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The arrested immunity hypothesis in an immunoepidemiological model of Chlamydia transmission

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HIGHLIGHTS

- We test the arrested immunity hypothesis using an immunoepidemiological framework.
- For each host, we model Chlamydia replication and the buildup of immune responses.
- Individual hosts are then connected in small networks.
- For individuals, early treatment inhibits immunity, maintaining susceptibility.
- Across networks, incomplete treatment coverage extends an outbreak's duration.

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ABSTRACT

For curable infectious diseases, public health strategies such as treatment can effectively shorten an individual's infectious period, and thus limit their role in transmission. However, because treatment effectively eliminates antigen impingement, these types of control strategies may also paradoxically impair the development of adaptive immune responses. For sexually transmitted *Chlamydia trachomatis* infections, this latter effect has been coined the arrested immunity hypothesis, and is discussed to carry significant epidemiological implications for those individuals who return to similar sexual networks with similar sexual behavior. Here, we examine the effect of antibiotic treatment on the spread of Chlamydia infection through a simple immunoepidemiological framework that characterizes the population as a collection of dynamically evolving individuals in small, paradigmatic networks. Within each individual there is an explicit representation of pathogen replication, accumulation and persistence of an immune response, followed by a gradual waning of that response once the infection is cleared. Individuals are then nested in networks, allowing the variability in the life history of their infection to be functions of both individual immune dynamics as well as their position in the network. Model results suggest that the timing and coverage of treatment are important contributors to the development of immunity and reinfection. In particular, the impact of treatment on the spread of infection between individuals can be beneficial, have no effect, or be deleterious depending on who is treated and when. Although we use sexually transmitted Chlamydia infection as an example, the observed results arise endogenously from a basic model structure, and thus warrant consideration to understanding the interaction of infection, treatment, and spread of other infectious diseases.

1. Introduction

The genus *Chlamydiae* encompasses a unique class of obligate intracellular bacteria that can cause disease in a wide range of animals (Bavoil et al., 2000). In humans, sexually transmitted *Chlamydia trachomatis* is an important public health concern largely because of its adverse effects on reproduction. For women,

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untreated Chlamydia infections can result in pelvic inflammatory disease, and can have long-term consequences such as scarring of the fallopian tubes and ovaries, ectopic pregnancy, chronic pelvic pain, and infertility.

Evidence from epidemiological research indicates that genital reinfection is common and plays a role in the development of the infection-related sequellae mentioned above (Brunham and Rey-Ladino, 2005). The high incidence of reinfection has led investigators to question whether there is protective immunity to chlamydial genital infection (Schachter et al., 1983), or conversely, whether clinically inapparent infections develop in some women (Su et al., 1999).

Inference by analogy with rodent models supports the existence of an effective immune response against Chlamydia infection (Bavoil et al., 2000; Brunham and Rey-Ladino, 2005; Morrison and Caldwell, 2002; Rank et al., 1988; Igietseme and Rank, 1991; Johansson et al., 1997; Su et al., 1999; Morrison and Morrison, 2005). These animal models of human genital tract infections demonstrate that a large proportion of animals resolve primary infection and are temporarily resistant to reinfection. When reinfection does occur, inflammation and disease are significantly shorter and bacterial load is either greatly reduced, or is non-existent (Rank et al., 2003).

One of the major immune mechanisms for controlling Chlamydia infection occurs through the depletion of cellular tryptophan (TRP) by indoleamine-2,3-dioxygenase (IDO)—a Th1 process that is mediated by interferon gamma (IFN-g) (Brunham and Rey-Ladino, 2005; Rey-Ladino et al., 2007; Debattista et al., 2003). A failed or weak Th1 response will allow Chlamydia RBs to respond to immune challenge by converting into a nonreplicating but revivable persistent state (Debattista et al., 2003; Leonhardt et al., 2007). In this persistent state, Chlamydia bacteria have been demonstrated to remain able to direct their own survival and still allow for antigen-presentation (Rey-Ladino et al., 2007). A direct consequence of this prolonged infection is antibody- or Th2-mediated hypersensitivity (Debattista et al., 2003). However, an over-stimulated Th1 response will lead to delayed-type hypersensitivity, and an increased risk of IFN-g-mediated tissue damage, that is likely a consequence of an initially dominant Th2 response.

Thus, significant biological differences may exist between mice and humans in their ability to generate a protective immune response to chlamydial infection (Su et al., 1999). This disparity might simply be the result of basic differences between species (Brunham and Rey-Ladino, 2005). Alternatively, it could also reflect the fact that humans, unlike other animal species, commonly receive antibiotic treatment (Su et al., 1999; Brunham and Rey-Ladino, 2005), an intervention that, in the previous immunological research, has been demonstrated to impair the development of an adaptive immune response (Bellahsene and Forsgren, 1985; Su et al., 1999). In epidemiological literature, this disruption of the immune response by antibiotic treatment has been coined *The Arrested Immunity Hypothesis* (Brunham and Rekart, 2008), and has been discussed as a reason for Chlamydia case notifications that now exceed those recorded before large-scale intervention strategies were implemented (Rekart and Brunham, 2008; Brunham and Rekart, 2008; Brunham et al., 2005; Lyytikainen et al., 2008).

As a public health policy, treating Chlamydia infections with antibiotics reduces the duration of infection, thus decreasing an individual's chances of developing adverse disease sequellae. However, since host and pathogen are tightly coupled, treatment policies that are specifically aimed at the pathogen will ultimately affect the host as well—you cannot do just one thing (Sterman, 2006). Infected cells increase through new infections and decrease by cell death and clearance by host immune responses; antibiotic treatment, however, also reduces the number of infected cells by eradicating Chlamydia bacteria; depletion of infected cells further removes the antigen impingement on the immune system. As a direct result, the arrested immunity hypothesis underscores the importance of gaining a better understanding of the interplay between the immunobiology of infection and the use of antibiotics (Gottlieb et al., 2010).

To our knowledge, the observed immunological effect of antibiotic treatment has only been directly observed in non-interacting individuals (Su et al., 1999). Conversely, the proposed counter-intuitive epidemiological implications of arrested immunity have been observed in the absence of detailed data on immunobiological characteristics (Brunham and Rey-Ladino, 2005). Therefore, questions remain about whether the effect of treatment on adapted immune responses propagates outward from within an infected host to their susceptible contacts.

In this paper, we develop an introductory link between Chlamydia infection and host immune responses, and we place an emphasis on how treatment impacts transmission. We do this by developing a simple immunoepidemiological model. Our approach includes strong simplifications due to this model being the first exploration of Chlamydia spread between hosts using an immunological perspective as its foundation. Individuals are nested in small, prototypical networks, which allow for building intuition of the interdependencies present both within hosts, and between hosts. It is important to note that this is an attempt to understand the arrested immunity hypothesis, not as a driver of epidemiological trends in human populations, but as something more fundamentally-linked to treatment (and spread) of infection—we just happen to use Chlamydia as our example.

2. Material and methods

2.1. Rationale for an immunoepidemiological modeling framework

Understanding the impact of public health efforts for infectious disease control is central to evidence-based public health policy (Brunham and Rekart, 2008). However, because complexity behind disease dynamics hinders our ability to discover the delayed and distal impacts of our actions, the outcome of many public health programs can be poorly understood (Sterman, 2006). Modeling has become a central tool in understanding the epidemiological processes underlying infectious disease transmission and aids the design of effective control strategies. For a wide range of infectious diseases, individual heterogeneity can be modeled effectively. For example, individuals can be represented as vertices in a network, where the connections between individuals represent potentially infectious contact. Models that use explicit network structures enable the study of how behavioral variability will impact diffusion processes, and have proved useful for understanding the spread of SARS, influenza, foot-and-mouth disease, tuberculosis, and quintessentially, STIs (Kiss et al., 2008). Network models represent an alternative approach to modeling infection spread by aggregate, compartmental models distinguished by their greater ability to capture behavioral heterogeneity and allow for the examination of various control strategies that take advantage of a given network structure (Lena et al., 2005), rather than assuming that the contact among susceptible and infected individuals is a random process (House and Keeling, 2010; Keeling and Eames, 2005). However, network models seldom incorporate individual representations of immunological differences.

Recent developments in immunoepidemiological modeling frameworks offer a chance to explore and explain mixed STI transmission dynamics that are linked not only to behavioral variability (i.e. network structures), but also to the variability in an individual's immunobiology. A number of previous methodologies have