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Observational study of vaccine effectiveness 20 years after the introduction of universal hepatitis B vaccination in Tunisia

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ABSTRACT

Objectives: The objectives of this study were to estimate the national prevalence of hepatitis B infection in Tunisia using data from a nationwide survey, to compare results with those obtained in 1996 survey and to evaluate the impact of vaccination twenty years after its introduction.
Methods: A National household-based cross sectional and serological survey was undertaken in 2015 from randomly selected districts using two-stage sampling. Data collection was performed using standardized and pretested questionnaires and collected blood samples were tested for markers of hepatitis B virus infection.
Results: National point prevalence of Hepatitis B surface antigen was 1.7% (95% CI [1.6–1.9%]). The highest prevalence was found in the Center and South regions with respectively 2.3% (95% CI [2.0–2.7%]) and 2.2% (95% CI [1.8–2.8%]). Vaccine effectiveness (VE) was 88.6% (95% CI [81.5–93.0%]) and was higher among population aged less than 20 years 96.1% (95% CI [70.1–99.5%]) than those aged more than 20 years 59.0% (95% CI [32.0–75.3%]). VE was 85.6% (95% CI [65.8–93.9%]) is hyper-endemic areas and 89.1% (95% CI [80.3–94.0%]) in meso-endemic and hypo-endemic areas.
Conclusions: The prevalence of Hepatitis B surface antigen decreased compared to previous estimations and classify Tunisia as a low endemic country as result to the introduction of vaccination since 1995.

1. Introduction

Hepatitis B virus (HBV) infection is a major public health problem. The world health organization (WHO) estimates that 257 million people have been exposed to this virus [1]. This is a viral infection that increases the risk of developing hepatocellular carcinoma (HCC) and cirrhosis, causing nearly one million deaths per year [2].

In Tunisia, the epidemiological context of HBV infection is characterized by the absence of accurate national data on the prevalence of HBV infection markers. The data available until now date from the 1990s and were obtained by combining different studies of various populations and regions and it classified Tunisia as a meso-endemic country [3–6].The results shown that the prevalence of Hepatitis B surface antigen (HBsAg) among blood donors varies from 5 to 10% and was 6.3% for young male military recruits aged between 20 and 25 years [4,7]. In another study of 17 children aged from 1 to 12 in the Sousse region the prevalence was 3.3% [8].

A first population study was conducted in 1996 in two governorates of the North and South of the country. It estimated the prevalence of HBsAg in the population at 4.2% in the North and 5.6% in the South with an heterogeneity within the same region varying from 0 to 19.6% [9]. The tests of HBsAg in blood donations in Tunisia within the last decade showed a relative decline in prevalence from 3.65% in 2001 to 1.98% in 2010 for 100 donations [10]. Therefore, no accurate national study has previously been conducted in our country.

As a part of the Expanded Programme on Immunization (EPI), hepatitis B vaccination was introduced in Tunisia in 1995. Initially, the schedule required vaccination of at the age of 3, 4, and 9 months in addition to serovaccination at birth of babies born to

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HBsAg positive mothers [11]. Since 2006, the schedule changed and vaccine doses became administrated systematically to newborns then at the ages of 2 and 6 months. Vaccination of health workers has been introduced since 1992 [12].

Our study is a part of a national survey on viral hepatitis seroprevalence (A, B and C). It aims to estimate the national and regional prevalences of the various markers of HBV infection in the Tunisian population and evaluate the impact of vaccination twenty years after its introduction.

2. Methods

2.1. Study design

A national cross-sectional survey based on the general population and covered all the 24 Tunisian governorates was undertaken between December 2014 and June 2015.

2.2. Study population

The source population was represented by the entire Tunisian population, regardless of age, sex and geographical origin.

Sampling as well as calculation of the sampling fractions was carried out using the data provided by the National Institute of Statistics (INS) basing on the national census of population of 2014.

According to the fact that HBsAg prevalence varies with the geographical area, a stratification of the Tunisian territory into 7 major regions was carried out. Furthermore, because of the impossibility of accessing a single survey base for all individuals, a two-stage cluster sampling plan was chosen. In the first stage of sampling, all governorates were included then a sample of districts weighted by estimated population size was randomly selected using unequal probability sampling. In the second stage, households were also randomly selected in each of the first-stage clusters and all family members present during the visit of interviewers were included. Members absent during the first visit were called for a second appointment and interviewed during the second visit of household within the same month.

The necessary sample size in the general population was calculated using the two-stage cluster sampling formula $(n = DE\left(z_{\frac{\alpha}{2}}^2 p(1-p)\right)/d^2)$ where d is the precision function, p is the prevalence of the infection, $Z_{\frac{\alpha}{2}}$ is the critical value (equal to 1.96 for α=0.05) and DE (design effect) is a correction factor.

Since our study is a part a national survey on three types of viral (A, B and C), the sample seize was calculated basing on hepatitis C infection prevalence estimation according to the choice made by the survey committee. If anti-HCV antibody expected prevalence p was 1.2%, DE was equal to 1.5%, d equal to 0.2% and at a significance level of 0.05 the estimated sample size is 21660.

2.3. Data and sample collection

Data was collected by visits to all houses within the study sample by beforehand trained doctors and interviewers using three standardized questionnaires. The first and second questionnaires included family general information (e.g. address, family size, socio-economic level, health care accessibility), risk factors related to HBV infection (e.g. sexual behaviour, transfusion, history of hospitalization, tattoo, drug use, scarification). The third and last questionnaire concerned subjects who already know their seropositivity for HBsAg and collected medical care related data. Vaccination status was assessed by consulting the up-to-date personal immunization record.

After obtaining subjects consent (parents for minors), questionnaires were filled out and a blood sample was properly collected for serological testing. These samples were transferred to Aziza Othmana Hospital at -20C temperature (cardice).

2.4. Hepatitis B serological screening

This part of study was performed at the Microbiology-Biochemistry laboratory of Aziza Othmana Hospital, Tunis. Blood samples were previously codified in order to be processed anonymously.

The plasma obtained by blood centrifugation at 3500 tr/min is the biological material used in this study. Sera were first tested for all subjects for hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti-HBc) using quantitative electrochemiluminescence immunoassay (ECLIA) method on the «Cobas e411» automate (Roche Diagnostics, Mannheim, Germany). This in vitro system provides a very high sensitivity and specificity and it is fully automated. Then, HBsAg screening was performed only for anti-HBc(+)/anti-HBs(−) subjects using the same technique on the same automate.

The following definitions of HBV status were used:

Isolated anti-HBc was defined as the presence of anti-HBc in the absence of HBsAg and anti-HBs. Vaccine immunity was defined as presence of anti-HBs in the absence of anti-HBc. Recovered hepatitis B infection was defined as presence of anti-HBc and anti-HBs. Doubtful HBV status was defined as the presence of anti-HBc and Anti-HBs with HBsAg rate less than the cut-off of positivity and more than the cut-off of negative given by the method.

The endemicity of different areas was defined as follow: High endemic areas, if HBsAg prevalence exceeds 8%; Low endemic regions, if HBsAg prevalence is less than 2%; Meso-endemic areas, if HBsAg prevalence is between 2% and 8%.

2.5. Data entry and analysis

Filled questionnaires were transferred to the Tunisian National Observatory of New and Emerging Diseases, coordinator of the survey, where data entry was performed after validation using Epi-Data 1.

The final data entry files were merged with HBV markers test results in the same database and multiple quality checks were done before data analysis using SPSS 20.0 software.

HBV infection prevalence was estimated with 95% confidence interval [CI] basing on the sample plan weights to allow comparisons between districts. The relation between HBV positivity and demographic, epidemiological, behavioral and clinical differences was examined by univariate analysis using chi-square test for percentages comparison and Odds Ratio for risk estimation with a 95% CI. All estimations and extrapolations were adjusted to the sample design based on the results of the 2014 national census using complex samples package.

2.6. Vaccine effectiveness

The Vaccine Effectiveness (VE) was calculated using the following formula: VE = 1 – Odds-Ratio (OR) [13], where OR is the ratio of odds of being vaccinated among subjects with positive HBsAg test results to the odds of being vaccinated among subjects with negative HBsAg test results.

2.7. Ethical considerations

The study was approved by the Higher Council of Statistics and National Ethic Committee of Pasteur Institute of Tunis and the National Instance of Personal Data Protection. It ensured confidentiality, anonymity and the right to refuse. Written informed

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