

Risk of pelvic inflammatory disease in relation to chlamydia and gonorrhoea testing,
repeat testing, and positivity: a population-based cohort study

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Key points: Gonorrhoea infection confers a substantially higher risk than chlamydia of hospitalisation or emergency department presentation for pelvic inflammatory disease. With emerging gonorrhoea antimicrobial resistance it is imperative that women in high prevalence areas receive timely and effective testing and treatment.

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Abstract

Background

There is uncertainty around whether the risks of pelvic inflammatory disease (PID) differ following *Chlamydia trachomatis* (chlamydia) and *Neisseria gonorrhoeae* (gonorrhoea) infection. We quantified the risk of PID associated with chlamydia and gonorrhoea infection and subsequent repeat infections in a whole-population cohort.

Methods

A cohort of 315,123 Western Australian women, born from 1974-1995, was probabilistically linked to chlamydia and gonorrhoea testing records and to hospitalisations and emergency department presentations for PID from 2002-2013. Time-updated survival analysis was used to investigate the association between chlamydia and gonorrhoea testing, and positivity, and risk of PID.

Results

Over 3,199,135 person-years, 120,748 women had pathology test records for both chlamydia and gonorrhoea, 10,745 chlamydia only, and 653 gonorrhoea only. Among those tested 16,778 (12.8%) had ≥ 1 positive chlamydia test, 3,195 (2.6%) ≥ 1 positive gonorrhoea test and 1,874 (1.5%) were positive for both. There were 4819 PID presentations (2222 hospitalisations, 2597 emergency presentations). Adjusting for age, Aboriginality, year of follow-up, health area, and socioeconomic status, compared to women 'negative for chlamydia and gonorrhoea' the relative risk (adjusted IRR) of PID was 4.29 (95%CI 3.66-5.03) in women who were 'both chlamydia and gonorrhoea positive', 4.54 (95%CI 3.87-5.33) in those only 'gonorrhoea positive', and 1.77 (95%CI 1.61-1.94) in those only 'chlamydia positive'.

Conclusion

Gonorrhoea infection conferred a substantially higher risk than chlamydia of hospitalisation or emergency department presentation for PID. The emergence of gonorrhoea antimicrobial resistance may have a serious impact on rates of PID and its associated reproductive health sequelae.

Introduction

Pelvic inflammatory disease (PID) is a common and potentially serious infection of the female reproductive organs. Approximately 4.1% of sexually active young women in the United States (US) report having been treated for PID in their life time[1]. If left untreated, PID can cause scarring and dysfunction of the genital tract, which may go on to cause ectopic pregnancy, chronic pelvic pain, and infertility[2-4]. PID has been commonly associated with the sexually transmitted infections *Chlamydia trachomatis* (chlamydia)[5-8] and *Neisseria gonorrhoea* (gonorrhoea)[9, 10], however other etiological agents such as *Mycoplasma genitalium*[10, 11], *Trichomonas vaginalis*[12], and organisms associated with bacterial vaginosis[13] have been reported in the literature.

Chlamydia and gonorrhoea are two of the most frequently reported sexually transmitted infections (STIs) globally[14]. While gonorrhoea notification rates are lower than those of chlamydia, gonorrhoea disproportionally affects discrete population groups. In the US in 2015 the rate of gonorrhoea in Blacks was 9.6 times the rate among Whites[15], while in Australia in 2015, the gonorrhoea notification rate in the Aboriginal and Torres Strait Islander population (hereafter referred to as Aboriginal) was 10 times that of the non-Aboriginal population, increasing to 72 times higher in remote areas[16]. Such disparities may be due to reduced access to health services and differences in testing patterns, as well as in sexual risk behaviours[17, 18]. There is also evidence of an emerging gonorrhoea epidemic among heterosexuals in some urban areas of Australia[19] although the reason underlying this increase is unknown.

Studies have suggested that PID following gonorrhoea infection may be more clinically severe[10, 20, 21]. With concerns over the emerging antimicrobial resistance of gonorrhoea[22] and a potential epidemic in some heterosexual populations[19], the role gonorrhoea plays in the development of PID is of increasing importance. Our aim was

therefore to compare the risks of PID associated with single and repeated chlamydia and gonorrhoea infections in a large cohort of reproductive age women.

Methods

Study population and linkage

This study was conducted using population-based record linkage in the Australian state of Western Australia (WA) (population 2.6 million). WA has Australia's oldest and most comprehensive record linkage system[23]. It maintains probabilistic linkages between core health datasets using personal identifiers such as name, date of birth, address, and sex. Linkage accuracy using this process is high with an error rate estimated at 0.11%[24].

A cohort comprising women of reproductive age residing in WA was constructed using two datasets; the WA Birth Registrations Data Collection, which contains a record of all children born and registered in WA from 1974 onwards, and the 2014 WA Electoral Roll. Registration on the electoral roll is compulsory in Australia. Eligible women were those with either a birth registration, or a record on the Electoral Roll with year of birth between 1974-1995.

The cohort was probabilistically linked to the Hospital Morbidity Data System, the Emergency Department Data Collection, laboratory chlamydia and gonorrhoea test records and death registrations.

Hospitalisation and emergency department presentation for PID

The Hospital Morbidity Data System is a statutory data collection including all hospitals in WA (public and private). It comprises inpatient hospital discharge (separation) records dating back to 1970, with every record assigned a principal diagnosis code and up to 20 additional diagnosis fields. The Emergency Department Data Collection contains data on emergency department presentations in WA's public hospitals as well as private hospitals under contract with the WA government from 2002 onwards. Women were classified as having a diagnosis of PID if they had a linked hospital admission or emergency department presentation record where the primary ICD-10-AM diagnosis was any of N70-73, N74.1-N74.8, or A18.1, A51.4, A52.7, A54.2 A56.1, with an additional diagnosis of N74.1-N74.8. If a hospitalisation for PID

occurred within seven days of the emergency department presentation then the diagnosis was classed as a hospitalisation and the hospitalisation date was selected. In all other cases the first PID presentation was selected.

Chlamydia and gonorrhoea testing

Records of all chlamydia and gonorrhoea nucleic acid amplification tests (NAAT) conducted between January 2001 and December 2013 at two large WA pathology laboratories were also linked to the cohort. The date of specimen collection, and test result (positive, negative, or equivocal/undetermined) were supplied to the research team. Multiple tests for the same infection on the same referral date were counted as one test and considered positive if any of the results were positive. Tests were then limited to one test per infection within a 30 day period.

Analysis

Time-updated survival analysis was used to investigate the association between chlamydia and gonorrhoea diagnoses and risk of emergency department presentation or hospitalisation for PID. For the main analysis women were classified into five categories:

1. Negative for chlamydia and gonorrhoea: women tested negative for both chlamydia and gonorrhoea, women tested negative for chlamydia and no linked record of a gonorrhoea test and women tested negative for gonorrhoea and no linked record of a chlamydia test;
2. Chlamydia positive: women with at least one positive chlamydia test and either no gonorrhoea test or a negative gonorrhoea test;
3. Gonorrhoea positive: women with at least one positive gonorrhoea test and either no chlamydia test or a negative chlamydia test;
4. Both chlamydia and gonorrhoea positive: women with at least one positive chlamydia test and at least one positive gonorrhoea test at some time during the study (not necessarily on the same date); and

5. No test record: women with no linked record of chlamydia or gonorrhoea test at either of the two laboratories

All women were initially classified as 'no test record' and contributed person-time in that category until such time as their first NAAT record. They then moved into another category and contributed person-time to that category depending on the test result. Only tests after the women's 15th birthday were included[25].

To investigate the association of repeat testing with PID, women were re-classified into eight categories according to the number of positive and negative tests they had during follow-up (1 negative test, 2 tests all negative, ≥ 3 tests all negative, 1 chlamydia positive test, ≥ 2 chlamydia positive tests, 1 gonorrhoea positive test, ≥ 2 gonorrhoea positive tests and no test record). Women both chlamydia and gonorrhoea positive were classified according to how many positive gonorrhoea tests they had.

Women were eligible for inclusion in analyses from their 15th birthday or 1st January 2002 (the first date Emergency Department Data Collection records were available), whichever was later. All women were followed until either a diagnosis of PID, death, or 31st December 2013 (the last date of complete records).

The incidence of PID was calculated in the categories outlined above. Poisson regression using generalized estimating equations was used to investigate the association with chlamydia and gonorrhoea diagnoses and risk of PID. In addition to chlamydia and gonorrhoea diagnoses, age (continuous), and year of follow-up (continuous) were included as time-updated variables. Models were also adjusted for Aboriginality, health area and socio-economic status (based on the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) 2011[26]). Aboriginality was determined from the Indigenous Status Flag variable[27]. Health area (metropolitan, rural, and remote) was determined through residential postcode information on their electoral roll record or most recent linked record. Women residing outside of WA or with no postcode information were excluded.

Subgroup analysis examined if chlamydia and gonorrhoea testing and positivity and risk of PID differed between Aboriginal and non-Aboriginal women, or by: attained age (15-24 versus 25+ years), socioeconomic group (low versus high), health area (metropolitan versus regional/remote), and year of testing (2002-2007 versus 2008-2013).

All analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina).

This study was approved by the Government of Western Australia Department of Health HREC (Ref #2012/73) and the Western Australian Aboriginal Health Ethics Committee (Ref 470).

Results

A total of 315,123 women born between 1974-1995, were included and followed for a total of 3,199,135 person-years (mean 10 years(SD 2.8)) (Figure 1). The demographic and testing characteristics of the cohort are summarized in Table 1. The mean age at entry was 18 years(SD 4.3), 14,521(4.6%) women were Aboriginal, and 67,613(21.5%) resided in rural or remote areas.

During follow-up 38.3%(120,748) had at least one linked test record for both chlamydia and gonorrhoea, 3.4%(10,745) had at least one linked chlamydia test but no gonorrhoea test and 0.2%(653) had at least one gonorrhoea test but no chlamydia test. Among those tested 16,778(12.8%) had at least one positive chlamydia test, 3,195(2.6%) had a least one positive gonorrhoea test and 1,874(1.6%) were positive for both chlamydia and gonorrhoea of which 1209(64.6%) tested positive for both concurrently (on the same day).

There were 4819 women diagnosed with PID during our study period (2222 hospitalisations and 2597 emergency department presentations); PID incidence 1.5(95%CI 1.5-1.6) per 1000 person-years. Among these women, 845(18%) had their first chlamydia and/or gonorrhoea test, and 381(8%) were positive (189 chlamydia, 141 gonorrhoea, and 51 both) on the same day as their PID diagnosis.

PID incidence per 1000 person-years was highest in those who were both 'chlamydia and gonorrhoea positive' (IR 24.4, 95%CI 21.3-27.5) and those only 'gonorrhoea positive' (23.9, 95%CI 20.6-27.2) followed by those only 'chlamydia positive' (7.6, 95%CI 7.0-8.2) and then those 'negative for chlamydia and gonorrhoea' (3.8, 95%CI 3.7-4.0). The incidence of PID was lowest among women with no record of a chlamydia or gonorrhoea test (0.5, 95%CI 0.5-0.6); Figure 2. Of women only 'gonorrhoea positive' and those both 'chlamydia and gonorrhoea positive' the proportion of PID presentations resulting in hospitalisation was 85% and 87% respectively compared to 43% in women only 'chlamydia positive' ($p < 0.0001$). Among women hospitalised for PID, those with positive tests for either chlamydia or

gonorrhoea spent a median of 2 days in hospital (IQR 1-3) compared to women 'never tested' and women 'negative for chlamydia and gonorrhoea' who spent a median of 1 day in hospital (IQR 0-2, $p < 0.0001$).

After adjusting for age, Aboriginality, year of follow-up, health area, and socioeconomic status the risk of PID compared to women 'negative for chlamydia and gonorrhoea' was over four times higher in women who were 'both chlamydia and gonorrhoea positive' (adjusted IRR 4.29, 95%CI 3.66-5.02, $p < 0.0001$) and those only 'gonorrhoea positive' (aIRR 4.54, 95%CI 3.87-5.33, $p < 0.0001$) (Table 2). Women who were only 'chlamydia positive' had a 1.77 times (95%CI 1.61-1.94, $p < 0.0001$) higher risk of PID compared to women 'negative for chlamydia and gonorrhoea'.

Table 2 shows there was also an increasing risk of PID with more testing. Compared to those with only one negative test, those with two negative tests and those with three or more negative tests were more likely to have PID (p -trend < 0.0001). Results also suggest a higher risk of PID in women who had ≥ 2 positive chlamydia tests compared to one positive chlamydia test and women who had ≥ 2 positive gonorrhoea tests compared to one positive gonorrhoea test although tests for statistical difference were non-significant ($p = 0.26$ and $p = 0.06$ respectively).

The rate of PID in Aboriginal women was double that of their non-Aboriginal counterparts (aIRR 2.00, 95%CI 1.82-2.20, $p < 0.0001$). Figure 3 shows that even among those women who were chlamydia and gonorrhoea negative, the incidence rates of PID in Aboriginal women were consistently higher compared to non-Aboriginal women. Figure 3 also shows that the relatively higher proportion of PID hospital admissions compared to emergency department presentations in 'gonorrhoea positive' women was observed in both Aboriginal and non-Aboriginal women. Despite differences in PID rates between Aboriginal and non-Aboriginal women, the relative risks of PID among those with positive gonorrhoea tests were consistently higher than among those with positive chlamydia tests (compared to women

'negative for chlamydia and gonorrhoea') for both Aboriginal and non-Aboriginal women (Supplementary Table 1).

Additional analyses stratified by attained age, socioeconomic group, health area, and time period during which tests were conducted, were also generally consistent (Supplementary Table 1).

Discussion

This large population-based study found that compared to women who had always tested negative, the risk of emergency department presentation or hospital admission for PID was over four times higher in women who had tested positive for gonorrhoea (either alone or with a coexisting chlamydia diagnosis) and 1.8 times higher in women positive only for chlamydia. Repeated infections appeared to further increase the risk of PID as did a history of repeat but negative tests. The lowest rate of PID was in women who had no test record for chlamydia or gonorrhoea.

Several European[5, 7, 28] and one Canadian study[6] have used similar methods to estimate the association between chlamydia infection and hospital presentations for PID with relative risk estimates of between 1.3 and 1.7. Our study of Australian women estimated the risk of PID to be around 1.8 times higher comparing chlamydia-only positive women to women negative for both chlamydia and gonorrhoea, a comparable yet slightly higher estimate. These earlier studies found repeat chlamydia diagnoses to be associated with an increased risk of PID compared to only one positive diagnosis[5, 6, 29].

Our study adds to these earlier findings that only investigated chlamydia infections. We were able to examine the association of gonorrhoea with PID and compare the risks to that of chlamydia. We demonstrated a substantially greater risk of PID with gonorrhoea. However, the effect was not additive and women positive for both chlamydia and gonorrhoea had a similar sized risk to those positive only for gonorrhoea. Also our results suggest that gonorrhoea-related PID was more clinically severe than that from chlamydia with a higher proportion of hospitalisations relative to emergency department presentations. To our knowledge, this is the first and largest cohort analysis using both testing and positivity data to quantify and compare the risks of gonorrhoea and chlamydia on incidence of PID hospitalisation and emergency department presentations. Two previous Australian studies, one using positive STI notifications[20], and a clinic based study[30] have reported a higher

risk of PID with gonorrhoea infection. Earlier studies have also suggested that gonococcal PID is more likely to be symptomatic than PID arising from a chlamydia infection[10]. However, it is worth noting that chlamydia infections are much more common than gonorrhoea[14] and therefore the population attributable risk of PID for gonorrhoea may still be lower than that for chlamydia.

An increase in the risk of PID was also observed in women with increasing numbers of negative chlamydia and gonorrhoea tests, a finding which to our knowledge has not previously been reported. STI screening guidelines recommend regular testing of young sexually active women at higher risk of STIs. Recommendations include those <30 years and Aboriginal populations in Australia and those <25 years in U.S.[25, 31]. We have previously demonstrated in this cohort significantly higher testing rates among both younger women and Aboriginals[32]. As by definition, this population recommended for testing would also be at higher risk of other infections such as *Mycoplasma genitalium* and Trichomoniasis, the higher PID risk observed associated with greater testing may reflect PID caused by a different etiological agent[33]. Therefore our observation of increased risk with increased negative tests may simply reflect this practice of testing higher risk women. This is supported by the finding that women with no test records for chlamydia or gonorrhoea had the lowest risk of PID and underlies the importance of considering STI testing history in epidemiological studies quantifying risks associated with chlamydia and gonorrhoea.

In Australia, gonorrhoea disproportionately affects Aboriginal people[16]. We estimated the absolute risk of PID hospitalisations and emergency department presentations in Aboriginal women to be almost double that of non-Aboriginal women, however, the relative risks of PID associated with chlamydia and gonorrhoea positivity were similar between Aboriginal and non-Aboriginal women. Possible reasons for the higher rate of PID hospitalisations and emergency department presentations in Aboriginal women could be attributed to poor diagnosis and inadequate treatment of PID in some primary care settings[34], a higher prevalence of other infections or risk factors associated with PID such as *Mycoplasma*

genitalium[17] or smoking[21] for which we could not account, or it may be that non-Aboriginal women are more likely to present with PID to other health care settings.

PID can be difficult to diagnose as symptoms are often subtle and non-specific[35]. Knowledge of a recent STI diagnosis may lead to detection bias for PID and this could result in an overestimate of effect sizes. However random misclassification of PID hospitalisations[36] could lead to underestimates. Further, mild to moderate PID is usually managed in the primary care setting[37] and therefore only more serious clinical cases, those with undiagnosed or inadequately treated PID[34] would likely present at the emergency department, with only the most severe hospitalised. Our analyses lacked primary care data; however, when we stratified analyses by factors affecting primary care access such as Aboriginality, socioeconomic status and region of residence, our results were consistent. Also some women in our cohort may have moved out of state however we know from census data this was relatively small in WA[38]. Finally our linked laboratory data did not capture all tests conducted in the state with previous analysis suggesting coverage of approximately 50% of all chlamydia and 80% of all gonorrhoea tests conducted in WA[32]. However our main comparisons are between women tested positive for chlamydia or gonorrhoea to those tested negative.

In Australia, gonorrhoea antimicrobial resistance has been shown to vary substantially between regions. While national surveillance data show that overall from 2011-2015 gonorrhoea antimicrobial resistance (measured as a decreased susceptibility to ceftriaxone (MIC 0.06–0.125 mg/L), has fluctuated between 1.8% and 8.8%[39], in WA over the same period, susceptibility to ceftriaxone ranged from 0.7% to 3.0%. Furthermore in remote WA Aboriginal communities, where gonorrhoea is endemic, penicillins continue to remain the first-line treatment as <5% of gonorrhoea isolates have been found to be penicillinase producing[40]. Despite this, as gonorrhoea infections in Australia are dominated by relatively few strains there is a significant potential for incursion of antibiotic resistant gonorrhoea into these communities[19]. While chlamydia infections are much more common than

gonorrhoea[14] our findings suggest that gonorrhoea infections confer a substantially higher risk of hospitalisation or emergency department presentation for PID. This, combined with concerns around increasing antimicrobial resistance and the potential for rapid spread, make it imperative that individuals in areas with high gonorrhoea prevalence are tested, diagnosed, and treated in a timely and effective manner in an effort to reduce both the risk of onwards transmission and the risk of PID and its serious health sequelae.

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Conflict of Interest

The authors have no conflicts of interest to declare

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References

1. National Centre for HIV/AIDS Viral Hepatitis STD and TB prevention, Division of STD Prevention. Pelvic Inflammatory Disease (PID): CDC Fact Sheet. Available at: <http://www.cdc.gov/std/pid/stdfact-pid-detailed.htm>. Accessed 10/11/2016.
2. Westrom L, Joesoef R, Reynolds G, Hagdu A, Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sexually transmitted diseases* **1992**; 19(4): 185-92.
3. Gray-Swain MR, Peipert JF. Pelvic inflammatory disease in adolescents. *Current opinion in obstetrics & gynecology* **2006**; 18(5): 503-10.
4. Wiesenfeld HC, Hillier SL, Meyn LA, Amortegui AJ, Sweet RL. Subclinical pelvic inflammatory disease and infertility. *Obstetrics and gynecology* **2012**; 120(1): 37-43.
5. Davies B, Turner KM, Frolund M, et al. Risk of reproductive complications following chlamydia testing: a population-based retrospective cohort study in Denmark. *The Lancet Infectious diseases* **2016**.
6. Davies B, Turner K, Ward H. Risk of pelvic inflammatory disease after Chlamydia infection in a prospective cohort of sex workers. *Sexually transmitted diseases* **2013**; 40(3): 230-4.
7. Low N, Egger M, Sterne JA, et al. Incidence of severe reproductive tract complications associated with diagnosed genital chlamydial infection: the Uppsala Women's Cohort Study. *Sexually transmitted infections* **2006**; 82(3): 212-8.
8. Ness RB, Smith KJ, Chang CC, Schisterman EF, Bass DC. Prediction of pelvic inflammatory disease among young, single, sexually active women. *Sexually transmitted diseases* **2006**; 33(3): 137-42.
9. Moore MS, Golden MR, Scholes D, Kerani RP. Assessing Trends in Chlamydia Positivity and Gonorrhea Incidence and Their Associations With the Incidence of Pelvic Inflammatory Disease and Ectopic Pregnancy in Washington State, 1988-2010. *Sexually transmitted diseases* **2016**; 43(1): 2-8.
10. Short VL, Totten PA, Ness RB, Astete SG, Kelsey SF, Haggerty CL. Clinical presentation of Mycoplasma genitalium Infection versus Neisseria gonorrhoeae infection among women with pelvic inflammatory disease. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **2009**; 48(1): 41-7.
11. Haggerty CL, Taylor BD. Mycoplasma genitalium: an emerging cause of pelvic inflammatory disease. *Infectious diseases in obstetrics and gynecology* **2011**; 2011: 959816.
12. Cherpes TL, Wiesenfeld HC, Melan MA, et al. The associations between pelvic inflammatory disease, Trichomonas vaginalis infection, and positive herpes simplex virus type 2 serology. *Sexually transmitted diseases* **2006**; 33(12): 747-52.
13. Ness RB, Kip KE, Hillier SL, et al. A cluster analysis of bacterial vaginosis-associated microflora and pelvic inflammatory disease. *American journal of epidemiology* **2005**; 162(6): 585-90.
14. World Health Organisation. Sexually transmitted infections (STIs); Fact sheet. Available at: <http://www.who.int/mediacentre/factsheets/fs110/en/>. Accessed 7/11/2016.
15. Centres for Disease Control and Prevention. Sexually Transmitted Diseases Surveillance 2015. Atlanta: U.S. Department of Health and human Services, **2016**.
16. The Kirby Institute. Bloodborne viral and sexually transmitted infections in Aboriginal and Torres Strait Islander people: Surveillance and Evaluation Report 2016: UNSW Australia, **2016**.

17. Graham S, Guy RJ, Donovan B, et al. Epidemiology of chlamydia and gonorrhoea among Indigenous and non-Indigenous Australians, 2000-2009. *The Medical journal of Australia* **2012**; 197(11): 642-6.
18. Newman LM, Berman SM. Epidemiology of STD disparities in African American communities. *Sexually transmitted diseases* **2008**; 35(12 Suppl): S4-12.
19. Trembizki E, Wand H, Donovan B, et al. The Molecular Epidemiology and Antimicrobial Resistance of *Neisseria gonorrhoeae* in Australia: A Nationwide Cross-Sectional Study, 2012. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **2016**; 63(12): 1591-8.
20. Reekie J, Donovan B, Guy R, et al. Hospitalisations for pelvic inflammatory disease temporally related to a diagnosis of Chlamydia or gonorrhoea: a retrospective cohort study. *PLoS one* **2014**; 9(4): e94361.
21. Li M, McDermott R. Smoking, poor nutrition, and sexually transmitted infections associated with pelvic inflammatory disease in remote North Queensland Indigenous communities, 1998-2005. *BMC women's health* **2015**; 15: 31.
22. Kirkcaldy RD, Harvey A, Papp JR, et al. *Neisseria gonorrhoeae* Antimicrobial Susceptibility Surveillance - The Gonococcal Isolate Surveillance Project, 27 Sites, United States, 2014. *MMWR Surveill Summ* **2016**; 65(7): 1-19.
23. Government of Western Australia Department of Health. Data Linkage Western Australia. Available at: <http://www.datalinkage-wa.org.au/>. Accessed 11 April 2016.
24. Holman CD, Bass AJ, Rouse IL, Hobbs MS. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Australian and New Zealand journal of public health* **1999**; 23(5): 453-9.
25. Royal Australian College of General Practitioners. Communicable diseases, STIs. Guidelines for preventative activities in general practice, 8th edition, East Melbourne RACGP, **2016**.
26. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA) 2011: Technical Paper, **2011** 28/03/2013.
27. Christensen D, Davis G, Draper G, et al. Evidence for the use of an algorithm in resolving inconsistent and missing Indigenous status in administrative data collections. *Aust J Soc Issues* **2014**; 49(4): 423-43.
28. Bakken IJ, Ghaderi S. Incidence of pelvic inflammatory disease in a large cohort of women tested for *Chlamydia trachomatis*: a historical follow-up study. *BMC infectious diseases* **2009**; 9: 130.
29. Hillis SD, Owens LM, Marchbanks PA, Amsterdam LF, Mac Kenzie WR. Recurrent chlamydial infections increase the risks of hospitalization for ectopic pregnancy and pelvic inflammatory disease. *American journal of obstetrics and gynecology* **1997**; 176(1 Pt 1): 103-7.
30. Goller JL, De Livera AM, Fairley CK, et al. Population attributable fraction of pelvic inflammatory disease associated with chlamydia and gonorrhoea: a cross-sectional analysis of Australian sexual health clinic data. *Sexually transmitted infections* **2016**.
31. Workowski KA, Bolan GA, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* **2015**; 64(RR-03): 1-137.
32. Reekie J, Donovan B, Guy R, et al. Trends in chlamydia and gonorrhoea testing and positivity in Western Australian Aboriginal and non-Aboriginal women 2001-2013: a population-based cohort study. *Sexual health* **2017**.
33. Lis R, Rowhani-Rahbar A, Manhart LE. *Mycoplasma genitalium* infection and female reproductive tract disease: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **2015**; 61(3): 418-26.
34. Silver BJ, Knox J, Smith KS, et al. Frequent occurrence of undiagnosed pelvic inflammatory disease in remote communities of central Australia. *The Medical journal of Australia* **2012**; 197(11): 647-51.

35. Soper DE. Pelvic inflammatory disease. *Obstetrics and gynecology* **2010**; 116(2 Pt 1): 419-28.
36. Scholes D, Satterwhite CL, Yu O, Fine D, Weinstock H, Berman S. Long-term trends in *Chlamydia trachomatis* infections and related outcomes in a U.S. managed care population. *Sexually transmitted diseases* **2012**; 39(2): 81-8.
37. Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. *American journal of obstetrics and gynecology* **2002**; 186(5): 929-37.
38. Australian Bureau of Statistics. 3105.0.65.001 - Australian Historical Population Statistics, 2014. **2014**.
39. Lahra MM, Enriques RP, Network. NN. Australian Gonococcal Surveillance Programme Annual Report, 2015, **2015**.
40. Speers DJ, Fisk RE, Goire N, Mak DB. Non-culture *Neisseria gonorrhoeae* molecular penicillinase production surveillance demonstrates the long-term success of empirical dual therapy and informs gonorrhoea management guidelines in a highly endemic setting. *The Journal of antimicrobial chemotherapy* **2014**; 69(5): 1243-7.

Table 1 Demographic characteristics and STI testing patterns of cohort

		N (% of total)
Total		315123 (100)
Year of birth	1974-1979	85172 (27.0)
	1980-1984	72698 (23.1)
	1985-1989	73971 (23.5)
	1990-1995	83282 (26.4)
Aboriginal	No	300602 (95.4)
	Yes	14521 (4.6)
Area of residence	Metropolitan	247510 (78.5)
	Rural	35827 (11.4)
	Remote	31786 (10.1)
Socioeconomic status	Lower	157116 (49.9)
	Higher	158007 (50.1)
STI Nucleic acid testing	Chlamydia and gonorrhoea	120748 (38.3)
	Chlamydia only	10745 (3.4)
	Gonorrhoea only	653 (0.2)
	No test record	182977 (58.1)
		N (% of those tested)
STI test positivity	Chlamydia and gonorrhoea	1874 (1.6)
	Chlamydia only	14904 (11.3)
	Gonorrhoea only	1321 (1.1)

Table 2 Association between chlamydia and gonorrhoea testing and risk of PID among women of reproductive age

Testing	PID	PYFU	Age adjusted		Fully adjusted*	
			IRR (95%CI)	p-value	IRR (95%CI)	p-value
Negative for chlamydia and gonorrhoea	2496	655709	1.00 (ref)		1.00 (ref)	
Chlamydia positive	573	75508	1.81 (1.65-1.99)	<.0001	1.77 (1.61-1.94)	<.0001
Gonorrhoea positive	201	8422	5.88 (5.05-6.84)	<.0001	4.54 (3.87-5.33)	<.0001
Chlamydia and gonorrhoea positive	238	9762	5.76 (5.01-6.62)	<.0001	4.29 (3.66-5.02)	<.0001
No test record	1311	2449733	0.12 (0.11-0.13)	<.0001	0.12 (0.11-0.13)	<.0001
	PID	PYFU	Age adjusted		Fully adjusted*	
			IRR (95%CI)	p-value	IRR (95%CI)	p-value
1 negative test	1274	403724	1.00 (ref)		1.00 (ref)	
2 tests all negative	600	142769	1.34 (1.24-1.51)	<.0001	1.40 (1.27-1.54)	<.0001
≥ 3 tests all negative	622	109217	1.90 (1.72-2.09)	<.0001	1.93 (1.75-2.14)	<.0001
1 chlamydia positive test~	487	65606	2.16 (1.95-2.40)	<.0001	2.17 (1.95-2.42)	<.0001
≥ 2 chlamydia positive tests~	86	9902	2.49 (2.00-3.11)	<.0001	2.50 (2.01-3.13)	<.0001
1 gonorrhoea positive test ⁺	316	13682	6.74 (5.92-7.68)	<.0001	5.52 (4.78-6.37)	<.0001
≥ 2 gonorrhoea positive tests ⁺	123	4502	8.12 (6.69-9.86)	<.0001	7.12 (5.75-8.81)	<.0001
No test record	1311	2449733	0.15 (0.14-0.16)	<.0001	0.14 (0.13-0.15)	<.0001

* fully adjusted model included age, Aboriginality, year of follow-up, health area, socio-economic status

~ included 'chlamydia positive only' women who were either negative for gonorrhoea or never tested for gonorrhoea

⁺ included 'gonorrhoea positive only' and 'both chlamydia and gonorrhoea positive' women

Figure 1 Formation of the cohort through data linkage

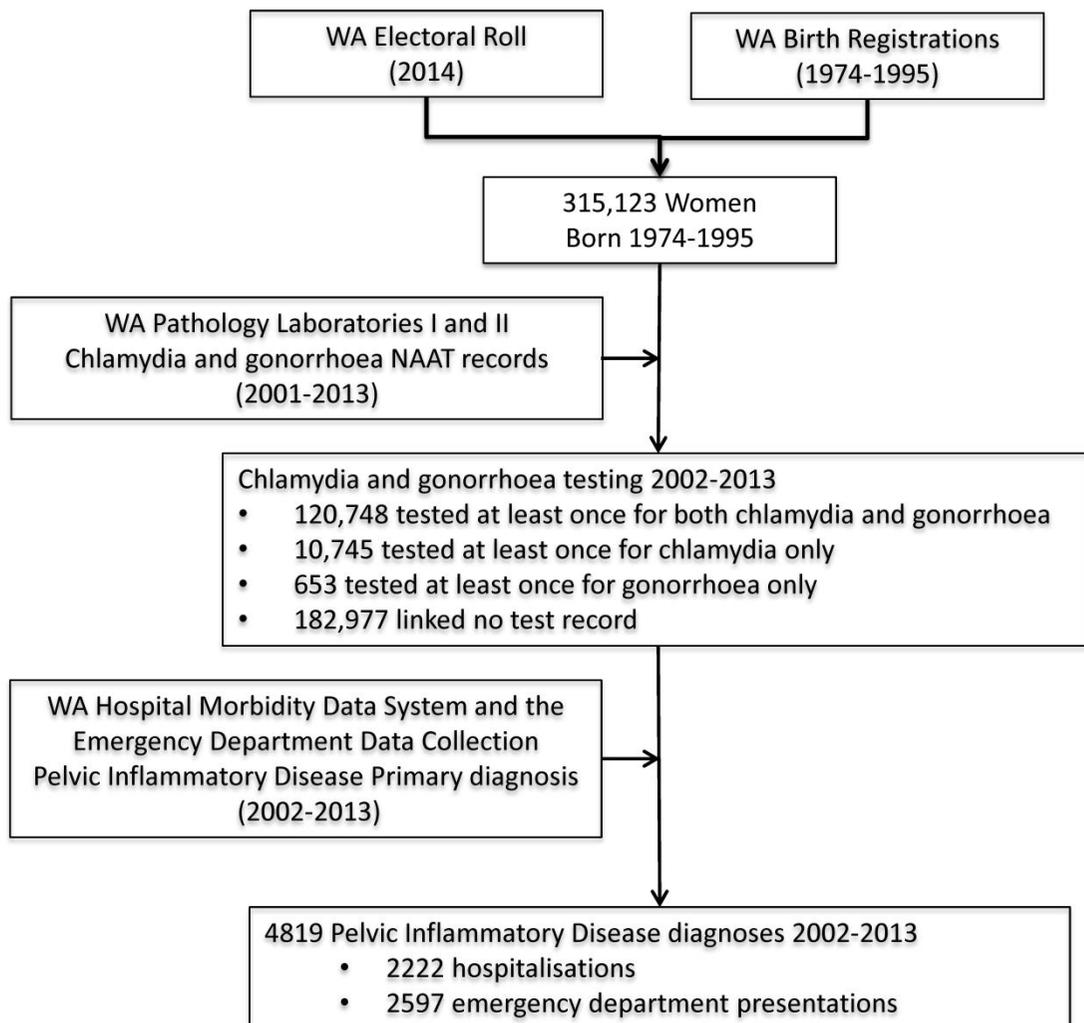


Figure 2 Crude incidence rate of PID by chlamydia and gonorrhoea testing and positivity

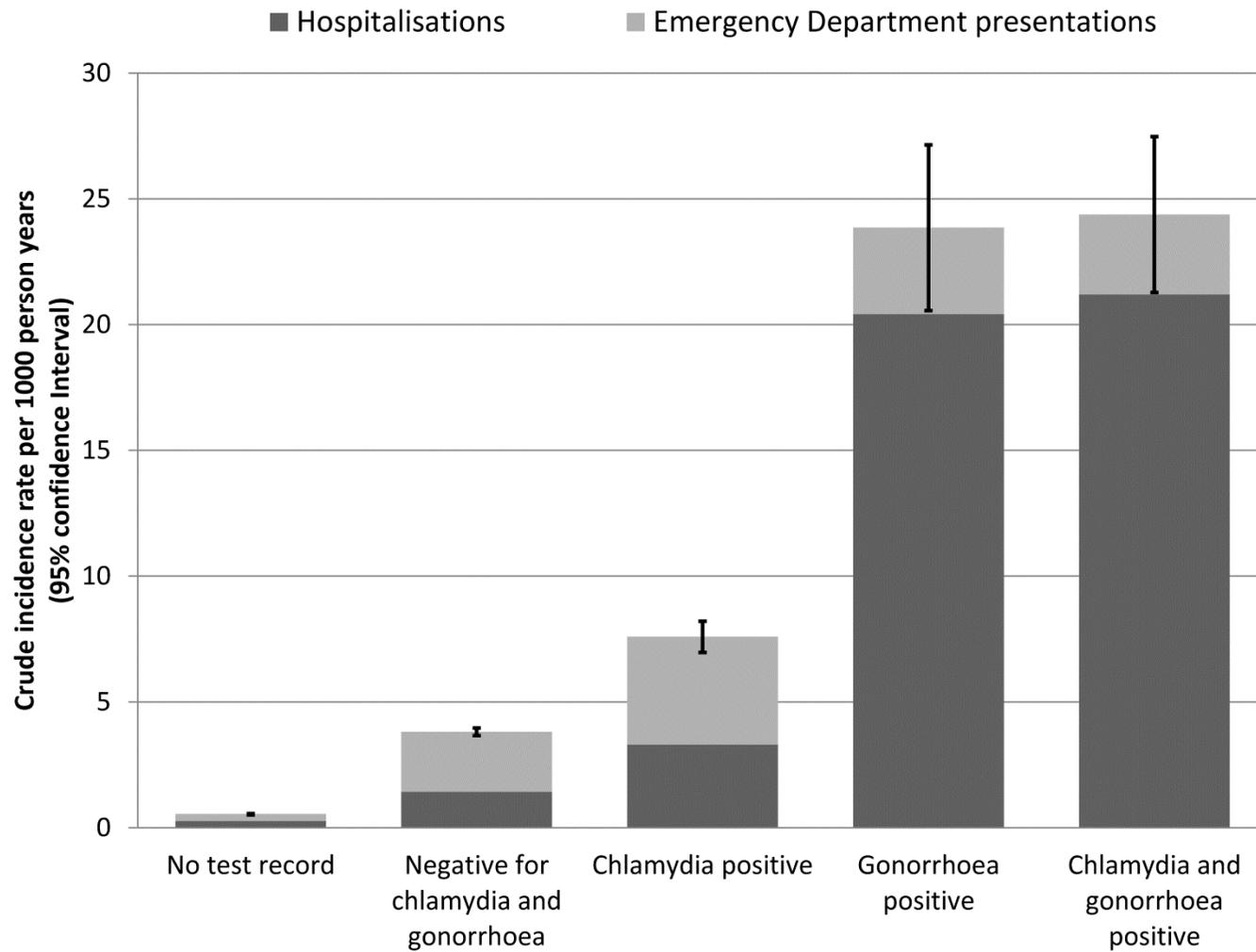
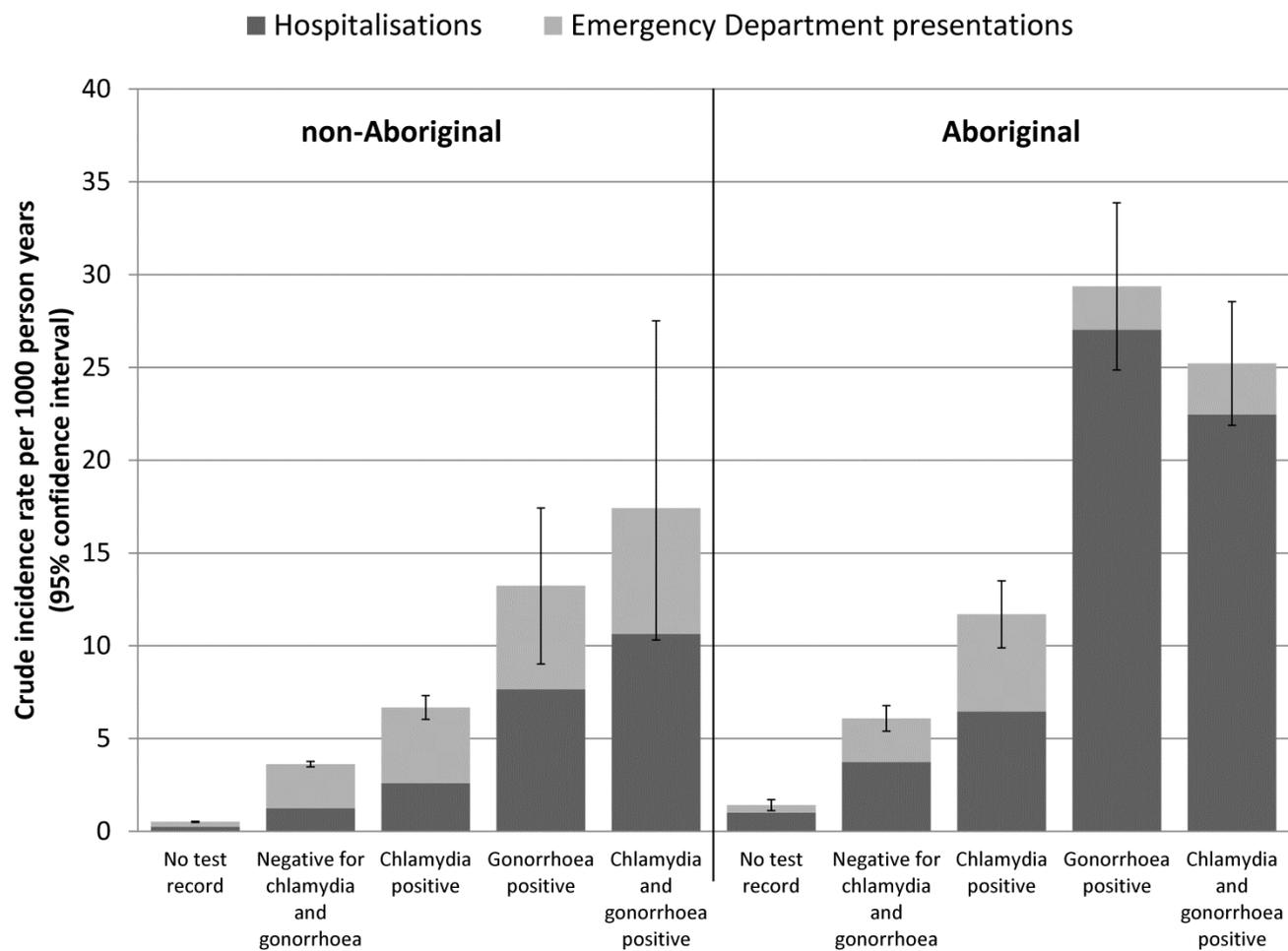


Figure 3 Crude incidence rate of PID by chlamydia and gonorrhoea testing and positivity, stratified by Aboriginality



Supplementary table

Table 2 Association between chlamydia and gonorrhoea testing and risk of PID, stratified by subgroup

Aboriginality	Fully-adjusted IRR (95%CI)	
	Non-Aboriginal	Aboriginal
Negative for chlamydia and gonorrhoea	1.00	1.00
Chlamydia positive	1.77 (1.59-1.97)	1.87 (1.54-2.28)
Gonorrhoea positive	3.39 (2.43-4.73)	5.20 (4.25-6.36)
Chlamydia and gonorrhoea positive	4.77 (2.94-7.76)	4.56 (3.80-5.47)
No test record	0.12 (0.11-0.13)	0.15 (0.12-0.20)

Age group	Fully-adjusted IRR (95%CI)	
	15-24 years	≥25 years
Negative for chlamydia and gonorrhoea	1.00	1.00
Chlamydia positive	1.84 (1.65-2.06)	1.46 (1.23-1.4)
Gonorrhoea positive	5.24 (4.29-6.39)	3.46 (2.64-4.53)
Chlamydia and gonorrhoea positive	4.94 (4.09-5.96)	3.00 (2.24-4.02)
No test record	0.07 (0.06-0.08)	0.20 (0.18-0.22)

Region	Fully-adjusted IRR (95%CI)	
	Metro	Rural/remote
Negative for chlamydia and gonorrhoea	1.00	1.00
Chlamydia positive	1.44 (1.21-1.71)	1.65 (1.38-1.98)
Gonorrhoea positive	3.06 (2.34-4.02)	5.15 (4.18-6.34)
Chlamydia and gonorrhoea positive	2.54 (1.90-3.39)	4.52 (3.73-5.48)
No test record	0.20 (0.18-0.22)	0.13 (0.11-0.15)

Year of follow-up	Fully-adjusted IRR (95%CI)	
	2002-2007	2008-2013
Negative for chlamydia and gonorrhoea	1.00	1.00
Chlamydia positive	1.95 (1.64-2.31)	1.69 (1.51-1.88)
Gonorrhoea positive	5.03 (3.99-6.34)	4.21 (3.39-5.22)
Chlamydia and gonorrhoea positive	5.25 (4.13-6.67)	3.85 (3.14-4.72)
No test record	0.12 (0.11-0.13)	0.12 (0.11-0.13)

Socio-economic status (SES)	Fully-adjusted IRR (95%CI)	
	Lower SES	Higher SES
Negative for chlamydia and gonorrhoea	1.00	1.00
Chlamydia positive	1.82 (1.63-2.04)	1.67 (1.42-1.97)
Gonorrhoea positive	4.91 (4.12-5.86)	3.60 (2.39-5.42)
Chlamydia and gonorrhoea positive	4.66 (3.92-5.52)	3.14 (1.99-4.96)
No test record	0.12 (0.11-0.13)	0.12 (0.11-0.14)

* fully adjusted model included age, Aboriginality, year of follow-up, health area, socio-economic status

