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# Exposure time to hepatitis B virus and associated risk factors among children in Edirne, Turkey

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## SUMMARY

Hepatitis B virus (HBV) infection is endemic in Turkey, but the main routes of transmission were not well established. This study aims to detect the exposure time to HBV and associated risk factors among children. In a sampling group of chıldren aged 0–19 years living in Edirne, antiHBc, antiHBs and HBsAg were screened by the microELISA method. A questionnaire was also completed for each child. In 717 children that were included in the study, the total antiHBc seropositivity was 5·4% and was 1·8, 0·8, 1·7, 6·8, 11·8% in 0–1, 2–5, 6–10, 11–14, 15–19 years age groups respectively. The overall HBsAg seropositivity was 1·7%. The risk of HBV infection increased after the age of 10 years (OR 7·79, 95% CI 3·01–20·16). Collective circumcision was the only independent factor according to regression analysis. Children living in Edirne should be vaccinated against HBV before reaching 11 years of age.

## INTRODUCTION

The epidemiology of hepatitis B virus (HBV) infection needs to be properly determined in order to establish an effective vaccination strategy. The epidemiological characteristics of HBV infection vary considerably in different parts of the world. In developed nations such as the United States and western Europe, the HBsAg prevalence is $<1$% and most of the cases are related to known risk factors [1]. However in Southeast Asia where HBsAg prevalence is 10–20%, perinatal transmission has been detected as the most important method of transmission [2]. In Africa and Middle East where HBsAg prevalence is also high, the main mode of transmission is horizontal, particularly among children [3, 4]. HBsAg carrier rates in different countries in the Middle East range from 2 to 18·5% and the majority of these countries include hepatitis B vaccination in their expanded programme on immunization (EPI) [5]. In 1997, HBV vaccination was begun for all newborns and this was accepted as the seventh vaccine in Turkey also. However, the deficient and disorganized data about the epidemiology of HBV infection makes it difficult to decide which age groups, apart from newborns, should be included in the target group for immunization.

In this study, the aim was to detect the age of exposure to HBV and the associated risk factors among children in Edirne, a city located at the border with Greece and Bulgaria in the northwestern part of Turkey.

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## MATERIALS AND METHODS

### Cases

The study was performed in a sampling group of children aged 0–19 years living in Edirne. The sample size calculation was based on the population data given by the Provincial Health Administration. The sampling group was weighted according to the population of primary health care units (PHUs). Different PHUs were also weighted by age group. The number of children in each age group were calculated in relation to the proportion of the population in those groups. The children to be included in the study were randomly chosen from household data sheets of the related PHUs. In the Turkish Health Organization, these units have demographic records of all the citizens in their regions and are responsible for primary health practice.

In Edirne city, the population aged between 0 and 19 years was 36162 and there were no data about HBsAg seroprevalence in this region. Therefore, the estimated mean seroprevalence of $8 \pm 2\%$ in Turkey [6] was assumed to be valid for Edirne also. As a result, sample size was calculated as 706 with 5% error. The number of children in each sampling group was 32, 117, 167, 184 and 206 for 0–1, 2–5, 6–10, 11–14 and 15–19 years age groups respectively.

### Design of the study

The study was performed after permission from the local Committee of Ethics in Science. Participation was on a voluntary basis and in accordance with the Guidelines of the Declaration of Helsinki II. Excluded from the study were: other children living in the same house, children with two doses of HBV vaccination in last 6 months or who had already completed their vaccination schedule and/or children with insufficient data necessary for statistical analysis.

### Factors affecting the exposure time

The children included the study, and their families, were invited to their local PHU, and a questionnaire for each child was completed by the child and/or the family in order to define the probable risk factors.

The questionnaire elicited information on demographic data as well as: where and how long the child has lived up to the time of the study; the person who took care of the child when she/he was a baby; number of siblings; whether the child shared a toothbrush or a razor with anybody; contact with an icteric case; presence of any known blood disease; history of blood transfusion; operation undergone and its type; history of hospitalization, dental treatment, approximate total number of injections; history of HBV vaccination, and – for boys – history of penile circumcision. History of sexual intercourse was not included because it was believed that the children would not correctly answer this question due to the crowded environment of the PHU as well as the presence of their family.

Table 1. *Socioeconomic criteria and scoring to determine the socioeconomic status of the family**

| Criteria | Score |
|---|---|
| Concrete house | 5 |
| Refrigerator | 5 |
| Piped water reaching the house | 3 |
| Private car | 2 |
| Sufficient calorie intake | 2 |
| Central heating system in the house | 1 |
| Toilet inside the house | 1 |
| Radio | 1 |
| Television | 1 |
| Washing machine | 5 |
| Dishwasher | 7 |
| Telephone | 5 |
| Own house | 2 |

* Adapted from Toukan et al. [7].

In addition, parents were also questioned about their age; place of birth; educational status; occupation; where and how long the father has lived; number of people living per room in the family home; history of icteric disease, diabetes mellitus, debility or mental retardation in the family, and known HBsAg seropositivity of the mother. Socioeconomic status of the family was determined using a socioeconomic status index (SEI) adapted from the scoring system as described by Toukan et al. [7] relevant to the features of the house and its contents (Table 1). All scores were totalled to calculate the SEI. Therefore, the SEI of all cases ranged between 0 and 40. Arbitrary cut-off points for socioeconomic status were as follows: lower, 0–20 points; lower-middle, 21–25 points; upper-middle, 26–30 points; and upper, 31–40 points.

In order to investigate the effect of the child's place of birth, and where and how long the child and father have lived so far on antiHBc seropositivity, a city scale arranged by the State Planning Organization according to gross domestic product *per capita* was

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Table 2. *AntiHBc seropositivity according to gender and age groups*

| Age group (years) | Boys | | Girls | | Total | |
|---|---|---|---|---|---|---|
| | *N* | AntiHBc (+) *n* (%) | *N* | AntiHBc (+) *n* (%) | *N* | AntiHBc (+) *n* (%) |
| 0–1 | 25 | 0 (0) | 32 | 1 (3·1) | 57 | 1 (1·8) |
| 2–5 | 67 | 1 (1·5) | 65 | 0 (0) | 132 | 1 (0·8) |
| 6–10 | 88 | 1 (1·1) | 90 | 2 (2·2) | 178 | 3 (1·7) |
| 11–14 | 79 | 5 (6·3) | 68 | 5 (7·4) | 147 | 10 (6·8) |
| 15–19 | 101 | 12 (11·9) | 102 | 12 (11·8) | 203 | 24 (11·8) |
| Total | 360 | 19 (5·3) | 357 | 20 (5·6) | 717 | 39 (5·4) |

used [8]. This scale was divided into four equal groups designated A, B, C and D (decreasing from A to D).

### HBV markers

The blood samples of the children were taken by a trained phlebotomist at the individual PHUs following the interview. They were immediately transported to the laboratory; sera were separated and stored at −70 °C, and antiHBc, HBsAg and antiHBs were tested using the micro-ELISA method (Organon Teknika, Boxtel, The Netherlands). AntiHBc seropositivity was accepted as an indication of HBV exposure. Positive results for both antiHBc and HBsAg were interpreted as chronic infection and such cases underwent further medical evaluation. Positive results for both antiHBc and antiHBs were considered as immunity by natural infection. When only antiHBc positivity was present, the test was repeated and recurrent positivity was accepted as evidence of exposure to HBV [9].

### Statistical methods

Sample size was calculated by using Epi-Info (version 6.0) software (CDC, Atlanta, GA, USA). The distribution of categorical data was tested by Pearson's $\chi^2$ test (Fisher's exact $\chi^2$ test if the expected value was $<5$ in a cell). For binary variable risk calculations and for differences between numeric values with multiple groups one-way ANOVA tests were used. The Tukey test was performed for the detection of the source of difference(s). Regression analysis was used to test numeric, ordinal or binary variables at the same time. All variables included in the model were assumed to be independent. All statistical evaluations were performed using SPSS for Windows (version 9.0).

## RESULTS

A total of 717 children were included in the study. Of these, 39 (5·4%) were antiHBc positive and the gender distribution was similar in all age groups (Table 2). There was only one child with antiHBc positivity in the 0–1 year age group, HBsAg and antiHBs were negative and the reason for the antiHBc seropositivity was most probably due to maternal antibodies. AntiHBc seropositivity differed among age groups ($\chi^2=28{\cdot}62$, $P<0{\cdot}01$) and the most significant difference was detected between the 6–10 and 11–14 years age groups (OR 7·79, 95% CI 3·01–20·16). The mean HBsAg positivity was 1·7%.

There was no difference in antiHBc seropositivity according to the districts where the PHUs were located ($\chi^2=7{\cdot}22$, $P=0{\cdot}41$).

Socioeconomic status did not affect seropositivity. The PHU districts were grouped according to SEI scores using one-way ANOVA and Tukey tests. Thus, the districts were divided into four groups with mean SEI scores ranging from 32·7 to 17·0 ($F=44{\cdot}7$, $P<0{\cdot}01$). There was no difference on the basis of antiHBc seropositivity in these four different groups of districts ($\chi^2=1{\cdot}93$, $P=0{\cdot}59$). When SEI scores of the children's family were evaluated, again no difference in frequency of antiHBc seropositivity was observed ($\chi^2=1{\cdot}13$, $P=0{\cdot}77$).

When sociodemographic data that might be responsible for exposure and, therefore, antiHBc seropositivity was analysed, it was found that the number of siblings and father's educational status were the two factors that affected antiHBc positivity. Being a single child was a positive factor for being seronegative. In the group of middle-school-educated father's children seropositivity was found to be high compared to the lower or higher groups of middle-school-educated father's children. However, the effect

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Table 3. *The effect of sociodemographic factors on antiHBc seropositivity*

| | AntiHBc (+) | | AntiHBc (−) | | | |
|---|---|---|---|---|---|---|
| Sociodemographic factor | *n* | % | *n* | % | $\chi^2$ | *P* |
| Gender | | | | | 0·85 | 0·87 |
| Girl | 19 | 5·3 | 341 | 94·7 | | |
| Boy | 20 | 5·6 | 337 | 94·4 | | |
| Place of birth* | | | | | 2·80 | 0·42 |
| A | 36 | 6·2 | 541 | 93·8 | | |
| B | — | — | 14 | 100·0 | | |
| C | 1 | 7·7 | 12 | 92·3 | | |
| D | 2 | 15·4 | 11 | 84·6 | | |
| Mother's educational level | | | | | 0·75 | 0·86 |
| Primary school or lower | 28 | 5·7 | 467 | 94·3 | | |
| Middle school | 4 | 6·2 | 61 | 93·8 | | |
| High school | 5 | 3·9 | 122 | 96·1 | | |
| University | 2 | 6·7 | 28 | 93·3 | | |
| Father's educational level | | | | | 8·43 | 0·04 |
| Primary school or lower | 16 | 4·3 | 355 | 95·7 | | |
| Middle school | 12 | 11·2 | 95 | 88·8 | | |
| High school | 7 | 4·6 | 145 | 95·4 | | |
| University | 3 | 4·0 | 72 | 96·0 | | |
| Number of siblings | | | | | 8·32 | 0·02 |
| 0 | 2 | 1·2 | 163 | 98·8 | | |
| 1–2 | 30 | 6·4 | 439 | 93·6 | | |
| >2 | 7 | 8·9 | 72 | 91·1 | | |
| Persons per room | | | | | 3·00 | 0·22 |
| <1·01 | 15 | 4·6 | 310 | 95·4 | | |
| 1·01–2 | 17 | 5·3 | 302 | 94·7 | | |
| >2 | 7 | 9·7 | 65 | 90·3 | | |

* Groups were created relevant to personal income in child's city of birth (prepared with data from ref. [8], see Methods section for description; A is the highest, D is the lowest).

of mother's educational status and the number of people living together with the child in the same house was not significant. Neither the place of birth nor its gross domestic product *per capita*, nor the gender of the children was a criterion for antiHBc seropositivity (Table 3). Only seven mothers were aware of their HBsAg seropositivity and none of their children were AntiHBc positive. A great majority of the mothers (58·7%) were unaware of their HBsAg status.

In this study, apart from sociodemographic data, 11 other parameters which were possible causes of transmission were also evaluated (Table 4). By comparing these parameters using single variable analysis methods, a significant effect for collective circumcision on antiHBc seropositivity was detected. Children circumcised collectively with other children had more risk compared to children not circumcised or circumcised alone (OR 2·81, 95% CI 1·28–6·19).

When all variables that could be responsible for transmission and their effect on antiHBc seropositivity were evaluated using logistic regression analysis, collectively circumcised children had a 3·06 times greater risk than children not circumcised or circumcised alone (95% CI 1·29–7·27). No other variable was significantly associated with being antiHBc seropositive in the regression analysis.

## DISCUSSION

There is no known study in the literature covering the prevalence of HBV infection in children in the Trakya region (European part of Turkey). The validity of our assumption that the estimated rate of HBsAg seropositivity for Turkey (8 ±2%) [4] could also be used for the Trakya region and specifically for the city of Edirne, was questionable since overall HBsAg

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Table 4. *AntiHBc seropositivity and the effects of factors that could be directly responsible for the transmission of HBV infection*

| | AntiHBc (+) | | AntiHBc (−) | | | |
|---|---|---|---|---|---|---|
| Risk factor | *n* | % | *n* | % | $\chi^2$ | *P* |
| Sharing toothbrush and/or razor | | | | | | 0·34* |
| No | 37 | 5·4 | 652 | 94·6 | | |
| Yes | 2 | 9·1 | 20 | 90·9 | | |
| Contact with an icteric patient | | | | | | 0·74* |
| No | 36 | 5·4 | 629 | 94·6 | | |
| Yes | 3 | 6·1 | 46 | 93·9 | | |
| History of blood transfusion | | | | | | 1·00* |
| No | 39 | 5·6 | 662 | 94·4 | | |
| Yes | 0 | — | 11 | 100·0 | | |
| Approximate number of injections | | | | | 3·76 | 0·44 |
| 0 | 3 | 3·2 | 91 | 96·8 | | |
| 1–10 | 10 | 5·0 | 192 | 95·0 | | |
| 11–25 | 15 | 7·1 | 195 | 92·9 | | |
| 26–50 | 4 | 3·6 | 108 | 96·4 | | |
| >50 | 4 | 10·2 | 44 | 89·8 | | |
| History of hospitalization | | | | | | 1·00* |
| No | 39 | 5·6 | 662 | 94·4 | | |
| Yes | 0 | — | 16 | 100·0 | | |
| History of operation | | | | | | 1·00* |
| No | 34 | 5·4 | 590 | 94·6 | | |
| Yes | 5 | 5·6 | 84 | 94·4 | | |
| An icteric case in the family | | | | | 1·05 | 0·59 |
| No | 30 | 5·1 | 559 | 94·9 | | |
| Close relative | 7 | 7·7 | 84 | 92·3 | | |
| Distant relative | 2 | 6·1 | 31 | 93·9 | | |
| Diabetes mellitus in the family | | | | | 1·13 | 0·29 |
| No | 35 | 5·9 | 557 | 94·1 | | |
| Yes | 4 | 3·4 | 112 | 96·6 | | |
| Person taking care of the child | | | | | 2·50 | 0·29 |
| Mother | 36 | 5·8 | 588 | 94·2 | | |
| Babysitter | 3 | 5·8 | 49 | 94·2 | | |
| Relative | 0 | — | 41 | 100·0 | | |
| Dental treatment | | | | | 0·81 | 0·37 |
| No | 24 | 4·9 | 462 | 95·1 | | |
| Yes | 15 | 6·6 | 213 | 93·4 | | |
| Circumcision | | | | | 7·72 | 0·02 |
| No | 22 | 4·5 | 470 | 95·5 | | |
| Alone | 8 | 6·2 | 121 | 93·8 | | |
| Collective | 9 | 12·5 | 63 | 87·5 | | |

* Analysed by Fisher's exact $\chi^2$ test.

seropositivity was found to be 1·7%. AntiHBc as an indicator of HBV exposure was detected at 5·4%. These data showed that the incidence of HBV infection during the childhood period in Edirne was lower than the predicted value prior to the study. On the other hand if the sampling group were calculated taking the 5·4% ratio of antiHBc seropositivity as a basis, the group to be formed would consist of 490 children with 5% error, therefore, 717 children are sufficient to represent Edirne city.

HBsAg seropositivity in other regions of Turkey ranges from 3·9% to 23%, and the antiHBs ratio ranges from 19·8% to 50% [6]. The two most important reasons for this great difference are the

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composition of the groups and the methodology. However, data from the childhood period shows that the HBV infection rate is generally very low in the first decade and the risk increases parallel with age in later periods. For instance, in a study performed with 24 108 people in Izmir, a Turkish city in western Anatolia, the prevalence of HBV infection was 5% for the first 10 years of age, showed an increase in the 11–15 years age group, and became $>50$% after the fifth decade [10]. Because our study group is composed of children $\leqslant 19$ years of age, we cannot say that a similar rise also existed in Edirne. However, the prevalence during the childhood period in Izmir is consistent with our data. In the above study [10], HBsAg seroprevalence remained below the 2% level in the first 10 years of age. In a study from Sivas, another Turkish city in central Anatolia, while no HBsAg was detected in the 3–10 years age group, it was present in 5·2% of the 11–20 years age group and antiHBs frequencies were 1·8 and 13·9% in the same groups respectively [11]. All these results support the view that the risk of exposure with HBV is uncommon until 10 years of age. On the other hand, in a study in the southeastern part of Turkey where the first 10 years of age had not been evaluated, HBsAg and antiHBs seropositivities in the 10–19 years age group were detected as 13·1% and 37·8% respectively [12]. These data also show that HBV seroprevalence has a regional variability in Turkey. However Degertekin et al. [13] have recently reported that the risk of HBV infection increased mostly between the ages of 7 and 11 years in this latter region.

In our study, the father's educational status and the number of siblings are associated with antiHBc seropositivity. It might be reasonable to think that with an increasing number of siblings, the risk for having a HBsAg-seropositive member in the family increases. However, in this study, the effect of number of people per room or socioeconomic level could not be shown. In the literature it has been shown that when the mother is HBsAg seropositive, the risk of HBV exposure increases up to 5·4-fold [14], and a similar ratio is detected if the brother or sister is a carrier [15]. However, in our study, HBV markers of other family members have not been evaluated. Regarding the effect of having a middle-school-educated father on antiHBc seropositivity, no reasonable explanation could be given.

The well-known risk factors for HBV such as blood transfusion, operation, sharing of toothbrush or razor, estimated number of injections and dental treatment [16] have not been found as important risk factors in the epidemiology of HBV infection for children in Edirne.

Multiple regression analysis yielded collective circumcision as the sole factor effective in the risk of HBV exposure. In Turkey only male children are circumcised because of religious reasons. When 24 boys with no data about circumcision were excluded, 201 out of 333 boys were circumcised and 72 of them (35·8%) had a history of collective circumcision. Collective circumcision is carried out in two different ways in Turkey. The common practice is collective circumcision of brothers or children of close relatives limiting the number of children to as few as 2–5. However, in cases of charity, this number is generally much higher; sometimes reaching up to hundreds. In such cases, the high probability of using the same surgical equipments for more than one child increases the risk of HBV infection. In addition the procedure is generally carried out by an informal professional circumciser. Even in European countries, collective circumcision by a professional circumciser is more common in Turkish Muslims than in others originating from different countries [17].

Recent epidemiological studies have shown that in high-risk populations in sub-Saharan Africa, male circumcision is associated with a reduced risk of HIV infection [18]. However, use of contaminated equipment during collective circumcision may cause the transmission of bloodborne viruses such as HBV [19], hepatitis C virus [20] or even HIV itself.

In Turkey, the age of circumcision is not standard but is generally performed before 11–12 years of age. In this study, it has been shown that the risk of HBV exposure increased fourfold in the 6–10 and 11–14 years age groups. Therefore, collective circumcision is seen as one of the most significant risk factors for HBV infection of boys in this age group. However, since no difference could be detected between boys and girls, additional factors must also be present. Horizontal transmission among children may explain the seropositivity of girls and boys, but we were unable to study this route. One of the most well-known ways of horizontal transmission is sexual intercourse [21]. However, the children were not asked such a question as it was thought that they would not answer correctly due to the crowded environment of the PHU and the presence of family members. However, a study among the students of Trakya University where most are from the vicinity, revealed that the age of first sexual intercourse was $19{\cdot}5 \pm 2{\cdot}2$ for girls and

17·7 ± 2·2 for boys [22]. Therefore, sexual intercourse cannot be stated as a risk factor for the 11–14 years age group in this region. Yet, sexual transmission may partly explain the seropositivity in the 15–19 years age group since 24 out of 39 (61·5%) antiHBc-seropositive children came from this age group. Horizontal transmission of HBV without apparent sexual or parenteral exposure is common in endemic areas. In most cases, the route of transmission is unknown [23]. The role of intra-familial horizontal spread (probably via saliva or open wounds) in households with a persistent carrier has been demonstrated well by epidemiological or molecular studies [24, 25]. While we did not serologically screen other family members, we enquired about the presence of known HBsAg seropositivity of mothers and the history of any icteric case in the family, however the great majority were uninformed. Contact infection as a horizontal transmission in everyday life in school is another explanation that is more difficult to prove [13, 26]. Cultural or behavioural factors which have been described in some communities, e.g. injections using unsterilized needles [27], sharing of personal and household articles [28], dental procedures and tattoos in unsafe circumstances [29] were enquired about directly or indirectly, but their effects could not be shown in this study.

Since it has been demonstrated that the 11–14 years age group had a significantly high risk for HBV exposure not only in Edirne but also in other regions of Turkey, it is possible that high risk might be related not only with age, but also with the years in which the high risk of exposure existed. Turkey started to take preventive measures for bloodborne diseases during the 1980s. Primary measures were serological screening tests of blood in the blood banks (in 1983) and use of disposable injectors for the first time in the expanded programme on immunization (in 1985), followed by the use of disposable syringes and other disposable materials in all health centres over the next 2–3 years. Finally, in 1994 the Municipality of Edirne made a decision that barbers and hair-dressing salons should maintain sterilizers for the sterilization of shaving and manicure/pedicure equipment. Our study was conducted in 1998 and children who were 10 years old then were born in 1987. Thus, the risk was for children born in 1986 and before. Since there were no precautions taken at that time, the risk could also have been high in this period. One way to prove this hypothesis is to repeat our study 5 years later. Finding a shift of the risk period to the 15–19 years age group from the 11–14 years age group will support this idea.

In conclusion, exposure risk for HBV increased after the age of 10 years in Edirne, however, risk factors detected in the United States or European countries could not explain the reason for that rise. In this study, however, the effect of a unique factor for Turkey, namely collective circumcision, has been stated for the first time. Therefore, use of sterilized equipment should be compulsory for each child during circumcision. Moreover, all children up to 11 years of age, in addition to the 0 years age group, should be vaccinated without the need for screening tests in Edirne.

HBV vaccination is free for newborns and the defined risk groups in the PHUs in Turkey, but others are not covered by the system. This study's results suggest the need for a catch-up strategy for older children in addition to universal infant vaccination in Turkey.

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