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ORIGINAL RESEARCH

Substantial underdiagnosis of lymphogranuloma venereum in men who have sex with men in Europe: preliminary findings from a multicentre surveillance pilot

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ABSTRACT

Objectives Understanding the public health impact of lymphogranuloma venereum (LGV) in Europe is hampered by inadequate diagnostics and surveillance systems in many European countries. We developed and piloted LGV surveillance in three European countries without existing systems and performed a preliminary investigation of LGV epidemiology, where little evidence currently exists.

Methods We recruited STI or dermatovenereology clinics and associated laboratories serving men who have sex with men (MSM) in Austria, Croatia and Slovenia, using the UK for comparison. We undertook centralised LGV testing of *Chlamydia trachomatis* (CT)-positive rectal swabs collected between October 2016 and May 2017 from MSM attending these clinics. Stored specimens from Austria (2015–2016) and Croatia (2014) were also tested. Clinical and sociodemographic data were collected using a standardised proforma. The *ompA* gene of LGV-positive specimens was sequenced.

Results In total, 500 specimens from CT-positive MSM were tested, and LGV positivity was 25.6% (128/500; 95% CI 22.0% to 29.6%) overall, and 47.6% (79/166; 40.1% to 55.2%) in Austria, 20.0% (3/15; 7.1% to 45.2%) in Croatia, 16.7% (1/6; 3.0% to 56.4%) in Slovenia and 14.4% (45/313; 10.9% to 18.7%) in the UK. Proformas were completed for cases in Croatia, Slovenia and in the UK; proformas could not be completed for Austrian cases, but limited data were available from line listings. Where recorded, 83.9% (78/93) of LGV-CT cases were HIV-positive compared with 65.4% (149/228) of non-LGV-CT cases; MSM with LGV-CT were more likely to have proctitis (Austria, 91.8% vs 40.5%, $p < 0.001$; Croatia, 100% vs 25%, $p = 0.04$; UK, 52.4% vs 11.7%, $p < 0.001$) than those with non-LGV-CT. Six different *ompA* sequences were identified, including three new variants; the L2 *ompA* sequence predominated (58.6%, 51/87).

Conclusions LGV is substantially underdiagnosed in MSM across Europe. Unified efforts are needed to overcome barriers to testing, establish effective surveillance, and optimise diagnosis, treatment and prevention.

INTRODUCTION

Lymphogranuloma venereum (LGV) is an STI caused by the L serovars of *Chlamydia trachomatis* (CT). LGV epidemics in men who have sex with men (MSM) have been reported in Europe, North America, Australia and Canada.¹ LGV infection can manifest as severe proctitis, proctocolitis, rectal bleeding, ulceration, tenesmus and other symptoms found in patients with inflammatory bowel disease,² which may lead to misdiagnosis. In prolonged infections, fissures and perirectal abscesses may arise, as well as systemic symptoms such as fever, fatigue and weight loss. Rectal LGV is typically more severe than rectal chlamydia infection, which is usually asymptomatic,³ although rectal LGV is also asymptomatic in approximately 27%–43% of cases.⁵ A correct diagnosis of LGV is important because of the distressing morbidities, and to ensure appropriate management, particularly treatment, which is currently of a longer duration compared with non-LGV rectal CT.⁶

The number of LGV cases reported to the the European Centre for Disease Prevention and Control (ECDC) increased by 15% in 2016 ($n = 2043$) compared with 2015 ($n = 1780$).⁷ However, the picture across the region is unclear because many countries have no national surveillance system for LGV, and the majority of cases reported since 2004 have been from just three countries: the UK (52%, 5234 cases), France (23%, 2317 cases) and the Netherlands (14%, 1449 cases).⁷ Limited or absent case reports from most European countries therefore suggest substantial underdiagnosis, mainly due to a lack of testing, rather than an absence of infection.⁸ Data are particularly sparse from Central and Eastern Europe, with only the Czech Republic⁹ and Hungary¹⁰ regularly performing LGV diagnostics and reporting cases to the ECDC.⁷ LGV surveillance data have shown that LGV transmission in MSM is strongly associated with HIV-positive status, HIV seroadaptive behaviours, a high turnover of sexual partners and dense sexual networks.^{7 11–13} Effective control of LGV requires good local, national and international understanding of infection frequency,

key groups affected and epidemiological trends, and more detailed and up-to-date understanding of the epidemiology of LGV is urgently required.

We developed and piloted LGV surveillance in three European countries without existing systems (Austria, Croatia and Slovenia) to determine the feasibility of establishing surveillance and provide preliminary data on LGV frequency, where little evidence exists. We used UK data for comparison as routine LGV diagnostics and surveillance have been routinely performed since 2003,¹³ and the study provided an opportunity to update the risk factors for LGV in the UK.

METHODS

Participating sites

Four countries spanning the Western, Central and Eastern European Union (EU) were recruited to the study. Suitable clinics and laboratories were identified through existing contacts in the European gonococcal antimicrobial surveillance programme (Euro-GASP) network,¹⁴ and were selected based on CT diagnostics capability and to maximise participation from European regions with limited data on LGV epidemiology. One to three STI or dermatovenereology (DV) clinics serving MSM, and their associated laboratories, were recruited from Vienna (Austria), Zagreb (Croatia), Ljubljana and Maribor (Slovenia), and London (UK), as follows: Austria: specimens from the Practice for General Medicine, Vienna, which offers services to MSM, were sent for testing to the Outpatients' Centre for Diagnosis of Infectious Venero-Dermatological Diseases (CDIVD) in Vienna; Croatia: the 'Afternoon Clinic' and laboratory based at the University Hospital for Infectious Diseases (Dr F Mihaljevic Hospital), Zagreb; Slovenia: the STI outpatient clinic at the Dermatovenereology Hospital, University Medical Centre, Ljubljana, and two outpatient clinics of the Surgical Center Zdrav splet, in Ljubljana and in Maribor—the participating laboratory was the Institute of Microbiology and Immunology at the University of Ljubljana; and the UK: the Mortimer Market Centre (MMC) in London and the University College London Hospital Laboratory.

Patient population and chlamydia testing

Between October 2016 (April 2017 in Slovenia) and May (April in the UK) 2017, any MSM attending the STI or DV clinic who was diagnosed with rectal CT using a nucleic acid amplification test (NAAT) was included in the study. CT testing in the Austrian and Croatian clinics was often performed due to signs and symptoms, and testing was also dependent on which diagnostic tests the patients were willing to pay for. In the UK, STI testing in National Health Service clinics is free for those attending for asymptomatic STI screening as well as for those with signs and symptoms. CT testing was performed using the Aptima Combo 2 (Hologic, San Diego, USA) in Austria and the UK, the RealTime CT/NG Assay (Abbott Molecular, Des Plaines, USA) in Croatia and for 17 Austrian specimens, and the cobas 4800 CT/GC assay (Roche Diagnostics, Rotkreuz, Switzerland) in Slovenia. To estimate CT and LGV positivity in rectal specimens from MSM tested at participating sites in Austria, Croatia and Slovenia, the total number of rectal CT tests in MSM performed during the study period at each setting was requested (a single lymph node punctate from Croatia was also available and included). In the UK, data on CT testing reported to the routine national STI surveillance system in England (Genitourinary Medicine Clinic Activity Dataset (GUMCAD)) were used to provide data on the number of CT tests performed in MSM at MMC.¹⁵ As triple site (rectal, genital and pharyngeal) testing is routine at MMC, tests

reported in GUMCAD were deduplicated to remove non-rectal site tests. The total number of rectal CT-positive specimens sent to Public Health England (PHE) by MMC for LGV testing was used to estimate the CT and LGV positivity in rectal specimens.

LGV testing and *ompA* sequencing

Consecutive rectal swabs from MSM who tested positive for CT by NAATs or residual DNA extracts (Slovenia only) (Austria=19, Croatia=14, Slovenia=6, UK=162) were stored locally at -20°C and sent in batches to PHE. In addition, CT-positive rectal swabs from Austria that had been collected during 2015 (n=62) and 2016 (n=85) and one CT-positive lymph node punctate specimen from Croatia collected in 2014 were also sent to PHE. LGV testing was performed at PHE using a multiplex real-time (RT)-PCR that incorporates LGV,¹⁶ CT and internal control¹⁷ targets. The *ompA* gene of LGV-positive specimens was sequenced,¹⁸ and the amplified fragment was trimmed to 950 base-pairs for sequence analysis.

Enhanced surveillance data collection

A standardised proforma for collecting enhanced demographic, clinical and behavioural data on all CT-positive patients was developed based on an LGV surveillance proforma used in the UK, updated to include questions on more recently identified risk factors (online supplementary technical appendix).^{13 19} The proforma was completed for clinic attendees in Croatia, Slovenia and the UK. Due to a lack of clinical resources, no proformas were completed for Austrian cases; however, some limited data were provided by the CDIVD and the referring physician in an electronic line listing: age (estimated from attendance date and year of birth with 1 January set as the date and month of birth), HIV status, symptoms, previous chlamydia and STI coinfection with *Neisseria gonorrhoeae*. No behavioural information was available.

Statistical analysis

LGV positivity (%) among CT-positive cases was estimated for each country and overall. CT positivity (%) in MSM tested was estimated where data were available. For each country, patient characteristics associated with LGV infection were investigated when variable completion was >80% using univariate logistic regression, expressed as OR with 95% CI. A Pearson χ^2 test, Fisher's exact test or Mann-Whitney test was used to test for statistical significance ($p < 0.05$). All statistical analyses were performed in STATA V.15.1.

RESULTS

Overall CT and LGV positivity in all MSM tested for CT was estimated as 9.0% (500/5581; 95% CI 8.2 to 9.7) and 2.3% (128/5581; 95% CI 1.9 to 2.7), respectively. Among 500 CT-positive rectal specimens collected from 500 MSM in the four countries, the overall LGV positivity was 25.6% (128/500; 95% CI 22.0% to 29.6%) (table 1).

Austria

In Austria, CT and LGV positivity in rectal specimens from MSM tested for CT was 14.6% (166/1135; 95% CI 12.7 to 16.8) and 7.0% (79/1135; 95% CI 5.6 to 8.6), respectively. LGV positivity among MSM with rectal CT was 47.6% (79/166; 95% CI 40.1% to 55.2%). Sixty-six MSM with LGV were treated, prior to the LGV diagnosis, with a single dose of cefixime and azithromycin for chlamydia and gonorrhoea treatment; treatment provided to the remainder of patients was not reported. A higher proportion

Table 1 Characteristics of men who have sex with men with confirmed rectal CT infection attending STI and dermatovenereology clinics in four European countries, stratified by LGV and non-LGV (CT) genotype, 2015–2017

	Austria			Croatia			Slovenia			UK			Total	
	n (%)	Crude OR (95% CI)	P value	n (%)	Crude OR (95% CI)	P value	n (%)	Crude OR (95% CI)	P value	n (%)	Crude OR (95% CI)	P value	n (%)	n (%)
Number of referred rectal CT-positive specimens	166			15			6			313			500	
Number of LGV-negative (%; 95% CI)	87 (52.4; 44.8 to 59.9)			12 (80.0; 54.8 to 93.0)			5 (83.3; 43.7 to 97.0)			268 (85.6; 81.3 to 89.1)			372 (74.4; 70.4 to 78.0)	
Number of LGV-positive* (%; 95% CI)	79 (47.6; 40.1 to 55.2)			3 (20.0; 7.1 to 45.2)			1 (16.7; 3.0 to 56.4)			45 (14.4; 10.9 to 18.7)			128 (25.6; 22.0 to 29.6)	
Median age	CT LGV	35 37	0.13†	26 34			27 40–49‡			37 44			36 37	0.05†
HIV-positive	CT LGV	57/75 (76.0) 57/67 (85.1)	1.0 1.8 (0.8 to 4.3)	4/11 (36.4) 3/3 (100)			1/5 (20.0) 0/1 (0.0)			87/137 (63.5) 18/22 (81.8)	1.0 2.6 (0.8 to 8.2)	0.09	149/228 (65.4) 78/93 (83.9)	
Symptoms at clinic attendance	CT LGV	34/79 (43.0) 67/73 (91.8)	1.0 14.8 (4.9 to 44.8)	6/12 (50.0) 3/3 (100)			5/5 (100) 0/1 (0.0)			33/140 (23.6) 10/22 (45.5)	1.0 2.7 (1.1 to 6.9)	0.03	78/236 (33.1) 80/99 (80.8)	
Proctitis	CT LGV	32/79 (40.5) 67/73 (91.8)	1.0 16.4 (5.3 to 50.7)	3/12 (25.0) 3/3 (100)			2/5 (40.0) 0/1 (0.0)			15/128 (11.7) 11/21 (52.4)	1.0 8.3 (2.8 to 24.7)	<0.001	52/224 (23.2) 81/98 (82.7)	
Previous CT	CT LGV	15/75 (20.0) 24/67 (35.8)	2.0 2.2 (1.03 to 4.8)	2/9 (22.2) –			0/5 (0.0) 0/1 (0.0)			28/124 (22.6) 7/21 (33.3)	1.0 1.7 (0.6 to 4.7)	0.29	45/213 (21.1) 31/89 (34.8)	
STI coinfection§	CT LGV	28/87 (32.2) 22/79 (27.9)	– –	3/10 (30.0) 1/3 (33.3)			3/5 (60.0) 0/1 (0.0)			49/134 (36.6) 12/19 (63.2)	1.0 3.0 (1.1 to 8.2)	0.03	83/236 (35.2) 35/102 (34.3)	
Chemsex (previous 3 months)	CT LGV	– –	– –	– –			0/5 (0.0) 0/1 (0.0)			30/119 (25.2) 6/19 (31.6)	1.0 1.4 (0.5 to 3.9)	0.56	30/124 (24.2) 6/20 (30.0)	
Sex abroad	CT LGV	– –	– –	3/12 (25.0)¶ 3/3 (100)**			3/5 (60.0)† 1/1 (100)‡‡			17/122 (13.9)§§ 2/18 (11.1)¶¶		1.0†	23/139 (16.5) 6/22 (27.3)	

No proformas completed for Austria, but some limited data available. Proformas were completed for 162 of 344 patients from the UK. Statistical analysis only performed when variable completion was >80%, and no analysis of the Slovenian data set due to low numbers. P-values in bold represent significance ($p < 0.05$).

*Includes a LGV-positive lymph node punctate from Croatia and three equivocal results: one in Austria and two in the UK.

†P value from Mann-Whitney test for age distribution or Fisher's exact test due to small cell sizes.

‡Age range listed to avoid deductive disclosure.

§Not including HIV; includes only rectal gonorrhoea for Austrian patients; one UK non-LGV-CT patient had concurrent *Shigella* sp. infection.

Number of patients who reported sex abroad in the previous 3 months and region;

¶13 EU.

**1 EU, 2 non-EU.

††2 EU, 1 non-EU.

‡‡1 both EU/non-EU.

§§10 EU, 6 non-EU, 1 both EU/non-EU.

¶¶2 EU.

CT, *Chlamydia trachomatis*; EU, European Union; LGV, lymphogranuloma venereum.

of MSM with LGV-CT compared with those with non-LGV-CT had proctitis (91.8% vs 40.5%, $p < 0.001$) or a previous CT infection (35.8% vs 20.0%, $p = 0.04$) (table 1).

Croatia

In Croatia, CT and LGV positivity in rectal (and one lymph node punctate) specimens from MSM tested for CT was 8.8% (15/171; 95% CI 5.4 to 14.0) and 1.8% (3/171; 95% CI 0.6 to 5.0), respectively. LGV positivity among MSM with rectal CT was 20% (3/15; 95% CI 7.1% to 45.2%). Based on clinical symptoms and CT results, MSM with rectal LGV were treated with 21 days of doxycycline, and one patient with cervical lymphadenitis was treated for 6 weeks with doxycycline as previously described.²⁰ MSM with LGV-CT were significantly older than those with non-LGV-CT ($p = 0.03$) (table 1). A higher proportion of MSM with LGV-CT compared with those with non-LGV-CT had proctitis (100% vs 25%, $p = 0.04$) or were HIV-positive (100% vs 36.4%), although the latter was not significant ($p = 0.19$). All patients were born and resided in Croatia. All MSM with LGV in the Croatian sample ($n = 3$) compared with a quarter of those with non-LGV-CT (3/12) reported sex abroad in the previous 3 months ($p = 0.04$) (table 1).

Slovenia

In Slovenia, CT and LGV positivity in rectal specimens from MSM tested for CT was 11.5% (6/52; 95% CI 5.4 to 23.0) and 1.9% (1/52; 95% CI 0.3 to 10.1), respectively. The single specimen positive for LGV out of the six CT-positive specimens gave an LGV positivity of 16.7% (1/6; 95% CI 3.0% to 56.4%) (table 1). The LGV case had been treated with azithromycin 1 g for CT, as LGV was not diagnosed at point of care (the patient at test of cure was CT-negative). All CT-positive MSM resided in Slovenia and one was not Slovenian-born. No statistical associations were investigated due to small numbers. None of the cases reported chemsex.

UK

In the UK, the CT and LGV positivity in rectal specimens from MSM tested for CT was estimated to be 7.4% (313/4223; 95% CI 6.7 to 8.4) and 1.1% (45/4223; 95% CI 0.8 to 1.4), respectively. LGV positivity among CT-positive MSM was 14.4% (45/313; 95% CI 10.9% to 18.7%), of whom 162 (51.8%) had completed proformas for subsequent analysis (22 with LGV and 140 with non-LGV-CT) (table 1). All 22 MSM with LGV were treated with either 21 days ($n = 13$) or 7 days ($n = 9$) of

doxycycline. MSM with LGV were significantly older than those with non-LGV-CT ($p = 0.05$), and a higher proportion had proctitis (52.4% vs 11.7%, $p < 0.001$) or were coinfecting with another STI (63.2% vs 36.6%, $p = 0.03$) (table 1). Higher (but not significant) proportions of MSM with LGV-CT compared with those with non-LGV-CT were HIV-positive (81.8% vs 63.5%, $p = 0.09$) or had a previous CT infection (33.3% vs 22.6%, $p = 0.29$). Most (70%, 14/20) MSM with LGV were UK-born, whereas less than half (48.0%, 61/127) of MSM with non-LGV-CT were UK-born; the remainder were born in countries representing all global continents. Most MSM with non-LGV-CT (135/138) were UK residents. Similar proportions of MSM with LGV compared with those with non-LGV-CT reported sex abroad in the previous 3 months (13% vs 11.8%) (table 1). The number of sexual partners involving receptive anal intercourse in the previous 3 months ranged from 0 to 20 (median=3, mode=2) for MSM with LGV and from 0 to 57 (median=3, mode=5) for MSM with non-LGV-CT. Almost a third of MSM with LGV (31.6%, 6/19) reported chemsex in the previous 3 months, mainly with mephedrone and/or gamma-Hydroxybutyric acid (GHB), although crystal meth use was also reported. Of those MSM with non-LGV-CT, 25.2% (30/119) reported chemsex with mephedrone (56.7%), GHB (50%) and/or crystal meth (50%); 3,4-Methylenedioxyamphetamine (MDMA), cocaine, ketamine and marijuana use was also reported.

ompA sequences

Six different *ompA* sequences were described, including three new variants: L2bV5 (accession number: MH253040), L2bV6 (MH253041) and L2h (MH253042) (table 2). The most common genovar according to the *ompA* sequence in the UK sample was L2b and the new L2b variant, L2bV5. The L2 reference strain L2/434/Bu *ompA* sequence predominated in the Austrian (in all years) and Croatian samples.

DISCUSSION

We present data from a multicentre surveillance pilot in three Central and Eastern European countries with no routine LGV diagnostics. A quarter of CT-positive MSM in our study were infected with an LGV genotype, suggesting a high prevalence and systematic underdiagnosis of LGV infection in these MSM populations. Although not without its challenges, this sentinel surveillance approach, supported by centralised LGV testing if necessary, could serve as a model for countries with limited

Table 2 LGV *ompA* sequences derived from LGV-positive specimens from four European countries

	Austria		Croatia		Slovenia		UK		Total	
	n	%	n	%	n	%	n	%	n	%
LGV <i>ompA</i> sequences (accession number)										
Number of LGV-positive	79		3		1		22		105	
L2/434/BU (AM884176)	48	67.6	2	66.7	–	–	1	8.3	51	58.6
L2b/UCH-1/proctitis (AM884177)	5	7.0	1	33.3	1	100	5	41.7	11	12.6
L2bV1 (JX971936)	16	22.5	0	0.0	–	–	0	0.0	16	18.4
L2bV1 and L2/434/BU*	1	1.4	0	0.0	–	–	0	0.0	1	1.1
L2bV5 (MH253040) (new; most similar to L2bV4 (KU518892) with G-A at 271 bp)	0	0.0	0	0.0	–	–	4	33.3	4	4.6
L2bV6 (MH253041) (new; most similar to L2b (AM884177) with G-A at 998 bp)	0	0.0	0	0.0	–	–	1	8.3	1	1.1
L2h (MH253042) (new; most similar to L2 (AM884176) with A-G at 997 bp)	1	1.4	0	0.0	–	–	1	8.3	2	2.3
LGV sequence not obtained†	8	10.1	0	0.0	0	0.0	10	45.5	18	17.1

*Two different sequences present in specimen; mixed infection.

†Includes one patient from Austria with genotype G according to *ompA* sequencing; possible dual LGV and non-LGV-CT infection. LGV, lymphogranuloma venereum; bp, base-pairs.

resources to assess the prevalence of LGV infection among MSM and inform the development of appropriate care pathways, especially in countries where routine CT testing already occurs.

Over 5500 MSM were tested for CT in our pilot in order to achieve around 500 CT specimens for LGV testing. As such, the pilot study was limited by small numbers of cases, particularly from Croatia and Slovenia, and LGV positivity CIs overlapped for all country comparisons other than between Austria and the UK. We experienced difficulties in collecting complete clinical and behavioural information, highlighting the challenges of introducing a new surveillance system. The differences in selection criteria, clinic formats, testing algorithms and case mix across countries, along with relatively poor data completeness, make comparisons between countries difficult and contribute to the large variation in LGV and CT positivity across the four countries. For example, the majority of MSM in Austria and Croatia had symptoms, which probably introduced a bias towards higher LGV prevalence, and the representativeness of the LGV cases detected is not known. Nevertheless, our study complements the very limited published LGV data available from these countries; LGV was reported from Austria during 2005–2006, but no LGV reports have been published since; a single LGV case has previously been reported in Slovenia,²¹ where LGV testing is available but rarely performed.

Despite these limitations, our data suggest considerable underdiagnosis of LGV may be occurring across many EU countries given the number of previously unidentified LGV cases detected and the poor availability of LGV diagnostics (and in some places CT testing).⁸ Moreover, recent studies suggest there may be a high prevalence of asymptomatic LGV infection, which is probably under-represented in our pilot study,^{4,5,22} and some cases of LGV are not treated according to the guidelines.⁶ Asymptomatic carriage of LGV does raise important questions in relation to whether this non-invasive state should be considered and treated differently from symptomatic invasive LGV infection.

In general, and although the epidemiological data collected were limited, the findings from our pilot are consistent with previous studies, suggesting similarities in the drivers of LGV transmission across Europe, including HIV seroadaptive behaviours.^{4,11} The high frequency of STI coinfections is indicative of high partner turnover, which suggests that men acquiring LGV are likely to be at risk of other sexual and general health morbidities. Recent sex abroad, including outside of the EU (table 1), was commonly reported, implying a high potential for intercontinental transmission of LGV and other STIs.

In accordance with a previous study,²³ we found that the L2b *ompA* variant was not the most common in the pooled data set^{5,24}; the L2 *ompA* sequence predominated. However, this varied by country as the L2 *ompA* sequence predominated in Austria, while the L2b *ompA* sequence predominated in the UK. We also observed more *ompA* sequence diversity^{23,25} than previously reported.^{5,24} This diversity may be due to more mixed infections and subsequent recombination, sampling from different MSM sexual networks, or the occurrence of single nucleotide polymorphisms through mutations over time. In any future surveillance exercise, whole-genome sequencing would assist in assigning genotype and assessing genetic diversity because the high level of CT recombination, particularly in *ompA*, compromises genotype assignment based on partial sequencing of this single gene.²⁴ Unfortunately it was not possible to obtain an *ompA* sequence for all LGV-positive specimens, especially from the UK, where DNA degradation may have contributed to the low *ompA* sequencing success, so the results should be interpreted with caution.

Routine LGV diagnostics are limited by the additional cost and availability of CE-marked LGV assays. The use of inhouse assays is not always possible due to laboratory accreditation requirements and/or the limitations some health insurance companies impose on the reimbursement of test costs. The lack of appropriate LGV diagnostics and surveillance hampers infection control measures, and it seems likely that LGV is continuing to be spread unchecked in MSM in many countries across Europe and beyond. Our findings, which suggest systematic underdiagnosis of LGV in Europe, should be cause for considerable public health concern given the associated morbidity of this infection, which is often misdiagnosed. This adds to the considerable health inequalities experienced by MSM who are well recognised as a vulnerable and marginalised community, even in countries which are more tolerant of same-sex behaviours.²⁶ Unified infection control efforts are needed to overcome barriers to implementing LGV testing, establish effective surveillance programmes, and optimise diagnosis, treatment and prevention of LGV.

Key messages

- ▶ Data on the prevalence of lymphogranuloma venereum (LGV) in men who have sex with men (MSM) in Europe are sparse.
- ▶ We piloted LGV surveillance in Austria, Croatia and Slovenia using a centralised testing model and with the UK for comparison.
- ▶ Of 500 specimens from chlamydia-positive MSM tested, LGV positivity was 25.6%; a diverse number of *ompA* sequences were identified, including three new variants.
- ▶ Efforts to address barriers to LGV testing in Europe are needed to enable surveillance and optimise diagnosis, treatment and prevention.

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Contributors MJC, NF, GS and GH designed and coordinated the study, with GS and AJA-G initiating the study. MJC, NF, RP and GH analysed and interpreted the data, and wrote the first draft of the manuscript. JB, PDF, DK, IK, SZL, KP, AS and HS coordinated the study in their associated clinic/s and laboratory, and were responsible for collecting patient specimens and/or data, as well as interpretation of local data. All authors read, commented and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All specimens were collected and all patients were managed and treated for CT and related symptom presentation according to clinical guidelines in their respective countries. The pilot protocol was reviewed by PHE's Research Ethics Governance Group, and in settings where swabs were collected according to routine clinical practice (Austria, Croatia and the UK) this was deemed a surveillance evaluation not requiring ethical approval. In Slovenia, where CT testing is not routinely performed, ethical approval was granted by the Slovenian National Ethics Advisory Committee (number:0120-646/2016-4).

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Data availability statement Data are available upon reasonable request.

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REFERENCES

- O'Byrne P, MacPherson P, DeLaplante S, et al. Approach to lymphogranuloma venereum. *Can Fam Physician* 2016;62:554–8.
- Stoner BP, Cohen SE, Venereum L. Clinical presentation, diagnosis, and treatment. *Clin Infect Dis* 2015;61:S865–73.
- Nwokolo NC, Dragovic B, Patel S, et al. UK national guideline for the management of infection with *Chlamydia trachomatis*. *Int J STD AIDS* 2015;2016:251–67.
- Saxon C, Hughes G, Ison C, et al. Asymptomatic lymphogranuloma venereum in men who have sex with men, United Kingdom. *Emerg Infect Dis* 2016;22:112–6.
- Spaargaren J, Fennema HSA, Morr  SA, et al. New lymphogranuloma venereum *Chlamydia trachomatis* variant, Amsterdam. *Emerg Infect Dis* 2005;11:1090–2.
- de Vries HJ, Zingoni A, Kreuter A, et al. European guideline on the management of lymphogranuloma venereum. *J Eur Acad Dermatol Venereol* 2013;2015:1–6.
- European Centre for Disease Prevention and Control. Lymphogranuloma venereum. in: ECDC. Annual epidemiological report for 2016, 2018. Available: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2016-lymphogranuloma-venereum.pdf [Accessed Jan 2019].
- European Centre for Disease Prevention and Control. STI laboratory diagnostics in Europe, 2013. Available: <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/STI-laboratory-diagnostics-survey-Europe-December-2013.pdf> [Accessed Jan 2019].
- Rob F, J zlov K, Krutkov H, et al. Steady increase of lymphogranuloma venereum cases, Czech Republic, 2010 to 2015. *Euro Surveill* 2016;21.
- Petrovay F, Balla E, Erd si T. Emergence of the lymphogranuloma venereum L2C genovariant, Hungary, 2012 to 2016. *Euro Surveill* 2017;22.
- Childs T, Simms I, Alexander S, et al. Rapid increase in lymphogranuloma venereum in men who have sex with men, United Kingdom, 2003 to September 2015. *Euro Surveill* 2015;20.
- R nn M, Hughes G, White P, et al. Characteristics of LGV repeaters: analysis of LGV surveillance data: Table 1. *Sex Transm Infect* 2014;90:275–8.
- Hughes G, Alexander S, Simms I, et al. Lymphogranuloma venereum diagnoses among men who have sex with men in the UK: interpreting a cross-sectional study using an epidemic phase-specific framework. *Sex Transm Infect* 2013;89:542–7.
- Cole MJ, Spiteri G, Jacobsson S, et al. Overall low extended-spectrum cephalosporin resistance but high azithromycin resistance in *Neisseria gonorrhoeae* in 24 European countries, 2015. *BMC Infect Dis* 2017;17.
- Savage EJ, Mohammed H, Leong G, et al. Improving surveillance of sexually transmitted infections using mandatory electronic clinical reporting: the genitourinary medicine clinic activity dataset, England, 2009 to 2013. *Euro Surveill* 2014;19.
- Morr  SA, Spaargaren J, Fennema JSA, et al. Real-time polymerase chain reaction to diagnose lymphogranuloma venereum. *Emerg Infect Dis* 2005;11:1311–2.
- Chen C-Y, Chi K-H, Alexander S, et al. The molecular diagnosis of lymphogranuloma venereum: evaluation of a real-time multiplex polymerase chain reaction test using rectal and urethral specimens. *Sex Transm Dis* 2007;34:451–5.
- Lan J, Walboomers JM, Roosendaal R, et al. Direct detection and genotyping of *Chlamydia trachomatis* in cervical scrapes by using polymerase chain reaction and restriction fragment length polymorphism analysis. *J Clin Microbiol* 1993;31:1060–5.
- Gilbart VL, Simms I, Gobin M, et al. High-risk drug practices in men who have sex with men. *The Lancet* 2013;381:1358–9.
- Gjurašin B, Lepej Snjezana Zidovec, Cole MJ, et al. *Chlamydia trachomatis* in Cervical Lymph Node of Man with Lymphogranuloma Venereum, Croatia, 2014¹. *Emerg Infect Dis* 2018;24:806–8.
- Mati i  M, Klavs I, Vide nik Zorman J, et al. Confirmed inguinal lymphogranuloma venereum genovar L2C in a man who had sex with men, Slovenia, 2015. *Euro Surveill* 2016;21:2–5.
- Haar K, Dudareva-Vizule S, Wisplinghoff H, et al. Lymphogranuloma venereum in men screened for pharyngeal and rectal infection, Germany. *Emerg Infect Dis* 2013;19:488–92.
- Peuchant O, Touati A, Sperandio C, et al. Changing pattern of *Chlamydia trachomatis* strains in lymphogranuloma venereum outbreak, France, 2010–2015. *Emerg Infect Dis* 2016;22:1945–7.
- Harris SR, Clarke IN, Seth-Smith HMB, et al. Whole-genome analysis of diverse *Chlamydia trachomatis* strains identifies phylogenetic relationships masked by current clinical typing. *Nat Genet* 2012;44:413–9.
- Rodr guez-Dom nguez M, Puerta T, Men ndez B, et al. Clinical and epidemiological characterization of a lymphogranuloma venereum outbreak in Madrid, Spain: co-circulation of two variants. *Clin Microbiol Infect* 2014;20:219–25.
- Mercer CH, Prah P, Field N, et al. The health and well-being of men who have sex with men (MSM) in Britain: evidence from the third national survey of sexual attitudes and lifestyles (Natsal-3). *BMC Public Health* 2016;16.