

## Original Article

## Seroprevalence and Risk Factors of Hepatitis A Virus Infection in Iran: a Population Based Study

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**Background:** In older studies, the seroprevalence of hepatitis A virus infection has been reported to be over 95% in Iranians. Most of these studies were performed on volunteer blood donors. Studies on the general population are sparse. The purpose of this study was to determine the current seroprevalence of hepatitis A virus infection in the general population of Iran.

**Methods:** During 2006, 1869 subjects between 18 and 65 years of age were randomly selected from the general population of three Iranian provinces (Tehran, Golestan, and Hormozgan). Subjects were interviewed and a plasma sample was obtained for serologic testing for anti-hepatitis A virus. Univariate and multivariate analysis was performed to identify risk factors.

**Results:** The seroprevalence of hepatitis A virus in Tehran, Golestan and Hormozgan was 85%, 99%, and 96%, respectively. The overall seroprevalence of hepatitis A virus in the general population of the three provinces studied was 86% and did not differ between the two genders. The prevalence in younger subjects and in urban populations was under 70%. In multivariate analysis, older age, being married, and level of the father's education was associated with hepatitis A virus seropositivity.

**Conclusion:** The seroprevalence of hepatitis A virus still appears to be too elevated for recommending routine vaccination in the general population. However, the trend towards a lower prevalence in younger age groups and people from urban areas points towards the possible benefit of vaccination in these subgroups.

*Archives of Iranian Medicine, Volume 13, Number 2, 2010: 99 – 104.*

**Keywords:** Hepatitis A • Iran • prevalence • seroepidemiologic studies

### Introduction

Hepatitis A (HAV) is one of the most common viral infections of the liver with a worldwide distribution. The pattern of this disease includes infection during early childhood followed by life-long immunity.<sup>1</sup> During recent decades, due to an improvement in

sanitation, the age of infection by this virus has shifted from early childhood to adolescence or even later.<sup>1-3</sup> Although this shift indicates better sanitation and hygiene, there is an important consequence. HAV, when acquired in childhood, is a very benign disease in which over 70% of the patients are asymptomatic and fulminant liver failure is extremely rare.<sup>4, 5</sup> Thus, vaccination for HAV is generally not recommended in communities where new infections are mainly limited to children. In contrast, when the infection occurs in adulthood a much more prolonged and aggressive course is seen. The rate of jaundice and fulminant liver failure is much higher.<sup>4-6</sup> Therefore, in communities where a significant percentage of adults have no immunity, the increased morbidity that occurs with HAV

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Accepted for publication: 13 January 2010

amongst adults might justify vaccination, especially when travelling to an endemic area.<sup>2</sup>

Despite the availability of a very effective and safe vaccine, prevention of HAV infection is still not on the health agenda of most developing countries based on the assumption that most individuals acquire natural immunity at an early age.

In Iran, a study in 1980 indicated that 95% of the blood donors had serologic markers of a previous infection with HAV.<sup>7</sup> Accordingly, routine vaccination against HAV is not currently recommended in Iran. However the current status, especially in the general population, is uncertain. During the last few decades, Iran has witnessed a substantial improvement in the standard of living and general health, even in remote rural areas.<sup>8</sup> Thus we might expect an increase in the percent of adults susceptible to HAV.<sup>9</sup> Such an increased susceptibility, if of a large enough magnitude, might justify routine vaccination of children.

The aim of the following study is to investigate the current seroprevalence of HAV in the general population of Iran.

## Patients and Methods

### Study population

Subjects were selected from the general population of three Iranian provinces. The three provinces were Golestan in northeastern Iran, Tehran north-central Iran, and Hormozgan in southern Iran. We included only subjects of Iranian nationality that were permanent inhabitants of the household whose ages were between 18 and 65. Subjects not consenting to the study were excluded. Information about Iran and the three provinces studied is given in Table 1.

### Sampling and sample size

The study was performed on sera collected during a larger study in 2006 which evaluated common liver disease in Iran. The original study was designed for diseases with an estimated prevalence as low as 0.5%, therefore a total

number of 6583 subjects were enrolled by clustered random sampling. In the original study, 100 clusters were selected from each province. Each cluster included the first 20 or 25 eligible subjects who lived within a block of adjacent households. The first household of each cluster was randomly selected using postal or family registry codes. Plasma samples were obtained from each subject and a questionnaire including common risk factors was completed. Further details of the sampling methods and data collection can be found elsewhere<sup>10</sup>.

The estimate of HAV seroprevalence in Iran, according to previous studies, was 95%.<sup>7,11</sup> A conservative sample size of 2000 was selected to estimate this rate with an alpha of 0.05. For our sample selection, we obtained the list of participants in the original study and chose 30% of this list by systematic random sampling. This method enabled us to overcome sampling bias.

### Laboratory tests

Serum samples from selected participants were transferred to the Iran Blood Transfusion Organization (IBTO) Research Center where they were tested for total anti-HAV (DiaPro Diagnostic Bioprobes srl, Milano, Italy).

### Statistical analysis

The age specific prevalence of HAV infection was calculated in each province. For the entire population, the prevalence of HAV infection was calculated using a weighted average proportional to the population size in each province. Weighted logistic regression was used to calculate the effect of potential risk factors on HAV prevalence. A weighted multivariate logistic regression model was used on the pooled data of Tehran and Hormozgan provinces in order to measure the independent effect of risk factors. Golestan was not included in this model since data on risk factors were missing for too many subjects in this province. In this analysis, data was weighted according to the proportion of rural and urban population within each province. In all analyses,

**Table 1.** Census information on the three Iranian provinces studied\*

	Area (km <sup>2</sup> )	Population	Percent urban	Percent male	Literacy
Iran	1,648,195	70,495,782	68.5%	50.9%	84.0%
Tehran	18,814	13,422,366	91.3%	51.4%	91.3%
Hormozgan	70,697	1,403,674	47.1%	51.7%	82.4%
Golestan	20,367	1,617,087	49.2%	49.7%	82.1%

\*Source: Iran National Population and Housing Census, 2006; [http://www.sci.org.ir/portal/faces/public/sci\\_en](http://www.sci.org.ir/portal/faces/public/sci_en), reproduced from Merat et al.<sup>10</sup>

the 95% confidence interval was adjusted for clustered sampling with cluster as the primary sampling unit. Analyses were done by STATA 10.0 (StatCorp, College Station, TX).

### Ethics

Data was saved with no reference to subjects' names. Written and informed consent was obtained from all subjects. The study protocol and consent forms were approved by the Institutional Review Board of the Digestive Disease Research Center, Tehran University of Medical Sciences.

### Results

A total of 1869 serum samples were studied. The characteristics of the study population and the proportion selected from each province are detailed in Table 2.

**Table 2.** Characteristics of participants

	Subjects interviewed	Samples randomly selected	Percent male	Percent rural	Mean age±SD (yr)
Tehran	2561	791	39.7%	2.7%	35.3±13.3
Hormozgan	1987	453	43.3%	0%	33.4±11.6
Golestan	2035	625	34.1%	37.6%	40.9±12.9
<b>Total</b>	<b>6583</b>	<b>1869</b>	<b>38.7%</b>	<b>13.7%</b>	<b>36.7±13.1</b>

The prevalence of anti-HAV in the three provinces ranged from 85% in Tehran to 99% in Golestan. There was no significant difference between the two sexes. After adjusting for the population of each province, the overall seroprevalence of anti-HAV for Iran was 86% (Table 3).

**Table 3.** The prevalence of positive anti-HAV in the three provinces

	Tehran	Hormozgan	Golestan	Total*
HAV-AB	85%	96%	99%	86%
Male	85%	95%	100%	86%
Female	85%	97%	99%	86%

\*Totals adjusted for population of provinces

We observed that in Golestan province, the prevalence of anti-HAV approximated 100% with almost no variation by age; whereas in Tehran, the younger age groups had a significantly less prevalence (Figure 1A). Similarly, all age groups in the rural population were virtually 100% anti HAV positive, whereas in the urban population, the younger age groups showed less prevalence (Figure 1B). The aggregated age-specific prevalence for the study population is depicted in Figure 1C. It is seen that in both males and females, the rate of HAV seropositivity rapidly increased by age and reached a plateau close to

100% near age 40.

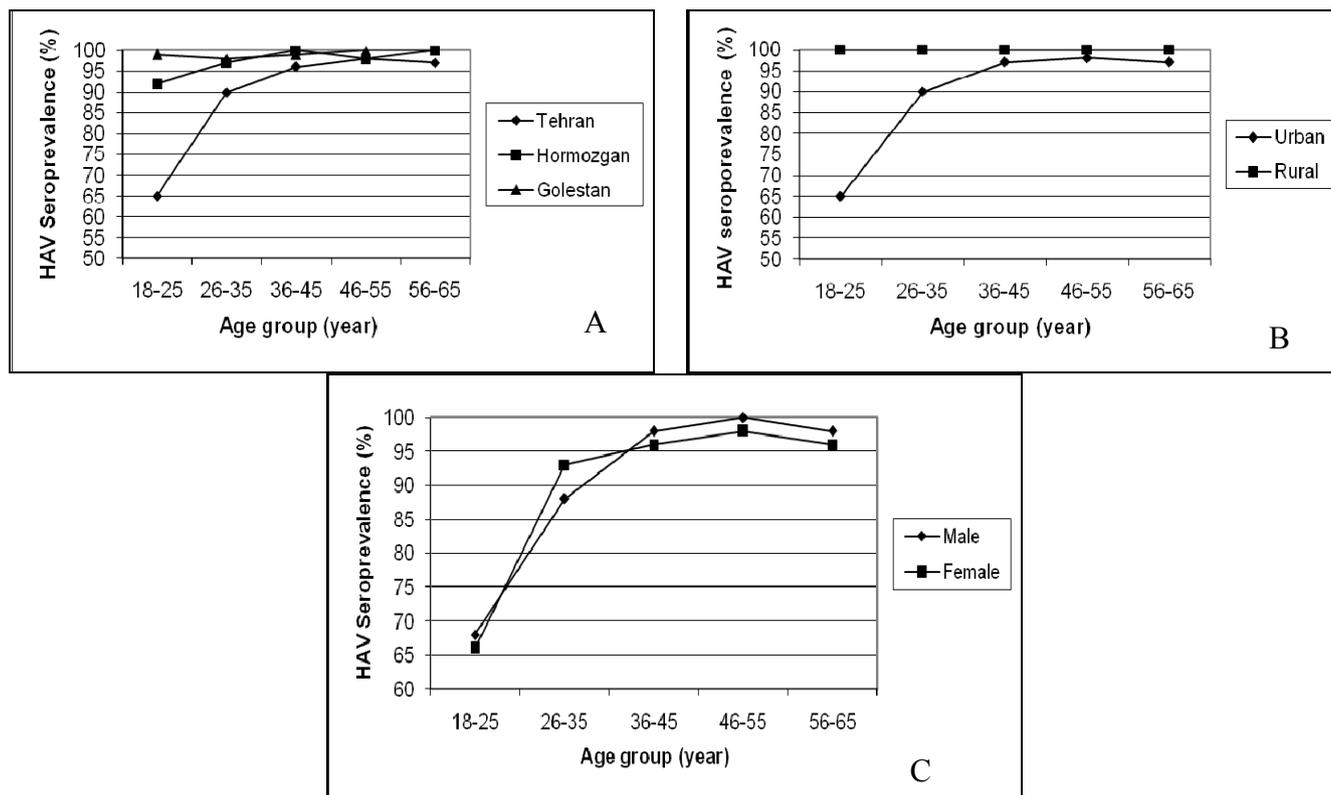
In univariate analysis, factors associated with anti-HAV included: living in a rural area, not living in Tehran, older age, married, a history of traditional phlebotomy (cupping), and less education of the subject, mother, or father (Table 4). In the multivariate analysis increased age, less father's education, and being married remained significant (Table 5). Risk-factor data for Golestan was not collected, thus this province has been excluded from most of the analyses in Tables 4 and 5.

### Discussion

HAV is highly prevalent in the Iranian population. Previous reports, mostly based on healthy blood donors, report a rate of 95% or more

in adults.<sup>7,11</sup> We have observed a slightly less seroprevalence of 86% almost 20 years later. Although our data has been collected from only three provinces, in the absence of better data, it is currently the best estimate for the seroprevalence of HAV in the Iranian general population. In agreement with our findings, a recent study on the

prevalence of anti-HAV in healthy blood donors has reported exactly the same figure of 86%.<sup>12</sup> This change might be related to the improvement in living conditions which has occurred in Iran during recent decades.<sup>8</sup> The improvement is most visible in younger subjects who live in urban areas where the prevalence is close to 65%. We did not study subjects younger than 18 years old, but in a study on children referring to pediatric hospitals in Tehran; the observed trend of a lesser prevalence in younger subjects continues to rates as low as 26% for children aged 10 – 15 and 21% for those younger than 10.<sup>13</sup>



**Figure 1.** Age-specific prevalence of HAV infection: **A)** by province, **B)** by location, and **C)** by sex

In multivariate analysis, father's education was found to be a negative predictor of anti-HAV (Table 5). A high prevalence of HAV has been frequently viewed as a marker of poor hygiene or socioeconomic status.<sup>1,9,14</sup> It would be conceivable that higher education levels of the father (and family) would lead to better socioeconomic status, better observation of sanitation, and subsequently, less chance of exposure to HAV. Another surrogate marker of poor general hygiene is infection with *Helicobacter pylori* (HP).<sup>15,16</sup> Interestingly, a recent study on the seroprevalence of HP in Tehran has similarly observed that better family education is associated with less prevalence of HP infection.<sup>17</sup> Similar patterns of spread for HP and HAV have been previously reported,<sup>18</sup> although conflicting reports exist.<sup>19</sup>

Another finding in our study was that married subjects had a significantly higher rate of HAV seropositivity. Previous studies from Iran have not studied or reported such an association. This finding might be explained by the fact that married subjects in Iran typically have a larger number of social and household contacts and are therefore, probably more exposed to HAV.

We also observed significant differences between the three provinces studied. The lowest seroprevalence was observed in Tehran, the

capital, and the highest in Golestan, with a more traditional life style.<sup>8</sup> Such differences in seroprevalence might well be attributed to the vast variations in living conditions and ethnicity.

It should be noted that we had no samples from the rural area of Hormozgan. Thus the reported numbers only represent the urban population of this province. The rate for the rural populations of Tehran and Golestan were both 100%. If we assume the same for rural Hormozgan, considering the ratio of rural population, we can presume a total seroprevalence of approximately 98% for this province which is quite close to Golestan. The socioeconomic development of Golestan and Hormozgan are roughly comparable.

Making decisions for controlling HAV and providing a national vaccination guideline is a complex process which depends on many variables including disease burden, feasibility, cost-effectiveness, and vaccine efficacy, among others.<sup>20</sup> The age at which vaccination should be performed and whether or not serologic testing is done before vaccination are questions which need to be addressed.<sup>21</sup> Universal vaccination of young children (2 – 4 years old) is probably the most effective strategy, but at the same time, the most expensive.<sup>22</sup> Furthermore, there are concerns that passive immunity induced at this age might not last

**Table 4.** Risk factors associated with HAV infection in univariate analysis

	Number (%)	Anti-HAV positive	
		Odds ratio (95%CI)	P-value
Province			
Tehran	674 (85%)	1	
Hormozgan	437 (96%)	4.7 (2.8–8.1)	<0.001
Golestan	621 (100%)	26.9 (9.9–73.4)	<0.001
Gender			
Female	1064 (86%)	1	
Male	668 (86%)	1 (0.7–1.5)	0.9
Location			
Urban	1476 (86%)	NA	
Rural	256 (100%)	NA	<0.001
Age group (years)			
18–29	573 (73%)	1	
30–45	644 (94%)	5.7 (3.4–9.5)	<0.001
46–65	515 (98%)	20.1 (7.4–54.9)	<0.001
Education*			
< 5 years	354 (98%)	1	
5–12 years	587 (83%)	0.08 (0.02–0.25)	<0.001
> 12 years	155 (77%)	0.05 (0.02–0.18)	<0.001
Marital status*			
Unmarried	248 (64%)	1	
Married	863 (94%)	8.4 (5.5–13.0)	<0.001
Traditional phlebotomy*			
No	998 (84%)	1	
Yes	110 (94%)	2.9 (1.3–6.4)	0.008
Father's education*			
< 5 years	862 (93%)	1	
5–12 years	213 (72%)	0.19 (0.12–0.29)	<0.001
> 12 years	33 (50%)	0.08 (0.04–0.15)	<0.001
Mother's education*			
< 5 years	934 (93%)	1	
5–12 years	160 (66%)	0.15 (0.10–0.24)	<0.001
> 12 years	11 (44%)	0.06 (0.02–0.18)	<0.001

into adulthood where it is most needed. Vaccination of older children (12 – 16 year olds) is another option. Depending on the epidemiology of HAV in the community in question, many children may have acquired natural immunity by this age. Thus, prior serologic testing might reduce costs.<sup>22</sup> The HAV seroprevalence of 86% which we have observed in this study is still high and might not justify a universal vaccination program. Nevertheless, it does indicate an increase in the number of susceptible subjects, especially in the younger urban population.

We conclude that although it is obvious that

Iran is experiencing a shift in the epidemiology of HAV infection, the seroprevalence is still very high. In rural or recently established urban areas that have more important health priorities, vaccination against HAV might not be warranted, especially for the older population. But in the urban population, especially in large cities such as Tehran, vaccination might be recommended for children or selected adult subjects and should be available in health centers.

#### Conflict of interest statement

No competing interest declared.

**Table 5.** Risk factors associated with anti-HAV in multivariate analysis\*

	OR (95% CI)	P-value
Age (for each 10 years)	2.2 (1.5–3.3)	<0.001
Hormozgan vs. Tehran	5.1 (2.9–8.9)	<0.001
Father's Education		
<5 years	1	
5–12 years	0.4 (0.2–0.6)	<0.001
>12 years	0.15 (0.07–0.33)	<0.001
Being married	2.1 (1.2–3.7)	0.008

Variables entered into model: age, province, personal education, father's education, mother's education, marital status, traditional phlebotomy

### Ethical approval this has previously been discussed in the Patients and Methods section.

The study protocol and the consent forms were reviewed and approved by the Institutional Review Board of the Digestive Disease Research Center, Tehran University of Medical Sciences.

### Acknowledgements

We wish to thank Bandar-Abbas NAJA Khatamol-Anbia Hospital and the Gonbad Cohort Study Center for their help in gathering data and blood samples. We also express our gratitude to Saideh Raman, Behnaz Amoohossein, Mina Moghtadaie, and Roshanak Shamriz from IBTO Research Center, for their technical assistance. The study was supported jointly by the Digestive Disease Research Center of Tehran University of Medical Sciences and Iran Blood Transfusion Organization Research Center.

### References

- Jacobsen KH, Koopman JS. Declining hepatitis A seroprevalence: a global review and analysis. *Epidemiol Infect.* 2004; **132**: 1005 – 1022.
- Hendrickx G, Van Herck K, Vorsters A, Wiersma S, Shapiro C, Andrus JK, et al. Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. *J Viral Hepat.* 2008; **15** (suppl 2): 1 – 15.
- Melnick JL. History and epidemiology of hepatitis A virus. *J Infect Dis.* 1995; **171** (suppl 1): S2 – S8.
- Centers for Disease Control and Prevention. Hepatitis Surveillance Report No. 58. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2003: 1.
- Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. *Vaccine.* 1992; **10** (suppl 1): S15 – S17.
- Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. *Am J Epidemiol.* 1985; **122**: 226 – 233.
- Farzadegan H, Shamszad M, Noori-Arya K. Epidemiology of viral hepatitis among Iranian population—a viral marker study. *Ann Acad Med Singapore.* 1980; **9**: 144 – 148.
- Pourshams A, Saadatian-Elahi M, Nouraie M, Malekshah AF, Rakhshani N, Salahi R, et al. Golestan cohort study of oesophageal cancer: feasibility and first results. *Br J Cancer.* 2005; **92**: 176 – 181.
- Jacobsen KH, Koopman JS. The effects of socioeconomic development on worldwide hepatitis A virus seroprevalence patterns. *Int J Epidemiol.* 2005; **34**: 600 – 609.
- Merat S, Rezvan H, Nouraie M, Jamali A, Assari S, Abolghasemi H, et al. The prevalence of hepatitis B surface antigen and anti-hepatitis B core antibody in Iran: a population-based study. *Arch Iran Med.* 2009; **12**: 225 – 231.
- Malekzadeh R, Khatibian M, Rezvan H. Viral hepatitis in Iran and the world: epidemiology, diagnosis, treatment, and prevention (in Persian). *J Med Council Iran.* 1997; **15**: 183 – 200.
- Elikaei A, Sharifi Z, Shooshtari MM, Hosseini M, Maroufi Y. Prevalence of HAV among healthy blood donors referring to Tehran transfusion center. *Iranian J Publ Health.* 2008; **37**: 126 – 130.
- Mehr AJ, Ardakani MJ, Hedayati M, Shahraz S, Mehr EJ, Zali MR. Age-specific seroprevalence of hepatitis A infection among children visited in pediatric hospitals of Tehran, Iran. *Eur J Epidemiol.* 2004; **19**: 275 – 278.
- McQuillan GM, Kruszon-Moran D, Kottiri BJ, Curtin LR, Lucas JW, Kington RS. Racial and ethnic differences in the seroprevalence of 6 infectious diseases in the United States: data from NHANES III, 1988 – 1994. *Am J Public Health.* 2004; **94**: 1952 – 1958.
- Webb PM, Knight T, Greaves S, Wilson A, Newell DG, Elder J, et al. Relation between infection with *Helicobacter pylori* and living conditions in childhood: evidence for person to person transmission in early life. *BMJ.* 1994; **308**: 750 – 753.
- Moreira ED Jr., Nassri VB, Santos RS, Matos JF, de Carvalho WA, Silvani CS, et al. Association of *Helicobacter pylori* infection and giardiasis: results from a study of surrogate markers for fecal exposure among children. *World J Gastroenterol.* 2005; **11**: 2759 – 2763.
- Nouraie M, Latifi-Navid S, Rezvan H, Radmard AR, Maghsudlu M, Zaer-Rezaei H, et al. Childhood hygienic practice and family education status determine the prevalence of *Helicobacter pylori* infection in Iran. *Helicobacter.* 2009; **14**: 40 – 46.
- Pretolani S, Stroffolini T, Rapicetta M, Bonvicini F, Baldini L, Megraud F, et al. Seroprevalence of hepatitis A virus and *Helicobacter pylori* infections in the general population of a developed European country (the San Marino study): evidence for similar pattern of spread. *Eur J Gastroenterol Hepatol.* 1997; **9**: 1081 – 1084.
- Webb PM, Knight T, Newell DG, Elder JB, Forman D. *Helicobacter pylori* transmission: evidence from a comparison with hepatitis A virus. *Eur J Gastroenterol Hepatol.* 1996; **8**: 439 – 441.
- Gentile A. The need for an evidence-based decision-making process with regard to control of hepatitis A. *J Viral Hepat.* 2008; **15** (suppl 2): 16 – 21.
- Wasley A, Fiore A, Bell BP. Hepatitis A in the era of vaccination. *Epidemiol Rev.* 2006; **28**: 101 – 111.
- Das A. An economic analysis of different strategies of immunization against hepatitis A virus in developed countries. *Hepatology.* 1999; **29**: 548 – 552.