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Hepatitis B Virus Infections Among Children and Adolescents in Germany

Migration Background as a Risk Factor in a Low Seroprevalence Population

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Background: *Data on hepatitis B (HB) infection prevalence among children and adolescents in Germany are scarce. We estimated seroprevalence of HB infection and assessed determinants for HB infection among children and adolescents in Germany from a representative population sample.*

Methods: *From 2003 to 2006, the Robert Koch Institute conducted a nationwide cross-sectional Health Interview and Examination Survey for Children and Adolescents in Germany. Data on age, gender, migration background, and socioeconomic status were collected through questionnaires. A child was defined as having a 2-sided migration background if both parents, or the child and 1 parent, immigrated, and a 1-sided migration background if only 1 parent immigrated. Among children with migration background, a first-generation migrant was defined as born outside Germany; a second-generation migrant was born in Germany. Information on HB vaccination status was obtained from vaccination cards. Serologic samples from participants were tested for anti-hepatitis B core antigen (anti-HBc) and hepatitis B surface antigen. We performed weighted univariable and multivariable logistic regression analyses to assess determinants for HB infection.*
Results: *Of 13,065 participants (3–17 years), 0.5% (95% confidence interval [CI], 0.4–0.7) were anti-HBc positive, among whom 38.7% (95% CI, 20.0 –57.5) were hepatitis B surface antigen positive. Two-sided migration background and being a first- or second-generation migrant were significantly associated with anti-HBc positivity (odds ratio [OR]: 8.3, 95% CI: 4.0 –17.4; OR: 11.0, 95% CI: 3.5–35.0; OR: 3.0, 95% CI: 1.2–7.3). No further determinants were found.*
Conclusions: *HB infection is rare among children and adolescents in Germany. First- and second-generation migrant children can be considered to be at risk for HB infection, 2-sided migration background or being a first-generation migrant carried the greatest risk. Targeted testing for HB infection and early HB vaccination should be provided to immigrants' children.*

Hepatitis B virus (HBV) infections acquired during childhood often run an asymptomatic course, but likely result in chronic infections that can progress to cirrhosis or hepatocellular carcinoma.[1–4]

Since 1995, the German Standing Vaccination Committee (STIKO) recommends HB vaccination for all infants from the age of 2 months, children and adolescents in Germany. Pre- and postvaccination serologic testing is not recommended for infants, children, and adolescents who are not at particular risk for HBV infection.5,6 Since 1994, hepatitis B surface antigen (HBsAg, a marker for a current HBV

infection) screening of pregnant women is mandatory in Germany. Newborns of HBsAg-positive mothers receive a first dose of HB vaccine and passive immunization with HB immunoglobulin immediately after birth.[5–8]

Even though there is knowledge on HB epidemiology among adults in Germany,[9,10] to date, neither representative data on HB prevalence nor on risk factors for HBV infection among children and adolescents in Germany are available. The prevalence of antibodies to hepatitis B core antigen (anti-HBc, a marker for a previous or current HBV infection) was 7.0% (95% confidence interval [CI], 6.4 – 7.6) and of HBsAg was 0.6% (95% CI: 0.4–0.8) among the adult population in Germany.[9] According to the World Health Organization, Germany is categorized as a country with low HB endemicity (prevalence of HBsAg <2%).[11] However,about 84% of adult immigrants residing in Germany migrated from countries with moderate to high HB endemicity (prevalence of HBsAg ≥2%). It has been estimated that 42% of all chronic HBV infections in Germany occur among immigrants, even though immigrants represent only 12.7% of the adult population in Germany.[12] Therefore, it is hypothesized that offspring of immigrants may be at risk for HBV infection through perinatal transmission or person-to-person contact within the household, reflecting HBV transmission modes shown to exist for children.[13,14] In some other countries, migration background has been already identified to be a risk factor for HBV infection among children.[15–19]

German clinical guidelines recommend testing persons migrated from regions with high HBsAg prevalence.[20] However, actually, immigrants in Germany are not routinely tested for HBV infection. Beyond the HB vaccination recommendation for infants, children, and adolescents, the STIKO defined several particular risk groups for HBV infection and recommends HB vaccination for them.[5] So far, the STIKO has not considered immigrants to be a particular risk group for HBV infection. Therefore, in Germany,
for immigrants, there is no specific recommendation other than the universal HB vaccination starting at 2 months of age, and no preor postvaccination serologic testing is currently recommended for immigrants or their children.[5]

The Robert Koch Institute conducted a large populationbased nationwide Health Interview and Examination Survey for Children and Adolescents (KiGGS) in Germany from 2003 to 2006.

The objectives of our study were to estimate seroprevalence of markers indicative for HBV infection among children and adolescents in Germany and to assess determinants for HBV infection to improve recommendations to prevent HBV infection for children.

Materials and Methods

The German Health Interview and Examination for Children and Adolescents (KiGGS)
We performed a secondary data analysis of the KiGGS database. Detailed descriptions of the KiGGS methodology have been published elsewhere.21–26 In brief, the KiGGS was a crosssectional study conducted from May 2003 to May 2006 aiming at a nationally representative sample of children and adolescents 0 to 17 years of age with main residence in Germany.

Participants of the KiGGS were enrolled in 2 steps. First, primary sample units were drawn from all German communities. Second, addresses of families per birth cohort were selected randomly from local resident registries.[21]

Data on gender, date of birth, migration background, educational and occupational status of parents, and household income were collected through self-completed questionnaires. A child was defined as having a 2-sided migration background if both parents, or the child and 1 parent, had immigrated into Germany. If only 1 parent had immigrated, the child was defined as having a 1-sided migration background.[22,23] Among the children and adolescents with a 1- or 2-sided migration background, a first-generation migrant was defined as being born outside Germany; a secondgeneration migrant was born in Germany. Only children and adolescents aged between 11 and 17 years were asked about their respective country of birth. Based on the data from the World Health Organization and the Centers for Disease Control and Prevention, children born in countries where prevalence of HBsAg is 2% or more were classified as being from countries with moderate or high HB endemicity (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A555).[11,27] Information on educational and occupational status of parents and household income was aggregated into a social status index.

Children were classified as being from families with high, medium, or low socioeconomic status according to this social status index.[24] Information on HB vaccination status was obtained from self-held vaccination cards. A child was categorized as having been completely vaccinated against HBV infection if he or she had received a 3-dose HB mono- or bivalent vaccine, or a 4-dose HB hexavalent vaccine with a pertussis component.[25] Nonmigrants and secondgeneration migrants were classified as being born before or after the HBsAg screening program was launched in pregnant women in 1994.

We included all KiGGS participants with known anti-HBc serology status in our study.

HB Testing

Serum samples of children and adolescents from 3 years of age were tested for anti-HBc, and if positive, HBsAg was tested. Tests for anti-HBc and HBsAg were qualitative, and both tests based on the electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics, Switzerland). Anti-HBc was determined at an automatic ELECSYS 2010 Analyzer. Details of the laboratory methods have previously been published.[26]

Statistical Analyses

To ensure that estimates derived from the KiGGS were representative at national level, survey weights had been developed to be applied throughout statistical analyses. This included weighting for sampling design as well as weighting to adjust for deviations between the design-weighted net sample and German population statistics (as of December 31, 2004)[28] based on crossclassifications by age, gender, residence in Western or Eastern Germany, and nationality (German vs. non-German). Weighting corrected for differences in age structure and for oversampling of individuals from Eastern Germany, which had been performed to ensure sufficient statistical power. Prevalences and odds ratios were calculated and presented with a 95% CI. We performed x^2 tests for trend to assess linear trend in HB-prevalence across different age groups and performed univariable and stepwise forward multivariable logistic regression analyses to assess determinants of HBV infection. Only variables indicating statistically significant associations with HBV infection in the univariable analysis were kept in a multivariable logistic regression model. We measured the impact of possible multicollinearity among migration background and migrants' generation and among age group and existence of HBsAg screening in pregnant women in a regression model by considering the variance inflation factor (VIF).[29] If the value of VIF was above 2.5, we created different multivariable logistic regression models to avoid possible multicollinearity and to estimate the separate effects of the variables on HBV infection. Two-sided tests were applied, and an alpha error level of 5% was considered acceptable. The data were analyzed using Stata (version 10, StataCorp LP, College Station, TX).

Results

Study Participants

A total of 17,641 children and adolescents (8656 girls and 8985 boys) participated in the KiGGS (response: 66.6%).24 Anti-HBc serology results were available for 13,065 (88.6%) children and adolescents aged between 3 and 17 years. An overview of information on gender, age group, migration status, socioeconomic status, HB vaccination status, and being born before or after the HBsAg screening in pregnant women among study population is presented in Table 1.

Anti-HBc Seroprevalence

Overall, 0.5% (95% CI, 0.4–0.7) of the children and adolescents aged between 3 and 17 years were anti-HBc positive, among whom 38.7% (95% CI, 20.0 –57.5) were HBsAg positive. Among the anti-HBc positive children and adolescents, 56.8% were girls, 77.0% were 11 to 17 years, and 1.1% showed a 1-sided and 73.7% a 2-sided migration background. Information on migrants' generation was available for 55.1% of the anti-HBc positive children and adolescents, of whom, 29.9% were first and 28.8% second-generation migrants. Among the anti-HBc positive children and adolescents, 48.0% were from families with low socioeconomic status. Information on HB vaccination status was present for 57.0% of the anti-HBc positive children and adolescents, of whom, 54.9% had been completely vaccinated against HBV infection. Among the anti-HBc positive children and adolescents born in Germany, 65.4% were born after the HBsAgscreening of pregnant women was introduced.

Anti-HBc prevalence increased with age in both genders (P = 0.001 for boys, P = 0.009 for girls). In each age group, the prevalence was higher in girls than in boys, however, the differences observed were not statistically significant (Fig. 1).

Univariable Analysis of Determinants of Anti-HBc Positivity

In univariable logistic regression analysis, the age groups 11 to 13 and 14 to 17 years, 2-sided migration background, being a first- or second-generation migrant, low socioeconomic status, and having no vaccination card were associated with anti-HBc positivity. The anti-HBc prevalence was 15 times higher in children or adolescents who were first-generation migrants, 13 times higher in those being with 2-sided migration background, and 3 times higher in second-generation migrants than the one in nonmigrants, respectively. Anti-HBc prevalence was significantly higher among children and adolescents from families with low socioeconomic status in comparison to those from families with high socioeconomic status. Anti-HBc prevalence was higher among children and adolescents having no vaccination card than those having information on HB vaccination status. No significant differences regarding anti-HBc prevalence were found according to existence of the HBsAg screening in pregnant women among those born in Germany (Table 2).

Multivariable Analysis of Determinants of Anti-HBc Positivity

As the VIF for migration background and migrants' generation was 6.5, we separated the both variables and created 2 different multivariable logistic regression models. Age group, socioeconomic status, and HB vaccination were included in both models. The VIF for age group and existence of HBsAg screening in pregnant women was 3.9, but since existence of HBsAg screening for pregnant women was not associated with anti-HBc positivity in univariable analysis, we did not consider it in the multivariable analysis.

In a multivariable logistic regression model involving migration background (1-sided, 2-sided, or none), the age group 14 to 17 years, having a 2-sided migration background as well as having no vaccination card were independently associated with anti-HBc positivity. In another model involving migrants' generation (first, second, or none), first- as well as second-generation migrant remained to be independently associated with anti-HBc positivity (Table 2).

Discussion

The population-based KiGGS survey enabled us to estimate nationwide and representative anti-HBc seroprevalence among children and adolescents in Germany.

According to the findings of our study, it can be assumed that approximately 48,000 to 85,000 children and adolescents aged between 3 and 17 years with previous or current HBV infection (presence of anti-HBc positivity) currently live in Germany. Of those, 20.0% to 57.5% are assumed to have a current, replicative HBV infection (presence of anti-HBc and HBsAg positivity), and thus, are capable of transmitting the infection. Compared with the anti-HBc prevalence in the adult German population,9 the prevalence among children and adolescents was substantially lower.

In our study, migrants' generation and migration background were closely related to one another and appeared to be multicollinear variables. One logistic regression model may not be able to reliably assess the independent contribution of each variable, therefore we investigated their impact separately.

The prevalence of anti-HBc among children and adolescents with a 2-sided migration background and among those who were first- or second-generation migrants, respectively, was higher than anti-HBc prevalence among nonmigrants. Of the anti-HBc positive children and adolescents, almost three-quarters showed a migration background, even though only 2807 (24.9%) participants in our study displayed a migration background, which is close to the proportion among children and adolescents in Germany (28.6%).[30]

There may be several reasons for the markedly higher HB prevalence among children and adolescents with a migration background compared with those without.

A migrant's health status normally reflects the disease profile of his or her country of origin at least in the first years after their immigration.[31,32] As the majority of the first-generation migrants in our study who indicated their country of birth had been born in countries with moderate or high HB endemicity, they presumably had been at risk for HBV infection in their countries of origin through perinatal transmission, person-to-person contact in household, kindergarten or school, or nosocomial transmission. This assumption is supported by our finding that anti-HBc prevalence among first-generation migrants was higher than among second generation migrants and nonmigrants.

Immigrants in industrialized countries are more likely to belong to a lower income class and to generally display lower living standards.[31,32] This may stand as a proxy for an increased risk of HBV infection for children of immigrant families: there may be lesser health care seeking behavior, and family members suffering from replicative HBV infection may not see a physician on time, and may not receive appropriate medical treatment to reduce viral load, resulting in a considerable probability that a child is in close contact with infected family members. If a family member suffers from replicative HBV infection, HB vaccination for an infant, according to the schedule recommended in Germany, may be too late in time, and be performed only after infection had occurred already. It is assumed that HBsAg screening of pregnant women is an effective public health measure, but does not protect infants born into families where another family member than the mother displays replicative HBV infection.

There is evidence that households with HB-infected family members represent a considerable hazard in terms of HBV infections.[13,14] Lower living standards with overcrowding, or cultural habits which entail closer physical contacts to infants and children in the family context may further increase infection risk. In our study, univariable analysis suggested that children and adolescents from families with low socioeconomic status were more likely anti-HBc positive; however, multivariate analysis suggested that these differences were probably due to confounding with migration background or migrants' generation.

The HB prevalence among children and adolescents who had a 2-sided migration background was higher than the ones with only 1-sided migration background, which might suggest a potentially higher degree of exposure to HB infected family members in the household when a 2-sided migration background was present. Furthermore, 2-sided migrant children were partly born outside Germany; they could have been at risk for HBV infection prior to immigration, as well. In our study, no association between antiHBc positivity and 1-sided migration background was found, however, low statistical power owing to the small sample size of children with a 1-sided migration background might also contribute to the lack of association.

Our finding regarding increasing HB prevalence with age of children and adolescents is in line with results from other studies[33,34]; however, this finding was not significant in a multivariable analysis involving migrants' generation, which likewise might reflect lower statistical power as not all children with a migration background could be defined as first- or second-generation migrants and the sample size of the multivariable logistic regression model involving migrants' generation was smaller. In Germany, children and adolescents aged 14 to 17 years in 2003 to 2006 were born before universal HB vaccination recommendation was implemented in Germany (1995) or before the HBsAg screening program for pregnant women was introduced (1994), and the HB vaccination catch-up campaign for adolescents is less successful. Indeed, among children and adolescents, the HB vaccination coverage was reported lower in older age group (11–17 years) than in younger age group (3–10 years).25 The higher prevalence of anti-HBc in older age groups may also suggest a cumulative risk for acquiring HBV infection over time. However, interpretation of these results are limited as the proportion of first-generation migrants was higher in older than in younger age groups23 and stratification by migration status revealed imprecise results owing to the small sample size.

In our study, no difference among being completely vaccinated and being unvaccinated or incompletely vaccinated regarding anti-HBc positivity was found. The KiGGS reported that more children and adolescents with a 2-sided migration background compared with those without a migration background could not provide complete vaccination cards (17.3% vs. 4.6%).22 They were therefore not considered in the analysis of the vaccination status and might have introduced a selection bias as children and adolescents with a 2-sided migration background, especially the first-generation migrant children, were possibly less likely to have received HB vaccination than nonmigrants due to lack of recommendations on universal HB vaccination in some countries,3 but they were more likely to be anti-HBc positive. This is in line with our finding regarding high anti-HBc prevalence among children and adolescents having no vaccination cards.

Limitations
In the KiGGS, information on HBV infection status in family members of infected children was not obtained. Therefore, based on our data, it was impossible to estimate the actual HBV transmission mode among anti-HBc positive children and adolescents.

Reflecting the inherent limitations of a cross-sectional study, it was impossible to determine the time of onset of HBV infection, or to distinguish whether infections of those participants with HBsAg were acute or already chronic, or to identify potential breakthrough infections.

In Germany, no representative data on adherence to the guidelines for HBsAg screening for pregnant women are available—a regional study reported that HBsAg screening had been performed in 79.0% of pregnant women.[35] Based on the data of KiGGS, it was impossible to identify whether the HBsAg screening was actually performed in mothers of the children. Classification was performed only by considering the year of childbirth among those born in Germany, most probably leading to some degree of misclassification.

Conclusions and Recommendations
Generally, HBV infection is uncommon among children and adolescents in Germany, but still, the prevalence findings from this study translate into several thousand children and adolescents suffering from replicative HBV infection.

Owing to the high probability that HBV infections in infants and children run a chronic course but go unnoticed, and likely impair the health status of the affected due to liver associated morbidity and mortality in the long run (liver cirrhosis, hepatocellular carcinoma), efforts need to be intensified in Germany to aim at preventing all cases of HBV infection in infants and children, particularly by taking into consideration the target group of infants and children with a migration background.

We conclude that those potentially at risk early in life, prior to the routinely recommended first dose of HB vaccine need to be identified and vaccinated as timely as possible.

On the basis of our analysis, first- and second-generation migrant children can be considered to be at risk for HBV infection, with 2-sided migration background or being a firstgeneration migrant the most risky categories. Therefore, adherence of existing preventive programs needs to be reinforced, eg, HBsAg screening for all pregnant women, and particularly efforts need to be intensified to provide this service to all mothers with a migration background. Every infant of an HBsAg-positive mother should receive HB vaccination plus HB immunoglobulin[5,8] and be followed up by serologic testing (anti-HBs) to avoid vertical transmission.

Additionally, we strongly recommend that local health departments, pediatricians, and general practitioners provide information on HBV infection prevention, consider targeted testing of immigrants from regions with moderate or high HB endemicity and their family members,[20,36] and perform HB vaccination especially to those immigrants' children in a timely and consistent manner to avoid horizontal transmission within the household.

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Tables and Figures

Table 1. Gender, Age Group, Migration Status, Socioeconomic Status, HB Vaccination Status, and Being Born Before or After the HBsAg Screening in Pregnant Women of Study Population

	N	Weighted Percentage
Study population	13,065	
Gender		
Boys	6709	51.3
Girls	6356	48.7
Age group (yr)		
3–6	3003	24.0
7–10	3697	25.2
11–13	2869	20.1
14–17	3496	30.6
Migration status		
Nonmigrant	10,205	75.1
1-sided migrant	880	7.7
2-sided migrant	1927	17.2
First-generation migrant*	381	3.8
Second-generation migrant	1887	18.4
Socioeconomic status		
High	3294	27.0
Medium	6038	46.0
Low	3414	27.0
HB vaccination		
Completely vaccinated	7949	60.0
Unvaccinated or incompletely vaccinated	4171	32.1
No vaccination card available	945	7.9
Existence of the HBsAg screening in pregnant women		
Birth before 1994	5451	48.7
Birth in or after 1994	6148	51.3

*Information on country of birth was available for 247 first-generation migrants, of whom, 225 (89.6%) were born in countries with moderate or high HB endemicity. HBsAg indicates hepatitis B surface antigen; HB, hepatitis B.

Table 2. Prevalence of Anti-HBc, Univariable, and Multivariable Logistic Regression Analyses for the Association Among Socio-demographic Variables, Vaccination Status, and HBsAg Screening in Pregnant Women With Anti-HBc Positivity Among Children and Adolescents, Germany, 2003–2006

	Prevalence of Anti-HBc Percent (95% CI)	Univariable Analysis Crude OR (95% CI)	Multivariable Analysis* Adjusted OR (95% CI)	Multivariable Analysis† Adjusted OR (95% CI)
Gender				
Boys	0.4 (0.3–0.6)	1	—	—
Girls	0.6 (0.4–0.8)	1.4 (0.8–2.4)	—	—
Age group (yr)				
3–6	0.2 (0.0–0.3)	1	1	1
7–10	0.3 (0.1–0.5)	1.8 (0.6–5.2)	1.9 (0.6–6.1)	2.0 (0.6–6.5)
11–13	0.6 (0.3–0.9)	3.5 (1.3–9.9)	2.3 (0.8–6.9)	1.1 (0.3–4.0)
14–17	0.9 (0.5–1.2)	5.2 (2.0–13.3)	4.2 (1.5–11.8)	2.8 (0.9–8.4)
Migration background				
Nonmigrant	0.2 (0.1–0.3)	1	1	—
1-sided migrant	0.1 (0.0–0.2)	0.4 (0.1–1.9)	0.4 (0.1–1.9)	—
2-sided migrant	2.1 (1.4–2.9)	13.0 (7.1–23.9)	8.3 (4.0–17.4)	—
Migrants' generation				
Non-migrant		1	—	1
First-generation migrant	2.4 (0.3–4.5)	15.2 (5.4–42.6)	—	11.0 (3.5–35.0)
Second-generation migrant	0.5 (0.2–0.8)	3.0 (1.3–6.8)	—	3.0 (1.2–7.3)
Socioeconomic status				
High	0.3 (0.1–0.4)	1	1	1
Medium	0.3 (0.1–0.5)	1.2 (0.5–3.1)	0.9 (0.4–2.1)	0.9 (0.3–2.5)
Low	0.7 (0.4–1.1)	2.9 (1.3–6.5)	1.0 (0.4–2.4)	1.0 (0.4–2.7)
HB vaccination				
Completely vaccinated	0.3 (0.1–0.4)	1	1	1
Unvaccinated or incompletely vaccinated	0.4 (0.1–0.7)	1.5 (0.7–3.4)	1.3 (0.6–2.9)	1.2 (0.6–2.6)
No vaccination card available	2.8 (1.6–3.9)	10.7 (5.8–19.8)	4.0 (2.1–7.6)	—
Existence of the HBsAg screening in pregnant women				
Birth before 1994	0.3 (0.1–0.4)	1	—	—
Birth in or after 1994	0.2 (0.1–0.3)	0.7 (0.3–1.7)	—	—

*In the multivariable logistic regression model, age group, migration background, socioeconomic status, and HB vaccination are included.
†In the multivariable logistic regression model, age group, migrants' generation, socioeconomic status, and HB vaccination are included. Anti-HBc indicates antibodies to hepatitis B core antigen; HBsAg, hepatitis B surface antigen; OR, odds ratio; CI, confidence interval.

Figure 1. Anti-HBc prevalence by age group and gender among children and adolescents, Germany, 2003–2006.