

2006 UK National Guideline for the Management of Genital Tract Infection with *Chlamydia trachomatis*

Introduction and Methodology

Scope and Purpose

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI, or undergoing investigation for possible infection.

Specifically:

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of *C. trachomatis*. It covers management of the initial presentation, as well as how to prevent transmission and future infection.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering level 3 care in STI management (see national strategy) within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

Stakeholder Involvement

This guideline has been produced by medical specialists from relevant disciplines with input from patients attending UK GUM clinics. Successive drafts have been reviewed by GUM patients, GUM physicians, nurses, health advisers and key professional organisations.

Rigour of Development

An extensive literature reviewed was carried out using Medline searches for the years 1970 to 2001 using keywords "Chlamydia trachomatis" in association

with "polymerase chain reaction" or "PCR" or "ligase chain reaction" or "lcr" or "lcx" and "immunoenzyme techniques" or "enzyme-linked immunosorbent assay". "Chlamydia trachomatis" combined with the following key words "detection", "diagnosis", "treatment". The Cochrane library: "Chlamydia trachomatis". This literature search was updated in 2005 and included nucleic acid amplification technique, Aptima, Probetec and SDA.

What's New?

NAATs to be used for medico-legal cases

EIAs to be replaced by NAATs

Update on performances of NAATs

Offer epidemiological treatment to contacts of *C. trachomatis* as per index case.

Azithromycin 1 gm stat in pregnancy recommended by WHO; unlicensed in UK (2006). BNF recommend use only if no other alternative available.

Recommendation for partner notification rates: 0.43 contacts per case in cities, 0.64 contacts per case elsewhere.

Aetiology

C. trachomatis is the most common curable sexually transmitted infection in Britain. Approximately 5-10% of sexually active women under 24 and men between 20-24 may be currently infected (1-4). Risk factors for infection includes age under 25yrs, new sexual partner or more than one sexual partner in the past year, a new sexual partner being more important than number of partners (4), and lack of consistent use of condoms (5-9). *C. trachomatis* is frequently asymptomatic in both men and women and ongoing transmission in the community is sustained by this un-recognised infection.

The natural history of *C. trachomatis* infections is poorly understood. Infection is primarily through penetrative sexual intercourse, however infection can be

detected at the conjunctiva and nasopharynx without concomitant genital tract infection (10;11).

If untreated, infection may persist or resolve spontaneously (12-17). Two thirds of sexual partners of chlamydia-positive individuals are also chlamydia-positive (18-21).

In response to the evidence of high and increasing rates of infection, the Government has introduced a national chlamydial screening programme (NCSP) (22;23).

Clinical features

Symptoms and Signs

Women

- Asymptomatic in approximately 70%
- Post coital or intermenstrual bleeding
- Lower abdominal pain
- Purulent vaginal discharge
- Mucopurulent cervicitis and/or contact bleeding
- Dysuria

Men

- Asymptomatic in over 50% in a community setting (3)
- Urethral discharge
- Dysuria

The severity of these two symptoms is variable and may be so mild as to be unnoticed by the patient.

Rectal infections

Usually asymptomatic, but may cause anal discharge and anorectal discomfort (proctitis) (24).

Pharyngeal infections

These are asymptomatic and are uncommon (24;25).

Complications

In the absence of treatment, 10-40% of infected women will develop pelvic inflammatory disease (PID) with a significant proportion of these cases being asymptomatic or having mild, atypical symptoms (26;27). PID can result in tubal factor infertility, ectopic pregnancy and chronic pelvic pain (26;28). The risk of developing PID increases with each recurrence of *C.trachomatis* infection, as does the risk of reproductive sequelae (29;30). Other complications include Fitz-Hugh-Curtis syndrome (perihepatitis), transmission to neonate (neonatal conjunctivitis, pneumonia), epididymo-orchitis, adult conjunctivitis and sexually acquired reactive arthritis /Reiter's syndrome (commoner in men). It is estimated that complications cost at least £100 million annually in the United Kingdom (22). The majority of health economic valuations demonstrate that chlamydia screening is cost effective (28;31;32).

Diagnosis

Nucleic Acid Amplification Technique

- Although the technology for diagnosing *C.trachomatis* continues to be a rapidly developing field, the standard of care for all cases, including medico legal cases, is a nucleic acid amplification technique (NAAT).
- NAATs are more sensitive and specific than enzyme immunoassays (EIAs) and the Department of Health has recently advised that the use of sub-optimal EIAs is no longer appropriate and has provided funding to support laboratories moving from EIAs to NAATs (33). However no test is 100% sensitive or specific (34).
- Reactive tests should be confirmed in the laboratory either using the same NAAT platform but if possible a second platform is to be preferred

(34;35). This improves specificity by countering processing errors but at the expense, which is usually judged acceptable, of a small reduction in sensitivity caused by specimens with a low organism load being missed at re-test (34). Thus therapy should be offered to all patients with unconfirmed reactive NAAT results but the significance of this result must be discussed with them (36). The laboratory report should request an additional specimen for further testing when reporting an unconfirmed reactive test, but this may not be possible (34;35).

- An inhibitory control should be used for each specimen (34;35) as substances may be present in biological fluids which can inhibit NAATs. Failure to use an inhibitory control with each specimen will lead to false negative results (37-39). The Gen-Probe Aptima system includes a nucleic acid extraction stage which removes the majority of inhibitors and thus the manufacturers state that no inhibitory control is needed (39).
- In general NAATs are 90-95% sensitive with the majority of studies indicating that as either the number of sites sampled increases, or the number of different NAAT used increases, the greater the detection of *C. trachomatis* in any given population.

Sites to be sampled

Women

- A cervical swab (Grade of recommendation B) or vulvo vaginal swab (Grade of recommendation C) are specimens of choice. To collect cervical specimens, a speculum examination is performed and as the sample must contain cervical columnar cells (40;41), swabs should be inserted inside the cervical os and firmly rotated against the endocervix. Inadequate specimens reduce the sensitivity of NAATs.
- The vulvo-vaginal swab has a sensitivity of 90-95% (47-50) and can be either taken by the patient or health care worker (43). Studies indicate that sensitivities similar to a cervical swab are obtainable. Currently,

only the APTIMA system (Gen-Probe Inc., San Diego, CA) has FDA approval for this specimen type.

- If a speculum examination is not possible then urine (Grade of recommendation B) samples can be utilized.
- Variable sensitivities (65-100%) have been reported using the first catch urine (FCU) specimen (42-46). When processed by inexperienced staff it may perform with sensitivity <90% (43). Patients should hold their urine for at least 1 hour (36) (maybe 2 hours with some kits, check manufacturer's instructions) before providing a FCU specimen.

Men

- First voided urine sample is reported to be as good as a urethral swab (44;51-54). Urine samples are easy to collect, do not cause discomfort and thus are preferable to urethral swabs. Urethral swabs should be inserted 2-4cm inside the urethra and rotated once before removal (Grade of recommendation C).
- Patients should hold their urine at least 1 hour before being tested (36), (maybe 2 hours with some kits, check manufacturer's instructions).

Rectal, Pharyngeal and Conjunctival specimens, men and women

- Currently none of the NAATs have FDA approval for these sites. Only Culture or DFA are recommended (Grade of recommendation A). However, in the absence of Culture or DFA tests, NAATs may be used (Grade of recommendation C).

Rectal swabs should be obtained via proctoscopy.

- Due to the emergence of rectal Lymphogranuloma venereum infection in men who have sex with men(55), the current (2006) recommended method of detecting rectal LGV infection is to perform a rectal NAAT which, if positive, is sent to the Health Protection Authority for confirmation.

Medico Legal Cases

For medico legal cases a NAAT should be taken from all the sites where penetration has occurred. This guideline recommends NAAT rather than culture due to the low sensitivity (60-80%) of culture and its lack of availability in many centres (Grade of recommendation D).

- A reactive NAAT result must be confirmed using a different NAAT (36). Ideally, two swabs should be taken from each site, one for testing and one for confirmation if the initial test is positive. This avoids potential compatibility problems when retesting specimens using a different platform (34). There is evidence that the Becton Dickinson ProbeTec ET strand displacement amplification (SDA) assay has a lower analytical sensitivity than Roche Cobas Amplicor PCR(56) for some serotypes, which means that SDA may not be suitable for the confirmation of PCR results. There are also data to suggest that Gen-Probe APTIMA system has a higher sensitivity than the other two assays discussed (57). Although, this system does have its own confirmatory assay with matching sensitivity it uses the same methodology, on the same specimen, thus theoretically some causes of false positives may not be eliminated.(36)

Cell culture

- Sensitivity 60-80%
- 100% specificity
- Expertise essential
- Expensive – and only limited availability nationally
- Can be used on all specimen types
- Routine use is not recommended due to high cost and low sensitivity.

Enzyme immunoassays (EIAs)

- The sensitivity of the majority of EIAs is probably only 40-70% and their use is not recommended. This guideline recommends laboratories to

move to the use of NAATs utilizing Department of Health dedicated funding (30).

- Should be not used on non-invasive specimens in women, nor on rectal or throat specimens in women or men.

Direct fluorescent antibody (DFA)

- Routine use is not recommended.
- Labour intensive, and although a >80% sensitivity is achievable, this requires skilled personnel using a cut off of 2 elementary bodies.
- Unsuitable for large numbers of specimens (>30/day).
- Will accommodate all specimen types including rectal and pharyngeal

Management

General Advice

Ideally, treatment should be effective (microbiological cure rate >95%), easy to take (not more than twice daily), with a low side effect profile, and cause minimal interference with daily lifestyle (Grade of recommendation C). Uncomplicated genital tract infection with *C.trachomatis* is not an indication for removal of an IUS or IUD.

Patients should be advised to avoid sexual intercourse (including oral sex) until they and their partner(s) have completed treatment (or wait 7 days if treated with Azithromycin). Advice regarding appropriate action if using hormonal contraceptives is also required.

Patients should be given detailed explanation of their condition with particular emphasis on the long-term implications for their and their partner(s). This should be reinforced by giving them clear, accurate written information.

Further Investigation

All patients diagnosed with *C.trachomatis* should be encouraged to have screening for other STIs, including an HIV test and, where indicated hepatitis B

screening and vaccination (Grade of recommendation C). If the patient is within the window period for HIV and syphilis, these should be repeated at an appropriate time interval. All contacts of *C.trachomatis* should be offered the same screening tests.

Treatment of genital, rectal and pharyngeal uncomplicated infection (see appropriate guidelines for treatment of complications) and epidemiological treatment

Recommended regimens: (Grade of recommendation A)

- Doxycycline 100mg bd for 7 days (contraindicated in pregnancy)

or

- Azithromycin 1gm orally in a single dose

Alternative regimens: (Grade of recommendation A)

For use if either of the above treatments are contraindicated.

- Erythromycin 500mg bd for 10-14 days

or

- Ofloxacin 200mg bd or 400mg once a day for 7 days

Studies of anti-microbial efficacy

Azithromycin and Doxycycline

Doxycycline and azithromycin are the most rigorously investigated. Comparative studies with follow-up periods from 2-5 weeks have demonstrated similar efficacy, with >95% being chlamydia-negative on re-testing with a NAAT or culture (58). However there is now good evidence that when patients, treated with azithromycin 1gm or doxycycline 100mgs bd 7 days, are followed up for longer, >10% will be chlamydia-positive on retesting (59-62). In the chlamydia re-infection study, there was no difference in the re-infection rates between women who received doxycycline (n=88) and those who received azithromycin (n=325) (HR 0.8, 95% CI:0.4-1.4) even after adjusting for all covariates (personal communication D Scott LaMontagne) (63).

Resistance to tetracycline and macrolides has been detected in vivo but appears to be rare (64). It has not been documented to be significant in vitro.

Other anti-microbials

The information from published studies on efficacy of other anti-microbials is considerably less than that available for azithromycin and doxycycline. It should not be assumed that these are more efficacious than either doxycycline or azithromycin.

***Ofloxacin* (Grade of recommendation B)**

- It is unknown whether 200mg twice a day is superior to 400mg once a day (65).
- Ofloxacin has similar efficacy to doxycycline and a better side-effect profile but is considerably more expensive, so is not recommended as first-line treatment.
- Resistance to ofloxacin has been demonstrated in vivo and in vitro, but appears to be rare (64).
- No long term follow up (>6 weeks) data.

***Erythromycin* (Grade of recommendation A)**

- Erythromycin is less efficacious than either azithromycin or doxycycline.
- When taken four times a day, 20-25% may experience side-effects sufficient to cause the patient to discontinue treatment (66).
- There are only limited data on erythromycin 500mg twice a day, with efficacy reported at between 73%-95%. A 10-14 day course appears to be more efficacious than a 1 week course of 500mg twice a day, with a cure rate >95% (59;67)
- Resistance to erythromycin has been demonstrated in vivo and appears to be rare. It has not been documented to be significant in vivo.

***Other tetracyclines* (Grade of recommendation A)**

- “Deteclo” (registered trademark) is probably as efficacious as Doxycycline (68). However, photosensitivity occurs more frequently and there is insufficient data on efficacy if compliance is poor.
- Oxytetracycline 500mgs bd 10 days has also been shown to be effective (59).

Pregnancy and breast feeding

Recommended regimens; (Grade of recommendation A)

- Erythromycin 500mg four times a day for 7 days

or

- Erythromycin 500 mg twice a day for 14 days

or

- Amoxicillin 500 mg three times a day for 7 days

or

- Azithromycin 1 gm stat (see caution below from BNF)

Due to higher positive chlamydia tests after treatment in pregnancy, attributed to either less efficacious treatment regime, non compliance or re-infection, it is recommended that pregnant woman must have a test of cure 5 weeks after completing therapy, 6 weeks later if given azithromycin.

- Doxycycline and ofloxacin are contraindicated in pregnancy
- Azithromycin; is probably less than 95% effective (69-71). The safety of azithromycin in pregnancy and lactating mothers has not yet been fully assessed, although available data indicate that it is safe (71). WHO Guidelines recommend 1gm stat to treat *C.trachomatis* in pregnancy, the BNF recommends its use in pregnancy and lactation only if no alternative is available.
- Erythromycin has a significant side effect profile and is less than 95% effective. There are no trials of erythromycin 500mg twice a day for 14

days, which would be better tolerated than four times a day although the follow-up data from the Portsmouth pilot study suggests it is efficacious (59).

- Amoxicillin had a similar cure rate to erythromycin in a meta-analysis and had a much better side effect profile (71). However, penicillin *in vitro* has been shown to induce latency and re-emergence of infection at a later date is a theoretical concern of some experts.

Compliance with therapy

In general compliance with therapy is improved if there is a positive therapeutic relationship between the patient and the doctor (72) and /or nurse.

This can probably be improved if the following are applied (Grade of recommendation C):

Discuss with patient and provide clear written information on:

- What *C. trachomatis* is and how it is transmitted
 - It is primarily sexually transmitted
 - If asymptomatic there is evidence that it could have persisted for months or years
- The diagnosis of *C. trachomatis*, particularly:
 - It is often asymptomatic in both men and women
 - Whilst tests are accurate, no test is absolutely so
- The complications of untreated *C. trachomatis*
- Side effects and importance of complying fully with treatment and what to do if a dose is missed.
- Advice regarding antibiotics and hormonal contraception.
- The importance of their sexual partner(s) being evaluated and treated.

- Advised to abstain from sexual intercourse until they and their partner(s) have completed therapy (and waited 7 days if treated with azithromycin).
- Advice on safer sexual practices, including advice on correct, consistent condom use.

Reducing the risk of individuals retesting chlamydia-positive following treatment.

Background

- Partner notification by practice nurses who receive brief training and ongoing support from a health adviser has been shown to be at least as successful as that achieved by referral to a genitourinary medicine clinic for individuals with chlamydia diagnosed in the community (73).
- NAATs may remain positive up to five weeks post treatment. This does not necessarily mean active infection as it may represent the presence of nucleic acid from non-viable organisms.
- Re-testing *C. trachomatis*-positive can result from either sub-optimal antimicrobial therapy (see above) or re-infection. Re-infection may result either from having sexual intercourse with an untreated, sub-optimally treated or a new partner who is *C. trachomatis* positive.
- Latency and antimicrobial resistance are areas currently being researched (74).

Recommendations

- Advise (and document that advice given) no genital, oral or anal sex, even with a condom, until both index patient and their partner(s) have completed treatment or if the partner(s) choose testing only until the partner(s) have a negative test.
- Abstain as above from sexual activity, for one week after azithromycin 1gm stat.

Management of sexual partners

- All patients identified with *C. trachomatis* should have partner notification discussed at time of treatment by a trained health care professional.
- The method of partner notification agreed for each partner/contact identified should be documented, as should partner notification outcomes.
- All sexual partners should be offered, and encouraged to take up a full STI screen, including HIV test and if indicated hepatitis B screening +/- vaccination.
- Epidemiological treatment for *C.trachomatis* should be offered. If declined, patients must be advised to abstain from sex until they have received a negative result. If found to be positive, any other potentially exposed partner(s) needs screening and the offer of epidemiological treatment.

Look back period

Only limited evaluation has taken place of the incubation period following exposure to the development of symptoms. In the United Kingdom a cut-off of 4 weeks is used to identify those sexual partner(s) potentially at risk if the index patient is symptomatic. If the index case is asymptomatic, an arbitrary cut off of 6 months, or until the last previous sexual partner (whichever is the longer time period), is used. Common sense needs to be used in assessing which sex partner(s) may have been at risk in these situations.

Those at risk should be informed and invited to attend for evaluation and epidemiological treatment even if tests are negative. This may be patient or provider-led.

Follow up

Follow up by phone may be both more efficacious and cost effective than by re-attendance.

This is an important part of the management of chlamydial infection and it has a number of objectives including:

- Following up partner notification
- Reinforcing health education
- Ensuring compliance with treatment and abstinence from sexual intercourse until partner(s) have completed antibiotics (if treated with azithromycin waiting seven days).
- There is evidence to suggest that follow-up by phone may be more efficacious than asking the patient to re-attend. It is therefore likely that the former method is more cost effective (75).
- Re-treat non-compliant and/or re-exposed individuals.

Test of Cure

A test of cure is not routinely recommended but should be performed in pregnancy or if non-compliance or re-exposure is suspected. It should be deferred for 5 weeks (6 weeks if azithromycin given) after treatment is completed.

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Auditable Outcome Measures

- Compliance with clinical standards of care.
- Partner notification recommendation: In 2004, a systematic review of UK GUM clinics' work showed that a mean of 0.43 contacts per case of chlamydia were screened in large city clinics and 0.64 contacts per case of chlamydia were screened in other clinics (76).

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Editorial Independence

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Updates 2002 clinical effectiveness guidelines for the management of genital tract infection with *Chlamydia trachomatis*.

References

- (1) Fenton KA, Koroivessis C, Johnson AM, McCadden A, McManus S, Wellings K et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital *Chlamydia trachomatis* infection. Lancet 2001 December 1; 358(9296):1851-4.
- (2) LaMontagne DS, Fenton KA, Randall S, Anderson S, Carter P, on behalf of the National Chlamydia Screening Steering Group. Establishing the National Chlamydia Screening Programme in England: results from the first full year of screening. Sex Transm Infect 2004 October 1; 80(5): 335-41.
- (3) McKay L, Clery H, Carrick-Anderson K, Hollis S, Scott G. Genital *Chlamydia trachomatis* infection in a subgroup of young men in the UK. Lancet 2003 May 24; 361(9371):1792.
- (4) Macleod J, Salisbury C, Low N, McCarthy A, Sterne JA, Holloway A et al. Coverage and uptake of systematic postal screening for genital *Chlamydia trachomatis* and prevalence of infection in the United Kingdom general population: cross sectional study. BMJ 2005 April 23; 330(7497):940.
- (5) Paz-Bailey G, Koumans EH, Sternberg M, Pierce A, Papp J, Unger ER et al. The effect of correct and consistent condom use on chlamydial and gonococcal infection among urban adolescents. Archives of Pediatrics & Adolescent Medicine 2005 June; 159(6):536-42.
- (6) Warner L, Macaluso M, Austin HD, Kleinbaum DK, Artz L, Fleenor ME et al. Application of the case-crossover design to reduce unmeasured confounding in studies of condom effectiveness. Am J Epidemiol 2005 April 15; 161(8): 765-73.
- (7) Brabin L, Fairbrother E, Mandal D, Roberts SA, Higgins SP, Chandio S et al. Biological and hormonal markers of chlamydia, human papillomavirus, and bacterial vaginosis among adolescents attending genitourinary medicine clinics. Sex Transm Infect 2005 April; 81(2): 128-32.
- (8) Miranda AE, Szwarcwald CL, Peres RL, Page-Shafer K. Prevalence and risk behaviors for chlamydial infection in a population-based study of female adolescents in Brazil. Sexually Transmitted Diseases 2004 September; 31(9):542-6.
- (9) Warner L, Newman DR, Austin HD, Kamb ML, Douglas JM, Jr., Malotte CK et al. Condom effectiveness for reducing transmission of gonorrhoea and chlamydia: the importance of assessing partner infection status.[see comment]. Am J Epidemiol 2004 February 1; 159(3):242-51.

- (10) Postema EJ, Remeijer L, van der Meijden WI. Epidemiology of genital chlamydial infections in patients with chlamydial conjunctivitis; a retrospective study. *Genitourinary Medicine* 1996 June; 72(3):203-5.
- (11) Stenberg K, Mardh PA. Treatment of concomitant eye and genital chlamydial infection with erythromycin and roxithromycin. *Acta Ophthalmologica* 1993 June; 71(3): 332-5.
- (12) Joyner JL, Douglas JM, Jr., Foster M, Judson FN. Persistence of *Chlamydia trachomatis* infection detected by polymerase chain reaction in untreated patients. *Sexually Transmitted Diseases* 2002 April; 29(4):196-200.
- (13) Morre SA, van den Brule AJ, Rozendaal L, Boeke AJ, Voorhorst FJ, de Blok S et al. The natural course of asymptomatic *Chlamydia trachomatis* infections: 45% clearance and no development of clinical PID after one-year follow-up. *International Journal of STD & AIDS* 2002 December; 13 Suppl 2:12-8.
- (14) Parks KS, Dixon PB, Richey CM, Hook EW, III. Spontaneous clearance of *Chlamydia trachomatis* infection in untreated patients. *Sexually Transmitted Diseases* 1997 April; 24(4):229-35.
- (15) Golden MR, Schillinger JA, Markowitz L, St Louis ME. Duration of untreated genital infections with *Chlamydia trachomatis*: a review of the literature. [Review] [84 refs]. *Sexually Transmitted Diseases* 2000 July; 27(6):329-37.
- (16) van den Brule AJ, Munk C, Winther JF, Kjaer SK, Jorgensen HO, Meijer CJ et al. Prevalence and persistence of asymptomatic *Chlamydia trachomatis* infections in urine specimens from Danish male military recruits. *International Journal of STD & AIDS* 2002 December; 13 Suppl 2:19-22.
- (17) Molano M, Meijer CJ, Weiderpass E, Arslan A, Posso H, Franceschi S et al. The natural course of *Chlamydia trachomatis* infection in asymptomatic Colombian women: a 5-year follow-up study. *Journal of Infectious Diseases* 2005 March 15; 191(6):907-16.
- (18) Clad A, Prillwitz J, Hintz KC, Mendel R, Flecken U, Schulte-Monting J et al. Discordant prevalence of *Chlamydia trachomatis* in asymptomatic couples screened using urine ligase chain reaction. *European Journal of Clinical Microbiology & Infectious Diseases* 2001 May; 20(5):324-8.
- (19) Lin JS, Donegan SP, Heeren TC, Greenberg M, Flaherty EE, Haivanis R et al. Transmission of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* among men with urethritis and their female sex partners. *Journal of Infectious Diseases* 1998 December; 178(6):1707-12.
- (20) Quinn TC, Welsh L, Lentz A, Crotchfelt K, Zenilman J, Newhall J et al. Diagnosis by AMPLICOR PCR of *Chlamydia trachomatis* infection in

urine samples from women and men attending sexually transmitted disease clinics. *J Clin Microbiol* 1996 June; 34(6): 1401-6.

- (21) Khan AM. The Prevalence of Chlamydia, Gonorrhoea, and Trichomonas in Sexual Partnerships: Implications for Partner Notification and Treatment. *Sexually Transmitted Diseases* 2005 April; 32(4): 260-4.
- (22) Department of Health. National Chlamydia Screening Programme in England: Programme overview. Department of Health 2004; (2nd) Available from: URL: <http://www.dh.gov.uk/assetRoot/04/09/26/48/04092648.pdf>
- (23) Hamlyn C. Roll out of the national chlamydia screening programme (NCSP). Department of Health 2005; Available from: URL: <http://www.dh.gov.uk/assetRoot/04/11/42/07/04114207.pdf>
- (24) Jones RB, Rabinovitch RA, Katz BP, Batteiger BE, Quinn TS, Terho P et al. *Chlamydia trachomatis* in the pharynx and rectum of heterosexual patients at risk for genital infection. *Ann Intern Med* 1985 June; 102(6): 757-62.
- (25) Winter AJ, Gilleran G, Eastick K, Ross JD. Comparison of a ligase chain reaction-based assay and cell culture for detection of pharyngeal carriage of *Chlamydia trachomatis*. *J Clin Microbiol* 2000 September; 38(9): 3502-4.
- (26) Paavonen J, Eggert-Kruse W. *Chlamydia trachomatis*: impact on human reproduction. *Hum Reprod Update* 1999 September 1; 5(5): 433-47.
- (27) Simms I, Stephenson JM. Pelvic inflammatory disease epidemiology: what do we know and what do we need to know? *Sex Transm Infect* 2000 April 1; 76(2): 80-7.
- (28) Hu D, Hook EW, III, Goldie SJ. Screening for *Chlamydia trachomatis* in Women 15 to 29 Years of Age: A Cost-Effectiveness Analysis. *Ann Intern Med* 2004 October 5; 141(7): 501-13.
- (29) Hillis SD, Joesoef R, Marchbanks PA, Wasserheit JN, Cates W, Jr., Westrom L. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. *American Journal of Obstetrics & Gynecology* 1993 May; 168(5): 1503-9.
- (30) Westrom LV. Sexually transmitted diseases and infertility. [Review] [30 refs]. *Sexually Transmitted Diseases* 1994 March; 21(2 Suppl): S32-S37.
- (31) Honey E, Augood C, Templeton A, Russell I, Paavonen J, Mardh PA et al. Cost effectiveness of screening for *Chlamydia trachomatis*: a review of published studies. *Sex Transm Infect* 2002 December 1; 78(6): 406-12.
- (32) van Valkengoed I, Morre SA, van den Brule AJ, Meijer CJ, Bouter LM, Boeke AJ. Overestimation of complication rates in evaluations of

- Chlamydia trachomatis* screening programmes--implications for cost-effectiveness analyses. *International Journal of Epidemiology* 2004 April; 33(2):416-25.
- (33) Department of Health. *Sexual health and HIV strategy: Chlamydia Screening*. London: DoH; 2003.
- (34) Skidmore S, Herring A, Horner P, Mallinson H, on behalf of the HPA Chlamydia Diagnosis Forum. Testing specimens for *Chlamydia trachomatis*. *Sex Transm Infect* 2006; submitted 2005.
- (35) Health Protection Agency. *Chlamydia Infection - Testing by Nucleic Acid Amplification Tests (NAATs) - minimum testing algorithm*. National Standard Method VSOP 37 Issue 1 2004; Available from: URL: <http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop37.pdf>
- (36) Johnson RE, Newhall WJ, Papp JR, Knapp JS, Black CM, Gift TL et al. Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections--2002. *Morbidity & Mortality Weekly Report* 2002 October 18; Recommendations & Reports. 51(RR-15):1-38.
- (37) Horner P, Skidmore S, Herring A, Sell J, Paul I, Caul EO et al. Enhanced Enzyme Immunoassay with Negative-Gray-Zone Testing Compared to a Single Nucleic Acid Amplification Technique for Community-Based Chlamydial Screening of Men. *Journal of Clinical Microbiology*, In press. 2005.
- (38) Mahony J, Chong S, Jang D, Luinstra K, Faught M, Dalby D et al. Urine specimens from pregnant and nonpregnant women inhibitory to amplification of *Chlamydia trachomatis* nucleic acid by PCR, ligase chain reaction, and transcription-mediated amplification: identification of urinary substances associated with inhibition and removal of inhibitory activity. *J Clin Microbiol* 1998 November; 36(11):3122-6.
- (39) Chong S, Jang D, Song X, Mahony J, Petrich A, Barriga P et al. Specimen processing and concentration of *Chlamydia trachomatis* added can influence false-negative rates in the LCx assay but not in the APTIMA Combo 2 assay when testing for inhibitors. *J Clin Microbiol* 2003 February; 41(2):778-82.
- (40) Loeffelholz MJ, Jirsa SJ, Teske RK, Woods JN. Effect of endocervical specimen adequacy on ligase chain reaction detection of *Chlamydia trachomatis*. *J Clin Microbiol* 2001 November; 39(11):3838-41.
- (41) Welsh LE, Quinn TC, Gaydos CA. Influence of endocervical specimen adequacy on PCR and direct fluorescent-antibody staining for detection of *Chlamydia trachomatis* infections. *J Clin Microbiol* 1997 December; 35(12):3078-81.

- (42) McCartney RA, Walker J, Scoular A. Detection of *Chlamydia trachomatis* in genitourinary medicine clinic attendees: comparison of strand displacement amplification and the ligase chain reaction. *British Journal of Biomedical Science* 2001; 58(4): 235-8.
- (43) Schachter J, McCormack WM, Chernesky MA, Martin DH, Van Der PB, Rice PA et al. Vaginal swabs are appropriate specimens for diagnosis of genital tract infection with *Chlamydia trachomatis*. *J Clin Microbiol* 2003 August; 41(8): 3784-9.
- (44) Van Der Pol B., Ferrero DV, Buck-Barrington L, Hook E, III, Lenderman C, Quinn T et al. Multicenter evaluation of the BDProbeTec ET System for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urine specimens, female endocervical swabs, and male urethral swabs. *J Clin Microbiol* 2001 March; 39(3): 1008-16.
- (45) Jensen IP, Thorsen P, Moller BR. Sensitivity of ligase chain reaction assay of urine from pregnant women for *Chlamydia trachomatis*. *Lancet* 1997 February 1; 349(9048): 329-30.
- (46) Moncada J, Schachter J, Hook EW, III, Ferrero D, Gaydos C, Quinn TC et al. The effect of urine testing in evaluations of the sensitivity of the Gen-Probe Aptima Combo 2 assay on endocervical swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: the infected patient standard reduces sensitivity of single site evaluation. *Sexually Transmitted Diseases* 2004 May; 31(5): 273-7.
- (47) Carder C, Robinson AJ, Broughton C, Stephenson JM, Ridgway GL. Evaluation of self-taken samples for the presence of genital *Chlamydia trachomatis* infection in women using the ligase chain reaction assay. *International Journal of STD & AIDS* 1999 December; 10(12): 776-9.
- (48) Macmillan S, McKenzie H, Flett G, Templeton A. Feasibility of patient-collected vulval swabs for the diagnosis of *Chlamydia trachomatis* in a family planning clinic: a pilot study. *British Journal of Family Planning* 2000 October; 26(4): 202-6.
- (49) Wiesenfeld HC, Heine RP, Rideout A, Macio I, DiBiasi F, Sweet RL. The vaginal introitus: a novel site for *Chlamydia trachomatis* testing in women. *American Journal of Obstetrics & Gynecology* 1996 May; 174(5): 1542-6.
- (50) Gaydos CA, Quinn TC, Willis D, Weissfeld A, Hook EW, Martin DH et al. Performance of the APTIMA Combo 2 assay for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in female urine and endocervical swab specimens. *J Clin Microbiol* 2003 January; 41(1): 304-9.
- (51) Chernesky MA, Martin DH, Hook EW, Willis D, Jordan J, Wang S et al. Ability of new APTIMA CT and APTIMA GC assays to detect *Chlamydia*

trachomatis and *Neisseria gonorrhoeae* in male urine and urethral swabs. J Clin Microbiol 2005 January; 43(1): 127-31.

- (52) Crotchfelt KA, Welsh LE, DeBonville D, Rosenstraus M, Quinn TC. Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in genitourinary specimens from men and women by a coamplification PCR assay. J Clin Microbiol 1997 June; 35(6): 1536-40.
- (53) Young H, Moyes A, Horn K, Scott GR, Patrizio C, Sutherland S. PCR testing of genital and urine specimens compared with culture for the diagnosis of chlamydial infection in men and women. International Journal of STD & AIDS 1998 November; 9(11): 661-5.
- (54) Sugunendran H, Birley HD, Mallinson H, Abbott M, Tong CY. Comparison of urine, first and second endourethral swabs for PCR based detection of genital *Chlamydia trachomatis* infection in male patients. Sex Transm Infect 2001 December; 77(6): 423-6.
- (55) French P, Ison CA, Macdonald N. Lymphogranuloma venereum in the United Kingdom. Sex Transm Infect 2005 April 1; 81(2): 97-8.
- (56) Chalker VJ, Vaughan H, Patel P, Rossouw A, Seyedzadeh H, Gerrard K et al. External Quality Assessment for Detection of *Chlamydia trachomatis*. J Clin Microbiol 2005 March 1; 43(3): 1341-7.
- (57) Schachter J, Hook EW, Martin DH, Willis D, Fine P, Fuller D et al. Confirming Positive Results of Nucleic Acid Amplification Tests (NAATs) for *Chlamydia trachomatis*: All NAATs Are Not Created Equal. J Clin Microbiol 2005 March 1; 43(3): 1372-3.
- (58) Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sexually Transmitted Diseases 2002 September; 29(9): 497-502.
- (59) Tobin JM, Harindra V, Mani R. Which treatment for genital tract *Chlamydia trachomatis* infection? International Journal of STD & AIDS 2004 November; 15(11): 737-9.
- (60) Lee VF, Tobin JM, Harindra V. Re-infection of *Chlamydia trachomatis* in patients presenting to the genitourinary medicine clinic in Portsmouth: the chlamydia screening pilot study - three years on. International Journal of STD & AIDS 2004 November; 15(11): 744-6.
- (61) Fortenberry JD, Brizendine EJ, Katz BP, Wools KK, Blythe MJ, Orr DP. Subsequent sexually transmitted infections among adolescent women with genital infection due to *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Trichomonas vaginalis*. Sexually Transmitted Diseases 1999 January; 26(1): 26-32.
- (62) Golden MR, Whittington WL, Handsfield HH, Hughes JP, Stamm WE, Hogben M et al. Effect of expedited treatment of sex partners on

recurrent or persistent gonorrhoea or chlamydial infection. [see comment]. *New England Journal of Medicine* 2005 February 17; 352(7):676-85.

- (63) La Montagne, D. S., Baster K, Emmet L, Randall, S., McClean, L., Meredith, P. and et al. For the Chlamydia Recall Study Advisory Group. The chlamydia recall study: investigating the incidence and re-infection rates of genital chlamydial infection among 16-24 year old women attending general practice, family planning and genitourinary medicine clinics, March 2002-August 2004, final report part 1. London: Health Protection Agency Centre for Infections; 2004 December.
- (64) Somani J, Bhullar VB, Workowski KA, Farshy CE, Black CM. Multiple drug-resistant *Chlamydia trachomatis* associated with clinical treatment failure. *Journal of Infectious Diseases* 2000 April; 181(4):1421-7.
- (65) Kitchen VS, Donegan C, Ward H, Thomas B, Harris JR, Taylor-Robinson D. Comparison of ofloxacin with doxycycline in the treatment of non-gonococcal urethritis and cervical chlamydial infection. *Journal of Antimicrobial Chemotherapy* 1990 November; 26 Suppl D: 99-105.
- (66) Linnemann CC, Jr., Heaton CL, Ritchey M. Treatment of *Chlamydia trachomatis* infections: comparison of 1- and 2-g doses of erythromycin daily for seven days. *Sexually Transmitted Diseases* 1987 April; 14(2): 102-6.
- (67) Ross JD, Crean A, McMillan A. Efficacy of anti-chlamydial therapy with oxytetracycline and erythromycin. *International Journal of STD & AIDS* 1996 August; 7(5):373-4.
- (68) Munday PE, Thomas BJ, Gilroy CB, Gilchrist C, Taylor-Robinson D. Infrequent detection of *Chlamydia trachomatis* in a longitudinal study of women with treated cervical infection. *Genitourinary Medicine* 1995 February; 71(1):24-6.
- (69) Jacobson GF, Autry AM, Kirby RS, Liverman EM, Motley RU. A randomized controlled trial comparing amoxicillin and azithromycin for the treatment of *Chlamydia trachomatis* in pregnancy. *American Journal of Obstetrics & Gynecology* 2001 June; 184(7): 1352-4.
- (70) Kacmar J, Cheh E, Montagnano A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of *Chlamydia trachomatis* in pregnancy. *Infectious Diseases in Obstetrics & Gynecology* 2001; 9(4): 197-202.
- (71) Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. *Cochrane Database of Systematic Reviews* 2000; (2): CD000054.

- (72) Sanson-Fisher R, Bowman J, Armstrong S. Factors affecting nonadherence with antibiotics. *Diagnostic Microbiology & Infectious Disease* 1992 May; 15(4 Suppl): 103S-9S.
- (73) Low N, Roberts T, Huengsberg M, Sanford E, McCarthy A, Pye K et al. Partner notification for chlamydia in primary care: randomised controlled trial and economic evaluation. *BMJ* 2006; 332: 14-8.
- (74) Hogan RJ, Mathews SA, Mukhopadhyay S, Summersgill JT, Timms P. Chlamydial Persistence: beyond the Biphasic Paradigm. *Infect Immun* 2004 April 1; 72(4): 1843-55.
- (75) Apoola A, Boothby M, Radcliffe K. Is telephone follow-up as good as traditional clinic follow-up in achieving the proposed national outcome standards for chlamydia management? *International Journal of STD & AIDS* 2004 June; 15(6): 376-9.
- (76) Low N, Welch J, Radcliffe K. Developing national outcome standards for the management of gonorrhoea and genital chlamydia in genitourinary medicine clinics. *Sex Transm Infect* 2004 June 1; 80(3): 223-9.