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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

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of the population at risk of developing symptomatic infection [3]. Cross-sectional studies on age-specific seroprevalence of HAV infection to determine endemicity level are helpful to highlight susceptible populations and are reliable measures for vaccine recommendation 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% immune 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 communities 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 population [5]. In recent years Iran has experienced significant 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 population 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 nationwide 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-based 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 demographic 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 sampling method from 27 of the 30 provinces of the country. 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 cohort 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 considering 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 assessment showed that some samples were unsuitable having 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 OD_{450nm} 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. χ^2 test and logistic regression analysis were used to identify associations of age, gender, place and region of residence with HAV seroprevalence.

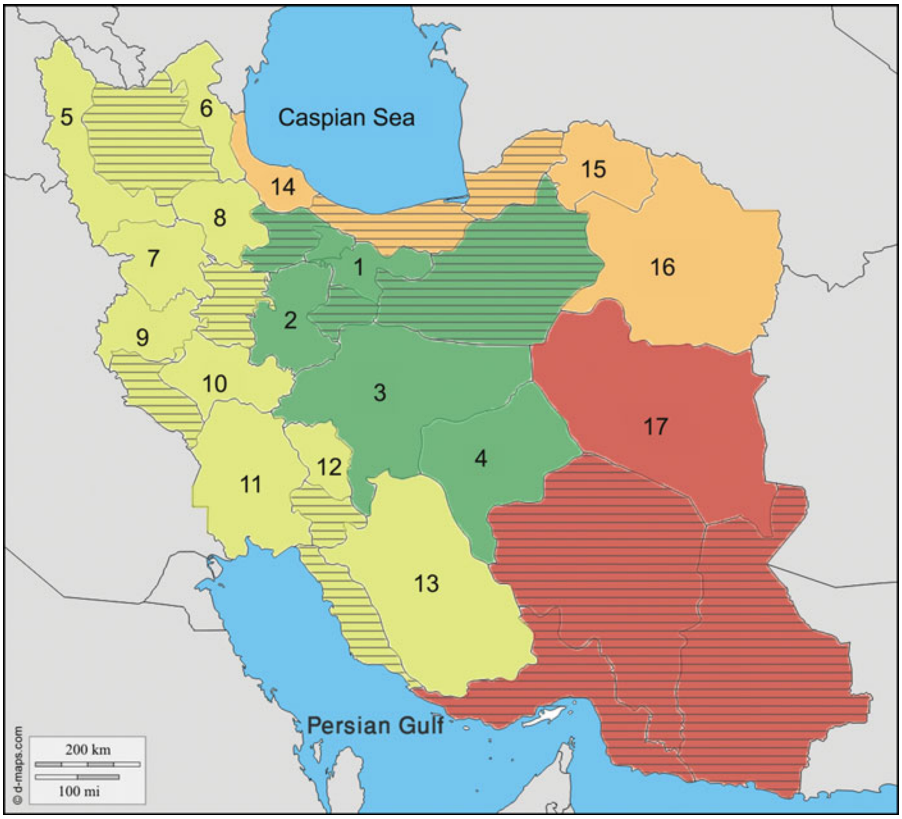

Fig. 1. Iran's provinces and regions. Green, Central; yellow, West; orange, North-Northeast; red, Southeast; shaded area, provinces not included in the study. 1, Tehran and Alborz (they were a single province at the time of this study); 2, Markazi; 3, Isfahan; 4, Yazd; 5, West Azerbaijan; 6, Ardabil; 7, Kordestan; 8, Zanjan; 9, Kermanshah; 10, Lorestan; 11, Khuzestan; 12, Chaharmahal and Bakhtiari; 13, Fars; 14, Gilan; 15, North Khorasan; 16, Razavi Khorasan; 17, South Khorasan.

Results were interpreted in the form of odds ratio (OR) and 95% CI. $P < 0{\cdot}05$ 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, $P < 0{\cdot}001$) and no relationship was documented between gender ($P = 0{\cdot}62$), place of residence ($P = 0{\cdot}55$), or SES of the region of residence ($P = 0{\cdot}23$) 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 χ^2 test was performed for different age groups across

Table 1. *Seroprevalence of hepatitis A in Iranian students*

Demographic characteristic	Positive cases, *n*/*N*	Percentage (95% CI)	OR (95% CI)	*P* value*
Age (years)			1·23 (1·19–1·27)	<0·001
10	12/81	14·8 (7–23)		
11	104/277	37·5 (32–44)		
12	244/432	56·5 (52–61)		
13	210/288	72·9 (68–78)		
14	125/176	71·0 (64–78)		
15	86/121	71·1 (62–79)		
16	277/393	70·5 (66–75)		
17	274/384	71·4 (67–76)		
18	265/342	77·5 (73–82)		
Gender†				0·623
Male	788/1250	63·0 (60–66)	1	
Female	808/1241	65·1 (62–68)	1·05 (0·88–1·23)	
Residency†				0·550
Urban	1045/1649	63·4 (61–66)	1	
Rural	550/843	65·2 (62–68)	1·06 (0·88–1·26)	
Region†				0·230
Central	427/635	67·2 (64–71)	1	
West	830/1314	63·2 (61–66)	0·82 (0·66–1·01)	
North-Northeast	261/ 420	62·2 (57–67)	0·79 (0·61–1·03)	
Southeast	79/125	63·2 (55–72)	0·83 (0·55–1·25)	
Total	1597/2494	64·0 (62–66)		

OR, Odds ratio; CI, confidence interval.
* By logistic regression analysis.
† Missing value present.

Table 2. *Hepatitis A seroprevalence in different regions and age groups of Iran*

	Positive cases, *n*/*N* (%)			
Region	Age 10–12 years	Age 13–15 years	Age 16–18 years	*P* value*
Central	97/199 (48·7)	123/159 (77·4)	207/277 (74·7)	<0·000
West	190/428 (44·4)	183/264 (69·3)	457/622 (73·5)	<0·000
North-Northeast	55/124 (44·4)	90/128 (70·3)	116/168 (69·0)	<0·000
Southeast	18/39 (46·2)	25/34 (73·5)	36/52 (69·2)	0·027
Total	360/790 (45·6)	421/585 (72·0)	816/1119 (72·9)	<0·000

* By χ^2 test.

the regions. This showed a significant difference between age groups in all regions ($P < 0{\cdot}05$) with seropositivity rates ranging from 44·4% to 48·7% 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

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 endemicity, 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 government, there is a need for studies of the cost-effectiveness of mass HAV vaccination as well as for the establishment of a comprehensive national surveillance system to closely monitor the incidence of the disease. Such measures are considered as an important health priority for the country, and should be considered 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 appropriate 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 provides 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 seropositivity 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 introducing 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 interpretation 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 infection in the forthcoming years. Therefore, universal HAV immunization as well as a campaign to vaccinate early adolescents would be efficient strategies to reduce the burden of HAV disease in the country.

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DECLARATION OF INTEREST

None.

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