Lymphogranuloma venereum rates increased and *Chlamydia trachomatis* genotypes changed among men who have sex with men in Sweden 2004–2016

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**Abstract**

This study aimed to determine the incidence of lymphogranuloma venereum (LGV) in Sweden since 2004 and to study in detail a consecutive number of *Chlamydia trachomatis* cases in men who have sex with men (MSM) during a 10 month period (September 2014 to July 2015). LGV increased from sporadic import cases in 2004 to comprise a spread within Sweden in 2016. Initially, only the L2b ompA genotype was detected, but in 2015 half of the genotyped LGV cases were L2 genotype. The changing genotype distribution in Sweden is linked to increased LGV spread in Europe. High-resolution multilocus sequence typing of 168 *C. trachomatis* cases from MSM in 2015 resulted in 29 sequence types, of which 3 accounted for 49 % of cases. The increased rates and different genotypes of LGV indicate that more concern for high-risk taking MSM is needed to avoid further spread of this invasive infection.

*Chlamydia trachomatis* is the most common of the detected sexually transmitted infections (STIs) among men who have sex with men (MSM). The invasive lymphogranuloma venereum (LGV) variant of *C. trachomatis* is increasing among high-risk groups of MSM in Europe [1–4]. The first cases were reported in 2003 from The Netherlands [5]. In contrast to classical LGV with inguinal buboes, which is rarely detected in Europe, LGV infections among MSM are commonly found in patients with *C. trachomatis* proctitis. However, mild cases of rectal LGV cannot be clinically distinguished from *C. trachomatis* infections caused by the other *ompA* genotypes D–K. It is important to diagnose LGV since this infection needs prolonged treatment and this can be established by specific LGV genotyping. A previous study using multilocus sequence typing (MLST) indicated that LGV infections in Europe are of a clonal nature, while in the USA several variants are prevalent [6]. This study describes the increase of LGV in Sweden in recent years and characterizes genetic variants of detected *C. trachomatis* infections among a high-risk population for LGV in 2015, and compares these results with previous findings from Sweden and Europe.

All diagnostic tests for LGV in Sweden are submitted from local laboratories to Uppsala University Hospital (Uppsala, Sweden). The individual physician decides when a positive test for *C. trachomatis* should be sent for LGV testing. Factors such as the following are all weighed in this decision: degree of rectal inflammation, sexual history, history of sex abroad and human immunodeficiency virus (HIV) status. The HIV/STI clinic for MSM, Venhälensan, in Stockholm accounts for about a third of all LGV tested samples in Sweden, while the other samples come from general STI clinics in Sweden, mainly from the two major cities Gothenburg and Malmö. Detected cases are reported according to the Swedish Communicable Diseases Act.

During a 10 month period (September 2014 to July 2015), 519 *C. trachomatis*-positive samples from 378 patients at the HIV/STI clinic for MSM, Venhälensan, Stockholm, were analysed for LGV (the ’LGV study’). After analysis by a LGV-specific PCR [7], samples were further genotyped by MLST of five target genes, and in addition the *ompA* gene [8]. The reference sequences used for *ompA* variants in LGV were: L2 AM884176; L2b AM884177.

Obtained MLST sequence types (STs) were analysed by BioNumerics software (version 7.0; Applied Maths) to construct minimum spanning trees of all entries in the study and for comparison with STs in the *C. trachomatis* MLST...
The number of detected LGV cases in Sweden increased substantially between 2004 and 2016. The number of LGV tests also increased during the same period (Fig. 1).

In the LGV study of 2014–2015, 31 LGV infections were detected in 307 (10 %) patients, with successful PCR results among all detected C. trachomatis cases in MSM at the Venhälssan clinic in Stockholm. The remaining cases of the 378 patients had other ompA genotypes (n=276) or were negative (n=71, excluded from further analysis) in the LGV-specific PCR. Sequence-based C. trachomatis genotyping results were obtained for 168 patients with the ompA distribution: L2, 4 % (n=7); L2b, 4 % (n=7); D, 29 % (n=48); E, 14 % (n=24); G, 30 % (n=51); H, 0.6 % (n=1); and J (18 %, n=30).

MLST genotyping of the same 168 C. trachomatis cases resulted in 29 STs of which 3 predominated and accounted for 49 % of the cases (ST52, 14 %; ST108, 14 %; and ST109, 22 %). Four STs were on an intermediate level (ST56, 8.8 %; ST58, 7.1 %; ST308, 5.9 %; and ST352, 5.9 %). The remaining 22 STs comprised between 0.6 and 2.4 %. Eleven STs were new when compared to the Uppsala University C. trachomatis MLST database (http://mlstdb.bmc.uu.se) comprising 540 STs from 3306 specimens. A total of 2 out of 168 patients had double genotypes (ompA D/MLST ST109 combined with ompA G/MLST ST346; and ompA J/MLST ST108 combined with ompA E/MLST ST553). The STs obtained in this study are related to previously found STs among MSM (Fig. 2).

The presence of clinical symptoms (proctitis, urethritis) in patients were analysed in relation to MLST STs. No association could be found between symptoms and specific STs. Similarly, no linkage could be found between STs and the presence of HIV infections except for ST58, which is confined to LGV strains.

Since the first report of LGV among MSM in The Netherlands in 2003, the ompA variant L2b has predominated in Europe [6], which was also the case in our previous study among MSM at the same clinic in 2006 [9]. This clonal nature of LGV spread supports the concept of an international high-risk MSM community with frequent sexual contacts within Europe.

In Sweden, LGV infections in 2004 were sporadic import cases, while in recent years, LGV has become an infection that also has spread within Sweden among sexually active MSM engaging in condomless sex. The increase in LGV infections in recent years can partly be explained by an increased number of tests. In the LGV study, the L2 and L2b variant each comprised half of the ompA sequenced cases. This is in agreement with recent reports of LGV variants other than L2b among MSM in Europe [3, 10], and is indicative that new variants have been introduced into the European MSM community and possibly also of an increased spread of LGV. New ompA variants based on single nucleotide differences may also emerge from mutations. High-resolution genotyping is based on more than a single gene and is important, which recently was highlighted when limited ompA sequencing caused confusion and misleading interpretation of results in studies of LGV [11]. A limitation in our study is that only 55 % of PCR-positive cases resulted in full MLST/ompA sequence determination. This is considerably lower than seen in previous studies [8], but no obvious reason for this has been identified.

In our study, MLST analysis showed one single ST among LGV cases, which is in agreement with a previous study [6], and among the non-LGV C. trachomatis strains a few variants predominated in our study, and they also predominated in previous studies from different countries [8]. While ST52 was the most common variant among MSM in Sweden 2006 (24 % [12]), it comprised 14 % of the cases in the present study. Similarly, ST14 decreased from 9 % to being absent in 2015. In the opposite direction, ST308 was not detected in 2006 but constituted 6 % of the cases in 2015, and ST56 increased its proportion from 2 to 9 % of all chlamydia cases with MLST analysis. It is obvious that some genotypes are clearly predominating [8] and it has been reported that tissue tropism explains why some chlamydia strains are more successful in spreading than others [13–15]. However, our present study indicates that different genotypes fluctuate in populations and is probably the result of epidemiological dissemination patterns. This is in agreement with our previous work [8] and a Dutch study [16] of
samples from different locations in MSM, which found no evidence for local tissue tropism and concluded that separate sexual networks explain the different distributions between heterosexuals and MSM. To better understand the role of tissue tropism and the impact of epidemiology, studies including whole genome sequencing are needed.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
The study (diary number 2014/107) was approved by the Regional Ethical Committee in Uppsala and patients gave informed consent to participate in the study.

References


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