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A mathematical model of Chlamydia infection of incorporating spatial movement of chlamydial particles

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Abstract
We present a spatiotemporal mathematical model of chlamydial infection, host immune response and spatial movement of infectious particles. The resulting partial differential equations model both the dynamics of the infection and changes in infection profile observed spatially along the length of the host genital tract. This model advances previous chlamydia modelling by incorporating spatial change which we also demonstrate to be essential when the timescale for movement of infectious particles is equal to or shorter than the developmental cycle timescale. Numerical solutions and model analysis are carried out and we present a hypothesis regarding the potential for treatment and prevention of infection by increasing chlamydial particle motility.

Keywords: chlamydia, partial differential equation, mathematical model, infectious diseases

1. Introduction

\textit{Chlamydia trachomatis}, an obligate intracellular bacterial pathogen that infects the genital and ocular mucosa of humans causing sexually transmit-
ted disease and trachoma, is the most common bacterial sexually transmitted disease in humans [4]. Women face the most serious consequences of the infection including chronic pain, tubal factor infertility, ectopic pregnancy and pelvic inflammatory disease resulting from genital tract infections [4, 18]. In a majority of cases, the infections are asymptomatic and may persist for months to years without treatment or diagnosis [4]. Such outcomes contribute to *C. trachomatis* being positioned as the most costly sexually transmitted infection besides HIV/AIDS with the health care costs in the United States alone rising to at least $US2 billion per year [11].

*C. trachomatis* is an intracellular pathogen that replicates via a unique biphasic developmental cycle involving eukaryotic cells and two distinctive forms of the bacteria: the Elementary Body (EB), which is the extracellular, metabolically inert, infectious form; and the Reticulate Body (RB), which is the intracellular, replicating structure [1]. In this developmental cycle (see Figure 1), the infectious but metabolically inactive elementary body, approximately 0.3 µm in diameter, is endocytosed by eukaryotic cells and resides within a cytoplasmic inclusion [1]. Within the inclusion, the EBs transform into the non-infectious but metabolically active reticulate body which is larger at approximately 1 µm in diameter. The RBs replicate via repeated cycles of binary fission, before differentiating back to the infectious EB form. The EBs are then released to the cell exterior upon cell lysis [1, 2].

Wilson [16] indicates that 200-500 new EBs are released from each infected cell following the replication process. This is an initial indicator of how the *C. trachomatis* infection can progress and subsequently reach the upper
genital tract. On the other hand, it is also important to note the competing defensive factors in the infection. In particular, the host immune system has a significant role in the clearance of *Chlamydia* throughout the infection period and the developmental cycle, and is able to respond both to intracellular and extracellular Chlamydia [3, 6]. Humoral immunity, through antibody-mediated neutralisation of infectious chlamydial particles and macrophages engulfing antibody-bound chlamydial particles, plays an important role in the host response to extracellular chlamydial particles. Cytotoxic T cells are instrumental in the host’s cell-mediated immune response to intracellular chlamydia through their role clearing infected cells. The relative importance of different arms of the immune system is debated in the literature with Morrison *et al.* discussing the importance of B cells and CD4+ T cells over CD8+ T cells [9], while Yang and Burnham for example argue that cell-mediated immunity plays the dominant protective role [19] and Wilson shows in a theoretical study that CD4+ T cells play a significant role in adaptive immunity to *Chlamydia trachomatis* infection of the genital tract [12].

Generally, the severe sequelae of chlamydial infections, such as damage to fallopian tube function, result from fibrosis and scarring following inflammation. In urogenital tract infection in women, while the initial infection develops in the lower genital tract, the chronic infection that leads to scarring and subsequently causes disease occurs in the upper regions of the genital tract. In this paper, we hypothesise and investigate a mechanism for the movement of the infection to the upper genital tract, a mechanism that is currently unknown.

Much of the mathematical modelling of Chlamydia that has been undertaken to date has been concerned only with dynamic issues related to the infection, the developmental cycle and the immune response. Wilson presented a mathematical framework for investigating chlamydial infection dynamics that summarises the basis for virtually all of the mathematical modelling of Chlamydia that has been carried out to date [13]. Wilson *et al.* developed a mathematical model and used real-time PCR data to obtain a better approximation for RB doubling times [14]. Hoare *et al.* presented a model that confirmed a hypothesis stating that increasing RB radius and/or the number of inclusions per infected cell contributes to the development of persistent infection [5]. Wilson *et al.* also carried out a modelling study that showed that there is an optimal number of inclusions within an infected cell for maximum release of infectious EBs due to spatial restrictions encountered for higher numbers of inclusions [16]. Wilson and coworkers also investigated
how the cell-mediated immune response to Chlamydia-infected cells changes over the developmental cycle, suggesting that persistent infection should be induced and sustained as a means of reducing severe disease sequelae [12], and also showed that treatment interventions will only be effective in preventing or mitigating pathologic response if the intervention change the time course prior to reaching peak infection forming loads [17]. Here we intend to build on such work by exploring spatial variations in the infection process.

In this paper we develop a mathematical model to investigate the interaction between extracellular *C. trachomatis* and epithelial cells of the genital tract that extends previous chlamydia modelling research by explicitly considering a spatial dimension and movement of chlamydial particles via diffusion. Previously, Mallet *et al.* [7, 8] presented cellular automata based computational models of chlamydial infection. While those models rely on ‘fuzzy’, individual level descriptions of cell-cell and cell-particle interactions, here we apply a continuum approach with its easier to quantify or estimate reaction kinetic and diffusion parameters. We present results regarding infection dynamics and obtain new insight into the effects of spatial progression of infection in the genital tract. We discuss how these effects may have potential application in effective infection control strategies.

In the following section we develop and briefly analyse the partial differential equation based mathematical model for *C. trachomatis* spatial progression and infection dynamics. In section 3 we present numerical solutions and analysis of the model, comparing it with experimental results and findings. Finally, we present a concluding discussion of the implications of the findings of our mathematical model of chlamydial infection in Section 4.

### 2. Model development

We present a one-dimensional spatiotemporal mathematical model of chlamydial infection in the genital tract. Here we use the structure employed by Wilson [13] that describes the infection using a basic set of important species: the extracellular chlamydial particles themselves, healthy epithelial cells and infected epithelial cells. We denote the density of free extracellular Chlamydia particles by $C(x, t)$, while the densities of uninfected and infected mucosal epithelial cells are denoted $E(x, t)$ and $I(x, t)$, respectively. The spatial coordinate, $x$, represents distance from the opening of the genital tract and $t$ represents time.
Following the work of Wilson [13], we include in the model the clearance of Chlamydia particles by macrophages, removal from the free population due to infection of epithelial cells and expansion due to lysis of infected cells. The density of the free extracellular Chlamydial particles is assumed to be increased through the lysis of infected epithelial cells containing Chlamydial particles that have completely passed through the development cycle. This lysis occurs with rate parameter $\kappa_2$ and results in a factor $P$ increase in the local density of particles. The density of particles is decreased due to clearance by macrophages with a rate $\mu$ and also when particles take part in infection events with rate parameter $\kappa_1$. The model developed in this research includes explicit spatial movement of particles via the inclusion of a diffusion-like term with diffusion coefficient $D_C$ that may or may not depend on space, time and/or the three species considered in the model. These phenomena are described using the equation

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x} \left(D_C \frac{\partial C}{\partial x}\right) + P\kappa_2 I - \mu C - \kappa_1 CE. \quad (1)$$

We allow for transformation of uninfected cells to the infected state with rate $\kappa_1$ when cells and particles come in contact. Unlike Wilson, who allowed for a constant influx of epithelial cells and natural death of uninfected epithelial cells, we assume that uninfected cells are produced in a logistic manner with carrying capacity $E_0$ and production rate $r_E$, modelling the regeneration of the epithelium to some normal level when no infectious particles are present. Together, these actions are described using the equation

$$\frac{\partial E}{\partial t} = r_E E (E_0 - E) - \kappa_1 CE. \quad (2)$$

For the infected epithelial cell density, we again follow [13] and consider density increases due to uninfected cell–free particle interactions with rate $\kappa_1$, decreases resulting from cell-mediated immunity clearance of infected cells with rate $\gamma$ and lysis of infected cells with rate $\kappa_2$. Hence for the infected cell density we have

$$\frac{\partial I}{\partial t} = \kappa_1 CE - \gamma I - \kappa_2 I. \quad (3)$$

Initially, the system supports the natural level of uninfected epithelial cells, $E_0$ throughout the domain, with no infected cells. We impose an initial innoculum, $C_0(x)$, of Chlamydial particles, the form for which will be
discussed later. These initial conditions are given mathematically by

\[ C(x, 0) = C_0(x), \quad E(x, 0) = E_0, \quad I(x, 0) = 0. \tag{4} \]

At both ends of the genital tract, we assume for simplicity that free particles cannot flow out of the region of interest. This gives boundary conditions of the form

\[ \frac{\partial C}{\partial x} = 0, \tag{5} \]

for both \( x = 0 \) and \( x = L \) where \( L \) is the length of the domain.

2.1. Steady states and stability analysis

We now consider the spatially homogeneous steady states of the system given by equations (1)–(3) (where \( \partial C/\partial x = \partial C/\partial t = \partial E/\partial t = \partial I/\partial t = 0 \)). For this model of Chlamydial infection there are three steady states: the trivial state, the Chlamydia-free state and the infected state.

We also investigate the stability of the steady states. To carry out the stability analysis, it is noted that the Jacobian matrix for the system (1)–(3) is given by

\[
J = \begin{bmatrix}
-(\mu + \kappa_1 E) & -\kappa_1 C & P \kappa_2 \\
-\kappa_1 E & r_E(E_0 - 2E) - \kappa_1 C & 0 \\
\kappa_1 E & \kappa_1 C & -(\gamma + \kappa_2)
\end{bmatrix}.	ag{6}
\]

2.1.1. Trivial steady state

Trivially, we have a steady state at

\[ \overline{C} = \overline{E} = \overline{I} = 0. \tag{7} \]

At this trivial steady state, the eigenvalues of the Jacobian matrix are

\[ \lambda_1 = -(\gamma + \kappa_2), \quad \lambda_2 = r_E E_0, \quad \lambda_3 = -\mu. \]

So the trivial steady state is always unstable since \( \lambda_2 > 0 \) always, and we have that the model predicts that infection is either always persistent (the infected steady state) or is cleared (the Chlamydia-free steady state).
2.1.2. Chlamydia-free steady state

The steady state corresponding with the absence of infection and infectious particles is characterised by the values.

\[ \overline{C} = \overline{T} = 0, \quad \overline{E} = E_0. \]  

At this steady state, the Jacobian matrix has eigenvalues

\[ \lambda_{1,2} = -\frac{1}{2} (E_0 \kappa_1 + \kappa_2 + \gamma + \mu) \pm \frac{1}{2} \sqrt{(E_0 \kappa_1 - \kappa_2 - \gamma + \mu)^2 + 4P \kappa_1 \kappa_2 E_0 \kappa_1 \kappa_2} \]  

\[ \lambda_3 = -r E_0. \]  

Since all of the system parameters are nonnegative, all three eigenvalues are always real. Furthermore, \( \lambda_1 \) and \( \lambda_2 \) will both be negative provided \( P < P_{\text{crit}} \), where

\[ P_{\text{crit}} = \frac{(\mu + E_0 \kappa_1)(\gamma + \kappa_2)}{E_0 \kappa_1 \kappa_2}. \]  

That is, given that the burst size of infected cells is capped at the value given on the right of equation (11), the infection is weak enough that it is cleared by the immune system. We may also write this expression in the form of a basic reproduction ratio, \( R_0 \), given by

\[ R_0 = \frac{P}{(1 + \mu/E_0 \kappa_1)(1 + \gamma/\kappa_2)}, \]  

and note that the Chlamydia-free steady state is stable when \( R_0 < 1 \). While the healthy epithelial cell reproduction dynamics are different from and slightly more complicated than those presented by Wilson [13], we point out that the resulting \( R_0 \) and \( P_{\text{crit}} \) values are equivalent.

The basic reproduction ratio provides a number of useful insights into clearance of infection. In particular, the ability to clear an infection can be increased in three ways. \( R_0 \) can be decreased first by reducing the burst size of lysing infected cells, second by increasing the rate of response of the humoral immune system compared with the rate of cell infection, and finally by increasing the rate of response of the cell-mediated immune response compared with the rate of lysis of infected cells.
2.1.3. Infected steady state

The nontrivial steady state corresponding with continued chlamydial infection is given by

\[
\begin{align*}
\overline{C} &= \frac{r_E \mu (\gamma + \kappa_2) + \kappa_1 E_0 (\kappa_2 + \gamma - P \kappa_2)}{\kappa_1^2 (\kappa_2 + \gamma - P \kappa_2)}, \\
\overline{E} &= \frac{\mu (\gamma + \kappa_2)}{\kappa_1 (P \kappa_2 - \kappa_2 - \gamma)}, \\
\overline{I} &= \frac{\mu (r_E \mu (\gamma + \kappa_2) + \kappa_1 E_0 (\kappa_2 + \gamma - P \kappa_2))}{\kappa_1^2 (\kappa_2 + \gamma - P \kappa_2)^2}.
\end{align*}
\]

The eigenvalues of the Jacobian matrix at this steady state were obtained using the computer algebra system Maple, however they are not shown here due to the length of the expressions involved. Further manipulation with Maple shows that two of the eigenvalues are always negative. The third vanishes when \( P = P_{\text{crit}} \) and is negative when \( P > P_{\text{crit}} \). Thus we have that the infected steady state is stable whenever

\[
P > \frac{\left( \mu + E_0 \kappa_1 \right) (\gamma + \kappa_2)}{E_0 \kappa_1 \kappa_2},
\]

or alternatively, when the basic reproduction ratio satisfies \( R_0 \geq 1 \).

3. Results

The mathematical model developed above along with the parameter values and ranges presented in Table 1 was solved numerically using MATLAB’s parabolic partial differential equation solver \textit{pdepe}. Simulations were run using baseline parameters as provided in the paper of Wilson [13], with numerical investigation of the parameter space carried out for those parameters provided only approximately (namely \( P, \gamma, \mu \) and \( \kappa_2 \)) and those parameters that are introduced in the current research (namely \( r_E \) and \( DC \)).

Our model calculated the number of extracellular chlamydial particles, healthy and infected cells over the length of infection commonly observed in experimental studies and over a spatial length on the order of the length of the genital tract of an animal model (the guinea pig). With this model we have successfully reproduced the qualitative and approximate quantitative form of infection time courses for chlamydial particles and proportion of cells infected observed in relevant experimental literature (such as [10]).
Table 1: Parameters values and ranges used in the numerical solution of equations (1)–(3). All parameters values/ranges are taken from [12, 13, 15], except $D_C$ and $r_E$, the ranges for which have been investigated numerically in the present study.

Numerical investigation has also demonstrated the key role of spatial spread of chlamydial particles in determining the peak and length of infection in the host.

In the subsections to follow, we first present a general discussion of the numerical solutions of the model followed by two representative solutions of biological interest, demonstrating key model outputs. While the model includes a spatial dimension representing depth in the genital tract, we also present spatially aggregated, time course results that can be compared with the type of results commonly reported in experimental studies. To construct time course plots of extracellular chlamydia particles we plot the quantity 

$$C(t) = \sum_{x^* \in \mathcal{D}} C(x^*, t)$$

against time, where $\mathcal{D}$ represents all spatial locations in the problem domain. Similarly, for plots of the percentage of all cells that are infected, we use 

$$\%I(t) = \frac{\sum_{x^* \in \mathcal{D}} I(x^*, t)}{\sum_{x^* \in \mathcal{D}} I(x^*, t) + E(x^*, t)}$$

plotted against time. It is also important to note that we have artificially moved the time axis to begin with day 3 as the first day of positive infection. This is an arbitrary but useful strategy employed in the experimental literature (for example [10]) to allow for statistical comparison of infection curves for different animals and different groups. We adopt this strategy here for consistency and ease of comparison with such experimental research.
3.1. Numerical solutions

We investigated the mathematical model developed in Section 2 by numerically solving equations (1)–(3) with parameter values sampled from Table 1. Particular attention was paid to investigating the parameter spaces for new parameters included in the model of this present paper. In particular, the chlamydial diffusion parameter $D_C$ and the rate of healthy cell division/replenishment, $r_E$.

Varying the diffusion parameter over the range 0.0001 up to 1 results in increases to the initial peak chlamydial load. While the time to peak particle load is similar, approximately 4 to 4.5 days, the length of the infection tail (the time period where a lower but nonzero level of particles remains in the system) is shortened as the diffusion rate is increased (see Figure 2). We explain this by noting that with higher diffusion rates, the infectious particles are more quickly transported away from the initial zone of infection to locations with high proportions of uninfected cells with which they can interact. There is a shorter waiting time, specifically the period of spatial diffusion, before the residual free particles can infect new cells than there is in situations of low chlamydial diffusion, where EBs must wait a full developmental cycle for new healthy cells to become available for infection. Hence, in a shorter time, more cells are infected and lysed resulting in higher initial peaks of both chlamydial particles and the proportion of infected cells. These higher peaks lead to a magnified response from the host immune system and therefore faster clearance of the infection. Figure 2(b) plots the length of time to clearance of infection against the chlamydial diffusion parameter demonstrating the dependence of the infection period on the rate of movement of the infectious particles.

The numerical solutions predict that greater chlamydial particle motility leads to increased infection peaks in the early stages of infection, but they also suggest that this leads to faster clearance of the infection by the host immune system. Keeping in mind the elementary form of this model and the elements of biology that is does not account for, these computational results suggest that there is potential for experimental investigations into strategies to speed up the movement of chlamydial particles, thereby increasing the initial infection and initiating a stronger response from the immune system with a view to inducing a faster clearance of infection.

We found that a stronger immune system modelled via increasing $\mu$ and/or $\gamma$ resulted, not surprisingly, in elimination of the infection within about 3 days post infection. With low chlamydial burst sizes the immune
Figure 2: The relationship between time to clearance of infection and the chlamydial diffusion parameter $D_C$. Other parameters used were selected to produce time courses qualitatively reflecting experimental results of Rank et al. [10].

System is able to clear the infection prior to any real increase in the chlamydial load – that is, there is no initial peak in the chlamydial particle population. This result further supports the findings of Wilson et al. [17] regarding the need for treatment interventions that have their effect early in the course of infection. But even at the relatively high end of the estimated burst sizes and rates of infected cell lysis, the initial peak in chlamydial load at around 5 days post infection is quickly depleted by the highly effective immune system of the host.

For higher rates of replenishment of healthy cells to the mucosal layer of the genital tract we observed solutions of the model where chlamydial particles initially peaked at around 5 days post infection, then settled to a high, nonzero steady state level. This coincided with a persistent infected cell population over the period shown in our solutions. We also noted that the chlamydial particles initially spread in a wave-like fashion with a peak of chlamydial particles moving up the genital tract. Eventually a approximately homogeneous nonzero level of particles is observed throughout the tract.

We found that varying the infected cell clearance parameter (that is, the immune system response to cells) results in reduced peaks for the chlamydial particle loads, but did not change the time to peak load or the length
of time chlamydial particles remain in the genital tract. Interestingly, for
the highest level of immune response, a second peak develops later in time
(approximately 15 days) after near complete clearance of infection. We be-
lieve that this is due to the immune response removing the infected cells
leading to a replenishment with healthy cells (through cell division) which
are then infected by the small number of remaining particles. This suggests
that too high a response to infected cells without a balanced response by the
immune system to the chlamydial particles themselves may lead to repeated
infections.

3.2. Clearance of infection

Experimental studies, such as those of Rank et al. [10], have found that
laboratory chlamydial infection of guinea pigs leads to an initial spike or peak
of chlamydial particles approximately one developmental cycle after positive
infection, followed by a longer period with lower particle levels recorded, a
second smaller peak and after approximately 15 – 21 days, nearly complete
clearance of particles from the area of interest. Figure 3 shows a number of
plots of inclusion forming units (represented in the present research by the
number of extracellular chlamydial particles) reported in the experimental
results of Rank et al. [10].

Figure 4 shows examples of the time courses of chlamydial particles and
proportion of cells infected for a cleared infection, produced by numerical so-
lution of equations (1)–(3). Figure 4(b) show an initial spike in infected cell
numbers (to approximately 10% of all cells), before a reduction in infection
due to the effects of the immune system, then a recovery in the infection near
13 days post infection, and finally immune clearance of the infected cell pop-
ulation. The chlamydial particle plot, shown in Figure 4(a), demonstrates a
similar initial peak of infection near 4.5 days post infection, then a period of
lower but non-zero chlamydial particle presence, and finally immune clear-
ance around 15 days post infection. Parameters used in the solution shown in
Figure 4 were $P = 350, \kappa = 0.33, \gamma = 6, \mu = 6, r_E = 0.005$, and $D_C = 0.01$,
with initial values of $\sum_{x^* \in D} C_0(x^*) = 1000, E_0 = 50$ and $I_0 = 0$.

Figure 5 shows the chlamydial particle distribution in space (along the
genital tract). Here we note that the initial innoculum of chlamydial particles
centred at the “lower tract” region undergoes both dispersion and internal-
isation within the first day and a half of the infection process. However
after approximately two days, a wave-like spike of particles is seen travelling
Figure 3: Number of inclusion forming units (IFUs) against time for female guinea pigs infected with various initial doses of chlamydiae or by sexual transmission, adapted from [10].

Figure 4: An example of cleared infection. Time course plots of (a) the total sum of Chlamydia particles throughout the domain at each point in time (here, $C_{\text{max}} = 3811$) and (b) the proportion of all cells in the domain that are infected at each point in time.
towards the upper region of the genital tract. The results presented in Figures 4 and 5, arising from the inclusion in this model of a diffusion term in the equation for chlamydial particles, suggest that it may be possible that ascension of chlamydial infection in the genital tract is caused by diffusive transport of the particles to the upper region of the tract.

3.3. Persistent infection

When both the immune response rates and the infection rates are high, numerical solution of the model predicts that a nonzero steady state of infection is reached. Figure 6 shows an example of this behaviour where we see, as in the previous example, an initial peak in the chlamydial particle population, before $C(t)$ oscillates and settles to a high, nonzero level. Similarly, the proportion of all cells that are infected undergoes an initial rise to around 15% of all cells, then settles to a lower but fairly constant value. Based on these numerical results, we hypothesise that experimental observations of persistent infection behaviour may be a result of this type of balance between strong cellular and humoral immune responses and a high infection rate. Parameters used in the solution shown in Figure 6 were as in Table 1 along with $P = 350, \kappa_2 = 0.6, \gamma = 10, \mu = 10, r_E = 0.05, E_{\text{max}} = 50,$ and $D_C = 1$ with initial values of $\sum_{x^* \in \mathcal{D}} C_0(x^*) = 1000, E_0 = 50,$ and $I_0 = 0.$
Figure 6: An example of persistent chlamydial infection. Time course plots of (a) the total sum of Chlamydial particles throughout the domain at each point in time (here, \( C_{\text{max}} = 7259 \)) and (b) the proportion of all cells in the domain that are infected at each point in time.

Figure 7 and 8 show spatial distributions of chlamydial particles for early times (Figure 7) and over a longer period (Figure 8). Here we again see a wavelike spreading of the initial inoculum of chlamydial particles from the “lower tract” region to the “upper tract” within the first 3 days of infection. Unlike the previous example, the wavelike peak here moves more quickly due to a higher rate of dispersion. Eventually, after approximately 9 days, the level of chlamydial particles reaches a nearly homogeneous, nonzero level throughout the genital tract. This dispersed load of infectious particles allows the infection to persist over time as seen in Figure 6.

4. Discussion

We have developed a mathematical model of chlamydial infection that couples spatial dispersion of chlamydial particles with a description of infection dynamics, implicit cell-mediated and humoral immune responses and the release of infectious particles at the completion of the intracellular developmental cycle. Numerical solution of the model shows that it can reproduce infectious particle and infected cell time courses that qualitatively mirror those observed in experimental studies of the chlamydial infection of guinea pigs. We have been able to generate numerically, both cleared infections and infections that persist over time.
Figure 7: Spatial distribution of chlamydial particles at five time points over the early course of the infection showing the wave-like spatial progression of a peak chlamydial particles from the lower to upper genital tract. Here, the maximum spatial value of $C$ is $C_{\text{max}} = 118$.

Figure 8: Spatial distribution of chlamydial particles at five timepoints over the course of the infection showing the moving peak of chlamydial particles reaching the upper end of the genital tract before settling to a homogeneous nonzero distribution throughout the tract. Here, the maximum spatial value of $C$ is $C_{\text{max}} = 118$. 

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Numerical solution of the mathematical model presented in the current research support recommendations of Wilson et al. [17] that treatment interventions that involve enhancing the host immune response should aim to do so early in the infection as this can prevent the formation of a chlamydial peak and result in rapid clearance.

By investigating spatial changes and incorporating spatial dispersion of infectious particles in our model, we have exposed a potentially important phenomenon. Firstly, we found that by increasing the diffusion of extracellular chlamydial particles the magnitude of the chlamydial load peak was boosted while the time to peak remained essentially unchanged. Interestingly, we found that this increase in diffusivity also resulted in a shortened ‘infection tail’ – that is, the period of time following chlamydial load peak up until clearance of the infection. We postulate that the earlier availability of a greater number of susceptible cells, caused by the movement of EBs away from the inoculation site toward the upper tract when the diffusion parameter increases, results in the increase load peak, while the shortened infection tail results from the heightened immune response to the higher chlamydial particle load and infected cell peaks.

Our model demonstrates that if the timescale of movement or dispersion of chlamydial particles over the length of the genital tract is near to or shorter than the intracellular chlamydial developmental cycle timescale, then it is essential that spatial phenomena be considered in future theoretical and experimental research.

The model also uncovers an avenue for experimental investigation of a potential treatment/prevention pathway. Numerical solutions of the model show that increased infectious particle motility leads to inflated magnitudes of infected cell and chlamydial load peaks, and in turn these inflated peaks lead to stronger host immune responses. We hypothesise that increasing the ability of particles to disperse will result in a faster clearance of the chlamydial infection by the immune system. If such a change in particle behaviour can be provoked, while simultaneously coping with the negative effects of increased intensity of the infection, this may be a useful method of treating chlamydial infection in the genital tract.

Obviously, this model is a simplified picture of the extremely complex chlamydial infection process and host immune response. As such the hypotheses proposed and the findings discussed in this paper must be considered in context and used to stimulate further theoretical and experimental research. This model does however provides a basis for the development
of more complicated models that capture more of the underlying processes involved in chlamydial infection. Current research being undertaken by a subgroup of the authors of the research presented in this paper involves extending the model developed by incorporating explicit descriptions of the immune response while another subgroup is developing more accurate models of the chlamydial burst size.

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References


