



Personal, partner and public health benefits of testing for *Chlamydia trachomatis* infections in women

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In view of personalised laboratory testing for the presence of infections with *Chlamydia trachomatis* the paper by Wiesenfeld fits perfectly (1). The paper starts with a case of a 19-year-old woman visiting her physician for preventive reasons. She is sexually active and has no complaints. The question is raised whether she should be screened for *Chlamydia trachomatis*. The answer is yes and Wiesenfeld gives a number of good arguments why women at the reproductive age or others at increased risk for infection should be (regularly) tested.

First of all, *C. trachomatis* infections often remain asymptomatic and infections can be cleared spontaneously, but they can still lead to, sometimes serious, complications such as pelvic inflammatory disease (PID) and infertility (2). Pre-term delivery is associated with a past infection. Acute PID does not develop in most women with chlamydial infection, either because they receive effective antibiotic treatment or because of spontaneous clearance, which occurs in one in five infected women (3).

Worldwide *C. trachomatis* has for decades been the most reported infection, with 1.5 million cases in the United States in 2015 (1). There are differences among ethnicities within a country, for example within the USA the prevalence of chlamydial infection among sexually active non-Hispanic black girls and women 14 to 24 years of age was 13.5%, as compared with 1.8% among non-Hispanic white girls and women (1). Also in Australia, impressive regional differences in *C. trachomatis* prevalence were noted, probably reflecting differences in the ethnicity of their populations (4). In the Northern Territory, with many aboriginals, 31.2% of women aged 16 to 29 years were positive for chlamydia

whereas this was only 4.0% positive in women of the same age group in Tasmania; all were tested during a yearly visit to their general practitioner (GP). Remarkable was the inverse relation with testing rate, which was the highest in Tasmania with 92.5% getting tested per GP visit versus 71% in the Northern Territory (4). But the prevalence may also vary for the same ethnicities in different countries. For example, among young women visiting a family planning clinic in Surinam (perceived low risk), the chlamydia prevalence was over 20% in 2009 (5), whereas in visitors of the STI clinic (high risk) in Amsterdam, the Netherlands, it was found in the same calendar period to be 18% among Surinamese young women compared to 11% for the native Dutch young women (6). And in a screening study in the Netherlands among (low risk) women aged 16 to 29 years, the positivity rate for *C. trachomatis* was in general 2% to 4% but higher in postcode areas with low versus high socioeconomic status scores (4.6% versus 2.4%) and higher among participants with non-Dutch background compared with a Dutch background (5.6% versus 3.4%) (7). These differences in chlamydia prevalence in different ethnicities and populations probably reflects the accessibility to health care, thus the possibility for women to get tested and treated for chlamydia (6).

People most at risk for chlamydia are young sexually active women (<25 years), those with inconsistent condom use and with new or multiple partners. In *Table 2*, Wiesenfeld provides a list of indications that warrant chlamydia screening in women (1). Regular testing has been reported to substantially reduce the incidence of PID (8). An important question is, however, how much of the

PID burden is caused by *C. trachomatis* infections. In the United Kingdom, the proportion of PID attributable to *C. trachomatis* was 20% in women aged 16–44 years and 35% in women aged 16–24 years (9). In a recently published systematic review the population excess fraction of treated chlamydia infection on PID at 12-months was compared in the absence and presence of a chlamydia screening program. In the absence of active chlamydia screening, 26.4% of PID at 12-month was attributable to untreated chlamydia infections whereas in the presence of testing and treatment this was less than 10% of PID, showing the effectiveness of screening (10). The overall importance of chlamydia in PID and infertility in the presence of appropriate therapy may however be lower and bacterial vaginosis associated bacteria may be as important or even more important than infection with *C. trachomatis* (11).

Symptomatic chlamydia may involve abnormal vaginal discharge, chronic pelvic pain, dysuria or mucopurulent cervicitis, and sampling with a swab may induce bleeding in the latter case (1). The vagina and cervix are the most obvious anatomical locations to screen for *C. trachomatis* infections in women but extra-genital *C. trachomatis* infections may also occur, such as in rectal tissue of women reporting receptive anal intercourse and in the oropharynx. For men, mostly (first catch) urine samples are tested but for women urine samples may be less reliable for testing (12). Wiesenfeld mentions the possibility of extra-genital infection but does not discuss chlamydia screening for these sites. In the Netherlands, the presence of chlamydial nucleic acids in rectal swabs in women were quite common, also in the absence of anal intercourse (13). So extra-genital testing and treatment should be encouraged for women as well as for men since transmission may occur solely via these anatomical locations and stay unnoticed otherwise (13). Genital *C. trachomatis* infections are very efficiently transmitted from women to men and vice versa with an approximate efficiency of 70%. Male partners should therefore always be notified in case of a positive test outcome and if possible, get tested, since many of them proved to be positive for *C. trachomatis* infection (14).

Treatment consists of either 1 g of azithromycin or 7 days of doxycycline, with both therapies being highly effective (15,16). For extra-genital infections, such as the pharynx or rectum, treatment with doxycycline is superior, but this antibiotic should not be used in pregnant women. Genetic resistance to azithromycin or other antibiotics has so far not been documented (17). A test of cure is recommended after 3 months, since in about 20% of cases recurrent chlamydia

infections occur. More data are needed however to decide if one test after 3 months is the optimal test of cure (18). A nice overview of guidelines and a testing algorithm for chlamydia (re)-screening is given by Wiesenfeld, which focuses on women (1) and is consistent with general guidelines to test for sexually transmitted infections (STIs) (19).

Recurrent infections may arise from either untreated partners or reflect persistence, for example due to treatment failure. Also, the transmission by using sex toys or auto-inoculation from rectal to urogenital sites is unknown. When performing tests of cure, it is important to realise that the used tests differ in sensitivity, with culture which demonstrates the presence of viable bacteria, being far less sensitive than the commonly used nucleic acid amplification assays. These molecular tests may remain (low) positive up to weeks and months after treatment, even though people deny having had recent unprotected sex (18). The meaning of the positivity of the (ultra) sensitive assays is not clear: are persons still infective if testing low positive? Is there still bacterial growth ongoing, leading to immune responses and later scarring? Another explanation for persistent infection is the possibility of dormant state *C. trachomatis* particles which were shown to occur *in vitro* (20) but may also occur in human mucosal cells lining the gastro-intestinal tract, as is known to occur for many members of the *Chlamydiaceae* family infecting birds and mammals (21).

Persons with previous chlamydia or other STIs, such as gonorrhoea, syphilis and trichomoniasis, should also be tested since these STI are a marker for risk behaviour. Disturbance of the vaginal microbiota and bacterial vaginosis are also predictors of *C. trachomatis* infection (11). Counselling is important and women at risk should be screened at least once a year according to Wiesenfeld or more often, if having complaints (1). During the last couple of years home-based testing has emerged as a good option for testing (22), and Wiesenfeld provides a website to order such tests (1). Reliable websites are important since the performance of some of the offered assays may be very low (23). An efficient and cost-effective way for screening for *C. trachomatis* infection is sampling at home using a validated assay and sending the sample to an accredited laboratory for subsequent testing (22).

The personal health of a woman may improve if she is tested timely and treated adequately, since this will avert future problems when conceiving and giving birth to a healthy child. It may also benefit the partner(s) of the infected woman, but most importantly, screening may reduce forward transmission and thus have broad public

health consequences.

A draw back of (over)diagnosis and treatment is the possibility of emerging antibiotic resistance in other bacteria as a side effect. Although *C. trachomatis* strains have so far not been identified as being resistant to azithromycin (17), this macrolide has been used very broadly. Possibly this broad use explains the sharp increase in the last decade of macrolide resistance in STI bacteria such as *Mycoplasma genitalium* and *Treponema pallidum* (causing syphilis) infections even though *T. pallidum* is not directly treated with azithromycin and infections with *M. genitalium* often remain untested and thus undiagnosed (24,25).

As discussed by Wiesenfeld, decades of testing with increasingly sensitive assays did not reduce the burden of *C. trachomatis* infection and in some areas it may have even increased, possibly by better case finding (1). Since the prevalence and incidence of *C. trachomatis* has not declined, the added benefit of increased testing is currently still unknown.

The paper of Wiesenfeld ends with the following conclusions. The woman in case should be screened using a vaginal or cervical swab (collected by respectively either the woman herself or the clinician) using a sensitive and specific nucleic acid amplification assay. If found positive, treatment with a single dose of either 1g azithromycin or 100 mg twice daily of doxycycline is recommended, with repeat testing after 3 months. All sexual partners of this woman should be tested and treated empirically if the sexual contact occurred within 60 days before testing. If the recommendations given in this comprehensive paper are followed it may be feasible that the transmission of *C. trachomatis* infections may finally be reduced or come to a halt in the next decade.

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