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Is it time to move to nucleic acid amplification tests screening for pharyngeal and rectal gonorrhoea in men who have sex with men to improve gonorrhoea control?

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Abstract. The use of nucleic acid amplification tests (NAAT), as well as or in preference to culture for non-genital sites is now recommended both in Australia and overseas because of their greater sensitivity and improved specificity. A survey of 22 Australian sexual health clinics who each year test over 14 500 men who have sex with men (MSM) show that culture remains the predominate method for detecting gonorrhoea at pharyngeal (64%) and rectal (73%) sites. This editorial discusses the potential disadvantages of using culture over NAAT in relation to optimal gonorrhoea control among MSM and advocates that significantly improved control would be achieved by moving to NAAT with the proviso that culture samples are taken wherever possible on NAAT-positive samples and from clients with urethritis to ensure continued surveillance for antimicrobial resistance.

Australia's ability to control gonorrhoea in men who have sex with men (MSM) may currently be hampered by the common use of culture rather than nucleic acid amplification tests (NAAT) to detect gonorrhoea infection in the pharynx and rectum. The use of insensitive culture techniques may not only be contributing to a higher prevalence of gonorrhoea, but may also be leading to higher rates of HIV transmission and its significant associated lifetime treatment costs.[1]

The data supporting the limited sensitivity of culture compared with NAAT from pharyngeal and rectal samples is well substantiated. In a recent study at Melbourne Sexual Health Centre, culture plated directly at the bedside failed to detect 20 (42%, 95% confidence interval (CI) 28–57%) of the 48 NAAT-positive samples among 1011 rectal samples.[2] Culture also failed to detect 25 (61%, 95% CI 45–76%) of 41 NAAT-positive samples among 1076 pharyngeal samples.[2] Care was taken to test samples with two targets, i.e. the *opa* and *por* A pseudogene.[3,4] A study in the USA of over 1000 MSM, reported a sensitivity of culture of only 55% for pharyngeal and 49% for rectal samples compared with NAAT testing.[5] Other studies have reported similar findings.[6]

It has been rightly argued that culture for gonorrhoea should be maintained because this technique allows surveillance for changes in antibiotic resistance. However, this important function can be successfully maintained if culture samples are taken at the time an individual returns for treatment of their NAAT-positive pharyngeal and rectal infections. The majority of these individuals would not have received treatment at the time of sampling because infections at these sites are largely asymptomatic, so treatment would only occur when individuals are recalled after a positive result.[7,8] Furthermore, culture could continue to be used with urethral infections, which are largely symptomatic.

The other concern with NAAT testing for gonorrhoea at extragenital sites is the specificity of some NAAT assays at these sites.[9] Specificity of NAAT assays is a concern, because closely related *Neisseriae* species may result in false-positive results.[10] This was highlighted in a study utilising the BDProbeTec ET System (Becton Dickinson, Franklin Lakes, NJ, USA) for detection of gonorrhoea in the Sydney-based Health in Men (HIM) study of homosexual men, where only 30% of pharyngeal and 74% of rectal samples were confirmed as true-positives using a supplemental *porA* pseudogene assay.[11] The *porA* pseudogene assay has been shown to be to be highly specific for the diagnosis of both genital and extragenital gonorrhoea.[12,13] Careful selection of primary assays and restricting screening to MSM, where the prevalence of gonorrhoea is high, will help to optimise specificity.

It is also recommended that any positive NAAT test is confirmed by a supplemental NAAT assay that targets

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different genes from those used in the screening assay.[14,15] This can be done utilising in-house assays or utilising commercial assays targeting different genes.[3,4]

There have been recent changes in Australian and international recommendations for gonococcal testing. The Australian STIGMA guidelines now recommend either NAAT testing or culture for both pharyngeal and rectal samples.[16] In the USA, after a 2009 expert consultation meeting at the Centers for Disease Control and Prevention, NAAT testing for both pharyngeal and anal samples was recommended, although it was noted that laboratories must first establish satisfactory performance specifications.[5,15] The UK Health Protection Agency also favours NAAT over culture for the detection of extragenital gonorrhoea in MSM.[17]

The effect of using culture, instead of NAAT testing, for pharyngeal and rectal samples on the prevalence of gonorrhoea in MSM depends on several factors, including the proportion of clinical services for MSM using culture or NAAT testing. We carried out a survey of Australia's 25 largest sexually transmissible infection (STI) clinics that form part of the Australian Collaboration for Chlamydia Enhanced Sentinel Surveillance (ACCESS) program.[18] We received data from 22 of these clinics, which together reported testing ~14 500 MSM annually, of which culture was used for 64% of pharyngeal specimens and 73% of rectal samples (C. K. Fairley, pers. comm., 2010).

Having established that culture is still relatively widely used for pharyngeal and rectal samples, the next key question is how significantly the use of culture adversely affects the prevalence of gonorrhoea in MSM. In other words, would changing to NAAT testing result in a significant fall in gonorrhoea prevalence in MSM. The prevalence of gonorrhoea in MSM is determined by the basic reproductive rate (Ro), which itself is dependent on a complex set of relatively poorly studied interactions between the duration of infection at each site, the transmissibility between different sites with different acts of sex and the rates of site-specific partner change. As moving from culture to NAAT will only change the duration of infection and not other components of Ro, so it is possible to crudely estimate this effect.

The duration of pharyngeal infection with gonorrhoea has been studied using culture among 18 pharyngeal positive individuals, who were left untreated, asked to refrain from new sexual partners and cultured every 2 weeks.[19] All 18 had become culture negative at 12 weeks (median time of 6 weeks), although how long they had been culture positive at the start of the observation period is unknown. If we assume that they were identified midway through their untreated infection, one could postulate that culture-detectable pharyngeal gonorrhoea could last on average for 12 weeks. Given that routine screening for pharyngeal gonorrhoea is recommended once a year, annual testing would detect on average only one in four infections while three out of every four infections would have resolved untreated. The one case in every four that was detected by screening would by chance be detected half way through its natural course and then treated, thereby halving its duration from 12 weeks to 6 weeks. Because culture testing is only half as sensitive as NAAT testing, culture would miss half of the cases detected by NAAT and therefore culture would only detect every eighth infection, while NAAT detected one in four. One can therefore postulate that, with yearly testing using only culture, there would be a reduction in the duration of pharyngeal infection by about one-sixteenth (i.e. halving the duration in every eighth infection). Similarly, with yearly testing using only NAAT there would be a reduction in the duration of pharyngeal infection by about one-eighth (i.e. halving every fourth infection). Thus, in simplistic terms, if NAAT testing was used instead of culture, this specifically would translate into a 6% reduction in Ro for pharyngeal gonorrhoea (i.e. 6% or can be regarded as the difference between 1/8th and 1/16th).

The duration of rectal infection with gonorrhoea has not been studied in the same way as pharyngeal gonorrhoea. However, there have been cohort studies that have looked at the prevalence and incidence of rectal infection.[20] One can estimate the duration if one assumes that it is roughly equivalent to the prevalence divided by the incidence in the same population. An Australian cohort study of homosexual men (HIM study) found a prevalence of rectal gonorrhoea at enrolment of 0.91% and an incidence in the following year of 0.96 per 100 person years.[20] This would roughly equate to a duration of about one per year. Using similar logic to pharyngeal swabs, and assuming screening would take place yearly, then NAAT testing would shorten the duration of rectal infection from 12 months to an average of 6 months. If culture was used and half of the cases were missed, the duration would be shortened to only 9 months. Thus, in simplistic terms, if NAAT were used instead of culture, it would translate into a 25% greater reduction in Ro for rectal gonorrhoea specifically (i.e. a difference between 9 months and 6 months duration).

Both of these assumptions are subject to unknown factors. For example, if the infectivity of NAAT-positive but culture-negative samples was lower than culture-positive samples, the effect on the basic reproductive rate of replacing culture with NAAT will be lower. However, if the duration of pharyngeal infection by NAAT was longer than estimated from the culture as studied in the 1970s, the magnitude of the reduction in Ro will be greater.[19]

Effective control of gonorrhoea can best be achieved when the basic reproductive rate is lowered to less than one. Many developed countries have achieved this in heterosexuals, primarily through the provision of accessible health care, which identifies and terminates infection early.[21] In Australian capital cities, the rates of gonorrhoea in women are ~5 per 100 000, which is similar to Scandinavian countries.[21] However, limited access to health care, and the resultant higher duration of infection, is responsible for the very high prevalence of gonorrhoea seen in remote Indigenous communities in Australia.[22]

It is not known how close to one the basic reproductive rate of gonorrhoea is among MSM, but recent significantly increased screening appears likely to be lowering prevalence. In a Victorian study between 2002 and 2009 among MSM, the proportion of pharyngeal, anal and urethral samples that were positive for gonorrhoea fell by about half, with a large rise in testing rates over this time suggesting that the basic reproductive rate for gonorrhoea in MSM had fallen (L. A. Vodstrcil *et al.*, unpubl. data).

The key public health issue then is: will a change from culture to NAAT result in a fall in the basic reproductive rate for gonorrhoea in MSM to less than one? We believe that it is time to move to universal screening of MSM for pharyngeal and rectal gonorrhoea using NAAT testing to minimise the morbidity associated with gonorrhoea and potentially to enhance control of HIV transmission. However, there are two important caveats: wherever feasible, individuals with positive-NAAT specimens have pretreatment culture samples for antibacterial surveillance and that all NAAT testing follow the recommendations for confirming all positive tests with supplemental assays.

Conflicts of interest

None declared.

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