ORIGINAL ARTICLE

A new approach to estimating trends in chlamydia incidence

Hammad Ali,[1] Ewan Cameron,[2,3] Christopher C Drovandi,[2] James M McCaw,[4] Rebecca J Guy,[1] Melanie Middleton,[1] Carol El-Hayek,[5] Jane S Hocking,[4] John M Kaldor,[1] Basil Donovan,[1,6] David P Wilson,[1] on behalf of the Australian chlamydia incidence estimation group

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[1]The Kirby Institute, UNSW Australia, Sydney, New South Wales, Australia
[2]School of Mathematical Sciences, Queensland University of Technology, Brisbane, Australia
[3]Spatial Ecology & Epidemiology Group, University of Oxford, Oxford, United Kingdom
[4]Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia
[5]Centre for Population Health, Burnet Institute, Melbourne, Australia
[6]Sydney Sexual Health Centre, Sydney Hospital, Sydney, Australia

Correspondence to
Dr Hammad Ali,
The Kirby Institute, UNSW Australia, UNSW, Sydney, NSW 2052, Australia;
hali@kirby.unsw.edu.au

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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.[1–3] 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.[4] 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[5] 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.[6] 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.[7 8] Modelling approaches have also been used to infer population incidence of other infectious diseases using routine surveillance data, for example, for HIV[9] but not for chlamydia.

Like some other countries, Australia routinely monitors chlamydia by the reported numbers and rates of notifications of diagnosed cases.[10] 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.[11] 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.[12] 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.

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[13] 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)[10] and
- National testing data collected by Medicare[14] (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.[14] Although tests conducted in public hospitals and most sexual health services are excluded, 82% of all chlamydia tests were conducted at GP clinics.[15]

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

Model calibration methods

A sequential Monte Carlo (SMC) approximate Bayesian computation (SMC-ABC) procedure[17] 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[18] (see online supplementary material for details).

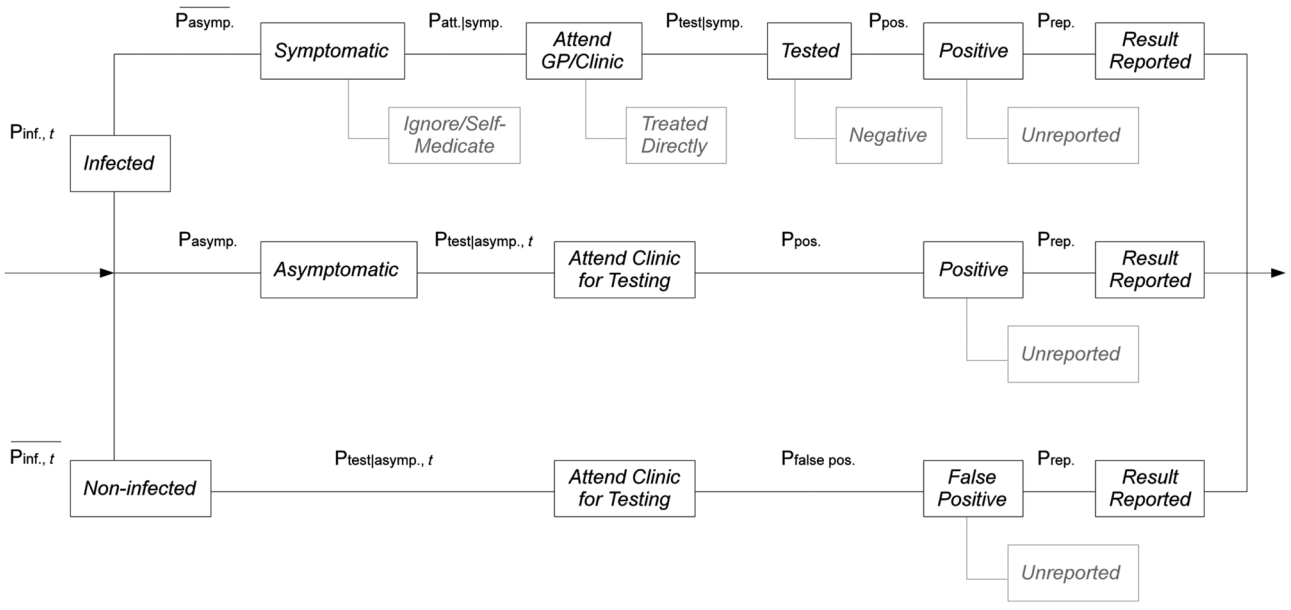

Figure 1 Pathways of chlamydia infection to be notified to the National Notifiable Diseases Surveillance System. Each parameter represents the (annualised) probability of progressing over a particular step. The light grey branches/boxes represent drop-outs from the notification count, but those reaching 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.[19] 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[15]). The model outcomes were also compared with a study which measured incidence and prevalence among a cohort of young women (see Discussion section).[5]

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.[20] 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.[10] Second, prevalence as notified by the ACCESS sentinel surveillance system at sexual health services across Australia[11] 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.[21]

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

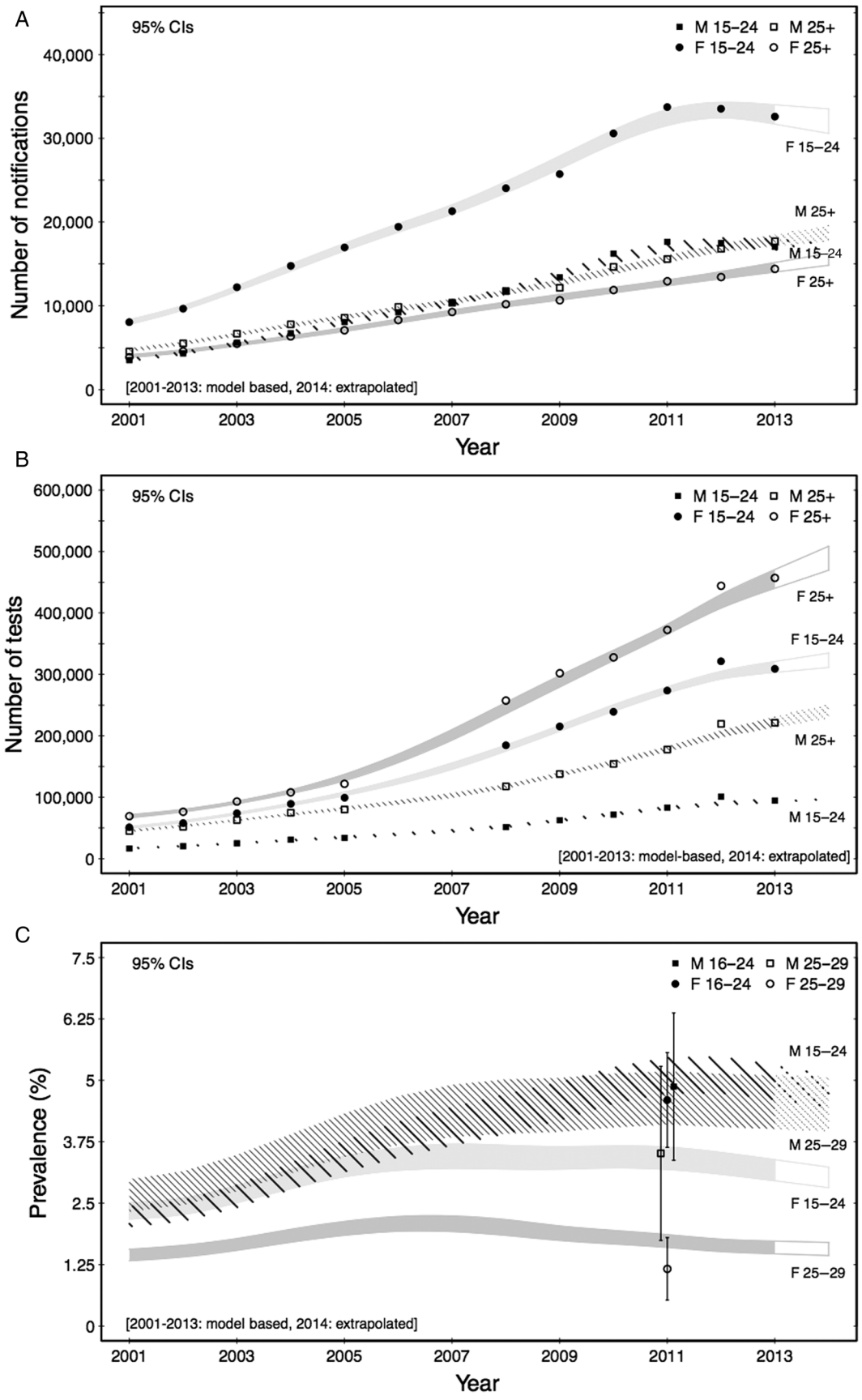

Figure 2 Model calibration and validation against chlamydia data, by age group and sex, 2001–2013: (A) notifications, (B) tests and (C) prevalence.

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

Sex	Men						Women					
Age	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).[5] 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*[22] 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)[23]) 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,[24 25] 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).[5] 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,[5] consistent with our study. CIRIS also reported that recent use of antibiotics was protective against incident infection.[5] 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.

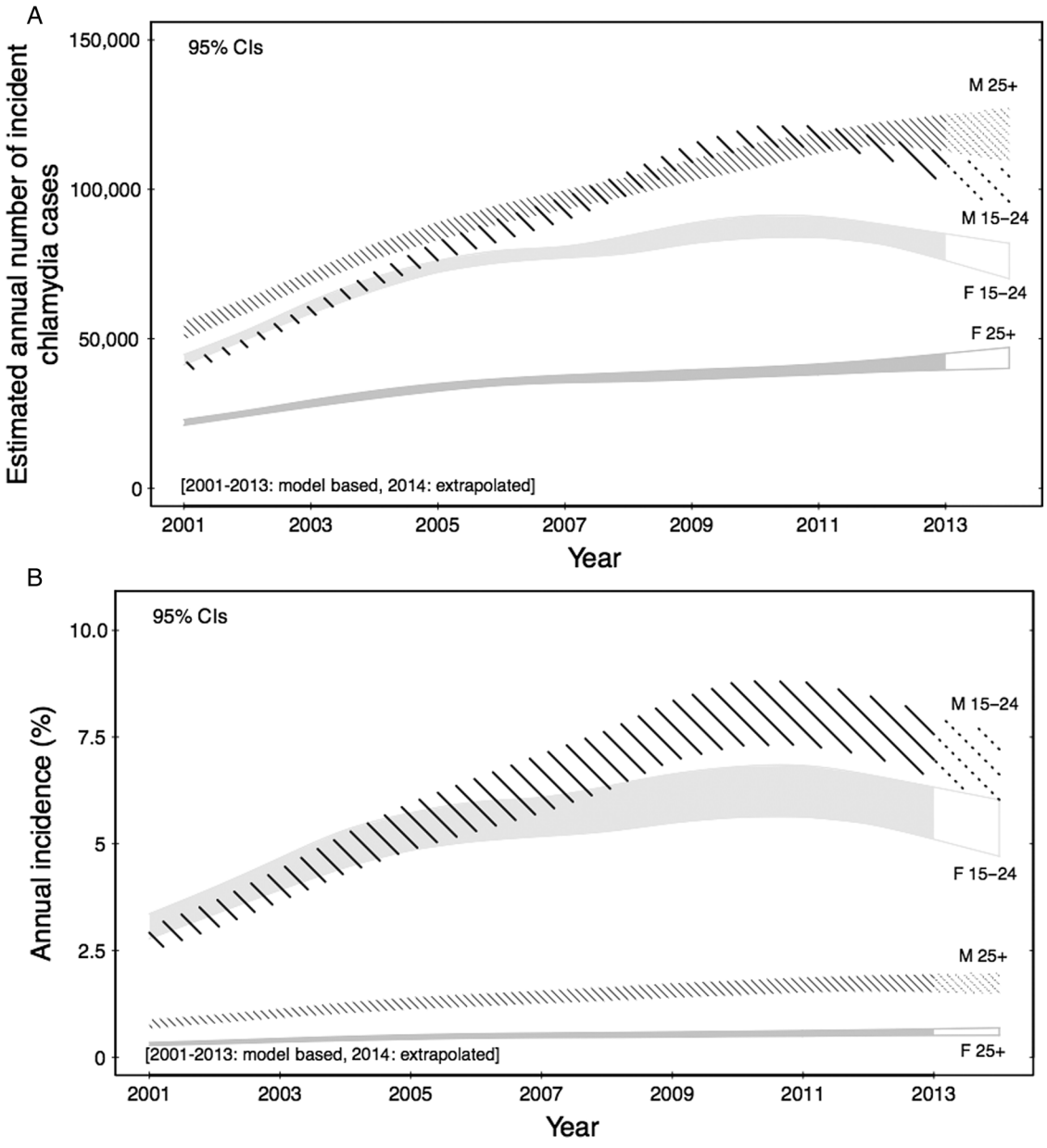

Figure 3 Estimates of chlamydia incidence in Australia, by sex and age group, 2001–2013: (A) number of incident infections and (B) incidence rate as a percentage per person per year.

Although there is a dearth of studies reporting on chlamydia incidence in the general population internationally, a study from the USA[26] 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.[11]

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.

Handling editor Jackie A Cassell

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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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