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Epidemiology of Hepatitis B Infection among Expatriates in Nigeria

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Adult expatriates in countries where hepatitis B virus (HBV) is highly endemic have an increased risk of HBV infection, but little is known about risks to their children or about patterns of spread. The epidemiology of HBV infection was studied among 124 unvaccinated Dutch missionaries and family members who lived in a rural area of Nigeria. Antibodies to hepatitis B core antigen were found in 5 (9.8%) of 51 adults (incidence rate, 1.7 per 1000 person-months at risk [PMAR]) and 9 (12.3%) of 73 children (incidence rate, 2.8 per 1000 PMAR). Vertical transmission of HBV was a likely source of infection in 1 child and was a possible source of infection in 2 others. The prevalence of HBV infection showed strong family clustering ($P < .0001$), was associated with a history of temporary adoption of Nigerian children ($P = .004$), and increased with both the number of adoptive children ($P = .009$) and the total time that these children had stayed in the family ($P = .036$). Horizontal transmission from adoptive Nigerian children probably played an important role in the spread of HBV infection in this expatriate community.

Several studies have reported increased risks of hepatitis B virus (HBV) infection—from 1% to 5% per year—among expatriates working in areas of high endemicity in sub-Saharan Africa and the Western Pacific [1–5]. For adult expatriates planning to work in areas where HBV is highly endemic, hepatitis B vaccination is increasingly recommended [6]. For children, the recommendations are often less straightforward. This is probably because the risk factors identified for HBV infection are age, health care work, and sexual contact [1, 2, 4], and, although one study [5] reported infections among children, no study has analyzed risk factors among them. On the other hand, once infected, children have an increased risk of chronic HBV infection, hepatic cirrhosis, and primary liver cell carcinoma [7]. Although most countries now routinely immunize infants, expatriate children from certain age groups and from certain countries still escape hepatitis B vaccination.

During a routine medical check-up of a missionary family that had lived for several years in Nigeria, both of the parents and 3 of 5 children were found to have markers of HBV infection [8]. One child was a hepatitis B e antigen (HBeAg)–positive carrier without symptoms. This family had been part of a group of largely unvaccinated Dutch missionaries that had lived in the same rural area of Nigeria since 1964. Nigeria is an area of high endemicity for hepatitis B; an estimated 78% of the population have evidence of past or chronic infection by the age of 40 years [9]. We expected to find more subclinical infections among these expatriates that might result in further transmission and chronic sequelae, and we undertook a retrospective cohort study to identify persons with markers of HBV infection, to

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describe its epidemiology, and to explain how transmission had occurred.

METHODS

All missionaries and their families who had lived in Nigeria for ⩾3 months were approached by the mission organization with information about the study and were requested to participate in it. Those who assented were visited at home in The Netherlands or in Nigeria (if they were still living there) to obtain blood samples, and they completed a self-administered questionnaire. Informed consent was signed by the parents for children under 12 years old and by both the child and the parents for children between 12 and 18 years old.

Questionnaires for the children were completed by the parents. A participant was defined as a child if aged <18 years during the entire period of their stay in Nigeria. All blood samples were centrifuged within 24 h after collection, and serum samples were kept at −20° C until testing. All serum samples were tested for antibody to HBV core antigen (anti-HBc) using a commercial ELISA (IMx; Abbott Laboratories) according to the manufacturer's instructions. Test results were reported to the study participants by one of the study directors (H.J.S.), and participants with positive test results were advised to undergo testing for markers of chronic infection. Questionnaires were checked manually, and inconsistencies were resolved with the participants.

Data were entered twice in EpiInfo, version 6.04 (Centers for Disease Control and Prevention), and discrepancies were checked against the raw data. Data analysis was performed using Stata, version 6 (Stata). All HBV infections were assumed to have been acquired in Nigeria. The person-time denominator was calculated to exclude all home leaves or other stays outside of Nigeria that were longer than 3 months and was censored for HBV-infected subjects at the halfway point of the stay in Nigeria (i.e., it was assumed that infection occurred halfway through the HBV-infected subject's stay). For participants who received hepatitis B vaccination, the at-risk period was censored from the date of the third vaccine dose (i.e., participants with <3 vaccine doses were still considered to be at-risk for HBV infection). A patient with HBV infection was defined as one who had received a positive anti-HBc test result. Incidences were expressed as incidence rates with approximate 95% confidence limits based on the standard errors, and the incidence rates were compared using the likelihood ratio test. For stratified analysis, summary incidence rate ratios were calculated by the Mantel-Haenszel method. Ages were calculated at the halfway point of the subjects' stay in Nigeria, on the basis of the dates of first arrival in and last departure from Nigeria. In the analysis of family clustering, the likelihood for each HBV-infected subject to have ⩾1 family member who was also infected was compared to this likelihood for each subject who was not infected.

RESULTS

Of a total of 192 eligible missionaries and family members, 162 consented to participate in our study. Of these, 151 submitted a blood sample, and 144 returned a questionnaire; complete data were available for 138 participants. One adult was excluded from the study because he was Nigerian by birth, 1 child was excluded because it did not have a parent participating in the study, and 1 child was excluded because it was born after its parents had returned from Nigeria. This left 135 study participants (i.e., 70.3% of the 192 eligible missionaries and family members approached about participating in the study), including 60 adults and 75 children. Of these 135, 26 (19.3%) had received ⩾3 doses of hepatitis B vaccine, and their person-time was censored accordingly. These included 11 (8.1%) who were vaccinated before their stay in Nigeria, leaving 124 subjects for the analysis (table 1).

Fourteen (11.3%) of these 124 subjects had serological evidence of HBV infection (95% CI, 6.3–18.2), resulting in an

Table 1. Demographic characteristics of 124 Dutch missionaries and family members who lived in Nigeria.

Characteristic	Value
Patient group	
Adults	51 (41.1)
Children	73 (58.9)
Sex	
Male	61 (49.2)
Female	63 (50.8)
Children born in Nigeria, no. (%) of children[a]	13 (17.8)
Family units, no.	36
Persons in family unit, no. (%) of family units[b]	
1	13 (36.1)
2	4 (11.1)
3	1 (2.8)
4	4 (11.1)
5	7 (19.4)
6	2 (5.6)
7	3 (8.3)
8	2 (5.6)
Duration of stay, months	
Median (IQR)	49.8 (22.9–86.8)
Range	3–434

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] $n = 73$.

[b] $n = 36$.

incidence rate of 2.3 cases of HBV infection per 1000 person-months at risk (95% CI, 1.3–3.8). These included 5 (9.8%) of 51 adults and 9 (12.3%) of 73 children ($P = .777$); incidence rates were 1.7 (range, 0.7–4.0) per 1000 person-months for adults and 2.8 (range, 1.4–5.3) per 1000 person-months for children. Table 2 summarizes the demographic characteristics of these 14 patients. Three patients had lived for ⩾3 months in another country of high endemicity for HBV infection (i.e., either Kenya or Indonesia). Two patients were single, and the remaining 12 patients belonged to 5 different family units. Among family units of >1 person, 11 (92%) of 12 patients who were positive for anti-HBc had ⩾1 family member who was infected with HBV, compared with 15 (15%) of 99 patients who were negative for anti-HBc ($P < .0001$), indicating strong family clustering. This was primarily due to family clustering among children only (7 [77%] of 9 children, compared with 11 [18%] of 62 adults, $P = .001$). Of 9 HBV-infected children (belonging to 5 different families), 4 had mothers who tested positive for anti-HBc ($n = 2$). Vertical transmission was the likely source of infection in 1 of these children. This child's Dutch mother was married to a Nigerian (who was not included in the study, but who tested positive for anti-HBc), and she had a history of acute hepatitis at the time of delivery. Vertical transmission was a possible source of infection in the other 3 children, except in the case of 1 who was born before the mother arrived in Nigeria. Vertical transmission was unlikely in the remaining 5 children, whose mothers tested negative for anti-HBc.

Of the 14 HBV-infected subjects, 7 (50%) reported ⩾1 episodes of jaundice, compared with 22 (20%) of 110 uninfected subjects ($P = .020$). Multiple episodes of jaundice were reported by 2 HBV-infected subjects (both of whom reported 3 episodes). The proportion reporting jaundice did not differ between adults (3 of 5) and children (4 of 9) ($P = 1.000$).

The 14 infected subjects were never all in Nigeria at the same time. There were 2 periods during which there was substantial overlap in time: around 1986 (at which time there were 8 cases) and from 1992 to 1996 (during which time there were 11 cases). During both periods, these cases involved members of 5 of the 7 family units with members who were infected.

The missionary community lived scattered among 12 villages and settlements, with frequent changes of residence. None of the affected family units ever lived in the same locality at the same time as any other affected family unit, but there were frequent gatherings that were attended by most of the community. HBV-infected subjects did not differ significantly from noninfected subjects in age. This was true both among all subjects (median age, 16.7 years for infected subjects versus 17.7 years for noninfected subjects; $P = .658$) and among children only (median age, 3.6 years for infected subjects versus 4.6 years for noninfected subjects; $P = .291$). Infected subjects reported a longer duration of stay in Nigeria than did noninfected subjects. Among subjects of all ages, the median duration of stay in Nigeria was 9.3 years, for infected subjects, versus 5.6 years, for noninfected subjects ($P < .001$). Among children only, the median duration of stay in Nigeria was 7.8 years, for infected subjects, versus 4.3 years, for noninfected subjects ($P = .026$). Table 3 shows univariate associations with other possible risk factors. Two of these risk factors were significant: a history of one or more Nigerian children living temporarily in the house-

Table 2. Demographic characteristics of 14 Dutch missionaries and family members with hepatitis B virus infection who lived in Nigeria.

Patient no.	Age in years[a]	Sex	Duration of stay, years	Family unit (no. of children)	Remarks
1	54.9	F	24.7	Single	…
2	48.2	F	36.2	Single	…
3	28.0	F	6.6	A (1)	Married to Nigerian who was also anti-HBc positive
4	1.0	M	2.0	A (1)	Son of patient 3, born in Nigeria; mother jaundiced at time of delivery
5	34.2	M	8.4	B (5)	Index family
6	32.9	F	6.6	B (5)	Wife of patient 5
7	8.8	F	8.4	B (5)	Daughter of patient 6, born before stay in Nigeria
8	4.6	F	5.5	B (5)	Daughter of patient 6, born in Nigeria
9	3.2	F	3.2	B (5)	Daughter of patient 6, born in Nigeria; HBeAg-positive carrier
10	6.7	M	8.3	C (5)	Both parents vaccinated before stay in Nigeria and anti-HBc negative
11	3.4	M	5.7	C (5)	Both parents vaccinated before stay in Nigeria and anti-HBc negative
12	5.6	M	8.2	D (3)	Both parents anti-HBc negative
13	3.9	F	8.3	D (3)	Both parents anti-HBc negative
14	11.7	F	5.7	E (6)	Both parents anti-HBc negative

NOTE. Anti-HBc, antibody to hepatitis B virus core antigen; HBeAg, hepatitis B e antigen.

[a] Age at the halfway point of the patient's stay in Nigeria.

Table 3. Univariate associations between potential risk factors and hepatitis B virus infection among Dutch missionaries and their families in Nigeria.

	All subjects (n = 124)				Children only (n = 73)			
Risk factor	No./person-months	Rate per 1000 person-months	Incidence rate ratio (95% CI)	P	No./person-months	Rate per 1000 person-months	Incidence rate ratio (95% CI)	P
Sex								
Male	5/3110	1.6	1.80 (0.61–5.38)	.283	4/1978	2.0	1.96 (0.53–7.28)	.309
Female	9/3103	2.9	1		5/1265	4.0	1	
Health care worker[a]								
Yes	2/913	2.2	1.50 (0.25–8.99)	.654	NA	NA	NA	NA
No	3/2057	1.5	1		…	…	…	
Orphanage worker[a]								
Yes	2/788	2.5	1.85 (0.31–11.05)	.495	NA	NA	NA	NA
No	3/2182	1.4	1		…	…	…	
Blood contact[a,b]								
Occasional	4/1251	3.2	5.50 (0.61–49.18)	0.086	NA	NA	NA	NA
Never	1/1719	0.6	1		…	…	…	
Nigerian children lived in household								
Yes	11/2511	4.4	5.41 (1.51–19.38)	.004	6/1397	4.3	2.64 (0.66–10.57)	.153
No	3/3702	0.8	1		3/1846	1.6	1	
Received gammaglobulin injections								
Yes	9/3290	2.7	1.60 (0.54–4.77)	.396	5/1254	4.0	1.98 (0.53–7.38)	.298
No	5/2923	1.7	1		4/1989	2.0	1	
Received other parenteral treatment								
Yes	4/1919	2.1	0.90 (0.28–2.85)	.851	3/802	3.7	1.52 (0.38–6.09)	.550
No	10/4294	2.3	1		6/2441	2.5	1	
Received dental treatment								
Yes	2/1422	1.4	0.56 (0.13–2.51)	.444	0/494	0	0	.203
No	12/4791	2.5	1		9/2749	3.3	1	
Received minor surgery[c]								
Yes	4/1723	2.3	1.04 (0.33–3.32)	.944	4/1158	3.5	1.44 (0.39–5.36)	.584
No	10/4490	2.2	1		5/2085	2.4	1	
Delivered child[d]								
Yes	2/453	4.4	3.06 (0.43–21.71)	.239	NA	NA	NA	NA
No	2/1385	1.4	1		…	…	…	
Nursed by Nigerian maid[e]								
Yes	NA	NA	NA	NA	5/1788	2.8	1.02 (0.22–5.13)	.989
No	…	…	…		4/1455	2.7	1	
Reported overnight stays with Nigerian families[e]								
Yes	NA	NA	NA	NA	3/874	3.4	1.36 (0.34–5.42)	.666
No	…	…	…		6/2369	2.5	1	
Attended local primary school[e]								
Yes	NA	NA	NA	NA	2/178	11.2	4.92 (1.02–23.68)	.028
No	…	…	…		7/3065	2.3	1	

NOTE. NA, not applicable.

[a] Adults only.
[b] Nonprofessional (e.g., provided first aid).
[c] Incision of superficial abscess, excision of onchocercoma, or other minor surgery.
[d] Women only.
[e] Children only.

hold (incidence rate ratio [IRR] among all ages, 5.41; P = .004), and having attended a local primary school for ⩾3 months (IRR among children only, 4.92; P = .028). The association with Nigerian children in the household was significant both if the Nigerian child was an infant (IRR, 3.45; 95% CI, 1.16–10.30) and if the child was older (IRR, 4.27; 95% CI, 1.34–13.62) at the time of residence with the family unit. The association was strongest for adults: among missionary children only, the association with Nigerian children in the household was not statistically significant. The 2 HBV-infected children who attended a local primary school were from the same family unit, and they were among the 3 HBV-infected children who had no history of Nigerian children staying in their families.

A history of nonprofessional blood contact during first aid

(e.g., dressing of wounds) showed a near-significant association (IRR, 5.50; $P = .086$). This data was obtained from adult subjects only, and all respondents reported that their history of nonprofessional blood contact involved contact with Nigerians. None of the respondents had major surgery or had received blood transfusions or intravenous fluids while in Nigeria. Parenteral treatment, gammaglobulin administration, dental treatment, and minor surgery were reported by all family units in which HBV infections were found. The questionnaire contained no questions on sexual risks. Multivariate analysis was not possible due to the small number of subjects.

The association with a history of Nigerian children in the family was further explored for dose-response relationship. Because our data did not allow us to ascertain whether a Dutch child had actually been exposed to a particular Nigerian child (i.e., whether the Nigerian child had lived with the family before the Dutch child's birth), the analysis was done by family unit (table 4). Not only the presence of a Nigerian child in the family ($P = .029$), but also the number of Nigerian children living with the family ($P = .009$) and the total duration of their stay ($P = .036$), significantly predicted HBV infection in $\geqslant 1$ family member.

DISCUSSION

The risk of HBV infection among these Dutch missionary families in Nigeria was 2.3 cases per 1000 person-months, or 2.8% per year. This is comparable to the 1%–2% per year reported for Canadian missionaries and Dutch expatriates in sub-Saharan Africa [2, 4], but it is somewhat lower than the 4%–5% per year for French development workers [1] or American missionaries in that region [3]. Two other studies that estimated HBV infection risk among expatriate children in Papua New Guinea and Taiwan suggested that the risk was less than among adults [5, 10]. In our study, however, infection risks among children were at least as high as they were among adults. If the clinical definition of HBV infection is based on a history of jaundice, 50% of the HBV infections in our study were subclinical. Because 20% of noninfected subjects also reported jaundice (probably caused by hepatitis A), the proportion of subclinical infections will be even greater than 50%.

This is the first study to describe in detail the epidemiology of HBV infection among an expatriate community. Sexual transmission was not investigated because of the expected low validity of questionnaire responses to this item. Although it cannot be ruled out from our data, the age distribution and family patterns of the infections make it unlikely that sexual transmission played a major role in the spread of HBV infection in this community. The analysis of risk factors showed no significant associations for other classical routes of transmission, such as transmission from mother to child, transmission as a result of parenteral treatment, and transmission as a result of health care work. Although these routes of transmission may have been implicated in some infections (e.g., mother-to-child transmission for subject 4 in table 2), they do not seem to explain the complete epidemiological picture. Regarding routes of transmission, 2 findings stand out in the analysis: first, strong family clustering, and, second, an association between risk of HBV infection and a history of Nigerian children living temporarily with the family (i.e., temporary adoption). In addition, 2 of 3 infected subjects who reported no temporary adoption had attended the same local primary school. These findings suggest horizontal transmission, and it is likely that this played a significant role in the spread of HBV infection in this expatriate community. Horizontal transmission is the main route of HBV infection for children in Africa [11–14], in-

Table 4. Associations between temporary adoption of Nigerian children and hepatitis B virus (HBV) infection among 36 Dutch missionary families in Nigeria.

Variable	No. (%) of families		*P*
	Without HBV infection	With $\geqslant 1$ HBV infection	
Nigerian children temporarily adopted by family			.029
No	22 (75.9)	2 (28.6)	
Yes	7 (24.1)	5 (71.4)	
No. of Nigerian children temporarily adopted			.009
0	22 (75.9)	2 (28.6)	
1 or 2	6 (20.7)	2 (28.6)	
$\geqslant 3$	1 (3.5)	3 (42.9)	
Duration of stay of Nigerian children with family, months			.036
0	22 (75.9)	2 (28.6)	
1–12	4 (13.8)	2 (28.6)	
>12	3 (10.3)	3 (42.9)	

cluding rural eastern Nigeria [9]. Horizontal transmission of HBV infection has also been described within families in the United States and Europe, particularly transmission from adopted children carrying hepatitis B surface antigen (HBsAg) and originating from countries with high endemicity [15–17]. Horizontal transmission from children probably occurs through exposure to blood (e.g., through contact with skin lesions) or saliva (e.g., through sharing of toothbrushes and candy) [18]. The high rates of horizontal transmission in sub-Saharan Africa suggest that the tropical environment presents additional transmission routes. Suppurative skin lesions are more common in that environment, and HBV may be detected in various man-biting insects, including bedbugs and *Culex* and *Anopheles* mosquitoes [19]. However, neither epidemiological nor experimental studies have provided evidence that these routes have an important role [20–22]. In some family units, HBV infection may have been introduced through horizontal transmission from an adoptive child and then spread onwards by one or more missionary children (e.g., the HBeAg-positive child [table 2, subject 9]).

There are a number of shortcomings to this study. Apart from the lack of data on sexual transmission, the assumption that all infections were acquired in Nigeria may not be correct. Infection in The Netherlands before deployment in Nigeria is highly unlikely. During the period 1989–1992, the prevalence of HBsAg among women seeking antenatal care outside of major urban centers was 0.33%, suggesting a prevalence of infection markers in the general population of 1%–2% [23]. Because these figures include immigrants from countries where infection is highly endemic or mesoendemic, and because the religious communities involved in this study condemn premarital sex, the prevalence of HBV infection among these Dutch-born missionaries will have been even lower than 1%-2%. However, 3 of 14 infected subjects had also stayed in other countries where hepatitis B infection is highly endemic.

We used only 1 marker of HBV infection. Testing for anti-HBc has high sensitivity for present or past HBV infection, but results may be negative for some patients with self-limiting infections [24]. In addition, anti-HBc levels may have declined below the threshold of detection in subjects who acquired a self-limiting infection several decades before testing [24]. The sensitivity for detecting past HBV infection may therefore have been lower than in similar studies that used antibody to HBsAg with or without anti-HBc as a marker [1, 3], and this may be an explanation for the lower prevalence of infection observed in our study.

Some specific exposures—in particular, parenteral exposure—may not have been recalled due to the long period covered by the retrospective study. However, this would not explain the family clustering, unless errors in recalling exposures were specific to some families. We found no evidence for this, because all of the family units involved in the study reported parenteral exposures.

Finally, the observed association with temporary adoption may be a chance finding, attributable to the large number of variables tested. The level of statistical significance ($P < .01$) and the finding of a dose-response relationship with both the number of adoptive children and the duration of their stay suggest, however, that this is a true association.

We conclude that both adults and children who stay in areas where HBV infection is highly endemic for a prolonged period may be at considerable risk for HBV infection, and should thus be offered hepatitis B vaccination, particularly when living in close contact with local children who may transmit HBV infection horizontally. Because HBV infections acquired during childhood often become chronic [7], and therefore carry a considerable risk of chronic sequelae and further transmission after return to the home country, screening of unvaccinated expatriate children after return should be considered, regardless of a history of jaundice or reported exposures.

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