Hepatitis B vaccination targeted at behavioural risk groups in the Netherlands: Does it work?


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1. Introduction

Hepatitis B virus (HBV) infections and the consequent increased risk for chronic infection with its sequelae cirrhosis and hepatocellular carcinoma can be prevented by a safe and effective vaccine. The WHO has advised worldwide universal vaccination since 1992, not only in countries where HBV is highly endemic but also in low-endemic countries [1].

The Netherlands is a low-endemic country with an estimated HBsAg prevalence of 0.3–0.5% [2], where HBV transmission is restricted mainly to risk groups. Therefore, the Netherlands, like Britain, and the Scandinavian countries, has adopted a policy of vaccination targeted at behavioural risk groups, rather than universal vaccination [3].

Before implementation of this targeted vaccination program, HBV prevention in the Netherlands consisted mainly of prenatal screening and vaccination of newborns with a chronically infected mother, vaccination of certain patient groups (e.g. hemophiliacs), and healthcare workers. These preventive measures are still ongoing and were extended with the targeted vaccination program and with the vaccination of newborns with at least one parent born in a country with a HBV prevalence over 2%, as of 2003.

Since the Netherlands did not implement universal HBV vaccination, it is important to monitor the effect of our current strategy targeted at behavioural risk groups. Such an evaluation may have implications for countries with a comparable vaccination strategy and even for countries with a universal vaccination program, since they have the same risk groups.

The pilot study preceding nationwide implementation of the vaccination program targeted at behavioural risk groups reached only a small number of people, most of whom were vaccinated in...
Amsterdam [4,5]. As Amsterdam is not representative for the rest of the Netherlands, we have evaluated the current risk group vaccination program 5 years after implementation, using nationwide epidemiological data of reported HBV cases and national vaccination data. Only acute cases were included in this study, because they give insight in the evolution of HBV transmission in the Netherlands. Molecular epidemiology was used to obtain insight into the impact of this targeted vaccination program, and on the dynamics of HBV transmission between and amongst behavioural risk groups and the general population.

2. Methods

2.1. Patients

In the Netherlands, all cases of HBV infection have to be reported to the local Public Health Service and subsequently to the National Centre of Infectious Diseases Control. The reporting criteria for acute HBV are: clinical signs and symptoms of acute hepatitis in combination with the presence of HBsAg in the serum. Reported patients are approached by public health nurses for source and contact tracing and for information about the most likely mode of infection. These data are stored in the national notification system databank (OSIRIS), as are demographic data on age, gender, country of origin and travel history for the past six months. For this study, epidemiological data from OSIRIS were obtained for acute cases reported between January 2003 and December 2007. On the basis of availability, we obtained sera of acute patients, since January 2004.

2.2. Vaccination coverage

Data were supplied by the national behavioural risk group HBV vaccination database. Compliance was defined as the proportion of people reached by the program, who tested negative for anti-HBc at first vaccination and completed their series of three vaccinations at 0, 1, and 6 months. Vaccination coverage was defined as the proportion of people who completed their vaccination series compared to the estimated population at risk. Susceptibles were defined as people negative for anti-HBc and not (completely) vaccinated. The pilot of the nationwide vaccination program for behavioural risk groups (October 1998 through October 2000) was included in the calculation of the coverage and the number of susceptibles [4].

To calculate the vaccination coverage and the susceptible proportion within the risk groups, population size estimates for each risk group were used. The total number of MSM in the Netherlands was based on a population survey in 2006, using the Internet panel Eurolicx, which estimated the percentage of MSM in the general population [6]. Response rate of this panel was 28%, and the outcome was weighted for age, sex, education, and urbanisation to obtain a representative estimate. The extrapolated 95% confidence interval was 278,000–392,000 MSM in the Netherlands. The estimation of the total number of CSWs is based on contacts in the field related to STI prevention or social work. The number of CSWs who work in the Netherlands in a given year was estimated to be 20,000–25,000 [7]. For the number of DUs, regionally capture-recapture estimates were used. The values for regions lacking estimations were supplied by the most likely estimates, using regression analysis, and population size was then calculated for the entire country [8]. The 95% confidence interval estimate for drug users in the Netherlands was 23,800–46,400. Since heterosexuals with multiple sex partners were mainly vaccinated at STI-clinics, the number of heterosexual visitors recorded at STI-clinics was used to calculate the vaccination coverage and number of susceptible heterosexuals (195,000) [9]. The proportion of anti-HBc positives within the various risk groups in the Netherlands has also been estimated in previous studies [10]. The estimates from the various studies and the proportion anti-HBc positives found in the vaccination program were widely divergent. Therefore, we used the range between the lowest and highest estimate.

2.3. Isolation, amplification and sequence analysis

HBV DNA was sequenced in three different laboratories, the Public Health Laboratory in Amsterdam, the Erasmus Medical Centre in Rotterdam, and the National Institute for Public Health and the Environment in Bilthoven. Each used its own protocol and primers, but all yielded PCR amplicons and sequencing data spanning the pre-S2 and S-region. PCR and sequencing conditions as well as the various primers used were previously described [11].

2.4. Phylogenetic analysis

A 648-nucleotide fragment of the pre-S2 and S regions, present in all amplicons, was isolated in the three laboratories and subjected to sequence alignment, using the BioEdit 5.0.9 software [12]. Neighbour-joining phylogenetic analysis was carried out on the nucleotide alignments as provided by the MEGA-4.0.1 software [13]. Nucleotide distances were calculated according to the Kimura 2-parameter model. Phylogenetic reproducibility was estimated by bootstrap analysis with 1000 replicates. In addition, minimum spanning trees were constructed, using the Bionumerics software package 5.1. The nucleotide sequence data have been deposited in the GenBank sequence database under accession numbers DQ988364–DQ988521 and FJ391525–FJ391918.

2.5. Statistical analyses

The basic demographic characteristics of patients for whom sera was available for sequencing were compared with patients for whom no serum was available, using the chi-square test. Median ages were compared among groups using Students T-test. P-values lower than 0.05 were considered to be significant. All analyses were done in SPSS 15.0.

3. Results

3.1. General characterization of acute HBV cases

From January 2003 through December 2007, 1386 patients acutely infected with HBV were reported in the Netherlands. Of these, 78% were men. The annual number of reported cases declined from 326 in 2003 to 220 in 2007, equivalent to a decline in reported incidence from 2.0 to 1.4 per 100,000 inhabitants. Based on interviews with public health nurses, patients were classified according to the most probable mode of transmission (Table 1). For both men and women sexual intercourse was the most frequently reported mode of transmission: 65% over the entire study period. MSM accounted for the largest group of HBV transmission throughout the study. The overall decrease in reported patients acutely infected with HBV occurred in all risk groups. The distribution of the various modes of transmission remained the same throughout the study period, although there seemed to be a slight increase in proportion of heterosexual cases. The median age remained stable throughout the study period for the various modes of transmission. The median age of MSM infected acutely with HBV was significantly higher than that of the heterosexuals, being 39 and 33 years, respectively. Most patients (84%) were infected with HBV within the Netherlands. Of all reported patients with an acute HBV infection, 245 (18%) were admitted to a hospital.
Table 1
Number and median age of all reported patients acutely infected with HBV, by most probable mode of transmission; the Netherlands, January 2003 through December 2007 (N = 1386).

<table>
<thead>
<tr>
<th>Most probable mode of transmission</th>
<th>Reported cases (%)</th>
<th>2003 Median age</th>
<th>2004 Median age</th>
<th>2005 Median age</th>
<th>2006 Median age</th>
<th>2007 Median age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homosexual</td>
<td>104 (31.9)</td>
<td>40</td>
<td>105 (35.5)</td>
<td>38</td>
<td>106 (35.1)</td>
<td>83 (34.3)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>84 (25.8)</td>
<td>33</td>
<td>74 (25.0)</td>
<td>33</td>
<td>89 (29.5)</td>
<td>75 (31.0)</td>
</tr>
<tr>
<td>Sexual</td>
<td>13 (4.0)</td>
<td>33</td>
<td>7 (2.4)</td>
<td>45</td>
<td>4 (1.3)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>IDU</td>
<td>7 (2.1)</td>
<td>35</td>
<td>3 (1.0)</td>
<td>33</td>
<td>1 (0.4)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (9.2)</td>
<td>49</td>
<td>33 (11.1)</td>
<td>34</td>
<td>13 (4.3)</td>
<td>15 (6.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>88 (27.0)</td>
<td>35</td>
<td>74 (25.0)</td>
<td>39</td>
<td>90 (29.8)</td>
<td>64 (26.4)</td>
</tr>
<tr>
<td>Total</td>
<td>326</td>
<td>36</td>
<td>296</td>
<td>37</td>
<td>302</td>
<td>242</td>
</tr>
</tbody>
</table>

Sexual: not further specified sexual transmission; IDU: injecting drug use; other: includes household and blood-blood contacts.

3.2. Molecular epidemiology

For molecular analysis, we included 620 sera (58%) from acute HBV patients sampled by the various laboratories in the Netherlands, from January 2004 through December 2007. HBV DNA could be isolated, amplified, and sequenced from 554 of these samples (89%). The demographic characteristics of patients whose sera were available for sequencing analysis did not significantly differ from those sera not available (all variables *P* > 0.05); except for country of birth (the majority of included sequences derived from patients born in the Netherlands. In none of these patients, a vaccine or immune escape mutation was present in the S-gene.

Constructing various phylogenetic trees (data not shown) revealed no major changes in phylogeny. By 2007, HBV genotypes A–F were still circulating in the Netherlands, and genotypes A and D were the predominant genotypes, as was the case in previous years [10].

The genotypes were differently distributed among the various modes of transmission as depicted in minimum spanning trees for each calendar year (Fig. 1). For genotype A, homosexual contact was the predominant mode of transmission (47%) throughout the study period. Overall, 54% of the identical strains in genotype A derived from MSM, as depicted by the pink portion within the main circle. There was a non-significant decline in the proportion of acute HBV infections caused by homosexual transmission within genotype A, from 53% in 2004 to 44% in 2007. The proportion of infections caused by heterosexual transmission within genotype A, on the other hand, significantly increased from 16% in 2004 to 30% in 2007.

During the study period, there were no major changes within genotype D. The patients infected with these strains could not be epidemiologically linked to one another. Heterosexual contact was the predominant mode of transmission of genotype D strains (51%). Of those infected with HBV genotype D, 28% could be linked to the Mediterranean area. They were either infected there or had had sexual contact with a person originating in that area. The proportion of women infected with a HBV genotype D strain increased significantly in the study period, from 27% to 58% respectively. Phylogenetic analysis showed that 38 patients (46%) infected with genotype D were infected with two strains linked to the Mediterranean area (e.g. Morocco and Turkey) (data not shown).

Phylogenetic analysis showed that there is sustained transmission of a genotype F strain in the Netherlands. Patients infected with this strain live across the Netherlands and could not be epidemiologically linked to one another. Transmission of this genotype F strain is not restricted to certain modes of transmission or to a single risk group.
HBV vaccination targeted at behavioural risk groups in the Netherlands, November 2002 until November 2007.

Table 2

<table>
<thead>
<tr>
<th>MSM</th>
<th>DU</th>
<th>CSW</th>
<th>Heterosex</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>18,510</td>
<td>13,482</td>
<td>9,391</td>
<td>39,297</td>
<td>80,680</td>
</tr>
<tr>
<td>2,576 (13.9)</td>
<td>2,048 (15.2)</td>
<td>1,346 (14.3)</td>
<td>2,017 (5.1)</td>
<td>7,987 (9.9)</td>
</tr>
<tr>
<td>13,718</td>
<td>9,458</td>
<td>5,959</td>
<td>28,805</td>
<td>57,940</td>
</tr>
<tr>
<td>10,732</td>
<td>6,269</td>
<td>3,744</td>
<td>19,855</td>
<td>40,600</td>
</tr>
<tr>
<td>74.6%</td>
<td>59.2%</td>
<td>50.7%</td>
<td>59.3%</td>
<td>61.7%</td>
</tr>
<tr>
<td>35</td>
<td>38</td>
<td>30</td>
<td>26</td>
<td>31</td>
</tr>
</tbody>
</table>

MSM: men having sex with men; DU: drug users; CSW: commercial sex workers; heterosex: heterosexuals with an indication for a STI exam.

a Participants positive for anti-HBc did not receive a second and third vaccination.

b Compliance is the percentage of anti-HBc negative participants that completed their series of vaccination. This percentage includes only those participants that were able to complete their vaccination within 6 months (first vaccination until May 1, 2007).

Table 3

<table>
<thead>
<tr>
<th>Estimated total population</th>
<th>Fully vaccinated</th>
<th>Estimated anti-HBc positive</th>
<th>Vaccination coverage (range)</th>
<th>Susceptibles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM 278,000–392,000</td>
<td>12,208</td>
<td>13–36%</td>
<td>6% (4–7%)</td>
<td>165,000–328,000 (59–84)</td>
</tr>
<tr>
<td>DU 24,000–46,000</td>
<td>6,723</td>
<td>15–53%</td>
<td>39% (17–60%)</td>
<td>4,600–32,000 (19–70)</td>
</tr>
<tr>
<td>CSW 20,000–25,000</td>
<td>4,010</td>
<td>14–33%</td>
<td>25% (19–30%)</td>
<td>9,400–17,000 (47–68)</td>
</tr>
<tr>
<td>Heterosex 195,000</td>
<td>23,763</td>
<td>5–42%</td>
<td>17% (13–21%)</td>
<td>89,000–161,000 (46–83)</td>
</tr>
<tr>
<td>Total 517,000–658,000</td>
<td>47,704</td>
<td>11–40%</td>
<td>12% (8–15%)</td>
<td>262,000–538,000 (51–82)</td>
</tr>
</tbody>
</table>

MSM: men having sex with men; DU: drug users; CSW: commercial sex workers; heterosex: heterosexuals with an indication for a STI exam.

3.3. Vaccination

From the start of the national HBV vaccination program targeted at behavioural risk groups in November 2002 until November 2007, 80,680 persons received the first of three HBV vaccinations (Table 2). Of the people participating in the program, 10% had been previously infected with HBV. The total number of people who were fully vaccinated in that period was 40,600 (62%). Compliance was highest among MSM (75%) and lowest among CSW (51%). An additional 17,340 participants received only two doses of the HBV vaccine; overall compliance for receiving two vaccinations was 80%.

The median age of the participants at first vaccination was lower than the median age of the patients acutely infected with HBV, being 31 and 39 years, respectively (Tables 1 and 2). For MSM, the median age at first vaccination and the age at infection were 35 and 40 years, respectively.

The estimated vaccination coverage of the current nationwide vaccination program targeted at behavioural risk groups, including the pilot, was 12% (range: 8–15%) and among MSM this was 6% (range: 4–7%) (Table 3). When the participants who received only two vaccinations were included in the coverage calculation, the overall vaccination coverage did not exceed 16%.

By the end of 2007, we estimated that 51–82% (equivalent to 262,000–538,000) of the people who should be vaccinated are currently susceptible for HBV, the majority being MSM. That risk group had the highest estimated number of susceptibles (165,000–328,000) and also the highest proportion of susceptibles (59–84%). For heterosexuals with an indication for an STI exam and CSW, the proportion of susceptibles was 46–83% and 47–68%, respectively. For DUs this proportion was somewhat lower, 19–70%. However, this range is wide due to the divergent estimations of anti-HBc proportions among DUs.

4. Discussion

In November 2002, the Netherlands adopted a HBV vaccination program targeted at behavioural risk groups, instead of implementing a universal vaccination program. Five years after its implementation, the total number of reported patients acutely infected with HBV has declined from 326 in 2003 to 220 in 2007 and has returned to the level of the 1990s. This decline could be observed in all risk groups. The largest decline was seen among MSM, although it was not significantly larger than in other groups. Sexual transmission, especially among MSM, is the most frequently reported mode of transmission in the Netherlands. Injecting drug use plays a minor role in HBV transmission, in contrast to other European countries; probably because injecting drug use has declined in the past decade [14–16].

The HBV genotype distribution remained equal over the study period, and genotypes A and D remained predominant in the Netherlands. Transmission of the genotype A strain that was observed for years is still ongoing, especially among MSM. There was a slight decrease in the proportion of MSM infected with this genotype, but it was not significant. The increase in the proportion of heterosexuals infected with this genotype, on the other hand, was significant. This is probably due to a better case registration, as the proportion of individuals infected via another mode of transmission has decreased significantly. The majority of infections with HBV genotype D strains were single introductions, and there was no sustained transmission. Remarkably, over the years, there seemed to be reintroduction of two genotype D strains, both linked to the Mediterranean area (e.g. Turkey and Morocco). However, patients infected with these two strains could not be epidemiologically linked to one another. These strains were probably single introductions by people from the same area in the Mediterranean, without ongoing transmission. One genotype F strain which has its origin in South America has been circulating in the Netherlands for at least 4 years. Patients infected with this strain could not be epidemiologically linked to one another, and it was not restricted to a certain risk group. It seems unlikely that circulation of this strain is restricted to the Netherlands, since an isolate with similar sequence has recently been found in Germany [17].

The median age at first vaccination of participants of the targeted program was high, at 30 years. For MSM, the median age at first vaccination was lower than the age at infection, but it was still high, at 35 years. Clearly, in the current vaccination approach, people are already involved in risk behaviour before they are vaccinated. After 5 years of vaccination, we can conclude that the important younger part of the various risk groups are hard to reach for vaccination.
HBV transmission is not sustained in the heterosexual population [5,11]. Therefore, as of November 2007, heterosexuals with an indication for a STI exam were no longer considered as a high-risk group for HBV infection to be offered HBV vaccination free of charge.

The estimated vaccination coverage was low (12%), especially among MSM (6%). Consequently, the estimated number of people being susceptible for HBV in the Netherlands remains high despite the targeted vaccination program. Among CSWs, the low vaccination coverage and the low compliance could be explained by their high turnover between residences in and outside the Netherlands. Among MSM, low perception of their susceptibility and the severity of HBV infection are important factors in the low uptake of vaccination in this group [18,19]. It is debatable whether DUs are still a high-risk group for HBV infection and whether extra effort should be put into vaccinating this group. HBV incidence among those using hard drugs in Amsterdam has strongly declined over time, and we know that injecting and non-injecting DUs in general get infected with the same genotype D strain (Van Houdt et al., manuscript in preparation), which has disappeared after 2000 [5]. Furthermore, the injecting DUs population has strongly decreased and become older, and most are immune or chronically infected with HBV. However, we must continue monitoring trends in drug use, to see whether DUs will again become a high-risk group in the near future.

The total number of acute HBV patients reported in the Netherlands is an underestimate of the true number of cases, since less than half of infected individuals have symptoms, and not all patients are reported. Some chronically infected patients might have been accidentally included in this study, due to our reporting criteria. However, testing a subset for anti-HBc-IgM, demonstrated that only a few chronic carriers could be identified [11]. The population sizes of the various risk groups in the Netherlands were roughly estimated, and the estimated anti-HBc seroprevalences have a large range. Furthermore, people vaccinated outside the targeted program were not included in our calculations. In a survey among MSM in the Netherlands, 45% of the respondents stated in their questionnaire to be vaccinated against HBV [20]. Although this survey was not representative for the entire MSM population in the Netherlands and might represent the population that is reached by the current program, it suggests that the actual vaccination coverage among MSM is somewhat higher than estimated in this study. Only the fully vaccinated participants were included for the calculation of the vaccination coverage, but a proportion of those receiving only two vaccinations might also be immune [21]. However, when participants receiving two dosages were included and the highest estimate for anti-HBc seroprevalence was used, the overall vaccination coverage remained low (16%).

Although a respectable number has been reached by the vaccination program, its coverage is too low to have a large impact on the HBV incidence among the various risk groups. Whether the vaccination program targeted at behavioural risk groups has contributed to the decline in the total number of reported acute HBV cases is unclear. A possible decline in sexual risk behaviour, reflected by a decline in proportion of STIs, especially gonorrhea and syphilis, in the Netherlands [22], might be an additional explanation for the decrease in reported HBV incidence.

As the current program continues, more effort is put into vaccinating more susceptible and younger people in the risk groups. Therefore, the coverage will somewhat increase, but this seems insufficient to substantially reduce HBV transmission in the Netherlands. This insufficiency to reduce transmission substantially has not only been suggested by this study, but also by mathematical modelling [23]. Therefore, low-endemic countries such as the Netherlands may need to reconsider introduction of universal vaccination against HBV.

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References


