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

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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.

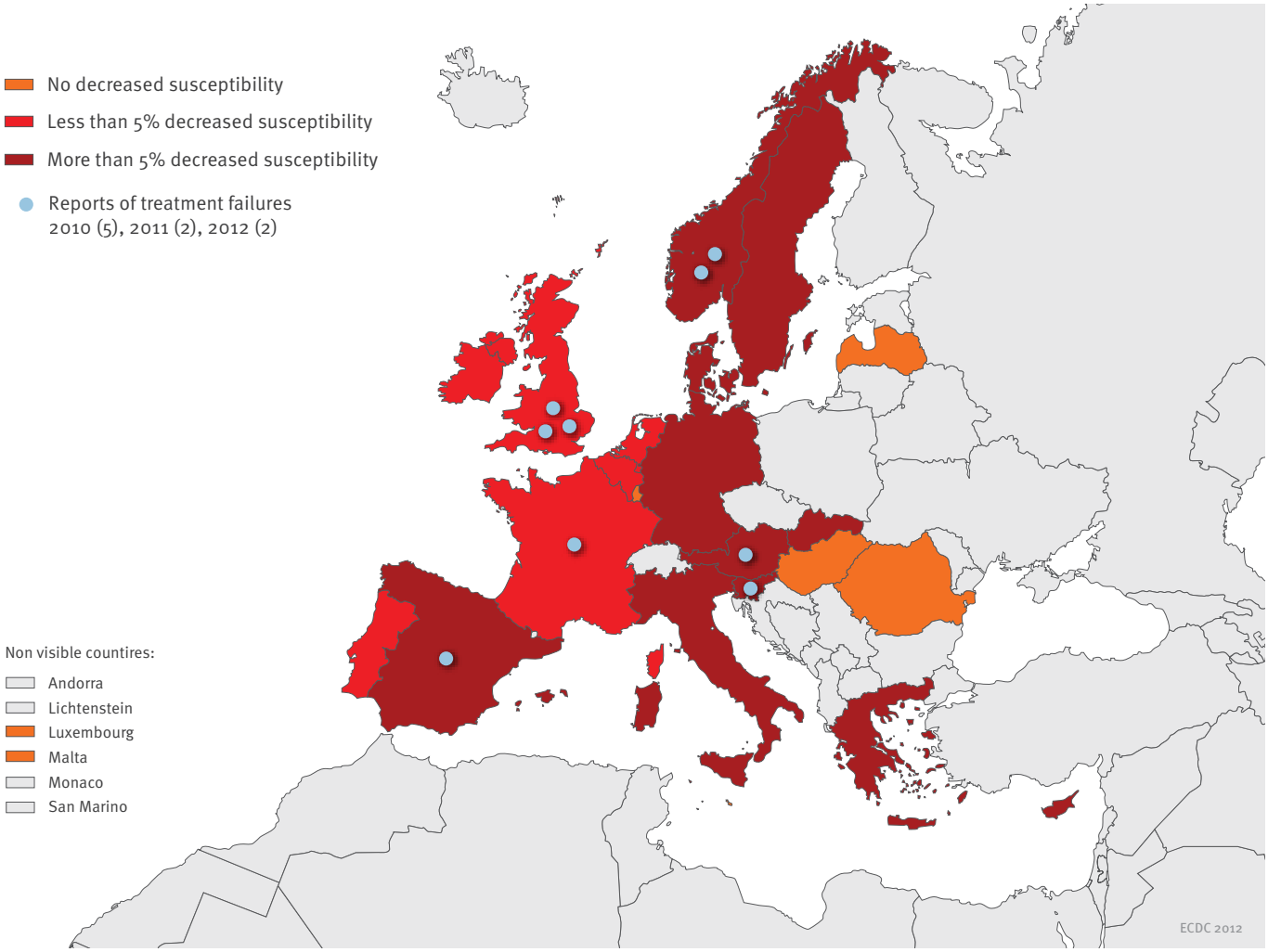
Effective control of gonorrhoea relies entirely on successful antimicrobial treatment. Untreated infections can lead to severe secondary sequelae, including pelvic inflammatory disease, first trimester abortions, ectopic pregnancy and infertility, and may contribute to facilitating HIV transmission. 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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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.

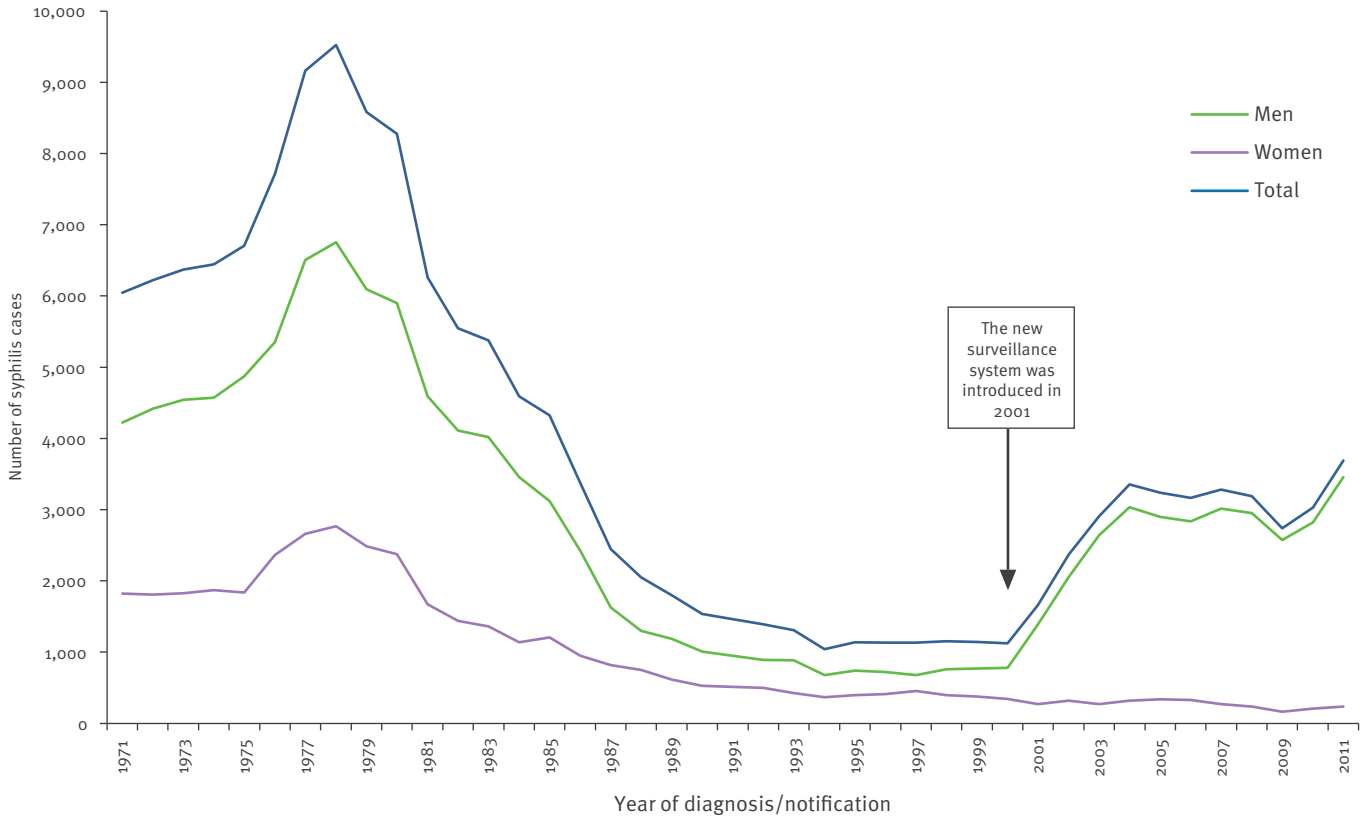
Results

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.

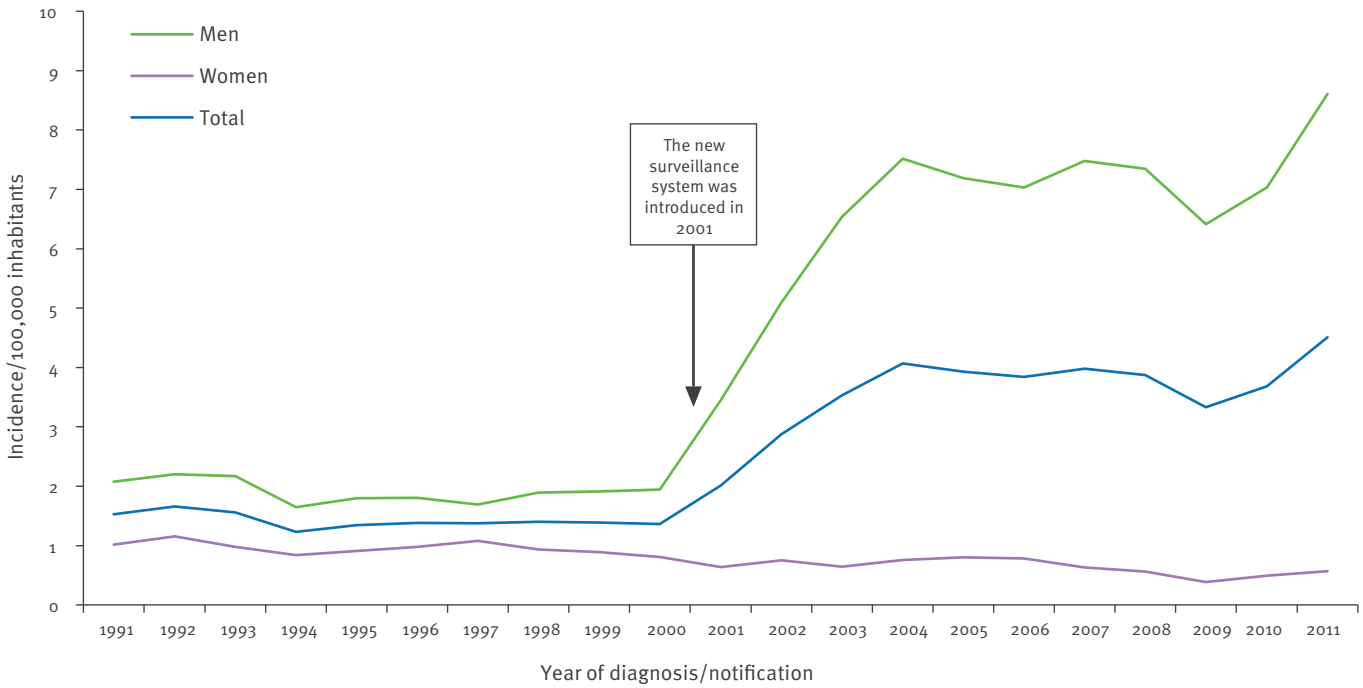
An increased incidence was observed in 11 of the 16 federal states, while it was stable in and decreased slightly in three federal states. The highest incidences were seen in the cities of Cologne (24.0/100,000), Frankfurt (21.0/100,000) and Berlin (18.0/100,000). Furthermore, we observed an unusual 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).

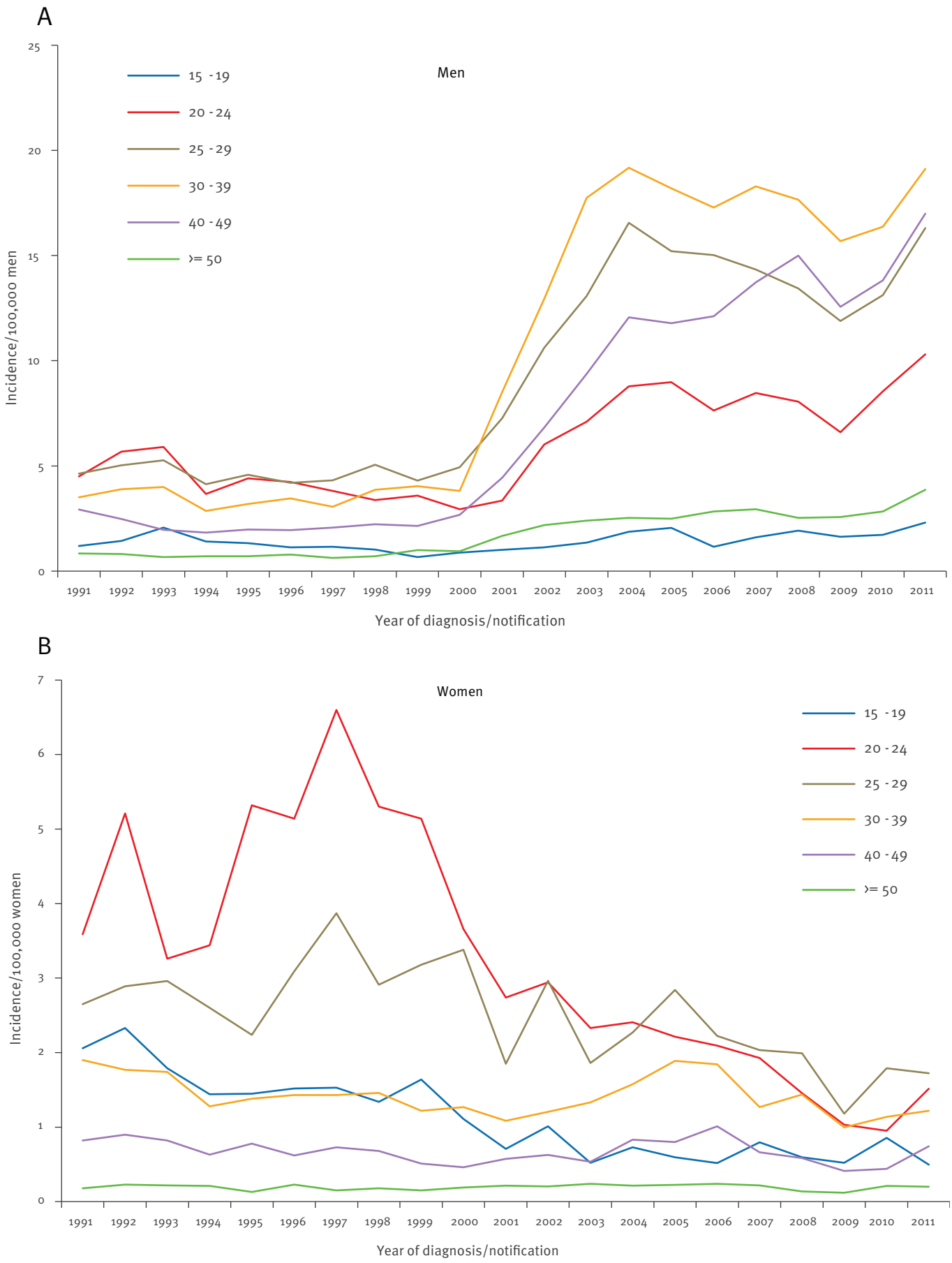
Until 2008, simultaneous increases and decreases of syphilis notifications in MSM in different regions had been observed. Following the country-wide decrease in syphilis case notifications in 2009, also the increase in 2011 in the MSM population seems to be occurring in most regions in Germany. From 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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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

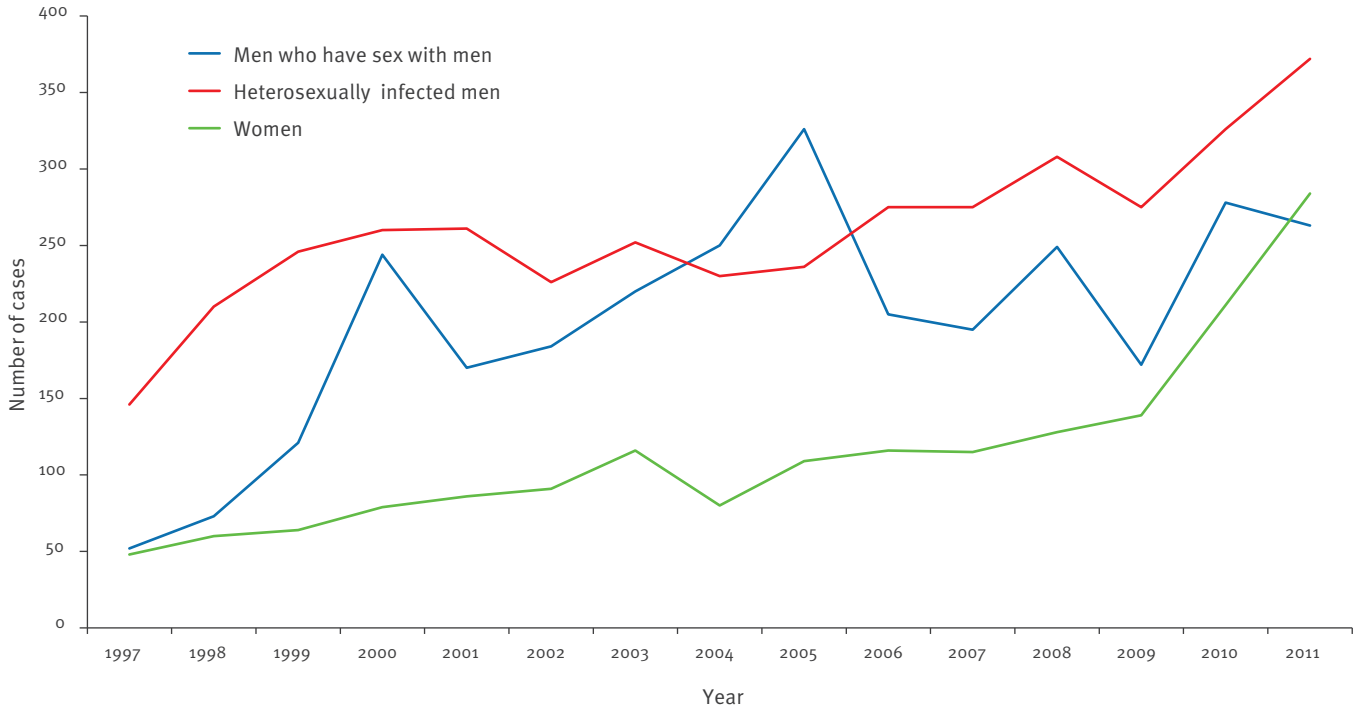
Trends in gonorrhoea and syphilis in Sweden, 2007 and 2011

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).

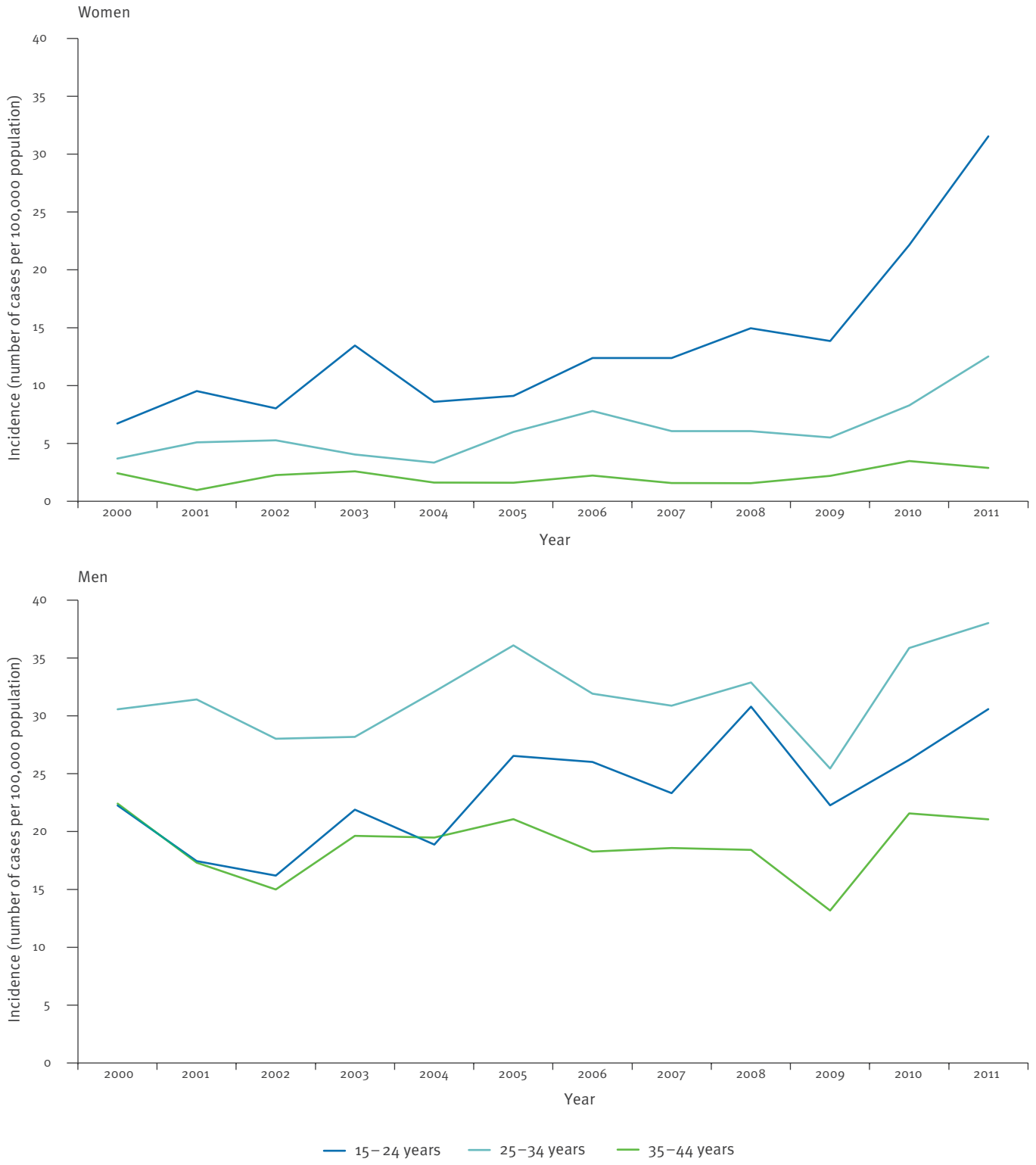
During 2007 to 2011, about 70% of all the cases became infected in Sweden: a mean of 74% of the 15–24 year-olds and 70% of the 25–34 year-olds. In the remaining age groups, more than a mean of 50% were infected abroad. Of all cases infected abroad, the countries where the infection was most commonly 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%.

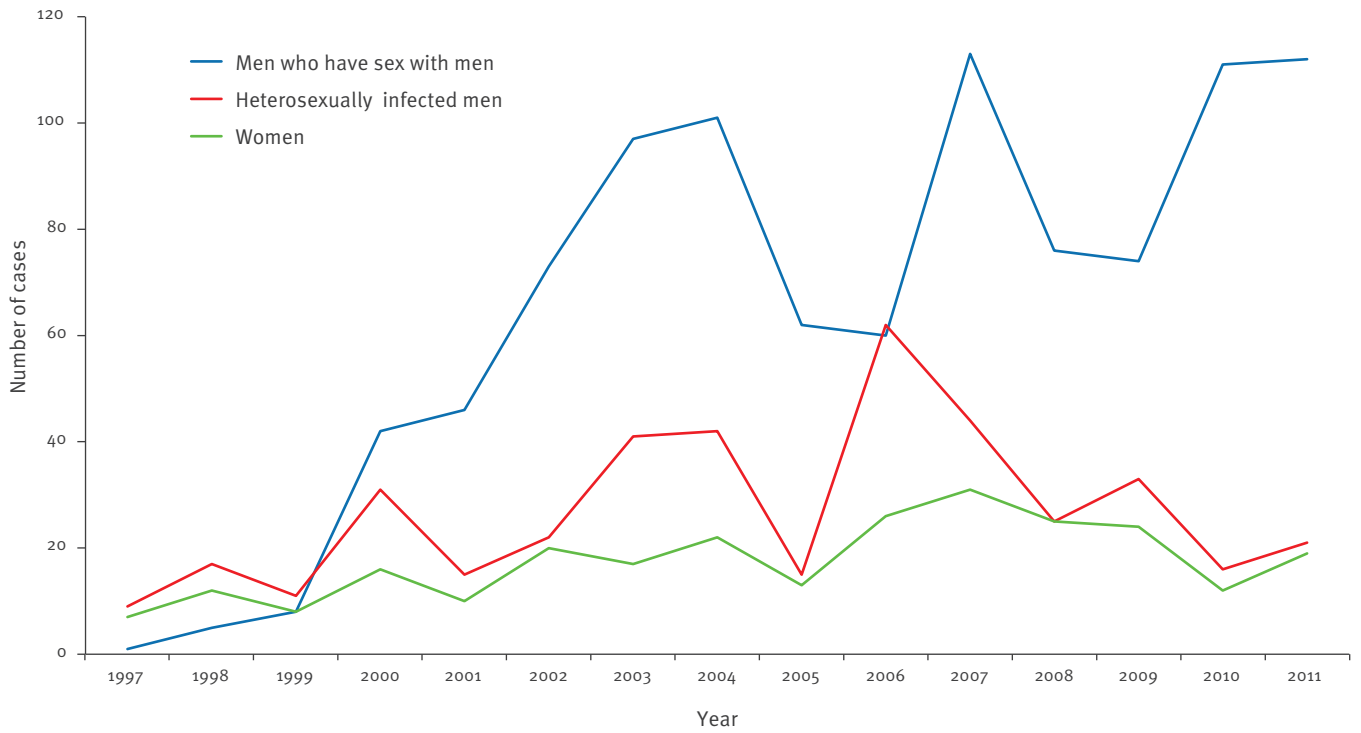
During 2007 to 2011, between 40% and 52% of all syphilis cases became infected in Sweden: a mean of 51% of the 15–24 year-olds and a mean of 51% of the 45–54 year-olds. In the remaining age groups, a mean of more than 50% were infected abroad. Of all cases infected abroad, the countries where the infection 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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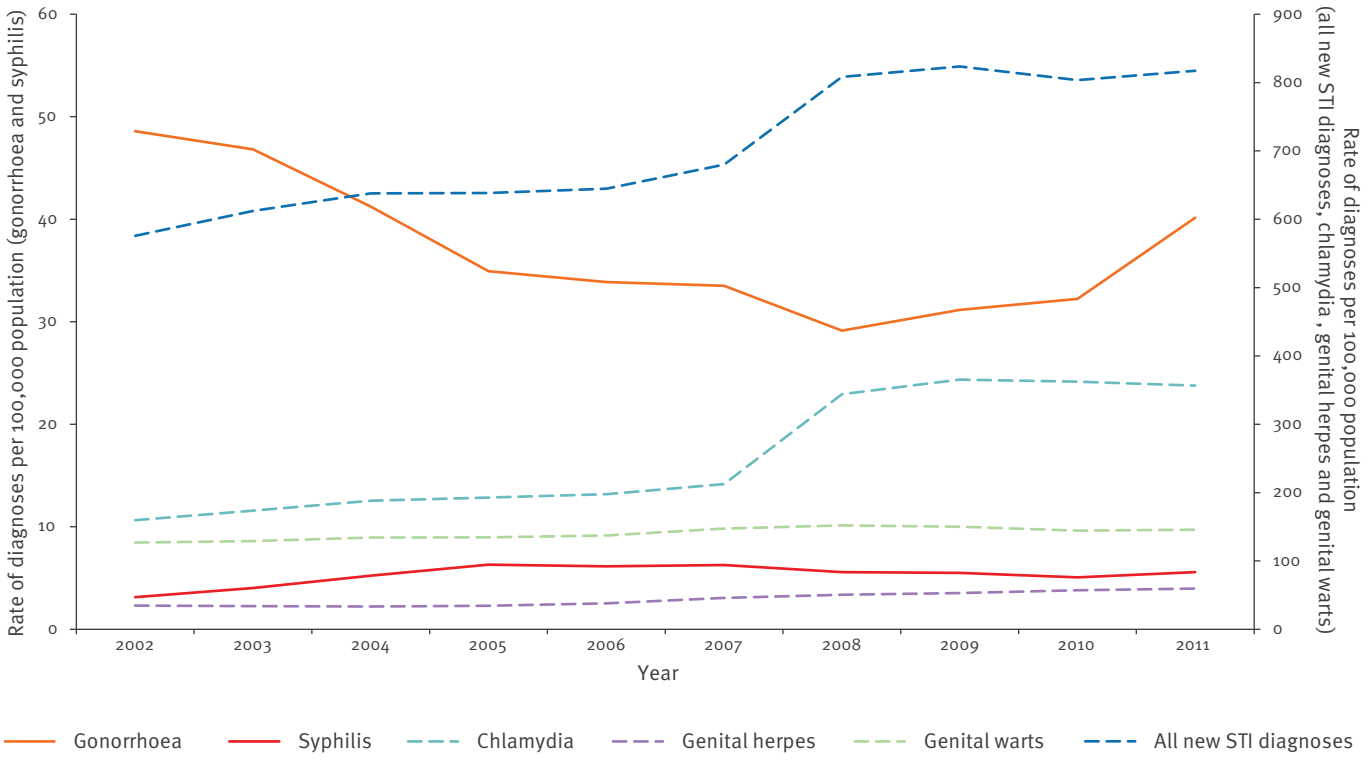
There has been a rapid rise in the number of gonorrhoea and syphilis diagnoses in England during 2011, an increase of 25% and 10% respectively. Large increases of both gonorrhoea (61%) and syphilis (28%) were observed among men who have sex with men. Although these rises can partly be attributed to increased 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

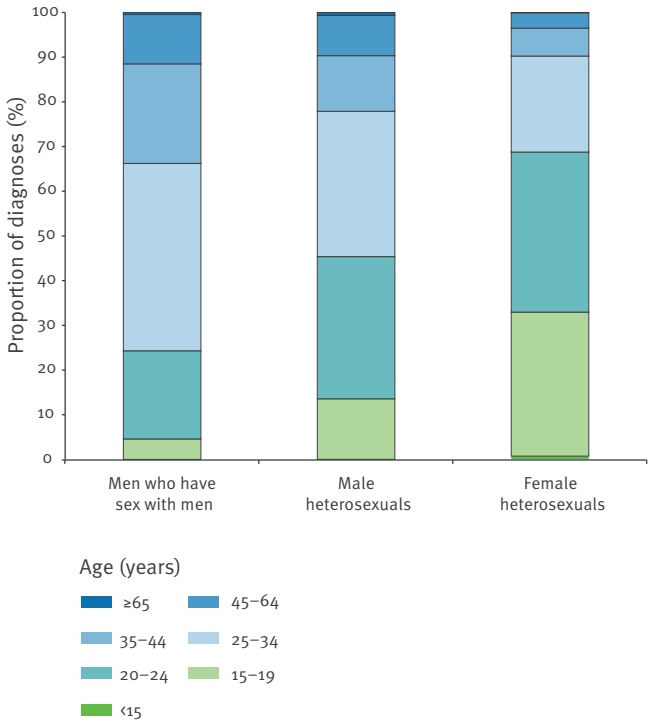
In England, all specialist sexual health clinics submit the mandatory Genitourinary Medicine Clinic Activity Dataset (GUMCAD) to the Health Protection Agency (HPA) every quarter. This dataset is an electronic pseudo-anonymised patient-level data return that contains information on all STI diagnoses made 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

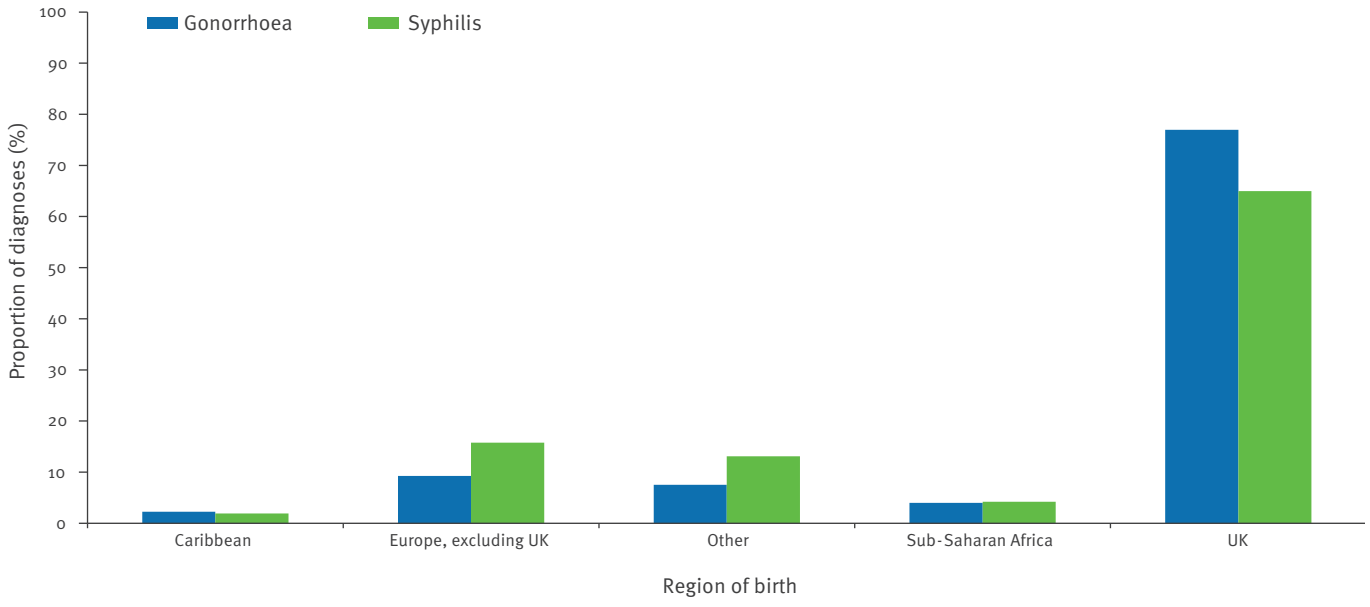
Proportion of gonorrhoea diagnoses in each age group by sexual orientation, England, 2011



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].

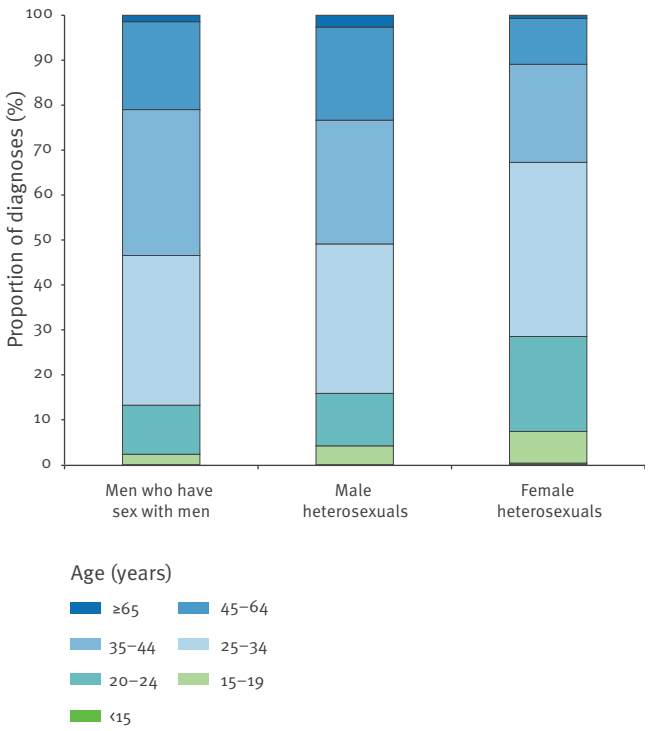
Trends in syphilis

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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An ongoing large outbreak of measles in Merseyside, England, January to June 2012

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From 1 January to 30 June 2012, 359 confirmed and 157 probable cases of measles were reported in Merseyside, England. The most affected age groups were children under five years and young adults from 15 years of age. Most cases have been sporadic. There have been few outbreaks in nurseries; however, no outbreaks have been reported in schools. Of the cases eligible for vaccination, only 3% of the confirmed cases were fully immunised.

From 1 January until 30 June 2012, 1,339 suspected cases of measles were reported by clinicians (family doctors or hospitals) to the Cheshire and Merseyside Health Protection Unit (CMHPU) in England. Of these, 359 (27%) were laboratory-confirmed and 522 (39%) were discarded after laboratory results showed them to be PCR-negative.

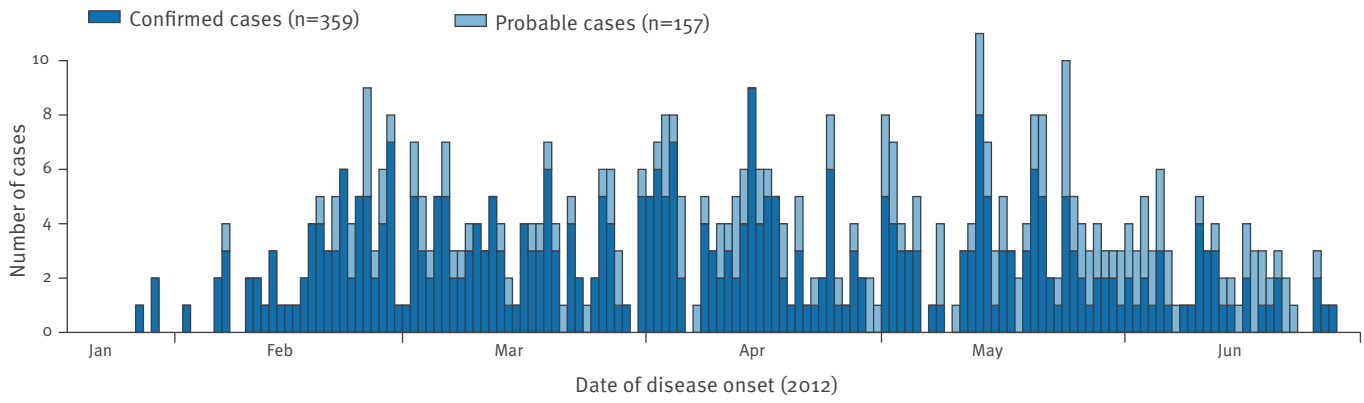
Background

Measles vaccination was introduced in the United Kingdom (UK) in 1968 with the combined measles-mumps-rubella (MMR) vaccine being used since 1988 [1]. As uptake of MMR vaccination increased, the numbers of confirmed cases of measles reduced. Confidence in the MMR vaccine has not always been good as controversies about potential links between MMR vaccine and autism in the late 1990s, which were later proved unfounded [2,3], show uptake in the UK reduced from 92% in 1996 to 80% in 2003 [4,5]. Outbreaks in recent years have mainly occurred in areas of the country or specific groups in which uptake of MMR vaccine is low [6-8].

Merseyside is an area in the north-west of England with a population of around 1.4 million people. Liverpool is

Figure 1

Number of confirmed and probable cases of measles by date of disease onset, Merseyside, England, January–June 2012 (n=516)



the largest metropolitan area in Merseyside. In recent years, uptake of the first dose of MMR vaccine (given from 13 months of age as part of the routine immunisation schedule in the UK) by 24 months of age has been over 92%. Uptake by the age of five years of the second dose (normally offered from the age of three years and four months to five years) has been around 85%. Despite recent small and localised outbreaks of measles in 2009 and 2011 in the neighbouring county of Cheshire, cases in Merseyside have been infrequent and sporadic.

Outbreak description

Case definition

A measles case definition was adapted from national guidelines to reflect local epidemiology [1]. A case was defined as probable when the three following criteria were fulfilled:

- Clinical presentation: fever and measles-like rash and one or more of the following symptoms: cough, conjunctivitis, coryza, or Koplik's spots.
- Residence / reported from: residence in Liverpool or adjacent areas, or being a close contact of a confirmed or probable case of measles, or history of recent travel to endemic or outbreak areas.
- MMR vaccination status: patients who had not received two doses of MMR vaccine (irrespective of age) or with unknown history of MMR vaccination. As most cases at the outset of the outbreak were unvaccinated and partially vaccinated, MMR vaccination status was considered in the case definition for practical purposes.

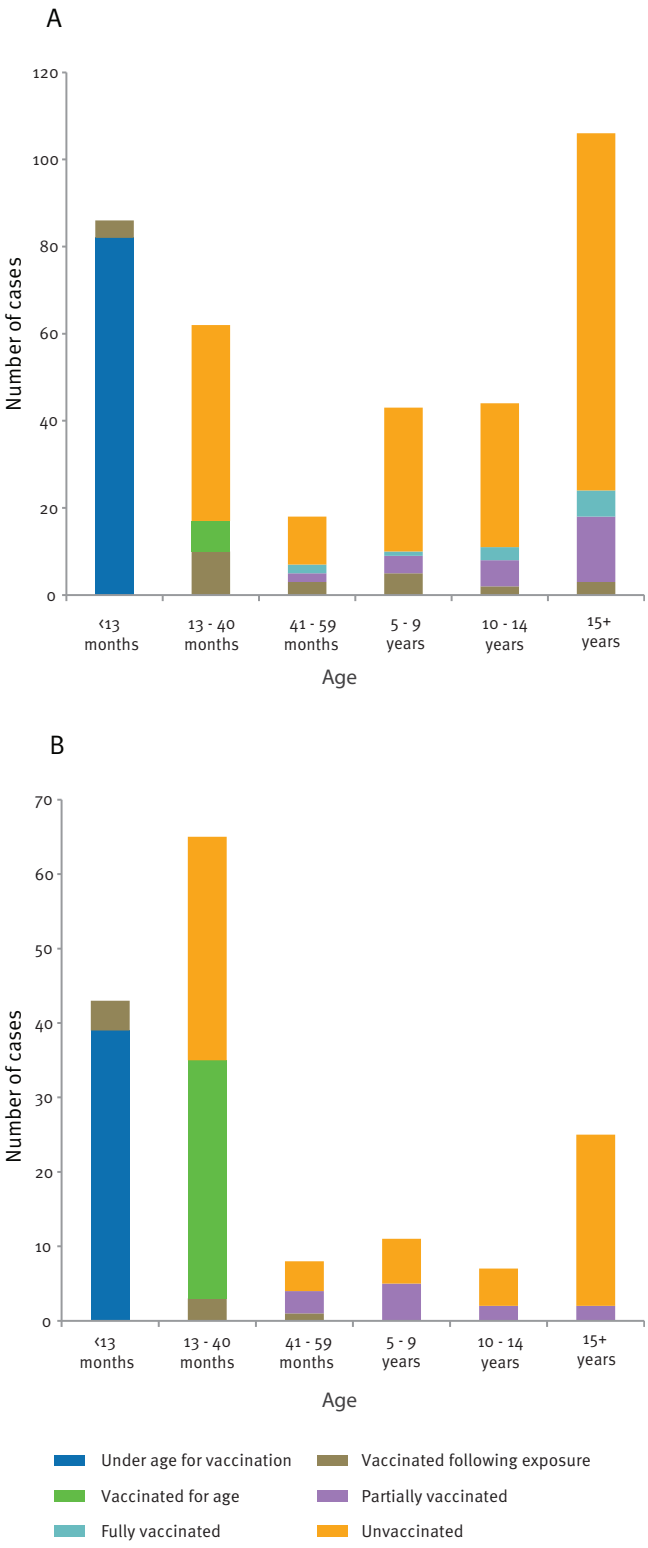
All reported cases not meeting the above criteria were considered as possible. All reported cases were sent a salivary self-testing kit by post or tested in healthcare settings. Cases were considered confirmed if they were measles IgM-positive on saliva, or if they had a positive PCR result from urine, saliva or throat swab. After the first confirmed case of measles in January 2012, all patients were also asked to respond to questions on age, sex, travel history, place of residence, vaccination status, and whether they had been in contact with vulnerable individuals.

Epidemiology

From 1 January until 30 June 2012, 1,339 suspected cases of measles were reported by clinicians (family doctors or hospitals) to CMHPU, of which 359 (27%) were laboratory-confirmed and 522 (39%) were discarded after laboratory results showed them to be PCR-negative. Of the remainder number of cases, based on the case definition, 157 (12%) were classified as probable cases and the rest of 301 cases (22%) were defined as possible. Although there is a statutory duty on doctors to report suspected cases of measles, the number of suspected cases that could have gone unreported is unknown. The epidemic curve shows a typical propagated outbreak pattern (Figure 1). Most cases

Figure 2

Measles-mumps-rubella vaccination status by age of (A) confirmed (n=359) and (B) probable (n=157) measles cases, Merseyside, England, January–June 2012



have been sporadic with very few outbreaks in nurseries. Some family clusters were also identified.
Of the 54 confirmed cases reported before March, at least 16 had documented exposure to another case in a healthcare setting (e.g. waiting rooms in clinics). To date, at least eight confirmed cases out of 359 (2%) occurred in medical staff exposed to cases at work.

The reproductive number (R_0), estimated through Poisson regression in week 3 after the start of the outbreak was R_0= 1.2 (95% CI: 1.1–1.3), which slowly came down to an R_0= 1.00 (95% CI: 0.986–1.018) for confirmed cases in week 26.

Of the 359 confirmed cases, 175 (49%) were female, 84 (23%) were under one year of age and too young to be vaccinated and 106 (30%) were 15-years-old or older. Of the cases aged less than 13 months, most were aged between 6 and 12 months (n=68) and only two cases were under three months of age. Most confirmed cases eligible for vaccination, i.e. >12 months old, were not fully vaccinated (38% had no previous MMR vaccination, 16% had only one dose of MMR) and information was not available for 68 (19%) cases (Figure 2). Twelve of the confirmed cases had been vaccinated with two doses of MMR vaccine. There have been no measles-related deaths to date.

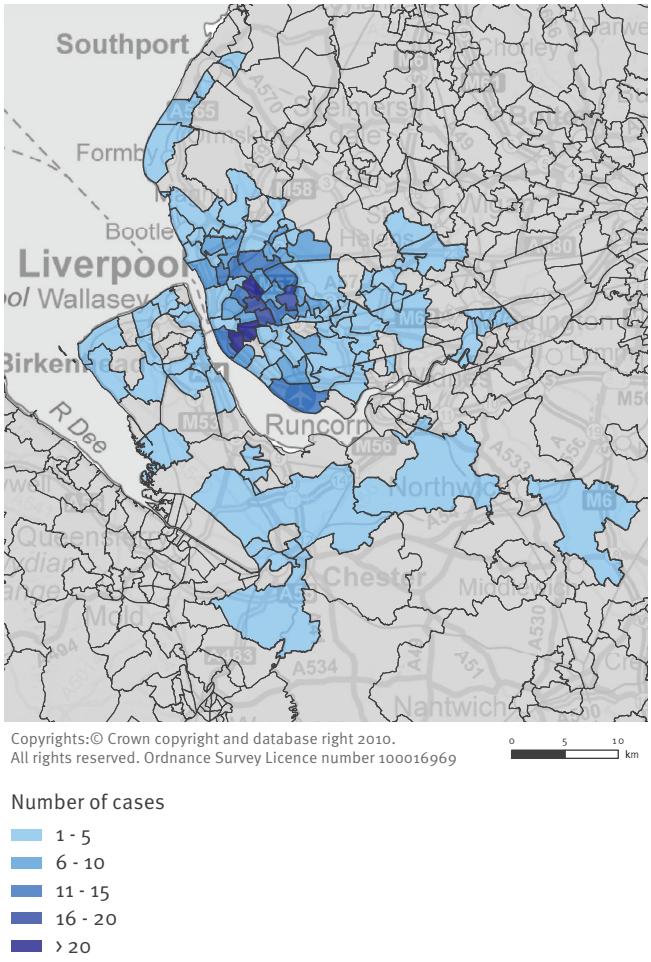
Overall, 63 (18%) of the confirmed cases required hospitalisation, whereas only three (2%) of the probable cases needed to be admitted to hospital. Hospitalisation rates in confirmed cases were higher in the very young (29% in children aged under one year) and older patients (41% of those aged 15 years and older). These figures are likely to underestimate true hospitalisation rates as admission to hospital after a case is reported is unlikely to be captured. Work is ongoing to accurately estimate the number of cases hospitalised during this outbreak.
Most confirmed cases were distributed in and around Liverpool and the neighbouring areas (60% in Liverpool, 15% in Knowsley and 12% in Sefton), although confirmed cases of measles have been reported in all eight of the Primary Care Trusts (PCTs) in Cheshire and Merseyside (Figure 3).

Laboratory results

The genotype of the measles virus identified in 86 cases in Merseyside is B3. This is the predominant genotype circulating in Africa, although it has been reported in 2011 in outbreaks in other parts of Europe [9,10]. Genotype D8 has been identified in seven of the cases reported in Cheshire. D8 strain has also been identified in neighbouring areas: an ongoing outbreak in North Wales and sporadic cases in the Greater Manchester area. Both genotypes are distinct from that previously predominant in the UK (D4) [11]. Although the strain of measles is assumed to have been imported, it has not been possible to confirm this yet, as none of initial probable or confirmed cases reported since January in this outbreak had travelled abroad in the incubation period.

Figure 3

Geographical distribution of confirmed (n=359) and probable (n=157) measles cases, Merseyside, England, January–June 2012



Public health actions

To minimise secondary spread and complications in vulnerable cases, individual risk assessment and contact tracing were conducted and, where appropriate, post-exposure prophylaxis (PEP) of vulnerable contacts (those under 13 months of age, pregnant women and immunocompromised persons) with either MMR vaccine or Human Normal Immunoglobulin (HNIG) was offered as per UK national guidelines [12]. Immunocompromised and pregnant contacts were offered HNIG if they were antibody-negative; infants from 0 to 5 months were offered HNIG, unless their mother was born before 1970 or if the mother had natural measles and was born between 1970 and 1984; infants from six months of age were offered MMR vaccination. Over 1,800 individual risk assessments have been conducted between January and June to ascertain vulnerable contacts and offer PEP. Over 1,000 contacts

were followed up, and over 150 doses of HNIG have been issued to vulnerable contacts.

A Measles Response Centre was set up with support from the eight PCTs in Cheshire and Merseyside to manage the increased workload associated with contact tracing and risk assessment and a clinic was set to facilitate urgent administration of PEP.

Increased vaccination efforts

Existing initiatives to increase MMR vaccination uptake in children and young people have been intensified by primary care and community healthcare staff. Families of children not fully vaccinated have been contacted to encourage vaccination during March and May. Effort has been made to make it as easy as possible for people to take up the opportunity to be vaccinated, e.g. through setting up community clinics at convenient times or home visits. Vaccination was offered at the small number of schools and nurseries where clusters of cases were reported. Coverage statistics for Liverpool, where the majority of the cases occurred, showed uptake improvements from the last quarter of 2011 (October to December) to the first quarter of 2012 (January to March): uptake for the first dose of MMR vaccine by two years of age improved from 95.1% to 95.5%, and for the second dose by five years of age from 85.6% to 88% [13]. Provisional figures for the quarter from April to June 2012 suggest further improvements to 96% and 90% respectively. Similar improvements have been seen in other areas in Merseyside. Additionally, in March alone, over 1,500 children and young adults (aged from 5 to 24 years) were vaccinated across Merseyside. Quarterly coverage data for the period April to June 2012 are not yet available.

Awareness campaign

An intensive media campaign has been mounted with regular press releases issued by the Health Protection Agency on behalf of the Multiagency Outbreak Control Team informing about the outbreak, persons at risk of getting the infection, what to do if infected to minimise exposure to others, and ongoing public health measures. This received coverage by most local and some national newspapers, radio and television on repeated occasions [14].

Discussion and conclusions

This measles outbreak is by far the largest in the North West of England at least since 1996 [15]. Around a quarter of cases have, so far occurred in children too young to be vaccinated. This age group is normally dependant on passive immunity (maternal antibodies) or herd immunity for protection. Given that the uptake of the first dose of MMR vaccine locally in recent years has been relatively high, this large number of cases can partially be explained by the lower levels of immunity in older children and teenagers, and by lower levels of maternal antibodies passed on to babies from vaccinated mothers [16]. Therefore a priority in the control of community outbreaks like this should be to target older children and young adults who missed vaccination in childhood. Lowering the age of the first MMR as a control measure was discussed by the outbreak control team but it was discarded as it was thought that it could divert attention and resources from improving uptake of the routine vaccination programme an the catch up of older children and younger adults.

The low proportion of cases seen in infants less than five months of age is likely to be the result of passive immunity, which wanes later in the infant period [16], hence the larger proportion of cases in children aged between 6 and 12 months.

Exposure to measles in healthcare settings is described in the literature as a risk for acquiring measles and propagating outbreaks [17,18]. In the outbreak described here, a number of measles exposures occurred in healthcare settings due to the difficulty in clinically differentiating measles, particularly in its early stages, from other viral systemic illnesses and the challenge of maintaining airborne precautions in waiting rooms. After isolation of suspected cases and cohorting were put in place in emergency rooms and community clinics, exposures and secondary transmission have been reduced.

Interestingly, the genotype (B3) of measles virus seen in this outbreak is distinct from that of outbreaks seen in the UK in 2010 and 2011. Circulation of B3 in the UK was uncommon before this outbreak, but it has caused outbreaks in Europe in the last three years [10]. The genotype is assumed to have been imported but it has not been possible to determine how it was introduced in Merseyside.

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