

The importance of imported infections in maintaining hepatitis B in The Netherlands

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SUMMARY

In The Netherlands, in May 1999 an enhanced surveillance of hepatitis B was begun to collect detailed information of patients with acute hepatitis B virus (HBV) infection. The objective was to gain insight in transmission routes and source of infection of new HBV cases. Through public health services, patients were interviewed on risk factors. It appeared that the majority (59%) acquired the infection through sexual contact; 52% of these by homosexual and 48% by heterosexual contact. In 60% of the heterosexual cases, the source of infection was a partner originating from a hepatitis B-endemic region. Sexual transmission is the most common route of transmission of acute hepatitis B in The Netherlands and introduction of infections from abroad plays a key role in the current epidemiology of HBV. As well as prevention programmes targeted at sexual high-risk groups, prevention efforts should focus more on the heterosexual transmission from HBV carriers.

INTRODUCTION

Hepatitis B virus (HBV) infection is an important cause of morbidity and mortality worldwide as it can lead to chronic hepatitis, liver cirrhosis and hepatocellular carcinoma [1]. The age at which infection takes place is inversely related to the risk of developing chronic infection [2]. In areas of high and intermediate endemicity for HBV infection (HBsAg carrier rate >2%) the infection is mainly transmitted from mother to child (vertical transmission) and in young children through household contact (horizontal transmission). In low endemic areas (HBsAg carrier rate <2%) most infections occur in adults with risk

behaviours such as injecting drug use (IDU) and high-risk sexual activity [1]. To achieve a large reduction in the carrier rate among children, the World Health Organization (WHO) advised all countries to integrate universal hepatitis B vaccination into their national immunization programmes by 1997 [3]. A number of western European countries with very low HBsAg carrier rates have been reluctant to do so (e.g. United Kingdom [4], The Netherlands [5]). It is unclear how effective such a universal vaccination programme would be in a situation with low prevalence and a substantial importation of people with HBV infections.

In the Dutch statutory notifications, approximately 50% of acute HBV infections are attributable to sexual contact [6]. Apart from sexual preference, more detailed information on sexual behaviour is not recorded in the notifications. In a substantial percentage

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of acute HBV infections (37% in 2000) the transmission route is unknown [6]. In The Netherlands, the surveillance was enhanced to gain more insight in the epidemiology of HBV. All patients with acute hepatitis B infection were investigated thoroughly to assess risk factors associated with transmission of HBV and the source of infection.

METHODS

Clinicians and microbiologists report patients with acute hepatitis B to their local municipal health services (MHS) as part of the Dutch notification system for communicable diseases. Patients are contacted routinely by the MHS to identify the source of infection and for contact tracing. Patients with acute hepatitis B reported between May 1999 and July 2000 and meeting the case definition were asked to participate in the study. Intake criteria included living in The Netherlands, a positive HBsAg test and elevated aminotransferase levels (>3 times normal). Patients with chronic infection causing this clinical picture were excluded. The MHS was also asked to register the notification number, the date of diagnosis, the sex, and year of birth of the patient. Additional data were collected by means of two questionnaires. During the contact tracing interview the public health nurse recorded details on the medical condition and possible risk factors in order to identify the most likely mode of transmission and source of infection. The patient supplied additional information on demographic variables and risk exposures on a self-administered questionnaire. For participants younger than 12 years of age, parents were asked to complete the questionnaire. Ethical permission was not granted to ask questions on sexual partnership to individuals under 18 years of age. Patients who did not agree to participate in the study were asked to fill out a non-response form. To determine the possible effects of non-response the cases in the study were compared with the notified cases of hepatitis B in the period of data collection. Written informed consent was obtained from all participants. The Medical Ethics Committee of The Netherlands Organization of Applied Scientific Research (TNO) approved the study.

Details on the number and nature of sexual partners in the past 6 months, commercial sexual contacts, drug use and needle sharing were collected in a face-to-face interview with the public health nurse. For each of the three most recent partners

the following information was included: type of partner (self-defined as casual or steady), sex, age, nationality and country of birth of partner, condom use (never, sometimes, mostly, always), country where sexual contact took place, intravenous drug use and commercial sex work of partner, other (homo)sexual contacts of partner in the last year. Details on demography (age, ethnicity, education), education, work, (para)medical history (including cosmetic treatment and tattoos/piercings), and international travel were recorded by the patient. In case of international travel, questions regarding (para)medical and cosmetic treatment while abroad were included. Most questions referred to the period of 6 months prior to diagnosis. Ethnicity was based on the country of birth of the patient and his/her parents; i.e. Dutch if the patient and both parents were born in The Netherlands and non-Dutch if the patient and/or at least one of the parents was born abroad. Educational levels were classified as 'low' (primary school, lower vocational or lower general secondary education), 'intermediate' (intermediate vocational or intermediate general secondary and higher general secondary education) and 'high' (higher vocational secondary education and university education). All variables concerning countries were classified according to the prevalence of HBsAg as defined by the WHO in low (<2%), intermediate (2–8%) and high (>8%) endemic countries. The final classification of the most probable route of transmission was based on the information obtained in the face-to-face interview and the additional questionnaire on risk exposure.

All statistical analyses were done with version 8.1 of the SAS software package (SAS Institute Inc., Cary, NC, USA). For comparison of the age distribution Student's *t* test was used. The χ^2 test or Fisher's exact test was used for comparing proportions.

RESULTS

Between May 1999 and July 2000 144 patients participated in the study and 20 patients completed a non-response form. In the same period, 289 acute HBV infections were notified. Because these cases were considered eligible for this study, the MHS were contacted to retrieve information on the missing 125 patients. Of those, 27 did not meet the case definition and were excluded. Reasons for non-response of the remaining 98 patients were that the MHS did not inform the patient of the study (e.g. the MHS did not

Table 1. *Characteristics of patients*

	Total		Men		Women		<i>P</i> value
	<i>n</i> = 144	100%	<i>n</i> = 108	75·0%	<i>n</i> = 36	25·0%	
Mean age in years (s.d.)	35		38	(12·5)	28	(13·7)	<0·001
Nationality							
Dutch	127	92·0	96	93·2	31	88·6	0·47
Non-Dutch	11	8·0	7	6·8	4	11·4	
Unknown	6	—	5	—	1	—	
Ethnicity							0·06
Dutch	105	77·2	82	81·2	23	65·7	
Non-Dutch	31	22·8	19	18·8	12	34·3	
Low endemic	7		5		2		
Intermediate endemic ^a	18		10		8		
High endemic	6		4		2		
Unknown	8	—	7	—	1	—	
Reason for HBsAg test							0·10
Symptoms	130	92·2	100	94·3	30	85·7	
Other	11	7·8	6	5·7	5	14·3	
Unknown	3	—	2	—	1	—	
Hospitalized for HBV							0·008
Yes	20	14·2	10	9·3	10	29·4	
No	121	85·8	97	90·7	24	70·6	
Unknown	3	—	1	—	2	—	
Transmission route							n.s.
Sexual	85	59·0	64	59·3	21	58·3	
Medical/dental treatment	9	6·3	9	8·3	0	0	
Blood contact (first aid, work)	11	7·6	10	9·3	1	2·8	
Contact with HBV carrier	8	5·6	4	3·7	4	11·1	
Percutaneous procedure ^b	6	4·2	3	2·8	3	8·3	
Other ^c	4	2·8	4	3·7	0	0	
Unknown	21	14·6	14	13·0	7	19·4	
Country of infection							0·14
The Netherlands	97	82·2	68	79·1	29	90·6	
Abroad	21	17·8	18	20·9	3	9·4	
Unknown	26	—	22	—	4	—	
Sexual contact (last 6 months) ^d							
Yes	115	92·7	90	91·8	25	96·2	
No	9	7·3	8	8·2	1	3·8	
Not filled in	6	—	5	—	1	—	

^a Countries: Morocco (3), Turkey (3), Surinam/Netherlands Antilles (6), other intermediate endemic countries (6).

^b Including (ear)piercing (2), acupuncture (2), tattoo (1), injection (1).

^c Including shaving at barber's shop (2), living in a high endemic country for 4 months (1), sharing toiletry in students' house (1).

^d Only patients aged 18 years and older.

participate at all, could not reach the patient, forgot to ask the patient, did not want to burden the patient) or the patient refused to participate. As a result, 144 (55%) of the total number of 262 eligible patients participated in the study. The sex distribution was similar for the participants (108 men and 36 women) and the non-participants ($P=0·32$). Also there was

no difference in the age distribution between participants and non-participants (t test men, $P=0·14$; t test women, $P=0·18$).

The age of the patients ranged from 2 to 75 years and the mean age of men was greater than that of women (Table 1). The majority of the patients (92%) were diagnosed because of symptomatic disease.

Other reasons for serological testing were medical examination ($n=6$), new sexual partner ($n=2$), contact tracing ($n=2$), pre-vaccination serology ($n=1$). An HBsAg confirmation test was performed for 108 patients (75%). Twenty patients (14%) were hospitalized due to their HBV infection, women more frequently than men (Table 1). The majority of the patients (92%) had Dutch nationality or Dutch ethnicity (77%). Of the patients with non-Dutch ethnicity, 77% (24/31) came from countries with an intermediate or high prevalence of hepatitis B. More women (34%) than men (18%) had non-Dutch ethnicity. For both genders, the educational level was low for 40%, intermediate for 36% and high for 24% of the patients. Intravenous drug use and commercial sex work in the 6 months prior to diagnosis were not reported.

The most likely route of transmission was sexual contact for 85 patients (59%). Other risk exposures were identified for another 38 patients (26%). In 21 cases (15%) the most likely transmission route could not be identified.

Of all patients who were probably infected through sexual contact, heterosexual contact was reported by 41 (48%) patients (21 women, 20 men), and men having sex with men (MSM) by 44 men (52%) (Table 2). Nineteen patients (22%) had non-Dutch ethnicity, less often for MSM (14%) compared to heterosexual men and women (32%, $P=0.06$), and more often for women (38%) compared to heterosexual men (25%, $P=0.08$). Compared to heterosexuals, MSM more often reported more than one sexual partner in the past 6 months (39% and 82% respectively, $P<0.0001$). Among heterosexuals more men than women reported more than one sex partner in the past 6 months but this difference was not significant. Eighty-nine per cent of MSM reported at least one sexual partner with known other sexual contacts in the previous year *vs.* 37% of heterosexuals ($P<0.0001$). Consistent condom use with the three most recent partners was reported by only 23% of the MSM ($n=10$ of whom six did not use condoms in oral sex), and by only 20% of the heterosexual men. Three patients had a concurrent sexually transmitted infection at the time of diagnosis (two MSM had HIV and one female had a chlamydial infection).

In all cases of sexual transmission the most probable source of infection was identified. Overall, 59% of the cases became infected through sexual contact with a casual partner. MSM more often (73%) than heterosexuals (44%, $P=0.01$), and heterosexual men

(60%) more often than women (29%, $P=0.01$). Women were more likely to become infected by a steady partner. The ethnicity of the source of infection was more often non-Dutch for heterosexual men (65%) and women (57%) than for MSM (30%, $P=0.01$). Almost all non-Dutch partners of heterosexuals, who were identified as the source of infection, originated from countries with a intermediate or high prevalence of HBV (92%); for MSM this was 54% ($P=0.004$). Comparison of the ethnicity of case and source (for heterosexuals only) revealed that a non-Dutch partner infected 16 of the 26 (62%) Dutch cases compared to 9 of the 12 (75%) non-Dutch cases ($P<0.05$). For MSM relatively little information is available on the source of infection.

Overall, 15% of the infections were acquired abroad, 25% (5/20) of the heterosexual men and 10% (2/21) of the heterosexual women acquired the infection in countries with an intermediate or high HBV prevalence.

In 38 cases (26% of the total) a variety of risk exposures was identified (see Table 1). The source of infection was only identified in eight of the 38 cases (21%) with non-sexual transmission routes. Five cases could be classified as horizontal transmission, of whom four were younger than 15 years of age. All these were non-Dutch and infected through household contact with carriers of the same ethnic group. For 21 cases (15% of total) the mode of transmission was not identified as no risk exposures could be determined. Fourteen cases with non-sexual or unknown transmission routes (24%) reported travel to countries with a middle or high HBV prevalence; six of them (43%) had probably acquired the infection abroad.

DISCUSSION

Sexual contact is the most common route of transmission of acute hepatitis B in The Netherlands. Approximately half of the sexually transmitted HBV infections was attributable to homosexual contact. A non-Dutch partner was often identified as the source of infection for heterosexuals (in 75% of the non-Dutch patients and in 62% of the Dutch patients).

Although the patients in the study were representative of the total group of notified HBV cases regarding sex and age distribution, they may not represent the total group of new infections with HBV. Due to subclinical infections, cases of acute HBV infections may not be recognized and, therefore,

Table 2. *Characteristics and sources of infection of patients infected through sexual contact*

	Total		Homosexual men		Heterosexual men		Women	
	n=85	100%	n=44	51·8%	n=20	23·5%	n=21	24·7%
Mean age in years (s.d.)	35·9	(12·0)	37·7	(10·6)	37·0	(10·2)	30·3	(14·9)
Mean age in years (partner) (s.d.)	31·7	(9·3)	33·2	(5·9)	29·4	(6·9)	31·9	(13·6)
Ethnicity (patient)								
Dutch	60	70·6	33	75·0	14	70·0	13	61·9
Non-Dutch	19	22·4	6	13·6	5	25·0	8	38·1
Intermediate-high endemic	17		5		5		7	
Unknown	6	7·1	5	11·4	1	5·0	0	0
Number of partners (previous 6 months) ^a								
1	31	37·8	8	18·2	11	55·0	12	70·6
2	14	17·0	6	13·6	5	25·0	3	17·6
3	11	13·4	8	18·2	2	10·0	1	5·6
4-9	18	22·0	15	34·1	2	10·0	1	5·6
≥10	5	6·1	5	11·4	0	0	0	0
Unknown	3	3·7	2	2·3	0	0	1	0
Did partner have other sexual contacts in previous year								
Yes	54	63·5	39	88·6	8	40·0	7	33·3
No	19	22·4	2	4·6	9	45·0	8	38·1
Unknown	12	14·1	3	6·8	3	15·0	6	28·6
Condom use (6 months) ^a								
Yes (always)	14	17·1	10	22·7	4	20·0	0	0
No (most of the time, sometimes, never)	63	76·8	31	70·5	16	80·0	16	88·9
Unknown	5	6·1	3	6·8	0	0	2	11·1
Source of infection								
Steady partner	35	41·2	12	27·3	8	40·0	15	71·4
Casual partner	50	58·8	32	72·7	12	60·0	6	28·6
Ethnicity of source								
Dutch	38	44·7	24	54·4	6	30·0	8	38·1
Non-Dutch	38	44·7	13	29·5	13	65·0	12	57·1
Intermediate-high endemic	30		7		12		11	
Unknown	9	10·6	7	15·9	1	5·0	1	4·8
Country of infection								
The Netherlands	62	72·9	31	70·5	14	70·0	17	81·0
Abroad	13	15·3	6	13·6	5	25·0	2	9·5
Intermediate-high endemic	9		2		5		2	
Unknown	10	11·7	7	15·9	1	5·0	2	9·5

^a Only patients aged 18 years and older (missing data for three women).

be under-reported. As the clinical expression of HBV is age-dependent [2, 7] children are more likely to be missed and under-reported. Children in migrant populations with a higher HBsAg carrier rate than the Dutch population are at increased risk of acquiring HBV through horizontal transmission. A study by Franks et al. showed that nearly half of the HBV infections in children born in the United States to Southeast Asian refugees were attributable to

horizontal transmission within and between families [8]. In The Netherlands, a screening programme of pregnant women and subsequent immunization of neonates of HBsAg-positive mothers has been in place since 1976. However, this programme is not effective in the prevention of horizontal HBV infections in later childhood in migrant populations. Therefore, the Dutch Ministry of Health has recently decided to offer HBV vaccination to all newborn infants having

at least one parent born in a country with an intermediate or high prevalence of hepatitis B.

None of the patients in our study acquired HBV through IDU. In the notification data of 2000, it was found that only 1% of all acute HBV infections could be attributed to IDU [6]. This is different from the United Kingdom, where IDU was the most common exposure for acquisition of acute HBV (21%) [9]. In Sweden 38% of all cases were attributed to IDU [10]. A study of IDU in The Netherlands showed that HBsAg prevalence rates in IDU vary between 3 and 7% [11]. Injecting drug users may be possibly under-represented in our study. This could be due to a bias in intake; injecting drug users may not be asked to participate in the study as it is assumed they are less willing to participate. In Amsterdam a large decline in prevalence and initiation of IDU was observed from 1986 to 1998 which might also partially explain the low number of acute HBV infections attributable to IDU [12].

Of the notified cases of acute HBV in the year 2000, 52% were infected through sexual contact [6], which is similar to the proportion in our study (59%). Within the notification system the proportion has even increased recently to 60% in 2002, probably due to improved data collection [13]. The contribution of sexual transmission may be underestimated as infections with an unknown transmission route may also partially be due to sexual contact. In a case-control study, carried out in the United States among HBV patients who had no known source of infection, an additional 14% of all HBV infections was likely to be attributed to multiple heterosexual partners [14].

The identification of the most likely route of transmission for acute hepatitis B is complicated. Nevertheless the proportion of cases with unknown transmission route in notification data from The Netherlands declined from 61% in 1993 to 37% in 2000 and 25% in 2002 [6, 13, 15]. This percentage was 46% in laboratory-reported cases in the United Kingdom and approximately 30% in US sentinel surveillance [9, 16]. Our study (15% unknown transmission route) demonstrates that enhanced surveillance can further reduce the proportion of unknown routes. This was previously noted by Struve et al. [10]. However, it must be emphasized that in case of non-sexual transmission the actual source of infection is only identified in a few cases, e.g. in our study mostly through horizontal transmission.

Although MSM have been recognized as an important risk group for HBV infection for over 30

years, several studies have shown an increase in the number of acute infections due to heterosexual activity during the last two decades [9, 17, 18]. The MSM in our study reported a large number of casual partners, who also had other numerous contacts, and were mostly of Dutch origin. A total of 60% of the heterosexual cases were infected by partners from medium or high endemic countries. This shows that the importation of new infections plays an important role in the epidemiology of HBV. These results support the findings of the mathematical model of HBV in The Netherlands [19]. The basic reproduction number (R_0) in the MSM population was 4.67, suggesting that HBV can maintain itself in MSM. In the heterosexual population, the R_0 is smaller than 1, suggesting that HBV cannot maintain itself without the introduction of new infections into the population [19]. This is also suggested by results from a molecular epidemiological study in Amsterdam [20].

Our study shows that the prevention of HBV infections in sexual high-risk groups is of the highest importance as more than half of all recognized new infections are attributable to sexual contact. The feasibility of an enhanced outreach programme of HBV vaccination of risk groups was demonstrated recently [21]. This programme for targeted risk group vaccination is now implemented throughout The Netherlands. The newly implemented vaccination programme for newborn infants having at least one parent born in a HBV-endemic country is aimed at the prevention of HBV in migrant populations. However, individuals with sexual partners from HBV-endemic countries are also at increased risk for HBV infection. Prevention should be focused more on the reduction of sexual transmission from HBV carriers.

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