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Impact of HBV Vaccination on Prevalence of Hepatitis B Virus Infection Among Volunteer Blood Donors in Tehran-Iran

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Background: Hepatitis B (HB) vaccination is the most effective measure for preventing hepatitis B virus (HBV) infection and its consequences. HB vaccination has been a part of the Expanded Program on Immunization (EPI) of Iran since 1993. To extend HBV immunization, mass HBV vaccination was planned for adolescents born during 1989-1992.

Objectives: The aim of the present study was to assess the prevalence of HBV infection in Tehran blood donors after implementing national *HB* vaccination program.

Patients and Methods: Prevalence of HBV infection was determined in all of Tehran blood donors born during 1989-1993 as cases and the ones born during 1986-1988 as controls. All the participants were recruited after medical interviews. Serum samples taken from the participants as well as other blood donors were tested according to the IBTO standards for hepatitis B surface antigen (HBsAg). Initially, positive samples were tested with appropriate confirmation methods. Statistical comparisons were performed using chi-square test. Prevalence estimates were age-adjusted by the direct method for comparisons across subgroups.

Results: The prevalence of HBV infection was 57/100 000, 350/100 000, and 265/100 000 among accepted blood donors born during 1989-1993 (cases), 1986-1988 (nonconcurrent controls), and 1989-1993 (concurrent controls), respectively. The prevalence of HCV infection in the same group of blood donors was 28/100 000, 38/100 000, and 31/100 000, respectively.

Conclusions: HBV prevalence was significantly lower among blood donors born during 1989-1993, which reflected the positive impact of EPI program and extended mass vaccination against HBV.

Keywords: Hepatitis B; Blood Donors; Vaccination

1. Introduction

Hepatitis B (HB) vaccination is the most effective method to prevent Hepatitis B virus (HBV) infection and its consequences, including cirrhosis, liver cancer, liver failure, and death. In neonates, HBV infection is transmitted from infected mothers in prenatal period; however, in adults, HBV transmission occurs primarily among unvaccinated persons with risk factors for HBV infection, predominantly (1, 2). National vaccination program was implemented in Iran since 1993 for all neonates (3, 4). World Health Organization (WHO) recommended that HB vaccination should be integrated to national immunization programs in all the countries, since 15 years ago (5, 6). The result of this worldwide implementation was reduction of acute and chronic hepatitis B infections. This outcome has been reported in our country by many studies (7-9). The efficacy of vaccination is determined by assessment of anti-HBsAg level (10, 11). In Iran, two sero-epidemiologic studies were carried out before and after the mass vaccination on a representative sample of 1/1000 persons. The overall seropositivity rate showed significant decline during 1991-1999 in the age group of 2-14 years (1.3% versus 0.8%, $P < 0.05$) (12). According to this study, the overall prevalence of HBsAg decreased within six years of implementation of HB vaccination program in neonates since 1993, which was probably mainly due to vaccination of newborns after 1993.

The epidemiology of infection is also changing from vertical to horizontal route. In a cohort study with historical controls, the prevalence of HBV infection increased after the age of 16 (13). Recent studies pointed out that in Iran, horizontal transmission was the most important route of HBV transmission in new cases (14,

15). The carrier rate significantly decreased among Iranian neonates and the average age of infected individuals was increased; thus, to expand the effect of HBV vaccine in other groups, mass vaccination for some groups was implemented in Iran in 2007 (16).

2. Objectives

The aim of this study was to evaluate the effect of HB public vaccination program among young adults. We conducted a sero-epidemiological study of HBV infection in blood donors in Tehran from January 2005 to December 2011.

3. Patients and Methods

3.1. Study Population

The participants were selected from volunteer blood donors attending TBTC (Tehran Blood Transfusion Center) during 2005-2011, based on date of birth. All the donors born during 1989-1993 were enrolled as cases and the ones born during 1986-1988 were selected as controls (birth cohort comparison). The participants were interviewed according to IBTO (Iranian Blood Transfusion Organization) guidelines for blood donation. These guidelines were constant over the study time. Donors selected by medical screening were sampled for transfusion transmitted infection (TTI) viruses detection. All serum samples of the blood donors were screened for HBV, hepatitis C virus (HCV), HIV, and syphilis. Hepatitis B surface antigen (HBsAg) was screened using third generation ELISA kits. The initially reactive samples were tested in duplicates. The repeatedly reactive results were considered positive for confirmation assay. Confirmatory tests were performed on all repeatedly reactive donations using hepatitis B core antibody (HBcAb) and HBsAg confirmatory assays.

3.2. Hepatitis B Immunization

HB vaccination has been a part of the EPI of Iran since 1993 (2). All infants received HBV vaccine as part of routine children immunization program at zero, two, and six months old. To extend *HB* immunization, *HB* mass vaccination has been planned for adolescents born during 1989-1992. The vaccination campaigns were implemented in three rounds for four consecutive years from 2007 to 2010. In each round, the adolescents received 20 μg of a recombinant-DNA-derived hepatitis B vaccine (Euvax B®, LG Life Sciences, Jeonbuc-do, South Korea), administered intramuscularly in the deltoid muscle.

3.3. Definitions

Cases were defined as blood donors who met the age criterion for *HB* vaccination according to Iranian immunization schedule including those born during 1989-1993. Blood donors were divided to two categorizes for control selection. The first group of controls included nonconcurrent blood donors and the second group of controls included concurrent blood donors. Both control groups did not met the age criterion for *HB* vaccination in campaigns.

3.4. Laboratory Methods

All the blood samples were tested in duplicates, using a commercial immunoassay (Behring Enzygnost HBsAg 5.0 assay [Dade Behring]), to detect HBsAg. The HBsAg positive samples were tested by confirmation method. All the participants were notified of the positive results and provided with an interpretation of their serological markers

3.5. Statistical Analyses

The data were analyzed using SPSS for windows version 19.5. Chi-square test and Fisher's exact test with 95% confidence intervals were used, when appropriate. Results were considered significant when P value was < 0.05. The prevalence estimates were age-adjusted by the direct method, using the age groups listed above, for comparisons across the subgroups.

4. Results

In total, 202 631 subjects aged 17-22 years were enrolled in the study. Characteristics of the participants is shown in Table 1. Except for marital status, characteristics did not show any significant differences between case and control groups (concurrent and nonconcurrent groups).

4.1. Overall Prevalence of Hepatitis B Virus and Hepatitis C Virus Infections Among Vaccinated and Nonvaccinated Blood Donors

The prevalence of HBV infection was 57/100 000, 350/100 000, and 265/100 000 among blood donors born during 1989-1993 (cases), 1986-1988 (nonconcurrent controls), and 1989-1993 (concurrent controls), respectively, with statistical significance ($P < 0.01$) (Tables 2 - 4). The prevalence of HCV infection in the abovementioned groups were 28/100 000, 38/100 000, and 31/100 000; $P = 0.01$. HBV and HCV coinfection in the same individuals was not observed.

4.2. Age-Adjusted Estimates of Prevalence of Hepatitis B and Hepatitis C Virus Infections Among Vaccinated and Nonvaccinated Blood Donors

The age-adjusted prevalence of HBV infection was 40/100 000, 361/100 000, and 272/100 000 among blood donors born during 1989-1993 (cases), 1986-1988 (nonconcurrent controls), and 1989-1993 (concurrent controls), respectively, with statistical significance ($P < 0.01$). The prevalence of HCV infection in the same groups were 26/100 000, 38.5/100 000, and 32/100 000; $P = 0.01$. The prevalence of HBV and HCV infections in both genders are shown in Table 5.

Table 1. Characteristics Information of the Participants [a,b]

Characteristics	Cases (Blood Donors Born During 1989-1993)	Nonconcurrent Controls (Blood Donors Born During 1986-1988)	Concurrent Controls (Blood Donors Born During 1989-1993)	P Value
Gender				
Male	54029	59841	69433	NS
Female	6003 (10)	6459 (9.7%)	6866 (8.6%)	NS
Donation status				
First	36045	48384	46291	NS
Repeated	4702 (8%)	3700 (5.6%)	5181 (6.8%)	NS
Regular	19285 (32%)	17216 (26%)	24728 (32.2%)	NS
Marital status				
Single	58319	51164	61927	0.01
Married	5345 (8.4%)	15136 (22.8%)	13616 (18%)	0.01
Education				
Illiterate	53	89	73	
< 12 years	7369 (11.4%0)	8898 (13.4%)	9689 (12.7%)	NS
≥ 12 years	56942 (88.5%)	57313 (86.5%)	66360 (87.2%)	NS

[a] Abbreviation: NS, not significant.
[b] Data are presented as No. (%).

Table 2. Overall Prevalence of Hepatitis B virus and Hepatitis C Virus Infections in Nonconcurrent Controls [a]

Age at Donation Time , y	Sample Size	No. of Donors With Positive HBsAg	Prevalence in 10^5 (95% CI)	No. of Donors With Positive HCV Ab	Prevalence in 10^5 (95% CI)
17	321	1	311 (261-361)	0	0
18	4441	27	608 (594-622)	3	67 (60-74)
19	10433	38	364 (355-373)	4	38 (34-42)
20	13595	36	265 (258-272)	2	15 (13-17)
21	17372	60	345 (338-352)	6	34 (31-37)
22	20138	70	347 (340-354)	10	50 (47-53)
Total	66300	232	350 (346-354)	25	38 (36-40)

[a] Abbreviations: CI, confidence interval; HBsAg, hepatitis B surface antigen.

Table 3. Overall Prevalence of Hepatitis B virus and Hepatitis C Virus Infections Among Cases [a]

Age at Donation Time, y	Sample Size	No of Donors With positive HbsAg	Prevalence in 10^5 (95% CI)	No of Donors With Positive HCV Ab	Prevalence in 10^5 (95% CI)
17	323	0	0	0	0
18	9951	14	141 (134-148)	5	50 (46-54)
19	16410	16	98 (92-104)	6	37 (34-40)
20	14900	3	20 (18-22)	4	27 (24-30)
21	11947	1	8 (6.4-9.6)	2	17 (15-19)
22	6501	0	0	0	0
Total	60032	34	57 (55-59)	17	28 (25-31)

[a] Abbreviations: CI, confidence interval; HBsAg, hepatitis B surface antigen.

Table 4. Overall Prevalence of Hepatitis B virus and Hepatitis C Virus Infections in Concurrent Controls [a]

Age at Donation Time, y	Sample Size	No of Donors With Positive HBsAg	Prevalence in 10^5 (95% CI)	No of Donors With Positive HCV Ab	Prevalence in 10^5 (95% CI)
17	476	3	630 (578-670)	0	0
18	0	0	0	0	0
19	5142	27	525 (511-539)	2	39 (34-44)
20	13387	31	233 (226-300)	6	45 (41-49)
21	22706	68	300 (294-306)	7	31 (27.5-33.5)
22	34588	73	211 (207-215)	9	26 (24 -28)
Total	76299	202	265 (262-268)	24	31 (28-34)

[a] Abbreviations: CI, confidence interval; HBsAg, hepatitis B surface antigen.

Table 5. Prevalence of *Hepatitis B* and Hepatitis C Virus Infections in Male and Female Blood Donors [a]

	HBV **Infection Rate in 10^5**		**P Value**	**HCV Infection Rate in 10^5**		**P Value**
	Female	**Male**		**Female**	**Male**	
Cases	50	57	NS	17	30	0.01
Concurrent Controls	170	270	0.01	30	31	NS
Non Concurrent Controls	330	350	0.043	0	42	1

[a] Abbreviation: NS, not significant.

5. Discussion

The *HB* vaccination program in Iran has been provided for all newborns since 1993. An extended vaccination program for adolescents born during 1989-1992 was performed during 2007-2010 (3). In the present study, we found a significant reduction of HBV infection prevalence among blood donors born during 1989-1993 in Tehran. HBsAg seropositivity in blood donors who received HBV vaccine (cases) compared with nonconcurrent controls, (longitudinal analysis) showed more than six times decrease; however, compared with concurrent controls (cross-sectional analysis), the prevalence of HBsAg decreased about 4.6 times. The observed differences in prevalence of HBsAg between case and control blood donors may be because of preventive applications, which lowered the prevalence of HBV infections in cases and concurrent controls. This significant time-dependent decrease (17) in the rate of HBV-positive blood donors was observed around the time of the study, probably due to implementing some strategies including expansion of educational programs, especially in the at-risk groups, as well as granting harm reduction establishments to reduce HBV transmission in IDUs and sex workers, prisoners and drivers. In addition, introducing new guidelines and regulations for high-risk professions should to be considered.

The differences between cases and concurrent controls were obviously due to *HB* vaccination in case blood donors. HCV Ab seropositivity rate among cases compared with nonconcurrent controls (longitudinal analysis) 1.4 times lesser; however, compared with concurrent controls (cross-sectional analysis), prevalence of HCV Ab decreased about 1.1 times. Therefore, in this study, the slight decrease in HCV prevalence revealed that preventive applications other than vaccination may not be enough to explain these differences; thus, the prevalence of HCV infection decreased at a slower rate due to lack of HCV vaccination.

The changing epidemiology of HBV infection from vertical to horizontal route in Iran after introducing the *HB* vaccination program may be a supportive document for effective role of horizontal transmission prevention of HBV in blood donors (18). However, in a cohort study (November 2001 to December 2003) with historical controls, the prevalence of HBV infection increased after the age of 16 (13). Low coverage of *HB* mass vaccination (less than 50%) was reported from three provinces of Iran including Kohkiloyeh-Boyerahmad, Qom, and Tehran (16). Therefore, if the study was performed on the total sample of blood donors in Iran, it might obtain more prominent results.

The greatest effect of *HB* vaccination in diminishing the HBsAg titer in blood donors was observed in 17 and 22-year-old age groups. This phenomenon in the age group of 17 years old may be due to *HB* vaccination in the neonatal period, since vaccination against HBV before the age of one year is more effective than before the first year (19); but, in age group of 22 years, we did not have any evidence; although, the root of HBV infection transmission in Iran seems to be changing from vertical to horizontal in the recent years, which may be an alternative evidence. Our results were similar to the previous studies (19-21); but in our study, we compared the prevalence were performed in historical (nonconcurrent) and concurrent control groups. It seems more possible to attribute the documented decline when comparison was done in concurrent control group.

In conclusion, universal HB immunization has successfully affected the prevalence rate in blood donors. The HBV infection (positive HBsAg) rates among blood donors in Tehran have shown significant decreases since the vaccination program has been launched. The HB immunization program should be proceeded to eradicate HBV infection. Further studies to evaluate the long-term benefits of HB vaccination (reduction in prevalence of severe chronic liver disease as well as the HCC associated with HBV infection) in Tehran will be required.

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Authors' Contributions

Seyed Mohammad Mirrezaie wrote the first manuscript; Hamid Reza Saber participated in data gathering, analysis, and manuscript revision; Bashir Hajibeigi, Ebadollah Salekmoghaddam and Ali Abbasian revised the manuscript, Seyed Moayed Alavian provided the idea and revised the manuscript.

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