RAPID RISK ASSESSMENT

Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men

Second update, 19 May 2017

Conclusions and options for response

Since June 2016, 1 173 confirmed hepatitis A cases infected with three distinct strains of sub-genotype IA virus have been reported by 15 EU countries. These include 499 new cases compared with the data reported in the last epidemiological update published on 28 April 2017 [1]. Two additional countries reported cases (compared to the first rapid risk assessment update published on 23 February 2017) [2]. Overall, most cases are reported among adult men who have sex with men (MSM); 80 women were also affected.

The main prevention measure in the context of the current outbreaks is hepatitis A vaccination of MSM. The ECDC guidance for HIV and sexually transmitted infection (STI) prevention among MSM encourages Member States to offer and promote vaccination of MSM against hepatitis A [3]. Information on vaccine availability should be included in health promotion programmes targeting MSM, particularly at sex venues [4].

Where hepatitis A vaccination is not universally offered to MSM, the following groups could be prioritised for vaccination:

- MSM living in areas of ongoing outbreaks
- MSM travelling to destinations reporting outbreaks of hepatitis A among MSM
- MSM that will attend WorldPride festival in Madrid, 23 June–2 July 2017 and are likely to engage in risky sexual practice
- MSM at risk of severe outcomes from hepatitis A, for example those with hepatitis B and/or hepatitis C and those who inject drugs.

In addition to vaccination, the following options should be considered for preventing transmission among MSM:

- Provide primary prevention advice and promote vaccination by engaging with civil society, social media, the gay press and gay-dating apps
- Increase awareness among healthcare providers about ongoing outbreaks of hepatitis A among MSM and promote vaccination in health clinics
- Emphasise the importance of partner notification with healthcare providers
- Provide post-exposure prophylaxis to identified sexual contacts, household contacts and other relevant close contacts of cases through the administration of hepatitis A vaccine and human normal immune globulin in accordance with national guidelines in order to prevent secondary cases
- Raise awareness among MSM about the risk of contracting hepatitis A through risky sexual behaviour

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- Educational efforts targeting MSM at high risk should emphasise the importance of hepatitis A vaccination and of personal hygiene (e.g. washing hands and genital areas before and after sex). The use of dental dams for oral-anal sex and of latex gloves during fingering or fisting may offer protection against hepatitis A; the use of condoms for anal sex may also offer protection against other STIs
- All hepatitis A cases among MSM should be referred to sexual health services for further STI/HIV testing
- In accordance with national legislation and guidance, hepatitis A cases should be notified to public health authorities and, where required, temporarily excluded from work.

Sharing of microbiological and epidemiological details of new cases and questionnaires used during outbreak investigations through the Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonoses (EPIS-FWD) is encouraged for monitoring the epidemiological situation.

Vaccine procurement and licensing agreements for the various hepatitis A vaccines differ between countries. It is therefore suggested that countries interact directly with marketing authorisation holders to enquire about supplies at the national level as early as possible, i.e. create forecasts of the number of doses required and make procurement arrangements. It is advisable that any changes in current hepatitis A vaccination policies and supplementary immunisation activities be planned as early as possible. At the national level, where hepatitis A vaccines have a marketing authorisation in accordance with national legislation, regulatory authorities should be informed of supply shortages.

Source and date of request

Internal ECDC decision dated 11 May 2017.

Public health issue

Ongoing transmission of hepatitis A virus (HAV) infection mainly affecting men who have sex with men (MSM) in EU/EEA countries.

This second update of the Rapid Risk Assessment includes:

- updated epidemiological figures
- information on hepatitis A vaccine supplies in the EU/EEA.

Consulted experts

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Disease background information

Hepatitis A is an acute, usually self-limiting infection caused by the hepatitis A virus (HAV). Transmission is predominately by the faecal-oral route, through contaminated water or food products and/or by person-to-person contact. Transmission through sexual exposure has been associated with outbreaks in men who have sex with men (MSM), and transmission through sharing of needles and syringes with outbreaks among people who inject drugs. Parenteral transmission through infected instruments or, rarely, blood components has been documented [5].

The infection is generally asymptomatic or mild in children, but the proportion of symptomatic infections and the severity of the presentation increases with age. Adults may develop jaundice and present with more severe clinical symptoms. The case-fatality ratio is generally 0.1%, but can be 1.8% in adults >50 years of age and in immunocompromised patients. The mean incubation period is 28 days, ranging from 15 to 50 days. The maximum infectivity is in the second half of the incubation period (i.e. while asymptomatic), and most cases are considered non-infectious after the first week of jaundice. The diagnosis is made by serology or molecular tests. Anti-HAV IgM serology and detection of HAV-RNA indicate acute infection. Almost all human hepatitis A viruses belong to genotypes I and III, with genotype I being divided into sub-genotypes IA and IB. Genotype I is the most prevalent, comprising at least 80% of circulating human strains [6,7].

No specific treatment is available for hepatitis A. Strict control measures such as enforcing personal hygiene, contact tracing and vaccination of exposed persons have been shown to be effective in reducing transmission. Active (receiving vaccine) and passive immunisation (receiving immunoglobulins) is effective if administered within two weeks of exposure. Several inactivated vaccines are available for prevention [8]. Post-exposure prophylaxis should be administered in accordance with national guidelines.

In 2015, 12 527 confirmed hepatitis A cases were reported to The European Surveillance System (TESSy) by 30 EU/EEA countries. Romania accounted for 41% of the cases and Bulgaria for 9%. Cases were reported among all age groups with most cases among 5–14-year-olds (39%) and 25–44-year-olds (19%). Male cases were more frequent than female ones, particularly in age groups 15 to 24 and 25 to 44 years, with a male-to-female ratio of 1.3:1 and 1.2:1, respectively. The majority (91%) of infections were acquired in the country of residence.

The percentage of travel-associated cases varied from zero to 100% across Europe. Syria, Morocco and Turkey were the most common travel destinations among travel-associated cases. Among the 479 cases related to travel within the EU/EEA for the period 2010–2015, the male-to-female ratio was 1.4:1.

There is a high degree of temporal and spatial variability in hepatitis A seroprevalence across the EU/EEA, with an increasing gradient of seroprevalence from the northern to the central and from the southern to the eastern parts of the EU/EEA. The susceptibility to infection among adults is highest in northern EU/EEA countries and lowest in eastern EU countries. There has been an overall decreasing trend in hepatitis A seroprevalence over the last four decades in most countries [5].

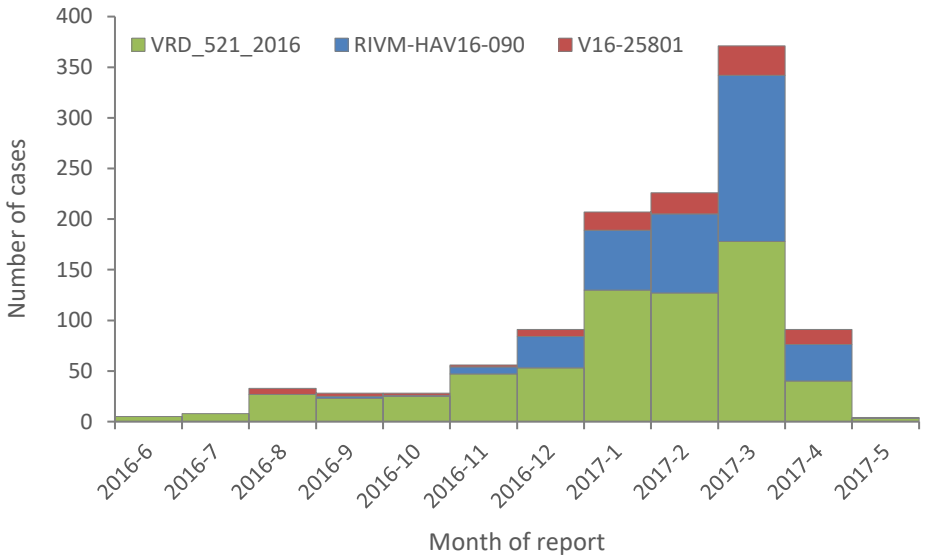
Outbreaks of hepatitis A among MSM have been recognised since the 1970s [9-12]. Several multinational outbreaks have been described, one of which involved at least eight cities across three countries and two continents (North America and Australia) and occurred between January and June 1991 [13]. Several European countries have reported national outbreaks in MSM in the past decades. The main risk factor is related to direct oral-anal contact during sex [14-17]. The current level of immunity among the MSM population in Europe is unknown. It has been estimated that a level of >70% immunity among the MSM population would prevent sustained transmission and future outbreaks [18].

Event background information

Epidemiology of genetically sequenced HAV cases

Between 1 June 2016 and 16 May 2017, 15 EU countries (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom) reported 1 173 HAV genotype IA-confirmed cases. The investigations identified three separate clusters based on genetic sequencing of HAV (Figure 1). The descriptive epidemiology is presented for each cluster as they indicate separate transmission chains.

Figure 1. Distribution of hepatitis A cases, by month of report and genetic sequence, June 2016, as of 15 May 2017, EU/EEA (n=1 148)



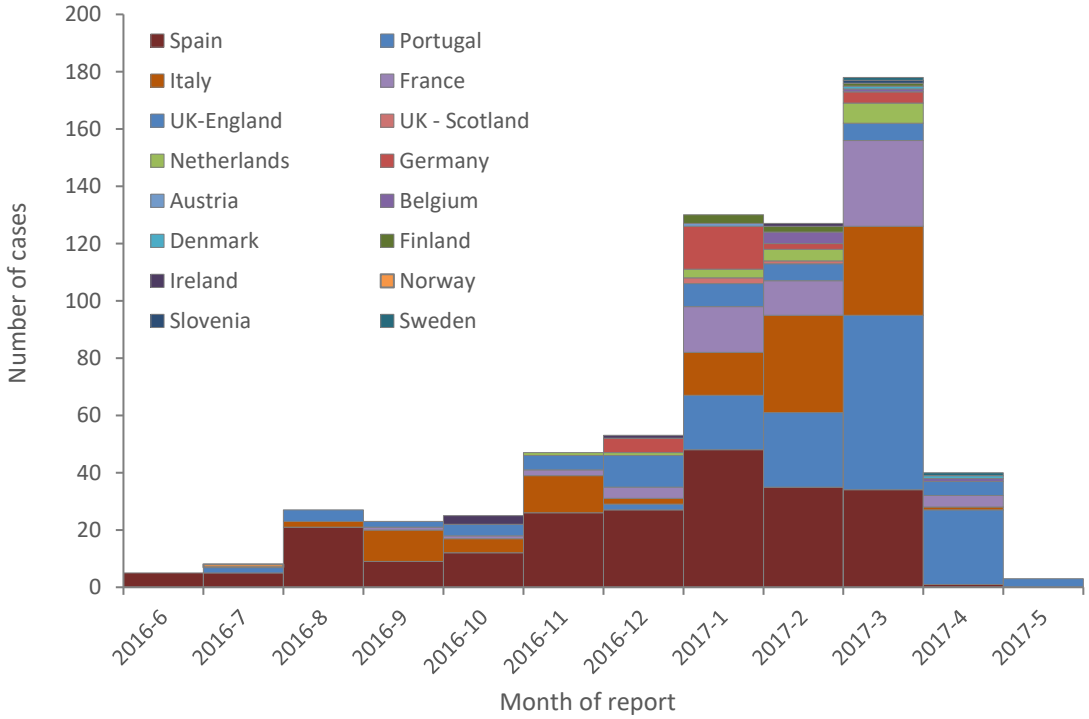
Note: 25 cases with missing date of report are not included.

Event 1 – Cluster VRD_521_2016

On 6 December 2016, through an EPIS FWD urgent inquiry, UK notified 15 hepatitis A cases, five of them with a travel history to Spain.

As of May 2017, 15 EU Member States have reported 598 cases with VRD_521_2016-identical virus sequence (Figure 2). Most cases were reported by Spain (223), Portugal (144), Italy (114), France (70), and the United Kingdom (56). Of the 588 cases with information on sex, 541 (92%) are male, and 189 of 221 documented cases (86%) identify themselves as MSM. The median age of cases is 33 years (range: 0–79 years of age). Twenty-two of the 51 cases with a travel history reported visiting Spain during the incubation period.

Figure 2. Distribution of cases associated with cluster VRD_521_2016, by reporting country and month of report (n=666), June 2016, as of May 2017, EU/EEA



Note: Ten cases with missing date of report are not included.
One female and one male cases reported by Spain in January and May 2016, respectively, and one case reported by Sweden in a female traveller to Spain with onset in March 2016 are not included.

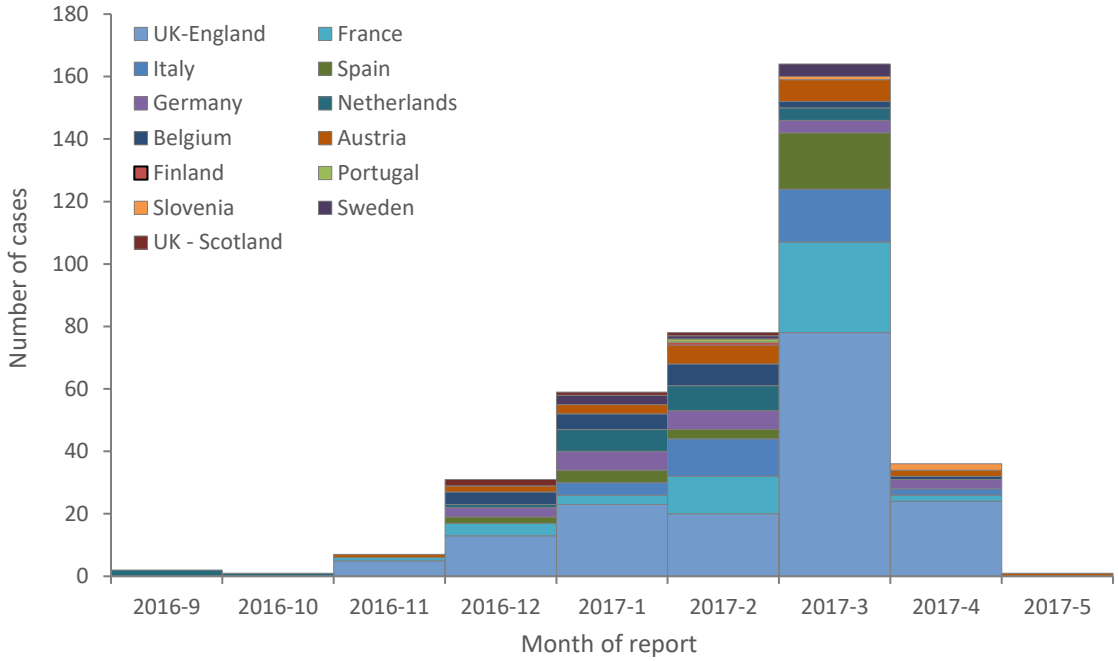
HAV strain VRD_521_2016 of sub-genotype IA is characterised by an identical viral RNA sequence of 505 nucleotides from the VP1/2A region. The complete VP1 fragment is available for comparison in HAVnet. The UK shared this sequence with the European FWD network, and ECDC informed the STI contact points through EPIS STI. The strain is phylogenetically related to strains derived from Central/South America, based on the analysis of European database (HAVNET).

Event 2 – Cluster RIVM-HAV16-090

On 14 October 2016, the Netherlands, using the Early Warning and Response System, notified two cases of hepatitis A among MSM who participated in the EuroPride festival in Amsterdam (23 July to 7 August 2016). The cases were infected with an indistinguishable IA genotype sequence RIVM-HAV16-090. At EuroPride, both visited the same dark room on 2 and 3 August 2016, where they reportedly engaged in anonymous sexual activities.

As of 16 May 2017, 12 EU Member States have reported 388 cases with an identical virus sequence (Figure 3). Most cases were reported by the United Kingdom (168), France (51) and Italy (35). Of the 375 cases with gender information, 347 (93%) are in males, and 198 of 239 documented cases identify themselves as MSM. The median age of cases is 33 years, ranging from 0 to 88 years. Of the 76 cases with a travel history during the incubation period, 28 travelled to Spain and nine to Germany.

Figure 3. Distribution of cases associated with cluster RIVM-HAV16-090, by reporting country and month of report (n=379), June 2016, as of May 2017, EU/EEA



Note: Nine cases with missing date of report are not included.

The sequence of HAV strain RIVM-HAV16-090 sub-genotype IA was shared with the respective networks in EPIS FWD and EPIS STI. The sequence is a 460-nucleotides-long fragment from region VP1/2A according to the HAVNET protocol [19]. The complete VP1 fragment is available for comparison in HAVnet. The sequence is closely related to strains reported by Japan and China and most probably originates from Asia. In 2015, the UK detected this sequence in a traveller returning from Hong Kong, China. Recently, the strain was found to be identical to the strain involved in the ongoing outbreak among MSM in Taiwan.

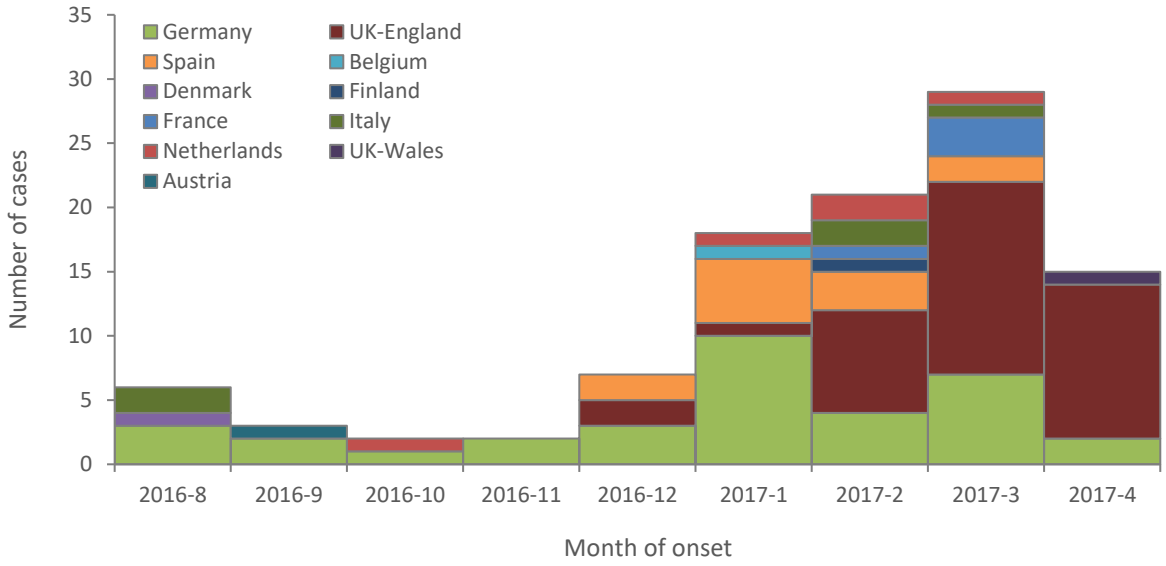
The sequence of RIVM-HAV16-090 is only 95.4% similar to the VRD_521_2016, suggesting unrelated transmission events.

Event 3 – Cluster V16-25801

On 11 January 2017, through an EPIS FWD urgent inquiry, Germany notified three clusters of hepatitis A, predominantly males, reported in Berlin in November and December 2016. Cases were related to the two clusters described above, but a new cluster was also described that included cases in Munich and Frankfurt (since August 2016). The distinct genotype IA was denoted V16-25801.

As of 17 May 2017, ten EU Member States have reported 109 cases with identical virus sequence: Germany (40) United Kingdom (39), Spain (12), Italy (5), the Netherlands (5), France (4), Austria (1), Belgium (1), Denmark (1) and Finland (1). Of the 109 documented cases, 104 are in males, and 38 of 42 documented cases identify themselves as MSM. The median age of cases is 33 years (range: 16–60 years of age). Six of 20 cases with information on travel visited Spain during the incubation period.

Figure 4. Distribution of cases associated with cluster V16-25801, by reporting country and month (n=103), June 2016, as of May 2017, EU/EEA



Note: Six cases with missing date of report are not included in the figure.

Germany shared the sequence of HAV strain V16-25801 sub-genotype IA in EPIS FWD and EPIS STI. The sequence is a 459-nucleotides-long fragment from region VP1/2A according to the HAVNET protocol [19].The complete VP1 fragment is available for comparison in HAVnet. The sequence of V16-25801 is only 96.1% similar to the VRD_521_2016 and 96.5% similar to the RIVM-HAV16-090, suggesting unrelated transmission events.

In 2014 and 2016, Italy detected two sequences very similar (2 nt differences) to V16-25801 from two female Ecuadorian patients: the 2014 case (sequence Acc. N. KU570286) acquired infection in Ecuador (no travel information for the other), which suggests relatedness between V16-25801 and strains from South America.

Additional information on national outbreaks

Both the United Kingdom (England) [20] and Portugal [21] have reported overall increases in hepatitis A cases among MSM, largely linked with the three clusters identified above, and have recommended the use of hepatitis A vaccine in specific groups. Some cases in England that are linked to the outbreaks have been reported in the general population, causing Public Health England to consider wider vaccination strategies to respond to this outbreak, which is occurring in the context of a global hepatitis A vaccine shortage.

In addition, Public Health England reported 17 cases identified in individuals who work in venues where food is prepared or served. Other countries also suspected cases in food handlers.

Six countries notified an overall increase in the number of HAV infection cases reported from January until May 2017 compared with the same period in 2016: Belgium (203 in 2017 vs. 37 during the same period in 2016), Estonia (10 vs. 2), Finland (14 vs. 2), Italy (20 vs. 11), Spain (1 539 vs. 236) and Sweden (45 vs. 33). These increases ranged from a slight increase up to a seven-fold increase. In addition, Italy reports 1 247 cases of hepatitis A from August 2016 to April 2017, a five-fold increase compared to cases reported in 2015. However, other HAV outbreaks may have also influenced in this increase and the effect might not be completely attributed to the ongoing MSM transmission.

Several countries, e.g. Belgium, Denmark, Finland and Sweden, reported that the current situation is stable or that case numbers are declining.

Hepatitis A vaccine availability in the EU

As reported by some of the affected EU/EEA Member States (e.g. Austria, Italy, Portugal and Spain), vaccine availability in the EU is currently limited, with some countries facing shortages. Other countries like the Czech Republic, Denmark, Estonia, Finland, Ireland, Slovenia and Sweden reported no shortages.

Supply information was obtained from three major hepatitis A vaccine marketing authorisation holders (MAH) in the EU/EEA. The information received confirmed observations made at the national levels. The supply of HAV vaccine, whether in single antigen presentation or as part of a combination vaccine with other antigens, is stretched at the global level, owing to a combination of past and ongoing production issues in MAH which resulted in reduced production along with an increased demand exceeding existing stocks. For some manufacturers, the situation is not expected to return to normal before the end of 2018.

Vaccine procurement and licensing agreements for the various hepatitis A vaccines differ between countries. It is therefore suggested that countries interact directly with marketing authorisation holders to enquire about supplies at the national level as early as possible, i.e. create forecasts of the number of doses required and make procurement arrangements. It is advisable that any changes in current hepatitis A vaccination policies and supplementary immunisation activities be planned as early as possible. At the national level, where hepatitis A vaccines have a marketing authorisation, regulatory authorities should be informed of supply shortages. Countries with limited vaccine availability are encouraged to bring that topic to the Health Security Committee in order to identify possible solutions.

ECDC threat assessment for the EU

The extent of the three reported clusters is likely to be underestimated, as reported cases are limited to those attending healthcare facilities and cases for which sequencing was performed. However, the reporting of confirmed cases provides a good indication of the outbreak dynamics. The definition of confirmed cases is based on viral RNA sequencing, and only a minority of EU countries sequence a sufficiently large proportion of strains in a timely fashion. Due to the challenges with regard to complete and timely reporting of sequencing results, the current figures will represent a significant underestimation of the true extent of these outbreaks. Therefore, considering the information provided by some EU countries on the number of confirmed and suspected cases, it is estimated that more than 3 000 cases are associated with this event.

Most cases are reported among HAV-unvaccinated adult MSM, but evidence exists for secondary cases among the general population. As cases have been also reported in food handlers, subsequent foodborne transmission would not be unexpected. Several reports of household transmission linked to these clusters highlight the need for early contact tracing and post-exposure prophylaxis of close contacts in order to avoid infections among unvaccinated household contacts.

Scientific articles on these clusters published after the ECDC rapid risk assessment of 19 December 2016 [22,23] indicate unvaccinated MSM as the European population group most at risk of being affected by these clusters. These articles also provide insights into the high-risk sexual practices associated with HAV transmission. In particular, they indicate anonymous sex, multiple sex partners, sex-on-premises venues and the use of dating apps as factors associated with these outbreaks.

The multinational dimension of these clusters may be explained by the highly interconnected sexual networks among MSM in Europe. In at least two EU Member States, the United Kingdom and Germany, secondary cases have been linked to travel-associated index cases. The circulation of three different HAV genotype IA strains in the MSM population is likely to be the result of several introductions into these networks.

Further transmission resulting from these clusters may be prevented by vaccination of MSM and post-exposure prophylaxis in contacts of cases. However, limited vaccine availability in some countries may have an impact on the implementation of such control measures. In addition, since many of the risk group contacts are anonymous, their timely vaccination is a particularly challenging task.

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