Surveillance studies on Infectious diseases: Evidence for action
van Rijckevorsel, G.G.C.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Risk of hepatitis B for travellers, is vaccination for all travellers really necessary?

Gerard JB Sonder,1,2,3 Gini GC van Rijckevorsel,1,3 Anneke van den Hoek 1,2

1. Public Health Service Amsterdam, Department of Infectious Diseases. Nieuwe Achtergracht 100, 1018 WT Amsterdam The Netherlands
2. Academic Medical Centre, Department of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and AIDS, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
3. LCR, National Coordination Centre for Travellers Health Advice, Nieuwe Achtergracht 100, 1018 WT Amsterdam The Netherlands

Journal of Travel Medicine, 2009; 16:18-22
Abstract

Objectives: Behavioural studies in travellers suggest that 33% to 76% of all travellers to hepatitis B virus (HBV)-endemic countries are at risk for HBV infection. We study the incidence and risk factors for HBV infection in travellers.

Methods: Retrospective analysis of the characteristics and risk factors of all reported acute HBV patients in Amsterdam, the Netherlands, from January 1, 1992, until December 31, 2003.

Results: The estimated incidence in travellers from Amsterdam to HBV-endemic countries is 4.5/100,000 travellers. Two thirds of these patients were immigrants who lived in Amsterdam and who had visited their friends and relatives in their country of origin. In 12 years, only three Dutch short-term tourists contracted HBV while travelling, all by heterosexual contacts.

Conclusions: Dutch tourists who travel to HBV-endemic countries run a very low risk of contracting HBV. Vaccination of short-term Dutch tourists is not necessary. Immigrants run a higher risk irrespective of travel or duration of travel. This group should be advised vaccination.
Introduction

The prevalence of hepatitis B (HBV) is not evenly distributed around the world. The world can be divided into three areas where the prevalence of chronic HBV infection is high (≥8%), intermediate (2%-8%), and low (<2%). In 1992, the World Health Organization recommended that by 1997, all countries should introduce a program of universal immunization against HBV. The Netherlands, like the UK and the Nordic countries, adopted a program of targeted HBV risk group vaccination rather than the universal vaccination practiced in most other countries in the world. In the Netherlands, these are risk groups as determined by their behaviour, such as injecting drug users (IDU), men who have sex with men (MSM), and male and female sex workers. Also, newborns from HBV surface antigen (HBsAg)-positive mothers and, since 2003, children with at least one parent from a country with HBV-endemicity ≥2% are offered free vaccination through the National Vaccination Program to prevent horizontal or sexual transmission in this group. These risk groups are offered free vaccination. The Dutch national HBV travellers’ guidelines advise HBV vaccinations together with other travellers’ vaccinations for all persons who travel to HBV-endemic countries for more than 3 months and for those who travel for less than 3 months but have other risk factors. These include sex tourists, people involved in dangerous sports, and frequent travellers. Travel vaccinations are not free of charge but, depending on the health insurer, partially reimbursed. Studies have indicated that travellers to HBV-endemic countries can be at risk for HBV infection. The only available prospective study found 2 of 7887 travellers infected. Both patients worked abroad, and no infections were found in 7317 short-term travellers. Retrospective serological studies among expatriates originating from low-endemic countries, who had lived in HBV-endemic countries for several years, found that 9% to 11% had been infected with HBV. Assuming no infections had occurred before departure, Steffen estimated an incidence of 80 to 420/100,000/month for expatriates, 2 to 10-fold higher than in short-term travellers. More recently, several questionnaire-based studies have examined the potential risk for HBV infection as determined by risky behaviours such as accidents, dental or medical treatment, tattooing, sporting activities, and sexual contact, reporting that 33% to 76% of all travellers to endemic countries are at risk. The World Tourism Organization estimated that worldwide in 2004, 461 million travellers had arrived in HBV-endemic countries. From the Netherlands, the
number of travellers to HBV-endemic countries has tripled between 1992 and 2003 from 540,000 to 1,611,000. These numbers are still rising. With the results of the behavioural studies, one would expect a large number of acute HBV infections among travellers.

To evaluate whether our current HBV vaccination guidelines for travellers are adequate, we retrospectively analyzed all acute HBV cases in Amsterdam between 1992 and 2003 to answer the following questions: which proportion of acute HBV infections are travel related and imported from endemic countries? Is HBV vaccination for all travellers necessary, or are particular groups more at risk of HBV than others while travelling?

**Methods**

In the Netherlands, each diagnosis of acute HBV has to be reported to the local public health service (PHS). Reporting criteria are clinical signs and symptoms in combination with findings of HBsAg or type M immunoglobulin antibodies to HBV in the serum. All reported patients are approached by public health nurses of the PHS, who provide active surveillance as to the source of infection for each patient and acquire information on specific risk factors in the 6 months prior to infection, as well as demographic data. An algorithm is used to classify sources of infection by probable mode of transmission. These include people with high-risk behaviour specifically for HBV: MSM, individuals having unprotected heterosexual contact with new or multiple partners, or IDU. People without such behaviours are classified as horizontal transmission, i.e., when a household or other contact is identified as a carrier of HBsAg or when such identification is likely, or as healthcare transmission if invasive procedures were performed in the 6 months preceding infection. If none of the above risks are identified, the transmission is classified as ‘unknown’.

If a person or one of his/her parents was born in a country endemic for HBV (HBsAg = 2%), the person was considered to be an ‘immigrant of endemic origin’ (‘immigrant’). All other patients were considered of ‘Dutch or other low-endemic origin’ (‘Dutch’).

All reported cases in Amsterdam in a 12-year period, between 1992 and 2003, were evaluated. Evaluation was done until 2003 because of a change and therefore inconsistency in data collection in 2004. We analyzed risk factors for contracting an acute HBV infection in an endemic country. We used univariable
and multivariable logistic regression to assess risk factors for travel-related infections. In multivariate modelling, all factors with p < 0.1 were included.

Results

Between January 1, 1992, and December 31, 2003, 342 patients with acute HBV were reported to the PHS of Amsterdam. Of these, 19 were excluded from analysis because no information could be obtained for a variety of reasons (no telephone number, language problems, and no patient consent to PHS involvement). Another seven were excluded because no information about travel in their incubation period was available, and two patients were excluded because they were immigrants who had very recently moved to Amsterdam and were already infected in their country of origin.

The remaining 314 HBV patients are shown in Table 1. The largest proportion of patients (128/314 = 41%) were infected by homosexual contacts and another 26 of 314 (8%) by IDU. Almost a third (100/314 = 32%) of all patients were immigrants from HBV-endemic countries. Excluding MSM and IDU, almost half (78/160 = 49%) of all patients were immigrants.

Of all patients, 52 of 314 (16%) had travelled to an HBV-endemic country during their incubation period, but half (25/52 = 48%) the patients who had travelled to an endemic country had a most likely source not related to that travel: of the 98 heterosexually infected patients, 25 (26%) had travelled to such countries, but 6 of them were infected by their own steady partner, and 2 reported unsafe sex contacts in the Netherlands but not abroad; of the 24 horizontally infected patients, 7 (29%) had travelled, but 2 had a source in their own family in the Netherlands, and 2 reported blood–blood contact in the Netherlands but not abroad; of the 10 medically infected patients, 6 (60%) had travelled, all 6 were most likely infected abroad, and of the 128 patients infected by homosexual contacts, 12 (9%) had visited an HBV-endemic country in their incubation period, but none mentioned sexual contacts exclusively while travelling. Of the IDU, none had travelled in their incubation period.

In conclusion, of only 27 of 314 (9%) it was likely that the infection was acquired in an HBV-endemic country.

Immigrants were significantly more likely to have contracted HBV in an endemic country (18/100 = 18%) than patients of low-endemic origin (9/214 = 4%). Also, patients infected by medical care or tattoos were significantly more likely to have
contracted their infection abroad (7/10 = 70%) than patients infected by other transmission routes (20/304 = 7%) (Table 1).

Of all reported patients, 15 of 314 (3.2%) were younger than 16 years old, and 14 of 15 originated from an endemic country. Of the 15, 9 were infected horizontally, of whom 1 was infected in her country of origin and 3 were infected by medical treatment in their country of origin (2 circumcisions and 1 injection). In three children, including the patient from Dutch origin, infection was not travel related and the transmission route was unknown.

Of the 27 patients who contracted HBV in an endemic country, according to the Dutch guidelines, 10 of 27 were advised vaccinations. Six were expatriates from low-endemic origin, of whom one had received only one HBV vaccination before travel because there was no more time and one had received an accelerated series of three vaccinations but apparently was not protected. The other four expatriates did not seek pre-travel health advice or chose not to be vaccinated. Four immigrants, who travelled to their country of origin for more than 12 weeks, would have been advised vaccinations according to the guidelines, but none of these sought pre-travel health advice.

Of the 17 of 27 patients who, according to the current Dutch guidelines, are not advised vaccinations before travel, 14 (82%) were immigrants. Of these 14 immigrants, 6 were most likely infected by heterosexual contact, 2 horizontally (both children), 5 by medical treatment (2 children), and 1 by a tattoo. The remaining three were Dutch tourists who travelled less than 3 months. All three were infected by local casual sex partners during a short holiday in the Gambia, Tanzania, and Thailand, respectively.
Table 1 Characteristics of all acute HBV patients who were most likely infected while travelling to an HBV-endemic country, reported in Amsterdam, the Netherlands, 1992 to 2003

<table>
<thead>
<tr>
<th>Total HBV patients</th>
<th>Source of infection HBV-endemic country (HBsAg &gt;2%)</th>
<th>univariable</th>
<th>multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 314</td>
<td>n = 27 (9%)</td>
<td>OR (95%CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Mean age (y), range</td>
<td>33 (1-75 y)</td>
<td>0.93 (0.66–1.32) per 10 y</td>
<td>0.687</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>235 (75%)</td>
<td>1.0</td>
<td>0.924</td>
</tr>
<tr>
<td>Female</td>
<td>79 (25%)</td>
<td>1.05 (0.42-2.57)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Origin (%)</td>
<td></td>
<td>5.0 (2.16-11.58)</td>
<td>&lt;0.033</td>
</tr>
<tr>
<td>Dutch /low-endemic</td>
<td>214 (68%)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Immigrant HBV-endemic</td>
<td>100 (32%)</td>
<td>5.0 (2.16-11.58)</td>
<td>&lt;0.033</td>
</tr>
<tr>
<td>Transmission route (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>98 (31%)</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Horizontal</td>
<td>24 (8%)</td>
<td>0.43 (0.09-2.02)</td>
<td>0.34 (0.07-1.61)</td>
</tr>
<tr>
<td>Medical care/tattoo</td>
<td>10 (3%)</td>
<td>11.12 (2.61-47.40)</td>
<td>10.67 (2.40-47.46)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28 (9%)</td>
<td>0.18 (0.02-1.39)</td>
<td>0.16 (0.02-1.27)</td>
</tr>
<tr>
<td>Homosexual</td>
<td>128 (41%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IDU</td>
<td>26 (8%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HBsAg = hepatitis B surface antigen; HBV = hepatitis B; OR = odds ratio; CI = confidence interval y = years.
Discussion

This study confirms the findings of an earlier prospective study that the HBV risk for short-term tourists to HBV-endemic countries is very low: in 12 years, only 17 such tourists from Amsterdam contracted HBV in an HBV-endemic country. In the same period, an estimated 13 million people have travelled to HBV-endemic countries from the Netherlands. Assuming that the same proportion of the Amsterdam population has travelled to such countries, this would mean that in the 12 years studied, more than 600,000 people would have visited an HBV-endemic country, making the estimated incidence 4.5/100,000 travellers. This is even lower than earlier estimations and suggests that only a very small proportion of travellers considered ‘at risk’ according to the behavioural studies (33-76% of all travellers) actually contracts the disease.

In our study, like in all studies based on reported cases of disease, underreporting may have led to an underestimation of incidences. In Amsterdam, where all laboratories report every positive HBsAg result to the PHS, we expect that the number of unreported infections is very low.

Of all acute HBV patients in Amsterdam, 9% were likely infected in an HBV-endemic country. In contrast, a national study in 1999 found that 18% of all HBV patients reported were infected abroad, another national study in 2002 to 2005 found 15%, and a similar study in the UK found 12%. These findings were probably higher than in the current study because in those studies, everybody reporting international travel during incubation was considered to have contracted their infection abroad. In our study, we found that half the patients who had travelled were not infected abroad.

HBV patients who were infected while travelling were significantly more often immigrants from endemic countries (18/27 = 67%) than people of low-endemic origin (9/27 = 33%), and these immigrants were, according to the current Dutch guidelines, significantly more often not advised vaccination. In contrast, in the 12 years studied, only three short-term Dutch tourists, according to the guidelines were not advised vaccination, contracted HBV, all three by sexual contacts. No HBV cases were reported in Dutch tourists caused by accidents, medical care, sports activities, or tattooing.

Long-term travellers from low-endemic origin are more likely to have sex with the local population than short-term travelers. A recent study among almost 2,000 short-term travellers from the Netherlands found that 5% had sexual contact with a
new partner, of whom 2 of 3 had sexual contact with a local partner and 1 of 3 did not always use condoms. This behavioural study shows that about 1% (those having unprotected sex with local partners) of all travellers were possibly at risk of HBV, but again, the actual incidence of HBV in this group is likely to be very much lower and not necessarily higher than in people who do not travel. Travelling without a steady partner and expecting a new sexual contact were the most important risk factors of having casual sex, whereas reading pre-travel information on sexually transmitted infections protected sex. Therefore, people who travel without their steady partner should receive STI information and be advised to take condoms along. HBV vaccination could also be advised, but these travellers should be informed that HBV risk is not necessarily higher while travelling and that vaccination only protects from HBV after a complete series of vaccinations.

That import of HBV by patients of Dutch origin plays a minor role in the epidemiology of HBV in the Netherlands was also confirmed by a recent molecular epidemiological study among 306 newly reported chronically infected HBV carriers in Rotterdam, the Netherlands: only 22 of 306 (7%) of these patients were born in the Netherlands and of Dutch origin, of whom only 1 was possibly infected in an HBV-endemic country because he had a history of travel in such countries.

A relatively large proportion in the immigrant group (14/18 = 78%) were short-term travellers (<12 weeks), a group currently not targeted by travellers’ vaccination guidelines. In contrast to Dutch short-term travellers, these immigrants were infected not only by sexual contacts but also horizontally and by medical care. This suggests that these immigrants are not only at higher risk but also run different risks, even though a higher proportion is already immune by previous infection.

This was also seen in a national study in the Netherlands. A Swiss study also found that immigrants from HBV-endemic countries who live in a low-endemic country and who visit friends and relatives (VFR) in their country of origin are a specific risk group for viral hepatitis.

Our study also confirms earlier retrospective studies that long-term travellers are at higher risk than short-term tourists: despite the fact that the current national guidelines for HBV vaccination for travellers recommend HBV vaccinations for all travellers who travel to HBV-endemic countries for more than 3 months, six Dutch long-term travellers contracted HBV. Only two of them were (partially) vaccinated.

Conclusion
Dutch tourists who travel to HBV-endemic countries run a very low risk of contracting HBV and their risk is probably not higher than those who do not travel.
The current national HBV guidelines for this group are adequate and do not need to be amended. The HBV risk for immigrants from endemic countries who VFR, however, is higher. This risk seems also irrespective of travel or the duration of travel. Because of the horizontal transmission risk for immigrants’ children, in the Netherlands, HBV vaccination is added to the National Vaccination Program for immigrants’ children born since 2003. Because the risk for older immigrants is also higher than for the indigenous population, older immigrants should be advised vaccination irrespective of travel. Our advice is to include all immigrants in the risk group vaccination campaign. Those who do seek pre-travel health advice should be advised HBV vaccination irrespective of duration of travel. The national HBV vaccination guidelines for immigrant travellers should be amended.

Acknowledgements
The authors would like to thank Roel Coutinho for critical review of the article, Merlijn Kramer for methodological advice, Ronald Geskus for advice on statistical analysis, and Lucy Philips for editorial review.
References

infection is via vertical transmission through mothers from endemic regions. [In Dutch] Ned Tijdschr Geneeskd 2007; 151:2389-94.


