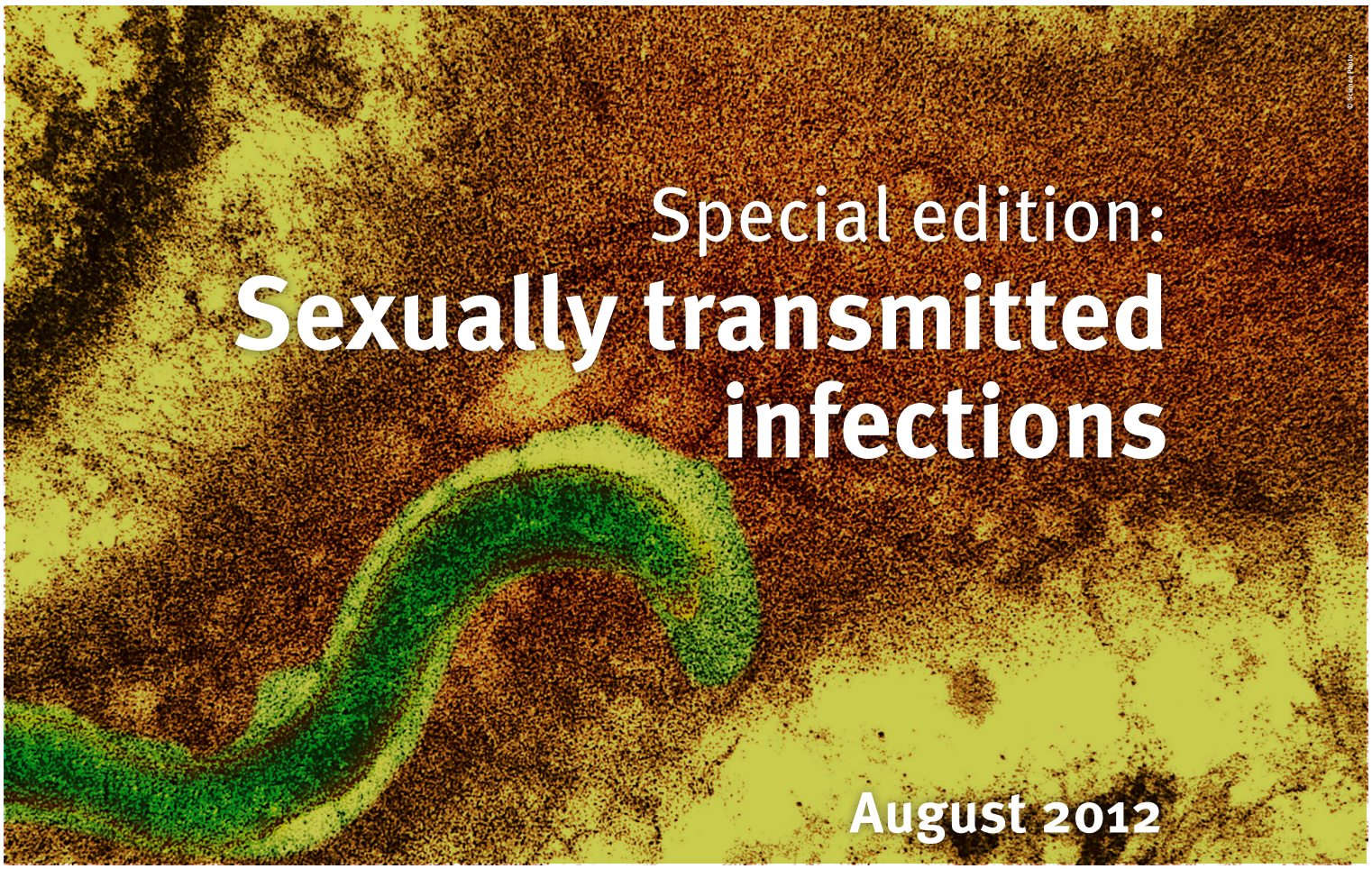
Impact factor 6.15

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control



Special edition:
Sexually transmitted infections

August 2012

- Reports highlighting increasing trends of gonorrhoea and syphilis and the threat of drug-resistant gonorrhoea in Europe.

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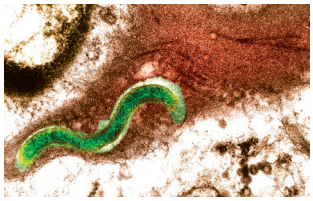

© Science Photos, Syphilis bacterium (Treponema pallidum)

Increasing trends of gonorrhoea and syphilis and the threat of drug-resistant gonorrhoea in Europe

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Citation style for this article:
Van de Laar M, Spiteri G. Increasing trends of gonorrhoea and syphilis and the threat of drug-resistant gonorrhoea in Europe. Euro Surveill. 2012;17(29):pii=20225. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20225

Article submitted on 18 July 2012 / published on 19 July 2012

Sexually transmitted infections (STI) notifications have been on the rise in several European countries since the early 2000s, most likely due to multiple factors like increased screening, use of more sensitive diagnostics, improved reporting and also due to high levels of unsafe sexual behaviour among certain subpopulations. Across Europe, 32,000 cases of gonorrhoea, 18,000 cases of syphilis and over 345,000 cases of chlamydia were reported in 2010 [1]. Certain subpopulations appear to be more affected than others: Men who have sex with men (MSM) are disproportionately affected by gonorrhoea and syphilis, and young people between 15 and 24 years of age are affected mainly by chlamydia and gonorrhoea. The increases in gonorrhoea and syphilis reported in this edition of *Eurosurveillance* are worrying as they are identified in MSM and young adults and seem to be associated with high levels of unsafe sexual behaviour and co-infection with human immunodeficiency virus (HIV). The increases in gonorrhoea are of particular concern as they coincide with decreasing susceptibility of *Neisseria gonorrhoeae* to currently used antimicrobial drugs in England [2] and across Europe [3].

The increases reported in this edition can be partly explained by increased testing of risk groups. Bremer et al. [4] report that the increase in syphilis diagnoses in Germany could be linked to increased uptake of screening by HIV-negative MSM and incorporation of syphilis testing in the clinical monitoring of HIV-positive MSM. In Sweden, the increase in gonorrhoea seen over the last five years, particularly among young women (who are more often asymptomatic than men) is similarly linked to the increasing use by youth clinics of nucleic acid amplification tests which are more sensitive and test for both chlamydia and gonorrhoea in the same sample [5]. Similarly, increased testing of MSM in the United Kingdom (UK) due to the recent increases in lymphogranuloma venereum (LGV), and new testing guidance is thought to have contributed to the increase in gonorrhoea notification there [6].

Intensified testing does not, however, completely explain the reported rises in STI notifications. Increased risk behaviour among both MSM and young adults may have contributed to these changes. The rise in gonorrhoea among heterosexuals in Sweden and the UK in particular cannot be linked solely to increased testing, and unsafe sexual behaviour is an important contributor. In addition, Velicko and Unemo [5] report that half of the diagnoses among heterosexual men in Sweden appear to be acquired outside Sweden; this adds to the risk of importation of resistant strains. These observations indicate the need to implement behavioural surveillance in addition to biological surveillance as a useful tool to gain more insight into current trends of unsafe sexual behaviour.

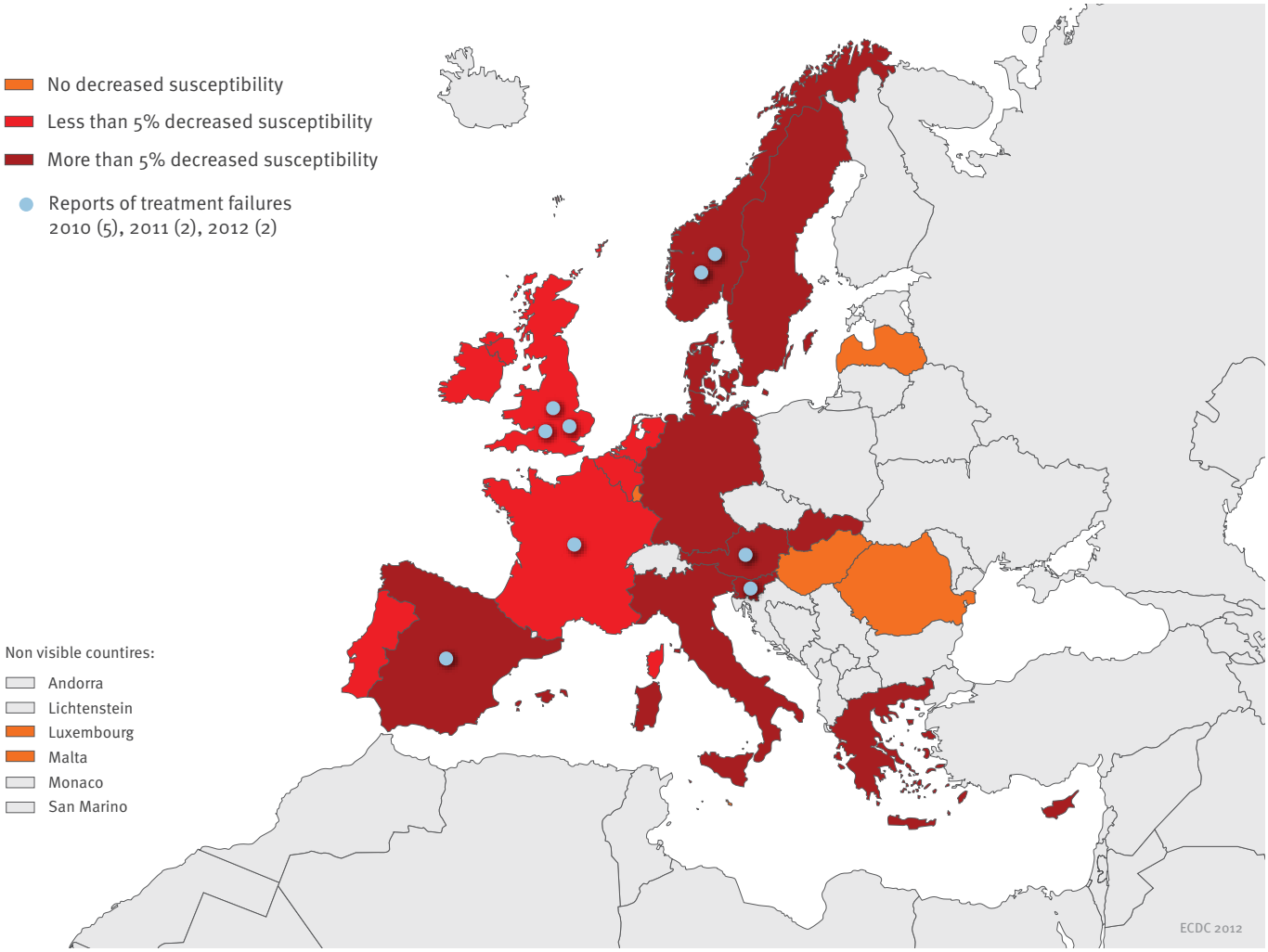
Effective control of gonorrhoea relies entirely on successful antimicrobial treatment. Untreated infections can lead to severe secondary sequelae, including pelvic inflammatory disease, first trimester abortions, ectopic pregnancy and infertility, and may contribute to facilitating HIV transmission. Current treatment guidelines in Europe recommend the use of single-dose injectable (ceftriaxone) or oral third-generation cephalosporins (cefixime) [7].

The upward trend in gonorrhoea cases is particularly worrying as it comes at a time when treatment failures with third generation cephalosporins are being reported, also in Europe. In June this year, the World Health Organisation has warned that drug-resistant gonorrhoea is becoming a major public health crisis [8]. The European Centre for Disease Prevention and Control (ECDC) has recently launched the first regional public health response plan to control and manage the threat of resistant gonorrhoea. [9]

N. gonorrhoeae has developed resistance to most of the antimicrobial drugs successively introduced for treatment over the years. The first treatment failures to the less potent cephalosporins were reported in 2000 in Japan [10] and other countries [11] with recent reports from Norway [12], England [13,14] and Austria [15]. The emergence of a highly ceftriaxone-resistant strain H041 in Japan in 2011 [16] triggered worldwide concerns as ceftriaxone is the last remaining option for

Figure

Decreased susceptibility to cefixime in 2010 and reported cefixime treatment failures in 2010-2012, EU/EEA



EU/EEA: European Union/European Economic Area.
Decreased susceptibility to cefixime is defined as a minimum inhibitory concentration (MIC)≥0.25 mg/L.
This figure has been is adapted with permission from a map published in [9].

empirical first-line treatment. Ceftriaxone treatment failures of pharyngeal gonorrhoea have been reported in Sweden [17] and Slovenia [18]; treatment failure for genital infection has been reported from France [19]. A suspected ceftriaxone-resistant strain has also been reported from Spain [20].

The European gonococcal antimicrobial surveillance programme (Euro-GASP) is a sentinel surveillance system implemented through the European STI network; it involved laboratories across 21 Member States of the European Union (EU) and European Economic Area (EEA). Euro-GASP results from 2009 and 2010 show that decreased susceptibility to cefixime is becoming more frequent and is spreading across Europe (Figure 1). Susceptibility to ceftriaxone also appears to be decreasing [3,21,22]. These results are extremely worrying as the loss of both cefixime and ceftriaxone as treatment options for gonorrhoea would have a significant impact on public health.

The ECDC plan details the response to this development across the EU/EEA and guides the individual Member States in their national interventions [9]. The goal of the plan is to minimise the impact of resistant gonorrhoea in Europe, and specific objectives are directed at national authorities as well as ECDC:

- Surveillance of gonococcal antimicrobial susceptibility in the EU/EEA will be strengthened to inform national treatment guidelines. ECDC plans to include another four to five countries in Euro-GASP in 2012 and 2013 in a capacity building project, to reinforce the collection of epidemiological and demographical information on patients. Through Euro-GASP, ECDC supports countries in performing antimicrobial

testing and ensures the comparability of results through training courses and an external quality assurance programme.

- Minimum capacity for bacterial culture and susceptibility testing will be either available or developed at national level in EU/EEA Member States.
- A strategy will be developed to rapidly detect patients diagnosed with gonorrhoea who experience a clinical treatment failure with recommended cephalosporins, including the clinical management of affected patients and their sexual partners. ECDC will implement treatment failure reporting to inform (inter)national authorities and professional societies to contribute to the revision of the European treatment guidelines.
- A set of recommended public health actions will be outlined for use in the EU/EEA Member States where resistant cases are detected. A communication strategy will be established to disseminate the surveillance results and increase awareness among public health authorities, professional societies, physicians and the public about the threat of resistant gonorrhoea.

The increasing rates of gonorrhoea and syphilis need to be closely monitored, and public health interventions need to be targeted at the affected groups. These intervention programmes need to be evidence-based and monitored rigorously and systematically to ensure their quality. Multidrug-resistant *N. gonorrhoeae* is a serious public health threat which could result in the loss of the last remaining options for effective treatment in the near future. The spread of strains with reduced antimicrobial susceptibility to third generation cephalosporins across Europe needs to be further investigated using tools such as molecular typing. Public health experts and clinicians need to be informed about the current critical situation and should be vigilant for treatment failures.

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Syphilis on the rise again in Germany – results from surveillance data for 2011

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Citation style for this article:
Bremer V, Marcus U, Hamouda O. Syphilis on the rise again in Germany – results from surveillance data for 2011. Euro Surveill. 2012;17(29):pii=20222. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2022

Article submitted on 9 July 2012 / published on 19 July 2012

In Germany, syphilis is notified anonymously. In 2011, 3,698 cases (incidence 4.5/100,000 inhabitants) were notified, an increase of 22% over 2010. The increase was higher in men (23%) than women (13%) and 94% of the cases were male. Information on the possible way of transmission was available for 72% of cases. Of these, 84% were men who have sex with men, who seem to play a major role in the renewed increase in syphilis cases.

Syphilis had become a rare disease in Germany in the 1990s. In 2001, the surveillance system changed and laboratories in Germany were required to notify each new syphilis diagnosis directly to the Robert Koch Institute in Berlin [1]. Before 2001, syphilis was notifiable according to the Geschlechtskranheitengesetz (Sexually Transmitted Diseases Act). Physicians were asked to report clinical syphilis cases and no case definition was used. The number of syphilis cases doubled between 2001 and 2004 and reached 3,364 [2]. This increase between 2001 and 2004 was only observed among men, many of them men who have sex with men (MSM). Since the increase was only seen among men, we assume it was not an effect due to the new surveillance system. Notifications then remained stable until 2008, decreased in 2009 to 2,742 [3], and rose again to 3,033 in 2010 [4], an increase of 10.6%. This report describes how syphilis cases have increased in Germany in 2011, in comparison to previous years.

Syphilis surveillance

In Germany, laboratories notify syphilis diagnoses directly and anonymously to the Robert Koch Institute. Physicians are required to complete the laboratory findings with clinical information. To identify possible double notifications, each incoming notification form is compared to previous notifications with regard to the month and year of birth of the case and the first three digits of the postal code of their place of residence. Since the notifications are completely anonymous and not identified by a code, potential double notifications are compared using the parameters date of diagnosis, antibody titres and reported clinical information, to differentiate between follow-up tests and new clinical episodes.

We used the following case definition:

- direct detection of *Treponema pallidum* by microscopic examination of fluid or smears from lesions, histological examination of tissues,
- or detection of antibodies against *T. pallidum* by screening test (*T. pallidum* haemagglutination assay (TPHA), *T. pallidum* particle agglutination assay (TPPA) or enzyme immunoassay (EIA)), confirmed by fluorescent treponemal antibody absorption (FTA-ABS) or IgG immunoblot,

and

- venereal disease research laboratory test (VDRL) titre ›4 (rapid plasma reagin ›8),
- or VDRL titre ›0 and ‹8, and clinical information consistent with primary syphilis,
- or detection of treponemal IgM antibodies (by IgM enzyme-linked immunosorbent assay (ELISA), IgM immunoblot or 19S(IgM) FTA-ABS).

We described syphilis cases by month of diagnosis or notification (in case date of diagnosis was missing), age, sex and residence. Where such information was available, we analysed the data by transmission category and country of infection and origin.

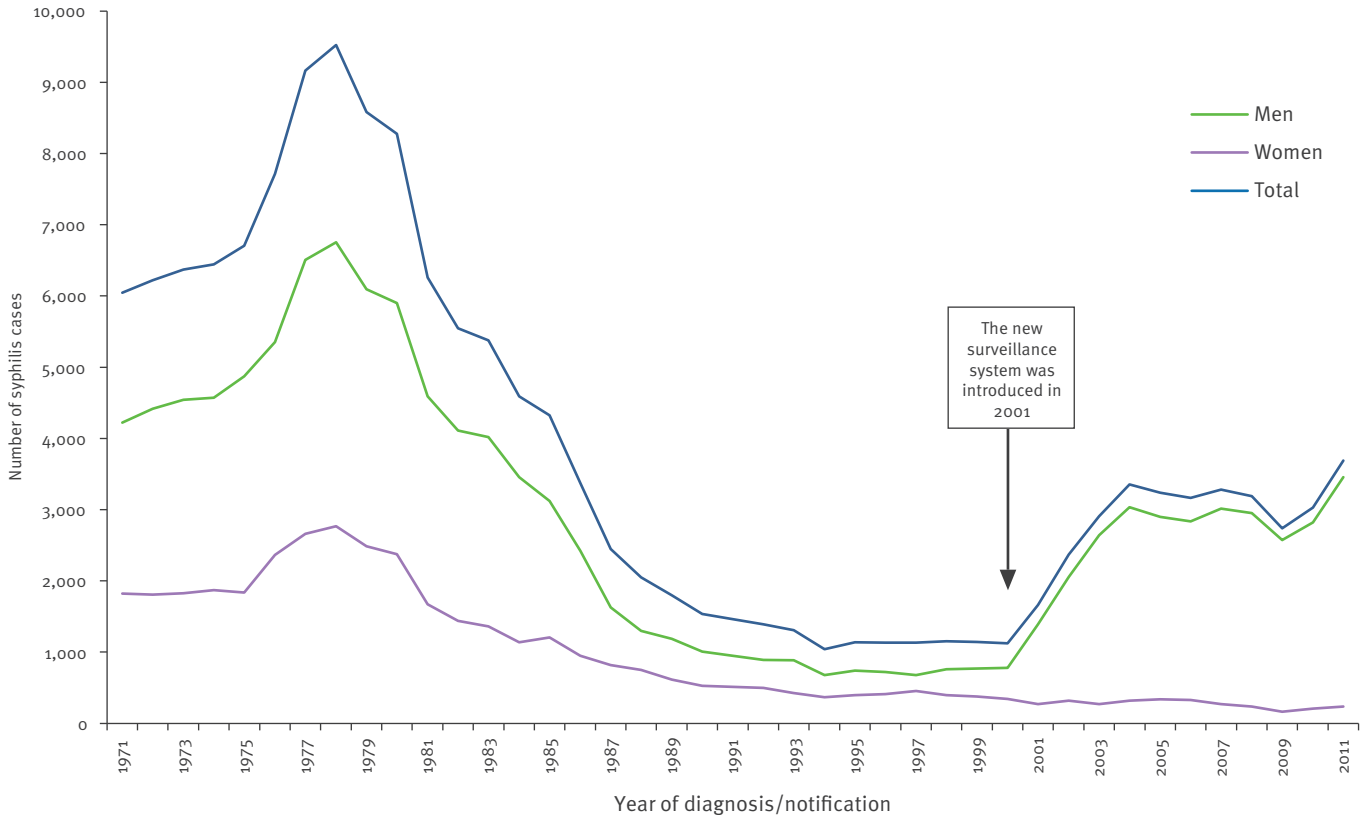
Results

In 2011, 3,698 syphilis cases were notified, an increase of 22% over the 3.033 cases in 2010. The observed increase was higher in men (23%) than in women (13%), and 94% of the cases were male (Figure 1). The overall incidence was 4.5 per 100,000 inhabitants (Figure 2).

The incidence in men was 14 times higher than in women (8.6 versus 0.6 per 100,000 inhabitants). The incidence rose in all age groups for men, while there was only a small increase in some age groups among women (Figure 3). The highest incidence in men (19.1/100,000) was observed in the 30-39 year-olds, and the highest incidence in women (1.7/100,000) in the 25-29 year-olds.

Figure 1

Notified syphilis cases by sex and year of notification or diagnosis, Germany, 1971-2011



We used month of notification in case the date of diagnosis was missing.
Notification data according to the Sexually Transmitted Diseases Act (before 2001) and the Infection Protection Act (after 2001).

Information on transmission category was available for 2,645 cases (72%) of the cases. In 84% of those, sex between men was mentioned as the probable route of transmission. Transmission through heterosexual contacts was mentioned in 16% of the cases. The largest increase in syphilis cases was observed in MSM, followed by cases without information on route of transmission and cases with probable heterosexual transmission. Information on country of infection was available for 2,659 cases (73%). Of those, 93% acquired their infection in Germany. Infections acquired in western Europe were mostly in MSM, while heterosexual transmission prevailed in infections acquired in central or eastern Europe. Also, two cases of congenital syphilis were registered.

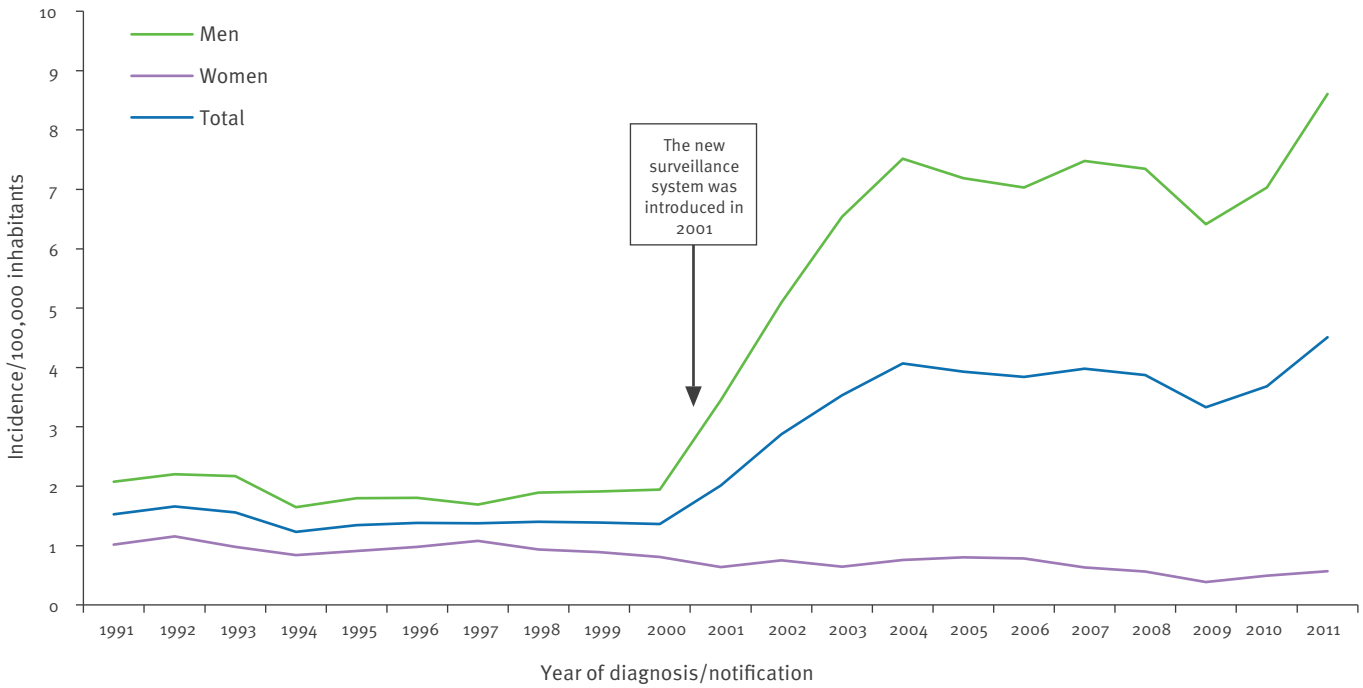
An increased incidence was observed in 11 of the 16 federal states, while it was stable in and decreased slightly in three federal states. The highest incidences were seen in the cities of Cologne (24.0/100,000), Frankfurt (21.0/100,000) and Berlin (18.0/100,000). Furthermore, we observed an unusual upsurge of syphilis cases among women and heterosexual men in the city of Dortmund in North Rhine-Westphalia and the surrounding area. The number of notified syphilis cases in women residing in Dortmund increased from two in 2009 to 10 in 2010 and 23 in 2011. At the same time, the number of notified syphilis cases in heterosexual men increased from eight in 2010 to 18 in 2011. Sex work or contact with sex workers was indicated as a possible way of transmission in nine of these cases. However, the available information was too incomplete to conclude that this outbreak was solely linked to sex work.

Discussion

We observed a considerable increase in notified syphilis cases in Germany in 2011. It has been the year with the highest number of notified cases since the introduction of the Infection Protection Act (Infektionsschutzgesetz) in 2001. Such a high level has not been observed since 1986, although comparability between surveillance data before and after 2001 is limited due to introduction of a case definition and a different reporting system. It is too early to know whether this is just a temporary rise or a new trend. However, we had already observed a moderate increase in notifications between 2009 and 2010. Since the notified syphilis cases continued to increase during the first three months of 2012, it is possible that a further increase in the number of syphilis cases in 2012 will be observed.

Figure 2

Incidence per 100,000 inhabitants of notified syphilis cases by sex and year of notification or diagnosis, Germany, 1991-2011



We used month of notification in case the date of diagnosis was missing.
Notification data according to the Sexually Transmitted Diseases Act (before 2001) and the Infection Protection Act (after 2001).

An increase in syphilis has been observed in several countries in western Europe between 1998 and 2005 [5,6]. Many of these syphilis cases were among MSM residing in large cities [7,8]. This has also been observed in Germany. Most syphilis cases among German MSM acquired their infection in Germany, which indicates that transmission is mainly occurring within the country. Part of the increase in cases among MSM could be explained by the inclusion of syphilis testing into the regular monitoring of human immunodeficiency virus (HIV)-positive MSM and a higher demand by HIV-negative MSM to get screened for sexually transmitted infections (STIs).

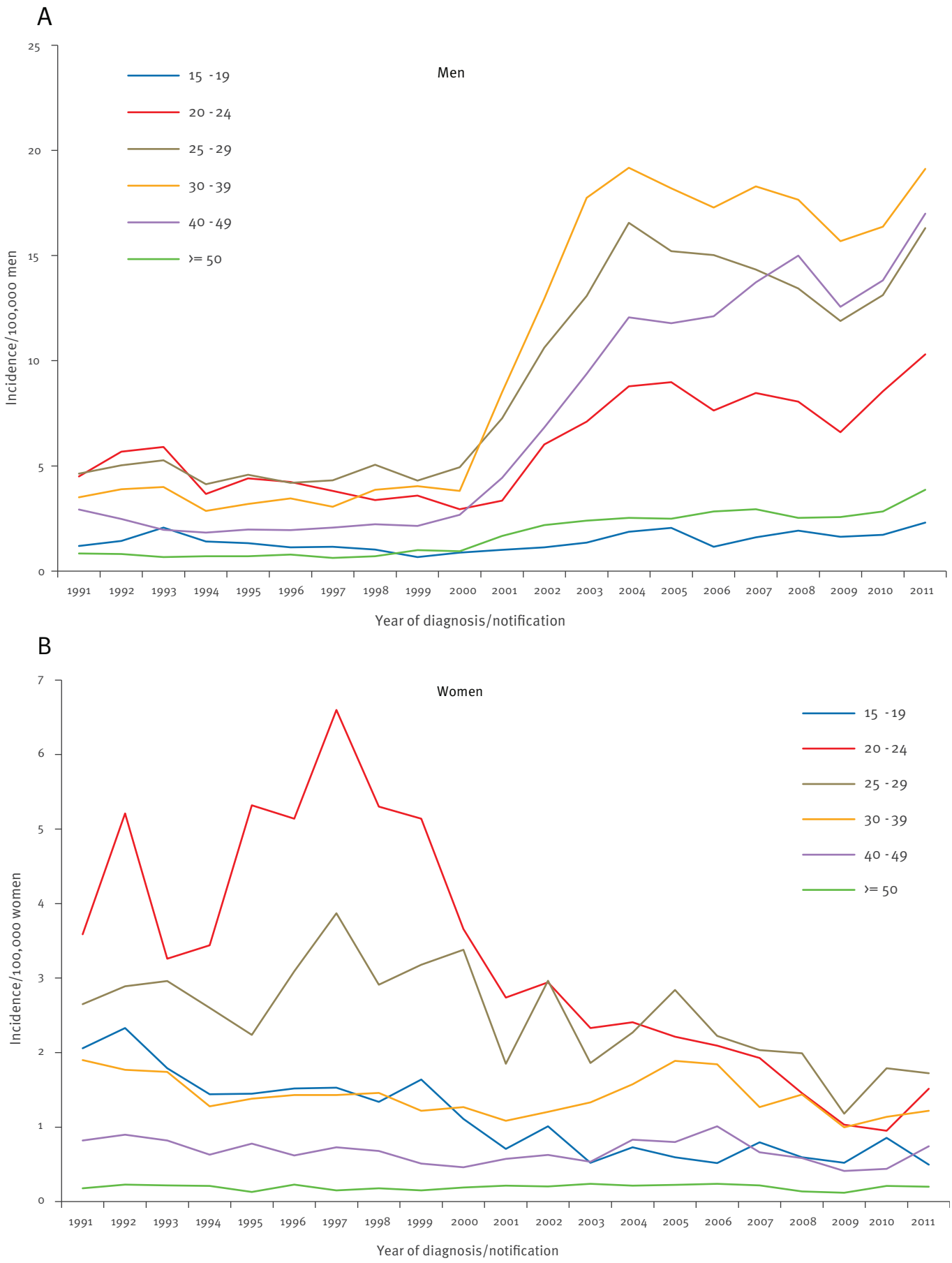
Until 2008, simultaneous increases and decreases of syphilis notifications in MSM in different regions had been observed. Following the country-wide decrease in syphilis case notifications in 2009, also the increase in 2011 in the MSM population seems to be occurring in most regions in Germany. From behavioural studies among MSM – the last larger survey (European MSM Internet Survey; EMIS) was conducted in 2010 [9] – there are no indications of any significant behavioural changes. Longer term trends towards increasing partner numbers and high levels of HIV serosorting (choosing sexual behaviour based on HIV status) particularly among MSM diagnosed with HIV may generally favour the spread of syphilis [10], but would not be sufficient to explain short term increases. Since undetected syphilis infections can increase the risk of HIV transmission [11], early diagnosis and treatment are important to minimise this risk. MSM with multiple partners should therefore be offered regular screening for syphilis and other STIs.

Although the large majority of cases in 2011 were observed among MSM, outbreaks among heterosexuals do occur. In Dortmund, we were not able to verify a possible link to sex work for the outbreak. Still, the local health authorities started to reinstate STI counselling and testing, aimed at sex workers. Private practitioners were informed about the outbreak. In 2012, only few syphilis cases among women and heterosexual men have so far been registered in Dortmund.

The increase of syphilis in MSM between 1998 and 2005 was observed in several European countries at the same time [6]. After that, surveillance data showed that the incidence of syphilis remained stable or declined in several western European countries, leading to an overall decrease of 7% in reported cases between 2006 and 2009 [12]. Since increases or decreases seem to be synchronised in several countries, it is possible that the recent development in Germany will be mirrored also in other western European countries.

Figure 3

Incidence per 100,000 men and women of notified syphilis cases by age groups and year of notification or diagnosis, Germany, 1991-2011



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Recent trends in gonorrhoea and syphilis epidemiology in Sweden: 2007 to 2011

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Citation style for this article:
Velicko I, Unemo M. Recent trends in gonorrhoea and syphilis epidemiology in Sweden: 2007 to 2011. Euro Surveill. 2012;17(29):pii=20223. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20223

Article submitted on 10 July 2012 / published on 19 July 2012

Gonorrhoea incidence in Sweden continued to increase during 2007–2011, while for syphilis, there was a very minor decrease, but no clear trend. Gonorrhoea incidence increased most among heterosexually infected men and women while for syphilis, the major burden was among men who have sex with men. *Neisseria gonorrhoeae* resistance to first-line antimicrobials increased annually. Surveillance of infection and antimicrobial resistance along with continuous analysis are needed, to develop prevention activities to reduce risk behaviours.

Recent reports from several European Union (EU) countries have revealed increases in gonorrhoea incidence, particularly in populations with higher frequency of spread of sexually transmitted infections (STIs), such as men who have sex with men (MSM) and young heterosexual individuals of both sexes (under 25 years of age), and stable or increasing syphilis incidence in MSM [1-4].

During the past couple of decades, Sweden has observed an increased incidence of gonorrhoea (since 1996) and syphilis (since 1999) [5-7]. MSM have been shown to be at increased risk of acquiring and spreading both gonorrhoea and syphilis [5,6]. Heterosexually infected men, especially those aged 25–34 years, also have a high gonorrhoea incidence compared with women [6]. During the last 10 years, women have constituted only approximately 20–30% of all gonorrhoea and syphilis cases in the country [5,6]. Disquietingly, during the past five years, gonorrhoea and syphilis incidences in heterosexually infected men and women, including those in younger age groups (under 25 years of age), have increased. Furthermore, as observed worldwide, antimicrobial resistance of *Neisseria gonorrhoeae* in Sweden has increased annually during this time, including to the recommended first-line cefixime and ceftriaxone [6,8,9]. One instance of treatment failure of pharyngeal gonorrhoea with ceftriaxone has been verified in Sweden [10].

In this report, we describe the trends from 2007 to 2011 for gonorrhoea, including antimicrobial resistance, and syphilis in Sweden, in order to identify recent changes in the epidemiology of the diseases and groups at risk.

Surveillance of gonorrhoea and syphilis in Sweden

The aetiologically based surveillance systems of the mandatorily reported gonorrhoea and syphilis in Sweden have been described elsewhere [5,6]. The gonorrhoea and syphilis case definitions used in Sweden are identical to those of the EU [11].

TABLE

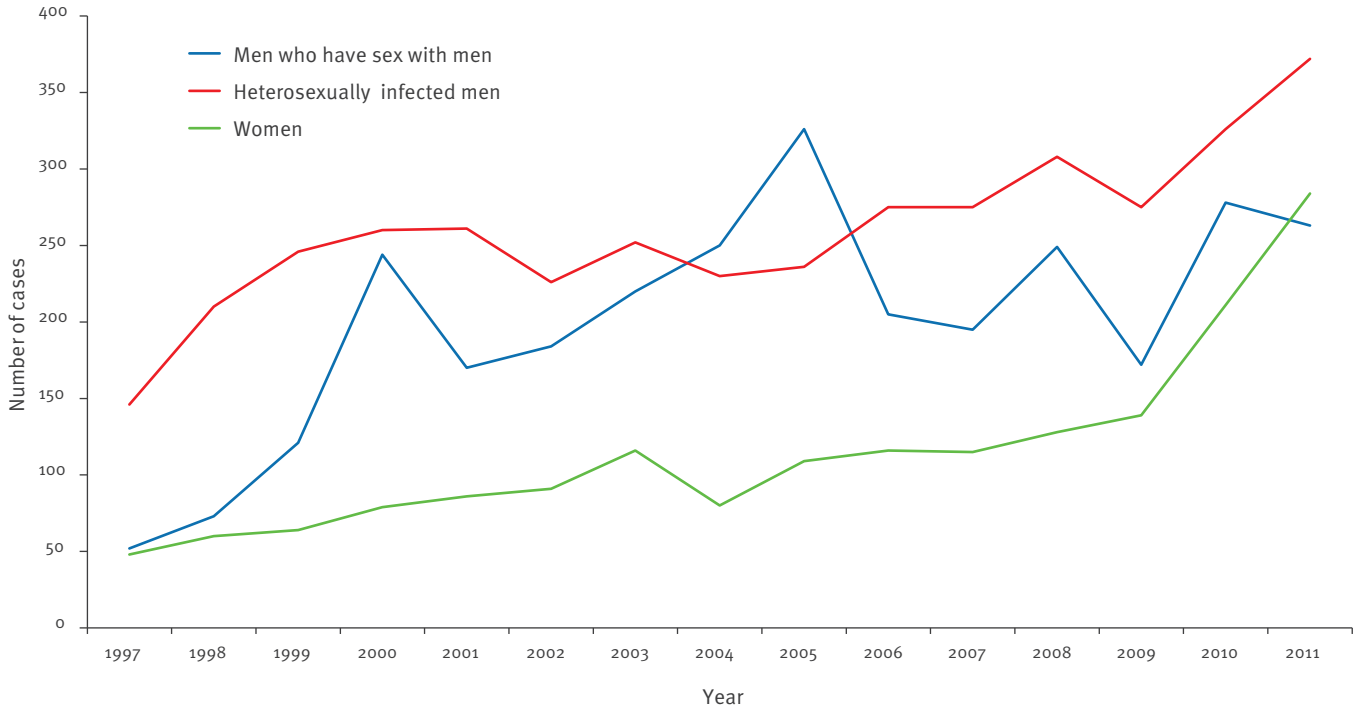
Trends in gonorrhoea and syphilis in Sweden, 2007 and 2011

Item	Gonorrhoea		Syphilis	
	2007	2011	2007	2011
Total number of cases	**642**	**951**	**239**	**206**
Total incidence (number of cases per 100,000 population)	7.1	10.0	2.6	2.2
Percentage of male cases among all cases	80%	69%	82%	82%
Percentage of MSM among all male cases	38%	40%	57%	66%
Percentage of adolescents and young adults of both sexes (aged 15–24 years) among all cases	34%	41%	8%	11%
Male-to-female case ratio	4.2:1	2.2:1	4.8:1	5.1:1
Percentage increase/decrease observed in heterosexual male cases in 2011 compared with 2007	+35%		−52%	
Percentage increase/decrease observed in MSM cases in 2011 compared with 2007	+35%		−1%	
Percentage increase/decrease observed in female cases in 2011 compared with 2007	+147%		−15%	

MSM: men who have sex with men.

Figure 1

Gonorrhoea cases by route of transmission, Sweden, 1997–2011 (n=8,626)[a]



[a] Cases with unknown or other transmission route were excluded (a total of 8,924 cases were reported during this time).

For this study, all reported cases were extracted from the national surveillance database SmiNet [12], which is maintained by the Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet. SMI). Surveillance data since 1997 are also presented as historical background of the gonorrhoea and syphilis incidences in Sweden. Population data for Sweden for the respective years were taken from Statistics Sweden [13].

Gonorrhoea in Sweden

From 2007 to 2011, the number of gonorrhoea cases increased by 48% (from 642 to 951 cases), reaching an incidence of 10.0 per 100,000 population in 2011 (Table). This increase was partly due to an increase (of 147%) in the number of cases among women (Figure 1). We also observed an increase of 35% in the number of cases among heterosexually infected men (Figure 1). The proportion of cases who were heterosexually infected men increased from 52% in 2007 to 57% in 2011, while the proportion of MSM among cases remained relatively stable (38–40%).

The increase among women was mostly observed in the age group 15–24 years, where the incidence increased by 154% (from 12.4 to 31.5 per 100,000 population) (Figure 2). During 2007 to 2011, a mean of 62% of all female cases was reported in this age group.

Among male cases, the largest increases were reported in the age groups 15–24 and 25–34 years (Figure 2), which constituted a mean of 30% and 34%, respectively, of all male cases during 2007 to 2011. During this time, the incidence increased by 31% (from 23.3 to 30.6 per 100,000 population) in men in the age group 15–24 years and by 23% (from 30.9 to 38.0 per 100,000 population) in men aged 25–34 years (Figure 2).

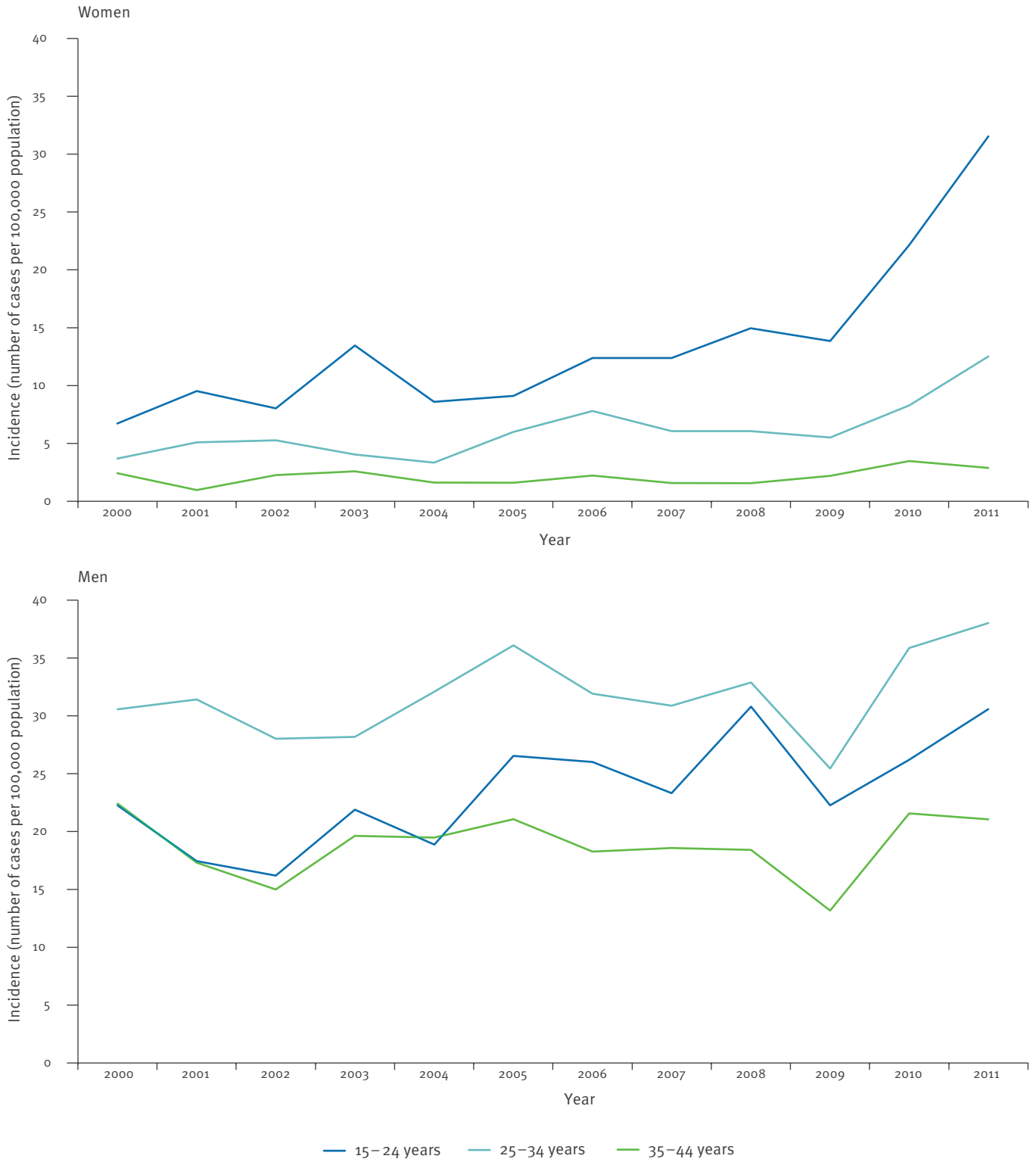
During 2007 to 2011, about 70% of all the cases became infected in Sweden: a mean of 74% of the 15–24 year-olds and 70% of the 25–34 year-olds. In the remaining age groups, more than a mean of 50% were infected abroad. Of all cases infected abroad, the countries where the infection was most commonly acquired were Thailand, Philippines, Spain, Denmark and Germany. Women and MSM were more frequently infected in Sweden (a mean of 79% and 80% of the respective cases) than heterosexually infected men (a mean of 50% of cases).

Neisseria gonorrhoeae resistance to antimicrobials

Resistance to the previous first-line antimicrobials for gonorrhoea treatment, ampicillin (24–44% of isolates were resistant) and ciprofloxacin (55–75%) remained high during 2007 to 2011. Azithromycin resistance ranged from 6% to 13% (11% in 2011). Decreased susceptibility or resistance to cefixime and ceftriaxone increased from less than 1% to 8% and 0%

Figure 2

Gonorrhoea incidence by sex and age group (from 15 to 44 years), Sweden, 2000–2011 (n=6,933)[a]



[a] Of the 7,908 cases reported during this time, 6,933 were aged 15–44 years.

to 2%, respectively. All isolates were susceptible to spectinomycin.

Syphilis in Sweden

From 2007 to 2011, the total incidence of syphilis showed a very minor decrease. However, due to the low number of cases and the large fluctuations in the number of cases annually (Figure 3), no clear trend in syphilis incidence could be observed. Thus the syphilis incidence, which started to increase in late-1990s, may now be stabilising. From 2007 to 2011, 172–277 cases were reported annually (incidence: 1.9–2.6 per 100,000 population) (Figure 3, Table). Most cases (a mean of 79%) were reported among men. A slight decrease (of 15%) in incidence among women has been observed since 2007. However, for women in age group 25–34 years, incidence increased particularly between 2009 and 2011 (by 94%). Among all female syphilis cases during 2007 to 2011, a mean of 41% were reported in this age group (25–34-years). In all other age groups, the incidence in women decreased during 2007–2011.

Among the male cases, the largest increase in incidence during the study period occurred between 2009 and 2011 and was mostly due to the increased incidences in the age groups 35–44 (4.5 to 9.3 per 100,000 population) and 55–64 years (2.5 to 3.8 per 100,000 population). From 2007 to 2011, of all male cases, those aged 25–34 years constituted a mean of 27% and those aged 35–44 years a mean of 31%.

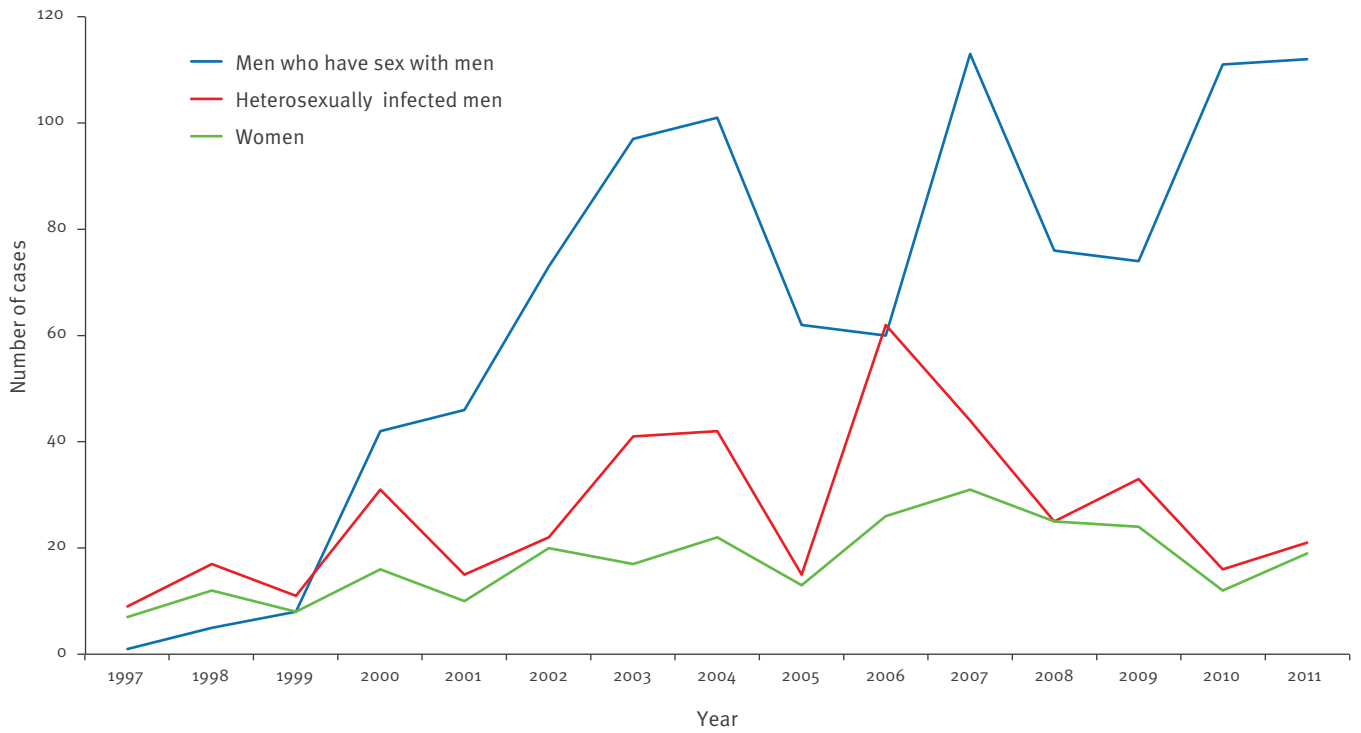
During 2007 to 2011, between 40% and 52% of all syphilis cases became infected in Sweden: a mean of 51% of the 15–24 year-olds and a mean of 51% of the 45–54 year-olds. In the remaining age groups, a mean of more than 50% were infected abroad. Of all cases infected abroad, the countries where the infection was most commonly acquired were Somalia, Iraq, Thailand, Germany and Denmark. Women and MSM were more frequently infected in Sweden (a mean of 45% and 67% of the respective cases) than heterosexually infected men (a mean of 34% of cases).

Discussion

The incidences of gonorrhoea and syphilis have been increasing since the mid/late-1990s in Sweden, as has also been observed in several other EU countries with well-functioning testing and surveillance systems [1-4]. However, the general trend in the EU, which contains many diverse countries, is a decline for both infections since the mid-2000s [14,15]. In Sweden, from 2007 to 2011 gonorrhoea incidence substantially increased among men (from both hetero- and homosexual transmission): in women, the increase was even more striking (Table). Observations of increased gonorrhoea (as well as syphilis) incidence in females and

Figure 3

Syphilis cases by route of transmission, Sweden, 1997–2011 (n=1,647)[a]



[a] Cases with unknown or other transmission route were excluded (a total of 2,078 cases were reported during this time).

males (heterosexually infected and MSM) have also been recently reported in some EU countries [1-3]. In Sweden, since the late 1990s, a general increase in syphilis incidence has been observed among hetero- and homosexual men, and women. However, from 2007 to 2011, the total incidence of syphilis showed a very minor decrease, but due to the low number of cases and the large variation in the number of cases annually, no clear trend could be determined. Nevertheless, the syphilis incidence in Sweden, which started to increase in late-1990s, may now be stabilising.

Many different factors might contribute to the divergent gonorrhoea and syphilis trends from 2007 to 2011 in Sweden. Firstly, the increase in risky sexual behaviour in young predominantly heterosexual individuals, such as increased number of sexual partners over time, increased number of new casual sexual partners, and low level of condom use with casual sexual partners [16,17], has presumably contributed to the increase in gonorrhoea in these highly sexually active young people. Gonorrhoea is also frequently imported from abroad by heterosexual men, which allows further spread of the infection domestically.

In these younger age groups of predominantly heterosexual individuals, syphilis remains relatively rare and does not have the same speed of spread, as it is mostly spreading among MSM in Sweden. In general, MSM are a group in which both gonorrhoea and syphilis are spread more easily due to more risky sexual behaviour such as unprotected anal intercourse, which makes them more prone to acquire STIs [5,18]. Some recent surveys among MSM in Sweden have demonstrated that an increased number of sexual partners during last year, unprotected anal intercourse during the last year, last sexual contact with a casual partner and sexual contact with an HIV-positive man are significantly associated with being diagnosed with chlamydia, gonorrhoea or syphilis during the last 12 months [18,19]. However, despite the large fluctuations in the exact number of cases annually among MSM in Sweden, the incidence of gonorrhoea and syphilis, which both started to increase in mid/late-1990s, may now be stabilising.

Other possible reasons for the observed trends is the increased awareness of healthcare workers in Sweden, which has contributed to increased uptake of testing, especially by young individuals being screened both for chlamydial infection and gonorrhoea [7] (an increasing number of youth health clinics in Sweden are offering screening for chlamydia infection and gonorrhoea from the same biological samples, using sensitive genetic tests for diagnosis). Syphilis testing is routinely only offered to new migrants, MSM, symptomatic patients, patients with unsafe sexual contacts with a syphilis-positive patient, and HIV-positive patients. The epidemiology of syphilis in Sweden is also substantially affected by importation of the infection as a result of syphilis-positive individuals migrating from countries with a higher syphilis prevalence than in Sweden, as well as importation of infection by Swedish travellers: this accounts for the large variation in reported cases annually [7].

The importation of gonorrhoea by heterosexually infected Swedish men, predominantly after travel in Asia, might also introduce multidrug-resistant *N. gonorrhoeae* strains (defined in reference 8) in Sweden. Treatment failures with cefixime have been verified in Norway [20], England [21], Austria [22], France [23] and Sweden (unpublished data). It is of concern that the first gonococcal strains with high-level resistance to ceftriaxone – the last remaining option for single antimicrobial empirical treatment of gonorrhoea – have been verified in Japan [24], France [23] and Spain [25]. In addition, ceftriaxone treatment failures of pharyngeal gonorrhoea have also been verified in Europe, in Sweden [10] and Slovenia [26]. In this emergent situation, the World Health Organization (WHO) has published a 'Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*' [27,28] and the European Centre for Disease Prevention and Control (ECDC) has launched a response plan for the European Union [29].

Continuous monitoring and thorough analysis of trends in sexually transmitted infections in general and in syphilis and gonorrhoea in particular, including antimicrobial resistance, should be maintained in order to identify risk groups involved in transmission of these infections. Ideally, this analysis should include denominators such as number of individuals tested (including also negative individuals) and diagnostic method (including specific tests) used. More knowledge is crucial to better understand the changing epidemiology of sexually transmitted infections and plan prevention activities to better target particular populations at risk.

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Rapid increase in gonorrhoea and syphilis diagnoses in England in 2011

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Citation style for this article:
Savage EJ, Marsh K, Duffell S, Ison CA, Zaman A, Hughes G. Rapid increase in gonorrhoea and syphilis diagnoses in England in 2011 . Euro Surveill. 2012;17(29):pii=20224. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20224

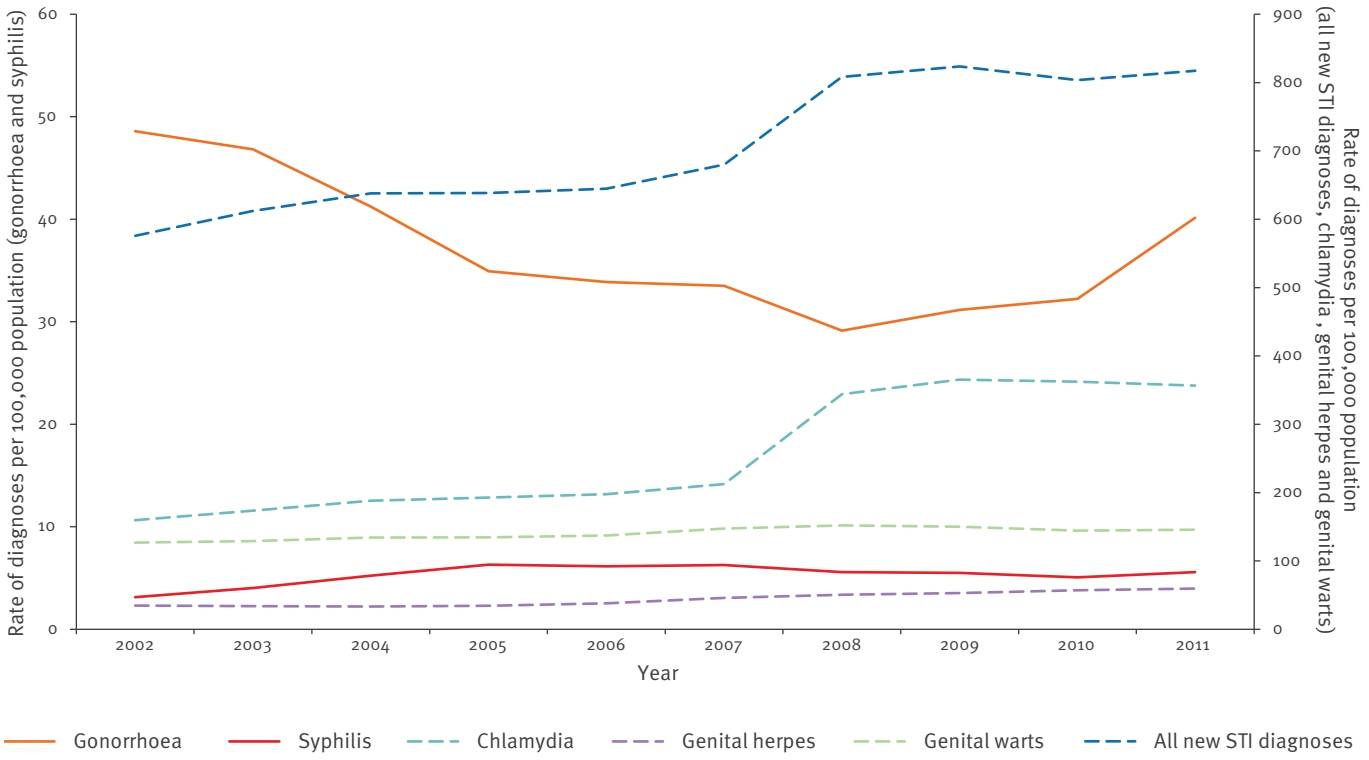
Article submitted on 13 July 2012 / published on 19 July 2012

There has been a rapid rise in the number of gonorrhoea and syphilis diagnoses in England during 2011, an increase of 25% and 10% respectively. Large increases of both gonorrhoea (61%) and syphilis (28%) were observed among men who have sex with men. Although these rises can partly be attributed to increased testing, ongoing high-levels of unsafe sexual behaviour probably contributed to the rise. The rise in gonorrhoea rates is worrying in an era of decreased susceptibility to treatments.

The number of new sexually transmitted infections (STIs) diagnosed in England during 2011 increased by 2% (419,773 to 426,867) from 2010. This rise in STIs followed a small decline in diagnoses seen in 2010 and is a return to the steady increase in STI diagnoses observed over the past decade. However, unlike previous years, in 2011 there was a particularly pronounced rise in the number of diagnoses of gonorrhoea (25%; 16,835 to 20,965) and infectious (primary, secondary and early latent) syphilis (10%; 2,650 to 2,915).

Figure 1

Rate of diagnoses per 100,000 population of selected sexually transmitted infections in England, 2002–2011



STI: sexually transmitted infection.

Source: Data from genitourinary medicine clinics; chlamydia data also include diagnoses made in the community. New STI diagnoses include chlamydia, gonorrhoea, syphilis (primary, secondary and early latent), genital herpes simplex (first episode), genital warts (first episode), non-specific genital infection/urethritis, chancroid, lymphogranuloma venerum (LGV), donovanosis, molluscum contagiosum, trichomoniasis, scabies, pediculus pubis, HIV new diagnoses, pelvic inflammatory disease (PID) and epididymitis (non-specific).

Only laboratory-confirmed diagnoses are reported. (Figure 1).

Surveillance of sexually transmitted infections in England

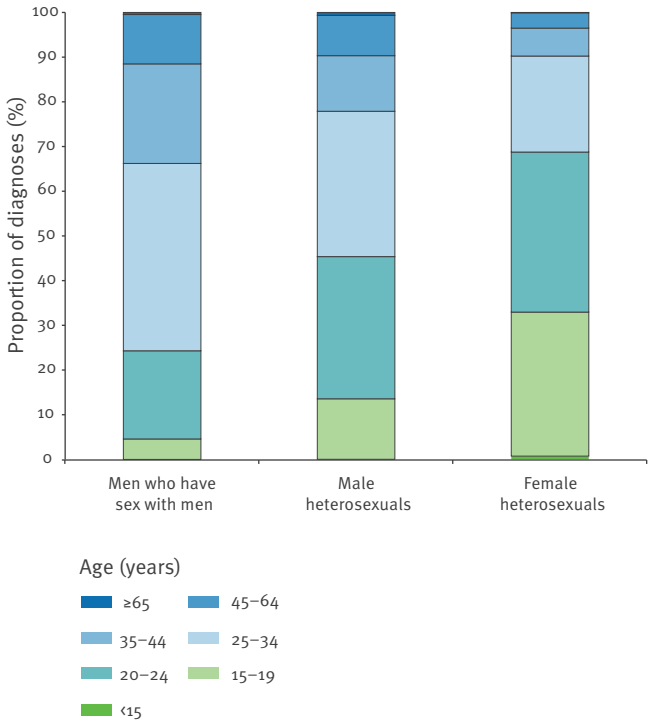
In England, all specialist sexual health clinics submit the mandatory Genitourinary Medicine Clinic Activity Dataset (GUMCAD) to the Health Protection Agency (HPA) every quarter. This dataset is an electronic pseudo-anonymised patient-level data return that contains information on all STI diagnoses made and services provided in the clinic (e.g. sexual health screening, HIV testing, hepatitis B vaccination and partner notification)along with patient demographic information (i.e. sexual orientation, age, sex, country of birth and patient-defined ethnicity, (based on national standard categories). GUMCAD is a new data return that started in 2009 and enables more detailed epidemiological analysis of STIs in England. Prior to GUMCAD, aggregated STI surveillance data were reported through a paper-based system. Data are also collected from community settings that carry out chlamydia screening as part of the National Chlamydia Screening Programme, which offers opportunistic chlamydia tests to people aged 15–24 years. The case definitions for gonorrhoea and syphilis are described in [1].

Trends in gonorrhoea

In 2011, gonorrhoea diagnoses increased by 25% with 20,965 cases reported (40.1 per 100,000 population). There were 14,992 male cases (58.2 per 100,000) and 5,972 female cases (22.6 per 100,000). Half of the male cases (7,487) were in men who have sex with men

Figure 2

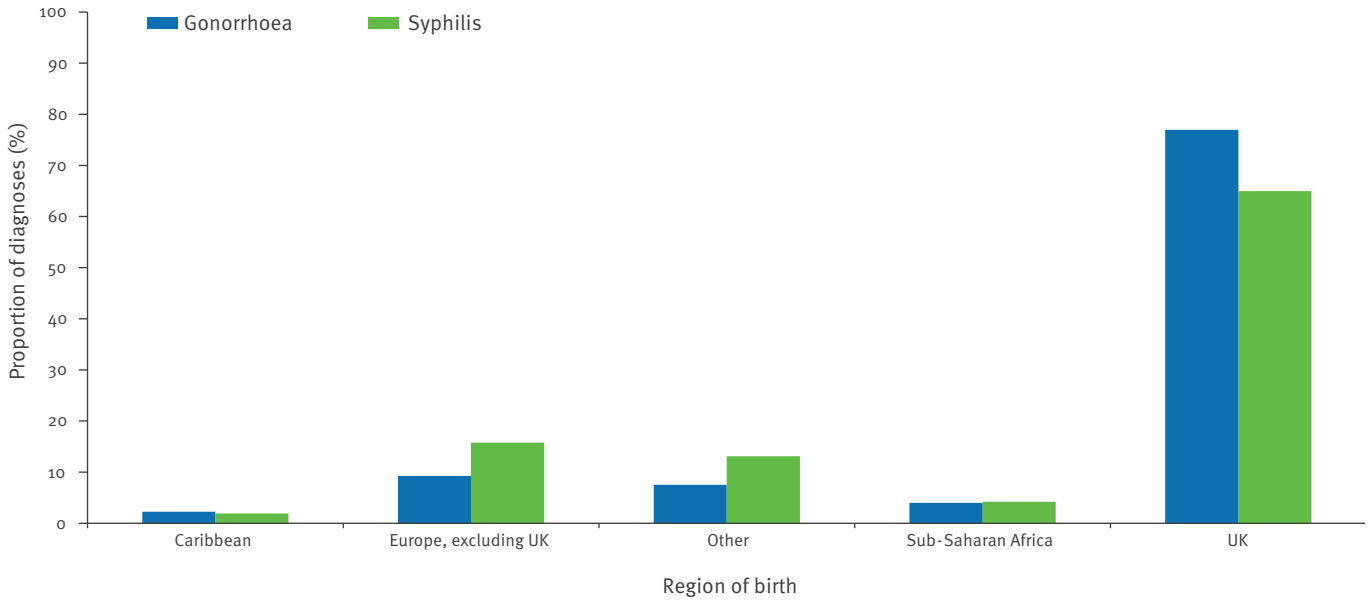
Proportion of gonorrhoea diagnoses in each age group by sexual orientation, England, 2011



Source: Genitourinary Medicine Clinic Activity Dataset (GUMCAD).

Figure 3

Proportion of gonorrhoea and syphilis diagnoses by region of birth, England, 2011



UK: United Kingdom.

Source: Genitourinary Medicine Clinic Activity Dataset (GUMCAD).

(MSM), among whom there was a substantial rise in diagnoses of 61% from 2010 (4,651 to 7,487). Among heterosexuals, 57% (6,678/11,778) of diagnoses were in those aged 15–24 years; however, in MSM, more diagnoses were reported in the older age groups, with 42% (3,128/7,487) of diagnoses in those aged 25–34 years (Figure 2). A total of 19% (1,389/7,487) of MSM diagnosed with gonorrhoea had previously been diagnosed with HIV infection.

For all gonorrhoea cases where country of birth was recorded, 77% (15,404/20,014) were born in the United Kingdom (UK) and 9% (n=1,854) were born elsewhere in Europe, primarily Italy (n=212), Poland (n=199), Spain (n=177), Ireland (n=173), France (n=169), Germany (n=127) and Portugal (n=101) and 4% were born in Sub-Saharan Africa (Figure 3). Rates of gonorrhoea were six times higher in those of black ethnicity compared with white ethnic groups.

A number of different factors will have contributed to the sharp increase in diagnoses particularly in MSM. Clinics are likely to have carried out more screening of extra-genital (rectal and pharyngeal) sites in MSM using nucleic acid amplification tests (NAATs) in response to new testing guidance [2] and the ongoing lymphogranuloma venerum (LGV) epidemic in England [3]. However, diagnoses among heterosexuals also increased by 14% in 2011 which cannot be attributed to changes in testing extra-genital samples, suggesting that there are continuing high levels of unsafe sexual behaviour among MSM and young adults in particular. The high rates of gonorrhoea infection are especially concerning given the backdrop of decreasing susceptibility to front-line antimicrobials seen in England [4] and across Europe [5] and the emergence of treatment failures [6-9].

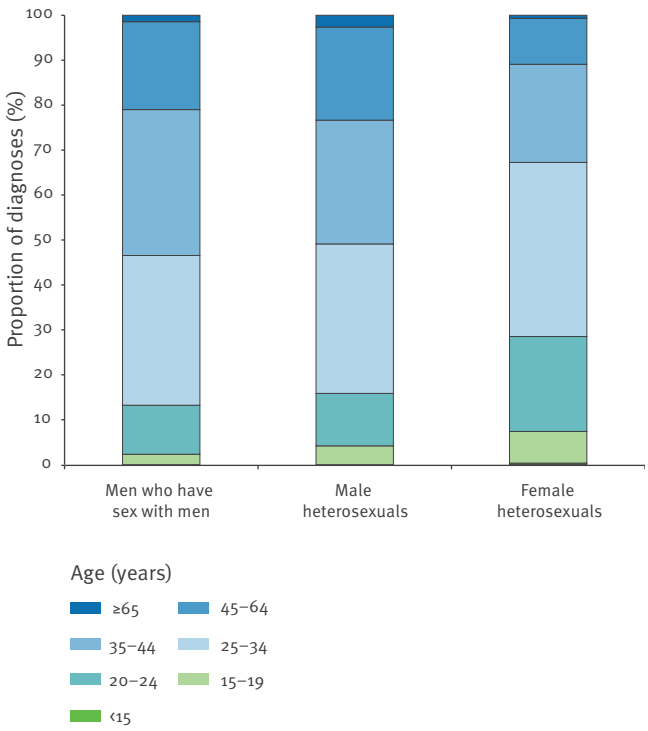
Trends in syphilis

Infectious syphilis diagnoses increased by 10% in 2011 with 2,915 cases reported (5.6 per 100,000 population). Rates of syphilis were nine times higher among men (10.2 per 100,000) than women (1.1 per 100,000 population). Syphilis continues to be predominantly seen in MSM, with 75% (1,955/2,622) of the male cases being in this group. Diagnoses among MSM rose by 28% (1,523 to 1,955) in 2011 but fell by 1% (749 to 739) among heterosexuals (Figure 4). Two thirds (1,283/1,955) of cases in MSM were in those aged 25–44 years. Almost a third (620/1,955) of MSM diagnosed with syphilis had previously been diagnosed with HIV infection.

For all syphilis cases where country of birth was recorded, 65% (1,789/2,753) were UK born and 16% (n=434) were born elsewhere in Europe, primarily Poland (n=59), Spain (n=50), France (n=43), Ireland (n=42), Italy (n=39) and Portugal (n=33). Just over 4% were born in Sub-Saharan Africa (Figure 3).

Figure 4

Proportion of syphilis diagnoses in each age group by sexual orientation, England, 2011



Source: Genitourinary Medicine Clinic Activity Dataset (GUMCAD).

Discussion

There was a large increase in the number of gonorrhoea and syphilis diagnoses reported in England during 2011. Of particular concern is the large rise in STIs observed in MSM. These rises can partly be attributed to increased STI screening and the testing of MSM for gonorrhoea and chlamydia at extra-genital sites and overall use of molecular testing for sexual health screens. However, the continuing LGV epidemic in England and outbreaks of other STIs such as shigellosis [10] suggests that ongoing high levels of unsafe sexual behaviour will have been an important factor behind the rise in diagnoses seen among MSM. People coinfected with HIV and other STIs are more likely to be infectious, facilitating HIV transmission [11] and in England, a considerable proportion of syphilis (32%), gonorrhoea (19%) and LGV (78%) cases in MSM were HIV positive. HIV-positive MSM diagnosed with gonorrhea are also more likely to report higher-risk sexual behaviours than HIV-negative MSM [4]. This suggests HIV sero-adaptive strategies may play an important role in STI transmission among MSM [12].

There is huge inequality in the distribution of gonorrhoea and syphilis across ethnic groups in England, with black ethnic minorities experiencing the highest rates of infection. This may be partly explained by higher levels of socio-economic deprivation although

other cultural influences on sexual behaviour may contribute [13,14].

Prevention efforts, such as greater STI screening coverage and easy access to sexual health services, need to be sustained and continue to focus on the groups at highest risk. Health promotion and education to increase public awareness and encourage safer sexual behaviour such as consistent condom use with all new and casual sexual partners remain vital in preventing STIs. This is of particular importance given the backdrop of emerging decreased susceptiblity to gonorrhoea treatments and the publication of both a European response plan [15] and global action plan [16]. The HPA recommends that MSM having unprotected sex with casual or new partners should have an HIV/STI screen at least annually, and every three months if changing partners regularly [17].

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Syphilis and the Internet

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Citation style for this article:
Noll-Hussong M. Syphilis and the Internet. Euro Surveill. 2012;17(33):pii=20249. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20249

Article submitted on 14 August 2012 / published on 16 August 2012

To the editor:

Based on surveillance data generated from national laboratory findings collected by the Robert Koch Institute, Bremer et al. [1] demonstrated that there was an increase in the incidence of syphilis in Germany in 2011. In their article, the authors focused on the persuasive power of traditional microbiologically-confirmed data. However, a recently evolving 'social' surveillance tool could also be considered: Internet search engine analytics.

The power of search engine analytics to detect infectious diseases (e.g. influenza) has been demonstrated [2], and it would make sense that this tool would be useful in the surveillance of other contagious diseases [3], especially sexually transmitted infections (STI). The ongoing stigmatisation of STIs, the perceived anonymity of Internet usage, and last but not least, the habits of the primary risk group, i.e. men who have sex with men (MSM) [4], who utilise the Internet to find sexual partners, makes it seem obvious that many individuals, when recognising new suspect symptoms, will first and foremost use information provided on the Internet, which is easily accessible via search engines. Indeed, and despite the inherent problems with Internet-based digital data retrieval [5], the interest for syphilis over time, in terms of web searches, can be for example investigated with Google Insights for Search (http://www.google.com/insights/search/) by enquiring on the search term 'syphilis', in Germany from 2004 to present, within the category 'Sexually Transmitted Diseases'. This allows graphical visualisation of the level of interest for 'syphilis' relative to that for ´Sexually Transmitted Diseases´ over this period in Germany. An increase in the searches for 'syphilis' relative to 'Sexually Transmitted Diseases´ can be observed from mid-2010.

Because, for example, various efforts to establish an effective partner notification system for syphilis patients have had differing levels of success, new methods for limiting or preventing the spread of syphilis should be developed, and these new methods should take into consideration the habits and reachability of young males in the 21st century. For example, when a person searches for the selected term, the top search results can be presented in the form of suggestions for counselling or therapy using the search patterns that Google computes for each of its search engine users for marketing purposes. In this scenario, these patterns would not be used for marketing but to promote health.

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Epidemiology of *Chlamydia trachomatis* endocervical infection in a previously unscreened population in Rome, Italy, 2000 to 2009

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Citation style for this article:
Marcone V, Recine N, Gallinelli C, Nicosia R, Lichtner M, Degener AM, Chiarini F, Calzolari E, Vullo V. Epidemiology of *Chlamydia trachomatis* endocervical infection in a previously unscreened population in Rome, Italy, 2000 to 2009 . Euro Surveill. 2012;17(25):pii=20203. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20203

Article submitted on 07 October 2011 / published on 21 June 2012

As reliable data on *Chlamydia trachomatis* infection in Italy are lacking and as there is no Italian screening policy, epidemiological analyses are needed to optimise effective strategies for surveillance of the infection in the country. We collected data from 6,969 sexually active women aged 15 to 55 years who underwent testing for endocervical *C. trachomatis* infection at the Cervico-Vaginal Pathology Unit in the Department of Gynaecology and Obstetrics of Sapienza University in Rome between 2000 and 2009. The mean prevalence of *C. trachomatis* endocervical infection during this period was 5.2%. Prevalence over time did not show a linear trend. Univariate analysis demonstrated a significant association of infection with multiple lifetime sexual partners, younger age (<40 years), never having been pregnant, smoking, use of oral contraceptives, and human papillomavirus and *Trichomonas vaginalis* infections. Multivariate stepwise logistic regression showed that *T. vaginalis* infection, age under 20 years and more than one lifetime sexual partner remained significantly associated with *C. trachomatis* infection in the final model. Prevalence of *C. trachomatis* in this study was high, even among women aged 25–39 years (5.1%): our data would suggest that a *C. trachomatis* screening policy in Italy is warranted, which could lead to a more extensive testing strategy.

Introduction

Chlamydia trachomatis endocervical/urethral infection, caused by serotypes D to K is the most common bacterial, treatable sexually transmitted infection worldwide [1,2]. As up to 80% of cases are asymptomatic, *C. trachomatis* can be spread unknowingly and remains largely undiagnosed [1,2]. The prevalence of the infection in Europe varies according to the population, setting, country, resource allocation for surveillance and prevention and national reporting system, if there is one. A systematic review of *C. trachomatis* infection among asymptomatic unscreened European women showed that the prevalence ranged from 1.7% (among women aged 15–40 years in the United Kingdom in the mid-1990s) to 17% (among women aged 15–55 years in France in the late 1980s) and was more than 5% in the majority of the countries examined [3,4]. More recently the European Centre for Disease Prevention and Control (ECDC) described surveys from seven countries, estimating a population prevalence of 1.4–3.0% in people aged 18–44 years [5]. They also reported that overall trends over time across Europe appeared to be increasing, from 1990 to 2009, although data were not available from Bulgaria, Czech Republic, France, Germany, Italy, Liechtenstein and Portugal [6]. Moreover, the organisation of the control of *C. trachomatis* infection varied widely, with many countries having no organised activities until 2009 [7].

Pelvic inflammatory disease, tubal sterility or infertility, newborn eye infection or pneumonia and, although controversial, sperm pathology, male sterility and spontaneous abortion or preterm labour, are well-known complications of untreated *C. trachomatis* infection [8-14].

Since treating complications is costly in both psychosocial and financial terms, and is often unsuccessful [15], screening is critical for the early detection and treatment of uncomplicated *C. trachomatis* infection, the control of the overall prevalence of the infection in the population and thus the reduction of transmission and finally for the reduction of treatment costs.

C. trachomatis screening programmes exist in only two European countries (England and the Netherlands) and in the United States: they are opportunistic or pro-active and are mostly directed at young women aged under 25 years [7,16]. Sweden, although lacking

nationally organised screening programmes, is the first country in the world to offer testing for *C. trachomatis* infection, treatment and partner notification – all free of charge – throughout the country. It is also the first to have a national diagnostic and reporting system [5]. In these four countries, after substantial decreases in complication rates of *C. trachomatis* infection at the end of the 1980s and early 1990s, further decreases in pelvic inflammatory disease and ectopic pregnancy rates after 2000 were observed [7,16-20].

Unfortunately, reliable and recent data concerning *C. trachomatis* control in Italy are lacking, except for those in studies such as that of the Italian MEGIC Group (Multicentre Epidemiology Group for Investigation of Chlamydia trachomatis) that reported a prevalence of *C. trachomatis* infection of 3.9% among 1,321 asymptomatic women [21] or that of the STD Surveillance Working Group, which described 809 female incident cases from mainly dermatology and venereology departments and a few gynaecological departments between 1991 and 1996 [22].

There is no screening policy for *C. trachomatis* infection in Italy. A national women's health report released in 2008 suggested for the first time that women should be tested for *C. trachomatis* when they have their first cervical smear test [23]. In order to understand if a screening strategy would be appropriate, the prevalence of the infection needs to be ascertained and there needs to be a preliminary analysis of the epidemiological variables in the population at risk, as well as a surveillance network. No existing epidemiological model can be applied to a different population without analysis and adjustment. New, larger epidemiological analyses are therefore needed in Italy to plan specific and effective strategies for the surveillance and screening of *C. trachomatis* infection in the country.

The purpose of this study was to investigate the prevalence of *C. trachomatis* endocervical infection and its determinants in a large population of sexually active women aged 15–55 years attending an outpatient service of a cervico-vaginal pathology unit in Rome over a 10-year period.

Methods

Patient population

Between January 2000 and December 2009, a total of 7,620 women (aged 13–58 years) attending the outpatient service of the Cervico-Vaginal Pathology Unit in the Department of Gynaecology and Obstetrics of Sapienza University in Rome were examined for genitourinary symptoms or routine gynaecological examination.

A team of gynaecologists collected socio-demographic and behavioural data, as well as clinical data, for each woman during this time, using our model of clinical record taking for sexually transmitted infections – a structured questionnaire. The data were archived as digital files.

The self-administered, structured, paper questionnaire comprised 25 questions on socio-demographic characteristics, sexual behaviour, reproductive history, and tobacco, alcohol and drug use.

Testing for *C. trachomatis* infection, along with testing for human papillomavirus (HPV) and N. gonorrhoeae infection and vaginal wet mount examination, was offered to all sexually active women presenting to the Unit.

Women who refused to be tested for *C. trachomatis* and/or to answer the questionnaire and/or were not sexually active were excluded from the study (n=651).

According to these criteria, a total of 6,969 sexually active women aged 15–55 years who were tested for cervical *C. trachomatis* infection were enrolled. The women were categorised as symptomatic if they presented with either dysuria or pelvic pain or both (symptoms typical of *C. trachomatis* infection). Women not exhibiting either of these symptoms were classified as asymptomatic. They were then further categorised according to whether they were seeking care for family planning, infertility routine gynaecological examination or matters related to pregnancy.

All participating women gave written informed consent. The research was carried out in compliance with the Declaration of Helsinki [24] and was approved by the local ethics committee (reference number 148/11, 2022). Data were stored and managed according to Italian privacy rules [25].

Examinations performed

On a scheduled visit, during the gynaecological examination, an unmoistened sterile speculum was inserted into vagina, so that vaginal walls, fornices and cervix could be evaluated for any erythema and colour and viscosity of any discharge. The pH of the vaginal walls was measured using colorimetric paper. For wet mount examinations, vaginal fluor samples were collected from lateral fornices by a wooden Ayre's spatula, mixed first with saline and then with 10% potassium hydroxide, on two different slides, and immediately observed under a phase contrast microscope [26].

A 'whiff test' using 10% potassium hydroxide was performed for each sample in order to detect abnormal amine production by anaerobes [27].

Wet mount examination allowed the vaginal microflora (predominance of lactobacillary morphotypes) to be assessed and *Trichomonas vaginalis* to be detected (in order to investigate coexisting sexually transmitted infections). In addition, we also looked for bacterial vaginosis-associated clue cells, aerobic

vaginitis-associated pleomorphic bacteria, yeasts and white blood cells.

Samples were taken from the endocervix for detection of *C. trachomatis* and from the ecto-endocervix for detection of HPV DNA, as described below.

Detection of microorganisms

Chlamydia trachomatis

Endocervical swabs were tested for the presence of *C. trachomatis* using the BD ProbeTec ET System (Becton, Dickinson and Company, United States). These assays amplify *C. trachomatis* DNA in separate wells and monitor inhibition of amplification for each specimen using strand displacement amplification and detection by fluorescent energy transfer probes, producing a method-other-than-acceleration (MOTA) score for each specimen The original algorithm involved retesting specimens with MOTA scores between 2000 and 9999. A negative repeat result (MOTA score ‹2000) was considered indeterminate [28].

Human papillomavirus

DNA was extracted from cervical samples using QIAampTissue Kit (Qiagen, Italy) and then genotyped by sequencing a 450-base pair fragment amplified from the L1 region of HPV DNA [29]. Sequence homology was determined using BLAST and ClustalW programs.

Neisseria gonorrhoeae

Identification of *N. gonorrhoeae* was carried out by growth on media selective for pathogenic *Neisseria* species (Oxoid) incubated for up to 48 hours in 5–10% CO_2 at 35–37 °C. Colonies obtained were identified by API NH (bioMérieux) [30].

Statistical analysis

The chi-square test was used to analyse contingency tables; the t-test was used to compare means and odds ratios (ORs), with 95% confidence intervals (CIs), in order to measure the strength of association between *C. trachomatis* infection and behavioural and clinical characteristics and age.

We used the Cochran–Armitage test to assess the possibility of a linear trend in the observed patterns for number of lifetime sexual partners and increasing age.

Statistical tests were considered significant if p was 0.05 or less. A stepwise backward logistic regression analysis, entering the variables significantly associated with *C. trachomatis* infection, was used to assess the effect of more than one variable at a time and to identify possible confounding factors in the range of test values under consideration. Statistical analysis was performed using SPSS version 18.0.

Results

A total of 366 (5.2%) of the 6,969 women sexually active women enrolled in the study tested positive for *C. trachomatis* endocervical infection (Table 1).

Prevalence of *C. trachomatis* infection by year is shown in the Figure: the p value for the chi-square statistic was not statistically significant (p=0.938) (the chi-square test for the resulting 2×10 contingency table tested the null hypothesis of no association against the alternative hypothesis of an association of some sort). Thus prevalence and time appeared not to be associated and were not expected to have a linear correlation over the study period.

A total of 4,620 (66%) of the women were asymptomatic for *C. trachomatis* infection: 256 (5.5%) of them tested positive. This prevalence was slightly higher than that in the 2,349 symptomatic women (4.7%), but the difference was not statistically significant (p=0.1289). Of the 366 women who were positive for *C. trachomatis* infection, 256 (70%) were asymptomatic.

Prevalence was also slightly higher among women without clinical signs of infection (238/4,328; 5.5% compared with those with signs (128/2,641; 4.8%), but this difference was also not statistically significant (p=0.2362).

Univariate analysis of sexual and reproductive history and of age (Tables 1 and 2) highlighted a significant association of *C. trachomatis* infection with age under 40 years, having never been pregnant, smoking, use of oral contraceptives and multiple lifetime sexual partners: women with two to four partners had a slightly higher risk of infection (in comparison with women who had had one partner); women with five to nine partners had double the risk; having had more than nine partners was linked to a threefold higher risk. The p value for the Cochran–Armitage test (p‹0.0001) suggested an underlying positive linear trend between number of lifetime sexual partners and prevalence of infection.

Comparison of the prevalence of *C. trachomatis* infection in stratified age groups with that in women over 49 years of age showed that teenage women aged 15–19 years had the highest increased risk of infection (OR: 4.55 (95% CI: 1.90–10.89); p=0.0002) and that the odds ratios for the remaining strata declined with increasing age. The p value for the Cochran–Armitage test (p‹0.0001) suggested an underlying negative linear trend between age and prevalence of infection.

Further univariate analysis showed that the prevalence of the infection was similar (no statistical significance) whatever the reason for seeking care (Table 2). Condom use was not found to be associated with *C. trachomatis* infection.

The frequency of *C. trachomatis* infection was significantly higher among patients who were also infected

with HPV (OR: 5.50 (95% CI: 4.39–6.89)) and *T. vaginalis* (OR: 4.97 (95% CI: 2.57–9.59)) (Table 3).

Multivariate stepwise logistic regression analysis shows that after backwards elimination, *T. vaginalis* infection (OR: 3.23 (95% CI: 1.61–6.46); p=0.001), age 15–19 years (OR: 2.33 (95% CI: 1.02–5.31); p=0.04) and more than one lifetime sexual partner (OR: 1.50 (95% CI: 1.21–1.87); p=0.000) remained significantly associated with *C. trachomatis* infection in the final model.

We found no cases of gonorrhoea among the first thousand patients referred to the clinic and systematically screened. We then tested *C. trachomatis*-positive cases only, if they showed symptoms or signs of cervicitis: none were positive for *N. gonorrhoeae*.

Discussion

To the best of our knowledge, this is the first study reporting on the epidemiology of *C. trachomatis* infection in Italy in a large sample of a diverse group of women over a long period of time. The mean prevalence of the infection was high (5.2 %) and showed no linear trend over time. The prevalence in asymptomatic women was higher than that observed in 1990 by the MEGIC group (5.5% vs 3.9%, respectively) [21]. In symptomatic women and in those seeking care for infertility the prevalence in our study (4.7% and 4.9% respectively) was similar to that reported by the same group (5.0% and 5.4%, respectively) [21]. These findings may reflect the lack of control and screening activities in Italy.

We also found a high prevalence of *C. trachomatis* infection in pregnant women (5.3%), i.e. those seeking obstetric care (Table 2) which has not been described in Italy and suggests we should consider screening in pregnancy according to CDC guidelines [16]. This strategy could also reduce the rate of obstetric complications due to *C. trachomatis* infection.

Two of the variables independently associated with *C. trachomatis* infection in our study, younger age and multiple lifetime sexual partners (particularly more

Table 1

Univariate analysis of age and sexual and reproductive history of women tested for *Chlamydia trachomatis* infection, Cervico-Vaginal Pathology Unit, Sapienza University, Rome, Italy, 2000–2009 (n=6,969)

Characteristic	Tested for *C. trachomatis* endocervical infection			Odds ratio[a] (95% CI)	P value (t-test statistic)[b]
	Number positive (%)[a]	Number negative[a]	**Total[a]**		
Mean age in years					
15–19	9 (10.8)	74	**83**	4.55 (1.90–10.89)	0.0002
20–24	71 (7.8)	835	**906**	3.18 (1.78–5.70)	0.0000
25–29	86 (5.6)	1,441	**1,527**	2.23 (1.26–3.96)	0.0049
30–34	84 (5.2)	1,519	**1,603**	2.07 (1.17–3.68)	0.0113
35–39	61 (5.1)	1,125	**1,186**	2.03 (1.12–3.66)	0.0166
40–44	29 (4.2)	656	**685**	1.65 (0.87–3.16)	0.1242[c]
45–49	12 (2.7)	429	**441**	1.05 (0.48–2.29)	0.9084[c]
≥50–55	14 (2.6)	524	**538**	1 Reference	–
Mean age per category	32.0 years	34.4 years	**33.2 years**	Difference (those positive vs those negative): −2.4	0.001 (t=−4.610)
Number of lifetime sexual partners					
1	89 (3.4)	2,508	**2,597**	1 Reference	–
2	71 (5.6)	1,191	**1,262**	1.68 (1.22–2.31)	0.0013
3	57 (5.1)	1,063	**1,120**	1.51 (1.08–2.12)	0.0167
4	41 (5.5)	702	**743**	1.65 (1.13–2.40)	0.0094
5–9	54 (7.9)	626	**680**	2.43 (1.71–3.45)	0.0000
≥10	54 (9.5)	513	**567**	2.97 (2.09–4.21)	0.0000
Mean number of lifetime sexual partners per category	2.9	1.7	**2.3**	Difference (those positive vs those negative): 1.2	0.02 (t=2.518)
Ever been pregnant					
Yes	115 (3.8)	2,896	**3,011**	1 Reference	–
No	251 (6.3)	3,707	**3,958**	1.71 (1.36–2.14)	0.0000
Total	**366 (5.2)**	**6,603**	**6,969**	–	–

CI: confidence interval.

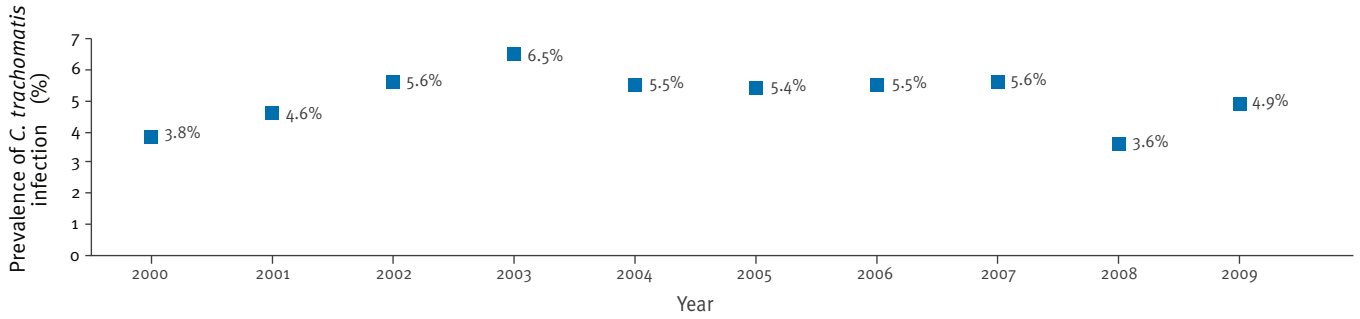
[a] Unless otherwise indicated.

[b] Where relevant. The t-test compares the mean values for women who tested positive for *C. trachomatis* and those who were negative.

[c] Not statistically significant.

Figure

Prevalence of *Chlamydia trachomatis* infection in women tested at the Cervico-Vaginal Pathology Unit, Sapienza University, Rome, Italy, 2000–2009 (n=6,969)



The overall chi-square statistic was 6.255 (the chi-square test for the resulting 2×10 contingency table tested the null hypothesis of no association against the alternative hypothesis of an association of some sort). The p value for the chi-square statistic (p=0.938) was not statistically significant.

Table 2

Univariate analysis of reasons for seeking care, clinical features, contraceptive use and smoker status of 6,969 women attending as outpatients the Cervico-Vaginal Pathology Unit, Sapienza University, Rome, Italy, 2000–2009

Characteristic	Tested for *Chlamydia trachomatis* infection			Odds ratio (95% CI)	P value
	Number positive (%)	Number negative	**Total**		
Reason for seeking care					
Gynaecological	207 (5.3)	3,666	**3,873**	1 Reference	–
Infertility	68 (4.9)	1,331	**1,399**	0.90 (0.68–1.20)	0.4852[a]
Obstetrics	50 (5.3)	889	**939**	1.00 (0.73–1.37)	0.9806[a]
Family planning	41 (5.4)	717	**758**	1.01 (0.72–1.43)	0.9427[a]
Symptoms of *C. trachomatis* infection[c]					
Yes	110 (4.7)	2,239	**2,349**	1.19 (0.95–1.50)	0.1289[a]
No	256 (5.5)	4,364	**4,620**	1 Reference	–
Signs of *C. trachomatis* infection[d]					
Yes	128 (4.8)	2,513	**2,641**	1.14 (0.92–1.42)	0.2362[a]
No	238 (5.5)	4,090	**4,328**	1 Reference	–
Contraceptive use					
None	269 (5.1)	5,025	**5,294**	1 Reference	–
Oral contraceptives	43 (7.3)	546	**589**	1.47 (1.05–2.05)	0.0226
Intrauterine device	20 (5.1)	372	**392**	1.00 (0.63–1,60)	0.9856[a]
Condoms	34 (4.9)	660	**694**	0.96 (0.67–1.39)	0.8370[a]
Smoker					
Yes	120 (6.1)	1,838	**1,958**	1.26 (1.01–1.58)	0.0402
No	246 (4.9)	4,765	**5,011**	1 Reference	–
Total	**366 (5.2)**	**6,603**	**6,969**	–	–

CI: confidence interval.

[a] Not statistically significant.

[b] Dysuria or pelvic pain.

[c] Cervical erythema, inflammation or discharge.

than five), have also been highlighted by research groups worldwide in various populations [7,16,31]. We found that the highest prevalence of infection (10.8%) was associated with a nearly fivefold increased risk of infection (as an independent factor, it showed a two-fold increased risk) in women aged 15–19 years.

Before 2008, *C. trachomatis* control activities in Italy consisted of case management in dermatovenereology clinics with Chlamydia testing for symptomatic people only [7]. C trachomatis testing is currently recommended for women at the time of their first cervical smear test, which takes place when women are 25 years of age in Italy. To the best of our knowledge, no report on the uptake and results of this testing recommendation is yet available. However, our data suggest that women aged under 25 years, and in particular those under 20 years, would be the core population of a good testing policy and a hypothetical *C. trachomatis* screening programme, as in other screening programmes worldwide [7,16]. Thus, the current Italian policy could be ineffective. The high prevalence of infection observed until the age of 40 years – which is a novel aspect of our findings – could also lead to a more extensive testing strategy. Although being aged 25–39 years was not an independent risk factor for infection, our data suggest that older women should also be tested.

Furthermore, as prevalence in women with signs or symptoms of infection did not differ statistically from that in women with no signs or symptoms in this study, case management appears to be an insufficient Chlamydia control activity.

The prevalence of infection among women seeking care for family planning was also high (5.4%): despite the low number of women in our study who sought advice for family planning, given the high number of women who usually attend this type of service and their young age, we suggest that family planning clinics could be sentinel for *Chlamydia* surveillance or an appropriate setting for *Chlamydia* opportunistic screening.

Our data also show that having HPV or *T. vaginalis* infection was associated with a fivefold higher risk of *C. trachomatis* coinfection, as expected in groups at higher risk as a result of age and behaviour [32,33]. In our logistic regression, HPV was not significantly associated with *C. trachomatis* infection, suggesting that age and multiple partners could be possible confounding factors, while *T. vaginalis* infection was an independent risk factor for *C. trachomatis* infection. It is possible that severe inflammation of the cervix due to *T. vaginalis* infection may make the cervix more susceptible to *C. trachomatis* infection. It could therefore be suggested that patients diagnosed with *T. vaginalis* infection should be tested for *C. trachomatis* or even given treatment for *C. trachomatis* infection without being tested, as proposed by Lo et al. [33].

Data on *N. gonorrhoeae* and *C. trachomatis* coinfection in Italy are limited, but our findings on *N. gonorrhoeae* seem to be consistent with those reported in 1998 by a dermatovenereology network, which found that fewer than 1% the infections in 44,438 individuals with sexually transmitted infections were *N. gonorrhoeae* cervical infections [22].

We also found a statistical association of *C. trachomatis* infection with absence of previous pregnancies, use of oral contraceptives and smoking. However, as they were not shown to be statistically associated with infection in the logistic regression final model, age, having multiple lifetime sexual partners and *T. vaginalis* infection are likely to be confounders, in contrast to the findings of others [34-36].

The lack of statistical association between *C. trachomatis* infection and condom use (as a protective factor) is unexpected, given the findings of others [21,37]. This could be considered a result of incorrect condom use and lack of health education. It could also be that some of the women were not entirely truthful when providing details of the type of contraception they used. There are probably some methodological limitations in the epidemiological study of condom effectiveness in

Table 3

Univariate analysis of other sexually transmitted infections in 6,969 women attending as outpatients the Cervico-Vaginal Pathology Unit, Sapienza University, Rome, Italy, 2000–2009

Other sexually transmitted organisms detected	Tested for *Chlamydia trachomatis* infection			Odds ratio (95% CI)	P value
	Number positive (%)	Number negative	**Total**		
Trichomonas vaginalis or HPV[a]	145 (16.9)	714	**859**	5.41 (4.33–6.77)	0.0000
Trichomonas vaginalis	11 (15.7)	59	**70**	4.97 (2.57–9.59)	0.0000
HPV	142 (17.1)	688	**830**	5.50 (4.39–6.89)	0.0000
Neither *Trichomonas vaginalis* nor HPV	221 (3.6)	5,889	**6,110**	1 Reference	–
Total	**366 (5.2)**	**6,603**	**6,969**	–	–

CI: confidence interval; HPV: human papillomavirus.

[a] Women coinfected with *T. vaginalis* and HPV (n=41) are not included.

preventing *C. trachomatis* infection, as has been highlighted by Warner et al. [37].

A new *C. trachomatis* variant was detected in 2006 following an unexpected 25% decrease in the number of infections in a Swedish county [38,39]. As we used the Becton Dickinson ProbeTec – which detects the new variant – the presence or absence of the variant in Italy has no impact on our prevalence data. However, as no data are available on the type and distribution of *C. trachomatis* diagnostic methods used in Italy, nor on whether this variant is present among Italian women, surveillance is also needed to provide such information.

In conclusion, the prevalence and determinants of *C. trachomatis* infection observed in this study seem to highlight the need for a focus on control activities in Italy, with special attention to standardisation of diagnostic tests and women aged under 25 years, who would be the core population of a screening programme.

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Identification of *Neisseria gonorrhoeae* isolates with a recombinant *porA* gene in Scotland, United Kingdom, 2010 to 2011

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Citation style for this article:
Eastick K, Winter A, Jamdar S. Identification of Neisseria gonorrhoeae isolates with a recombinant porA gene in Scotland, United Kingdom, 2010 to 2011. Euro Surveill. 2012;17(9):pii=20101. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20101

Article published on 1 March 2012

Three isolates of *Neisseria gonorrhoeae* have been identified in Scotland in 2010 and 2011, which lack sequences in the *porA* pseudogene commonly used as the target for confirmatory gonorrhoea polymerase chain reaction assays. Two isolates were clustered temporally and geographically and have the same sequence type and *porA* sequence. A similar strain was reported in Australia during early 2011. The other Scottish isolate was identified separately and is different in sequence type and *porA* sequence.

Introduction

We report three isolates of two different *Neisseria gonorrhoeae* multi-antigen sequence typing (NG-MAST) types in Scotland in 2010–2011 which lack the oligonucleotide binding sites for a *porA* polymerase chain reaction (PCR) in common use as a confirmatory assay for *N. gonorrhoeae* [1].

Nucleic acid amplification tests (NAATs) for *N. gonorrhoeae* are increasingly used in screening and diagnosis of gonorrhoea. They have a number of advantages over culture, particularly increased sensitivity when used on non-invasive and extra-genital specimens and where rapid transport of the specimen to the laboratory is not possible. However, concerns about the specificity of commercially-available NAATs have led to widespread recommendations for the confirmatory testing of reactive specimens [2,3]. This should be performed using a NAAT amplifying a different gene target to the original test.

In Scotland, specimens positive for *N. gonorrhoeae* by NAAT may be referred to the Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL) for confirmation. In addition, all *N. gonorrhoeae* isolates and those NAAT specimens confirmed locally are referred to SBSTIRL for typing by NG-MAST [4] and antimicrobial susceptibility testing (isolates only). Isolates are stored indefinitely on Microbank beads (Pro-Lab).

Confirmatory *N. gonorrhoeae* NAAT testing at SBSTIRL is performed using a real-time PCR targeting the *porA* pseudogene [1] with an internal inhibition control [5]. Specimens producing indeterminate or negative results are generally tested using Aptima GC (Gen-Probe). However, some referred specimens are insufficient in volume for Aptima GC or are in an incompatible transport medium [6].

In May 2011, two isolates of *N. gonorrhoeae* from the same patient, which harboured a recombinant *porA* gene were reported in Australia [7]. These isolates were NG-MAST type 5377, and were not amplifiable using the PCR primers used also by SBSTIRL.

Patients and isolates

In October 2011, a rectal *N. gonorrhoeae* isolate (GC1) and rectal swab positive by NAAT from the same male patient were referred to SBSTIRL. The NAAT specimen was negative by *porA* PCR, but was insufficient for testing by Aptima GC. A nucleic acid extract of the isolate was tested by the *porA* PCR and was also negative. The identity of the isolate was confirmed as *N. gonorrhoeae* serogroup WII/III by Phadebact Monoclonal GC test (Bactus AB), by carbohydrate utilisation test and by Aptima GC. GC1 was NG-MAST type 5967, and exhibited chromosomal resistance to penicillin, tetracycline and ciprofloxacin, while being sensitive to cefixime, ceftriaxone, azithromycin and spectinomycin. A database search for NG-MAST type 5967, revealed a stored rectal isolate (GC2) from a male patient from the same area of Scotland, diagnosed with gonorrhoea one month previously. The patient reported multiple male partners who remain untraced. There was no NAAT specimen for this patient, and no link was found between him and the previously described patient. GC2 had a similar antimicrobial susceptibility profile to GC1 and also failed to amplify using the *porA* PCR. No further identifications of NG-MAST type 5967 strains have been made in Scotland to date.

A further urethral isolate of *N. gonorrhoeae* (GC3) was identified through a search for *porA*-negative, Aptima GC-positive specimens. The male patient was diagnosed with gonorrhoea in December 2010, by both culture and NAAT, in a different region of Scotland to the previous patients. He reported one male partner who was not traced. GC3 was confirmed to be *N. gonorrhoeae* using the same methods as GC1 and GC2, was serogroup WII/III, NG-MAST type 3149, and exhibited chromosomal resistance to penicillin, tetracycline and ciprofloxacin, while being sensitive to cefixime, ceftriaxone, azithromycin and spectinomycin.

Sequencing of *porA*

The *porA* gene was sequenced bidirectionally using the primers described by Whiley et al. [7] (Figure). Basic Local Alignment Search Tool (BLAST) searches were performed via National Center for Biotechnology Information (NCBI), GenBank. Sequences were aligned using Seqscape software (Applied Biosystems).

Sequences from GC1 (European Molecular Biology Laboratory (EMBL) accession number: HE681884)* and GC2 (EMBL accession number: HE681885)* were identical, and very similar to the sequence previously reported [7]. The sequence from GC3 (EMBL accession number: HE681886)* was quite different from these, but the primer sites for the *porA* PCR were again missing and the sequence aligns most closely with a *porA* sequence from *N. meningitidis*.

Discussion

Similarly to the strain reported in Australia, the *N. gonorrhoeae* strains that we identified in this study have undergone an apparent recombination event with *N. meningitidis* in the *porA* region and therefore lack the sequences targeted by a published PCR assay [1] which may be commonly used in reference laboratories.

In contrast to the *porA* of *N. meningitidis*, the related sequence in *N. gonorrhoeae* is an unexpressed pseudogene. Whilst the consequently low selection pressure appears to have produced a rather conserved sequence, the apparent lack of function may make it vulnerable to mutation, including recombination with *porA* genes of other *Neisseria* species that may coexist with *N. gonorrhoeae*.

The sequences obtained from GC1 and GC2 are identical, and circumstantial evidence suggests that they

Figure

Alignment of *porA* nucleotide sequences derived from Scottish isolates of *Neisseria gonorrhoeae* with the *porA* sequence of *Neisseria gonorrhoeae* FA1090 strain and with *porA* sequences of *Neisseria meningitidis* strains, United Kingdom, 2010–2011

Shaded characters indicate differences to the *Neisseria gonorrhoeae* FA1090 strain *porA* pseudogene sequence.

[a] *Neisseria gonorrhoeae* strain FA1090, *porA* pseudogene; GenBank accession AJ223447. Italicised regions indicate polymerase chain reaction primer and probe binding sites.

[b] *Neisseria meningitidis* strain 278, *porA* gene; GenBank accession GQ173789.

[c] *porA* sequence derived from an isolate *of Neisseria gonorrhoeae* in this study.

[d] *Neisseria meningitidis* strain NGE31, *porA* gene; GenBank accession AF226348.

may have been acquired as part of the same chain of transmission. No further epidemiologically connected cases have been identified and there is no known history of sex abroad or with a person from outside Scotland from either patient. However, the histories supplied by the patients are incomplete.

Isolate GC3 was NG-MAST type 3149, which is not uncommon in Scotland, with sixteen isolates identified by SBSTIRL to date since July 2010, of which GC3 was the fourth to be found. All fifteen other NG-MAST type 3149 isolates are either *porA* PCR-positive or are from patients episodes where there was also a NAAT specimen which was *porA* PCR-positive. It is therefore possible that the *porA* recombination event occurred either in the patient from whom the isolation of GC3 was made, or within a very short chain of transmission. It is very likely, from the history reported by the patient, that this infection was acquired in Scotland from someone resident in Scotland, who has unfortunately not been identified.

NG-MAST type 5967, as represented by isolates GC1 and GC2, comprises alleles por 3558 and transferrin binding protein B (tbp) 4. These alleles are 99.8% and 99.7% similar to alleles por 1297 and tbp 983, respectively (representing in each case one nucleotide difference), which make up NG-MAST type 5377, the sequence type of the *porA*-recombinant strain reported in Australia [7]. In contrast, alleles por 1903 and tbp 110, which make up NG-MAST type 3149 are 92.5% and 79.8% similar to por 3558 and tbp 4, respectively. This represents significant sequence divergence and provides additional evidence that strain GC3 is unrelated to GC1, GC2 and the previously-reported strain.

All patients reported in Scotland and Australia were either men who have sex with men (MSM), or were infected rectally. The most likely site of co-colonisation with *N. gonorrhoeae* and *N. meningitidis*, and therefore of genetic exchange, is the pharynx, which is also the least amenable site to successful eradication of *N. gonorrhoeae* and is a frequent site of infection in MSM. It is notable that we have not so far identified pharyngeal infections with these unusual strains, but important that they are recognised if and when they occur in future.

No partners of any of the patients identified in Scotland are known to have been traced and tested or treated. While important for the interruption of gonorrhoea transmission and a mainstay of the public health response to sexually transmitted infections, partner notification remains a challenge in settings where contacts are frequently anonymous or semi-anonymous.

Due to the isolation of *N. gonorrhoeae*, all three patients were correctly diagnosed and adequately treated despite any difficulty with NAAT confirmation. The antimicrobial susceptibility pattern of all three isolates is typical of gonococci seen regularly in Scottish patients. None of the *N. gonorrhoeae* NAAT tests in use in Scotland for primary diagnosis target the *porA* gene [8] and therefore it appears that false-negative results are unlikely with these strains.

There is a small likelihood that patients exist who have been infected with *N. gonorrhoeae* strains similar to those described, in whom culture was unsuccessful and the original NAAT result was unconfirmed. The SBSTIRL records are currently being reviewed with the help of referring laboratories to attempt to identify such patients, and this work to date suggests that they are very few, if any.

We recommend that laboratories performing *porA*-based PCR to confirm positive *N. gonorrhoeae* NAAT results consider the use of a third NAAT, with an alternative target gene where the confirmatory assay is negative. This third target could alternatively be included as a duplex with the *porA* assay.

Laboratories and clinicians alike should be alert to the propensity of *N. gonorrhoeae* to develop unusual variations in genotype, as well as the well-established phenotypic variations.

Acknowledgments

The authors would like to acknowledge the help of laboratory staff from SBSTIRL and the DNASHEF sequencing service, of those clinicians who interviewed patients in the course of their care, particularly Kirsty Abu-Rajab, and those who submitted *N. gonorrhoeae* material.

The work of SBSTIRL is funded by Health Protection Scotland.

*Addendum

The European Molecular Biology Laboratory (EMBL) accession numbers of the nucleotide sequences derived from the reported isolates were added on 08 March 2012.

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Clinical *Neisseria gonorrhoeae* isolate with a *N. meningitidis porA* gene and no prolyliminopeptidase activity, Sweden, 2011 – danger of false-negative genetic and culture diagnostic results

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Citation style for this article:
Golparian D, Johansson E, Unemo M. Clinical Neisseria gonorrhoeae isolate with a N. meningitidis porA gene and no prolyliminopeptidase activity, Sweden, 2011 – danger of false-negative genetic and culture diagnostic results.
Euro Surveill. 2012;17(9):pii=20102. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20102

Article published on 1 March 2012

We describe a *Neisseria gonorrhoeae* strain, found in Sweden in 2011, that harbours a *N. meningitidis porA* gene causing false-negative results in PCRs targeting the gonococcal *porA* pseudogene. Furthermore, the strain had no prolyliminopeptidase (PIP) activity that many commercial biochemical kits for species verification in culture rely on. Enhanced awareness of the spread of such strains and screening for them can be crucial.

Gonorrhoea remains a global public health threat and the World Health Organization (WHO) estimated that 88 million new gonorrhoea cases occurred in 2005 [1]. In many laboratories worldwide, commercial or in-house nucleic acid amplification tests (NAATs) have rapidly replaced culture of the aetiological agent *Neisseria gonorrhoeae* for the diagnosis of gonorrhoea. The gonococcal *porA* pseudogene is possibly the most common target in in-house PCRs currently used for primary detection and/or verifying detection of *N. gonorrhoeae* globally. This is because the pseudogene is highly conserved and has so far been considered to be present in all gonococcal strains. It is also sufficiently diverse from the meningococcal *porA* gene, and commensal *Neisseria* species are lacking the *porA* gene/pseudogene [2-5]. However, recently the first case of a clinical *N. gonorrhoeae* isolate was found in Australia, in which the gonococcal *porA* pseudogene was replaced with a *N. meningitidis porA* gene sequence, which caused a false-negative result in a gonococcal *porA* pseudogene PCR [6].

This report describes the identification and detailed characterisation of the second case of a *N. gonorrhoeae* isolate harbouring a *N. meningitidis porA* gene that causes false-negative results in PCRs targeting the *N. gonorrhoeae porA* pseudogene.

Case report

In May 2011, a pharyngeal specimen from a woman in her 30s presenting to a dermatovenerological clinic in Sweden was culture-positive for *N. gonorrhoeae*. The patient had recently had oral sex with a man in Sweden who could not be traced. She had no recent trips abroad. She was given therapy with cefixime (400 mg oral dose) and seven days later a test-of-cure using culture was negative, which indicated a successful treatment. However, it is known that culture, especially of pharyngeal specimens, has a suboptimal sensitivity compared to NAATs [7,8].

Characterisation of the *N. gonorrhoeae* strain with a meningococcal *porA* gene

The *N. gonorrhoeae* isolate was initially identified by typical colonies on selective culture medium, rapid oxidase production, presence of Gram-negative diplococci in microscopy, and two phenotypic species-verifying assays, i.e. an in-house sugar utilisation test and Phadebact GC Monoclonal Test (Bactus AB, Sweden).

When screening 200 clinical gonococcal isolates from 2011 with a PCR targeting the gonococcal *porA* pseudogene [2], the isolate obtained from the case above was repeatedly negative. Nevertheless, the phenotypic methods remained positive for *N. gonorrhoeae*, and additional phenotypic methods such as matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF-MS; bioMérieux, France) and API NH (bioMérieux, France) confirmed this species. However, the isolate did not show any prolyliminopeptidase (PIP) activity in the API NH. According to Etest (bioMérieux, Sweden), the isolate was susceptible to cefixime, ceftriaxone, ampicillin, ciprofloxacin and spectinomycin, but resistant to azithromycin (Table). The isolate was also identified as *N. gonorrhoeae* in

APTIMA Combo 2 and APTIMA GC NAATs (Gen-Probe, United States).

For genetic characterisation, DNA was isolated in the robotised NorDiag Bullet (NorDiag ASA Company, Norway) using BUGS n'BEADS STI-*fast* kit (NorDiag ASA Company). The 16S rRNA gene in the isolate showed 100% sequence identity with other *N. gonorrhoeae* strains in a GenBank BLAST search. The strain was assigned to *N. gonorrhoeae* multi-antigen sequencing typing (NG-MAST) ST2382 (*porB* allele 1480 and *tbpB* allele 4) and multilocus sequence typing (MLST) ST7367 (*abcZ* allele 109, *adk* 39, *aroE* 67, *fumC* 111, *gdh* 148, *pdhC* 153, *pgm* 133), performed as previously described [9,10]. However, two gonococcal *porA* pseudogene PCRs [2,4] gave negative results. Sequencing of the full-length gonococcal *porA* pseudogene, performed as previously described [3], identified instead a meningococcal *porA* gene sequence (94% sequence identity with the genome-sequenced meningococcal reference strain MC58 [11]), which was assigned to meningococcal genosubtype P1.21-6,2-48,35-1 (Table). This meningococcal *porA* sequence had multiple mismatches in the target sequences for both the primers and probe used in the two gonococcal *porA* pseudogene PCRs [2,4]. The monoclonal antibody 4BG4-E7 multivalent PorA (which is described and can be obtained at www.nibsc.ac.uk) verified that the meningococcal PorA protein was also expressed.

Discussion

There is one previously published report from Australia on a *N. gonorrhoeae* isolate that lacks the highly conserved gonococcal *porA* pseudogene [6]. We describe here the identification and characteristics of a *N. gonorrhoeae* isolate from Europe lacking the gonococcal *porA* pseudogene. The results from the present study together with the data from the Australian report [6] show that gonococcal strains can harbour a *N. meningitidis porA* sequence instead of the gonococcal *porA* pseudogene that causes false-negative results using *N. gonorrhoeae porA* pseudogene PCRs [2,4], which are commonly used in many laboratories globally. The isolate described in the present study also lacked PIP activity, which might challenge the species verification in culture if commercial biochemical kits such as API NH, RapID NH, Gonocheck II, Bacticard Neisseria and Neisseria Preformed Enzyme Test (PET) are used [12]. These kits are used worldwide and rely entirely or in part on the gonococcal PIP activity. This is of major concern, in particular because global transmission of PIP-negative gonococcal strains has previously been described [12]. The isolate described in the present study was assigned to MLST ST7367 (differing in two of the seven alleles from the previously described strain from Australia [6], i.e. which had *aroE* 170 and *pgm* 65) and to NG-MAST ST2382 (differing from the previously described strain from Australia [6] by 65 bp in a sequence alignment of the *porB* alleles and by 1 bp in the *tbpB* allele). Accordingly, this clone was not identical to the gonococcal clone reported from Australia, which was assigned to MLST ST1901 and NG-MAST ST5377 [6]. Thus it is clear that more than one gonococcal clone has acquired a meningococcal *porA* sequence, most likely through horizontal gene transfer and subsequent recombination.

It is worrying that the sexual contact of the present case could not be traced and this gonococcal strain could therefore be circulating in a larger sexual network. The findings of the present study have prompted us to carry out systematic screening of isolates from the past 10 years, which is currently ongoing.

In conclusion, the identification of a *N. gonorrhoeae* isolate harbouring a *N. meningitidis porA* gene as well as lacking PIP activity highlights the limitations and challenges using NAATs for diagnosis of gonorrhoea as well as in species verification in culture diagnostics for gonorrhoea. The presence of these two genetic changes in the same strain, which allow the strain to escape commonly used diagnostic tests, clearly illustrates how versatile the *N. gonorrhoeae* species is. Enhanced awareness of the spread of such strains is needed, and screening for them can be crucial. The opportunities to use combinations of different diagnostic methods (such as NAAT and culture) and multi-target NAATs in a laboratory remain exceedingly valuable.

Table

Characteristics of a *Neisseria gonorrhoeae* strain harbouring a *N. meningitidis porA* gene that causes false-negative results in gonococcal *porA* pseudogene PCRs, Sweden, 2011

NG-MAST	MLST	PIP activity[a]	Ampicillin MIC (mg/L)	Ciprofloxacin MIC (mg/L)	Spectinomycin MIC (mg/L)	Ceftriaxone MIC (mg/L)	Cefixime MIC (mg/L)	Azithromycin MIC (mg/L)	*porA*[b]	*porA* genosubtype
ST2382	ST7367	Negative	0.064	<0.002	8	0.002	<0.016	8	94% MC58	P1.21-6, 2-48,35-1

MIC: minimum inhibitory concentration (Etest was used); MLST: multilocus sequence typing; NG-MAST: *Neisseria gonorrhoeae* multi-antigen sequence typing; PIP: prolyliminopeptidase.

[a] The *N. gonorrhoeae* strain did not show any prolyliminopeptidase (PIP) activity, which might challenge the species-verification in culture if commercial biochemical kits are used that rely entirely or in part on the gonococcal PIP activity, such as API NH, RapID NH, Gonocheck II, Bacticard Neisseria and Neisseria Preformed Enzyme Test (PET). This is of particular concern because global transmission of PIP-negative gonococcal strains has previously been described [12].

[b] The *porA* gene in the *N. gonorrhoeae* strain showed 94% sequence identity with the *porA* gene in the genome-sequenced *N. meningitidis* reference strain MC58 [11].

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Treatment failure of pharyngeal gonorrhoea with internationally recommended first-line ceftriaxone verified in Slovenia, September 2011

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Citation style for this article:
Unemo M, Golparian D, Potočnik M, Jeverica S. Treatment failure of pharyngeal gonorrhoea with internationally recommended first-line ceftriaxone verified in Slovenia, September 2011. Euro Surveill. 2012;17(25):pii=20200. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20200

Article submitted on 13 June 2012 / published on 21 June 2012

We describe the second case in Europe of verified treatment failure of pharyngeal gonorrhoea, caused by an internationally occurring multidrug-resistant gonococcal clone, with recommended first-line ceftriaxone 250 mg in Slovenia. This is of grave concern since ceftriaxone is last remaining option for empirical treatment. Increased awareness of ceftriaxone failures, more frequent test-of-cure, strict adherence to regularly updated treatment guidelines, and thorough verification/falsification of suspected treatment failures are essential globally. New effective treatment options are imperative.

Background

Neisseria gonorrhoeae has developed resistance to all antimicrobial drugs previously used as first-line treatment for gonorrhoea [1]. Resistance to currently recommended first-line third-generation cephalosporins – cefixime and ceftriaxone – is emerging [1-3], and treatment failures with cefixime have been verified in Japan [4] and several European countries, namely Norway [5], the United Kingdom [6], Austria [7] and France [8]. One failure to treat pharyngeal gonorrhoea with ceftriaxone, the last remaining option for empiric treatment, has also been verified in Europe (Sweden) [9]. It is likely that treatment failures with ceftriaxone will initially accumulate for pharyngeal gonorrhoea because these infections are harder to treat than urogenital infections [1,10,11]. It is of grave concern that during the past year, the first three extensively drug-resistant (XDR) [1] *N. gonorrhoeae* strains that also had high-level ceftriaxone resistance were reported from Japan, France and Spain [8,12,13].

In this emergent situation of fear that gonorrhoea may become untreatable [1,8,12], the European Centre for Disease Prevention and Control (ECDC) has prepared a response plan for the European Union [14]. The World Health Organization (WHO) has published the 'Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae*' [15].

This report describes a ceftriaxone treatment failure of pharyngeal gonorrhoea in Slovenia in 2011, which is the second one strictly verified in Europe (and possibly globally).

Case description

In early September 2011, a Slovenian bisexual woman in her early 30s visited a dermatovenereologist in Ljubljana, Slovenia (Day 1). She had no symptoms of gonorrhoea, however, she was sampled and administered the internationally recommended first-line treatment of 1×250 mg ceftriaxone intramuscularly (Table), based on the fact that she had had unprotected oral and vaginal sex with gonorrhoea-positive casual male partner in late August 2011 in Belgrade, Serbia. The partner could later not be traced in Serbia.

Microscopy of Gram-stained smear of a cervical specimen was negative for *N. gonorrhoeae*. However, two days later (Day 3), a pharyngeal culture was shown to be positive for *N. gonorrhoeae*, while the cervical culture was negative. *Chlamydia trachomatis* DNA was identified in an additional cervical sample, using the COBAS TaqMan CT Test v2.0 (Roche Diagnostics). During a follow-up visit seven days after the initial visit (Day 8), a test-of-cure (TOC) pharyngeal culture was taken and examination showed no signs or symptoms of pharyngeal gonorrhoea, and she was given doxycycline at a dosage of 100 mg twice a day, for seven days, for a concomitant chlamydial infection. However, two days later (Day 10) the TOC culture confirmed gonococci in a pharyngeal sample. About three weeks later (Day 30), the patient returned with symptoms of acute pharyngitis (pain, inflammation and fever) and was given one dose of 250 mg ceftriaxone intramuscularly and

one oral dose of 1 g azithromycin. Finally, a follow-up examination after about four months (Day 173) showed no signs of infection, and a pharyngeal TOC culture was negative for *N. gonorrhoeae* (Table). The patient repeatedly reassured that she had not had any sexual contacts between the ceftriaxone therapy and the TOC.

Characterisation of *N. gonorrhoeae* isolates

The pre- and post-treatment *N. gonorrhoeae* isolates were species-confirmed by sugar utilisation test and Phadebact Monoclonal GC Test (Pharmacia Diagnostics). The isolates were indistinguishable using serovar determination (Bpyut), full-length *porB* gene sequencing, multilocus sequence typing (MLST; ST1901 [12]), and *N. gonorrhoeae* multiantigen sequence typing (NG-MAST; ST1407 [16]). Using Etest (AB bioMérieux), both isolates showed a ceftriaxone minimum inhibitory concentration (MIC) of 0.125 mg/L (Table), and overall indistinguishable antibiograms (cefixime 0.25 mg/L, spectinomycin 16 mg/L, azithromycin 0.5 mg/L, and ciprofloxacin >32 mg/L) and were beta-lactamase-negative. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [17], the MIC of ceftriaxone for these isolates were equal to the resistance breakpoint (>0.125 mg/L). Sequencing of resistance determinants for third-generation cephalosporins [1,8,12,18,19] showed that both isolates contained an identical *penA* mosaic allele XXXIV [12], which has been correlated with decreased susceptibility or resistance to third-generation cephalosporins and treatment failure with cefixime [5,20,21]. In addition, they contained *mtrR* and *penB* alterations that further increase the MICs of third-generation cephalosporins [1,8,12,19].

Discussion

This study describes the second verified case in Europe (possibly globally) of treatment failure of pharyngeal gonorrhoea with the internationally recommended first-line treatment of 250 mg ceftriaxone, the last remaining treatment option. The failure was strictly verified in accordance with WHO recommendations [1,15], i.e. detailed clinical records were obtained, reinfection was excluded as much as possible, pre- and post-treatment isolates were indistinguishable using highly discriminatory typing, ceftriaxone MICs were elevated, and the isolates contained well-known cephalosporin resistance determinants. The reporting of the case was unfortunately delayed because it took several months before the patient returned for follow-up examination and TOC after the third antimicrobial treatment (to prove successful eradication of infections).

This case shows that ceftriaxone at a dosage of 1×250 mg may in rare cases not be enough for treatment of pharyngeal gonorrhoea caused by gonococcal strains with ceftriaxone MICs of 0.125 mg/L. A 250 mg ceftriaxone dose also results in median times of free ceftriaxone above the MIC of only 24.1 h (range: 10.5–52.2 h) for the detected MIC of 0.125 mg/L [22], and rare treatment failures may happen in the lower range. Nevertheless, these cases are likely to be treatable with enhanced ceftriaxone doses or dual antimicrobial treatment that has already been introduced as first-line empiric treatment in the United States [10] and the United Kingdom [23]. It may be crucial to promptly revise also other national and regional treatment guidelines, and a revision of the European guidelines from the International Union against Sexually Transmitted Infections (IUSTI) and WHO [2] are currently in progress.

Table

Details of verified ceftriaxone treatment failure of one case of *Neisseria gonorrhoeae* pharyngeal infection, Slovenia, September 2011

Age (years)/ Sex	Place of exposure	Healthcare clinic (day of presentation)	Symptoms (signs)	Positive diagnostics	Negative diagnostics	MIC (mg/L)[a] Ceftriaxone	MLST (NG-MAST)[a]	Treatment
32/ female	Serbia (Belgrade)	STD (1)	- (-)	GC culture (pharynx) and CT PCR (cervix)	GC culture (cervix) and microscopy (cervix)	0.125	ST1901 (ST1407)	Ceftriaxone 250 mg×1 IM
		STD (8)	- (-)	GC culture (pharynx)	NA	0.125	ST1901 (ST1407)	Doxycycline 100 mg b.i.d., 7 days PO[b]
		STD (30)	Pharyngitis (inflammation in pharynx)	NA	NA	NA	NA	Ceftriaxone 250 mgx1 IM and azithromycin 1 gx1 PO
		STD (173)	- (-)	NA	GC culture (pharynx), CT PCR (cervix)	NA	NA	NA

b.i.d.: twice a day; CT: *Chlamydia trachomatis*; GC: *Neisseria gonorrhoeae*; IM: intramuscular administration; MIC: minimum inhibitory concentration; MLST: multilocus sequence typing; NA: not applicable; NG-MAST: *Neisseria gonorrhoeae* multi-antigen sequence typing; PCR: polymerase chain reaction; PO: per oral administration; STD: sexually transmitted diseases.

[a] MIC (mg/L) as determined by Etest, MLST [12] and NG-MAST [16] of *N. gonorrhoeae* pre- and post-treatment isolates.

[b] Treatment of concomitant *C. trachomatis* infection.

It is worrying that the gonococcus causing this treatment failure was assigned to MLST ST1901 and NG-MAST ST1407, which is a multidrug-resistant gonococcal clone that also shows decreased susceptibility and resistance to cefixime and is spreading worldwide [5,7,8,13,20,21,24-28]. The previously reported treatment failures with cefixime in Norway [5], Austria [7], France [8] and likely in the United Kingdom [6], were caused by this gonococcal clone or its evolving subtypes. This clone has also shown its capacity to develop high-level resistance to ceftriaxone [8,13].

In conclusion, the second case in Europe (possibly worldwide) of clinical failure using standard ceftriaxone treatment for pharyngeal gonorrhoea, caused by an internationally occurring multidrug-resistant gonococcal clone, has been strictly verified in Slovenia. An increased awareness of treatment failures with ceftriaxone, more frequent TOC (all cases of pharyngeal cases may be crucial), strict adherence to appropriate treatment guidelines, which need to be regularly updated based on antimicrobial resistance surveillance data, and thorough verification/falsification of suspected treatment failures (including subsequent tracing of sexual contacts of the index case with the treatment failure) are essential globally. A stronger focus on pharyngeal gonorrhoea, including increased sampling of pharyngeal specimens and promotion of condom use also when practising oral sex, is also crucial because pharyngeal infection is harder to treat than urogenital infection, relatively common, and is frequently an asymptomatic reservoir for infection and emergence of resistances [1,5]. Ultimately, new options for effective treatment of gonorrhoea are imperative.

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Lymphogranuloma venereum: a hidden emerging problem, Barcelona, 2011

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Citation style for this article:
Vargas-Leguas H, Garcia de Olalla P, Arando M, Armengol P, Barberá MJ, Vall M, Vives A, Martín-Ezquerra G, Alsina M, Blanco J, Muñoz C, Caballero E, Andreu A, Ros M, Gorrindo P, Dominguez A, Caylà JA. Lymphogranuloma venereum: a hidden emerging problem, Barcelona, 2011.
Euro Surveill. 2012;17(2):pii=20057. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20057

Article published on 12 January 2012

From the beginning of 2007 until the end of 2011, 146 cases of lymphogranuloma venereum (LGV) were notified to the Barcelona Public Health Agency. Some 49% of them were diagnosed and reported in 2011, mainly in men who have sex with men. Almost half of them, 32 cases, were reported between July and September. This cluster represents the largest since 2004. This article presents the ongoing outbreak of LGV in Barcelona.

From 1 January 2007 to 30 December 2011, a total of 146 cases of lymphogranuloma venereum (LGV) were notified to the Barcelona Public Health Agency. Of those, 72 cases (49%) were diagnosed and reported in 2011. The figure shows the epidemic curve of the 139 cases who were residents of Barcelona. Of the 70 cases in 2011 who were resident in Barcelona, 31(44%) were reported between July and September.

Surveillance

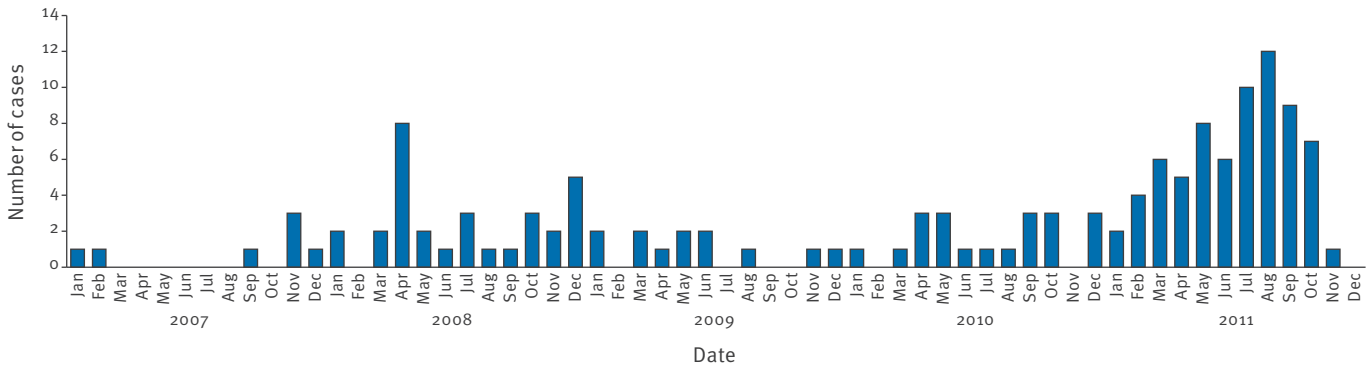
LGV surveillance in Barcelona is part of the sexually transmitted infections (STI) register, which has been active since 2007 and collects information about diagnoses in individuals tested in public or private facilities. Clinicians complete a standard data questionnaire to collect demographic, clinical and epidemiological key parameters, including date of consultation, sex, year of birth, sexual orientation, testing for human immunodeficiency virus (HIV), previous STIs, and sexual behaviour.

All data were collected by the Barcelona STI registry and were handled in a strictly confidential manner according to the requirements of the Spanish data protection Law [1].

Chlamydia trachomatis was detected by nucleic acid amplification tests. Positive samples were then confirmed with a second real-time multiplex polymerase

Figure

Cases of lymphogranuloma venereum by date of diagnosis, Barcelona residents, January 2007–December 2011 (n=139)



chain reaction that allows to differentiate serovars A-K from the L serovars [2].

Epidemiological data

After two decades without LGV notifications, a new case was diagnosed in Barcelona in 2004. It was a homosexual man who was a sexual partner of a case diagnosed in Amsterdam [3]. No further cases were detected in Barcelona until September 2007.

The median number of cases reported per month increased from two in 2010 to six in 2011. A comparison of data from the period 2007–2010 with the year 2011 showed that patients in 2011 were younger (p=0.01) and more of them had documented HIV infection (Table).

Of the 70 cases of LGV reported in 2011 that were resident in Barcelona, all were men who have sex with men (MSM), at least 66 were HIV-positive (HIV status was unknown in two cases), and 39 cases were born in Spain, 17 in South America, 12 in other countries of Western Europe and North America and one in another region. In four cases, HIV diagnosis was known at the time of the LGV diagnosis, and 22 of the cases were diagnosed with another STI in the previous 12 months. *C. trachomatis* was detected in the anal or perianal region in 67 cases, in the genital area in two cases, and for one case no data was available. Regarding the presence of symptoms, 64 cases had at least one symptom, two cases were asymptomatic, and in three cases this information was not recorded.

The time between the onset of the symptoms and the diagnosis ranged from two to 530 days, with a median of 29 days.

The mean number of new sexual partners in the 12 months before diagnosis was 26 (range: 1–100) for the 31 cases in 2011 for whom this information was obtained. Only four cases reported using a condom in the most recent sexual relationship, and three cases engaged in casual sexual intercourse while abroad. For the 27 patients whose information on location of sexual activity was available, 10 reported having had numerous sexual partners, at home or at private parties. The majority of these contacts had been established anonymously by Internet and some of them by mobile applications based on geolocation.

Control measures

To deal with the increase in LGV cases, control measures were implemented in Barcelona from September 2011: alerting STI clinics, HIV specialists and hospitals of the existence of the current outbreak of LGV; active case finding in clinical care units and microbiology laboratories; contact with patients to monitor treatment and implement partner notification; preventive

Table

Epidemiological and clinical characteristic of lymphogranuloma venereum cases, Barcelona residents, comparison of 2007–2010 with 2011 (n=139)

		2007–2010 n=69 Number (%)[a]	2011 n=70 Number (%)[a]	p value
Median age (interquartile range)		38 (34–43)	35 (29–41)	0.01
Country of birth: Spain		40 (58)	39 (56)	0.78
Sexual behaviour	MSM	64 (93)	70 (100)	
	HTS	1 (1)		
	Unknown	4 (6)		
HIV-infected	Yes	55 (80)	66 (94)	0.04
	No	8 (12)	2 (3)	
	Unknown	6 (9)	2 (3)	
Another STI diagnosed in the previous 12 months	Yes	26 (38)	22 (31)	
	No	29 (42)	23 (33)	
	Unknown	14 (20)	25 (36)	
Use of condom the last time they had sex	Yes	8 (12)	4 (6)	
	No	46 (67)	48 (69)	
	Unknown	15 (22)	18 (26)	
Contact tracing	Yes	29 (42)	42 (60)	
	No	18 (26)	9 (13)	
	Unknown	22 (32)	19 (27)	
Median of days between symptoms and diagnosis (interquartile range)		35 (14–90)	29 (13–45)	0.68
Proctitis	Yes	62 (90)	67 (96)	0.17
	No	7 (10)	3 (4)	

HIV: human immunodeficiency virus; MSM: men who have sex with men; HTS: heterosexual; STI: sexually transmitted infection.

[a] All cases were male.

activities targeting risk groups with the collaboration of non-governmental organisations.

Discussion and conclusion

This cluster represents the largest cluster of LGV cases since 2004. A previous outbreak in Barcelona, reported in 2008, had 18 cases in the course of seven months [4].

LGV is an emerging sexually transmitted infection in Europe and in North America. Occasionally, clusters of cases suggest ongoing low-level transmission in these areas [5]. However, since the first outbreak was reported in the Netherlands in 2003, new cases have been reported regularly in various European countries [6-12]. Since 2010, the United Kingdom reported an increase in cases of LGV to over 550 cases, most of them in London. The Netherlands reported 66 cases in 2010 [13,14].

Certain characteristics of LGV support the concept that it is a hidden disease: it affects vulnerable groups, is often self-treated, and misdiagnosis or delayed diagnosis is common. Early diagnosis and treatment of cases are very important because the period of communicability can vary from weeks to years, as long as active lesions are present [15].

As in other parts of Europe, the significant increase in cases of LGV in Barcelona in the last year affected the MSM population, most of them HIV-infected. The infrequent use of condoms in the last years and the high proportion of anonymous sexual contacts make this group active transmitters of STIs, including HIV. Clinicians, epidemiologists and those most susceptible to infection such as MSM, should be aware that this disease is still present in European countries, and that it could manifest in a gradual increase in cases or as outbreaks. Existing efforts to promote awareness and prevention of LGV, especially among HIV-infected patients and among physicians, should be strengthened. New technologies (e.g. Intenet, global positioning system) favour risk practices, but also provide opportunities for new prevention strategies. These new media could be used to disseminate information about preventive measures and, in the case of applications using georeferences, to facilitate the identification of contacts and tracing of patients with LGV who would benefit from timely notification. Some publications have welcomed this initiative aimed at groups of MSM who seek sexual contacts through websites [16,17]. Other experiences in STI centres, such as human sexuality seminars for MSM have proven effective in reducing risk practices in this group [18].

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First detection of *Chlamydia trachomatis* LGV biovar in the Czech Republic, 2010–2011

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Citation style for this article:
Vanousova D, Zákoucká H, Jilich D, Rozsypal H, Stankova M, Zufanova S, Vojackova N, Hercogova J, Marvan J, Machala L. First detection of Chlamydia trachomatis LGV biovar in the Czech Republic, 2010–2011. Euro Surveill. 2012;17(2):pii=20055.
Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20055

Article published on 12 January 2012

We present four cases of proctitis in HIV-infected men having sex with men (MSM) living in the Czech Republic. The causative agent in all cases was the lymphogranuloma venereum (LGV) biovar of *Chlamydia trachomatis*. The spread of proctitis caused by *C. trachomatis* serovars L1–3 among MSM has been observed in several European countries, the United States and Canada since 2003. To our knowledge, no LGV cases in eastern Europe have been published to date.

Between February 2010 and February 2011, four men who have sex with men (MSM) infected with human immunodeficiency virus (HIV), who were under regular observation for HIV infection at the Bulovka University Hospital AIDS Center in Prague, Czech Republic, developed symptoms of acute proctitis. The most prominent symptom in all four patients was intensive rectal pain lasting on average 10 days (range: 7–21 days). Other symptoms included blood in the stool or pinkish mucous discharge, constipation and tenesmus. Case 1 also had one enlarged, painful inguinal lymph node. Anoscopies were performed on Case 1 and Case 3 and revealed congested, irritated mucous membranes with a whitish coating. None of the patients had urethritis, fever, or other systemic symptoms (see Table).

To our knowledge, these cases are the first LGV infections detected in the region.

Background

Lymphogranuloma venereum (LGV) is a sexually transmitted disease (STD) caused by *Chlamydia trachomatis* serovars L1–3 [1]. Rare in industrialised countries, LGV is most often restricted to Africa, Asia, South America and the Caribbean [1,2]. Outbreaks of LGV proctitis in HIV-infected MSM have, however, been reported in several European countries, the United States and Canada [3-9]. Infections with LGV serovars, mainly L2, have been reported in North America and in Belgium, Denmark, France, the Netherlands, Portugal, Spain, the United Kingdom and Sweden, but to the best of our knowledge, there have been no publications to date reporting cases in eastern Europe.

Clinical and behavioural information

Three cases were regular visitors of gay clubs where they repeatedly had protected receptive anal intercourse with casual partners, but also used sex toys without condoms. One case reported having had unprotected anal sex and used sex toys with only one partner during the year before diagnosis. The identity and possible symptoms of the partner remain unknown to us. All but one of the cases were taking combination antiretroviral therapy (cART) and their mean CD4+ T cell count was 540/µL (range: 414–602/µL). Their median age was 46 years (range: 39–47 years) and the average time since the diagnosis of HIV infection was 27.75 months (range: 9–39 months). Three of them had already been treated for one episode of STD in the past (Table).

Laboratory investigation

Rectal swabs were taken from all cases for culture and PCR for *Neisseria gonorrhoeae* and for PCR for *C. trachomatis* (Cobas CT/NG, Roche). All cases were screened serologically for syphilis. The PCR tests for *C. trachomatis* were positive in all four cases. In Case 1, PCR was also positive for *N. gonorrhoeae*. The samples positive for *C. trachomatis* were stored at -80 °C for further identification of the LGV genotype, which became available in the Czech Republic in May 2011.

The LGV genotype was identified by PCR amplification of a 262 bp fragment of target DNA using the dual-priming oligonucleotide primers (DPO) test. This method targets the *pmp-H* gene and enables simultaneous detection of LGV-serovars and differentiation of L1–3 from other serovars [10].

Treatment

Therapy with oral azithromycin 1 g once per week for three weeks was started in Case 1, who had been concomitantly diagnosed with a *N. gonorrhoeae* infection. The anorectal symptoms resolved, but the lymph node abscessed and needed to be punctured. The puncture was also PCR-positive for *C. trachomatis*. A consecutive treatment with oral doxycycline, 100 mg twice per day for five weeks, was started, with the enlarged lymph node eventually regressing after this therapy. The other three cases were treated with oral doxycycline, 100 mg twice per day for 14 to 21 days, and in all of them the symptoms resolved during the therapy. The post-treatment rectal swabs for PCR of *C. trachomatis* were negative in all four patients. The Table summarises details of the patients' risk factors, clinical symptoms and therapy.

Table. Risk factors, clinical symptoms, therapy and sexually transmitted disease history of lymphogranuloma venereum cases, Czech Republic, February 2010 to February 2011 (n=4)

Discussion and conclusions

The Czech cases of LGV infection were very similar to the cases reported both in North America and western Europe [4]. All cases were HIV-infected MSM who used sex toys; three of them had had numerous sexual contacts. Furthermore, the clinical symptoms were very similar and their intensity corresponded to what is typical for LGV proctitis [11]. Although the method we used to identify LGV DNA cannot differentiate between L1, L2 and L3 genotypes, it distinguishes L1–3 from other serovars; the presence of the LGV infections in the region of eastern Europe is therefore evident.

The recommended therapy for LGV proctitis is oral doxycycline, 100 mg orally twice per day for three weeks [12]. Two of our cases were treated with the recommended dose of doxycycline, but only for two weeks. This shorter regimen was chosen because the LGV aetiology was not known, as the method for the identification of LGV biovars was introduced in the Czech Republic in May 2011. Nevertheless, even the two-week therapy with doxycycline proved effective enough in our cases.

The increased frequency of identification of LGV serotypes of *C. trachomatis* in developed countries in recent years is certainly connected to the introduction of modern molecular diagnostic methods into routine practice; on the other hand, it also closely correlates with the rapid increase in the incidence of syphilis among MSM in the same regions, including the Czech Republic [13-15]. This situation probably demonstrates decreasing awareness on the part of MSM about the risk of transmission of STDs. The frequent use of sex toys among patients with LGV proctitis indicates that these objects may play an important role in the transmission of LGV biovars of *C. trachomatis* [16,17].

This new epidemiological situation requires thorough analysis in order to adapt interventional strategies especially for population groups at particular risk such as HIV-infected MSM. Active case-finding and contact tracing for LGV infection should be included in routine healthcare for such high-risk populations.

In addition, the cases described here document that the spread of LGV strains of *C. trachomatis* has reached eastern Europe, and further reports of the identification of this pathogen in this region can be expected soon after the introduction of appropriate diagnostic methods in this region.

Table

Risk factors, clinical symptoms, therapy and sexually transmitted disease history of lymphogranuloma venereum cases, Czech Republic, February 2010 to February 2011 (n=4)

Case	Risk factors	Symptoms	Therapy	Other STDs	cART
1	Protected sexual intercourse with multiple sexual partners, use of sex toys	Rectal pain, constipation, blood in stool, tenesmus, unilateral inguinal painful lymphadenopathy	Azithromycin (1 g orally every five days for three weeks); doxycycline (100 mg twice per day for five weeks)	Coinfection with *N. gonorrhoeae*, syphilis in anamnesis	Lopinavir/ritonavir + zidovudin + lamivudin
2	Unprotected sexual intercourse with a stable partner, use of sex toys	Rectal pain, constipation, mucous discharge with blood, tenesmus	Doxycycline (100 mg orally twice per day for two weeks)	Syphilis in anamnesis	Tenofovir + zidovudin + lamivudin
3	Protected sexual intercourse with multiple sexual partners, use of sex toys	Mucous pinkish stool, constipation, tenesmus	Doxycycline (100 mg orally twice per day for two weeks)	No	Lopinavir/ritonavir + tenofovir + emtricitabine
4	Protected sexual intercourse with multiple sexual partners, use of sex toys	Rectal pain, mucous pinkish stool, constipation, tenesmus	Doxycycline (100 mg orally twice per day for three weeks)	Gonorrhoea in anamnesis	No

cART: combination antiretroviral therapy; STD: sexually transmitted disease.

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Ongoing outbreak of *Shigella flexneri* serotype 3a in men who have sex with men in England and Wales, data from 2009–2011

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Citation style for this article:
Borg ML, Modi A, Tostmann A, Gobin M, Cartwright J, Quigley C, Crook P, Boxall N, Paul J, Cheasty T, Gill N, Hughes G, Simms I, Oliver I. Ongoing outbreak of Shigella flexneri serotype 3a in men who have sex with men in England and Wales, data from 2009–2011.
Euro Surveill. 2012;17(13):pii=20137. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20137

Article published on 29 March 2012

Diagnoses of *Shigella flexneri* in the United Kingdom (UK) are usually travel-related. However, since 2009, there has been an overall increase in UK-acquired cases. The Health Protection Agency has been investigating a national outbreak of *S. flexneri* detected in 2011 and which is still ongoing. Cases occurred mostly in men who have sex with men and were of serotype 3a. The investigation aimed at obtaining epidemiological data to inform targeted outbreak management and control.

Cases of *Shigella flexneri* in the United Kingdom (UK) usually originate from travel or contact with travellers from higher incidence regions such as Indian subcontinent, North and East Africa and South America [1]. Following analyses of laboratory data, an increase in UK-acquired *S. flexneri* cases was detected in London in November 2010. A subsequent rise in UK-acquired cases was also noted in Manchester in May 2011. The initial cases reported were predominantly of serotype 3a and mostly among men who have sex with men (MSM) aged between 30 and 50 years, some of whom were HIV positive. Pulsed field gel electrophoresis (PGFE) performed on initial stool specimen showed that some of the isolates were indistinguishable, however preliminary investigation failed to identify a common venue or point source [2,3].
In response, a national outbreak control team was formally established in September 2011 to investigate and manage the outbreak of *S. flexneri*. Enhanced surveillance was initiated in order to:

- describe the epidemiology of *S. flexneri* infection in individuals who had no travel history or who had travelled to countries with low risk for infection;
- estimate the proportion of UK-acquired cases or cases associated with travel in low-risk countries that are explained by transmission in MSM;
- identify risk factors for transmission of *S. flexneri* between MSM.

Sexual transmission of *Shigella* was first described in the United States during the 1970s [4]. Since then, several outbreaks of sexually transmitted *Shigella*, predominantly in MSM, have been reported [5-8]. In 2006, an outbreak of *Shigella* among MSM in London coincided with a similar outbreak in Berlin suggesting that travel plays a role in introducing *Shigella* species to populations at risk [9,10].

Outbreak investigation

National enhanced surveillance of *S. flexneri* was conducted from September to December 2011 inclusive, in order to describe and monitor the epidemiology of the outbreak. The population under surveillance consisted of UK-acquired *S. flexneri* infection cases and reported cases associated with travel in low-risk countries.

Low-risk travel-associated individuals were defined as individuals who returned to the UK in the four days before onset of illness after travel to countries with low risk for *Shigella* infection (Europe, North America and Australia). High-risk travel-associated diagnoses were defined as individuals who returned to the UK in the four days before onset of illness after travel to countries with high risk for *Shigella* infection (South America, Asia and Africa) [1].

A confirmed case was defined as a laboratory-confirmed case of *S. flexneri* with a specimen date

between 1 September and 31 December 2011 with no recent travel or who reported recent travel to low-risk countries.

A probable case was defined as a laboratory-confirmed case of *S. flexneri* with an unknown travel history.

Cases of *S. flexneri* among people who had travelled to high-risk countries or secondary cases of *S. flexneri* who were contacts of high risk travel-associated cases were excluded.

All laboratories were asked to notify *Shigella* isolations and to send stool specimens to the national reference laboratory (Gastrointestinal Infections Reference Unit, Health Protection Agency - Colindale, London) for serotyping, PFGE analysis and sensitivity testing. Weekly updates on laboratory-confirmed *S. flexneri* diagnoses were forwarded to the respective regions for further follow-up.

Local health protection units confirmed the travel history for every reported *S. flexneri* diagnosis and conducted an interview using a surveillance questionnaire for UK-acquired or low-risk travel-associated diagnoses of *S. flexneri*. The questionnaire contained additional questions on exposures such as travel, food history, contact with symptomatic individuals and sexual contact to assist with case management. In-depth interviews with confirmed MSM cases were also conducted to identify potential risk factors for infection.
S. flexneri reports from the national laboratory databases, regions and local units were collected and analysed and feedback was disseminated to the regional units and identified leads through epidemiological update reports.

Increased awareness and guidance for health professionals and people at risk of infection was issued through HPA briefings, information leaflets and press releases [11].

S. flexneri diagnoses reported by the national laboratories between 2001 and 2011 were also analysed to provide context to the current outbreak and to produce historical time trends.

Results

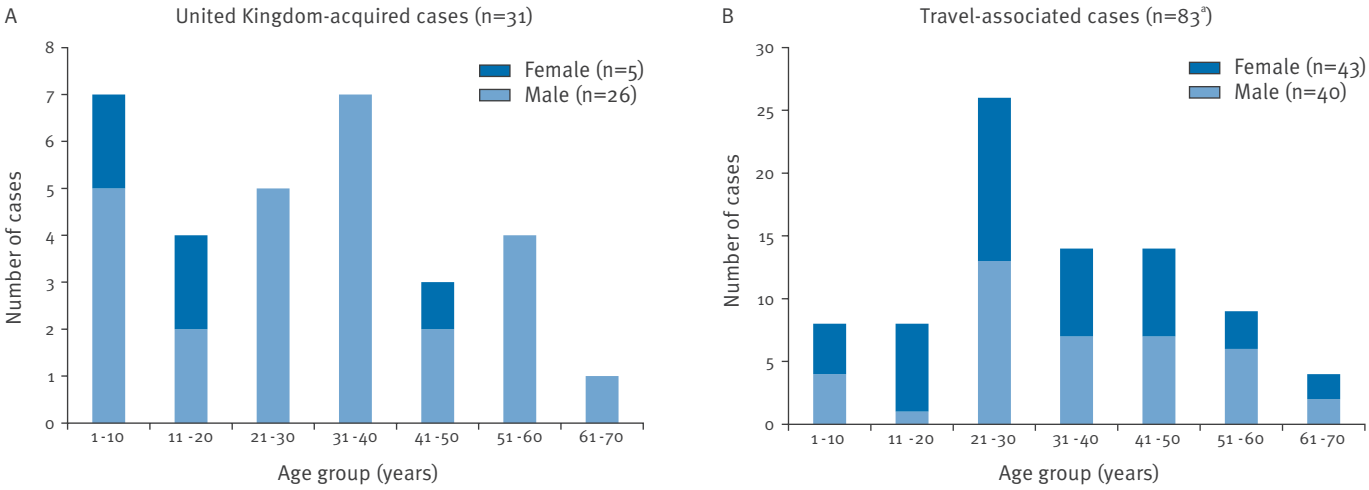
During the enhanced surveillance period between September and December 2011, 145 *S. flexneri* diagnoses were reported of which 37 (25.5%) were non-travel related. Thirty-one cases were confirmed as being UK-acquired whereas six reported diagnoses were likely to be secondary cases linked to a symptomatic contact with recent travel to a high-risk country.

Eighty-six cases (59.3%) were associated with travel to high-risk countries and the travel history was unknown for 22 individuals (15.2%). No low-risk travel-associated cases of *S. flexneri* were reported during the enhanced surveillance period.

The UK-acquired cases were predominantly male (n=26) whereas travel-associated *S. flexneri* diagnoses were equally distributed between both sexes: 48% male (n=40) and 52% female (n=43) as shown in Figure 1. The sex and age of three travel-associated cases was not known.

Figure 1

Cases of *Shigella flexneri* reported during the enhanced surveillance period by age group and sex, England and Wales, September – December 2011



[a] The gender and age of three travel-associated cases was not known.

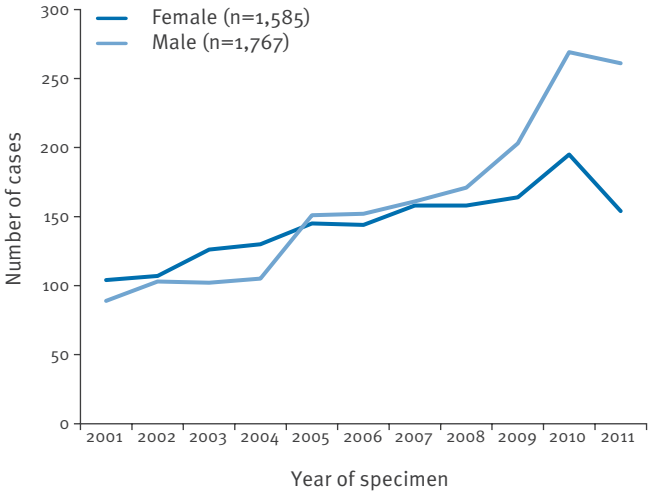
Source: National reference laboratory database (GDW- Gastro Data Warehouse), Health Protection Agency, Colindale, United Kingdom.
National laboratory reporting database (LabBase 2), Health Protection Agency, Colindale, United Kingdom.

Eleven male cases with UK-acquired *S. flexneri* reported MSM activity in the week before developing gastroenteritis. Three individuals refused to disclose their sexual orientation.

Ten of the 31 reported UK-acquired *S. flexneri* cases were serotype 3a, seven were serotype 1b, five were serotype 2a, three were serotype 6 and one case was reported for serotypes 1a, 1c, 2b and 3b. The serotype was unknown for two reported *S. flexneri* diagnoses. More than half (n=5) of the infections in MSM were caused by serotype 3a, four by serotype 1b, one by serotype 2a and one by serotype 6.

Figure 2

Shigella flexneri cases with no or unknown travel history stratified by year and sex, England and Wales, 2001–2011 (n=3,352)



Source: National laboratory reporting database (LabBase 2), Health Protection Agency, Colindale, United Kingdom.

In depth interviews with seven MSM cases showed that they all had one long term partner and attended regular medical examinations. However, all cases reported having a casual sexual partner in the week preceding illness. These interviews revealed lack of awareness about *Shigella* and of the risks associated with unprotected oral and oral-anal sex.

Trends in *S. flexneri* diagnoses reported between 2001 and 2011 showed a gradual increase in the number of cases with no or unknown history of travel since 2001, with a similar trend in both sexes until 2008 (Figure 2). However, from 2009 onwards, numbers of diagnoses rose far more rapidly in men (Figure 2).

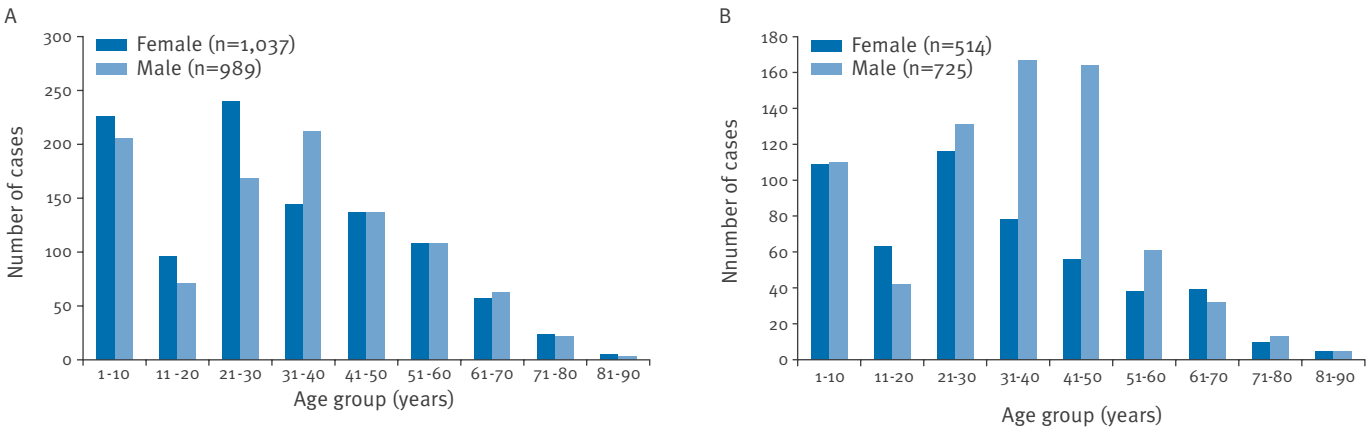
Data analysis revealed similar trends in cases between sexes and within the same age group, however, since 2009 the increase in the number of *S. flexneri* cases reported was attributable to an overrepresentation of men aged between 31 and 50 years (Figure 3).

Figure 4 shows the number of *S. flexneri* diagnoses by serotype from 2004 to 2011. The number of cases infected with serotype 3a has increased considerably and as from 2009 it has become as predominant as the 2a serotype and accounted for the increase in *S. flexneri* cases between 2009 and 2011.

The increase in serotype 3a since 2009 was mostly attributable to diagnoses among men aged 30-50 years which constituted 65% (211/324) of all *S. flexneri* 3a reports with no or unknown travel history between 2009 and 2011. When focusing on the male adult cases with serotype 3a, the number of monthly *S. flexneri* diagnoses in 2007/2008 fluctuates between 1 and 7 cases. The number of monthly reports increases to between 5 and 15 from 2009 onwards. The following graph shows the number of monthly diagnoses from

Figure 3

Shigella flexneri cases by sex and age group, England and Wales, (A) 2001–2008 (n=2,026) and (B) 2009–2012 (n=1,239)



Source: National laboratory reporting database (LabBase 2), Health Protection Agency, Colindale, United Kingdom.

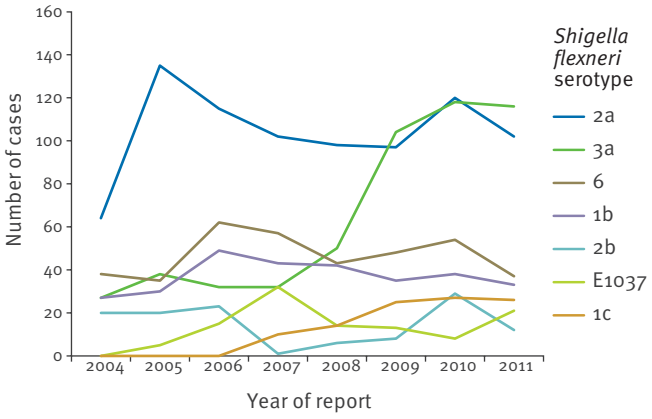
2007-2012 and a three-month moving average (Figure 5).

Control measures

The outbreak control team introduced control measures which focused on actions aimed at prompt and effective management of cases to prevent onward transmission. They included increasing awareness among clinicians and MSM and prompt diagnosis and treatment, increased testing of MSM with diarrhoea and treatment of laboratory-confirmed cases with ciprofloxacin [12] subject to antimicrobial sensitivity.

Figure 4

Shigella flexneri serotype by year of report for cases with *S. flexneri* infection with no or unknown travel history, England and Wales, 2004-2011 (n=2,350)



Source: National reference laboratory database (GDW- Gastro Data Warehouse), Health Protection Agency, Colindale, United Kingdom.

These actions also included recommendations regarding behaviours that may contribute to prevent further transmission:

- wash hands after using toilet, before preparing or eating food and after sexual activity;
- avoid anal sex, oral-anal sex, scat and rimming whilst symptomatic and until test for infection shows clearance;
- use of condoms, gloves, dental dams during sex;
- avoid sharing douching materials and sex toys;
- avoid swimming pools and spa centres whilst ill and for two weeks after recovery.

Work is ongoing to identify risk factors for infection and evaluate other possible control measures such as screening of asymptomatic contacts.

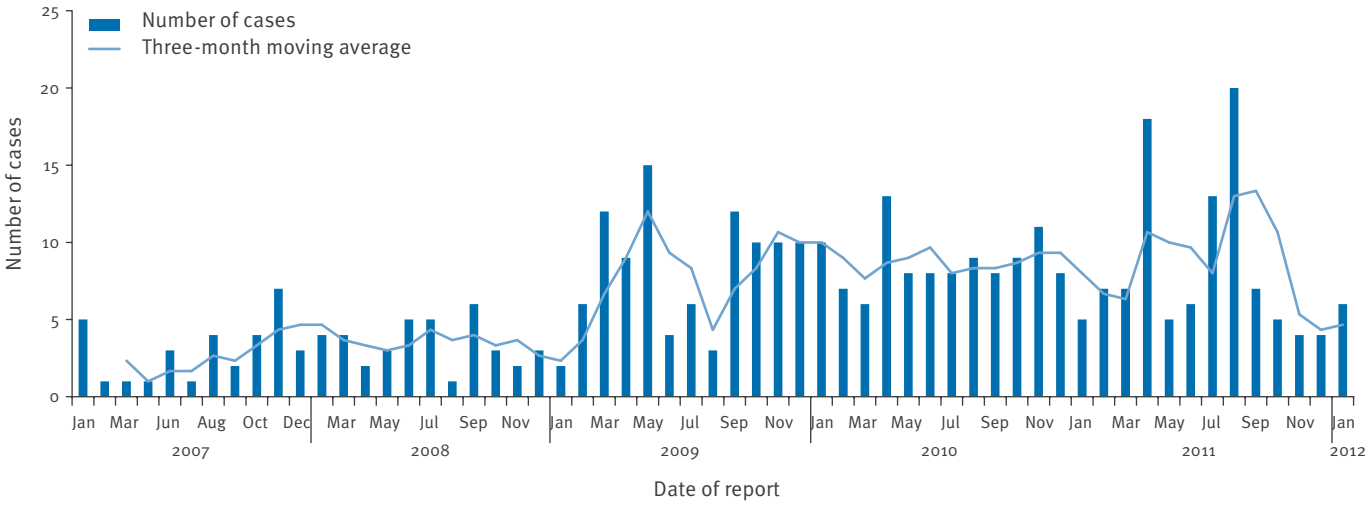
Discussion and conclusion

As the outbreak is still ongoing and no similar *S. flexneri* outbreaks have recently been reported by other countries, increased vigilance and monitoring by other European countries is recommended in order to promptly and effectively detect any change in the reported trends of *S. flexneri*.

Although some people may have been reluctant to disclose details about their sexual orientation, the enhanced surveillance revealed a strong association between UK-acquired *S. flexneri* and transmission in MSM. The outbreak will continue to be monitored through routine arrangements and information on cases occurring in MSM will continue to be collected in order to effectively describe the epidemiology of the disease in MSM and identify any potential risk factors to inform public health action.

Figure 5

Adult male cases of *Shigella flexneri* 3a infection with no or unknown travel history, England and Wales, January 2007–January 2012 (n=381)



Source: National reference laboratory database (GDW- Gastro Data Warehouse), Health Protection Agency, Colindale, United Kingdom.

Although the *S. flexneri* outbreak first emerged in 2009 and has been sustained since then, it has only been detected relatively recently. An evaluation of *Shigella* infection surveillance will therefore be carried out in order to identify factors leading to the delay in outbreak identification and to explore new approaches to routine surveillance of sexually-transmitted *Shigella* infection.

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