they are still capable of transmitting the infection by shedding MAP in milk and manure. When infected animals enter the clinical phase, the rate and amount of shedding increases. Recent research evidence suggests that there is a peak in shedding shortly after the initial MAP infection in calves, and the shedding continues throughout the infection. This variability in shedding/infectivity can be captured by an time-since-infection epidemiological model.

Transmission of MAP infection typically occurs through the fecal-oral route when animals ingest manure or milk, contaminated with the bacteria. Calves younger than one year old are considered most susceptible to MAP infections, however, recent evidence indicate that MAP infections in adult cattle (2 year old or more) may also occur. It is unknown whether infected animals recover, or whether they retain immunity after recovery. Consequently, we consider an SI model. Typically in an infected herd only a small proportion of the animals develops clinical signs; most animals remain asymptomatic. Once the symptoms appear, paratuberculosis is progressive and affected animals eventually die. The disease-induced mortality rate is approximately 3% [7].

In addition to the horizontal transmission through MAP-contaminated environment, vertical transmission of MAP also occurs in an estimated 20-40% of offspring from animals with clinical Johne's disease.

Control of Johne's disease is primarily through maintaining MAP-free environment and culling. Treatment with multiple antibiotics is possible but since it is expensive and the medications have to be given every day, it is cost-prohibitive and infeasible.

Prior epidemiological models have divided the population in many classes, and have considered separate classes corresponding to the latent stage and the disease stage. However, in our immuno-epidemiological model the variability in infectivity corresponding to the different phases can be accounted for by a time-since-infection transmission rate dependent of the bacterial load. Hence, a simple SI model will capture the essential features and the variability in the shedding during the various clinical stages. To introduce the model (see Figure 4), let $S(t)$ be the number of susceptible animals. The variable $i(\tau,t)$ denotes the density of infected animals with time-since-infection τ. Infected individuals in the *i*-stage pass through both the sub-clinical phase and the clinical phase. To account for the animals who remain asymptomatic, we introduce $J(t)$ – the number of asymptomatic animals who do not progress to clinical stage.

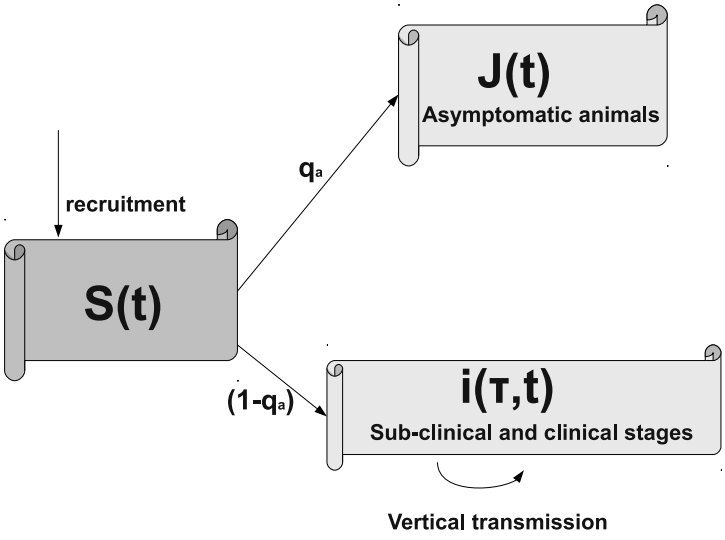

FIGURE 4. Flowchart of the time-since-infection epidemiological model.

The time-since-infection epidemiological model with vertical transmission takes the form:

$$\begin{aligned}
&\frac{dS}{dt} = \lambda_p(S(t)+J(t)) + p_v\lambda_p I(t) - S(t)\int_0^\infty \beta(\tau)i(\tau,t)d\tau - \beta_a S(t)J(t) - \mu_p S,\\
&\frac{dJ}{dt} = q_a\left(S(t)\int_0^\infty \beta(\tau)i(\tau,t)d\tau + \beta_a S(t)J(t)\right) - \mu_p J(t),\\
&\frac{\partial i}{\partial \tau} + \frac{\partial i}{\partial t} = -\gamma(\tau)i(\tau,t) - \mu_p i(\tau,t),\\
&i(0,t) = (1-p_v)\lambda_p I(t) + (1-q_a)\left(S(t)\int_0^\infty \beta(\tau)i(\tau,t)d\tau + \beta_a S(t)J(t)\right)
\end{aligned} \tag{2}$$

where λ_p is the birth/recruitment rate, p_v is the proportion of progeny of infected animals that is susceptible, q_a is the proportion of newly infected animals who progress to the purely asymptomatic stage, β_a is the transmission rate of asymptomatic animals, μ_p is the natural death rate. The total infected population in i-stage is

$$I(t) = \int_0^\infty i(\tau,t)d\tau.$$

The total population size $N = S(t) + I(t) + J(t)$ satisfies the equation $N' = \lambda_P N - \mu_P N$. We assume that $\lambda_P = \mu_P$ so that the total population size is constant. Furthermore, we assume that the initial conditions are chosen so that $N = 1$.

The time-since-infection dependent transmission rate is $\beta(\tau)$ and time-since-infection dependent disease-induced death rate is $\gamma(\tau)$. We link the time-since-infection epidemiological rates to the immunological dependent variables: bacterial load and antibody response. In particular, the time-since-infection dependent transmission rate $\beta(\tau)$ is assumed proportional to the bacterial load:

$$\beta(\tau) = \sigma B(\tau)$$

where σ is the transmission efficiency of the infection. Furthermore, we split the virulence $\gamma(\tau)$ into two components:

$$\gamma(\tau) = \gamma_1(\tau) + \gamma_2(\tau)$$

where $\gamma_1(\tau)$ is the additional host mortality due to parasite growth:

$$\gamma_1(\tau) = crB(\tau)(1 - B(\tau)/K)$$

with c being the parasite cost coefficient. Furthermore, $\gamma_2(\tau)$ is the additional host mortality due to immune response:

$$\gamma_2(\tau) = \kappa\eta A(\tau)$$

where κ is the immune response cost coefficient.

To compute the immune-response-dependent epidemiological reproduction number, we compute the epidemiological reproduction number of asymptomatic infection:

$$\mathscr{R}_a = \frac{q_a\beta_a S^*}{\mu_P} < 1$$

and we assume that it is smaller than one. Furthermore, we define

$$\mathscr{R}_0 = (1-p_v)\lambda_P \int_0^\infty \pi(\tau)d\tau + (1-q_a)\frac{S^*}{1-\mathscr{R}_a}\int_0^\infty \sigma B(\tau)\pi(\tau)d\tau$$

where S^* is the disease-free susceptible population, with $S^* = 1$. Furthermore, we have

$$\pi(\tau) = e^{-\mu_P\tau}e^{-\int_0^\tau (crB(\tau)(1-B(s)/K)+\kappa\eta A(s))ds}.$$

Note that $\pi(\tau)$ depends on the bacterial load and the antibody immune response. The first term in $\mathscr{R}_0$ accounts for the new infections caused by the vertical transmission, the second – accounts for the cases caused by horizontal transmission.

DISCUSSION

In this paper we introduce an immuno-epidemiological model of Johne's disease – a deadly disease of ruminants, which has a significant impact on the dairy herd production. We use a nested approach to compose the model. Our immunological model is linked to the time-since-infection epidemiological model through the time-since-infection variable and the parameters of the epidemiological model. Within-host models of Johne's disease do not exist in the literature. In that sense our immunological model is novel. The model captures the switch of the immune response from T-cell mediated to antibody mediated. Epidemiological models of Johne's disease exist in the literature, but our model is the first one that captures the latent and clinical stage through time-since-infection structure.

The nested approach for linking immunological to the epidemiological models that we have used has multiple advantages:

1. The link with the time-since-infection allows the immunological dynamics to have its own time-scale.
2. Linking through time-since-infection allows for unrestricted increase in complexity of the immunological model.
3. The time-since-infection epidemic models are mathematically well studied – many things about their dynamics are known.
4. The epidemiological reproduction number of the disease $\mathscr{R}_0$ can be computed in terms of the parasite load or the immune response. In this article we compute the immune-response-dependent epidemiological reproduction number for our immuno-epidemiological model of Johne's disease.
5. The mechanistic description of the within-host host-pathogen dynamics is used to derive, rather than impose, population-level life-history parameters.
6. The framework allows for easy incorporation of parasite genetic diversity in various regimes: competitive exclusion, co-infection, super-infection.

At this point one particular disadvantage of the nested approach is that all infected animals in the i-stage experience the same immunological dynamics. This disadvantage can be remedied if a multi-group epidemic model is considered but expanding model (2) to a multi-group model will increase the complexity of the immuno-epidemiological model significantly.

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