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(a) Title: *Chlamydia trachomatis* incidence using self-reports and serology by gender, age period and sexual behavior in a birth cohort

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There are no conflicts of interest to declare.

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SHORT SUMMARY

A third of women born in Dunedin, New Zealand had evidence of chlamydia by age 38, with risk more strongly determined by behavior than age to the early thirties.

ABSTRACT

Background: While understanding chlamydia incidence assists prevention and control, analyses based on diagnosed infections may distort the findings. Therefore, we determined incidence and examined risks in a birth cohort based on self-reports and serology.

Methods: Self-reported chlamydia and behavior data were collected from a cohort born in New Zealand in 1972/3 on several occasions to age 38 years. Sera drawn at ages 26, 32 and 38 years were tested for antibodies to *C. trachomatis* Pgp3 antigen using a recently developed assay, more sensitive in women (82.9%) than men (54.4%). Chlamydia incidence by age period (first coitus to age 26; 26–32; and 32–38 years) was calculated combining self-reports and serostatus and risk factors investigated by Poisson regression.

Results: By age 38, 32.7% of women and 20.9% of men had seroconverted or self-reported a diagnosis. The highest incidence rate was to age 26, 32.7 and 18.4 per 1,000 person-years for women and men, respectively. Incidence rates increased substantially with increasing number of sexual partners. After adjusting age period incidence rates for partner numbers, a relationship with age was not detected until 32–38 years, and then only for women.

Conclusions: Chlamydia was common in this cohort by age 38, despite the moderate incidence rates by age period. The strongest risk factor for incident infection was the
number of sexual partners. Age, up to 32 years, was not an independent factor after accounting for partner numbers, and then only for women. Behavior is more important than age when considering prevention strategies.

KEY WORDS:

Chlamydia; epidemiology; sexual behavior; chlamydia serology
INTRODUCTION

While the prevalence of chlamydia, which gives an indication of untreated persisting infection and guides recommendations on testing, is relatively straightforward to measure, incidence is a more useful indicator of risk but much harder to determine.¹ The rate of clinically diagnosed infections has been used as a marker of incidence, but this is likely to distort the underlying trends, not only through variations in methods and patterns of testing, but also because many infections are asymptomatic and resolve spontaneously.²,³

The most robust studies of infection incidence are cohort studies, as rates can be determined directly over a specific period. However, when based on self-reports, this will underestimate true incidence due to unrecognized infections.³,⁴ Examining chlamydia incidence using serology has been hampered by lack of sensitive markers of past infection and the loss of detectable antibody as time since treatment increases.⁵,⁶ However, we have shown that a recently developed double-antigen sandwich enzyme-linked immunosorbent assay (ELISA) to detect antibodies to Pgp3, a C. trachomatis-specific antigen, is more sensitive than current major outer membrane protein (MOMP) assays.⁷

We have previously examined all sexually transmitted infection (STI) incidence in the Dunedin Multidisciplinary Health and Development Study (DMHDS) birth cohort.⁸,⁹ Based on self-reports of all STIs up to 32 years of age, we showed the period up to age 21 is the time of highest infection rate for women, and for men from age 21–26 years.

Here we report further analyses, using repeated assessments of self-reported chlamydia diagnosis and serology to estimate incidence more completely than either measure alone. The specific aims are to: a) estimate the cumulative incidence of chlamydia (self-reported and/or seroconversion) by age 26, 32 and 38 years; and b) calculate the incidence rates
and compare the risks of chlamydia for the three age periods from first coitus to age 26, 26–32 and 32–38 years.

MATERIALS AND METHODS

Population and data

Participants are members of the DMHDS, a birth cohort born between April 1972 and March 1973 in Dunedin, New Zealand and assessed on a number of occasions up to age 38 years. Information on self-reported STIs, including chlamydia, and sexual behavior information were collected by computerized interview at ages 21, 26, 32 and 38 years as part of the module on sexual and reproductive health. Age at first coitus was based on the self-reported age of first experience of vaginal intercourse or same-sex contact. At age 26, the total numbers of reported opposite-sex and same-sex sexual partners since first coitus were summed and grouped as: 0–1; 2–4; 5–9; and 10 or more. At ages 32 and 38, the number of partners reported in the past six years was similarly calculated. Highest educational qualification reported at age 26 was grouped as: low (none or secondary school); medium (post-secondary or overseas qualification); and high (university bachelors or higher degree). At age 26, ever reporting same-sex sexual contact was used to identify same-sex contact in the age period, and at ages 26 and 38, any same-sex sexual contact in the past six years.

At the age 21 interview, the participants were asked if they had ever had an STI, and at the age 26, 32 and 38 interviews, if they had one since the previous assessment. If so, they were asked to specify which STI(s) from a list which included chlamydia.
Sera collected at the age 26, 32 and 38 assessments were tested for antibodies to Pgp3 using a double-antigen sandwich ELISA, as previously reported. When the assay was assessed in individuals with confirmed infection recruited at various times since treatment from UK genitourinary medicine clinics, the assay was 82.9% (95% confidence interval [CI] 77.0–88.8%) sensitive in women and 54.4% (64.5–78.6%) sensitive in men. Using a reference standard of sera from micro-immunofluorescence assay negative children aged 2–13 years, the Pgp3 assay was 97.8% specific. The Pgp3 antibody response has also been shown to persist in 83.8% in men and 96.5% in women at least 12 years after seroconversion. Participants were considered to have evidence of chlamydia if they self-reported a diagnosis and/or had positive serology.

Ethical approval was obtained from the Otago and Southern Regional Ethics Committees for all assessments (reference numbers 97/12/109=126, 03/08/066-93 and 10/03/012).

**Analysis of cumulative incidence (objective a)**

The cumulative incidences and 95% CIs to the end of each data collection period when serological testing was conducted (26, 32 and 38 years) were calculated per 100 people. The calculation of cumulative incidence was limited to those who had experienced coitus and was based on any evidence of chlamydia, seropositivity and/or self-reported chlamydia, at that or any previous assessment. For the calculation of cumulative incidences by age 32 and 38, those who had not provided full information on chlamydia infection (self-reports and serology) at all previous assessments were excluded.

**Analysis of incidence rates and risk (objective b)**

Incidence rates of chlamydia infection in the three age periods (first coitus to age 26, age 26–32 and 32–38 years) were calculated per 1,000 person-years of observation. All those
who had ever experienced coitus, completed interview questions on number of partners and provided sera were included. At age 26, all participants who self-reported a diagnosis and/or had positive serology were considered an incident case. At ages 32 and 38, those who self-reported a diagnosis or had become seropositive, but who had not already seroconverted, were considered incident cases. Person-years (the exposure time) were calculated as the number of years from first coitus to age 26, from age 26 to 32 and age 32 to age 38; in each age period, the midpoint was used to assign exposure time for participants who seroconverted and/or self-reported a diagnosis. An alternate person year measure was also calculated, whereby those who seroconverted and/or self-reported a diagnosis were assigned the full follow-up time for the age period.

Incidence rates ratios (IRR) were calculated using multilevel mixed-effects Poisson regression with robust standard errors. This accounted for repeated observations of the same individuals by including a random effect of participants’ study identifier and exaggerated random errors arising from deviation from the underlying assumptions of Poisson regression. Models were run separately for women and men. However, incidence and risk of chlamydia infection were not compared by gender due to the marked difference in the sensitivity of the serological assay among women and men.\(^7\)

Adjusted incidence rate ratios (AIRR) were re-calculated by including, stepwise, in a multivariate model age period, the number of sexual partners in the age period, same-sex sexual contact in the age period and educational level at age 26. A separate model, limited to the period from first coitus to age 26 years, investigated the effect of age of first coitus in women due to the \textit{a priori} hypothesis that women are more susceptible to infection when they are younger.\(^{12}\) For all models, sensitivity analyses were conducted to identify any difference in the interpretation of the models if those who had evidence of chlamydia
were assumed to have been infected at the end of the age period, instead of being assigned half of the person-years for that age period.

STATA 12.1/SE was used for all analyses and p-values calculated using $X^2$ tests, unless Poisson modelling was indicated. Poisson models were evaluated by comparing Akaike information criterion values and the significance of each parameter was assessed using a Wald test.

RESULTS

Response rates and eligibility by age period

Figure 1 summarizes the numbers in the cohort available at the end of each data collection period. Of the surviving cohort who had experienced first coitus at the age 26 assessment, 82.4% (399/484) of women and 82.0% (420/512) of men had sera tested and sufficiently completed the sexual health questionnaire by answering questions on partner numbers. At age 32, this was true for 86.7% (425/490) of women and 82.9% (431/520) of men; and at age 38 for 90.0% (440/489) of women and 86.8% (448/516) of men. There were no significant differences between eligible study members who did and did not provide sera (Supplementary Table).

The cumulative incidence of chlamydia

By age 38, 32.7% (95% CI 27.9–37.8%) of women and 20.9% (17.0–25.5%) of men showed evidence of past chlamydia infection, based on ever being seropositive and/or having self-reported chlamydia (Figure 2). While at all ages women had a markedly higher cumulative incidence than men, this does not compare true differences due to the lower sensitivity of the assay in men and differences in the likelihood of clinical assessment of
chlamydia. The patterns of cumulative incidence for self-reports mirrored that for seropositivity, with the majority of first infections occurring before age 26.

Of those who had seroconverted by age 38, 38.1% and 16.7% of women and men, respectively, had ever self-reported a diagnosis chlamydia. Of those who had ever self-reported a diagnosis, 80.0% and 29.0% of women and men, respectively, had seroconverted by age 38.

**Incidence rates and risk of chlamydia by age period and sexual behavior**

Incidence rates for were highest in the period from first coitus to age 26 for both women and men, 32.7 (27.0–39.5) and 18.4 (14.4–23.5) per 1,000 person-years, respectively (Table 1), then dropped significantly with increasing age (X² for trend tests both p<0.001).

A consistent pattern of increasing incidence with increasing numbers of sexual partners was seen for all age periods in both women and men. Incidence rates from first coitus to age 26 increased with decreasing age of first coitus, significantly so for men (p=0.003), but not women (p=0.063). There was no discernable trend of statistical association after age 26. For women who had same-sex sexual contact, the incidence was higher in each age period, significantly so from age 26–32 (p=0.047) and age 32–38 (p=0.050). However, for men who had same-sex contact the incidence was lower up to age 32, although not statistically significant. For women only, the rates were generally lower in those with medium or high educational attainment compared with those with low attainment, but this was only significant in the period from first coitus to age 26 (p=0.003).

Comparisons of the crude incidence rates by age period expressed as the IRR are shown in Table 2, together with the comparison by number of partners and any same-sex contact in each period, and education. Accounting for numbers of sexual partners, same-sex sexual contact and education had a marked effect on the age period IRR estimates. For
women, the adjusted IRR for 26–32 years increased from being significantly lower (0.45) than the baseline (first coitus to age 26 years) to no difference (1.04), and for 32–38 years from 0.17 to 0.53, the latter remaining significant. For men, with adjustment the IRRs changed from 0.69 to 1.04 for 26–32 years and from 0.38 to 0.81 for 32–38 years. Increasing numbers of sexual partners remained strongly associated with increasing rates (p<0.001) for both genders, with only a slight decrease in the adjusted IRRs. For women, rates remained significantly lower among those with higher education (p=0.015). For men, same-sex sexual contact became associated with a decrease in rates (p=0.036).

The effect of age of first coitus was investigated for the period from first coitus to age 26 years for women (Table 3). While the unadjusted IRRs were significantly elevated for first coitus at younger ages; however, this association disappeared after simultaneously considering other behavioral factors and education in the model.

Sensitivity analyses showed the interpretation of these incidence rates and risk analyses was not sensitive to the underlying assumption of infection occurring at the midpoint in the age period. If infection was assumed to occur at the end of the age period the patterns of association were the same, although the difference by age period in women was not significant after adjusting (data now shown). However, under this assumption the overall incidence rates, especially for women up to age 26, were slightly lower than when using the midpoint for the timing of infection.

**DISCUSSION**

In this birth cohort, evidence of infection with chlamydia, based on either self-reporting or serology, was common and occurred in a third of sexually experienced women by age 38. For men, the cumulative incidence was lower (a fifth), although not directly
comparable to the figure for women due to gender differences in the sensitivity of the assay. Incidence rates were highest up to age 26 years and dropped for both women and men in the subsequent age periods. Incidence rose with the number of sexual partners in all age periods, behavior that differed markedly with age. After simultaneously adjusting for age period and behavior, increasing risk with more partners remained highly significant. However, with adjustment, the age effect was greatly attenuated and no longer a significant factor for men, and for women from age 32 only. Higher education in women and same-sex contact in men were protective. Among women, there was no evidence that age of first coitus influenced risk of infection in the age period from first coitus to age 26 years after accounting for partner numbers.

**Strengths and weaknesses**

The Dunedin cohort study is unique in having been followed up to age 38 years with detailed questions on STIs and sexual behavior, as well as having serology available at three time points. Confidential computer-presented questions at each assessment, the trust built up with study members over a long period and the study's high retention of participants minimizes the likelihood of information and response bias. After exclusions for the current analysis, data for 80–90% of the surviving cohort was retained at each age period assessment; comparisons between those included with those excluded based on lack of sera did not indicate any introduction of a response bias. The use of a sensitive assay in women to detect past chlamydial infection reduces the under-estimation of the incidence of chlamydia in women that is inevitable with self-reports, as many infections remain undiagnosed. As serum specimens were correctly stored at -80°C, it is unlikely that the assay performance would have been compromised by antibody decay.
Weaknesses include the relatively small sample size which reduced the ability to investigate chlamydia risk and may have resulted in insufficient power to detect age-related risk. The exact age of self-reported diagnosis was not collected and there were no data from which these reports could be validated. It is unknown how likely participants were to have been tested for chlamydia and, therefore, self-reported a clinically diagnosed infection, and how changes in the likelihood of testing changed as the cohort has aged. Lack of sera from assessments before age 26 limited our ability to look at risk among younger women. Not all infections will be included via self-report or serology, as even in women the latter is around 80% sensitive. Lower assay sensitivity and probable differences in the likelihood of infection being diagnosed in men precludes direct comparison of incidence between men and women. Incidence will have been further under-estimated particularly from age 26 onwards as: 1) it is currently not possible to distinguish individuals who have had single versus multiple infections using serology and at least 20% of women are likely to have been re-infected at least once;\textsuperscript{4,13,14} and 2) those who had already seroconverted were not removed from the denominator after seroconverting, as they were still able to self-report diagnosis. A lack of sufficiently detailed data on condom use and of partners’ behavior prevented further investigation of these drivers of risk.

**Comparison with other studies**

Chlamydia incidence will be expected to vary by population and time, and be influenced by how incidence is determined. Repeat testing in samples have found incidence rates of 3.4 per 100 person-years in London tertiary education students, 4.4 and 4.9 in general practice populations in Australia and the UK, respectively, and 34 per 100 person-years in high-risk young women aged 14–17 years attending primary care in the US.\textsuperscript{4,15-17} By
modelling data from multiple sources, the annual incidence in UK women aged 16–24 years for 2001–05 was estimated to be 5.0 per 100 person-years (95% credible interval 3.5–7.1).\textsuperscript{18} Bayesian modelling of Australian testing and diagnosis data produced an estimated incidence of 2.7 per 100 person-years in women aged 15–24 years in 2001, increasing more than two-fold by 2013.\textsuperscript{19} In the age group 25–34 years, the estimates from this modelling for women were 1.1 and 1.7 per 100 person-years in 2001 and 2013, respectively. Our measured incidence in 1998/1999 of 3.3 per 100 person-years for women up to age 26 is slightly higher than the modelled Australian rates for 15–24 year-olds in 2001. Rates in the age period 26–32 years are very similar to Australian estimates for 25–34 years-olds. However, the incidence rate in this age period was probably underestimated in our study.

**Interpretation of the findings**

We have shown that modest incidence rates culminating in a high cumulative exposure to chlamydia is a reflection of the prolonged risk period due to on-going partner change; 70% of men and 54% of women reported multiple partners in the age period 26–32; as did 50% and 35% respectively when aged 32–38 years. As found in other cohort studies in the UK, US and Australia, the risk of incident chlamydia was strongly related to the number of sexual partners and age.\textsuperscript{15-17} In this study, after accounting for the differences in partner numbers by age, the relationship between chlamydia incidence and age was strongly attenuated. There was no evidence of a decline in risk with age until women were aged in their thirties, and no evidence for men. This gender difference in age-related risk is probably in part due to differences in sexual mixing patterns and the prevalence of chlamydia in partners.
A reduction in sexual risk taking among men who had sex with men was noted in the late 1980s in many countries, following the emergence of Human Immunodeficiency Virus. Available data from behavioural surveys in gay and bisexual men suggest these changes have been sustained in New Zealand,\(^\text{21}\) the protective effect of same-sex sexual contact for men in the Dunedin cohort is consistent with these survey findings. A protective effect for higher education has been found in other studies (for both genders), and may reflect both engagement with health services and differences in safe sex practices.\(^\text{20}\)

**Conclusions**

Evidence of chlamydia infection at least once by age 38 was common in this cohort of New Zealand born women and men, yet comparisons with studies in the UK, USA and Australia do not suggest our participants had an unusually high incidence of chlamydia. Our finding that a major determinant of risk is the number of sexual partners aligns with other studies. Furthermore, we showed that most of our observed decrease in incidence in the older age periods could be explained by fewer partners.

Our findings emphasize that chlamydia prevention strategies should be aimed at a wide age group of men and women whose behavior puts them at increased risk. Larger population-based incidence studies are needed to assess further risk for those aged in their mid-twenties and older accounting for behavior and to assess the performance of the Pgp3 assay for serologically determining incidence rates.

**REFERENCES**


15. Aghaizu A, Reid F, Kerry S, et al. Frequency and risk factors for incident and redetected Chlamydia trachomatis infection in sexually active, young, multi-ethnic


TABLES
Supplementary Table: Frequency of self-reported behaviours and missing information by number and proportion providing sera, by age period for women and men interviewed and eligible to be included in analyses based on self-reported information (had first coitus and reported partner numbers).

Table 1: Incidence rate of chlamydia (per 1000 person-years) by age period, sexual behavior and education for women and men.

Table 2: Poisson regression derived incident rate ratios for chlamydia by age period, number of partners, same-sex contact and education for women and men.

Table 3: Poisson regression derived incident rate ratios for chlamydia by age at first coitus, number of partners, same-sex contact and education, for women from first coitus–age 26.

FIGURES

Figure 1: Cohort retention and data collection at the age 26, 32 and 38 assessments.

Foot notes for Figure 1:

* At age 21 information sexual behavior and self-reported STIs were collected by interview, but no sera were available.

† Eligible sample for analysis were those who had reported first coitus, those who did not attend the assessment were assumed to have experienced coitus for the purpose of estimating the response rate.

‡ Considered sufficient if questions on partner numbers were answered.
Figure 2: Cumulative incidence of chlamydia by self-report, seroconversion, and combined evidence at each age period for women and men.

Footnote for Figure 2:

* At age 21 no serological data were available.