Public Health Agency of Canada
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# Lymphogranuloma venereum (LGV) in Canada: Recommendations for Diagnosis and Treatment and Protocol for National Enhanced Surveillance

Canada

**Our mission is to promote and protect the health of Canadians through leadership, partnership, innovation and action in public health.**

Ce document est aussi offert en français sous le titre :
*Lymphogranuloma venereum (LGV) au Canada : Recommandations pour son diagnostic et son traitement Protocole de surveillance accrue à l'échelle nationale*

# Interim Statement on the Diagnosis, Treatment and Reporting of Lymphogranuloma venereum (LGV) In Canada

Lymphogranuloma venereum (LGV) is a sexually transmitted infection caused by *C. trachomatis* serotypes L1, L2, and L3. Unlike serovars A-K, LGV serovars are invasive, preferentially affecting the lymph tissue. LGV can be transmitted through vaginal, anal or oral sexual contact, and can be prevented through the use of condoms or other barrier methods. If left untreated, LGV can cause serious complications such as swelling, deformity/destruction of the genitals/rectum (including rectal stricture), and can uncommonly lead to meningoencephalitis, hepatitis and death. Having LGV can increase the chances of acquiring or transmitting HIV, other STIs and other blood-borne pathogens, such as hepatitis C.

## Epidemiology

Until recently, LGV has been a rare infection in industrialized countries, and was usually acquired in endemic areas. LGV is endemic to parts of Africa, Asia, South America and the Caribbean, and is thought to account for approximately 2-10% of genital ulcer disease in areas of Africa and India. However recent cases have been reported in men having sex with men (MSM) in Europe, starting in 2003 in the Netherlands, and more recently in North America. Cases have been reported in:

- the Netherlands
- Belgium
- France
- Germany
- Sweden
- UK
- USA

Recent cases in MSM have been associated with concurrent STI including HIV as well as hepatitis C, casual sex gatherings (leather scene parties) and higher risk sexual activities such as “fisting”.

## Clinical Picture and Diagnostic Features

LGV is commonly divided into 3 stages:

1. Primary LGV
    - incubation period of 3-30 days
    - small, painless papule at site of inoculation (vagina, penis, rectum, occasionally cervix), that may ulcerate
    - self-limited and may go unnoticed
2. Secondary LGV
    - begins within 2-6 weeks of primary lesion
    - often accompanied by significant systemic symptoms such as low-grade fever, chills, malaise, myalgias, arthralgias; occasionally by arthritis, pneumonitis or hepatitis/perihepatitis; rarely with cardiac involvement, aseptic meningitis and ocular inflammatory disease
    - abscesses and draining sinuses possible (< 1/3 of patients)
    - involves the inguinal/femoral lymph nodes OR anus and rectum
        - Inguinal Secondary LGV characterized by painful inguinal and/or femoral lymphadenopathy (usually unilateral) – painful lymph nodes are referred to as buboes
            - “groove sign” – inguinal nodes above and femoral nodes below the inguinal ligament(once considered pathognomonic for LGV)
        - cervical lymphadenopathy has been described in cases with oral contact

- Anorectal Secondary LGV characterized by acute haemorrhagic proctitis
  - bloody, purulent or mucous discharge from the anus

3. Tertiary LGV (chronic, untreated LGV)

- more common in females than males
- chronic inflammatory lesions lead to scarring:
  - lymphatic obstruction causing genital elephantiasis
  - rectal strictures and fistulae
- possible extensive destruction of genitalia (*esthiomene*)

## Diagnosis

The diagnosis of LGV is not always straightforward. The symptoms and signs of LGV significantly overlap those of other STI, other infections, drug reactions and malignancies. The diagnosis is often based on the history and clinical picture and is supported by laboratory testing, although in Canada confirmatory testing for LGV is now readily available in some laboratories (see Laboratory Testing below).

### *Diagnostic Procedures*

- anoscopy/sigmoidoscopy/proctoscopy
  - pattern similar to ulcerative colitis
  - granular or ulcerative proctitis
- bubo aspiration
  - buboes in LGV usually contain small amount of milky fluid
  - may require injection of 2-5ml of sterile saline for aspiration
  - buboes should be aspirated through healthy skin

### *Specimen Collection*

For a definitive diagnosis of LGV, emphasis should be placed on clinical specimens such as swabs and aspirates. Serology, though less definitive, may provide support for the diagnosis.

The following section describes the types of specimens that may be collected for the diagnosis of LGV by stage. For more information and detailed descriptions of the testing modalities see the Laboratory Testing section below.

- Primary
  - swab of lesion for:
    - culture *or*
    - NAAT

    Because the invasive nature of LGV has not yet manifested in the primary stage of the infection, serology at this stage is unlikely to be helpful

- Secondary
  - bubo aspirate for:
    - culture *or*
    - NAAT

    Identification of *C. trachomatis* in bubo fluid is highly suggestive of LGV, even prior to or without identification of LGV serovars

  - rectal, vaginal or urethral swab for:
    - culture *or*
    - NAAT*

    * NAAT not officially approved in Canada for use with rectal or oropharyngeal swabs. Repeat testing is advised to confirm a positive test

  - urine for:
    - NAAT
  - serology (method varies by laboratory)
    - microimmunofluorescence (MIF) test
    - complement fixation (CF) test
      - See note in Laboratory Testing below
- Tertiary
  - as for secondary (see above)

## *Laboratory testing*

The availability and type of testing for LGV varies by laboratory. Some local laboratories are able to test specifically for LGV while others will need to involve the National Microbiology Laboratory (NML) via their Provincial Laboratory. Please check with your local laboratory for more information on how to collect and transport specimens. Where possible, suspected cases of LGV should have both swab and sera samples submitted for laboratory testing.

For samples being sent to NML, the following storage and shipping recommendations apply:

- dry swabs should be stored and shipped frozen
- swabs stored in viral or chlamydial transport media should be kept frozen at -80°C if culture will be done, or at -20°C if culture will not be done
- urine samples should be stored frozen

Many laboratory testing modalities do not distinguish between LGV and non-LGV serovars of *C. trachomatis.* Some methods are suggestive of LGV. Two methods, restriction fragment length polymorphism (RFLP) and DNA sequencing, are available in Canada to definitively diagnose LGV (availability varies by laboratory).

## *Non-specific tests*

- Culture for *C. trachomatis*
  - does not definitively distinguish between LGV and non-LGV serovars; however, LGV serovars will yield a positive culture without centrifugation (non-LGV serovars require centrifugation)
    - dilution (1:10) of anal/rectal swabs may be required because of fecal toxicity
    - positive cultures may be sent for further definitive testing to identify LGV serovars (see below)
- Nucleic acid amplification testing (NAAT) for *C. trachomatis*
  - include polymerase chain reaction (PCR), ligase chain reaction (LCR), transcription mediated amplification (TMA) and strand displacement amplification (SDA)
  - differences in sensitivity and specificity in detecting LGV and non-LGV serovars is unknown
  - does not differentiate between LGV and non-LGV serovars
    - positive specimens may be sent for further definitive testing to identify LGV serovars (see below)
- Serology
  - because of the invasive nature of LGV, serology titres are in general significantly higher in LGV vs. non-LGV *C. trachomatis* infections
  - serology can be suggestive of LGV infection but is not definitive
  - testing modalities vary by laboratory:
    - microimmunofluorescence (MIF) test for *C. trachomatis*: high titre (titre ≥ 1:256)
    - complement fixation (CF) test for chlamydiae: positive (titre ≥ 1:64)
      - MIF is a more specific test for LGV than CF
      - cross-reactivity may be an issue with CF
- Frei skin test is no longer used

## *LGV specific tests (Confirmatory)*

- DNA sequencing
  - samples that test positive for *C. trachomatis* with NAAT or culture can be sent for DNA sequencing
  - definitively identifies LGV serovars

- Restriction fragment length polymorphism (RFLP)
  - samples that test positive for *C. trachomatis* with NAAT or culture can be sent for RFLP testing
  - definitively identifies LGV serovars

Laboratories sending samples to NML for confirmatory testing, please note that it is the original sample that must be tested by PCR for *omp*1, and this PCR product is what must be sent for sequencing to NML.

## Treatment

- First line:
  - Doxycycline 100 mg PO BID x 21 days (B2)
- Alternative:
  - Erythromycin 500 mg PO QID x 21 days (C3)
- Possible:
  - Azithromycin 1g PO once weekly for three weeks* (C3)

*While some experts believe azithromycin to be effective in the treatment of LGV, clinical data are lacking.

Erythromycin dosage refers to the use of erythromycin base. Equivalent dosages of other formulations may be substituted (with the EXCEPTION that the estolate formulation is contraindicated in pregnancy).

Erythromycin (NOT the estolate formulation) should be used in pregnancy.

- Aspiration of buboes may help symptomatically. However, incision/drainage or excision of nodes is not helpful and may delay healing.

### *Treatment of partners*

Sexual partners from the last 60 days should be contacted and treated (regardless of whether signs/symptoms are present) as follows:

- Azithromycin 1g PO in a single dose (C3) OR
- Doxycycline 100mg PO BID x 7 days (C3)

**Level and Quality of Evidence**

| | |
|---|---|
| **Level** | |
| A | Good evidence (benefit substantially outweighs harm) |
| B | Fair evidence (benefit outweighs harm) |
| C | Too close to justify a general recommendation |
| D | Ineffective (harm outweighs benefit) |
| I | Insufficient evidence (lacking, poor quality, conflicting) |
| **Quality** | |
| I | Evidence from ≥ 1 RCT |
| II | Evidence from ≥ 1 clinical trial without randomization (cohort, case-control, time-series, dramatic results in uncontrolled experiment) |
| III | Expert opinion |

## Reporting and Partner Notification

- LGV is not a nationally reportable disease; however, in light of recent cases an enhanced surveillance system was initiated by the Public Health Agency of Canada in partnership with the provinces and territories in February 2005.
  - LGV should be reported by local public health authorities to the appropriate regional and provincial/territorial authorities. The provinces and territories have agreed to report LGV to the Sexual Health and STI Section of the Public Health Agency of Canada at (613) 946-8637 (please see Enhanced Surveillance Protocol and case guide below).

## Follow-up

- Patients should be followed until chlamydial tests such as culture or NAAT are negative (test of cure). Serology should not be used to monitor treatment response as the duration of antibody response has not been defined.
  - Test of cure should be performed at 3 to 4 weeks after the completion of effective treatment to avoid false positive results due to the presence of non-viable organisms (especially if using NAAT).
- Sexual partners from the last 60 days should be contacted and treated (see Treatment section).
- Surgery may be required to repair genital/rectal damage of tertiary LGV.

## Consideration for other STI

- Because of rates of co-infection, testing for HIV, syphilis, HSV, gonorrhea, hepatitis B, and hepatitis C is recommended in patients with LGV.
- Testing for chancroid and donovanosis (granuloma inguinale) should also be considered in patients with LGV, especially if there has been travel to regions where these infections are endemic.
- In general, HIV appears to have little effect on the clinical presentation though atypical presentations in HIV+ patients have been rarely reported.
  - disease duration may be prolonged in HIV+ patients.
- In pregnancy, erythromycin should be used for the treatment of LGV.
- The estolate formulation of erythromycin is contraindicated in pregnancy.
- Immunization for hepatitis B should be offered to non-immune patients.
- The opportunity to provide safer-sex counselling should not be missed.

# Protocol for LGV Enhanced Surveillance

## Summary

In light of recent LGV cases reported internationally, an enhanced surveillance system for LGV was initiated by the Public Health Agency of Canada in partnership with the provinces and territories in February 2005. The following describes the working case definition for this LGV enhanced surveillance system.

## Working Case Definition

### *Probable Case*

Positive *C. trachomatis* culture, NAAT* or serology (MIF≥1:256, CF≥1:64) PLUS

Proctitis OR
Inguinal/femoral lymphadenopathy OR
Sexual partner with LGV

### *Confirmed Case*

DNA sequencing OR RFLP for *C. trachomatis* confirming serovars of L1, L2, or L3 present.

Cases which fit a probable case definition but test negative for LGV serovars on confirmatory (genotype) testing are not considered probable cases; cases which fit a probable case definition and whose test results are inconclusive on confirmatory (genotype) testing are considered probable cases.

*NAAT is not officially approved in Canada for use with rectal or oropharyngeal swabs. Repeat testing is advised to confirm a positive test.

NOTE: Where possible, suspected cases of LGV should have both a swab and sera submitted for laboratory testing. Please contact your local laboratory or the National Microbiology Laboratory for more information and advice regarding specimen collection and transport.

**All probable or confirmed cases should be reported** by local public health authorities to the appropriate regional and provincial/territorial authorities. The provinces and territories have agreed to report LGV to the Sexual Health and STI Section of the Public Health Agency of Canada at (613) 946-8637.

Once cases of LGV are reported to the Public Health Agency of Canada, PHAC will be responsible for collating and analyzing the data from the enhanced surveillance program and will include this analysis within quarterly reports posted on our Web site.

**An LGV enhanced surveillance form is attached below in Appendix I. This guide is intended to serve as a helpful tool for healthcare professionals in collecting key epidemiological information on suspected cases.**

# Appendix I

## LGV Enhanced Surveillance Form

Until recently, LGV has been a rare infection in industrialized countries, and was usually acquired from endemic areas. In light of recent cases, the Public Health Agency of Canada is coordinating national enhanced surveillance of LGV in an effort to rapidly identify and describe outbreaks in Canada. This form is intended to serve as a helpful tool for health care providers in collecting key epidemiological information on suspected cases.

| | |
|---|---|
| **1.** | Sex: ☐ Male ☐ Female ☐ Transgender ☐ Unknown |
| **2.** | Date of Birth: |
| **3.** | City of Residence: |
| **4.** | What ethnic origin does the patient consider him/herself to be? |
| **5.** | Date of clinic visit: (yyyy/mm/dd) |
| **6.** | Date of onset of LGV symptoms: (yyyy/mm/dd) |
| **7.** | Date of 1st presentation at the clinic for this episode: (yyyy/mm/dd) |
| **8.** | What were the patient's presenting symptoms? Please mark an answer for each:<br>Yes ☐ No ☐ Unknown ☐ Proctitis<br>Yes ☐ No ☐ Unknown ☐ Malaise<br>Yes ☐ No ☐ Unknown ☐ Inguinal lymphadenopathy<br>Yes ☐ No ☐ Unknown ☐ Genital papule/lesion<br>Yes ☐ No ☐ Unknown ☐ Bloody stools<br>Yes ☐ No ☐ Unknown ☐ Other (Please specify): _____ |
| **9.** | Has the patient experienced any of the following symptoms? Please mark an answer for each:<br>Yes ☐ No ☐ Unknown ☐ Proctitis<br>Yes ☐ No ☐ Unknown ☐ Malaise<br>Yes ☐ No ☐ Unknown ☐ Inguinal lymphadenopathy<br>Yes ☐ No ☐ Unknown ☐ Genital papule/lesion<br>Yes ☐ No ☐ Unknown ☐ Bloody stools<br>Yes ☐ No ☐ Unknown ☐ Other (Please specify): _____ _____ |

| | |
|---|---|
| **10.** | How does the patient define him/herself?<br>☐ Gay or homosexual ☐ Two spirited<br>☐ Bisexual ☐ Straight or heterosexual<br>☐ Other _____ |
| **11.** | At the time the individual was infected with LGV, was he/she co-infected with any of the following? If yes, please provide the date of that diagnosis:<br>Yes No Unknown Date of diagnosis _____<br>☐ ☐ ☐ None<br>☐ ☐ ☐ Genital warts/HPV _____<br>☐ ☐ ☐ Gonorrhoea _____<br>☐ ☐ ☐ Genital Herpes _____<br>☐ ☐ ☐ Chlamydia (not LGV) _____<br>☐ ☐ ☐ Syphilis _____<br>☐ ☐ ☐ HIV _____<br>☐ ☐ ☐ Hepatitis C _____<br>☐ ☐ ☐ Hepatitis B _____<br>☐ ☐ ☐ Other _____ |
| **11a.** | If Hepatitis C positive, was the infection:<br>Acute ☐ Yes ☐ No ☐ Unknown<br>Chronic ☐ Yes ☐ No ☐ Unknown |
| **11b.** | If Hepatitis B positive, was the infection:<br>Acute ☐ Yes ☐ No ☐ Unknown<br>Chronic ☐ Yes ☐ No ☐ Unknown |
| **12.** | Was the patient Hepatitis C antibody positive?<br>☐ Yes ☐ No ☐ Unknown<br>If yes, the date of this test: (yyyy/mm/dd)_____ |
| **13.** | Was the patient Hepatitis C PCR positive?<br>☐ Yes ☐ No ☐ Unknown<br>If yes, the date of this test: (yyyy/mm/dd)_____ |
| **14.** | Has the patient engaged in drug use with shared needles, spoons, straws and other drug-related equipment?<br>☐ Yes ☐ No ☐ Unknown |

| | |
|---|---|
| **15.** | Does the patient have a history of blood transfusion or blood product receipt prior to 1992?<br>☐ Yes ☐ No ☐ Unknown |
| **16.** | Has the patient had tattooing or body piercing with dirty or un-sterile needles and ink?<br>☐ Yes ☐ No ☐ Unknown |
| **17.** | Has the patient engaged in sexual activities where exchange of blood may have occurred (sex during menstruation/S&M/unprotected anal or rough sex)?<br>☐ Yes ☐ No ☐ Unknown |
| **18.** | During any travel outside of the reporting jurisdiction in the 60 days prior to symptom onset, did the case have sex with a person from the area of travel or another traveler while there?<br>☐ Yes ☐ No ☐ Unknown<br>If yes, city/geographic location: _____ |
| **19.** | Up to 60 days prior to the onset of LGV symptoms, what was the circumstance(s) in which sexual activity took place? (Tick all that apply)<br>☐ No sexual contacts 60 days prior to LGV symptoms ☐ Private residence<br>☐ Rave/circuit party ☐ Sex trade<br>☐ Leather scene party ☐ Internet partnering<br>☐ Bathhouse/sauna ☐ Unknown<br>☐ Other, please specify: _____ |
| **20.** | How many sexual partners did the patient have in the 60 days prior to the onset of LGV symptoms?<br>Total number of female sexual partners: _____<br>Total number of male sexual partners: _____ |
| **21.** | Has the patient ever had a sexual partner with known LGV infection?<br>☐ No ☐ Yes, a femal partner<br>☐ Yes, a male partner ☐ Unknown |
| **22.** | If the patient had a sexual partner with known LGV, does he or she recall when the sexual contact took place?<br>_____<br>_____ |
| **23.** | In the 60 days prior to the onset of LGV symptoms, did the patient engage in the following activities:<br>Rectal enema ☐ Yes ☐ No ☐ Unknown<br>Rectal use of recreational drugs ☐* Yes ☐ No ☐ Unknown<br>*If yes, which drug(s) were used rectally: _____ |

**24.** Please indicate if the patient engaged in any of the following, within 60 days prior to the onset of LGV symptoms: "*Protected*" *refers to the use of condoms or other barrier methods.*

| | No | Yes, protected | Yes, unprotected | Unknown |
|---|---|---|---|---|
| Receptive anal intercourse | ☐ | ☐ | ☐ | ☐ |
| Insertive anal intercourse | ☐ | ☐ | ☐ | ☐ |
| Receptive oral sex | ☐ | ☐ | ☐ | ☐ |
| Insertive oral sex | ☐ | ☐ | ☐ | ☐ |
| Sharing sex toys | ☐ | ☐ | ☐ | ☐ |
| Receptive fisting | ☐ | ☐ | ☐ | ☐ |
| Insertive fisting | ☐ | ☐ | ☐ | ☐ |
| Vaginal intercourse | ☐ | ☐ | ☐ | ☐ |

Other relevant sexual activity (Please specify): _____

**25.** Type of lab test(s) done and results:

| Type of test | Specimen (including site) | Date of Collection (yyyy/mm/dd) | Results |
|---|---|---|---|
| **Non-specific** Culture for *C. trachomatis* | | | ☐ + ☐ – ☐ unknown |
| NAAT for *C. trachomatis* | | | ☐ + ☐ – ☐ unknown |
| **Serology** Microimmunoflourescence (MIF) | | | Titre: |
| Complement Fixation (CF) | | | Titre: |
| **Confirmatory** DNA Sequencing | | | ☐ + ☐ – ☐ unknown Serovar: ☐ L1 ☐ L2 ☐ L2b ☐ L3 |
| RFLP | | | ☐ + ☐ – ☐ unknown Serovar: ☐ L1 ☐ L2 ☐ L2b ☐ L3 |
| Other (Please specify): _____ _____ _____ | _____ _____ _____ _____ | _____ _____ _____ _____ | _____ _____ _____ _____ |