



## First Outbreak of Hepatitis A Associated with Sexual Transmission among Men who have Sex with Men (MSM) in Puglia, South Italy, 2017

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### Abstract

The introduction of the universal routine vaccination against hepatitis A virus in Puglia (South Italy) has significantly changed the natural history of the disease with a drastic reduction of the number of infections. In 2016, only 9 cases of acute viral hepatitis A were reported. From February 2016 to February 2017, 287 confirmed hepatitis A cases have been reported by 13 European countries. In Italy, between August 2016 and February 2017, 583 cases of hepatitis A infection were reported. Most cases in Europe and Italy involved adult men who have sex with men (MSM). In Puglia region (South Italy) from January to March 2017, 33 cases of hepatitis A were reported. Of these cases, 93.9% were male aged between 26 and 52 years (median age 38 years). Fifteen subjects reported having had sexual contacts with men (MSM) in the 8 weeks preceding the onset of symptoms and 4 of these were HIV-positive. The molecular characterization was performed on 20 samples. Eight sequences were identical to the strain VRD\_51\_2016 and 4 to the strain RIVM-HAV16-090, which are related to the epidemic of HAV in MSM in Italy and Europe. In Puglia, as well as in Europe, anonymous sex, multiple sex partners, use of dating apps and international travel are the main risk factors for infection. Vaccination among at-risk group and specific communication strategies through social media, apps and venues seem to be the main public health strategies to contain this outbreak.

### Introduction

Hepatitis A is an acute infection of the liver, usually self-limited, caused by the hepatitis A virus (HAV) and occurs sporadically and in epidemics worldwide. HAV is mostly transmitted through the fecal-oral route, either by consumption of contaminated food and water or by person-to-person contact. Parenteral transmission through sharing of needles and syringes among injecting drug users has been documented [1]. The sexual transmission has been associated with epidemics among men who have sex with men (MSM). These outbreaks have been reported since the 1970s [2-5]. The main risk factor is related to unprotected oral-anal contacts during sex [6-9]. Active and passive immunization within 2 weeks of exposure are the main public health action to contain the spread of HAV during an outbreak [10]. The most common human HAV strains belong to genotypes I and III. Genotype I is the most prevalent (responsible for at least 80% of cases) [11].

Italy has gradually shifted from a high endemicity level to a low/intermediate endemicity level for HAV infection as a result of improvements in sanitation and socioeconomic advancements [12].

Puglia region (South Italy) has been an intermediate endemicity region for hepatitis A for a long time [13]. In Puglia over the period 1996-1997, an epidemic occurred with more than 11,000 HAV cases (incidence of 130 per 100,000 people). After this event, anti-hepatitis A vaccination was introduced for all newborns in the second year of life and for adolescents. From 1998 to 2015, the vaccination covered 29 birth cohorts with an average coverage of 65% in children and young adults (2-32 years) (data from Regional Epidemiologic Observatory). This coverage rate is slightly above the threshold level considered sufficient to stop human-to-human transmission of the virus [14]. The introduction of the universal routine vaccination has significantly changed the natural history of the disease in the region. In the year 2015, 39 cases of hepatitis A were reported (notification rate:

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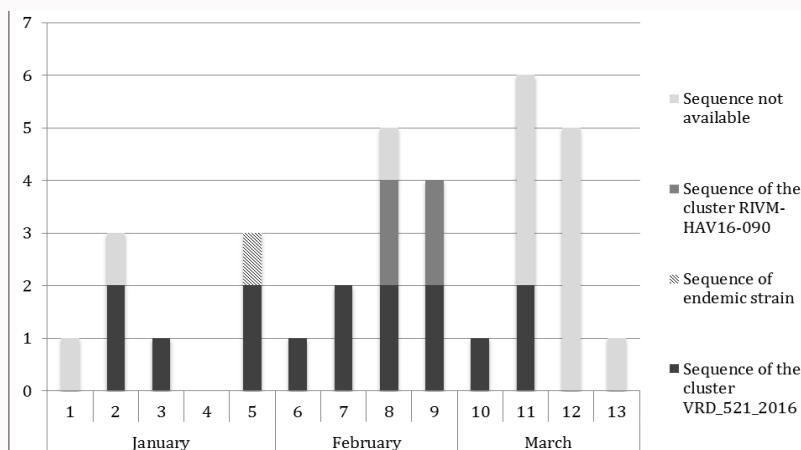


Figure 1: Epidemic curve of hepatitis A outbreak in Puglia region (South Italy), Jan-Mar 2017.

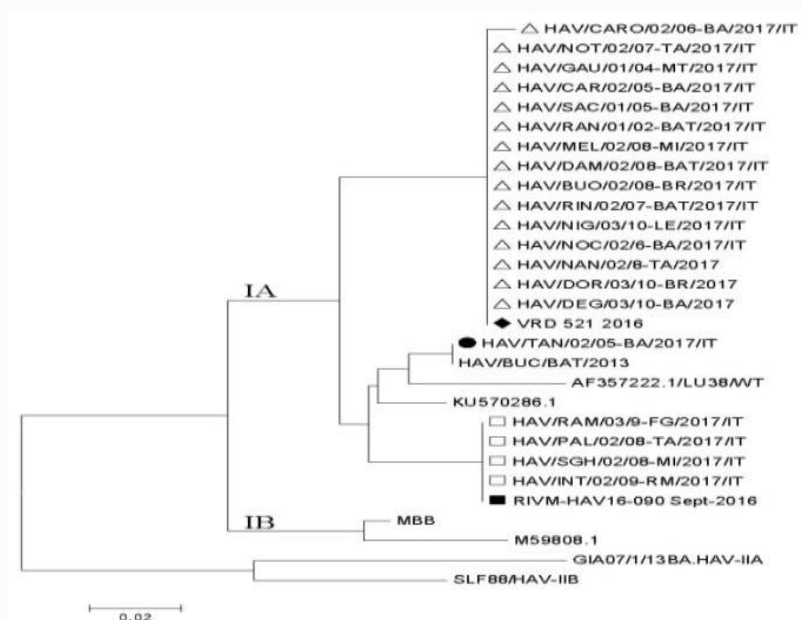


Figure 2: Phylogenetic analysis of VP1/P2 junction region of HAV strains identified in Puglia, Jan-Mar 2017. Empty triangles and empty squares indicate the sequences of the outbreak. The black rhombus and the black squares indicate the references strain VRD\_521\_2016 and RIVM-HAV16-090.

0.96 per 100,000) and in 2016 only 9 cases were notified (data from Regional Epidemiologic Observatory). In addition, in Puglia region, strains circulating in recent decades belonged to genotype IA [11,15].

From February 2016 to February 2017, 287 confirmed hepatitis A cases have been reported by 13 European countries [10]. Three different clusters have been identified based on HAV sequences, probably indicating distinct transmission chains. All the strains belonged to the sub-genotype IA. Most cases involved adult MSM. Only nine female subjects were involved [10]. In Italy, between August 2016 and February 2017, 583 cases of hepatitis A infection were reported. This number of infections is about 5 times higher than the number of hepatitis A infections identified in the same period of the last year. Among the cases, 85% were males and 61% of these were MSM [16].

Here we describe the current outbreak of hepatitis A in the Puglia region (South Italy) occurred in MSM and report the findings of molecular characterization of HAV strains from the reported cases.

The epidemic is ongoing at the current time.

### Material and Methods

Notification of hepatitis A in Italy is mandatory (Italian Ministerial Decree of 15/12/1990) [17]. A sentinel surveillance system for acute viral hepatitis (SEIEVA – Sistema Epidemiologico Integrato Epatiti Virali Acute) was implemented in 1984 [18]. Case definition is based on clinical and serologic criteria and a standard questionnaire is filled for collecting data on risk factors [18].

Epidemiological surveillance in Puglia is carried out by monitoring all hepatitis cases notified at the regional SEIEVA. Personal variables and risk factors are analyzed by using data collected in the standard questionnaire. In Puglia, the epidemiological surveillance of hepatitis A is accompanied by the systematic collection of a stool sample from each infection case [19]. The samples are analyzed and typed at the regional reference laboratory (Unità Operativa Igiene - Policlinico, Bari, Italy).

RNA was extracted from 200 µl of fecal extract using a commercial kit (High Pure Viral Nucleic Acid, Roche Diagnostics, Milan, Italy). Elution was performed in a volume of 50 µl. The region at the VP1/2A junction of the HAV genome was amplified. HAV-RNA was amplified by reverse-transcription PCR (RT-PCR), followed in the case of negativity by second-round PCR. PCR products were purified using the QIA quick Purification kit (Qiagen).

For positive samples, nucleotide sequence analysis was performed directly on the purified first or second PCR products using primers for amplification and an ABI PRISM Big Dye Terminator Cycle Sequencing Kit (Applied BioSystems, Foster City, CA) in an ABI PRISMA 3130 XL DNA Analyzer (Applied BioSystems).

Phylogenetic analysis was performed using MEGA7 (Molecular Evolutionary Genetics Analysis software –<http://www.megasoftware.net>). The evolutionary history was inferred using the neighbor-joining method. The evolutionary distances were computed using the Maximum Composite Likelihood method.

## Results and Discussion

From January to March 2017, 33 cases of hepatitis A were reported in the Puglia region (Figure 1). Of these cases, 93.9% were male aged from 26 to 52 years (median age 38 years). Three cases were not resident in the Puglia region and 4 were resident in the region but living in Milan (3 cases) and Rome (1 case). Hospitalization was required for all but one case (30 cases were hospitalized in Puglia and 2 cases were hospitalized outside the region). For one case, no data were available since hospitalization was refused. HIV infection was documented in the case of four subjects, HIV-HCV co infection in one subject. HBV infection and syphilis were reported in one case. Fifteen subjects reported having had sexual contacts with men (MSM) in the 8 weeks preceding the onset of symptoms and 4 of these were HIV-positive. Among MSM, international travels were reported in 4 cases and travels in Italy in 8 cases. Two cases reported contacts with a confirmed case of hepatitis A in the 8 weeks before the onset of symptoms. Five MSM reported sexual intercourses with men met through smart phone apps and dating websites and other 5 MSM reported sexual intercourses with occasional anonymous partners.

Of the 16 cases who did not present the sexual risk factor, 14 reported the consumption of raw/undercooked shellfish and 4 international travels. In one case, neither sexual contact nor consumption of unsafe food or travel outside the region was reported.

The molecular characterization was performed on 20 samples (Figure 2). All the analyzed strains belonged to genotype IA; 15 were highly related to each other (Figure 2, empty triangles). In particular, 8 sequences were identical to the sequence VRD\_51\_2016 strain, which is responsible for one of the three clusters of hepatitis A among MSM in Germany and England and for cases in other Italian regions. The sequences of 7 other cases of the same clade showed a similarity rate ranging from 99.3% to 99.8% with other strains and with the VRD\_51\_2016 strain. The high rate of similarity suggests that all cases belong to the same international outbreak in MSM. Seven documented cases were found to be MSM and 3 were positive for HIV-1 infection. In 8 cases, no sexual risk factor was reported; one was positive for HIV-1 infection.

The sequence of 4 cases (Figure 2, empty squares) showed a 100% similarity with the strain RIVM-HAV16-090, which is also related to the epidemic of HAV in MSM in Italy and Europe. All these cases referred to be MSM; one of these was positive for the HIV-1 infection.

In one case (Figure 2, black dot), the sequence showed a high similarity rate with the endemic strains circulating in Puglia in previous years. Seven cases identified between 14 and 21 March reported being MSM and international travel as risk factors. The molecular characterization of these sequences is not available.

Almost all HAV strains characterized in Puglia over the period of January to March 2017 were linked to the outbreaks reported in Europe and Italy among MSM. In Italy, an outbreak of hepatitis A among MSM was reported in 2008-2009 [8]. This outbreak occurred in Rome metropolitan area and almost all HAV infections in MSM were due to a unique strain belonging to genotype IA. HAV strains were phylogenetically related to HAV strains detected before in MSM from Germany and France and also in MSM in Tuscany [8,20]. A high proportion of acute hepatitis A cases was represented by HIV-infected men (14/55). Being MSM and HIV+ were the main risk factors for HAV infection also in the Puglia region.

All cases showed an age ranging from 30 to 50 years. This age class seems to be more at-risk for HAV infection than other age classes probably due to the lack of natural immunity caused by the lower circulation of the virus in recent years in the region. Furthermore, anti-HAV vaccination was not offered to the older age classes in the immunization program of Puglia.

Active and passive immunization within 2 weeks of exposure are strongly recommended as preventive measures for hepatitis A control during an outbreak [10]. In Italy, from the beginning of 2016 the vaccine against hepatitis A for adults is lacking (report from the Italian Agency of Drugs – AIFA). Even in Puglia, the vaccine is currently not available in different provinces.

Although in Puglia the risk of introducing HAV in the food chain is possible due to the particular eating behaviors (consumption of raw seafood) [11,21], infant and children vaccination may have contributed to maintain a “herd effect”. This effect probably has prevented the spread of the epidemic of hepatitis A from imported frozen berries occurred in recent years in Europe and also in Italy and Puglia [22] but could be not sufficient to contain the current epidemic considering the peculiar risk factor associated with this epidemic.

## Conclusions

In this study, we report an ongoing hepatitis A outbreak among MSM in the Puglia region that has started in Italy since 2016. This is the first outbreak of the disease related to such a risk factor in Puglia as anonymous sex, multiple sex partners, use of dating apps and international travel are the main risk factors for infection also in Puglia.

The control of the spread of the infection among MSM, the identification and the vaccination of sexual contacts can be a challenge in this population because of the high risk sexual practices and the need to investigate about the private information [23].

This outbreak highlights the need to improve awareness about hepatitis A among MSM. Condom use is not a safeguard against HAV infection because it does not interrupt the fecal-oral transmission route [24]. The use of other protection tools such as dental dam for oral-anal contacts should be encouraged to avoid HAV transmission. Vaccination among at-risk group and specific communication strategies through social media, apps and venues seem to be the main public health strategies to contain this outbreak.

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