

LYMPHOGRANULOMA VENEREUM IN EUROPE, 2003-2008

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Lymphogranuloma venereum, caused by the L serovars of *Chlamydia trachomatis*, emerged in Europe in 2003 and a series of outbreaks were reported in different countries. The infection presents as a severe proctitis in men who have sex with men, many of whom are co-infected with HIV and other sexually transmitted infections. This paper reviews the number of cases reported over a five year period, from 2003 to 2008, from countries that were part of the European Surveillance of Sexually Transmitted Infections (ESSTI) network. Reports were received from Belgium, Denmark, France, Germany, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom. It appears that after five years the characteristics of the patients infected has overall remained unchanged, although the total number of cases has increased and more countries in Europe have now identified cases of LGV.

Introduction

After initial case reports in late 2003, an outbreak of lymphogranuloma venereum (LGV) among men who have sex with men (MSM) was described in the Netherlands in 2004 [1-3]. MSM with LGV have presented with severe proctitis, the majority were co-infected with HIV and other sexually transmitted infections (STI) such as Hepatitis C, and reported unprotected anal intercourse [2-5]. Prior to 2003, LGV had been unusual in Western Europe for many years with most cases being imported. Classically, LGV presents as genital ulceration with lymphadenopathy and a secondary anorectal syndrome in tropical and subtropical countries in Africa, Asia, Central and South America [6]. The causative agent of LGV is *Chlamydia trachomatis* belonging to the L serovars and the current outbreak in Europe has been almost exclusively attributed to L2 genotype.

LGV was not a notifiable disease in many countries but enhanced surveillance has been established since 2004 in the Netherlands (January) and the United Kingdom (UK, October), and sentinel surveillance was set up in Germany (May). France introduced sentinel surveillance in January 2005 while LGV reporting in Sweden was performed via the mandatory *Chlamydia* laboratory reporting system since 2004. Other EU Member States did not change their

national STI notification systems and LGV cases were reported through routine clinical or laboratory observations. From June 2003, the European Surveillance of Sexually Transmitted Infections (ESSTI) network enabled epidemiologists and microbiologists to communicate, share information and raise alerts on emerging STI or outbreaks of STI via ESSTI_ALERT. This platform was also used to disseminate information about LGV. This report collates data collected through the ESSTI network and comments on the situation regarding LGV five years on from the apparent start of the outbreak in 2003.

Methods

In June 2008, the focal points of 24 countries participating in the ESSTI network were asked to provide information on LGV since 2003 for their respective countries (by short questionnaire). Countries were asked to provide available data on: monthly/quarterly number of cases, their sexual orientation, HIV status, age, sex, concurrent STI, travel abroad, clinical syndrome i.e. anorectal or inguinal, clinical symptoms, number of sexual partners in the last three months, and any other information available which they felt was relevant. Where no data or only incomplete data was available, information was compiled from reports of LGV submitted to ESSTI_ALERT during 2004 and 2008.

The ESSTI_ALERT system was developed as an informal system for epidemiologists and microbiologists to facilitate sharing and dissemination of early information on unusual events or outbreaks of STI across Europe. The system is based on a monthly active notification of unusual STI transmission events to the ESSTI coordinating centre meaning that notifications were requested actively each month from the coordination centre and were made using a standard reporting form.

Results

Nine countries (Belgium, Denmark, France, Germany, the Netherlands, Portugal, Spain, Sweden and the UK) provided data on LGV cases. For three additional countries: Ireland, Italy, and

Norway information was compiled using ESSTI alerts from 2007 and 2008.

Trends

From 2002 to 2007, the total number of cases reported was 1,693 (the UK 648 cases, France 556, the Netherlands 255, Germany 159, Belgium 45, Denmark 18, Portugal 8, Spain 4). LGV cases were already reported between 2002 and 2004 in Belgium, the UK, France, the Netherlands and Germany from where cases continued to be diagnosed. The highest number of cases was reported in the third quarter of 2005 with 96 cases diagnosed in the UK. The number of cases in the UK declined in 2006 but increased again in 2007 (Figure 1) and 2008 (191 cases) (data not shown). The Netherlands also saw an increase in the number of LGV cases reported starting towards the end of 2006. In France, the number of cases increased each year since 2002 until 2007 and seemed stable in 2008 with 170 and 174 cases respectively. Denmark, Portugal and Spain - countries that had not seen LGV cases early in the outbreak - started to report cases in 2006 and 2007 (Figure 2).

Characteristics

Characteristics of recent cases were similar to those in early outbreak reports. LGV cases were predominantly found among MSM with between 80-100% of cases in all countries reporting, except for Portugal (Table 1). In France, information on sexual orientation is not available; however, all French cases were male and *C. trachomatis* serovar L2 was identified from anorectal samples.

The majority of the European cases were co-infected with HIV, with the proportion of HIV-positives ranging from 40% in one sentinel site in Spain (Bilbao) to 100% in Sweden (Table 1).

Data on concurrent infections other than HIV was available from Belgium, Denmark, the Netherlands, Portugal, Spain (Bilbao), and the UK (Table 1). For gonorrhoea the proportion ranged from 0% in Portugal to 25% in the Netherlands and for syphilis co-infections the range was between 6% in the UK where a large number of LGV cases had been detected, to 40% in Portugal.

The clinical presentation was anorectal syndrome in the majority of cases: all cases in Netherlands, both cases in Portugal where the clinical syndrome was known, and 31 out of 36 cases in Denmark. Thirty-eight of 45 cases in Belgium had proctitis. In six cases, LGV was reported as inguinal manifestation (Denmark 5 cases, Spain 1 case).

LGV was mostly diagnosed in MSM aged above 25 years, with the exception of an outbreak in Catalonia where 25 of 28 cases of LGV were in MSM younger than 25 years (Table 1). High numbers of sexual partners were noted for cases in Spain, with more than 20 partners in the last six months reported for three of five cases; while more than five partners in the last six months were reported for eight of 15 cases in Belgium.

Only few male heterosexual cases were reported: two in Portugal, one in Spain (female partner also infected), and three in the UK. In Germany, cases were reported without additional information on sexual orientation.

Reports to ESSTI_ALERT

Reports to ESSTI-ALERT were received from Ireland; two LGV cases, both MSM, one HIV-positive; from Italy, three cases, all MSM, two of whom were HIV-positive; and from Norway, four cases,

without additional information. These reports, however, do not necessarily represent the total number detected in each of these countries. Sweden described an LGV cluster of five cases with domestic transmission in a sexual network in Stockholm.

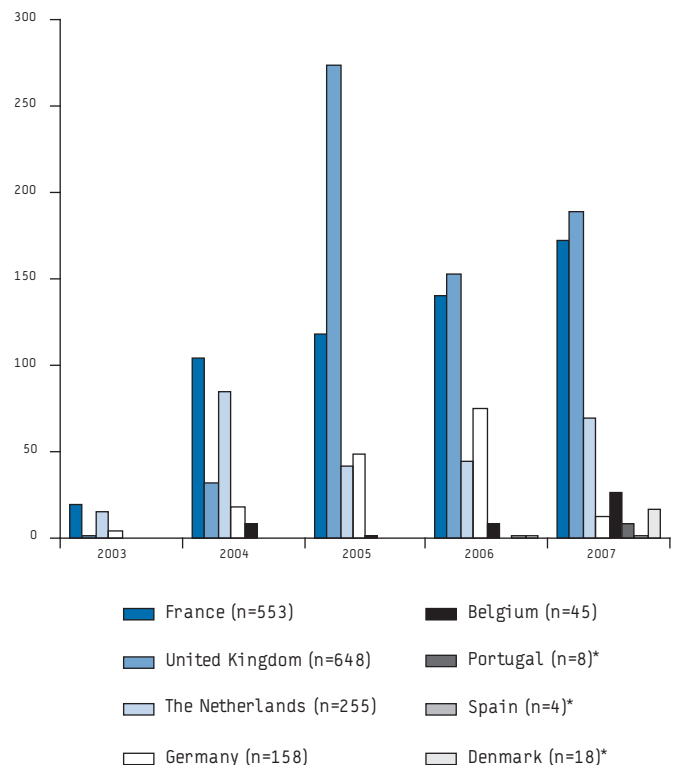
Discussion

From 2003 to 2008 the number of reported cases of LGV has increased in different countries in Europe, with the largest numbers reported in the UK, France, the Netherlands and Germany [7-10]. Moreover, since 2006 LGV has been reported in additional countries including Italy, Austria, Denmark, Portugal and Spain although often with a small total number of cases [11-15]. The profile of infected individuals, MSM with proctitis over 25 years of age and predominantly co-infected with HIV, has remained largely unchanged throughout the epidemic. Only some exceptions were reported, such as a small number of heterosexual cases detected by systematic screening in Portugal, with only few cases in total [14]. In the UK, where over 800 cases were detected, 13 presented with unusual clinical features: five cases of urethral LGV, three cases of LGV-associated inguinal buboes, one case of a solitary LGV penile ulcer and another case with a penile ulcer and bubonulus [16]. A case of bubonulus has also been reported from France [17].

The number of LGV cases continued to increase in several European countries and the characteristics of the patients appear to have remained unchanged, despite a few exceptions. Countries have reported actively on the number of cases detected, however, the reporting is largely influenced by the existence of a national

FIGURE

Cases of lymphogranuloma venereum in selected European countries, 2002-2007



*Data for 2006 and 2007.

sentinel surveillance system for LGV and the active case finding practices in clinical care across and within countries. The LGV cases presented here are probably largely underestimated due to the fact that cases may not be recognised, remain undiagnosed or are not reportable to national surveillance systems. Furthermore, ESSTI_ALERTS have increased awareness throughout the network but did not involve clinicians in the participating countries. Another weakness in our data and in the literature is a lack of a consistent case definition across Europe and the lack of LGV genotyping in some countries particularly early in the outbreak. Nevertheless, the consistency in the characteristics of patients infected with LGV across Europe suggests that this is a distinct entity.

There is little evidence that the LGV outbreak in MSM has spread to a wider population since 2003. LGV still seems to occur amongst a core group of individuals infected with HIV and with high-risk sexual behaviour [18-20]. The low number of cases among HIV-negative and heterosexual men indicates little bridging between the core MSM and other sexual networks. Molecular typing studies have shown that, where the data is available, the infecting LGV strain belongs primarily to serovar L2b [21] and although variants have been found, these differ from the parent strain by only a few base pairs [22]. This seems to point towards transmission within a closed network but data needs to be interpreted with caution as the molecular typing methods are poorly discriminatory at present. Spaargaren et al. [21] compared strains from the current European

outbreak with strains collected in the 1980s in the United States and found both belonging to serovar L2b. The conclusion from this might be that the outbreak has not emerged recently but may rather have gone undetected due to the lack of specific screening for LGV genotypes.

The reasons for the re-emergence of LGV in Europe over the last five to six years remain unclear and it has been suggested that it is the result of the increased availability of molecular diagnostic tests [23]. While there has certainly been considerable development [24-27] and increased use of molecular tests to directly detect *C. trachomatis* belonging to the L serovars [28], this appears to have been largely in response to a clinical need [29]. There do remain a number of elusive questions regarding the reservoir and mode of transmission that perpetuates the ongoing outbreak. Data regarding the existence of an asymptomatic reservoir are conflicting with only a small number of asymptomatic cases detected in the UK compared to a larger number in the Netherlands [28,30-32], although this may simply reflect variation in protocols for screening and testing of MSM patients across Europe. The inability to detect *C. trachomatis* serotypes causing LGV in the urethra points at possible transmission through inanimate objects such as sex toys, or the inability of the pathogen to colonise the urethra. High-risk behaviour is now well documented as a characteristic of individuals infected with LGV but the use of enemas and increased number of partners are the only risk factors currently identified [22]. There

TABLE
Risk factors of LGV cases in selected countries in Europe, 2004-2008

Country	Period	Number of male cases	No. MSM (%)	HIV positive (% of known status)	HIV unknown serostatus (% of total)	Concurrent STI (%)					Age Years
						Syphilis	Gonorrhoea	Hepatitis B	Hepatitis C	Chlamydia infection	
Belgium	2004-2008	43	42* (97.7)	41 (95.3)	0	6 (14)	5 (11.6)	-	-	-	Mean age 38 (range 20-58)
Denmark	2006-2008	43	42 (97)	15 (35)	6 (16.7)	3 (7)	2 (5)	NA	NA	NA	Mean age 38 (range 24-52)
France	2002-2008	725	NA	280 (90)	415 (57)	-	-	-	-	-	Median age 37 (range 20-58)
The Netherlands	2004-2007	225	224 (99.6)	117 (55)	14 (6.2)	27 (12)	56 (24.9)	3 (1.3)	-	-	Mean age 41
Portugal	2007-March 2008	5	3 (60)	3 (100)	2 (40)	2 (40)	-	-	-	3 (60)	Mean age 42 (range 29-52)
Spain: Bilbao	2006-June 2008	5	4* (80)	2 (40)	0	0	1 (20)	0	0	2 (40)	Mean age 35 (range 33-39)
Spain: Catalonia	2007-June 2008	17	17 (100)	16 (94)	0	-	-	-	-	-	Age group 15-24(n=25) 25-44 (n=3)
United Kingdom	2004-2008	848 (763 with further epidemiological data)	756 (99.1)	566 (74)	33 (4)	49 (6)	135(18)	1 (0.1)	112 (15)	-	Mean age 38 (range 19-67)
Sweden	2007-August 2008	9	9 (100)	9 (100)	0	-	-	-	-	-	NA

MSM: men who have sex with men; STI: sexually transmitted infections; NA: not available
*Includes 1 bisexual

is other epidemiological evidence that STI such as syphilis and resistant gonorrhoea are increasing in MSM in many countries, showing that STI infections can spread in sexual networks of MSM across Europe [33].

Sharing of information through the ESSTI has raised awareness for the problem of LGV in MSM. However, cases continue to be detected in many European countries, implying that control and prevention strategies which have so far concentrated on accurate diagnosis and treatment of cases and their sexual partners, have not been optimal. Activities also included raising awareness amongst healthcare professionals and the gay community in some countries. This is in contrast to the situation which occurred in the late 1990s when outbreaks of syphilis were first reported in Western Europe among MSM. A variety of control measures targeting MSM were introduced by countries such as health education and promotion, increased clinic capacity, syphilis screening at social venues and clinics and at HIV treatment centres, distribution of free condom packs, and contact tracing [34]. Despite all these efforts, syphilis rates have reached high levels almost equal to the pre-AIDS era in many countries. Although the numbers of LGV remain small in comparison to the number of syphilis cases reported, it is clear that LGV is becoming endemic in particular sexual networks and alternative approaches to the control of LGV should possibly be considered. Surveillance and monitoring of LGV is currently implemented at EU level by the European Centre for Disease Prevention and Control (ECDC) as part of the enhanced surveillance for STI as agreed with the Member States. Reporting to one European surveillance system shall contribute to the availability of more comparable data on LGV, and STI in general, in the future.

Members of the European Surveillance of Sexually Transmitted Infections, listed in alphabetical order by countries, are:

Austria: Angelika Stary, Outpatients' Centre for Diagnosis of Infectious Venero-Dermatological Diseases, Reinhold Strauss, FM for Health, Family and Youth; Belgium: Tania Crucitti, Institute of Tropical Medicine; Cyprus: Chrystalla Hadjianastasiou, Ministry of Health; Denmark: Susan Cowan, Statens Serum Institut; Estonia: Anneli Uusküla, Tartu University Clinics, Rutta Voiko, West Tallinn Central Hospital; Finland: Eija Hiltunen-Back, National Public Health Institute; France: Véronique Goulet, Institut de Veille Sanitaire, Patrice Sednaoui, Institut Alfred Fournier; Bertille de Barbeyrac, National Reference Centre of Chlamydia Infection; Germany: Peter Kohl, Dept. of Dermatology and Venerology, Vivantes Klinikum Neukölln; Greece: Vasileia Konte, Hellenic Centre for Infectious Disease Control, Eva Tzelepi, National Reference Center for N.gonorrhoeae, Hellenic Pasteur Institute; Iceland: Guðrún Sigmundsdóttir, Centre for Infectious Disease Control, Directorate of Health, Guðrún Hauksdóttir, Landspítali University Hospital; Ireland: Aidan O'Hara, Health Protection Surveillance Centre, Helen Barry, St. James Hospital; Italy: Paola Stefanelli, Barbara Suljoi, Istituto Superiore di Sanità; Latvia: Judite Pirska, Elvira Lavrinovica, State Centre of Sexually Transmitted and Skin Diseases; Malta: Christopher Barbara, St Luke's Hospital, Jackie Maistre Melillo, Infectious Disease Prevention and Control Unit, Department of Health Promotion and Disease Prevention; Netherlands: Ineke Linde, GGD Amsterdam; Norway: Hilde Klovstad, Norwegian Institute of Public Health, Vegard Skogen, UNN Tromsø Universitetssykehuset; Portugal: Jacinta Azevedo, General Directorate of Health (DGS); Slovak Republic; Jan Mikas, National Public Health Agency of the Slovak Republic; Slovenia: Irena Klavs, Centre for Communicable Diseases, Institute of Public Health of the Republic of Slovenia, Alenka Andlovic, Institute of Microbiology and Immunology, University of Ljubljana; Spain: Julio Vazquez, Instituto de Salud Carlos III; Sweden: Anders Blaxhult, Inga Velicko, Swedish Institute for Infectious Disease Control, Hans Fredlund, Swedish Reference Laboratory for Pathogenic Neisseria, Örebro University Hospital; Turkey: Peyman Altan, General Directorate of Primary Care Services, Ministry of Health; United Kingdom: Lesley Wallace, Health Protection Scotland, Hugh Young, Scottish Bacterial Sexually Transmitted Infections Reference Laboratory, Mike Catchpole, Michelle Cole, Health Protection Agency..

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