RAPID RISK ASSESSMENT

Invasive meningococcal disease among men who have sex with men

3 July 2013

Summary

On 25 June 2013, Germany reported three cases of invasive meningococcal disease (IMD) among men who have sex with men (MSM) caused by *N. meningitidis* serogroup C. All three isolates were serogroup C, PorA-VR1: 5-1; PorA-VR2: 10-8 and FetA: 3-6 and confirmed as ST-11/ET-15. On 26 June, Belgium retrospectively reported (via EPIS-VPD) a single case of IMD in a homosexual male diagnosed in March 2013; infection was due to a strain of the same sequence type as the German strain. The patient had reported travel to London in the three weeks prior to onset of illness. On 26 June, France reported three cases of IMD among MSM living in the Paris area. The three isolates were also of the same sequence type as the German and Belgian strains.

Three similar outbreaks have been previously reported among MSM in Canada and US. The last one involved 22 cases in New York between 2010 and 2013. All cases were caused by *Neisseria meningitidis* serogroup C.

Conclusions and recommendations

- The occurrence of clusters of invasive meningococcal disease among MSM in European metropolitan centres caused by a strain that has been associated with a similar outbreak with a high case-fatality rate in New York City indicates an increased risk of IMD among MSM in such settings in Europe.
- Increased travel and international contact in these settings, including sexual contact with partners from abroad, also in the context of Gay Pride and other festivals, may be factors facilitating the spread of the disease among MSM.
- Further microbiological studies are needed to provide laboratory evidence of direct or indirect transmission between the European cases, as well as between the European and US cases.
- More epidemiological studies and better understanding of common risk factors in the European clusters is needed in order to identify groups of MSM at higher risk. Enhanced surveillance over the summer period should be considered at the European level in order to quickly detect possible spread and to coordinate any required response.
- Member States should consider retrospective investigations of cases of serogroup C IMD in young men in order to identify similar cases in the past.
- Increasing awareness among MSM, through the use of social media and community networks, as well as among healthcare providers is essential for the prevention and early identification of further cases.
- Vaccination with conjugate meningococcal vaccine against serogroup C constitutes an effective prevention intervention, and Member States should consider vaccination as a means of outbreak control where clusters in specific target populations are identified.

Source and date of request

ECDC internal decision, 28 June 2013.

Public health issue

This assessment is related to clusters of cases of invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroup C affecting men who have sex with men (MSM) in Germany and France.

ECDC internal response team

Niklas Danielsson, Lara Payne Hallström, Diamantis Plachouras, Otilia Sfetcu, Gianfranco Spiteri, Marc Struelens, Piotr Wysocki.

Consulted experts

Sophie Bertrand, Tine Grammens, Daniel Levy-Bruhl, Ulrich Marcus, Alison Ridpath, James Stuart, Annie Velter, Ulrich Vogel, Don Weiss, Ole Wichmann.

Background information

Neisseria meningitidis is a common bacterial commensal of the pharyngeal mucosa. The organism can cause invasive meningococcal disease (IMD), which presents as septicaemia, meningitis, or both. Most cases in Europe are caused by *N. meningitidis* serogroups B and C. Overall, IMD has a case-fatality rate of around 10%; however, case fatality rates are sometimes higher in outbreaks and among cases due to serogroup C [1].

The incidence of IMD is decreasing in Europe. The largest reduction is in IMD caused by serogroup C as a result of the introduction of MenC vaccines in a number of countries, but the incidence of cases due to serogroup B has also been falling. Meningococcal serogroup C conjugate vaccine is highly effective in preventing serogroup C meningococcal disease [2], although the effectiveness one year after vaccination can be relatively low when given as a primary course below four months of age.

Carriage of *N. meningitidis* is common and ranges from below 5% in young children to a peak of 20–30% in young adults [3]. Carriage is usually asymptomatic, can last for months, and generally leads to immunity [4]. If illness results, this usually occurs within a few days of acquisition [5]. The risk of disease following infection varies, and is higher for serogroup C than other serogroups [3]. Nasopharyngeal carriage of *N. meningitidis* among men who have sex with men (MSM) has been reported to be higher than for heterosexual men [6], with rates of 15–43% reported. Lower urethral and rectal colonisation has also been reported [6-8].

The risk of IMD is higher in infancy with age-specific rates reaching 13.4 per 100 000 persons in the EU/EEA in 2010 and decreasing with age; the age-specific rates from 20 years of age and above are below 1 per 100 000 population. Other risk factors include passive smoking [9] and overcrowding [10]. The role of HIV infection in IMD is not clear. A study from South Africa suggest that HIV infection increases the risk of IMD by 11 times and increases the case-fatality ratio [9]; it is also reported that the cumulative average incidence of meningococcal disease among patients aged 25 through 64 years with acquired immune deficiency syndrome (AIDS) is 12 times higher than for persons of the same age group in the general population [10].

Typing methods for *N. meningitidis* in Europe have been agreed and standardised across all national reference laboratories by the European Meningococcal Disease Society and implemented through the ECDC-funded Invasive Bacterial Disease Laboratory Network (IBD-LabNet) [11]. The fine typing of *N. meningitidis* includes determination of serogroup, multilocus sequence typing (MLST) at least at clonal complex level, and sequence-based analysis of *por*A variable regions (VRs), VR1 and VR2, and FetA.

Clusters and outbreaks of serogroup C IMD are not infrequent [12-15] and have also affected mass gatherings, like football and rugby games [16, 17] as well as dance parties [18]. In recent years, the emergence of a new virulent strain of *N. meningitidis* serogroup C, belonging to the clonal complex ST-11 has been associated with clusters of more severe disease in France [19]. Response to outbreaks has included chemoprophylaxis and vaccination.

Since 2000, 14 out of 31 EU Member States have introduced meningococcal vaccines in their routine immunisation programmes. Only few countries conducted catch-up campaigns at the time of introduction, and vaccine-induced immunity in the adult population is likely to be low in most countries.

Documented outbreaks of MenC among MSM

- In 2001, six cases were reported among MSM in Toronto, Canada. Cases were between 23 and 39 years of age and did not have direct links with each other; five had direct or indirect contact with bathhouses. Two of the cases were fatal. The outbreak was caused by a genetic variant of the C:2a:P1.2 meningococci; the phenotype of the strain was C:NT:P1.2. Multilocus enzyme electrophoresis demonstrated that all six outbreak strains belonged to the ET-15 clone in the ET-37 complex [20].
- In 2003, six cases of IMD were reported among MSM in Chicago, United States. The cases were between 27 and 42 years of age and had attended a number of MSM-oriented social venues in the city in the 10 days prior to infection. Four had visited the same bar, two had kissed, and two might have had anonymous sex with each other. Three cases were fatal. Five of the cases had positive cultures which showed *N. meningitidis* serogroup C. All of the isolates were indistinguishable on molecular characterisation, but distinct from the Toronto clone. All of the isolates were of MLST sequence type 11 (ST-11). Sequencing of porA VR1 and VR2 resulted in type P1.5-1,10-8 [21].
- Between August 2010 and February 2013, 22 cases of IMD were reported among MSM in New York City, United States. The mean age was 34 years, and 12 were infected with HIV, with a median CD4 cell count of 525 × 10^9 cells/L. There were seven deaths, five of which were among HIV-positive cases. A number of cases had met multiple sexual partners online through the use of mobile phone apps and social networking sites. All were caused by serogroup C and most were indistinguishable by pulsed-field gel electrophoresis (PFGE). The outbreak strain has not been fully described; however, it is related to an outbreak of serogroup C IMD among intravenous drug users in Brooklyn and their close contacts [22]. During 2012, the estimated incidence among MSM aged 18–64 years in New York was 12.6 per 100 000 persons, compared with 0.16 among non-MSM in the same age group. In addition, four cases of IMD have been reported among MSM in Los Angeles since the beginning of 2013 [22-24].

In response to the outbreaks, public health authorities tried to increase awareness in the MSM community and among healthcare workers, and provided chemoprophylaxis and MenC vaccinations for identified contacts. The identification of contacts was especially challenging in the outbreaks among MSM due to the anonymous nature of some of the contacts, particularly those made through smartphone applications:

- During the Toronto outbreak, an immunisation campaign was organised to prevent further cases of IMD. More than 50 immunisation clinics were held in a variety of locations, including bathhouses, an MSM community centre, a sexually transmitted disease clinic, and hospital-based immunodeficiency clinics. Between 25 July and 18 August 2001, more than 3 850 doses of quadrivalent polysaccharide vaccine were administered free of charge to eligible persons (homosexual or bisexual men with one or more of the following risk factors: 20 to 44 years old, sex with more than one partner, visits to bathhouses/gay bars, or has a condition which seriously affects the immune system).
- In response to the Chicago outbreak, authorities distributed health alert notices and fact sheets to healthcare providers serving the MSM community. An eight-day vaccination and prophylaxis campaign was organised, which targeted patrons of MSM-oriented venues in Chicago. Through the six identified sites, 14 267 doses of quadrivalent meningococcal polysaccharide vaccine were provided.
- Following the identification of the New York outbreak, the New York Department of Health and Mental Hygiene initially recommended vaccination of HIV-infected male NYC residents who had intimate contact with any man met online, through a smartphone application, or at a bar or party since 1 September 2012. The recommendation was eventually widened to include HIV-uninfected men with the same high-risk behaviours who reside in areas of Brooklyn where recent cases had clustered. The outbreak was also publicised among the population at risk through advertising, mass e-mail messages on MSM websites, posters distributed at MSM bars and clubs, advertisements on social networking applications for mobile phones, and outreach to community leaders and physician's groups. Vaccinations were also offered through events at bars frequented by MSM.

MSM travel and sexual contact

A number of cases in the New York outbreak reported meeting sexual partners through social networking sites and mobile phone apps. Data collected through the European Men-Who-Have-Sex-With-Men Internet Survey [25] show that among interviewed MSM, 25% reported having sex while travelling with a person not resident in the respondent's country of residence in the previous 12 months. Older men (>25 years), those with a higher education, from large cities, or with HIV infection were more likely to report sex abroad. The countries where respondents most commonly had sex abroad were Spain (18%), Germany (11%), the USA (7%), and France (7%). The most common way of meeting sexual partners abroad was through the internet (32%), gay saunas (13.6%), or gay nightclubs and discos (12.6%).

Gay Pride festivals and other events in 2013

Some of the concern surrounding the reported cases of IMD is due to the opportunities for transmission across Europe over the summer and autumn of 2013. Between June 2013 and October 2013, the European Region of the International Lesbian, Gay, Bisexual, Trans and Intersex Association lists 210 Gay Pride and similar events across Europe [26]. Large numbers of persons attend some of these events, with, for example, two million participants expected in Madrid on 6 July.

Event background information

On 25 June 2013, Germany reported three cases of IMD among MSM due to *N. meningitidis* serogroup C through the Epidemiological Information System for Vaccine-Preventable Diseases (EPIS-VPD). Two of the cases, both 24 years old, presented within two days in May 2013 and had direct contact with each other; one case was fatal, the other remains in a coma. A third, also fatal case, aged 22, was retrospectively identified in a homosexual man who had onset of disease in Berlin in February 2013. All cases were HIV negative. None of the cases or investigated contacts reported travel to New York. Germany estimated the incidence among MSM to be 3.8/100 000 MSM, markedly higher than among young adults in general (0.8 cases/100 000 among 20–24-year-olds). The retrospectively detected case is reported to have visited bars in Berlin commonly frequented by visitors of the international MSM community. For one case, nasal cocaine insufflation was reported. All three cases were due to serogroup C, PorA-VR1: 5-1; PorA-VR2: 10-8 and FetA: 3-6, and confirmed as ST-11/ET-15.

On 26 June, Belgium reported on EPIS-VPD a single case of IMD due to a strain with similar characteristics as the German strain in a homosexual male in March 2013. The patient had returned from a three-week stay in London one week prior to onset of illness. This case was identified retrospectively, following a search prompted by the German post on EPIS VPD.

On 26 June, France reported three cases of IMD among MSM living in the Paris area through the Early Warning and Response System (EWRS). The cases, all frequent visitors of gay bars in the city, were 29, 31 and 45 years of age, and were reported between 13 and 20 June 2013. All three cases were HIV negative. The three isolates were of the same MLST sequence type as the German and Belgian strains. No direct links with the New York City outbreak were identified in the investigation.

European surveillance data

During 2006–2011, 427 cases of meningococcus serogroup C, cc11 (ST-11) were reported to The European Surveillance System (TESSy), accounting for 66% of the 648 serogroup C cases for which the sequence type was reported. In 2011, 123 cases were reported, with the majority from France (57) and Denmark (28). The trend in reported cases caused by ST-11 appears to be increasing; however, this could be attributed to improved reporting. In 2011, 54% of cases were reported among males. Among 20–50-year-olds, males accounted for 54% of cases, which is similar to the proportion of males in this age group among other sequence types reported to TESSy (58%) [27].

Threat assessment for the EU

IMD is a severe infection with a high fatality ratio that occurs either as sporadic cases or in small outbreaks among people who have had direct contact. A limited number of outbreaks among MSM have been reported worldwide and so far none of them have occurred in Europe. However, IMD among MSM is probably underreported because sexual orientation and sexual activities may not be widely recognised as a risk factor for the disease.

A slowly evolving outbreak of IMD among MSM in New York City, which started in 2010, has been linked to the use of mobile phone applications for contacts between MSM and visits to gay bars and clubs. There is so far no convincing evidence of increased IMD transmission in MSM networks outside of New York City. The seven cases in Europe were reported from metropolitan areas and may be a reflection of increased travel and international contact in these settings. So far, the cases in Europe have been sporadic or small clusters. There is no evidence of links between the two clusters and the sporadic cases, nor is there evidence of links to the MSM community in New York City. Experience from the US suggests that such outbreaks may evolve slowly and there is consequently a risk that they go unnoticed in the absence of increased vigilance and awareness.

There is a possibility that the seven cases in Europe were caused by the same strain circulating in the MSM community in New York City, but this remains to be established. The numerous Gay Pride and other events in Europe during the summer season raise concern for increased transmission and outbreaks of IMD.

Conclusions and recommendations

- The occurrence of clusters of invasive meningococcal disease among MSM in European metropolitan centres caused by a strain that has been associated with a similar outbreak with a high case-fatality rate in New York City indicates an increased risk of IMD among MSM in such settings in Europe.
- Increased travel and international contact in these settings, including sexual contact with partners from abroad, also in the context of Gay Pride and other festivals, may be factors facilitating the spread of the disease among MSM.
- Further microbiological studies are needed to provide laboratory evidence of direct or indirect transmission between the European cases, as well as between the European and US cases.
- More epidemiological studies and better understanding of common risk factors in the European clusters is needed in order to identify groups of MSM at higher risk. Enhanced surveillance over the summer period should be considered at the European level in order to quickly detect possible spread and to coordinate any required response.
- Member States should consider retrospective investigations of cases of serogroup C IMD in young men in order to identify similar cases in the past.
- Increasing awareness among MSM, through the use of social media and community networks, as well as among healthcare providers is essential for the prevention and early identification of further cases.
- Vaccination with conjugate meningococcal vaccine against serogroup C constitutes an effective prevention intervention, and Member States should consider vaccination as a means of outbreak control where clusters in specific target populations are identified.

References

1. Meningococcal Reference U, Gray SJ, Trotter CL, Ramsay ME, Guiver M, Fox AJ, et al. Epidemiology of meningococcal disease in England and Wales 1993/94 to 2003/04: contribution and experiences of the Meningococcal Reference Unit. J Med Microbiol. 2006 Jul;55(Pt 7):887-96. PubMed PMID: 16772416.

2. Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet. 2004 Jul 24-30;364(9431):365-7. PubMed PMID: 15276396.

3. Trotter CL, Gay NJ, Edmunds WJ. The natural history of meningococcal carriage and disease. Epidemiol Infect. 2006 Jun;134(3):556-66. PubMed PMID: 16238823. Pubmed Central PMCID: 2870423.

4. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. II. Development of natural immunity. J Exp Med. 1969 Jun 1;129(6):1327-48. PubMed PMID: 4977281. Pubmed Central PMCID: 2138665.

5. Edwards EA, Devine LF, Sengbusch GH, Ward HW. Immunological investigations of meningococcal disease. III. Brevity of group C acquisition prior to disease occurrence. Scand J Infect Dis. 1977;9(2):105-10. PubMed PMID: 408918.

6. Russell JM, Azadian BS, Roberts AP, Talboys CA. Pharyngeal flora in a sexually active population. Int J STD AIDS. 1995 May-Jun;6(3):211-5. PubMed PMID: 7647127.

7. Carlin EM, Hannan M, Walsh J, Talboys C, Shah D, Flynn R, et al. Nasopharyngeal flora in HIV seropositive men who have sex with men. Genitourin Med. 1997 Dec;73(6):477-80. PubMed PMID: 9582465. Pubmed Central PMCID: 1195929.

8. Chapel TA, Gatewood C, Keane MB. *Neisseria meningitidis* in the anal canal of homosexual men. J Infect Dis. 1977 Dec;136(6):810-2. PubMed PMID: 411836.

9. Cohen C, Singh E, Wu HM, Martin S, de Gouveia L, Klugman KP, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. AIDS. 2010 Jun 1;24(9):1351-60. PubMed PMID: 20559040.

10. Cohn AC, MacNeil JR, Clark TA, Ortega-Sanchez IR, Briere EZ, Meissner HC, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013 Mar 22;62(RR-2):1-28. PubMed PMID: 23515099.

11. Harrison OB, Brueggemann AB, Caugant DA, van der Ende A, Frosch M, Gray S, et al. Molecular typing methods for outbreak detection and surveillance of invasive disease caused by *Neisseria meningitidis*, *Haemophilus influenzae* and *Streptococcus pneumoniae*, a review. Microbiology. 2011 Aug;157(Pt 8):2181-95. PubMed PMID: 21622526.

12. Mayoral Cortes JM, Torres Butron E, Garcia Fernandez M, Herrador Ortiz Z, Huarte Osakar S, Santos Luque R, et al. Community cluster of meningococcal disease by *Neisseria meningitidis* serogroup C in Andalusia, Spain, March to May 2011. Euro Surveill. 2012;17(36):20261. PubMed PMID: 22971329.

13. Stefanelli P, Fazio C, Neri A, Isola P, Sani S, Marelli P, et al. Cluster of invasive *Neisseria meningitidis* infections on a cruise ship, Italy, October 2012. Euro Surveill. 2012;17(50). PubMed PMID: 23241233.

14. Fazio C, Neri A, Tonino S, Carannante A, Caporali MG, Salmaso S, et al. Characterisation of *Neisseria meningitidis* C strains causing two clusters in the north of Italy in 2007 and 2008. Euro Surveill. 2009;14(16). PubMed PMID: 19389338.

15. Skoczynska A, Kadlubowski M, Knap J, Szulc M, Janusz-Jurczyk M, Hryniewicz W. Invasive meningococcal disease associated with a very high case fatality rate in the North-West of Poland. FEMS Immunol Med Microbiol. 2006 Mar;46(2):230-5. PubMed PMID: 16487304.

16. Orr H, Kaczmarski E, Sarangi J, Pankhania B, Stuart J, Outbreak Investigation Team. Cluster of meningococcal disease in rugby match spectators. Commun Dis Public Health. 2001 Dec;4(4):316-8. PubMed PMID: 12109402.

17. Reintjes R, Kistemann T, MacLehose L, McKee M, Gill N, Weinberg J, et al. Detection and response to a meningococcal disease outbreak following a youth football tournament with teams from four European countries. Int J Hyg Environ Health. 2002 May;205(4):291-6. PubMed PMID: 12068748.

18. Gorla MC, de Lemos AP, Quaresma M, Vilasboas R, Marques O, de Sa MU, et al. Phenotypic and molecular characterization of serogroup C *Neisseria meningitidis* associated with an outbreak in Bahia, Brazil. Enferm Infecc Microbiol Clin. 2012 Feb;30(2):56-9. PubMed PMID: 22078548.

19. Deghmane AE, Parent du Chatelet I, Szatanik M, Hong E, Ruckly C, Giorgini D, et al. Emergence of new virulent *Neisseria meningitidis* serogroup C sequence type 11 isolates in France. J Infect Dis. 2010 Jul 15;202(2):247-50. PubMed PMID: 20515410.

20. Tsang RS, Kiefer L, Law DK, Stoltz J, Shahin R, Brown S, et al. Outbreak of serogroup C meningococcal disease caused by a variant of *Neisseria meningitidis* serotype 2a ET-15 in a community of men who have sex with men. J Clin Microbiol. 2003 Sep;41(9):4411-4. PubMed PMID: 12958279. Pubmed Central PMCID: 193786.

21. Schmink S, Watson JT, Coulson GB, Jones RC, Diaz PS, Mayer LW, et al. Molecular epidemiology of *Neisseria meningitidis* isolates from an outbreak of meningococcal disease among men who have sex with men, Chicago, Illinois, 2003. J Clin Microbiol. 2007 Nov;45(11):3768-70. PubMed PMID: 17728467. Pubmed Central PMCID: 2168499.

22. Simon MS, Weiss D, Gulick RM. Invasive meningococcal disease in men who have sex with men. Ann Intern Med. 2013 Jun 17. PubMed PMID: 23778867.

23. Centers for Disease C, Prevention. Notes from the field: serogroup C invasive meningococcal disease among men who have sex with men – New York City, 2010–2012. MMWR Morb Mortal Wkly Rep. 2013 Jan 4;61(51-52):1048. PubMed PMID: 23282863.

24. Weiss D, Stern EJ, Zimmerman C, Bregman B, Yeung A, Das D, et al. Epidemiologic investigation and targeted vaccination initiative in response to an outbreak of meningococcal disease among illicit drug users in Brooklyn, New York. Clin Infect Dis. 2009 Apr 1;48(7):894-901. PubMed PMID: 19231975.

25. European Centre for Disease Prevention and Control (ECDC). EMIS 2010: The European Men-Who-Have-Sex-With-Men Internet Survey. Stockholm: ECDC; 2013. Available from: http://ecdc.europa.eu/en/publications/Publications/EMIS-2010-european-men-who-have-sex-with-men-survey.pdf.

26. International Lesbian G, Bisexual, Trans and Intersex Association. Calendar of European pride events 2013 [cited 2013 1 July 2013]. Available from: http://ilga-europe.org/home/issues/assembly_prides/pride_events_in_europe/calendar.

27. European Centre for Disease Prevention and Control (ECDC). Surveillance of invasive bacterial diseases in Europe 2008/09. Stockholm: ECDC; 2011. Available from: http://www.ecdc.europa.eu/en/publications/Publications/1107_SUR_IBD_2008-09.pdf.