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Title page

TITLE

Intensified partner notification and repeat testing can improve the effectiveness of screening in reducing *Chlamydia trachomatis* prevalence: a mathematical modelling study.

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Abstract

BACKGROUND

The Australian Chlamydia Control Effectiveness Pilot (ACCEPt) was a cluster randomised controlled trial designed to assess the effectiveness of annual chlamydia testing through general practice in Australia. The trial showed that testing rates increased among sexually active men and women aged 16-29 years but, after three years, estimated chlamydia prevalence did not differ between intervention and control communities. We developed a mathematical model to estimate the potential longer-term impact of chlamydia testing on prevalence in the general population.

METHODS

We developed an individual-based model to simulate the transmission of *Chlamydia trachomatis* in a heterosexual population, calibrated to ACCEPt data. A proportion of the modelled population is tested for chlamydia and treated annually at coverage achieved in the control and intervention arms of ACCEPt. We estimate the reduction in chlamydia prevalence achieved by increasing retesting and by treating the partners of infected individuals up to nine years after introduction of the intervention.

RESULTS

Increasing the testing coverage in the general Australian heterosexual population to the level achieved in the ACCEPt intervention arm resulted in reduction in the population-level prevalence of chlamydia from 4.6% to 2.7% in 16-29 years-olds after 10 years (a relative reduction of 41%). The prevalence reduces to 2.2% if the proportion re-tested within 4 months of treatment is doubled from the rate achieved in ACCEPt intervention arm (a

relative reduction of 52%), and to 1.9%, if the partner treatment rate is increased from 30%, as assumed in the base-case, to 50% (a relative reduction of 59%).

CONCLUSION

A reduction in *C. trachomatis* prevalence could be achieved if the level of testing as observed in the ACCEPt intervention arm can be maintained at a population level. More substantial reductions can be achieved with intensified case management comprising re-testing of those treated and treatment of partners of infected individuals.

KEYWORDS

Chlamydia trachomatis, chlamydia testing, mathematical model, randomised controlled trial, testing coverage, re-testing, partner testing, case management.

KEY MESSAGES

- Our model, which is calibrated to testing and prevalence data from the control and intervention arms of a trial of chlamydia testing in general practice (ACCEPt), estimates the potential impact of screening interventions in the medium to long term.
- The model predicts a moderate reduction in *C. trachomatis* prevalence over 10 years if testing coverage is increased to the level achieved in ACCEPt.
- More substantial reductions in prevalence can be achieved through retesting of previously diagnosed/treated individuals and testing/treating the partners of infected individuals.

Main text

BACKGROUND

Chlamydia is the most commonly reported sexually transmissible infection (STI) in Australia, with more than 400 notifications per 100 000 population in 2018.(1) The sequelae of infection can be serious, and include pelvic inflammatory disease, ectopic pregnancy and infertility in women, and epididymo-orchitis in men.(2, 3) Regular screening of sexually active young adults in the general population is recommended to detect asymptomatic infection and reduce ongoing transmission and complications.(4, 5) The effectiveness of screening interventions to reduce transmission of *Chlamydia trachomatis* (*C. trachomatis*) are unclear.(6-8) A Cochrane review of randomised controlled trials, published in February 2016, found only one relevant trial of a screening intervention in the general population.(9) In this trial (Chlamydia Screening Implementation project), there was no difference in *C. trachomatis* positivity between intervention and control communities after three years in the Netherlands, but uptake of screening interventions was very low.(10)

The Australian Chlamydia Control Effectiveness Pilot (ACCEPt) was a cluster randomised controlled trial of annual opportunistic chlamydia testing in general practice across Australia, conducted between 2010 and 2015.(11) Clinics in the intervention arm received a multifaceted intervention designed to increase chlamydia testing, while clinics in the control arm were asked to continue their usual chlamydia testing practice. The underlying premise of the trial was that if testing rates increased, chlamydia prevalence in the underlying population would decline. The annual testing coverage among men and women aged 16-29 years increased from 8% to 20% in the intervention arm and from 8% to 13% in the control arm over a 3-years period (absolute difference 4.6%; 95%CI: 3.3, 6.0). However, chlamydia prevalence, estimated amongst primary care clinic attenders at baseline and the end of the

trial period, fell in both intervention and control arms and the absolute change in prevalence was only -0.5% (95% confidence interval: -2.6 to 1.5), in favour of the intervention arm. The possible reasons for the limited impact of the intervention on prevalence were that: 1) testing rates either did not reach high enough levels or were not sustained for long enough; 2) the proportion of individuals retested three to four months after treatment did not increase over time, and 3) uptake of partner notification and treatment might have been too low. Both re-testing individuals with a positive diagnosis at around three months after treatment, and notification and treatment of sexual partners of infected individuals are recommended in Australian STI management guidelines to minimise the risk of reinfection and to reduce ongoing transmission and complications.(4, 12) The ACCEPt intervention did not result in an increase in re-testing after treatment, while data on partner notification were not collected.

Mathematical models of transmission can be used to predict the long-term impact of preventive interventions, such as those assessed in ACCEPt. While many published chlamydia transmission models were designed to investigate the impact of increased chlamydia testing, the differences in assumed sexual partnership dynamics and infection parameter estimates between models mean that predicted outcomes may vary.(13) We developed a mathematical model of chlamydia transmission for the general heterosexual population in Australia. The objectives of the study were to estimate the potential longer term impact on chlamydia prevalence at the population-level if partner notification and/or re-testing among 16-29 years old were improved on top of the increased annual testing coverage achieved under ACCEPt.

METHODS

We developed an individual-based model of *C. trachomatis* transmission in a population of heterosexuals aged 14 to 59 years.

We adopt an SEIR framework whereby individuals can be Susceptible to infection, Exposed (infected but not yet infectious), Infected (and infectious), or Recovered (and immune to reinfection). Age, infection status, sexual partner history, and sexual behaviour of individuals are tracked and updated in the model on a daily basis. A brief description of the model follows, with further detail provided in the Technical Appendix.

The modelled population consists of 92,000 heterosexual individuals, stratified by sex (male/female) and age (14-59 years), with 1000 individuals for each one-year gender-age stratum. Upon reaching the age of 60 years, individuals are removed from the model and replaced with a new individual of the same gender aged 14 years. Individuals begin to seek sexual partners at age 16 years. We did not model sexual partnerships for individuals below age 16 years explicitly because reliable data are not available for this age group.

We used data about sexual behaviour, as reported by female and male heterosexual participants in the second Australian Study of Health and Relationships (ASHR2), a national population-based survey of the sexual behaviour and sexual attitudes of Australian adults aged 16-69 years during 2012-13.(14) The process of formation and dissolution of sexual partnerships in the model is informed by participant-reported data about the mean number of partners in the last 12 months at different ages, the age of the sexual partner, partnership duration, condom use and numbers of sex acts per week (Technical Appendix, section 3).Data collection in ASHR2 took place during 2012-2013 in the period between ACCEPt Survey 1 in December 2010 and Survey 2 in September 2015.(11, 14)

The model is calibrated against chlamydia prevalence, estimated from the ACCEPt baseline survey by adjusting the per-sex-act probability of *C. trachomatis* transmission using a Nelder-Mead simplex procedure.(15) The procedure involved minimising the sum of squared differences between gender- and age-specific prevalence measured in ACCEPt and those

generated by the baseline model. The per-act transmission probabilities inferred by calibration, and other parameters related to *C. trachomatis* natural history, are given in Table A6 of the Technical Appendix. For model calibration, the annual chlamydia testing coverage for males and females is set to the testing coverage observed in the control arm of ACCEPt in Year one of the trial (Table A7, Technical Appendix). We refer to this calibrated model as the 'baseline model' (Scenario A below), against which intervention scenarios are compared.

We used the model to investigate different scenarios about chlamydia testing coverage, re-testing after treatment, based on what was observed in ACCEPt, and treatment of partners, based on the limited information available from an interview with general practitioners.(16) We predicted the impact on chlamydia prevalence if these scenarios were extended to the entire Australian population beyond the end of the trial period. In ACCEPt, clinics in the intervention arm achieved higher annual testing coverage over the course of the trial (20% across both genders, corresponding to 26% in females and 13% in males by trial end) than those in the control arm (13% across both genders, corresponding to 17% in females and 7% in males).(11) Chlamydia test coverage from the ACCEPt control arm is very similar to that estimated from STI testing coverage (measured in terms of Medicare rebated chlamydia tests) in Australia in 2017.(17)

The scenarios investigated in this study are summarised in Table 1. Each scenario is run for ten years, which includes the four years between the baseline and post-trial prevalence surveys conducted for ACCEPt, followed by six years of continued intervention, to estimate the impact on chlamydia prevalence in the population over that period. It is assumed that diagnosis of chlamydia is performed with a 100% sensitive test, and that all individuals who receive a positive diagnosis are successfully treated. This is a simplifying assumption about treatment that likely overestimates the impact of the testing strategies slightly as it is

believed that around 93% of people in general population with a positive chlamydia test result receive treatment.(18)

Table 1: Summary of scenarios investigated in this study. (Table created by the authors)

Scenario	Annual testing coverage for individuals aged 16-29 years	Proportion retested after a positive diagnosis	Partner notification/treatment rate[1]
A (Baseline)	Same as the coverage in the control arm of ACCEPt over the first 4 years, maintained at 17% for females and 7% for males from Year 5 onwards	24% within 4 months, as in control arm of ACCEPt	30%
B	Same as the coverage in the intervention arm of ACCEPt over the first 4 years, maintained at 26% for females and 13% for males from Year 5 onwards	28% within 4 months, as in intervention arm of ACCEPt	30%
C	Same as Scenario B	56% within 4 months	30%
D	Same as Scenario B	28% within 4 months	50%
E	Same as Scenario B	56% within 4 months	50%

1.We assume partner notification rate for the base-case as 30% as no data were collected to inform this from ACCEPt.

For Scenarios A and B, the results of 100 simulations were included in this study. The 100 simulations were selected from 1000 simulations in which chlamydia prevalence amongst sexually experienced individuals (defined as having had at least one lifetime sexual partner) aged 16-29 years had the smallest square differences to the prevalence reported in survey 1 and 2 from of ACCEPt.(11) The non-scenario specific parameters (e.g. the seed for the

random number generator that governs partnership formations) from selected 100 simulations from Scenario B were then reused to generate simulations for the other scenarios.

Testing for *C. trachomatis*

Under Scenario A, testing coverage in the model was set to the testing coverage achieved in the ACCEPt control arm over the four years of the trial (Table 1). Under Scenarios B, C, D and E testing coverage was set to match the testing coverage achieved in the ACCEPt intervention arm over the same period. The testing coverage in both arms over the 4 years of the trial are given in Table A7 of the Technical Appendix. We assumed the screening coverage to be same as the Year 0-1 coverage under Scenario A prior to intervention. Beyond the trial period, we assume that, for all scenarios, testing coverage was maintained at the fourth-year level until the end of each simulation run.

Re-testing after treatment for chlamydia

Australian STI management guidelines recommend re-testing after three months for anyone receiving a positive chlamydia diagnosis.(4) In practice, however, the rate of re-testing is very low in general practice where most chlamydia is diagnosed (about 25% of those receiving a positive diagnosis).(19) In ACCEPt, and for the purpose of this analysis, re-testing is defined as a chlamydia test carried out within four months of a positive diagnosis. We used four months as the cut off as it allows clinics up to 4 weeks to recall patients for re-testing. The rate of re-testing in ACCEPt was also observed to be low. In the final year of the trial, the rate of re-testing within four months of diagnosis was 28% in the intervention arm compared with 24% in the control arm. We use the re-testing rate observed in the control arm in our baseline model (Scenario A) and predicted the impact on chlamydia prevalence if the rate of re-testing is increased to the rate observed in the intervention arm (Scenario B

and D). We further examine the impact of increasing the proportion retested to double that observed in the intervention arm (i.e., to 56%) in Scenario C.

Partner treatment

Data on whether partners of those with a positive diagnosis were notified and treated were not routinely collected in the ACCEPt trial and thus the effectiveness of partner treatment could not be measured. We used our model to investigate the potential impact of partner treatment on chlamydia prevalence by assuming that a proportion of partners of patients diagnosed with chlamydia are tested and treated. We assume that 30% of current partners of patients diagnosed with chlamydia are successfully treated in Scenarios A, B and C (our base-case assumption), and increase this to 50% for Scenario D.

Finally, in Scenario E, we examine the combined effect of increasing both retesting and partner treatment (i.e. combining Scenario C and D).

RESULTS

The prevalence outcomes of Scenario A and B, together with the corresponding prevalence from ACCEPt, are summarised in Table 2. Similar to the prevalence measured in the ACCEPt trial, the relative reduction in modelled prevalence among those of aged ≥20 is greater than among those aged <20 in both scenarios. Note the simulation results at Year 0 are the same for all scenarios as scenarios only differ after Year 0.

Table 2: Chlamydia prevalence amongst sexually active individuals aged 16-29 years from the model compared to the prevalence observed in ACCEPt. (Table created by the authors)

Age (years)	Median prevalence from 100 selected simulations (IQR)		Prevalence from ACCEPt (11) (95% confidence interval)	
	Year 0	Year 4	Survey 1	Survey 2

Control (Scenario A in the model)				
16-19	8.4 (7.7, 9.3)	6.6 (5.4, 7.6)	6.7 (4.4, 9.1)	5.4 (3.0, 7.9)
20-24	5.2 (4.4, 5.9)	3.6 (2.8, 4.5)	5.9 (3.9, 7.9)	4.0 (2.6. 5.4)
25-29	1.3 (0.9, 2.0)	0.7 (0.5, 1.1)	1.7 (1.0, 2.4)	1.3 (0.2, 2.5)
All, 16-29	4.6 (1.8, 5.8)	3.4 (2.8, 4.0)	4.6 (3.5, 5.7)	3.4 (2.4, 4.5)
Intervention (Scenario B in the model)				
16-19	8.4 (7.7, 9.3)	6.0 (4.9, 6.8)	8.1 (5.3, 10.9)	6.0 (3.9, 8.1)
20-24	5.2 (4.4, 5.9)	3.0 (2.4, 3.8)	6.0 (4.0, 8.0)	3.1 (1.9, 4.3)
25-29	1.3 (0.9, 2.0)	0.7 (0.4, 1.1)	2.0 (1.0, 3.1)	1.9 (1.0, 2.9)
All, 16-29	4.6 (1.8, 5.8)	3.1 (2.4, 3.6)	5.0 (3.8, 6.2)	3.4 (2.7, 4.1)

IQR: Interquartile range

Chlamydia prevalence from the model for all sexually active individuals aged 16-29 years in the fourth year and the tenth year under each scenario is summarised in Table 3. These results suggest that, although increased screening coverage in Scenario B will result in lower prevalence compared with Scenario A, the absolute difference in median prevalence at the fourth year is only 0.3%. If testing coverage is maintained from the fourth year, then by the tenth year, the absolute difference in median prevalence between Scenario A and B is still only 0.6%. The reduction in prevalence when the partner treatment rate is increased from 30% to 50% (Scenario D) is greater than when the re-testing rate is doubled (Scenario C). As expected, the reduction in prevalence is greatest if both the partner treatment rate and the re-testing rate are increased (Scenario E). Comparison of the interquartile ranges presented in Table 3, using the technique described in McGill *et al.* (20), suggests that the median prevalences for Scenarios C to E are significantly different from the median for Scenario A (at the 5% significance level) at the fourth and tenth year. Similar to the findings

from ACCEPt, the model-predicted median prevalences for Scenario A and Scenario B are not significantly different (at the 5% significance level) at the fourth year. However, the model-predicted median prevalence for Scenario B is significantly different to the median for Scenario A (at the 5% significance level) at the tenth year.

Table 3: Chlamydia prevalence among individuals aged 16-29 years and sexually active in the modelled population at the fourth and tenth year under each scenario (see Table 1 for definition of each scenario). IQR: interquartile range. (Table created by the authors)

Scenario	Median prevalence, % at the fourth year (IQR)	Median prevalence, % at the tenth year (IQR)
A	3.4 (2.8, 4.0)	3.3 (2.5, 4.0)
B	3.1 (2.4, 3.6)	2.7 (2.0, 3.1)
C	2.6 (2.2, 3.0)	2.2 (1.8, 2.7)
D	2.1 (1.8, 2.6)	1.9 (1.4, 2.3)
E	1.8 (1.4, 2.1)	1.5 (1.0, 1.7)

Chlamydia prevalence by age (16-19 and 20-29) and gender at the tenth year under each scenario is summarised in Figure 1. The results show a similar pattern to those presented in Table 3, with the median chlamydia prevalence lowest under Scenario E, followed by Scenario D then Scenario C. Under all scenarios the prevalence of chlamydia in those aged $\geq$30 years is <0.5% and hence not shown in Table 3 and Figure 1.

DISCUSSION

This individual-based mathematical model of *C. trachomatis* transmission in the general Australian heterosexual population was informed by data from a cluster-randomised controlled trial (ACCEPt), and was designed to evaluate the potential impact of increased

testing, re-testing and partner treatment on chlamydia prevalence in the longer term. We found that increasing testing coverage to the level achieved in the ACCEPt intervention arm could reduce prevalence among 16-29 years old from 4.6% to 3.1% within 4 years (corresponding to a relative reduction of 33%), compared with a reduction from 4.6% to 3.4% under the testing coverage achieved in the control arm (a relative reduction of 26%). If, in addition to increased testing coverage, the proportion of those retested within 4 months after positive diagnosis is doubled from 28% to 56%, the prevalence is predicted to be reduced further to 2.6% with 4 years (a relative reduction of 43%), whereas increasing the partner notification-treatment rate from 30% to 50% is predicted to reduce prevalence to 2.1% within 4 years (a relative reduction of 54%). Doubling the proportion retested as well as increasing the partner notification-treatment rate from 30% to 50% is predicted to reduce prevalence to 1.8 % within 4 years (a relative reduction of 61%).

In ACCEPt, the observed reduction in prevalence between Survey 1 and Survey 2 (spanning roughly 4 years) was from 5.0% to 3.4% in the intervention arm (1.6% corresponding to a relative reduction of 32%), and from 4.6% to 3.4% in the control arm (1.2% corresponding to a relative reduction of 26%).(11) The reductions in prevalence predicted by our model (1.5% for the intervention arm and 1.2 % for the control arm) are thus consistent with the decreases in prevalence observed in both arms of ACCEPt. It is worth noting that in ACCEPt, the prevalence measure in both the intervention and control arms was essentially the same at Survey 2, but the control arm had lower prevalence to begin with in Survey 1 due to sampling variability. The findings from our model suggests that if the baseline prevalence was similar in the control and intervention arms, then the differences between arms at Survey 2 would have been more noticeable. However, our findings also suggest that even if the levels of testing coverage achieved in ACCEPt are sustained for up to 10 years, the additional reduction in chlamydia prevalence due to the intervention will only be around 0.6%.

Re-testing rates were low in both arms of the ACCEPt trial, with less than 30% of people with a positive diagnosis re-tested within four months, consistent with other measures of retesting for chlamydia in Australia.(18) Our findings suggest that doubling the rate of re-testing achieved in ACCEPt would lead to larger reductions in chlamydia prevalence. However, given that the package of support provided to clinics in the ACCEPt intervention arm did not lead to a significant increase in the re-testing rate, more intensive case-management of patients, such as mailed self-sampling kits and reminders, may be needed to increase the rate of re-testing.(21, 22)

Our model predicts that if the partner treatment rate can be increased from 30% to 50% in addition to increasing testing coverage to the level achieved in the ACCEPt intervention arm, chlamydia prevalence could be reduced from 4.6% to 2.1% within 4 years (a relative reduction of 54%), and to 1.9% after ten years (a relative reduction of 59%). By comparison, results from a previously published individual-based modelling study predicted a 60% reduction of the baseline population prevalence within 5 years if 50% of partners were treated.(13) This suggests our model prediction is consistent with results from previous modelling studies, even if the baseline testing rate and prevalence differs between models.(7) However, achieving high rates of partner treatment is notoriously difficult in practice,(23, 24) and determining the most efficient means to deliver partner treatment is challenging,(25) but additional support using online tools shows promises.(26, 27) One of the main limitations in ACCEPt was the absence of a direct measurement of the partner treatment rate, and it is not known whether the intervention affected partner treatment. Our baseline assumption of a partner treatment rate of 30% is an estimate based on a survey of general practitioners in which 40% of participants reported actively engaging in partner notification activities, and more than 90% reported that they will ask their patients to contact their partners and encourage them to seek treatment.(16) While it is unlikely that all patients

will contact their partners upon general practitioners' advice, it is also possible that the partner treatment rate of 30% applied in this study is an underestimate, especially in the context of the ACCEPt trial where the STI awareness was enhanced.

Reviews of chlamydia transmission models have suggested that they often overestimate the impact of screening interventions.(28, 29) With this model we attempted to reduce the overestimation by calibrating the model against prevalence and screening coverage as measured in the control and intervention arms of ACCEPt simultaneously. While the testing coverage measured in ACCEPt does not include all STI testing carried out in the population (e.g., testing sought by individuals away from their usual general practitioner is not included), it does provide a measure of the level of increase in testing coverage achievable at the population level. For our analysis, we attempted to reduce the uncertainties by only including simulations that match the prevalence reported from ACCEPt, resulting in a more modest reduction in prevalence from the screening intervention in our model. While this approach means our outcomes more closely match the prevalence measured in ACCEPt, there is a risk of overfitting, with the selected simulations not being representative of the true underlying dynamics and the results therefore less applicable outside the conditions described in ACCEPt. Furthermore, other factors that might lead to overestimation of impact of screening interventions, such as uncertainties in *C. trachomatis* natural history (e.g., duration of untreated infections, transmission probability per contact, partial immunity after natural clearance) and underlying assortative mixing across age and risk groups, remain in our model.

The primary outcome from ACCEPt and the findings of this modelling study address effects on chlamydia prevalence. Mathematical modelling of the effects of the ACCEPt intervention on chlamydia-associated morbidities such as PID, ectopic pregnancy, infertility and epididymo-orchitis, and the cost effectiveness of increased testing have not yet been

investigated. However other studies have focused on investigations of these issues, including the cost and feasibility of population screening and other interventions and approaches.(30) For ACCEPt, a cost-effectiveness evaluation of increased testing, as informed by findings from the ACCEPt trial and the output of this modelling study, is underway and will be published separately.

The focus of this study was to model the effects of expanding chlamydia screening to the general population. A parsimonious representation of the Australian general heterosexual population was adopted due to the limited availability of detailed sexual behaviour data and to reduce model complexity. We have therefore not considered a range of Issues related to heterogeneity in sexual behaviour such as the frequency of one-off casual partnerships and possible changes in sexual practices as partnerships progress to long term partnerships, as data to inform these was not collected in the surveys used to inform the models. We also restricted the model to the general heterosexual population, even though bridging from other populations with higher prevalence (e.g., bisexual, remote communities) is possible.

In summary, our modelling suggests that increased annual testing coverage, sustained at the levels achieved in a trial setting, has the potential to lead to modest reductions in chlamydia prevalence in the general Australian population in the medium to long term. Additional measures, such as increasing re-testing and partner treatment combined with increased annual testing coverage, are needed to provide greater reductions in prevalence.

AUTHOR CONTRIBUTIONS

BBH, JSH, NL and DGR contributed conceptualization of the study. BBH developed the model. BBH, JSH, NL and DGR discussed the main model findings. BBH and DGR wrote the original manuscript. JSH and DGR supervised the work and contributed resources. All authors reviewed and edited the manuscript.

COMPETING INTERESTS

No competing interests declared.

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