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Confirmed inguinal lymphogranuloma venereum genovar L2c in a man who had sex with men, Slovenia, 2015

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A laboratory-confirmed lymphogranuloma venereum (LGV) case in Slovenia was reported in 2015, in a human immunodeficiency virus (HIV)-negative man presenting with inguinal lymphadenopathy. He reported unprotected insertive anal intercourse with two male partners in Croatia. Variant L2c of *Chlamydia trachomatis* was detected in clinical samples. Although the patient was eventually cured, the recommended treatment regimen with doxycycline had to be prolonged.

We describe a laboratory-confirmed case of lymphogranuloma venereum (LGV) in Slovenia, reported to the National Institute of Public Health (NIPH) in 2015 according to the Communicable Diseases Act that provides for mandatory universal reporting of all diagnosed LGV cases.

Clinical case management

In August 2015, a man who had sex with men in his late 40s with no medical history presented at the Clinic for Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, with a one-week history of painful swelling in the left groin, and sore throat. He reported no urethral discharge, no genital ulcers and no systemic symptoms. The baseline leukocytes and C-reactive protein (CRP) were normal and serology excluded infectious mononucleosis, toxoplasmosis and cat scratch disease. Fine needle aspiration tested negative for malignant cells. No antibiotics were prescribed. One week later he presented with fever (›38.5°C), malaise and unilateral inguinal erythema above the much increased swelling. Ultrasound of the left groin revealed two necrotic lymph nodes with abscess formation. Since LGV was suspected a bubo aspirate as well as urethral, pharyngeal and rectal swabs, and a urine sample were obtained for *Chlamydia trachomatis* (CT) DNA detection by real-time polymerase chain reaction (PCR). The urethral sample, bubo aspirate and urine tested positive for CT, meanwhile a real-time PCR specific for serovars of CT causing LGV (PCR LGV) tested positive for a urethral sample and a bubo aspirate. According to the 2013 European guideline on the management of LGV [1], doxycycline 100 mg twice daily (bid) was prescribed for 21 days (Figure). Infections with *Neisseria gonorrhoeae*, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), *Treponema pallidum*, and urogenital mycoplasmas were excluded.

After five days of doxycycline, the patient's general condition improved, but the swelling increased and fluctuated with no spontaneous perforation, so a drainage incision of the swollen lymph node was performed, with pus testing positive by PCR LGV. Sixteen days after surgical incision, pus secretion from the incision wound still tested positive by PCR LGV, while culture yielded no CT isolates. The treatment with doxycycline was prolonged to 24 days by which time the incision wound was clean so the antibiotic therapy was stopped. However, two days later, the patient presented once more with painful erythematous swelling in the same area and abscess formation within necrotic lymph nodes, confirmed by ultrasound. Pus that was evacuated via a Penrose drain tested positive by PCR LGV, therefore the patient was again started on doxycycline. Despite the extended doxycycline treatment and drainage, the inguinal bubo did not subside and ultrasound examination revealed a new suppuration. Thirty-four days after the start of antibiotic therapy three necrotic lymph nodes were extirpated. The lymph node tissue proved positive in CT culture as well as by real-time PCRs for CT DNA and LGV-specific DNA. The doxycycline treatment was prolonged and subsequently stopped after clinical improvement, which occurred 54 days after initial administration. Six days later, the patient presented again with new buboes,

Figure

Timeline of clinical management of a human immunodeficiency virus-negative patient with lymphogranuloma venereum, Slovenia, 2015

Day	-21	1	7	11	12	28	31	33	39	42	62	68	81	123	163
Signs/ symptoms	Infection	Painful unilateral inguinal swelling	Fever, malaise, unilateral inguinal erythema above extremely increased swelling	Sore throat with no pharyngitis	Increased swelling with fluctuation; improvement of general condition	Decreased swelling, no fluctuation, no erythema; pus in incision wound	Clean incision wound	Painful swelling with erythema of the same area	Increased swelling, persistent erythema	Persistent swelling and erythema	No swelling, no erythema, no fluctuation	New swelling medially to previous one	Persistent swelling	Complete scaring of the wounds, no swelling no erythema	Cured
US	–	–	Necrosis of two lymph nodes, abscess formation	–	Large necrotic suppurative lymph nodes	–	–	Abscess formation within necrotic lymph nodes of the same area	Suppuration of another lymph node	–	–	Necrotic lymph node medially to previous ones	Necrotic lymph node persists	No area of inflammation	–
CT DNA & LGV DNA	–	–	**Pos:** urethra, pus from lymph node **Neg:** rectum	**Neg:** pharynx	**Pos:** pus aspirate	**Pos:** pus of incision wound	–	**Pos:** pus aspirate	–	**Pos:** lymph node tissue **&pos isolation**	–	**Neg:** pus aspirate, swab of incision wound	–	–	–
Antibiotic therapy	–	**None**	**Doxy**	**Doxy**	**Doxy**	**Doxy**	**None**	**Doxy**	**Doxy**	**Doxy**	**None**	**Doxy**	**Doxy**	**None**	–
Intervention	–	–	Pus aspiration	–	Drainage incision	–	–	Penrose drain	Penrose drain	Extirpation of the affected lymph nodes	–	Pus aspiration	–	–	–

CT: *Chlamydia trachomatis*; CT DNA: DNA specific for CT detected by real-time polymerase chain reaction (PCR); doxy: doxycycline; LGV: lymphogranuloma venereum; LGV DNA: specific DNA sequence for CT serovars causing LGV detected by a real-time PCR; Neg: negative; Pos: positive; US: ultrasound.

medially from the previous ones, and the ultrasound examination confirmed necrotic lymph nodes. Doxycycline was re-administered. Pus aspiration was negative for CT DNA and LGV-specific DNA by PCR. Clinical and ultrasound follow-up was continued on a two-week basis and the doxycycline treatment was stopped after 116 days, when clinical and ultrasound examination showed no remaining inflammation in the left inguinal region. On follow-up visit 40 days after latest treatment cessation no clinical relapse was noted.

Laboratory confirmation

Urethral, rectum and throat swabs, urine and pus aspirated from the suppurative lymph node, were tested for CT using COBAS TaqMan CT test, v2.0 (Roche, Germany) according to manufacturer's instructions. All except rectum and throat swabs tested positive. Subsequently, LGV infection was identified by a real-time PCR using *pmp*-H gene specific primers together with a specific MGB probe for LGV biovar, including serovars L1, L2, L2b, L3 (Applied Biosystems, US), as described previously [2]. Sequencing of the *omp*A gene was performed to confirm LGV infection and to specify the biovar L strain. Analysing the obtained 1,003 bp double stranded consensus sequence by basic local alignment search tool (BLAST) algorithm showed a 100% match to the CT genotype variant L2c.

Lymph node tissue was cultured for 72 hour with monolayers of cycloheximide-treated McCoy cells. Only for one specimen were very small CT inclusions detected by using MOMP specific monoclonal antibodies conjugated with fluorescein (Trinity Biotech, Ireland).

Microimmunofluorescence test was performed for detection of CT IgG, IgA and IgM specific antibodies (FOCUS Diagnostics, US). High IgG (1:1,024) and IgA (1:128) titres were detected with CT specific antibodies. However, no IgM antibodies were found.

Risk-behaviour and public health response

Our patient reported sex with two male partners four weeks preceding the diagnosis, both of whom he had met on the same day through a mobile phone app. This occurred on the northern Croatian islands. One partner was a Croat, living in Germany, and the other a Slovenian, who had recently travelled to New York and to the coast of mid-western Africa. Our patient reported unprotected insertive anal and oral intercourse and no receptive anal intercourse, fisting or use of sex toys and no use of any drugs. He had no history of previous sexually transmitted infections (STI). The patient was counselled regarding prevention of other STI, including HIV and hepatitis C. Since the identity of contacts was not known, they could not be notified.

Information about the laboratory-confirmed LGV case in Slovenia was published in the last NIPH STI quarterly report. It was also included into the information about LGV in the 'Questions and Answers' format on the NIPH website as there have been no documented LGV cases in our country previously. Safer sex promotion, including condom use promotion, as well as promotion of seeking healthcare when having signs and symptoms of any STI among men who have sex with men (MSM) has been ongoing within the framework of the National strategy for HIV prevention and control according to plans and allocated resources. Information about the case was also forwarded to the three key Slovenian MSM non-governmental organisations for possible dissemination through their communication channels.

Background

Lymphogranuloma venereum is caused by CT strains of serovars L1, L2 and L3. Since 2003 several European countries reported a series of LGV outbreaks among the population of MSM [3]. These cases mostly presented with proctitis, caused by L2b variant and the majority of these MSM were co-infected with HIV and other STI [1,3]. In 2010, a case of LGV in a MSM was detected in a central European country, the Czech Republic [4]. Together with Hungary, these are the only two central European countries that reported LGV cases to the European Centre for Prevention and Control of Disease (ECDC) by the end of 2013 [5]. The number of reported LGV cases to ECDC underestimate true LGV incidence, since many countries do not routinely report LGV cases and because genotyping, which is necessary to confirm cases, is not always available [5].

Discussion

The laboratory-confirmed LGV case reported here was different from the majority of LGV cases in Europe [3,5]. It occurred in a HIV-negative MSM who presented with inguinal lymphadenopathy and who was infected with CT genotype variant L2c. The infection proved difficult to treat with doxycycline according to the current European guidelines [1].

Indeed, in contrast to our case, the majority of LGV cases reported in Europe occur in HIV-positive individuals [3,5]. In 2013, information on HIV status was available for 520 LGV cases (50%) reported to ECDC, of whom 62% occurred in HIV-positive individuals and only 14% in HIV-negative (for 24% HIV status was unknown) [5].

Moreover, while most LGV cases among MSM in Europe present as severe proctitis our case presented as inguinal lymphadenopathy [3].The diagnosis of LGV can easily be missed in the first stages of infection as well as with overt clinical signs, especially, if it is uncommon in a particular geographic area. Knowledge of high-risk sexual behaviours of a patient may be crucial for correct diagnosis. The differential diagnosis of inguinal lymphadenopathy must include LGV, particularly in MSM.

As opposed to our case where disease was caused by CT genotype variant L2c, most LGV cases among MSM in Europe are infected with CT serovar L2b [1]. Although cases of LGV caused by this new LGV L2c variant, that originates from a recombination of L2 and D strains of

CT, have been reported, they all clinically manifested as proctitis and not as inguinal lymphadenopathy [6,7].

In addition, our patient did not respond to treatment with doxycycline 100 mg bid for 21 days, according to the 2013 European guideline on the management of lymphogranuloma venereum [1]. Eventually, prolonged treatment with doxycycline (109 days), drainage of pus and extirpation of necrotic lymph nodes resulted in cure. Several studies have shown the failure of the recommended treatment regimen [8,9]. The new LGV variant L2c with inguinal clinical presentation might be more aggressive compared with the variant L2b, as it also was present in the anorectal region. Thus this may require a different treatment approach with extended doxycycline regimen or new antimicrobial options [7]. Revision of the current clinical guideline on the management of LGV, possibly distinguishing between the two variants, could be considered.

In Slovenia the national guidelines for treatment of STIs follow the European STI treatment guidelines [10], yet taking into account the national particularities. Careful clinical and microbiological monitoring of future LGV cases within the network of STI outpatient services will be crucial in evaluating any need to change the current LGV treatment guidelines. Since in Slovenia clinicians treating MSM with signs and symptoms of possible LGV rarely demand confirmation of LGV infection even when CT has been confirmed in a clinical specimen, the occurrence of LGV among Slovenian MSM is most likely underestimated. Although there exists laboratory capacity to diagnose LGV, the Institute of Microbiology and Immunology, Faculty for Medicine, University of Ljubljana that performs the vast majority of STI tests in Slovenia, reported only five LGV test requests in 2015. In addition to the notification of the presented laboratory-confirmed LGV case in Slovenia, in 2015 the NIPH received also a notification of three suspected LGV cases that occurred in HIV-positive MSM, all presenting with clinical signs and symptoms consistent with LGV, including proctitis. Being managed at a private medical facility they did not wish the suggested microbiological testing (in one case CT infection was confirmed) because this would incur additional expenses to them, therefore they opted for empirical treatment. Their symptoms resolved after administration of doxycycline 100 mg bid for 21 days.

Enhanced awareness of LGV together with promoting national LGV testing might unveil a hidden LGV epidemic among MSM in Slovenia. The proposed diagnostic algorithm for any MSM presenting with clinical signs and symptoms suggesting a possible LGV and a laboratory-confirmed CT infection, includes LGV confirmation at any of the STI outpatient services. However, additional resources are required for its realisation. Similar approaches in other central European countries with no cases reported to ECDC up to date might unveil hidden LGV epidemics among MSM.

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Conflict of interest

None declared.

Authors' contributions

MM, IK and DK wrote the manuscript together. MM, JVZ, DVV treated the patient. DK, RK performed microbiological testing.

References

1. de Vries HJC, Zingoni A, Kreuter A, Moi H, White JA, European Branch of the International Union against Sexually Transmitted Infections, et al. 2013 European guideline on the management of lymphogranuloma venereum.J Eur Acad Dermatol Venereol. 2015;29(1):1-6. DOI: 10.1111/jdv.12461 PMID: 24661352
2. Morré SA, Spaargaren J, Fennema JS, de Vries HJ, Coutinho RA, Peña AS. Real-time polymerase chain reaction to diagnose lymphogranuloma venereum.Emerg Infect Dis. 2005;11(8):1311-2. DOI: 10.3201/eid1108.050535 PMID: 16110579
3. Savage EJ, van de Laar MJ, Gallay A, van der Sande M, Hamouda O, Sasse A, et al. Lymphogranuloma venereum in Europe, 2003-2008. Euro Surveill. 2009;14(48):19428.PMID: 20003898
4. Vanousova D, Zakoucka H, Jilich D, Rozsypal H, Stankova M, Zufanova S, et al. First detection of Chlamydia trachomatis LGV biovar in the Czech Republic, 2010-2011. Euro Surveill. 2012;17(2):20055.PMID: 22264863
5. European Centre for Disease Prevention and Control (ECDC). Sexually transmitted infections in Europe 2013. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/sexual-transmitted-infections-europe-surveillance-report-2013.pdf
6. Stary G, Meyer T, Bangert C, Kohrgruber N, Gmeinhart B, Kirnbauer R, et al. New Chlamydia trachomatis L2 strains identified in a recent outbreak of lymphogranuloma venereum in Vienna, Austria. Sex Transm Dis. 2008;35(4):377-82. DOI: 10.1097/OLQ.0b013e31815d6df8 PMID: 18209688
7. Somboonna N, Wan R, Ojcius DM, Pettengill MA, Joseph SJ, Chang A, et al. Hypervirulent Chlamydia trachomatis clinical strain is a recombinant between lymphogranuloma venereum (L(2)) and D lineages. MBio. 2011;2(3):e00045-11. DOI: 10.1128/mBio.00045-11 PMID: 21540364
8. Méchaï F, de Barbeyrac B, Aoun O, Mérens A, Imbert P, Rapp C. Doxycycline failure in lymphogranuloma venereum.Sex Transm Infect. 2010;86(4):278-9. DOI: 10.1136/sti.2009.042093 PMID: 20660591
9. Oud EV, de Vrieze NH, de Meij A, de Vries HJ. Pitfalls in the diagnosis and management of inguinal lymphogranuloma venereum: important lessons from a case series.Sex Transm Infect. 2014;90(4):279-82. DOI: 10.1136/sextrans-2013-051427 PMID: 24787368
10. The International Union against Sexually Transmitted Infections (IUSTI). Available from http://www.iusti.org/regions/europe/euroguidelines.htm

Emergence of influenza A(H1N1)pdm09 genogroup 6B and drug resistant virus, India, January to May 2015

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To investigate the aetiology of the 2015 A(H1N1)pdm09 influenza outbreak in India, 1,083 nasopharyngeal swabs from suspect patients were screened for influenza A(H1N1)pdm09 in the state of Madhya Pradesh. Of 412 positive specimens, six were further characterised by phylogenetic analysis of haemagglutinin (HA) sequences revealing that they belonged to genogroup 6B. A new mutation (E164G) was observed in HA2 of two sequences. Neuraminidase genes in two of 12 isolates from fatal cases on prior oseltamivir treatment harboured the H275Y mutation.

An epidemic of influenza A(H1N1)pdm09, affecting over 39,000 persons and causing more than 2,500 deaths occurred in India in 2015 [1]. We show that genotype 6B strains forming two sub-lineages circulated during the outbreak. Comparison of the sequences of six outbreak strains recovered in this work, to other published genotype 6B sequences, also reveals a unique combination of previously-reported mutations in the haemagglutinin (HA) gene. Two of the six sequences additionally display a E164G mutation in HA2, which has not been reported to date, moreover a N129D mutation in HA1 is observed for two sequences derived from patients with severe disease. Among strains analysed from 12 fatal cases on prior oseltamivir treatment, two harbour the H275Y mutation in the neuraminidase (NA) gene, which confers resistance to this antiviral.

Description of the study

Sampling and testing for influenza A(H1N1) pdm09

A total of 1,083 acute phase nasopharyngeal swab specimens from patients suspected of influenza (as prior defined [2]), were referred by 13 district health authorities of Madhya Pradesh, India between 29 January and 7 May 2015. Upon specimen collection, the travel history, treatment status, and symptoms of the patients were recorded in addition to age, sex and place of residence. The samples were handled in a designated biosafety level (BSL) 3 laboratory and viral RNA was extracted using QIAamp viral RNA mini kit (Qiagen). The RNA samples were screened by World Health Organization (WHO)–Centers for Disease Control and Prevention (CDC) approved quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) for influenza A(H1N1)pdm09 [3].

Molecular analyses of the strains

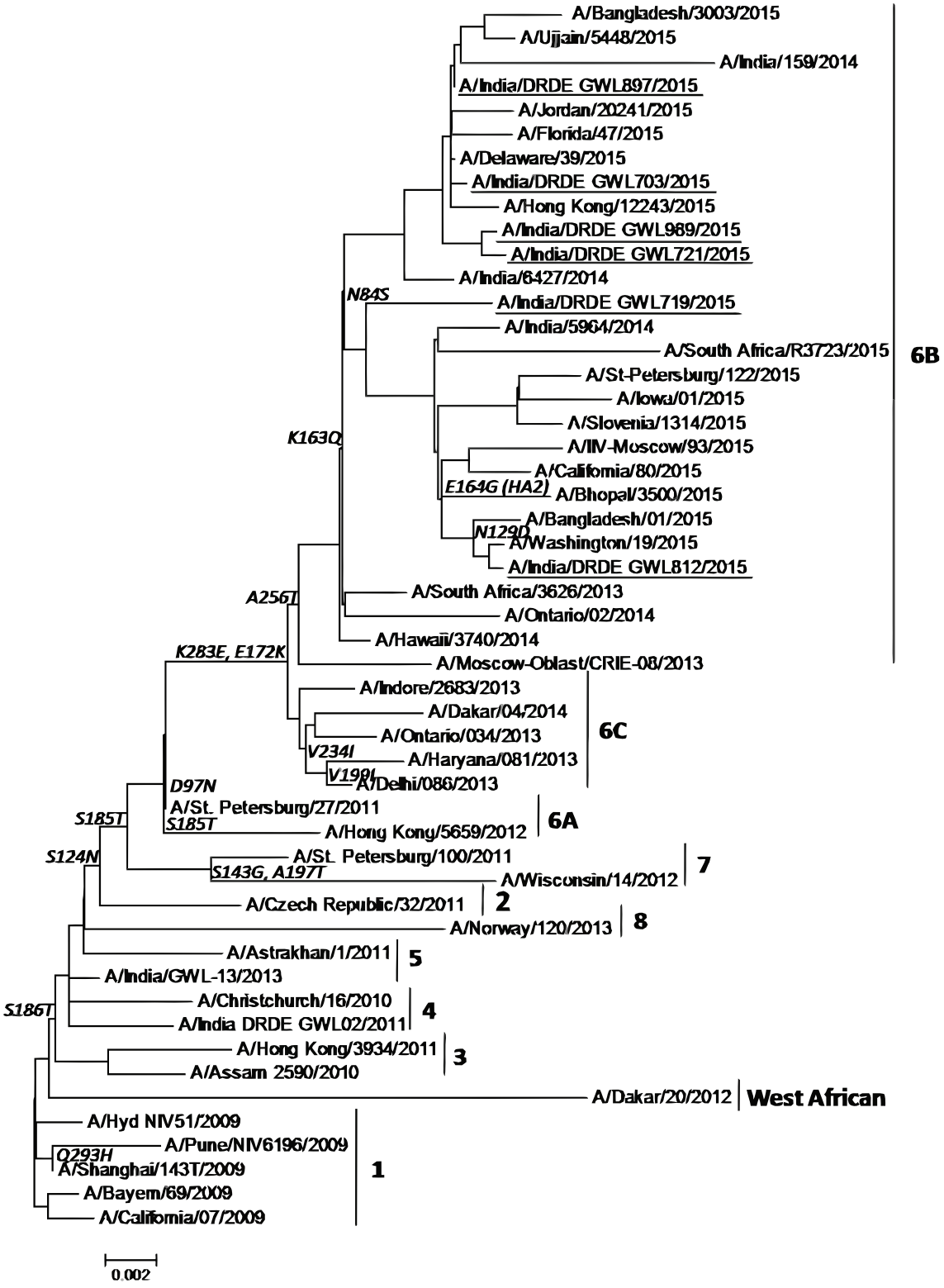
Six clinical samples testing positive for influenza A(H1N1)pdm09 by qRT-PCR were selected based on patients' disease severity category A (n=2; A/India/DRDE_GWL897/2015 and A/India/DRDE GWL721/2015), B (n=2; A/India/DRDE_GWL703/2015, A/India/DRDE_GWL989/2015), and C (n=2; A/India/DRDE GWL719/2015 and A/India/DRDE_GWL812/2015) as previously described [2], and used for direct nucleotide (nt) sequencing of the haemagglutinin (HA) gene. A phylogenetic analysis was performed by comparing with nt sequence of 45 globally diverse influenza A(H1N1)pdm09 viruses retrieved from GenBank (as further shown in the phylogenetic tree) and the Global Initiative on Sharing Avian Influenza Data (GISAID) (Table 1). The phylogenetic tree in this analysis was constructed with maximum likelihood and bootstrap analysis of 1,000 replicates using Mega 5.03 software [4]. Further the amino acid substitutions were marked at the major branches for better clarity.

Influenza A(H1N1)pdm09 HA amino-acid sequences were inferred from the genetic sequences obtained in this study, and the protein structures were modelled using Modeller software and compared to prototype A/California/07/2009 through Discovery studio client 4.1.

The qRT-PCR positive samples from 12 fatal cases, all on prior oseltamivir therapy, were also tested for a mutation (H275Y) conferring resistance to this antiviral by PCR–restriction fragment length polymorphism (RFLP)

Figure 1

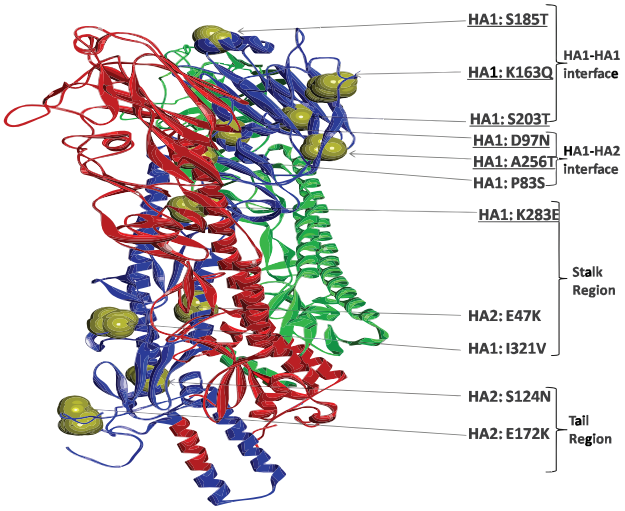
Phylogenetic analysis of influenza A(H1N1)pdm09 viral sequences derived from an outbreak in India, 2015



Amino acid substitutions are depicted on the major branches at the nodes. Samples recovered in this study are underlined. GenBank accession numbers of sequences in the tree are: A/Bhopal/3500/2015 (KT426698); A/California/80/2015 (KT836680); A/Delaware/39/2015 (KT836926); A/Delhi/086/2013 (KP317290); A/Florida/47/2015 (KT836928); A/Haryana/081/2013 (KP317285); A/Hawaii/3740/2014 (CY187658); A/India/DRDE_GWL703/2015 (KT867221); A/India/DRDE_GWL719/2015 (KT867219); A/India/DRDE_GWL721/2015 (KT867223); A/India/DRDE_GWL812/2015 (KT867224); A/India/DRDE_GWL897/2015 (KT867220); A/India/DRDE_GWL989/2015 (KT867222); A/India/GWL-13/2013 (KF683625); A/Indore/2683/2013 (KF886296); A/Iowa/01/2015 (KT836709); A/Moscow-Oblast/crie--08/2013 (KF013860); A/Ontario/02/2014 (KP864396); A/Ontario/034/2013 (KF886365); A/Ujjain/5448/2015 (KT369727); A/Washington/19/2015 (KT836815); A/Wisconsin/14/2012 (KC891394); A_Assam_2590_2010 (JN600357); A_Hyd_NIV51_2009 (GU292350); A_India_DRDE_GWL02_2011 (JQ319657); A_Pune_NIV6196_2009 (GU292352); A_Shanghai_143T_2009 (GQ411907).

Figure 2

Three-dimensional quaternary structure of trimeric haemaglutinin protein, identifying mutations compared to A/California/07/2009 in the proteins in this study, India, 2015



In this structure two monomers are coloured green and red. In the third monomer, residues are coloured blue and amino acid residues differing from A/California/07/2009 are denoted as yellow spheres. The mutations are listed to the right of the molecule, along with the four structural regions that contain the mutations. Mutations characterising genogroup 6B are underlined.

analysis of the NA gene [5]. Of these 12 cases, one (with corresponding sample: A/India/DRDE GWL719/2015) also belonged to the group of six patients, from whom the HA gene was sequenced. The PCR–RFLP positive samples were further confirmed through nt sequencing of the target sites of the NA gene.

Results of screening for influenza A(H1N1) pdm09

A total of 1,083 patients, including 525 males, were screened for influenza A(H1N1)pdm09 by qRT-PCR. The age range of these patients varied from 0 to 90 years-old, with age groups between 21 and 30 year-old (n=284) as well as between 31 and 40 year-old (n=179) representing 26% and 17% of the total respectively (Table 2). Of the 1,083 clinical samples tested, 412 (38%) were found positive for influenza A(H1N1)pdm09 virus. Similar to patients screened, most of those testing positive were from young age groups, with 21 to 30 years-old (n=104; 25%) representing the majority, followed by 31 to 40 year-olds (n=69; 17%). The positivity rate among the different age groups varied from 25 to 59% (Table 2). The female to male sex ratio of PCR positive patients was found to be 1.20:1.

The clinical features of PCR confirmed patients revealed presence of cough (n=378; 92%), fever >38°C (n=350; 85%), sore throat (n=331; 80%), shortness of breath (n=271; 66%) and catarrh (n=253; 61%).

Molecular characteristics of outbreak strains

HA sequences from six samples of influenza A(H1N1) pdm09-positive patients in this study were recovered and deposited in National Center for Biotechnology Information (NCBI)-GenBank under the accession numbers KT867219, KT867220, KT867221, KT867222, KT867223 and KT867224. The HA open reading frame was found to be 1,701 nt in length.

Phylogenetic analysis of the six sequences, together with geographically diverse global influenza A(H1N1) pdm09 viral sequences, including sequences recovered in India in previous years, revealed that the six sequences clustered with genogroup 6B sequences. Sequences from India in 2014 also belonged to this genogroup (e.g. A/India/159/2014, A/India/6427/2014 and A/India/5964/2014). Moreover, within this genogroup, two distinct lineages could be observed (Figure 1).

Four study sequences (A/India/DRDE GWL703/2015, A/India/DRDE GWL721/2015, A/India/DRDE GWL897/2015 and A/India/DRDE GWL989/2015), which were derived from patients with disease severity categorised as A and B, were found grouped into one lineage (lineage 1) of genogroup 6B. Lineage 1 additionally included some Indian sequences (A/India/159/2014 and A/India/6427/2014) from 2014. The two remainder study sequences (A/India/DRDE GWL719/2015 and A/India/DRDE GWL812/2015), both originating from category C patients, segregated into the other genogroup 6B lineage (lineage 2). A 2014 Indian sequence (A/India/5964/2014) also belonged to lineage 2. The two lineages differed by an amino acid substitution at position 84 in HA1, whereby lineage 1 sequences had an N and lineage 2 sequences an S.

No clear difference was observed between 2015 and 2014 Indian sequences included in the analysis, except that 2015 strains in lineage 2 (A/India/DRDE GWL719/2015 and A/India/DRDE GWL812/2015) encoded a N129D mutation in HA1 (HA1 numbering system).

The comparative analysis of inferred peptide-sequences confirmed that the 2015 Indian viruses harboured the signature amino acid substitutions of genogroup 6B (D97N, K163Q, S185T, S203T, A256T and K283E) [6,7].

In addition to the six substitutions defining genotype 6B, all HA-sequenced viruses in this study presented five mutations compared to prototype A/California/07/2009, namely, P83S, I321V in HA1, as well as E47K, S124N, and E172K in HA2 (Figure 2). Further to these total 11 mutations, N129D was found in HA1 sequences of two specimens (A/India/DRDE GWL719/2015 and A/India/DRDE GWL812/2015) from patients with severe disease (both category C including one fatal case). Also, E164G was found in HA2 of A/India/DRDE GWL721/2015 and A/India/DRDE GWL812/2015.

Table 1

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing Avian Influenza Data (GISAID)'s EpiFlu Database for complete haemagglutinin-gene-based phylogenetic analysis in this study

ID	S	Country	Collection date	Isolate name	Originating laboratory	Submitting laboratory	Authors
EPI624748	HA	Russian Federation	2015-Feb-26	A/St-Petersburg/122/2015	WHO National Influenza Centre Russian Federation	Crick Worldwide Influenza Centre	–
EPI630634	HA	Hong Kong (SAR)	2015-Jun-14	A/Hong Kong/12243/2015	Government Virus Unit	Crick Worldwide Influenza Centre	–
EPI630684	HA	South Africa	2015-Jun-29	A/South Africa/R3723/2015	Sandringham, National Institute for Communicable Diseases	Crick Worldwide Influenza Centre	–
EPI630652	HA	Slovenia	2015-Mar-05	A/Slovenia/1314/15	Laboratory for Virology, National Institute of Public Health	Crick Worldwide Influenza Centre	–
EPI624704	HA	Russian Federation	2015-Mar-10	A/IIV-Moscow/93/2015	Ivanovsky Research Institute of Virology RAMS	Crick Worldwide Influenza Centre	–
EPI589565	HA	Jordan	2015-Mar-22	A/Jordan/20241/2015	Laboratory Directorate	Crick Worldwide Influenza Centre	–
EPI253705	HA	Germany	2009-Jan-01	A/Bayern/69/2009	Robert-Koch-Institute	Robert-Koch-Institute	Biere, B; Schweiger, B
EPI278607	HA	New Zealand	2010-Jul-12	A/Christchurch/16/2010	Canterbury Health Services	WHO Collaborating Centre for Reference and Research on Influenza	Deng, Y-M; Iannello, P; Caldwell, N; Leang, S-K; Komadina, N
EPI319590	HA	Russian Federation	2011-Feb-28	A/Astrakhan/1/2011	WHO National Influenza Centre Russian Federation	National Institute for Medical Research	–
EPI319527	HA	Russian Federation	2011-Feb-14	A/St. Petersburg/27/2011	WHO National Influenza Centre Russian Federation	National Institute for Medical Research	–
EPI416411	HA	Norway	2013-Jan-02	A/Norway/120/2013	WHO National Influenza Centre	National Institute for Medical Research	–
EPI390473	HA	Hong Kong (SAR)	2012-May-21	A/Hong Kong/5659/2012	Government Virus Unit	National Institute for Medical Research	–
EPI326206	HA	Hong Kong (SAR)	2011-Mar-29	A/Hong Kong/3934/2011	Government Virus Unit	National Institute for Medical Research	–
EPI466626	HA	South Africa	2013-Jun-06	A/South Africa/3626/2013	Sandringham, National Institute for Communicable Diseases	National Institute for Medical Research	–
EPI539474	HA	Senegal	2014-Feb-05	A/Dakar/04/2014	Institut Pasteur de Dakar	National Institute for Medical Research	–
EPI417122	HA	Senegal	2012-Dec-09	A/Dakar/20/2012	Institut Pasteur de Dakar	National Institute for Medical Research	–
EPI319447	HA	Czech Republic	2011-Jan-18	A/Czech Republic/32/2011	National Institute of Public Health	National Institute for Medical Research	–
EPI320141	HA	Russian Federation	2011-Mar-14	A/St. Petersburg/100/2011	Russian Academy of Medical Sciences	Centers for Disease Control and Prevention	–
EPI626148	HA	Bangladesh	2015-May-04	A/Bangladesh/3003/2015	Institute of Epidemiology Disease Control and Research (IEDCR) & Bangladesh National Influenza Centre (NIC)	Centers for Disease Control and Prevention	–
EPI626140	HA	Bangladesh	2015-May-10	A/Bangladesh/01/2015	Institute of Epidemiology Disease Control and Research (IEDCR) & Bangladesh National Influenza Centre (NIC)	Centers for Disease Control and Prevention	–
EPI176620	HA	United States	2009-Apr-09	A/California/07/2009	Naval Health Research Center	Centers for Disease Control and Prevention	–
EPI536832	HA	India	2014-May-24	A/India/5964/2014	National Institute of Virology	Centers for Disease Control and Prevention	–
EPI537951	HA	India	2014-Mar-06	A/India/6427/2014	National Institute of Virology	Centers for Disease Control and Prevention	–
EPI644248	HA	India	2014-Feb-05	A/India/159/2014 (H1N1)	National Centre for Disease Control	National Centre for Disease Control (NCDC)	–

S: segment.

We acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's EpiFlu Database on which this research is based. All submitters of data may be contacted directly via the GISAID website www.gisaid.org.

Table 2

Age distribution of persons with confirmed influenza A(H1N1)pdm09 positive samples, Madhya Pradesh, India, 29 January–7 May 2015 (n=412)

Age group in years	Positivity rates n/N (%)[a]
0–5	31/92 (34)
6–10	13/30 (43)
11–20	44/111 (40)
21–30	104/284 (37)
31–40	69/179 (38)
41–50	56/150 (37)
51–60	48/134 (36)
61–70	27/69 (39)
71–90	20/34 (59)

[a] Where in each age group, n is the number of positive samples and N the total number of samples screened and the percentage is the positivity rate.

A thorough *in silico* analysis revealed that all of the 11 mutations common to the 2015 Indian sequences studied here, have been reported in different strains of influenza A(H1N1)pdm09 virus isolated from various parts of the world in the past [8-10]. However, to date, no single strain was reported to possess all these 11 mutations together, except the Indian 2015 strains sequenced in this study. Moreover, the E164G mutation found in HA2 of A/India/DRDE GWL812 and A/India/DRDE GWL721 has not previously been reported.

Modelling reveals that mutations are found in the head, stalk and tail region of HA protein but the majority were found in the head region which covers the major antigenic binding region. The HA2 E172K mutation showed distinct structural changes in the tail region compared to the influenza A(H1N1)pdm09 virus prototype [11].

Two influenza A(H1N1)pdm09 strains from 12 fatal cases were found to possess H275Y oseltamivir resistance mutation.

Discussion

Influenza A viruses have been responsible for four influenza pandemics in last century viz., Spanish influenza (H1N1) in 1918, Asian influenza (H2N2) in 1957, Hong Kong influenza (H3N2) in 1968 and pandemic influenza (H1N1) in 2009, which was caused by influenza A(H1N1)pdm09. During the 2009 pandemic period (2009–2010), India was affected with around 50,000 cases and a case fatality of 6% [12]. After the end of the 2009 pandemic, the virus continued to circulate at low level in the population, and during the period from 2011 to 2014 the circulation of the virus declined [13]. From January to May 2015 however, over 39,000 persons in India were affected by a new epidemic of influenza A(H1N1)pdm09, with more than 2,500 deaths [1]. The outbreak spread across 22 of the 29 states in the country, making it the largest since 2009. This sudden re-emergence and wide spread simultaneous reporting of influenza A(H1N1)pdm09 along with higher number of hospitalisations and deaths was a major public health concern.

By further characterising the strains infecting patients positive for influenza A(H1N1)pdm09 through HA phylogeny, this study finds that sequences of genogroup 6B were circulating during the 2015 epidemic. The genogroup 6B was found to evolve from a Russian isolate (A/Moscow-Oblast/CRIE-08/2013) and is since then circulating in many parts of the world. However, this is the first report from India regarding circulation of genogroup 6B, coinciding with a large scale outbreak [1].

Researchers from Massachusetts Institute of Technology (MIT) have recently reported mutations D225N, and T200A in a 2014 Indian strain (A/India/6427/2014, which also clusters with genogroup 6B sequences in the phylogenetic tree Figure 1) making the virus more infectious [14]. Although we did not find these two mutations in our study, all the sequences that we characterised harboured five mutations (P83S, I321V in HA1, as well as E47K, S124N, and E172K in HA2), which although previously described, have not been reported in combination. Moreover, two isolates from patients with severe disease harboured a N129D mutation in HA1 and two isolates had a mutation in HA2, E164G, that has not been observed to date. These unique features of the viruses found here may have played a role in shaping the large scale epidemic with cases of severe disease. On the other hand, the 2015 epidemic in India may be attributed to lack of immunity among an immune-naïve population. It is also noteworthy that seasonal influenza vaccination is not very common in India.

Some limitations of the study include that the samples were only tested for influenza A(H1N1)pdm09 virus, whereby only 38% of samples tested were positive. Therefore, co-circulation of other influenza subtypes or types could not be ruled out. Moreover the sequence analysis was conducted with only few positive samples that did not cover other gene segments than the HA and NA genes.

The influenza A(H1N1)pdm09 virus represents a quadruple reassortment of two swine, one human, and one avian strain of influenza virus [15]. The largest proportion of genes comes from swine influenza viruses (30.6% from North American swine strains, 17.5% from Eurasian swine strains), followed by North American avian strains (34.4%) and human influenza strains (17.5%). It will be interesting to investigate the involvement of any gene reassortment in the 2015 outbreak in India through complete genome sequencing.

Two of 12 strains from fatal cases were found to harbour a mutation conferring resistance to oseltamivir. Learning more about the 2015 strains circulating

in India could help public health officials determine treatment options and inform on vaccines for the next influenza season, which is likely to include currently circulating strains [16].

Our findings show the importance of systematic molecular surveillance to provide insight into strains circulating during influenza epidemics.

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Conflict of interest

None declared.

Authors' contributions

Manmohan Parida: Design & supervision; Paban Kumar Dash: Sequence and Phylogeny; Jyoti S Kumar: RT-PCR; Gaurav Joshi: Sample processing, modeling & phylogeny; Kundan Tandel: Sample processing; Shashi Sharma: RT-PCR; Ambuj Srivastava: Sample processing; Ankita Agarwal: Sample processing; Amrita Saha: Sample processing; Shweta Saraswat: Sample processing; Divyanshi Karothia: Sample processing; Vatsala Malviya: Sample processing.

References

1. Cousins S. Death toll from swine flu in India exceeds 2500.BMJ. 2015;351:h4966. DOI: 10.1136/bmj.h4966 PMID: 26384378
2. Pandemic influenza (h1n1) 2009. CD Alert. 2009; 13(2). Available from: http://www.ncdc.gov.in/writereaddata/linkimages/Aug-Sep_092813460594.pdf
3. World Health Organization (WHO), Centers for Disease Control and Prevention (CDC). CDC protocol of real-time RTPCR for swine influenza A(H1N1). Geneva: WHO; 2009. [Accessed 15 Mar 2015]. Available from: http://www.who.int/csr/resources/publications/swineflu/CDCrealtimeRTPCRprotocol_20090428.pdf
4. Tamura K, Peterson D, Peterson N, Stecher G, Nei M, Kumar S. MEGA5: molecular evolutionary genetics analysis using maximum likelihood, evolutionary distance, and maximum parsimony methods.Mol Biol Evol. 2011;28(10):2731-9. DOI: 10.1093/molbev/msr121 PMID: 21546353
5. Nukiwa N, Suzuki A, Furuse Y, Shimabukuro K, Odagiri T, Khandaker I, et al. Simplified screening method for detecting oseltamivir resistant pandemic influenza A (H1N1) 2009 virus by a RT-PCR/restriction fragment length polymorphism assay. J Virol Methods. 2010;170(1-2):165-8. DOI: 10.1016/j.jviromet.2010.09.005 PMID: 20833206
6. Spanish Influenza Sentinel Surveillance System (SISS),Jiménez-Jorge S, Pozo F, de Mateo S, Delgado-Sanz C, Casas I, García-Cenoz M, et al. . Influenza vaccine effectiveness in Spain 2013/14: subtype-specific early estimates using the cycEVA study.Euro Surveill. 2014;19(9):20727. DOI: 10.2807/1560-7917.ES2014.19.9.20727 PMID: 24626206
7. European Centre of Disease Prevention and Control (ECDC). Surveillance Report. Influenza virus characterization. Summary Europe, December 2013. Stockholm: ECDC; 2013. Available from: http://www.ecdc.europa.eu/en/publications/Publications/influenza-virus-characterisation-dec-2013.pdf
8. Castelán-Vega JA, Magaña-Hernández A, Jiménez-Alberto A, Ribas-Aparicio RM. The hemagglutinin of the influenza A(H1N1) pdm09 is mutating towards stability.Adv Appl Bioinform Chem. 2014;7:37-44. DOI: 10.2147/AABC.S68934 PMID: 25328411
9. Dakhave M, Khirwale A, Patil K, Kadam A, Potdar V. Whole-genome sequence analysis of postpandemic influenza A(H1N1)pdm09 virus isolates from India.Genome Announc. 2013;1(5):e00727-13. DOI: 10.1128/genomeA.00727-13 PMID: 24051317
10. European Centre of Disease Prevention and Control (ECDC). Surveillance Report. Influenza virus characterization, summary Europe, September 2015. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/influenza-virus-characterisation-september-2015.pdf
11. Deem MW, Pan K. The epitope regions of H1-subtype influenza A, with application to vaccine efficacy.Protein Eng Des Sel. 2009;22(9):543-6. DOI: 10.1093/protein/gzp027 PMID: 19578121
12. Cases of Influenza A H1N1 (Swine Flu) – State/UT- wise, Year-wise for 2009, 2010, 2011 and 2012; Ministry of Health & Family Welfare, Govt. of India. Available from: http://mohfw.nic.in/showfile.php?lid=2121
13. Broor S, Krishnan A, Roy DS, Dhakad S, Kaushik S, Mir MA, et al. Dynamic patterns of circulating seasonal and pandemic A(H1N1)pdm09 influenza viruses from 2007-2010 in and around Delhi, India. PLoS ONE. 2012;7(1):e29129. DOI: 10.1371/journal.pone.0029129 PMID: 22235265
14. Tharakaraman K, Sasisekharan R. Influenza surveillance: 2014-2015 H1N1 "swine"-derived influenza viruses from India.Cell Host Microbe. 2015;17(3):279-82. DOI: 10.1016/j.chom.2015.02.019 PMID: 25766285
15. Neumann G, Noda T, Kawaoka Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus.Nature. 2009;459(7249):931-9. DOI: 10.1038/nature08157 PMID: 19525932
16. Ortiz JR, Sotomayor V, Uez OC, Oliva O, Bettels D, McCarron M, et al. Strategy to enhance influenza surveillance worldwide. Emerg Infect Dis. 2009;15(8):1271-8. DOI: 10.3201/eid1508.081422 PMID: 19751590

Research article

Evaluation of a temporary vaccination recommendation in response to an outbreak of invasive meningococcal serogroup C disease in men who have sex with men in Berlin, 2013–2014

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Meningococcal serogroup C (MenC) vaccination of men who have sex with men (MSM) was temporarily recommended to control an outbreak of invasive MenC disease among MSM in Berlin in 2012–2013. Vaccination was offered to HIV-infected MSM free of charge; others had to request reimbursement or pay out of pocket. We aimed to assess (i) awareness and acceptance of this recommendation through an online survey of MSM, (ii) implementation through a survey of primary care physicians and analysis of vaccine prescriptions, and (iii) impact through analysis of notified cases. Among online survey respondents, 60% were aware of the recommendation. Of these, 39% had obtained vaccination (70% of HIV-infected, 13% of HIV-negative/non-tested MSM). Awareness of recommendation and vaccination were positively associated with HIV infection, primary care physicians' awareness of respondents' sexual orientation, and exposure to multiple information sources. Most (26/30) physicians informed clients about the recommendation. Physicians considered concerns regarding reimbursement, vaccine safety and lack of perceived disease risk as primary barriers. After the recommendation, no further outbreak-related cases occurred. To reach and motivate target groups, communication of a new outbreak-related vaccination recommendation should address potential concerns through as many information channels as possible and direct reimbursement of costs should be enabled.

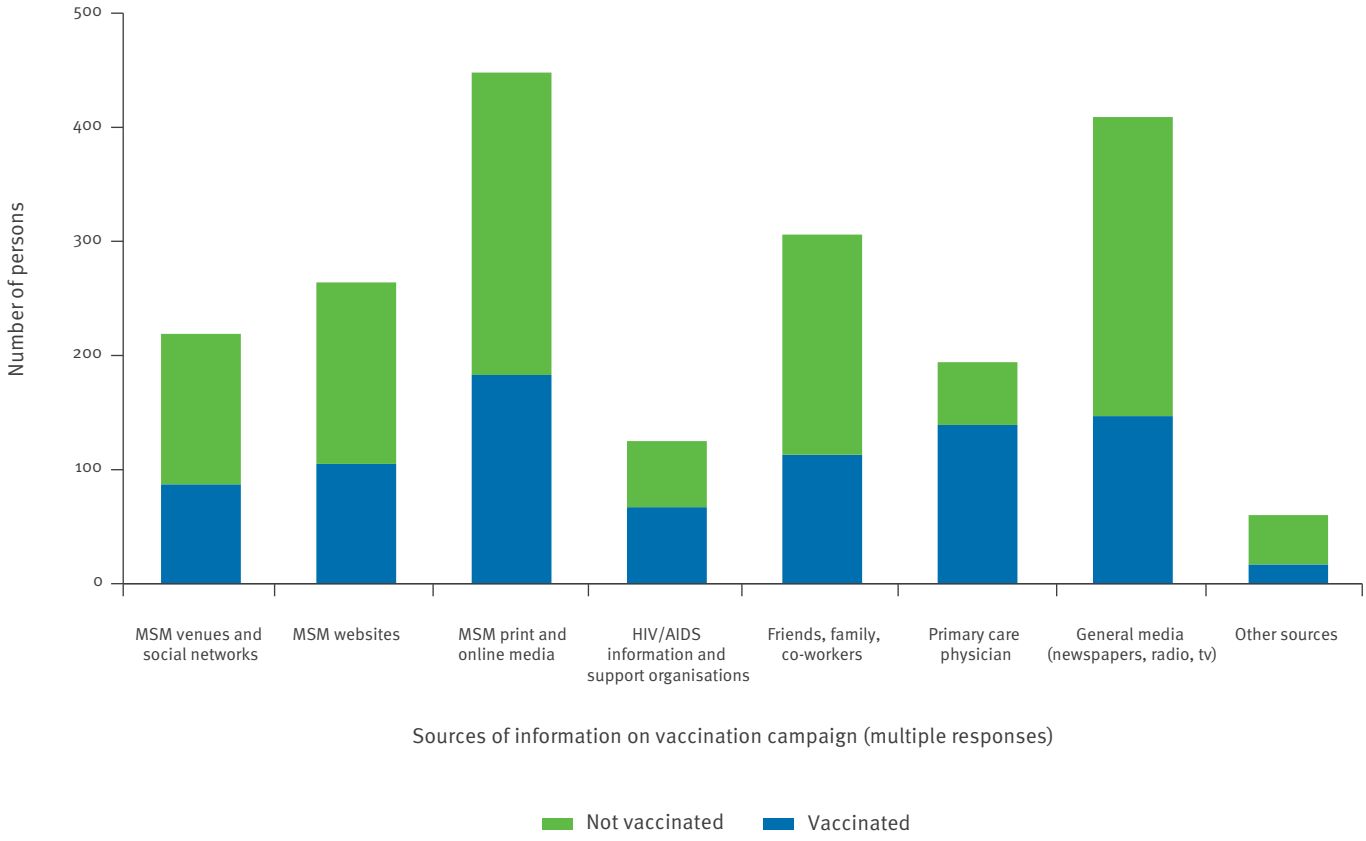
Introduction

Neisseria meningitidis (Nm) is a gram-negative diplococcus that commonly colonises the human pharynx and respiratory tract [1]. Nm can sometimes cause invasive meningococcal disease (IMD), presenting as meningitis and/or sepsis. Thus far, 13 serogroups have been identified; of these A, B, C, W, X and Y cause virtually all IMD [2]. Similar to other European and North American countries [3], serogroup B, followed by C, predominate in Germany, with IMD incidence showing a decreasing trend, from 0.95 cases/100,000 inhabitants in 2001 to 0.45/100,000 in 2011 [4]. Overall case fatality from 2009 to 2011 was 7.8%, significantly higher for meningococcal C (MenC) (10.9%) than for meningococcal B (MenB) disease (7.6%). Incidence was highest in infants (8.1 cases/100,000 inhabitants) and toddlers (4.8), with a second, smaller peak in 15-19 year-old adolescents (2.0) [4].

The overall prevalence of nasopharyngeal meningococcal carriage is about 10%, but varies markedly in different age and population groups [5-8]. Very high Nm carriage rates of over 40% have been reported in men who have sex with men (MSM) [9-10], and one study reported higher carriage rates in MSM (23.8%) than in heterosexual men (11.6%) [11]. Further known risk factors for meningococcal disease, such as exposure to tobacco smoke and crowding [12, 13], may also be more prevalent in venues where MSM meet. Since 2001, IMD clusters in MSM have been reported in Toronto (2001) [14], Chicago (2003) [15] and New York City (2010–2013) [16-17]. All outbreaks were caused by MenC and were of the multilocus sequence type (MLST) 11 (ST-11) [18]. The outbreaks in Toronto and Chicago (six cases each) ended rapidly after carrying out targeted MenC vaccination campaigns in the gay communities affected.

Figure 1

Number of men who have sex with men reached by various information sources and vaccination status after meningococcal serogroup C vaccination recommendation, Berlin, November 2013–January 2014



MSM: men who have sex with men.

However, the New York outbreak (22 cases) was more protracted despite intensive efforts to vaccinate MSM.

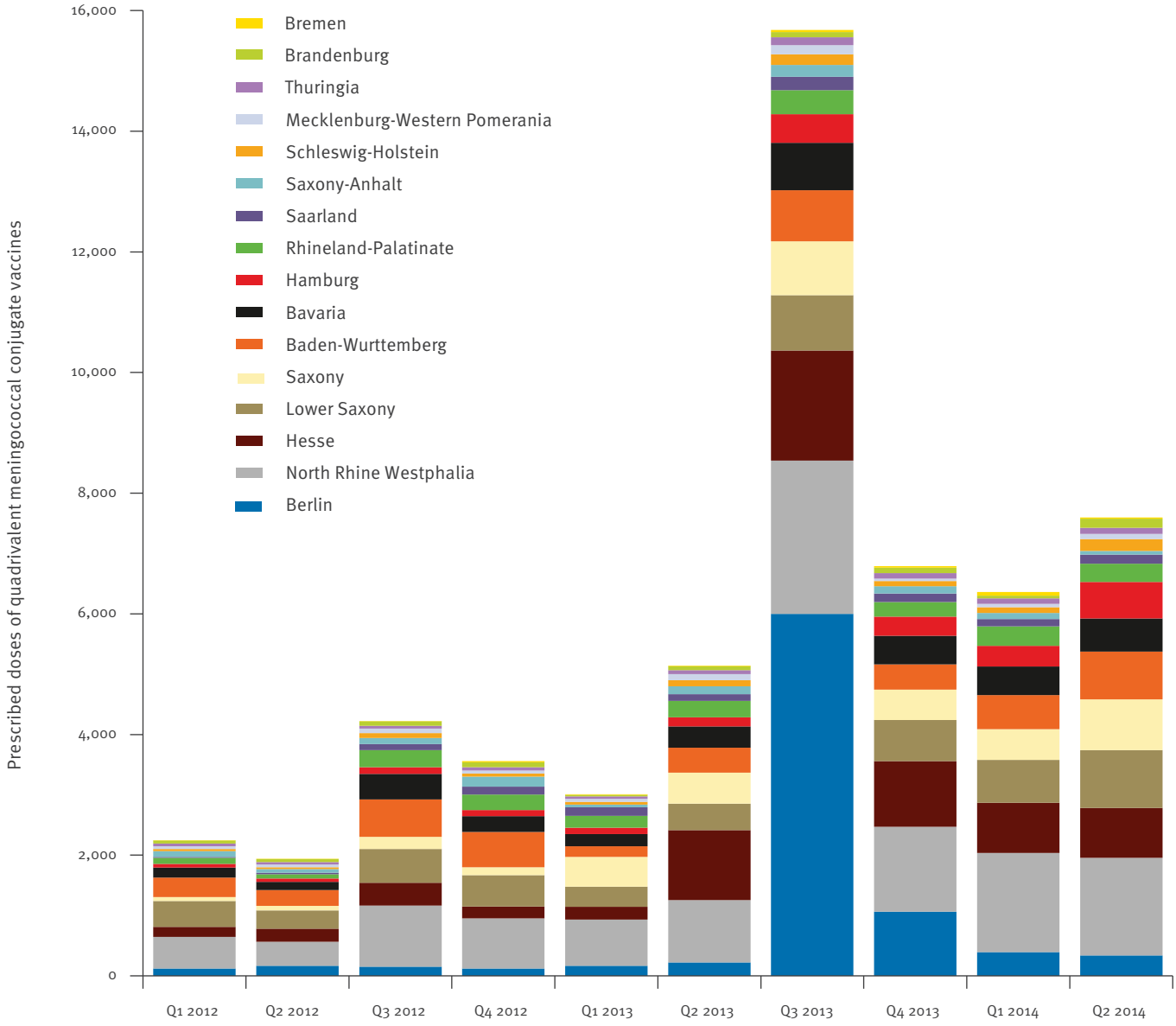
From October 2012 to May 2013, five IMD cases in MSM living in Berlin were notified to local health authorities (LHA). The patients were between 22 and 28 years old; none were HIV-positive. All cases were caused by MenC strains belonging to ST-11 of the fine type PorA(P)1.5-1,10-8:FetA(F)3-6 [19]. In addition, four of the five strains from these patients had fHbp allele 766, that had not been described previously. All five cases presented with severe sepsis; four died. Only two of the cases had a definite epidemiological link, having spent a night together shortly before illness onset [19]. In this time period MenC clusters among MSM were also reported from New York, Los Angeles and Paris and a single case from Belgium. All European strains showed similar characteristics [20].

It has been estimated that 80,000 MSM (95%CI 74,000–104,000) aged 20–59 years live in Berlin [21-22]. Among these, an estimated 10,800 MSM had been diagnosed with HIV as of the end of 2013 [22]. Assuming the age distribution among MSM is similar to that of men in the general population, an estimated 18,000 MSM aged 20–29 years live in Berlin, among whom four MenC IMD cases occurred in the first half of 2013. The resulting incidence of 11 cases/100,000 inhabitants [23] was markedly higher than the nationwide incidence of 0.7/100,000 in 20–29 year old men in 2012 [24].

Prevention of IMD with meningococcal conjugate vaccines is highly effective [25]. In Germany, MenC vaccination was recommended for all one year-old children in 2006; older children can obtain the vaccine on an individual basis free-of-charge. Vaccination coverage of adolescents increased gradually, reaching 59% among 15-17 year-olds in 2013 based on statutory health insurance (SHI) claims data (Thorsten Rieck, personal communication, January 2015). In addition, vaccination against serogroups ACWY (MenACWY) is recommended for persons with congenital or acquired immunodeficiencies with residual T- and/or B-cell function, especially complement/properdin deficiencies, hypogammaglobulinaemia, and asplenia. While HIV infection is not explicitly listed, it is considered to be an indication for meningoccal vaccination under this rubric. Quadrivalent meningococcal vaccination is also recommended for travellers to endemic areas. Finally, vaccination is recommended to control regional IMD outbreaks when three or more cases of an identical

Figure 2

Number of prescribed doses of quadrivalent meningococcal serogroups ACWY conjugate vaccines according to quarter and federal state, Germany, 1 January 2012–30 June 2014



Q: quarter.

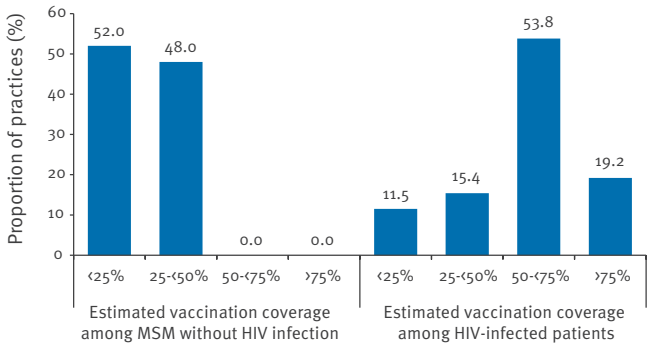
For information on the prescribed doses, see Text.

serogroup occur in a specific age group in a particular region within three months in conjunction with an attack rate of 10 or more cases per 100,000 inhabitants in the respective population [26].

Thus, in response to this outbreak, the competent authorities of the federal state of Berlin recommended meningococcal vaccination for all MSM with a vaccine licensed for adults to protect against serogroup C as of 27 July 2013, following advice from the Berlin Advisory Board for Immunisation and announced in a press release on 18 July 2013 [27]. Female partners of MSM were not targeted in this recommendation. The recommendation was to remain in effect until 31 January 2014, but was subsequently extended to 31 December 2014, pending an evaluation of its impact. The recommendation did not entail reimbursement of the vaccine by SHI. However, most insurance companies adopted a policy of individual evaluation and reimbursement upon request. The gay community and physicians were informed via internet forums as well as by radio, TV and the print media. The recommendation was promoted in counselling centres of the gay and lesbian community in Berlin, by the German and Berlin AIDS service organisations (DAH and BAH, respectively), the AIDS working group of practicing physicians in Berlin (AK AIDS), the German association of practising physicians treating

Figure 3

Vaccination coverage for meningococcal serogroups C and ACWY vaccination as estimated by physicians at the time of the survey in participating practices for men who have sex with men without HIV-infection and HIV-infected patients



MSM: men who have sex with men.

HIV-infected patients (DAGNÄ) and via regional and national gay Internet portals.

Our goal was to evaluate the awareness and implementation of the temporary MenC vaccination recommendation for MSM in Berlin by surveying MSM and physicians. In addition, we analysed IMD cases notified in Berlin after implementation of the recommendation, including the molecular epidemiology of MenC cases, to confirm that the outbreak had been interrupted.

Methods

Internet-based survey among men who have sex with men

Starting in the late 1980s, anonymous knowledge, attitude and behaviour (KAB) surveys on HIV/AIDS were conducted every two to four years among MSM in Germany [28]; from 2007 onwards these were carried out online exclusively. Questions on the Berlin vaccination recommendation were included in the nationwide survey made available online from November 2013 until mid-January 2014. Participants living in Berlin were asked how they obtained information on the MenC vaccination campaign and whether they obtained vaccination. They were recruited by personalised instant messages and banners on social networking and dating websites for MSM. Two multivariable logistic regression models were constructed to analyse factors potentially associated with awareness of the recommendation and with MenC vaccine uptake, respectively. The following factors were investigated: demographic and behavioural characteristics such as age, educational status, income, reported sexual orientation, openness regarding sexual orientation towards colleagues and their physician, affinity to gay subculture (visiting gay venues), information seeking pertaining to HIV, HIV testing, and HIV status, number of sexual partners in the previous year, and sources used to obtain information on the Berlin vaccination recommendation. Respondents who reported MenC vaccination before the recommendation was issued were excluded from this analysis.

The online survey protocol was evaluated and approved by the ethical review board of the Charité University Clinic in Berlin (EA1/266/13).

Prescription of meningococcal conjugate vaccines

The number of monovalent MenC or quadrivalent MenACWY conjugate vaccine doses prescribed within SHI from July 2013 to March 2014 was analysed based on data from Insight Health (http.//insight-health.de/). This database contains data from pharmaceutical data-processing centres on all directly reimbursed prescriptions for › 99% of persons insured by SHI (85% of the population) in Germany. However, data on recipients' age and sex are not available. SHI reimburses all prescriptions for vaccinations recommended by the German Standing Committee for Vaccination (STIKO). Thus, prescriptions for meningococcal vaccination of people living with HIV (PLWHIV) were included in the Insight Health database, since vaccination was already recommended by STIKO for this group before the outbreak. However, meningococcal vaccination for non-HIV-infected, otherwise-healthy MSM living in Berlin as recommended by the Berlin authorities was not covered directly by SHI and thus not registered in this database. Rather, patients had to fill individual private prescriptions that SHI reimbursed on a voluntary basis.

Survey of primary care physicians

In February 2014 we conducted a cross-sectional survey among privately practicing physicians belonging to AK AIDS, who represent almost all primary HIV care providers and are known as MSM-friendly. We assumed that most MSM would seek vaccination from one of these practices, which covered a range of relevant medical specialties. The study was presented in January 2014 at the AK AIDS working group meeting to motivate members to participate. Since most members worked in group practices, we conducted the survey per practice. We used a written anonymous questionnaire eliciting participants' demographics (age, sex, physician specialty, location and type of practice), the number of MSM clients and HIV-infected patients in the practice population, information channels used to inform patients, vaccination practices in general and MenC vaccination practices in particular, including type of vaccine used, possible obstacles to immunisation and vaccine uptake by MSM. After pre-testing, the questionnaire was distributed on 14 January 2014 to all 45 practices, with a total of about 70 practicing physicians. Returned questionnaires were entered electronically using Microsoft Excel 2010. We conducted a descriptive analysis, including calculation of proportions and 95% confidence intervals (CI).

Surveillance of invasive meningococcal disease cases in men who have sex with men after meningococcal C vaccine recommendation

In Germany, surveillance of IMD is based on statutory notification by physicians and laboratories to LHAs [29]. LHAs transmit laboratory-confirmed and epidemiologically linked IMD cases to the Robert Koch Institute (RKI) via the federal state authorities according to a standardised case definition. These data are routinely matched to data of invasive meningococcal strains that undergo molecular genetic typing at the national reference laboratory for meningococci and *Haemophilus influenzae* (NRLMHi) as described previously [30]. During the outbreak, all LHA in Berlin were requested to elicit sexual orientation of IMD cases in men which is otherwise not routinely done. Ethical approval was not necessary since according to the Protection against Infection Act, local health authorities are authorised to request information on any risk factors relevant to outbreak control in patients and forward this information anonymously to the Robert Koch Institute. Possible outbreak-related cases were defined as follows: All MenC IMD in MSM aged 20-49 years, living in Berlin with illness onset from 1 July 2013 to 31 August 2014.

Results

Internet-based survey among men who have sex with men

MenC-related questions were answered by 1,471 online survey participants. Of these, 42 (2.9%) reported MenC vaccination before the recommendation was published and were excluded from further analysis, leaving a study sample of 1,429 men.

The median age of respondents was 40 years (range: 16–78 years); 72% had at least a high school diploma. The majority (78%) reported exclusively male sexual partners in the previous 12 months, but only 37% reported regularly visiting gay venues. About half (52%) stated that they were single, 44% reported having a steady male partner, and 4% a steady female partner. Most (81.5%) had been tested for HIV at least once; among those tested (n = 1,199), 23% were HIV-positive. Table 1 presents demographic, behavioural and information-seeking characteristics stratified according to awareness of the recommendation and vaccine uptake.

Of all participants, 852 (59.6%) were aware of the recommendation and 333 (23.3%) obtained MenC vaccination. Positive HIV status, the primary healthcare provider being aware of the respondent's sexual orientation, having received information about the recommendation from a larger number of different information channels, higher educational level, and › 10 sexual partners in the past year were independently associated with both awareness of the recommendation and obtaining vaccination (Table 2). Frequent visits to gay venues were also significantly associated with awareness, while men who reported having mainly female partners were less likely to have heard of the recommendation (Table 2). Over two-thirds (69.6% (183/263) of HIV-infected MSM, but only 12.9% (150/1,166) of non-tested or HIV-negative participants reported obtaining MenC vaccination.

MSM whose physicians personally recommended MenC vaccination during a healthcare visit had the highest vaccine uptake, followed by those who learned of the recommendation through HIV/AIDS information and support organisations. However, only 18.8% (268/1,429) of all survey participants and 31.5% of survey participants aware of the vaccination recommendation (268/852) were exposed to these sources. The highest number of MSM was reached through MSM online and print media, followed by general print and broadcast media, but vaccine uptake among these MSM was lower (Figure 1).

Prescription of meningococcal conjugate vaccines

From Q1 2012 to Q2 2014, the number of monovalent conjugate MenC vaccine doses (Menjugate Kit, NeisVac-C and Meningitec) prescribed and directly reimbursed by SHI fluctuated between 159,000 and 213,000, with peak values in Q3 2012 as well as Q3 2013 in all federal states and the lowest number in Q1 2013. In contrast, the number of prescribed and directly reimbursed doses of quadrivalent conjugate ACWY vaccines (Nimenrix and Menveo) increased markedly in Q3 of 2013 (Figure 2). By far the largest increase (ca 37-fold, from a mean of 159 doses per quarter in Q1 2012 to Q2 2013 to 6,001 in Q3 2013) was seen in Berlin, but increases were also seen in other states. Thereafter, the number of prescriptions for MenACWY vaccines decreased rapidly, but remained two- to three-fold higher in most federal states than prior to Q3 2013. In Berlin, 7,798 doses of quadrivalent vaccine were prescribed in Q3 2013 to Q2 2014, compared with 635 expected doses based on the mean of 159 per quarter in Q1 2012 to Q2 2013. If we assume the 7,163 excess doses were mainly used to vaccinate MSM known to be HIV-positive, this implies up to 66% of the estimated 10,800 MSM with HIV diagnoses living in Berlin received meningococcal vaccination.

Survey of primary care physicians

Of 45 distributed questionnaires, 30 (66.7%) were returned completed. The respondents' median age was 50 years (range: 41–64 years), 22 were male and six female. The two most common disciplines of the surveyed practices were family (n=12) and internal medicine (n=13), followed by dermatology (n=4). This was similar to the distribution of disciplines among all contacted practices. Of responding physicians, 22 worked in group practices and eight in solo practices. Practice size was highly variable, and thus also the number of patients with an existing or new indication for MenC vaccination. Based on the participants' estimates, an average of 480 HIV-infected patients (median: 425; range 1–2,000) and 530 MSM without HIV-infection

Table 1

Demographic and behavioural characteristics of Internet survey respondents resident in Berlin stratified according to awareness of vaccine recommendation and vaccine uptake, November 2013–January 2014 (n=1,429)

		Unaware of campaign n=577		Aware, not vaccinated n=519		Aware, vaccinated n=333		Row totals N = 1,429	Pearson's chi-squared test
		n	%	n	%	n	%		
Age group (years old)	<25	89	15.4%	68	13.1%	14	4.2%	171	<0.001
	≥25	488	84.6%	451	86.9%	319	95.8%	1,258	
Education	<High school diploma	176	31.2%	131	25.5%	84	25.7%	391	0.075
	≥High school diploma	389	68.8%	382	74.5%	243	74.3%	1,014	
Monthly income	<€1,000	125	23.2%	89	18.2%	56	17.7%	270	0.062
	≥€1,000	413	76.8%	401	81.8%	260	**82.3%**	1,074	
Openness regarding sexual orientation towards co-workers	≥50% know	275	50.3%	369	**73.8%**	252	79.5%	896	<0.001
	<50% know	272	49.7%	131	26.2%	65	**20.5%**	468	
Openness regarding sexual orientation towards primary care provider	Is informed	211	36.6%	285	54.9%	294	88.3%	790	<0.001
	Does not know/unsure	366	63.4%	234	45.1%	39	11.7%	639	
Visiting gay venues	Infrequent	435	75.5%	212	34,2%	153	45.9%	894	<0.001
	Frequent	141	24.5%	306	59.1%	180	54.1%	533	
Sexual orientation	Exclusively male sex partners	401	69.5%	424	**81.7%**	291	87.4%	1,116	<0.001
	Predominantly male sex partners	101	17.5%	77	14.8%	41	12.3%	219	
	Predominantly female sex partners	75	13.0%	18	3.5%	1	0.3%	94	
HIV test status	HIV-positive	38	6.7%	42	8.1%	183	55.0%	263	<0.001
	HIV-negative recent test ≤12 months	216	**37.4%**	229	44.1%	112	33.6%	557	
	HIV negative test >12 months ago	152	**26.3%**	157	30.3%	29	8.7%	338	
	Never tested	171	**29.6%**	91	17.5%	9	2.7%	271	
Number of information sources on MenC recommendation	None, unaware of vaccination recommendation	577	100.0%	0	0.0%	0	**0.0%**[a]	577	<0,001
	1–2	NA	NA	342	66.3%	187	56.3%	529	
	3–4	NA	NA	141	27.3%	99	29.8%	240	
	≥5	NA	NA	33	6.4%	46	13.9%	79	
Number of sexual partners in previous 12 months	≤1	159	27.9%	102	19.8%	32	**9.7%**	293	<0.001
	2–5	221	38.8%	159	**30.8%**	64	19.3%	444	
	6–10	85	14.9%	96	18.6%	56	16.9%	237	
	>10	105	18.4%	159	30.8%	179	54.1%	443	

MenC: meningococcal C; NA: not applicable.

[a] Men already vaccinated before the vaccination recommendation targeting men who have sex with men were excluded from this analysis

(median: 200; range 1-3,000) attended each practice annually.

As summarised in table 3, surveyed physicians learned of the vaccination recommendation most frequently through the Berlin Senate press release (n=30) or HIV-specific medical networks (n=14). Of the 30 practices, 26 actively informed their patients about the new MenC vaccination recommendation, usually during routine consultations. Before the recommendation was issued, 20 practices regularly vaccinated certain patient groups against MenC. International travel was the most common indication (19/20), with only 5/20 reporting HIV-related immunodeficiency as being an indication.

Responding physicians estimated MenC vaccine uptake to be markedly higher among HIV-infected patients than HIV-non-infected patients in February 2014, ca 6 months after implementation of the recommendation (Figure 3). They administered quadrivalent MenACWY vaccine almost exclusively (28/29) rather than a monovalent vaccine. Twenty-two practices reported that MSM patients sometimes declined MenC vaccination despite the recommendation, most commonly due to a lack of perceived risk, a negative attitude towards vaccination, or fear of side effects (Table 3). Half the responding physicians believed that concerns regarding reimbursement of vaccination costs by SHI led to refusal of the recommended vaccination in approximately onethird of eligible patients in these practices.

Table 2

Results of two multivariable logistic regression models analysing factors associated with awareness of the vaccination recommendation and uptake of the MenC vaccine, Berlin, November 2013–January 2014

Factors	Awareness of vaccination campaign (n=1,346)				Vaccine uptake (n=786)			
	Number of individuals	OR	95% CI	p	Number of individuals	OR	95% CI	p
Primary care physician								
Unaware of patient's sexual preference(s)	766	Ref.	NA	NA	542	Ref.	NA	NA
Aware of patient's sexual preference(s)	580	2.1	1.6-2.8	<0.000	244	2.6	1.7–4.2	<0.000
HIV status								
HIV-positive	257	Ref.	NA	NA	209	Ref.	NA	NA
HIV-negative ≤12 months	532	0.4	0.3-0.6	<0.000	316	0.1	0.1–0.2	<0.000
HIV-negative >12 months	315	0.4	0.3-0.7	<0.000	172	0.1	0.03–0.1	<0.000
Never tested for HIV (status unknown)	242	0.3	0.2-0.4	<0.000	89	0.1	0.02–0.1	<0.000
Number of partners within past 12 months								
2–5 partners	410	Ref.	NA	NA	202	Ref.	NA	NA
≤1 partner	278	0.8	0.6–1.2	0.294	129	0.5	0.3–1.0	0.044
6–10 partners	229	1.3	0.9–1.8	0.226	138	1.0	0.6–1.7	0.978
>10 partners	429	1.8	1.3–2.5	0.001	317	1.6	1.0–2.5	0.057
Number of information sources on the vaccination campaign								
1–2 sources	NA	NA	NA	NA	482	Ref.	NA	NA
3–4 sources	NA	NA	NA	NA	226	1.3	0.9–1.9	0.214
≥5 sources	NA	NA	NA	NA	78	2.5	1.4–4.5	0.003
Level of education								
≤Secondary school	376	Ref.	NA	NA	199	Ref.	NA	NA
≥High-school diploma	970	1.6	1.2–2.1	0.001	587	1.7	1.1–2.7	0.012
MSM venues: infrequent or no visits								
Infrequent or no visits	837	Ref.	NA	NA	421	NS	NS	NS
Regular visits	509	1.7	1.3–2.2	<0.000	365	NS	NS	NS
Sexual partner(s)								
Male only	1,057	Ref.	NA	NA	665	NS	NS	NS
Majority male	201	0.8	0.6–1.1	0.138	104	NS	NS	NS
Majority female or female only	88	0.3	0.2–0.5	<0.000	17	NS	NS	NS

NA: not applicable; NS: not significant; OR: odds ratio; 95%CI: 95% confidence interval; Ref: reference group.
Factors excluded from the model as non-significant: income (≤ EUR1,000 /month vs > EUR 1,000/month); age (≤25 years-old vs >25 years-old).

Invasive meningococcal disease cases in men who have sex with men after meningococcal C vaccine recommendation

No further outbreak-related cases occurred in Berlin from July 2013 to August 2014. Only four men with MenC IMD were notified in Berlin from July 2013 to August 2014, aged 37–48 years. None were MSM. While strains from two of these cases had the fine type P1.5-1,10-8:F3-6, the other two did not. None had fHbp allele 766. MenC incidence in 20–29-year old men in Berlin decreased from 1.58 cases/100,000 inhabitants in the first half of 2013 (four cases) to none in the second half of 2013, and none in the first half of 2014. From 2008 to 2012, annual MenC incidence in this age group in Berlin ranged from 0 to 0.79 (1–2 cases/year). The outbreak strain with fHbp 766 was not identified in any female cases.

Discussion

We evaluated the implementation, acceptance and impact of a temporary MenC vaccination recommendation issued in response to a MenC outbreak among MSM in Berlin in 2013. In the 13 months following endorsement of the recommendation, no further outbreak-related cases were reported among MSM. As LHA elicited sexual orientation of all reported IMD cases, it is unlikely that cases in MSM were missed. The recommendation led to enhanced meningococcal vaccination activities among MSM, but primarily among those with an HIV diagnosis. It seems plausible that the targeted vaccination campaign reduced meningococcal transmission in the population at risk. However, due to the rare and sporadic nature of IMD occurrence, it is possible that the outbreak would have also ended without enhanced vaccination activities.

Table 3

Survey results of physicians of the working group on AIDS regarding the temporary implementation of meningococcal serogroup C vaccine recommendation for men who have sex with men in Berlin Berlin, Germany, February 2014 (n=30)

Question	n	%	95% CI
How did you learn of the MenC vaccination recommendation for MSM in Berlin? (n=30)			
Press release by the Senate of Berlin	20	66.7	50.2–83.8
German association of practising physicians treating HIV-infected patients (DAGNÄ)	14	46.7	29.1–64.9
German AIDS service organisation (DAH)	10	33.3	16.2–49.8
Berlin AIDS service organisation (BAH)	9	30.0	13.6–46.4
From patients	6	20.0	7.9–38.1
Gay community counselling centres in Berlin	7	23.3	5.7–34.3
Gay community Internet portals	4	13.3	1.0–25.0
Have you informed your MSM patients of the temporary MenC vaccination recommendation? (n=30)			
Yes	26	86.7	75.0–99.9
No	4	23.3	1.0–25.0
If yes, how did you inform your patients? (n=26)			
During routine consultation	24	92.3	81.6–102.4
Information sheets and/or poster	7	26.9	9.9–44.1
Patient letter	3	11.5	-0.5–24.5
Did you regularly vaccinate certain groups of patients against meningococcal disease prior to the announcement of the recommendation? (n=29)			
Yes	20	69.0	52.2–85.8
No	9	31.0	14.2–47.8
What were the indications for vaccination against meningococcal disease?(n=20)			
Travel vaccination	19	95.0	95.4–104.6
HIV infection independent of a immunodeficiency	5	25.0	6.0–44.0
Immunodeficiency due to HIV infection	4	20.0	2.5–37.5
Routine childhood immunisation	3	15.0	-0.6–30.6
General immunisation of MSM	0	0.0	-
What vaccine did you use for the MenC vaccination? (n=29)			
Quadrivalent MenACWY conjugate vaccine	28	96.6	90.8–96.6
Monovalent MenC conjugate vaccine	1	3.4	-3.2–9.2
Did any patients decline the recommended MenC vaccination? (n=28)			
Yes	22	78.6	63.9–94.1
No	6	21.4	5.9–36.1
If yes, why? (n=22)			
Patient considered themselves to be not at risk	20	90.9	79.0–103.0
General refusal of vaccinations	17	77.3	59.4–94.6
Fear of side effects	16	72.7	54.4–91.6
Concerns that cost of vaccine would not be reimbursed	14	63.6	43.9–84.1
MenC disease not perceived as dangerous	8	36.4	15.9–56.1
Feared stigmatisation	4	18.2	1.9–34.1
Others advised against vaccination	4	18.2	1.9–34.1
Doubts about the effectiveness of the vaccine	3	13.6	-0.5–28.5

CI: confidence interval; MenC: meningococcal serogroup C; MSM: men who have sex with men.

As IMD clusters in the MSM community seem to be a recurring problem [14-16,18], heightened awareness should be upheld during routine surveillance to ensure early detection of and response to outbreaks in this group. All IMD cases should be reported promptly to responsible LHA and sexual orientation elicited during epidemiological case investigation.

The results of the surveys among MSM and physicians and vaccine prescription data showed both directly and indirectly that targeting information to the relevant groups was effective, reaching an estimated 60% of MSM according to the internet-based survey. Preventive measures such as pneumococcal and influenza vaccination were well established in the everyday practice of physician members of the working group on AIDS, likely facilitating the prompt response to the new recommendation. Almost all responding practices reported offering the recommended MenC vaccine during patient visits. The conditions for the

implementation of a new vaccination recommendation were particularly favourable in this network of competent and dedicated physicians with an interest in treatment of HIV-infected patients. For MSM who did not routinely consult such practices, the situation might be different. Their doctors may not have offered meningococcal vaccination due to a lower level of awareness of the recommendation. Nonetheless, estimated vaccination coverage according to participating physicians was similar to that based on analysis of prescription data and the online survey.

The majority of meningococcal vaccinations were administered to HIV-positive MSM, over two thirds of whom were vaccinated based on the internet survey and prescription data, versus only 13% of the HIV-negative or untested internet survey participants. This may reflect less frequent physician contacts in the latter group. In addition, primary care providers also faced healthcare system- and patient-related barriers to vaccine delivery, including uncertainty regarding reimbursement of vaccination costs, fear of side effects and scepticism towards vaccination in general. Being required to at least indirectly reveal their sexual orientation to SHI to receive reimbursement for MenC vaccination may have been a further barrier for patients. In future similar situations, it might be helpful to communicate more detailed information on vaccine safety and requirements for reimbursement during the initial promotion of the campaign. Convincing SHI companies to directly reimburse vaccination costs in the case of outbreak-related vaccination recommendations and/or to provide funding for anonymous and free community-based vaccination sites would likely increase willingness to receive vaccination in similar situations.

In agreement with other studies, our survey among MSM showed that personal advice from the physician is pivotal in influencing willingness to be vaccinated [31-32]. In this case of a vaccination recommendation being limited to MSM, the physicians' recommendation had an even greater impact when the sexual orientation of the patient was known, emphasising the importance of a trusting doctor-patient relationship. In addition, vaccination could be conveniently obtained at routine healthcare visits, at least in HIV-positive MSM. In the implementation of a preventive measure such as a vaccination campaign, it is a particular challenge to reach the population most at risk. Our results show that repeated information via different sources led to higher vaccination uptake, similar to the findings of Friedman et al. during a community-wide hepatitis A vaccination campaign [33]. Nonetheless, 40% of MSM who participated in the online survey were unaware of the campaign. These men tended to be less open about their sexual orientation, reported less risky sexual behavior and visited gay venues less often. It would still be important to reach this group for targeted prevention measures, and for this, other channels of information must be identified.

Despite the long-standing STIKO recommendation to vaccinate immunocompromised patients against IMD, the majority of HIV-positive online survey participants (96%) were not vaccinated prior to the Berlin MenC vaccination recommendation. Only 20% of physicians in the practice-based survey stated that HIV-related immunodeficiency was an indication for meningococcal vaccination prior to the recommendation. Rather, travel abroad was the most common indication for meningococcal vaccination of MSM. The prescription data showed that MenC vaccine uptake increased in states other than Berlin as well. While this suggests that the Berlin MenC vaccination recommendation increased awareness for the pre-existing STIKO recommendation to immunise HIV-infected persons, more widespread education of physicians is required.

Our study has several limitations. Firstly, the impact of the vaccination campaign could only be determined indirectly through an observed decrease in the number of cases. Due to the sporadic nature of meningococcal clusters, we cannot say definitively that no further cases would have occurred even without vaccination. Studies to investigate the direct impact of vaccination on circulation of the pathogen in the gay community would be extremely difficult to perform since colonisation with MenC is very rare compared to other serogroups [5]. In addition, for population groups such as MSM it is impossible to determine the representativeness of an online sample. It is likely that MSM participants in the survey were more socially and sexually active, as well as more open about their sexual orientation, than MSM who did not participate. Such MSM may be more easily reachable by a vaccination campaign promoted through gay media [34-35]. However, the remarkable agreement in the estimated proportion of HIV-positive MSM vaccinated after the Berlin recommendation based on the internet survey with prescription data and physicians' estimates suggests that at least HIV-positive MSM were well represented in the survey.

Conclusion

In conclusion, the vaccination campaign launched to control the IMD outbreak in Berlin achieved a marked increase in vaccination coverage in MSM with HIV. The much lower coverage achieved in non-tested or HIV-negative MSM reflects known challenges of outbreak control in specific social groups such as MSM compared to in institutional settings [28]. Nonetheless, no further IMD cases occurred in MSM, and ongoing molecular genetic monitoring at the NRLMHi did not detect the outbreak strain in any IMD cases from Germany. A key finding of our study was that receiving information on the campaign from several sources increased vaccination uptake; thus widespread promotion of a new recommendation through all possible venues is crucial to reach target groups. Promotion of such a recommendation should also directly motivate persons in the target group to visit their physician and contact specific support groups, as these measures were associated

with the highest vaccine uptake. In particular, the long-standing and effective network of MSM-friendly physicians was crucial in implementing the vaccination campaign. Since lack of perceived risk for IMD and concerns regarding adverse vaccine effects were identified as important barriers to vaccination uptake, these issues should be more specifically addressed in future vaccination campaigns. Finally, in addition to direct reimbursement of physician-based vaccination, offering free and preferably anonymous vaccination at community-based vaccination sites might improve uptake, especially among those targeted persons who rarely consult a physician.

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Conflict of interest

None declared

Authors' contributions

JK designed and coordinated the survey of the general practitioners, analysed the data and drafted the manuscript. WH contributed to the questionnaire and data analysis of the survey of the general practitioners, and performed the analysis of the statutory health insurance prescription data. UM, JD and MK designed the questions for the MSM internet survey, which was implemented by JD and MK. The survey data were analysed by UM, SS, JD and MK. UM, WH and SS contributed to the manuscript draft. AC supported the execution of the physician's survey and reviewed the physicians' questionnaire. OW and MS critically reviewed the physicians' questionnaire and the manuscript. HC performed molecular genetic analysis of meningococcal strains and critically reviewed the manuscript. All authors read and approved the final manuscript.

References

1. Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, et al. The changing and dynamic epidemiology of meningococcal disease. Vaccine. 2012;30(Suppl 2):B26-36. DOI: 10.1016/j.vaccine.2011.12.032 PMID: 22178525
2. Harrison OB, Claus H, Jiang Y, Bennett JS, Bratcher HB, Jolley KA, et al. Description and nomenclature of Neisseria meningitidis capsule locus. Emerg Infect Dis. 2013;19(4):566-73. DOI: 10.3201/eid1904.111799 PMID: 23628376
3. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease.Vaccine. 2009;27(Suppl 2):B51-63. DOI: 10.1016/j.vaccine.2009.04.063 PMID: 19477562
4. Robert Koch Institut (RKI). Invasive Meningokokken-Erkrankungen, 2009 – 2011 [Invasive meningococcal disease, 2009-2011]. Epidemiologisches Bulletin. 2012;(39):389-97. German. Available from : http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2012/Ausgaben/39_12.pdf?__blob=publicationFile.
5. Trotter CL, Gay NJ, Edmunds WJ. The natural history of meningococcal carriage and disease.Epidemiol Infect. 2006;134(3):556-66. DOI: 10.1017/S0950268805005339 PMID: 16238823
6. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis.Lancet Infect Dis. 2010;10(12):853-61. DOI: 10.1016/S1473-3099(10)70251-6 PMID: 21075057
7. Claus H, Maiden MC, Wilson DJ, McCarthy ND, Jolley KA, Urwin R, et al. Genetic analysis of meningococci carried by children and young adults. J Infect Dis. 2005;191(8):1263-71. DOI: 10.1086/428590 PMID: 15776372
8. Ala'aldeen DA, Oldfield NJ, Bidmos FA, Abouseada NM, Ahmed NW, Turner DP, et al. Carriage of meningococci by university students, United Kingdom. Emerg Infect Dis. 2011;17(9):1762-3. DOI: 10.3201/eid1709.101762 PMID: 21888817
9. Faur YC, Wilson ME, May PS. Isolation of N. meningitidis from patients in a gonorrhea screen program: a four-year survey in New York City.Am J Public Health. 1981;71(1):53-8. DOI: 10.2105/AJPH.71.1.53 PMID: 6789687
10. Janda WM, Bohnoff M, Morello JA, Lerner SA. Prevalence and site-pathogen studies of Neisseria meningitidis and N gonorrhoeae in homosexual men.JAMA. 1980;244(18):2060-4. DOI: 10.1001/jama.1980.03310180026026 PMID: 6776296
11. Russell JM, Azadian BS, Roberts AP, Talboys CA. Pharyngeal flora in a sexually active population.Int J STD AIDS. 1995;6(3):211-5.PMID: 7647127
12. Baker M, McNicholas A, Garrett N, Jones N, Stewart J, Koberstein V, et al. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. Pediatr Infect Dis J. 2000;19(10):983-90. DOI: 10.1097/00006454-200010000-00009 PMID: 11055601
13. Fischer M, Hedberg K, Cardosi P, Plikaytis BD, Hoesly FC, Steingart KR, et al. Tobacco smoke as a risk factor for meningococcal disease. Pediatr Infect Dis J. 1997;16(10):979-83. DOI: 10.1097/00006454-199710000-00015 PMID: 9380476
14. 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;41(9):4411-4. DOI: 10.1128/JCM.41.9.4411-4414.2003 PMID: 12958279
15. 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;45(11):3768-70. DOI: 10.1128/JCM.01190-07 PMID: 17728467
16. Simon MS, Weiss D, Gulick RM. Invasive meningococcal disease in men who have sex with men.Ann Intern Med. 2013;159(4):300-1. DOI: 10.7326/0003-4819-159-4-201308200-00674 PMID: 23778867
17. Centers for Disease Control and Prevention (CDC),. 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;61(51-52):1048.PMID: 23282863
18. Weiss D, Varma JK. Control of recent community-based outbreaks of invasive meningococcal disease in men who have sex with men in Europe and the United States. Euro Surveill. 2013;18(28):20522. DOI: 10.2807/1560-7917.ES2013.18.28.20522 PMID: 23870094
19. Marcus U, Vogel U, Schubert A, Claus H, Baetzing-Feigenbaum J, Hellenbrand W, et al. A cluster of invasive meningococcal disease in young men who have sex with men in Berlin, October 2012 to May 2013. Euro Surveill. 2013;18(28):20523. DOI: 10.2807/1560-7917.ES2013.18.28.20523 PMID: 23870095
20. European Centre for Disease Prevention and Control (ECDC). Invasive meningococcal disease among men who have sex with men. Stockholm: ECDC; 2013. Available from: http://www.ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-invasive-meningococcal-disease-among-MSM.pdf.
21. Marcus U, Schmidt AJ, Hamouda O, Bochow M. Estimating the regional distribution of men who have sex with men (MSM) based on Internet surveys.BMC Public Health. 2009;9(1):180. DOI: 10.1186/1471-2458-9-180 PMID: 19519888
22. Robert Koch Institut. HIV/AIDS in Berlin – Eckdaten der Schätzung [HIV/AIDS in Berlin – Key figures of the estimates]. 2012 [Accessed 24 Oct 2014]. German Available from: http://www.rki.de/DE/Content/InfAZ/H/HIVAIDS/Epidemiologie/Daten_und_Berichte/EckdatenBerlin.pdf?__blob=publicationFile.
23. Office for Health and Social Affairs Berlin (LAGeSo). [Cases of invasive meningococcal infection by a particular type of sequence of N. meningitidis type C in MSM in Berlin 2012-2013]. Epi-Info-Wochenbericht. 2013(28):17-23. German.
24. Robert Koch Institut (RKI). Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten für 2013 [Yearboook for notifiable diseases 2013, Invasive meningococcal disease]. Berlin: RKI; 2014:154-9. German. Available from: http://www.rki.de/DE/Content/Infekt/Jahrbuch/Jahrbuecher/2013.html?nn=2374622
25. Campbell H, Andrews N, Borrow R, Trotter C, Miller E. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of

serological correlates of protection, and modeling predictions of the duration of herd immunity.Clin Vaccine Immunol. 2010;17(5):840-7. DOI: 10.1128/CVI.00529-09 PMID: 20219881

26. German Standing Committee on Vaccination (STIKO),. (Recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute). Epidemiol Bull. 2013;(34):313-44.
27. Senatsverwaltung für Gesundheit und Soziales. Empfehlung des Berliner Impfbeirates zur Impfung gegen Meningokokken-Erkrankungen [Recommendation of vaccination against meningococcal disease by the Berlin Advisory Board for Immunisation] [press release]. Berlin: Senatsverwaltung für Gesundheit und Soziales; 18 Jul 2013. German. Available from: http://www.berlin.de/sen/gessoz/presse/pressemitteilungen/2013/pressemitteilung.150750.php
28. Bochow M, Lenuweit S, Sekuler T, Schmidt AJ. Schwule Männer und HIV/AIDS: Lebensstile, Sex, Schutz- und Risikoverhalten [Gay Men and HIV/AIDS: lifestyles, sex, protection and risk behavior 2010], AIDS Forum DAH Berlin: Deutsche AIDS-Hilfe; 2011. German Available from: http://www.emis-project.eu/sites/default/files/public/publications/emis_nationalreport_germany.pdf
29. Krause G, Altmann D, Faensen D, Porten K, Benzler J, Pfoch T, et al. SurvNet electronic surveillance system for infectious disease outbreaks, Germany. Emerg Infect Dis. 2007;13(10):1548-55. DOI: 10.3201/eid1310.070253 PMID: 18258005
30. Hellenbrand W, Elias J, Wichmann O, Dehnert M, Frosch M, Vogel U. Epidemiology of invasive meningococcal disease in Germany, 2002-2010, and impact of vaccination with meningococcal C conjugate vaccine.J Infect. 2013;66(1):48-56. DOI: 10.1016/j.jinf.2012.09.008 PMID: 23043893
31. Böhmer MM, Walter D, Krause G, Müters S, Gösswald A, Wichmann O. Determinants of tetanus and seasonal influenza vaccine uptake in adults living in Germany.Hum Vaccin. 2011;7(12):1317-25. DOI: 10.4161/hv.7.12.18130 PMID: 22108034
32. Weigel M, Weitmann K, Rautmann C, Schmidt J, Bruns R, Hoffmann W. Impact of physicians' attitude to vaccination on local vaccination coverage for pertussis and measles in Germany.Eur J Public Health. 2014;24(6):1009-16. DOI: 10.1093/eurpub/cku013 PMID: 24599940
33. Friedman MS, Blake PA, Koehler JE, Hutwagner LC, Toomey KE. Factors influencing a communitywide campaign to administer hepatitis A vaccine to men who have sex with men.Am J Public Health. 2000;90(12):1942-6. DOI: 10.2105/AJPH.90.12.1942 PMID: 11111274
34. EMIS network,Marcus U, Hickson F, Weatherburn P, Schmidt AJ. Age biases in a large HIV and sexual behaviour-related internet survey among MSM.BMC Public Health. 2013;13(1):826. DOI: 10.1186/1471-2458-13-826 PMID: 24020518
35. EMIS Network,Marcus U, Hickson F, Weatherburn P, Schmidt AJ. Prevalence of HIV among MSM in Europe: comparison of self-reported diagnoses from a large scale internet survey and existing national estimates.BMC Public Health. 2012;12(1):978. DOI: 10.1186/1471-2458-12-978 PMID: 23151263

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European public health policies for managing contacts of invasive meningococcal disease cases better harmonised in 2013 than in 2007

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In 2007, a European survey identified variation in country policies on public health management of invasive meningococcal disease (IMD). In 2009–10, the European Centre for Disease Prevention and Control (ECDC) published evidence-based guidance on IMD. We therefore surveyed again European countries to describe policies for managing IMD cases and contacts in 2013. We asked national IMD public health experts from 32 European countries to complete a questionnaire focusing on post-exposure prophylaxis (PEP) for IMD contacts and meningococcal vaccination. Proportions in 2007 and 2013 were compared using the chi-squared test. All 32 countries responded, with responses from two regions for Belgium and Italy; half stated having used ECDC guidance to update national recommendations. PEP was recommended to close contacts in 33 of 34 countries/regions, mainly ciprofloxacin for adults (29/32 countries) and rifampicin for children (29/32 countries). ECDC guidance for managing IMD contacts in airplanes was strictly followed by five countries/regions. Twenty-three countries/regions participated in both surveys. Compared with 2007, in 2013, more countries/regions recommended i) ceftriaxone for children (15/23 vs 6/20; p = 0.03), ii) PEP for all children in the same preschool group (8/23 vs 17/23; p = 0.02). More countries/regions recommended evidence-based measures for IMD public health management in 2013 than 2007. However, some discrepancies remain and they call for further harmonisation.

Introduction

Invasive meningococcal disease (IMD) is associated with high case fatality (9% in 26 European countries in 2011 [1]) and substantial risk of long-term sequelae among survivors [2-4]. This explains the high level of concern associated with cases of IMD despite a low incidence in Europe of under one case per 100,000 population annually in the past decade [4,5]. Close contacts of IMD patients have a 200- to 1,200-fold increased risk of developing the disease [6-9]. Post-exposure prophylaxis (PEP) and, in case of a vaccine-preventable strain in the index case, vaccination of close contacts, are evidence-based measures to reduce the risk of secondary IMD cases. However, while the former is based on direct evidence showing decreased incidence among household contacts if they receive PEP [10], the latter rests on indirect evidence only, consisting of the observed increased risk for IMD in household contacts despite chemoprophylaxis during the 14 to 365 days after contact with the index case [7,11]. A survey in 2007, performed by the public health management working group of the European Meningococcal Disease Society (EMGM), documented that recommendation of these and other public health control measures varied widely among European countries [12]. This heterogeneity was thought to reflect uncertainty on effectiveness of public health measures, but also pragmatic, economic or legal constraints of policymakers in different countries.

A consistent and evidence-based public health policy on the management of IMD cases and their contacts across Europe is desirable to facilitate communication among countries in case of cross border case management. Therefore, the EMGM working group developed evidence based guidance for good practice in public health management of sporadic cases of meningococcal disease and their contacts [10]. In 2010,

Box

ECDC guidance on public health management of sporadic cases of invasive meningococcal disease[a] and risk assessment of infectious diseases transmitted on aircraft[b]

ECDC guidance

- Chemoprophylaxis with an antibiotic regimen that eradicates carriage is recommended for household contacts of a case of IMD. (**Strong recommendation**)
- Sharing drinks, cigarettes or similar contact (implying a low level of salivary contact) with a case of IMD is not in itself an indication for chemoprophylaxis. (**Weak recommendation**)
- Attending the same preschool as a case of IMD is an indication for chemoprophylaxis, depending on risk assessment. (**Weak recommendation**)
- Attending the same school/college (including the same class) as a case of IMD is not in itself an indication for chemoprophylaxis. (**Weak recommendation**)
- Sharing the same transport vehicle as a case of IMD is not, in itself, an indication for chemoprophylaxis. (**Weak recommendation**)
- Rifampicin, ciprofloxacin, ceftriaxone, azithromycin and cefixime can be advised for chemoprophylaxis. (**Strong recommendation**) Ciprofloxacin, azithromycin and ceftriaxone are preferred. (**Weak recommendation**) In children, all these antibiotics can be advised. (**Strong recommendation**) In pregnant women, ceftriaxone, azithromycin and cefixime can be advised. (**Weak recommendation**)
- If a case of meningococcal disease is caused by a strain that is preventable by an available licensed vaccine, an appropriate course of vaccination – in addition to chemoprophylaxis – is recommended for household contacts unless considered to be protected by previous vaccination. (**Strong recommendation**)

RAGIDA

- Besides fellow travellers who may be household (-like) contacts of an index case, passengers and crew with close contact to pharyngeal secretions should be considered for contact tracing.
- Close contacts of IMD cases should be traced if the index cases were travelling while infectious (seven days before the onset of symptoms; up to 24 hours after the onset of effective treatment).

ECDC: European Centre for Disease Prevention and Control; IMD: invasive meningococcal disease; RAGIDA: risk assessment of infectious diseases transmitted on aircraft.

[a] Source: [10].

[b] Source: [13,14].

Grading of Recommendations Assessment, Development and Evaluation (GRADE) [23] was used for ECDC guidance on public health management of IMD, but not in RAGIDA.

this document was adopted as European Centre for Disease Prevention and Control (ECDC) guidance [10]. In addition, in 2009–10, risk assessment guidelines for diseases transmitted on aircraft (RAGIDA) including recommendations on the management of contacts to an IMD case were published by ECDC [13,14] (Box). The EMGM working group repeated the survey on IMD public health policies in 2013. Our objectives were to describe current public health policies for managing cases of meningococcal disease and their contacts in European countries, to track changes in national public health policies since 2007 and to assess to what extent measures outlined in the ECDC guidance were implemented in the respective countries.

Methods

We conducted a cross-sectional study, addressing 32 national IMD public health experts from all 28 European Union (EU) Member States and four European Free Trade Association (EFTA) countries (Iceland, Liechtenstein, Norway, and Switzerland). Participants from national public health institutes were identified from the previous survey in 2007 and from member lists of the ECDC Vaccine Preventable Diseases Network and EMGM. We invited potential participants via email to complete either a word or a web-based version (voozanoo by Epiconcept) of a structured questionnaire. The questionnaire comprised 40 questions and covered the following topics: clinical and laboratory diagnostic case definition criteria for confirmation of a case; the definition of a close contact for control measures; the use and choice of PEP for persons with contact to IMD cases in different settings; the use of meningococcal vaccines in routine schedules and after exposure to an IMD case; the perceived usefulness of the ECDC guidance document in updating national recommendations. The questionnaire was similar to the one used in 2007, but questions on criteria for defining cases and contacts and on policies for managing contacts in school and day care settings as well as in transport vehicles were expanded (questionnaire available from the authors upon request). Comparison of answers between 2007 and 2013 was restricted to countries participating in both surveys. Countries with missing data for a particular item were excluded when calculating proportions. Proportions were compared using chi-squared and Fisher's exact tests. Differences were considered statistically significant at $p<0.05$.

Results

All 32 countries responded to the 2013 survey. Two responses each were obtained from Belgium and Italy, reflecting sub-national policies. These were included as separate entities in the analysis, bringing the total number of respondents to 34. The following 23 of the 34 countries/regions responded to both surveys: Austria, Belgium (Flanders and Wallonia), Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Lithuania, Malta, the Netherlands, Norway, Poland, Romania, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom (UK).

Table 1

Criteria for definition of IMD cases for the purpose of control measures in 2007 and 2013, European survey on public health policies for managing cases of meningococcal disease and their contacts, 2013

Case definition criteria	Countries/regions applying criteria in 2013 (N=34)	Countries/regions responding to both surveys and applying criteria 2007 (N=23) and 2013 (N=23)		P value for comparison 2007 vs 2013
	n	n (2007)	n (2013)	
Isolation of *Neisseria meningitides* from sterile site	34	22	23	1.000
Isolation of meningococcal DNA from sterile site	32	20	22	0.608
Isolation of antigen from CSF[a]	32	19	21	0.665
Isolation of gram negative diplococci from sterile site	30	20	19	0.608
Detection of high titre in convalescent serum	2	6	2	0.243
Clinically compatible	21	16	13	0.542
Purpura fulminans	24	16	15	1.000
Official notification	15	12	9	0.554

CSF: cerebrospinal fluid; IMD: invasive meningococcal disease.

European Centre for Disease Prevention and Control (ECDC) or risk assessment guidelines for diseases transmitted on aircraft (RAGIDA) recommendations are highlighted in grey.

[a] This criterion differed slightly in the 2007 questionnaire: 'Isolation of meningococcal antigen from sterile site'.

Case definition criteria

There were only slight changes between 2007 and 2013 for laboratory and other case definition criteria (Table 1). The only case definition criterion for laboratory diagnosis used by all countries in 2013 was 'isolation of *Neisseria meningitidis* from sterile site', but a high proportion also used 'isolation of meningococcal DNA from a sterile site', 'meningococcal antigen from CSF' and 'gram-negative diplococci from sterile site'.

Definition of close contacts

In 2013, 33 of 34 countries/regions recommended PEP to close contacts of an IMD case. This included all 23 countries/regions that also participated in the 2007 survey, when all respondents recommended PEP for close contacts after an IMD case (22/22; data missing for one country). However, the definition of close contact varied across countries/regions, with 11 of 34 countries/regions including sharing cups and glasses with an index case and 23 of 34 kissing on the mouth (Table 2). The maximum period after contact with a case in which initiation of PEP was recommended varied from seven days (n=9/33) to one month (n=5/33) (median 10 days; IQR 8–14).

Recommended chemoprophylaxis

Of the 33 countries/regions recommending PEP for close contacts of an IMD case in 2013, only one did not have specific guidelines on the choice of antibiotic for PEP. As in the 2007 survey, the most commonly recommended antibiotic in non-pregnant adults was ciprofloxacin (Table 3), most frequently administered as either 500 mg (26/29) or 750 mg (3/29), usually as a single dose (27/29), followed by rifampicin (usually as four 600 mg doses (26/27)). From 2007 to 2013, the proportion of countries/regions recommending use of ceftriaxone and azithromycin increased, but not significantly (Table 3). In 2013, 29 of 34 countries/regions recommended PEP during pregnancy, most commonly intramuscular ceftriaxone (Table 3). One country additionally recommended cefixime in pregnancy and for children.

Most countries/regions recommended rifampicin as PEP for one year-old children both in 2007 and 2013 (Table 3). Ciprofloxacin was recommended for this age in nine of 32 countries/regions in 2013 (starting from birth (4/9) or from one month (2/9) of age; the remaining three countries did not specify a minimum age). In addition, two countries recommended ciprofloxacin in older children, one starting from the age of two and the other from the age of 14 years. The only statistically significant change from 2007 to 2013 was an increase in the proportion of countries/regions recommending ceftriaxone for one year-old children (Table 3).

A few countries/regions additionally recommended antibiotics not included in the guidance for various target groups, namely spiramycin (2/34), penicillin (4/34), cotrimoxazole (1/34) and ofloxacin (1/34).

Settings

In 2013, 32 of 34 countries/regions reported specific policies for PEP in preschool and school settings and 33 of 34 in university settings. Twenty-two of 32 countries/regions recommended prophylaxis for all children sharing the same classroom following the occurrence of an IMD case in preschool. This increased significantly

Table 2

Criteria for definition of close contacts of IMD cases for the purpose of control measures in 2007 and 2013, European survey on public health policies for managing cases of meningococcal disease and their contacts, 2013

Definition of close contacts	Countries/regions applying criterion in 2013 (N=34)	Countries/regions responding to both surveys and applying criterion in 2007 (N=23) and 2013 (N=23)		P value for comparison 2007 vs 2013
	n	n (2007)	n (2013)	
People sharing the same household	34	23	23	1.0
People with equivalent level of close contact	30	22	22	1.0
Attending the same preschool facility[a]	28	NA	NA	NA
Kissing on mouth	23	20	15	0.17
People sharing cups and glasses	11	9	5	0.34
Kissing on cheek	4	3	1	0.61
Period in which index patient is considered infectious				
7 days before onset of illness	21	14	14	1.0
10 days before onset of illness	10	7	8	1.0

ECDC: European Centre for Disease Prevention and Control; IMD: Invasive meningococcal disease; NA: not applicable; RAGIDA: Risk assessment guidelines for diseases transmitted on aircraft.

ECDC or RAGIDA recommendations are highlighted in grey.

[a] This criterion was not included in the 2007 questionnaire.

Table 3

Choice of post-exposure prophylaxis for contacts of IMD cases in different target groups, European survey on public health policies for managing cases of meningococcal disease and their contacts, 2013

Target group	Antibiotic	Countries/regions recommending the antibiotic in 2013 (N=34)	Countries/regions responding to both surveys and recommending the antibiotic 2007 (N=23) and 2013 (N=23)		P value for comparison 2007 vs 2013
		n	n (2007)	n (2013)	
Adults	Ciprofloxacin	29	20	21	1.0
	Rifampicin	27	14	19	0.30
	Ceftriaxone	22	13	15	0.76
	Azithromycin	6	1	3	0.61
Children of one year of age	Ciprofloxacin	9	5	7	0.75
	Rifampicin	29	16	20	0.69
	Ceftriaxone	21	6	15	**0.03**
	Azithromycin	6	3	4	1.0
Women in the first trimester of pregnancy[a]	Ciprofloxacin	2	0	2	0.49
	Rifampicin	3	4	3	0.69
	Ceftriaxone	25	12	18	0.21
	Azithromycin	5	2	5	0.42

ECDC: European Centre for Disease Prevention and Control; IMD: invasive meningococcal disease; PEP: post-exposure prophylaxis.

[a] Number of countries that recommended specifically certain antibiotics for PEP in pregnancy in 2013: n=27/34 (79%). In 2007 n=18/23 vs n=20/23 in 2013.

ECDC recommendations are highlighted in grey.

from 2007 to 2013 in countries participating in both surveys (Table 4). In school and university settings, most countries/regions recommended PEP only to close contacts within the class (Table 4).

In 2013, 20 of 32 countries/regions recommended PEP to contacts after an IMD case on a plane either in general or under specific circumstances (e.g. sitting next to the case, travel of a certain duration, overnight travel), a non-significant increase compared with 2007 (Table 5). In 2013, of the 20 countries/regions that recommended PEP after the occurrence of an IMD case on an aircraft, one implemented contact tracing for all passengers and 14 only for persons they considered eligible for PEP (Table 5). Five countries strictly followed the criteria recommended by RAGIDA. Fifteen of 31 countries/regions recommended PEP to contacts after an IMD case on a train or bus.

Vaccination

In 2007 eight of 23 countries recommended meningococcal serogroup C vaccination in their national childhood vaccination programme, compared with 11 of 23 in 2013. Of all respondents to the 2013 survey (n=34), 18 countries/regions recommended serogroup C vaccination in their routine schedule. Of these, five recommended vaccination starting in the first six months of life and 13 at 12 months of age and older. Six countries/regions recommended a booster dose for adolescents.

Vaccination of household contacts after the occurrence of an IMD case due to a vaccine-preventable serogroup was recommended by 24 of 34 countries/regions in 2013. Among countries participating in both surveys, this increased slightly from 2007 (15/22) to 2013 (17/22; p=0.46). Of the 24 countries/regions recommending post-exposure vaccination in 2013, seven recommended this for close contacts after a serogroup C IMD case and 15 after an IMD case due to serogroups A, C, W or Y; serogroups were not specified by two countries. Countries/regions with meningococcal C vaccination in their childhood immunisation schedule were somewhat more likely to recommend post-exposure vaccination (14/18) than countries/regions not having a routine childhood meningococcal vaccination policy (8/16, p=0.15).

Perceived usefulness of ECDC guidance

Twenty-eight of 31 countries/regions found the ECDC guidance [12] document useful. Half (17/34) reported having used the ECDC guidance to update recommendations in their country/region. The following topics were indicated as helpful: choice of medication for prophylaxis (4/17); management of contacts in transport vehicles (4/17); increased emphasis on contact with pharyngeal secretions as a criterion for defining close contact (1/17); and criteria for laboratory diagnosis (1/17). Nine additional countries/regions stated they were planning to use the ECDC guidance document to update their country policy.

Cross border communication

In case of IMD occurring in a resident of another country, 28 of 32 countries/regions reported having a policy in place in 2013 for contacting the source country for contact tracing, if indicated. This was already the case for 19 out of 22 countries/regions in 2007.

Discussion

Comparison of the results of the 2007 [12] and 2013 surveys reveals increasing harmonisation of public health policies for the management of sporadic IMD cases and a relatively high level of adherence to evidence-based guidance as published by ECDC in the period between the two surveys [10,13,14]. This applied to the two laboratory diagnostic case definition criteria considered to be gold standard [10], meningococcal culture and DNA isolation from a sterile site, and, in particular, to the choice of antibiotics for PEP and their use in preschools, elementary and secondary schools, and universities. Recommendations for the management of contacts of an IMD case on transport vehicles remained heterogeneous, possibly reflecting the low level of evidence available in this area.

ECDC guidance [10,13,14] emphasises that exposure to respiratory droplets or pharyngeal secretions of a case is essential for the transmission of meningococcal disease. Thus, a casual social contact, even if involving sharing drinks or cigarettes, is not in itself an indication for PEP [10]. Although not statistically significant, fewer countries/regions considered such contacts to warrant a recommendation for PEP in 2007 than in 2013. In addition, 'kissing on the mouth' was also considered by fewer countries/regions in 2013 than in 2007 to be a criterion for close contact. ECDC guidance states that exchange of pharyngeal secretions is likely to occur during intimate mouth-to-mouth kissing, which was found to be a risk factor for carriage or disease in observational studies [15-17]. However, a brief kiss on the mouth is unlikely to lead to significant exchange of pharyngeal secretions. Interpretation of our finding is difficult, as the wording of 'kissing on the mouth' was possibly interpreted to mean intimate mouth-to-mouth kissing by some, but not all countries/regions. Future surveys should define both types of kissing. In addition, we would like to stress that no contact indicator should be considered in isolation; rather, the overall contact history of each person must be evaluated to assess the likelihood of contact with pharyngeal secretions of the index case.

As concluded in the ECDC guidance [10], none of the recommended regimens (rifampicin, ciprofloxacin, ceftriaxone, azithromycin and cefixime) can be considered superior in terms of effectiveness to eradicate meningococcal carriage [10,11]. However, ciprofloxacin, azithromycin and ceftriaxone have the advantage of low reported rates of side effects and can be given as single dose, although the latter must be given intramuscularly [10]. Most countries/regions recommended ciprofloxacin and rifampicin, followed by ceftriaxone,

Table 4

Use of post-exposure prophylaxis in IMD contacts in different educational settings, European survey on public health policies for managing cases of meningococcal disease and their contacts, 2013

Recommendation of chemoprophylaxis		Countries/regions applying recommendation in 2013 (N = 32)[a]	Countries/regions responding to both surveys and applying recommendation 2007 (N=23) and 2013 (N=23)		P value for comparison 2007 vs 2013
		n	n (2007)	n (2013)	
Preschool	For all children	5	3	2	1.0
	for all children of the same group	22	8	17	0.02
	For close contacts in the same group	1	0	1	1.0
	No chemoprophylaxis	3	12	3	0.01
Elementary school[b]	For all pupils	0	NA	NA	NA
	For all pupils in the same class	7	NA	NA	NA
	For close contacts in the same class	17	NA	NA	NA
	No chemoprophylaxis	7	NA	NA	NA
Secondary school[b]	For all pupils	0	NA	NA	NA
	For all pupils attending the same class	6	NA	NA	NA
	For close contacts in the same class	19	NA	NA	NA
	No chemoprophylaxis	7	NA	NA	NA
University[b]	For all students of the same class	1	NA	NA	NA
	For close contacts in the same group	25	NA	NA	NA
	No chemoprophylaxis	6	NA	NA	NA

ECDC: European Centre for Disease Prevention and Control; IMD: invasive meningococcal disease.

[a] Number of countries responding to the question on pre-, elementary and secondary school in 2013: n = 32; responding to questions on university settings: n = 33.

[b] This criterion was not included in the 2007 questionnaire.

ECDC recommendations are highlighted in grey.

for adults. Despite rifampicin requiring four doses and being associated with the development of resistance [11], most countries/regions still recommended it. Only four countries/regions specifically recommended single-dose ciprofloxacin or azithromycin and not rifampicin for adults.

Rifampicin was the antibiotic most commonly recommended for children, followed by ceftriaxone, the recommendation for which significantly increased from 2007 to 2013. Ciprofloxacin was recommended for PEP in children by nine of 32 countries/regions in 2013, with little change since 2007. Although ciprofloxacin is considered safe in children [10], reluctance to use this antibiotic is likely related to the warning of a theoretical risk of arthropathy in children in the product information. In addition, 'chemoprophylaxis of IMD' is listed as an indication for adults, but not for children in the summary of product characteristics (SPC) for ciprofloxacin [18]. In contrast, rifampicin is licensed for prophylaxis of meningococcal disease at all ages [10]. While ceftriaxone is not explicitly licensed for meningococcal prophylaxis, it is widely used for treatment of IMD.

We are not aware that meningococcal prophylaxis is included as an indication in the SPC of the other antibiotics for which there is evidence that they eradicate meningococcal carriage (azithromycin, cefixime). This, together with a lower level of evidence for the use of these antibiotics for prophylaxis, likely explains why only few countries/regions recommended these at all. Although the effectiveness of azithromycin and cefixime were comparable to rifampicin each in one randomised controlled trial [19,20], no trials compared these two antibiotics with placebo. In contrast, high eradication rates were shown for rifampicin, ciprofloxacin and ceftriaxone in various randomised placebo-controlled trials, providing a more robust evidence base [10]. Furthermore, while very low resistance rates have been reported for ciprofloxacin, rifampicin and ceftriaxone in European countries [1], routine sensitivity testing of *N. meningitidis* for azithromycin and cefixime has not been widely implemented. Thus there is a paucity of data regarding development of resistance against these antibiotics, with no such data reported by EARS (European Antimicrobial Resistance Surveillance; hosted by ECDC) thus far [1,21]. Some countries/regions recommended rifampicin and ciprofloxacin for

Table 5

Criteria defining eligibility for post-exposure prophylaxis in countries/regions recommending chemoprophylaxis for fellow passengers of an IMD case on a plane, European survey on public health policies for managing cases of meningococcal disease and their contacts, 2013

Criteria for chemoprophylaxis in fellow passengers on a plane[a]	Countries/regions applying criteria in 2013 (N=20)[b]	Countries/regions responding to both surveys and applying criteria 2007 (N=9)[c] and 2013 (N=13)[c]		P value for comparison 2007 vs 2013
	n	n (2007)	n (2013)	
Duration of travel				
Four hours or more	2	2	23	1.0
Seven hours or more	1	1	0	0.41
Eight hours or more	8	3	5	1.0
Overnight travel	0	2	0	0.16
Time not taken into account[d]	9	1	6	0.17
Proximity to the case				
Seated next to the case	6	4	4	0.66
Seated in the same row, row in front/back	7	1	4	0.61
Contact with pharyngeal secretions of the case	5	1	4	0.61
Undefined	2	3	1	0.26

ECDC: European Centre for Disease Prevention and Control; IMD: invasive meningococcal disease; RAGIDA: Risk assessment guidelines for diseases transmitted on aircraft.

[a] Responses were free-text in the 2007 questionnaire and multiple choice in the 2013 version.

[b] Countries/regions recommending post-exposure prophylaxis to passengers with contact to an IMD case on a plane in 2013: n=20/32 (63%).

[c] Countries/regions recommending post-exposure prophylaxis to passengers with contact to an IMD case on a plane; 2007: n=9/22 (41%); 2013: n=13/23 (57%).

[d] For 2007: time criteria not mentioned by one country.

ECDC or RAGIDA recommendations are highlighted in grey.

pregnant women despite theoretical risk to the foetus based on animal studies. Although this risk is considered low, the use of ceftriaxone, cefixime and azithromycin in pregnancy is considered safer [10]. Finally, there is no supporting evidence to use antibiotics such as spiramycin, penicillin, cotrimoxazole and ofloxacin, still occasionally recommended for PEP in European countries [10].

The proportion of countries/regions recommending PEP in preschool settings increased significantly from 2007 to 2013. This is in agreement with the weak recommendation in the ECDC guidance to provide PEP to contacts in the same preschool group, depending on risk assessment, despite availability of only low-quality evidence [10,22]. In older children and students most countries/regions only recommended PEP to close contacts within the class, also in agreement with ECDC guidance.

In 2013, about two-thirds of countries/regions recommended PEP to contacts after a case on a plane in various circumstances. Risk of transmission of meningococcal disease on airplanes is generally low [13] and sharing the same transport vehicle as an IMD case should not in itself justify PEP [10,14]. As in other settings, contact with pharyngeal secretions of a case qualifies for the administration of chemoprophylaxis, yet this criterion played a role in only one quarter of countries/regions' recommendations concerning air travel. However, RAGIDA does state that, based on expert opinion and given the severity of the disease, contact tracing can be considered for persons sitting next to the suspected or laboratory-confirmed case [13].

In spite of a strong recommendation for post-exposure vaccination for serogroups A, C, W and Y in addition to PEP [7,10], 10 of 34 countries/regions did not have a respective policy in place, with little change from 2007 to 2013. This may be due to the very low level of evidence behind this recommendation [10].

Communication between countries/regions in case of transborder IMD case management is an important issue given the steadily increasing mobility throughout Europe. Almost 90% of countries/regions reported having a policy in place ensuring such communication. In addition, a high level of adherence to ECDC guidance in many areas – as observed in the 2013 survey – facilitates this task.

ECDC guidance on public health management of sporadic IMD was found useful by most participating countries/regions at the national level. However, only half of the countries/regions used the guidance to change

recommendations. Besides, some of these countries having most recommendations already in place, a possible explanation is that the time interval between publication of the guidance and the survey was less than three years and may have been insufficient to achieve changes in national policies. This could explain persistence of significant discrepancies between country recommendations, for instance in the management of contacts in schools and public transport vehicles and the vaccination of close contacts. It is likely that practical issues, policy constraints related to use of antibiotics, reluctance to recommend antibiotics not explicitly licensed for PEP as well as economic considerations continue to contribute to these residual differences. In addition, some countries/regions may view recommendations based on very low levels of evidence more critically than others; however, it is unlikely that higher level of evidence will be obtainable in most of these areas, as the very large studies that would be required are not feasible in a setting of overall low disease incidence. Nonetheless, increasing awareness of available evidence, for instance through translation of guidance documents into the respective languages, might improve adherence. It is also possible that the overall low incidence in European countries/regions may partly explain reluctance to adopt recommendations that contribute with relatively low effectiveness to prevention of subsequent cases in the same setting. For instance, it has been estimated that to prevent one subsequent case, PEP must be administered to 300 household contacts, but to 1,900 same-group preschool contacts [10], and ca 1,000 household contacts need to be vaccinated [7].

There may be other reasons for persistent differences as well, such as logistic and economic considerations related to the structure of a particular healthcare system that might influence the feasibility of implementing certain public health measures even when recommended by international guidance. For instance, some antibiotics are more expensive than others or might be centrally procured at a reduced rate, and post-exposure vaccination can be logistically challenging as vaccination may not be performed by the public health authority making the recommendation. Furthermore, countries may be reluctant to recommend antibiotics without routine resistance testing. All of these factors should be addressed in future similar surveys.

Comparisons between the two surveys were limited by the smaller number of countries/regions that participated in 2007. Nonetheless, comparability between the surveys was high due to the similar method used and their being undertaken by almost the same team. The respective participants gave us information on the official national policy of their countries/regions. However, we could not assess to what extent policies were legally binding and actually implemented in the respective country. We tried to address this by carefully identifying the person best placed to participate for each country. Further research on the actual implementation of recommendations would be useful.

In conclusion, public health policies for the management of sporadic IMD cases were better harmonised among European countries/regions in 2013 compared with 2007. This is notably reflected by good adherence to evidence-based recommendations regarding the most important target groups requiring PEP as well as the choice of antibiotics for PEP published in 2010, suggesting that guidance disseminated by an international public health agency can have an important impact on public health policy. However, some discrepancies remained, e.g. only a minority of countries/regions strictly followed ECDC guidance for IMD contacts in airplanes. Future surveys should specifically aim to identify possible reasons for persistent discrepancies in public health management of IMD that might help achieve further harmonisation, as this is desirable in the context of increasing mobility across European societies.

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Conflict of interest

None declared.

Authors' contributions

Sabine Vygen: protocol writing, carrying out of the survey, data analysis and writing up of the manuscript;

Wiebke Hellenbrand and Pawel Stefanoff: discussions and scientific input on protocol, data analysis and manuscript;

Germaine Hanquet, Sigrid Heuberger, and James Stuart: scientific input on protocol and manuscript.

References

1. European Centre for Disease Prevention and Control (ECDC). Surveillance of invasive bacterial diseases in Europe, 2011. Stockholm: ECDC; 2013. Available from: http://www.ecdc.europa. eu/en/

publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=994.
2. Heymann DL. Control of communicable disease manual, nineteenth edition. American Public Health Association, 2008.
3. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The disease burden of invasive meningococcal serogroup B disease in Canada. Pediatr Infect Dis J. 2013;32(1):e20-5. Available from: DOI: 10.1097/INF.0b013e3182706b89 PMID: 22926207
4. Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol. 2012;11(9):774-83. DOI: 10.1016/S1474-4422(12)70180-1 PMID: 22863608
5. European Centre for Disease Prevention and Control (ECDC). Surveillance of invasive bacterial diseases in Europe 2008/2009. Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/1107_SUR_IBD_2008-09.pdf
6. Hastings L, Stuart J, Andrews N, Begg N. A retrospective survey of clusters of meningococcal disease in England and Wales, 1993 to 1995: estimated risks of further cases in household and educational settings.Commun Dis Rep CDR Rev. 1997;7(13):R195-200.
7. Hoek MR, Christensen H, Hellenbrand W, Stefanoff P, Howitz M, Stuart JM. Effectiveness of vaccinating household contacts in addition to chemoprophylaxis after a case of meningococcal disease: a systematic review.Epidemiol Infect. 2008;136(11):1441-7.
8. De Wals P, Hertoghe L, Borlée-Grimée I, De Maeyer-Cleempoel S, Reginster-Haneuse G, Dachy A, et al. Meningococcal disease in Belgium. Secondary attack rate among household, day-care nursery and pre-elementary school contacts. J Infect. 1981;3(1) Suppl;53-61. Available from: DOI: 10.1016/S0163-4453(81)80009-6 PMID: 7185953
9. Munford RS, Souza De Morais J, De EA, Taunay AE, Fraser DW, Feldman RA. Spread of meningococcal infection within households.Lancet. 1974;303(7869):1275-8. Available from: DOI: 10.1016/S0140-6736(74)90022-1 PMID: 4134961
10. European Centre for Disease Prevention and Control (ECDC). Public health management of sporadic cases of invasive meningococcal disease and their contacts. Stockholm: ECDC; 2010. Available from: http://ecdc.europa.eu/en/publications/Publications/1010_GUI_Meningococcal_guidance.pdf
11. Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections.Cochrane Database Syst Rev. 2011; (8):CD004785. DOI: 10.1002/14651858.CD004785.pub4 PMID: 21833949
12. Hoek M, Hanquet G, Heuberger S, Stefanoff P, Zucs P, Ramsay M, et al. A European survey on public health policies for managing cases of meningococcal disease and their contacts. Euro Surveill. 2008;13(10):8060.PMID: 18445439
13. European Centre for Disease Prevention and Control (ECDC). ECDC technical report. Risk assessment guidelines for infectious diseases transmitted on aircraft. Stockholm: ECDC; 2009. Available from: http://www.ecdc.europa.eu/en/publications/publications/0906_ter_risk_assess ment_guidelines_for_infectious_diseases_transmitted_on_aircraft.pdf
14. European Centre for Disease Prevention and Control (ECDC). Risk assessment guidelines for diseases transmitted on aircraft. PART 2: Operational guidelines for assisting in the evaluation of risk for transmission by disease. Stockholm: ECDC; 2010. Available from: http://ecdc.europa.eu/ en/publications/publications/1012_gui_ragida_2.pdf
15. Stanwell-Smith RE, Stuart JM, Hughes AO, Robinson P, Griffin MB, Cartwright K. Smoking, the environment and meningococcal disease: a case control study.Epidemiol Infect. 1994;112(02):315-28. Available from: DOI: 10.1017/S0950268800057733 PMID: 8150006
16. United Kingdom Meningococcal Carriage Group,MacLennan J, Kafatos G, Neal K, Andrews N, Cameron JC, Roberts R, et al. . Social behavior and meningococcal carriage in British teenagers.Emerg Infect Dis. 2006;12(6):950-7. Available from: DOI: 10.3201/eid1206.051297 PMID: 16707051
17. Tully J, Viner RM, Coen PG, Stuart JM, Zambon M, Peckham C, et al. Risk and protective factors for meningococcal disease in adolescents: matched cohort study. BMJ. 2006;332(7539):445-50. Available from: DOI: 10.1136/bmj.38725.728472.BE PMID: 16473859
18. European Medicines Agency (EMA). 2008. Summary of product characteristics for Ciprofloxacin Bayer and associated names. London: EMA. [Accessed 30 Mar 2015]. Available from: http://www.ema.europa.eu/docs/en_GB/document_ library/Referrals_document/Ciprofloxacin_Bayer_30/WC500008075.pdf
19. Girgis N, Sultan Y, Frenck RW, El-Gendy A, Farid Z, Mateczun A. Azithromycin compared with rifampin for eradication of nasopharyngeal colonization by Neisseria meningitidis. Pediatr Infect Dis J. 1998;17(9):816-9. DOI: 10.1097/00006454-199809000-00013 PMID: 9779768
20. Podgore JK, Girgis N, El-Refai M, Abdel-Monheim A. A double-blind randomized trial of cefixime compared to rifampin in the eradication of meningococcal pharyngeal carriage in a closed population.J Trop Med (Cairo). 1993;2(5):41-5.
21. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2013. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2013.pdf
22. Hellenbrand W, Hanquet G, Heuberger S, Nielsen S, Stefanoff P, Stuart JM. What is the evidence for giving chemoprophylaxis to children or students attending the same preschool, school or college as a case of meningococcal disease?Epidemiol Infect. 2011;139(11):1645-55. Available from: DOI: 10.1017/S0950268811001439 PMID: 21835067
23. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-25.

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Resources and latest news about Zika virus disease available from ECDC

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On 1 February 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) following a meeting of the recently established 'International Health Regulations (2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations' and the rapid spread of the disease in the Americas [1]. At the meeting, the Committee advised that the recent cluster of microcephaly cases and other neurologic disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, constitutes a PHEIC.

The European Centre for Disease Prevention and Control (ECDC) has monitored the Zika outbreaks in the Pacific Region and Latin America since onset of the respective outbreaks, and provides updates and resources in various formats such as daily updated maps of the countries and territories with reported confirmed autochthonous cases of Zika virus infection [2], fact sheets for professionals, risk assessments and epidemiological updates reflecting changes in the evolution of the epidemic [3] on its website. The weekly ECDC communicable disease threat report, summarises information gathered through epidemic intelligence by ECDC regarding communicable disease threats of concern to the European Union. It also includes updated information on the global situation and changes in the epidemiology of Zika virus [4].

As of 4 February 2016, no autochthonous Zika virus transmission had been reported in the continental European Union (EU). In 2015 and 2016, in several EU countries there were imported cases who had recently travelled in affected countries/territories. Several outermost EU regions continue to report Zika virus autochthonous circulation: French Guiana Guadeloupe, Martinique, Saint Martin and, Curacao (an independent state and part of the Kingdom of the Netherlands) reported an autochthonous case [2]. Widespread transmission is also present in Cape Verde and sporadic Zika virus outbreaks have been described in Africa and South Asia since the virus was discovered for the first time in Uganda in 1947. In 2013–14 a large outbreak occurred in the Pacific region, especially in French Polynesia. In 2015, the Pacific region experienced another outbreak and in May 2015, the Pan American Health Organization (PAHO) and several Latin American authorities reported cases. The recent outbreaks in French Polynesia, Brazil and other Latin America countries led to reports of potential neurological and autoimmune complications of Zika virus disease. Moreover, in Brazil and in other countries in Latin America, there were signals that a strong association between Zika virus infection and congenital abnormalities, including microcephaly, could exist when pregnant women were infected.

Read more in the articles published on Zika virus infection in *Eurosurveillance*.

References

1. World Health Organization (WHO). WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. Geneva: WHO; 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/
2. European Centre for Disease Prevention and Control (ECDC). Epidemiological update: Outbreaks of Zika virus and complications potentially linked to the Zika virus infection. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?ID=1350&List=8db7286c-fe2d-476c-9133-18ff4cb1b568&Source=http%3A%2F%2Fecdc%2Eeuropa%2Eeu%2Fen%2FPages%2Fhome%2Easpx
3. European Centre for Disease Prevention and Control (ECDC). Zika virus infection. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/Pages/index.aspx
4. European Centre for Disease Prevention and Control (ECDC). Communicable Disease Threat Reports. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/surveillance_reports/communicable-disease-threats-report/Pages/cdtr.aspx

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