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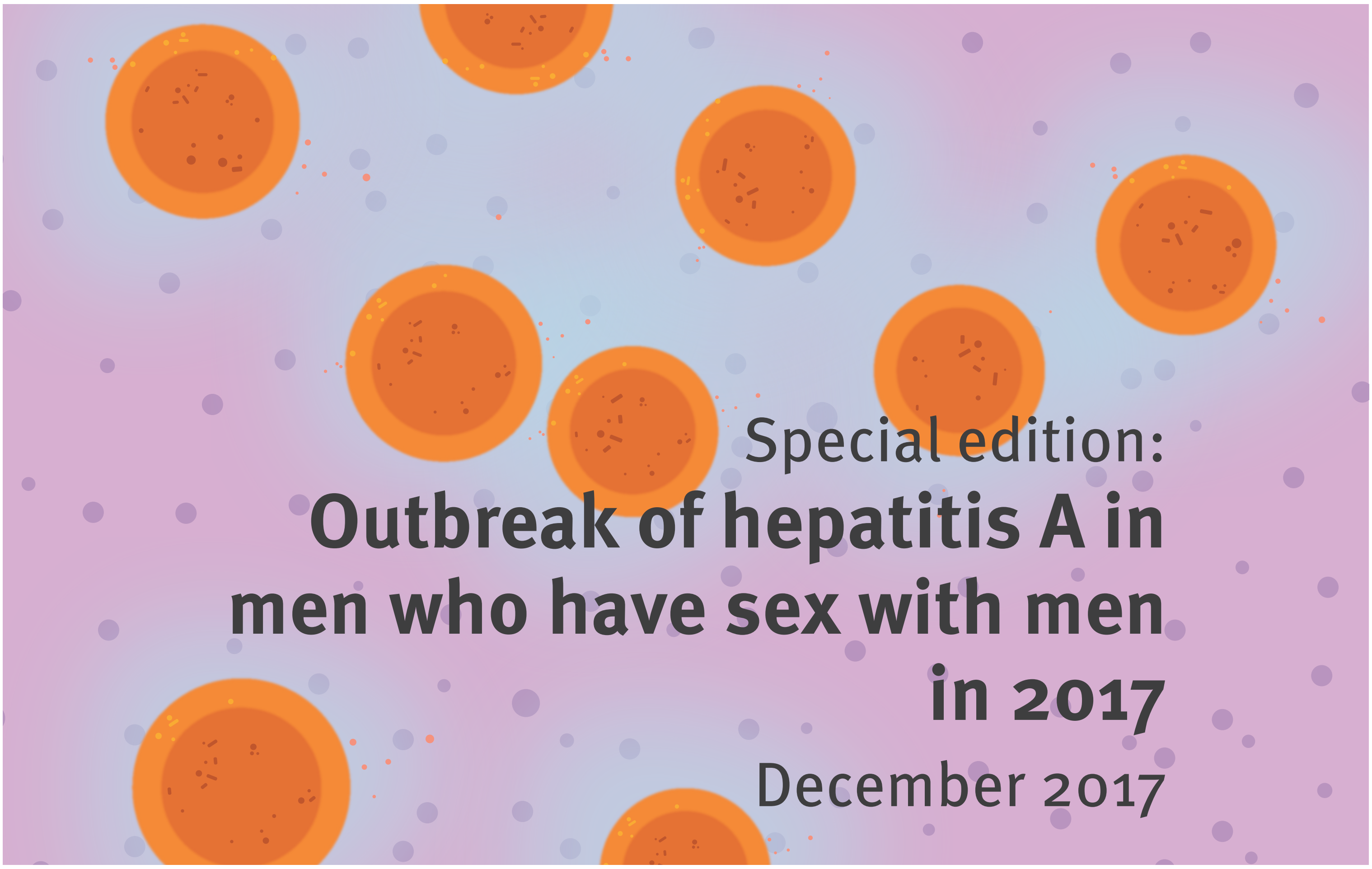

Special edition:

Outbreak of hepatitis A in men who have sex with men in 2017

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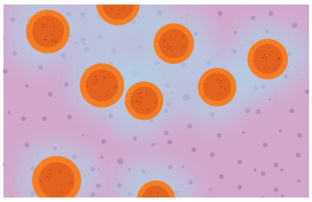

Hepatitis A outbreak in HIV-infected MSM and in PrEP-using MSM despite a high level of immunity, Lyon, France, January to June 2017

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Since 2016, an increase in the number of hepatitis A cases affecting mainly men who have sex with men (MSM) has been reported in low endemic countries in Europe. We calculated the attack rate in Lyon, France, in populations considered at high-risk: HIV-infected MSM and HIV-negative MSM receiving HIV pre-exposure prophylaxis (PrEP). In these populations, high level of immunity did not prevent the outbreak, indicating that vaccination should be reinforced, particularly in younger individuals.

Several outbreaks of acute hepatitis A among men who have sex with men (MSM) have been recently reported in different European countries [1-4]. Since the end of 2016, an important increase in the number of acute hepatitis A cases in MSM has been also notified in France through the national mandatory reporting system [5]. The aim of this study was to evaluate the proportion of hepatitis A virus (HAV)-susceptible individuals and the attack rate of acute hepatitis A in HIV-infected MSM and in HIV-negative MSM receiving HIV pre-exposure prophylaxis (PrEP).

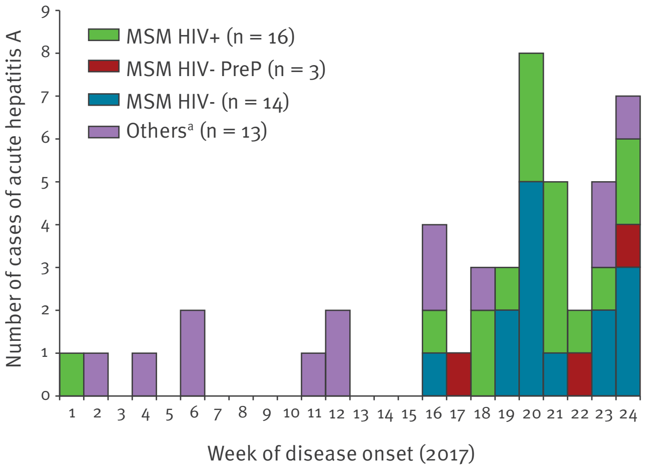
Case definition and cohort description

The infectious diseases department of the Hospices Civils de Lyon follows ca 3,800 HIV-infected patients per year, representing 94% of HIV-infected patients followed in the Rhône department. Additionally, 415 MSM who used PrEP in the Rhône department were followed in the infectious diseases department during the study period. All cases of acute hepatitis A diagnosed in the Hospices Civils de Lyon virology laboratory between 1 January and 30 June 2017 were included. Diagnosis was based on the detection of serum HAV-specific IgM antibodies (ADVIA Centaur HAV assays, Siemens, Canada) along with elevated liver enzymes. HAV sequencing from IgM-positive samples was performed by the HAV national reference centre in Villejuif, France, as previously reported [6].

All 2,023 HIV-infected MSM and 415 PrEP users followed during the period were enrolled. Demographics (age, HIV status, PrEP use), HAV and hepatitis B virus (HBV) serological status, previous history of HAV infection and HAV vaccination history were retrieved from the clinical database and are compiled in the Table. The proportion of HAV-susceptible patients was determined based on medical, serological and vaccination history. Criteria for HAV immunity were: (i) past documented acute hepatitis A or (ii) past positive test for HAV total antibodies or (iii) administration of at least one dose of hepatitis A vaccine before January 2017. Evaluation of the attack rate in HIV-infected susceptible patients was determined by category of age. To take into account the patients with unknown HAV immune status, sensitivity analyses were performed assuming that patients with unknown HAV immune status were considered as susceptible (best case scenario), and that patients with unknown HAV immune status were considered as immune (worst case scenario). The hepatitis A attack rate was not determined by category of age in PrEP users due to the limited number of cases. HAV cases in HIV-negative MSM not enrolled in the PrEP programme were not considered for the determination

Figure 1

Epidemic curve of total hepatitis A cases, January–June 2017, Lyon, France (n = 46)



HIV+: HIV infected; HIV-: HIV negative; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis

[a] The category ‘Others’ includes women, children and heterosexual men.

Table

Characteristics of HIV-infected MSM (n = 2,023) and MSM PrEP users (n = 415), January–June 2017, Lyon, France

Characteristic	HIV-infected MSM (n = 2,023)		MSM PrEP users (n = 415)	
Age **median (IQR)**	**49** **(40–57)**		**36** **(29–44)**	
CD4 cells count / mm^3 **median (IQR)**	**676** **(515–857)**		NA	
Antiretroviral treatment	n	%	**NA**	
	2,006/2,022[a]	99.2		
HIV viral load < 40 copies/mL	n	%		
	815/1,963[a]	92.5		
HBV status	n	%	n	%
Chronic hepatitis B	67	3.3	1	0.2
Cured hepatitis	693	34.3	18	4.3
Vaccinated	1,041	51.5	349	84.1
Non immune	175	8.6	31	7.5
Unknown	47	2.3	16	3.9
HAV status	n	%	n	%
Immune	1,219	60.3	305	73.5
• Vaccinated	417	20.6	158	38.1
• Previous history of hepatitis A	109	5.4	14	3.4
• Positive serology	1,037	51.3	210	50.6
Non immune	442	21.8	101	24.3
Unknown status	362	17.9	9	2.2
Acute hepatitis A during outbreak (attack rate %)				
Best scenario	2		2.7	
Worst scenario	3.8		3	
Hepatitis A strain (n = 19)				
1a_RIVM_HAV16–90 (EuroPride)	6		0	
1a_VRD_521_2016 (UK/Spain)	10		2	
1a_V16–25801	0		1	

IQR: interquartile range; MSM: men who have sex with men; NA: not applicable; PrEP: pre-exposure prophylaxis; UK: United Kingdom.

[a] Number of patients with information available for this variable.

of the attack rate, since the denominator for this population is unknown. The study was approved by the local ethics committee.

Description of the outbreak

From 1 January 2017 to 30 June 2017, 46 cases of acute hepatitis A were diagnosed in the laboratory (Figure 1) among whom 34 occurred between May and June. Two cases occurred in children under 15 years old. Among 44 adult cases, 38 were men (sex ratio M/F: 6.3); 33 were MSM, including 17 HIV-negative (among whom three were PrEP users) and 16 HIV-infected. Two cases in HIV-infected MSM who did not live in the Rhône department were excluded from the attack rate analysis. In all but one case occurring in MSM, sequencing identified one of the three epidemic strains circulating among MSM in many European countries [2-4]: 1a_VRD_521_2016 (UK/Spain; 18/33), 1a_RIVM_HAV16–090 (EuroPride; 12/33), and 1a_V16–25801 (2/33) (Table).

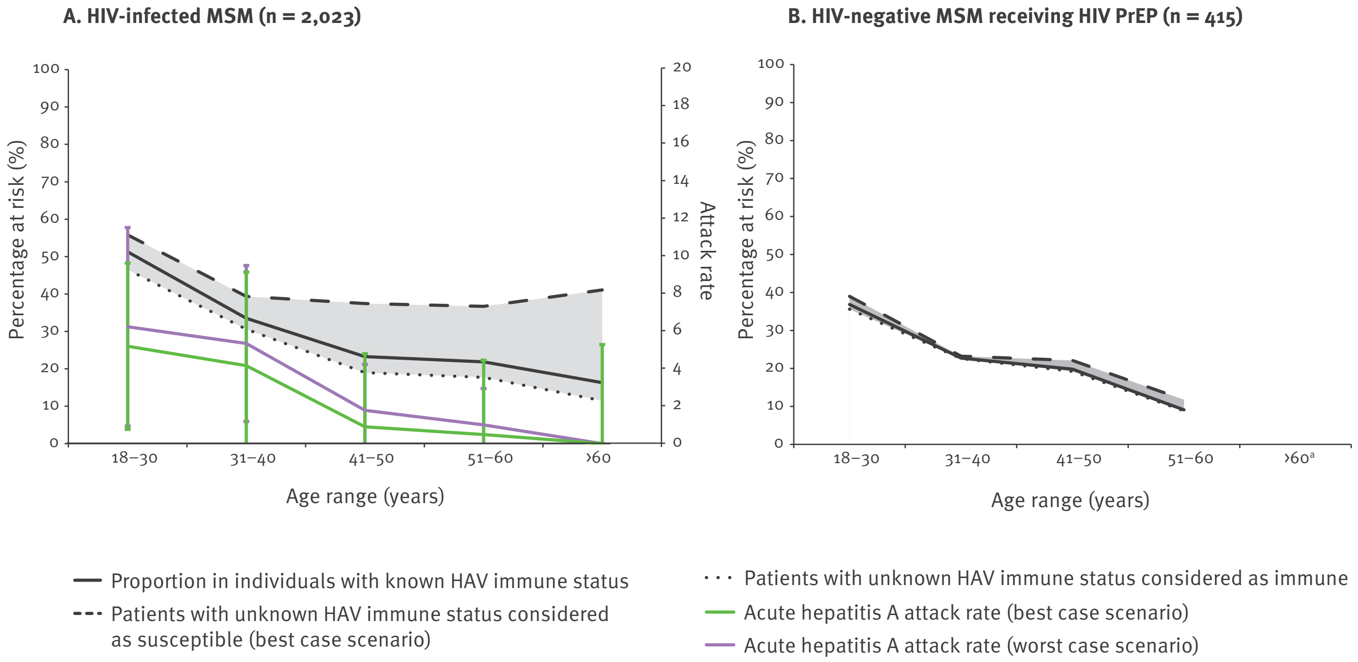
HIV-infected MSM were significantly older than PrEP users ($p < 0.001$). Among those with information available, the proportion of HAV-susceptible patients was not significantly different between groups (HIV-infected MSM: 26.6%, PrEP users: 24.9%, $p = 0.48$). The attack rate irrespective of age was similar in HIV-infected MSM (best case scenario: 2%; worst case scenario: 3.8%) and in PrEP users (best case scenario: 2.7%; worst case scenario: 3%; Table). HAV susceptibility in patients with a known immune status was higher in patients aged 18–30 years, both among PrEP users (36%) and in HIV-infected MSM (47%) and decreased with age. The best and worst case scenario gave results that were close, except for the older HIV-infected group, in which a greater number of unknown status led to an increase in susceptibility in the best case scenario (Figure 2). The attack rate in HIV-infected MSM was highest in those aged 18–30 years (best case scenario: 5.2%; worst case scenario: 6.3%) and decreased with age to reach 0% in those aged 60 years or more.

Discussion

In high-income countries the prevalence of anti-HAV antibodies in the general population is usually low (<50% by the age of 30 years) [7] Therefore, the high proportion of susceptible individuals among adults

Figure 2

Proportion of individuals susceptible to HAV and acute hepatitis A attack rate according to age, January–June 2017, Lyon, France



A. HIV-infected MSM (n = 2,023)

B. HIV-negative MSM receiving HIV PrEP (n = 415)

HAV: hepatitis A virus; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis.

[a] Number too small to calculate the percentage at risk.

Black lines: proportion of individuals susceptible to HAV.

Error bars: 95% confidence intervals.

could theoretically allow transmission, but usually hygiene measures limit the circulation of the virus and the risk of acquiring infection remains low. However, if HAV is introduced in groups at particular high-risk of transmission, outbreaks may occur according to level of immunity. Due to faeco-oral transmission during sexual activities, in particular bucco-anal, digital-anal, digital-rectal, and genito-oral activities following anal sex, MSM are at a high risk of HAV transmission. Moreover, as HAV transmission from sharing needles has also been described [8], intravenous injection of recreational drugs along with anal intercourse (also known as slamming) may increase the risk of HAV transmission in some groups of MSM. For these reasons, anti-HAV vaccination is routinely recommended in France in HIV-infected MSM and PrEP users [9], contributing to a high level of immunity compared with the general population. For example, in a recent survey, 78% of adults aged 20–29 years were susceptible to HAV, as opposed to 31% of HIV-infected MSM and 29% of PrEP users in the present study [10]. Nevertheless, this high level of immunity did not prevent HAV outbreak in the present study.

Between 1 January 2017 and 30 June 2017, 57 cases of acute hepatitis A were notified through the mandatory reporting system in the Rhône department. Among these 57 cases, 46 were diagnosed in our laboratory, suggesting a satisfying representativeness of the cases analysed here for the overall outbreak in the department. As previously reported, the outbreak described here affected mainly MSM with a similar attack rate in HIV-positive MSM and PrEP users, suggesting a comparable transmissibility in both groups considered at high risk of transmission.

One limitation of the study is that HAV immune status remained unknown in 17.9% of HIV-infected MSM and in 2.2% of PrEP users. However, in the best case scenario sensitivity analysis attack rates were high, confirming that both populations were engaged in at-risk sexual behaviour, as previously described [11,12]. Another limitation is that HAV immune status was not systematically confirmed serologically. Moreover, a single dose of hepatitis A vaccine may not be sufficient to provide immunity in a HIV-positive patients [13]. However, during the study period, no case of acute hepatitis A was reported in our centre among patients who received a single dose of vaccine.

Predictions from a modelling study suggested that population immunity must exceed 70% to prevent future person-to-person transmission of hepatitis A virus among MSM [14]. According to this model, the immunity level in the study population should have conferred protection against HAV outbreaks. However, HAV-susceptibility was much higher in younger individuals, which is likely to explain the higher attack rate observed before 40 years of age. Additionally, differences in risk practices among age groups may also have influenced transmission of the virus and the attack rate.

As immunity threshold of 70% seems to be insufficient to prevent HAV outbreaks, it should be adjusted considering behavioural characteristics, socio-demographic characteristics, and different age structures. Promotion of HAV vaccination should be reinforced, especially in young MSM who are at high risk of HAV transmission.

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Conflict of interest

None declared.

Authors' contributions

Caroline Charre, Christophe Ramière, Caroline Scholtes performed laboratory diagnostics.

Anne-Marie Roque Afonso performed sequencing data analysis.

Christian Chidiac, Fabien Zoulim, Matthieu Godinot, Joseph Koffi, Jean-Michel Livrozet, Laurent Cotte provided clinical care.

Caroline Charre, Christophe Ramière, Laurent Cotte analysed the data and drafted the manuscript.

All authors reviewed the manuscript before submission.

Members of the HAV study group contributed to the acquisition of the clinical or biological data, revised the work, and approved the submitted version.

References

1. World Health Organization (WHO). Hepatitis A outbreaks mostly affecting men who have sex with men – European Region and the Americas. Geneva: WHO; 7 Jun 2017. Available from: http://www.who.int/csr/don/07-june-2017-hepatitis-a/en/
2. Werber D, Michaelis K, Hausner M, Sissolak D, Wenzel J, Bitzegeio J, et al. Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 - linked to other German cities and European countries. Euro Surveill. 2017;22(5):30457. https://doi.org/10.2807/1560-7917.ES.2017.22.5.30457 PMID: 28183391
3. Beebeejaun K, Degala S, Balogun K, Simms I, Woodhall SC, Heinsbroek E, et al. Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017. Euro Surveill. 2017;22(5):30454. https://doi.org/10.2807/1560-7917.ES.2017.22.5.30454 PMID: 28183392
4. Freidl GS, Sonder GJ, Bovée LP, Friesema IH, van Rijckevorsel GG, Ruijs WL, et al. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveill. 2017;22(8):30468. https://doi.org/10.2807/1560-7917.ES.2017.22.8.30468 PMID: 28251892
5. Sante publique France. Epidémie d'hépatite A en France et en Europe - Point de situation au 11 septembre 2017. [Hepatitis A outbreak in France and in Europe – Situation as at 11 September 2017]. Paris: Sante publique France. [Accessed 27 Sep 2017]. French. Available from: http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/Hepatites-virales/Hepatite-A/Points-d-actualite/Epidemie-d-hepatite-A-en-France-et-en-Europe-Point-de-situation-au-11-septembre-2017
6. Schwarz NG, Revillion M, Roque-Afonso AM, Dussaix E, Giraud M, Liberpre C, et al. A food-borne outbreak of hepatitis A virus (HAV) infection in a secondary school in Upper Normandy, France, in November 2006. Euro Surveill. 2008;13(22):18885. PMID: 18761959
7. Carrillo-Santisteve P, Tavoschi L, Severi E, Bonfigli S, Edelstein M, Byström E, et al. ECDC HAV Expert Panel. Seroprevalence and susceptibility to hepatitis A in the European Union and European Economic Area: a systematic review. Lancet Infect Dis. 2017;17(10):e306-19. https://doi.org/10.1016/S1473-3099(17)30392-4 PMID: 28645862
8. Spada E, Genovese D, Tosti ME, Mariano A, Cuccuini M, Proietti L, et al. An outbreak of hepatitis A virus infection with a high case-fatality rate among injecting drug users. J Hepatol. 2005;43(6):958-64. https://doi.org/10.1016/j.jhep.2005.06.012 PMID: 16143420
9. Morlat P, editor. Prise en charge médicale des personnes vivants avec le VIH. Recommandations du groupe d'experts. Actualisation 2017. [Medical management of people living with HIV. Recommendations from the group of experts. 2017 update]. Paris: la Documentation Française; 2017. [Accessed 24 Nov 2017]. French. Available from: https://cns.sante.fr//wp-content/uploads/2017/07/experts-vih co-infections.pdf
10. Lepoutre A, Antona D, Fonteneau L, Halftermeyer-Zhou F, Baudon C, Dorléans F, et al. Séroprévalence des maladies à prévention vaccinale et de cinq autres maladies infectieuses en France. Résultats de deux enquêtes nationales 2008-2010. [Seroprevalence of vaccine-preventable diseases and five other infectious diseases in France. Results of two national surveys 2008-2010]. Bull Epidemiol Hebd (Paris). 2013; (41-42):526-34. French.
11. Molina J-M, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. ANRS IPERGAY Study Group. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015;373(23):2237-46. https://doi.org/10.1056/NEJMoa1506273 PMID: 26624850
12. Velter A, Sauvage C, Saboni L, Sommen C, Alexandre A, Lydié N, et al. Estimation de la prévalence du VIH chez les hommes ayant des relations sexuelles avec des hommes fréquentant les lieux de convivialité gay de cinq villes françaises – PREVAGAY 2015. [HIV prevalence estimate among men who have sex with men attending gay venues in five French cities – PREVAGAY 2015]. Bull Epidemiol Hebd (Paris). 2017; (18):347-54. French. Available from: http://invs.santepubliquefrance.fr/beh/2017/18/2017_18_1.html
13. Phung B-C, Launay O. Vaccination against viral hepatitis of HIV-1 infected patients. Hum Vaccin Immunother. 2012;8(5):554-9. https://doi.org/10.4161/hv.19105 PMID: 22634451
14. Ali H, Regan DG, Guy RJ, Robertson P, Watchirs-Smith L, McNulty AM, et al. Increasing hepatitis A immunity in men who have sex with men in Sydney, 1996-2012. Vaccine. 2015;33(38):4745-7. https://doi.org/10.1016/j.vaccine.2015.01.090 PMID: 25720793

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Ongoing hepatitis A among men who have sex with men (MSM) linked to outbreaks in Europe in Tel Aviv area, Israel, December 2016 – June 2017

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Between December 2016 and June 2017, 19 Hepatitis A virus (HAV)-positive cases, 17 of which were among men who have sex with men (MSM) were identified in the Tel Aviv area. Seven of the 15 sewage samples collected between January and June 2017 were also HAV-positive. All sequences clustered with two of the three strains identified in the current European HAV outbreak. We demonstrate that despite an efficient vaccination programme, HAV can still be transmitted to an unvaccinated high-risk population.

An ongoing hepatitis A outbreak involving 15 European countries with the first case identified in June 2016 in the United Kingdom (UK) [1], was recently reported [2]. By June 2017, 1,173 hepatitis A virus (HAV) infections mainly among men who have sex with men (MSM) were notified. In December 2016, when the first hepatitis A cases in Tel Aviv district were diagnosed, the local public health authority was notified and an ongoing virological, epidemiological and environmental surveillance has commenced. Here we report the current findings of 1 June 2017.

Identification of hepatitis A virus 1a in clinical and environmental samples

Hepatitis A is a notifiable disease in Israel and only 17 sporadic cases were reported between March 2013 and December 2016 in the Tel Aviv district, when the first case of the current hepatitis A outbreak was identified in a hospitalised man. A case was defined as a report of an individual who had been in the Tel Aviv health district (covering the Tel Aviv metropolitan region) with a clinical presentation of abrupt onset of hepatitis (fatigue, nausea, anorexia, abnormal liver function tests) and laboratory confirmed anti-HAV (immunoglobulin M, IgM positivity) serology. By June 2017, 19 cases of HAV infection confirmed by serology were notified to the Tel Aviv district health office (Figure 1). Seventeen cases were men, aged 22 to 41 years, who self-identified as MSM. One was a woman with a travel history to India during the incubation period. Of the 15 MSM, three had travelled to Europe, and one to the United States (US) in the two months before symptom onset. Fifteen infections were also confirmed by RT-PCR and sequencing: eight MSM were infected by the HAV 1a_ RIVM_HAV16–90 (EUROPRIDE) and six by the HAV 1a_ VRD_521_2016 (UK/SPAIN) strain; the woman was infected with an HAV 1b_India strain. The Table shows the characteristics of the patients, none of whom were vaccinated.

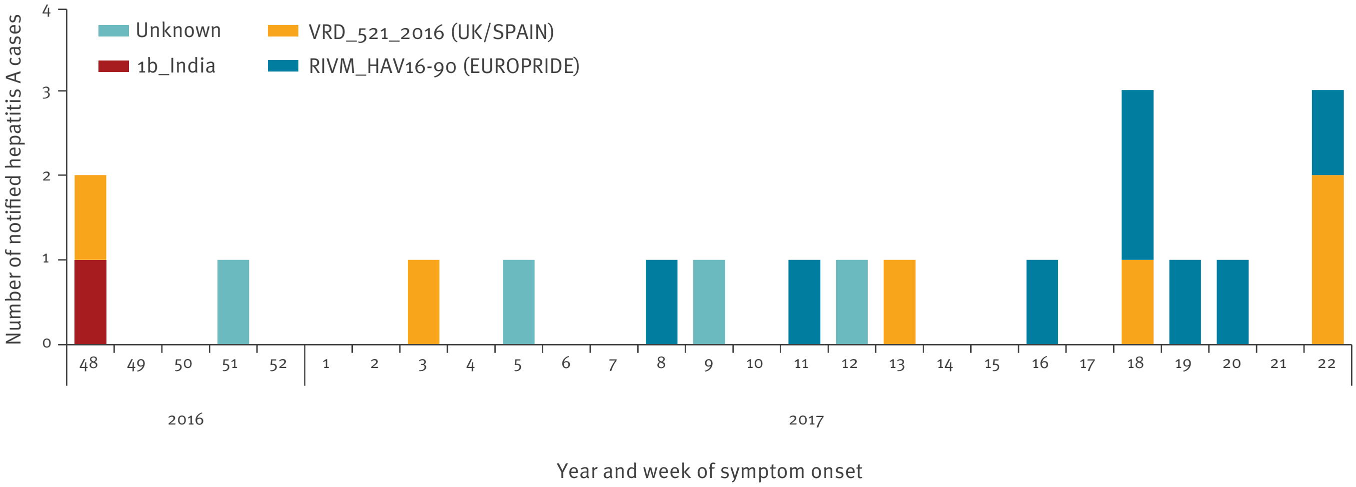
To support the outbreak investigation, the presence of HAV sequences was assessed in sewage samples (n = 23) collected between August 2016 and June 2017 as part of the routine polio surveillance programme [3] from three facilities located in the Tel Aviv area.

All sewage samples collected between August and the end of December 2016 were HAV- negative. Seven of the fifteen samples (3/7 from the Shafdan, the sewage treatment plant of Tel Aviv, and 4/4 samples from a southern Tel Aviv pipeline), collected between January and June 2017, were found to be HAV-positive.

Phylogenetic analysis of clinical and sewage HAV-positive samples showed that all sequences from the current outbreak among MSM in Israel and the seven positive sewage samples, clustered with either RIVM_HAV16–90 (EUROPRIDE) or VRD_521_2016 (UK/SPAIN)

Figure 1

Epidemic curve of hepatitis A cases by risk group, week of onset of illness, and viral strain, December 2016–June 2017, Israel (n = 19)



UK: United Kingdom.

isolates identified in the 2016–2017 European HAV outbreak [1,4,5].

Three MSM were infected with the VRD_521_2016 (UK/SPAIN) strain and epidemiologically-linked to the same non-household venue. Moreover, sequencing results were available for three of four MSM who reported travelling in the 2 months before symptoms onset. One of them, identified with the VRD_521_2016 (UK/SPAIN) strain in December 2016 (week 52), was most likely infected in Berlin. Another adult MSM, harbouring the RIVM_HAV16–90 (EUROPRIDE) strain and diagnosed in May 2017 (week 18), reported a stay in Poland during the incubation period. The third MSM, diagnosed in late May (week 22), presented with acute hepatitis two weeks after returning from New York and carried the VRD_521_2016 (UK/SPAIN) strain. All other cases had not travelled abroad and were infected in Israel.

HAV isolates from sewage also clustered with both HAV strains implicated in the ongoing European outbreak. In two of the sewage samples (9,794 and 9,773), both strains could be identified together. HAV sequences from past outbreaks in Tel Aviv formed a separate cluster with HAV 1b sequences (Figure 1, 2).

Laboratory investigation

Serum or plasma samples from acute hepatitis A cases positive for anti-HAV IgM were transferred to the national centre of HIV and viral hepatitis in the central virology laboratory of the Ministry of Health. Total nucleic acids were purified from 400 µL of plasma (or from 500 µL of filtered and concentrated sewage samples) and real-time PCR for HAV detection was performed as described previously [6]. PCR and sequencing primers of a 460-nt fragment located within the VP1/P2A region were chosen according to the HAVNET unified typing protocol [7]. Sequencing was performed on an ABI 3500 Genetic Analyzer (Applied Biosystems, Foster City, California, US) using an ABI PRISM BigDye Terminator Cycle Sequencing kit (Applied Biosystems). Raw sequence data was analysed corrected and trimmed to generate a 427-nt consensus sequence using Sequencher 5.4 (GeneCodes, Ann Arbor, Michigan, US). The resulting HAV sequences were aligned with the three distinct HAV 1a strains representing the current HAV MSM outbreak in Europe and with sequences from previously identified HAV infections in Israel. Phylogenetic analysis was conducted using a neighbour-joining algorithm in MEGA, version 6 [8], with 1,000 replicates for bootstrap testing.

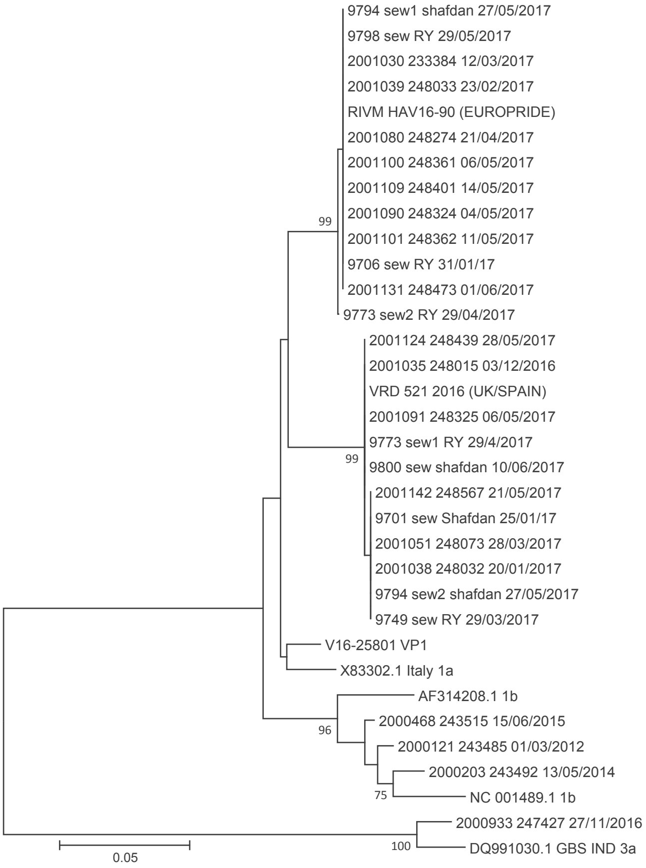
Discussion

Hepatitis A virus infection causes a substantial number of viral hepatitis cases worldwide. It is an acute self-limiting illness, associated with fever, malaise, nausea, anorexia and jaundice, mainly transmitted via the faecal-oral route [9]. A two-dose universal toddler's vaccination programme at 1.5 and 2 years of age, was initiated in Israel in 1999 and has led to an over 90% decline in incidence of the disease [10]. However, the programme cannot prevent HAV infection in high risk groups like MSM born in Israel before 1999.

Between March 2012 and March 2013, there was an outbreak in the Tel Aviv district with 75 cases of acute hepatitis, of which 73% were in non-vaccinated young men. HAV 1b was the predominant subtype identified in clinical as well as in sewage samples collected during the outbreak [6]. In the ongoing HAV outbreak occurring in the Tel Aviv district, in non-vaccinated, MSM in the age-group of 20-45 years, two of the three strains currently circulating in MSM in Europe were identified. They were detected in clinical samples from patients

FIGURE 2

Phylogenetic analysis of virus strains from hepatitis A cases and sewage isolates, 2012–2017, Israel



Neighbour-joining tree of sequences of 427 nt of the VP1/P2A region of hepatitis A virus strains. The tree was constructed in MEGA 6.0. Strains are identified by sample number, patient number (or sewage facility name) and date of infection (or date of sewage sampling). For comparison, hepatitis A virus strains detected in recent years in Israel and several reference strains (denoted by GeneBank number) were included. Numbers at the nodes indicate bootstrap values.

TABLE

Characteristics of notified hepatitis A cases, Tel-Aviv, December 2016-June 2017 (n = 19)

	Other	MSM cluster[a]
Cases	2	17
Median Age (range)	48.5 (35–62)	31 (22–41)
Male sex	1	17
Hospitalised	2	17
Travel in 2 months before symptom onset (detination)	1 (India)	4 (3 Europe, 1 United States)
HIV infection	0	1
Sexual contacts in non-household venues	0	3[b]
Hepatitis A vaccination	0	0
Hepatitis A strain (n = 15)		
1a_ RIVM_HAV16–90 (EUROPRIDE)	NA	8
1a_ VRD_521_2016 (UK/SPAIN)	NA	6
1b_India	1	NA

MSM: men who have sex with men; NA: not applicable; UK: United Kingdom.

[a] Self-identified as MSM.

[b] All were infected with RIVMHAV1690 (EUROPRIDE).

and in samples collected from sewage facilities located in the Tel Aviv area. Interestingly, none of the sewage samples collected in the 5 months before the first HAV case was identified, were HAV-positive. We therefore assume that these strains did not circulate in Tel Aviv before December 2016. Moreover, a different HAV subtype, HAV 1b, dominated in the 2012–13 outbreak that affected mainly non-vaccinated injecting drug users and not MSM. The identification of individuals that reported being infected while abroad also supports the conclusion that the current outbreak was imported to Israel by travelling MSM.

Anti-HAV vaccine is routinely recommended by the Israeli Ministry of Health to various risk groups, including MSM [11]. Following the identification of the first hepatitis A cases in MSM in Tel Aviv, we communicated about the outbreak through social media and offered free of charge vaccinations at all public health offices and sex clinics in Israel. Leaflets explaining HAV transmission and calling for anti-HAV vaccination were distributed at the venue where three infections occurred. Controlling the outbreak and protecting those who are not immune is complicated by undernotification as well as by possible asymptomatic HAV infection leading to continuous virus circulation. The abundance of HAV isolates in the environmental samples indicates that not all HAV cases have been identified.

In the past, molecular and phylogenetic analysis of HAV-positive cases in Israel was only done in specific cases. Following the 2012-13 outbreak, the need for a national diagnostic laboratory to support public health decisions on hepatitis A was emphasised. In June 2017, the viral hepatitis reference laboratory in the central virology laboratory of the Ministry of Health was formally established and an official requirement to send IgM-positive HAV samples for molecular confirmation put in place. Thus future outbreaks are expected to be better assessed. Our findings in the MSM population together with the current reports from Europe and recently also in North America [12] call for introduction of new methodologies aiming to increase vaccination coverage specifically within this risk group.

Acknowledgements

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Conflict of interest

None declared.

Authors' contributions

All the authors contributed to the outbreak investigations described here, the presentation of information and reviewed and commented on the manuscript.

References

1. Beebeejaun K, Degala S, Balogun K, Simms I, Woodhall SC, Heinsbroek E, et al. Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017. Euro Surveill. 2017;22(5):30454. DOI: 10.2807/1560-7917.ES.2017.22.5.30454 PMID: 28183392
2. European Centre for Disease Prevention and Control (ECDC). Communicable Disease Threats Report (CTDR): Week 23, 4-10 June 2017. ECDC. Jun 2017. Available from https://ecdc.europa.eu/sites/portal/files/documents/Communicable-disease-threats-report-9-june-2017.pdf
3. Manor Y, Shulman LM, Kaliner E, Hindiyeh M, Ram D, Sofer D, et al. Intensified environmental surveillance supporting the response to wild poliovirus type 1 silent circulation in Israel, 2013. Euro Surveill. 2014;19(7):20708. DOI: 10.2807/1560-7917.ES2014.19.7.20708 PMID: 24576473
4. Werber D, Michaelis K, Hausner M, Sissolak D, Wenzel J, Bitzegeio J, et al. Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 - linked to other German cities and European countries. Euro Surveill. 2017;22(5):30457. DOI: 10.2807/1560-7917.ES.2017.22.5.30457 PMID: 28183391
5. Freidl GS, Sonder GJ, Bovée LP, Friesema IH, van Rijckevorsel GG, Ruijs WL, et al. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveill. 2017;22(8):30468. DOI: 10.2807/1560-7917.ES.2017.22.8.30468 PMID: 28251892
6. Manor Y, Lewis M, Ram D, Daudi N, Mor O, Savion M, et al. Evidence for Hepatitis A virus endemic circulation in Israel despite universal toddlers' vaccination since 1999 and low clinical incidence in all age groups. J Infect Dis. 2016;215(4):574-80. Available from: https://doi.org/10.1093/infdis/jiw611PMID: 28013247
7. National Institute of Public Health and the Environment (RIVM) Hepatitis A Lab Network. (HAVNET). Protocol: Molecular detection and typing of VP1region of Hepatitis A vius (HAV). RIVM.[Accessed Jun 2017]. Available from: http://www.rivm.nl/en/Topics/H/HAVNET/Protocols/Typing_protocol_HAVNET_VP1P2A.org.
8. Tamura K, Stecher G, Peterson D, Filipski A, Kumar S. MEGA6: Molecular Evolutionary Genetics Analysis version 6.0.Mol Biol Evol. 2013;30(12):2725-9. DOI: 10.1093/molbev/mst197 PMID: 24132122
9. Lavanchy D. Viral hepatitis: global goals for vaccination.J Clin Virol. 2012;55(4):296-302. DOI: 10.1016/j.jcv.2012.08.022 PMID: 22999800
10. Levine H, Kopel E, Anis E, Givon-Lavi N, Dagan R. The impact of a national routine immunisation programme initiated in 1999 on Hepatitis A incidence in Israel, 1993 to 2012.Euro Surveill. 2015;20(7). DOI: 10.2807/1560-7917.ES2015.20.7.21040 PMID: 25719962
11. Israel MoH. Refreshing the Ministry of Health guidelines concerning immunization against Viral Hepatitis (Hepatitis A). [Accessed June 18, 2017]; Available from: http://www.health.gov.il/English/News_and_Events/Spokespersons_Messages/Pages/07022013_1.aspx.
12. World Health Organization (WHO). Hepatitis A outbreaks mostly affecting men who have sex with men – European Region and the Americas. WHO. Jun 2017. Available from: http://www.who.int/csr/don/07-june-2017-hepatitis-a/en/.

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Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017

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Between July 2016 and February 2017, 48 male cases of hepatitis A were notified in the Netherlands. Of these, 17 identified as men who have sex with men (MSM). Ten of the 13 cases for whom sequencing information was available, were infected with a strain linked with the EuroPride that took place in Amsterdam in 2016. This strain is identical to a strain that has been causing a large outbreak among MSM in Taiwan.

In December 2016, the European Centre for Disease Prevention and Control (ECDC) issued a Rapid Risk Assessment reporting of two distinct hepatitis A virus (HAV) genotype IA strains circulating among men who have sex with men (MSM) in the United Kingdom (UK) and the Netherlands in 2016. Germany, Italy and Spain had also reported a recent increase in male HAV cases [1].

The outbreak is ongoing with 37 cases reported in the UK between July 2016 and January 2017 [2] and 30 cases in Berlin between mid-November 2016 and end of January 2017 [3]. Here we describe the current situation in the Netherlands including potential links to this international hepatitis A outbreak.

Case definition

A case was defined as a person who (i) met the surveillance definition of a case of hepatitis A, (ii) self-identified as MSM or had MSM contact i.e. sexual contact with another man two months before the onset of symptoms, (iii) developed symptoms after mid-2016 (3 July 2016) and (iv) was a resident in the Netherlands. The surveillance case definition comprises (i) non-specific symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting), (ii) fever or jaundice and (iii) laboratory confirmation or an epidemiological link with a laboratory-confirmed case i.e. either hepatitis A-specific IgM antibodies in serum or detection of HAV in serum or stool by means of PCR [4].

Surveillance of hepatitis A in the Netherlands

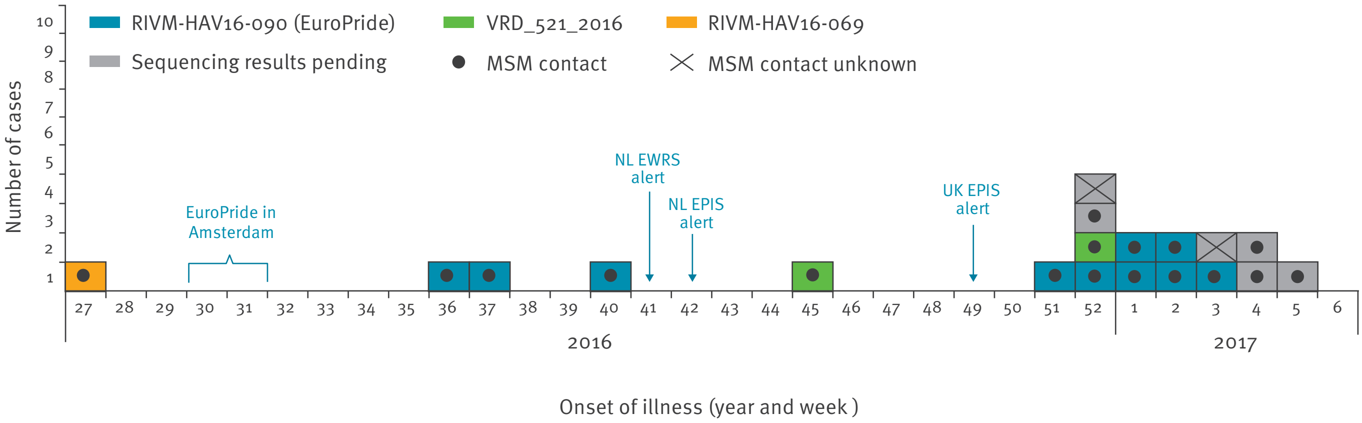
In the Netherlands, hepatitis A is a notifiable disease. Laboratories and physicians report HAV infections within one working day to the regional Public Health Services (PHS). The PHS then collect epidemiological information on demographics, occupation, symptoms, suspected source / country of infection, MSM contact (for males only) and consumption of specific food items. The PHS reports all information in the national surveillance system for notifiable diseases. In addition, serum and / or stool samples of HAV cases are routinely sent to the National Institute of Public Health and the Environment (RIVM) for molecular analysis. In case men did not explicitly report having had MSM contact two months before disease onset, MSM status was assessed by asking whether they identified themselves as MSM.

Molecular analyses

HAV IgM-positive serum samples were analysed by sequence analysis of a 460 nt PCR fragment in the VP1/P2A region according to a shared protocol available through Hepatitis A Lab-Network HAVNET [5].

Figure 1

Epidemic curve of hepatitis A cases by MSM status and week of onset of illness, July 2016–February 2017, the Netherlands (n = 19)



EPIS: Epidemic Intelligence Information System; EWRS: Early Warning and Response System; MSM: men who have sex with men; NL: the Netherlands; UK: United Kingdom.

Two cases for whom MSM status was unknown at the time of the investigation, are also included.

Outbreak description

In the first half of 2016 (including week 26), 22 sporadic hepatitis A cases were notified through the Dutch national surveillance system. Half of these were men and none reported MSM contact.

On 19 September 2016 (week 38), the outbreak investigation was triggered by the notification of two male cases of hepatitis A, in their 30s and 40s, who fell ill in mid-September. Both cases reported having had MSM contact during the EuroPride. The EuroPride, which took place in Amsterdam between 29 July and 6 August, is an international event to celebrate equality rights of the lesbian, gay, bisexual and transgender community. In 2016, this event attracted over half a million visitors [6]. Sequencing showed that strains from both cases were identical (RIVM-HAV16–090). Given the international character of the EuroPride, alerts were placed on the Early Warning and Response System (EWRS) and on ECDC's Epidemic Intelligence Information System for Food- and Waterborne diseases (EPIS-FWD) to inform other European countries.

From mid-2016 (week 27) to 7 February 2017, 48 male cases of hepatitis A were reported nationally. Of these, 17 identified as MSM. Two cases did not (yet) meet the case definition, as MSM status was unknown at the time of the investigation. For comparison, in 2013, 2014 and 2015, 56, 58 and 45 male cases of hepatitis A were reported each year, respectively. Among these, none were identified as MSM.

The Table shows the characteristics of the cases recorded in the current outbreak. The onset of illness ranged from week 27, 2016 to week 5, 2017 (Figure 1).

Of the 17 cases, 11 were born outside the Netherlands (Argentina, Brazil, Canada, France, Italy, Lebanon, Peru, Spain (n = 3), Surinam). The median age of the 17 cases was 33 years (range: 26–52). None of the cases were vaccinated and about a third was hospitalised (Table). Sequence information was available for 13 of the 17 cases, which showed co-circulation of three different hepatitis A strains (Table, Figure 2).

Ten of the 13 cases with available typing information were infected with the EuroPride strain. The majority of cases (n = 11), irrespective of sequence type, clustered in the Public Health Service region of Amsterdam, whereas other Public Health Service regions only reported incidental cases (Table, Figure 3).

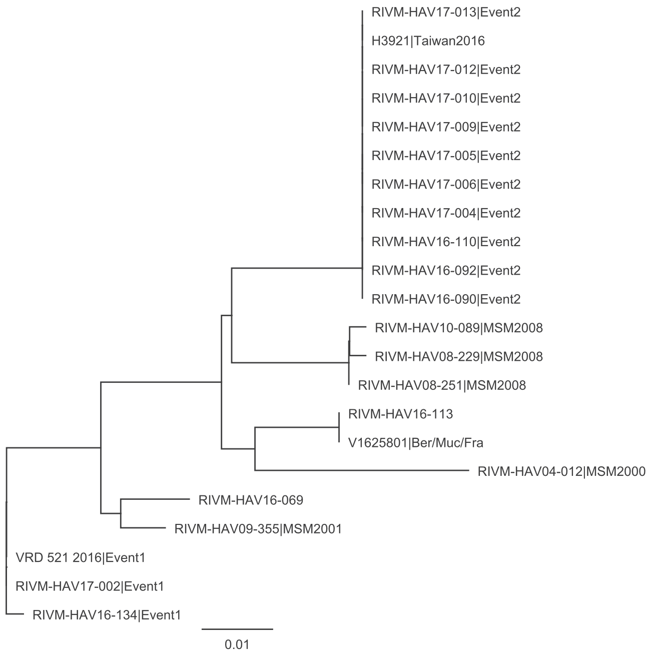
In comparison, among the 29 male cases who became ill after mid-2016 and were not MSM (median age: 20.5 years, range: 0–82) we found strains that were unrelated to the current outbreak. We detected genotype IA and IB strains from Morocco, IB strains from Egypt, Turkey, West Africa and East Africa, a IIA strain from Cameroon, a IIIA strain from Romania or no hepatitis A virus, respectively. As none of these cases was infected with a strain involved in the current outbreak, we are confident that these cases reported their MSM status truthfully.

EuroPride strain RIVM-HAV16–090

When comparing sequence information of the EuroPride strain with available sequences in the databases HAVNET [5] and GenBank, we found that the EuroPride strain was 99.57% identical to a sequence submitted by Japan (accession number: AB020565, release date: 14 August 2001). In addition, in response to a post on ProMED-mail from May 2016 that reported

Figure 2

Phylogenetic analysis of virus strains from hepatitis A cases who self-identified as men who have sex with men, the Netherlands, 2000–2017

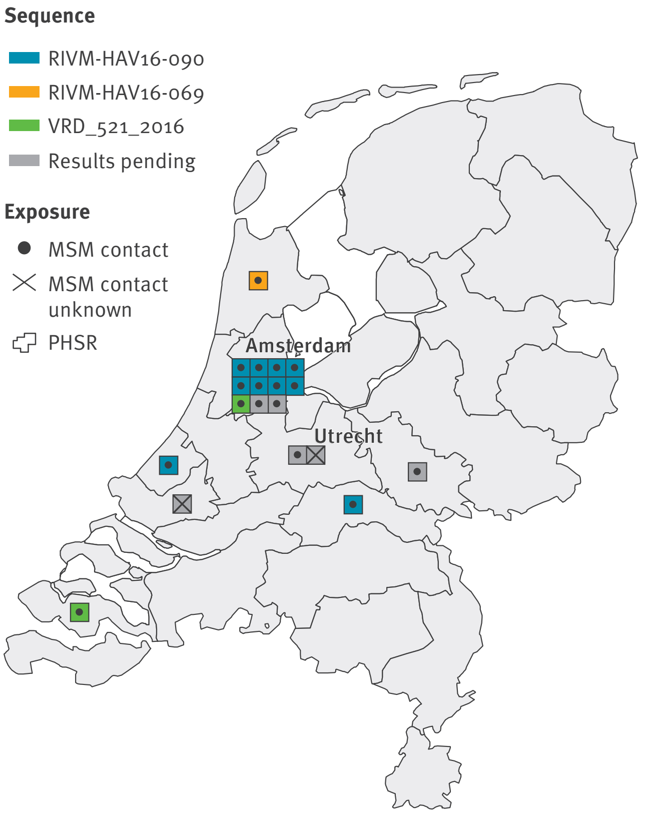


Neighbour-joining tree of sequences of 445 nt of the VP1/P2A region of hepatitis A virus strains.

The tree was constructed in PHYLIP (DNADIST) (Joe Felsenstein, Department of Genome Sciences, University of Washington, Seattle, USA). Strains are identified by sample number and cluster. Event 1 and Event 2 refer to terminology used in the Rapid Risk Assessment published by the European Centre for Disease Prevention and Control (ECDC) [1]. Event 1 refers to strains detected in the United Kingdom and Spain [2]. Event 2 refers to the EuroPride strain detected in the Netherlands and the strain circulating in Taiwan in 2016, respectively. One asymptomatic case is identical to a sequence that caused a cluster in Germany (Ber/Muc/Fra) [3]. For comparison, we also included older hepatitis A virus strains detected in men who have sex with men (MSM) in 2000, 2001 and 2008, respectively.

Figure 3

Geographic distribution of hepatitis A cases who self-identified as men who have sex with men, by available sequence information, the Netherlands, July 2016–February 2017 (n = 19)



MSM: men who have sex with men; PHSR: Public Health Service region.

Two cases for whom MSM status was unknown at the time of the investigation, are also shown. Notified cases are centred in the respective Public Health Service region. The majority of cases (n = 11) occurred in the PHSR Amsterdam.

on a hepatitis A outbreak among MSM in Taiwan with 275 notified cases [7], we investigated whether the EuroPride strain might be related to the Taiwanese outbreak strain. Direct comparison and phylogenetic analyses showed that the Taiwanese outbreak strain was identical to the EuroPride strain (Figure 2). Eight of the ten cases reported to have likely been infected in the Netherlands, and a further two cases were likely infected in Barcelona, Spain (n = 2; onset of illness for both cases: week 2, Figure 1).

Strains VRD_521_2016 and RIVM-HAV16–069

Two cases were infected with strain VRD_521_2016, first reported by the UK in December 2016 and likely imported from Spain several times [1,2]. One of the Dutch cases reported having travelled to Spain (onset of illness in week 45), whereas the other case stated to have likely been infected in the Netherlands (onset of illness week 52, Figure 1).

One case infected with strain RIVM-HAV16–069 reported having travelled to Argentina and became ill shortly before the EuroPride (week 27). The UK also reported one MSM case with the same sequence [2].

Discussion

Here we report on an ongoing hepatitis A outbreak among MSM in the Netherlands that started in 2016. Hepatitis A is an acute, self-limiting liver disease which is transmitted via the faecal-oral route. Infection occurs via contaminated food or water, or through person-to-person contact, including sexual contact. The average incubation period is 28 days (range: 15–50 days) [8]. In western Europe hepatitis A endemicity is low [9] and is primarily associated with travelling to endemic countries [10] or consumption of contaminated, imported food [11]. Outbreaks among MSM have also been described [12]. In Europe, the last outbreak of hepatitis A among MSM occurred between 2008 and 2011 [13].

TABLE

Characteristics of hepatitis A cases by MSM status and strain, the Netherlands, July 2016–February 2017 (n = 19)

	Men who have sex with men (MSM)					Sequence information and MSM status unknown / pending
Hepatitis A strain	RIVMHAV16090 (EuroPride)	VRD_521_2016 (UK / Spain)	RIVM-HAV16–069	Sequence information pending	Total	
Number of cases	10	2	1	4	17	2
Number per 10-year age group	20–29 (n = 3) 30–39 (n = 4) 40–49 (n = 3)	20–29 (n = 1) 40–49 (n = 1)	20–29 (n = 1)	20–29 (n = 2) 30–39 (n = 1) 50–59 (n = 1)	33 (26–52) Median (min–max)	20–29 (n = 1) 40–49 (n = 1)
Number of cases hospitalised	3	1	1	0	5	0
Number of cases vaccinated against hepatitis A	0	0	0	0	0	0
Suspected place of infection	The Netherlands (n = 8) Spain, Barcelona (n = 2)	The Netherlands (n = 1) Spain (n = 1)	Argentina (n = 1)	The Netherlands (n = 3)[a] Germany, Berlin (n = 1)	4	The Netherlands (n = 1)[b]

MSM: men who have sex with men; UK: United Kingdom.

[a] One case reported Portugal as second suspected country of infection.

[b] For one case information on suspected place of infection was not available.

Ages were estimated because only year of birth was known.

Characteristics of two male cases of hepatitis A for whom MSM status was unknown at the time of the investigation, are shown separately.

Between 2012 and mid-2016, hepatitis A infection in MSM was only notified twice in the Netherlands.

In the currently ongoing outbreak in the Netherlands, the majority of cases for whom sequence information was available, were infected with strain RIVM-HAV16–090. This strain had only been detected once before in 2010 and was absent in the Netherlands until it was detected in two MSM cases who attended the EuroPride in 2016. The strain is identical with a strain causing an ongoing outbreak among MSM in Taiwan. As at 29 September 2016, Taiwan reported 845 hepatitis A cases among MSM, of which 56% were HIV-positive or had another sexually transmitted diseases [14].

In the Netherlands, information on HIV status is not routinely collected for hepatitis A surveillance purposes. In the course of this outbreak investigation, in week 43, we detected one HAV infection in a HIV-positive MSM who was asymptomatic and therefore did not meet the case definition. Sequencing showed infection with a strain identical to the Berlin/Munich/Frankfurt HAV cluster in Germany (V16–25801) [3]. Asymptomatic individuals, even if they do not fulfil the case definition, can still be epidemiologically relevant and should therefore be included in epidemiological analyses.

In the Netherlands, besides risk groups, i.e. persons with chronic liver disease or occupational exposure to HAV, hepatitis A vaccination is recommended to individuals who travel to HAV endemic countries. Hepatitis A vaccine uptake is unknown. Because of several outbreaks among European and Dutch MSM [15,16], hepatitis A vaccination is also recommended to MSM in the Netherlands. For MSM, vaccination against HAV is available at reduced costs and is administered in combination with hepatitis B vaccine that is free of charge for this risk group. The uptake of hepatitis B vaccination among MSM in Amsterdam is high and hepatitis B incidence has dropped markedly since 2005 [17]. In contrast, financial aspects might hamper wide uptake of hepatitis A vaccination. Vaccination coverage among MSM is unknown.

In the Netherlands, hepatitis A control is based on vaccination of household- and other close contacts [4]. Tracing and vaccination of sexual contacts of MSM can be challenging due to anonymous sexual contacts. To better understand transmission chains and the epidemiology of this outbreak, we recently introduced an additional, more detailed questionnaire for hepatitis A-positive MSM to complement routinely collected epidemiological data. Given the high outbreak potential of hepatitis A in the MSM community and the high interconnectedness through global travel of this risk group [18], increasing awareness of hepatitis A among MSM as well as health professionals at sexually transmitted disease clinics and public health services should be emphasised. To increase hepatitis A vaccination uptake, the Regional Public Health Services and ‘STI AIDS the Netherlands’ (centre of expertise for HIV and other sexually transmitted infections) have been engaging in activities to remind professionals and the Dutch MSM community of the availability of hepatitis A vaccination within the hepatitis B vaccination programme.

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Conflict of interest

None declared.

Authors’ contributions

GSF analysed epidemiological data and wrote the manuscript. LPMJB, FvS, ECS and GJBS interviewed cases and coordinated outbreak investigation within the Public Health Service region GGD Amsterdam. IHMF, WLMR, GGCvR were involved in the outbreak management and coordination of the outbreak response. J-YY provided sequence information from Taiwan. HV conducted molecular analyses. All authors commented on the manuscript.

References

1. European Centre for Disease Prevention and Control (ECDC). Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men. Stockholm: ECDC; 19 Dec 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/13-12-2016-RRA-Hepatitis%20A-United%20Kingdom.pdf
2. Beebeejaun K, Degala S, Balogun K, Simms I, Woodhall SC, Heinsbroek E, et al. Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017. Euro Surveill. 2017;22(5):30454. DOI: 10.2807/1560-7917.ES.2017.22.5.30454 PMID: 28183392
3. Werber D, Michaelis K, Hausner M, Sissolak D, Wenzel J, Bitzegeio J, et al. Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 - linked to other German cities and European countries. Euro Surveill. 2017;22(5):30457. DOI: 10.2807/1560-7917.ES.2017.22.5.30457 PMID: 28183391
4. National Coordination Centre for Communicable Disease Control. (Landelijke Coordinatie Infectieziektenbestrijding (LCI). LCI-richtlijn Hepatitis A. [LCI directive on hepatitis A]. Bilthoven: LCI. [Accessed: 5 Feb 2017]; Dutch. Available from: http://www.rivm.nl/Documenten_en_publicaties/Professioneel_Praktisch/Richtlijnen/Infectieziekten/LCI_richtlijnen/LCI_richtlijn_Hepatitis_A
5. National Institute of Public Health and the Environment (RIVM). HAVNET Hepatitis A Lab Network. Bilthoven: RIVM; [Accessed 5 Feb 2017]. Available from: http://www.rivm.nl/en/Topics/H/HAVNET
6. Nieuws RTL. Recorddrukte Canal Parade geëvenaard: 560.000 mensen op de been. [Record visitor numbers at Canal pride: 560.000 people present]. Hilversum: RTL Nieuws; 2016. Dutch. Available from: http://www.rtlnieuws.nl/nederland/recorddrukte-canal-parade-geevenaard-560000-mensen-op-de-been
7. ProMED-mail. Hepatitis A - Taiwan: Increased MSM incidence. Archive. 2016;4230111(: 20160518):18. Available from: http://www.promedmail.org/post/20160518.4230111
8. World Health Organization (WHO). Hepatitis A vaccines.Wkly Epidemiol Rec. 2000;75(5):38-44.PMID: 10693358
9. World Health Organization (WHO). The Global Prevalence of Hepatitis A Virus Infection and Susceptibility: A Systematic Review. Geneva: WHO; Jun 2009. Available from: http://apps.who.int/iris/bitstream/10665/70180/1/WHO_IVB_10.01_eng.pdf
10. Wu D, Guo CY. Epidemiology and prevention of hepatitis A in travelers.J Travel Med. 2013;20(6):394-9. DOI: 10.1111/jtm.12058 PMID: 24165384
11. Gossner CM, Severi E. Three simultaneous, food-borne, multi-country outbreaks of hepatitis A virus infection reported in EPIS-FWD in 2013: what does it mean for the European Union?Euro Surveill. 2014;19(43):20941. DOI: 10.2807/1560-7917.ES2014.19.43.20941 PMID: 25375903
12. Urbanus AT, van Houdt R, van de Laar TJ, Coutinho RA. Viral hepatitis among men who have sex with men, epidemiology and public health consequences.Euro Surveill. 2009;14(47):19421.PMID: 19941800
13. Bordi L, Rozera G, Scognamiglio P, Minosse C, Loffredo M, Antinori A, et al. . Monophyletic outbreak of Hepatitis A involving HIV-infected men who have sex with men, Rome, Italy 2008-2009.J Clin Virol. 2012;54(1):26-9. DOI: 10.1016/j.jcv.2012.01.009 PMID: 22341552
14. Centers for Disease Control (CDC) R.O.C. Taiwan. As Taiwan CDC to expand target groups for government-funded hepatitis A vaccination beginning October 1, 2016, eligible individuals urged to get vaccinated at contracted healthcare facilities. Press release. Taipei: CDC R.O.C. Taiwan; 30 Sep 2016. Available from: http://www.cdc.gov.tw/english/info.aspx?treeid=bc2d4e89b154059b&nowtreeid=ee0a2987cfba3222&tid=557BA6C13262600C
15. van Steenbergen JE, Tjon G, van den Hoek A, Koek A, Coutinho RA, Bruisten SM. Two years’ prospective collection of molecular and epidemiological data shows limited spread of hepatitis A virus outside risk groups in Amsterdam, 2000-2002.J Infect Dis. 2004;189(3):471-82. DOI: 10.1086/381152 PMID: 14745705
16. Stene-Johansen K, Tjon G, Schreier E, Bremer V, Bruisten S, Ngui SL, et al. Molecular epidemiological studies show that hepatitis A virus is endemic among active homosexual men in Europe. J Med Virol. 2007;79(4):356-65. DOI: 10.1002/jmv.20781 PMID: 17311331
17. van Rijckevorsel G, Whelan J, Kretzschmar M, Siedenburg E, Sonder G, Geskus R, et al. Targeted vaccination programme successful in reducing acute hepatitis B in men having sex with men in Amsterdam, the Netherlands. J Hepatol. 2013;59(6):1177-83. DOI: 10.1016/j.jhep.2013.08.002 PMID: 23954670
18. Lee VC, Sullivan PS, Baral SD. Global travel and HIV/STI epidemics among MSM: what does the future hold?Sex Health. 2017;14(1):51. DOI: 10.1071/SH16099 PMID: 28055822

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Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 – linked to other German cities and European countries

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Since 14 November 2016, 38 cases of hepatitis A have been notified in Berlin; of these, 37 were male and 30 reported to have sex with men (MSM). Median age of MSM cases is 31 years (range: 24–52 years). Phylogenetic analysis revealed three distinct sequences, linking cases in Berlin to those in other German cities and to clusters recognised in other European countries in 2016.

On 14 December 2016, the local public health authority (LPHA) of the Berlin district Mitte informed the State Office for Health and Social Affairs (SOHSA) in Berlin, of two male cases of hepatitis A, notified in calendar week 50, who identified themselves as men who have sex with men (MSM). At that time, no increase in hepatitis A cases was apparent in the notification data.

Immediately following this information, we enhanced epidemiological and virological surveillance of hepatitis A in Berlin and report here preliminary findings.

Enhanced surveillance and molecular analyses

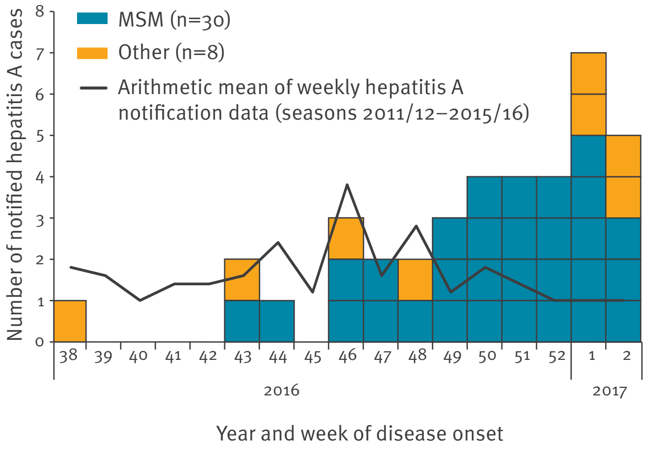
In the absence of an increase of hepatitis A in the notification data of Berlin in calendar week 50/2016, we (arbitrarily) considered a possible outbreak beginning as of calendar week 46/2016 (starting 14 November), i.e. four weeks (mean incubation period of hepatitis A) before the hepatitis A cases in MSM were first recognised. This coincided with when notified hepatitis A cases started to be predominantly male adults. We applied the case definition that is also used for surveillance purposes in Germany, i.e. symptomatic disease defined as fever or one of the following: abdominal discomfort, increase in serum transaminases, jaundice, plus laboratory confirmation, i.e. detection of hepatitis A virus (HAV) nucleic acid or HAV-specific IgM or a distinct increase in IgG [1]. We requested all 12 LPHAs in Berlin to systematically collect additional information on hepatitis A cases, notified as of calendar week 46/2016, in a specifically designed spreadsheet, including information on sexual contacts, sex in non-household venues and drug use, during their assumed period of infection. SOHSA collated case information submitted electronically by LPHAs.

LPHAs were also asked to organise sequencing of hepatitis A virus (HAV) from IgM positive serum samples or stool samples of cases notified as of calendar week 50 at the National Consultant Laboratory for Hepatitis A and Hepatitis E in Regensburg. Nucleic acid isolation, quantitative reverse transcription PCR (RT-qPCR) and sequencing were conducted as described elsewhere [2]. Sequencing primers were chosen according to the HAVNET unified typing protocol [3]. We queried GenBank for sequences with high similarity using the BLAST algorithms. A rooted maximum likelihood phylogenetic consensus tree for sequences of a 437 nucleotide (nt) long fragment in the VP1/P2A junction region was inferred using MEGA version 7.0.18 software.

In order to obtain information about possibly linked cases in other European Union countries, we communicated the information about the increase of hepatitis A in Berlin together with sequence information via the European Centre for Disease Prevention and Control

Figure 1

Notified cases of hepatitis A, stratified by sexual orientation and sex by week of symptom onset, Berlin, Germany, 14 November 2016–20 January 2017 (n=38)



(ECDC)'s Epidemic Intelligence Information System (EPIS) for food- and waterborne diseases and zoonoses (FWD) and the EPIS for sexually transmitted infections.

Description of the outbreak

As at 20 January 2017, 38 cases of hepatitis A have been notified in Berlin since 14 November 2016 (calendar week 46). Of these, 37 are male, and one is female (Table).

Sexual orientation is known for 32 cases (31 men, one woman); 30 identified themselves as MSM, one as heterosexual and the woman as having sex with women (WSW). Median age of the 30 MSM cases is 31 years (range: 24–52 years); they live in seven of the 12 districts in Berlin, and most of them in Mitte (n = 10). Disease onset of MSM cases ranges over an 11-week period (calendar weeks 43/2016–2/2017, Figure 1), which is incompatible with a common exposure to a point source. Three cases are epidemiologically linked to three other notified cases, supporting the assumption of transmission by interpersonal spread. Six cases have a travel history outside Germany (Spain (n = 2), Austria, Greece, Malta, Taiwan (n = 1 each) during the assumed period of infection, but the majority was apparently infected in Germany (likely in Berlin).

None of the MSM cases reported intravenous drug use. One MSM case was vaccinated with one dose of a monovalent hepatitis A vaccine 11 months before disease onset (a second dose within 6 to 12 months after the first dose is usually recommended by manufacturers to provide long-term protection); all others for which information on vaccination is available (n = 27) were unvaccinated (n=23) or their vaccination was incomplete (n=3, single doses of HAV/HBV combination vaccine or unknown vaccine more than one year before disease onset) or outdated (n=1, last dose in 2001).

Sequencing results and phylogenetic analysis show three distinct clusters of MSM-related HAV strains currently circulating in Berlin (Figure 2).

The five sequences in the cluster Ber/Muc/Fra (including the WSW) are identical (100% match in the investigated 437 nt long fragment) to the HAV strain first observed in a MSM patient in August 2016 in Munich and later in a MSM patient in Frankfurt (prototype sequence V16–25801). The HAV sequences of three cases in the cluster Ber/NL are identical to the previously reported MSM-related HAV sequence RIVM-HAV16–090, which was isolated from two patients in September 2016, who had visited the EuroPride in Amsterdam in August 2016 [4]. Two of the identified cases fit in the third cluster Ber/UK with also identical sequences as compared with the MSM HAV outbreak strain UK VRD 521 circulating in the United Kingdom (UK) and reported in 2016 [4]. The closest match in the National Center for Biotechnology Information (NCBI) sequence database for the Ber/Muc/Fra cluster was isolated in 2013 in Italy during a multi-country European food-borne outbreak (IZSLER-005, acc. KU570286.1, 99.5% identity) [5], matches for the other clusters are described in [4].

Through EPIS-FWD, colleagues from Austria, Denmark and the Netherlands reported sporadic cases with sequence identity to the Ber/Fra/Muc-Cluster, some of which reported having sex with men in Berlin before disease onset.

Background

HAV is predominantly transmitted via the faecal-oral route through person-to-person contact or contaminated food and water. The mean incubation period is 28 days (range: 15 to 50 days). Infected persons are most likely to transmit HAV before the onset of jaundice, when HAV concentration in stool is highest [6]. Transmission through sexual contact, particularly in MSM [7] as well as through sharing of needles and syringes has also been described [8]. Hepatitis A is a vaccine preventable disease and the German Standing Committee on Vaccination recommends vaccination of people with sexual behaviour at high-risk for HAV infection (such as homosexual contacts) [9]. Recommended vaccinations are paid for by health insurances in Germany.

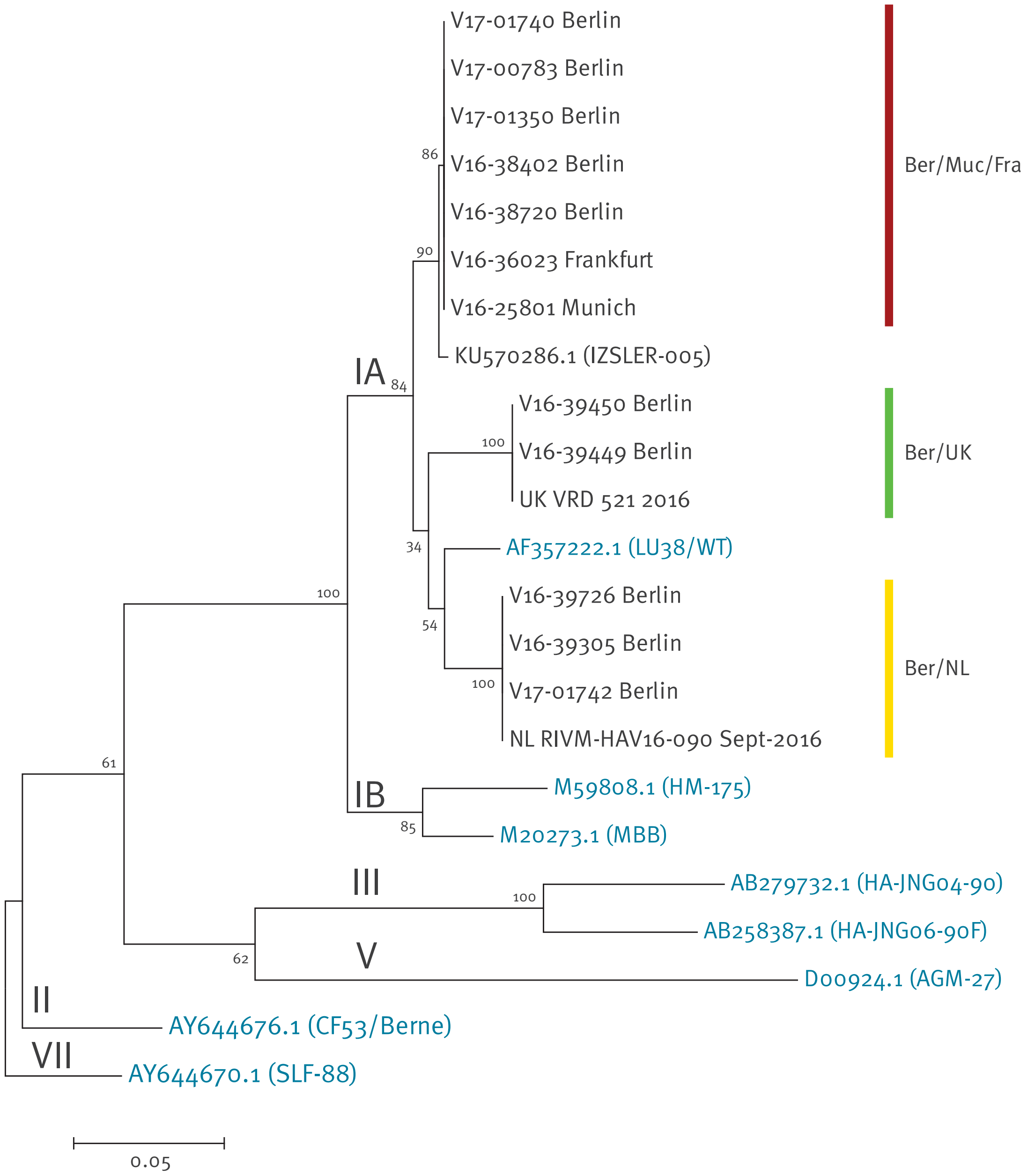
Germany is a low incidence country with 0.9 notified cases per 100,000 population in 2016. Virtually all HAV infections are directly or indirectly imported [10].

General and specific public health measures in Germany

In response to the present outbreak, LPHAs educated cases about personal hygiene, traced cases and their contacts and recommended vaccination or post-exposure prophylaxis to contacts according to their risk profile. In addition, LPHA's, the SOHSA and the Robert Koch Institute (RKI, German national public health institute) formulated prevention recommendations to

Figure 2

Phylogenetic analysis of hepatitis A viruses, outbreak among men who have sex with men, Berlin, Germany, 14 November 2016–20 January 2017



HAV: hepatitis A virus.

Molecular Phylogenetic analysis of the VP1/P2A junction region of selected HAV isolates by Maximum Likelihood method. Genotype VII was used as an outgroup. Sequences are denoted by GenBank ID (reference strains in blue) or isolate ID. Roman numerals indicate genotype; numbers at the nodes indicate bootstrap values.

The evolutionary history was inferred by using the Maximum Likelihood method based on the Tamura-Nei model. All positions containing gaps and missing data were eliminated. There were a total of 437 positions in the final dataset. Sequences from the Netherlands and the United Kingdom are from [4].

TABLE

Characteristics of notified hepatitis A cases, Berlin, 14 November 2016–20 January 2017 (n=38)

	MSM	Others[a]	Total
Number	30	8	38
Male patients	30 of 30	7 of 8	37 of 38
Median age (range) in years	31 (24–52)	34 (11–50)	31 (11–52)
Hospitalised	6 of 30	2 of 7[b]	8 of 37[b]
Sexual contacts in non-household venues	12 of 24[b]	NA	NA
Migration background	13 of 25[b]	1 of 4[b]	14 of 29
Drug use	1 of 25[b]	NA	NA

MSM: men who have sex with men; NA: not applicable.

[a] This category includes one heterosexual patient, one homosexual female patient and six male patients with unknown status.

[b] Information missing for some patients.

reinforce offering (i) vaccination to people with sexual behaviour at high-risk for HAV infection [10], and (ii) post-exposure prophylaxis to exposed contacts (active and passive immunisation is effective if administered within two weeks after exposure) [11].

This information was sent to practitioners who focus on treating HIV patients in Berlin, as well as to gay-oriented magazines, newsletters, webpages and specialised healthcare organisations. Furthermore, information was published in the weekly newsletter of the SOHSA and the Epidemiological Bulletin of the RKI [12].

Discussion

We report on a recent increase of notified hepatitis A cases in Berlin, attributable to cases in MSM. The age distribution of MSM is comparable to that of MSM in previously described hepatitis A outbreaks [7,13]. The vast majority of cases was not vaccinated against hepatitis A indicating a need for targeted risk communication and vaccination campaigns. Of note, condom use is not a safeguard against HAV infection because it does not block the faecal-oral transmission route.

Interestingly, two different HAV sequences detected in cases from Berlin were recently identified in clusters of MSM in the Netherlands and in the UK [7]. The third sequence was identified in a cluster of six MSM cases in Munich and Frankfurt from August through October (data not shown). It is unclear why three different HAV strains concurrently circulate in Berlin among MSM. Apparently, Berlin's MSM scene is nationally and internationally well connected allowing for 'importation' and 'exportation' of HAV strains from or to various places in Europe.

For hepatitis A, the German electronic notification system does not capture sexual orientation. Thus, the magnitude of sexually transmitted hepatitis A is likely underestimated. The outbreak described here highlights the interconnectedness of MSM in Europe and the need to increase coverage of hepatitis A vaccination in this group.

Acknowledgements

We would like to thank colleagues from the local public health authorities for collecting case data and organising to forward blood and stool specimens for strain typing. We also would like to acknowledge the following colleagues who reported to EPIS on possibly linked cases in other countries: Luise Müller (Denmark), Solveig Jore (Norway), Franz Allerberger (Austria), Lelia Thornton (Ireland), Harry Vennema (The Netherlands) and Lena Sundqvist (Sweden).

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Conflict of interest

None declared.

Authors' contributions

DW JB and DSa have conducted enhanced surveillance of hepatitis A in Berlin, DW has written the manuscript MH and DSi have discovered the link of recent hepatitis A cases and MSM in Berlin Mitte and provided detailed case information. KM has monitored the situation at the federal level and communicated with European colleagues via EPIS. AB has investigated the cluster in Munich with links to Frankfurt, JW conducted the sequencing of hepatitis A viruses in this outbreak. MF has conducted the phylogenetic analysis and co-written the manuscript. All authors have revised the manuscript.

References

1. Robert Koch Institut (RKI). Falldefinitionen des Robert Koch-Instituts zur Übermittlung von Erkrankungs- oder Todesfällen und Nachweisen von Krankheitserregern, Ausgabe 2015. [Case definitions of the Robert Koch Institute for the surveillance of notifiable infectious diseases in Germany, Edition 2015]. German. Available from: http://www.rki.de/DE/Content/Infekt/IfSG/Falldefinition/Downloads/Falldefinitionen_des_RKI.pdf?__blob=publicationFile
2. Harries M, Monazahian M, Wenzel J, Jilg W, Weber M, Ehlers J, et al. Foodborne hepatitis A outbreak associated with bakery products in northern Germany, 2012. Euro Surveill. 2014;19(50):20992. DOI: 10.2807/1560-7917.ES2014.19.50.20992 PMID: 25597541
3. National Institute for Public Health and the Environment (RIVM). Ministry of Health, Welfare and Sport. Protocol. Molecular detection and typing of VP1-2A region of Hepatitis A Virus (HAV). Bilthoven: RIVM. [Accessed 19 Jan 2017]. Available from: http://www.rivm.nl/dsresource?objectid=87925ed7-72d0-4d4f-8b53-fa309fe45b87&type=org&disposition=inline
4. European Centre for Disease Prevention and Control (ECDC). Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men. Stockholm: ECDC. 19 Dec 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/13-12-2016-RRA-Hepatitis%20A-United%20Kingdom.pdf
5. Bruni R, Taffon S, Equestre M, Chionne P, Madonna E, Rizzo C, et al. , Italian National Task Force on Hepatitis A. Key Role of Sequencing to Trace Hepatitis A Viruses Circulating in Italy During a Large Multi-Country European Foodborne Outbreak in 2013.PLoS One. 2016;11(2):e0149642. DOI: 10.1371/journal.pone.0149642 PMID: 26901877
6. Mao JS, Yu PH, Ding ZS, Chen NL, Huang BZ, Xie RY, et al. Patterns of shedding of hepatitis A virus antigen in feces and

of antibody responses in patients with naturally acquired type A hepatitis. J Infect Dis. 1980;142(5):654-9. DOI: 10.1093/infdis/142.5.654 PMID: 6257794

7. Cotter SM, Sansom S, Long T, Koch E, Kellerman S, Smith F, et al. Outbreak of hepatitis A among men who have sex with men: implications for hepatitis A vaccination strategies. J Infect Dis. 2003;187(8):1235-40. DOI: 10.1086/374057 PMID: 12696002
8. Spada E, Genovese D, Tosti ME, Mariano A, Cuccuini M, Proietti L, et al. An outbreak of hepatitis A virus infection with a high case-fatality rate among injecting drug users. J Hepatol. 2005;43(6):958-64. DOI: 10.1016/j.jhep.2005.06.012 PMID: 16143420
9. Robert Koch Institut (RKI). Statement of the German Standing Committee on Vaccination at the RKI. Recommendations of the Standing Committee on Vaccination. (STIKO) at the Robert Koch Institute/Effective: August 2015.Epidemiol Bull. 2015;332(34). Available from: http://www.rki.de/EN/Content/infections/Vaccination/recommandations/34_2015_engl.pdf?__blob=publicationFile
10. Faber MS, Stark K, Behnke SC, Schreier E, Frank C. Epidemiology of hepatitis A virus infections, Germany, 2007-2008.Emerg Infect Dis. 2009;15(11):1760-8. DOI: 10.3201/eid1511.090214 PMID: 19891863
11. Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med. 2007;357(17):1685-94. DOI: 10.1056/NEJMoa070546 PMID: 17947390
12. Robert Koch Institut (RKI). Gehäuftes Auftreten von Hepatitis-A-Erkrankungen bei Männern, die Sex mit Männern haben [Increased incidence of hepatitis A among men who have sex with men].Epidemiol Bull. 2017;2:28. German. Available from: http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2017/Ausgaben/02_17.pdf?__blob=publicationFile
13. Sfetcu O, Irvine N, Ngui SL, Emerson C, McCaughey C, Donaghy P. Hepatitis A outbreak predominantly affecting men who have sex with men in Northern Ireland, October 2008 to July 2009. Euro Surveill. 2011;16(9):19808.PMID: 21392487

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Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017

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Between July 2016 and January 2017, 37 confirmed cases of hepatitis A with two unique IA genotype strains primarily among men who have sex with men, were reported across eight areas in England and Northern Ireland. Epidemiological and laboratory investigations indicate that these strains may have been imported several times from Spain, with secondary sexual transmission in the United Kingdom. Local and national public health services are collaborating to control this ongoing outbreak.

Infection with the hepatitis A virus (HAV) is most commonly acquired through ingestion of contaminated food and water, and through faeco-oral contact. In the United Kingdom (UK) hepatitis A is a rare and mainly travel-associated disease, preventable by vaccination [1,2]. Sexually transmitted hepatitis A outbreaks among men who have sex with men (MSM) are well documented [3-6]. We describe an ongoing outbreak in the UK, primarily affecting MSM, caused by two concurrently circulating HAV strains previously not seen in the UK, as well as the intervention strategies that have been instigated to control the outbreak. Cases with the identical strains have been reported in other European countries, prompting the European Centre for Disease Prevention and Control (ECDC) to issue a rapid risk assessment in December 2016 [7].

Case definition

A confirmed case was defined as a laboratory-confirmed HAV infection with the specific outbreak sequence of either VRD_521_2016 Strain 1 (Event 1) or RIVM-HAV16–090 Strain 2 (Event 2) and symptom onset after 31 June 2016 [7]. A probable case was defined as a laboratory-confirmed HAV infection (not yet sequenced) with symptom onset after 31 June 2016, with contact with a confirmed case and/or who identifies as MSM.

Outbreak description

Between July 2016 and January 2017, 37 confirmed cases with either strain 1 or 2 were detected across England as well as Northern Ireland (Figure 1), of which 28 identified as MSM. Of the 37 cases, 24 were Strain 1 and 13 were Strain 2. In addition, 15 probable cases (all MSM), primarily in London, were identified, and typing results are awaited.

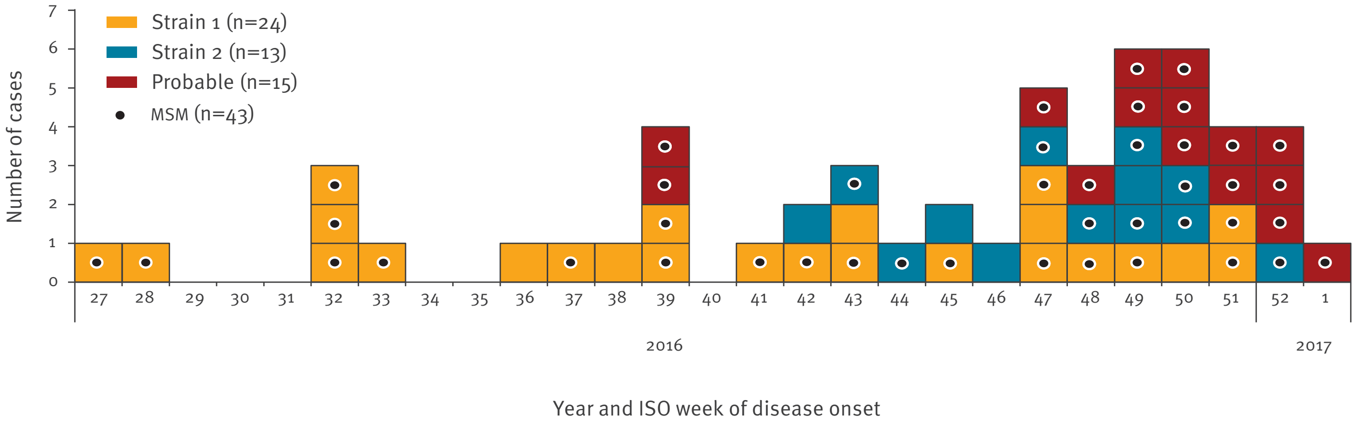
Strain 1 was first identified by the Virus Reference Department, Public Health England, London, in July 2016. The sequence had not been seen previously in the UK and phylogenetic analysis (Figure 2) showed a clear relation to sequences derived from travellers returning from Central and South America.

Strain 1 cases were reported in eight geographically distinct areas in England and Northern Ireland (Figure 3).

Of 24 Strain 1 cases, 22 were male, median age 35 years (19–63 years), 19 identified as MSM and eight reported travel within the incubation period, seven of which to Spain (Table).

Figure 1

Probable and confirmed cases of hepatitis A among men who have sex with men, England and Northern Ireland, July 2016–January 2017 (n=52)



ISO: International Organization for Standardization; MSM: men who have sex with men.

Strain 2 was first notified through the European Union Early Warning and Response System (EWRS) message from the Netherlands in October 2016 related to two MSM cases at EuroPride 2016, which took place in Amsterdam in July/August 2016. This genotype sequence was detected in 13 cases across six regions in England between November 2016 and January 2017 (Figure 3). Of the 13 cases, 12 were male, median age 39 years (range: 29–78), nine identified as MSM and 11 travelled during the incubation period, of which seven to Spain and two to Germany (Table). Of note, Strain 2 has mainly been reported in MSM in London to date. Characteristics of concern among cases were noted, including infection in a sex worker with multiple partners, co-infection with sexually transmitted infections (STIs) and use of sex-on-site premises and apps (Grindr, Recon) (Table).

Control measures

Public Health England (PHE) declared a national incident in December 2016. Local and national laboratory, epidemiology and health protection teams contributed to the response, which comprised: (i) enhanced surveillance for MSM-associated cases through an adapted questionnaire [8], (ii) a joint letter with the British Association for Sexual Health and HIV (BASHH) to all members alerting them to the outbreak and recommending vaccination of at-risk MSM in outbreak areas, according to national guidelines [9,10], testing cases for other STIs and partner notification, (iii) disease information and targeted hygiene advice to the public through the National Health Service web portal [11], (iv) liaising with lesbian, gay, bisexual, and transgender (LGBT) and sexual health charities, gay-dating apps and gay venues to raise awareness through social media and health promotion visuals, and (v) giving post-exposure prophylaxis to household and sexual contacts.

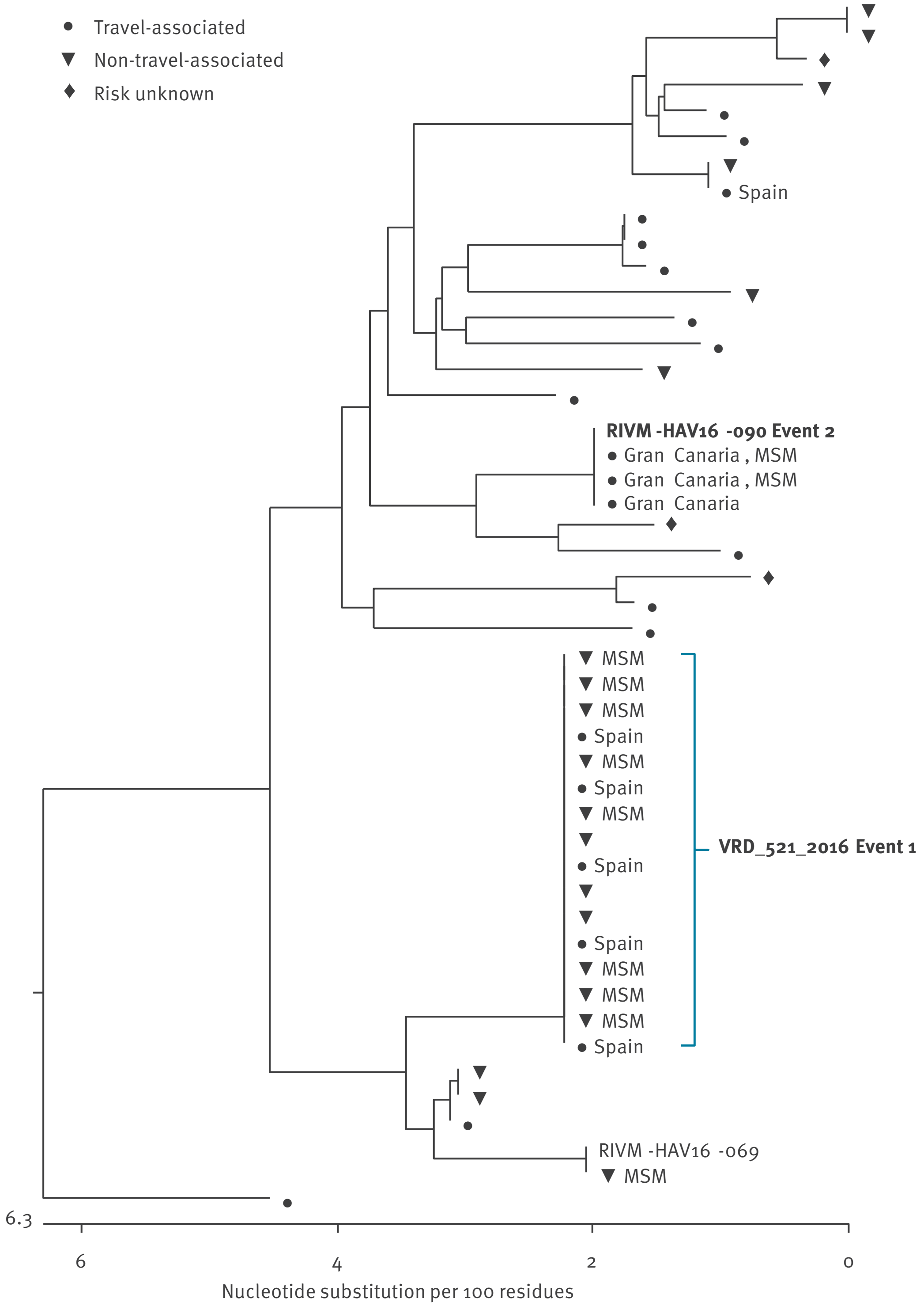
Discussion

As at 24 January 2017, 37 HAV infections with two sequences have been identified in eight UK areas, mostly among MSM (median age: 35 years; range: 19-56). HAV infection is most commonly acquired through contaminated food or water. In this outbreak however, epidemiological and laboratory investigations suggest multiple importations from several regions of Spain with secondary sexual transmission within the MSM population in the UK, as nine of the confirmed MSM cases reported travelling to Spain during the incubation period. Ireland, Sweden, Luxembourg and Germany have reported hepatitis A cases with identical viral sequences, some with history of travel to Spain during the incubation period. Spain has reported an increase in male HAV infections, but no further details were available [7]. This outbreak highlights the key role sequencing can play in outbreak detection, as well as the added value of a common European platform to share epidemiological and virological information.

While the two concurrently circulating strains are virologically distinct, the public health response is intended to address both. Although it has not been possible to establish epidemiological links between all cases within geographical clusters, it is likely that cases are related either through undisclosed sexual contacts or other routes since neither strain is commonly circulating in England. These missing epidemiological links are not unexpected when trying to capture sexual history via short questionnaires, particularly since some cases reported anonymous sex with multiple partners. However, the questionnaires revealed sex-on-premises venues (saunas, clubs) and social networking (dating apps) as potential drivers of the outbreak. While these findings can help focus interventions, they are of particular concern in areas with

Figure 2

Phylogenetic analysis of virus strains from hepatitis A cases in England and Northern Ireland, July 2016–December 2016



HAV: hepatitis A virus; MSM: men who have sex with men.

The tree was constructed in MegAlign (DNAstar) using Clustal Key.

Figure 3

Geographical distribution of hepatitis A cases among men who have sex with men, England and Northern Ireland, July 2016–January 2017 (n=52)

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TABLE

Characteristics of hepatitis A cases associated with the outbreak, England and Northern Ireland, July 2016–January 2017 (n=52)

Region	Case status (strain)	Cases (n)	Median age (years)	MSM (n)	Spain	Notable characteristics
East Midlands	**Confirmed (Strain 1)**	9	28	6	2	One cluster of three cases of Strain 1 transmitted in a factory through environmental exposure.
	Confirmed (Strain 2)	3	55	2	2	
	Probable	0	NA	0	0	
	Total	**12**	**36**	**8**	**4**	
South West	**Confirmed (Strain 1)**	4	45	3	1	One case operated a private meeting place, used by contacts and multiple anonymous men.
	Confirmed (Strain 2)	1	NA	0	1	
	Probable	0	NA	0	0	
	Total	**5**	**46**	**3**	**2**	
Hampshire	**Confirmed (Strain 1)**	3	35	3	1	Probable case is index case in this area. This case was diagnosed in Spain but never sequenced. Further spread through household and sexual contacts.
	Confirmed (Strain 2)	0	NA	0	0	
	Probable	1	NA	1	1	
	Total	**4**	**32**	**4**	**2**	
North East	**Confirmed (Strain 1)**	3	41	3	1	First identified case with likely importation from Spain. Further spread to two cases through household and sexual transmission.
	Confirmed (Strain 2)	0	NA	0	0	
	Probable	0	NA	0	0	
	Total	**3**	**41**	**3**	**1**	
London	**Confirmed (Strain 1)**	2	31	2	0	One Strain 1 case was a sex worker with multiple sexually-transmitted co-infections who reported sex in several gay saunas in London. Three cases reported using apps and websites to meet partners. One Strain 2 case reported 20 sexual contacts within the eight weeks prior to disease onset.
	Confirmed (Strain 2)	6	35	4	3	
	Probable	12	34	12	1	
	Total	**20**	**32**	**18**	**4**	
Yorkshire and Humber	**Confirmed (Strain 1)**	1	NA	0	0	All but one case reported travel; three to Spain and to Germany. One Strain 2 case reported sexual contact with multiple partners at a gay sauna in London.
	Confirmed (Strain 2)	1	NA	1	1	
	Probable	1	NA	1	0	
	Total	**3**	**NA**	**2**	**1**	
North West	**Confirmed (Strain 1)**	0	NA	0	0	
	Confirmed (Strain 2)	1	NA	1	0	
	Probable	1	NA	1	0	
	Total	**2**	**43**	**2**	**0**	
East of England	**Confirmed (Strain 1)**	0	NA	0	0	
	Confirmed (Strain 2)	1	NA	1	0	
	Probable	0	NA	0	0	
	Total	**1**	**NA**	**1**	**0**	
South Midlands	**Confirmed (Strain 1)**	1	NA	1	1	
	Confirmed (Strain 2)	0	NA	0	0	
	Probable	0	NA	0	0	
	Total	**1**	**NA**	**1**	**1**	
Belfast	**Confirmed (Strain 1)**	1	NA	1	1	
	Confirmed (Strain 2)	0	NA	0	0	
	Probable	0	NA	0	0	
	Total	**1**	**NA**	**1**	**1**	
Grand total		**52**	**36**	**43**	**16**	

MSM: men who have sex with men; NA: not applicable.

large, active MSM populations, such as London, where several of the recent cases have been reported.

This outbreak also highlights the need for HAV awareness among MSM and sexual health professionals and the need for health promotion materials that focus on both infection and vaccination. Innovative and evaluated communication strategies with targeted messaging through social media, apps and venues also need to be readily available to public health agencies.

Hepatitis A vaccination for MSM in England is currently a risk-based recommendation [9,10]. For the purpose of this investigation, the vaccination status of the cases was not included in the analysis. While some may advocate for a universal MSM vaccination policy, it may not be cost-effective or affordable for local governments who commission sexual health services. Vaccine availability also needs to be taken into account as it may impact the ability to vaccinate a large number of individuals in a short timeframe. Enhanced surveillance for HAV in MSM will allow monitoring of the evolving outbreak as well as evaluating intervention impact, and gain a better understanding of HAV transmission in this population.

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Conflict of interest

None declared.

Authors' contributions

All the authors contributed to the outbreak investigations described here, the presentation of information and the final drafting of the manuscript.

References

1. Public Health England. Laboratory reports of hepatitis A infection, and hepatitis C: 2015. Health Protection Report. 2016;10. [Accessed 16 Dec 2016]. Available from: https://www.gov.uk/government/publications/laboratory-reports-of-hepatitis-a-and-c-2015
2. European Centre for Disease Prevention and Control (ECDC). Hepatitis A virus in the EU/EEA, 1975-2014. ECDC technical report. Stockholm: ECDC. 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/hepatitis-a-virus-EU-EEA-1975-2014.pdf
3. Bell A, Ncube F, Hansell A, Davison KL, Young Y, Gilson R, et al. An outbreak of hepatitis A among young men associated with having sex in public venues. Commun Dis Public Health. 2001;4(3):163-70.PMID: 11732354
4. Mindel A, Tedder R. Hepatitis A in homosexuals.Br Med J (Clin Res Ed). 1981;282(6277):1666. .DOI: 10.1136/bmj.282.6277.1666 PMID: 6786425
5. Sfetcu O, Irvine N, Ngui SL, Emerson C, McCaughey C, Donaghy P. Hepatitis A outbreak predominantly affecting men who have sex with men in Northern Ireland, October 2008 to July 2009. Euro Surveill. 2011;16(9):19808. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19808PMID: 21392487
6. Stene-Johansen K, Tjon G, Schreier E, Bremer V, Bruisten S, Ngui SL, et al. Molecular epidemiological studies show that hepatitis A virus is endemic among active homosexual men in Europe. J Med Virol. 2007;79(4):356-65. .DOI: 10.1002/jmv.20781 PMID: 17311331
7. European Centre for Disease Prevention and Control (ECDC). Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men. Stockholm: ECDC. 19 Dec 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/13-12-2016-RRA-Hepatitis%20A-United%20Kingdom.pdf
8. Public Health England (PHE). Hepatitis A: case questionnaire. London: PHE. 2016. [Accessed 16 Dec 2016]. Available from: https://www.gov.uk/government/publications/hepatitis-a-case-questionnaire
9. Public Health England (PHE). Green Book, Immunisation against infectious disease: Chapter 17, Hepatitis A. London: PHE. [Accessed 16 Dec 2016]. Available from: https://www.gov.uk/government/publications/hepatitis-a-the-green-book-chapter-17
10. Brook G, Bhagani S, Kulasegaram R, Torkington A, Mutimer D, Hodges E, et al. , Clinical Effectiveness Group British Association for Sexual Health and HIV. United Kingdom National Guideline on the Management of the viral hepatitides A, B and C 2015.Int J STD AIDS. 2016;27(7):501-25. DOI: 10.1177/0956462415624250 PMID: 26745988
11. NHS Choices. Sexual health for gay and bisexual men - Live Well - NHS Choices. Hepatitis A. [Accessed 16 Dec 2016]. Available from: http://www.nhs.uk/Livewell/LGBhealth/Pages/Sexualhealthgaymen.aspx#hepa

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Bulletin of the National Centre of Infectious and Parasitic Diseases, Sofia
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http://www.ncipd.org/

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Bulletin épidémiologique hebdomadaire
Institut de veille sanitaire, Saint-Maurice Cedex
Weekly, print and online. In French.
http://www.invs.sante.fr/beh/default.htm

Germany

Epidemiologisches Bulletin
Robert Koch-Institut, Berlin
Weekly, print and online. In German.
http://www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html

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HCDCP Newsletter
Hellenic Centre for Disease Control and Prevention (HCDCP/KEELPNO), Athens
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http://www2.keelpno.gr/blog/?lang=en

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Epinfo (az Országos Epidemiológiai Központ epidemiológiai információs hetilapja)
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Weekly, online. In Hungarian.
http://www.oek.hu/oek.web?to=839&nid=41&pid=7&lang=hun

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http://www.landlaeknir.is

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Health Protection Surveillance Centre, Dublin
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http://www.hpsc.ie/hpsc/EPI-Insight

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Notiziario dell'Istituto Superiore di Sanità
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome
Monthly, online. In Italian.
http://www.iss.it/publ/noti/index.php?lang=1&tipo=4

Bolletino Epidemiologico Nazionale (BEN)
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome
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http://www.epicentro.iss.it/ben

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Užkreciamuju ligu profilaktikos ir kontroles centras
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Infectieziekten Bulletin
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Sporadic, print only. In Romanian.
http://www.insp.gov.ro/cnscbt/index.php?option=com_docman&Itemid=12

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http://revista.isciii.es

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https://www.gov.uk/government/collections/health-protection-report-latest-infection-reports

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http://www.cdscni.org.uk/publications

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http://ec.europa.eu/health/

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European Centre for Disease Prevention and Control (ECDC)

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