

Hepatitis A outbreak affecting men who have sex with men (MSM) in South Italy

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SUMMARY

From April to October 2017, 27 cases of Hepatitis A (HA), 22 male and 5 female, were reported in Cosenza (South Italy). The median age of cases was 32 years (range 3-49 years). Out of 21 male adults, 14 were identified as men who have sex with men (MSM). Phylogenetic analysis was conducted in 15 cases and revealed two distinct sequences of genotype IA linking to clusters recognised in MSM in other European countries in 2016; genotype IB was recognized in only 2 cases. The report confirms that HA is an emerging issue among MSM. As suggested by the WHO, in countries with low HAV circulation, vaccination programmes should be tailored on local epidemiological patterns to prevent outbreaks among high risk groups and eventual spill-over of the infection into the general population.

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Hepatitis A virus (HAV) infection is usually transmitted by ingestion of contaminated food or water, but sexual transmission among MSM has been described (CDC Sexual transmission and viral Hepatitis Feb. 2018). The burden of HAV infection on communities and nations is highly linked to average age at infection. In high endemic countries, nearly all children become infected at an early stage (when asymptomatic infection is likely) and almost no adolescents and adults are susceptible. In intermediate endemic areas (such as Central and South America, Eastern Europe, and parts of Asia), childhood transmission is less frequent, more adolescents and adults are susceptible to infection, and outbreaks are common. In low endemic countries, the incidence rate is very low, few individuals become infected in childhood, and a high proportion of adults are susceptible. (Jacobsen, K.H. and Wiersma, 2010).

Despite a significant decrease in HAV in European Union countries (ECDC Hepatitis A virus in the Eu/EEA, 1975-2014 A systematic review of seroprevalence and incidence comprising European surveillance data and national vaccination recommendations. Stockholm ECDC 2016. Available from http://ecdc.europa.eu/en/publication_data/hepatitis-virus-eueea_1975-2014; Carrillo-santistev, *et al.*, 2017), in December 2016, the European Centre for

Disease Prevention and Control (ECDC) issued a Rapid Risk Assessment reporting of 3 HAV genotype IA outbreak strains (VDR_521_2016, RIVM-HAV16-090, V16-25801) among MSM in the UK and the Netherlands (Beebejann K., Degala S. *et al.* 2017; Werber D., Michaelis *et al.*, 2016; <https://ecdc.europa.eu/en/publications-data/rapid-risk-assessment-hepatitis-outbreak-eueea-mostly-affecting-men-who-have-sex>). Between 1 June 2016 and 7 September 2018, 22 European Union and European Economic Area reported 4475 cases associated with a multi-country hepatitis A outbreak. In particular, outbreaks of hepatitis A among MSM are ongoing in Europe (<https://ecdc.europa.eu/en/news-events/epidemiological-update-hepatitis-outbreak-eueea-mostly-affecting-men-who-have-sex-men-2>). Italy and Spain have also reported a recent increase in male HAV cases. (Rodriguez *et al.*, 2018; Loconsole *et al.*, 2017; Comelli A., Izzo *et al.*, 2018; Greco *et al.*, Lanini *et al.*, 2017; Rossati *et al.*, 2017). In Italy, HAV is mandatorily reported to the Italian National Surveillance System (Ministerial Decree (DM) of 15/12/1990. Gazz. Uff. 8/01/1991, n.6 Rome: Ministero della Salute Italiana. Available from http://www.salute.gov.it/imgs/C_17_normativa_1357_allegato.pdf).

Italy is a low endemic country for HAV infection characterized by low annual incidence rate: in the last decades, according to A Sentinel Surveillance System for Acute Viral Hepatitis-SEIEVA- (Tosti *et al.*, 2008) data, incidence decreased from 10 to 3.6 cases per 100,000 inhabitants per year between 1985 and 2004, up to 1.1 cases in 2010 and 0.8 cases in 2016 (Ansaldi *et al.*, 2017) (5/100,000 inhabitants) and a progressive shift in the average age of infection was recorded toward adulthood.

In the past 2 decades, the general risk of HAV infection has changed due to better hygiene and sanitation, but contam-

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inated food like berries, shellfish and raw seafood were the most frequently reported risk factor (Lopalco *et al.*, 2005; Pontrelli *et al.* 2008; Montano *et al.* 2013).

Hepatitis E virus (HEV) is a fecal-oral route transmitted pathogen and HEV infection is one of most common causes of enteric transmitted hepatitis in countries with low and intermediate healthcare standards (European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection, 2018). In industrialized countries, autochthonous cases of acute infection with HEV are often reported as sporadic cases occurring in clusters associated with occupational exposure (mainly pig handlers) (Backer *et al.*, 2012; Chaussade *et al.*, 2013) and consumption of contaminated water or food. The increased risk for HEV infection among MSM is noteworthy, though not unexpected (Payne *et al.*, 2013). Recent studies suggest that direct human-to human contact, such as for sexually transmitted disease, may play a significant role in HEV spread (Colson *et al.*, 2011; Lanini *et al.*, 2015) and analogy with the transmission of HAV in MSM would be considered.

We describe an outbreak of 27 patients with HAV in Cosenza. In 15/27 cases a phylogenetic analysis was also conducted at the Istituto Superiore di Sanità (ISS).

The outbreak started in April 2017 and the last case was recorded in October 2017: a total of 27 cases were reported, a considerable increase in HAV cases compared with the last six years. In Cosenza (about 700,000 inhabitants) in 2010-2016 only 12 HAV cases were recorded (8 children and 4 adults with a clear food-borne acquisition) and from June 2018 to January 2019 only 4 cases were reported (two were travellers returning from countries at risk and 2 were adult males without clear risk factors).

A case was defined as a symptomatic person who met surveillance criteria of HAV:

- 1) Possible cases were those diagnosed with HAV with epidemiological link to confirmed cases;
- 2) sequence-confirmed cases were those with strains of hepatitis A of MSM outbreaks.

None of the cases were vaccinated with hepatitis A vaccine (HAV vaccine). Among the 27 cases described there were 3 family outbreaks (3 adult females, 2 children, 1 adult male): a heterosexual (HS) couple that declared to have eaten uncooked fish, and mother/daughter, mother/son didn't confirm any clear risk factors. The remaining 21 cases were 20 men (14 MSM) and a woman HS. Interestingly, among adult patients, HAV infection outbreak affects men in a 5:1 ratio. Among affected men 67% (14/21) identified themselves as MSM and 3 out of 14 MSM were affected by other sexually transmitted infections (HAV/HIV, HAV/syphilis, HAV/HBV). All 27 patients resulted positive for HAV-IgG and HAV-IgM. None of the patients reported HEV infection. None of the MSM reported intravenous drug use. Median value of ALT peak during hospitalization was 2245±2022 U/L. One patient reported acute liver failure with ALT levels of 7019 U/L, AST levels 4354 U/L, bilirubin 6.6 mg/dL, albumin 3 g/dL, cholesterol 109 mg/dL. Average length of hospital stay was 5.1 days.

Out of 27 cases, 15 samples of serum (1 HS couple, 1 mother/daughter couple, 1 mother/son couple, 1 HS woman, 8 MSM) were collected and phylogenetic analyses for HAV were conducted at ISS. The remaining 12 sera were not analysed because the sample was insufficient.

The region that was amplified by RT-PCR corresponded to a 406 nt amplicon comprising the viral protein1/protease

2A (VP1/2 A) region of the HAV genome (HAVNET). Genotype was assigned by phylogenetic analysis of a dataset HAV reference sequences of genotypes and subgenotypes (IA IB, II, IIIA, IIIB) (Vaughan *et al.*, Lemon *et al.*). Results of the phylogenetic analysis showed that the strains were:

- 2 genotype IB: HS couple;
- 6 genotype IA RIVM-HAV16-090: mother/daughter couple, mother/son couple and 2 MSM;
- 7 genotype A VRD_521_2016: 1 HS woman and 6 MSM.

According to previous reports (Beebejaun *et al.*, 2017; Rodriguez-Taies *et al.*, 2018; Werber *et al.*, 2016, Comelli *et al.*, 2016; Greco *et al.*, 2018; Lanini *et al.*, 2017; Rossati *et al.*, 2017), our data show that most cases of HAV (70%) are reported among MSM. In particular, results of the phylogenetic analysis (even if conducted on only 8 MSM) showed that the strain mostly affecting MSM in our city is VRD1-521-2016, as described in other European outbreaks in MSM; the same strain was reported in the HS woman. In our results, two MSM are affected by IA RIVM-HAV16-090, another strain described in Europe in MSM. The same strain is also reported in 2 families (mother/daughter couple, mother/son couple) included in this study. The VRD1-521-2016 and RIVM-HAV16-090 genotypes were also detected in non-MSM: these results show that the outbreaks within the risk-group, MSM, spill over into the general population in a country with a low prevalence of HAV (Friesema *et al.*, 2018). In regions with a low incidence of HAV infection, sequencing of HAV RNA can be used to link apparently sporadic cases and outbreaks (Ngu SL, Granerod J *et al.*, 2008).

In the HS couple, a phylogenetic analysis revealed an IB genotype. The couple claims to have eaten uncooked food (shellfish) and a different transmission source should be hypothesized. Previous cases of hepatitis A IB, related to food consumption, have been reported (Costantino *et al.*, 2017; Chironna *et al.*, 2004; Petrigiani *et al.*, 2010). Italy, just as other EU/EEA countries, is recording an unusual increase in the number of HAV cases, particularly among MSM. These events could contribute to the spread of the outbreak strains in population groups at increased risk of infection or in the community. Avoidance of faecal-oral exposure during sexual activity and safer sex practices (e.g., use of barrier methods) play an important role, but typical measures for preventing most sexually transmitted infection are not sufficient to prevent HA transmission. Information campaigns are very important and a safe and effective vaccine exists: its use is recommended to prevent further transmission and future outbreak (Ndumbi *et al.*, 2018).

The prevention of HAV for non-MSM rests largely on the availability of contamination-free potable water, adequate hand-washing, safe sewage disposal and hygienic handling of food throughout the chain from production to consumption.

The main prevention in the context of the current outbreaks is HAV vaccine for MSM (none of our patients were vaccinated). HAV vaccine is recommended, not only for MSM, but also for people traveling to or working in countries that have high or intermediate HAV endemicity, and it has been shown to be immunogenic in adults and children (Lopalco, Prato, 2008, Furesz, Scheifelet, 1995). The outbreak described here highlights the need to increase coverage of HAV vaccination, in particular in MSM, and to increase surveillance programs, because the outbreak reported in various European countries demonstrates the risk of a resurgence of the disease.

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