Seroprevalence of hepatitis A in Iranian adolescents: is it time to introduce a vaccine?

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SUMMARY

Universal vaccination of children for hepatitis A virus (HAV) has emerged as a cost-effective strategy to prevent this infection in regions with high incidence of symptomatic disease. Age-specific seroprevalence surveys are practical and reliable methods to estimate the rate of susceptibility in populations, and to help the implementation of vaccination policies. We surveyed the age-specific HAV seroprevalence in a nationally representative sample of Iranian adolescent students aged 10-18 years. Serum samples (n = 2494) were tested by enzyme immunoassay for total anti-HAV antibody. The overall rate of HAV seropositivity was 64% [95% confidence interval (CI), 62–66], which increased sharply from 14.8% (95% CI 7–23) at age 10 years to 72.9% (95% CI 68–78) at age 13 years, without a significant increase up to age 18 years. No significant difference in HAV seroprevalence was observed between males and females (63% vs. 65.1%), or urban and rural areas (63.4% vs. 65.2%); the seropositivity rate was similar in four different socioeconomic regions of Iran. We conclude that the seroconversion rate of HAV is high in Iranian adolescents and therefore mass vaccination of children may be necessary and should be considered by national health authorities.

Key words: Adolescence, hepatitis A, Iran, seroprevalence, vaccination.

INTRODUCTION

Hepatitis A virus (HAV) infection is a major health concern worldwide with a global disease incidence of about 1.5 million cases annually but the rate of asymptomatic infection can be tenfold higher [1]. Clinical symptoms are often age related as infections in children aged <6 years are usually asymptomatic or mild but older children and adults are more likely to present with acute hepatitis sometimes requiring hospital admission; acute liver failure and death are generally rare [2].

Effective and safe vaccines have been available for HAV since 1992, but HAV mass vaccination is only recommended for communities with a high proportion...
of the population at risk of developing symptomatic
disease [3]. Cross-sectional studies on age-specific
seroprevalence of HAV infection to determine en-
demicity level are helpful to highlight susceptible
populations and are reliable measures for vaccine rec-
ommendation by the World Health Organization
(WHO) [4].

According to the WHO recommendation, HAV
mass vaccination is suggested for communities with
a mixed endemicity rate of intermediate (≥50% im-
une by age 15 years, with <90% immune by age 10
years) or low (≥50% immune by age 30 years,
with <50% immune by age 15 years) and also for com-
unities in transition from high (≥90% immune by age 10
years) to intermediate endemicity which are
generally middle-income countries [3]. In these areas
HAV transmission occurs in older age groups with a
high incidence of apparent infection. Community-
wide outbreaks with a significant degree of clinically
important disease are frequently encountered in
these populations [3].

The level of endemicity of HAV infection varies
considerably between countries depending on the
socioeconomic and sanitary conditions of the popula-
tion [5]. In recent years Iran has experienced signifi-
cant improvements in sanitation in both rural and
urban regions [6], which has no doubt impacted on
HAV seroprevalence and therefore re-evaluation of
the national strategy on HAV vaccination is necessary.

To date there is no published nationwide survey on
age-specific seroprevalence of HAV in Iran. A recent
systematic review and meta-analysis performed by
our research group revealed that major seroprevalence
studies in Central and North-Northeast regions of the
country reported conflicting results and were confined
to specific cities, age groups or subpopulations with no
demonstrable trends except high seropositivity [7]. For
instance, more than 85% of the >18-year-old popula-
tion in Tehran, Hormozgan, and Golestan provinces
were seropositive in 2006 [8], which was consistent
with the results of another study in Tehran in 2007
(90-0% seropositivity in those aged 1–83 years) [9]
and in Ghom province in 2011 (78-6% seropositivity
in those aged >15 years) [10].

The objective of this study was to estimate the HAV
seroprevalence rate in adolescents aged 10–18 years
according to their demographic characteristics in a na-
tionwide cluster sampling survey in order to provide
data on levels of endemicity in different regions of
Iran, and inform the evaluation and implementation
of vaccination policies.

METHODS

A multicentre cross-sectional study was conducted on
serum samples obtained and stored during a school-
unbased nationwide health survey (CASPIAN-III)
which was conducted in Iranian students aged 10–18
years from urban and rural areas [11]. CASPIAN-III
was approved by ethics committees and other relevant
national regulatory organizations. Written informed
consent was obtained from parents of students for
venepuncture and use of blood samples and demo-
graphic data in research projects. The current study
was approved by the ethical committee of Isfahan
University of Medical Sciences, Isfahan, Iran (project
no. 292221).

Samples were selected by a multistage, cluster sam-
ping method from 27 of the 30 provinces of the coun-
try. Stratification was performed in each province
according to area of residence (urban/rural), and
school grade (elementary/intermediate/high school).
The sampling was proportional to the size of the co-
hort with equal sex ratio in numbers of boys and
girls from each province, and proportional to their
ratios in urban and rural areas in each school grade.
Cluster sampling with equal clusters was used in
each province to reach the necessary sample size.

The minimum sample size was calculated by consider-
ing the level of confidence of 95%, with an expected
prevalence of 40%, and a precision of 10%, multiplied
by age groups, which was calculated as 830 samples.

In the primary study, serum samples were tested in
regional laboratories and samples frozen at -70 °C,
with datasets, were sent to the Infectious Diseases
and Tropical Medicine Research Centre, Isfahan
University of Medical Sciences. A preliminary assess-
ment showed that some samples were unsuitable hav-
ing been previously used for biochemical tests or were
not identifiable due to errors in coding. Consequently
samples and representative data from 17 provinces
were available for the current study and represented
coverage of about 70% of the Iranian population.
Total anti-HAV antibody (IgG and IgM) was detected
using a competitive enzyme immunoassay (ELISA) kit
(EIA; Dia.Pro, Italy). A ratio of cut-off value to
OD450nm of the sample >1·1 was considered as
positive.

Data were analysed by SPSS-PC v. 16·0 (SPSS Inc.,
USA). The 95% confidence interval (CI) was calculated.
χ2 test and logistic regression analysis were
used to identify associations of age, gender, place
and region of residence with HAV seroprevalence.
Results were interpreted in the form of odds ratio (OR) and 95% CI. \( P < 0.05 \) was considered statistically significant.

The provinces of Iran have been categorized into four regions (Fig. 1) based on a combination of geography and socioeconomic status (SES) such as years of education, employment rates, and family assets [12]. The Central region (seven provinces with \(~32.4\)% of the total national population) has the highest SES; the West region (14 provinces, 38.4% of the population) has moderately high SES; the North-Northeast region (five provinces, 19% of population) moderately low SES, and the Southeast region (four provinces, 10.2% of population) has the lowest SES [12–13].

**RESULTS**

Overall, 2562 subjects were included from the CASPIAN-III project database, but 68 stored samples were excluded owing to insufficient volumes for testing. Finally, samples of 2494 subjects (50.2% boys, 49.8% girls) from urban (66.2%) and rural (33.8%) populations were included in the study. Sex and residence ratios were consistent with the ratios of the national population in the year of the study, which were 50.9% vs. 49.1% for males and females, and 68.4% vs. 31.6% for urban and rural areas, respectively [13].

The overall rate of HAV seropositivity was 64% (95% CI 62–66). The seroprevalence rate increased from 14.8% (95% CI 7–23) in subjects aged 10 years to 72.9% (95% CI 68–78) at age 13 years. No significant change in seroprevalence was documented up to the age of 18 years. In the logistic regression analysis, only the increase in age was a risk factor for HAV seropositivity (per years: OR 1.23, 95% CI 1.19–1.27, \( P < 0.001 \)) and no relationship was documented between gender (\( P = 0.62 \)), place of residence (\( P = 0.55 \)), or SES of the region of residence (\( P = 0.23 \)) with HAV infection (Table 1). To determine if a rapid increase in HAV seroprevalence in subjects aged 13–15 years was common in all regions a \( \chi^2 \) test was performed for different age groups across
This showed a significant difference between age groups in all regions ($P < 0.05$) with seropositivity rates ranging from 44.4% to 70.0% at age 10–12 years and rising to ∼70% at age 13–15 years in all regions (Table 2).

**DISCUSSION**

This study revealed that the overall HAV seroprevalence in Iranian children and adolescents aged 10–18 years was 64% with specific rates of 14.8% in those aged 10 years, and 71.1% in those aged 15 years. Iran can therefore be considered to be a country with an intermediate HAV endemicity level according to the WHO definition [3]. Furthermore, while the majority (85.2%) of school children aged 10 years were susceptible to HAV infection, more than 60% of them had become infected by age 13 years. In this situation, the risk of symptomatic and complicated HAV infection in adolescents in the future is proposed to be high.

Prevention of HAV can be achieved by universal immunization of children. Until now, more than 20 countries including Bahrain, Iraq, Saudi Arabia and

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Positive cases, $n/N$</th>
<th>Percentage (95% CI)</th>
<th>OR (95% CI)</th>
<th>$P$ value*</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>10</td>
<td>12/81</td>
<td>14.8 (7–23)</td>
<td>1.23 (1.19–1.27)</td>
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<tr>
<td>11</td>
<td>104/277</td>
<td>37.5 (32–44)</td>
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<tr>
<td>12</td>
<td>244/432</td>
<td>56.5 (52–61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>210/288</td>
<td>72.9 (68–78)</td>
<td></td>
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<tr>
<td>14</td>
<td>125/176</td>
<td>70.0 (64–78)</td>
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<td>15</td>
<td>86/121</td>
<td>71.1 (62–79)</td>
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<td>16</td>
<td>277/393</td>
<td>70.5 (66–75)</td>
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<td>17</td>
<td>274/384</td>
<td>71.4 (67–76)</td>
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<tr>
<td>18</td>
<td>265/342</td>
<td>77.5 (73–82)</td>
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<td></td>
</tr>
<tr>
<td>Gender†</td>
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</tr>
<tr>
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<td>788/1250</td>
<td>63.0 (60–66)</td>
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<tr>
<td>Female</td>
<td>808/1241</td>
<td>65.1 (62–68)</td>
<td>1.05 (0.88–1.23)</td>
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<tr>
<td>Residency†</td>
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<td>1045/1649</td>
<td>63.4 (61–66)</td>
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<tr>
<td>Rural</td>
<td>550/843</td>
<td>65.2 (62–68)</td>
<td>1.06 (0.88–1.26)</td>
<td></td>
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<tr>
<td>Region†</td>
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<td></td>
<td></td>
<td>0.230</td>
</tr>
<tr>
<td>Central</td>
<td>427/635</td>
<td>67.2 (64–71)</td>
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<tr>
<td>West</td>
<td>830/1314</td>
<td>63.2 (61–66)</td>
<td>0.82 (0.66–1.01)</td>
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</tr>
<tr>
<td>North-Northeast</td>
<td>261/ 420</td>
<td>62.2 (57–67)</td>
<td>0.79 (0.61–1.03)</td>
<td></td>
</tr>
<tr>
<td>Southeast</td>
<td>79/125</td>
<td>63.2 (55–72)</td>
<td>0.83 (0.55–1.25)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1597/2494</td>
<td>64.0 (62–66)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, confidence interval.

* By logistic regression analysis.

† Missing value present.

<table>
<thead>
<tr>
<th>Region</th>
<th>Age 10–12 years</th>
<th>Age 13–15 years</th>
<th>Age 16–18 years</th>
<th>$P$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>97/199 (48.7)</td>
<td>123/159 (77.4)</td>
<td>207/277 (74.7)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>West</td>
<td>190/428 (44.4)</td>
<td>183/264 (69.3)</td>
<td>457/622 (73.5)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>North-Northeast</td>
<td>55/124 (44.4)</td>
<td>90/128 (70.3)</td>
<td>116/168 (69.0)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Southeast</td>
<td>18/39 (46.2)</td>
<td>25/34 (73.5)</td>
<td>36/52 (69.2)</td>
<td>0.027</td>
</tr>
<tr>
<td>Total</td>
<td>360/790 (45.6)</td>
<td>421/585 (72.0)</td>
<td>816/1119 (72.9)</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

* By $\chi^2$ test.
Qatar in the Middle East have integrated HAV vaccination in their national immunization programmes [14]. Several studies have demonstrated that introducing a two-dose inactivated HAV vaccine for children would result in a marked decrease in acute HAV incidence in all age groups. Such studies in the United States [15, 16] and China [17] have shown a reduction of about 90% in acute HAV incidence a few years after introduction of mass vaccination. Likewise in Argentina, with an intermediate endem-icity, implementation of a single-dose vaccine schedule in 12-month-old children in 2005, resulted in reduction of incidence of HAV from 6–12 cases to <1 case/100,000 population per year in 2010 [18]. Furthermore, cost-effectiveness studies generally support the use of universal vaccination in regions with high incidence of the disease [19].

In Iran, hepatitis A is a substantial disease, but as the reporting system is mainly hospital-based, it is difficult to identify the true incidence of this infection. As vaccination programmes are totally funded by gov-ernment, there is a need for studies of the cost-effectiveness of mass HAV vaccination as well as for the establishment of a comprehensive national surveil-lance system to closely monitor the incidence of the disease. Such measures are considered as an important health priority for the country, and should be consid-ered further by healthcare authorities. As similar rates of infection existed at different ages between regions with diverse SES, all of which were in the category of intermediate endemicity, the current findings suggest that a single vaccination strategy would be appro-priate for the whole country.

In this study, the rate of HAV seropositivity was not related to the place of residence. Currently about 98% of urban and 90% of rural populations in Iran are supplied with hygienic drinking water, and almost the whole population has access to sanitation facilities [6]. Moreover, the national primary healthcare system pro-vides personal and environmental training specifically in rural areas. Such measures together might explain the non-significant differences in HAV seroprevalence between urban and rural areas of the country.

Our study showed that the seroprevalence of HAV in Iranian adolescents was comparable in both sexes which is consistent with several studies in Iran [7] and other reports from the Middle East, e.g. Egypt [20], Iraq [21], and Saudi Arabia [22], suggesting a similar exposure to contaminated food and water.

The reason for the sharp increase in HAV sero-positivity from ages 10 (14.8%) to 13 (72.9%) years remains to be determined. It might be explained by a previous large outbreak of HAV infection, but no related evidence was found in review of local literature and governmental data, and therefore might reflect asymptomatic infection in younger age groups. Our findings propose that a campaign to vaccinate high-risk age groups, i.e. adolescents aged <13 years should be performed in Iran, as well as integration of HAV vaccination in the national vaccination programme.

Our study has some limitations; we were unable to include inhabitants of all provinces as some samples originating from the earlier project were already used or were not identifiable, thus possibly introduc-ing a bias towards high-rank provinces. However, as coverage exceeded 70% of the national population from different SES, our findings can be extrapolated to the national level. Furthermore, although inclusion of subjects in other age groups could have made inter-pretation of the data more clear, we focused on the most important age group (10–15 years) for determining the level of endemicity.

In conclusion, the results of this study show an intermediate endemicity for HAV infection in Iran. We found significant susceptible early adolescent populations which could experience symptomatic in-fection in the forthcoming years. Therefore, universal HAV immunization as well as a campaign to vaccin-ate early adolescents would be efficient strategies to re-duce the burden of HAV disease in the country.

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DECLARATION OF Interest
None.

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