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The Use of Mathematical Models of Chlamydia Transmission to Address Public Health Policy Questions: A Systematic Review

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Abstract

Background: Mathematical models of chlamydia transmission can help inform disease control policy decisions when direct empirical evaluation of alternatives is impractical. We reviewed published chlamydia models to understand the range of approaches used for policy analyses and how the studies have responded to developments in the field.

Methods: We performed a literature review by searching Medline and Google Scholar (up to October 2015) to identify publications describing dynamic chlamydia transmission models used to address public health policy questions. We extracted information on modeling methodology, interventions, and key findings.

Results: We identified 47 publications (including two model comparison studies), which reported collectively on 29 distinct mathematical models. Nine models were individual-based, and 20 were deterministic compartmental models. The earliest studies evaluated the benefits of national-level screening programs and predicted potentially large benefits from increased screening. Subsequent trials and further modeling analyses suggested the impact might have been overestimated. Partner notification has been increasingly evaluated in mathematical modeling, whereas behavioral interventions have received relatively limited attention.

Conclusions: Our review provides an overview of chlamydia transmission models and gives a perspective on how mathematical modeling has responded to increasing empirical evidence and addressed policy questions related to prevention of chlamydia infection and sequelae.

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Chlamydia trachomatis is the most commonly reported bacterial sexually transmitted infection (STI) in high-income countries.[1] Chlamydia prevalence is relatively consistent across high-income economies, with 1 study from 6 countries finding pooled prevalence estimates for women and men between ages 18 and 26 years at around 4.3% and 3.6%, respectively, with minimal heterogeneity across countries.[2] Untreated chlamydia infection can result in pelvic inflammatory disease (PID) in women, which can lead to ectopic pregnancy and tubal factor infertility. Chlamydia can cause epididymitis in men.[3,4] The association between chlamydia and PID has contributed to an emphasis in prevention efforts on screening of young women to prevent sequelae of chlamydial infection.[5] The introduction of highly sensitive, noninvasive, nucleic acid amplification techniques (NAATs) for chlamydia diagnosis has probably also contributed to increases in screening over time.[6] Despite the introduction of public health interventions aimed at detecting and treating infections, chlamydia prevalence persists, due in part to existence of a significant asymptomatic reservoir.[4]

For infectious diseases, like chlamydia, mathematical models are often used to examine transmission dynamics, synthesize knowledge about natural history and disease outcomes to predict future events, and quantify the potential impact of interventions. One use of such analyses is to inform policy decisions, especially where there are limited empirical data available for comparative evaluation of different interventions.[7] For example, mathematical models of chlamydia can be used to assess the cost-effectiveness of novel strategies that have not yet been deployed on a large scale, such as routine screening of men,[8] or to estimate risks of PID and long-term reproductive sequelae following infection.[9] Some of the first mathematical modeling studies of chlamydia were published in 1989 and 1990 by Buhaug et al.[10,11] These groundbreaking studies used a simulation model of infection and progression to consider the potential benefits achieved through screening asymptomatic women. In these earliest models, the incidence of infection was defined as an exogenous parameter rather than as a dynamic function of the number of infectious individuals in the population. An important benefit of the latter approach, which characterizes “dynamic transmission models,” is that it allows models to capture both direct effects of interventions on infected persons and indirect effects relating to transmission. For this reason, dynamic transmission models are recommended when assessing interventions that impact disease transmission.[12]

A number of dynamic transmission models of chlamydia have been developed, and in this study, we present a review of the published literature on dynamic transmission models of chlamydia that have been used to answer public health and policy questions. We compare models in terms of their methodology, interventions considered and key findings. We map the models in relation to the accumulating evidence on chlamydia interventions derived from clinical trials.

METHODS

Search Strategy

We performed a systematic literature review by searching Medline through PubMed with the following search terms: (“transmission dynamics” OR “mathematical model” OR

"transmission model" OR "dynamic model" OR "simulation model" OR "computer model" OR "cost-effectiveness") AND chlamydia, without further limits on the search. The search terms were selected to reflect the variety in nomenclature around mathematical models of infectious diseases. To assure that recent publications and publications not indexed in Medline were covered, we performed an additional search in Google Scholar. Google Scholar performs a search through the Internet and the full text of the articles. Therefore, we used more specific search terms and a shorter time period to limit false positives. We used the advanced search function to identify articles with the following words: ("chlamydia trachomatis" AND transmission AND dynamic AND "mathematical model") AND (deterministic OR compartmental OR stochastic OR agent OR individual OR network). No timeline restrictions were set for PubMed, whereas Google Scholar was limited to after 1995. In both cases, the end date for inclusion was October 2015.

Figure 1 summarizes the substantive inclusion criteria used in selecting models: we included analyses that were based on dynamic transmission models of chlamydia in humans and assessed the impact of at least 1 public health intervention. This review did not include in-host models, static models, or theoretical analyses that did not address a policy question.

Data Analysis

The lead author performed the search, identified the articles and coordinated the data extraction, at least 2 people reviewed any extracted material. A mathematical model was defined as an "original" in the first publication in which a novel model was described or when substantial changes were made to an existing model structure. Original models could be applied in subsequent publications, such as decision analysis using outputs from the dynamic transmission model, the same model could be reparameterized to a different setting, or there could be a variation of the model (minor change in structure or variation in key assumptions). Where substantial changes were made to the original model structure, it was considered a new model.

For each study, we collected data on modeling framework, natural history assumptions, setting and population, intervention (s), outcomes, and conclusions of the study. Whereas we are not aware of guidelines for reporting of systematic reviews of modeling studies, we were guided by recommendations for good research practice in infectious disease modeling from two sources.[12,13] Emphasis was given to Pitman et al,[12] which focuses on transmission models. Our inclusion criteria only included studies using dynamic transmission models, which can capture the indirect effects, filling an important criterion for modeling interventions against infectious diseases.[12] We also measured reporting items to assess methodological rigor; specifically, we looked for the presence of differential equations (for deterministic compartmental models), or a detailed description of the individual-based model (IBM) for model reproducibility. We then evaluated whether the model had been calibrated using a statistical or other explicit approach as opposed to ad hoc tuning of the model to produce a particular outcome (usually prevalence). Finally, we evaluated whether a probabilistic sensitivity analysis had been conducted including key biological and behavioral parameters of the model (and not merely analyzing the impact of the intervention at different

levels of coverage, for example); an important consideration because there are likely a number of parameter combinations that can create any given pattern in the model.

To place the findings of the review within the context of major empirical developments in the field, we extracted relevant information from five sources: 3 reviews of clinical trials of the effects of chlamydia screening on chlamydia transmission and PID incidence,[14–16] a review of partner notification (PN) strategies on STI/human immunodeficiency virus prevention[17] and a more recent randomized clinical trial of the effects of PN on chlamydia transmission.[18]

RESULTS

We found 272 publications through PubMed and 402 articles on Google Scholar. Supplementing those searches with the reference lists of the identified articles and applying our inclusion criteria led to a final sample of 47,[19–29,31s–66s] publications in the review, 2 of which were model comparison exercises that involved multiple models (supplemental references, http://links.lww.com/OLQ/A160). The publications collectively reported on 29 original dynamic transmission models, summarized in Table S1 (supplemental content, http://links.lww.com/OLQ/A158)).

The 2 model comparison exercises by Kretzschmar et al. (2009)[65s] and Althaus et al. (201 l)[66s] were considered as landmark studies, and we organized the results accordingly in Figure 2: clinical trials in Figure 2A and the mathematical transmission models identified in Figure 2B. Both are ordered by publication year. Because models of chlamydia are informed by clinical trials of chlamydia screening and other empirical evidence, we first review major advances in the empirical evidence, followed by the chronology of the chlamydia models and key measures identified across the studies.

Empirical Evidence Base

Early clinical trials by Scholes et al (1996)[67s] and Østergaard *et al.* (2000)[68s] found a halving in PID risk among women 12 months postscreening in comparison to the control (usual care) group. In 2010, the prevention of pelvic infection trial reported a nonsignificant decrease in relative risk (RR) of PID in those screened (RR, 0.65; 95% confidence interval [CI], 0.34–1.22) after 12 months of follow-up.[69s] The study had low statistical power but a more rigorous design than earlier studies (women and clinicians diagnosing PID were blinded to the patients' study arm). Overall, a 2016 Cochrane review of the impact of screening for genital chalmydia[16] determined there to be a moderate evidence base for screening on reduced risk of PID at 12 months post chalmydia test (RR, 0.68; 95% CI, 0.49–0.94; pooling 4 studies[67s–70s]).

In contrast, there is limited evidence from trials on the impact of screening on chlamydia transmission. Two cluster-randomized trials in high prevalence communities investigated the impact of screening on transmission,[71s,72s] and found a statistically significant reduction in positivity in at least one of the groups measured post-screening. The 2016 Cochrane review included two randomized trials.[73s,74s] A nonrandomized cluster Chlamydia Screening Implementation (CSI) trial in the Netherlands investigated a population-level active

screening program. CSI included yearly screening invitations, but screening uptake was low and no reduction in chlamydia positivity was observed (RR, 0.96; 95% CI, 0.84–1.09).[73s] A community-randomized trial in urban areas of Peru provided syndromic STI management for female sex workers and observed a significant decline in chlamydia positivity over the two-year follow-up (RR, 0.72; 95% CI, 0.54–0.98).[74s] The 2016 Cochrane review determined there to be low evidence base to estimate the impact of screening on chlamydia prevalence.

Trials of PN on chlamydia transmission[18,75s–78s] have focused on patient-delivered partner therapy (PDPT) in comparison to traditional PN services. Based on a Cochrane 2013 review, [17] PDPT can be more effective than traditional partner referral at reducing re-infection in index cases when “any curable STI” (chlamydia, gonorrhea or trichomonas) is used as the outcome measure (RR, 0.71; 95% CI, 0.56–0.89; pooling 6 studies) but no evidence was found for chlamydia (RR, 0.90; 95% CI, 0.60–1.35; pooling 2 studies[75s,78s]). For chlamydia, the most encouraging results come from a community randomized clinical trial, which suggested that PDPT of the partners of female index cases may decrease ongoing transmission of chlamydia at the community level based on positivity in women over time, however the prevalence rate ratio was not statistically significant (RR, 0.89; 95% CI, 0.77–1.04).[18]

Overview of Models

Models Focusing on Screening Interventions—The earliest dynamic chlamydia transmission models focused on the impact of screening interventions. Several models were developed for public health agencies to help evaluate the benefits of implementing a screening program, such as the Turner[55s–57s] and Kretzschmar[49s,50s] models in the United Kingdom and the Netherlands, respectively. Low’s model[59s,60s] was developed as part of an economic evaluation of chlamydia screening studies in the United Kingdom. A modeling analysis by Townshend,[19] for the Department of Health in the United Kingdom, estimated opportunistic screening to be cost-saving after 5 years as did a cost-effectiveness analysis for the Netherlands based on the Kretzschmar model.[51s] Both assumed high proportions of the population visiting a primary care provider annually, high screening uptake among those targeted (eg, women <25 years, varied in model scenarios), and high probability of PID per chlamydia infection (25%). A modeling analysis conducted to inform potential screening strategies in Australia by Reagan et al.[25] suggested screening women and men younger than 25 years old could reduce chlamydia prevalence by more than 80% with 40% coverage maintained over 10 years.

Model comparison exercises[65s,66s] were motivated by the differences seen in the effects of screening interventions predicted by the IBMs of Kretzschmar, Turner and Low.[49s,56s,59s] In the study published in 2009[65s] the impact of a standardized chlamydia screening program was compared (35% of sexually active 16- to 24-years-olds were tested for chlamydia, and 45% of partners were treated; 20% in the Turner model). The models differed in assumptions about treatment seeking behavior, levels of testing, and PN occurring before the intervention, and these were thought to drive the differences in predicted impact of interventions. The combined evidence from the model comparison exercises suggested that

screening all sexually active young adults every 2 to 5 years (at coverage, 20–40%) could reduce chlamydia prevalence after 5 to 10 years.

The comparison exercises advocated for development of simpler models to promote better understanding of the model behavior, combined with exploring parameter uncertainly in sensitivity analyses. Studies have since considered the type of model framework chosen (individual-based, frequency dependent or pair-formation models),[28,38s,39s,44s] and the effects on transmission dynamics from varying key natural history parameters such as duration of infection in asymptomatic persons, and duration of transient immunity,[27] where the former increases and the latter reduces the estimated impact of a chlamydia screening program. Assumptions regarding PID development during infection also affect the impact of a screening program (screening is more effective when there is a longer time window for screening to detect and treat the infection before sequelae occurs).[35s]

The increasing empirical evidence and developments in chlamydia modeling are both evident in a model by Schmid and colleagues (2013)[61s] which used Dutch CSI trial data.[62s] Declining participation, as observed in the active screening arm, resulted in less optimistic screening predictions in the modeling analysis. The cost-effectiveness ratio estimated for a national screening program was unfavorable (comparing screening with existing strategy),[62s] and the evidence contributed to a decision not to implement active chlamydia screening at the national level in the Netherlands.

Other Strategies Used—In the modeling studies, screening interventions often included PN services, predicting that adding PN to screening would further improve health outcomes. PN as an independently beneficial intervention has received increased attention in mathematical modeling over the last 10 years.[38s,39s,45s,47s,63s] Clarke et al.[44s] suggested that partner tracing could provide more value for the money than screening, and Althaus et al. (2014)[47s] found reducing delay to PN (such as in PDPT) would reduce the reinfection rate (median reinfection rates, 7.6%, 2.3%, and 0.8% for a delay of 14, 3, and 1 days, respectively).

Behavioral interventions and increased condom use have received limited attention in chlamydia modeling. Condom use was included in the first Kretzschmar model,[49s] and in 2 studies in South Africa.[42s,43s] In the analyses, increased condom use limited transmission and reduced prevalence. Studies that examined interventions in Sub-Saharan Africa also examined periodic presumptive treatment and syndromic management, with influence of STIs on human immunodeficiency virus transmission as a focal point.[41s–43s]

By definition, full coverage of a perfectly efficacious vaccine would outperform screening in terms of preventing new infections.[20] Two models have assessed the potential impact of a hypothetical vaccine at different levels of efficacy and coverage.[40s,48s] Assuming a highly efficacious vaccine (efficacy ≥ 75%), vaccination would be a cost-effective addition to screening in the United States,[40s] whilst reducing susceptibility to infection among vaccinated individuals would have a greater impact on prevalence than reducing infectiousness once infected.[48s]

Key Measures Across the Chlamydia Models—Table S2 (supplemental content, http://links.lww.com/OLQ/A159) summarizes measures across 45 studies (excluding the 2 model comparison exercises). Twenty-one publications[44s,46s,64s] reported on IBMs and 26 publications[19–29,31s–45s] included deterministic compartmental models. Among the 26 publications reporting on deterministic models, the majority (25/26) modeled sexual contacts as frequency dependent (assuming instantaneous partnership formation and dissolution), and 4 of 26 used a pair formation modeling approach (explicitly modeling partnerships and their duration). Four publications included multiple modeling frameworks in the same study.[28,38s,39s,44s] Age and sexual risk behavior are risk factors for chlamydia, and 20 of 45 publications included model stratification to capture both of these factors. Less than half of all published studies (17/45) assumed natural immunity as part of chlamydia's natural history.

Apart from 3 publications[41s–43s] that examined Sub-Saharan African settings, all articles in this review were set in high-income countries (Fig. 2). The most common settings were the United Kingdom (n = 10), the Netherlands (n = 10) and the United States (n = 8). The trials identified were conducted in high-income countries except Garcia et al. (2012) in Peru.[74s]

The most common outcome examined was chlamydia infection (38/45; 84%) followed by sequelae (20/45; 44%). Costs were estimated in 21, and 11 considered quality-adjusted life years. In comparison, there were 4 trials,[71s–74s] estimating the impact of screening on chlamydia transmission (Fig. 2), of which 2 had sufficient quality to be included in the 2016 Cochrane review. Six trials[67s–70s,79s,80s] had measured the impact of screening on PID incidence of which 4 were included in the Cochrane review. Half of the modeling studies had estimated sequelae outside of the model whilst the others incorporated sequelae directly in the model. The latter allows, in theory, more flexibility in exploring the natural history and timing of sequelae development.

Twenty-eight publications included PN with or without screening. These suggested chlamydia prevention would benefit from increased PN whether traditional or partner-delivered. The 5 trials identified[18,75s–78s] give us evidence only of the increased benefit of PDPT in comparison to the standard of care (with traditional PN), with unclear evidence on the benefits to chlamydia reinfection rates.

We also examined the completeness of reporting in the studies, applying three criteria: explicit reporting of model equations or IBM specification, statistical calibration and inclusion of sensitivity analyses. Reporting score were calculated for each modeling analysis in Table S1 excluding decision analysis studies and the model comparisons. There were 5 modeling analyses,[27,29,32s,41s,55s] fulfilling all three of the criteria. Four of these were published since 2009, likely reflecting a combination of improvement in reporting of transmission models of infectious diseases in general, as well as possibly responding to recommendations from the chlamydia model comparison studies. Studies that fulfilled 0 or 1 of the reporting criteria were published before 2009, with 2 exceptions.

Baseline assumptions about existing interventions are likely to have an influence on the relative impact of interventions tested. Most analyses assumed testing of symptomatic cases,

or did not report baseline assumptions (Table S1). Nine models[24,31s,32s,36s,39s,40s,44s,45s,59s] had 10% or higher screening at baseline before intervention roll-out. Of these, 3[39s,44s,45s] concluded that screening linked to PN is an efficacious strategy, 3[24,31s,32s] focused in higher risk populations and found targeted screening of core groups to be an effective strategy in reducing transmission, whereas 2,[36s,59s] which examined screening of the general population, concluded that screening at levels observed in empirical data was not a cost-effective strategy compared with baseline level (the remaining analysis investigated a hypothetical vaccine together with screening[40s]).

DISCUSSION

Chlamydia modeling has proliferated since Buhaug's mathematical models of chlamydia screening.[10,11] This proliferation is shown in the 47 transmission dynamic modeling studies summarized in this review, which date back to Kretzschmar's first chlamydia transmission model in 1996.[49s] The influence of Kretzschmar's IBM for chlamydia can be traced not only to subsequent analyses using the 2001[50s] version of the model[51s,54s] but also to models developed by Low,[59s] Turner[55s] and Schmid[61s] which have utilized the original framework in their respective IBMs.

Based on results from two model comparison studies in 2009 and 2012, we would conclude that screening all sexually active young adults every 2 to 5 years (at coverage, 20–40%) could reduce chlamydia prevalence after 5 to 10 years. If we relied on evidence from studies with the most comprehensive reporting, we would conclude that screening, and periodic presumptive treatment, could be effective depending on the setting in question. If we assumed the studies with 10% or greater baseline screening before program implementation represent a more realistic scenario, we would conclude that the effect of screening comes from linked PN, and that targeted screening of higher-risk communities within the population is likely beneficial in reducing transmission.

Our review is limited by our broad aim, which led to a variety of outcomes measured in the included studies. Sources of variability in the models are difficult to assess in the absence of comparable results, which is why model comparison studies with standardized interventions across the models may represent the most robust approach in synthesizing modeling evidence. Although reporting of the mathematical models has evidently improved, the transparency of the analyses could be enhanced by more standardized reporting practices. The strength of our review is that we included only transmission dynamic models, which are in general better suited to evaluate chlamydia prevention interventions than static models.

Evidence synthesis exercises have helped advance our understanding of the natural history of chlamydia and the potential impact of screening on the incidence of PID.[81s–83s] Recent cohort analyses indicate that repeated chlamydia infections may increase the risk of adverse reproductive health outcomes.[84s,85s] Further, theoretical modeling suggests repeat infections may help maintain chlamydia at endemic levels.[86s] Modeling can help to evaluate the potential health benefits of strategies to reduce chlamydia reinfection rates, and studies that collect data on PID incidence on a routine basis could help to inform such models. Future modeling efforts can also be used to inform the development of strategies to increase the

yield of chlamydia testing, as opposed to strategies which simply aim to increase the amount of testing. We can continue working to improve on screening coverage while also investigating the potential benefits of targeting higher risk individuals, improving PN strategies and repeated testing for those with a known previous chlamydia infection. Empirical studies should aim to measure both positivity and sequelae occurrence to better understand the impact of the interventions. Dynamic transmission models can help us understand the potential costs and benefits of these interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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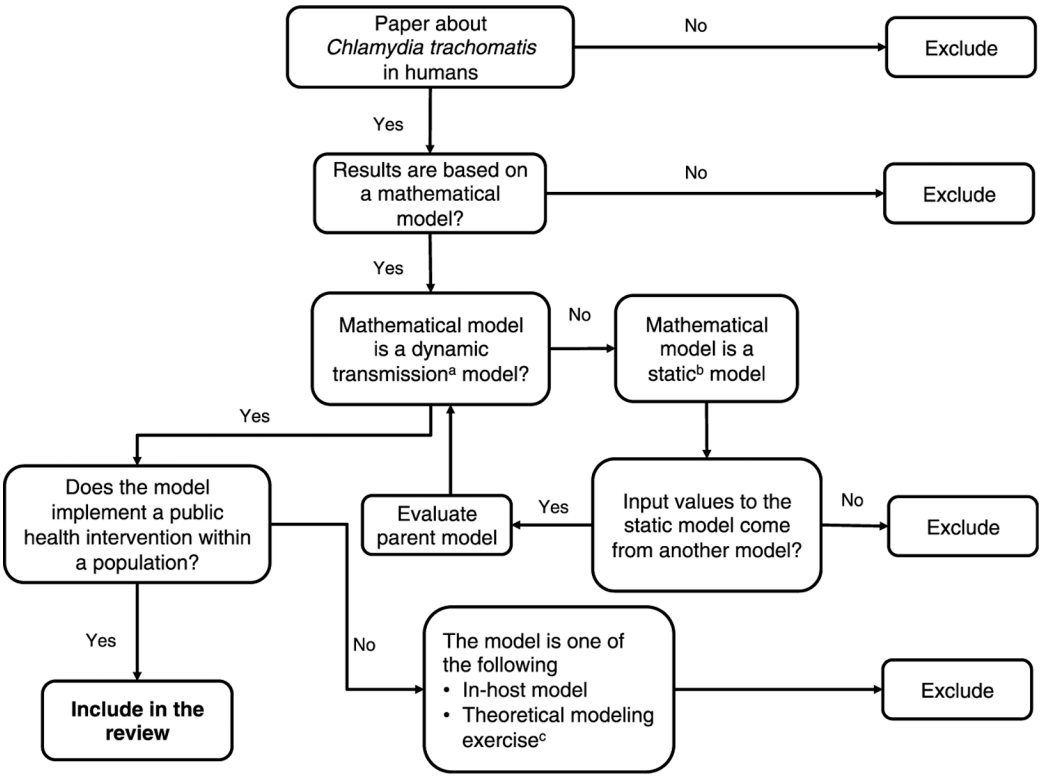

Figure 1.

Algorithm used to select chlamydia transmission models for the review. [a]Dynamic transmission models are mathematical models in which transmission is determined endogenously. In dynamic models force of infection is defined by the size of the susceptible population, prevalence of infection and risks of transmission given contact between infected and susceptible persons. [b]Static models incorporate a fixed force of infection for a given state (such as in Markov Models), whereas dynamic transmission models account for underlying population prevalence and infectivity and allow for indirect effects (such as herd immunity after vaccination) to be incorporated in the analysis. [c]Theoretical models are used to understand transmission dynamics, but the impact of an intervention at population level is not their primary aim.

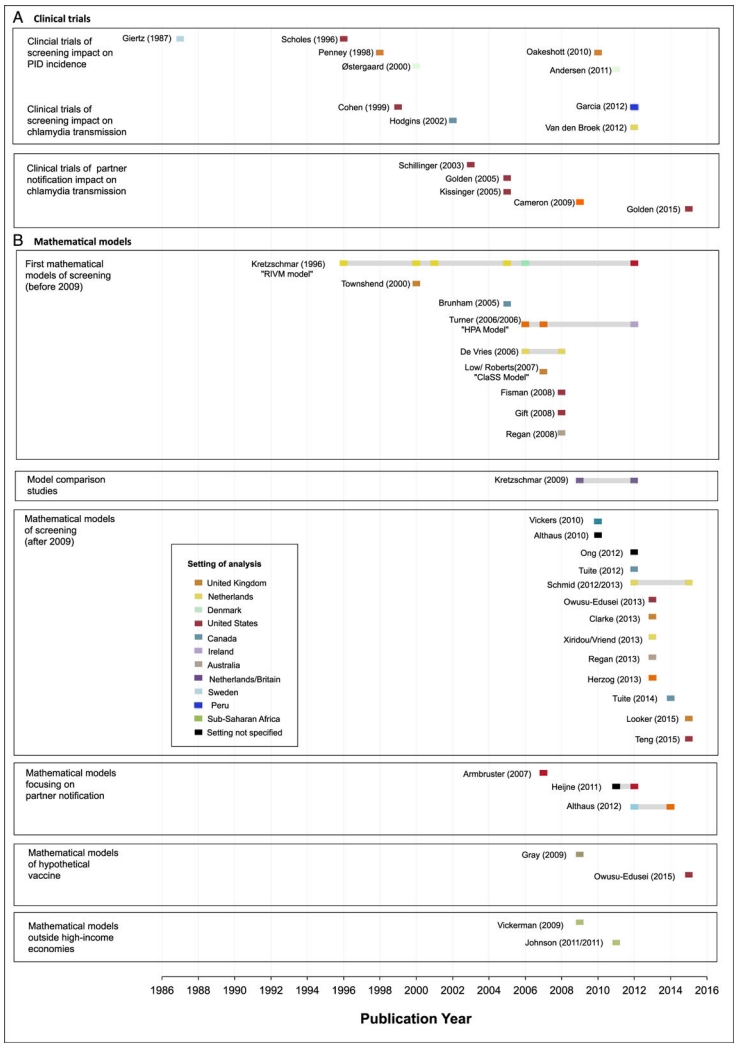

Figure 2.

Timeline of publications forming the evidence base for chlamydia interventions: A, Clinical trials of chlamydia. B, The dynamic chlamydia transmission models used to address public health questions. Publications are ordered by publication year and are named after the first model paper. Figure 2 can be viewed online in color.