RAPID RISK ASSESSMENT

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

Third update, 28 June 2017

Conclusions and options for response

Since June 2016, 1 500 confirmed hepatitis A (HAV) cases and 2 660 probable or suspected cases have been reported in the EU, predominantly among adult men who have sex with men (MSM).

EU/EEA countries should consider enhancing national hepatitis A surveillance in order to ensure timely monitoring of this outbreak and rapid detection of critical developments, such as the extension of the outbreak into other population groups at increased risk of infection or the introduction into the food chain.

Sharing of anonymised 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 in order to monitor the epidemiological situation.

The main prevention measure in the context of the current outbreaks is hepatitis A vaccination of MSM. 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 [1]. Information on vaccine availability should be included in health promotion programmes targeting MSM, particularly at sex venues [2].

Where hepatitis A vaccination is not universally offered to MSM, the following groups could be prioritised for vaccination, in line with the national vaccine recommendations:

- MSM living in areas where there are ongoing outbreaks;
- MSM travelling to destinations reporting outbreaks of hepatitis A among MSM;
- MSM attending Pride festivals this summer, where the likelihood of contact with HAV-infected individuals could be elevated (provision of vaccination at Pride festival venues could be considered);
- MSM at risk of severe outcome as a result of hepatitis A, for example those with chronic liver disease, hepatitis B and/or hepatitis C and those who inject drugs.

In the context of the current outbreaks of hepatitis A, it is suggested that vaccination be promoted and offered to MSM attending the WorldPride festival in Madrid, 23 June–2 July 2017 and other Pride festivals this summer, where the likelihood of contact with HAV-infected individuals could be elevated. However, limited HAV vaccine availability in some countries may have an impact on the implementation of these measures.

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

Suggested citation: European Centre for Disease Prevention and Control. Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men – third update, 28 June 2017. Stockholm: ECDC; 2017.

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 marketing of hepatitis A vaccines is authorised in accordance with national legislation, regulatory authorities should be informed of supply shortages.

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 by administering hepatitis A vaccine or human normal immune globulin in accordance with national guidelines to prevent secondary cases.
- Raise awareness among MSM about the risk of contracting hepatitis A.
- Emphasise the importance of hepatitis A vaccination and personal hygiene (e.g. washing hands and genital areas before and after sex) in educational efforts targeting MSM at high risk. 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.

National competent authorities for substances of human origin (SoHO) should be aware and informed about an outbreak of hepatitis A in the country.

In donors with an increased-risk of HIV, HBV and HCV infection due to MSM sexual practice, permanent or temporary (12 months after sexual contact with men) deferral from blood donation, or individual risk assessment of candidate MSM donors – including individual deferral from donation for four months to lifelong deferral – may be considered sufficient to prevent HAV transmission through blood donations from HAV-infected MSM [3,4].

Candidate MSM donors of organs, tissues and cells who have had sexual exposure in the last 12 months are considered as increased-risk donors. In countries with an outbreak of hepatitis A among MSM, increased-risk donors who have had sexual exposure two months before donation or deceased donors should be also tested for HAV infection by NAT and not accepted if positive. Previous vaccination or anti–HAV status of the recipient should be considered as part of the individual risk assessment of the donor.

Source and date of request

Internal ECDC decision on 20 June 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 [5-8].

This third update of the Rapid Risk Assessment was triggered in order to provide:

- Updated epidemiological figures;
- Scenarios and critical developments;
- Information on hepatitis A vaccine supplies in the EU/EEA;
- Information on the use of hepatitis A vaccine in the context of supply shortages
- Risk of hepatitis A virus transmission via substances of human origin (SoHO) i.e. blood, tissues and cells, organs.

Consulted experts

ECDC internal response team in alphabetical order: Sergio Brusin, Mike Catchpole, Denis Coulombier, Tarik Derrough, Dragoslav Domanovic, Margot Einöder-Moreno, Joana Haussig, Kaja Kaasik Aaslav, Piotr Kramarz, Otilia Mardh, Ettore Severi, Gianfranco Spiteri, Bertrand Sudre.

External experts consulted by country in alphabetical order:

- Austria: Stephan Aberle (Medical University of Vienna, Austria), Franz Allerberger, Lukas Richter, Daniela Schmid (Austrian Agency for Health and Food Safety, Austria), Karin Haar (Federal Ministry of Health and Women's Affairs).
- Belgium: Sofieke Klamer, Virginie Maes, Sophie Quoilin (Scientifc Institute of Public Health, Belgium), Vanessa Suin (Viral Hepatitis National Reference Laboratory, Scientifique Institute of Public Health, Belgium).
- Denmark: Sofie Elisabeth Midgley, Luise Mueller (Statens Serum Institut, Denmark).
- Germany: Mirko Faber (Robert Koch Institute, Germany), Jürgen Wenzel (National Consultant Laboratory for HAV and HEV, Germany), Dirk Werber (State Office for Health and Social Affairs, Berlin, Germany).
- Greece: Kassiani Mellou (Hellenic Centre for Disease Control and Prevention).
- Ireland: Lelia Thornton (HSE Health Protection Centre, Ireland).
- Italy: Roberto Bruni, Anna Rita Ciccaglione, Caterina Rizzo, Maria Elena Tosti (Istituto Superiore di Sanita, Italy).
- Netherlands: Ingrid Friesema, Eelco Franz, Harry Vennema (National Institute for Public Health and the Environment, the Netherlands).
- Portugal: Rita de Sousa (National Institute of Health Dr Ricardo Jorge, Portugal).
- Spain: Ana Avellon Calvo (Viral Hepatitis Reference and Research Laboratory, Carlos III Health Institute, Spain), Patricia Ndumbi (EPIET fellow at Carlos III Health Institute, Spain), Carmen Varela Martinez (Carlos III Health Institute, Spain).
- Sweden: Josefine Ederth, Lena Sundqvist (Public Health Agency of Sweden).
- United Kingdom (UK): Koye Balogun, Kazim Beebeejaun, Michael Edelstein, Siew Lin Ngui, Sema Mandal (Public Health England, UK).

ECDC issued this risk assessment document according to Article 10 of Decision No 1082/13/EC and Article 7 of Regulation (EC) No 851/2004 establishing a European Centre for Disease Prevention and Control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter with their respective advantages and disadvantages. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written under the coordination of an Internal Response Team at the ECDC. All data published in this risk assessment are correct to the best of our knowledge as at 26 June 2017. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

Disease background information

Hepatitis A is an acute, usually self-limiting infection caused by the hepatitis A virus (HAV). Transmission is predominantly via 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 MSM, and transmission through the sharing of needles and syringes with outbreaks among people who inject drugs. Parenteral transmission through infected instruments or, rarely, blood components has been documented [9].

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 which are further divided into sub-genotypes A and B. Genotype I is the most prevalent, comprising at least 80% of circulating human strains [10,11].

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 (receiving immunoglobulins) immunisation is effective if administered within two weeks of exposure. Several inactivated vaccines are available for prevention [12]. Post-exposure prophylaxis should be administered in accordance with national guidelines.

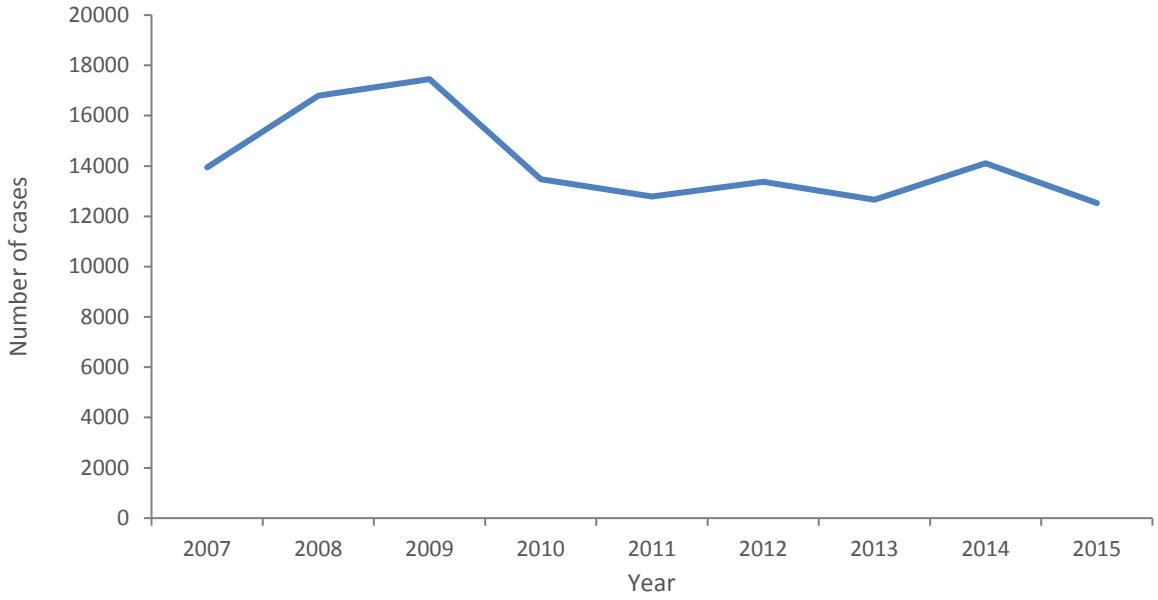
In 2015, 12 527 confirmed hepatitis A cases were reported to The European Surveillance System (TESSy) by 30 EU/EEA countries. Romania accounted for 41% of the cases and Bulgaria for 9%. Cases were reported among all age groups, with most cases among 5–14-year-olds (39%) and 25–44-year-olds (19%). Male 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 and 1.2, 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.

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 [9].

Outbreaks of hepatitis A among MSM have been recognised since the 1970s [13-16]. Several multinational outbreaks have been described, one of which between January and June 1991 involved at least eight cities across three countries and two continents (North America and Australia) [17]. Several European countries have reported national outbreaks among MSM in recent decades. In 2008 and 2009, different and probably related hepatitis A outbreaks affecting MSM were identified in several EU countries [18-21]. Other population groups at increased risk of infection (i.e. people who inject drugs and Roma communities) were also simultaneously affected by outbreaks, resulting in the highest number of reported cases during the period 2007-2015 (Figure 1) [22]. The main risk factor is related to direct oral-anal contact during sex [18-21]. 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 [23].

Figure 1. Distribution of hepatitis A cases, by year of report, 2007–2015, EU/EEA



Source: ECDC

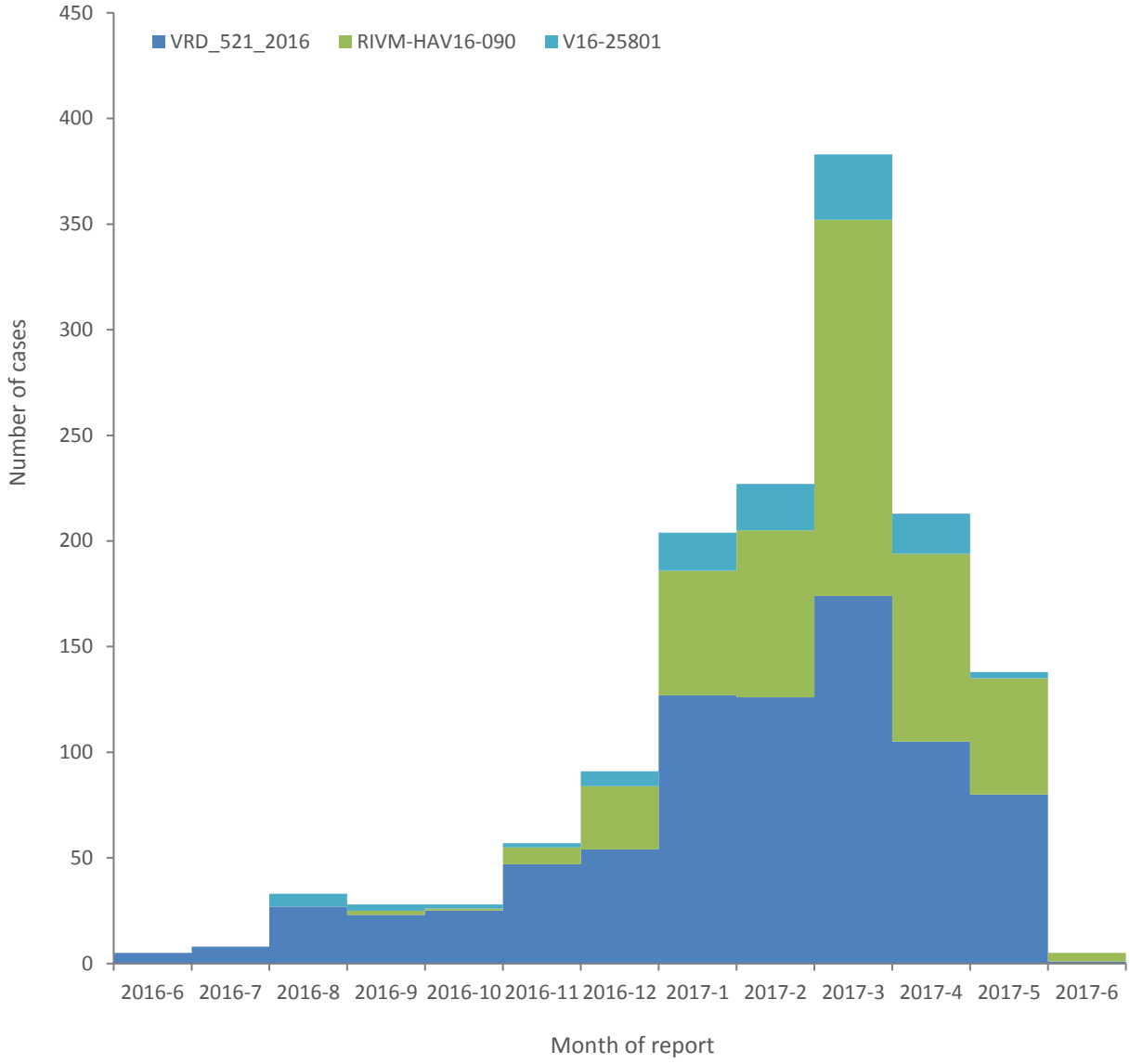
Event background information

Epidemiology of genetically-sequenced HAV cases

Between 1 June 2016 and 26 June 2017, 16 EU countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom) reported 1 500 HAV genotype IA-confirmed cases, belonging to three separate clusters based on genetic sequencing of HAV (Figure 2). Of these, 66 were reported to be infected with one of the cluster strains without specific cluster information. The descriptive epidemiology is presented below for each cluster as they indicate separate transmission chains. No deaths have been reported in confirmed cases.

Data on reported cases in April and thereafter should be interpreted with caution, as data is not yet available for several countries due to reporting delays. Thus, the numbers represented in this report underestimate the true extent of the clusters for these months.

Figure 2. Distribution of hepatitis A cases, by month of report and genetic sequence, June 2016 to June 2017, as of 26 June 2017, EU/EEA (n=1 420*)



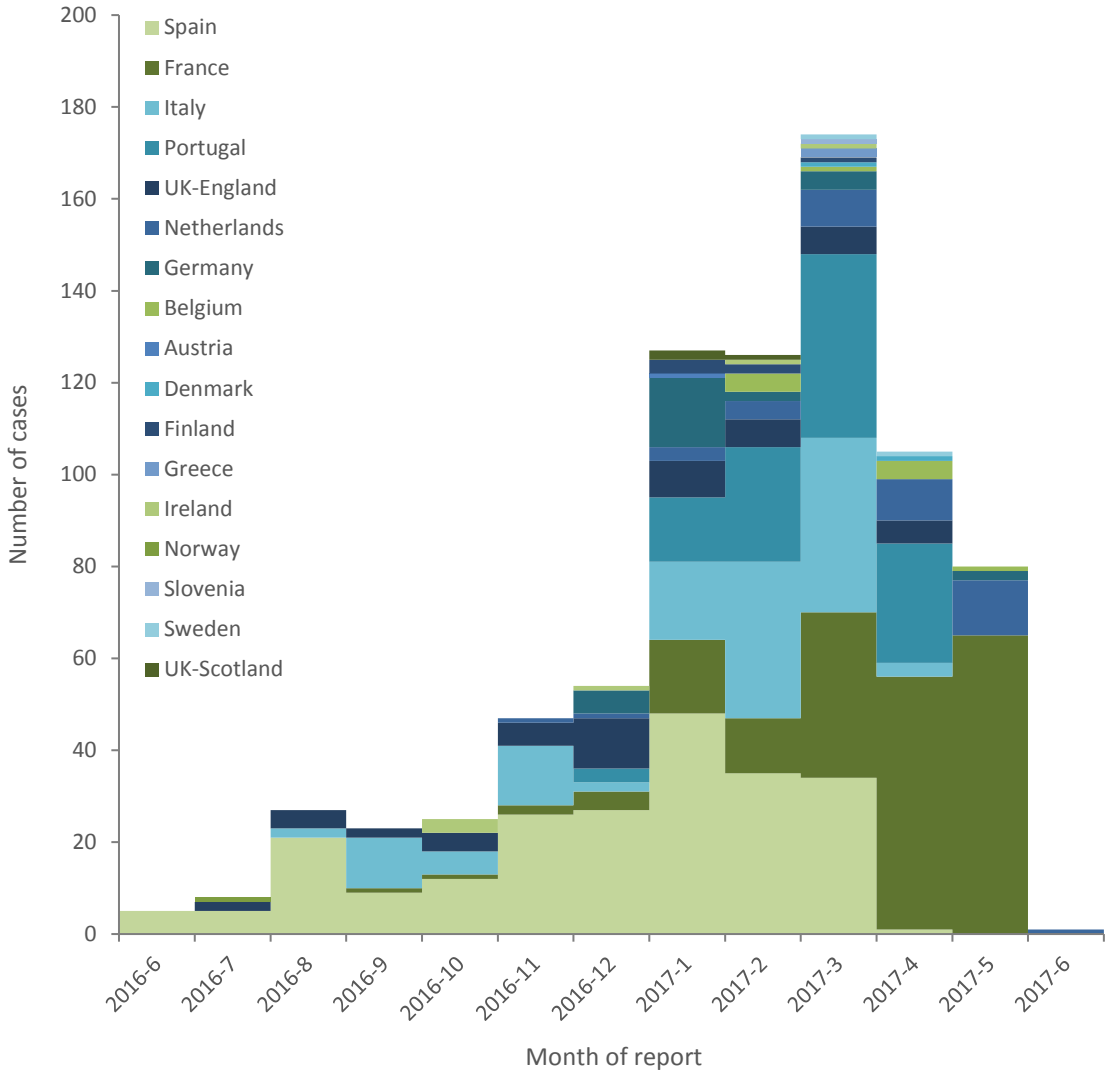
** An additional 80 cases with missing date of report are not included, 66 of which were also lacking information on cluster.*

Event 1 – Cluster VRD_521_2016

On 6 December 2016, UK gave notification of 15 cases of hepatitis A by means of an urgent inquiry through EPIS FWD. Five of these cases had a travel history to Spain.

As of 26 June 2017, 16 EU Member States had reported 806 cases infected with a viral RNA sequence matching the VRD_521_2016 sequence or with a maximum of two nucleotides difference (Figure 2). Most cases were reported by Spain (223), France (193), Italy (125), Portugal (144) and the United Kingdom (56). Of the 796 cases with gender information, 742 (93%) are male and 288 (85%) of 339 documented cases identify themselves as MSM. The median age of cases is 33 years, ranging from 0 to 79 years. Twenty-seven of the 71 cases with a travel history reported visiting Spain during the incubation period.

Figure 3. Distribution of cases associated with cluster VRD_521_2016, by reporting country and month of report (n=802*), June 2016 to June 2017, as of 26 June 2017, EU/EEA



**Four additional cases with missing date of report are not included.*
Note: One female and one male case 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.

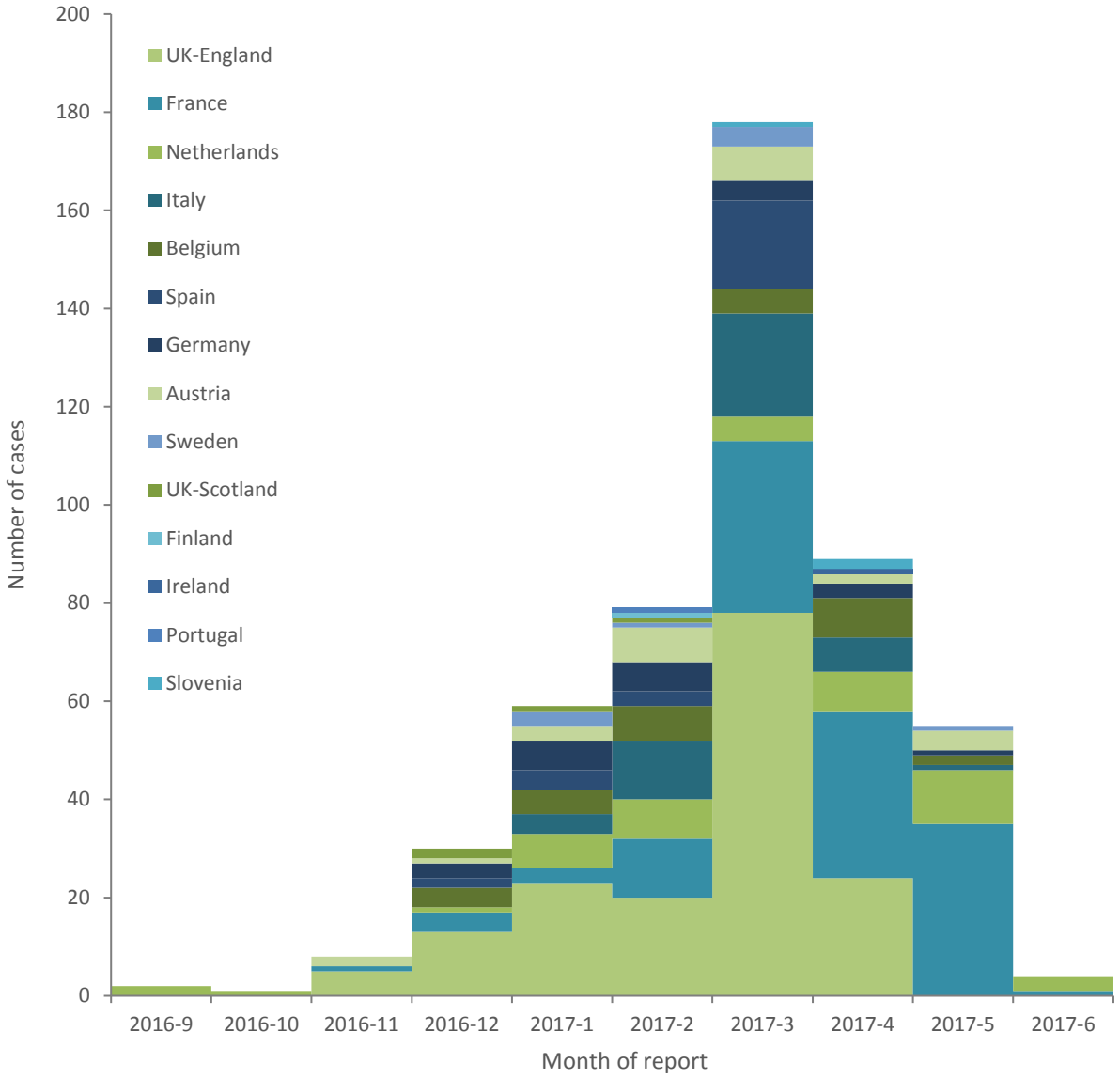
HAV strain VRD_521_2016 of sub-genotype IA is characterised by a viral RNA sequence of 505 nucleotides from the VP1/2A region. The complete VP1 fragment is available for comparison in HAVNET. The UK shared this sequence with the European FWD network and ECDC informed the STI contact points through EPIS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

Event 2 – Cluster RIVM-HAV16-090

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

As of 26 June 2017, 13 EU Member States have reported 509 cases with a viral RNA sequence matching RIVM_HAV16_090, or with a maximum of two nucleotides difference (Figure 3). Most cases were reported by the United Kingdom (168), France (125), the Netherlands (46), Italy (45) and Belgium (31). Of the 501 cases with gender information, 461 (92%) are in males, and 243 (80%) of 302 documented cases identify themselves as MSM. The median age of cases is 34 years, ranging from<1 to 88 years. Of the 88 cases with a travel history during the incubation period, 26 travelled to Spain and 11 to Germany.

Figure 4. Distribution of cases associated with cluster RIVM-HAV16-090, by reporting country and month of report (n=505*), June 2016 to June 2017, as of 26 June 2017, EU/EEA



**Four additional 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. According to the HAVNET protocol, the sequence is a 460-nucleotide-long fragment from region VP1/2A [24]. 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 large ongoing outbreak among MSM in Taiwan.

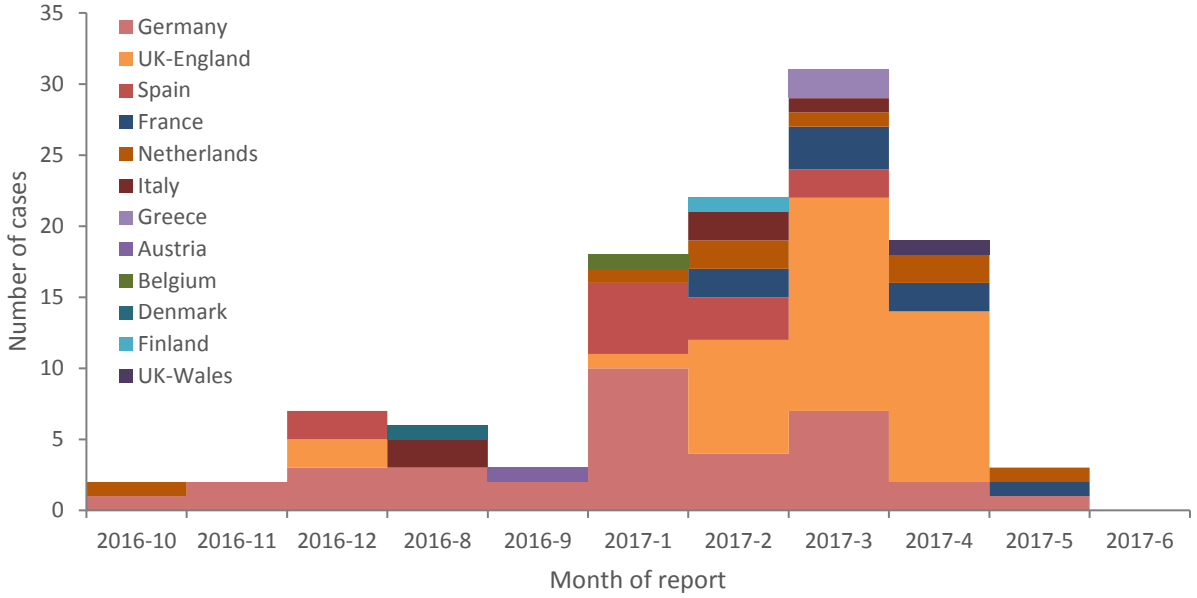
The sequence of RIVM-HAV16-090 is only 95.4% similar to the VRD_521_2016, suggesting unrelated transmission events.

Event 3 – Cluster V16-25801

On 11 January 2017, Germany gave notification of three clusters of hepatitis A via an EPIS FWD urgent inquiry. These cases, predominantly in males, were 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 as V16-25801.

As of 26 June 2017, 11 EU Member States had reported 119 cases with a viral RNA sequence matching V16_25801 or with a maximum of two nucleotides difference. Most cases were reported from Germany (41), the United Kingdom (39) and Spain (11). Of the 119 cases, 112 (94%) are in males, and 41 of 47 documented cases identify themselves as MSM. The median age of cases is 34 years and ranges from 16 to 61 years. Nine of 24 cases with information on travel had visited Spain during the incubation period.

Figure 5. Distribution of cases associated with cluster V16-25801, by reporting country and month (n=119*), June 2016 to June 2017, as of 26 June 2017, EU/EEA



**Six additional 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. According to the HAVNET protocol, the sequence is a 459-nucleotide-long fragment from region VP1/2A [24]. 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 nucleotide difference) to V16-25801 from two female Ecuadorian patients. Information on sequence (Acc. N. KU570286) is only available for the 2014 case who acquired infection in Ecuador, suggesting relatedness between V16-25801 and strains from South America.

Additional information on national investigations

In addition to the above-mentioned confirmed cases, Austria, Denmark, Greece, Ireland, Italy, Malta, the Netherlands and Spain reported 2 660 hepatitis A cases, probably or suspected to be associated with this outbreak. Sequencing had not been performed for these cases and it could therefore not be confirmed whether they were part of the outbreak. Of the 2 660, 938 (35%) were considered to probably be associated with this outbreak, because they were reported in individuals who had had contact with a confirmed case, self-identified as MSM, reported having sexual contact with MSM or attending MSM venues or events. Spain reported 537 (57%) and Italy 350 (37%) of these cases. The remaining 1 722 (65%) were considered suspected to be associated with this outbreak, because they were reported in males between 18-45 years of age without identified exposure to contaminated food or water. Spain reported 1 338 (78%) and Italy 294 (17%) of these cases.

The United Kingdom (England) [25] and Portugal [26] have reported overall increases in hepatitis A cases among MSM, largely linked to the three clusters identified above, and have recommended the use of hepatitis A vaccine in specific groups. Some cases in England 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, the UK reported 18 cases identified in food handlers and one instance of foodborne transmission associated with one of the outbreak strains. Ireland reported one food handler infected with the VRD_521_2016 sequence, with no reported secondary cases. Other countries have reported suspected cases in food handlers. Greece, reported one food handler infected with V16-25801 out of five confirmed cases, one food handler among the probable cases and two among the suspected cases. Foodborne transmission has not been reported.

So far no cases in other risk groups, such as people who inject drugs or ethnic minorities have been reported and these strains have not been identified in the food chain.

Ten countries have notified an increase in the number of HAV infection cases reported in 2017 compared with the same time period or 2016: Austria, Belgium, Estonia, Finland, Italy, Ireland, the Netherlands, Portugal, Spain and Sweden. These increases ranged from a slight increase up to a seven-fold increase. Other hepatitis A outbreaks may have influenced these increases and the effect might not be completely attributed to the ongoing MSM transmission.

Hepatitis A vaccine availability in the EU

Hepatitis A vaccine availability in the EU is currently limited, with some countries having reported shortages (e.g. Austria, Denmark, Italy, Portugal, Spain and Sweden). Other countries, such as the Czech Republic, Estonia, Finland, Germany, Ireland, Luxembourg and Slovenia, have reported no shortages.

Supply information was obtained from three major hepatitis A vaccine marketing authorisation holders in the EU/EEA. The information received confirmed observations made at the national level. 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. This is due to a combination of past and ongoing production issues with marketing authorisation holders that has 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.

In the EU/EEA, HAV vaccines exist as stand-alone or in combination with HBV antigen or typhoid antigen. All vaccines considered in this assessment are listed below (Table 1). None of the monovalent HAV vaccines have been licensed at EU level through a centralised procedure, therefore national licence agreements and national summaries of product characteristics need to be consulted for further information where available.

HAV vaccines exist in adult and children/adolescents formulation that vary in antigen content (Table 1). All HAV vaccines available in the EU/EEA are formaldehyde-inactivated vaccines.

Table 1. Monovalent HAV vaccines available in the EU/EEA, 2017

Trade name	HAV antigen dose/injection		Manufacturer
	Paediatric	Adults	
AVAXIM [27]	80 Units[1]	160 Units[1]	Sanofi Pasteur
HAVRIX [28,29]	720 ELISA Units	1440 ELISA Units	GlaxoSmithKline (GSK)
VAQTA [30,31]	25 Units[2]	50 Units[2]	Merck Sharp & Dohme Limited (MSD)

[1] In the absence of an international standardised reference, the antigen content is expressed using a Sanofi Pasteur in-house reference
[2] Units measured according to the in-house method of the manufacturer-Merck Sharp & Dohme Corp

Monovalent HAV vaccines are licensed for use from one year of age for the paediatric formulation. Adult formulations are licensed from 16 years for AVAXIM or from 18 years for HAVRIX and VAQTA.

The current hepatitis A vaccination schedules applicable in EU/EEA Member States are available from the ECDC vaccine schedule platform [32]. Apart from Austria (recommended in childhood but not funded) and Greece, none of the EU/EEA countries includes HAV vaccination as part of their national general recommendation.

HAV vaccination policy usually targets individuals who are at increased risk of HAV exposure or those at risk of serious health outcomes after infection. National recommendations vary and may include, in addition to MSM, the following groups:

- travellers to areas of intermediate or high endemicity;
- people who inject drugs;
- contact persons of confirmed HAV cases;
- exposed immunocompromised persons;
- persons with chronic liver disease at risk of severe adverse consequences of HAV infection;
- occupational groups including food handlers, those working with non-human primates;
- individuals living in institutions for persons with developmental disabilities.

A complete vaccination schedule consists of two doses with, in general, an interval of six to twelve months between the first and booster dose. The interval between two doses is flexible and can be extended from six months up to 4-5 years, as per WHO recommendations. Two doses are believed to provide life-long protection [33].

It is accepted that all inactivated HAV vaccines are interchangeable, highly immunogenic and produce comparable immune response [33].

In light of the limited supply of HAV vaccines in some EU countries, the vaccination of MSM will have to be prioritised with the other groups where vaccination is also recommended, in accordance with national recommendations and guidelines. In addition, the limited availability of HAV vaccine adult formulation has meant that some EU/EEA Member States have reviewed the use of paediatric formulation vaccine as a temporary measure rather than no vaccination at all.

The following scenarios have been designed to provide options for mitigation measures. The final decision of prioritisation groups for vaccination or to use vaccination off-label (e.g. use of paediatric formulation vaccine in adults) will have to be decided by national technical advisory groups or regulatory authorities (both referred as national authorities). It is up to national authorities to decide whether the vaccination of MSM is to be prioritised.

Scenario 1: HAV-inactivated vaccine adult formulation available, no supply constraints

- No prioritisation action required, vaccination activities performed as usual. The vaccination of MSM is to be reinforced.

Scenario 2: HAV-inactivated vaccine adult formulation available but with a limited supply

It is suggested that in order to spare doses, national authorities may:

- Review the list of people for which HAV vaccine is recommended and propose a temporary priority list.
- Consider using a single dose and delaying booster doses until stocks resume to normal, given that the interval between two doses can be extended. This option is further supported in light of available evidence suggesting that a single dose of HAV vaccine can successfully control outbreaks [33-36] and demonstrating the long-term efficacy of one-dose hepatitis A vaccination [37-39].
- Consider serological testing of immunity for those with uncertain vaccination history or past exposure.

Scenario 3: HAV inactivated vaccine adult formulation NOT available. HAV paediatric formulation available

- According to limited published evidence on the immune response of some of the paediatric formulation vaccine in adults, a single dose of paediatric vaccine could be used as pre-exposure prophylaxis as a temporary measure. As part of the clinical investigations of HAV vaccine, the immunogenicity of varying schemes and antigen content of HAV vaccines were studied [40-43]. The proportion of individuals that seroconverted after one dose was above 90%. However, evidence on the duration of protection provided by a single paediatric dose is lacking. There will be a need to boost adults who would have received a paediatric vaccine with an adult formulation as soon as stocks resume to normal in order to increase antibody titre and ensure long-term protection.
- There is no published evidence of using paediatric formulation vaccine in adults as post-exposure prophylaxis.

Scenario 4: HAV inactivated vaccine adult formulation NOT available. HAV paediatric formulation available but with a limited supply

- In this scenario, suggestions for Scenario 2 and 3 should be considered.

Scenario 5: HAV vaccine adult and paediatric formulation not available

- This is the worst-case scenario where no vaccine is available. Information targeting healthcare professionals and the public would be required to reinforce prevention activities. There would be a need to liaise with regulatory authorities and manufacturers to enquire about upcoming supply. If HAV combination vaccines are available, consider usage on an individual basis.

According to national recommendations and availability, the use of HAV immunoglobulins may be considered for post-exposure prophylaxis.

ECDC threat assessment for the EU

An outbreak of hepatitis A is ongoing in the EU/EEA. Between June 2016 and June 2017, 16 EU/EEA countries reported 1 500 confirmed outbreak cases infected with a viral RNA sequence matching or closely related to one of three circulating HAV clusters. Confirmed cases peaked in March 2017. However, the peak of the outbreak is unlikely to have passed yet as confirmed cases from April 2017 onwards have not yet been reported from some of the affected countries, notably Spain and Portugal, which reported a large proportion of the overall number of confirmed cases up to March 2017. Confirmed cases significantly underestimate the true extent of the outbreak due to the challenges with regard to complete and timely reporting of sequencing results. Only a minority of EU countries sequence a sufficiently large proportion of strains in a timely fashion.

In addition to the outbreak confirmed cases, 2 660 hepatitis A cases are also considered probably or suspected to be associated with this outbreak. Reported cases are limited to those attending healthcare facilities and a very large proportion of mild or asymptomatic infections associated with this outbreak may not have been identified or reported.

Risk of spread in the high risk groups

Scientific articles on these clusters published after the ECDC rapid risk assessment of 19 December 2016 [44,45] provide insights into the high-risk sexual practices associated with HAV transmission in MSM. In particular, they indicate anonymous sex, multiple sex partners, sex-on-premises and the use of dating apps as factors associated with these outbreaks. The anonymous and therefore unidentifiable sexual contacts make partner notification and control of the outbreak particularly challenging. The spread of the epidemic among MSM seems not to have peaked yet, and more cases are expected to be reported in the coming weeks and possibly months.

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.

There is a risk of spread into other groups that are at increased risk of infection, particularly people who inject drugs and other population groups (e.g. Roma population) that can sustain transmission for a prolonged period in extended networks, as was the case in 2008 and 2009 [22].

Risk of spread to the general population

Transmission in the community can be related to secondary transmission to contacts of infected cases in the high-risk groups, contamination of food items by infected food handlers and possibly via substances of human origin e.g. blood transfusion or tissue and organ donation.

Most of the cases reported are among HAV-unvaccinated adult MSM, but evidence exists for secondary cases among the general population. As cases have also been 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. The contamination of a food item early in the food chain may lead to wide-scale transmission into the general population.

A change in the profile of cases, such as an increase in the proportion of cases in females or in age-groups under 18 years of age or over 45 years of age, could indicate a possible increased transmission in the general population.

There is also a risk of HAV transmission through asymptomatic or incubating viraemic donors of substances of human origin (SoHO) [46,47]. Most symptomatic cases are considered non-infectious after the first week of jaundice [10].

There is no risk of HAV transmission through plasma-derived medicinal products because human plasma (pooled and treated for virus inactivation) is tested by nucleic acid testing (NAT) for HAV and the production process effectively reduces the HAV in plasma-derived medicinal products [48].

References

1. European Centre for Disease Prevention and Control. HIV and STI prevention among men who have sex with men. Stockholm: ECDC; 2015.
2. European Centre for Disease Prevention and Control. Communication strategies for the prevention of HIV, STI and hepatitis among MSM in Europe Stockholm: ECDC, 2016.
3. European Commission. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. Official Journal of the European Union. 2004 (L 91/25).
4. Suligoi B, Pupella S, Regine V, Raimondo M, Velati C, Grazzini G. Changing blood donor screening criteria from permanent deferral for men who have sex with men to individual sexual risk assessment: no evidence of a significant impact on the human immunodeficiency virus epidemic in Italy. Blood Transfus. 2013 Jul;11(3):441-8.
5. European Centre for Disease Prevention and Control. Rapid Risk Assessment: Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men. 19 December 2016. Stockholm: ECDC; 2016.
6. European Centre for Disease Prevention and Control. Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men - First update, 23 February 2017. 2017. Stockholm: ECDC; 2017.
7. European Centre for Disease Prevention and Control. Epidemiological update: Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men - 28 April 2017. Stockholm: ECDC; 2017.
8. European Centre for Disease Prevention and Control. Rapid Risk Assessment: Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men - Second update, 19 May 2017. Stockholm: ECDC; 2017.
9. European Centre for Disease Prevention and Control. Hepatitis A virus in the EU/EEA, 1975-2014. ECDC, 2016.
10. Nainan OV, Xia G, Vaughan G, Margolis HS. Diagnosis of Hepatitis A Virus Infection: a Molecular Approach. Clin Microbiol Rev. 2006 Jan;19(1):63-79.
11. Costa-Mattioli M, Di Napoli A, Ferre V, Billaudel S, Perez-Bercoff R, Cristina J. Genetic variability of hepatitis A virus. J Gen Virol. 2003 Dec;84(Pt 12):3191-201.
12. Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines, 6th Edition: Elsevier Inc; 2012.
13. Corey L, Holmes KK. Sexual transmission of hepatitis A in homosexual men: incidence and mechanism. N Engl J Med. 1980 Feb 21;302(8):435-8.
14. Hoybye G, Skinhoj P, Hentzer B, Faber V, Mathiesen L. An epidemic of acute viral hepatitis in male homosexuals. Etiology and clinical characteristics. Scand J Infect Dis. 1980;12(4):241-4.
15. Mindel A, Tedder R. Hepatitis A in homosexuals. Br Med J (Clin Res Ed). 1981 May 23;282(6277):1666.
16. Dritz SK, Ainsworth TE, Back A, Boucher LA, Garrard WF, Palmer RD, et al. Patterns of sexually transmitted enteric diseases in a city. Lancet. 1977 Jul 02;2(8027):3-4.
17. Centers for Diseases Control and Prevention. Hepatitis A among homosexual men in United States, Canada, and Australia. MMWR 1992, 155:161-4.
18. 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 Mar 03;16(9).
19. Tortajada C, de Olalla PG, Diez E, Pinto RM, Bosch A, Perez U, et al. Hepatitis a among men who have sex with men in Barcelona, 1989-2010: insufficient control and need for new approaches. BMC Infect Dis. 2012.
20. 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 5//;54(1):26-9.
21. Mazick A, Howitz M, Rex S, Jensen IP, Weis N, Katzenstein TL, et al. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. Euro Surveill. 2005 May;10(5):111-4.
22. Payne L, Coulombier D. Hepatitis A in the European Union: responding to challenges related to new epidemiological patterns. Euro Surveill. 2009 Jan 22;14(3).
23. Regan DG, Wood JG, Benevent C, Ali H, Smith LW, Robertson PW, et al. Estimating the critical immunity threshold for preventing hepatitis A outbreaks in men who have sex with men. Epidemiol Infect. 2016 May; 144(7):[1528-37 pp.]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26566273.

24. National Institute for Public Health and the Environment (RIVM). Ministry of Health WaS. Molecular detection and typing of VP1-2A region of Hepatitis A Virus (HAV). [Protocol]. Bilthoven: RIVM; [cited 20 February 2017]. Available from: http://www.rivm.nl/en/Topics/H/HAVNET/Protocols/Typing_protocol_HAVNET_VP1P2A.org.
25. Public Health England. Health protection Report: Hepatitis A outbreak in England under investigation 2017. Vol. 11 No. 17 Published: 12 May 2017. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/613909/hpr1717_hepA.pdf.
26. Direção-Geral da Saúde e Instituto Nacional de Saúde. Boletim epidemiológico. HEPATITE A EM PORTUGAL. Situação a 8 de maio de 2017: Semana 19 (7 – 14 maio 2017)2017. Available from: http://www.dgs.pt/ficheiros-de-upload-2013/hepatite-a-boletim-epidemiologico-8-de-maio-pdf.aspx
27. electronic Medicines Compendium (eMC). AVAXIM. Sanofi Pasteur. Summary of Product Characteristics [Internet]. 2017 [updated 28 February 2017 cited 21 June 2017]. Available from: https://www.medicines.org.uk/emc/medicine/6206.
28. electronic Medicines Compendium (eMC). Havrix Junior Monodose Vaccine. GlaxoSmithKline UK. Summary of Product Characteristics [Internet]. 2017 [updated 9 December 2016 cited 21 June 2017]. Available from: https://www.medicines.org.uk/emc/medicine/2040.
29. electronic Medicines Compendium (eMC). Havrix Monodose Vaccine. GlaxoSmithKline UK. Summary of Product Characteristics [Internet]. 2017 [updated 9 December 2016 cited 21 June 2017]. Available from: https://www.medicines.org.uk/emc/medicine/2041.
30. electronic Medicines Compendium (eMC). VAQTA Adult. Merck Sharp & Dohme Limited. Summary of Product Characteristics [Internet]. 2017 [updated 3 February 2017 cited 21 June 2017]. Available from: https://www.medicines.org.uk/emc/medicine/6210.
31. electronic Medicines Compendium (eMC). VAQTA Paediatric. Merck Sharp & Dohme Limited. Summary of Product Characteristics [Internet]. 2017 [updated 3 February 2017 cited 21 June 2017]. Available from: https://www.medicines.org.uk/emc/medicine/6211.
32. European Centre for Disease Prevention and Control. Vaccine Scheduler from the European Centre for Disease Prevention and Control 2017 [cited 22 June 2017]. Available from: http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx.
33. World Health Organization (WHO). WHO position paper on hepatitis A vaccines – June 2012. Weekly Epidemiological Record. No. 28-29, 2012, 87, 261–2762017 13 July 2012.
34. World Health Organization (WHO). The immunological basis for immunization series: module 18: hepatitis A. 2017. Available from: http://apps.who.int/iris/bitstream/10665/44570/1/9789241501422_eng.pdf.
35. Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. N Engl J Med. 1992 Aug 13;327(7):453-7.
36. Zamir C, Rishpon S, Zamir D, Leventhal A, Rimon N, Ben-Porath E. Control of a community-wide outbreak of hepatitis A by mass vaccination with inactivated hepatitis A vaccine. Eur J Clin Microbiol Infect Dis. 2001 Mar;20(3):185-7.
37. Iwarson S, Lindh M, Widerstrom L. Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. J Travel Med. 2004 Mar-Apr;11(2):120-1.
38. Hatz C, van der Ploeg R, Beck BR, Frosner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis a vaccine delayed up to 11 years. Clin Vaccine Immunol. 2011 May;18(5):885-7.
39. Vacchino MN. Incidence of hepatitis A in Argentina after vaccination. J Viral Hepat. 2008;15:47-50.
40. Jilg W, Bittner R, Bock HL, Clemens R, Schatzl H, Schmidt M, et al. Vaccination against hepatitis A: comparison of different short-term immunization schedules. Vaccine. 1992;10 Suppl 1:S126-8.
41. Andre F, Van Damme P, Safary A, Banatvala J. Inactivated hepatitis A vaccine: immunogenicity, efficacy, safety and review of official recommendations for use. Expert review of vaccines. 2002 Jun;1(1):9-23.
42. Theilmann L, Kallinowski B, Gmelin K, Hofmann F, Scheiermann N, Wohland B, et al. Reactogenicity and immunogenicity of three different lots of a hepatitis A vaccine. Vaccine. 1992;10 Suppl 1:S132-4.
43. Garin D, Vidor E, Wallon M, Fanget B, Brasseur P, Delolme H, et al. Good immunogenicity of GBM strain inactivated hepatitis A vaccine in healthy male adults. Vaccine. 1995 Feb;13(2):220-4.
44. 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 Feb 02;22(5).

45. 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 Feb 02;22(5).

46. Hollinger FB, Khan NC, Oefinger PE, Yawn DH, Schmulen AC, Dreesman GR, et al. Posttransfusion hepatitis type A. JAMA. 1983 Nov 04;250(17):2313-7.

47. Foster MA, Weil LM, Jin S, Johnson T, Hayden-Mixson TR, Khudyakov Y, et al. Transmission of Hepatitis A Virus through Combined Liver-Small Intestine-Pancreas Transplantation. Emerg Infect Dis. 2017 Apr;23(4):590-6.

48. European Medecines Agency. Guideline on plasma-derived medicinal products. London: EMA; 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500109627.pdf