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Serosurveillance of hepatitis A in a region which adopted the universal mass vaccination

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Abstract

Hepatitis A is a common infectious disease worldwide that was endemic in many regions of Southern Italy, such as Apulia region. After a large hepatitis A outbreak occurred between 1996 and 1997, in Apulia an active-free immunization program that was targeted to new-borns and adolescents was started. The aim of this study is to investigate the hepatitis A seroprevalence in the adult Apulian population 18 years after the immunization program introduction, in order to evaluate the risk of new epidemics onset.

The study was carried out from May 2011 to June 2012 among blood donors from Department of Transfusion Medicine and Blood Bank of Policlinico General Hospital in Bari. Participants signed a written consent and filled out a questionnaire including items on demographic characteristics, risk factors, disease memory, and raw food consumption. Serum samples, collected from each patient, were tested for anti-HAV using the chemiluminescent microparticle immunoassay. Vaccination status against hepatitis A was checked on Regional Digital Immunization Registry (GIAVA).

In total 1827 donors agreed to participate (77.7% male) with a mean age of 38.4 ± 11.7 years. However, 1172 (64.1%) donors were seropositive with no difference by sex. The highest proportion of seronegative subjects was in the 27 to 35 years age group. 91.8% of 1-dose vaccinated subjects (n = 190/207; 95%CI = 87.2–95.1) and 96.1% (n = 171/178; 95%CI = 92.1–98.1) of 2-doses vaccinated subjects were immune to the disease. Sensitivity of disease memory in unvaccinated subjects was 14.4% (95%CI = 12.2–16.7), specificity was 97.8% (95%CI = 96.3–98.8), positive predictive value was 91% (95%CI = 85.3–95), and negative predictive value was 42.6% (95%CI = 40–45.2). Raw seafood consumption in unvaccinated subjects was associated with the anti-HAV IgG positivity (OR = 2.1; 95%CI = 1.7–2.7; $z = 7.4$; $P < 0.0001$).

The vaccination program seems to have changed the virus circulation pattern, with a higher seronegativity rate among subjects not included in the vaccination strategy: 67% of susceptible subjects were among younger people aged 27 to 35 years. Immunization program implementation with a catch-up strategy may be needed to avoid a possible increase of hepatitis A incidence and outbreaks in Apulia. Epidemiological surveillance should be continued and vaccination should actively be offer for free to all the cases contacts, in order to prevent new outbreaks onset.

Abbreviations: CO = stored cut-off RLU, GMT = geometric mean titre, HAV = hepatitis A virus, RLU = relative light units, S = sample relative lights units, WHO = World Health Organization.

Keywords: blood donors, food consumption, hepatitis A antibodies, prevalence, seroepidemiological studies

1. Introduction

Hepatitis A is the most common acute viral hepatitis. It is spread throughout the world and is a significant public health problem in many countries, especially in those of low socio-economic level. The estimated incidence by the World Health Organization (WHO) is about 1.4 million cases per year.[1,2] The real burden of infection would be 3 to 10 times higher because hepatitis A is usually asymptomatic in 95% of children under the age of 4 and less than 90% under the age of 6.[3]

The burden of hepatitis A in Europe changes in accordance with the socio-economic level of the countries, with a very low prevalence in Western Europe where less than 50% of population is immune within the age of 30 and intermediate (≥50% is immune within the age of 15) to low (≥50% is immune within the age of 30) prevalence in Eastern and Central Europe countries.[4] Recently 3 important outbreaks of hepatitis A have been described in Europe and during the largest of these epidemics, most cases occurred in Italy (>1200 cases as of March 31, 2014).[5]

Until 2000, WHO classified Italy as a country with an intermediate level of endemicity,[4] but in the last decades, according to SEIEVA (Integrated Epidemiological System for Acute Viral Hepatitis) 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.[6] It was higher in southern Regions most likely because of the common and widely spread habit to eat raw seafood and to the higher environmental fecal contamination.[7]

Apulia is a South-Eastern Region of Italy with a population of about 4 million people. In Apulia, hepatitis A has been endemic

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for a long time and several outbreaks occurred in the past years, with an incidence of more than 30 cases per 100,000 inhabitants during interepidemic periods. Until 1998, a percentage ranging from 12% to 60% of all Italian cases was reported in Apulia and regional seroprevalence rate achieved a value being close to the 50% of the 18-year-old population.[8–9]

A large outbreak occurred in the biennium 1996 to 1997, during which nearly 11,000 cases of hepatitis A and an incidence higher than 130 cases per 100,000 people per year[8] were registered in Apulia. After the outbreak, the Health Regional Authority of Apulia started an active and free immunization program against hepatitis A targeted to new-borns (aged 15–18 months) and adolescents (12 years) in accordance with the WHO recommendations.[9]

Vaccination coverage estimated in 2008 by ICONA survey (National Survey of Vaccination Coverage among Children and Adolescents) were 64.8% (95% CI: 52.7–76.9%) for children born 2006 and 12 to 24 months and 67.6% (95% CI: 58.4–76.8%) for 12-year-old adolescents born in 1992. Routine data from the Local Health Unit vaccination registers are similar: in the cohorts born between 1997 and 2005 the average coverage was 54.1%, while in the cohorts born between 1985 and 2005 it was 60.7%.[10]

Despite the suboptimal immunization coverage achieved, an important reduction of hepatitis A incidence rate was described, that can be explained because of the vaccine-induced herd immunity.[10]

The low incidence rate and suboptimal vaccination coverage achieved between 2005 and 2014 together with the increase of susceptible subjects and the permanence of environmental and behavioral risk factors may determine the onset of new epidemics in the case of re-entry of the pathogen, as Ajelli et al[11] theorized through a mathematical predictive dynamic model.

In this epidemiological context, the authors designed the present study, which investigates the hepatitis A seroprevalence in the adult population of Apulia.

2. Materials and methods

The present study was carried out from May 2011 to June 2012 in the Department of Transfusion Medicine and Blood Bank of Policlinico General Hospital in Bari.

The protocol of the study was approved by the Regional Committee for the Epidemiology (Osservatorio Epidemiologico Regione Puglia). In accordance with Apulian Regional Laws, permission from the Ethics Committee to carry out this study was not necessary given that both data and sera from patients were collected for routine diagnostic testing. The research was carried out in accordance with the Helsinki declaration.

Subjects were enrolled by a convenience sampling. A physician explained the aim of the study to blood donors; a written informed consent was requested and obtained from blood donors who accepted to participate in the survey. The enrolled subjects also answered a short questionnaire, which investigated vaccination, memory of disease, and eating habits.

The sample size was calculated considering the distribution of Apulian population by age classes (18–26; 27–35; 36–45; 46–55; 56–65) in 2012, using seroprevalence data from the first 100 subjects enrolled with a margin of error of 5% and a confidence interval of 95%.[12]

The ARCHITECT HAVAb-IgG chemiluminescent microparticle 2 phases immunoassay technique by Abbott Diagnostics was used to measure anti-HAV antibodies concentration in blood samples. The Architect ARCHITECT HAVAb-IgG assay protocol calculates a result based on the ratio of the sample Relative Lights Units (S) to the stored cut-off RLU (CO) for each sample and control (S/CO = Sample RLU (S) /Cut-off RLU (CO)). We considered reactive (positive) those samples with a relative light units (RLU) ratio (sample RLU/cutoff RLU) ≥ 1.

After the enrolment, we verified vaccination status against hepatitis A checking Regional Digital Immunization Registry (GIAVA).

Questionnaires, forms, and information about vaccination status were computerized using a database created by FileMaker Pro and data were analyzed by STATA MP11.

For data analysis, the chi-square test was used to compare the proportion of subjects who were positive to anti-HAV IgG by the gender and by the age group.

Univariate logistic analysis was performed to evaluate association between the raw seafood consumption and anti-HAV IgG positivity through OR calculation with 95% confidence intervals and the z test. A multivariate analysis was performed in order to consider the possible confounding effect of age and memory of the disease. For all tests, a P value < 0.05 was considered as significant.

3. Results

We enrolled 1827 subjects; 1420 (77.7%) were male. The mean age was 38.4 ± 11.7 years (range: 17–65), and was not different in males (39.4 ± 11.3) and in females (35 ± 12.2; $t = 6.8$, $P = 0.6$). Table 1 shows the distribution of enrolled subjects by the age group and the gender.

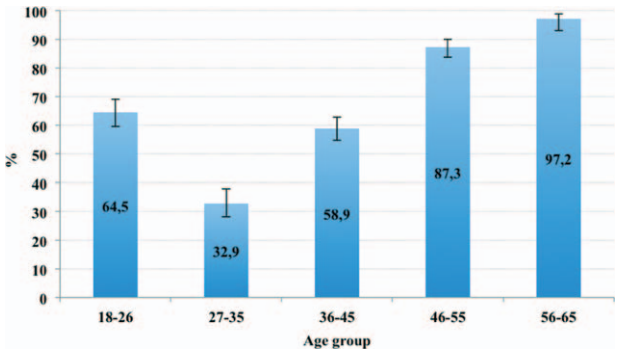
The 64.1% (95% CI = 61.9–66.4) of enrolled subjects was positive for anti-HAV IgG. The proportion of positive subjects was similar both in females (n = 259/407; 63.6%; 95% CI = 58.9 – 68.2) and in males (n = 913/1420; 64.3%; 95% CI = 61.8 – 66.7; chi-square = 0.06; $P = 0.807$).

Table 1

Distribution of enrolled subjects by the age group and the gender.

	Female		Male		Total	
Age group	N	%	n	%	n	%
18–26	142	34.9	233	16.4	375	20.5
27–35	78	19.2	278	19.6	356	19.5
36–45	86	21.1	471	33.2	557	30.5
46–55	83	20.4	311	21.9	394	21.6
56–65	18	4.4	127	8.9	145	7.9
Total	407	100.0	1420	100.0	1827	100.0

Chi-square = 76.2; $P < 0.0001$.



Graph 1. Proportion of HAV IgG positive subjects by age group. HAV = hepatitis A virus.

A higher proportion of immune individuals to hepatitis A was observed in the older age groups and in younger than 26, whereas the highest proportion of seronegative subjects and potentially susceptible to infection was observed in the 27 to 35 years age group (Graph 1; chi-square = 319.2; $P < 0.0001$).

The 11.3% (n = 207; 95%CI = 9.9–12.9) of enrolled people was vaccinated against hepatitis A with at least 1 dose of vaccine and 91.8% of vaccinated subjects (n = 190/207; 95%CI = 87.2–95.1) was immune to the disease. The 9.7% (n = 178; 95%CI = 8.5–11.2) of the sample received 2 doses of vaccine and 96.1% (n = 171/178; 95%CI = 92.1–98.1) of these group showed a protective titer. 1% (n = 2/207; 95%CI = 0.3–3.5%) of vaccinated people had memory of the disease, whereas this proportion rises to 9.6% (n = 155/1620; 95%CI = 8.2–11.1; chi-square = 15.5, $P = 0.00$) in the unvaccinated.

The 54% (n = 113/207; 95%CI = 47.8–61.2) of all the enrolled subjects who got vaccinated with at least 1 dose of vaccine stated they used to eat raw seafood; among unvaccinated subjects this proportion was 65.7% (n = 1064/1620; 95%CI = 63.3–68.0; chi-square = 2.2; $P = 0.13$).

The sensitivity of memory of the disease of hepatitis A in unvaccinated subjects was 14.4% (95%CI = 12.2–16.7), the specificity was 97.8% (95%CI = 96.3–98.8%), the positive predictive value was 91% (95%CI = 85.3–95), and negative predictive value was 42.6% (95%CI = 40–45.2).

Raw seafood consumption in unvaccinated subjects was associated with the positivity of IgG (OR = 2.2; 95%CI = 1.8–2.7; $z = 7.4$; $P < 0.0001$). This association was also confirmed from the multivariate model, which considered the possible confounding effect of age and memory of the disease (OR = 2.1; 95%CI = 1.7–2.7; $z = 6.0$; $P < 0.0001$).

4. Discussion

In our study, carried out in a Region that adopted universal mass vaccination against Hepatitis A since 1998, we detected a seroprevalence rate of 64.1%. Seroprevalence is linked to the age of subjects: only 3% of subjects older than 55-year old people was susceptible to the disease, whereas the highest proportion (67%) of susceptible subjects was among younger people aged 27 to 35 years.

This high seroprevalence in the older people (>55 years) was due to the highest spread of the disease in the pre-vaccination period, which was a consequence of the habit to consume contaminated food matrices (raw sea food).[13]

The highest proportion of susceptible subjects was among young people because they were not included in the vaccination program, started in 1998 and targeted to newborns and 12-years-old people. This was an expected finding and concordant with other previous studies carried out in Europe, which reported 70% to 94% susceptibility rate of those aged <30 years.[14] In other hands, this group revealed a lower seroprevalence because people were not target of vaccination program but experimented the effect of the reduction of HAV circulation due to the vaccination program.

On the other hand, effects of routine immunization program against hepatitis A are evident in the targeted cohorts, that are 18 to 26 year-old people.[5]

The outcomes of our study confirmed the high effectiveness of the hepatitis A vaccine reported in the scientific literature.[15] The collected data showed that this product is immunogenic in more than 90% of people vaccinated with a single dose, and more of 95% of those who received the full course.

The comparison of disease memory and immunity status against hepatitis A among enrolled subjects confirmed the high frequency of the asymptomatic cases, especially in the pediatric age. The finding that many unvaccinated persons have a positive titer, even if they do not remember the got the disease, is concordant with results of other studies.[3] The reliability of the disease memory in symptomatic cases, confirmed by the high values of the specificity and the positive predictive value, is a proof that this people do not require either a further investigation of the immunization status, or the vaccine administration because most of this subjects would be immune against hepatitis A. As a consequence, any preventive intervention is unnecessary.

One of the main strengths of our work was the large sample size enrolled thanks to a high compliance of the donors that joint the study. The opportunity for susceptible donors to get free vaccination against hepatitis A was one of the reasons of the high compliance. A further element to consider was that blood donors are people who usually care for themselves and their own health and what sometimes motivates them to donate blood besides altruism is the possibility to check their health status: in fact, 1 factor that increases their decision to donate is the opportunity to have free blood tests.[16–18] In all likelihood, this could be one of the reasons they easily gave their consent to the study.

At the same time, this element was one of the limitations of this work. As donors are usually healthy people, persons with low socio-economic and health problems may have been under-represented. Considering that hepatitis A seroprevalence is frequently associated with both a low socio-economic and education level and that blood donors are a population generally in good health and middle-high social status.[19–27]

A further limitation consisted in the low proportion of the enrolled female subjects who were significantly less than males because they are allowed to donate half the times than males.

Another limitation of this study was related to the use of a semiquantitative enzyme immunoassay, which is unable to determine Geometric Mean Titre (GMT) of antibodies anti-HAV. The availability of the antibody titer values allows assessing if antibody GMT is related to age and date of vaccination, what is the Long Term Immunogenicity of vaccination and if there are any difference of anti-HAV IgG concentrations between vaccinated subjects and those in possession of natural immunity.

Finally another critical aspect was related to the research of information about immunization status of the enrolled people: the Regional Digital Immunization Registry (GIAVA) was started in 2008 and it includes data about vaccinations that was administered since that time so verification of immunization

status, especially for older subjects, took a longer time because it needed to consult paper registries located in the local vaccination services.

Despite these limitations and on account of the dimension of sample size and the inclusion of people from all areas of Apulia region, the distribution of anti-HAV immunity that came out of our study describes the prevalence in the different age groups and areas of our region and highlights some public health priorities.

During the study period, no specific preventive measures were adopted against Hepatitis A, as it could have had an effect on the disease control. Immunization program implementation with a catch-up strategy may be needed to avoid a possible future increase of hepatitis A incidence and outbreaks in Apulia.[10] Epidemiological surveillance should be continued and vaccination should be actively offered for free to all the contacts of the cases, in order to prevent new outbreaks onset.

Vaccination should also be offered to all susceptible adults each time they happen to get in contact with the vaccination service for other vaccinations, or for certification, licenses renewal and children vaccination. This is very important because in the age group between 27 and 35 years, given the consistent rate of susceptibility found in this study, the danger of propagation of an epidemic event is very high.

Food matrices surveillance, such as seafood, which is a potential vehicle of infection, should be strengthened. Our data show that the consumption of this kind of food is very widespread in Apulia, as it is a tradition and a part of the cultural heritage of this land that should be protected. Several studies showed a minimal viral circulation in mussels that are produced in Apulia and this evidence is confirmed by the low endemicity of the disease. However risk of new epidemics could be related to mussels coming from Spain and Greece that are often sold during periods with higher demand (Christmas, Summer) and that could be a source of infection despite they are declared to be conform to the microbiological food quality indicators.[13]

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