Surveillance studies on infectious diseases: Evidence for action
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Citation for published version (APA):

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Targeted vaccination program successful in reducing acute hepatitis B in men having sex with men in Amsterdam, the Netherlands

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Submitted
Abstract

Background: In the Netherlands, transmission of hepatitis B virus (HBV) occurs mainly within behavioural high-risk groups, such as in men who have sex with men (MSM). Therefore, a vaccination programme has targeted these high-risk groups. This study evaluates the impact of the HBV vaccination programme targeting Amsterdam's large population of MSM from 1998 through 2011.

Methods: We used data from all MSM in Amsterdam registered in the national database of the vaccination programme for high-risk groups (January 1, 1998 to December 31, 2011). Programme and vaccination coverage were estimated with population statistics. The incidence of acute HBV was analyzed with notification data from the Amsterdam Public Health Service (1992 to 2011). Mathematical modelling accounting for vaccination data and trends in sexual risk behaviour was used to explore the impact of the programme.

Findings: At the end of 2011, programme coverage was estimated at 41% and vaccination coverage 30% to 38%. Most participants (67%) were recruited from the outpatient department for sexually transmitted infections (STI) and outreach locations such as saunas and gay bars. The incidence of acute HBV remained stable over time, but dropped sharply after 2005. The mathematical model in which MSM who engage most in high-risk sex are vaccinated, best explained the decline in incidence.

Interpretation: HBV transmission among Amsterdam's MSM has decreased, despite ongoing high-risk sexual behaviour. Vaccination programmes targeting MSM do not require coverage of all MSM; they are effective when MSM who engage most in high-risk sex are reached, such as via STI clinics.
Introduction

Worldwide, an estimated two billion people are infected with hepatitis B virus (HBV). More than 240 million have chronic liver infections, and approximately 600,000 die each year from HBV-associated cirrhosis or hepatocellular carcinoma. The endemicity of HBV differs greatly by geographical region; depending on the prevalence of hepatitis B surface antigen (HBsAg) in the population, countries may be classified endemically as high (>8%), intermediate (2-8%), or low (<2%). In high- and intermediate-endemic countries, HBV transmission occurs mainly perinatally or in early childhood, whereas in low-endemic areas, HBV is more often contracted later in life, either through sexual contact or use of contaminated needles. In 1982 a safe, effective vaccine became available, and many countries have since implemented a national infant immunization programme. In the Netherlands, HBV prevalence in the general population is very low (HBsAg = 0.2%; 95% confidence interval; 95%CI 0.1-0.4%). Since 1983, vaccination programmes have been implemented for health care workers (1983), newborns of HBsAg-positive mothers (1989), and newborns with at least one parent from a high- or intermediate-endemic country (2003). In addition, in 2002, as transmission occurred mainly within behavioural high-risk groups (injecting drug users, men who have sex with men (MSM), and commercial sex workers), a vaccination programme targeting behavioural high-risk groups was implemented nationally, after a pilot programme from 1998 to 2000 in several regions, including Amsterdam. Because more recent insights have shown that vaccination of the general population is cost-effective and more beneficial in the long term than those only in the high-risk groups, a nationwide infant vaccination programme was initiated in August, 2011. As no catch-up campaign will be instituted, the 'high-risk group' policy must be continued for at least another 20 to 30 years. This study evaluates the impact of the HBV vaccination programme targeting the behavioural risk group of MSM in Amsterdam. The Dutch capital, with about 800,000 inhabitants, is a popular residence for MSM from the world all over, totalling at least 26,000. The seroprevalence of HBsAg in MSM in Amsterdam in 2004 was estimated at 2.3% versus 0.4% in the general population, and the incidence of acute HBV in MSM was on average 15 times higher than in the general population. This study aims to describe incidence trends of acute HBV in the MSM population in Amsterdam from 1992 through 2011 and the impact of the targeted HBV
vaccination campaign that began in 1998. We used a mathematical model, taking into account vaccination data, demographic aspects, and changes in sexual risk behaviour, to explore potential explanations for these trends.

**Methods**

**Population statistics**

Yearly age- and gender-specific population data were obtained from the Research and Statistics Department of Amsterdam. The number of MSM residing in Amsterdam was estimated as 10% of the male population aged 15-69 years as registered on December 31 of each calendar year. The differential effect of migration in and out of the population was accounted for; however, the changing proportions of immune, vaccinated, or susceptible MSM were unknown.

**Targeted vaccination programme MSM**

To evaluate the programme targeting MSM in Amsterdam, data were used from the national database of the vaccination programme for high-risk groups (November 1, 2002 until December 31, 2011, including follow-up data from 2012) and the pilot project (October 1, 1998 to May 1, 2000). Details of the programme are described elsewhere. Male residents aged 15 to 69 years who were registered in Amsterdam and indicated a same-sex preference were eligible for inclusion. Demographic data, date and location of inclusion (first contact), number and dates of vaccination, and results of testing for antibodies against hepatitis B core antigen (anti-HBc+) and, if applicable, consecutive HBsAg testing were used. Programme coverage was estimated as the fraction of MSM included in the program and the estimated number of MSM aged 15-69 years residing in Amsterdam. Vaccination coverage was calculated as the number of participants effectively vaccinated divided by the number of susceptible MSM in Amsterdam (the number of MSM residing in Amsterdam per calendar year, minus the assumed number of MSM immune/anti-HBc+ by previous natural infection). Since approximately 20% (range, 10-36%) are thought to be immune by previous infection, we used a range of 10% to 30%. Compliance was defined as the proportion of susceptible participants completing the series of three vaccinations. Vaccine efficacy increases from 40% after one dose to 70% after two doses to 90% after three doses, and it was estimated in this study by the number of susceptible participants receiving one to three doses.
Acute hepatitis B infections
In the Netherlands, all new patients with laboratory-confirmed acute HBV infection must be reported to the Public Health Service (PHS). Criteria, which were consistent during the 20-year period of analysis, include clinical signs and symptoms, combined with findings of HBsAg and/or type M immunoglobulin antibodies to hepatitis core antigen in the serum. Public health nurses collected data from all patients on the source of infection, demographic data, and information on specific risk factors, including travel prior to infection, sexual preference, and risk behaviour.
From January 1992 to January 2012, 534 patients with acute HBV were reported to the PHS in Amsterdam. Patients were ranked hierarchically into five transmission groups: sexual transmission; injecting drug use; horizontal transmission; health care transmission; and patients in whom none of those risks were identified. With this classification, 220 (41%) acute HBV infections in MSM were identified and included in the analysis, together with baseline characteristics, including age and year of birth.

Statistical analyses
Analysis was conducted with Intercooled Stata 11.1 for Windows (Stata Corp., College Station, Texas, USA). Incidence rates were estimated as the annual number of new cases per 100,000 persons-at-risk. Incidence rate ratios (IRR) with 95%CI were estimated via Poisson regression, separately for calendar time, age, and birth year, respectively. When modelling the IRR, we used natural splines to obtain smoothed trends. In each model, we tested whether the null hypothesis of constant infection rates could be rejected.
Because the variables of age, period, and cohort were linearly related, an age-period-cohort (APC) model was used for the multivariable analysis. The incidence of acute HBV was modelled in (log) rates as a sum of (non-linear) age-, period- (date of diagnosis), and cohort- (date of birth) effects. The model was constructed with ‘apcfit’ in Stata which uses natural splines to estimate each of the three effects that are then combined to give estimated rates. For details, see Carstensen 2007 and Rutherford 2010.13,14 As we were interested in the age effects related to birth cohort effects, the model was parameterized to constrain the period effect to have a slope of zero and to be zero on average on the log scale. After adjustment for period effects, age-specific rates were estimated for the median birth cohort (1966). The cohort effect (cohort rate ratios) was similarly estimated and reported relative to the median 1966 birth cohort.
The mathematical model

The current model, which was derived from previous models by Williams et al. and Kretzschmar et al., demonstrates the course of the HBV epidemic among MSM in Amsterdam since 1992, taking into account demographic aspects, effects of the targeted vaccination programme, and changes in sexual risk behaviour. The model population consisted of the annual number of MSM residing in Amsterdam and was stratified by age (15 to 64 years) and 6 sexual activity classes. Migration in and out of the MSM population was incorporated into the model and occurred at a constant rate stratified by age group (mean rate more than 12 years). Vaccination rates stratified by age were calculated from the numbers of vaccinations averaged during the years since 1998 per age category. Only a sexual mode of transmission was considered. Partner change rates were based on data from sexual behaviour surveys and calibrated so that the model reproduced the observed incidence of notified acute hepatitis B infections averaged over the pre-vaccination years 1992-1998. Trends in sexual risk behaviour were based on data on behaviour (i.e., proportion of MSM practicing unprotected anal intercourse (UAI)) among MSM in the Amsterdam Cohort Studies (1984-2009). The trends show steadily increasing sexual risk behaviour from the mid-1990s after the introduction of combination antiretroviral therapy, with a plateau from 2004 coinciding with increasing sexual risk behaviour among MSM. We assumed that incidence of infection was six times the incidence of notified cases, where a factor three is due to subclinical infection and a factor two to underdiagnosis and underreporting.

Three different scenarios are processed in the model. The endemic equilibrium is based on the incidence of patients of notified acute HBV infection before the start of the vaccination programme in 1998. The first scenario describes the trend of acute HBV infection without a targeted vaccination programme in a context of increasing sexual risk behaviour (partner change rates increased by 10% in 1997, followed by an annual increase of 5% until 2004, and stable risk behaviour from 2005 onwards). Scenario two describes the effect of the current vaccination programme targeting all MSM. Scenario three describes the effect of the vaccination programme targeting the 20% of the population with higher partner change rates, i.e., the proportion of the model population in the four highest levels of sexual activity.
Results

Targeted vaccination programme MSM
From 1998 to 2012, a total of 12,273 MSM in Amsterdam participated in the targeted HBV vaccination campaign. The median age at inclusion was 34 years (interquartile range (IQR) 27-41 years, range 14-83 years). Most participants were born in the Netherlands (71%) or other low-endemic countries (9%). Fifty-one percent of the participants (6306) were recruited from the outpatient department for sexually transmitted infections (STI-OPD) of the PHS in Amsterdam and 22% (2719) from the department for infectious diseases of the PHS. Other recruitment sites included outreach locations (i.e. saunas and gay bars,1965 or 16%), general practitioners’ offices (6%), and penitentiaries and hospitals (4%). Almost all participants (98%) were tested for anti-HBc, and 18.3% were positive (95%CI 17.6-19.0%). Anti-HBc seroprevalence decreased over time (Table 1a). Results of consecutive HBsAg testing were available from 2002 onwards for 1573 anti-HBc-positive samples; 106 participants were chronic HBsAg carriers (6.7%; 95%CI 5.5-8.0%), and HBsAg seroprevalence in all participants was 1.2% (95%CI 1.0-1.4%), decreasing over time. Results of both anti-HBc and HBsAg testing were associated with the location of recruitment. Participants recruited at STI-OPD and outreach locations were significantly more often immune by previous infection (anti-HBc+: 19-21%) compared to those recruited elsewhere, and 78% of the HBsAg-seropositive MSM were recruited at these locations (data not shown).

Compliance, vaccine efficacy and vaccination coverage
Table 1a shows the programme coverage per calendar year, which increased from 2% in 1998 to 41% in 2011. Table 1b shows programme compliance and vaccine efficacy. At the time of inclusion, 82% of the participants were still susceptible to infection and received a first dose of the vaccine; of those, 84% received two doses, and 71% received the full series of three vaccinations. In 2011, 7952 participants were effectively vaccinated. Assuming that 10% to 30% of the total MSM population (29,751 in 2011) was already immune by previous infection, we estimated vaccination coverage at 30% to 38%, leaving 12,875 to 18,825 MSM still susceptible to infection at the end of 2011.
Table 1a. Programme coverage of the HBV vaccination campaign targeting MSM in Amsterdam and the proportion of immune and MSM chronic carriers, 1998-2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Population size</th>
<th>Number of inclusions (cumulative)</th>
<th>Programme coverage (%)</th>
<th>% AntiHBc+</th>
<th>% HBsAg+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>27,078</td>
<td>549 (549)</td>
<td>2%</td>
<td>16.8%</td>
<td>-</td>
</tr>
<tr>
<td>1999</td>
<td>27,486</td>
<td>2049 (2598)</td>
<td>9%</td>
<td>20.0%</td>
<td>-</td>
</tr>
<tr>
<td>2000</td>
<td>27,692</td>
<td>577 (3175)</td>
<td>11%</td>
<td>21.9%</td>
<td>-</td>
</tr>
<tr>
<td>2001</td>
<td>27,851</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>27,890</td>
<td>291 (3466)</td>
<td>12%</td>
<td>21.6%</td>
<td>2.5%</td>
</tr>
<tr>
<td>2003</td>
<td>27,919</td>
<td>1302 (4768)</td>
<td>17%</td>
<td>24.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>2004</td>
<td>28,067</td>
<td>1091 (5859)</td>
<td>21%</td>
<td>23.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>2005</td>
<td>28,269</td>
<td>1028 (6887)</td>
<td>24%</td>
<td>20.7%</td>
<td>1.2%</td>
</tr>
<tr>
<td>2006</td>
<td>28,286</td>
<td>941 (7828)</td>
<td>28%</td>
<td>19.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>2007</td>
<td>28,313</td>
<td>1103 (8931)</td>
<td>32%</td>
<td>17.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>2008</td>
<td>28,513</td>
<td>920 (9651)</td>
<td>35%</td>
<td>14.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>2009</td>
<td>28,893</td>
<td>688 (10,539)</td>
<td>36%</td>
<td>10.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>2010</td>
<td>29,331</td>
<td>948 (11,487)</td>
<td>39%</td>
<td>10.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>2011</td>
<td>29,751</td>
<td>732 (12,219)</td>
<td>41%</td>
<td>9.1%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Table 1b. Compliance and vaccine efficacy of the HBV vaccination campaign targeting MSM in Amsterdam, the Netherlands, 1998-2011

<table>
<thead>
<tr>
<th>Number of MSM with</th>
<th>Number of MSM who received</th>
<th>Compliance</th>
<th>Vaccine efficacy #</th>
<th>Effectively immunized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 vaccine</td>
<td>10,021</td>
<td>1 vaccine</td>
<td>1604</td>
<td>642</td>
</tr>
<tr>
<td>≥ 2 vaccines</td>
<td>8417</td>
<td>2 vaccines</td>
<td>1328</td>
<td>930</td>
</tr>
<tr>
<td>≥ 3 vaccines</td>
<td>7089</td>
<td>3 vaccines</td>
<td>7089</td>
<td>6380</td>
</tr>
</tbody>
</table>

# 40% protected after 1 vaccine, 70% protected after 2 vaccines, and 90% protected after 3 vaccines.

Acute hepatitis B infections

From January 1992 to January 2012, 220 MSM with acute HBV infection were reported to the Amsterdam PHS. The annual number of new patients ranged from 5 to 21 (median 12). The median age at diagnosis was 34 years (IQR 29-40 years, range 19 to 72 years). Figure 1a shows the measured and fitted incidence and the growing MSM population over calendar time. The incidence (mean 39.5 per 100,000 MSM, range 14.0-74.8) remained stable until 2005, but then dropped sharply from 60 to 20 out of 100,000 in 2011 (p <0.001). Age-specific incidence
peaked at 35 to 44 years (Figure 1b), yet its distribution shifted over calendar time (Figure 2a). In the period 1992-1996 the highest incidence was in those 25 to 29 years old, whereas in 2007-2011 it was in those aged 40 to 44 years. This is reflected in the incidence rates specific to birth year (Figure 1c), which peaked in the years between 1960 and 1969, irrespective of the period of diagnosis (Figure 2b).

**Figure 1** Acute HBV per 100,000 person years in MSM in Amsterdam (1992-2011)

(A) Acute HBV incidence per 100,000 MSM in Amsterdam per calendar year (1992-2011). The measured incidence is represented by the line with dots, and the fitted incidence by the smooth line with its 95%CI (striped area). The grey shaded area is the population denominator data of the Amsterdam MSM population. (B) Age-specific rate per 100,000 MSM of acute HBV in Amsterdam (1992-2011). (C) Year of birth-specific rate of acute HBV per 100,000 person years in Amsterdam (1992-2011). The measured rate is represented by the dots, and the fitted rate by the smooth line with its 95%CI (striped area).
Figure 2 Age-and year-specific rates of acute HBV per 100,000 person years in MSM in Amsterdam

(A) Age-specific rates of acute HBV per 100,000 person years in MSM in Amsterdam stratified by 4 periods of diagnosis (’92-’96, ’97-’01, ’02-’06, ’07-’11). (B) Year of birth-specific rates of acute HBV (per 100,000 person years) in MSM in Amsterdam stratified by 4 periods of diagnosis (’92-’96, ’97-’01, ’02-’06, ’07-’11).

These findings are supported by the multivariable APC-analysis (Figure 3). The left graph shows the age-specific (longitudinal) incidence for those born in 1966, which peaked at 20 and 40 years. After adjustment for age and period, the cohort effect is evident: all rate ratios in the graph are less than one, and the highest rate is the 1966 birth cohort (centre graph). The right graph shows the non-linear effects of period, independent of age or cohort effects.
Figure 3. Results from the multivariable APC-analysis of the acute HBV incidence per 100,000 MSM in Amsterdam, the Netherlands 1992-2011, shown as line graphs representing log rates, with its 95% confidence interval (grey shaded area).

(A) demonstrates the age-specific rates (per 100,000 person-years on left Y-axis) in the reference birth cohort (1966), after adjusting for period. The age-specific rate for this cohort peaks at age 20 and 40. (B) The cohort effect is evident from the centre graph (calendar year versus rate ratio on the right Y-axis). After adjusting for age and period, the highest rate is in the 1966 birth cohort, i.e. all rate-ratios before and after this year are lower (i.e. <1, and the 95%CI do not include 1 for a major part of the calendar time). (C) represents the period effect, describing the non-linear effects of period, and acts like a residual effect (because it is constrained to be 0 on average with 0 slope) unexplained by the other two terms.

Mathematical Model

Figure 4 shows the effect of vaccination and changed sexual risk behaviour on the incidence of acute HBV infection in three different scenarios. In the first scenario, (no vaccination programme), the incidence sharply increased due to increasing risk behaviour from 1997 to 2004. In the second scenario (dashed line) the effects of the vaccination campaign directed at all MSM in the population counterbalance the increase of risk behaviour to some extent, but the vaccination programme cannot reverse the increasing trend in incidence. However, if vaccination is targeted to the population with the highest risk levels (scenario three), the current coverage is sufficient to reduce the incidence to below the baseline of the pre-vaccination era.
Figure 4. Effect of vaccination and increased sexual risk behaviour on the incidence of acute HBV.

The endemic equilibrium (black solid line) is based on the incidence of notified acute HBV 1992-1998 before the initiation of vaccination and before changes in sexual risk behaviour. Scenario 1: (green line): effect of increasing sexual behaviour from 1997 to 2004 if no MSM were vaccinated. Scenario 2: (red line) the effect of the vaccination programme targeting all MSM. Scenario 3: (black line) the effect of the vaccination programme targeting high-risk MSM only.
Discussion

From 2004 to 2012, the incidence rate of HBV infection in MSM in Amsterdam decreased by 78% (from 75 to 17/100,000), indicating that transmission among MSM has decreased.\textsuperscript{8,23} As in the past eight years, high-risk sexual behaviour among MSM has stabilized, and the reduced transmission is a probable effect of the targeted MSM risk-group vaccination programme started in 1998.\textsuperscript{18} Earlier evaluations of the programme (up until 2006) did not find evidence that this programme had an impact, partly because of the coincident increase in risk behaviour among MSM since the mid-1990s that counterbalanced the positive effects of the programme and partly because the uptake was too low at that time.\textsuperscript{5,18,19,23,24} In 2008, a mathematical model by Xiridou et al. predicted a greater benefit if MSM engaging most in high-risk sex (i.e. having a higher rate of partners or having more UAI) could be reached.\textsuperscript{24}

The mathematical model in our study demonstrates that the current decline in incidence is best explained by the scenario in which high-risk MSM (approximately 20% of the MSM population) are vaccinated. More than two thirds of our participants were MSM recruited at STI-OPD (51%) and at saunas and gay bars (16%). These participants were significantly more often immune by previous infection (anti-HBc+: 19-21%), and 78% of the HBsAg-seropositive (infectious) MSM were recruited at these locations. Furthermore, analysis of acute HBV infection in MSM showed that those born between 1960 and 1970 have been at highest risk for the disease in the past 20 years. This aging cohort has contributed heavily to transmission of HBV in the last two decades and therefore can be considered a high-risk core group. Whether this is because they have more UAI than others is unknown, but it is possible that in their social network more acute and chronic HBV infection has occurred, meaning more infectious partners have been present. The vaccination programme included almost 4000 MSM born between 1960 and 1970, and the estimated programme coverage was highest (62%) within this group (data not shown). If we assume that this core group has become immune either by infection or vaccination, we have a potential explanation for the declining HBV incidence, despite ongoing sexual high-risk sexual behaviour.

The reduced transmission of HBV infection among MSM in Amsterdam because of the targeted vaccination programme is also supported by several molecular epidemiological studies of circulating HBV genotypes in this population in...
Amsterdam and in the rest of the Netherlands. For the past two decades, an identical HBV genotype A strain has been circulating among MSM in Amsterdam.\textsuperscript{5,25} In 2009, the analysis of molecular DNA sequences revealed a significant decrease in genetic diversity of the HBV genotype A viral sequences collected from the same population (1992-2006) within a few years after the start of the programme, indicating a lower transmission rate of the virus.\textsuperscript{26}

This is the first time that a targeted HBV vaccination programme has been proven to be effective.\textsuperscript{27} Our findings have important policy implications. In the past the programme aimed to include as many MSM possible. Since 2005, as the average age of recruitment was 39 years and similar to the average age of infection, much effort was made to reach young MSM. However, this study shows that the epidemic is driven by older MSM, and young, non-immune MSM have no particular increased risk of infection. As long as a programme reaches MSM networks in which the virus circulates, it is effective.

Previous evaluations of this programme up until 2006 (incidence trend analysis, mathematical modelling and molecular sequence models) could prove no impact. Concern also exists about the effectiveness of such programmes when the uptake or coverage remains low.\textsuperscript{28,29} This study proves that a targeted vaccination programme can be effective with vaccination coverage below 40%, as long as MSM who engage most in high-risk sex, such as clients of STI clinics, are reached.

In conclusion, the targeted Amsterdam HBV vaccination programme has been successful in reducing transmission among MSM, despite ongoing high-risk sexual behaviour. HBV vaccination programmes targeting MSM do not require coverage of all MSM, but can have a substantial effect on the incidence, if those who engage most in high-risk sex and those who contribute most to transmission are reached.

To make a targeted vaccination programme successful, policy decisions should focus on identifying MSM networks responsible for continued HBV transmission.

Acknowledgements

The authors would like to thank Mark Rutherford for his comments on the statistical procedures regarding the age-period-cohort (APC) model; and Sally Hebeling for editing the final manuscript. Furthermore the authors would like to thank the nurses of the Public Health Services in Amsterdam for their data collection on hepatitis B.
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