

Hepatitis A in Sfax, Tunisia, from 2000 to 2017: A prominent epidemiological shift among blood donors population

Hépatite A à Sfax, Tunisie, de 2000 à 2017: Un changement épidémiologique majeur au sein de la population des donneurs de sang

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ABSTRACT

Objective: To assess the evolution of the epidemiological pattern of HAV infection in Sfax through the determination of HAV seroprevalence in 2017 and the comparative analysis with data of 2000 and 2007.

Methods: A total of 378 blood donors sampled in 2017 were included. In line with the previous adopted methodology, blood donors belonged to three age groups: 18-20, 21-25 and 26-30 years and are originating from Sfax governorate (urban and rural areas) and different governorates of South Tunisia. Total anti-HAV antibodies were assessed in serum samples. Comparative analysis between 2000, 2007 and 2017 was performed using SPSS version 20.0 Software.

Results: The overall HAV seroprevalence in 2017 was 65.1% with a significant increase with older age (50.8%, 65.9% and 78.6% in the 18-20, 21-25 and 26-30 years age groups, respectively). HAV seroprevalence was significantly lower in urban areas of Sfax than in rural settings and South Tunisia (31%, 80.2% and 84.1%, respectively). In the age group 18-20 years, seroprevalence was 14.3%, 64.3% and 73.8% in Sfax's urban areas, Sfax's rural areas and South Tunisia, respectively. In Sfax's urban areas, only 45.2% of blood donors in the age group 26-30 years had anti-HAV immunity. A significant decrease in HAV seroprevalence was documented in all regions as compared to 2000 and 2007.

Conclusion: The present study confirmed the epidemiological shift in HAV infection in Sfax governorate and South Tunisia with a mix of intermediate-low endemicity. Further epidemiological surveillance of the incidence of hepatitis A during the vaccination era is crucial to guide national policies.

Key words: Hepatitis A virus; Blood donors; Epidemiological shift; Tunisia

RÉSUMÉ

Objectif : Analyser l'évolution du profil épidémiologique de l'infection par le virus de l'hépatite A (VHA) dans le gouvernorat de Sfax à travers la détermination de la séroprévalence des anticorps anti-VHA en 2017 et la comparaison avec les données de 2000 et 2007.

Méthodes : Étude transversale incluant 378 donneurs de sang recrutés en 2017. Les participants ont été répartis en trois classes d'âge (18-20 ans, 21-25 ans et 26-30 ans) et provenaient du gouvernorat de Sfax (milieu urbain et rural) ainsi que d'autres gouvernorats du sud tunisien. Les anticorps totaux anti-VHA ont été recherchés dans des échantillons sériques. L'analyse comparative des données de 2000, 2007 et 2017 a été réalisée à l'aide du logiciel SPSS version 20. Les comparaisons statistiques ont été effectuées avec un seuil de significativité fixé à $p < 0,05$.

Résultats : La séroprévalence globale du VHA en 2017 était de 65,1 %, de manière significative avec l'âge (50,8 %, 65,9 % et 78,6 % respectivement). Elle était significativement plus faible en milieu urbain à Sfax (31 %) qu'en milieu rural (80,2 %) et dans le sud tunisien (84,1 %). Chez les 18-20 ans, la séroprévalence était de 14,3 % en milieu urbain, 64,3 % en milieu rural et 73,8 % dans le sud tunisien. Une diminution significative a été observée par rapport aux années 2000 et 2007.

Conclusion : Ces résultats confirment une transition vers une endémicité intermédiaire à faible du VHA à Sfax et dans le sud tunisien, soulignant la nécessité d'une surveillance épidémiologique continue à l'ère vaccinale.

Mots clés: Virus de l'hépatite A, donneurs de sang, Changement épidémiologique, Tunisie

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INTRODUCTION

Hepatitis A virus (HAV) infection is a global health problem with approximately 1.5 million people infected annually in the world [1]. The clinical outcome of hepatitis A is known to be highly age-related. Indeed, in young children, this infection is usually asymptomatic with only 30% of those under the age of 6 years develop symptomatic disease [2]. However, in older age groups, clinical manifestations of hepatitis are more common, and even in some cases, fulminant hepatitis with fatal outcome can occur [1,3].

HAV infection is primarily acquired through the fecal-oral route, either directly via person-to-person transmission or indirectly via ingestion of contaminated food and water [4]. Therefore, the prevalence of HAV infection is strongly correlated with socioeconomic conditions in each area; lower prevalence is associated with increasing incomes and adequate sanitation. According to the World Health Organization (WHO) [1], four levels of endemicity of hepatitis A worldwide are defined on the basis of seroprevalence : high ($\geq 90\%$ by age 10 years); intermediate ($\geq 50\%$ by age 15 years, with $< 90\%$ by age 10 years); low ($\geq 50\%$ by age 30 years, with $< 50\%$ by age 15 years); and very low ($< 50\%$ by age 30 years). In low-resource countries with high endemicity due to very poor hygienic conditions, HAV infection occurs at an early age when the disease is often asymptomatic, hence, these areas are characterized by low disease burden and potential for outbreaks [5,6]. By contrast, in resource-rich countries, because of good sanitation and hygienic conditions, there is little circulation of HAV with the occurrence of occasional outbreaks especially among specific adult risk groups such as intravenous drug users and men having sex with men (MSM) [7,8]. Interestingly, in some regions of the world which have known a rapid socioeconomic development, such as Eastern Europe, some parts of Asia and Latin America [9,10], an epidemiological shift with transition from high to intermediate-low endemicity has been described, due to improvement in sanitary conditions. Consequently, in these areas HAV infection occurs primarily in adolescents and young adults, leading paradoxically to a higher rate of symptomatic disease with the occurrence of community-wide outbreaks.

In Tunisia, several studies have been conducted in order to evaluate the HAV epidemiology trend in different regions of the country [8,11–15]. Specifically, a serological survey carried out in blood donors from Sfax governorate (Center East of Tunisia), has shown a significant decrease in the global seroprevalence of HAV infection, which dropped from 94.9% in 2000 to 85.9% in 2007 [16]. According to this study, the decline in HAV seropositivity among blood donors was observed only in urban areas of Sfax. Interestingly, from 2007 to 2018, a high number of symptomatic HAV infections resulting in community large-scale outbreaks have been described in Sfax governorate [17] and in Tunisia in general [18]. During these outbreaks, both urban and rural settings of Sfax were involved with the occurrence of fulminant hepatitis, suggesting probably the changing pattern in the HAV epidemiology. To assess the epidemiological trend

of HAV infection, we estimated the HAV seroprevalence in Sfax blood donors population in 2017, and we next compared it with data previously reported in 2000 and 2007 in the same population.

METHODS

In order to compare the HAV seroprevalence rates between the three different years, 2000, 2007 and 2017, the same methodology, based on a multistage cluster sampling of blood donors, was performed in this study as previously described [16].

Study population

This is a cross-sectional study including 378 randomly selected healthy blood donors, aged between 18 and 30 years, at the Regional Blood Transfusion Center of Sfax in 2017. A two-stage cluster sampling was used for random selection of regions that was proportional to the number of blood donors in each region. As it was previously described in 2000 and 2007 [16], the same stage process was performed in the current study, using a sampling according to age in the first stage, followed by a sampling of regions from each age group in the second stage. Indeed, blood donors were divided into three age groups: 18-20 years; 21-25 years and 26-30 years. As for the urbanization level, the distribution of the regions was taken into account during sampling. Regions of blood donors were allocated to three groups: Group 1 from the city of Sfax (urban area); Group 2 from different delegations of Sfax (rural area); and Group 3 from different governorates of South Tunisia: Gabès, Gafsa, Sidi Bouzid, Medenine, Guebelli, Tataouine and Tozeur (urban and rural areas). Blood donors positive for hepatitis B virus, hepatitis C virus, human immunodeficiency virus and syphilis were not included in the study. Serum samples from all included blood donors were frozen at -20°C until use.

Anti-HAV antibodies testing

Quantitative determination of total anti-HAV antibodies in serum samples was performed using an electrochemiluminescence immunoassay on the Cobas e411 analyzer (Elecsys Anti-HAV assay, Roche Diagnostics, Germany). Samples with concentrations ≥ 20 IU/L were considered reactive according to the manufacturer's instructions.

Statistical analysis

All calculations were performed with SPSS.20. Software. The HAV seroprevalence data of the previously published study [16] were included in the 2017 statistical file for comparative analysis. The Chi-square test was used to assess the differences in the prevalence of anti-HAV antibodies according to gender, age and origin of blood donors. A multivariate analysis with logistic regression including the 378 blood donors in 2017 was performed to determine the impact of the aforementioned variables on the HAV seroprevalence. A second multivariate analysis was then performed including a total of 1130

blood donors (376, 376 and 378 in 2000, 2007 and 2017, respectively) to assess the variables age, origin and the year of the study. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated for these variables. A *p* value of < 0.05 was considered statistically significant.

RESULTS

HAV seroprevalence in 2017

The overall rate of HAV seropositivity in the year 2017 was 65.1% (95% CI 0.60 – 0.70). No significant difference in the HAV seroprevalence was found according to gender (66.7% and 63.5% for male and female, respectively, *p* = 0.517). A significant increase in the seroprevalence rate with age was observed (percentages were 50.8% (95% CI 0.42 – 0.59), 65.9% (95% CI 0.58 – 0.74) and 78.6% (95% CI 0.71 – 0.86) in the 18–20 years, 21–25 years and 26–30 years age groups, respectively, *p* < 0.001). Considering the origin of blood donors, the seroprevalence of anti-HAV antibodies in the city of Sfax was significantly lower than in rural regions and other governorates of South Tunisia, with rates of 31% (95% CI 0.23 – 0.39), 80.2% (95% CI 0.73 – 0.87) and 84.1% (95% CI 0.78 – 0.9), respectively, *p* < 0.001. Specifically, the seroprevalence rate in the city of Sfax in the 26–30 years age group do not exceed 45.2%. The results of the HAV seroprevalence according to both age groups and origin are shown in Table 1.

Table 1. HAV seroprevalence in blood donors according to age groups and origin in 2017

Positive cases, n/N (%)				
Age group (years)	Group 1	Group 2	Group 3	p value
18-20	6/42 (14.3)	27/42 (64.3)	31/42 (73.8)	< 0.001
21-25	14/42 (33.3)	33/42 (78.6)	36/42 (85.7)	< 0.001
26-30	19/42 (45.2)	41/42 (97.6)	39/42 (92.9)	< 0.001
Total	39/126 (31)	101/126 (80.2)	106/126 (84.1)	< 0.001

Group1: city of Sfax; Group2: rural areas of Sfax; Group3: governorates of South Tunisia.
^a n: number of anti-HAV positive cases, ^b N: total number of tested cases.

In the logistic regression analysis (Table 2), only age and origin of blood donors were associated with anti-HAV seropositivity and no relationship was documented between gender and HAV infection (*p* = 0.434).

Comparative study of HAV seroprevalence in the years 2000, 2007 and 2017

A significant decrease in the overall HAV seroprevalence rate among blood donors was shown in 2017 as compared to 2007 and 2000 (65.1%, 85.9% and 94.9%, respectively, *p* < 0.001). This significant reduction was observed in all age groups (Table 3) and in all regions (Table 4). Specifically, a decline in the HAV seroprevalence by nearly the half was observed in 2017 in the city of Sfax as compared to 2007, with rates of 31% and 62.7%, respectively (Table 4).

Table 2. Logistic regression analysis for the association between age, gender or origin and anti-HAV seropositivity in 2017

Anti-HAV Seropositivity		
Variables	Odds Ratio (95% CI)	p value
Age group (years)		
18-20	1	
21-25	2.4 (1.3-4.5)	0.005
26-30	5.9 (3-11.8)	<0.001
Gender		
Male		
Female	0.8 (0.4-1.3)	0.434
Origin		
Group 1	1	
Group 2	11.7 (6.2-22)	<0.001
Group 3	15.6 (8-30.5)	<0.001

CI: confidence interval ; Group 1: city of Sfax; Group 2: rural areas of Sfax; Group 3: governorates of South Tunisia ; 1: reference category.

Table 3. Comparison of HAV seroprevalence in blood donors according to age groups in 2000, 2007 and 2017

Positive cases, n/N (%)				
Age group (years)	2000 [16]	2007 [16]	2017	p value
18-20	114/124 (91.9)	100/124 (80.6)	64/126 (50.8)	< 0.001
21-25	118/126 (93.7)	107/126 (84.9)	83/126 (65.9)	< 0.001
26-30	125/126 (99.2)	116/126 (92.1)	99/126 (78.6)	0.001
Total	357/376 (94.9)	323/376 (85.9)	246/378 (65.1)	< 0.001

^a n: number of anti-HAV positive cases, ^b N: total number of tested cases.

Table 4. Comparison of HAV seroprevalence in blood donors according to origin in 2000, 2007 and 2017

Positive cases, n/N (%)				
Origin	2000 [16]	2007 [16]	2017	p value
Group 1	112/126 (88.9)	79/126 (62.7)	39/126 (31)	< 0.001
Group 2	124/126 (98.4)	121/126 (96)	101/126 (80.2)	< 0.001
Group 3	121/124 (97.6)	123/124 (99.2)	106/126 (84.1)	< 0.001
Total	357/376 (94.9)	323/376 (85.9)	246/378 (65.1)	< 0.001

n: number of anti-HAV positive cases, N: total number of tested cases. Group1: city of Sfax; Group2: rural areas of Sfax; Group3: governorates of South Tunisia.

In the logistic regression analysis including 1130 blood donors (Table 5), the variables age, origin and year of study were associated with anti-HAV seropositivity.

DISCUSSION

The prevalence of HAV infection worldwide is closely related to hygienic and sanitary conditions and other indicators of the level of socioeconomic development [4,5,19]. Therefore, improvements in the hygienic conditions can consequently lead to an epidemiological shift in the HAV infection [3,20,21].

Table 5. Logistic regression analysis for the association between age, origin or year and anti-HAV seropositivity in 2000, 2007 and 2017, including a total of 1130 blood donors

Anti-HAV Seropositivity		
Variables	Odds Ratio (95% CI)	p value
Age groups (years)		
18-20	1	
21-25	1.8 (1.2-2.9)	0.004
26-30	5.4 (3.2-9)	<0.001
Origin		
Group 1	1	
Group 2	11.5 (7.1-18.8)	<0.001
Group 3	16.9 (9.9-28.8)	<0.001
Year		
2000	1	
2007	0.2 (0.1-0.4)	<0.001
2017	0.04 (0.02-0.08)	<0.001

CI: confidence interval ; Group 1: city of Sfax; Group 2: rural areas of Sfax; Group 3: governorates of South Tunisia ; 1: reference category.

Transition from high-endemicity pattern to intermediate/low-endemicity pattern in a given area of the world is very important to recognize, since it can potentially lead to a serious public health problem due to the increase in the incidence of symptomatic cases, hospitalizations and mortality due to hepatitis A, despite a reduction in HAV transmission rate [22]. Ideally, this can be achieved through repeated and updated serological surveys that measure age-specific seroprevalence of anti-HAV antibodies and that are able to illustrate changes in immunity over time [2]. In the present study, seroprevalence rates among blood donors from Sfax governorate (Center East of Tunisia) and South Tunisia are assessed ten years later, based on a previous published study [16]. Although the given epidemiological information derived from a specific population (blood donors aged ≥ 18 years), this study provided updated serological data and illustrated the epidemiological transition of HAV infection in both Sfax governorate and South Tunisia with an intermediate/low endemicity pattern, depending on the socioeconomic development of the regions considered.

The previous study conducted during the years 2000 and 2007 has shown a significant decrease in the overall prevalence of antibodies to HAV from 94.9% to 85.9%, respectively [16]. Taking into account the origin of blood donors, the shift in HAV epidemiology was observed only in Sfax city, wherein seroprevalence rates in 2000 and 2007 declined from 88.9% to 62.7%, respectively. However, in the rural settings of Sfax and in the governorates of South Tunisia, high prevalence of HAV infection was documented during both years, ranging from 96% to 99.2%. In the year 2017, a significant decline in the global HAV seropositivity (65.1%) among blood donors as compared to 2000 and 2007 was observed, with a significant increase with older age, up to 78.6% by age of 30 years. Interestingly, both urban and rural settings of Sfax governorate as well as the other governorates of the South have experienced a

significant decrease in HAV seroprevalence as compared to 2000 and 2007. However, this epidemiological transition was markedly more pronounced in Sfax city than in the other areas, with only 31% of blood donors being anti-HAV antibodies positive, corresponding to a decline in the HAV seroprevalence by nearly the half as compared to 2007. Furthermore, in the age group 18-20 years, the seroprevalence was estimated to 14.3%, 64.3% and 73.8% in urban areas of Sfax, rural areas of Sfax and the governorates of the South, respectively. Importantly, in the city of Sfax, only 45.2% of blood donors in the age group 26-30 years had anti-HAV immunity. Altogether, these findings confirm the changing pattern of HAV epidemiology in Sfax governorate and in Tunisia in general, with a mix of intermediate (rural areas of Sfax and South Tunisia) and even low prevalence (urban areas of Sfax). Indeed, HAV epidemiological shift has been mainly attributed to improved socioeconomic status, sanitary conditions, access to improved water sources and improvements in sewage treatment methods [24]. Theoretically, urban areas may benefit the most from this hygienic development, which explain the rapidity of the decline in HAV seroprevalence rates in the city of Sfax as compared to the rural areas in our country. According to the nationwide seroprevalence study of hepatitis A which was carried out in total population in Tunisia in 2015 [8], the HAV seroprevalence was 78.8%, with significant differences between and within regions. Indeed, in line with our findings, an East-West gradient of HAV transmission was documented in this study, with lower rates in northern and eastern coastal regions (72% in Center East part of the country, including Sfax governorate). Nevertheless, in the national study, Sfax was classified as having an intermediate-high endemicity level. This difference is mainly due to the age groups included (seroprevalence was 97.8% for those aged > 30 years) and to the criteria used for the endemicity assignment.

The prominent change in HAV epidemiology in Sfax and South Tunisia can result in a higher proportion of susceptible adolescents and adults among whom increased rates of clinical disease may occur. In fact, any gap in the sanitary conditions may potentially lead to the introduction of HAV in susceptibles, resulting in a rapid spread of the virus through serial waves of transmission [22]. As a consequence, small localized or even community-large outbreaks of hepatitis A can occur, often with a cyclical trend, which is typical of epidemiological transition in HAV infection, and could explain what happened in Tunisia from 2007 to 2017 [9,18]. In general, these epidemics are mainly due to the presence of a common-source through contaminated food or water, with secondarily an extended person-to-person transmission. Indeed, epidemiological investigations carried out during three successive large outbreaks recorded between 2007 and 2010 in both urban and rural settings of Sfax governorate [17] have shown that the most likely sources of contamination were inadequate water supplies from wells or tanks in addition to direct transmission. The contamination of the environment has been also recently described in

central regions and coastal areas of Tunisia, mainly due to inadequate wastewater treatment [25].

The decreasing trend of HAV seropositivity with subsequently higher incidence of acute symptomatic hepatitis A stresses the need to implement adequate preventive measures. In addition to standard hygiene measures enhancement, like hand washing, accessibility to clean water supplies and implementation of food-safety measures, introduction of HAV vaccination programs has played a key role in the significant drop in the incidence of acute hepatitis A, as it was documented in several countries in the world [5,20,21]. According to the WHO recommendations, integration of universal mass vaccination in national immunization schedules for children aged ≥ 1 year in regions with declining endemicity from high to intermediate must be considered [1]. Given the HAV epidemics which have occurred in 2016, 2017 and 2018 in many parts of Tunisia [18], vaccination against HAV for school children aged of 6 years was introduced in the national immunization schedule in september 2018 [25], alongside reinforcement of access to sanitation facilities especially hygienic drinking water, in order to reduce the burden of the disease in the country.

The present study has several limitations. First, it was based on healthy blood donors aged 18–30 years, which limits the generalizability of the findings to the overall population. Second, its cross-sectional design allows only the estimation of HAV seroprevalence and precludes assessment of incidence or temporal relationships between exposure and infection. In addition, individual vaccination status and other potential risk factors were not available, limiting a more comprehensive analysis of determinants. Although blood donor selection procedures remained essentially unchanged across study periods and no major population migration shifts were documented, these factors may still represent potential residual confounders affecting temporal comparability. Despite these limitations, the study provides strong evidence of an ongoing epidemiological transition of HAV endemicity in Sfax and southern Tunisia.

CONCLUSION

The present study brings a new insight into the epidemiological evolution of hepatitis A in Tunisia through comparative HAV seroprevalence rates among Sfax blood donors, providing updated serological data and contributing to a better understanding of the HAV endemicity pattern in our country before vaccination implementation. Our findings illustrated a prominent and heterogeneous epidemiological shift in HAV infection in Sfax governorate and South Tunisia among blood donors from high to intermediate-low endemicity, according to the socioeconomic development of the regions considered. Further epidemiological studies to evaluate hepatitis A incidence in Tunisia are strongly needed to assess and optimize the national vaccination strategy.

Conflict of interest: none.

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