New Zealand Guideline for the Management of Gonorrhoea, 2014, and Response to the Threat of Antimicrobial Resistance

Gonorrhoea Guideline Writing Group on behalf of the New Zealand Sexual Health Society

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Glossary of abbreviations

BASHH	British Association for Sexual Health and HIV
CDC	Centers for Disease Control and Prevention
CLSI	Clinical Laboratory Standards Institute
DGI	disseminated gonococcal infection
DHB	District Health Board
DSAC	Doctors for Sexual Abuse Care
DTT	dithiothreitol
EQAP	external quality-assurance programme
ESR	Institute of Environmental Science and Research
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FVU	first-void urine
GASP	Gonococcal Antimicrobial Surveillance Programme
GRASP	Gonococcal Resistance to Antimicrobials Surveillance Programme
нιν	human immunodeficiency virus
НРА	Health Protection Agency
IM	intramuscularly
IV	intravenously
MIC	minimum inhibitory concentration
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NG-MAST	N. gonorrhoeae multi-antigen sequence typing
NPAAC	National Pathology Accreditation Advisory Council
NPV	negative predictive value
NZRM	New Zealand Reference Culture Collection, Medical Section
NZSHS	New Zealand Sexual Health Society
PCR	polymerase chain reaction
PFGE	pulsed-field gel electrophoresis
PID	pelvic inflammatory disease
РО	orally
PPV	positive predictive value

Sens	sensitivity
Spec	specificity
stat	immediately
STI	sexually transmitted infection
STIGMA	Sexually Transmissible Infections in Gay Men Action Group
WHO	World Health Organisation

Executive summary

This guideline was developed by a multidisciplinary group in response to a request from the World Health Organisation (WHO) for all countries to have guidelines in place to support optimal management of gonorrhoea in an era of decreasing antimicrobial susceptibility and emergence of resistance to currently used antibiotics.

- Gonorrhoea is not a notifiable disease in New Zealand. Disease control requires good communication between all stakeholders.
- Nucleic acid amplification tests (NAATs) have become the first-line testing methodology for gonorrhoea in New Zealand.
- Culture needs to be maintained because this is the only method available for detecting new mutations. NAATs are currently available only for detection of known mutations. Recommendations for culture need to be determined on a regional basis, with good communication between laboratory and clinical personnel.
- NAATs are very sensitive but have a low positive predictive value (PPV) in low-prevalence populations. Testing for gonorrhoea requires knowledge of both local epidemiology and individual behavioural factors to reduce the impact of false positive results. Widespread testing in low-prevalence populations is not recommended.
- The recommended NAAT specimens are vulvovaginal swabs for women and first-pass urine samples for men. Rectal and pharyngeal swabs are recommended in all men who have sex with men (MSM) and in others with risk factors for non-genital infection. Gonorrhoea testing should be carried out in conjunction with testing for other sexually transmitted infections (STIs).
- Ceftriaxone 500 mg intramuscularly (IM) immediately (stat) and azithromycin 1 g orally (PO) stat are the first-line treatments for gonorrhoea in New Zealand.
- Advice should be given to people with gonorrhoea on how to notify their sexual contacts, and formal contact tracing should be reserved for cases where that is not feasible.
- Follow-up is recommended at 7 days (by phone or consultation) to check on treatment compliance and on partner notification. Patients with persistent symptoms require further assessment to detect treatment failure.
- Follow-up testing at 3 months is recommended in all cases of gonorrhoea to detect re-infections.
- Early notification of possible or suspected treatment failure to specialist services is essential for early detection and containment of antibiotic-resistant cases.

Foreword

This guideline has been developed to promote optimal management of gonorrhoea in New Zealand as the threat of ceftriaxone resistance emerges globally. It is aimed at all stakeholders involved in the management of gonorrhoea, including clinicians, microbiologists and epidemiologists.

The WHO's *Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in Neisseria gonorrhoeae* has a vision of enhancing the prevention, diagnosis and control of gonorrhoea, and mitigating the impact of antimicrobial resistance through enhanced, sustained, evidence-based and collaborative multi-sectoral action (WHO 2012). The WHO calls for all countries to take a multidisciplinary co-operative approach to containment of antimicrobial resistance. This guideline covers the testing of *Neisseria gonorrhoeae* and its clinical management, including suspected cases of treatment failure and enhanced surveillance of antimicrobial susceptibility. The guideline should be used in conjunction with the New Zealand Sexual Health Society (NZSHS) best-practice guidelines (NZSHS 2012a).

The guideline has been developed by a multidisciplinary Writing Group, which was set up following a gonorrhoea workshop held in conjunction with the annual NZSHS Conference in Palmerston North in 2012. The project has been supported by a grant from the Ministry of Health. The guideline development followed the process used for the New Zealand *Chlamydia Management Guidelines* (Ministry of Health 2008) developed by the disestablished Sexual Health Advisory Group. A Medline search and a review of international gonorrhoea management guidelines were undertaken. Feedback from consultation has been incorporated into the final guideline.

The guideline is intended as a reference document. There is some intentional overlap between sections because it is anticipated that different professional groups will consult the sections relevant to their disciplines.

Introduction

Commonly known as 'the clap' – most likely after the Parisian district 'Les Clapiers', which housed prostitutes in the Middle Ages – *N. gonorrhoeae* infection (that is, gonorrhoea) is a common and treatable perinatally and sexually transmitted infection. Throughout history, from biblical times onwards, there has been an awareness of gonorrhoea, but it has been poorly understood until fairly recent times. Neisser's description of *N. gonorrhoeae* in 1879 and Leistikow's and Löffler's subsequent culture of the organism in 1882 have led us to where we are today. The introduction of sulfonamides in 1936 and penicillin in 1943 provided the first real therapeutic options for gonorrhoea (Sparling 2005). Worldwide, gonorrhoea is the second most common bacterial STI after chlamydia.

The primary sites of infection are the urethra, rectum, pharynx and conjunctiva in both genders and the endocervix in the female. In infants, the conjunctiva is the most common site of infection.

N. gonorrhoeae has traditionally been detected by culture, before measurement of antibiotic susceptibilities. This method is highly specific for *N. gonorrhoeae* but is time consuming and subjective, and it relies on organism viability, which reduces the sensitivity of the test. Over the last 10 years, there has been a shift in New Zealand towards NAAT for STIs. In 2008, the New Zealand *Chlamydia Management Guidelines* recommended polymerase chain reaction (PCR) as best practice for detection of chlamydia in New Zealand (Ministry of Health 2008). NAAT for *N. gonorrhoeae* has the advantage of higher sensitivity than culture but has less reliable specificity. Since 2008, the reliability of NAAT for *N. gonorrhoeae* has improved, and NAAT is now the usual first-line test for *N. gonorrhoeae* in New Zealand laboratories. However, NAATs are currently unable to provide antibiotic susceptibility information data to referring clinicians or for monitoring of resistance patterns. This is significant in an environment of emerging multidrug-resistant *N. gonorrhoeae*.

For years, gonorrhoea has been easily treated with a single oral dose of antibiotics. However, *N. gonorrhoeae* has progressively acquired resistance to each new agent: sulphonamides in the 1940s, penicillins and tetracyclines in the 1970s and 1980s, and fluoroquinolones in the last decade. Since 2007, third-generation cephalosporins have been the only antibiotics recommended for empirical treatment of gonorrhoea (Workowski and Berman 2007). Clinicians now face emergence of third-generation–cephalosporin-resistant *N. gonorrhoeae*, without any well studied, effective, back-up treatment options (Kirkcaldy et al 2013).

Given the potentially serious social and medico-legal issues arising from the diagnosis of gonorrhoea, and in the face of increasing antibiotic-resistant strains of *N. gonorrhoeae*, it is essential that up-to-date research and ongoing efforts to effectively detect, report and treat this disease are promoted in New Zealand. In particular, the maintenance of *N. gonorrhoeae* culture is vital, as this is currently the only modality by which antimicrobial resistance can be monitored – and it will, for the foreseeable future, be the only route to discovery of new resistance mechanisms.

Epidemiology of gonorrhoea in New Zealand

Surveillance of gonorrhoea in New Zealand is undertaken via laboratory notification and is collated by the Institute of Environmental Science and Research (ESR). The change from culture to NAAT methodology has led to a recent increase in testing and notifications. There is regional variation in the incidence, with the highest rates being reported in the Tairawhiti region. There have been no confirmed cases of ceftriaxone resistance so far in New Zealand, but isolates with reduced ceftriaxone susceptibility have been identified. There are high rates of ciprofloxacin resistance.

Infection with *N. gonorrhoeae* has only ever been notifiable in New Zealand as 'ophthalmia neonatorum' (subsequently termed 'neonatal eye infection due to gonococcus') and then only until 31 May 1996.

Therefore, information on the epidemiology of gonorrhoea in New Zealand must be drawn from various data sources.

National and regional gonorrhoea rates

Laboratory-based STI surveillance data collated by ESR provide the best information on more recent trends in the rates of gonorrhoea infection in New Zealand. Gonorrhoea data are available from all laboratories in the Auckland, Waikato and Bay of Plenty/Lakes regions for 1998 onwards (Figure 1). These three regions all showed an increase in the gonorrhoea rate from 1998 until 2006, followed by a steady decline. However, in contrast to the other two regions, the reported gonorrhoea rate in the Auckland region increased sharply in 2012, following a smaller increase in 2011. The increase in the gonorrhoea rate in the Auckland region followed the introduction of NAAT for gonorrhoea testing at LabPlus in 2011 and at Labtests in 2012. There was an increase of 80 percent in the gonorrhoea rate in the Auckland region between 2010 and 2012 [from 65 per 100,000 population to 117 per 100,000] (ESR 2013a). Laboratories in the Waikato and Bay of Plenty/Lakes regions were not yet using NAAT routinely for gonorrhoea at the time of the ESR report.

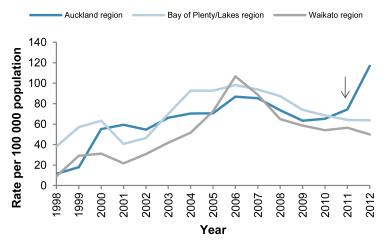


Figure 1: Gonorrhoea rates in the Auckland, Bay of Plenty/Lakes and Waikato regions, 1998–2012

Notes

- The Auckland region comprises the Waitemata, Auckland and Counties Manukau District Health Boards (DHBs).
- Nucleic acid amplification tests (NAATs) were introduced in the Auckland region in 2011 (at LabPlus) and 2012 (at Labtests).

Source: (ESR 2013a).

Estimated national gonorrhoea rates are available for 2009–2012 (Figure 2). As in the Auckland region, there was an obvious, but smaller, increase in the estimated national gonorrhoea rate in 2012, consistent with the introduction of NAAT by some laboratories. According to laboratory data from 17 of the 20 district health boards (DHBs) in New Zealand, the estimated national rate increased by approximately one-third to 89 per 100,000 population in 2012, from a previously stable rate [66 per 100,000 in 2009] (ESR 2013a).

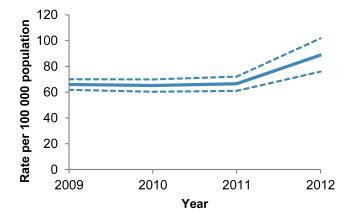


Figure 2: Estimated national gonorrhoea rates, 2009–2012

Note: The solid line denotes the gonorrhoea rate. The dashed lines denote the 95% confidence interval.

Source: (ESR 2013a).

Demographic and behavioural risk factors

Historically, the burden of gonorrhoea was considerably greater in males than in females, with a male : female case ratio of 4.5 : 1 in the late 1950s (Lyttle 1994). However, the gap has narrowed over time, and in 2012 there was little difference in the gonorrhoea rates between males and females [90 and 86 per 100,000 population, respectively] (ESR 2013a).

From recent laboratory-based STI surveillance data, the gonorrhoea rate in males has consistently been highest in the 20- to 24-year age group, followed by the 15- to 19-year age group. In females, the order of the two age groups with the highest rates is reversed, with the 15- to 19-year age group generally experiencing the highest rate (Figure 3). In 2012, there was a sharp increase in the gonorrhoea rate in females in this age group. At 533 per 100,000 population, this group experienced a higher rate than the male age group with the highest rate [20–24 years: 395 per 100,000] (ESR 2013a). This conspicuous increase and the smaller increases observed in other sex–age groups in 2012 are likely to be the result of greater use of NAAT for gonorrhoea in 2012.

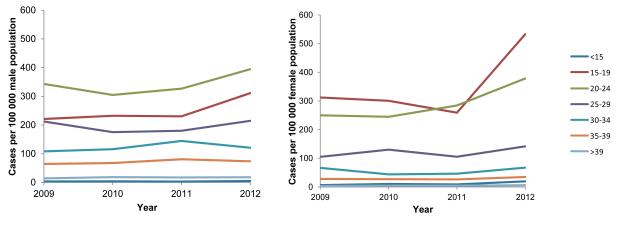


Figure 3: Gonorrhoea rates per 100,000 population by sex and age group (from <15 years to >39 years), 2009–2012

Source: (ESR 2013a).

From the current laboratory-based surveillance data, it is not possible to estimate national rates of gonorrhoea by ethnic group. STI surveillance data from sexual health clinics suggest that Māori bear a disproportionate burden of gonorrhoea, but valid rates cannot be calculated from these data. A Bay of Plenty DHB study confirmed that in 2007, both Māori males and Māori females had more than double the age-standardised rates of gonorrhoea, compared with European males and females, respectively (Aspin et al 2010). Similarly, a case–control study of Auckland Sexual Health Service gonorrhoea patients in 2003 and 2004 found that patients with gonorrhoea were more likely to be of Māori or Pacific ethnicity than patients who had negative STI screens, and this association was statistically significant [p < 0.001] (Azariah and Perkins 2007).

Considerable variation in gonorrhoea rates between DHBs in New Zealand is evident in laboratory-based STI surveillance (Figure 4). Tairawhiti DHB has consistently experienced the highest rate by a substantial margin. At 408 per 100,000 population, the 2012 rate for Tairawhiti DHB was more than four times the national rate and more than double the next highest DHB rate [Hawke's Bay DHB, 174 per 100,000] (ESR 2013a).

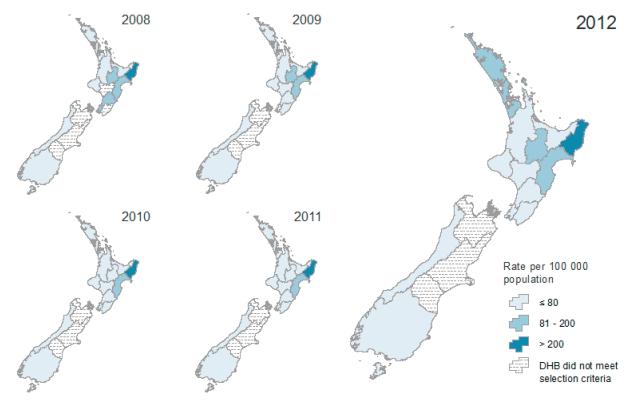


Figure 4: Gonorrhoea rates by district health board (DHB), 2008–2012

Notes

- In 2010, nucleic acid amplification tests (NAATs) were introduced in the Wellington region (at Hutt Hospital Laboratory).
- In 2011, NAATs were introduced in the Auckland region (at LabPlus), Lakes DHB (at Taupo Southern Community Laboratory), Hawke's Bay DHB (at Hawke's Bay Southern Community Laboratory) and Southern DHB.
- In 2012, NAATs were introduced in the Auckland region (at Labtests), Wellington region (at Aotea Pathology), Northland DHB (at Northland Pathology) and Tairawhiti DHB.

Source: Adapted from (ESR 2013b).

Surveillance data on the sexual orientation of gonorrhoea-positive individuals are not available in New Zealand. In the 2008 Gay Auckland Periodic Sex Survey, 2.9 percent (40) of the men surveyed reported a diagnosis of gonorrhoea within the previous 12 months (Saxton et al 2010). The Auckland Sexual Health Service case–control study found no association between sexual orientation and the likelihood of a gonorrhoea diagnosis (Azariah and Perkins 2007). In recent years, gonorrhoea diagnoses have been increasing in MSM in a number of countries, including the US (CDC 2013) and the UK (HPA 2011).

Sites of infection

In New Zealand, laboratory-based STI surveillance from 26 laboratories shows that gonorrhoea is most commonly diagnosed via urethral samples in males (53.1 percent of positive specimens) and via cervical specimens in females (46.7 percent of positive specimens) [Figure 5 and Figure 6]. However, in 2012, there was a large increase in the number of positive urine specimens in both males and females, which made up 29.6 percent and 11.1 percent of positive male and female specimens, respectively. The greater use of NAAT for gonorrhoea will be driving this increase in positive urine specimens. In 2012, fewer than 3 percent of positive specimens in males were either anorectal or throat specimens, and in females, fewer than 1 percent were anorectal specimens. There were no positive throat specimens in women in 2012 from the 26 laboratories (ESR 2013a).

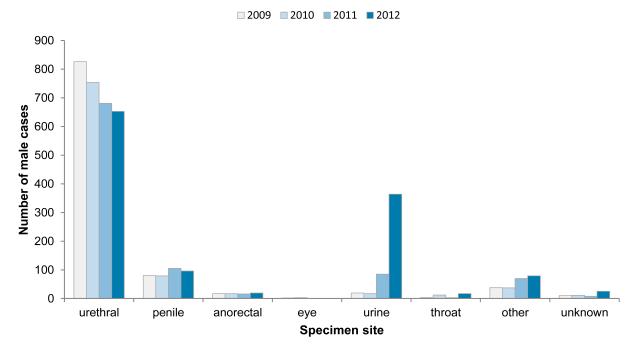
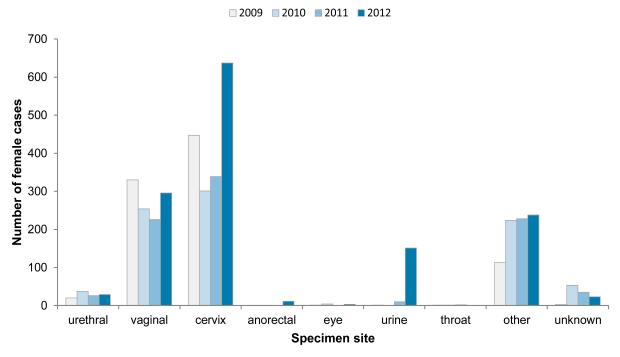
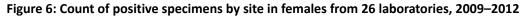


Figure 5: Count of positive specimens by site in males from 26 laboratories, 2009–2012

Source: (ESR 2013a).





Source: (ESR 2013a).

Gonococcal antimicrobial susceptibility

Diagnostic laboratories submit their gonococcal antimicrobial susceptibility data to ESR on an annual basis. Data on β -lactamase production, penicillin resistance, ciprofloxacin resistance and tetracycline resistance are collated to produce national estimates of resistance. Data on ceftriaxone resistance are not currently collected. In 2011, 11.6 percent of *N. gonorrhoeae* cases in New Zealand were penicillin resistant, 40.8 percent were ciprofloxacin resistant and 47.0 percent were tetracycline resistant. The rates of penicillin and ciprofloxacin resistance vary considerably throughout the country. In 2011, penicillin resistance ranged from 28.7 percent in the Auckland region to 3.5 percent in Bay of Plenty DHB, and ciprofloxacin resistance ranged from 53.5 percent in MidCentral and Whanganui DHBs to 7.3 percent in Southern DHB. For more information, see *STI Surveillance: Annual Report* at http://www.surv.esr.cri.nz/surveillance/annual_sti.php (Public Health Surveillance 2014).

While no ceftriaxone resistance has been confirmed among *N. gonorrhoeae* cases in New Zealand to date, isolates with decreased susceptibility to ceftriaxone (see 'Antimicrobial susceptibility testing', page 26) have been identified in the Auckland region, and in 2012 they accounted for 20 percent of gonococcal isolates recovered from patients attending local sexual health clinics. Molecular typing of isolates with decreased ceftriaxone susceptibility from the Auckland region showed that a number of the isolates belonged to one of two predominant strains (Roberts et al 2013). One of these strains was *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST) type 1407, the type associated with decreased ceftriaxone susceptibility in Europe and also with the three ceftriaxone-resistant gonococci isolated to date in Europe (Cámara et al 2012, Unemo et al 2012).

Biology and pathology

N. gonorrhoeae is a non-motile, non-spore-forming, intracellular, Gram-negative diplococcus. Humans are the only reservoir for *N. gonorrhoeae*. *Neisseria meningitidis* is a closely related pathogen, which, along with several other non-pathogenic *Neisseria* species, forms part of normal human flora (Sparling 2005).

N. gonorrhoeae is a highly adapted pathogen. It adheres to mucosal surfaces lined with columnar, cuboidal or non-cornified epithelial cells (the urethra, endocervix, rectum, pharynx and conjunctiva). It withstands phagocytosis by white blood cells. It is also capable of breaching mucosal surfaces to invade the bloodstream and cause systemic disease (Hook and Handsfield 2005).

N. gonorrhoeae readily acquires novel chromosomal and plasmid-mediated antimicrobial resistance within and across antibiotic classes. Resistance is retained even when use of the antibiotic has been discontinued. *N. gonorrhoeae* can do this because its genome undergoes continual mutation and internal recombination, resulting in rapidly evolving gonococcal populations. *N. gonorrhoeae* can:

- Acquire all or part of external resistance or virulence genes from other Neisseria species.
- Frequently release DNA or efficiently incorporate exogenous DNA acquired from other *Neisseria* species and closely related bacteria (WHO 2012).
- Generate both false negative and false positive results as a result of genome sequence variation (Whiley et al 2006).

The rectum and pharynx are emerging as significant reservoirs of exogenous DNA for *N. gonorrhoeae* (Park et al 2012). The rate of rectal gonorrhoea among women who report anal intercourse may be similar to that of urogenital infections (Javanbakht et al 2012).

Co-infection

Commonly, *N. gonorrhoeae* co-infects with other pathogens. Data from England and Wales in 2008 demonstrated that *Chlamydia trachomatis* accompanies *N. gonorrhoeae* infection in 35 percent of heterosexual men and in 41 percent of women (HPA 2009). A local study reported that 42 percent of those infected with *N. gonorrhoeae* had a concurrent *C. trachomatis* infection (Bromhead et al 2013). *N. gonorrhoeae* is more common in the presence of bacterial vaginosis (Wiesenfeld et al 2003) and facilitates infection with human immunodeficiency virus (HIV). *Trichomonas vaginalis* and *Candida albicans* may also be present.

Transmission

N. gonorrhoeae survives for only a short time outside the human body. Infection is by direct inoculation onto the mucosal surface, usually by sexual activity (vaginal, rectal or oral sex) and rarely by direct digital transfer of infected secretions onto susceptible mucosa. Transmission rates have been estimated (Holmes et al 1970, Hooper et al 1978, Lin et al 1998), but there are no reliable studies of transmission rates following single episodes of sexual exposure. Transmission may be more efficient from the penis to the vagina or to the rectum than vice versa, because of retention of infected ejaculate. Vertical transmission may lead to conjunctival infection in 30 percent of neonates of infected mothers.

Incubation

The incubation time for male urethral infection is usually between 2 and 5 days but ranges from 1 to 14 days. The incubation time of endocervical *N. gonorrhoeae* may be longer, with symptoms occurring at closer to 10 days. The incubation times for rectal and pharyngeal infection are more uncertain. Vertically transmitted neonatal ophthalmia is usually symptomatic within 2–7 days, though it may present later (Hitti and Watts 2005, Hook and Handsfield 2005, Kohlhoff and Hammerschlag 2005).

Natural history

Without treatment, urethral gonorrhoea in men becomes asymptomatic over several weeks to 6 months. Infection with *N. gonorrhoeae* does not confer immunity against re-infection.

Symptoms and signs

The majority of men with urethral gonorrhoea are symptomatic. Fifty percent of women with urogenital infection are likely to be symptomatic. Non-genital infections in both genders are usually asymptomatic.

Symptoms and signs are not sensitive predictors of *N. gonorrhoeae* infection, because other STIs, such as chlamydia, may produce similar syndromes. The prevalence of asymptomatic infections is influenced by the reason for presentation (for example, contacts versus index cases) and the sensitivity and specificity of the test (see 'Laboratory standards for NAAT', page 21). With the exception of male urethral gonorrhoea, studies that discuss symptoms differ in their definition of 'symptoms' [for example, symptoms are undefined (Gaydos et al 2003, Van Der Pol et al 2001) or warts are included as a symptom (Martin et al 2000, Schachter et al 2008)] and/or they pool symptoms from all sites when comparing results [for example, genital and rectal (Schachter et al 2008)]. Replicated studies using consistent criteria are scarce.

A summary of the symptoms and signs associated with *N. gonorrhoeae* infection is provided by site of infection in Table 1. The frequencies quoted in this table are based on the more reliable data or the only data available, and they are therefore approximate.

Site of infection	Symptoms ¹	% with symptoms	Signs ¹
Male urethra	Urethral discharge Dysuria Pain or swelling in the glans penis or testis	≈90%	Discharge Swollen, red glans penis Inguinal lymphangitis
Adult female genitourinary tract	Vaginal discharge	≈50%	Purulent cervical discharge
genitournary tract	Abdominal/pelvic pain	\downarrow	Friable cervix
	Dysuria Dysmenorrhoea Menstrual changes Dyspareunia Urethral discharge Bartholin's abscess	Rare	Cervical excitation Tender adnexae
Prepubertal female genitourinary tract	Vaginal discharge	Nearly always	Vaginal discharge
8	Vulvovaginal swelling and pain	\downarrow	Vulvovaginitis
	Dysuria	Rare	Urethral discharge
Conjunctiva (neonatal) Conjunctivitis		Nearly always	Oedema of eyelids Purulent discharge Conjunctivitis
Rectum Anal discharge Mucus on bowel motions Anal pain		<10%	Discharge Inflamed rectal mucosa
Pharynx	Sore throat	<5%	Pharyngitis
Other site or systemic	Lump(s) in groin Backache Rash Arthralgia	Rare	Lymphadenopathy Rash Septic arthritis

Table 1: Symptoms and signs that may be present in patients with Neisseria gonorrhoeae infection

1 Symptoms and signs may also indicate other sexually transmitted infections – for example, chlamydia.

Complications

A potential complication of infection in women is pelvic inflammatory disease (PID), which in turn can lead to Fitz-Hugh–Curtis Syndrome (perihepatitis), subfertility and ectopic pregnancy.

Possible sequelae of infection in males include epididymo-orchitis and prostatitis. Penile lymphangitis, periurethral abscess, seminal vesiculitis and infection of Tyson's and Cowper's glands are seen but are uncommon (Handsfield and Sparling 2005).

In both men and women, haematogenous spread can lead to disseminated gonococcal infection (DGI), involving the skin and the musculoskeletal system. To date, the risk of developing complicated gonococcal infection has not been studied, but recent data from the UK indicate that it is uncommon.

N. gonorrhoeae infection is associated with adverse outcomes in pregnancy: spontaneous abortion, premature rupture of membranes, premature delivery, acute chorioamnionitis and endometritis.

Conjunctivitis presents with purulent conjunctivitis in neonates and may also occur in adults. If untreated, it can lead to corneal ulceration and visual impairment, and may result in disseminated infection.

Laboratory testing for N. gonorrhoeae

NAATs have become the first-line testing method for gonorrhoea and are usually combined with chlamydia testing. NAATs are very sensitive, but there are some limitations in specificity. The PPV may be low in low-prevalence populations. Recent advances in NAAT technology have improved the specificity and have reduced the need for supplementary testing for all positive NAAT results. Supplementary testing should be considered for positive NAAT results from non-genital sites and must be undertaken when positive NAAT results are obtained in paediatric cases. There needs to be good communication between clinical and microbiology teams to develop local testing guidelines, taking into consideration knowledge of local epidemiology and sexual networks.

Detection of *N. gonorrhoeae* has traditionally has been performed by culture to isolate, biochemical tests to definitively identify, and antimicrobial susceptibility testing to determine antimicrobial susceptibility of the organism. There are now several commercial *N. gonorrhoeae* NAATs in use in New Zealand, and many platforms offer combined testing for *C. trachomatis* and *N. gonorrhoeae*. The currently available next-generation NAAT assays are more sensitive than culture and are more sensitive and specific than the predecessor NAAT assays, and they provide the option of testing using noninvasive specimens, such as urine and self-collected vaginal swabs. However, none are yet approved for use on non-genital sites, and there are currently no NAATs able to offer reliable information on antibiotic susceptibility.

Nucleic acid amplification tests (NAATs)

NAATs have several advantages over culture. The ability to test self-collected vaginal swabs and urine by NAATs increases the accessibility of testing for those who would otherwise decline an invasive swab sample. Other advantages include enhanced sensitivity and detection of non-viable organisms, allowing for less stringent collection and storage requirements for specimens.

There are disadvantages of NAATs. The first is reduced specificity due to false positives from commensal *Neisseria* species incorporating *N. gonorrhoeae* DNA that corresponds to the gene targets of the NAATs (see 'Biology and pathology', page 18). While the specificity of new-generation dual-target assays is higher than that of earlier assays, false positive results remain a possibility. This is particularly an issue for non-genital specimens, such as throat and rectal swabs (Fairley et al 2011). The other disadvantage of NAATs is the inability to perform concurrent culture for susceptibility testing. The swab lysis buffers that are utilised for many commercial *N. gonorrhoeae* assays destroy the organism in order to gain access to the nucleic material of the cell.

Despite these limitations, NAATs are the tests of choice in asymptomatic men and women with a genital, throat or rectal infection (BASHH 2012, Best Practice Advocacy Centre 2013, Fairley et al 2011, Schachter et al 2008). Because of the impact of false positive results, non-genital site testing should be considered on the basis of individual behavioural risk and knowledge of sexual networks.

Laboratory standards for NAATs

Laboratories must ensure that testing conforms to International Accreditation New Zealand requirements, including in-house methods or testing algorithms (for example, between commercial platforms) used for supplementary testing. Testing should include a control for inhibition in all tests (National Pathology Accreditation Advisory Council 2012). Laboratories must also participate in external quality assurance testing relevant to NAATs. The Australian National Pathology Accreditation Advisory Council (NPAAC)

Requirements for Medical Testing of Microbial Nucleic Acids may be used for guidance on performing testing (National Pathology Accreditation Advisory Council 2012).

Any molecular testing algorithm used by a laboratory should aim to give a PPV of >90 percent (Dimech et al 2004, National Pathology Accreditation Advisory Council 2012, Palmer et al 2003). The PPV of a diagnostic test is driven by both prevalence and specificity. In low-prevalence populations, more than one test may be required for adequate PPV (Whiley et al 2008). Figure 7 shows PPVs by prevalence for increasing specificity values. Note the steep decrease in the PPV at lower prevalence levels. Conversely, the negative predictive value (NPV) can be expected to decrease steeply as the prevalence increases. As with all laboratory tests, therefore, correct interpretation of results is critically dependent on knowledge of the prevalence of the disease in the particular population undergoing testing.

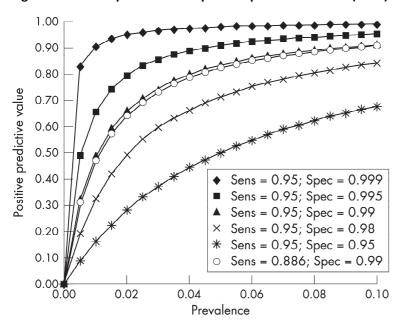


Figure 7: Effect of prevalence on positive predictive values (PPVs)

Note: Calculated PPVs for a test with sensitivity (Sens) of 0.886–0.95 and specificity (Spec) of 0.95–0.99 in theoretical populations with a disease prevalence of 0.00–0.10.

Source: Reproduced from (Zenilman et al 2003), with permission from BMJ Publishing Group Ltd.

First-line assays

There are several commercial NAAT assays currently available in New Zealand. Their performance in approved specimens, performance in non-genital sites and reported cross-reacting species vary. Because of the potentially negative social implications of false positive results, all positive results from first-line assays require supplementary testing to confirm the result, unless:

• The first-line assay is a current next-generation assay;

AND

• The sample was taken from a urogenital site;

AND

• Validation of the first-line method shows that more than 90 percent of positive samples in the screening method are confirmed by either a supplementary assay or culture, and the validation has been

conducted as per relevant guidelines [for example, (Dimech et al 2004) or (National Pathology Accreditation Advisory Council 2012)];

AND

 The validation is carried out in the target population – for example, it is not reliant on data from outside New Zealand;

AND

• The approach does not otherwise deviate from the manufacturer's instructions, unless separate (and appropriate) validation data are produced by the laboratory.

Supplementary assays

Supplementary testing is complex because of variability in specificity/sensitivity but also because of different buffering systems between platforms. Any supplementary assay must be directed at a different genetic target (or targets) from that of the first-line assay. Ideally, the supplementary assay should be at least as sensitive as the first-line assay and must have discriminatory value in identifying *N. gonorrhoeae*. If the supplementary assay on a sample that is positive in a first-line assay meets the above criteria and is negative, the result should be flagged and the report should include the following information:

'INCONCLUSIVE (or EQUIVOCAL). Initial positive result not confirmed by subsequent supplementary testing. Interpretation requires clinical correlation, and discussion with a clinical microbiologist is recommended.'

An equivocal or inconclusive result is a reminder to re-assess the patient's risk and communicate the uncertainty of the results to the patient. A diagnosis of gonorrhoea can precipitate a personal or relationship crisis – therefore, as high a level of confirmation as possible is desirable within the available resources and the limitations of the tests. For clinical management of unexpected results or inconclusive positive results, see 'Clinical interpretation of results', page 34.

Note that if the supplementary assay has lower sensitivity than the first-line assay, this will increase the number of results reported as being inconclusive or equivocal. The relative diagnostic sensitivities of the first-line assay and the supplementary assay must therefore be taken into account in interpretation of these results. Table 2 provides information on gene targets that have been used in supplementary assays, and their performance.

Supplier/reference for in-house	False positive results	False negative results	Comments	
(Tabrizi et al 2005)	None published	See comments	False negative results	
(Whiley and Sloots 2005)		porA negative strain (Whiley et al 2011)	using these genes were found during RCPA surveys of Australian	
(Goire et al 2008)		lab	and New Zealan laboratories in 2011/2012	laboratories in
GenProbe (Chui et al 2008, Farrell 1999, Van Dyck et al 2001)	Neisseria meningitidis in GenProbe assay (Walcher et al 2013)	See comments		
TIB MolBiol LightMix kit (Airell et al 2005, Ho et al 1992)	None published	(Chui et al 2008)	Not commonly used	
(Ho et al 1992)	<i>Neisseria cinerea</i> (Palmer et al 2003)	(Geraats-Peters et al 2005, Lum et al 2005, Palmer et al 2003)	Not recommended, because of a high rate of false negative results	
(Liebling et al 1994)	Various commensal strains (Palmer et al 2003)	None published	Not commonly used	
(Chaudhry and Saluja 2002)	<i>Neisseria subflava</i> (Whiley et al 2006)	None published	Not commonly used	
	in-house (Tabrizi et al 2005) (Whiley and Sloots 2005) (Goire et al 2008) GenProbe (Chui et al 2008, Farrell 1999, Van Dyck et al 2001) TIB MolBiol LightMix kit (Airell et al 2005, Ho et al 1992) (Ho et al 1992) (Liebling et al 1994) (Chaudhry and Saluja	in-house(Tabrizi et al 2005)None published(Whiley and Sloots 2005)Since al 2008(Goire et al 2008)Neisseria meningitidis in GenProbe (Chui et al 2008, Farrell 1999, Van Dyck et al 2001)TIB MolBiol LightMix kit (Airell et al 2005, Ho et al 1992)None published (Walcher et al 2013)(Ho et al 1992)Neisseria cinerea (Palmer et al 2003)(Liebling et al 1994)Various commensal strains (Palmer et al 2003)(Chaudhry and SalujaNeisseria subflava	in-house(Tabrizi et al 2005)None publishedSee comments(Whiley and Sloots 2005)porA negative strain (Whiley et al 2011)(Goire et al 2008)Neisseria meningitidis in GenProbe (Chui et al 2008, Farrell 1999, Van Dyck et al 2001)Neisseria meningitidis in GenProbe assay (Walcher et al 2013)TIB MolBiol LightMix kit (Airell et al 2005, Ho et al 1992)None published (Chui et al 2008)(Ho et al 1992)Neisseria cinerea (Palmer et al 2003)(Liebling et al 1994)Various commensal strains (Palmer et al 2003)(Chaudhry and SalujaNeisseria subflavaNone publishedNone published	

Table 2: Supplementary tests for confirming positive first-line assay results for Neisseria gonorrhoeae

RCPA = Royal College of Pathologists of Australia.

Invalid test results

NAAT may occasionally yield an invalid test result, either because of a pipetting error/clot in the specimen (on automated platforms) or because of amplification failure (presence of inhibitors).

It has been reported that a high proportion of specimens yielding pipetting errors/clots are from gonorrhoea-infected patients. The mucopurulent discharge caused by *N. gonorrhoeae* infection may interfere with automated testing platforms (Hopkins et al 2012, Miller et al 2012). Therefore, patients with invalid NAAT results should be tested by an alternative method, such as culture, to confirm their infection status.

When alternative methods are not available routinely, it is recommended that laboratories consider methods to resolve mucus interference, such as treatment with dithiothreitol [DTT] (Miller et al 2012), and referring clinicians should be advised that such results may be clinically significant.

Extra-genital specimens

Extra-genital sites are considered to include the rectum, pharynx, conjunctiva and sterile fluids.

The high levels of commensal *Neisseria* species in non-genital sites may compromise the specificity of NAAT, leading to false positive results. Most commercial screening assays are not licensed for these specimen types – therefore, supplementary testing for *N. gonorrhoeae* is necessary for all non-genital sites.

To avoid false negative results due to sequence variation in supplementary assay gene targets, a minimum of two supplementary targets should be tested for when extra-genital specimens are positive on the first-line NAAT assay. If either supplementary target is positive, the first-line assay result should be considered to be confirmed as positive (D Whiley, personal communication, 2013).

This is a modification of the three-gene target test evaluation criteria that have been recommended by the Australian Public Health Network for diagnostic non-genital site testing since 2005 (Smith et al 2005). It continues to be a recommendation, as NAAT has gradually been introduced for non-genital site testing in Australia (Whiley 2012). The recommendation from the UK is for supplementary testing using a test with a different target (HPA 2010, HPS 2012). The 2010 guidance qualifies this recommendation by stating that a NAAT that exhibits little cross-reactivity should be chosen and that testing should be undertaken in low-prevalence populations 'with extreme caution'. Decisions regarding supplementary testing need to consider the testing methodology and local prevalence, taking into account the fact that the latter may be dynamic during epidemics (HPS 2012). Both the first-line assay and the laboratory's confirmatory testing strategy should be validated as a single protocol prior to introduction (Alexander et al 2011).

Culture and identification

To facilitate detection and management of antibiotic resistance in *N. gonorrhoeae*, it is necessary to maintain culture capabilities and expertise, where possible. The culture of an isolate enables appropriate antimicrobial susceptibility testing to be undertaken.

Swabs taken for culture should be processed within 6 hours of collection. Where this timeframe can be met, there is no advantage of direct inoculation at the clinic (Olsen et al 1999). The initial inoculation should be onto a selective medium, such as New York City or Thayer–Martin agar. After inoculation, the plates should be incubated for 48 hours in a CO_2 -enriched environment at 35°C before being discarded as negative.

Oxidase-positive Gram-negative diplococci should be confirmed as *N. gonorrhoeae* by biochemical, immunological or molecular methods.

Suitable culture samples

The following are suitable culture samples:

- Clinician-collected female endocervical swabs and male urethral swabs (**note:** female urethral swabs are suitable only after hysterectomy).
- Rectal and pharyngeal samples (**note:** NAAT has considerably higher sensitivity for both of these sites, and culture may not yield an isolate).
- Vaginal swabs in prepubertal girls are acceptable for culture, as the presence of columnar epithelial cells in the vagina means that the vaginal mucosa can be infected.
- Ophthalmic sites.
- Bartholin's abscess purulent material expressed from the Bartholin's duct.

Note: Urine is not suitable for culture.

For more details, see 'When, where, from whom and what specimens to take for *N. gonorrhoeae* testing', page 27.

Laboratory culture recommendations

Laboratory culture should be considered in the following instances:

- Where patients are treated at the time of presentation because they are symptomatic.
- In patients who are contacts of a confirmed case of *N. gonorrhoeae*.
- Where possible, in cases of gonorrhoea diagnosed by NAAT prior to antibiotics being given, so that susceptibility testing can be performed and resistant strains can be identified (BASHH 2012).
- In patients with persisting symptoms or signs after treatment (to exclude antimicrobial resistance). Culture MUST be performed in this situation.
- In patients with allergy to empirical treatment, necessitating antimicrobial susceptibility testing.
- If it may be required for medico-legal reasons.
- For sentinel surveillance as defined regionally (see 'Enhanced surveillance of antimicrobial resistance in *N. gonorrhoeae*: roles and responsibilities', page 45).

Microscopy

Gram staining of urethral smears can be useful as point-of-care testing in symptomatic male patients when it is available. In asymptomatic patients, microscopy of Gram-stained endocervical and urethral smears has low (40–60 percent) sensitivity and is not recommended.

Antimicrobial susceptibility testing

All antimicrobial susceptibility testing should be performed by a standard method, such as that of the Clinical Laboratory Standards Institute [CLSI] (CLSI 2013) or that of the European Committee on Antimicrobial Susceptibility Testing [EUCAST] (EUCAST 2013).

Because of high rates of resistance, penicillin and ciprofloxacin are no longer choices for empirical treatment of gonorrhoea. Therefore, it is not necessary to test susceptibility to these two antibiotics routinely. However, some laboratories may wish to test ciprofloxacin susceptibility, since oral ciprofloxacin therapy may be considered as a treatment option when the *N. gonorrhoeae* isolated from the patient or their contact is known to be susceptible. In addition, if susceptibility testing of a range of antimicrobial agents is not performed routinely, it is recommended that such testing is undertaken periodically to determine local susceptibility profiles.

Ceftriaxone is currently recommended for empirical treatment of gonorrhoea. At present, isolates that have decreased susceptibility to ceftriaxone are usually resistant to other antimicrobials, including penicillin, ciprofloxacin and tetracycline. Therefore, laboratories that test penicillin susceptibility and ciprofloxacin susceptibility routinely could opt to only test the ceftriaxone susceptibility of isolates that are penicillin resistant and ciprofloxacin resistant. Such an approach may not be valid in the future if ciprofloxacin-susceptible isolates with decreased ceftriaxone susceptibility emerge. However, importantly, ceftriaxone susceptibility testing should be performed in all cases of apparent treatment failure, particularly when re-infection is unlikely.

The ceftriaxone susceptibility testing method that is used should be capable of detecting decreased susceptibility. In addition to use of a standard method, such as the CLSI method or the EUCAST method, the following recommendations should be noted when ceftriaxone susceptibility is being tested:

- Ideally, ceftriaxone susceptibility should be tested by a method that determines the minimum inhibitory concentration (MIC), such as an Etest or agar dilution, rather than by disc testing. Neither the CLSI standards nor the EUCAST standards currently provide MIC breakpoints for decreased ceftriaxone susceptibility, with CLSI only defining a ceftriaxone MIC ≤0.25 mg/L as susceptible and EUCAST defining a ceftriaxone MIC ≤0.12 mg/L as susceptible and >0.12 mg/L as resistant. The Australian Gonococcal Surveillance Programme recommends that isolates with MICs in the range of 0.06–0.25 mg/L should be categorised as having decreased ceftriaxone susceptibility (Australian Gonococcal Surveillance Programme 2008).
- If ceftriaxone susceptibility is determined by disc testing, a low-strength 0.5 µg ceftriaxone disc, rather than the standard 5 µg disc, should be used. As an indicative guide, *N. gonorrhoeae* isolates with zone diameters of ≤24 mm with a 0.5 µg disc may have decreased ceftriaxone susceptibility.
- Quality-control strains with defined MIC values should be used in every run of susceptibility testing. These strains need to produce results that are consistent with established or published expected ranges (Unemo et al 2009). When ceftriaxone susceptibility is being tested by either an MIC or disc method, a reference strain with decreased ceftriaxone susceptibility should be used, such as the WHO K strain, which is available from the ESR Culture Collection as Accession Number NZRM 4543.
- Any isolates showing decreased susceptibility or resistance to ceftriaxone should be sent to ESR for confirmatory susceptibility testing and further characterisation.

When, where, from whom and what specimens to take for *N. gonorrhoeae* testing

Introduction to this section

This advice is based on the British Association for Sexual Health and HIV (BASHH) United Kingdom National Guideline for Gonorrhoea Testing 2012 (BASHH 2012) and the Centers for Disease Control and Prevention (CDC) Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae – 2014 (CDC 2014) adapted for New Zealand conditions in specialist Sexual Health Services and in primary care practices in the community. They are consistent with the New Zealand sexually transmitted disease testing guidelines (Best Practice Advocacy Centre 2013, NZSHS 2012a) and the Australasian testing guidelines for MSM (STIGMA 2014).

The prevalence of gonorrhoea in New Zealand is not sufficiently high to justify unselected random testing. Testing should occur on the basis of epidemiological and behavioural risk factors.

Please refer to A How to Guide for a Sexual Health Checkup (Best Practice Advocacy Centre 2013) for a full discussion of sexual history and STI testing in New Zealand.

NAAT shows high sensitivity (>96%) in both symptomatic and asymptomatic infection (BASHH 2012). Firstline testing in most situations requires the following specimens for NAAT:

- First-void urine (FVU) in men after a minimum of 1 hour since the last void.
- Vulvovaginal swabs in women, either self-collected (see 'Appendix 1: how to take your vaginal swab', page 56), or clinician-collected if self-collected swabs are declined or in the presence of symptoms.
- Rectal and pharyngeal swabs in MSM and in others with epidemiological and behavioural risk factors for gonorrhoea infection. In some situations (or if NAAT is not available), swabs for culture are essential.

For more detailed discussion, see 'Laboratory testing for N. gonorrhoeae', page 21, and the following text.

The following should be noted:

- The recommendations in this section apply to male, female, and sex- and gender-minority adults postpuberty in New Zealand.
- For prepubertal sampling, see 'Management of gonorrhoea in children', page 40.
- For testing of adults where recent sexual assault is a consideration, please consult your local Sexual Abuse Assessment and Treatment Service. Contact details are available from your local specialist Sexual Health Service or through the National Office of Doctors for Sexual Abuse Care (DSAC).

General advice

- Please refer to A How to Guide for a Sexual Health Checkup (Best Practice Advocacy Centre 2013) for a full discussion of sexual history and STI testing in New Zealand.
- There are five potential anatomical sites that may be tested: the cervix, urethra, rectum, pharynx and conjunctivae. Symptoms, the presenting history and a sexual history (particularly within the previous 2 months) of 'What went where, when, with whom' determine appropriate samples and tests.
- A history of past sexual infection, lifestyle or occupational risks, past or present sexual assault or intimate relationship violence may be significant. Demographic variations in infection rates related to age, sex, region and ethnicity may need to be considered. (See 'Demographic and behavioural risk factors', page 14).
- Sampling is affected by the availability of tests in a particular region and at the workplace of the clinician, and/or the need for antimicrobial susceptibility testing.
- Less intrusive or self-collected samples are often preferable for example, FVU for male urethral
 infection or vulvovaginal swabs for cervical infection (see 'Appendix 1: how to take your vaginal swab',
 page 56). However, in some situations, clinician examination and collection of samples is essential for
 quality results. An examination should be undertaken in the presence of symptoms to guide empirical
 treatment and to exclude other pathology.
- FVU is the first 30 mL of voided urine collected ≥1 hour after the last voiding, if possible.
- If multiple specimens are being collected from an anatomical site, *N. gonorrhoeae* culture specimens should be obtained first; this sequence increases the likelihood of a successful culture (CDC 2014).

A culture (via a swab in Amies transport medium or plated directly):

- Is desirable in all cases of gonorrhoea diagnosed by NAATs prior to antibiotics being given, where possible, so that susceptibility testing can be performed and resistant strains can be identified (BASHH 2012, Whiley 2012). This is particularly important when there is allergy to empirical or first-line treatment, and to ensure efficient treatment of sexual contacts.
- May be required for medico-legal reasons [sexual assault advice is given in Chapter 6 of *The Medical Management of Sexual Assault*, available from http://www.dsac.org.nz/dsac-manual.php (DSAC 2006)] or for sentinel surveillance. See 'Enhanced surveillance of antimicrobial resistance in *N. gonorrhoeae*: roles and responsibilities', page 45.

Swabs for culture MUST be taken from all patients with persisting symptoms or signs after treatment to investigate treatment failure, rule out resistant organisms (BASHH 2012) and direct further treatment options.

Appropriate use of N. gonorrhoeae testing

Overall, the prevalence of gonorrhoea in New Zealand is not high enough to warrant widespread, unselected screening of individuals. In low-prevalence populations, the PPV decreases with increasing impact of a false positive result. The impact of a false positive test increases (see Figure 7).

The relatively high prevalence of chlamydia in New Zealand means that 'screening' for chlamydia with NAAT is recommended for certain populations (Ministry of Health 2008), while gonorrhoea screening would not be recommended for the same population. When NAAT samples from these patients are automatically dual tested for gonorrhoea as well as chlamydia, practitioners need to be alert to the possibility of false positive gonorrhoea results. (See 'Laboratory standards for NAAT', page 21).

An adequate sexual history [as per *A* How to Guide for a Sexual Health Checkup (Best Practice Advocacy Centre 2013)] prior to testing helps balance the risk of not detecting asymptomatic carriage against the impact of a false positive result. For advice on managing unexpectedly positive or ambivalent results, see 'Clinical interpretation of results', page 34.

How soon to test

It is recommended that STI testing should be deferred for 2 weeks after the last sexual contact or after a specific event of concern, to allow for the appropriate incubation period for chlamydia testing. However, if the patient has symptoms or is unlikely to come back for testing, testing should be done at the time of presentation (Best Practice Advocacy Centre 2013, NZSHS 2012a).

Testing for other sexually transmitted infections (STIs)

Any person who is at risk of *N. gonorrhoeae* infection, and/or is found to be positive for gonorrhoea, should also be tested for other STIs (Best Practice Advocacy Centre 2013, NZSHS 2012a, STIGMA 2014).

- **Chlamydia:** Most laboratories perform dual gonorrhoea and chlamydia NAATs. Additional NAAT swabs for chlamydia alone are necessary only if gonorrhoea testing is done by culture. Testing and treatment for chlamydia should be provided routinely to all adult patients with gonorrhoea (Bignell et al 2011).
- Women should have a high vaginal swab for trichomoniasis/*Candida*/bacterial vaginosis, *PLUS* an offer of serology for HIV, syphilis and hepatitis B.
- Men whose sexual partners are female should have serology for HIV, syphilis and hepatitis B.
- MSM should have multi-site testing for *N. gonorrhoeae* and *C. trachomatis* (urethra, rectum and pharynx), *PLUS* serology for HIV, syphilis, and hepatitis A and B (Ministry of Health 2011, STIGMA 2014) [see 'Co-infection', page 18].
- Hepatitis C serology should be performed if indicated by a risk history of injecting drug use, imprisonment or medical intervention in a developing country. MSM are at higher risk of hepatitis C, particularly if they are HIV positive or have multiple sexual partners.

Sites for testing

With rare exceptions, the types of test to be taken are determined by presenting symptoms and a history of sexual exposure at each site. The Sexually Transmissible Infections in Gay Men Action Group (STIGMA) STI testing guidelines for MSM recommend that all MSM should be offered annual urethral, pharyngeal and rectal NAAT for *N. gonorrhoeae* (STIGMA 2014).

With the advent of NAAT, specimen requirements have changed.

In women it has been demonstrated that self-collected vulvovaginal swabs are better than cliniciancollected cervical swabs (Stewart et al 2012). (See 'Appendix 1: how to take your vaginal swab', page 56.)

Specimen collection by site and method

Notes

- Clinicians should refer to local laboratory instructions for details of specimen swabs and processes. There are a number of different NAAT systems in use in New Zealand, with varying swab and urine container requirements.
- In most areas of New Zealand, NAATs are the choice for first-line testing with culture for specific indications. Refer to local management pathways and laboratory guidelines for indications for culture.
- In patients who are symptomatic, external genital, speculum or anoscopic examinations may be required.
- If NAAT and culture swabs are being collected, culture swabs should be taken first.
- See 'Testing for other sexually transmitted infections (STIs)', page 29, for other specimens to take for full STI testing.
- **Rectal and pharyngeal testing:** NAATs are not approved by the US Food and Drug Administration (FDA) for testing on non-genital sites (BASHH 2012), but they have considerably higher sensitivity for both of these sites (Ota et al 2009, Page-Shafer et al 2002, Schachter et al 2008), and culture may not yield an isolate. NAATs are therefore the test of choice. Supplementary testing is recommended for positive results (BASHH 2012, Whiley et al 2008) [see 'Extra-genital specimens', page 24].
- Systemic sites: It can be difficult to prove infection in patients with suspected DGI. The diagnosis of DGI is made on the basis of positive blood or synovial culture or, in a patient with the typical clinical syndrome and negative blood or synovial culture results, on the basis of gonococci isolated from another site. Genital and pharyngeal samples have a higher yield in identifying the presence of *N. gonorrhoeae* than blood cultures (BASHH 2012). Diagnostic testing of patients with suspected DGI should be discussed with a sexual health specialist or an infectious diseases physician prior to antibiotic treatment. Genital and pharyngeal samples should be taken.
- In women who have had a hysterectomy, urethral swabs (in Amies transport medium or plated directly) offer a better yield than high vaginal culture (Judson and Ruder 1979). "No comparative data are available regarding the use of cultures versus NAATs, or of testing urine, urethral swab and vaginal swabs by NAATs in samples from patients who have had a hysterectomy" (BASHH 2012).
- In pregnancy, a selective approach is recommended and should be considered in the following instances:
 - In patients aged <25 years.
 - Where no previous testing has been done in the current relationship.
 - In patients with a partner change within the previous 6 months or during pregnancy.
 - In the presence of symptoms.
 - In patients with a history of previous gonorrhoea infection.

Site	NAAT	Culture
Urine	Specimen of choice in men	Not suitable
	FVU (first 30 mL) with minimum of 1 hour since last void	
	Usually a dual gonorrhoea/chlamydia test	
	Not recommended in women, because of lower sensitivity than vulvovaginal swab; offer only if swabs are declined	
Cervical	Not recommended (lower sensitivity than vulvovaginal NAAT)	Endocervical swab is the specimen of choice in women when culture is required
		Insert Amies swab into cervical canal and rotate
		In specialist settings, direct plating is an alternative to use of transport medium
Urethral	Not recommended except in women post-	Suitable
	hysterectomy Although suitable, noninvasive testing is	Insert Amies transport medium swab into urethral meatus and rotate
	associated with greater testing rates	Direct plating is an alternative to use of transport medium in specialist settings
Vulvovaginal	Specimen of choice for NAAT in women	Not recommended except in prepubertal girls
ano aginar	Self-collected for opportunistic testing or if examination is declined (see 'Appendix 1: how to take your vaginal swab', page 56)	
	Clinician-collected if patient is symptomatic or requests clinical examination	
	Sweep NAAT swab around inner labia (including external urethral meatus), insert into vagina 3– 5 cm (touching the wall of the vagina) and rotate for a minimum of 5 seconds	
	Usually a gonorrhoea/chlamydia dual test	
Anorectal	Suitable	Suitable
	Insert NAAT swab gently 4 cm into anal canal and rotate	Insert Amies transport medium swab gently 4 cm into anal canal and rotate
	Usually a dual gonorrhoea/chlamydia test	In specialist settings, direct plating is an alternative to use of transport medium
Pharynx	Suitable	Suitable
	Wipe NAAT swab across posterior pharynx, tonsils and tonsillar crypts	Wipe Amies transport medium swab across posterior pharynx, tonsils and tonsillar crypts
	Usually a dual gonorrhoea/chlamydia test	In specialist settings, direct plating is an alternative to use of transport medium
Conjunctiva	Not recommended and not validated	Specimen of choice from this site
	There are insufficient data to recommend sampling from this site	Wipe excess exudate from around eye, then take Amies transport medium swab from each eye by rolling over lower tarsal conjunctiva,
	Gonorrhoea NAAT result may be given with dual gonorrhoea/chlamydia NAATs	avoiding eyelid border and lashes (or plate directly in specialist settings)

Table 3: Summary of clinical specimen collection by site and method

FVU = first-void urine; **NAAT** = nucleic acid amplification test.

Specimen collection by clinical history and risk stratification

Table 4: Summary of which specimen to take from which site, by gender

Note: If NAAT is unavailable, follow the instructions for culture under the highest-risk criteria.

Clinical criteria for testing	Collection of samples
Females	
Females at highest risk of gonorrhoea:Symptoms or signs of gonorrhoea	Vulvovaginal swab for <i>Neisseria gonorrhoeae/Chlamydia trachomatis</i> NAATs
• Sexual contact of someone with gonorrhoea	PLUS
Suspected PIDSuspected treatment failure	Endocervical swab via speculum examination (in Amies transport medium or plated directly) for culture, <i>PLUS</i> Gram stain if available
	Note: An endocervical swab MUST be taken for culture in cases of suspected treatment failure
	PLUS
	Tests for other STIs and at other sites:
	 Vaginal swab (in Amies transport medium) for <i>Trichomonas</i> vaginalis/bacterial vaginosis/<i>Candida</i> and serology as appropriate for hepatitis B, syphilis and HIV
	• Tests at other sites as per sexual history, for example:
	 Anorectal/pharyngeal swabs for <i>N. gonorrhoeae/C. trachomati</i> NAATs in cases of non-genital sex with more than one partner, <i>PLUS</i> Amies transport medium swabs for gonorrhoea culture if symptomatic or in cases of suspected treatment failure
	 Urethral swab for N. gonorrhoeae/C. trachomatis NAATs if previous hysterectomy or urethral symptoms predominate, PLUS urethral swab for gonorrhoea culture if indicated by histor
Females at moderate risk of gonorrhoea:	Vulvovaginal swab for N. gonorrhoeae/C. trachomatis NAATs:
 Unprotected vaginal sex with a new partner since the last test 	 Clinician-collected if nonspecific genital symptoms, if patient requests genital check or at time of cervical smear
Requested an STI check	• Self-collected if opportunistic or if examination is declined (see
 Past history of gonorrhoea or another STI 	'Appendix 1: how to take your vaginal swab', page 56)
 Commercial sex work (no condoms) 	FVU for <i>N. gonorrhoeae/C. trachomatis</i> NAATs if the patient declines
 Pregnancy – antenatal testing (see text for indications) 	a swab, but it has lower sensitivity than NAAT PLUS
 Prior to termination of pregnancy 	
 History of sexual assault or intimate partner abuse 	 Tests for other STIs and at other sites: Vaginal swab (in Amies transport medium) for <i>T. vaginalis</i>/bacteria
HIV-positive status	vaginosis/ <i>Candida</i> serology as appropriate for hepatitis B, syphilis and HIV, and test at other sites as per sexual history
Note: If NAAT is positive for N. gonorrhoeae,	 Test at other sites as per sexual history, for example:
consider recall for culture before prescribing medication, especially if there is allergy to first- line treatment	 Anorectal/pharyngeal swabs for <i>N. gonorrhoeae/C. trachomati</i> NAATs in cases of non-genital sex with more than one partner
	 Consider urethral swab for <i>N. gonorrhoeae/C. trachomatis</i> NAATs in women post-hysterectomy
Females at very low risk of gonorrhoea	Testing for gonorrhoea is not recommended but is an automatic result given with dual <i>N. gonorrhoeae/C. trachomatis</i> NAATs

Clinical criteria for testing

Collection of samples

Males

Note: All MSM should have annual testing with *N. gonorrhoeae/C. trachomatis* NAATs on FVU and pharyngeal and rectal swabs (STIGMA 2014)

Males at highest risk of gonorrhoea:	FVU for N. gonorrhoeae/C. trachomatis NAATs
• Symptoms or signs of gonorrhoea	PLUS
 Sexual contact of someone with gonorrhoea Suspected epididymo-orchitis Suspected treatment failure 	Urethral swab for culture (in Amies transport medium or plated directly), <i>PLUS</i> Gram stain if available
	PLUS
	Tests for other STIs and at other sites:
	 Serology as appropriate for hepatitis B, syphilis, and HIV and hepatitis A in MSM
	• Tests at other sites as per sexual history
	 All MSM should be offered anorectal and pharyngeal swabs for <i>N. gonorrhoeae/C. trachomatis</i> NAATs, <i>PLUS</i> Amies transport medium swabs for culture if symptomatic or in cases of suspected treatment failure
Males at moderate risk of gonorrhoea:	FVU for N. gonorrhoeae/C. trachomatis NAATs
 Unprotected sex with a new partner ALL MSM Requested an STI check Past history of <i>N. gonorrhoeae</i> or other STI HIV-positive status Unprotected sex with a commercial sex worker Note: If NAAT is positive for N. gonorrhoeae, consider recall for cultures before prescribing medication, especially if there is allergy to first-line treatment 	 PLUS Clinical examination if nonspecific symptoms, PLUS tests for other STIs and at other sites: Serology as appropriate for hepatitis B, syphilis, and HIV and hepatitis A in MSM Test at other sites as per sexual history All MSM should be offered anorectal and pharyngeal swabs for <i>N. gonorrhoeae/C. trachomatis</i> NAATs
Males at low risk of gonorrhoea	Testing for gonorrhoea is not recommended but is an automatic result given with dual <i>N. gonorrhoeae/C. trachomatis</i> NAATs
Transgender	Test specific sites according to risk as per sexual history
Suspected gonorrhoea prepuberty	See 'Testing for <i>N. gonorrhoeae</i> in prepubertal children', page 40, and seek specialist advice
	In children, NAAT has been shown to have high sensitivity and specificity
	In girls presenting with vaginal discharge, an Amies transport medium swab AND vulvovaginal NAAT swab are suitable

FVU = first-void urine; **HIV** = human immunodeficiency virus; **MSM** = men who have sex with men; **NAAT** = nucleic acid amplification test; **PID** = pelvic inflammatory disease; **STI** = sexually transmitted infection.

Clinical interpretation of results

NAAT 'false positive' results, or 'invalid or inconclusive' *N. gonorrhoeae* results, may cause problems, while false negative results are more common when only *N. gonorrhoeae* culture samples have been taken.

Management of unexpectedly positive NAAT results

An unexpectedly positive NAAT result should be managed with caution, particularly if the patient is in a 'very low risk of gonorrhoea infection' category. This will usually be when dual chlamydia and gonorrhoea NAATs have been done in a population where the prevalence of chlamydia warrants this test but the *N. gonorrhoeae* prevalence may not. Initial steps to resolve this include:

- Review of the patient's sexual history. Check their risk factors for infection (see Table 4 and the text above).
- Discussion with the clinical microbiologist and/or molecular biologist at the laboratory. It is prudent to have this discussion prior to any conversation with the patient.
- Discussion with a sexual health medicine specialist.

Repeat NAAT and/or additional samples for culture may be required. If still in doubt, treat empirically and follow up accordingly.

Management of invalid and/or inconclusive or equivocal NAAT results

Also see 'Supplementary assays', page 23, and 'Invalid test results', page 24.

- For all of these patients, specific advice on further testing should be sought from a clinical microbiologist and/or from a sexual health medicine specialist.
- Culture swabs may clarify the situation, but it should be noted that culture has lower sensitivity than NAAT.
- Supplementary testing may yield further information but is expensive. Because of the varying sensitivity of different NAAT methodologies, the effect of different buffering systems when further testing is undertaken and the impact of treatment on those previously treated, a definitive result may not be available.
- The limitations of testing should be explained to patients, and treatment should be offered on the basis of doubt when infection cannot be excluded in the presence of epidemiological and behavioural risk.

Management of N. gonorrhoeae infection

The first-line treatment for uncomplicated gonorrhoea is **ceftriaxone 500 mg IM stat** *PLUS* **azithromycin 1 g PO stat.**

Treatment for chlamydia should be included in all regimens for gonorrhoea treatment. Dual therapy may delay the onset of antimicrobial resistance, and co-infection is common.

Patients with gonorrhoea should be advised on how to notify sexual contacts over the previous 2 months or as per their history. Formal provider contact tracing should be reserved for cases where this is not feasible or where there are concerns about treatment failure.

Follow-up should occur at 7 days to check on resolution of symptoms and partner notification. Follow-up testing is recommended at 3 months to detect re-infections.

Where there are concerns about treatment failure, prompt referral to a specialist service is recommended.

Qualifying statement

Decisions to follow these recommendations must be based on professional clinical judgement, consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure publication of the correct dosages of medication and routes of administration. However, it remains the responsibility of prescribing clinicians to ensure the accuracy and appropriateness of the medication they prescribe.

Management of gonorrhoea in adults

Resistance of gonococcus to penicillin, tetracycline and ciprofloxacin is common in most of New Zealand, and these antibiotics are not suitable as empirical agents.

This treatment guideline follows the protocols recommended by BASHH, as commissioned and edited by the Clinical Effectiveness Group, and has been adapted to take into account the availability of suitable antibiotics in New Zealand.

Penicillin should not be used for treatment. Although *N. gonorrhoeae* may be sensitive to penicillin, it is suboptimal for treating pharyngeal and rectal infection.

Partner notification is an important part of managing infection.

Indications for therapy

The indications for therapy are as follows:

- Purulent urethritis in males, which should be considered for empirical treatment after samples have been obtained.
- A laboratory diagnosis of *N. gonorrhoeae* infection and recent sexual partner(s) of confirmed cases of gonococcal infection.
- Identification of intracellular Gram-negative diplococci on microscopy of a genital tract smear in symptomatic males.

- Identification of intracellular Gram-negative diplococci on cervical microscopy from women in a high-prevalence setting for example, sexual health clinics.
- Consider offering treatment on epidemiological grounds following sexual assault (Bignell et al 2011). *The Medical Management of Sexual Assault* [available from http://www.dsac.org.nz/dsac-manual.php] (DSAC 2006) provides current advice on epidemiological treatment in this situation.

Treatment

To maximise compliance, immediate once-only doses are often given at the point of diagnosis.

Note: Azithromycin is recommended as co-treatment irrespective of the results of chlamydia testing, in an effort to delay the onset of widespread resistance to cephalosporins (Bignell et al 2011). This is also the rationale behind the increased recommended dose of ceftriaxone. There is some evidence of synergy between azithromycin and cephalosporins (Furuya et al 2006), and there have been reports of improved treatment of pharyngeal infections with dual therapy (Sathia et al 2007).

Uncomplicated anogenital infection in adults

In cases of uncomplicated anogenital infection in adults, the treatment options are as follows:

- Ceftriaxone 500 mg IM stat (reconstituted with 1% lidocaine as per the data sheet) *PLUS* azithromycin 1 g PO stat.
- Ciprofloxacin 500 mg PO stat *PLUS* azithromycin 1 g PO stat where the organism is known to be susceptible to ciprofloxacin (but not in pregnancy or lactation).
- Other single-dose cephalosporin regimens for example, cefotaxime 500 mg IM stat or cefoxitin 2 g IM stat. (Cefotaxime is not listed for use in the community in New Zealand, and cefoxitin is subsidised only for cystic fibrosis or dialysis in the community.) There is no clinical evidence that other extended-spectrum cephalosporins, either parenteral or oral, are more efficacious than ceftriaxone. The addition of probenecid 1 g PO stat may increase and prolong circulating antibiotic levels.

Uncomplicated infection where resistance to first-line therapy may be an issue in adults

Cases must be discussed with a sexual health or infectious diseases specialist, and the information must be passed onto the clinical microbiologist at the referring laboratory to facilitate testing.

- The first choice, where appropriate, should be high-dose azithromycin 2 g PO stat. This is based on good trial evidence but has poor gastrointestinal tolerance (Handsfield et al 1994).
- It should be noted that there is already evidence of resistance to azithromycin in China (Yuan et al 2011). A routine test of cure should be offered.
- Spectinomycin 2 g IM stat *PLUS* azithromycin 1 g PO stat: At the time of writing, spectinomycin is not available in New Zealand. Should this situation change, details of administration are given on the BASHH website [see Pfizer Trobicin[®] package leaflet at http://www.bashh.org/documents/3574.pdf] (Durbin PLC 2004).
- Gentamicin 240 mg IM stat *PLUS* azithromycin 2 g PO stat: Gentamicin regimens are currently under further evaluation. A review of currently available evidence concluded that gentamicin regimens have an efficacy of over 90 percent and not the 95 percent required by the CDC as a criterion for recommendation as an alternative treatment (Dowell and Kirkcaldy 2012). Gentamicin is subsidised in New Zealand only for cystic fibrosis, dialysis or complicated urinary tract infection in the community.

Specific situations (in adults)

Allergy

Individuals who are allergic to penicillins may also be allergic to cephalosporins. This is particularly the case with first-generation cephalosporins. As ceftriaxone is a third-generation cephalosporin, the risk of an allergic reaction is significantly reduced (Pichichero 2005). Ceftriaxone is contraindicated as a treatment option only in patients who have genuine hypersensitivity – with immediate and/or severe hypersensitivity – to penicillin or other beta-lactam drugs (Best Practice Advocacy Centre 2011, Gruchalla and Pirmohamed 2006, Pichichero 2006). These patients should be treated with alternative antibiotics and should be considered for referral to clinical immunology.

The treatment options for patients at risk of severe hypersensitivity are:

• Ciprofloxacin 500 mg PO stat if the organism is known to be ciprofloxacin susceptible, *PLUS* azithromycin 1 g PO stat;

OR

• Azithromycin 2 g PO stat;

OR

• Gentamicin 240 mg IM stat *PLUS* azithromycin 1 g PO stat.

Pregnancy and breastfeeding

- The treatment for pregnant or breastfeeding patients is ceftriaxone 500 mg IM stat *PLUS* azithromycin 1 g PO stat.
- Infants born to mothers who have not been treated with gonococcal infection should be managed prophylactically with single-dose ceftriaxone as for neonatal uncomplicated infection (see 'Gonococcal infection in neonates', page 43).

Pharyngeal infection

• The treatment for pharyngeal infection is ceftriaxone 500 mg IM stat *PLUS* azithromycin 1 g PO stat.

Monotherapy has shown lower efficacy (\leq 90 percent) in pharyngeal infection than in treating genital infection with *N. gonorrhoeae*. Failure with ceftriaxone in treating pharyngeal infection has been reported in Australia – therefore, a test of cure is recommended in this group (Tapsall et al 2009).

Human immunodeficiency virus (HIV) infection

• The treatment for gonorrhoea in HIV-infected individuals is the same as in those who are not HIV infected (CDC 2011).

Azithromycin and long-QT syndrome

 Risk factors for long-QT syndrome should be considered (Medsafe 2010), particularly in patients on other medications that may affect the QT interval (Medsafe 2012). Doxycycline 100 mg PO twice daily for 7 days is an alternative to azithromycin if an alert is raised on checking interactions in the New Zealand Formulary [see http://nzformulary.org] (NZF 2014).

Complicated infection in adults

Gonococcal pelvic inflammatory disease

See the *Pelvic Inflammatory Disease Management Summary* at http://www.nzshs.org/guidelines/PID-guideline.pdf (NZSHS 2012b). The treatment for gonococcal PID is as follows:

- Ceftriaxone 500 mg IM stat reconstituted with 1% lidocaine (as per the data sheet) *PLUS* doxycycline 100 mg PO twice daily for 14 days *PLUS* metronidazole 400 mg twice daily for 14 days.
- Severe PID should be referred to gynaecology in-patient services.

Gonococcal epididymo-orchitis

See the *Epididymo-Orchitis Management Summary* at http://www.nzshs.org/guidelines/Epididymo-orchitis-guideline.pdf (NZSHS 2012c).

• The treatment for gonococcal PID is ceftriaxone 500 mg IM stat *PLUS* doxycycline 100 mg PO twice daily for 14 days.

Gonococcal conjunctivitis

- Hospitalisation is recommended. The eye should be irrigated with saline/water (Bignell et al 2011). A 3day systemic regimen is recommended in the case of corneal involvement (especially as this is a relatively avascular area):
 - Ceftriaxone 500 mg IM daily for 3 days.
 - For non-anaphylaxis allergy: ceftriaxone as above.
 - For patients with a history of severe anaphylaxis with penicillin or cephalosporin allergy: azithromycin
 2 g PO stat *PLUS* doxycycline 100 mg twice daily for 7 days *PLUS* ciprofloxacin 50 mg daily for 3 days.

Disseminated gonococcal infection (DGI)

- Referral to hospital is recommended, and treatment is as follows:
 - Ceftriaxone 1 g IM or intravenously (IV) every 24 hours;

OR

- Ciprofloxacin 500 mg IV every 12 hours (if the infection is known to be susceptible).
- Treatment should be continued for 7 days but may be switched to ciprofloxacin 500 mg PO twice daily after 24–48 hours if the infection is known to be susceptible.

Partner management

Partner notification is the process by which sexual contacts of a person with an STI are informed of their possible exposure and are given information on how to access appropriate services. It is an essential part of the management of gonorrhoea to prevent ongoing transmission and re-infection.

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Patient referral of sexual contacts is the most cost-effective method of partner notification, but clinicians need appropriate training, and patients should be offered written materials to give to sexual contacts.

Sexual contacts over the previous 2 months, or as per the sexual history, should be notified.

Provider notification of sexual contacts should be reserved for difficult cases and where there is concern about decreased antimicrobial susceptibility. Availability of resources may limit the extent of provider notification.

Partner notification should be discussed with all patients who have a confirmed gonococcal infection, preferably by a healthcare professional with specific training and expertise. The discussion and outcome should be documented. It has been demonstrated that nurses with appropriate training in teaching patients how to disclose to partners can be effective in general practice (Low et al 2006).

Systematic reviews have shown that provider referral may be more effective than patient referral, but it is resource intensive (Hogben 2007).

It should be noted that there is no legal provision for patients to give treatment to partners in New Zealand. There are a number of barriers to patients telling partners, including shame, disclosure of infidelity, fear of rejection and anger.

The following practical advice has been adapted from the *Gonorrhoea Management Summary* [available at http://www.nzshs.org/guidelines/Gonorrhoea-guideline.pdf] (NZSHS 2012d).

Partner notification

- Be clear about language: 'partner' implies a relationship.
- Contacts should be treated without waiting for their test results; if the results are positive, their recent contacts need to be informed.
- Most patients choose to tell their contacts themselves.
- It is helpful to provide written information (Trelle et al 2007).
- Encourage patients to bring their current partners to the clinic at the time of treatment.
- Notifying all contacts may not be possible for example, if there insufficient information or a threat of violence.

Management of sexual partners/contacts

- Perform a full sexual health check.
- Do not wait for test results treat empirically for gonorrhoea.
- If the susceptibility profile of the isolate from the index case is known, treat accordingly.

Management of gonorrhoea in children

Because of the medico-legal implications, robust processes are required for specimen collection, transportation, testing and supplementary testing in children.

Where there are concerns about sexual abuse, assessment should be undertaken only by doctors with appropriate training.

If a diagnosis of gonorrhoea is made in a pre-pubertal child, treatment should be withheld until the child has been fully assessed by a child protection team.

This section pertains to the management of gonorrhoea in children, and the need for testing for other STIs should be taken into consideration. The medical and legal testing of STIs in children has been summarised by Hammerschlag and Guillén (Hammerschlag and Guillén 2010).

Testing for *N. gonorrhoeae* in prepubertal children

Sexual abuse is the most common mode of transmission of gonorrhoea in prepubertal children (Kelly 2002). Overall, children with a history of sexual abuse have a low incidence of STIs. As in adults, rectal and pharyngeal gonococcal infections are commonly asymptomatic. A retrospective analysis in three different countries, including New Zealand, gave a detection rate of 0.4–1.8 percent for both gonorrhoea and chlamydia (Hammerschlag 2011).

Because of the medico-legal implications, robust processes are required for specimen collection, transportation (see below) and testing, and supplementary testing is needed in the event of a positive diagnosis. In neonates and infants, maternal foetal transmission at the time of delivery should be considered. It should be noted that there is no defined upper age limit for the diagnosis of gonorrhoea as a result of vertical transmission from the mother to the baby.

Details of clinical assessment of suspected sexual abuse are contained in *The Medical Management of Sexual Assault* [available from http://www.dsac.org.nz/dsac-manual.php] (DSAC 2006). Clinical assessments in this situation should be undertaken only by doctors who have received appropriate training. Where there is a suspicion of sexual abuse, a chain-of-evidence procedure is required for collection of specimens. This requires documentation of all persons handling the specimens, together with the dates, places and conditions of storage. When a diagnosis of gonorrhoea is made in prepubertal children, laboratories should retain specimens for further supplementary testing.

When should *N. gonorrhoeae* testing be undertaken in prepubertal children?

N. gonorrhoeae testing should be undertaken in prepubertal children in the following instances:

- In children who have symptoms but who have no other indicators of sexual abuse at the time of the initial presentation. This includes girls with vaginal discharge and children of both genders with perianal symptoms. Such specimens can be collected without a chain-of-evidence procedure. If any tests are positive for gonorrhoea, the child should not be treated but should be referred urgently to a paediatric child protection service for repeat testing and ongoing management.
- In children where there is a reasonable suspicion of sexual abuse.
- In children with symptoms for which an STI is a possible differential diagnosis.
- In children who have made a disclosure of sexual abuse that includes allegations of anal or vaginal penetration.
- In children in whom there has been an STI diagnosis.

Which specimens should be taken, and which tests should be requested?

Genital and non-genital sites can be sampled for *N. gonorrhoeae*, using culture or NAAT. In young children, the level of co-operation and the degree of discomfort felt by the child need to be considered. On occasion, children are examined under a general anaesthetic because of other concerns. A general anaesthetic is rarely required for the purpose of STI testing only. Initially, collection of urine for dual *N. gonorrhoeae* and *C. trachomatis* NAATs is the most feasible and least invasive option, with multi-site testing being reserved for those with a confirmed STI. It should be noted that there has been limited experience of NAAT in non-genital sites in children, and the few studies that have been published included a high proportion of girls.

The following sites can be sampled, and swabs can be pre-moistened with normal saline to reduce discomfort:

- Vaginal swabs can be taken for culture and NAAT. Because of the non-acidic pH in the vagina in prepubertal girls, *N. gonorrhoeae* can be cultured from a standard vaginal swab placed in transport medium, and a speculum examination is not required. The swab will also be cultured for opportunistic organisms that may cause vulvovaginitis in prepubertal girls. Microscopy ± culture may detect *T. vaginalis*. A vaginal swab can be taken from discharge that has pooled distal to the hymen. Alternatively, swabs can be taken through the hymen, using a fine perinasal swab. The inner hymen is exquisitely tender in prepubertal girls, and touching it should be avoided if possible.
- Urine collection (first-pass or clean-catch, preferably after abstaining from voiding for a minimum of 1 hour) can be taken for dual *N. gonorrhoeae* and *C. trachomatis* testing. Although studies of NAAT in children are limited, there is evidence that such testing has high specificity. It should be noted that not all NAAT methods have been evaluated, and supplementary testing of positive results is required (Girardet et al 2009, Hammerschlag 2011).
- Rectal and pharyngeal swabs can be taken for culture and NAAT. Rectal swabs should be inserted into the anal canal. Supplementary testing is required for positive results.
- Urethral swabs in prepubertal boys are rarely necessary and only in the presence of urethral discharge. A urine sample is the preferred first sample.

Positive NAATs should be followed by taking of swabs for culture for typing and supplementary testing prior to treatment, if this was not done at the time of the initial assessment.

Additional testing

Gonorrhoea typing

In order to confirm or exclude strain relatedness between the child and other family members or potential contacts, gonorrhoea cultures are sent to the Nosocomial Infections Laboratory at ESR in Wellington for DNA macrorestriction analysis. On occasion, it may be necessary to determine prevalent stains of gonorrhoea in the community. Because of the expense, this would only be arranged if considered relevant to the case and with agreement on payment from the Police.

NAAT

Supplementary testing is required for all paediatric cases. Testing with a number of tests using different gene targets is advisable (HPA 2012), and a minimum of three separate genes known to have discriminatory capacity is recommended (see 'Testing for *N. gonorrhoeae* in prepubertal children', page 40).

Management of gonorrhoea in prepubertal children (excluding neonates)

If possible, treatment should be withheld until specimens for supplementary testing have been collected and the child has been assessed. Where the diagnosis has been made on testing because of symptoms and without disclosure or suspicion of sexual abuse, referral to Child Youth and Family and the Police is mandatory and an urgent inter-agency case conference is required, with discussion on how to keep the child safe. Voluntary testing of parents and other household members is required, with explanation of the significance of a positive result. A guideline has been developed in Auckland for co-ordination of such investigations (Whaitiri and Kelly 2011) and is available on the Starship Children's Health website [see 'Abuse & Neglect' at http://www.adhb.govt.nz/starshipclinicalguidelines/Abuse%20and%20Neglect.htm] (ADHB 2010). All contact tracing must be done in the context of the Police and Child Youth and Family investigation. Advice should be sought from a local Sexual Abuse Assessment and Treatment Service paediatrician.

For uncomplicated anogenital and pharyngeal gonorrhoea (not in neonates)

Ceftriaxone: 50 mg/kg (maximum 500 mg) IM can be used as a single dose, using the adult dilution as per the data sheet [available at http://www.medsafe.govt.nz/profs/datasheet/c/ceftriaxoneaftinj.pdf] (Medsafe 2013). It has been demonstrated that the plasma concentration—time curves after IV and IM administration are equivalent up to 24 hours. IV administration can be used where appropriate (Medsafe 2013);

PLUS

• Azithromycin: A single oral dose of 20 mg/kg could be used in children weighing less than 45 kg, although there are no published data on its use in this situation (DSAC 2006).

Alternative treatments

Ciprofloxacin is relatively contraindicated in children because of concerns about arthropathy, based on animal studies. However, it has been used in other childhood conditions without adverse sequelae. It may be considered in children with a history of major penicillin anaphylaxis where the organism is susceptible. A dose of <20 mg/kg in children weighing <45 kg is recommended on the basis of the treatment used for pyelonephritis (DSAC 2006).

Contact tracing

Testing of parents, household contacts and siblings is indicated as determined by the history and an interagency case conference, as discussed above. This testing should include culture, so that *N. gonorrhoeae* isolate(s) are available from any contact(s) with gonorrhoea. Such isolates can then be typed at ESR and compared with isolates from the child.

Management of gonorrhoea in postpubertal adolescents

Gonorrhoea in postpubertal adolescents should be managed as per management in adults. For young women who are being assessed for possible sexual abuse and who are not otherwise sexually active, a speculum examination may not be necessary. Vaginal swabs can be taken for NAAT. A chain-of-evidence procedure may be required in younger adolescents with no history of other sexual activity.

Gonococcal infection in neonates

Gonococcal ophthalmia neonatorum is the most common manifestation of vertical transmission of gonorrhoea. It presents at 2–5 days of age, with profuse purulent discharge and oedema. If it is untreated, corneal ulceration and blindness may result. Disseminated infection may occur, including skin lesions and septic arthritis. Other presentations include subcutaneous abscesses – for example, at the site of a foetal scalp electrode monitoring clip. All infants with suspected gonococcal ophthalmia neonatorum must be assessed by a paediatrician.

For a summary of testing, see Table 3, Table 4 and Table 5.

Treatment

All infants should be discussed with a paediatrician and require hospitalisation and evaluation for systemic infection (CDC 2011). At least one dose of ceftriaxone 50 mg/kg up to 125 mg (IM or IV) is recommended. Longer courses are used in severe or disseminated gonococcal infection (ADHB 2000).

Ceftriaxone remains first-line treatment, and this is one of the few explicit indications for neonatal ceftriaxone. Cefotaxime is used only for infants with hyperbilirubinaemia or during prolonged antibiotic courses when required.

Immediate and frequent eye hygiene is important, with use of hourly saline irrigation until exudates clear.

Follow-up

All patients should be followed up at 7 days. Important outcomes include:

- Confirmation of treatment compliance.
- Ensuring resolution of symptoms.
- Enquiring about adverse reactions.
- Taking a further sexual history and exploring the possibility of re-infection and the need for further contact tracing.
- Partner notification and health promotion.

This can be done by phone or in person.

If there is reported re-exposure, the patient should be offered re-treatment.

It is recommended that all patients diagnosed with a bacterial STI should be offered routine follow-up testing at 3 months to detect re-infection (Table 5). Those with ongoing symptoms, pregnant women and those who have had non-first-line treatment require earlier testing.

Table 5: Summary of indications, timing and specimen collection for follow-up testing

Clinical scenario	Timing of follow-up testing	Specimens required (see Table 3 and Table 4 for more information)
Uncomplicated asymptomatic urogenital or rectal infection treated with first-line treatment <i>PLUS</i> 3-month follow-up of the scenarios listed below	Follow-up STI testing at 3 months to exclude re-infection	 NAAT: FVU in males Vulvovaginal swab in females Rectal swab if previously infected at this site
Complicated urogenital infection (PID, epididymo-orchitis) and symptoms resolved at follow-up review (at 1–2 weeks)	Follow-up STI testing at 3 months to exclude re-infection	NAAT:FVU in malesVulvovaginal swab in females
Pharyngeal infection	Routine follow-up testing at 2 weeks for <i>Neisseria gonorrhoeae</i> only, or at 5 weeks post- completion of treatment (to give adequate time to allow for chlamydia NAAT to revert to negative)	Pharyngeal swab for NAAT
Non-first-line treatment	Follow-up testing at 2–5 weeks post-completion of treatment	NAAT:FVU in malesVulvovaginal swab in females
Pregnant women	Follow-up testing in third trimester and at least 2–5 weeks post-completion of treatment	Vulvovaginal swab for NAAT
Persistent vaginal discharge	At 72 hours post-completion of treatment	Cervical swab in Amies transport medium for culture
Persistent proctitis	At 72 hours post-completion of treatment	Rectal swab in Amies transport medium for culture
Urethritis, persistent discharge or dysuria	At 72 hours post-completion of treatment	Urethral swab in Amies transport medium for culture
Infection at any site with known decreased antimicrobial susceptibility, or contact of such a case	At 72 hours post-completion of treatment	Swab for culture in Amies transport medium

FVU = first-void urine; **NAAT** = nucleic acid amplification test; **PID** = pelvic inflammatory disease; **STI** = sexually transmitted infection.

It should be noted that NAAT for *N. gonorrhoeae* usually becomes negative by 2 weeks post-treatment (Hjelmevoll et al 2012). This is earlier than for chlamydia testing, which may take up to 4–6 weeks post-treatment (BASHH 2010).

Suspected treatment failure

Suspected treatment failure requires urgent discussion with a specialist sexual health service and microbiologist.

Anonymous reports of suspected treatment failures should be sent to ESR.

Working case definitions for 'confirmed' and 'probable' treatment failure have been defined in the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) Action Plan for England and Wales (HPA 2013).

A probable case:

- May be asymptomatic or have ongoing genital symptoms following diagnosis of *N. gonorrhoeae* and adequate treatment with ceftriaxone.
- May deny the possibility of re-infection.
- Has confirmation of ongoing infection on culture, the presence of intracellular diplococci on microscopy on a urethral specimen after 72 hours post-treatment, or positive NAAT after 2–3 weeks post-treatment.

A confirmed case includes the above criteria plus a laboratory result indicating decreased ceftriaxone susceptibility (see 'Antimicrobial susceptibility testing', page 26).

Testing is summarised in Table 3, Table 4 and Table 5.

For alternative treatment options, see 'Uncomplicated infection where resistance to first-line therapy may be an issue in adults', page 36.

Enhanced surveillance of antimicrobial resistance in *N. gonorrhoeae*: roles and responsibilities

The following section outlines the roles and responsibilities of laboratories, clinicians, ESR and the Ministry of Health in monitoring antimicrobial resistance in *N. gonorrhoeae*, and the responses required when there is treatment failure or when gonococci with decreased susceptibility or resistance to ceftriaxone are identified. It should be noted that *N. gonorrhoeae* is not notifiable in New Zealand. Enhanced surveillance of syphilis and HIV infection is on a voluntary basis.

Local level

Roles and responsibilities of diagnostic laboratories

Antimicrobial susceptibility testing

Laboratories should culture sufficient specimens to obtain an adequate number of gonococcal isolates to determine local antimicrobial susceptibility rates and to detect emerging resistance (see 'Laboratory culture recommendations', page 26). The antimicrobial susceptibility testing methods that are used should

be capable of detecting decreased susceptibility and resistance to ceftriaxone. Laboratories should use appropriate quality-control strains to monitor the performance of their antimicrobial susceptibility tests to ensure reliable results. (See 'Antimicrobial susceptibility testing', page 26, which discusses the methodology for ceftriaxone susceptibility testing).

Laboratories should participate in an appropriate external quality-assurance programme (EQAP) for gonococcal antimicrobial susceptibility testing. One such programme is provided by the Australian WHO Collaborating Centre for Sexually Transmitted Diseases. For this Centre's contact details, contact ESR or seethe WHO Collaborating Centres Global Database at http://apps.who.int/whocc/Detail.aspx?cc_ref=AUS-72&cc_ref=aus-72& (WHO 2014).

Laboratories should immediately notify the clinician of any isolates with decreased susceptibility or resistance to ceftriaxone. Such isolates should be referred to ESR for confirmation of their resistance and for strain typing.

All gonococci isolated from cases of treatment failure should be referred to ESR for antimicrobial susceptibility testing.

Analysis and reporting of antimicrobial susceptibility test results

Laboratories are requested to provide their gonococcal antimicrobial susceptibility results to ESR as part of the national laboratory STI surveillance system.

To guide empirical therapy, laboratories should ensure that they generate or have access to data on local susceptibility rates and should make these data available to local clinicians. Such local data will be available from ESR for laboratories who report their gonococcal antimicrobial susceptibility results as part of the laboratory STI surveillance system.

Roles and responsibilities of clinicians

Cases of treatment failure

Clinicians should ensure that for every patient with treatment failure, appropriate specimens are collected for culture and antimicrobial susceptibility testing (see Table 3, Table 4 and Table 5). A phone call should be made to the clinical microbiologist at the referring laboratory to inform them of a potential treatment failure; this will ensure that the appropriate testing is carried out. 'FOR CULTURE' and 'GONORRHOEA TREATMENT FAILURE' should be noted on the test request form to ensure that adequate testing is undertaken.

General practitioners should make contact with their nearest sexual health clinic (which may be in a neighbouring DHB) to discuss and/or refer the case. This is to ensure that the case is managed appropriately and that a surveillance case report form is completed (see 'Appendix 2: gonorrhoea treatment failure surveillance case report form', page 57).

Cases with decreased susceptibility or resistance to ceftriaxone with or without treatment failure

Clinicians should make contact with their nearest sexual health clinic (which may be in a neighbouring DHB) to discuss and/or refer the case. This is to ensure that the case is managed appropriately and that a surveillance case report form is completed (see 'Appendix 2: gonorrhoea treatment failure surveillance case report form', page 57).

National level

Roles and responsibilities of the Institute of Environmental Science and Research (ESR)

Routine surveillance of gonococcal antimicrobial susceptibility

As part of ESR's role in national surveillance of STIs and antibiotic resistance, ESR should collate gonococcal antimicrobial susceptibility testing data from diagnostic laboratories, including ceftriaxone susceptibility data (see 'Antimicrobial susceptibility testing', page 26). Analysis and reporting of these data should occur in a timely manner to ensure that appropriate policy changes or control measures can be implemented promptly. Ceftriaxone susceptibility testing data should be reviewed as they are submitted to ensure that any isolates with decreased susceptibility or resistance to ceftriaxone are identified early and followed up. National gonococcal antimicrobial susceptibility data should be published regularly and could be incorporated into the quarterly laboratory STI surveillance reports that are already produced. These reports are generally published within 2 months of the end of each quarter.

Surveillance of cases of gonorrhoea treatment failure or cases with decreased susceptibility or resistance to ceftriaxone

Routine collection, analysis and reporting of demographic and risk factor information on cases of gonorrhoea treatment failure or cases of gonorrhoea with decreased susceptibility or resistance to ceftriaxone will assist with the detection and control of outbreaks of antimicrobial-resistant gonorrhoea and will help identify priority population groups for health promotion activities. Surveillance of these cases could include just those managed by or referred to sexual health clinics. This would be acceptable, given that many 'higher risk' individuals will attend sexual health clinics; treatment failures and cases with known decreased ceftriaxone susceptibility or resistance occurring in general practice should be discussed with a sexual health physician (see 'Suspected treatment failure', page 45), and there is at least one sexual health clinic in each DHB region (except for Wairarapa).

ESR should co-ordinate the surveillance, including maintaining a standard case report form, storing case report form data in an appropriate database, contacting sexual health clinics to provide data, and reporting data in a timely manner. The gonorrhoea treatment failure case report forms used by the CDC (CDC 2013) in the US and the Health Protection Agency (HPA) in England (HPA 2013) have been used as the basis for a proposed New Zealand surveillance case report form (see 'Appendix 2: gonorrhoea treatment failure surveillance case report form', page 57). Sexual health clinics already report data to ESR routinely and have experience completing anonymised detailed case report forms for syphilis cases.

National surveys of gonococcal antimicrobial susceptibility

ESR should undertake periodic national point-prevalence surveys of gonococcal antimicrobial susceptibility, using isolates collected from diagnostic laboratories throughout New Zealand. The survey isolates should be tested for susceptibility to an extended range of antimicrobials, including antimicrobials currently used to treat gonorrhoea, 'legacy' antimicrobials (for example, spectinomycin) and antimicrobials that could potentially be used in the future if treatment failures occur because of decreased susceptibility to ceftriaxone or if ceftriaxone resistance emerges (for example, carbapenems and gentamicin). The susceptibility testing method that is used should determine the MICs. Resistant isolates should be typed to determine whether the resistance is associated with a limited number of strains or is widespread.

Submission of New Zealand gonococcal antimicrobial susceptibility data to international surveillance systems

ESR should co-ordinate the submission of New Zealand data to international gonococcal susceptibility surveillance systems, including the WHO Gonococcal Antimicrobial Surveillance Programme (GASP) for the Western Pacific Region for laboratories not currently participating. These data could be submitted from the national laboratory STI surveillance system or directly from individual laboratories. The most recent data from the WHO Western Pacific Region GASP are usually published in the *Communicable Diseases Intelligence* journal, which is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-cdi-cdiintro.htm (DOH 2014).

Provision of reference antimicrobial susceptibility testing services and qualitycontrol strains

ESR's national reference laboratory offers confirmatory antimicrobial susceptibility testing for gonococcal isolates and advice on susceptibility testing methods. ESR's New Zealand Reference Culture Collection, Medical Section (NZRM) maintains and supplies suitable quality-control strains for antimicrobial susceptibility testing.

Typing services

ESR provides molecular-typing services, including pulsed-field gel electrophoresis (PFGE) and NG-MAST, to identify gonococcal strains to assist in investigating and describing the epidemiology of gonorrhoea and gonococcal resistance in New Zealand. This typing service is also available, where appropriate, to assist the Police and forensic services in the investigation of cases of sexual abuse.

Monitoring of international trends in gonococcal antimicrobial susceptibility

ESR should monitor international trends in gonococcal antimicrobial susceptibility and ensure that it has the laboratory capability to identify and characterise any new resistance. ESR should also be able to adapt its national STI surveillance system to capture any new, emerging resistance.

Roles and responsibilities of the Ministry of Health

In conjunction with ESR, the Ministry of Health should monitor international trends in gonococcal antimicrobial susceptibility and support the surveillance and management of gonococcal resistance in New Zealand.

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Appendix 1: how to take your vaginal swab

(Reproduced with permission from Leeds Teaching Hospitals NHS Trust, Leeds, UK)

How to take your Vaginal swab

Wash and dry your hands first.

The pack contains a swab stick and a plastic container.

Do not place the swab stick directly on any surface.

Do not touch the cotton wool tip of the swab.

Ask for a new kit if you drop the swab or touch the tip or spill any of the liquid in the container

1. Getting Ready:

out the container, carefully unscrew the top and place Peel open the pack. Take it on a flat surface



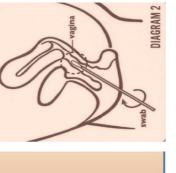
2. How to hold the swab: Take the swab stick out of its packet and hold the



3. Taking the sample

- Rub the cotton bud around the upper part of the entrance to the • With your legs apart, spread the opening of your vagina.
 - vagina (where the red arrow is) a couple of times.
- Then insert it 1-2 inches into your vagina. Your fingers on the middle of the shaft will stop you going in too far.
- Rotate the swab around your vagina, making sure it touches the inside wall of your vagina for 5 seconds (count to 5 slowly)







Make sure you do not spill any Put the swab in the container. 4. To finish off:



Snap the stick off at the black line



Screw the lid back on tightly.



Appendix 2: gonorrhoea treatment failure surveillance case report form



Gonorrhoea ceftriaxone treatment failure and/or infection with a *Neisseria gonorrhoeae* strain with decreased susceptibility or resistance to ceftriaxone

1. Reporter details

Name of clinician	
City or town of clinic	

2. Patient details and risk factors

Patient ID code	First	Second	First		Date of birth				
Note: For the first two letters of the surname, do not use any prefix such as 'Mac', 'Mc', 'van der', etc. If the surname starts with a prefix, use the letters immediately after it.	letter of surname	letter of surname	letter of first name	Sex	Da	ау	Mont	th	Year
Gender	🗌 Male	E Fem	ale 🗌 Tra	nsgende	er				
Ethnicity Self-identified – may tick more than one box	NZ Euro		Chinese	and Māo	ri	_	āori ngan		Indian Niuean
Country of birth									
Current city or town of residence									
Was gonorrhoea most likely acquired in NZ?	Yes If 'no', spec	No likely	Unkn U country of		on:				
Gender of sexual contacts in the last 12 months	🗌 Same g	ender only	🗌 Ор	posite ge	ender o	nly	🗌 Во	oth ge	nders
Is the patient a sex worker?	Yes	🗌 No	🗌 Unkn	own					

3. Clinical details – first presentation

Date on which the patient first presented	Day Month Year	
Primary reason for the first presentation	STI symptoms Contact of a case	Other
Laboratory confirmed site(s) of infection Tick as many sites as are applicable	SiteCCervixIEyeIPenisIRectum/anusIThroatIUrethraIUrineIVulva/vaginaIOther site (specify):IUnknown siteI	Culture positive NAAT positive
Was antimicrobial susceptibility testing performed?	Yes No Unknown If 'yes', provide details below: Specimen site Antibiotic Specimen site Antibiotic Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen site Image: Specimen s	MIC (mg/L) Zone diameter (mm)



What treatment was prescribed?	Provide details of the initial treatment:
Did the symptoms resolve after the initial treatment?	 Not applicable (asymptomatic infection) Yes No Unknown If 'yes', section 4 will need to be completed.
Was a test of cure performed?	Yes No Unknown If 'yes', section 4 will need to be completed.

4. Clinical details – subsequent presentation i.e. due to persistent symptoms or recall for a test of cure

Date of subsequent visit	Day Month Year Image: Constraint of the patient refused to return for a second	nd visit, and skip to question 5.
Reason for subsequent visit	Persistent symptoms Test of cure If symptomatic, provide details:	Unknown
Laboratory confirmed site(s) of infection	Site Cu	ulture positive NAAT positive
Tick as many sites as are	Cervix	
applicable.	Еуе	
	Penis	
	Rectum/anus	
	Throat	
	Urethra	
	Urine	
	Vulva/vagina	
	Other site (specify):	
	Unknown site	



Was antimicrobial susceptibility testing	Yes No Unknown						
performed?	If 'yes', provide details below:						
	Specimen site	Antibiotic	MIC (mg/L)	Zone diameter (mm)			
What treatment was prescribed?	Provide details of t	he second treatment:					
Did the symptoms resolve after the second	Not applicable (asymptomatic infection)						
treatment?	Yes No Unknown						
Was a test of cure	Yes No Unknown						
performed?	If 'yes', provide details of the sites that were sampled and the results:						

5. Comments

Any other relevant comments:						

Please return this completed form by email, mail or fax to ESR:

Email: STISurv@esr.cri.nz

Mail: Health Intelligence Team, ESR, PO Box 50348, Porirua 5240

Fax: 0-4-978 6690