Parran Award Lecture

Insights Into the Epidemiology of Sexually Transmitted Diseases From $R_o = \beta cD$

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Because the Thomas Parran Award is the highest honor in the field of sexually transmitted disease (STD) prevention and research, I am humbled and honored to be this year's recipient. I want to express my thanks to the Association and the Award Committee for this great honor. Any lifetime achievement award results from a lifetime of influences and my experience is no different. I owe an extraordinary debt of gratitude to King Holmes, Allan Ronald, and Roy Anderson. They have shaped how I think about STD research and their ideas repeatedly appear in my work. I also owe thanks to the many colleagues and students with whom I have worked over the years. In particular, I want to acknowledge the pleasures of working with Frank Plummer, Stephen Moses, Joshua Kimani, Fred Aoki, Jamie Blanchard, Rosanna Peeling, Grant McClarty, Michael Rekart, David Patrick, Babak Pourbohloul, and Craig Cohen. My 23-year career as an academic physician entirely depended on the constant support that I received from my wife and 2 sons. I am forever thankful for their unending patience and encouragement.

The basic reproduction number (R_o) is fundamental to understanding infectious disease epidemiology. R_o describes the average number of secondary infections that an infected individual generates when entering a fully susceptible population, and when greater than one, it defines ecologic success for a pathogen. Natural selection acts to optimize R_o when an emerging infectious disease newly enters a species population, thus shaping the genotypic and phenotypic properties of a microbe. A range of R_o values have been computed for different pathogens depending on factors such as routes and density dependence of transmission and susceptibility of the pathogen to innate and adaptive immune defenses.[1,2]

The concept of the reproduction number has been critical to understanding the epidemiology of sexually transmitted infections (STIs)[3] and has helped rationalize prevention strategies.[4] R_o is determined by 3 parameters: β, which represents the per-capita transmissibility of the agent; D, the average annualized duration of

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infection; and c, the pattern of contact between susceptible and infectious persons:

$$R_o = \beta cD$$

STI prevention programs can be aligned with each of these parameters. For instance, condoms, microbicides, and vaccines reduce susceptibility (β); behavioral interventions are aimed at altering sexual behavior and sexual networks (c); and antimicrobials reduce the average duration of infection (D). A distinctive characteristic of infectious disease epidemiology (as opposed to the epidemiology of chronic disease) is that incidence depends on prevalence, and therefore case detection and treatment is a major approach in bacterial STI prevention efforts. In short, treatment is prevention.

β captures the effects of host resistance and susceptibility factors, which are determined by innate defenses and by adaptive immunity. STIs are often thought to engender little or no immunity in part because they have evolved mechanisms to successfully penetrate innate defenses and replicate in hosts even after the development of adaptive immunity. As examples, they can display extraordinary antigenic variation (*Neisseria gonorrhoeae*), evade the actions of interferon-γ (*Chlamydia trachomatis*), present few surface proteins to the immune system (*Treponema pallidum*), infect immunologically privileged sites (herpes simplex virus and human papilloma virus), or directly disable the adaptive immune response (human immunodeficiency virus). Clearly, immune evasion mechanisms for sexually transmitted pathogens are varied and elegant, illustrating that the immune responses elicited by an STI must be intense because such forces have shaped molecular characteristics of the pathogen. Overall, STI immunity is better viewed as robust but complex that waxes and wanes as demographic forces alter the populations in which STIs are spreading.

An example of complex immunity to an STI is that seen with syphilis in which ongoing infection is necessary to sustain immunity to reinfection. This phenomenon was experimentally documented in the infamous Sing Sing prison study in which individuals with untreated early-latent syphilis resisted intradermal challenge with *T. pallidum,* but individuals with treated latent syphilis were fully susceptible to challenge infection.[5] This phenomenon is also seen with other infectious diseases such as cutaneous Leishmaniasis and is called concomitant immunity.[6] Concomitant immunity is the result of the fact that immune effector lymphocytes secreting IFN-γ are necessary for clearance of the

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pathogen, but T regulatory lymphocytes secreting IL-10 that are necessary to modulate the extent of collateral tissue damage down-regulate T cell-mediated clearance of the parasite. These immune mechanisms may also be at work during syphilis and account for the cyclical nature of syphilis epidemiology.[7] Syphilis cycles with a decadenal frequency, likely in part driven by immune forces and in part by population-level demographic changes in the host population.

Similarly, complex immune forces shape the immunobiology of *C. trachomatis* infection. The natural history of *C. trachomatis* infection is characterized by an extended duration of infection with 50% of persons remaining infected at 1 year and 10% after 3 years.[8] Presumably, the many immune evasion mechanisms of the organism allow it to persist in hosts despite the development of immune responses.[9] Nonetheless, *C. trachomatis* is highly susceptible to immune defenses as seen among sex workers who make IFN-γ responses to chlamydial antigen and highly resist infection.[10] Interestingly, sex workers who make IL-10 responses exhibit increased susceptibility to infection. Thus, immunity to *C. trachomatis*, like that to Leishmania and syphilis, may depend on acquiring the correct balance between antigen specific IFN-γ and IL-10-producing lymphocytes and takes some time to acquire after natural infection. Given that chlamydia immunity takes time to acquire, it is of interest that experiments in murine models of chlamydia infection clearly show that early antibiotic treatment abrogates the acquisition of immunity and heightens susceptibility to reinfection.[11]

Do these observations have implications for the effectiveness of current chlamydia prevention programs? Among other strategies, chlamydia prevention depends in large part on case detection and antimicrobial treatment, which aim to shorten the average duration of infection. This strategy targets improving reproductive health by preventing the development of pelvic inflammatory disease (PID) and its sequela. Excellent data have documented that detection and treatment of chlamydia infection reduces PID rates,[12] and in many jurisdictions with longstanding chlamydia prevention programs, sustained declines in PID, ectopic pregnancy, and tubal infertility rates have been seen. However, paradoxically, it is also commonly observed that infection rates, although initially declining following the introduction of chlamydia prevention programs, are now rising, producing a U-shaped epidemiologic curve.

How can we explain the key effects of a chlamydia control program? In general, disease detection programs are more successful at finding prevalent than incident infection, and because PID appears to depend on persistent chlamydia infection,[13] it can be argued that by reducing prevalent infection, chlamydia prevention programs should also reduce PID rates. Although it is not fully elucidated as to how persistent chlamydia infection induces inflammatory disease, it is likely correlated with immunopathogenesis mechanisms mobilized after chlamydia infection. Thus, limiting immunopathology by shortening the average duration infection may be the mechanistic basis for reducing the risk for chlamydial PID and its sequelae.

However, why are infection rates now increasing? Studies in Sweden where similar U-shaped epidemiologic curves for chlamydia case rates have also been recorded after the introduction of chlamydia prevention control programs have concluded that neither changes in sexual behavior nor diagnostic testing account for the sustained recent rise in case rates.[14] Rather, the authors concluded that there has been a true rise in prevalence but were unable to determine what caused this rise.

Recently, we examined the epidemiology of chlamydia in British Columbia during the era of chlamydia prevention and noted that there has been a striking rise in reinfection rates in the latter part of the prevention era.[15] Using a Cox proportional hazard model, it was determined that there has been an annual 4.6% increase in the relative risk of chlamydia reinfection over the 14 years of the program. The rise in relative risk was greater among younger than older persons and greater for women than for men. We interpreted these changes to suggest that there have been changes in population susceptibility to reinfection, in effect a reduction in herd immunity.

To test this interpretation, a compartmental standardized incidence ratio mathematical model was constructed in which we compared the effects of treating individuals at earlier and earlier stages after infection. An underlying assumption in the model was that immunity to chlamydia takes time to occur after acquisition of infection. Over a wide range of scenarios, including the proportion of infections treated, the model reproduced the observed U-shaped trend seen in the British Columbia data, that is, a period of initial decline in case rates is followed by a rebound in rates. Thus, the model is consistent with the notion that the current approach to chlamydia prevention based on shortening the average duration of infection has caused an unexpected effect on the population level of chlamydia immunity. Overall, we conclude that improvements in reproductive health can occur after the introduction of chlamydia prevention programs, but infection rates will paradoxically rise as a result of effects on time-dependent acquisition of immunity. We also conclude that prevention for chlamydia and likely other STIs will depend on the development of vaccines, and vaccine research needs to remain a central objective for STI researchers if better control and elimination is to be achieved.

In the mathematical model described here (and likely also true in life), one of the reasons that chlamydia rates rebound after antimicrobial intervention is that individuals reenter unchanged sexual networks with heightened susceptibility to reinfection. Thus, changes in sexual networks can also be expected to produce substantial gains in STI prevention, but we currently understand little about the structure of sexual networks or how infection spreads through them. Sexual networks are inherently a population-level phenomenon, and network analysis of human sexual behavior is also another prime area for STI research. Social scientists working with mathematicians are now beginning to make significant contributions to understanding sexual networks.[16]

The provocatively entitled article "Chains of Affection: The Structure of Adolescent Romantic and Sexual Networks" empirically revealed the network structure of teenage relationships.[17] These networks were characterized by long chains and few cycles in which a small number of micromechanisms such as rules around how partners chose one another determine how the networks are generated. Other social scientists have shown that the web of human sexual contacts at the whole population level has a power law "scale-free" degree distribution in the number of sexual partners.[18] This means that many persons have one or a few partners, whereas a few persons have many partners. This produces the "fat tail" phenomenon in the recorded numbers of sexual partners so frequently observed in population-level surveys of sexual behavior.

A rigorous mathematics exists to characterize network phenomena in which graph theory is used to define the architecture of a network and percolation theory is used to model the spread of infection on the network. A network approach to understanding and modeling the epidemiology of STIs should shed considerable light on the epidemiology of infection. For instance, modeling suggests that different network structures are very different in terms of their susceptibility to epidemic spread of disease.[19] Interestingly, power law scale-free networks are much more resistant to introduction of infection than are random or Poisson networks, and depending on the network structure, different networks have different epidemic thresholds.

In general, there are 2 bifurcation patterns in network architecture, one in which the branching pattern is constantly growing outward with little clustering and the other in which the branching pattern feeds back on itself generating cycles. These 2 patterns resemble disassortative and assortative social mixing patterns. Interestingly, molecular epidemiologic studies suggested that different STIs appear to transmit differently in different networks in which gonorrhea appears to be able to transmit in assortative networks and chlamydia in disassortative networks.[20]

Networks can be connected to one another over long geographic distances creating "small-world" effects. This was clearly seen with SARS in which intense transmission in a single hotel in Hong Kong generated transmitters who spread the infection globally through air travel.[21] "Small-world" effects are also apparent in STI epidemiology in which syphilis epidemics have become increasingly spatially synchronized in different U.S. cities over time.[7] This suggests that local sexual networks in one city share links with one another, and that linkages among sexual networks are increasing through time. In fact, we may be moving to an era of globalization of sexual networks with this being be one of the critical factors in the emergence of the global HIV pandemic.

Network theory offers a real opportunity to map the spread of STI through behavioral networks, allowing for prediction of community vulnerability and identification of early intervention strategies. Nonetheless, major challenges exist for network research. For example, approaches to modeling of STI transmission on heterogeneous networks in which different persons have different levels of immunity and different types of sexual contact will need to be developed.[22] To date, network analysis has focussed on homogeneous networks in which all vertices (persons) and links (sexual contacts) are assumed to be identical. Clearly, heterogeneous networks more accurately capture the biologic and sociological characteristics of STI transmission.

Thus, $R_o = \beta cD$ offers deep insights into the biology and epidemiology of STI. The formula accents how immunity is a major (and underappreciated force) shaping the epidemiology and ecologic success of STIs. Research on the immunoepidemiology of STIs will require the tools of network analysis as well as immunology, and the future for STI control will increasingly depend on acquiring an ability to develop STI vaccines as well as change sexual networks. Already, vaccines exist for hepatitis B and human papilloma virus; they are on the horizon for herpes simplex virus; they may be just over the horizon for *C. trachomatis*, *N. gonorrhoeae,* and *T. pallidum;* and a vaccine for HIV remains the single most important goal for all of public health. Prevention of STI/HIV will require coordinated collaboration of a broad array of life scientists, social scientists, and mathematicians. This can be facilitated by sharing a common theoretical framework such as that described here and is united in one of the grand challenges of global public health.

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