Estimation of the risk of tubal factor infertility associated with genital chlamydial infection in women: a statistical modelling study

Kimberley Kavanagh,1* Lesley A Wallace,2 Chris Robertson,1,2,3 Phil Wilson4 and Anne Scoular5

1Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK, 2Health Protection Scotland, Glasgow, UK, 3International Prevention Research Institute, Lyon, France, 4Centre for Rural Health, University of Aberdeen, Inverness, UK and 5NHS Greater Glasgow and Clyde, Glasgow, UK

*Corresponding author. Department of Mathematics and Statistics, Level 9, 26 Richmond Street, University of Strathclyde, Glasgow, G1 1XH, UK, E-mail: kim.kavanagh@strath.ac.uk

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Objectives Using a statistical modelling approach, our study aim is to determine reliable age-related estimates of the risk of all-cause tubal factor infertility (TFI) following past or current chlamydial infection in women in Scotland.

Method Using data from several sources, a Markov-Chain Monte Carlo model was used to estimate the age-related risk of TFI given genital chlamydia infection at any time. The analysis is based on the probability of a woman ever having chlamydia infection, ever having TFI and ever having a previous chlamydial infection given a diagnosis of TFI. The model was programmed and evaluated using WinBugs14.

Results By the age 44 years, the overall risk of a woman having at least a single chlamydial infection is estimated at 42.9% (95% credible interval 30.0, 59.0%). The risk of a woman having TFI increased from 0.5% in those aged 16–19 years to 0.8% in those aged 40–44. The overall estimated probability of TFI, based on lifetime infertility, given a past or current chlamydial infection, is relatively consistent across all five age groups from 16–44 years, being 0.9% among those aged 25–29 and 1.4% in those aged 35–39; The estimates were found to be sensitive to the definition of infertility, with the estimate increasing from 1.3% in the youngest age group to 2.8% and 4.5% for 24-month primary infertility and primary or secondary infertility, respectively.

Conclusions At the population level, the likelihood of all-cause TFI in those with past or current chlamydial infection is low. These findings have relevance both at the policy level, in the development of control programmes, and also at an individual level, particularly for clinicians supporting women undergoing testing or with a positive diagnosis.

Keywords Genital chlamydia, tubal factor infertility, MCMC model
**Introduction**

*Chlamydia trachomatis* is a highly prevalent sexually transmitted bacterial infection. Although there is clear evidence that genital chlamydial infection in women is associated with reproductive morbidity, including tubal factor infertility (TFI), the probability that TFI will occur in individuals who have been infected with *C. trachomatis* is uncertain.\(^1,2\) Estimates of the probability of late sequelae of chlamydial infection, including TFI, impact upon the cost effectiveness of chlamydial screening programmes,\(^3,4\) highlighting the need for accurate estimation.

A recently published review\(^4\) suggests that, when combining published progression rates, the risk of tubal infertility after chlamydial infection is low (0.1–6%). An alternative approach,\(^5\) based on deterministic estimation of probabilities and recombination using Bayes theorem, uses Dutch registration data and data from local studies to calculate the maximum probability of TFI after chlamydia infection and estimates the probability to be 0.02%. This deterministic approach does not attempt to capture the variability in the model components and provides no age stratification.

We used statistical modelling to estimate the age-related probability, accounting for uncertainty and variability, of TFI for women of reproductive age in Scotland with current or previous chlamydial infection. Such an approach, using available evidence from existing data, allows us to estimate the association between all-cause TFI and chlamydial infection at a population level when we are unable to perform randomised controlled trials in the context of widespread chlamydia testing.\(^6\) Given that we do not consider the role of other STIs in our model structure, we provide an upper bound on the modelled probabilities.

**Methods**

**Modelling approach**

We constructed a Markov-Chain Monte Carlo (MCMC) model to estimate the probability of TFI given past or current chlamydial infection for women of reproductive age in Scotland. This model extended the approach used in women in The Netherlands\(^5\) by introducing age dependence. The model comprised three components: (i) the probability that a woman in each 5-year age group from 16–19 to 40–44 has been infected with *C. trachomatis* in the past or is currently infected, denoted \(P(Ct^+, \text{Age } i)\); (ii) the probability that a woman in each age group has TFI, denoted \(P(TFI, \text{Age } i)\); and (iii) the probability of having had \(Ct \) in women with TFI in each age group, denoted \(P(Ct^+, \text{TFI, Age } i)\).

Each component of the model was derived from several data sources (Figure 1). These were combined, according to Equation 1, to estimate the probability of TFI given past/current chlamydial infection \(P(TFI|Ct^+, \text{Age } i)\):

\[
P(TFI|Ct^+, \text{Age } i) = \frac{P(Ct^+|TFI, \text{Age } i)P(TFI, \text{Age } i)}{P(Ct^+, \text{Age } i)}
\]

(1)

Age-stratified (point) estimates are presented with 95% Bayesian credible intervals (CrI), which state with 95% probability that the true value lies within the given range. The model was programmed and evaluated in WinBugs 14 software using two chains and 100,000 iterations.\(^7\) Convergence of the MCMC estimates was assessed by monitoring the Gelman and Rubin convergence diagnostic, and by using different starting points.\(^8\)

**Probability of ever having had chlamydial infection, \(P(Ct^+, \text{Age } i)\)**

The estimate of the probability that a woman has a current chlamydial infection uses estimates of the proportion of women testing positive in the population undergoing testing, with adjustments made for repeat tests, and population prevalence (Figure 1). Two data sources were used: (i) genital chlamydia testing data obtained from Scottish microbiology laboratories; and (ii) UK chlamydia prevalence estimates based on urine testing of a stratified random sample of the general population within the second National Survey of Sexual Attitudes and Lifestyles (NATSAL II) (Figure 2).\(^9,10\) Both data sources have limitations; the NATSAL samples have limited power to detect age trends in prevalence and did not include 16- and 17-year-olds. The proportion testing positive calculated from the chlamydia testing data is upwardly biased due to: repeat testing of anonymized samples; women going for testing possibly having higher levels of risk behaviour;\(^11\) and over-sampling of younger women (although age is taken into account in the model).

In an attempt to correct the bias in the laboratory samples, associated with repeat testing, information on chlamydia re-infection rates in the USA and the UK was used\(^12,13\) in the absence of data on repeat testing rates. Age-stratified yearly re-infection rate predictions, with their associated variability, were estimated for the UK and used to adjust the crude population-based testing rate downwards by splitting the number tested into repeat and incident infections based upon the reinfection rate in that age-band, thus generating a more robust estimate of the probability that an individual in each age group is tested (see Supplementary Appendix S1, available as Supplementary data at IJE online). This assumes that re-infection rates, from cohort studies which attempted to follow up all women, can be used to represent repeat testing rates among women who present for testing.

The estimates of prevalence from NATSAL II and proportion of positive tests from the Scottish laboratory data together with the estimates of the proportion of individuals who have a repeat test are used...
together in a model to provide estimates of chlamydia prevalence by age as described in Supplementary Appendix S2 (available as Supplementary data S2 at IJE online). This process models the change in prevalence with age as a logistic regression model, with the laboratory data primarily determining the slope (i.e. the rate of the change of prevalence with increasing age) as the numbers tested are greater, and the unbiased NATSAL II data primarily used to determine the intercept (i.e. the prevalence in the 16–19-year-old group).

Using these estimates of genital *C. trachomatis* population prevalence by age, the cumulative incidence of ever infected with chlamydia was calculated by dividing the age-stratified prevalence into incident and repeat infections, based upon the yearly rate of re-infection in that age group, and summing incident infections over the total number of years under consideration. This approach assumed that the age-specific prevalence, and incidence, remained constant over time. Making such an assumption, the probability of ever having chlamydia, \( P(C_t^+) \), and associated credible intervals can then be simulated. To consider the possibility of a temporal shift in age-specific incidence, the incidence of chlamydia in the 16–19-year-old group is varied. Our approach also assumes that re-infection is a rate based on 1 year of follow-up for each age-band rather than ever re-infected, and therefore when calculating cumulative incidence of chlamydia infection under this assumption, we provide an upper bound for the estimate. In addition, older individuals have a low re-infection rate but may have been infected when younger so these are not truly incident infections. To investigate the possible over-estimation of cumulative incidence of chlamydia, a sensitivity analysis is conducted by lowering the estimate of cumulative incidence by 5 and 10 percentage points.

**Probability of having TFI, \( P(TFI, \text{Age } i) \)**

The prevalence of infertility, defined here as primary unresolved infertility by the end of a woman’s reproductive lifetime, was estimated from four population-based UK surveys, two of which were identified from the review article of Boivin et al. and two from a search on subsequently published UK-based surveys. Estimates of prevalence were pooled using a Bayesian random-effects meta-analysis as described in Supplementary Appendix S3 (available as Supplementary data at IJE online). The prevalence of infertility varies according to definition which may affect the measured outcome; therefore the use of alternative definitions of infertility (24 months of primary and 24 months of primary or secondary infertility) were considered by the sensitivity analysis.
and on testing women aged 18–19 for the NATSAL data source and the prevalence from the UK NATSAL II survey test data. Note: In the youngest age group (<20), the data are based on mydial infection estimated from Scottish laboratory testing. The probability of tubal factors as the underlying cause of infertility in those seeking treatment is estimable via data from the Human Fertilisation and Embryology Authority. This data provides a breakdown by age but aggregate information for the 18-34 year old age group. Age-stratified data provided by a large Scottish infertility treatment centre provides a more detailed breakdown with stratification for those under 30 and infertility treatment centre provides a more detailed breakdown with stratification for those under 30 and 30–34 years and is therefore used. As information on TFI in women under 30 seeking treatment was not available, our model assumes an equal probability of developing TFI in such women. The increasing proportion of women with TFI with age, reported by Maheshwari et al., indicates that this approach may over-estimate the proportion of women with TFI in the younger age groups. We address this possibility in the sensitivity analysis by using a general additive model to predict the proportion of women with TFI in the 16–19- and 20–24-year age groups and using these predicted proportions in the model. In contrast, the HFEA (Human Fertilisation and Embryology Authority) data show a decrease in TFI attributable in the 40–44-year-old age group which was not observed in the Maheshwari et al. study. To account for this possibility the HFEA data are used in a sensitivity analysis. More information is available in Supplementary Appendix S3, available as Supplementary data at *IJE* online.

### Probability of ever having had chlamydial infection given a woman has TFI, $P(C^+\mid TFI, \text{Age } i)$

A random-effects meta-analysis of published studies was performed to investigate the association between chlamydial antibodies via serology and TFI (for literature search strategy details see Supplementary Appendix S4, available as Supplementary data at *IJE* online). This analysis does not take into account any potential bias induced by low sensitivity and specificity of these tests.

The odds ratios from each of the selected studies are combined into a single estimate. The use of a random-effects model accounts for the between-study heterogeneity in the diagnostic procedures used to detect chlamydia and also to diagnose TFI. For details of the model specification see Supplementary Appendix S4, available as Supplementary data at *IJE* online.

In terms of probabilities for chlamydia and TFI, the odds ratio can be written as:

$$OR = \frac{P(C^+\mid TFI, \text{age group } i)/P(C^+\mid \text{No TFI, age group } i)}{P(C^+\mid \text{No TFI, age group } i)/P(C^+\mid \text{No TFI, age group } i)}$$

where a ‘case’ is a subject with TFI and a ‘control’ is a subject without TFI. Comparing the odds of chlamydial infection between the cases and controls then gives the overall odds of having had a previous chlamydial infection.

The pooled estimate of $OR$ from the random-effects meta-analysis can then substituted into Equation 2. As TFI is rare, it is assumed that $P(C^+\mid \text{No TFI})$ can be estimated by the cumulative incidence of chlamydia over age, $P(C^+)$, which is estimated previously. Given that $P(C^+\mid \text{No TFI})$ is the complement of $P(C^+\mid \text{No TFI})$ this can be estimated also. With these estimates, Equation 2 can then algebraically manipulated to solve for $P(C^+\mid TFI)$.

### Sensitivity analysis

A sensitivity analysis (Table 1) was conducted to examine the effect of modelling assumptions on the overall risk estimate. The factors considered were: (i) the baseline prevalence of chlamydial infection; (ii) changes in the way re-infection is modelled and the lowering of the estimates of cumulative incidence; (iii) how the proportion of women with TFI varies with age; (iv) the definition of infertility; and (v) the potential influence of large studies in the random-effects meta-analysis and other changes in the odds ratio.

### Results

#### Model components

**Probability of ever having had chlamydial infection, $P(C^+\mid \text{Age } i)$**

The yearly prevalence of chlamydial infection was highest in the 16–19-year age group and declined with age, irrespective of the data source used (Figure 2). The estimated prevalence of chlamydial infection ranged from 4.2% (95% CrI: 2.7, 6.2%) in the 16–19 age group to 0.5% (95% CrI: 0.1, 1.2%) in the 40–44 age group. The cumulative reproductive lifetime risk of a woman ever having been infected...
with genital chlamydia was estimated at 42.9% (95\% CrI: 30.0, 59.0\%) (Table 2).

**Probability of having TFI, P(TFI)**

A single pooled estimate of the population prevalence of infertility [3.1\% (95\% CrI: 2.8, 3.4\%)], derived from four UK population-based studies\textsuperscript{14,15,17,18} was used. There was evidence of heterogeneity ($I^2 = 74.1\%$) in the results attributed to a single study with a large sample size having smallest probability of unresolved infertility,\textsuperscript{16} with data on the reported prevalence of TFI among infertile women which ranged from 14.7\% in those aged <30 years to 24.2\% in those aged >40 years.\textsuperscript{20} The age-stratified risk of a woman having TFI ranged from 0.5\% (95\% CrI: 0.4, 0.6\%) in those aged 16–19 to 0.8\% (95\% CrI: 0.6, 0.9\%) in those aged 40–44 (Table 2).

**Probability of ever having had chlamydial infection given a woman has TFI, P(Ct\textsuperscript{+}jTFI, Age i)**

The search as described in Supplementary Appendix S4 generated 555 citations (Figure 3) with 47 fully screened for eligibility and 8 studies\textsuperscript{21–28} found to be relevant. A significant association between previous chlamydial infection and the development of TFI was found (random-effects odds ratio 3.96 (95\% CrI: 1.57, 8.53\%)) with significant between-study heterogeneity ($I^2 = 79.7\%$). The probability of past chlamydial infection in those diagnosed with TFI ranged from 33.7\% (95\% CrI: 14.2, 58.5\%) in the youngest age group to 71.8\% (95\% CrI: 49.5, 88.7\%) in the oldest age group (Table 2).

**Modelling result: probability of TFI given past or current chlamydial infection**

Given the high lifetime cumulative incidence of chlamydial infection and the low incidence of TFI, the overall estimated probability of TFI given past or present chlamydial infection in women in Scotland was found to be consistent and low across all age groups, ranging from 0.9\% to 1.4\%. The widest variability was observed in those aged 16–19 years (0.6–2.3\%) (Table 2).

**Sensitivity analysis**

The definition of infertility was found to be the most influential on the estimate of the probability of TFI given previous or current chlamydial infection (Sensitivity analyses 1 and 2 respectively, Figure 4; for numerical estimates relating to the sensitivity analyses, see the Supplementary Table 1, available as Supplementary data at IJE online). These broader definitions of infertility, 24 months of primary infertility and 24 months of primary or secondary infertility, increase the probability of TFI following chlamydial infection across all age groups. The greatest increases are observed with the 24 months primary or secondary definition where estimates of $P(TFIjCt\textsuperscript{+})$ increased approximately 3-fold from the baseline estimate, ranging from 3.1\% to 4.8\% with no distinct age-related pattern. Accounting for variability, the estimates range from 2.0\% to 7.9\% with the widest range in the 95\% CrI occurring in the 16–19-year age group.

There is a lack of data on how the proportion of women with TFI varies with age in the younger age

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>Change made</th>
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<tr>
<td>1 Infertility definition: 24 months primary</td>
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<tr>
<td>2 Infertility definition: 24 months primary or secondary</td>
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<td>3a TFI age distribution using generalised additive model</td>
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<td>3b TFI age distribution using HFEA data</td>
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<td>4 Removal of large study from meta-analysis</td>
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<tr>
<td>5a Effect of reducing the odds ratio, $OR = 3$</td>
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<td>5b Effect of reducing the odds ratio, $OR = 6$</td>
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<tr>
<td>6a Odds ratio decreases with age</td>
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<td>6b Odds ratio increases with age</td>
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<tr>
<td>7a Effect of a five-percentage-point increase in the baseline incidence of chlamydial infection in those aged 16–19 years</td>
<td></td>
</tr>
<tr>
<td>7b Effect of a five-percentage-point decrease in the baseline incidence of chlamydial infection in those aged 16–19 years</td>
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<td>8 Re-infection definition: re-infection within 6 months</td>
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<td>10a Lowering the cumulative incidence of chlamydia by 5 percentage points</td>
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Table 1 Details of the sensitivity analyses performed
groups. An alternative approach to our baseline assumption of constant prevalence in those aged under 30 years, is to extrapolate the increasing trend of TFI with age to the youngest age groups using a general additive model (GAM). Using this approach, estimates of \( P(\text{TFI}|\text{Ct}^+) \) for the 20–24- and 16–19-year age groups decrease marginally. All credible intervals overlap with the baseline, suggesting that the lack of information on TFI prevalence in those aged <30 years is unlikely to have a large effect on the estimates of \( P(\text{TFI}|\text{Ct}^+) \). Use of the HFEA data (Sensitivity analysis 3b) gives more uncertain estimates for the younger age groups, as expected due to the aggregation of the data for the 18–34-year-old age group. However, results are generally of a magnitude similar to the baseline (Figure 4).

When evaluating \( P(\text{Ct}^+|\text{TFI}) \), one of the eight suitable studies illustrated a much lower association between TFI and past chlamydial infection.\(^{24}\) We have no reason to believe that this result is inaccurate, since the study has a more robust, population-based design than the other studies. We examined the effect of removing this study from the meta-analysis (Sensitivity analysis 4, Figure 4). Removal leads to an increase in the odds ratio calculated from the meta-analysis from 3.96 (95% CrI: 1.57, 8.53) in the baseline model to 4.82 (95% CrI: 1.84, 10.71). This stronger association is reflected in the narrower range of the point estimates of \( P(\text{Ct}^+|\text{TFI}) \) across age (Supplementary Table 1, available as Supplementary data at IJE online) but the change is minimal. This study does not unduly influence the overall results.

To consider the possibility that the search strategy did not identify studies which would alter the overall odds ratio from the baseline, the effect of decreasing the odds ratio to a fixed value of 3 and increasing it to 6 was considered (Sensitivity analyses 5a and 5b, Figure 4). As before, the overall effect was minimal with the observed decrease in the width of the CrIs being an artefact of the manual parameterisation of the odds ratio.

The meta-analysis conducted did not adjust for age due to a lack of available data. Sensitivity analyses 6a and 6b model age variation in the odds ratio while maintaining the level of the pooled estimate. If the odds of chlamydial infection in those with TFI increases with age, the estimate of \( P(\text{TFI}|\text{Ct}^+) \) in those aged 16–19 years reduces from 1.4% to 0.6%, whereas if the converse is assumed, the estimate in the same age group increases from 1.4% to 2.1%. Figure 4 illustrates that the credible intervals for these changes overlap with the baseline intervals so, although the effect may seem substantial, it is within the variability estimated when using the baseline assumptions.

It is possible that secular changes in the prevalence of chlamydial infection in young people could affect baseline estimates of lifetime incidence. To model this we varied baseline incidence in the 16–19-year age group by ±5% which carries through to cumulative
incidence (Sensitivity analyses 7a and 7b respectively, Figure 4). The relative insensitivity of the overall risk to relatively large shifts in cumulative incidence implies that the assumption of constant incidence over time is unlikely to influence the overall result unduly.

The final sensitivity analyses consider changes to the way re-infection is modelled and the level of cumulative incidence. Under the baseline model the number of tested individuals is adjusted by the modelled re-infection rate within 1 year. This makes a number of assumptions: (i) that tested individuals have a potential 1-year follow-up to contribute to the testing numbers; (ii) that all those who are re-infected are retested; and (iii) that all those re-tested are re-infected. The 1-year follow-up assumption is addressed in Sensitivity analysis 8, which illustrates that using an average 6-month follow-up reduces the probability in the 16–19-year- and 20–24-year-age groups by 0.1% and the probability in older age groups is unchanged. Assumptions (ii) and (iii) are addressed in Sensitivity analysis 9, producing estimates of $P(\text{TFI} | \text{Ct}^+)$ similar to the baseline level. Sensitivity analysis 10 considers that the estimates of cumulative incidence may be inflated by the way infections are split into incident and repeat infections. Reducing the cumulative incidence across all ages by 5 and 10 percentage points had only a small effect on the baseline estimates increasing the estimate in the youngest age group from 1.3% to 1.5% if 5 percentage points of over-estimation was assumed and to 1.7% if a 10 percentage points of over-estimation was considered.

Discussion

Our study estimates that the likelihood of all-cause tubal factor infertility associated with chlamydial infection is low. We have estimated that the probability of infertility in women with past chlamydial infection is between 0.9% and 1.4%, with no significant variation with age. Changes to wider definitions of infertility increase this estimate to 3% and then to 5%.

Our study augments a growing body of recent research in this area and provides estimates within a similar range. Van Valkengoed et al. estimated the risk of tubal factor infertility in women with serological evidence of chlamydial infection at 0.02%, whereas Land et al., in their review of women with
chlamydial infection, estimated the risk of developing TFI after chlamydial infection at between 0.1% and 6%. Considering mathematical models of progression from chlamydia to PID and then TFI, the work of Turner et al. and Adams et al. based on an individually based stochastic network model of chlamydia transmission and a static decision tree model of progression to TFI, estimate the probability of TFI in the English population given exposure to chlamydia at 0.034%. Similar work from Denmark finds estimates of 0.19%.

Our study is a contribution to the evidence in its application of a modelling approach to routinely available data. Using a MCMC approach allows us to account for both the variability that may arise in published estimates and also the uncertainty around the limited available data. Our estimates take into account the variability present at all stages of the modelling process but are still subject to biases that we have not been able to control for such as sensitivity and specificity of the serology tests and using repeat infections in a cohort as a surrogate for repeat testing among women going for voluntary testing.

Three prevalence estimates within our model contain inherent uncertainty: firstly, chlamydia prevalence estimates in the general population; secondly, data on the cumulative lifetime incidence of chlamydial infection; and thirdly, TFI prevalence in younger women. With regard to the first, we believe that the prevalence estimates are valid, for the following reasons: both diagnosed and undiagnosed chlamydial infection are considered, and age is factored into the statistical analysis. Although the two sources of data (NATSAL and testing data) generated different estimates, these likely reflect inherent differences in the two source populations (those at higher risk of infection seek testing which accounts for the higher proportion of positive results in the laboratory data set, which gives higher statistical power, compared with NATSAL II). Although the NATSAL date from the year 2000, they provide the most robust population prevalence from which to extrapolate our probability estimate—our own local data indicate no evidence of a decrease in prevalence despite the increased levels of testing.

Our approach to estimate the cumulative lifetime incidence assumed that the incidence of chlamydial infection over time remains constant. The sensitivity analysis used to adjust for secular trends in both laboratory testing and the uptake of chlamydia-specific

**Figure 4** Change in the estimates of $P(\text{TFI}|C_t^+)$ for each sensitivity analysis. The grey band shows the baseline credible interval.
healthcare services demonstrated no substantial effect. In addition, it was assumed that the proportion of repeat tests in the annual laboratory tests, used in the prevalence and incidence calculations, could be represented by re-infection data. There are limitations with this assumption though the sensitivity analysis using different assumptions showed no substantial effect on the estimates obtained. Estimates of population-based seropositivity for C. trachomatis at the end of a woman’s reproductive lifetime are lacking. A Swedish-based study found seroprevalence of 24.7% in sexually active women aged 19–25 years, with a prevalence of current infection of 2.7%. Such an estimate of seroprevalence is consistent with our estimate of 25.8% in the 20–24 year-group based on 3.4% prevalence. In the absence of ever re-infection rates, we made use of yearly rates. This could lead to an inflation of the overall cumulative incidence if individuals are re-infected more than 1 year after the initial infection. As reinfection is most common in the youngest age groups, this may have an effect on the accumulation of incident infections in this group. Sensitivity analysis showed that if the cumulative incidence was lowered by 5 and 10 percentage points across all ages, the effect on the overall estimate was small.

Our modelling approach is limited by its inability to distinguish TFI caused by chlamydia and that caused by other STIs. In this way our study may provide an upper bound on the association. An alternative approach would be to calculate the aetiological fraction, that is the proportion of TFI cases in which chlamydia played a role during its development. Such an approach using serological evidence adjusted for test sensitivity and specificity found that 45% of TFI episodes were due to chlamydia with a credible range from 28% to 62%. Following a similar approach but without adjustment for sensitivity and specificity, our data (using OR = 3.96 and a lifetime cumulative incidence of chlamydia of 42.9%) would give an aetiological fraction of 62.9% which is just above the upper bound published. This value could be a reflection of the odds ratio being overinflated due to chlamydia test sensitivity being higher for TFI cases compared with controls, the odds ratio being unadjusted for the influence of other STIs in the occurrence of TFI or due to an overinflation of the level of lifetime chlamydia incidence or a combination of all of the above.

With respect to the paucity of published data on TFI prevalence in younger women, our sensitivity analysis demonstrated that changing the assumptions regarding TFI prevalence in the young age groups had a negligible effect on estimated risk. There was also an absence of age-stratified estimates for the probability of previous chlamydial infection in those with TFI, \( P(C_{t}^{+}|\text{TFI}) \). We applied the assumption of an age-related trend in the odds ratio from the case-control studies in the sensitivity analysis, and this led to an age-related trend in \( P(C_{t}^{+}|\text{TFI}) \). As there are no age-specific data to validate this approach for our model, the use of a single odds ratio across all age groups is justified.

Many of the original serological studies on the detection of chlamydia antibodies, which were used to estimate \( P(C_{t}^{+}|\text{TFI}) \), were undertaken in the 1980s to 1990s. It was acknowledged that the available tests had poor sensitivity and often lacked species specificity. This could result in misclassification of patients in case-control studies and thus bias the results. Sensitivity analysis on the odds ratio has shown limited effect on the conclusions produced by the model, with large increases required to increase the estimates.

Our estimated risk of TFI following chlamydia infection was sensitive to the definition of infertility with each definition having caveats attached. Our baseline definition of involuntary childlessness by the end of a woman’s reproductive lifetime was strict and this estimate could be inflated if those who managed to conceive due to infertility treatment were included. The alternative definitions used considerably shorter periods of infertility which are likely to include individuals who seek treatment, those who never do and those who have no diagnosed clinical infertility problems. The results found under the alternative fertility definitions may be more applicable in an economic context when quality of life and costs to the health service are considered. Using the alternative definition gave estimates consistent with the upper estimates in the review of Land et al. A further limitation of the model is that treatment for chlamydial infection is not explicitly considered. As most diagnosed chlamydial infections are routinely and effectively treated, the progression of the infection to pelvic inflammatory disease and onwards to TFI may occur at a lower rate than in the past. In this case the levels of TFI observed today may overestimate the levels which will be observed in the future for those aged 16–19 years now. If this is so, the model estimates of infertility following chlamydial infection for this age group are also likely to be an over-estimate. However the commentary of Peterman et al. suggests that given current testing levels, most detected infections will have been present for too long to interrupt ascending infection, so this may not be the case. In addition, there is a perception that more sexual risks (more risk-taking behaviour, for example concurrent partners, increase in the number of partners) are being taken in recent years and therefore women may be prone to more repeat chlamydial infections which may be associated with an increased risk of progression to TFI compared with single episodes. These factors together lead to uncertainty which cannot be explicitly modelled in the framework proposed and must simply be considered when using the results of such an analysis to inform policy.
trials with long-term follow-up. Such studies are probably now impractical given the easy availability of chlamydia testing to asymptomatic young women. Our findings add to the evidence that rates of progression from chlamydial infection to TFI are low. Given that TFI may be attributable to the presence of other STIs which we do not model, the estimates could potentially be lower. These estimates add to the knowledge base for those conducting cost-effectiveness analyses. Our findings may also be helpful to clinicians: patients testing positive for *C. trachomatis* can be provided with a reliable age-specific estimate of the risk of TFI following their diagnosis, with these estimates being lower than those seen in many information leaflets available in clinical settings.

### Supplementary Data
Supplementary data are available at IJE online.

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**Conflict of interest:** None declared.

### KEY MESSAGES
- The risk of TFI in individuals with past or current chlamydial infection is low (0.9–1.4%) and varies little with age.
- Using a broader infertility definition (24 months primary or secondary infertility) the risk increases to 4.5%.
- These findings have relevance both at the policy level and also at an individual level, particularly for clinicians, supporting women undergoing testing or with a positive diagnosis.

### References
fertility-treatment-trends.html (6 August 2012, date last accessed).


Commentary: Participatory interventions reduce maternal and child mortality among the poorest, but how do they work?

Cesar G Victora

Federal University of Pelotas, CP 464 96100 Pelotas, RS, Brazil. E-mail: cvictora@gmail.com

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In this issue of IJE, Houweling et al1 report a remarkable impact of a participatory intervention in India on neonatal mortality, particularly among the poorest families in the study population. Coming out on the year of John Snow’s bicentenary, this article made me feel as puzzled as I think Snow did, when he made his groundbreaking observations on cholera transmission. Without any question, Snow detected a clear and strong association, but he could not describe the biological mechanism behind the observed effect, because micro-organisms were yet to be discovered. This also applies to the present paper. Houweling et al1 add an equity dimension to a previously published trial. The earlier report provided