REVIEW ARTICLE

Systematic review and meta-analysis on the age-specific seroprevalence of hepatitis A in Iran

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Background: Hepatitis A virus (HAV) is a major cause of acute viral hepatitis worldwide. Annual medical and work loss costs of hepatitis A are significant even in low-endemic countries. It is recommended that each country should collect and review the information needed to estimate its national burden of hepatitis A to provide evidence for health policy makers to implement appropriate and cost-effective preventive strategy for HAV infection. The objective of this study was to estimate accurate prevalence of HAV infection in Iran for best preventive measures. **Materials and Methods:** MEDLINE, Institute of Scientific Information, Scopus, Iranmedex, Irandoc, Magiran and Scientific Information Database were searched. The seroprevalence of HAV were pooled by age, sex and residence using fixed and random effect models. **Results:** Sixteen papers representing 11857 subjects were included. The overall HAV seroprevalence was 51% (confidence interval [CI] 95%: 50-52%) in fixed and 66% (95% CI: 50-79%) in random effects models. The prevalence was 32% (CI 95%: 11-63%) in less than 20, 50% (CI 95%: 24-75%) in 20-30, and 67% (CI 95%: 17-95%) in more than 30 years of age. The difference was not significant in gender or residence subgroups. **Conclusion:** HAV infection in Iran may be considered as low or very low. Therefore, targeted vaccination of high-risk groups and more improvement in environmental sanitation would be the best preventive measure.

Key words: Hepatitis A, Iran, seroprevalence

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INTRODUCTION

Hepatitis A virus (HAV) is a major cause of acute viral hepatitis world-wide.[1] It is mainly transmitted by ingestion of contaminated food or water or through contact with an infected patient.[2,3]

The expression of clinical symptoms varies greatly with the age of the infected person. While children with less than 6 years of age often have asymptomatic infection, older persons usually experience some specific signs of this illness, e.g., jaundice and dark urine lasting for several weeks, and rarely acute liver failure and death.[1] Annual medical and work loss costs of hepatitis A are significant even in low-endemic countries.[4] The incidence rate in a country is closely correlated with the socio-economic conditions, hygiene status, and access to safe drinking water.[1-3]

Active immunizations are highly effective and safe measures in reducing the burden of the HAV infection in communities.[5-7] Hepatitis A vaccines are inactivated forms, which contain antigens derived from attenuated HAV strains grown in cell culture.[8] Inactivated hepatitis A vaccines are licensed for use in people ≥12 months of age. A complete vaccination schedule consists of two doses administered commonly 6-12 months apart into the deltoid muscle.[8] The effectiveness of hepatitis A vaccines was shown in immunization program in North America, region of Puglia (Italy), and North Queensland, Australia resulting in 94-97% reduction in the incidence of acute hepatitis A within 6-10 years.[8]

The best recommendation program on active immunization in a country is highly related to the average age at infection.[9] In highly endemic areas (>90% by the age of 10 years), universal vaccination of children is not cost-effective and therefore, not recommended. In communities with intermediate endemicity (>50% until 15 years, with <90% by the age of 10 years), where incidence of the infection is high enough to yield significant risk of infection in adolescents and adults, but low enough that children would not usually develop immunity at an early age, universal vaccination programs are considered

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to be cost-effective. In low (>50% till 30 years, with <50% by age 15) and very low (<50% until 30 years) endemic countries, targeted vaccination of high-risk groups is usually recommended, e.g., for travelers to high-endemic countries, intravenous drug abusers, persons with coagulopathy, and patients with chronic liver disease.[8]

Global reports so far have considered the Islamic Republic of Iran (I.R. Iran) as an intermediate endemic country for hepatitis A.[1,8] Recent studies showed that the prevalence of the HAV infection in various parts of the country is declining.[10-12]

The World Health Organization also emphasizes that each country should collect and review the information needed to estimate its national burden of hepatitis A to provide evidence for health policy makers to implement appropriate and cost-effective preventive strategy for HAV infection.[8]

Categorizing the seroprevalence by the age enables indirect measurement of age-specific incidence rates of HAV infection, and is considered as the best way to describe the hepatitis A situation in a country.[9] To the best of our knowledge, any nation-wide study has not been conducted about the prevalence of the HAV infection in Iran. Therefore, to estimate a more comprehensive data on the burden of this infection in the community, we conducted a systematic review and meta-analysis on the literature reporting the age-specific prevalence of hepatitis A in the I.R. Iran during the last 10 years.

MATERIALS AND METHODS

The current review was conducted from January 2013 to May 2013 on studies conducted from January 2003 to January 2013.

Sources

We searched PubMed and the NLM Gateway (for MEDLINE), Institute of Scientific Information, and Scopus as the main international electronic data sources (by RN), as well as Iranmedex, Irandoc, Magiran and Scientific Information Database for Persian-language documents (by RN, FJ, and SGH). These main domestic databases have systematic search capability and the most coverage of Iranian scientific journals. For finding the gray literatures, all the Iranian scientific journals of medical universities, as OPAC and Civilica, were reviewed (by RN).

The search strategy was based on the terms "Hepatitis A" AND "Iran" in English sources. For the Iranian search engines, both the Persian and English keywords were searched.

All pertinent articles were retrieved and the reference lists were also systematically reviewed to identify further reports, which could be included in the meta-analysis. Proceedings of scientific meetings were not included. Other potentially relevant reports or unpublished data were explored by contacting experts in the field of HAV infection, e.g., specialists in infectious diseases, public health, and hepatology, as well as the related public health units such as Iranian Centers for Disease Control.

Study selection

An initial screening in titles and abstracts of the articles was performed by two independent observers (FJ, ZN) to exclude citations deemed irrelevant. Articles which report seroprevalence of HAV infection in a general population or I.R. Iran were included in the study. The representativeness of the studied population for the entire population in that community was the main determinant for including or excluding the study in the systematic review. Reasons for exclusion are categorized and reported [Figure 1]. Full texts of included articles were retrieved and screened by two independent reviewers (SGH, SNM). Redundant articles, reviews, those papers reporting incidence of acute hepatitis A and those containing data from prior to January 2003 were excluded. Articles meeting full defined criteria were selected for quality assessment and data extraction. Discrepancies were resolved through discussion.

Quality assessment

The quality of included studies was assessed by a scoring system through a predesigned checklist adopted from

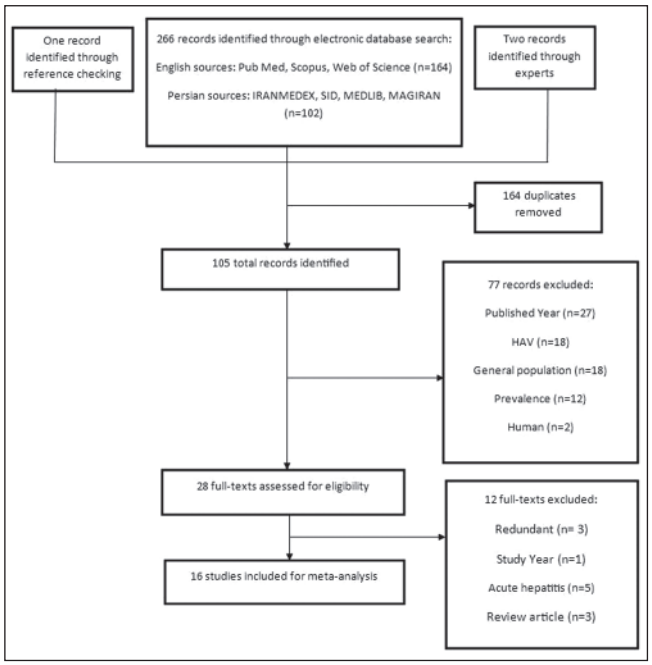


Figure 1: Summary of literature search and study selection

available critical appraisal forms by two independent reviewers (SGH, SNM).[13,14] Items for quality assessment and their scores were as follows:

Sampling method (cluster sampling proportional to rural and urban population size: 10, simple random cluster sampling: 8, Simple random sampling: 5, non-random sampling: 1, not reported: 0), studied age groups: A percent was calculated based on age range of study participants, which was 100% if it covered from age 1 to 80 years (over 80%: 5, 60-80%: 4, 40-60%: 3, 20-40%: 2, under 20%: 1), study level (national: 5, provincial: 4, district: 3, sub-district: 1), diagnostic methods (appropriate: 2, not appropriate: 1, not reported: 0).

We defined the quality of selected studies according to the mean and standard deviation (SD) of numbers achieved by the scoring system. Thus, the articles with scores more than one SD above the mean were defined as high quality, less than one SD under the mean as low quality, and other articles were classified as medium quality.

Data extraction

From the included reports, data were independently abstracted according to the study and participants' characteristics (by PM, FJ, and SGH). Data on age-, sex-, and residence- specific prevalence of HAV antibody were extracted for Iranian population.

We categorized the age of participants by two methods: The first method consisted of the following age groups: Under 20, 20-30 and more than 30 years. The second method was based on the age ranges of fewer than 10, 10-20 and more than 20 years.

Seroprevalence data from age groups of fewer than 6 months were omitted because of confounding maternal antibodies.

Data analysis

To calculate the point prevalence of HAV infection, numbers of subjects were aggregated across all studies. Pooled estimates with 95% confidence intervals (CI) were calculated both within age, sex, and residence categories, and overall across all studies, using both fixed and random effects models, by comprehensive meta-analysis V2.exe software (Biostat, USA). Homogeneity across studies was assessed using I square statistic. Wherever a significant heterogeneity was detected (I2 >50%), Cochrane's Q test was applied. A level of <0.1 was considered as significant.

In addition, in order to assess the impact of study design, the same analysis was conducted according to study quality category. Furthermore, to evaluate the publication bias, Egger's linear regression and Begg tests were used. $P > 0.05$ indicated no publication bias.

Iran regions

For comparing the HAV prevalence in various regions of the country, we used the definition used in a previous epidemiologic study, in which all provinces of Iran are categorized to four regions in accordance to their geographical and socio-economic status (SES). Based on this study, provinces were categorized to southeast, north-northeast, west, and central regions.[15]

The Southeast region consists of South Khorasan, Kerman, Hormozgan, Sistan-Baloughestan provinces and has the lowest SES. North-Northeast region consisted of RazaviKhorasan, North Khorasan, Golestan, Mazandaran, and Guilan provinces and defined as moderate low socio-economic states. Tehran, Qom, Qhazvin, Central, Isfahan, Semnan, and Yazd provinces were classified as central regions. These areas had the highest socio-economic state. Other provinces grouped as west regions and had moderate high SES.[15]

RESULTS

After screening 105 potentially relevant citations and reviewing 28 full-text study articles, 16 papers were included in the systematic review [Table 1, one of the studies (Merat 2010) included three distinct provinces, thus each region was considered as a separate study in the analysis]. Common reasons for exclusion at the screening stages are summarized in Figure 1. All included studies were cross-sectional. A total of 11857 cases were included in the studies, and totally 6880 positive cases were found (58% seropositivity). The quality scores of the considered studies ranged from 5 to 21, and the average score for all 16 studies was 13.6 (SD = 5.4). From 16 included articles, three were classified as high quality, eight as medium quality and five as low quality articles. Details of characteristics of the selected studies are shown in Table 1.

Data on the prevalence of HAV were extracted from the 16 included articles. Most of the studies reported the sex-specific prevalence. Eleven studies contained age-specific seroprevalence data,[11,12,16-18,20,21,23,25,27,28] and 6 studies reported urban versus rural seroprevalence rates,[10-12,20,25,28] which could be used in our study. Pooling of the results derived from all included reports, independent of study design, yielded an event estimation of 51% for fixed effect model (95% CI: 50-52), and 66% (95% CI: 50-79) for random effects model ($Q^2 = 3136$, df = 17, $P < 0.0001$, $I^2 = 99.4$) [Figure 2].

Sensitivity analysis was performed with removing low quality articles from the analysis in the first step and the medium quality ones in the next step. With removing low and medium quality articles, the point estimate of HAV prevalence in random effect model shifted from 66% to 89%, respectively. Therefore, it seems that lower quality articles had under-estimated the prevalence.

Eleven studies included in the meta-analysis provided the data regarding gender of the subjects. The pooled HAV prevalence among females was slightly higher than males (59% vs. 49% in fixed and 73% vs. 71% in random effect models). The difference was not statistically significant in any of models.

The weighted mean HAV prevalence in three age groups in random effect model was 32% (95% CI: 11-63) in under 20, 50% (95% CI: 24-75) in 20-30, and 67% (95% CI: 17-95) in above 30 years. According to second classification, the prevalence in under 10 years was 23% (CI 95%: 10-40%), in 10-20 years was 40% (CI 95%: 15-70%), and in the last group (more than 20) it was 75% (CI 95%: 60-80%). Figure 3 shows information about HAV prevalence among different age groups.

The pooled estimation of HAV prevalence in rural areas was higher than urban regions (68% [95% CI: 31-90] vs. 54% [95% CI: 20-84]). However, this difference was not statistically significant ($P = 0.59$).

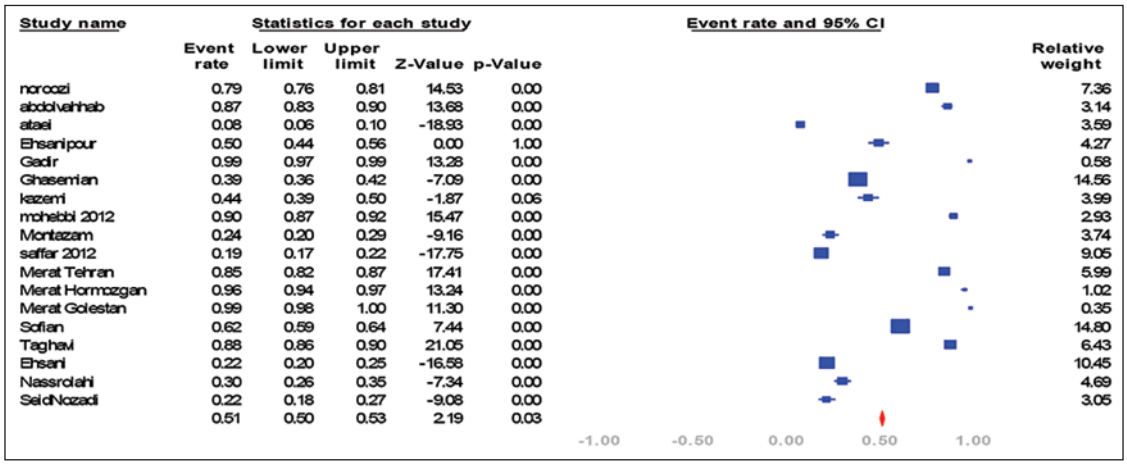
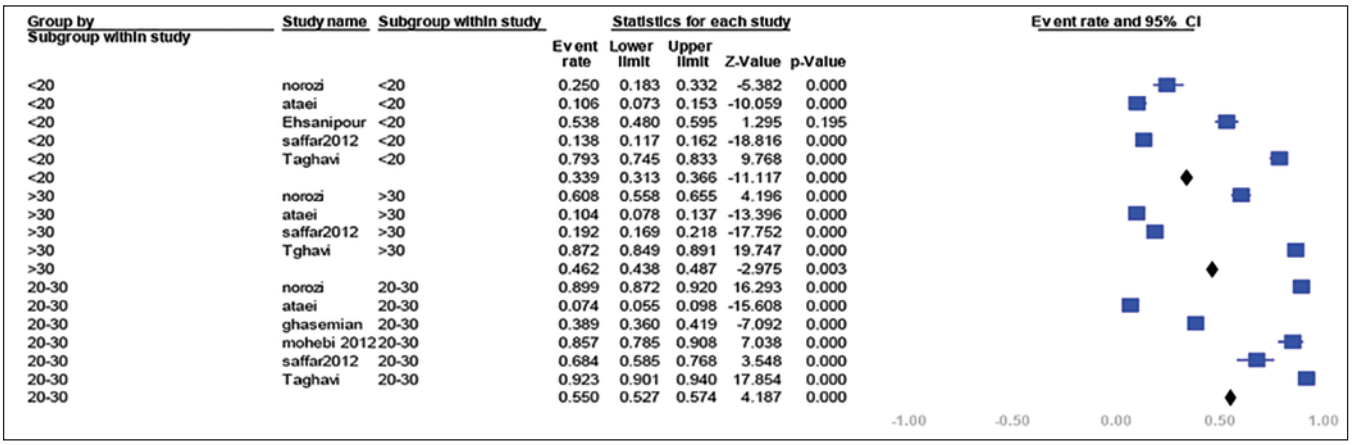


Figure 2: Forest plot of hepatitis A virus infection prevalence in islamic republic of Iran

Table 1:Characteristics of the selected studies

Sources	City/state	Population	Prevalence %	No. of cases	Quality score
Abdolvahhab 2010[16]	Golestan province	17-year-old referred for mass vaccination of hepatitis B virus	86.76	461	7
Ataei *et al*. 2007[11]	Isfahan province	General population >6 years	8.09	816	21
Ehsani 2002[17]	Tehran	Hospital patients, 0.5-15 years	22.3	1018	8
Ehsanipour *et al*. 2006[18]	Tehran	Hospital outpatients, 0.5-20 years	50	288	6
Ghadir *et al*. 2007[19]	Golestan province	General population, 18-76 years	98.6	697	18
Ghasemian and Alian 2011[20]	Sari city	General population, 1-25 years	38.9	1034	18
Kazemi *et al*. 2007[21]	Zanjan city	School children, 7-10 years	44.3	273	11
Merat 2010[22]	Tehran province	General population, 18-65 years	85	791	19
Merat 2010[22]	Hormozgan province	General population, 18-65 years	96	453	19
Merat 2010[22]	Golestan province	General population, 18-65 years	99	625	19
Mohebbi *et al*. 2012[23]	Tehran province	General population, 1-83 years	90	551	16
Montazam *et al*. 2007[10]	Malecan city	General population	23.9	346	13
Nassrolahi 2004[24]	Sari city	Participants of a health check program, 3-81 years	30.5	374	16
Noroozi *et al*. 2012[25]	Qhum province	General population >15 years	78.6	740	21
Saffar *et al*. 2012[12]	Savadkuh district	General population, 1-30 years	19.2	984	17
SeidNozadi 2005[26]	Mashhad	Hospital outpatients, 20-50 years	22	300	5
Sofian 2010[27]	Tehran	Hospital outpatients, 0.5-20 years	61.6	1056	8
Taghavi 2011[28]	Fars province	Screening before marriage, 15-63 years	88.2	1050	14



Group by Subgroup within study	Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Z-Value	p-Value
<20	norozi	<20	0.250	0.183	0.332	-5.382	0.000
<20	ataei	<20	0.106	0.073	0.153	-10.059	0.000
<20	Ehsanipour	<20	0.538	0.480	0.595	1.295	0.195
<20	saffar2012	<20	0.138	0.117	0.162	-18.816	0.000
<20	Taghavi	<20	0.793	0.745	0.833	9.768	0.000
<20			0.339	0.313	0.366	-11.117	0.000
>30	norozi	>30	0.608	0.558	0.655	4.196	0.000
>30	ataei	>30	0.104	0.078	0.137	-13.396	0.000
>30	saffar2012	>30	0.192	0.169	0.218	-17.752	0.000
>30	Tghavi	>30	0.872	0.849	0.891	19.747	0.000
>30			0.462	0.438	0.487	-2.975	0.003
20-30	norozi	20-30	0.899	0.872	0.920	16.293	0.000
20-30	ataei	20-30	0.074	0.055	0.098	-15.608	0.000
20-30	ghasemian	20-30	0.389	0.360	0.419	-7.092	0.000
20-30	mohebi 2012	20-30	0.857	0.785	0.908	7.038	0.000
20-30	saffar2012	20-30	0.684	0.585	0.768	3.548	0.000
20-30	Taghavi	20-30	0.923	0.901	0.940	17.854	0.000
20-30			0.550	0.527	0.574	4.187	0.000

Figure 3: Forest plot of hepatitis A virus infection prevalence among different age groups in islamic republic of Iran

Egger's and Begg tests showed no indication of asymmetry among studies (Egger's test [intercept: 11.9, standard error: 8.1, 95% CI: 5.3-29.3, $P = 0.1$], Begg test [Kendall's S statistic: 13, $P = 0.6$]).

DISCUSSION

The finding of this study revealed that the seroprevalence of hepatitis A has significant variations in different parts of the country. While estimates of HAV seroprevalence in general population was as low as 8.09-19.20% in some areas,[10,11] reports as high as 78.6-99% were found in other studies.[16,19,22,23,25,28] This heterogeneity in prevalence of HAV infection could be due to different selection methods or different socio-economic and hygienic states in the studied populations. Similar within-country regional differences in anti-HAV seroprevalence of the infection had been reported from other countries as Brazil,[29] China,[30] Italy,[31] Saudi Arabia,[32] and Turkey.[33] In Brazil prevalence of HAV were higher in northern regions compared with southern cities.[29] Similarly, the prevalence was higher in southern areas of Italy than central regions and in central areas than northern districts.[31] Furthermore, HAV were more prevalent in eastern regions compared with western and central areas of Turkey.[33] Total prevalence of infection in China had been reported to be greater than 90% in some regions while in some other areas, it was lower less than 70%.[30] In Saudi Arabia HAV prevalence of as high as 80% was found in some regions, while in other areas, the prevalence was as low as 19%.[32]

Thus, there is a need for additional studies in sub-national level to make an appropriate decision about HAV vaccination in inhabitants of various regions of the country.

The study elucidates that I.R. Iran currently might be considered as a low-endemic area for HAV infection. We could not accurately estimate the HAV seroprevalence at ages of 15 and 30, because of different designs of the studies in this age group. Nearly40% of the population aged 10-20 years and 55.4% of the population aged 20-30 years were HAV sero-positive, it can be concluded that infected population by age of 15 are less than 50% and by age of 30 years are approximately near 50%. Therefore, actually the I.R. Iran should be considered as a low or very low-endemic area. In the last global reports on the prevalence of HAV infection, the I.R. Iran had been considered as an intermediate endemic area.[1,8] Improvement in SES along with environmental sanitation especially in water supply during recent years could explain the changing prevalence of the infection in the I.R. Iran.

Studies from some other regions of the world have found similar decreases in the endemic occurrences of infectious hepatitis along with improvement in socio-economic markers of life. Reports from Egypt[34-36] and Saudi Arabia[37-41] in the Middle East and North Africa elucidate decrease in prevalence of the infection in recent 5 years compared with previous estimates. In Egypt the prevalence of HAV in the age group of 10-19 had been reported to be 97% in 1994[34] and 90% and 73.8% in 2007[36] and 2008,[35] respectively. Prevalence as high as 52.4% in 1-10 years in 1989-1990[38] and 90% in 12-17 years during 1987-1999[39] had been reported in Saudi Arabia, while the amount in 12-14 years in 2004[40] and 2005[37] were 28.4-30%, and in 16-18 years age group in 2007-2008[41] was 18.6%. In contrast, reports from Turkey[42,43] show no significant difference between the prevalence of the infectious hepatitis in previous years.

With regard to low endemicity of hepatitis A infection in recent years in the I.R. Iran, it seems logic that efforts should be made to vaccinate high-risk populations along with more improvement in environmental hygiene and sanitations. This is true especially for travelers to neighboring countries. The I.R. Iran is located in the vicinity of countries of Middle East and south Asia with high endemicity of HAV infection.

In Iraq,[44] Syria,[45] Pakistan,[46,47] Turkey,[48] Egypt,[34,36] and Lebanon[49] borders more than 90% of subjects tested are reported to be sero-positive with significant infection in children aged less than 10 years of age. Studies from some countries in the 2000s show a lower rate in children, with less than 50% of the 15 years old individuals being immune in studies conducted in Kuwait,[50] Saudi Arabia,[32,37,40] and the United Arab Emirates.[51]

Regardless of the age, the seroprevalence rates for HAV in the I.R. Iran were lower in urban than in rural areas, however the difference was not statistically significant. Nearly 68% of rural populations and 54% of urban inhabitants were HAV seropositive. Urban populations had lower rates of HAV infection than rural populations in some parts of the world. Lower level of parental[38,43,52,53] or personal[54,55] education, and larger family size[56,57] as well as use of wells, rivers, springs, and tanker-delivered water in rural areas had been associated with increased risk of HAV infection in these areas.[58,59] Insignificant difference of hepatitis A prevalence between rural and urban areas of I.R. Iran probably is associated to both improved SES and improved sources of drinking water during recent years.

Although in the current study, the seroprevalence of anti-HAV in females was slightly greater than male subjects, the difference was not statistically significant. It seems that there is no difference in predisposition of both genders to HAV infection in the country. This finding was consistent with other reports from Egypt,[35,36] Iraq,[44] and Saudi Arabia.[37,39] Comparing to men, women are more involved in food preparing works in home and so, they are more prone to direct contact with infected raw foods. This could explain mild increase of HAV infection in females.

This study elucidates scarce data on the seroprevalence of HAV infection in various parts of Iran. The major studies were performed in two regions of the country (central and north-northeast) and few data exist from the two other regions (southeast and west). Furthermore in the most published research reports, the results were restricted to a specific city in a province, age group, and or a sub-population. These limitations require the conservative interpretation of some results because the prevalence estimates could not be representative of the whole population of the country. Despite these limitations, this study is the first systematic review in the subject which represents clear and up to date information in the seroprevalence of the HAV infection in different age, gender and geographic areas in studied populations of Iran.

The results of our study showed that actually the I.R. Iran might be considered as a low or very low-endemic area for HAV infection. Therefore, targeted vaccination programs for groups at risk for the infection along with more improvement in environmental sanitations would be the best cost-effective preventive measure. This is true especially for travelers to neighboring countries with high HAV prevalence. Furthermore, new surveys are needed to detect HAV infection prevalence in different regions of I.R. Iran to provide more accurate recommendation in different socio-economic and geographic regions of the country.

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AUTHORS' CONTRIBUTION

All authors have contributed in designing and conducting the study. SNM, SGH, FJ, ZN, RN, PM, and SH collected the data and ZF and RK did the analysis. All authors have assisted in preparation of the first draft of the manuscript or revising it critically for important intellectual content. All authors have read and approved the content of the manuscript and are accountable for all aspects of the work.

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