

Estimating the effect of chlamydia and gonorrhea screening programs on the incidence of pelvic inflammatory disease and ectopic pregnancy in Washington State, 1988-2010

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Abstract

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Chlamydia and gonorrhea infection can cause serious sequelae in women, including pelvic inflammatory disease (PID) and ectopic pregnancy. We assessed how trends in chlamydia positivity and gonorrhea incidence corresponded to trends in PID and ectopic pregnancy incidence in Washington State between 1988 and 2010 when large-scale screening programs for these infections were in place. We used various sources of surveillance data to capture trends in each condition over time. Without direct information on outpatient-treated cases of PID and ectopic pregnancy in Washington State, we estimated these cases based on outpatient data from surrogate or sentinel populations. Chlamydia positivity and gonorrhea incidence significantly declined from 1988 to 1997 before gradually increasing. Inpatient and estimated total PID and ectopic pregnancy incidence also declined. Associations in trends between the infection rates and each outcome were strong. These results support the conclusion that chlamydial screening has diminished serious reproductive health outcomes in Washington women.

Introduction

Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (GC), the two most common reportable conditions in the United States, cause serious reproductive complications in women, such as pelvic inflammatory disease (PID) and ectopic pregnancy [1-3]. These conditions can have additional consequences, from chronic pelvic pain to infertility, or in the case of ectopic pregnancy, even death. However, much remains unknown about the relationship between these two infections and their sequelae. For one, the risk of developing either condition among women infected with CT or GC is not clear. Estimates of the proportion of untreated CT infections that lead to PID range from 9.5 to 40% [4-7], though some modeling studies suggest that the proportion could be as low as 0.6% [8]. Likewise, studies estimate that somewhere between 25-50% of PID cases and 40% of ectopic pregnancy cases are attributable to CT infection [6,8,9]. There is some evidence that GC-associated PID is more often symptomatic than CT-associated PID, but even less is known about the specific risks of PID and ectopic pregnancy attributable to GC infection [5,6,8-10].

The timing of these reproductive sequelae relative to the course of infection also remains unclear. While the risk of sequelae increases with an increasing number of infections, it is not known whether this is a multiplicative or an additive risk [9,11,12]. Though it is difficult to determine when infection begins, it is believed that PID can develop relatively quickly and that the risk of PID is highest soon after the onset of CT infection and wanes as the infection persists [4,6,11]. Similarly, the immune-induced molecular changes to the Fallopian tubes that are thought to precipitate ectopic pregnancy can occur relatively rapidly, with modeling studies suggesting a 1-3 year lag between CT infection and ectopic pregnancy [13,14].

Because of these risks, screening programs for CT and GC have been implemented in an attempt to prevent PID and associated conditions. The Infertility Prevention Project (IPP), funded by the US Centers for Disease Control and Prevention (CDC), provided CT testing to low-income, sexually active women from 1988 to 2012. IPP began in US Public Health Service Region X (Alaska, Idaho, Oregon, and Washington) in 1988 as a demonstration project before being expanded throughout the country.

In Washington (WA) State, as in the rest of the country, screening criteria, participating clinics, and testing practices changed over the course of the IPP program. Because the number of cases detected is dependent on the population being screened and the number of screening tests performed [15,16], these changes have made it difficult to determine the true incidence or prevalence of CT. In particular, young age and non-white race are associated with CT infection [17], and the age and racial distribution of the screened population may differ from that of all women in WA. The switch to nucleic acid amplification tests (NAAT) in the late 1990s also substantially increased the likelihood of a positive CT test, especially for asymptomatic infections [18,19]. Therefore, measures of CT burden must be appropriately adjusted when determining the impact of screening practices.

The primary purpose of efforts to control bacterial sexually transmitted diseases (STDs) is to avert the serious sequelae these infections cause in women. Despite the investment of many millions of dollars in screening and treatment programs, the extent to which public health control efforts have resulted in meaningful benefits remains controversial [20]. For one, important outcomes such as PID and ectopic pregnancy can be difficult to measure, as treatment for these conditions has increasingly shifted to the outpatient setting in the past twenty years [21,22], making it difficult for U.S. public health authorities to monitor the burden of these conditions over time; in particular, accurate counts of ectopic pregnancy cases have not been available nationally since 1992 [23,24]. Additionally, studies on the benefits of screening have been mixed. Three randomized control trials (RCTs) have found a lower incidence of PID in women screened and treated for CT than in the control groups, though the results of these studies were not always statistically significant [7,25,26], and all three trials have been criticized for methodological or other flaws [9,27]. There are currently no data from RCTs of ectopic pregnancy prevention [8] and observational studies have not consistently corroborated the results of the randomized trials [28,29]. Many ecological studies have found an association between the increase in CT testing and population-level declines in PID and ectopic pregnancy [14,19,30-32], though not all have adequately accounted for outpatient cases. Many of these studies also do not take into account the incidence of GC in the population over the same time period.

Because the benefits of chlamydial screening remain a point of controversy, we sought to assess the relationship between trends in CT and GC infection and the occurrence of two sequelae. Unlike

previous studies of surveillance data, this analysis includes an effort to estimate the contribution of outpatient cases to the overall incidence of PID and ectopic pregnancy and to evaluate statewide trends over the entire time period that screening programs were in place. The results of this analysis will allow us to assess the trends of each infection and associated outcomes in women in WA over time, as well as independently evaluate the contributions of CT and GC to the occurrence of PID and ectopic pregnancy in the state. Results may also contribute to the debate about the appropriateness of large-scale screening programs for CT and GC.

Methods

We performed an ecological analysis with a time-series design to assess the relationship in trends between CT positivity, GC incidence, and the incidence of PID and ectopic pregnancy in WA State between 1988 and 2010. Data on each measure were collected from a variety of surveillance sources (summarized in Table 1). In addition, we estimated the contribution of outpatient cases of PID and ectopic pregnancy to overall state trends using information from surrogate or sentinel populations, as direct data on all outpatient-treated cases in the state are unavailable.

IPP Data and Chlamydia Positivity

Positivity, the proportion of positive tests out of all tests performed, is frequently used as an alternative to prevalence or incidence when estimating CT burden [33]. We used IPP data from Washington State to calculate CT positivity among women aged 15-25 screened for the infection from 1988-2010 (Table 1). Additionally, we included tests from women attending Planned Parenthood of Western Washington (PPWW) clinics from 2008-2010, as PPWW tests were included in IPP only until 2008.

In addition to crude CT positivity, we calculated an adjusted positivity to account for changes over time in screening criteria, participating clinics types, and test type used. We used a generalized linear mixed model (GLMM; the SAS GLMMIX procedure, SAS Institute Inc., Cary, NC) with a random intercept and binary outcome, which calculates the conditional probability of a positive test given a combination of fixed and random effects, to adjust positivity [34]. In this model, we adjusted for age (15-17 and 18-20), race/ethnicity (black, Hispanic, American Indian/Alaska Native, Asian/Pacific Islander, other), test type

(NAAT vs. non-NAAT), and year as fixed effects, and a clinic identifier as a random effect. To calculate yearly adjusted positivity, we first determined the overall frequencies of the various age, test type, and race categories. We then used these to solve the regression equation, allowing only the coefficient for year of test to vary.

Gonorrhea Incidence

As a common co-infection with CT and an independent cause of PID and ectopic pregnancy, GC infections should ideally be taken into account when assessing reasons for changing PID and ectopic pregnancy incidences over time. However, IPP did not initially collect data on GC infections. Therefore, we used notifiable conditions data to capture GC incidence in women over time. Medical providers and laboratories are required to report all GC cases to the local health jurisdiction in WA State. The Washington State Department of Health (WADOH) provided the number of female cases of GC in WA State from 1988-2010 (Table 1). Age-level GC data are not available for cases reported before 1992, so we included cases from all women, which were available for the entire study period. We calculated incidence using the Washington State Office of Financial Management (OFM) intercensal female population estimates as the denominator.

Inpatient PID and Ectopic Pregnancy Incidence

We identified hospitalized cases of PID and ectopic pregnancy among women aged 15-44 using WA State's Comprehensive Hospital Abstract Reporting System (CHARS) database (Table 1). We used the following ICD-9 diagnosis codes to determine instances of PID:

098.10, 098.16, 098.17, 098.19, 098.30, 098.36, 098.37, 098.39, 098.86, 099.56, 614.0-614.5,
614.7-614.9, 615.0, 615.4, 615.9

and ectopic pregnancy: 633-633.91, 761.4x.

Non-Washington State residents were excluded from analysis. We used OFM intercensal population estimates of all women 15-44 years old as the denominator for annual PID incidence and all pregnancies among women aged 15-44, recorded in WA State vital statistics records, as the denominator for annual ectopic pregnancy incidence. All pregnancies include all live births, fetal deaths, abortions, and ectopic pregnancies recorded during the year.

Outpatient PID and Ectopic Pregnancy Incidence in Surrogate and Sentinel Populations

Pelvic Inflammatory Disease

Because state-level data were not available, we calculated the annual incidence of outpatient-treated PID nationally as a proxy for the outpatient incidence in WA. The annual number of outpatient cases of PID in this surrogate population is estimated through the National Disease and Therapeutic Index (NDTI) and is published by the CDC [24]. NDTI captures the practices of a representative sample of over 500,000 primary and specialty care office-based physicians throughout the US; participating physicians are randomly assigned two consecutive calendar days each quarter in which they report on all patient contact on those days [35]. These estimates incorporate standard errors based on uncertainties from the sampling process. We calculated the incidence of outpatient PID nationally using these NDTI estimates as the numerator and US Census mid-year estimates of the female population 15-44 years old in the United States as the denominator (Table 1).

In addition, we calculated the incidence of hospitalized PID nationally using information from the National Hospital Discharge Survey (NHDS), also published by the CDC [24,36], and the same denominator as for outpatient incidence, based on the annual national female population aged 15-44.

Ectopic Pregnancy

No state-level data on rates of outpatient ectopic pregnancy are available. Therefore, we obtained information on outpatient ectopic pregnancy cases based on data collected for a previously published study of treatment practices at Group Health Cooperative, a non-profit, mixed-model health maintenance organization that serves over 540,000 residents of WA and western Idaho. Data collection and case identification have been described previously [21]. The ICD-9 codes used to identify ectopic pregnancy in that study and here are similar. Study authors provided us with yearly counts of inpatient and outpatient ectopic pregnancy cases seen in Group Health healthcare facilities, as well as all pregnancies (live births, induced abortions, and ectopic pregnancies) in the Group Health population, between 1993 and 2007, which was the time frame of the previous study. We used the information from this sentinel population to calculate annual outpatient and inpatient incidences of ectopic pregnancy in Group Health (Table 1).

Estimation of Total PID and Ectopic Pregnancy Incidence

We used a Bayesian multi-parameter evidence synthesis approach to estimate the incidence of total cases of PID and ectopic pregnancy in WA, using the inpatient incidence calculated from CHARS and the outpatient incidence calculated from the Group Health and national populations. Multi-parameter evidence synthesis can be used to generate estimates of unknown or hard-to-measure quantities by combining data from multiple sources related to that quantity. The Bayesian approach uses any prior information on a model parameter, as well as the observed data, to create a posterior distribution for each parameter, allowing for the propagation of uncertainty in each component of the model into the final estimated quantity [37,38]. This technique has been used previously to estimate the symptomatic infection attack rate of influenza in the Netherlands, as well as hepatitis C prevalence, HIV prevalence, and likelihood of severe cases of influenza in England and Wales [38-41]. It is also commonly used in healthcare decision making and meta-analysis [37].

Using our data for inpatient and estimated outpatient incidence (basic parameters in the model), we then defined the total incidence of each condition as the sum of inpatient and outpatient incidence for that condition (making total incidence a functional parameter). We made the assumption that the incidence of outpatient cases, or at least the trend in incidence over time, would be the same in WA as in each surrogate or sentinel population. The outpatient incidence of ectopic pregnancy in the Group Health population was first adjusted to reflect the age distribution in WA State. This adjusted outpatient incidence was used in the evidence synthesis model for total ectopic pregnancy incidence. The PID analysis could not be age-adjusted because we lacked information on this variable. Both the PID and ectopic pregnancy models were run for each year of the analysis.

Model Specification

Pelvic Inflammatory Disease:

We assumed hospitalized PID incidence (IR_{hospPID}) was binomially distributed:

$$N_{\text{hospPID}} \sim \text{Binomial}(N_{\text{femaleWA}}, IR_{\text{hospPID}}),$$

where N_{hospPID} represents the number of hospitalized PID cases, and N_{femaleWA} represents the number of women aged 15-44 in WA State. We assigned this parameter an informative prior Beta distribution based on national estimates of hospitalized PID derived from the NHDS.

In order to incorporate the reported uncertainties in the estimated cases derived from NDTI, we used a normally distributed likelihood for the outpatient incidence, incorporating the reported estimated mean number of outpatient cases from NDTI and the variance of this estimate:

$$N_{\text{outPID}} \sim \text{Normal}(M_{\text{PID,NDTI}}, V_{\text{PID,NDTI}}),$$

where N_{outPID} represents the number of outpatient cases of PID nationally, and $M_{\text{PID,NDTI}}$ and $V_{\text{PID,NDTI}}$ represent the mean and variance of outpatient PID cases reported by NDTI, respectively. To account for the additional uncertainty of using national outpatient PID incidence as a stand-in for WA outpatient incidence, we doubled the variance reported in NDTI for our model. This parameter had an uninformative normal prior, $\text{Normal}(0, 10^{-6})$, because we had no previous data on outpatient incidence.

This model then required two functional parameters, one to estimate the outpatient incidence (IR_{outPID}) from the parameter for outpatient cases:

$$IR_{\text{outPID}} = N_{\text{outPID}}/N_{\text{femaleNat}},$$

where $N_{\text{femaleNat}}$ represents the number of women 15-44 years old in the US, and another to estimate the total incidence of PID:

$$IR_{\text{totalPID}} = IR_{\text{hospPID}} + IR_{\text{outPID}}.$$

Ectopic Pregnancy:

We assumed both outpatient and inpatient ectopic pregnancy incidence (IR_{outEP} and IR_{hospEP} , respectively) to be binomially distributed:

$$N_{\text{outEP}} \sim \text{Binomial}(N_{\text{pregGH}}, IR_{\text{outEP}})$$

$$N_{\text{hospEP}} \sim \text{Binomial}(N_{\text{pregWA}}, IR_{\text{hospEP}}),$$

where N_{outEP} and N_{hospEP} represent the number of outpatient and hospitalized ectopic pregnancy cases, respectively, and N_{pregGH} and N_{pregWA} represent the number of pregnancies in Group Health and WA, respectively.

We used an uninformative prior distribution, $\text{Beta}(1, 1)$, for IR_{outEP} , indicating that we had no prior information on the parameter. We used an informative prior Beta distribution for IR_{hospEP} , based on the incidence of ectopic pregnancy hospitalization in the Group Health population.

We then estimated the total incidence of ectopic pregnancy (IR_{totalEP}) from these basic parameters:

$$IR_{\text{totalEP}} = IR_{\text{hospEP}} + IR_{\text{outEP}}.$$

Statistical Inference

We estimated the posterior distributions for each parameter using the Markov Chain Monte Carlo (MCMC) simulation procedure using the open-source program WinBUGS version 1.4 [42]. In both the PID and ectopic pregnancy models, we ran two independent chains for 100,000 iterations, with the first 50,000 iterations discarded as burn-in. We assessed satisfactory chain convergence by examining Brooks-Gelman-Rubin diagnostic plots.

Outpatient PID Cases in the Public Health-Seattle & King County STD Clinic

We examined cases of PID identified among patients at a local STD clinic in order to assess how the trend in outpatient PID incidence that we estimated for WA compared to the trend in PID in an actual outpatient facility in the state. We examined de-identified clinic records for every visit among women 15-44 years old made to the clinic between 1993 and 2010 for instances of PID (electronic records before 1993 were not available). We identified PID based on the presence of the following signs and symptoms: abdominal pain (from abdominal exam), cervical motion tenderness, or adnexal tenderness. Visits made by the same patient within a 42-day window were counted as one case of PID [43]. We calculated annual clinic prevalence from the number of PID cases out of all clinic visits made by women 15-44 years old.

Analysis for Association between CT Positivity, GC Incidence, and Rates of PID and EP

To assess the influence of declining CT positivity and GC incidence on rates of PID and ectopic pregnancy, we developed a linear regression model with auto-correlated errors (the SAS AUTOREG procedure), which takes year-to-year correlation in regression residuals into account when fitting the data. We developed separate models for each of the outcomes of interest: inpatient PID incidence, inpatient ectopic pregnancy incidence, total PID incidence, and total ectopic pregnancy incidence. In addition, we developed models where CT positivity and GC incidence were included individually as predictors, as well as those with both predictors together. We used a first order autoregressive error process and maximum-likelihood estimation for each model. Additionally, we decided *a priori*, based on previous literature [14], to include a 2-year lag in the ectopic pregnancy analyses, such that CT positivity and GC incidence for 1988 would relate to ectopic pregnancy incidence in 1990 and so on. Given the acute nature of PID, a lag was

deemed not necessary for the PID analysis [4-6]. We used a significance level of $\alpha=0.01$ for regression coefficients to compensate for the model's tendency to underestimate standard errors in small samples [44].

Estimated Population Attributable Risk of Chlamydia and Gonorrhea Infection on PID and Ectopic Pregnancy

Using the linear regression models with auto-correlated errors, we estimated a population attributable risk (PAR) of CT or GC infection on the incidence of inpatient PID and ectopic pregnancy using the methods described previously for PAR estimation in ecological studies [45-47]. Briefly, we modeled inpatient PID and ectopic pregnancy incidence as a function of the proportion of the population exposed to either CT or GC and then used the model to estimate the incidence of either outcome in a fully exposed (R_1) and a fully unexposed (R_0) population. The difference of these two values (R_1-R_0) represents the attributable risk (AR) of that exposure. The PAR is then calculated as:

$$PAR=AR \times P_e,$$

where P_e represents the proportion of the population exposed to either CT or GC (for CT, the test positivity in the screened population; for GC, the proportion of reported cases among all WA women). We calculated the PAR for each exposure and each outcome for the beginning and end of the study period.

Statistical analyses were performed in SAS version 9.3.

Study procedures were determined to be exempt from review by the University of Washington Institutional Review Board.

Results

Adjustment and Trends in Chlamydia Positivity

From 1988-2010 there were 928,980 and 61,725 CT tests performed at IPP and PPWW sites in WA respectively, of which a total of 61,139 (6.2%) were positive. Adjustment of CT positivity for age, race, test type, year, and clinic led to much higher estimates of positivity during the first ten years of surveillance, as compared to the crude measurement (Figure 1A). In more recent years, adjusted

positivity has been similar and even slightly lower than the crude positivity. Further references to positivity will be based on the adjusted estimates.

During the surveillance period, positivity initially declined substantially, from a peak of 14.2% in 1988 to a low of 5.4% in 1997, a drop of 62% (test for negative linear trend: $p=0.0003$). Since that time, CT positivity has slowly but steadily increased, reaching 6.7% in 2004 and 6.3% in 2010. Overall, positivity increased 16.9% between 1997 and 2010 (test for positive linear trend: $p=0.045$).

Gonorrhea Incidence

A total of 36,500 GC cases in women were reported to WADOH between 1988 and 2010. GC incidence in WA women showed an even more extreme initial decline than CT, dropping by nearly 80% from 1998-98 (Figure 1A) (test for negative linear trend: $p<0.0001$). GC incidence then climbed through the mid-2000's, peaking at 64.7 cases per 100,000 women in 2006, though this increase was non-significant (test for positive linear trend: $p=0.93$). The subsequent decline resulted in the lowest incidence during the entire study period, at 28.2 cases per 100,000 women in 2009.

Incidence of PID and Ectopic Pregnancy Hospitalizations

There were 31,512 cases of hospitalization with PID and 16,454 instances of inpatient ectopic pregnancy in WA during the study period. Hospitalized PID incidence declined almost continuously each year since 1988 (Figure 1B). Incidence of PID was 244.7 cases per 100,000 women aged 15-44 in 1988 and decreased steeply until 1999. From 1999 to 2004, incidence remained relatively steady, but since 2005 there has been a renewed decrease, reaching 61.8 per 100,000 in 2010, for an overall decrease of 75% since 1988 (test for negative linear trend: $p<0.0001$).

Unlike PID, the incidence of hospitalized ectopic pregnancy did not begin to decrease until two years into the study period, with stable rates around 1,410 cases per 100,000 pregnancies in 1988 and 1989 (Figure 1B). Incidence rapidly decreased in the 1990s before leveling off, with only a small peak of cases in 2001 at 518.7 per 100,000. Incidence in 2010 was 417.3 per 100,000, an almost 70% decrease since 1988 (test for negative linear trend: $p<0.0001$).

Proportion of PID and Ectopic Pregnancy Cases Treated in an Outpatient Setting

We compared rates of inpatient and outpatient cases of PID and ectopic pregnancy in the national and Group Health populations, respectively, in order to calculate the proportion of cases over time treated in the outpatient setting. We found in both instances that outpatient-based cases represented a substantial proportion of all detected cases in these populations. Nationally, an average of 71% of PID cases were treated in the outpatient setting between 1988 and 2010, and this proportion varied between 59.4% and 77.6% over time. Overall, the proportion of women with PID treated as outpatients declined slightly over the study period, dropping 6.2% between 1988 and 2010 (Figure 2A) (slope for linear trend line: -0.41%, $p=0.008$).

In the Group Health population, the average proportion of ectopic pregnancy cases treated in outpatient facilities was 64.3%, and ranged from 46.4% and 76.8% between 1993 and 2007. Over time, there was a trend towards an increasing proportion of cases being treated in the outpatient setting (Figure 2B) (slope for linear trend line: +1.04%, $p=0.02$).

Estimated Incidence of Total PID and Ectopic Pregnancy Cases

Using the Bayesian evidence synthesis approach, we estimated the total incidence of PID and ectopic pregnancy, including both inpatient and outpatient treatment. We assessed the appropriateness of the assumption that the WA outpatient rates would be similar to those in the national/Group Health population by comparing trends in hospitalization rates for each condition. Comparison of the national and WA inpatient PID incidence rates shows that the incidence per 100,000 women is slightly higher nationally than in WA State. However, the trends in cases over time are largely similar between the two populations, with only a few deviations over time (Figure 3A). National outpatient incidence for PID during this time period showed similar declining trends. Comparison of Group Health and WA inpatient ectopic pregnancy incidence rates shows a remarkable degree of similarity in magnitude and trend over time (Figure 3B). Over this same time period, outpatient incidence of ectopic pregnancy in the Group Health population remained largely unchanged. However, the number of cases of ectopic pregnancy treated through Group Health each year was small (40-91 outpatient cases), and rates in that sentinel population fluctuated over the study period. These findings suggested that the assumption of similar rates, or at least

trends in rates, in outpatient cases of PID and ectopic pregnancy in the populations being analyzed was appropriate and could be applied in the construction of the evidence synthesis model.

Results of the evidence synthesis technique indicate a declining trend in estimated total PID incidence in WA State (test for negative linear trend: $p < 0.0001$) (Figure 4A). The estimated total incidence was much higher than that of hospitalized cases alone, with a four-fold greater total incidence than inpatient incidence in 1988 and in 2010. The estimated total incidence was 988 per 100,000 women in 1988 and 243.3 per 100,000 in 2010. The Bayesian credible intervals include the uncertainty due to sampling in the NDTI data and uncertainties for the difference between the national and WA populations.

Trends in estimated total ectopic pregnancy incidence similarly showed a decrease over time (test for negative linear trend: $p = 0.017$) (Figure 4B). Again, total incidence was much higher than what was calculated for inpatient cases alone, at 1,922 per 100,000 pregnancies in 1993 and 1,392 per 100,000 in 2007. This represents a two-fold difference in incidence in 1993 and a three-fold difference in 2007 compared to inpatient incidence.

Trends in PID Cases at the Public Health-Seattle & King County STD Clinic

The number of cases of PID identified at the PHSKC STD clinic declined rapidly from 1993 to 2010, with an accompanying decline in total number of visits by women (Figure 5A). We compared the trend in clinic prevalence at this one outpatient facility with the incidence of outpatient cases in the whole state, derived from the estimated total incidence generated from the multi-parameter evidence synthesis model. The trends over time between STD clinic cases and all outpatient cases in the state were remarkably similar (Figure 5B).

CT and GC as Predictors of Reproductive Outcomes

Tables 2 and 3 show the results of the regression models with auto-correlated errors relating CT positivity and GC incidence to either PID or ectopic pregnancy incidence. The linear regression model with auto-correlated errors was separately fit with both inpatient PID/ectopic pregnancy incidence and with total PID/ectopic pregnancy incidence as the outcome of interest. All models were originally fit with both CT positivity and GC incidence as predictors; however, models of total PID and ectopic pregnancy incidence displayed issues with collinearity when CT and GC were modeled together. Therefore, results

of models of total incidence are unadjusted for the other infection. Models of inpatient incidence are presented as adjusted for the other pathogen, as well as unadjusted to provide more ready comparisons to results of the models of total incidence.

Adjusted models of inpatient PID and ectopic pregnancy incidence

Both CT and GC were strongly associated with inpatient PID and ectopic pregnancy incidence, though not all of the associations were statistically significant. Interpretation of regression coefficients is based on one standard deviation change in CT positivity or GC incidence during the study period; the standard deviation for CT positivity was 2.1% and for GC incidence was 32.3 cases per 100,000 women. Therefore, the adjusted hospitalized PID model indicates that for every 2% decrease in CT positivity, mean inpatient PID incidence decreases by 18.36 cases per 100,000 (95% confidence interval (CI): 8.23-28.48, $p=0.001$) after adjusting for GC, while for every decrease of 32 per 100,000 GC cases, PID incidence decreases by 14.57 cases per 100,000 (95% CI: 2.72-26.41, $p=0.018$), on average, after controlling for CT (Table 2). The adjusted hospitalized ectopic pregnancy model indicates that for every 2% decrease in CT positivity, ectopic pregnancy incidence 2 years later will decrease by 59.88 cases per 100,000 pregnancies (95% CI: 4.71-115.04, $p=0.033$) on average, adjusting for GC incidence, and for every 32 cases per 100,000 decrease in GC incidence, mean ectopic pregnancy incidence will decrease by 102.87 per 100,000 pregnancies (95% CI: 36.13-169.62, $p=0.005$), adjusting for CT positivity, after two years (Table 3). The coefficients of the other models presented in Tables 2 and 3 should be interpreted similarly.

Total R^2 , which measures how well the model can predict the next value in the series using both the structural component of the model as well as residuals for the previous value, and so provides a measure of model fit, was high for both the PID and ectopic pregnancy model. Total R^2 for the PID model was 97.7% and was 97.3% for the ectopic pregnancy model.

Unadjusted models of inpatient PID and ectopic pregnancy incidence

From 1988 to 2010, CT and GC were each more strongly associated with PID and ectopic pregnancy hospitalization alone than after adjustment for the other infection (Tables 2 and 3). The association with CT positivity increases by almost a third when not adjusting for GC, while the magnitude

of the association of GC with PID nearly doubles when not adjusting for CT. The relationship of GC and PID also changes from being slightly non-significant when adjusting for CT to highly significant when not adjusting for the other infection. The total R^2 was 97% for the model with CT positivity and 96% for the model with GC incidence.

For ectopic pregnancy, the total R^2 was 95.8% for the model with CT positivity and 96.5% for the model with GC incidence. As with the PID models, the magnitude of the associations between CT or GC alone and ectopic pregnancy were approximately 1.5 to 2 times larger than when these estimates were adjusted for the other infection.

In both the unadjusted and the adjusted models, CT and GC seemed to be equally associated with inpatient PID incidence, while GC appeared to be more strongly associated with inpatient ectopic pregnancy incidence than did CT.

Unadjusted models of total PID and ectopic pregnancy incidence

Compared to the associations with hospitalized incidence, there was a larger magnitude of association between CT positivity and both total PID and total ectopic pregnancy incidence (Tables 2 and 3). However, while the magnitudes of these associations were large, they were non-significant. Similar results were observed for GC, though those associations were only marginally non-significant using the more conservative alpha cut-off of >0.01 . Interestingly, while the difference in the magnitude of the association between GC and inpatient versus total PID was quite large (almost 4-fold higher for total PID), there was much less difference in the associations of GC and inpatient versus total ectopic pregnancy. Total R^2 for the model of CT positivity and total PID incidence was 89.6%, but was only 16.6% for the model of CT positivity and total ectopic pregnancy incidence. Likewise, the total R^2 for the model of GC incidence and total PID incidence was 90.8%, and only 38.9% for the model of GC positivity and total ectopic pregnancy incidence. Importantly, models for total EP incidence had many fewer data points, given that fewer years of data were available for analysis (1993-2007), making it more difficult to assess the association in trends over time.

PAR Calculations for Inpatient PID and Ectopic Pregnancy

The PAR indicates the amount by which the incidence of a given outcome in the population will decrease given the complete elimination of a particular exposure. Table 4 presents the results of PAR calculations for inpatient PID and ectopic pregnancy incidence. Calculations were not performed for total PID and ectopic pregnancy because of the poor fit of the regression models for these outcomes, as detailed above. In 1988, when CT and GC exposure were at their highest, the complete elimination of CT would result in a decline of 122 cases of PID per 100,000 women and 399 cases of ectopic pregnancy per 100,000 pregnancies. Likewise, the complete elimination of GC would result in 67 fewer cases of PID per 100,000 women and 472 fewer cases of ectopic pregnancy per 100,000 pregnancies. The PARs for each infection in 2010 were lower for both inpatient PID and ectopic pregnancy.

Discussion

This study demonstrates that CT test positivity, GC incidence, and PID and ectopic pregnancy diagnoses all concurrently declined among women in WA between 1988 and 2010. The drop in PID and ectopic pregnancy rates was evident in an analysis that includes both inpatient and outpatient diagnoses, demonstrating that the declining trends in these important reproductive tract sequelae were not simply a consequence of changing patterns of medical management. We observed strong ecological associations between trends in CT positivity and GC incidence and trends in hospitalizations for PID and ectopic pregnancy. However, our findings associating STD trends with rates of all PID and ectopic pregnancy cases, including outpatient diagnoses, were more equivocal. Including outpatient diagnoses in the analyses increased the magnitude of the association between CT and GC trends and trends in PID and ectopic pregnancy but these larger associations were not consistently statistically significant. Overall, our results suggest that trends in ectopic pregnancy are more strongly associated with trends in GC than with trends in CT positivity, though this pattern was less evident with PID. The population attributable risk of CT and GC on hospitalized PID and ectopic pregnancy showed substantial declines between 1988 and 2010, perhaps reflecting declines in the occurrence of GC and CT, with a rising proportion of the remaining, smaller number of cases attributable to other causes.

Several of our findings merit comment. First, we observed significant decreases in both inpatient and total ectopic pregnancy incidence, while prior published studies have not consistently observed this

trend. Analyses of data from Group Health Cooperative in Washington and from British Columbia, Canada did not observe declines in the occurrence of ectopic pregnancy over time [19,32]. However, those studies began in 1997 and 1992, respectively. We observed that the majority of the decline in ectopic pregnancy occurred in the late 1980s and early 1990s, and the failure to observe a trend in ectopic pregnancy in these prior reports may simply reflect the period of observation included in those studies. In contrast, a study in Sweden that began in 1985 did observe declines in ectopic pregnancy for the majority of age groups [14]. Interestingly, the drop in total ectopic pregnancy we observed was primarily the result of a decline in inpatient ectopic pregnancy diagnoses. Outpatient ectopic pregnancy incidence in Group Health remained essentially unchanged between 1993 and 2007, even as the proportion of cases treated in the outpatient setting increased by approximately 30%. We were not able to calculate total ectopic pregnancy incidence between 1988 and 1993, but given that the years for which we had no data on total incidence correspond to the years during which declines in CT positivity, GC incidence, and the incidence of hospitalized ectopic pregnancy were greatest, we suspect that our analysis underestimates the magnitude of the true decline in ectopic pregnancy over the full study period.

Our study highlights the importance of including both inpatient and outpatient PID and ectopic pregnancy data in monitoring these conditions. We observed that a large proportion of PID and ectopic pregnancy cases were treated in the outpatient setting and those proportions changed over time. Therefore, failing to include outpatient cases may substantially underestimate the incidence of each condition in the population and distort trends in incidence over time. It would also bias associations with trends in CT and GC, though the direction of that bias is difficult to predict. Many previous ecological analyses have failed to adequately capture outpatient cases [14,30,31] or done so only in a subset of the population [19]. By including outpatient incidence of PID and ectopic pregnancy, we developed a more complete picture of PID and ectopic pregnancy burden in WA and their association with trends in CT and GC over time.

Finally, we were able to validate our estimates of total PID and ectopic pregnancy and the assumptions that were necessary to generate those estimates. By comparing the inpatient incidence of PID or ectopic pregnancy in WA and in the national or Group Health populations, respectively, we were more confident in the assumption that the incidence of outpatient treatment for each condition would be

similar between these populations. Additionally, the decline in estimated total PID we observed was further supported by declines seen in the PHSKC STD clinic. While this is only one source of outpatient PID data in the state, it suggests that PID incidence in the outpatient setting is in fact decreasing in WA. It also indicates the potential utility of sentinel surveillance data for hard-to-measure outcomes such as PID.

There were several limitations to our study. First, we were unable to collect information on outpatient cases in WA and instead had to rely on previously collected data from the U.S. and sentinel data from Group Health. As a result, our estimates of total incidence of PID and ectopic pregnancy may not reflect the true incidence of each condition in the state. However, while there are some differences between the Group Health population and that of WA, particularly in insurance status, overall Group Health is representative of the underlying population in WA in other demographics, such as race [21,48]. Second, as noted above, the Group Health data we used missed a crucial time period of potential decline in ectopic pregnancy. This limited in our ability to assess the relationship in STD trends and total ectopic pregnancy incidence; with the incorporation of the lag in ectopic pregnancy incidence, the models of total ectopic pregnancy were missing over half of the potential data points. During the time period where data were available, CT and GC were primarily increasing over time, while none of the initial decreases were captured in the models. This may account for the poor model fit between each outcome and both CT and GC, and for our failure to observe statistically significant associations between trends in STDs and trends in total PID and ectopic pregnancy. Third, our analysis was limited by the different age ranges used when assessing CT and GC infection over time; we used total GC incidence for women because GC incidence by age was not available for the whole study period. Because GC incidence in women ages 15-29 is greater than in all women, magnitudes of association between GC and PID/ectopic pregnancy may be underestimated. Finally, to the extent that we observed associations between two sexually transmitted infections and PID and ectopic pregnancy, we cannot conclude that these ecologic associations are causal. For this reason, the PARs calculated here should also be interpreted cautiously [47].

In summary, we observed that both PID and ectopic pregnancy declined concurrently with a drop in GC incidence and CT positivity in WA. The association between this encouraging drop in reproductive health sequelae and the trend in GC was of borderline statistical significance, while we did not observe a significant association between CT positivity and trends in total PID and ectopic pregnancy. The extent to

which this absence of association reflects the failure of chlamydial control activities to affect reproductive tract sequelae in women versus limitations in our data and study design is not clear. Thus, our findings demonstrate that important reproductive health morbidity among women is declining without clearly supporting the hypothesis that improved STD control is the cause of that decline.

Figures and Tables

Table 1: Summary of data sources used to calculate trends in chlamydia test positivity, gonorrhea incidence, and the incidence of PID and ectopic pregnancy in Washington State, 1988-2010.

Condition	Data Type	
	Numerator	Denominator
CT	IPP	IPP
GC	WA notifiable conditions data	WA OFM for number of women age 15-44
PID – hospitalized	<ul style="list-style-type: none"> CHARS, 1988-2010 NHDS, 1988-2010 for national hospitalization rate 	<ul style="list-style-type: none"> WA OFM for number of women, 15-44 US mid-year census estimates of women, 15-44
PID – outpatient	<ul style="list-style-type: none"> NDTI, 1988-2010 PHSKC STD clinic records of PID cases in women 15-44, 1993-2010 	<ul style="list-style-type: none"> US mid-year census estimates of women, 15-44 PHSKC STD clinic visits by women 15-44
Ectopic Pregnancy – hospitalized	<ul style="list-style-type: none"> CHARS, 1988-2010 Group Health Cooperative, 1993-2007 (previously reported, Trabert et al. [21]) 	<ul style="list-style-type: none"> WA vital statistics records for number of pregnancies among women age 15-44 Number of pregnancies, Group Health Cooperative, 1993-2007
Ectopic Pregnancy – outpatient	Group Health Cooperative, 1993-2007	Number of pregnancies, Group Health Cooperative, 1993-2007

Abbreviations: IPP=Infertility Prevention Project; CHARS=Comprehensive Hospital Abstract Reporting System; NHDS=National Hospital Discharge Survey; NDTI=National Disease and Therapeutic Index; WA=Washington State; OFM=Office of Financial Management; PHSKC=Public Health-Seattle & King County

Table 2: Results of linear regression with autocorrelated errors testing the association between chlamydia positivity and gonorrhea incidence on the incidence of PID in Washington State, 1988-2010. Mean change in PID incidence is based on a one standard deviation change in CT positivity or GC incidence.

	PID								
	Hospitalized cases only (adjusted)*			Hospitalized cases only (unadjusted)			All cases (unadjusted)		
	Mean change in PID incidence**	95% CI	p-value	Mean change in PID incidence**	95% CI	p-value	Mean change in PID incidence**	95% CI	p-value
Chlamydia	18.36	8.23–28.48	0.001	25.18	16.15–34.20	<0.0001	55.34	-23.03–134.02	0.153
Gonorrhea	14.57	2.72–26.41	0.018	28.08	15.49–40.67	0.0001	107.25	23.75–190.76	0.014

*Associations between each infection and outcome adjusted for the other infection

**Incidence presented per 100,000 women 15-44; mean change in PID incidence is based on a one standard deviation change in CT positivity or GC incidence.

Abbreviations: PID=pelvic inflammatory disease; CI=confidence interval

Table 3: Results of linear regression with autocorrelated errors testing the association between chlamydia positivity and gonorrhea incidence on the incidence of ectopic pregnancy in Washington State, 1988-2010.

	Ectopic pregnancy								
	Hospitalized cases only (adjusted)*			Hospitalized cases only (unadjusted)			All cases (unadjusted)**		
	Mean change in EP incidence†	95% CI	p-value	Mean change in EP incidence†	95% CI	p-value	Mean change in EP incidence†	95% CI	p-value
Chlamydia	59.88	4.71–115.04	0.033	106.17	52.90–159.45	0.0005	176.32	-101.01–453.66	0.201
Gonorrhea	102.87	36.13–169.62	0.005	146.61	88.15–205.06	<0.0001	160.88	33.05–288.72	0.021

*Associations between each infection and outcome adjusted for the other infection

**Model includes data from 1993-2007 only

†Incidence presented per 100,000 pregnancies; mean change in ectopic pregnancy incidence is based on a one standard deviation change in CT positivity or GC incidence.

Abbreviations: EP=ectopic pregnancy; CI=confidence interval

Table 4: Results of calculations of PAR for PID and ectopic pregnancy based on estimates from a linear regression with autocorrelated errors model. The PAR is calculated for both the first year and the last year of the study period. Results for each infection are based on adjustment for rates of the other infection.

	Inpatient PID Incidence*†	CT PAR*	GC PAR*
1988	244.68	122.23	66.78
2010	61.81	52.39	13.99
	Inpatient EP Incidence†‡	CT PAR‡	GC PAR‡
1988	1410.47	398.72	471.65
2010	417.27	170.88	98.79

*Incidence and PAR estimates presented per 100,000 women 15-44

†Inpatient incidence as presented in Figure 1B

‡ Incidence and PAR estimates presented per 100,000 pregnancies

Abbreviations and definitions: CT=chlamydia; GC=gonorrhea; PID=pelvic inflammatory disease; EP=ectopic pregnancy; PAR=Population attributable risk

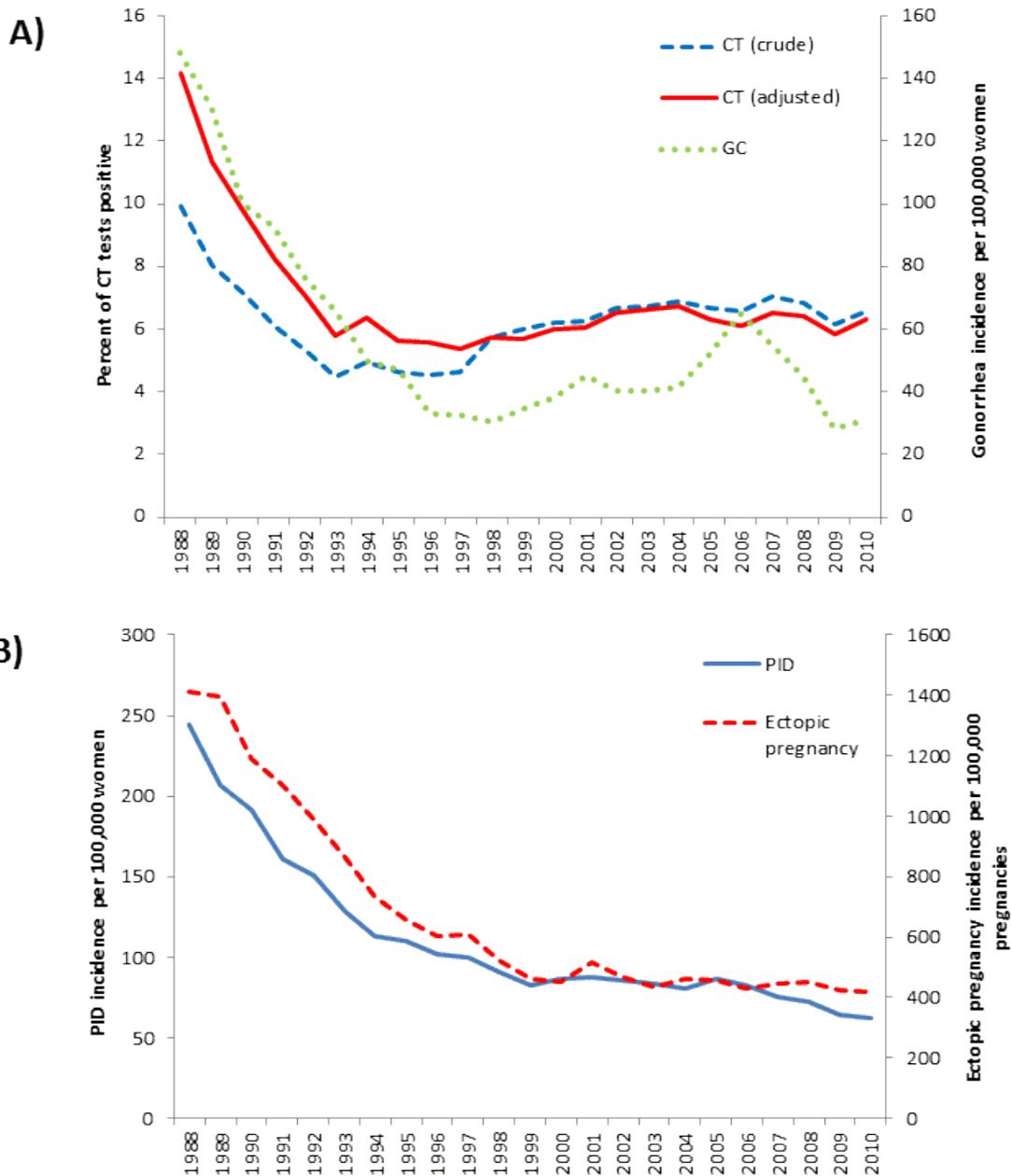


Figure 1: Trends by year, Washington State, 1988-2010. A) Crude and adjusted chlamydia positivity in women, 15-25, from the Infertility Prevention Project, and gonorrhea incidence in all women from Washington notifiable conditions records, B) incidence of inpatient PID and ectopic pregnancy, women 15-44 years old, from Washington hospital discharge records. Positivity is adjusted for age, race/ethnicity, test type, year and clinic.



Figure 2: Proportion of A) PID cases in the US population and B) ectopic pregnancy cases in the Group Health population treated in an outpatient setting. Proportions for PID are available for the entire study period, while treatment setting data are only available for ectopic pregnancy from 1993-2007. A linear trend line of best fit and accompanying equation are also displayed for each graph to summarize the overall trend over time.

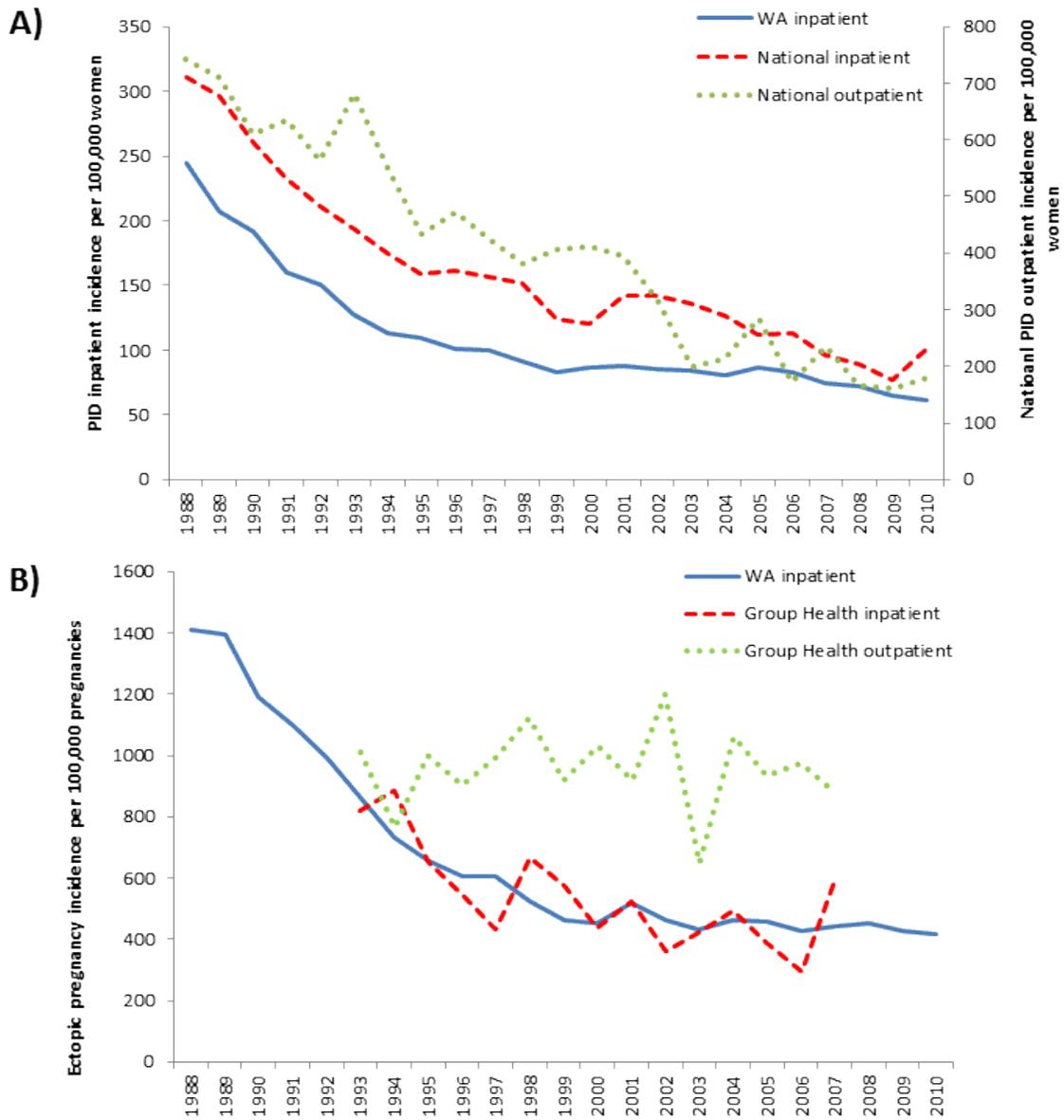


Figure 3: Comparison of trends over time in inpatient incidence of A) PID and B) ectopic pregnancy between the Washington State population and the national or Group Health populations, respectively. Also displayed is the outpatient incidence of PID and ectopic pregnancy nationally or in Group Health. Washington State inpatient incidence is derived from Washington State hospital discharge records. National inpatient PID incidence is derived from the National Hospital Discharge Survey, while trends in ectopic pregnancies in the Group Health population were collected from Group Health hospitalization and claims records and reported in Trabert et al. [21]. Group Health data were only available from 1993-2007.

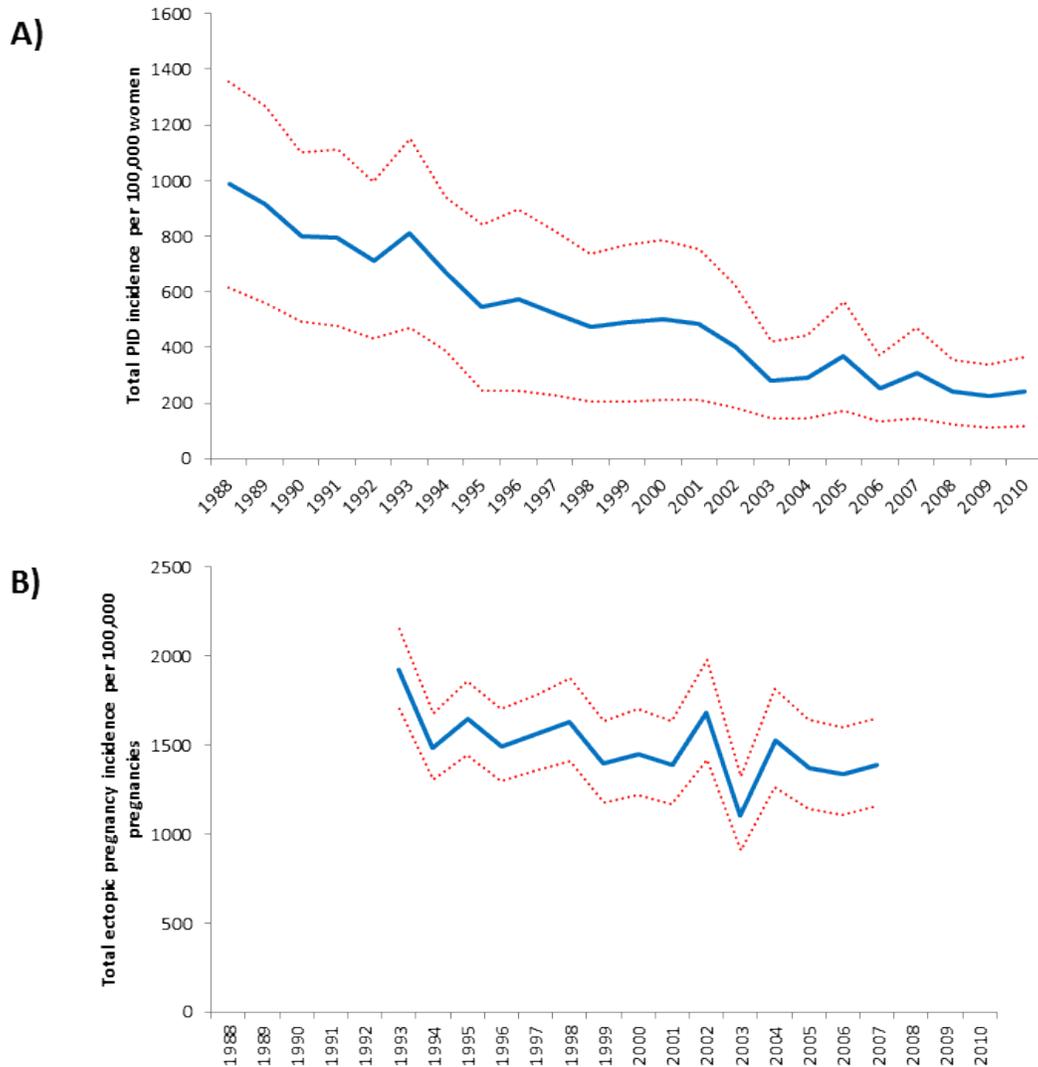


Figure 4: Estimated trends in total incidence of A) PID and B) ectopic pregnancy in Washington State derived from the multi-parameter evidence synthesis procedure, combining inpatient incidence of each condition in Washington with outpatient incidence in the national or Group Health populations, respectively. Trends include 95% Bayesian credible intervals. Group Health data are only available from 1993-2007.

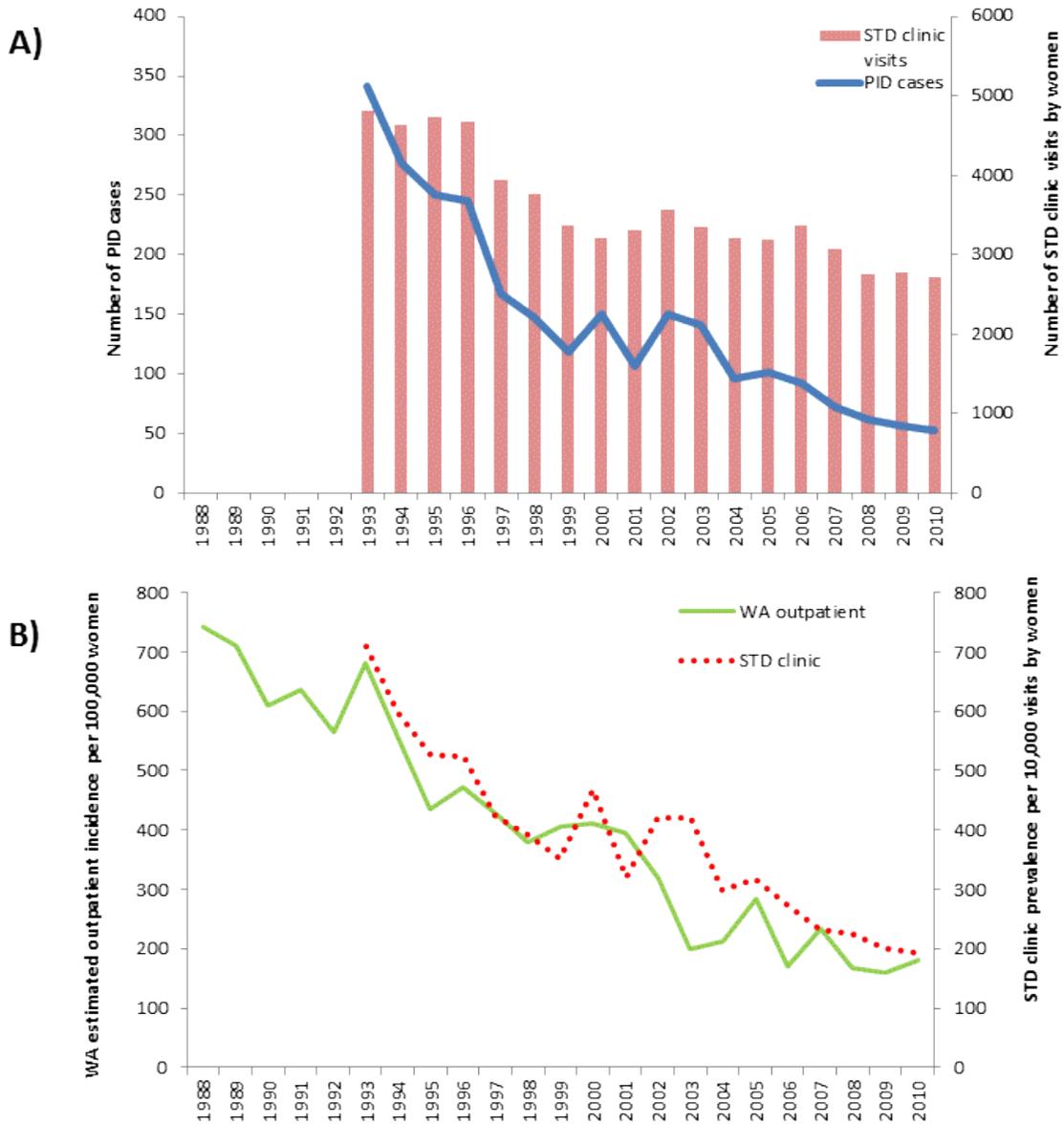


Figure 5: Cases of PID detected in female patients 15-44 years old, visiting the Public Health-Seattle & King County STD clinic between 1993 and 2010. A) Number of cases detected compared to number of visits made to the clinic by women over the same time period, B) comparison of trends in STD clinic prevalence per 10,000 visits by women 15-44 and estimated outpatient incidence per 100,000 women in the state.

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