

ORIGINAL ARTICLE

# A new approach to estimating trends in chlamydia incidence

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## ABSTRACT

**Objectives** Directly measuring disease incidence in a population is difficult and not feasible to do routinely. We describe the development and application of a new method for estimating at a population level the number of incident genital chlamydia infections, and the corresponding incidence rates, by age and sex using routine surveillance data.

**Methods** A Bayesian statistical approach was developed to calibrate the parameters of a decision-pathway tree against national data on numbers of notifications and tests conducted (2001–2013). Independent beta probability density functions were adopted for priors on the time-independent parameters; the shapes of these beta parameters were chosen to match prior estimates sourced from peer-reviewed literature or expert opinion. To best facilitate the calibration, multivariate Gaussian priors on (the logistic transforms of) the time-dependent parameters were adopted, using the Matérn covariance function to favour small changes over consecutive years and across adjacent age cohorts. The model outcomes were validated by comparing them with other independent empirical epidemiological measures, that is, prevalence and incidence as reported by other studies.

**Results** Model-based estimates suggest that the total number of people acquiring chlamydia per year in Australia has increased by ~120% over 12 years. Nationally, an estimated 356 000 people acquired chlamydia in 2013, which is 4.3 times the number of reported diagnoses. This corresponded to a chlamydia annual incidence estimate of 1.54% in 2013, increased from 0.81% in 2001 (~90% increase).

**Conclusions** We developed a statistical method which uses routine surveillance (notifications and testing) data to produce estimates of the extent and trends in chlamydia incidence.

## INTRODUCTION

Chlamydia is the most frequently reported notifiable infection in Europe, North America and Australia with steadily increasing trends over the last decade.<sup>1–3</sup> These trends are concurrent with increases in chlamydia screening rates. Because of the asymptomatic nature of chlamydia infection, the number of diagnoses depends on testing patterns.<sup>4</sup> Consequently, it is not known whether current response efforts are having an impact on community chlamydia incidence and prevalence,

particularly since neither parameter can be easily measured. Incidence is particularly difficult to measure directly, because it requires repeat testing. Prospective longitudinal studies of the same individuals<sup>5</sup> can almost never be incorporated into routine national surveillance due to cost, and retrospective cohorts are currently not feasible as levels of repeat testing are low in the general population.<sup>6</sup> An alternative approach to direct measurement is to infer prevalence and incidence by using all relevant and available data coupled with a quantitative framework which links these data to the epidemiological indicators. This epidemiological modelling approach is appealing because it does not require additional primary data collection, is not costly and can produce estimates that can be applied repeatedly every year. Modelling approaches have been used to assess the potential impact of chlamydia screening programmes and their cost-effectiveness.<sup>7–8</sup> Modelling approaches have also been used to infer population incidence of other infectious diseases using routine surveillance data, for example, for HIV<sup>9</sup> but not for chlamydia.

Like some other countries, Australia routinely monitors chlamydia by the reported numbers and rates of notifications of diagnosed cases.<sup>10</sup> However, the systematic increase in testing rates in Australia over the last decade is believed to be largely responsible for the increasing number of notifications.<sup>11</sup> Despite increases, testing rates still remain relatively low with only about 10% of the most affected age group, 16–29-year-olds, tested each year.<sup>12</sup> There are no estimates of incidence trends available in the general population in Australia. There are also no methods available from similar countries which estimate incidence from notification and testing data. Hence, we aimed to develop a method for inferring chlamydia incidence in Australia using routinely collected surveillance data (primarily national notifications and testing), ensuring consistency with other relevant data sources, and to apply these estimates to assess trends over time.

## METHODS

We estimated chlamydia incidence in the Australian population from 2001 to 2013 using a Bayesian statistical method based on a decision-pathway model.

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## Model

The decision-pathway of this approach is a probabilistic tree to represent the branches along which people in the population can end in each calendar year as either acquiring or not acquiring chlamydia infection, developing symptoms, being tested and treated and being notified as a case. Stratified by age and sex, each individual in the population has an assigned probability of each step along the branch over the course of each year (figure 1). For some branches, the model parameters (probabilities) are strongly constrained a priori from estimates in the literature, while other parameters must be informed by fitting the model to the surveillance data of numbers of people tested and numbers diagnosed with chlamydia.

To follow the effects of an evolving disease burden and changes in public awareness of, and access to, relevant public health programmes, we allowed the annual infection and asymptomatic screening probabilities to vary yearly by age group and sex using a flexible, stepwise Gaussian process model, while all other input parameters were fixed in time.

## Priors

Following a standard Bayesian approach, we adopted independent beta distributions for priors on the time-independent probability parameters; the two shape variables of each beta distribution were chosen so that the beta prior was closest (using the Kullback–Leibler divergence) to a triangular distribution for the corresponding parameter, which requires only an initial estimate of the minimum, mode and maximum for its characterisation (sourced directly from peer-reviewed literature or obtained from expert opinion). To best facilitate the calibration without sacrificing model flexibility, we adopted multivariate Gaussian priors on (the logistic transforms of) the time-dependent parameters, using the Matérn covariance function<sup>13</sup> to favour small changes over consecutive years and across adjacent age cohorts (with independence between the sexes). Online supplementary table S1 summarises the values chosen to specify the priors on the time-dependent and time-independent parameters.

## Calibration data sources

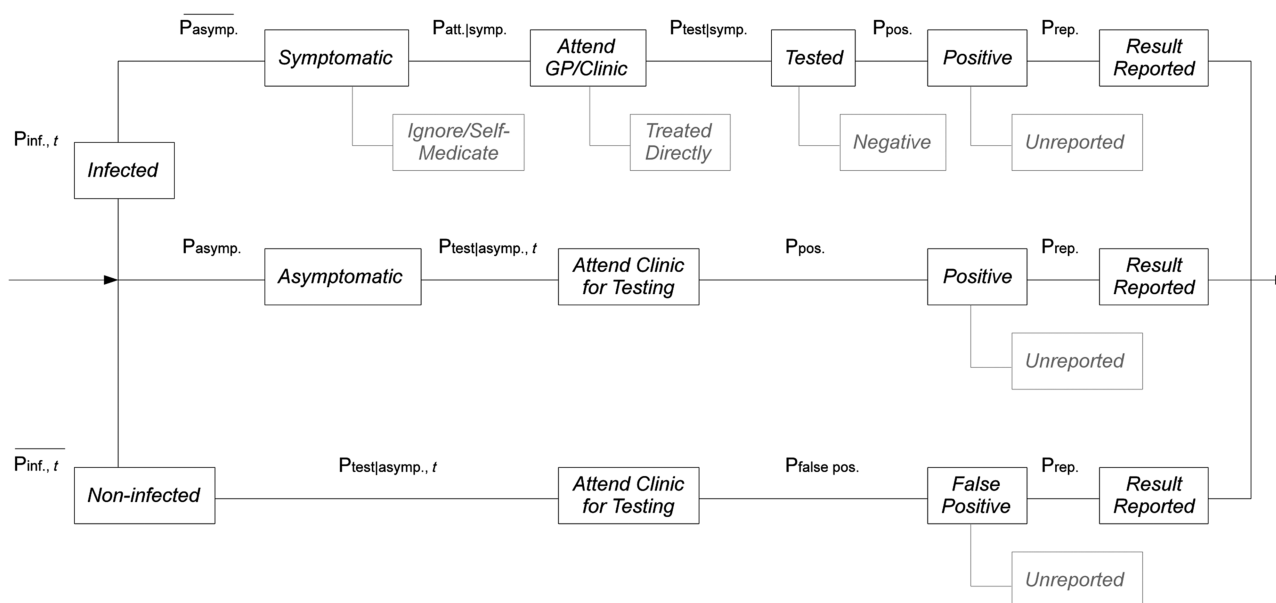
The two main data sources used to calibrate the model were:

- ▶ National notification data (numbers of reported diagnoses per year) published by the Australian National Notifiable Diseases Surveillance System (NNDSS)<sup>10</sup> and
- ▶ National testing data collected by Medicare<sup>14</sup> (the Australian universal health insurance scheme that rebates tests conducted by the majority of health providers). They include unique codes for a chlamydia test. However, tests conducted in public hospitals and most sexual health services are excluded, as these are funded separately and are not centrally collated. Medicare data on chlamydia tests were not available from November 2005 to April 2007 because the unique codes for identifying a chlamydia test were temporarily removed and any chlamydia tests conducted were recorded using a non-specific code that included tests for other genital organisms.<sup>14</sup> Although tests conducted in public hospitals and most sexual health services are excluded, 82% of all chlamydia tests were conducted at GP clinics.<sup>15</sup>

In addition, annual population census estimates published by the Australian Bureau of Statistics (ABS)<sup>16</sup> were used for sex and age group population sizes.

## Model calibration methods

A sequential Monte Carlo (SMC) approximate Bayesian computation (SMC-ABC) procedure<sup>17</sup> was used to identify the optimal fit of parameters, infer annual incidence and gauge uncertainties when comparing the model with observed notifications and testing surveillance data. The model simulations were matched to (i) the annual notification counts reported and (ii) the annual test counts reported by Medicare for 2001–2005 and 2008–2013. The ABC algorithm allows for rigorous statistical inference from complex systems for which the true likelihood function may be computationally intractable but simulation from the model is comparatively cheap<sup>18</sup> (see online supplementary material for details).



**Figure 1** Pathways of chlamydia infection to be notified to the National Notifiable Diseases Surveillance System. Each parameter represents the (annualised) probability of progressing over a particular step. The light grey branches/boxes represent drop-outs from the notification count, but those reaching the testing phase will (if correctly reported) nevertheless contribute to the total test count.

## Model validation

Model outcomes were compared with independent empirical epidemiological measures. Chlamydia prevalence among 16–29-year-olds was measured in 2011 by the Australian Chlamydia Control Effectiveness Pilot (ACCEPt)—a randomised controlled trial of a chlamydia testing intervention in 150 general practice clinics.<sup>19</sup> Since ACCEPt was conducted among sexually active 16–29-year-olds, prevalence estimates from the study were scaled down to account for the prevalence of sexual activity in these age groups (the Australian study of health and relationships found that 66%, 89% and 95% of men and 56%, 90% and 97% of women aged 15–19, 20–24 and 25–29 years, respectively, have been sexually active<sup>15</sup>). The model outcomes were also compared with a study which measured incidence and prevalence among a cohort of young women (see Discussion section).<sup>5</sup>

## RESULTS

### Data trends

The number of chlamydia notifications in Australia increased markedly over the study period, with 82 484 notifications in 2013 compared with 20 224 in 2001 (>300% increase). During the same period, the number of chlamydia tests recorded by Medicare increased by ~500% with 1 090 705 tests rebated in 2012 compared with 184 024 in 2001 (see online supplementary figure S1).

### Model calibration

To assess the accuracy of our calibrated model, we compared the 95% credible intervals (CIs) from the model output with the corresponding NNDSS and Medicare data in 15–24 and ≥25-year-old men and women. The comparison showed a close agreement between the model outcomes and the actual data (figure 2A, B).

### Model validation

Figure 2C presents a comparison between the model-based (median and 95% CI) estimates of chlamydia prevalence and measured prevalence among 16–24-year-old men and women in 2011 from the ACCEPt study (scaled down to adjust for rates of sexual activity). The comparison shows broad agreement between the model estimates and the measured prevalences for younger men and older women. The ACCEPt estimate for older men is so uncertain that it covers almost our entire credible range for all age–sex cohorts but has a mean below our estimate. Of greater concern is the relatively narrow range of the ACCEPt estimated prevalence for young women at 3.6–5.6% (95% CI), which lies above our model-based estimate of 3.2–3.6%; however, the quoted CI for the former excludes uncertainty in the estimate of the sexually active proportion in this cohort, which together with some additional variance contribution from the particular geographical coverage of the ACCEPt pilot study could reasonably account for the discrepancy here.

### Incidence estimates

The model inferred that the estimated total number of people acquiring chlamydia per year in Australia has increased from 160 000 (95% CI 157 000 to 164 000) in 2001 to 356 000 (344 000 to 367 000) in 2013, a 120% increase. This population chlamydia incidence corresponds to a per-person rate of 2.0% (1.9% to 2.1%) in men and 1.1% (1.1% to 1.2%) in women in 2013 overall.

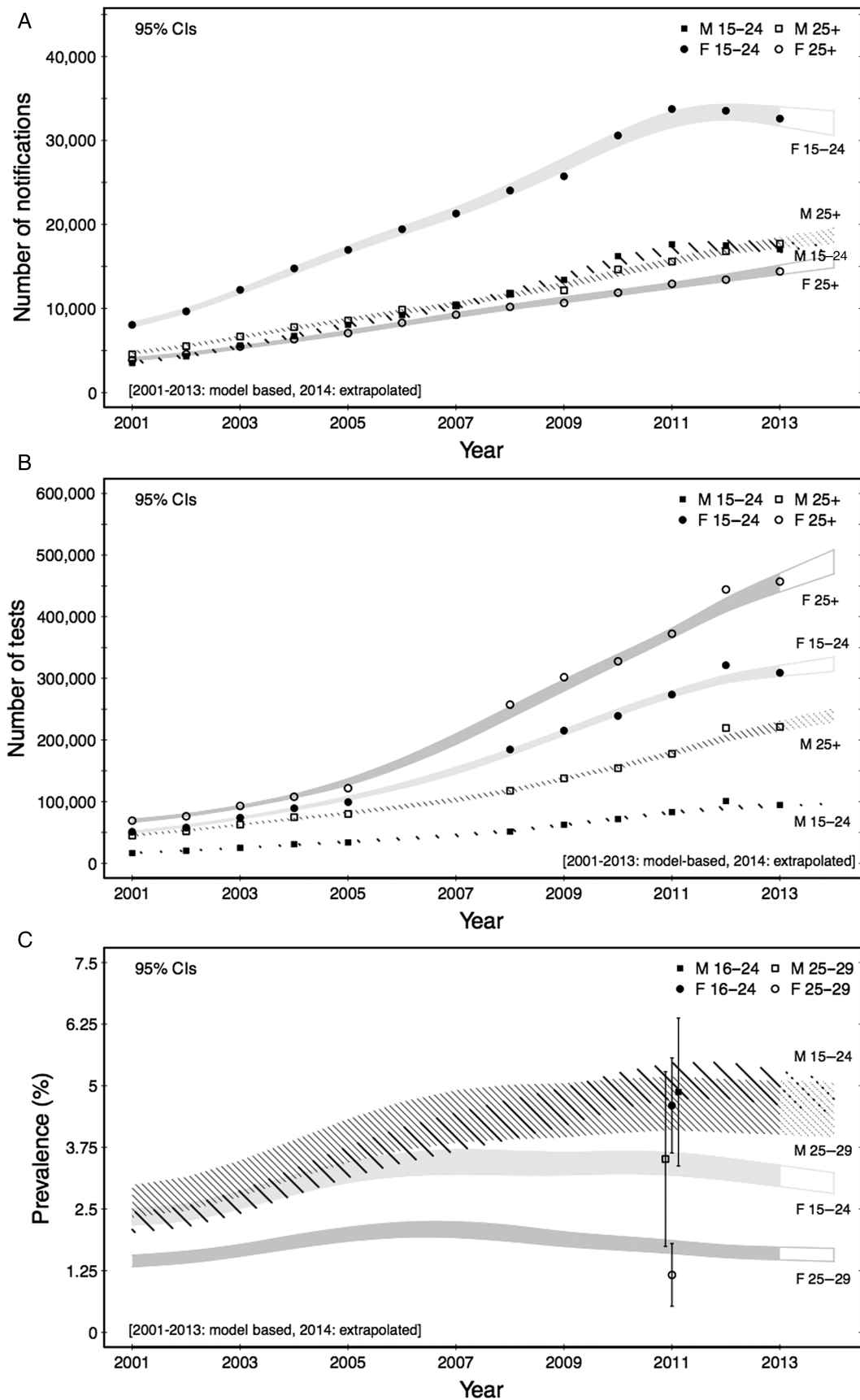
The model outcomes suggest that chlamydia incidence has been generally increasing over the past decade among both sexes and across all reported age groups (table 1 and figure 3). Incidence rates were greatest in people aged 15–24 years and increased historically: from 2.7% in 2001 to 7.0% in 2013 for men and from 3.1% to 5.6% for women, but appears to have levelled off in the last 2 years (figure 3). Among 25–34-year-olds, estimated incidence increased from 2.2% to 4.1% in men and 1.1% to 1.7% in women; in those aged 35 years or older, estimated incidence increased from 0.39% to 1.0% in men and 0.1% to 0.27% in women from 2001 to 2013.

## DISCUSSION

This study provides a new approach to estimate trends in chlamydia incidence in the general population. It uses a simple model which translates routinely available surveillance data and a limited number of key assumptions into estimates of incidence. Since this method relies only on routinely available data, chlamydia incidence can now be estimated easily on an ongoing basis; non-routine data (eg, prevalence or incidence studies) can be used for model calibration or reserved for validation. A recent modelling study, from the UK, used two separate methods to estimate incidence of chlamydia.<sup>20</sup> The first method used existing incidence estimates, while the other used prevalence estimates; neither of which is a routine data source, and hence cannot be used for routine incidence estimation.

Our model shows large increases in incidence. We believe such increases are plausible. First, there has been an increase in the number of notifications.<sup>10</sup> Second, prevalence as notified by the ACCESS sentinel surveillance system at sexual health services across Australia<sup>11</sup> showed increasing trends in young people aged 15–29 between 2006 and 2010—which when expanded to the whole time period will be more pronounced. Third, positivity among 15–24-year-old men, as calculated by notification-to-testing ratio has remained roughly constant. Simple mathematics (not presented here) suggest that (a) if incidence increases but testing stays constant, the positivity must increase; (b) if testing increases but incidence stays constant, positivity must decrease and (c) positivity can only remain constant, if both incidence and testing decrease or both increase or both remain unchanged. Since we know that testing rates have increased substantially and positivity rates are estimated to have remained steady, incidence must have increased for this age group. We note that other sex–age groups did not have constant positivity rates over time despite increased testing. Fourth, there is a relationship between changes in testing rate, prevalence and positivity rate. Online supplementary figure S2 demonstrates this relationship. Here, we observe the ‘positivity contour’ association between prevalence and testing rates. It infers how prevalence has likely changed over time while maintaining a steady positivity rate and increasing testing rates for 15–24-year-olds. This figure also relates testing and positivity rates to prevalence, had there been other testing or positivity data for this age group. In addition, there has been an increase in reported sexual risk-taking behaviour in young people in Australia. The Australian sexual health surveys among secondary students show that condom use at the most recent sexual encounter decreased over the last 10 years; and the proportion of young people reporting three or more sexual partners increased over this period.<sup>21</sup>

Like all Bayesian analyses, this study relies on both the validity of the modelling assumptions and the suitability of the prior distributions adopted. Perhaps the greatest limitation arising from the former is that the model does not take into account



**Figure 2** Model calibration and validation against chlamydia data, by age group and sex, 2001–2013: (A) notifications, (B) tests and (C) prevalence.



**Table 1** Estimates of annual chlamydia incidence, by sex and age group, 2001–2013

Sex Age	Men						Women					
	15–24 years		25–34 years		>34 years		15–24 years		25–34 years		>34 years	
	Incidence (%)	95% CI	Incidence (%)	95% CI	Incidence (%)	95% CI	Incidence (%)	95% CI	Incidence (%)	95% CI	Incidence (%)	95% CI
2001	2.7	2.5 to 3.0	2.2	1.9 to 2.4	0.39	0.32 to 0.46	3.1	2.8 to 3.4	1.1	0.96 to 1.2	0.11	0.09 to 0.13
2002	3.3	3.0 to 3.7	2.5	2.2 to 2.7	0.44	0.38 to 0.50	3.6	3.4 to 4.0	1.2	1.1 to 1.3	0.12	0.10 to 0.13
2003	4.0	3.7 to 4.4	2.9	2.6 to 3.1	0.50	0.45 to 0.57	4.2	3.9 to 4.7	1.4	1.3 to 1.5	0.13	0.12 to 0.15
2004	4.7	4.3 to 5.2	3.3	2.9 to 3.5	0.58	0.51 to 0.66	4.8	4.4 to 5.3	1.5	1.4 to 1.7	0.15	0.13 to 0.17
2005	5.3	4.9 to 6.0	3.5	3.0 to 3.7	0.64	0.57 to 0.74	5.2	4.8 to 5.7	1.6	1.5 to 1.8	0.16	0.15 to 0.19
2006	5.8	5.3 to 6.6	3.6	3.2 to 3.8	0.71	0.64 to 0.81	5.4	5.1 to 6.0	1.7	1.5 to 1.8	0.18	0.16 to 0.21
2007	6.2	5.7 to 7.1	3.7	3.2 to 3.9	0.77	0.69 to 0.89	5.5	5.2 to 6.1	1.7	1.5 to 1.8	0.20	0.18 to 0.23
2008	6.8	6.3 to 7.6	3.8	3.4 to 4.1	0.82	0.73 to 0.94	5.7	5.3 to 6.3	1.7	1.5 to 1.8	0.22	0.19 to 0.25
2009	7.5	7.0 to 8.3	4.0	3.5 to 4.2	0.88	0.78 to 1.0	5.9	5.5 to 6.6	1.7	1.5 to 1.8	0.23	0.20 to 0.26
2010	7.8	7.3 to 8.8	4.1	3.6 to 4.3	0.94	0.82 to 1.1	6.1	5.6 to 6.8	1.7	1.5 to 1.8	0.24	0.21 to 0.28
2011	7.7	7.3 to 8.8	4.2	3.7 to 4.4	0.99	0.89 to 1.1	6.0	5.6 to 6.8	1.7	1.5 to 1.8	0.25	0.22 to 0.29
2012	7.5	7.1 to 8.5	4.2	3.7 to 4.5	1.0	0.92 to 1.2	5.9	5.5 to 6.6	1.7	1.6 to 1.9	0.26	0.23 to 0.30
2013	7.0	7.0 to 6.8	4.1	3.6 to 4.4	1.0	0.91 to 1.2	5.6	5.1 to 6.3	1.7	1.5 to 1.9	0.27	0.24 to 0.33
% increase	160		86		156		80		54		170	

any re-infections or re-testing. High repeat positive test rates have been reported for chlamydia in young women in Australia (22.3 per 100 person-years).<sup>5</sup> In our analyses, all repeat positive tests were considered incident infections since the end point of this model's pathway was notification of infection. Since a vast majority of infections are asymptomatic and undiagnosed (and hence only cured naturally or by background antibiotic use), the contribution of re-infections has been assumed to be small for this study. A study by Althaus *et al*<sup>22</sup> reported that re-infections have little impact on the estimates of the average duration of infection.

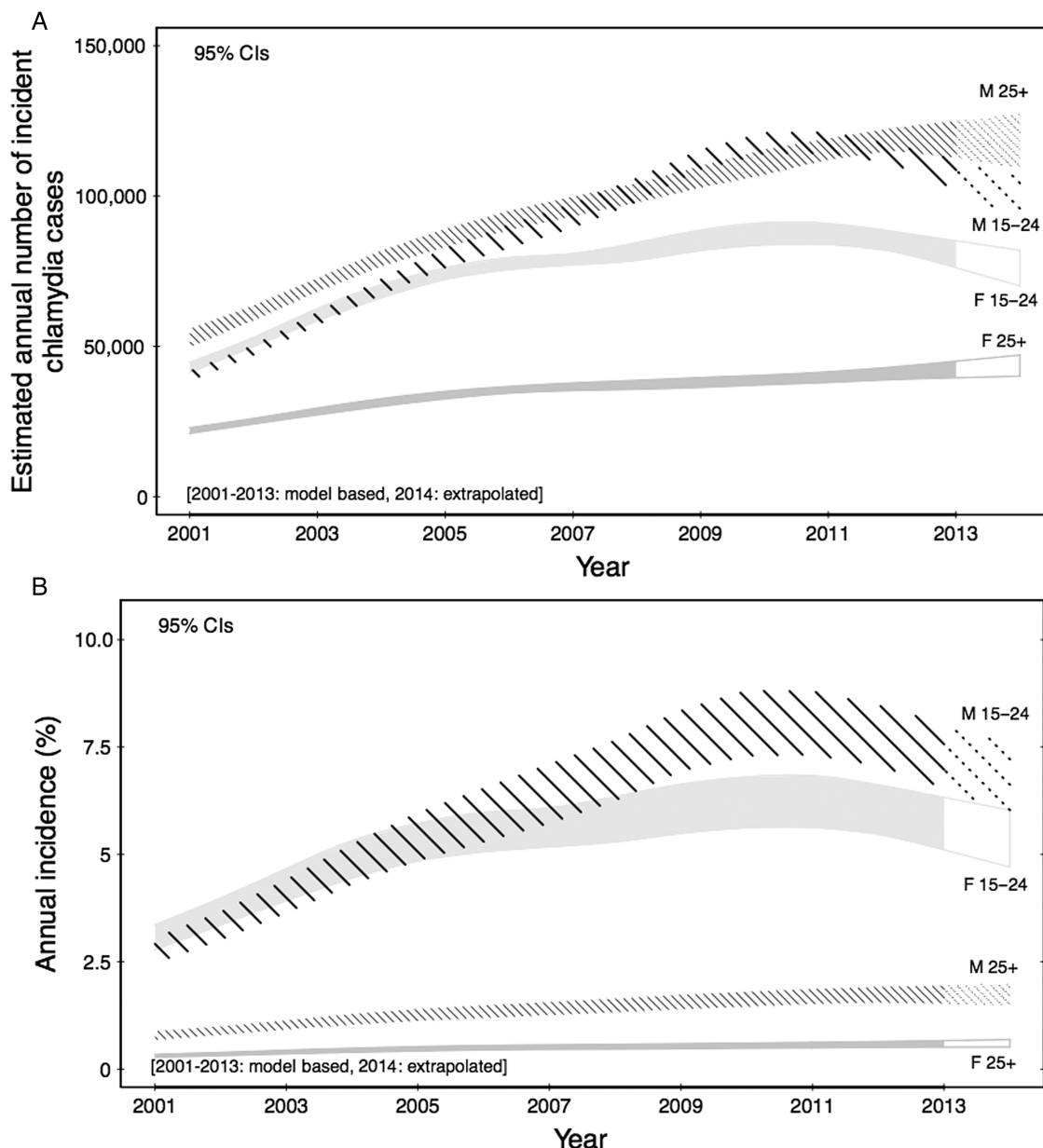
Another key assumption is that the designated time-independent parameters of our model are indeed time independent. These can be divided into (A) those related to disease (the proportions of asymptomatic infections in men and women and the probability of naturally clearing the infection within a year); (B) those related to testing (true positive and false positive test rates in the context of the same underlying diagnostic technology since 1999/2002 when Australia adopted nucleic acid amplification testing (NAAT)<sup>23</sup>) and (C) those related to behaviour and practices (probabilities of being tested for chlamydia, the rate of background antibiotic use and case reporting completeness). The parameters in group A are strongly expected to be truly time independent given no evidence for biological changes in the pathogen; likewise for the parameters in group B as NAATs have been used over the study period. However, the time independence of the parameters in group C is an assumption representing the simplest hypothesis in the absence of relevant data. Although there may be some minor differences, it was assumed that all these time-independent parameters (except for the proportions of those with symptoms) were the same for both sexes.

Our model suggests that incidence increased at a faster rate in men. Although incidence was higher in women than men aged 15–24 years until 2005, it was higher in men after 2005. Also, it was higher in men than women aged 25–34 and >34 years for all years. More chlamydia diagnoses occur among women, reflecting a higher rate of asymptomatic testing among women. However, as there is little known about the natural history of chlamydia infection in men, with most studies reporting on

natural history conducted in women,<sup>24 25</sup> it seemed reasonable to assume that the probability of natural clearance of infection over a year is the same for both sexes. It is also notable that our model does not differentiate between heterosexual versus homosexual men nor other sexual mixing patterns.

Through a careful sensitivity analysis, presented in the online supplementary material, we have confirmed the robustness of our results against moderate changes to our input priors. For four of our nine time-independent parameters, the data are highly informative (and our results are largely insensitive to our prior assumptions); these are the asymptomatic proportions in men and women, the probability of natural clearance over a year and the false positive rate of testing. The remaining five time-independent parameters for which our prior assumptions dominate are (a and b) the probabilities of attending and consequently testing for symptomatic infections, (c) the true positive rate of the diagnostic test, (d) the rate of background antibiotic use and (e) the probability of reporting a test. Of these, all except the second and third (the focus of our prior sensitivity analysis) have narrow prior ranges based on reliable references and thus would not be expected to substantially alter our overall quantitative findings.

Until now, only one prospective cohort study of chlamydia in the general population has ever been conducted in Australia: the chlamydia incidence and re-infection study (CIRIS).<sup>5</sup> This study included only young women aged 16–25 years and reported a chlamydia prevalence of 4.9% (95% CI 3.7% to 6.4%) and an incidence of 4.4 per 100 person-years (3.3–5.9) in 2007–2008. The incidence reported by CIRIS is similar to the estimates produced by our model: 5.6% (5.2% to 6.1%) and 5.7% (5.3% to 6.3%) in 15–24-year-old women in 2007 and 2008, respectively. Multivariate analysis from CIRIS showed that younger women (16–20 years) were more likely to have an incident infection,<sup>5</sup> consistent with our study. CIRIS also reported that recent use of antibiotics was protective against incident infection.<sup>5</sup> We accounted for background antibiotic use as a model parameter to allow for self-cure when antibiotics were taken for any reason, although the assumed level in our analyses may differ from actual levels of use.



**Figure 3** Estimates of chlamydia incidence in Australia, by sex and age group, 2001–2013: (A) number of incident infections and (B) incidence rate as a percentage per person per year.

Although there is a dearth of studies reporting on chlamydia incidence in the general population internationally, a study from the USA<sup>26</sup> estimated that there were about 2.86 million incident infections in the USA in 2008. The number of chlamydia notifications in 2008, in the USA, was 1.2 million, which gives an incidence-to-notification ratio of 2.4. This is less than the incidence-to-notification ratio of 4 for Australia based on our estimates. The difference in ratios between the USA and Australia could reflect differences in testing patterns or epidemiology between these settings and/or the methods used to calculate the ratios. It would be valuable to compare these factors in future studies.

Historically, Australia has based its chlamydia prevention strategies on the number of diagnoses notified. However, in 2013 the number of notifications among people aged 15 years and older ( $n=82\,484$ ) represents only 23% of all estimated incident

infections ( $n=356\,000$  according to this study) in the year. Thus, the estimated incidence-to-notification ratio in Australia was 4.3 in 2013. This also implies that 77% of new chlamydia infections remain undiagnosed. Our findings also suggest that incident infections of chlamydia more than doubled between 2001 and 2013, from 160 000 to 356 000 infections. However, this relative change (120%) is substantially less than the increase ( $>300\%$ ) in numbers of chlamydia notifications reported during the same time. This clearly demonstrates that the increase in the scale of the infection as observed by the trends in notification numbers has been misleading and is somewhat an artefact of increased testing.<sup>11</sup>

This study has reported a new approach to estimating chlamydia incidence in the general population using routine testing and notification data. Other countries that collate and report data on chlamydia diagnoses and testing numbers can also use this method to estimate chlamydia incidence.

## Key messages

- ▶ The estimated total number of people acquiring chlamydia per year in Australia has increased by ~120% over 12 years.
- ▶ The estimated ratio of incidence to notification in Australia was 4.3 in 2013.
- ▶ A Bayesian statistical approach, using routine testing and notification data, can be employed to estimate incidence.

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**Contributors** DPW and BD conceptualised the study; HA collected data for the study with input from MM and CE-H; EC designed and ran the model with assistance from JMM and CCD and DPW, RJG, JSH, JMK and BD provided input on the model estimate; HA drafted the manuscript with assistance from EC and DPW and input from JMM, CCD, RJG, CE-H, JSH and BD.

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**Competing interests** None.

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## A new approach to estimating trends in chlamydia incidence

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## Supplementary Material

In this Appendix we present further mathematical details of our approach for estimating chlamydia incidence.

### Decision pathway probabilistic model

In this study we adopt a pragmatic approach to inferring the annual variation in the incidence and screening rates, in which we simulate its link to the observed routine surveillance counts of chlamydia diagnoses reported, and chlamydia tests conducted, through a conditional probability model (as represented by the decision pathway diagram shown in Figure 1 of the main text). According to age and sex, each individual in the population is assigned a particular probability of acquiring chlamydia infection, developing symptoms, being tested and treated, and being notified as a case, over the course of each year. For a symptomatic infection to be notified we suppose the individual must seek medical care (with probability  $p_{\text{att.}|\text{symp.}}$ ), the clinician tests the patient for chlamydia (with probability  $p_{\text{test}|\text{symp.}}$ ), the test returns a true positive result ( $p_{\text{pos.}}$ ), which in turn is reported ( $p_{\text{rep.}}$ ). Patients with asymptomatic infection, or even those who do not acquire chlamydia infection at all, may also be notified (erroneously, in the latter case) if they are screened for chlamydia (with annual probability,  $p_{\text{test}|\text{asympt.}}$ ) and the diagnostic test returns a true positive ( $p_{\text{pos.}}$ ) or false positive ( $p_{\text{false pos.}}$ ) result, respectively.

Untreated infections may clear naturally over the course of a year (with probability  $p_{\text{self cure, n.}}$ ), or as a consequence of background antibiotic use (with probability  $p_{\text{self cure, a.}}$ ); those that do not clear infection are carried over to the following year, introducing a non-negligible (anti-)correlation in the notification and test counts across both calendar years and age groups (i.e., the more cases treated in a given year, the fewer that will carry over to the following year). Hence, although we allow the annual infection and asymptomatic screening probabilities to vary yearly we anticipate a degree of correlation, as reflected by our multivariate Gaussian priors on these parameters. All other input parameters, as summarized in Table S1, are taken to be constant in time.

If it is assumed that *all* untreated infections clear within the calendar year, estimates of the parameters in the model can be obtained by solving equations involving the model parameters and also the observed routine surveillance counts. In particular, the following equations are obtained when equating the observed value with that predicted by the conditional probability model:

Number of notifications/Total population [in a given age–sex cohort] =

$$P_{rep.} \left[ P_{inf.} P_{pos.} \left\{ (1 - P_{asympt.}) P_{att.,symp.} P_{test|symp.} + P_{asympt.} P_{att.,asympt.} \right\} + (1 - P_{inf.}) P_{att.,asympt.} P_{false\ pos.} \right];$$

and

Number of tests/Total population [in a given age–sex cohort] =

$$P_{rep.} \left[ P_{inf.} \left\{ (1 - P_{asympt.}) P_{att.,symp.} P_{test|symp.} + P_{asympt.} P_{att.,asympt.} \right\} + (1 - P_{inf.}) P_{att.,asympt.} \right].$$

Given input values for each of our time-independent model parameters and using the available NNDSS notification and Medicare test data to compute the left-hand side of each equation allows for simultaneous solution for the two unknown time-dependent parameters: the probability of acquiring infection per year (or incidence) and the proportion of asymptomatic people who are tested each year. In particular, taking the positive solution of the resultant quadratic equation yields:

Probability of acquiring chlamydia per year =

$$\frac{\text{Number of notifications/Total pop.} - P_{false\ pos.} \times \text{Number of tests/Total pop.}}{P_{rep.} \left( (1 - P_{asympt.}) P_{att.,symp.} P_{test|symp.} + P_{asympt.} P_{att.,asympt.} \right) (P_{pos.} - P_{false\ pos.})}.$$

With untreated infections allowed to progress (realistically) from year-to-year under our full model, this approximate solution needs adjusting; the corresponding likelihood function for Bayesian inference when infections are carried forward each year is not readily tractable (analytically or computationally). Instead we require an approximate Bayesian approach

based on a comparison of data simulated from the model and the actual data (referred to as approximate Bayesian computation, or ABC).

### Simulations

The simulation of datasets—i.e., annualized time series of notification and test counts by age and sex from 2001 to 2013—from our conditional probability model proceeds as follows. For a given set of (both time-dependent and time-independent) input parameters we draw (from the binomial distribution) in each year only the necessary annual totals of new symptomatic and asymptomatic infections in each age–sex cohort, adding these to the burden of uncured infections carried over (and aged) from the previous year, and we then simulate observations following our decision pathway diagram. With each simulation step there emerges a slight stochasticity from the binomial sampling process (i.e. counts of ‘successes’ within a fixed sample of common ‘success’ probability), while the ageing of uncured infections across cohorts yields a modest degree of year-to-year correlation. To initialize the model at an equilibrium prevalence level we run these simulations over a lead-in period of seven years (which are discarded) under our starting parameter set (for the year 2001). All code for running these simulations was built in the R statistical computing environment and is available from the authors upon request.

### Approximate Bayesian Computation via the Sequential Monte Carlo Algorithm

Originally developed in the late 1990s to solve complex inference problems in the study of population genetics (e.g. [1]) the statistical basis of ABC is the replacement of direct likelihood evaluation in Bayes’ theorem with a proxy based on the comparison of simulated and observed datasets (or, more commonly, key summary statistics thereof). In effect, the complete-likelihood Bayesian posterior,

$$posterior \propto likelihood \times prior:$$

$$\pi(\theta|y) \propto \pi(y|\theta)\pi(\theta)$$

is approximated by the ABC posterior,

$$ABC \text{ posterior} \propto \text{simulation} \times \text{thresholding} \times \text{prior}$$

$$\pi_{ABC}(\theta, y_s | y) \propto \pi(y_s | \theta) \text{Ind}(\rho[S(y_s), S(y)] < \varepsilon) \pi(\theta)$$

That is, the prior,  $\pi(\theta)$ , is weighted not directly by the likelihood,  $\pi(y|\theta)$ , but indirectly by the proportion of simulations,  $y_s$ , from a given set of input parameters,  $\theta$ , that produce simulated datasets,  $S(y_s)$ , that are ‘close’ enough to the observed data’s summary statistic,  $S(y)$ . Here ‘close’ is defined through the distance metric,  $\rho[\cdot, \cdot]$ . In our notation,  $\text{Ind}(\cdot < \varepsilon)$  represents the Indicator function, which is equal to 1 if the distance between the observed and simulated data is below a user-chosen threshold  $\varepsilon$  and 0 otherwise. Note that the above ABC posterior is defined as a joint distribution over  $\theta$  and  $y_s$ , so that samples from the corresponding marginal ABC posterior distributions for  $\theta$  and  $y_s$  are also obtained as a by-product. For an introductory review of ABC methods (with a focus on their application in evolutionary biology) the interested reader is referred to [2]; and see [3] for a pioneering application in epidemiology. The discrepancy distance metric adopted for our particular ABC analysis was the sum of the absolute fractional differences of notification and test counts in each of the age-sex cohorts between the model and the data; i.e.,

$$\rho[S(y_s), S(y)] = \sum |y_{s,i} - y_i| / y_i$$

Since there is a limited amount of stochasticity in our model, we are able to compare observed and simulated datasets directly without any summarisation.

As is typical in most Bayesian problems, the ABC posterior is not available in closed form. Instead, an algorithm is developed in order to generate samples from the ABC posterior and use these samples to approximate quantities of interest. In our application, we are interested in the posterior mean of the incidence level over time for various sub-populations and also the corresponding credible intervals, which quantifies the most likely values of incidence based on prior information and also the information contained in the observed data. The simplest algorithm available to sample from the ABC posterior, is the ABC rejection algorithm (see [5]). Under ABC rejection one simply draws a sample of  $N$  parameter vectors,

$\{\theta\}^N$ , from the prior, simulates a dataset for each, computes the corresponding vector of discrepancy distances,  $\{\rho\}^N$ , and then accepts as the ABC posterior only those  $\{\theta\}$  with  $\{\rho\}$  in the lower  $q$  quantile of the  $\{\rho\}^N$ . The choice of  $q$  ultimately reflects a trade-off between the ‘closeness’ of the ABC posterior to the true (i.e. complete likelihood) posterior and the Monte Carlo error associated with how many samples are kept in the ABC posterior. The major issue with the ABC rejection algorithm is that it is highly inefficient if the posterior distribution of interest is very different from the prior distribution. This problem is exacerbated when there is a large number of parameters being estimated. For our application, there is simply far too much computation required to reduce  $\varepsilon$  down to an acceptable level. Therefore we seek a more computationally efficient approach.

The sequential Monte Carlo (SMC) family of statistical learning algorithms offers a powerful means for generating computational approximations to complex (posterior) probability distributions and has been successfully applied in ABC applications. In the context of ABC, SMC ABC algorithms involve defining a sequence of ABC posterior distributions with a decreasing sequence of ABC tolerances,  $\varepsilon_1 > \varepsilon_2 > \dots > \varepsilon_T$  (our algorithm determines this sequence adaptively), where  $\varepsilon_T$  is the target ABC tolerance or the best tolerance that can be achieved within a reasonable computational budget. The main idea is to refine the distribution from which parameter values are drawn (instead of the prior) so that parameter values with non-negligible posterior support are drawn more often, leading to an overall much higher acceptance rate than is usually obtained in ABC rejection. The reader is referred to [23] of the main paper for full details of the SMC ABC approach we adopt.

Despite the improved efficiency of SMC ABC, it was also necessary to be reasonably precise in our prior specification regarding the expectation of moderate correlations year-to-year in the incidence rate of each age-sex cohort, and between those of nearby age-sex cohorts at fixed year; and likewise for the time dependent asymptomatic testing (screening) rate. To this end, we chose a multivariate Gaussian prior with Matérn covariance structure (given a correlation range of 12 years and a smoothness index of 1.5) acting on the logistic



transformed analogues of  $p_{\text{inf., } t}$  yearly (or  $p_{\text{test|asympt., } t}$  accordingly). Here the logistic transform,  $q_{\text{inf., } t} = \log(p_{\text{inf., } t} / [1 - p_{\text{inf., } t}])$ , transforms standard probabilities to random variables that have no upper or lower bound. The choice of the Matérn function here is not significant in of itself; rather its use was motivated by convenience since the Matérn guarantees a positive-definite covariance matrix and its properties are familiar from its routine use in geostatistical analysis. Interestingly, even though we then adopt broad, relatively non-informative prior variances in these (logistic transformed) Gaussian priors (as specified in Table S1) the effective reduction in the “volume” of the prior predictive distribution introduced by our implementation of a well-motivated correlation structure in the prior (as opposed to the naïve default of strict independence year-to-year) was observed to yield great improvements in the ABC convergence rate. Using our SMC ABC method we are able to reduce the ABC tolerance to less than a 5% mean fractional error in the fit to each of the 224 notification and test counts in our observed NNDSS benchmark.

Finally, it is important to emphasise that although at face value our application to the estimation of chlamydia incidence and prevalence amongst the Australian population using the chlamydia notification and testing data might appear highly specialised, the ABC-based methodology presented here should in fact be viewed as rather more general than this. With the defining characteristic of the ABC algorithm being to allow indirect inference of model parameters from complex datasets—especially where the likelihood function formally connecting the two is rendered intractable by complex selection effects or (as in this case) a third-party monitoring network—one might expect the approach to be useful in revealing the long-term trends of other transmissible infections. While the only direct, large-scale estimate of Australian chlamydia prevalence available from the ACCEPt study was here reserved for validation purposes, it is important to note that it could also have been used for model fitting simply by incorporating this data into our ABC discrepancy distance. In this sense, the power of ABC for enabling inference from multiple, heterogeneous datasets remains to be properly

explored in the epidemiological context (though see [45] for a first step in this direction) and should be recommended as an important direction for future research.

### Prior-Sensitivity Analysis

As in all Bayesian analyses it is important to bear in mind the possible sensitivity of the target posterior estimates to the assumed priors. Of principal concern for the present study is that although the inferred *trends* in our time-dependent parameters,  $p_{inf., t}$  and  $p_{test|asympt., t}$  are overwhelmingly data-driven, their absolute normalisation could potentially be quite sensitive to the priors on our time-independent parameters. To investigate this issue, we begin by comparing priors against posteriors for the nine time-independent parameters of our model in Figure S3. This comparison reveals four of these parameters ( $p_{asympt. [M]}$ ,  $p_{asympt. [F]}$ ,  $p_{false pos.}$  and  $p_{self cure, n.}$ ) as tightly constrained by the available data, and the remaining five ( $p_{att.|symp.}$ ,  $p_{test|symp.}$ ,  $p_{pos.}$ ,  $p_{self cure, a.}$  and  $p_{rep.}$ ) as relatively unconstrained (i.e., prior dominated). Our priors on  $p_{att.|symp.}$ ,  $p_{self cure, a.}$  and  $p_{rep.}$ —of which only the latter is without support from literature review (cf. Table S1)—enforce tight constraints on these parameters whereas our priors on  $p_{test|symp.}$  and  $p_{pos.}$  are comparatively broad.

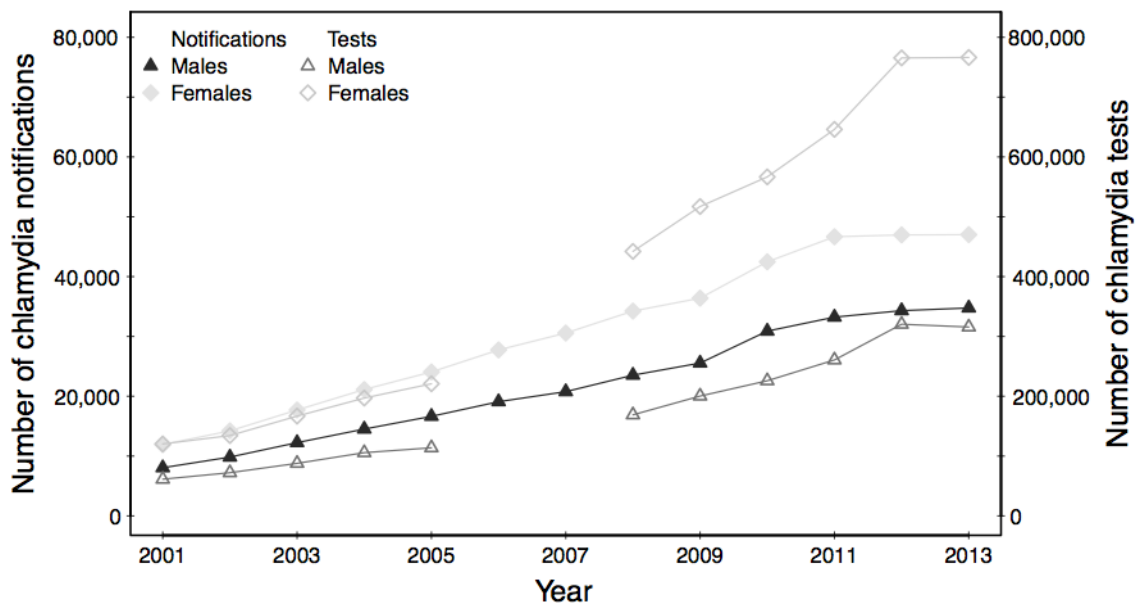
We conduct an in-depth prior sensitivity analysis by considering two alternative prior distributions for each of the five parameters,  $p_{att.|symp.}$ ,  $p_{test|symp.}$ ,  $p_{pos.}$ ,  $p_{self cure, a.}$  and  $p_{rep.}$ , separately (dotted red and blue lines in Figure S3) where the modes of these new priors have been shifted. Instead of having to run an additional  $2 \times 5 = 10$  ABC analyses, we run only another single ABC analysis using the broad (relaxed) prior distributions as indicated by the dashed lines in Figure S3. Then, the posterior results for a particular prior configuration can be obtained by simply applying importance sampling re-weighting of the ABC results obtained with the relaxed prior distributions. The first point we note upon examination of the posteriors under our relaxed priors on  $p_{att.|symp.}$ ,  $p_{self cure, a.}$  and  $p_{rep.}$  is that for the  $p_{rep.}$  parameter is quite similar to that for our original prior, revealing that in fact this parameter is well constrained by the data in a sense harmonious with our expectations (Figure S3). This

significant degree of constraint by the available data is again reflecting in the limited response of our prevalence estimates to reweighting of the  $p_{\text{rep.}}$  parameter by our shifted priors, despite  $p_{\text{rep.}}$  being degenerate with no other model parameter (cf. Figure 1). Conversely, although  $p_{\text{att. | symp.}}$ , and  $p_{\text{self cure, a.}}$  are only weakly constrained by the available data, they are each to some extent degenerate with  $p_{\text{asympt., M/F}}$  and  $p_{\text{self cure, n.}}$  respectively, such that forcing each in turn towards higher and lower values using our shifted priors forces the corresponding degenerate parameter(s) in the opposite direction while our data-driven prevalence estimates remain unchanged (Figure S4). The only parameter to notably respond to our shifted priors was  $p_{\text{pos.}}$ , which is only weakly degenerate with  $p_{\text{asympt., M/F}}$  and  $p_{\text{false pos.}}$ ; though the resulting shifts in the normalisations of our prevalence estimates are ultimately much smaller than the differences identified between our various age-sex cohorts.

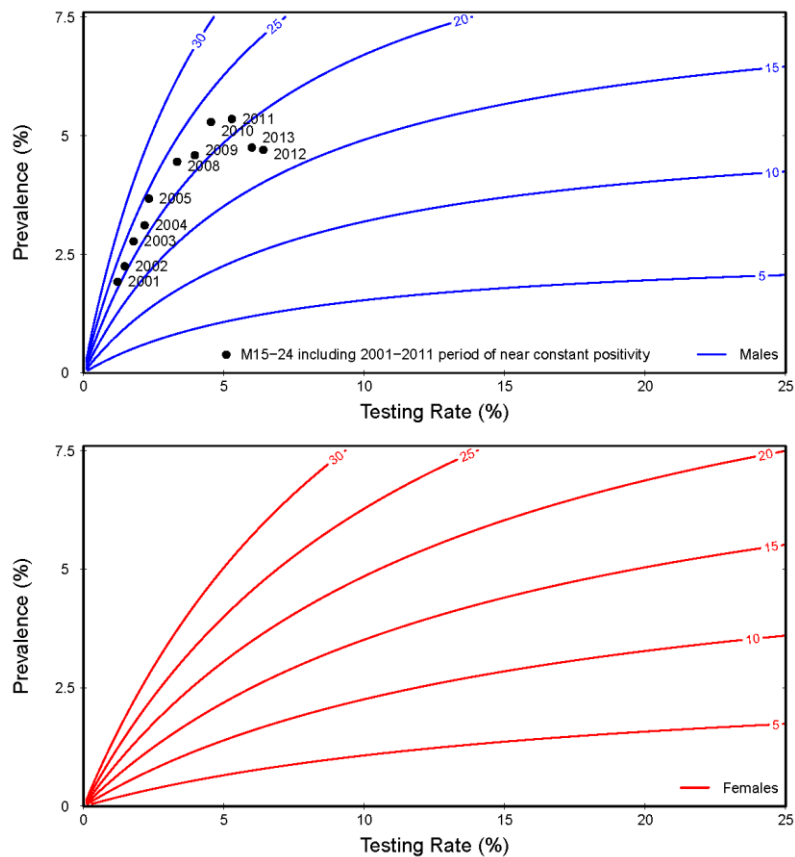
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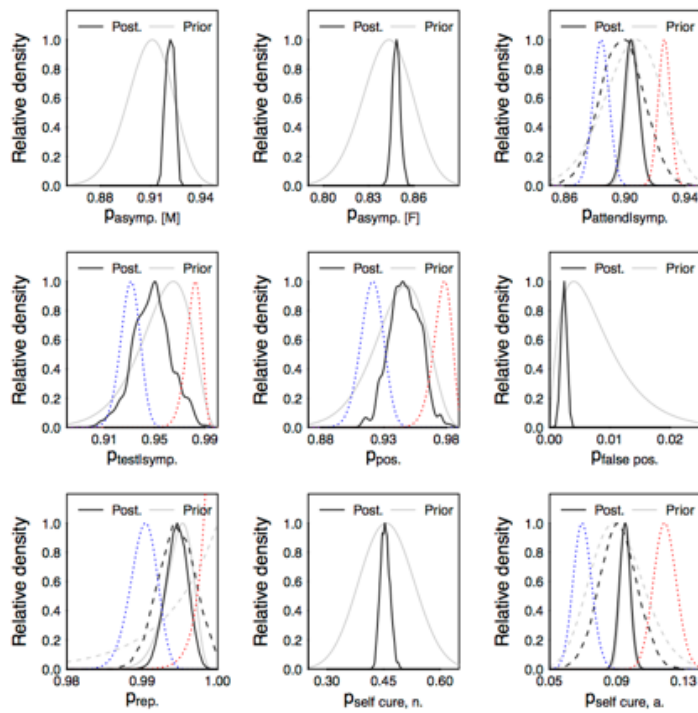
**Figure S1: Number of chlamydia notifications, and chlamydia tests rebated by Medicare, in Australia, 2001-2013**



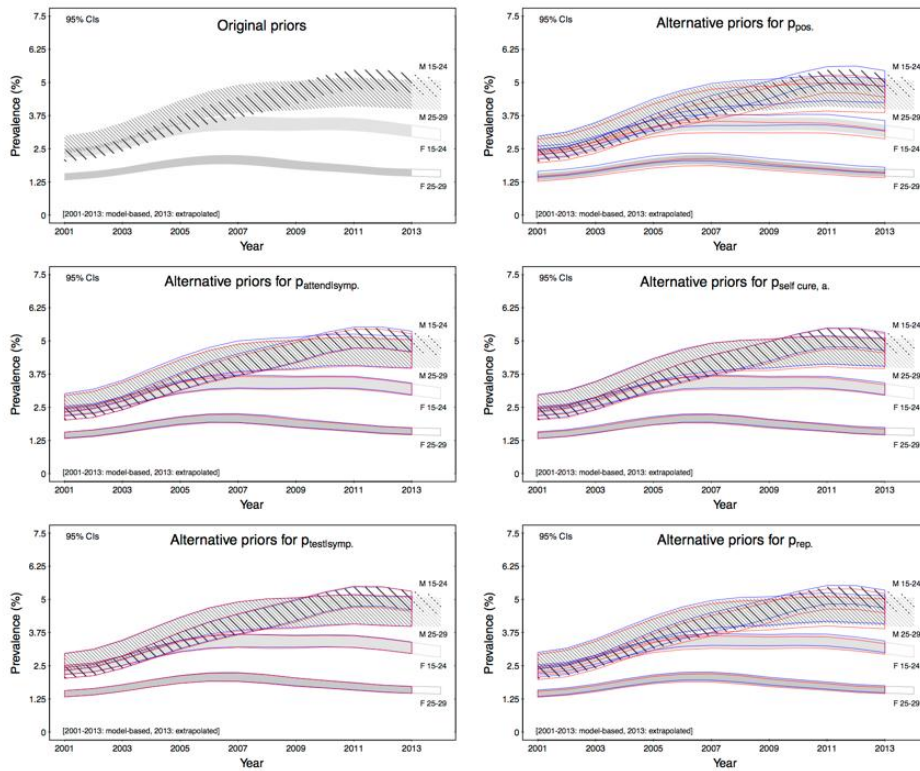
**Figure S2: Simple model deduced relationship between prevalence rates and testing rates for different levels (contours) of positivity**



**Figure S3: Comparison of prior and posterior densities for the nine time independent parameters of our decision pathway diagram**



**Figure S4: Prior-sensitivity in our prevalence estimates explored by importance sample reweighting under alternative, shifted priors**





**Table S1: Key parameters for prior specification in our Bayesian model for chlamydia**

*Time-independent Parameters*

Parameter*	Description of parameter	2.5% Q.	Mode	97.5% Q.	Beta params	Reference(s)
$p_{\text{asympt. [M]}}$	Proportion of asymptomatic infections (males)	0.881	0.910	0.934	400 40	[1, 2]
$p_{\text{asympt. [F]}}$	Proportion of asymptomatic infections (females)	0.808	0.843	0.873	400 75	[3]
$p_{\text{att.   symp.}}$	Proportion of symptomatic infections who seek medical care	0.896	0.905	0.913	4000 420	[4, 5]
$p_{\text{test   symp.}}$	Proportion of symptomatic patients (who visit a clinic) tested	0.901	0.957	0.987	83 4	Expert opinion
$p_{\text{pos.}}$	True positive rate of diagnostic test	0.891	0.943	0.975	110 7	[6, 7]
$p_{\text{false pos.}}$	False positive rate of diagnostic test	0.001	0.007	0.022	2 250	[6, 7]
$p_{\text{self cure, a.}}$	Proportion of infections cleared by background antibiotic use	0.090	0.095	0.101	1050 10000	[8]
$p_{\text{self cure, n.}}$	Proportion of infections that clear naturally	0.321	0.458	0.599	22 26	[9, 10]
$p_{\text{rep.}}$	Proportion of tests that are reported to NNDSS by labs	0.990	0.995	0.998	1500 8	Expert opinion

*Time-dependent Parameters*

Parameter <sup>†</sup>	Description of parameter	Matérn Covariance Parameters (w/ Logistic Trans.)			
		Expectation	Variance	Range	Smoothness
$p_{\text{inf., t}}$	Probability of experiencing chlamydia infection in a given year	-3.5	2	12	1.5
$p_{\text{test   asympt., t}}$	Probability of attending asymptomatic testing in a given year	-2.75	2	12	1.5

<sup>†</sup> With the probabilities of infection and screening in each of six age-based cohorts for each sex given the freedom to vary each year in our model, we encode our *a priori* expectation of relatively gradual changes over time (with some correlation between similar age groups) via a multivariate Gaussian prior structure with Matérn covariance function. To ensure probabilities between zero and one we in fact apply this prior to logistic transformed versions of each parameter,  $y = \log(p)/(1 - \log(p))$ . Specification of the Matérn covariance function is by way of its prior expectation, variance, range, and smoothness; our choice of a large prior variance for (the logistic transformed version of) each of these parameters gives a deliberately broad, non-informative range, allowing the dataset to “speak for itself” most clearly here (see Supplementary Material for more details).

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