Background review for the ‘2015 European guideline on the management of Chlamydia trachomatis infections’

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Abstract

Chlamydia trachomatis infections are major public health concerns globally. Of particular grave concern is that the majority of persons with anogenital Chlamydia trachomatis infections are asymptomatic and accordingly not aware of their infection, and this silent infection can subsequently result in severe reproductive tract complications and sequelae. The current review paper provides all background, evidence base and discussions for the 2015 European guideline on the management of Chlamydia trachomatis infections (Lanjouw E, et al. Int J STD AIDS 2015). Comprehensive information and recommendations are included regarding the diagnosis, treatment and prevention of anogenital, pharyngeal and conjunctival Chlamydia trachomatis infections in European countries. However, Chlamydia trachomatis also causes the eye infection trachoma, which is not a sexually transmitted infection. The 2015 European Chlamydia trachomatis guideline provides up-to-date guidance regarding broader indications for testing and treatment of Chlamydia trachomatis infections; clearer recommendation of using validated nucleic acid amplification tests only for diagnosis; advice on (repeated) Chlamydia trachomatis testing; recommendation of increased testing to reduce the incidence of pelvic inflammatory disease and prevent exposure to infection and recommendations to identify, verify and report Chlamydia trachomatis variants. Improvement of access to testing, test performance, diagnostics, antimicrobial treatment and follow-up of Chlamydia trachomatis patients are crucial to control its spread.

Keywords

Chlamydia trachomatis, Europe, diagnosis, treatment, antibiotic

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Aetiology, transmission and epidemiology

Chlamydia trachomatis is an obligate intracellular bacterium that is estimated to infect over 100 million people each year worldwide by sexual transmission.¹

C. trachomatis most frequently infects the lower urogenital tract in men and women, and it is the aetiologic agent of several common genital tract syndromes such as urethritis, cervicitis and pelvic inflammatory disease (PID) in women. However, C. trachomatis can also cause extra-genital infections by sexual transmission,

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such as rectal, pharyngeal and ocular infections. Moreover, C. trachomatis causes trachoma and pneumonia in newborns and the elderly, but these infections lie beyond the scope of this guideline. Of particularly grave concern is that the majority of persons with anogenital C. trachomatis infection are not aware of their infection because it might frequently result in minimal or no symptoms. Urogenital chlamydial infection is usually an easily treatable sexually transmitted infection (STI) but, if not successfully detected and/or treated, it can lead to serious adverse outcomes in women, e.g. ascend to the upper genital tract to cause PID that can result in tubal factor infertility, ectopic pregnancy and chronic pelvic pain. Reinfection after treatment is common, and there might be long delays until some reproductive tract complications in women become apparent. Urogenital chlamydial infections do not result in any sustained immunity. As a result, reinfection and possibly persistent infection are common.2

Since the 1990s, an increase of urogenital C. trachomatis infections has been reported from several countries, e.g. the USA, Canada, United Kingdom (UK) and the Scandinavian countries.3-5 The prevalence of C. trachomatis in population-based studies has ranged from 0.1% to 12.1% in men and from 1.1% to 10.6% in women depending upon country, age group, national or sub-national coverage and inclusion of all or only sexually experienced participants. The prevalence estimates in nationally representative samples of sexually experienced 18–26-year olds in Europe have been relatively similar in women and men (estimated ranging between 3–5.3% and 2.4–7.3%, respectively) and statistically consistent with those in other high-income countries.4-7 Selection bias in C. trachomatis prevalence surveys is likely, with over-estimation of prevalence being more likely than under-estimation. The incidence of diagnosed C. trachomatis cases reported to the European Centre for Disease Prevention and Control (ECDC) from 26 European Union (EU) and European Economic Area (EEA) countries in 2013 was 182 per 100,000 population (384,555 cases). Accordingly, C. trachomatis is the most commonly reported bacterial STI in Europe, especially among young adults.5 Young age (usually below 25 years of age) and behavioural risk factors such as prior C. trachomatis infection, lack of consistent condom use and new or multiple partners per year are the main risk factors for acquisition of C. trachomatis infection.8 Nevertheless, there was substantial variation across the EU/EEA countries in the incidence of reported C. trachomatis cases, with rates ranging from below 1 to more than 600 cases per 100,000 population.5 Comparison between countries is considerably challenged by differences in the surveillance systems, the diagnostic methods used, the access to and amount of testing and screening (general screening programme or opportunistic testing) for chlamydial infection and the proportion of underreporting.4 4

Transmission of C. trachomatis usually takes place by direct mucosal contact between two individuals during sexual intercourse (vaginal, anal or oral sex) or at birth through an infected cervical canal. It is difficult to estimate the risk of sexual transmission and there is also a lack of an agreed methodology on how to estimate transmissibility of C. trachomatis from cross-sectional sexual partnership studies. It has been estimated using data from heterosexual couples attending an STD clinic in the USA that the transmission probability per vaginal coitus was 39.5% from men to women and 32.3% from women to men.9 However, the infection status of the couples was observed during the partnership and not at the end, and so the estimated transmission probabilities do not represent the per partnership transmission probability. Furthermore, the natural history of chlamydial infection where spontaneous clearance and reinfection within sexual partnerships can occur was not taken into account. One transmission dynamic mathematical modelling study provided estimates,10 based on data from a cross-sectional heterosexual partnership study in clinical attendees.11 The model estimated a median transmission probability of around 10% for a single act of vaginal coitus and around 55% over the course of a partnership in a population that has two partnerships in a six-month period. Partners of people with C. trachomatis infection are very likely to be infected themselves,11 so contact notification and subsequent treatment are very important. Cervical ectopy, especially in young women, has been reported to increase the susceptibility to chlamydial infection. Cervical ectopy can also be more common in women using oral contraceptives,12 and hormonal contraceptives are associated with an increased risk of chlamydial infection.13-14 However, many confounding factors are involved and a strong evidence base is difficult to obtain. Vaginal douching is associated with bacterial vaginosis and HIV, both increasing the risk for other STIs including chlamydial infection;15 however, a direct association between douching and chlamydial infection is less consistent.16 As for HIV, the positive impact of circumcision on the risk of acquiring C. trachomatis and thus prevention of C. trachomatis by circumcision is more and more supported by the evidence in medical literature.17

C. trachomatis belongs to the genus Chlamydia (phylum Chlamydiae, order Chlamydiales, family Chlamydiaceae) together with Chlamydia muridarum and Chlamydia suis. Other chlamydiae infecting humans, Chlamydia pneumoniae and Chlamydia psittaci, are currently classified in a separate genus.18 However, this subdivision of the family
One page of a document, including some extracted raw text, is shown. The text refers to the infection caused by *Chlamydia trachomatis* and discusses the duration of infection in untreated individuals. It mentions that earlier reports of quick clearance of infections can be based on insensitive culture tests on one hand, while on the other hand, culture is the ultimate proof of viability. The long duration of undetected and untreated infection in women can result in that the bacteria cross the cervix and uterus, ascend into the upper genital tract, adhere, and ultimately result in associated complications and sequelae such as PID, ectopic pregnancy, and tubal factor infertility. Appropriate testing of asymptomatic and asymptomatic sexually active individuals is accordingly recommended to identify and treat the *C. trachomatis* infections. The direct medical costs of *C. trachomatis* infections were estimated at $516.7 million in 2008 in the USA, among the non-viral STIs the most costly infection. Also of importance are the tangible costs, including the lost labour productivity, and the intangible costs, including psychological and emotional injury caused by infertility and ectopic pregnancy.

### Clinical features, complications and sequelae

A primary urogenital chlamydial infection is mostly asymptomatic, and accordingly infected individuals are not prompted to seek medical care. Frequently referred figures for the proportion of asymptomatic infections, ~70% in women and ~50% in men, are from historical contact tracing studies which used tests with suboptimal sensitivity. In a recent review by Davies et al., it was concluded that asymptomatic infections can be even more common, i.e. estimated from 70% to 95.5% in women and from 25% to 100% in men. To measure the true range in duration of infection in untreated *C. trachomatis*-infected patients in observational studies is unfortunately basically impossible, because the timing of infection is required. However, Molano et al. described a *C. trachomatis* clearance (from the point of detection of the infection) in 54% of untreated asymptomatic women at one year of follow-up, 82% at two years, and 94% at four years. In another study examining untreated asymptomatic women, the clearance rate was similar (45%) during the first year. A significant proportion of the used parameter values regarding natural course of infection is also referenced back to the early chlamydial literature, before the introduction of nucleic acid-based methods for diagnosis and the widespread testing of asymptomatic individuals. This means that earlier reports of quick clearance of infections can be based on insensitive culture tests on one hand, while on the other hand, culture is the ultimate proof of viability. The long duration of undetected and untreated infection in women can result in that the bacteria cross the cervix and uterus, ascend into the upper genital tract, adhere, and ultimately result in associated complications and sequelae such as PID, ectopic pregnancy, and tubal factor infertility. Appropriate testing of asymptomatic and asymptomatic sexually active individuals is accordingly recommended to identify and treat the *C. trachomatis* infections. The direct medical costs of *C. trachomatis* infections were estimated at $516.7 million in 2008 in the USA, among the non-viral STIs the most costly infection. Also of importance are the tangible costs, including the lost labour productivity, and the intangible costs, including psychological and emotional injury caused by infertility and ectopic pregnancy.

### Urogenital infections

**Symptoms and signs in women**
- 70–95% asymptomatic;
- Mucopurulent cervicitis with or without contact bleeding;
- Cervical friability;
- Cervical oedema;
- Endocervical ulcers;
- Urethritis;
- Dysuria;
- Vaginal discharge;
- Postcoital bleeding and intermenstrual bleeding;
- Poorly differentiated abdominal pain or lower abdominal pain.

**Symptoms and signs suggestive of PID**
- Lower abdominal tenderness and pain – usually bilateral;
- Cervical motion tenderness on bimanual vaginal examination;
- Adnexal tenderness on bimanual vaginal examination;
- Deep dyspareunia – particularly of recent onset;
- Abnormal bleeding – intermenstrual bleeding, post coital bleeding and menorrhagia can occur secondary to associated cervicitis and endometritis;
Abnormal vaginal or cervical discharge – as a result of associated cervicitis, endometritis or bacterial vaginosis;
Fever (>38°C) – in moderate to severe PID.

Complications in women
- PID (endometritis, salpingitis, parametritis, oophoritis, tuboovarian abscess and/or pelvic peritonitis);
- Chronic pelvic pain;
- Tubal infertility;
- Ectopic pregnancy;
- Sexually acquired reactive arthritis (SARA) (<1%);
- Fitz-Hugh-Curtis syndrome (PID and perihepatitis).

Symptoms and signs in men (may be so mild that they are not noticed)2,39,42,43
- Usually more than 50% (25–100%) asymptomatic;
- Urethritis;
- Dysuria;
- Urethral discharge;
- Epididymitis;
- Testicular pain.

Complications in men
- SARA (<1%);
- Epididymitis, epididymo-orchitis.

Rectal and pharyngeal infections
* C. trachomatis* infections of the rectum in men and women can result from unprotected anal intercourse and are typically asymptomatic. However, the infections may cause anal discharge and anorectal discomfort and also progress to proctocolitis.44,45 The rates of rectal chlamydial infection in men who have sex with men (MSM) have been reported to be between 3% and 10.5% in some sexual settings.46,47 Recent studies have shown an 8.4% prevalence of anorectal *C. trachomatis* in women and almost all (94.5%) of these women also had urogenital *C. trachomatis*.48,49 Pharyngeal chlamydial infections are also usually asymptomatic, but symptoms of a mild sore throat can occur.50 The rates of *C. trachomatis* detection in the pharynx in MSM can range from 0.5% to 2.3%.47,51,52

Ocular infections
Ocular infections can result in conjunctivitis in neonates and adults. In adults, this can be caused by auto-inoculation, genito-ocular or ocular-ocular contact2,3,53–56 and can lead to chronic conjunctivitis and persist for several months if left untreated.

Neonatal infections
Infants born to mothers through an infected birth canal may become colonised and may develop conjunctivitis and/or pneumonia.55 The vertical transmission risk for a newborn is 50–75%.56

Lymphogranuloma venereum (LGV)
Lymphogranuloma venereum (LGV) is an invasive ulcerative disease caused by the serovars L1, L2 or L3 of *C. trachomatis*.57 LGV was rare in Western Europe and USA for many years. However, since the detection of an outbreak in 2003 in Rotterdam, the Netherlands LGV outbreaks have been verified amongst MSM in also several other European countries.58,59 Most cases have occurred in HIV-positive MSM.59–61 Most patients have presented with proctitis62 or tenesmus, anorectal discharge (often bloody) and discomfort, diarrhoea or altered bowel habits. Due to similarities between LGV and inflammatory bowel disease (IBD), LGV should be considered as a differential diagnosis in patients with proctitis or IBD-related symptoms, especially among HIV-positive men. Long-lasting examination, mistreatment and surgery can then be reduced.63,64

In contrast to the early reports, it has now been shown that approximately 25% of LGV infections can be asymptomatic and form an easily missed undetected reservoir.65 The majority of reported infections in MSM are found in the anorectal canal and not urogenital, which leaves the mode of transmission within the MSM network unclear.66 Given the increasing trend in several larger European cities, the LGV endemic is clearly not under control. Therefore, directed testing of LGV must be intensified.67 For additional information on LGV, see the latest version of the ‘European Guideline on the Management of Lymphogranuloma Venereum’68 (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

Complications and sequelae
Women. Untreated *C. trachomatis* infections can lead to serious complications. In older observational treatment studies, up to 30% of women with untreated urogenital *C. trachomatis* infections developed PID.69,70 The reported incidence of PID has fallen in several countries over the last decades,3,71–74 and the risk of complications has been reported to be lower than previously estimated.75–77 PID is assumed to be the necessary
intermediate condition between lower genital tract chlamydia infection and late sequelae. PID is a clinical syndrome, which results from ascending infection from the vagina and endocervix. Criteria for PID diagnosis are neither sensitive nor specific. Even when present, clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is frequently around 65–90% compared to laparoscopic diagnosis). A diagnosis of chlamydial PID is usually inferred from the findings of a positive C. trachomatis test result in the lower genital tract in the presence of a compatible clinical picture. Lower abdominal pain and adnexal tenderness, which form the basis of the clinical diagnosis of PID, are non-specific. Laparoscopy is considered the gold standard diagnostic tool, but this is an invasive investigation that requires general anesthetics. It is rarely used for routine diagnosis of mild or moderate symptoms and signs. Indications for laparoscopy should be a symptomatic patient with suspicion of pelvic or tuboovarian abscess, whenever differential diagnoses cannot be excluded, and whenever there is no improvement of clinical symptoms and infect parameters within 72 h despite adequate antibiotic therapy. Laparoscopy also helps to confirm the correct diagnosis and also offers the chance to perform adequate therapies such as rinsing and suctioning, adhesiolysis, salpingostomy or salpingectomy or placing drainages for subsequent irrigation.

Regardless of symptom intensity, the consequences of PID are severe. Of those with symptomatic PID, about 20% are subsequently infertile; 18–42% will experience debilitating, chronic pelvic pain; and 1–9% will have a life-threatening tubal pregnancy. The importance of subclinical PID became apparent with observations that most of the women with tubal factor infertility or ectopic pregnancy who had serologic evidence of chlamydial infection apparently had no history of PID. C. trachomatis infection during pregnancy might lead to infant conjunctivitis and pneumonia and maternal postpartum endometritis. Furthermore, FitzHugh-Curtis syndrome (PID and perihepatitis) could develop.

Men. Among men, urethritis is the most common syndrome resulting from C. trachomatis infection. Complications (e.g. epididymitis, epididymo-orchitis) affect a minority of infected men and rarely result in reproductive health sequelae. There is no strong evidence base that C. trachomatis causes infertility in men. However, C. trachomatis has been indirectly associated with male subfertility or infertility as a result of a direct effect on sperm production, maturation, motility and viability. This could at least partly explain poor in vitro fertilisation outcome or fertilisation failure, and therefore all patients should be screened and treated for C. trachomatis prior to assisted conception.

**Sexually acquired reactive arthritis (SARA)**

SARA has also been reported as a possible consequence of C. trachomatis infection (30–40/100,000 infections). There is much in favour of a causal relationship between C. trachomatis and SARA, although true evidence is still lacking. SARA is a multisystem disease, which predominantly occurs in human leukocyte antigen B27-positive young males, and includes a combination of urethritis, conjunctivitis and arthritis. The fact that the causative agents are found in the synovial membrane or synovial fluid is indicative of infectious rather than reactive arthritis. To diagnose and treat non-gonococcal urethritis as soon as possible should be the aim in order to prevent the development of reactive arthritis. For additional information regarding the management of SARA, see the latest version of the ‘European guideline for the management of sexually acquired reactive arthritis’ (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

**Indications for laboratory testing (level of evidence IV; Grade C recommendation)**

- Risk factor(s) for C. trachomatis infection and/or other STIs (age < 25 years, new sexual contact in the last year, more than one partner in the last year);
- Symptoms or signs of urethritis in men;
- Cervical or vaginal discharge with risk factor for STI;
- Acute epididymo-orchitis in a male aged < 40 years or with risk factor for STI;
- Acute pelvic pain and/or symptoms or signs of PID;
- Proctitis/proctocolitis according to risk;
- Purulent conjunctivitis in a neonate or adult;
- Atypical neonatal pneumonia;
- Persons diagnosed with other STI;
- Sexual contact of persons with an STI or PID;
- Termination of pregnancy;
- Any intrauterine interventions or manipulations.

**Laboratory diagnostics**

**Recommended diagnostic assays**

- Nucleic acid amplification tests (NAATs), identifying C. trachomatis-specific nucleic acid (DNA or RNA) in clinical specimens, are recommended to be used for diagnostics, due to their superior sensitivity, specificity and speed (I; A).
Only if *C. trachomatis* NAATs are not available or affordable, isolation of *C. trachomatis* in cell culture or identification of *C. trachomatis* by direct fluorescence assays (DFA) can be used for diagnosis of acute *C. trachomatis* infection.

NAATs have detected 10–30% more *C. trachomatis*-positive specimens than culture in studies comparing the two methods.\(^{11,103}\) It is not known whether the natural history of NAAT-positive *C. trachomatis* infections in people without symptoms and at low *C. trachomatis* loads is the same as that of culture-positive chlamydial infections.\(^{31}\) Evidence on the minimum period necessary before testing can be recommended is lacking, although clinical experience suggests that positive NAAT results may be observed within 1–3 days of *C. trachomatis* exposure. Nevertheless, in these situations mainly the infectious inoculum is detected. Thus, patients should be tested when they first present, however, if there is concern about a sexual exposure within the last two weeks they should have a repeat NAAT test two weeks after the exposure (IV; C). For adequate performance characteristics of all NAATs and other diagnostic methods, it is crucial to follow precisely the recommendations from the manufacturer concerning collection, transportation and storage of samples, as well as performance of the specific assay, including quality controls and participation in an appropriate external quality assessment (EQA) scheme. Furthermore, all diagnostic laboratories should have a quality assurance system and strive towards accreditation.

**NAAT**

Validated and quality assured NAATs are recommended due to their superior sensitivity, specificity and speed of diagnosis of both symptomatic and asymptomatic chlamydial infections compared to all other diagnostic techniques (I; A).\(^{97,104–110}\) Due to the high specificity of the appropriately validated *C. trachomatis* NAATs (resulting in a high positive predictive value) and risk of losing low positive results in repeated testing, confirmatory testing of positive specimens is not recommended.\(^{78,111}\) Many commercially available NAATs can detect *C. trachomatis* and *Neisseria gonorrhoeae* simultaneously, the NAATs can use less invasively collected specimens such as urine samples in men or vulvo-vaginal swabs in women and anorectal swabs in both genders,\(^{112}\) and the assays are well suited to automation, which results in increased standardisation and quality assurance of extraction and detection, as well as significantly increased throughput.\(^{113}\)

Nevertheless, it is crucial to realise that the performance characteristics of individual commercial as well as laboratory-developed (in house) *C. trachomatis* NAATs differ. Given the rigorous evaluation required before approval of a diagnostic test by the United States of America Food and Drug Administration (FDA), which includes multisite clinical trials with comparisons against appropriate standards, FDA-approved *C. trachomatis* NAATs are primarily recommended for diagnosis. However, globally, including in Europe, there are many additional commercially available or laboratory-developed *C. trachomatis* NAATs in use.\(^{114–116}\) If non-FDA-approved NAATs are used, regional (such as EU), and/or other national validation and regulatory processes should provide safeguards on the quality and performance of the diagnostic NAAT. If validated and approved NAATs cannot be used, it is strongly recommended that the effectiveness of the proposed NAAT for the local settings is validated and quality assured before use against at least one internationally approved NAAT and subsequently used with appropriate positive, negative, and inhibition controls; participation in appropriate EQA system is strongly recommended as well.

It is important to also be aware that substances in the biological sample may inhibit the NAAT.\(^ {117–119}\) It is therefore advisable to include an inhibition control to prevent false-negative results. Some commercial NAATs include internal controls from DNA extraction to amplification, other assays have no or only extraction controls. External inhibition controls are recommended to be added to the sample to solve this lack of inhibition control. Most modern nucleic acid extraction assays will remove most inhibitors;\(^ {120}\) however, users should still be aware of potential inhibition and invalid test results.

**Point-of-care tests (POCTs)**

Rapid point-of-care tests (POCTs) provide a quick and easy test result, and diagnosis and subsequent treatment can be provided at the same visit at clinic or even in remote settings. However, compared to NAATs the sensitivity of the current, mostly immuno-chromatographic, tests is clearly insufficient.\(^ {121–125}\) POCT with increased sensitivity has been developed, and newer POCT NAATs are under development.\(^ {122,126–128}\) These new POCT might be suitable for genital and extra-genital samples and evaluations are on-going.\(^ {129}\) Currently available rapid POCT cannot be recommended in Europe, unless other more sensitive tests are unavailable and results are interpreted with caution.

**Detection of *C. trachomatis* variants**

A new variant of *C. trachomatis* was detected in Sweden (nvCT or swCT) in 2006. This variant has a 377 bp
deletion in the cryptic plasmid, which is used by some commercial assays as amplification target.\textsuperscript{130–132} The nvCT resulted in thousands of false-negative \textit{C. trachomatis} tests in Sweden. The nvCT has mainly been reported in the Scandinavian countries and rarely in other countries. All major commercial assays used in Europe have now been redesigned to ensure detection of the new variant.\textsuperscript{133} Plasmid-free \textit{C. trachomatis} variants have been found, but they are rare.\textsuperscript{134} It is believed that the plasmid-free variants are less virulent (IIb).\textsuperscript{135–138} Laboratories are advised to use NAATs capable of detecting all known \textit{C. trachomatis} variants and to further investigate any unexplained significant increases or declines in the local incidence or positivity rate (I; A).

Since anorectal LGV needs different management as opposed to non-LGV infections, it is recommended to identify LGV patients by testing all MSM who report receptive anal sex in the previous six months for ano-rectal \textit{C. trachomatis} infection with a commercially available NAAT.\textsuperscript{139} Subsequently, MSM who are ano-rectal \textit{C. trachomatis} positive are recommended to be tested for LGV proctitis using a genovar L-specific NAAT.\textsuperscript{68} For additional information on LGV, see the latest version of the ‘European Guideline on the Management of Lymphogranuloma Venereum’\textsuperscript{68} (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

It is recommended that laboratories participate in quality assurance programmes, including appropriate EQA programme, to identify genetic variants and unusual clinical presentations (IA).\textsuperscript{140,141} Expert networks, such as the ECDC European STI Network or International Union Against Sexually Transmitted Infections (IUSTI), can help to quickly assess new \textit{C. trachomatis} variants or clinical presentations, and can be used to rapidly disseminate information to other professionals worldwide. It is recommended that laboratories participate in international STI expert networks.

**Specimens**

**Urogenital specimens.**

- The recommended first-choice specimens for diagnosis of urogenital chlamydial infections with NAATs are first-void urine for men and (self-collected) vulvo-vaginal swabs for women (I; A).

First-void urine (up to 20 ml sampled > 1 h after previous micturition) is highly acceptable for men as this is easy to collect and does not cause discomfort. In men, first-void urine also contains the highest \textit{C. trachomatis} load.\textsuperscript{142–144} Specialised swabs, collection units and transportation units have been developed to optimise the yield of Chlamydia, either by collection in the clinic or self-collection at home.\textsuperscript{106,145–150} First-void urine should be used to diagnose \textit{C. trachomatis} infections with NAATs in men (I; A).

Sensitivity of first-void urine testing in women is less compared to in males.\textsuperscript{102} Women have more often a cervico-vaginal infection than a urethral infection and the \textit{C. trachomatis} load in urine samples is substantially lower than in men.\textsuperscript{144} In women, a vulvo-vaginal swab (health-care worker or self-collected) is the preferred specimen for detection of \textit{C. trachomatis} (I; A).\textsuperscript{104,147,151–154} and also well accepted by women.\textsuperscript{151,155} Patients can send dry vulvo-vaginal swabs by mail to the laboratory without significant loss of sensitivity.\textsuperscript{156} If clinical examination is performed, a cervical specimen can be sampled. However, according to recent data NAATs on a (self-collected) vulvo-vaginal specimen is at least as sensitive. First-void urine from women should only be used if other specimens are not available (II; B).\textsuperscript{110,143}

The use of Pap-smears is not recommended for screening, case finding or other diagnostic purposes, even though several methods to optimise detection in Pap-smears have been published.\textsuperscript{157,158} Penile skin swabs cannot currently be recommended.\textsuperscript{78,102,159}

**Pharyngeal, rectal and conjunctival specimens**

No manufacturer of \textit{C. trachomatis} NAATs has licensed extra-genital specimens for diagnosis. However, NAATs are the preferred test for all these specimens and some NAATs have been adequately validated for these specimens (IIa; B).\textsuperscript{160–164} These specimens should not replace appropriate urogenital specimens, but should be used additionally when indicated by risk or sexual practice. In general, collecting pharyngeal and rectal specimens should always be considered in MSM and in heterosexuals according to risk.\textsuperscript{78,165}

Cell culture and DFAs are not suitable for rectal specimens, due to suboptimal sensitivity as well as cytotoxicity and possible cross-reactions, respectively. Accordingly, NAATs are recommended for testing of rectal specimens, although laboratories should be aware that sensitivity and specificity can be lower compared to urogenital specimens.\textsuperscript{162,166–169} Confirmation of the positive results with an independent assay may be appropriate (II).\textsuperscript{162,166,167}

With the increase (or persisting presence) of rectal LGV infections, especially in MSM,\textsuperscript{50,170,171} it is recommended that positive rectal specimens from MSM are genotyped for LGV, irrespective of the presence of anorectal symptoms (II; B), for instance by a reference laboratory. For additional information on LGV,

**Semen specimens**

NAATs can detect *C. trachomatis* in semen, however, there is a good correlation between first-void urine positivity and semen positivity, first-void urine is easier to obtain, and it is exceedingly difficult to exclude that the *C. trachomatis* detected in semen is not only from the urethra that is passed during semen sampling. Accordingly, testing of semen specimens has not proven to be of any main value and is not recommended (II; B).

**Serology**

Serology is not recommended for screening or diagnosis of acute uncomplicated anogenital *C. trachomatis* infections. In many patients, only invasive *C. trachomatis* infections will lead to detectable levels of antibodies and antibody levels might also remain positive for years. However, when NAATs are not available detection of specific antibodies to *C. trachomatis* may support the diagnosis of invasive disease, such as LGV involving the lymph nodes and neonatal pneumonia (I; A).

**C. trachomatis serology – key points**

- Differences in serological responses between men and women have been described, as well different *C. trachomatis* serovars resulting in different serological responses;
- Duration of antibody levels is unknown and may differ between persons. Detectable antibody levels may persist for a long time after clearance of the infection, which may result in false-positive results in testing;
- No value in the diagnosis of uncomplicated lower urogenital tract infections;
- Limited value in the diagnosis of ascending infections and for infertility work-up;
- Chlamydia antibody titres may predict development of tubal pathology, but this is under debate;
- LGV serovars tend to infect draining lymph nodes, resulting in greater chances of a detectable systemic antibody response. All MSM with rectal LGV infections develop high antibody titres may be used as a diagnostic tool, but NAATs are preferable.
- Detection of *C. trachomatis*-specific IgM can be a diagnostic tool in neonatal chlamydial pneumonia;
- Reports on Chlamydia antibody testing are extremely difficult to assess. The microimmunofluorescence (MIF) is claimed to be the test of choice, but only few laboratories are capable of performing the test adequately. Specificity has been greatly enhanced by using peptide-based assays. They are very useful in detecting infections in the past, for instance as testing assays in infertility work-up.

**Quality assurance**

Quality assurance is a requirement for high-quality and valid laboratory results, and all diagnostic laboratories should have a quality assurance system and strive towards accreditation. Reference standards and internal controls (positive, negative and, if required in NAATs, inhibition controls) should be an integral part of all tests. Laboratories should participate in national and international EQA programmes to assess proficiency and laboratory performance to assure quality of testing. Re-evaluation of random samples by an independent laboratory with an independent test will help reduce false-positive and false-negative results. Assay performance problems might be missed when following the manufacturer’s instructions, but are likely to be detected in a quality control programme. It should be noted that when specimens are self-collected, especially at home, quality assurance is limited before the specimens are received in the mail. Errors and manipulation before will remain unnoticed.

**Testing in STI and sexual health clinics and repeat testing**

- Annual *C. trachomatis* testing in STI and sexual health clinics is recommended for sexually active young women and men (<25 years of age), and should be considered for MSM (2a; B).
- Repeated testing in 3–6 months should be offered to young women and men (<25 years of age) who test positive for *C. trachomatis* (III; C).

Clinical guidelines in many countries recommend annual *C. trachomatis* testing for all sexually active young (<25 years of age) women and extend to young men in some countries. However,
in recent years, mathematical modelling studies have suggested that to achieve population level impact on *C. trachomatis* transmission, screening programmes need to achieve very high testing coverage and also high rates of partner notification and repeated testing for reinfection after treatment. Mathematical modelling also suggested that treating symptomatic men and women and screening 38% of women aged 15 to 24 years annually would significantly reduce the average number of secondary infections and that screening men and women aged up to 29 years may affect *C. trachomatis* transmission. Modelling by Althaus et al. also estimated that in a population-wide screening programme, the treatment of current partners is the most effective strategy for reducing *C. trachomatis* transmission at the population level. A recent systematic review showed that *C. trachomatis* screening in educational settings is a feasible approach to screen large numbers of young people and to identify and treat new infections. The review demonstrated that screening has been conducted in a range of educational facilities in a number of countries and screened a large number of both male and female students, although some strategies seemed to reach a greater number of students than others. However, only a few programmes reported on important outcomes such as treatment, partner notification and retesting after treatment. Future evaluations of school-based programme should also focus on collection and reporting of these important programme outcomes. The main rationale for current *C. trachomatis* screening or opportunistic testing is, however, that early detection and treatment will prevent or interrupt reproductive tract morbidity, particularly in women.

Mathematical modelling studies in the USA have shown that repeat infection rates peak at 2–5 months after the initial infection, supporting the US CDC recommendation that any person diagnosed as having *C. trachomatis* infection should be retested within 3–12 months of treatment. The English National Chlamydia Screening Programme (NCSP) guidelines recommend retesting annually or on change of sexual partner for all sexually active under 25 years of age and, in 2013, began to include recommendations of retesting around three months after a positive test. This guidance is based on evidence that young adults who test positive for *C. trachomatis* are 2–6 times more likely to have a subsequent positive test and that repeated chlamydial infection is associated with an increased risk of complications such as PID and tubal infertility. Recently, the frequency and risk factors for incident and redetected *C. trachomatis* infection in a community-based cohort of English women who provided follow-up samples in the Prevention of Pelvic Infection (POPI) Chlamydia screening trial have been examined. These results showed that the annual incidence and redetection rates of *C. trachomatis* infection in women in the community were high, particularly among sexually active teenagers. They highlighted the need for targeted screening among those with a new sexual partner or recent history of infection.

However, also the timing of progression from endocervical *C. trachomatis* infection can affect the impact of a Chlamydia control programme. If *C. trachomatis* ascends to infect fallopian tube cells immediately after endocervical infection and inflammation follows soon after, opportunistic testing and treatment would, in most cases, be too late to prevent tubal pathology. The reduction in the incidence of PID in randomised clinical trials (RCTs) comparing women receiving chlamydia screening interventions with control groups suggests that there must be an interval after endocervical infection during which screening can prevent or limit clinical PID. In four RCTs performed in EU Member States (Denmark, The Netherlands and the UK) that examined the effect of Chlamydia screening on the incidence of PID, the Chlamydia screening intervention was done on a single occasion. All trials found lower number of PID cases in the intervention group compared to the control group. The pooled average risk ratio of PID in the intervention compared with the control group was 0.64 (95% CI 0.45, 0.90), and there was exceedingly small statistical heterogeneity between results of the different trials. Accordingly, these RCTs suggest there is a window of opportunity in which treatment for screening-detected *C. trachomatis* can interrupt tubal pathology. For the outcome, PID the GRADE tool found moderate quality evidence of efficacy from the same four RCTs that Chlamydia screening reduces the incidence of PID when compared to control groups receiving usual care. The estimated absolute risk reduction was four cases of PID per 1000 women screened. The level of evidence was downgraded from high to moderate because of the high risk of selection bias in the methods used in the earliest trials. For the outcome of a change in *C. trachomatis* incidence, the GRADE tool found low quality of evidence from two effectiveness trials. The quality of evidence from non-randomised study designs begins as low. The risk of selection bias, which was greatest for the trial by Cohen et al., was a factor that downgraded the quality, but this was balanced by the finding of a dose response relationship in the effects of the two trials. Assumptions about model structure and about the probability of complications of Chlamydia in several studies tend to favour screening.
Management of patients

Information, explanation and advice for the patient

- Patients with positive *C. trachomatis* test should be advised to abstain from sexual contact for seven days after they and their partners have completed treatment and their possible symptoms have resolved (IV; C);
- Patients with positive *C. trachomatis* test (and their sexual contacts) should be given information about their infection, including details about transmission, prevention and complications. It is recommended that both verbal and written information be provided (IV; C);
- Information for patients is available on the IUSTI Europe website for guidelines (http://www.iusti.org/regions/Europe/euroguidelines.htm);
- Patients with positive *C. trachomatis* test should be considered for and encouraged to have testing for other STIs, including gonorrhoea, syphilis and HIV (IV; C).

Indications for therapy (IV; C)

- Identification of *C. trachomatis* or *C. trachomatis*-specific nucleic acid (DNA or RNA) in a clinical specimen;
- On epidemiological grounds, if a recent sexual contact has confirmed chlamydial infection (NAAT specimen should also be sampled for testing);
- On epidemiological grounds, mother of neonate with confirmed chlamydial infection (NAAT specimen should also be sampled for testing);
- On epidemiological grounds, treatment can be considered following sexual assault (NAAT specimen should also be sampled for testing);
- On demonstration of a purulent urethral discharge in men or mucopurulent cervicitis in women when diagnostic tests are not available and after specimen collection for laboratory testing. In this circumstance, dependent on local gonorrhoea incidence combined treatment for chlamydial infection and gonorrhoea should be considered.

Therapy

Treatment of individuals with *C. trachomatis* urogenital infection prevents sexual transmission and complications, including PID. Treatment of pregnant women will prevent the transmission of infection to infants during delivery. Furthermore, prompt treatment of persons with chlamydial infection is important; by decreasing the interval between *C. trachomatis* diagnosis and treatment complications can be limited. *C. trachomatis* is susceptible to many antibiotics such as tetracyclines, macrolides, penicillins and fluoroquinolones, which all are drugs that have been used for treatment of human chlamydial infection. Induced resistance to antimicrobials in *C. trachomatis* has been demonstrated in vitro. However, there is still no evidence of any stable, homotypic genetic and phenotypic resistance to any therapeutic antimicrobial in clinical *C. trachomatis* strains that affects the treatment in humans.218–222 Nevertheless, in recent years concerns have been raised over clinical failures in *C. trachomatis*-infected patients treated particularly with azithromycin 1g single oral dose.223–226 Some of these treatment failures can be explained by reinfection, poor compliance or tolerance of treatment or detection of nucleic acid from non-viable *C. trachomatis* due to test-of-cure (TOC) performed too early.227 However, the reasons for the remaining treatment failures remain unclear,228 though a suboptimal duration of exposure to azithromycin after the 1g single dose and a low-level absorption of azithromycin in some patients may be involved.219 Some earlier work suggested that a prolonged course of azithromycin is likely to be sufficiently bactericidal to *C. trachomatis*.229 and in respiratory tract infections azithromycin 1.5g administered over 3 to 5 days has been reported to achieve therapeutic levels in target tissues for up to 10 days.230,231 Based on the half life (68 h) of azithromycin, it has been suggested that increasing the dose of azithromycin to 3g (1g single dose then 500mg once daily for four days) would likely maintain tissue levels for over 12 days. Further, it has been suggested that use of azithromycin 1g stat increases the risk of inducing macrolide resistance in *Mycoplasma genitalium*.232–235 Accordingly, when a concomitant *M. genitalium* infection has been verified or can be suspected, treatment with azithromycin 500mg day 1, followed by azithromycin 250mg once a day for four days should be considered (III; C). Recently, it was shown that this five days azithromycin treatment regimen can effectively eradicate also *C. trachomatis*, that is, the eradication rate for *C. trachomatis* was 98.8% (79 of 80 patients infected with both *M. genitalium* and *C. trachomatis*).236 Nevertheless, appropriate large and well-designed RCTs using the five days azithromycin regimen to examine the eradication frequency of both *M. genitalium* and *C. trachomatis* are crucial, and when using this regimen TOC for both bacteria should be considered.

Recommended treatment for uncomplicated urogenital *C. trachomatis* infections

First-line (Ia; A).

- Doxycycline 100 mg twice a day for seven days (oral; contraindicated in pregnancy) or
• Azithromycin 1 g stat (oral)

Second-line (II; B) (TOC should be subsequently performed).
• Erythromycin 500 mg twice a day for seven days (oral) or
• Levofloxacin 500 mg once a day for seven days (oral; contraindicated in pregnancy) or
• Ofloxacin 200 mg twice a day for seven days (oral; contraindicated in pregnancy)

Third-line (II; B) (TOC should be subsequently performed).
• Josamycin 500 mg three times or 1000 mg twice a day for seven days (oral)

For many years, the two accepted first-line oral antimicrobial therapies for uncomplicated urogenital chlamydial infections have been azithromycin 1 g stat and doxycycline 100 mg twice daily for seven days. A meta-analysis of 23 RCTs comparing these regimens for urogenital chlamydial infections showed a statistical superiority in favour of doxycycline. However, the difference in efficacy was small at 1.5%–2.6% (approximately 97% versus 95% efficacy). This difference is not clinically significant and both azithromycin and doxycycline can be recommended as first-line regimens (Ia; A). When a concomitant *M. genitalium* infection has been verified or is suspected, treatment with azithromycin 500 mg day 1, followed by azithromycin 250 mg once a day for four days, should be considered (III; C).

The quinolones ofloxacin and levofloxacin and the macrolides erythromycin and, where available, josamycin, have also been shown to be effective. As there is substantially less published, particularly recent, data on the effectiveness of these agents they are only recommended second-line (ofloxacin, levofloxacin, and erythromycin) or third-line (josamycin), and if used a TOC should be performed (II, B).

The rate of compliance is of major concern and has been shown to be substantially higher in the case of a single dose of azithromycin, in both patients and their sexual contacts (I). Adverse side effects affect compliance negatively as well, making erythromycin, which is well known for its gastro-intestinal side effects, an unattractive alternative. Rifalazil 25 mg has been suggested to be a promising well-tolerated single dose oral alternative in women. However, a recent small study (including 82 *C. trachomatis* women) showed a suboptimal microbiologic cure rate of only 84.8% with rifalazil, versus 92.1% with azithromycin (Ib; A).

People living with HIV infection should be treated in the same way as HIV negative ones (IV; C).

Recommended treatment for uncomplicated *C. trachomatis* non-LGV rectal and pharyngeal infections
• Doxycycline 100 mg twice a day for seven days (oral) (I; A) (preferred if rectal infection)

Or alternatively
• Azithromycin 1 g stat (oral) (IIa; A) (if rectal infection, a TOC should be subsequently performed).

No RCTs for the treatment of non-LGV rectal or pharyngeal chlamydial infections have been performed. The results of the treatment trials for urogenital infection have been extrapolated to support the recommendation that the same regimens be used for treating infections at other sites.

For rectal infections four non-randomised studies have been published which showed higher efficacy rates for doxycycline (98.8–100%) than for azithromycin (74–87%) at this anatomical site. Conversely, another study (also non-randomised) showed azithromycin to be 94% effective; a similar rate to that for urogenital infections. However, all these five studies had important limitations; none was randomised, only one was prospective, only two had information on both regimens and in three less than half the patients had a TOC performed. Because of the low quality of the data supporting the superiority of doxycycline over azithromycin for treating rectal infections both regimens continue to be recommended as first-line. However, pending further studies and ideally double-blinded, placebo-controlled RCTs, if rectal chlamydia is treated with azithromycin then a TOC should be performed (IIa; A).

Recommended treatment for uncomplicated LGV infections
First-line (IIb; B).
• Doxycycline 100 mg twice a day for 21 days (oral)

Second line (III; B).
• Erythromycin 500 mg four times a day for 21 days (oral)

Azithromycin in single- or multiple-dose regimens has also been proposed, but evidence is lacking...
to currently recommend azithromycin (IV; C). Doxycycline is contraindicated in pregnancy and breast feeding.

**Adjunctive therapy**

1. If fluctuant buboes appear they should be aspirated promptly through healthy adjacent skin (IV; C);
2. Surgical incision of buboes is not usually recommended due to potential complications such as chronic sinus formation (IV; C);
3. Patients with residual fibrotic lesions or fistulae do not benefit from further courses of antibiotics so surgical repair, including reconstructive genital surgery, should be considered (IV; C).

LGV is an invasive *C. trachomatis* infection and can, if left untreated, have serious and permanent adverse sequelae. Most of these complications are preventable if treatment is initiated in the early stages (IV; C).

Despite a paucity of robust evidence regarding the efficacy of therapy for any rectal chlamydial infections (LGV or non-LGV), 3 weeks of oral doxycycline 100 mg twice daily to treat LGV is recommended.78,259,260

The vast majority of recent MSM case reports have observed complete responses to this therapy; shorter courses may not eradicate the organism.261

For detailed and updated information regarding the management of LGV, see the latest versions of the ‘European Guideline on the Management of Lymphogranuloma Venereum’68 and the ‘European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens’139 (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

**Pregnancy**

*C. trachomatis* infections also occur during pregnancy. Infection can be associated with premature labour, preterm birth and neonatal conjunctivitis and pneumonia.262–267 The choice of drugs for treatment is important because of their possible adverse effects on foetal development and pregnancy outcome.

**Recommended treatment for uncomplicated urogenital C. trachomatis infection in pregnancy and during breast feeding (TOC should be subsequently performed)**

**First-line (I; A)**78,195,268,269

- Azithromycin 1 g stat (oral)

**Second line.**

- Amoxicillin 500 mg three times a day for seven days (oral)
  or
- Erythromycin 500 mg 4 times a day for 7 days (oral)

**Third line.**

- Josamycin 500 mg three times or 1000 mg twice a day for 7 days (oral)

Doxycycline and fluoroquinolones are contraindicated. Azithromycin has been considered safe and an effective antibiotic with a short period of treatment according to clinical experience and in some studies,269–271 and azithromycin is also recommended by the WHO in pregnancy. Unfortunately, in some countries azithromycin is not permitted to be administered in pregnancy, and therefore erythromycin or amoxicillin is regarded as an option.269,272 In countries, where josamycin is available, it is regarded as an alternative drug with a well-tolerated regimen.243 In the first trimester, it is only recommended under strict conditions.

**PID**

PID is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tuboovarian abscess and/or pelvic peritonitis. *C. trachomatis* and *N. gonorrhoeae* have been identified as causative agents,38 whilst *M. genitalium* and anaerobes can also be implicated. PID may be symptomatic or asymptomatic.38–40

- Mild and moderate cases should be treated as outpatients with oral therapy (Ib; A): otherwise ceftriaxone 500 mg single dose intramuscularly (or cefoxitin 2 g single dose intramuscularly with probenecid 1 g orally) followed by doxycycline 100 mg twice daily orally plus metronidazole 400 mg twice daily for 14 days orally or
- Ofloxacin 400 mg twice daily orally plus metronidazole 500 mg twice daily for 14 days orally2,39,85,273,274 (ofloxacin may be replaced by levofloxacin 500 mg once daily orally275) (Ib; A)

For more complicated PID cases, inpatient or alternative treatment, follow-up and partner notification see the latest version of the ‘European guideline for the management of pelvic inflammatory disease’276 (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).
Ocular manifestations associated with acute or chronic follicular conjunctivitis. \(^{195}\) Differential diagnosis in sexually active individuals pre-

These differences are due to different socioeconomic, legal, ethical, privacy and human rights, cultural and religious frameworks. \(^{195, 277, 278}\) Patient notification should prompt for testing for genital \(C.\ trachomatis\) infection and other STIs such as HIV, gonorrhoea and syphilis.

**Recommended treatment for \(C.\ trachomatis\) conjunctivitis**

- Azithromycin 1 g stat (oral) \(^{279}\) (IIa; A) or alternatively:
- Doxycycline 100 mg twice a day for 7 days (oral) (I; A)

**Contact notification and management of sexual contact(s)**

- Contact notification should be performed and documented by appropriately trained professionals at the time of diagnosis to improve outcome (Ib; A);
- Sexual contacts should be contacted and offered (and encouraged) testing together with treatment and, if infected, counseling (as index patient) for chlamydial infection and other STIs (IV; C); \(^{78, 218, 280–282}\)
- All sexual contacts within the preceding 6 months of onset of symptoms or diagnosis should ideally be evaluated, tested and treated (IV; C); \(^{78, 192, 218, 282, 283}\)
- If sexual contact(s) does not attend for evaluation and testing, epidemiological treatment should ideally be offered (IV; C); \(^{78, 218, 282}\)

Infected and untreated sexual contacts may reinfect the index patient as well as be at risk of adverse outcome of the \(C.\ trachomatis\) infection. Therefore, contact notification is recommended, as it is important to reduce onward transmission of infection and it may reduce persistent and recurring infections. \(^{284}\) Contact notification strategies, including the subsequent management of contacts, differ widely between countries. \(^{285}\) These differences are due to different socioeconomic, legal, ethical, privacy and human rights, cultural and religious frameworks. \(^{192, 282, 285}\) Patient notification (where the index patient notifies the sexual contact(s)) and provider notification (where the healthcare provider notifies the sexual partner(s)) are currently the most commonly used methods. The ease of traveling means that sexual contacts may not only have come from the local region, but also nationally and internationally. Efforts should be made to ideally trace all local, national, and international sexual partners. All sexual partners (as far as practically and legally possible) should be notified of a possible \(C.\ trachomatis\) infection, and offered testing and treatment. Sexual health counselling during the clinic visits reduces sexual risk taking and increases health awareness. \(^{280, 281}\)

This counselling should be offered where possible. Studies on the duration of human urogenital \(C.\ trachomatis\) infections have shown that \(C.\ trachomatis\) clearance increases over time, with approximately half of infections spontaneously resolving one year after initial positive test. \(^{286}\) However, the evidence base regarding ideal look-back period is limited and legal and practical considerations have to be taken into account when deciding a feasible look-back period. In many countries, these considerations limit the look-back period to two to three months, reducing the overall impact of contact notification strategies.

Where no regulatory barriers exist, expedited partner therapy or patient-delivered partner therapy can be an efficient way to treat partners and reduce the infection rates. \(^{284, 287–293}\) However, local, practical and legal restrictions may prevent the introduction of such methods. \(^{192, 287, 294}\) The main concerns are the lack of supervision of administration of prescription drugs, lack of monitoring of therapeutic effect, side-effects and adverse outcomes, the lack of opportunity to clinically examine and test for \(C.\ trachomatis\) or other STIs, as well as the lack of onwards contact notification, and safe sex education. It appears, however, well accepted by patients and partners. \(^{295–297}\) Patient delivered therapy should therefore only be implemented as part of a larger system of contact notification strategies. Given the wide differences between countries, no definitive recommendation can be given regarding expedited partner therapy or patient-delivered partner therapy.

For further information, see the latest version of the ‘European guidelines for the management of partners of persons with sexually transmitted infection’ \(^{282}\) (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

**Follow-up and test-of-cure (TOC)**

- A TOC is not recommended to be routinely performed in patients treated with recommended first-line regimens but should be performed in pregnancy, in complicated infections, if symptoms persist, if second-line or third-line regimens have
been used, and if non-compliance to therapy or re-exposure of infection is suspected (IV; C). It should also be considered in extra-genital infections, particularly when azithromycin 1 g stat has been administered for treatment of rectal infections. When indicated, TOC using NAATs should be performed 4 weeks after completion of therapy (III; B).\textsuperscript{78,194,218,250,298–300}

- Repeated testing in 3–6 months should ideally be offered to young women and men (≤25 years of age) who test positive for \textit{C. trachomatis}.\textsuperscript{78,192–198}

There is still no evidence of any homotypic genetic and phenotypic resistance to any therapeutically antimicrobial in \textit{C. trachomatis} that results in treatment failure in humans.\textsuperscript{218–222} A positive TOC may be due to non-compliance to treatment, reinfection from an untreated or new contact, inadequacy of treatment, and a false-positive result (mainly due to detection of nucleic acid from non-viable \textit{C. trachomatis} because retesting was performed too early).\textsuperscript{227} The diagnostic NAATs cannot discriminate between viable and dead \textit{C. trachomatis}. Accordingly, NAATs can remain positive more than three weeks (and possibly up to eight weeks due to intermittent shedding of nucleic acid) after treatment; due to detection of residual, non-viable chlamydial DNA or RNA that have not been cleared by the host.\textsuperscript{78,218,298–300} Recent years, major concerns have been raised over clinical failures in >5% of individuals treated for chlamydial infection with azithromycin 1 g single oral dose.\textsuperscript{223–225} The reasons for these treatment failures remain unclear,\textsuperscript{228} though a short duration of exposure may be responsible.\textsuperscript{219} Further work is crucial to establish whether routine TOC should be recommended as suggested by some authors (IV; C).\textsuperscript{219,223}

TOC should be differentiated from repeated testing for reinfection. Reinfection, particularly in young women and men (≤25 years of age), is common, frequently occurs within two to five months of the previous infection, and repeated chlamydial infection is associated with an increased risk of complications such as PID and tubal infertility.\textsuperscript{194,198,205,210,301–303} Accordingly, repeated testing in 3–6 months should be offered to young women and men (≤25 years of age) who test positive for \textit{C. trachomatis} (III; C).\textsuperscript{78,192–194,196,198,200,276} Asymptomatic infections have also been increasingly identified in MSM.\textsuperscript{304} Accordingly, repeated testing for TOC of asymptomatic MSM with rectal chlamydia after treatment for uncomplicated chlamydial infection (azithromycin 1 g single oral dose or doxycycline 100 mg, 7 days) should be considered to ensure that any LGV infection is not missed.

For further information, see the latest version of the ‘European guidelines for the management of partners of persons with sexually transmitted infection’\textsuperscript{282} and the ‘European Guideline on the Management of Lymphogranuloma Venereum’\textsuperscript{68} (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

**Notification of \textit{C. trachomatis} cases**

\textit{C. trachomatis} infections should be notified to local, regional and national authorities as mandated by statute. The ECDC is responsible for the EU/EEA-wide surveillance of communicable diseases including \textit{C. trachomatis} infections.

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**Search strategy**

Evidence was provided by a thorough and systemic review of the literature in the databases Embase.com, Medline (OvidSP), PubMed (articles supplied by publishers not yet indexed in Medline), Web-of-science, Scopus, Cinahl, Cochrane DARE, and Google Scholar. Searches were performed on 18 March 2014 and on 28 November 2014, and the following broad search terms were used: \textit{Chlamydia trachomatis}, systematic review, meta-analysis, guideline, protocol. After deduplication, 3041 articles published from 1992 to 2014 were screened on title/abstract, which resulted in 824 references considered for inclusion when the guideline was written. Relevant STI guidelines produced by the US Centers for Disease Control and Prevention (www.cdc.gov/std/treatment/2015/) and the British Association for Sexual Health and HIV (www.bashh.org) were also reviewed.

**Levels of evidence and grading of recommendations**

Tables of levels of evidence and grading of recommendations that were used in the present guideline can be found at: http://www.iusti.org/regions/Europe/pdf/2013/Levels_of_Evidence.pdf

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