


## GUIDELINES

# 2019 European guideline on the management of lymphogranuloma venereum

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## Abstract

New or important issues in this updated version of the 2013 European guideline on the management of lymphogranuloma venereum (LGV):

### Epidemiology

- Lymphogranuloma venereum continues to be endemic among European men who have sex with men (MSM) since 2003.
- Lymphogranuloma venereum infections in heterosexuals are extremely rare in Europe, and there is no evidence of transmission of LGV in the European heterosexual population.

### Aetiology and transmission

- *Chlamydia trachomatis* serovars/genovars L2b and L2 are the causative strains in the majority of cases in Europe.

### Clinical features

- Among MSM, about 25% of the anorectal LGV infections are asymptomatic.
- Genital infections among MSM are rare; the ratio of genital vs. anorectal LGV infections is 1 in 15.

### Diagnosis

- To diagnose LGV, a sample tested *C. trachomatis* positive with a commercial nucleic acid amplification test (NAAT) platform should be confirmed with an LGV discriminatory NAAT.

### Treatment

- Doxycycline 100 mg twice a day orally for 21 days is the recommended treatment for LGV.
- This same treatment is recommended also in asymptomatic patients and contacts of LGV patients. If another regimen is used, a test of cure (TOC) must be performed.

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## Conflicts of interest

The authors have no conflicts of interest related to this guideline.

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None.

## Epidemiology

Lymphogranuloma venereum (LGV) is endemic among European men who have sex with men (MSM) since 2003.<sup>1,2</sup> It is a

relatively common cause of proctitis, but rarely causes genital or oro-pharyngeal infections.<sup>3–5</sup> Although other strains like serovar/genovar L2 have been identified,<sup>5–7</sup> subvariant L2b is the

causative strain in the majority of cases in Europe, and a high degree of clonal relatedness has been found with genome sequencing techniques.<sup>8–11</sup> It is speculated that the LGV epidemic among MSM in Europe caused by the L2b subvariant may have been imported to Europe from the United States by the end of the previous century via the global highly interconnected network of sexual contacts among MSM.<sup>12,13</sup> Endemic acquired cases of LGV in heterosexuals are extremely rare in Europe, and there is no evidence of transmission of LGV within the European heterosexual population.<sup>14–17</sup>

### Aetiology and transmission

- Causative pathogen: *Chlamydia trachomatis* genovars L1, L2 and L3. Subvariants have been described such as L2b, currently frequently spreading among MSM. Confusion in identifying new and emergent strains stress the importance of adhering stringently to the nomenclature rules developed by the International Committee on Systematics of Prokaryotes Subcommittee on the taxonomy of the Chlamydiae.<sup>18</sup>
- Heterosexual transmission of the strains found in MSM is extremely rare.<sup>14–16</sup>
- In contrast to genovars A–K, which remain confined to the mucosa, genovar L strains are invasive and can disseminate via underlying connective tissue and spread to regional lymph nodes.
- Mixed infections with genovar L plus D–K strains<sup>19</sup> and mutant strains with recombinant DNA from L plus D–K strains<sup>20</sup> have been described with unknown clinical relevance.
- Worldwide, LGV is thought to account for 2–10% of genital ulcerative disease in areas such as South-East Asia and Africa, although these figures are based on older studies.<sup>21</sup> In many high income countries, LGV is endemic among MSM, mainly those co-infected with HIV.<sup>22</sup>
- Neither the degree of infectiousness nor the reservoir of disease has been accurately defined. Transmission has been attributed largely to asymptomatic carriers.<sup>23</sup>
- Transmission in the MSM population can partially be explained via anogenital contact. Since the ratio of genital vs. anorectal LGV infections has been shown to be 1 in 15 in some settings,<sup>4</sup> other modes of transmission are suspected.<sup>24</sup>

### Clinical features

- In MSM, about 25% of the anorectal LGV infections are asymptomatic.<sup>3,23,25</sup>
- Depending on the site of inoculation, LGV can cause inguinal disease (after inoculation of the genitalia or anal area), or the anorectal syndrome (after inoculation via the rectum).<sup>2</sup>
- The incubation period is 1–4 weeks, after which three subsequent stages can follow: a primary ulcerative stage, a

secondary stage with loco-regional dissemination with buboes and fistulae, and a tertiary more complicated fibrotic stage with irreversible lymphedema.<sup>21</sup>

### Genital symptoms

- Primary stage: Initially, a small painless papule or pustule appears that may erode to form a small herpetiform ulcer. Usually, it heals within 1 week and often remains unnoticed, but may present as a chancre also. Depending on the inoculation site, mucopurulent discharge may be present, affecting the rectum or, rarely, the urethra or the cervix.<sup>21,26</sup>
- Secondary stage: ‘inguinal stage’ – begins 2–6 weeks after onset of primary lesion, and causes painful inguino-femoral lymphadenopathy. Typically, this produces unilateral enlargement, inflammation, suppuration and abscesses. These ‘buboes’ may become fluctuant and rupture in one third of patients. Some patients develop the ‘groove sign’, which results from enlargement of the inguinal nodes above, and the femoral nodes below the inguinal ligament (Poupart’s ligament).<sup>21,26</sup>
- In low- and middle-income countries, inguino-femoral lymphadenopathy is the typical presentation of LGV. It is mainly seen in male patients.<sup>21</sup>
- Genital infections are rarely seen in MSM.<sup>4</sup>

### Anorectal symptoms

- Proctitis is the main manifestation of infection in the current LGV epidemic among MSM. It can be characterized by severe symptoms of anorectal pain, haemopurulent discharge and bleeding per rectum; tenesmus and constipation are also seen due to the mucosal and perirectal oedema. Yet, the severity and extent of symptoms varies between patients. Anoscopic examination may reveal a distal granular or haemorrhagic proctitis with purulent exudate, mucosal ulceration and tumorous masses. LGV proctitis is usually not accompanied by inguino-femoral lymphadenopathy; however, radiological imaging may demonstrate pelvic and lower abdominal lymph node involvement.<sup>2</sup>
- Lymphogranuloma venereum proctitis can mimic chronic inflammatory bowel diseases like Crohn’s disease, both clinically and in the histopathological features.<sup>27,28</sup>
- In women, usually the rectum, upper vagina, cervix, or urethra are involved. These body locations drain to the deep iliac or perirectal nodes resulting in lower abdominal pain or lower back pain. Inguino-femoral lymphadenopathy is often absent.<sup>21,26</sup>

### Physical signs

- Reactive inflammatory responses can result in constitutional symptoms, such as low-grade fever, chills, malaise, myalgia, arthralgia.<sup>21,26</sup>

- Pharyngeal infections can cause submandibular and cervical lymphadenopathy, although these are rare.<sup>29</sup>

### Complications

- The tertiary stage of disease in LGV is often called the ‘anogenitoretal syndrome’ and is more often present in women. Patients initially develop proctocolitis followed by perirectal abscess, fistulas, strictures and stenosis of the rectum, possibly leading to ‘lymphorrhoids’ (haemorrhoid-like swellings of obstructed rectal lymphatic tissue). Without treatment, chronic progressive lymphangitis leads to chronic oedema and sclerosing fibrosis, resulting in strictures and fistulas of the involved region, which can ultimately lead to elephantiasis, esthiomene (the chronic ulcerative disease of the external female genitalia)<sup>30</sup> and the frozen pelvis syndrome.<sup>21,26</sup> If left untreated, LGV proctitis can lead to rectal strictures, with subsequent sequelae of soiling, pain, constipation and the possible development of mega colon.<sup>21</sup>
- Rare reactive complications include sexually acquired reactive arthritis, aseptic cardiac involvement, meningitis and ocular inflammatory disease.<sup>21,26</sup>
- Rare septic complications include arthritis, pneumonitis or (peri)hepatitis.<sup>21,26</sup>

### Diagnosis

#### Who should be tested?

- Lymphogranuloma venereum testing is not available in all settings, and recommendations on who to test can therefore be limited by availability. Ideally, appropriate LGV routine molecular diagnostics should be available in all European countries, which could also be centralized at some national reference, or similar type of expert laboratory.
- Irrespective of symptoms, all MSM with a *C. trachomatis* positive anorectal sample should be tested for LGV.
- Contacts of confirmed LGV index cases.
- Patients with symptoms suspected of having LGV.
- According to local or national policies, priority should be given to HIV-positive MSM, or MSM who are eligible for HIV Pre-Exposure Prophylaxis (PrEP) (1,A).<sup>31–34</sup>
- Other *C. trachomatis* positive sites (urethra/urine/pharynx) can be tested for LGV if symptoms persist despite having used recommended treatment options (2,D).

#### When should be tested?

- Lymphogranuloma venereum testing should be performed on a *C. trachomatis* nucleic acid amplification test (NAAT) positive sample and considered in patients with signs of proctitis/proctocolitis, femoro-inguinal lymphadenopathy or bubo’s, and/or (a history of) genital ulcers.<sup>35,36</sup>

- In asymptomatic MSM, a window phase of at least 2 weeks after exposure should be considered (2,D).

#### Which test should be used?

- The diagnosis of LGV should be confirmed by the detection of genovar-specific *C. trachomatis* DNA.
- For sensitive and specific detection of LGV genovar (L1, L2 and L3, including subvariant)-specific *C. trachomatis* DNA, laboratories are currently recommended to use a two-step procedure (1,B):
  - A commercially available NAAT is used to detect *C. trachomatis* DNA/RNA in suspected clinical samples. These tests cannot discriminate between LGV and non-LGV genovars. Although no commercially available *C. trachomatis* NAATs are FDA-cleared for extragenital specimens, for several NAATs sufficient evidence supports the use of these tests for the detection of *C. trachomatis* DNA/RNA also in rectal and pharyngeal *C. trachomatis* infections.<sup>31–34,37–39</sup> Some *C. trachomatis* NAAT are CE-labelled for use on rectal and pharyngeal samples in Europe.
  - If *C. trachomatis* DNA/RNA is detected, LGV genovar-specific *C. trachomatis* DNA should be detected from the same specimen.<sup>31,33,34,38</sup> There are multiplex NAATs for genital ulcerative disease that detect LGV but these have not yet been appropriately evaluated in the context of rectal LGV. Different in-house or laboratory-developed NAATs have been designed and used.<sup>7,25,35,40–46</sup> The sensitivities of these NAATs are generally lower than the commercially available *C. trachomatis* screening NAAT.<sup>19</sup>

#### General considerations

- For clinical management, identification of the LGV genovar should be performed in a timely manner (preferably within 1 week).
- In the absence of thoroughly validated commercially available LGV genovar-specific NAATs, it is of utmost importance that laboratories performing LGV diagnostics implement only carefully validated and quality assured laboratory-developed NAATs and/or perform a strict validation for local requirements and subsequently use the NAAT with appropriate internal and external quality controls.

#### Alternative diagnostic methods

- In the absence of LGV genovar-specific *C. trachomatis* NAAT, a presumptive LGV diagnosis can be made using validated and quality-assured Chlamydia genus-specific serological assays. A high antibody titre (particularly IgA anti-MOMP antibodies) in a patient with symptoms suggestive of LGV supports the diagnosis.<sup>31,33,34,47–49</sup> Importantly, a low titre does not exclude LGV, nor does a high titre in a patient without LGV symptomatology confirm

LGV infection.<sup>25,31,33–35,38,49</sup> It should be noted that the diagnostic sensitivity and specificity of serology are suboptimal, serologic test interpretation for LGV is not standardized, tests have not been appropriately validated for clinical proctitis/proctocolitis presentations, comparative data between different serologic tests are lacking, and serology cannot necessarily distinguish past from current LGV infection (1,B).

- Isolation of *C. trachomatis* in cell culture with subsequent specific detection of the LGV genovar can be used for diagnosis but the method has a suboptimal sensitivity,<sup>21</sup> is labour intensive, expensive, rarely available and now outdated.
- The identification of rectal polymorphonuclear leucocytes (PMNLs) in rectal swabs from symptomatic patients is predictive of LGV proctitis, especially in HIV-positive MSM. A PMNL number of  $>10^{35}$  and  $>20^{31}$  per high-power field both show to be significant, however, the sensitivity and especially specificity of this measurement can be suboptimal (1,B).

#### Which specimens can be used to diagnose LGV?

Samples include: (i) swab of ulcer base, or exudate from primary anogenital lesions; (ii) rectal mucosal specimens (swabs or biopsies, ideally collected from the mucosal lining under proctoscopic vision, but also self-collected rectal swabs in asymptomatic MSM); (iii) lymph node or bubo aspirates using a 21-gauge needle after topical disinfection (in suspected cases of inguinal LGV); (iv) urethral swab or first-catch urine specimen when LGV is suspected; and (v) pharyngeal swabs from MSM and women exposed at those sites.

#### Management

- The prevalence of HIV among MSM with LGV ranges from 67% to 100% in 13 descriptive studies. There is a significant association between HIV and LGV (odds ratio, 8.19, 95% CI, 4.68–14.33) (1,A).<sup>22,50</sup> Moreover, hepatitis C is associated with LGV in the current epidemic among MSM.<sup>51–53</sup>
- Therefore, tests for other STIs (at a minimum syphilis and gonorrhoea), including HIV (if not already known HIV-positive), hepatitis B and hepatitis C should be offered before starting therapy (1,B).<sup>54</sup>
- If no LGV diagnostic test is readily available, consider LGV treatment in case of severe proctitis in MSM with a *C. trachomatis* positive anorectal test result (2,C).

#### Information, explanation and advice for the patient

- Patients should be informed that LGV is a sexually transmitted infection that can invade connective tissue and regional lymph nodes but is curable with antibiotics. Left untreated it can have serious and permanent adverse

sequelae. Most of these complications are preventable if treatment is initiated at an early stage (2,C). Patient information leaflets focused on the LGV epidemic among MSM are available from IUSTI (<https://www.iusti.org/regions/europe/euroguidelines.htm>) and provided by several national organizations like the Terrence Higgins Trust (United Kingdom) and SOA AIDS Nederland (The Netherlands).

- In anorectal disease, symptoms should resolve within 1–2 weeks of commencing antibiotic therapy (2,C).<sup>55</sup>
- In inguinal disease, symptoms might persist for many weeks and follow-up visits should be implemented (2,C).<sup>36</sup>
- Patients should abstain from any sexual contact until they have completed therapy (2,D).
- Screening for STIs (at a minimum syphilis and gonorrhoea), including HIV (if not already known HIV-positive), hepatitis B and hepatitis C should be advised during a follow-up visit 3 months after an LGV diagnosis to cover window periods and exclude reinfections (2,D).<sup>54</sup>

#### Therapy

##### Which antibiotic should be used to treat symptomatic LGV?

- Doxycycline 100 mg twice a day orally for 21 days (1,B) (Table 1).<sup>36,56,57</sup>
- Azithromycin in single- or multiple-dose regimens or shorter course of doxycycline (100 mg twice a day orally for 7–14 days) has also been proposed, but consistent and concluding evidence is lacking to currently recommend these drug regimens as first-line options (2,D).<sup>58,59</sup> If alternative treatment regimens are used, it is advised to perform a test of cure (TOC) (2,D).
- There is no indication nor evidence that HIV co-infection requires a different therapeutic approach.

##### Which antibiotic should be used to treat asymptomatic LGV?

- Doxycycline 100 mg twice a day orally for 21 days is the first-line recommended therapy (1,C).<sup>36,56,57</sup>
- There is some data on alternative (shorter) treatment regimens for asymptomatic LGV (2,D).<sup>59</sup> If alternative treatment regimens are used, it is advised to perform a TOC (2,D).

##### Alternative regimens to treat LGV

- Erythromycin (ethylsuccinate) 400 mg 4 times daily 21 days, orally (2,D).
- Many guidelines mention erythromycin as an alternative treatment option in patients with a contraindication to doxycycline, based on expert opinions.<sup>31–33</sup> However, no trials evaluating erythromycin in LGV treatment have been reported and high rates of gastrointestinal effects are

**Table 1** Summary of different antibiotics currently or previously used in the treatment of lymphogranuloma venereum

Drug	Recommendation	Treatment regimen	Mechanism of effect	Side effects/contraindications	References
<b>Doxycycline</b>	First-line option	100 mg twice daily for 21 days, orally	Binds to the 30S and 50S ribosomal subunits in bacteria, inhibiting protein synthesis	Gastrointestinal effects: dyspepsia, nausea, diarrhoea hyperpigmentation of teeth, nails, skin, eyes Contraindicated in pregnant and lactating women	56–59
<b>Erythromycin†</b>	Alternative option	400 mg four times daily for 21 days, orally	Blocks dissociation of peptidyl tRNA in ribosomes, inhibiting bacterial growth	Gastrointestinal effects: dyspepsia, nausea, diarrhoea Pseudomembranous colitis Vertigo, convulsions, reversible deafness Cyp3A4 inhibitor, interactions with medication metabolized by Cyp3A4	31–34
<b>Azithromycin†</b>	Alternative option	1 g once, or 1 g once a week for 3 weeks, orally	Binds to the 50S subunit of ribosomes in bacteria, inhibiting protein synthesis	Gastrointestinal effects: dyspepsia, nausea, diarrhoea, flatulence Headaches, rash paraesthesia	57,58
<b>Minocycline†</b>	Escape option	300 mg loading dose, followed by 200 mg twice daily for 21 days, orally	Binds to the 30S and 50S ribosomal subunits in bacteria, inhibiting protein synthesis	Vertigo, tinnitus, intercranial hypertension Gastrointestinal effects: dyspepsia, nausea, diarrhoea hyperpigmentation of teeth, nails, skin, eyes Contraindicated in pregnant and lactating women	63,64
<b>Rifampicin†</b>	Escape option	600 mg once daily for 3 weeks, orally	Blockage of DNA dependent RNA polymerase in susceptible bacteria	Gastrointestinal effects: dyspepsia, nausea, diarrhoea Hepatitis. Dizziness, headaches Interaction with cytochrome p450 metabolized medicines.	65
<b>Moxifloxacin†</b>	Escape option	400 mg once daily for 21 days, orally	Bactericidal through blocking DNA gyrase enzyme, thus inhibiting DNA repair	QT elongation, tachycardia, atrial fibrillation Dizziness, headaches Hepatotoxicity (very rare)	61,62

†In case of alternative and escape options, a test of cure is recommended.

described in patients treated with erythromycin for other indications.<sup>60</sup> Treatment success has been reported in a few cases with anorectal infections using moxifloxacin (2, D),<sup>61,62</sup>; however, great care should be undertaken before using the broad-spectrum moxifloxacin widely, because of its importance in the treatment of, for example, *Mycoplasma genitalium* infections. Treatment success has also been documented in small older trials for inguinal LGV using minocycline (2,D)<sup>63,64</sup> and rifampicin (2,D).<sup>65</sup> Thus, it is suggested to only use moxifloxacin, minocycline or rifampicin if other options are unavailable.

### Adjunctive therapy

- Apart from oral antibiotic therapy, fluctuant buboes should be drained via needle aspiration through healthy overlying skin (2,D). Repeat visits might be necessary to ensure re-emerging buboes are drained.
- Surgical incision of buboes is not recommended due to potential complications such as chronic sinus formation (2, D).
- Patients with residual fibrotic lesions or fistulae do not benefit from further courses of antibiotics. Surgical repair,

including reconstructive genital surgery, should be considered (2,D).

### Partner notification and treatment

Partner notification should be initiated when the diagnosis is made. Sexual contacts within the last 3 months should be offered testing from all exposed sites for *C. trachomatis*/LGV and empiric treatment with doxycycline commenced until *C. trachomatis*/LGV has been excluded in the partner. It is not evident if alternative shorter course regimens are as effective in asymptomatic partners; case reports suggest treatment failure of contacts of LGV index patients treated with azithromycin 1 g single oral dose (2,D).<sup>36</sup>

### Follow-up

All patients diagnosed with LGV should be followed up at the end of treatment:

- to ensure treatment compliance, assess side effects, and ensure resolution of symptoms and signs of infection (2,D);
- to check that adequate partner notification has been completed (2,D);
- to address any patient concerns (2,D);

- to arrange suitable follow-up testing for syphilis, gonorrhoea and blood-borne viruses including hepatitis B, C and HIV (2,D);
- Although one case of doxycycline failure in LGV has been reported,<sup>61</sup> a TOC for LGV is not considered necessary if the recommended 21-day course of doxycycline is completed (2,C). However, if alternative treatment regimens are used, it is advised to perform a TOC 4–6 weeks after the end of treatment (2,D).

### Prevention/health promotion

Patients diagnosed with LGV should be counselled regarding prevention of other STIs including HIV and hepatitis C:

- Offer regular sexual health screening including HIV testing.
- Condom use should be demonstrated and promoted.
- Offer hepatitis A and B vaccination for MSM.
- HIV-negative patients should be advised of the availability of PrEP to prevent HIV infection.
- In particular, HIV-positive MSM should be made aware of recent trends in hepatitis C epidemiology and warned of the risks of unprotected anal sex, serosorting, recreational drug use [chemsex, Party and Play (PnP)] and mucosally traumatic sexual practices such as the use of toys and fisting. Enema use does not seem associated with STI infection.<sup>66</sup> It is prudent to advise against sharing any enema/douching equipment and to wash equipment thoroughly after use. If patients engage in chemsex, associated problems should be addressed and referral to substance use care offered.

### Notification of LGV cases

According to local, regional and national regulations, it might be required that LGV cases need to be reported to authorities. The European Centre for Disease Prevention and Control (ECDC) is responsible for the European Union/European Economic Area (EU/EEA)-wide surveillance of communicable diseases including LGV.

### Auditable outcome measures (target 95% for all)

- All cases of suspected LGV should be subjected to appropriate laboratory investigations.
- All patients should be interviewed for the purpose of partner notification and this should be documented in the case notes. Sexual contacts within at least the last 3 months should be traced, tested and treated.
- In all patients, screening for concomitant STIs should be offered before starting therapy and after 3 months.
- Suspected or confirmed cases of LGV should be reported and relevant surveillance data collected according to local and national guidelines.

### Search strategies and level of evidence grading

Appendix I.

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### Composition of the European Guideline Editorial Board

Current composition can be found at <https://www.iusti.org/regions/europe/euroguidelines.htm>.

### List of contributing organizations

Current list can be found at: <https://www.iusti.org/regions/europe/euroguidelines.htm>.

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## Appendix

### Search strategies

For the literature search (except for therapy), the following string was used in MEDLINE and PubMed on 3 August 2018: ct serovars I1-I3 OR CT infection\* L1-L3 OR chlamydia I1-I3 OR chlamydiosis I1-I3 OR LGV OR lymphogranuloma venereum OR chlamydia trachomatis serovar I1-I3 OR chlamydia trachomatis biovar I1-I3

For the literature search on therapy, the following string was used in MEDLINE and PubMed on 3 August 2018: ((lymphogranuloma venereum[MeSH Terms]) OR (LGV[TiAb]) OR (lymphogranuloma venereum[TiAb]) OR (Chlamydia trachomatis I1[TiAb]) OR (Chlamydia Trachomatis I2[tiab]) OR (Chlamydia Trachomatis I3[tiab]) OR (Chlamydia Trachomatis

I2b[tiab])) AND ('drug therapy'[MeSH Subheading] OR therapy[MeSH Subheading] OR (Treatment) OR (Antibiotics) OR (azithromycin) OR (erythromycin) OR (doxycycline) OR (Therapy) OR (Drug therapy))

### Levels of evidence

All key recommendations made for diagnosis and management should be graded for the level of evidence.<sup>67</sup>

A *Grade 1* recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording: 'We recommend ...' or 'It is recommended ...'

A *Grade 2* recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording: 'We suggest ...' or 'It is suggested ...' The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences, and, where appropriate, resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and is defined as follows:

- *Grade A* evidence means high-quality evidence that comes from consistent results from well-performed randomized controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.
- *Grade B* evidence means moderate-quality evidence from randomized trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias.
- *Grade C* evidence is low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias.
- *Grade D* evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate.