Breaking the chain of transmission: Immunisation and outbreak investigation

Whelan, Jane

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Targeted vaccination programme successful in reducing acute Hepatitis B in men having sex with men in Amsterdam, The Netherlands

Gini van Rijckevorsel
Jane Whelan
Mirjam Kretzschmar
Evelien Siedenburg
Gerard Sonder
Ronald Geskus
Roel Coutinho
Anneke van den Hoek

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Abstract

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

Methods
We used Amsterdam data from 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. Incidence of acute hepatitis B was analyzed with notification data from the Amsterdam Public Health Service (1992–2011). Mathematical modelling accounting for vaccination data and trends in sexual risk behaviour was used to explore the impact of the programme.

Results
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 and outreach locations such as saunas and gay bars. Incidence of acute hepatitis B dropped sharply after 2005. The mathematical model in which those who engage most in high-risk sex are vaccinated, best explained the decline in incidence.

Conclusions
Transmission of hepatitis B virus among Amsterdam's men who have sex with men has decreased, despite ongoing high-risk sexual behaviour. Vaccination programmes targeting men who have sex with men do not require full coverage; they may be effective when those who engage most in high-risk sex are reached.
CHAPTER 3 HEPATITIS B IN MSM

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 HBV 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. In this study we describe trends in the incidence of acute HBV in the MSM population in Amsterdam from 1992 through 2011 and evaluate the impact of the HBV vaccination programme targeting MSM that began in 1998. The Dutch capital, with about 800,000 inhabitants, is a popular residence for MSM from all over the world, totalling at least 26,000. 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 15–69 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 HBV 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. Compliance was defined as the proportion of susceptible participants completing the series of three vaccinations. The numbers of susceptible participants who received one to three doses, in combination with the known vaccine efficacy after one dose (40%), two doses (70%), and after three doses (90%) were used to calculate the number of effectively immunised MSM. Vaccination coverage was calculated by dividing this number of effectively immunised MSM by the assumed number of susceptible MSM (the number of MSM residing in Amsterdam per calendar year, minus the assumed number of MSM immune [anti-HBc positive] 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%.

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 HBV (anti-HBc) 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 according to risk of transmission into one of five transmission groups: sexual transmission (with high-risk sexual behaviour specific for HBV transmission, i.e. making distinction between sub-groups having unprotected homosexual and heterosexual contact with new and/or multiple partners); 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 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). HBV 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 birth 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. 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 (15–64 years) and 6 sexual activity classes. The activity classes were distinguished by their rates of partner change and were parameterized to reflect the large heterogeneity in partner change rates in the population. We assumed proportionate mixing by age and activity level, and that transmission takes place with a per partnership transmission probability. We do not explicitly specify transmission routes, but assume that transmission is largely driven by unprotected anal intercourse (UAI) and the contribution of transmission via injecting drug use or other modes is negligible. Migration in and out of the MSM population was incorporated into the model as 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.
Partner change rates were based on data from sexual behaviour surveys and calibrated so that
the model reproduced the observed incidence of notified acute HBV infections averaged over
the pre-vaccination years 1992–1998. Partner change rates increased by 10% in 1997, followed by
an annual increase of 5% until 2004, and a stable risk behaviour from 2005 onwards.16 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).17 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.17,18 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 under-diagnosis and under-reporting.19-21 The model and its parameters are
explained in detail in the Supplementary Data. Three different scenarios are processed in the
model. The endemic equilibrium is based on the incidence of notified acute HBV infections
before the start of the vaccination programme. Scenario one describes the trend of acute HBV
without a targeted vaccination programme in the context of increasing sexual risk behaviour.
Scenario two describes the effect of the current programme targeting all MSM. Scenario three
describes the effect of the 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.15 This choice was motivated by our observation that men participating in vaccination
often reported higher risk behaviour than other MSM and that we estimated the high risk core
group to be around 10% of the Amsterdam MSM population.

Results

Targeted vaccination programme MSM

From 1998 to 2012, a total of 12,273 MSM in Amsterdam participated in the targeted HBV
vaccination programme. Table 1 shows the programme coverage per calendar year, which
increased from 2% in 1998 to 41% in 2011. 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%). The relative distribution of
recruitment location did not change significantly over time. Anti-HBc seroprevalence decreased
over time (Table 1). 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, number of effectively immunized MSM and vaccination coverage

At the time of inclusion, 82% of all participants were susceptible to infection and received a first dose of the vaccine (10,021/12,273); of those, 84% received two doses, and 71% received the full series of three vaccinations. Table 2 shows compliance with the vaccination schedule, and in 2011, after taking the vaccine efficacy after 1, 2, and 3 doses into account, the number of effectively immunized MSM was estimated at 7952. Assuming that 10%–30% of the total MSM population (29,751 in 2011) was already immune by previous infection, we estimated vaccination coverage at 30%–38%, leaving 12,875–18,825 MSM still susceptible to infection at the end of 2011.

Table 1. Programme coverage of the HBV vaccination campaign targeting MSM in Amsterdam and the proportion of immune MSM, 1998-2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Population size (cumulative)</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>2,049 (2,598)</td>
<td>9%</td>
<td>20.0%</td>
<td>-</td>
</tr>
<tr>
<td>2000</td>
<td>27,692</td>
<td>577 (3,175)</td>
<td>11%</td>
<td>21.9%</td>
<td>-</td>
</tr>
<tr>
<td>2001</td>
<td>27,851</td>
<td>No vaccination programme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>27,910</td>
<td>291 (3,466)</td>
<td>12%</td>
<td>21.6%</td>
<td>2.5%</td>
</tr>
<tr>
<td>2003</td>
<td>27,919</td>
<td>1,302 (4,768)</td>
<td>17%</td>
<td>24.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>2004</td>
<td>28,067</td>
<td>1,091 (5,859)</td>
<td>21%</td>
<td>23.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>2005</td>
<td>28,269</td>
<td>1,028 (6,887)</td>
<td>24%</td>
<td>20.7%</td>
<td>1.2%</td>
</tr>
<tr>
<td>2006</td>
<td>28,286</td>
<td>941 (7,828)</td>
<td>28%</td>
<td>19.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>2007</td>
<td>28,313</td>
<td>1,103 (8,931)</td>
<td>32%</td>
<td>17.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>2008</td>
<td>28,513</td>
<td>920 (9,851)</td>
<td>35%</td>
<td>14.3%</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>10.1%</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 2. Compliance and number of MSM effectively immunized against HBV in Amsterdam, the Netherlands, 1998-2011.

<table>
<thead>
<tr>
<th>Vaccine number in HBV series</th>
<th>Number entering the programme</th>
<th>Number vaccinated</th>
<th>Compliance</th>
<th>Number effectively immunized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number who withdrew/ left the programme after vaccine</td>
<td>Vaccine efficacy after vaccine</td>
</tr>
<tr>
<td>i</td>
<td>$n_i (= m_{i-1})$</td>
<td>$m_i (= m_{i-1}w_i)$</td>
<td>$c (m_i/n_i)$</td>
<td>$w_i$</td>
</tr>
<tr>
<td>1</td>
<td>12,273</td>
<td>10,021a</td>
<td>0.82</td>
<td>1,604</td>
</tr>
<tr>
<td>2</td>
<td>10,021b</td>
<td>8,417</td>
<td>0.84</td>
<td>1,347</td>
</tr>
<tr>
<td>3</td>
<td>8,417</td>
<td>7,089</td>
<td>0.71</td>
<td>7,089</td>
</tr>
</tbody>
</table>

a. Of those who were recruited ($n=12,273$), 2252 were previously immune.
b. Only those who received the 1st vaccine in the series were eligible for the second vaccination, ditto 2nd & 3rd vaccinations.
c. Vaccine efficacy is assumed to be 40% after one dose, 70% after 2 doses and 90% after three doses. 10,11
d. Those who were vaccinated a 3rd time then left the programme.

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 19–72 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 35–44 years (Figure 1b), yet its distribution shifted over calendar time (Figure 2a). In the period 1992–1996 the highest incidence was in those 25–29 years old, whereas in 2007–2011 it was in those aged 40–44 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). 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 1. Acute HBV in MSM in Amsterdam (1992-2011).
A: Incidence (per 100,000 MSM) per calendar year. The measured incidence is represented by the line with dots, and the fitted incidence by the smooth line with its 95% confidence interval (striped area). The grey shaded area is the population denominator data of the Amsterdam MSM population.
B: Age-specific rate (per 100,000 MSM).
C: Year of birth-specific rate (per 100,000 person years) The measured rate is represented by dots, and the fitted rate by the smooth line with its 95% confidence interval (striped area); py, person years.

Figure 2. Acute HBV rates. (A) Age-specific and (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); py, person years.
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) Age-specific rates adjusted for period (per 100,000 person-years on left Y-axis) for the 1966 birth cohort, which peaks at age 20 and 40. (B) Cohort effect adjusted for age and period (calendar year versus rate ratio on the right Y-axis). The highest rate is in the 1966 birth cohort, i.e. all other rates ratios are <1. (C) represents the period effect (the non-linear effects of period unexplained by the other two terms), and acts like a residual effect; py, person years.

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.
CHAPTER 3 HEPATITIS B IN MSM

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. 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. 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. 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.

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. A limitation of the model is the assumption of proportionate mixing by age and activity level. However, with more preferred mixing the impact of targeted vaccination would even be stronger, because dilution of transmission via lower activity levels would be less influential. Another limitation is our lack of sexual behaviour data from the Amsterdam MSM population, which prevented us from directly estimating partner change rates from data for that population and led us to only indirectly determine these rates via a calibration process. While the model is a simplification of reality in the sense that it does not take other transmission routes except UAI into account and that it assumes perfect targeting to the high risk core group, the qualitative differences between scenarios are robust to uncertainty in parameter values. Vaccination will also reduce transmission via other transmission routes and we already took the targeted population to be broader – namely 20% of the population – rather than the 10% estimated from data. Our aim was not to predict the future course of HBV incidence, but to identify which vaccination scenario best explained the observed trends. Those trends could not be explained by assuming equally distributed vaccination, but could well be explained by assuming a targeted vaccination approach.

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.

This is the first time that a targeted HBV vaccination programme has been proven to be effective. Our findings have important policy implications. Previous evaluations of this programme up until 2006 (incidence trend analysis, mathematical modelling and molecular sequence models) could prove no impact.22-24 Concern also exists about the effectiveness of such programmes when the uptake or coverage remains low,25,26 and in the past the programme aimed to include as many MSM possible. This study shows that the targeted vaccination programme in Amsterdam is effective with vaccination coverage below 40%, most likely because MSM who engaged mostly in high-risk sex, such as clients of STI clinics, were reached.
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.

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
This study was conducted within the Sarphati Initiative: Academic Collaborative Center on Public Health of Noord-Holland and Flevoland, the Netherlands. The Sarphati Initiative is financially supported by the Netherlands Organization for Health Research and Development (ZonMw; grant number 125010001). 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 HBV.
References


Supplementary Data

This appendix is modified from the appendix published as a supplementary information file with Xiridou et al.¹

A.1. Model equations

The model was developed by Kretzschmar et al.²,³ to describe the transmission of acute hepatitis B (HBV) in the Netherlands, for the whole population (heterosexuals and MSM). The submodel for the MSM population is described by the following system of partial differential equations in time $t$ and age $a$

$$\frac{\partial X_s}{\partial t} + \frac{\partial X_s}{\partial a} = -[\lambda_s(t,a) + (1 - u_mV_s)\gamma_s\beta_s(a) + \Phi(a) + \Phi_m(a) + \zeta_s(a) + \theta d(a)]X_s(t,a)$$

$$\frac{\partial H_s}{\partial t} + \frac{\partial H_s}{\partial a} = [\lambda_s(t,a) + (1 - u_mV_s)\gamma_s\beta_s(a)]X_s(t,a) - [\sigma_1 + \theta d(a)]H_s(t,a)$$

$$\frac{\partial Y_s}{\partial t} + \frac{\partial Y_s}{\partial a} = \sigma_1 H_s(t,a) - [\sigma_2 + \theta d(a)]Y_s(t,a)$$

$$\frac{\partial Z_s}{\partial t} + \frac{\partial Z_s}{\partial a} = [1 - p(a)]\sigma_2 Y_s(t,a) + \sigma_2 C_s(t,a) - \theta d(a)Z_s(t,a) + \rho \theta y_s d(a)w_s N$$

$$\frac{\partial C_s}{\partial t} + \frac{\partial C_s}{\partial a} = p(a)\sigma_2 Y_s(t,a) - [\sigma_3 + \theta d(a)]C_s(t,a) + \rho \theta y_s d(a)w_s N$$

$$\frac{\partial V_s}{\partial t} + \frac{\partial V_s}{\partial a} = [\Phi(a) + \Phi_m(a) + \zeta_s(a)]X_s(t,a) - \theta d(a)V_s(t,a)$$

where the subscript $s = 1, ..., 6$ denotes sexual activity group. $X_s(t,a)$ denotes the density of uninfected individuals, $H_s(t,a)$ the density of individuals with latent infection, $Y_s(t,a)$ the density of individuals with acute HBV, $C_s(t,a)$ the density of carriers (chronic HBV), $Z_s(t,a)$ the density of immune individuals, and $V_s(t,a)$ the density of vaccinated individuals, of activity group $s$, age $a$, at time $t$. The size of activity group $s$ is $N_s = X_s + H_s + Y_s + Z_s + C_s + V_s$ and the total population size is $N = \sum_s N_s$. The force of infection is given by

$$\lambda_s(t,a) = \frac{c_s(a)\sum_r \int_{a_1}^{a_2} c_r(a')[\beta_1 Y_r(t,a') + \beta_2 C_r(t,a')]d\alpha'}{\sum_r \int_{a_1}^{a_2} c_r(a')N_r(t,a')d\alpha'}$$

where we assume proportionate mixing by age and activity class.
Births into the population were assumed to balance the death rate such that the population size remains constant. Death or removal from the population is assumed to occur at age 65 such that the age distribution over the population is uniform. Men are assumed to become sexually active at the age of 15. The fraction of infected individuals of age $a$ who become carriers is given by the function $p(a) = \exp\left(-x_1a^{x_2}\right)$, with $x_1 = 0.645$ and $x_2 = 0.455$.

Immigration rates for the Amsterdam population were estimated from population statistics. Definitions of parameters and default values are described in the following and summarized in Table 1. The model equations were solved numerically using the Escalator Boxcar Train method implemented in the package EBT tool.

A.2. Partner change rates and model calibration

The rates of formation of new partnerships, $c_{ij}(a,s)$, for men of age $a$ and sexual activity group $s$ were calibrated such that the incidence of acute HBV infections in endemic steady state in the model fitted the prevaccination incidence among MSM in Amsterdam for each of the eight age categories 15–19, 20–24, ..., 45–49, and 50+, as shown in Table 2. Hereby the MSM population was subdivided into six subgroups defined by the fractions $W = (0.451, 0.353, 0.125, 0.06, 0.01, 0.001)$ – see Tables 1 and 2. This subdivision defines the sizes of the six sexual activity groups, for example, group 1 is 45.1% of the population and group 2 is 35.3% of the population. This subdivision is arbitrary, but is chosen to reflect a skewed distribution of numbers of partners and is as defined elsewhere.

In the years before 1998, when vaccination was introduced, HBV incidence was relatively stable at approximately 12 cases of acute HBV cases among MSM per year being reported to the Public Health Service Amsterdam. Assuming that a third of the cases are clinical and that there is 50% underreporting, it implies that the reported number of acute HBV cases should be multiplied by a factor of 6, to give the actual number of new HBV cases. This means that there were around 72 new cases of HBV in MSM per year. The total number of MSM in Amsterdam was estimated to be around 28,000. Dividing the 72 new cases by this estimate of the MSM population size, results in an incidence of around 260 new infections per 100,000. We calibrated the model by adjusting the partner change rates, such that the incidence and the age distribution of incident cases from the model in steady state would match those from the data. The resulting partner change rates are shown in Table 2. The age distribution of incident infections from the model (at the steady state without vaccination) and the age distribution of the notified acute HBV cases (in the years before the introduction of vaccination 1992–1998) are shown in Figure 1.
A.3. Vaccination rates

The vaccination rate $\Phi(a)$ represents universal vaccination and is given by the following function

$$\Phi(a) = \int_a^{a+\Delta a} u d(a - P) d,$$

where $d$ denotes the Dirac function, $u$ the vaccinated fraction, and $P$ is the age of vaccination at puberty. The rate $\Phi_m(a)$ of vaccinating children of immigrants is given by a similar function (see reference 3 for details).

The rates of risk-group vaccination, $\mathbf{Z}_s(a)$, were calculated as follows. The size of the MSM population in Amsterdam was assumed to be 28,000. At the start of the vaccination campaign, 81% of them are susceptible for HBV and, hence, eligible for vaccination. Therefore, the number of men eligible for vaccination is given by the product of the total number of MSM and the fraction found susceptible, divided by the number of years the vaccination programme is ongoing: $28000 \times 0.81 / 12 = 2062$. During the 12 years of the vaccination campaign (1998 – 2009), 8500 men received at least one dose of HBV vaccine. The annual vaccination rates $\mathbf{Z}_i$ per age category $i$ were estimated as

$$\zeta_i = -\ln\left(1 - \frac{n_i}{12 \times 2062}\right),$$

where $n_i$ is the number of vaccinations of antiHBc negative persons in age category $i$ during the course of the vaccination campaign (see Table 4). For the default scenario, it was assumed that this vaccination rate is the same for all activity groups, meaning $\mathbf{Z}_i = \mathbf{Z}_s(a)$, for all ages in age category $i = 1, ..., 12$ (see Table 3) and all activity groups $s = 1, ..., 6$. The effective immunization rate is then given as the product of vaccination rate and vaccine efficacy $v_a$ (Table 4).
References

Table 1. Model parameters and baseline values.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1$</td>
<td>per partnership with acutely infected man</td>
<td>0.46</td>
<td>[6]</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>per partnership with carrier</td>
<td>0.3</td>
<td>[6]</td>
</tr>
<tr>
<td>$\beta_3 (a)$</td>
<td>horizontal from household contacts, age $a &lt; 15$</td>
<td>0.013</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>$a \geq 15$</td>
<td>0</td>
<td>[7]</td>
</tr>
<tr>
<td>$\sigma_1$</td>
<td>from latent to acute HBV</td>
<td>8.667</td>
<td>[6]</td>
</tr>
<tr>
<td>$\sigma_2$</td>
<td>from acute to chronic HBV</td>
<td>3.467</td>
<td>[6]</td>
</tr>
<tr>
<td>$\sigma_3$</td>
<td>from chronic to immune HBV</td>
<td>0.015</td>
<td>[6]</td>
</tr>
<tr>
<td>$p(a)$</td>
<td>Proportion of acute cases aged $a$ becoming carriers</td>
<td>$\exp(-0.645a^{0.455})$</td>
<td>[4]</td>
</tr>
<tr>
<td>$\zeta_s (a)$</td>
<td>Vaccination rate for men of age $a$, activity class $S$</td>
<td></td>
<td>Table 3</td>
</tr>
<tr>
<td>$\nu_a$</td>
<td>Vaccine efficacy for adult vaccination</td>
<td>0.75</td>
<td>[1]</td>
</tr>
<tr>
<td>$\nu_e$</td>
<td>Vaccine efficacy for children</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>$k_m$</td>
<td>Fraction of children eligible for risk group vaccination</td>
<td>0.15</td>
<td>[7]</td>
</tr>
<tr>
<td>$u_m$</td>
<td>Fraction of eligible migrant children vaccinated</td>
<td>0.9</td>
<td>[7]</td>
</tr>
<tr>
<td>$u$</td>
<td>Proportion of recruits to sexually active population being vaccinated</td>
<td>0.85</td>
<td>[2]</td>
</tr>
<tr>
<td>$\gamma_c$</td>
<td>Prevalence of chronic carriers among immigrants</td>
<td>0.047</td>
<td>[7]</td>
</tr>
<tr>
<td>$\gamma_z$</td>
<td>Prevalence of immune persons among immigrants</td>
<td>0.3</td>
<td>[7]</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Per capita immigration rate</td>
<td>0.066</td>
<td></td>
</tr>
<tr>
<td>$\rho$</td>
<td>Fraction of males among immigrants</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>$d$</td>
<td>Age distribution of immigrants</td>
<td></td>
<td>[3]</td>
</tr>
<tr>
<td>$\nu(a)$</td>
<td>Fertility of age $a$</td>
<td></td>
<td>[2]</td>
</tr>
</tbody>
</table>
### Table 2. Rates of formation of sexual partnerships after model calibration.

<table>
<thead>
<tr>
<th>Sexual activity group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion in class, $w_i$</td>
<td>0.45</td>
<td>0.353</td>
<td>0.125</td>
<td>0.060</td>
<td>0.010</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>Partner change rates $c_i(a)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>0.06</td>
<td>0.28</td>
<td>0.64</td>
<td>1.13</td>
<td>1.98</td>
<td>3.22</td>
<td>0.29</td>
</tr>
<tr>
<td>20-24</td>
<td>0.07</td>
<td>0.63</td>
<td>2.19</td>
<td>5.32</td>
<td>12.62</td>
<td>26.95</td>
<td>1.00</td>
</tr>
<tr>
<td>25-29</td>
<td>0.17</td>
<td>1.28</td>
<td>3.89</td>
<td>8.53</td>
<td>18.33</td>
<td>35.81</td>
<td>1.75</td>
</tr>
<tr>
<td>30-34</td>
<td>0.27</td>
<td>2.20</td>
<td>6.79</td>
<td>15.13</td>
<td>33.00</td>
<td>65.16</td>
<td>3.05</td>
</tr>
<tr>
<td>35-39</td>
<td>0.18</td>
<td>1.61</td>
<td>5.34</td>
<td>12.59</td>
<td>28.96</td>
<td>60.17</td>
<td>2.42</td>
</tr>
<tr>
<td>40-44</td>
<td>0.12</td>
<td>1.26</td>
<td>4.59</td>
<td>11.59</td>
<td>28.51</td>
<td>62.90</td>
<td>2.12</td>
</tr>
<tr>
<td>45-49</td>
<td>0.15</td>
<td>0.73</td>
<td>1.68</td>
<td>3.00</td>
<td>5.30</td>
<td>8.70</td>
<td>0.78</td>
</tr>
<tr>
<td>50+</td>
<td>0.06</td>
<td>0.36</td>
<td>1.00</td>
<td>2.03</td>
<td>4.05</td>
<td>7.43</td>
<td>0.45</td>
</tr>
</tbody>
</table>

### Table 3. Age-dependent annual vaccination rates among MSM in Amsterdam, 1998-2009.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age range</th>
<th>Number with first vaccination, all years*</th>
<th>Distribution</th>
<th>Annual vaccination rate, $Z_i$, Not targeted</th>
<th>Annual vaccination rate, $Z_i$, Targeted to core</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;15</td>
<td>0</td>
<td>0.00</td>
<td>0.000000</td>
<td>0.000000</td>
</tr>
<tr>
<td>2</td>
<td>15-19</td>
<td>277</td>
<td>0.08</td>
<td>0.01126</td>
<td>0.05882</td>
</tr>
<tr>
<td>3</td>
<td>20-24</td>
<td>1,230</td>
<td>0.17</td>
<td>0.05099</td>
<td>0.29255</td>
</tr>
<tr>
<td>4</td>
<td>25-29</td>
<td>1,695</td>
<td>0.16</td>
<td>0.07097</td>
<td>0.43006</td>
</tr>
<tr>
<td>5</td>
<td>30-34</td>
<td>1,626</td>
<td>0.15</td>
<td>0.06798</td>
<td>0.40842</td>
</tr>
<tr>
<td>6</td>
<td>35-39</td>
<td>1,437</td>
<td>0.14</td>
<td>0.05983</td>
<td>0.35144</td>
</tr>
<tr>
<td>7</td>
<td>40-44</td>
<td>1,057</td>
<td>0.06</td>
<td>0.04366</td>
<td>0.24586</td>
</tr>
<tr>
<td>8</td>
<td>45-49</td>
<td>528</td>
<td>0.06</td>
<td>0.02157</td>
<td>0.11528</td>
</tr>
<tr>
<td>9</td>
<td>50-54</td>
<td>327</td>
<td>0.04</td>
<td>0.01330</td>
<td>0.06981</td>
</tr>
<tr>
<td>10</td>
<td>55-59</td>
<td>187</td>
<td>0.04</td>
<td>0.00759</td>
<td>0.03932</td>
</tr>
<tr>
<td>11</td>
<td>60-64</td>
<td>105</td>
<td>0.03</td>
<td>0.00425</td>
<td>0.02189</td>
</tr>
<tr>
<td>12</td>
<td>65-69</td>
<td>31</td>
<td>0.03</td>
<td>0.00125</td>
<td>0.00641</td>
</tr>
<tr>
<td>13</td>
<td>70+</td>
<td>0</td>
<td>0.05</td>
<td>0.00000</td>
<td>0.00000</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8500</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data from the HBV Vaccination Campaign 1998-2009. In the untargeted scenario, 2062 men per age class were eligible for vaccination; in the targeted scenario 404 men per age class were eligible for vaccination. It was assumed that 19% of MSM were antiHbc+ and hence not eligible for vaccination.
Figure 1. Age distribution of new HBV infections from the model and from data, before the introduction of vaccination. Green columns: the age distribution of reported acute HBV infections among men who have sex with men in Amsterdam in the years 1992–1998, from notification data. Blue columns: the age distribution of new infections as calculated from the model, at the steady state without vaccination; for these results, the parameters shown in Table 1 and partner change rates in Table 2 were used.