Emily's Thesis Title

Emily Pollock

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Abstract

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Emily Pollock

Chair of the Supervisory Committee:
Title of my chair Steven M. Goodreau
Biological Anthropology

"Here is my abstract"

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“My acknowledgments”

Dedication

"My dedication"

Introduction

Anthropologists have long recognized the importance of social connections and behavioral variation among humans and our nonhuman primate relatives. Indeed, the ability for us to participate in distinct but potentially interlocking complex social networks has fueled our evolution as a species and made our uniquely elaborate life possible. Network analysis has often been utilized as a way to visually and quantitatively represent these ties in order to understand their effects on those connected to each other, from kinship, social support and social capital, to the diffusion of information and transmission of disease. These latter networks are crucially important to our understanding of how human biosocial variation influences our health, where the oft-beneficial complex social networks we maintain and navigate every day can also put us at risk of exposure to infection.

transition to STIs

In order to understand the complex patterns by which sexually transmitted infections (STIs) are transmitted throughout populations, we first need to understand the behavior of human relationships and how these behaviors generate the dynamic sexual network across which these types of infections can spread.

This work is guided by the theoretical framework of the human ecology of infectious disease, the investigation of how human behavior, social patterns, and built environments interact with the broader pathogen environment to influence our health. Of particular interest is not just aggregate behavior, but also how variation in individual behavior influences social patterns and alters the landscape through which diseases spread, particularly as this variation relates to biological age. Syndemic theory will also be

used as a guide to understand how variation in behaviors and patterns act synergistically to increase vulnerability and exacerbate existing health disparities of certain population subgroups (Singer et al., 2006).

can I pull some stuff from my PAA abstract about age?

- transition to a history of the evolution of epidemic models (ie. from compartmental where everything is basically independent and exponential through to ERGMs where formation can be quite elaborate but we've never spent much time thinking about dissolution)

Mathematical models are quantitative representations of real-life systems and the processes within these systems important to the outcome of interest. This form of inquiry is particularly useful when classic scientific experiments to understand disease spread or intervention efficacy cannot be conducted for either practical or ethical reasons, or when specific processes or parameter values in a system are unknown. In these situations, we use mathematical modeling as an in-silico laboratory to explore ideas and test hypotheses. Of course, the form and complexity of these models are determined by a variety of factors including the type of question that needs answering and the natural history of the infection of interest, but many types of mathematical models rely on similar underlying assumptions. Without diving too deep into the history of epidemic modeling, here I give a brief overview of the various model forms to highlight some key similarities and differences.

Initial mathematical models for epidemics were deterministic and compartmental in nature. They did not represent people individually, rather they group them into homogenous compartments representing specific states of interest, a portion of which transitioned between compartments at each time step based on a rate. In the most basic models, the compartments are usually "susceptible" and "infected" and the rate of transition from susceptible to infected depends on the rate of contact between the groups and the size of the infected group relative to the whole population. Additional complexity can be added by adding more compartments or states, like breaking down the state of susceptible and infected into demographic states like race or age groups, adding compartments for vector populations like mosquitoes, or by representing a more complex natural history of the pathogen by including states for groups such as "exposed but not infectious", "recovered", "infected and symptomatic", or "infected and asymptomatic"

to name a few. These models were deterministic in nature because the transitions between compartments rely on unchanging rates: the same proportion of each component transitions at each time point and if you run a deterministic compartmental model (DCM) multiple times you will alway have the same result.

Stochastic models grew out of this original framework as a way to capture variability and uncertainty in the systems we wish to study. In this scenario, some or all transitions between states were based on a *probability* of transitioning rather than a set rate, meaning that not the same proportion of a state transitioned at every time step, but on *average*

Notice the assumptions implicit in the way transitions occur in these models - it is memoryless, generating an exponential distribution (or geometric if using discrete time).

- dynamic networks require information about relationship duration
- why doing a bit better on dissolution/duration, especially by age, will be extra important for thinking about certain interventions for certain relatively short-lived infections (e.g. partner services in chlamydia).
- additionally, while births and deaths have been a part of models, only recently are we adding explicit age-dependent formation terms – and age changes over the simulation – what is this effect?
- including age in dynamic models may sound straightforward but as we're going to see adds a surprising amount of complexity

Notes from NME intro to modeling

exponential – memoryless survival function, exchangeability

all models have three basic components - elements (actors), states (attributes), transitions (rates of movements between states)

DCMs within each compartment, people are homogenous flows are represented by rates - the fraction of the aggregate count that moves from one compartment to another any any time point each run gives the

same results

at the most basic level - what do you need to transmit infection? one infected and one susceptible and some assumption(s) about the transmission process (acts, transmissibility, etc)

“contacts” somewhat misleading because multiple acts with same person makes a huge difference - but DCMs treat all contacts as independent, and/or contacts estimated as a full complete partnership

move into stochastic modeling (can be have stochastic and deterministic components)- rates become probabilities

1

Survival Analysis of Relationship Duration

- main goal here to understand where in the distribution we may not be capturing when we use models based on a memoryless process, and explore some ways to do better within the constraints of feasibility imposed by epidemic models
- so we primarily use the exponential distribution in the SA analyses
- discuss survey data and censoring / truncation issues
- And then flesh out the details of the analyses with a clear narrative and you have the core of a chapter!

The duration of sexual relationships across a population generates the network structure largely responsible for either exposing individuals to or protecting individuals from sexually transmitted infections

(STIs). In addition to dictating this period of possible exposure, relationship durations relative to the pathogen-specific duration of infection are an important driver of how quickly STIs can spread throughout a population. Transmission beyond a pair of actors for infections with short durations relative to relationship lengths is challenging and slow, and it is more likely that an infection will be detected and treated or resolved naturally prior to the dissolution of the relationship. If the duration of infection and duration of relationships are more equal, there is a greater chance that the infection can spread to future partners and throughout the network. When partnerships overlap, transmission pathways increase even among those individuals with few lifetime partners, and this effect is even greater when the duration of overlap is large (Armbruster, Wang, and Morris 2017; Morris and Kretzschmar 1997).

The pattern of relationship durations across the life-course is also important because STIs often have distinct age patterns in terms of prevalence. Individual age is often used as a predictor for risky sexual behavior, but there is additional complexity when considering the effect of age on the duration of relationships across the life-course. Young age likely influences the immediate intentions for relationships (i.e. serious or casual), and the frequency at which individuals form new relationships, but somewhat paradoxically it is also true that the only people who can report extremely long relationships are those who started them at young ages. This also introduces complex sampling issues because most data on relationship durations is collected cross-sectionally or retrospectively – not longitudinally. Given the importance of relationship duration to features of STI epidemiology discussed above, there is growing interest in improving the representation of relational durations in dynamic network models used to study epidemics. This study demonstrates the ways in which the current literature fails to represent this distribution and proposes a new modeling framework to better capture these relationships across the life-course.

One common class of models used to understand network influences on patterns of STI transmission is known as separable temporal exponential-family random graph models (STERGMs). These models are governed by two expressions: one that represents the set of processes that influence the formation of relationships, and a comparable one for dissolution (Krivitsky and Handcock 2014). The current standard practice for the dissolution models in this modeling framework assumes that once a relationship begins, its persistence is governed by a constant hazard. This memoryless process is a convenient simplifying

assumption, adopted because most hypotheses being explored relate to processes impacting network formation or cross-sectional structure. However, it is unlikely that this assumption faithfully represents the distribution all relationship durations we observe across a wide range of ages.

Several recent models have begun to address this issue by splitting out relationships into two categories: the first, marriages and cohabitations or main partnerships, and the second, persistent or casual partnerships. These are then modeled as separate networks simultaneously. By structuring the model in this fashion, each network has a hazard of dissolution specific to its type. (These models often have a third network for one-time sexual contacts which last only one time-step, but this network is not the focus of our study). While these models are indeed able to reproduce the mean relationship lengths drawn from empirical data, it remains unknown how well these strategies reproduce the full distribution of lengths observed. In particular, the memoryless assumption means that the modal length of main partnerships remains near zero across all ages, which basic intuition says is not true and descriptive data analysis confirms. Other work has considered disaggregating relational durations by a single demographic attribute of their members related to a hypothesis or prevention modality being explored, but again with no further effort to capture the full distribution, particularly by age (Goodreau et al. 2017; Jenness et al. 2017).

In this ongoing study, we seek to understand the changing distribution of relationship duration over the life-course using data from the National Survey of Family Growth, to evaluate which features the above dissolution assumptions are capable of replicating and which they cannot. We then introduce an alternative framework designed to more faithfully represent these data and the different demographic and data-collection processes that impact them in an age-structured population over time. We use tools from both event history analysis and network analysis to answer the following questions: First, under what circumstances, if any, can an exponentially distributed time-to-event model reasonably approximate empirical relationship duration data? Second, does it make sense to lump marriages and cohabitations into one network with the same dissolution probability? And third, can we better capture the age-wise relationship distribution by using one network where (1) relationships can transition between states (e.g. from a cohabitation into a marriage) rather than modeling several types separately, and (2) where relational formation probabilities depend on current relational status.

Data

The empirical data used in this study are drawn from the 2006-2010 and 2011-2015 waves of the National Survey of Family Growth (NSFG). The NSFG surveys men and women aged 15-44 on many aspects of family life, including but not limited to marriage and divorce, pregnancy, contraception use, infertility, and other aspects of sexual and reproductive behavior. In addition to the demographic information recorded for each respondent and their sampling weights, in this study we use the data collected in section C of the public use files on each respondent's recent sexual partnerships with opposite-sex partners in the last year, with a maximum of three partnerships reported. These data include the century-month of first sexual contact, the century-month of last sexual contact, whether the respondent considers this sexual partnership to be ongoing, and the partnership status (marriage, cohabitation, or other). We limit the combined data set to those respondents who report at least one partnership in the last year. Out of the original 43,303 respondents, our subset contains 32,516 respondents who report on 40,443 sexual partnerships. Due to the study design, all relationships that respondents report as ongoing on the day of interview have right-censored relationship lengths, and there is left-truncation present due to the large number or relationships that started prior to the observation window but continued into it.

Methods

First the empirical relational duration data (using the start and end dates of all reported relationships in NSFG) will be investigated using histograms (overall and stratified by age category). Then, due to the issues of right censoring and left truncation as a result of survey design in NSFG, a reference survival curve will be constructed from the empirical data using a Modified Kaplan-Meier model following (Burington et al. 2010) and using the R package 'survival'. Next, exploratory parametric models will be estimated from the data (with corrections for right-censoring and left-truncation) using a variety of distributions (namely and latent mixture components) to gain intuition about the underlying generative processes. Initial models will be covariate-free (representing the effects of relationship duration only on the chances of survival) and additional models will begin to examine the influence of age on relationship duration, including (but not limited to) the ego's age category, the reported current age difference between ego and alter, and the ego's age category at the beginning of each reported relationship. All models without latent

components will be fit using the R package 'flexsurv' and the likelihood functions for all models with latent components will be personally developed and models will be fit using the maxLik package (Jackson 2016; Henningsen and Toomet 2011).

From PAA abstract: In our preliminary work, we first checked the assumption that relationship duration can be modeled by a simple memoryless process, and then explored some natural extensions to this framework. In order to generate the reference distribution, we fit a Kaplan-Meier model using a modified estimator to account for both right-censoring and left-truncation following Burington et al (2010). We then fit several parametric models (all adjusted for the above sampling issues): first a simple exponential model to represent the memoryless process assumption, then a Weibull distribution and Gamma distribution, all with and without additional covariate attributes. Model fit was evaluated primarily using the Akaike Information Criterion (AIC) and visuals to understand which relationship lengths were represented better than others, given our ultimate goal of adapting these into dynamic network simulations. Below is a selection of explored models; parametric models with covariate categories are displayed in color, with their Kaplan-Meier reference curves plotted in black. All parameters in these fitted models are statistically significant ($p < 0.001$).

Results

The first takeaway is that an exponential distribution alone is not sufficient to capture the relationship distribution – it overestimates the survival of short relationships and underestimates the survival of long relationships (top left figure, below). The Weibull and Gamma perform better and capture more of the short relationships, suggesting that there is important heterogeneity in the data, but like the first models they also fail to capture the longest relationships. The age category of the reporting individual is not explanatory across all age categories (top right). This is perhaps not surprising, in that the age distribution of relationship lengths is at least partly an emergent property rather than a causal one. That is, no individual can have a relationship that has lasted longer than they have been sexually active, so the range of relationship lengths for young age categories is relatively small. Meanwhile, the older age categories are challenging to represent because the possible range of relationships is so much larger, and are likely influenced not only by dissolution probabilities but also by the changing formation probabilities over the

lifecourse – that is, older people in long-term relationships do not start new relationships at the same rate as others, and thus have relatively few relationships that are short.

The next two models test how appropriate it is to group relationships defined as marriages and cohabitations into the same dissolution model, as has been done in recent STERGMs. We see clear evidence that marriages and cohabitations have distinct hazards of dissolution and the combined marriage and cohabitation curve, like the simple exponential for all relationships, dramatically fails to capture both the shortest and longest relationships of these types (bottom right and bottom left figures, respectively. These results are similar to other work in family demography that has shown significant differences in the risk of dissolution between cohabitations and marriages due to variation in joint lifestyles (van Houdt and Poortman 2018). These results suggest to us that previously developed STERGM dissolution models that only capture the mean relationship length are not appropriate approximations of the data, and that cohabitation represents a distinctly separate type of relationship from marriages and other casual relationships and should be treated as such in our networks.

2

Demography and Dynamic Network Simulations

needs better title

Having gained insights about factors important (and not important) to the patterns of relationship length over the age course from survival analysis, the next steps initially seemed straightforward. First, I was going to build a two-network simulation model comparable to recently published models (where the casual/shorter relationships are represented on one network and marriages and cohabitations are represented on another) and analyze the patterns of relationship duration across the simulated age range to understand the ways in which we are able to recreate the empirical distribution and the ways in which we are not. Second, I was going to build a network model with a new structure: instead of modeling relationships on separate networks, I would begin all relationships as casual relationships and have them

transition over time into cohabitations and marriages. Relationship dissolution probability, as in the first model, would be based on relationship type. By transitioning relationships over time – a process much closer to reality - instead of classifying certain relationships as, say, marriages, at their onset, I hoped to match certain features of the empirical distribution better. In particular: the increasingly uniform distribution of relationship lengths at older ages as some individuals maintain long-lasting marriages and others maintain cohabitations or begin entirely new relationships.

Suffice it to say that I did not get to step two.

In mathematical models, the choice of model terms depends on the question of interest and the underlying patterns in the data and this is no less true for network models of sexual partnerships developed to understand disease transmission. Several previously published models using ERGMs and EpiModel to simulate epidemics focused on men who have sex with men (MSM) populations in a narrow age range, 18-35 (*cite papers and also double check that this is true*). These models focused on terms related to mixing patterns between races, the propensity to form relationships with individuals relatively close in age, and the likelihood of concurrent partnerships. Because prevalence of both main and casual relationships remained relatively stable over the small age range, the models did not include terms that used age as a predictor of relationship formation. However, in this project, we focus on heterosexual relationships over a larger age range (15-45). Unlike MSM, there are large clear differences in the prevalence of main and casual partnerships over this age range (insert figure), so we will need to include terms that include age in our model. In addition to influencing the distribution of relationship duration, these differences are likely to be especially important if we want to use this type of model to understand the processes that generate the large observed differences in bacterial STI prevalence by age - originally one of the broader goals of this dissertation.

- insert figure of mean degree by age (with unrestricted alters)

As it turns out, adding age-related formation terms and other important demographic processes to a dynamic network simulation has some unexpected consequences.

2.1 Model Overview & STERGM fit

several general trends in relationship formation (finish write-up and cite) –

- individuals often select partners that are not their exact age
- this difference in partner ages often increases over the life course (i.e. adults usually have wider age differences between their partners than do adolescents)
- it is common for men to partner with younger women (although the sex differences in relationship formation are not explored in this model, it's important to note that in a more realistic model the effect of aging out would disproportionately affect the women whose partners age out before them

The terms in the model are relatively simplistic so I did not expect to hit the degree-by-age distribution exactly, but the aging process within the network simulation and artificial node death at age 45, when many nodes are in relationships, heavily influences the degree distribution at the tail end of the age range in several ways.

(include model terms and coefs and explain terms) (full description of EpiModelHIV module flow w/ parameters in appendix, brief overview here)

2.2 Diagnostic Results

(to demonstrate closed-system effectiveness, assumes fixed nodal attributes)

The final step in evaluate the performance of an estimated STERGM prior to the simulation is to run a dynamic diagnostic. In this diagnostic, we simulate the STERGM for X repetitions of Y time steps and evaluate the network statistics over time. At each time step, ties can form and ties can dissolve based on the model coefficients. If the model is estimated properly and sufficient MCMC intervals are used, the network formation statistics should hover around their estimated targets. In this diagnostic we also evaluate the duration of ties and the rate of tie dissolution to ensure the dissolution targets are met. It is

important to note that this diagnostic is an indicator of model performance in a closed system: all nodal attributes are fixed, no nodes exit, and no new nodes enter the population.

2.3 Overview of Demographic Processes

The simulations run using the EpiModel API are distinct from the above dynamic diagnostic in that in addition to tie formation and dissolution at every time step, a series of modules is run that govern important demographic processes: node departure, node entry, aging, and sexual debut. Nodes automatically depart the model at age 45. This boundary was determined by two things: 1) individuals this point contribute almost a negligible amount of the yearly bacterial STI incidence [CDC figure] and 2) the National Survey of Family Growth, the empirical data from which we estimate our model, only surveys adults aged 15-45. There are likely other sources of information that we could use to increase the age range, but it did not seem necessary to our questions of interest. Note that implicit in this decision is the elimination of all reported relationships among egos aged 15-45 whose *partners* are outside of this age range. The degree distribution that we actually use to estimate the model (and are trying to maintain during simulation) looks rather different than the original distribution shown above, particularly in the marriage/cohabitation network. [insert figure]. We will consider the consequences of effect a later section. In addition to the age boundary at 45, all individuals experience the possibility of dying at each time step. Each node belongs to a class based on their 5-year-age-category and their sex, and is evaluated for death at every time step with the probability determined by data from published in U.S. Vital Statistics documents (cite). Given that our age range is relatively young, departures due to background mortality are uncommon relative to the effect of the age boundary on which nodes depart the model. Nodes enter at age 15 at a rate based on the expected number of departures per time step in order to keep the population size relatively stable. Like ASMR, the actual number of entires per time step is stochastic but maintains a population size within 1-2% of the starting size of 50,000 nodes. (Do I need to explain why we want to keep the pop stable?). Each time step in the simulation represents one week, so nodes age by 1/52 per time step. The sexual debut process is somewhat trickier to estimate and dynamically represent.

- Sexual Debut

- dynamic process, nodal attribute not necessarily monotonic in cross-sectional data - gets into period/cohort stuff that is interesting but not addressed here
- debut vs "eligibility" and what information we need for model vs what we have in the data now, in this model setup, the rate of sexual debut does not influence the birth/arrival rate in the model - as mentioned above the model is designed to have a relatively stable population with an arrival rate based on the expected number of departures at each time step. Sexual debut however does dictate whether an individual is allowed to form a relationship, and the number of un-debut persons is jointly estimated in the model, so deviations from the original distribution will influence the likelihood of tie formation...

the underlying population structure is not particularly complex...so it's not the act of aging (or migration etc) that generates problems but the fact that age is so tied to the probability of having (or not having) a certain type of relationship.

2.4 Original Simulation

Narrative order:

1. Cross network terms - we're going to avoid them due to complications

2. Older Partner

* offset for older partner

* keeping people in

* conclusion: we keep offset in all future scenarios but not older partners

3. Sexual Debut

* Debut

* eligibility

* conclusion: debut not eligibility

4. let's think about why we're seeing the things we are

* both networks have too few edges, particularly in early years

* both dissolution rates slightly too low

* marriage/cohab network: duration far too low

* casual network: duration too high

* tests:

* marriage/cohab – adj formation for earlier edges and longer durations

* casual – adj formation for earlier edges but also departure for too long relationships

`Edapprox`

5.

asides / future work

* cross-network terms - probably going to do most analysis on the independent networks but will show both and point at where there are holes (hey by the time this gets finished maybe Chad will have already figured this out)

* what distribution of formation terms / debut parameters will generate the desired mean degree by age distribution

* need to think about race and sex differences in formation and absdiff(age) by sex if we want to use this for applied work

3

Chlamydia, Acquired Immunity, & Expedited Partner Therapy?

copying over some text from diss proposal:

C. trachomatis is an obligate intracellular bacterium transmitted through sexual contact among humans. Chlamydial infections are most often asymptomatic. Untreated infections in women are an additional public health concern because they can lead to a variety of sequalae including pelvic inflammatory disease, scarring of ovaries and fallopian tubes, ectopic pregnancies, chronic pain, and infertility. Repeat infections are common and are an additional risk factor for the development of the above sequelae (Brunham and Rey-Ladino 2005). There is a great deal of uncertainty regarding the natural history of chlamydia, but the

duration of infection for untreated individuals is generally thought to be up to 6 months for men and a year or more for women (Golden et al. 2000; Satterwhite et al. 2013). Chlamydia is usually treated with azithromycin or doxycycline, and unlike other common STIs like syphilis and gonorrhea, true antibiotic resistance is rare (Kong et al. 2015).

Chlamydia is the most common reportable disease in the United States and incidence, particularly adolescents and young adults aged 15-29, is increasing nationwide. The Centers for Disease Control and Prevention (CDC) estimates that half of all new STI infections (including gonorrhea, syphilis, and others) occur in those aged 15-24 despite them making up only a quarter of the sexually active population. Even in places like King County, Washington, where overall rates have remained stable, longstanding acknowledged disparities in prevalence by race are marked and continue to increase (2015 SKCPH STD Report). These rates are particularly distressing in light of the fertility consequences of long-term infection and reinfection: it is estimated that in King County, over 60% of non-Hispanic Black women have had at least one chlamydia infection by age 34 (a rate 5x higher than non-Hispanic White women) and 1 in 500 of non-Hispanic Black women develops chlamydia-associated tubal factor infertility over their life-course (Chambers et al. 2018).

The United States has some of the highest STD rates in the industrialized world, and despite this, funding for public health programs dedicated to these issues has largely declined (CDC 2016 STD Report). As a result, few health departments are able to offer traditional partner notification services, where a patient who tests positive for an STI gives the contact information of their recent sex partners to the health department, and the department then contacts their partners with the hope that these partners will then get tested and, if necessary, treated. Expedited partner therapy (EPT) was developed with this scenario in mind (See figure 2). Under EPT, a patient who tests positive, upon receipt of their own treatment, receives either additional antibiotic pills for their recent sexual partners or prescriptions for treatment that their partners can fill. The patient then is expected to hand-deliver either the treatment or prescription to their partner(s), who take the medicine at their own discretion and without the need for a positive lab test. By using these actors to essentially leverage their sexual network in reverse, this system hopes to decrease the time to treatment for all possible infected partners and increase the total number of partners treated.

It can also reduce re-infection among the index patients if the partnerships are ongoing. There have been several clinical trials of EPT across the US (and Europe), including Washington State. These trails demonstrated that relative to traditional referral practices, EPT provision increased the proportion of partners who were ultimately treated, reduced the number of individuals who were re-infected at follow-up, and was less costly if at least 30% of partners were treated via EPT (CITE). Despite these results and a growing body of evidence in support, widespread implementation of EPT has been slow and there are still many questions to be answered.

Annals of Internal Medicine Article High Incidence of New Sexually Transmitted Infections in the Year following a Sexually Transmitted Infection: A Case for Rescreening - Peterman et al

Arrested Immunity Hypothesis One of the paradoxes in era of modern public health is that chlamydia incidence has actually increased overall in the presence of mass control programs. In Sweden, Norway, Finland and Canada the rates initially decreased but then resumed increasing, and in Australia, United States, and the United Kingdom the rates never stopped increasing even after program initiation, although this second pattern has been attributed to the challenges of implementing control programs consistently throughout a large population (Brunham and Rekart 2008). These areas now experience incidence rates higher than rates prior to introduction of control programs. Additionally, a regression analysis using data from family planning clinics in Region X of the United States (Alaska, Washington, Idaho, and Oregon) found that, after controlling for any changes in demographics, sexual behaviors, and increased sensitivity of clinical tests, there was a remaining 5% 'true' and unexplained annual increase in chlamydia positivity from 1997-2004 (Fine et al. 2008). In response to these and other examples of unabated chlamydia infection in the presence of control programs, Brunham and Reckart have proposed the arrested immunity hypothesis (Brunham and Rekart 2008). Under this hypothesis, early detection and treatment of chlamydia interrupts the development of acquired immunity, making treated individuals particularly vulnerable to reinfection almost immediately after treatment. While we have no natural history studies of chlamydia infection in humans that address the development, duration, and extent of immunity, there is growing evidence beyond rodent models and trends in incidence that partial immunity can develop and play a role. Rodent models of chlamydial infection suggest that a high proportion are able to resolve their primary

infection and are temporarily resistant to infection. Rodents that then eventually become reinfected with chlamydia have a shorter duration of disease, lower pathogen load and decreased inflammatory response (Rank et al. 2003). However, it has also been shown that treatment early in the course of infection interrupts the development of this protective immunity (Su et al. 2002). There is also some indirect evidence in humans. A 2010 review article acknowledged that in several studies of infection status among couples, the rates of discordance (i.e. one partner is infected while the other is not), are higher for chlamydia than for gonorrhea and that this discordance increases with age, providing indirect evidence for some level of protective immunity to chlamydia that increases with age, likely due to exposure over time. There is little immunity that develops to gonorrheal infection due to high levels of antigenic variation (Batteiger et al. 2010). Recent modeling using data from both the UK and United States has demonstrated that at least some immunity to chlamydia following natural clearance is necessary to generate observed patterns in incidence (Omori, Chemaitelly, and Abu-Raddad 2019). These questions are particularly relevant in the context of expedited partner therapy, where the goal is to interrupt transmission by treated individuals and their partners as quickly as possible. However, due to the arrested immunity of those treated quickly, if the timing of delivery and uptake of partners is not sufficient, the initially treated is likely at higher risk of reinfection than under the standard referral scenario. If sufficient numbers of partners are treated effectively and quickly and transmission throughout the network is greatly diminished, then EPT may be able to overcome the effects of this arrested immunity.

Conclusion

We conclude.

A

The First Appendix

additional figures?

B

The Second Appendix

more technical stuff in here?

Colophon

This document is set in EB Garamond, Source Code Pro and Lato. The body text is set at 11pt with *EBGaramond*(3).

It was written in R Markdown and *LaTeX*, and rendered into PDF using huskydown and bookdown.

This document was typeset using the XeTeX typesetting system, and the University of Washington Thesis class class created by Jim Fox. Under the hood, the University of Washington Thesis LaTeX template is used to ensure that documents conform precisely to submission standards. Other elements of the document formatting source code have been taken from the Latex, Knitr, and RMarkdown templates for UC Berkeley's graduate thesis, and Dissertate: a LaTeX dissertation template to support the production and typesetting of a PhD dissertation at Harvard, Princeton, and NYU

The source files for this thesis, along with all the data files, have been organised into an R package, xxx, which is available at `https://github.com/xxx/xxx`. A hard copy of the thesis can be found in the University of Washington library.

This version of the thesis was generated on 2020-08-26 10:25:30. The repository is currently at this commit:

The computational environment that was used to generate this version is as follows:

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- Session info ---------------------------------------------------------------
 setting  value
```

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 system   x86_64, darwin15.6.0
 ui       X11
 language (EN)
 collate  en_US.UTF-8
 ctype    en_US.UTF-8
 tz       America/Los_Angeles
 date     2020-08-26

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 fansi         0.4.1   2020-01-08 [1] CRAN (R 3.6.0)
 fs            1.5.0   2020-07-31 [1] CRAN (R 3.6.2)
 generics      0.0.2   2018-11-29 [1] CRAN (R 3.6.0)
```

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ggplot2       3.3.2   2020-06-19 [1] CRAN (R 3.6.2)
git2r         0.27.1  2020-05-03 [1] CRAN (R 3.6.2)
glue          1.4.1   2020-05-13 [1] CRAN (R 3.6.2)
gtable        0.3.0   2019-03-25 [1] CRAN (R 3.6.0)
htmltools     0.5.0   2020-06-16 [1] CRAN (R 3.6.2)
huskydown   * 0.0.5   2020-08-06 [1] Github (benmarwick/huskydown@a909835)
knitr         1.29    2020-06-23 [1] CRAN (R 3.6.2)
lifecycle     0.2.0   2020-03-06 [1] CRAN (R 3.6.0)
magrittr      1.5     2014-11-22 [1] CRAN (R 3.6.0)
memoise       1.1.0   2017-04-21 [1] CRAN (R 3.6.0)
munsell       0.5.0   2018-06-12 [1] CRAN (R 3.6.0)
pillar        1.4.6   2020-07-10 [1] CRAN (R 3.6.2)
pkgbuild      1.1.0   2020-07-13 [1] CRAN (R 3.6.2)
pkgconfig     2.0.3   2019-09-22 [1] CRAN (R 3.6.0)
pkgload       1.1.0   2020-05-29 [1] CRAN (R 3.6.2)
prettyunits   1.1.1   2020-01-24 [1] CRAN (R 3.6.0)
processx      3.4.3   2020-07-05 [1] CRAN (R 3.6.2)
ps            1.3.4   2020-08-11 [1] CRAN (R 3.6.2)
purrr         0.3.4   2020-04-17 [1] CRAN (R 3.6.2)
R6            2.4.1   2019-11-12 [1] CRAN (R 3.6.0)
remotes       2.2.0   2020-07-21 [1] CRAN (R 3.6.2)
rlang         0.4.7   2020-07-09 [1] CRAN (R 3.6.2)
rmarkdown     2.3     2020-06-18 [1] CRAN (R 3.6.2)
rprojroot     1.3-2   2018-01-03 [1] CRAN (R 3.6.0)
rstudioapi    0.11    2020-02-07 [1] CRAN (R 3.6.0)
scales        1.1.1   2020-05-11 [1] CRAN (R 3.6.2)
sessioninfo   1.1.1   2018-11-05 [1] CRAN (R 3.6.0)
stringi       1.4.6   2020-02-17 [1] CRAN (R 3.6.0)
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 stringr       1.4.0   2019-02-10 [1] CRAN (R 3.6.0)
 testthat      2.3.2   2020-03-02 [1] CRAN (R 3.6.0)
 tibble        3.0.3   2020-07-10 [1] CRAN (R 3.6.2)
 tidyselect    1.1.0   2020-05-11 [1] CRAN (R 3.6.2)
 usethis     * 1.6.1   2020-04-29 [1] CRAN (R 3.6.2)
 vctrs         0.3.2   2020-07-15 [1] CRAN (R 3.6.2)
 withr         2.2.0   2020-04-20 [1] CRAN (R 3.6.2)
 xfun          0.16    2020-07-24 [1] CRAN (R 3.6.2)
 yaml          2.2.1   2020-02-01 [1] CRAN (R 3.6.0)

[1] /Library/Frameworks/R.framework/Versions/3.6/Resources/library
```

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