The impact of the COVID-19 pandemic on hepatitis B virus vaccination and transmission among men who have sex with men: a mathematical modelling study

SUPPLEMENT

We used a deterministic compartmental model that we have earlier developed to investigate the impact of hepatitis B virus (HBV) vaccination on HBV transmission among men who have sex with men (MSM). The model accounts for HBV vaccination via the National HBV Vaccination Programme for Risk Groups. MSM have been included in the programme since its start in 2002 [1, 2]. The model and data used for parameterisation have been described in detail in our earlier publication [3]. In this appendix, we repeated all relevant information from our earlier publication [3], as well as new data from 2020 and 2021, as explained below.

S1. Data sources

Several model parameters were estimated using data from cohorts or studies among MSM in the Netherlands. The following data sources were used:

- Amsterdam Cohort Study (ACS) on HIV among MSM in Amsterdam was initiated in 1984 [4, 5]. It is an open, prospective cohort study. Participants visit the facilities of ACS every six months. They complete self-administered questionnaires (with questions about socio-demographic characteristics, sexual behaviour, recreational drug use etc.) and they are tested for HIV and other STIs. In this study, we used the 44th questionnaire completed by participants between January and June 2017,

because this specific questionnaire included also questions about the number of sex acts with each separate sexual partner.

- National HBV Vaccination Programme of Risk Groups. In 2002, a selective vaccination programme was initiated in the Netherlands, providing HBV vaccination free of charge for population subgroups at increased risk of HBV, including MSM, drug users, commercial sex workers, and heterosexuals who change partners frequently. MSM have been included in the programme since its start [1, 6]. The number of MSM receiving three doses of HBV vaccination are shown in Table S2 and were used for model validation (Figure S2). Furthermore, the numbers of vaccinations from March 2020 were used to calculate the change in vaccination rates during the pandemic (Table 2 in main text).
- Online National System for Registration of Infectious Diseases (OSIRIS). OSIRIS is a national computer system where data from the whole country about diagnoses of infectious diseases are registered [7]. We used data from this database for the annual number of diagnoses of acute HBV for model fitting (Figure S2).
- National STI Surveillance Database (SOAP). In this database, surveillance data of STI consultations from all 26 STI clinics in the Netherlands are accumulated [8, 9]. STI clinics in the Netherlands provide free and anonymous STI testing for MSM. At each STI consultation, information on demographics, sexual behaviour, STI history of the past two years, and STI test results are registered. According to the current protocol, MSM are tested for HIV, HBV, syphilis, gonorrhoea, and chlamydia. From this database, we used the number of HBV tests to estimate the testing rates before the pandemic (Table S1) and the change in testing during the pandemic (Table 2 in main text). Testing rates were stratified according to sexual activity level based on the number of partners in the preceding six months (low activity: 0-2 partners; moderately high activity: 3-10 partners; very high activity: >10 partners).
- COVID-19, Sex, and Intimacy Survey: This online repeated cross-sectional survey assessed COVID-19-related changes in sexual activity, number and types of partners and condomless anal intercourse among adult MSM in the Netherlands [10, 11]. The

first round of data collection was carried out from end July to beginning of September 2020 [10], with recruitment via social media advertisements on Facebook and Instagram. Respondents reported on their sexual-related behaviors during three two-month periods: before the first lockdown (January-February 2020), during the first lockdown (mid-March to mid-May 2020), and in the first relaxation period (following the first lockdown: mid-May to mid-July 2020). The model parameters accounting for the COVID-19-related change in sexual activity during the first lockdown and the first relaxation period were based on data from this survey round. In our previous publication [12], the parameters for sexual activity during the second lockdown were consensus estimates we established in consultation with experts working with the MSM population. In the present study, we used the same consensus estimates as they were validated by preliminary results from the second round of the COVID-19, Sex, and Intimacy Survey [11]. The second round was conducted in Spring 2021, and collected data on behaviours in five periods from January 1st 2020 until mid-February 2021.

S2. Model equations

The model is described by the following system of ordinary differential equations, with $i = 1,2,3$ denoting the i-th sexual activity group:

$$\frac{dX_i}{dt} = -(\lambda_i + \zeta_i + \pi_i + \mu)X_i + \mu N_i$$

$$\frac{dV_i}{dt} = (\zeta_i + \pi_i)X_i - \mu V_i$$

$$\frac{dZ_i}{dt} = (1-\sigma)\theta_1(Y_{1i} + W_{1i}) + \sum_{k=2}^{4} \theta_{kz}(Y_{ki} + W_{ki}) - \mu Z_i$$

$$\frac{dY_{1i}}{dt} = (1-f_s)\lambda_i X_i - (\theta_1 + \delta_1 + \gamma_i + \pi_i + \mu)Y_{1i}$$

$$\frac{dY_{2i}}{dt} = \sigma\theta_1 Y_{1i} - (\theta_{23} + \theta_{24} + \theta_{2z} + \delta_2 + \gamma_i + \pi_i + \varphi_2 + \mu)Y_{2i} + \theta_{32}Y_{3i}$$

$$\frac{dY_{3i}}{dt} = \theta_{23}Y_{2i} - (\theta_{32} + \theta_{3z} + \delta_3 + \gamma_i + \pi_i + \varphi_3 + \mu)Y_{3i}$$

$$\frac{dY_{4i}}{dt} = \theta_{24}Y_{2i} - (\theta_{4z} + \theta_{45} + \delta_4 + \gamma_i + \pi_i + \varphi_4 + \mu + \mu_4)Y_{4i}$$

$$\frac{dW_{1i}}{dt} = f_s\lambda_i X_i + (\delta_1 + \gamma_i + \pi_i)Y_{1i} - (\theta_1 + \mu)W_{1i}$$

$$\frac{dW_{2i}}{dt} = \sigma\theta_1 W_{1i} + (\delta_2 + \gamma_i + \pi_i)Y_{2i} - (\theta_{23} + \theta_{24} + \theta_{2z} + \varphi_2 + \tau_2 + \mu)W_{2i} + \theta_{32}W_{3i}$$

$$\frac{dW_{3i}}{dt} = \theta_{23}W_{2i} + (\delta_3 + \gamma_i + \pi_i)Y_{3i} - (\theta_{32} + \theta_{3z} + \varphi_3 + \mu)W_{3i}$$

$$\frac{dW_{4i}}{dt} = \theta_{24}W_{2i} + (\delta_4 + \gamma_i + \pi_i)Y_{4i} - (\theta_{4z} + \theta_{45} + \varphi_4 + \tau_4 + \mu + \mu_4)W_{4i}$$

$$\frac{dW_{5i}}{dt} = \theta_{45}(Y_{4i} + W_{4i}) - (\varphi_5 + \tau_5 + \mu + \mu_5)W_{5i}$$

$$\frac{dW_{6i}}{dt} = \sum_{k=2}^{4} \varphi_k(Y_{ki} + W_{ki}) + \varphi_5 W_{5i} + \varphi_T T_i - (\tau_6 + \mu + \mu_6)W_{6i}$$

$$\frac{dT_i}{dt} = \tau_2 W_{2i} + \sum_{k=4}^{6} \tau_k W_{ki} - (\varphi_T + \mu + \mu_T)T_i$$

The parameters and variables in these equations are explained in the following sections and in Tables 1 and S1.

S3. The course of HBV infection

In the model, MSM are divided into several classes according to state of HBV infection and immunity. First, we distinguish:

- Individuals who are uninfected and unvaccinated (X_i).
- Individuals who are immune to HBV due to HBV vaccination (V_i).
- Individuals who are immune to HBV after HBsAg seroconversion (Z_i).
- Individuals infected with HBV who receive antiviral treatment and have suppressed viral load (T_i).
- Individuals infected with HBV and not-immune; these are further subdivided into the following phases of HBV infection, according to international guidelines [13, 14]:
    1. Acute HBV infection, undiagnosed (Y_{1i}) or diagnosed (W_{1i}): a short period with very high levels of transmissibility. In adults, a small fraction σ of acute infections progresses to chronic infection, while the rest, $1-\sigma$, clears the infection and becomes immune.

2. Active chronic HBV infection or chronic hepatitis B (CHB), undiagnosed (Y_{2i}) or diagnosed (W_{2i}): This phase is characterised by active replication of the virus, moderate to high levels of serum HBV DNA and of contagiousness, and elevated ALT. In this phase, individuals can be hepatitis B e-antigen (HBeAg) positive or negative, but mostly HBeAg-negative, since HBeAg-positive is rare among those infected as adults. Virus replication may get under control and individuals progress to the inactive phase. Individuals with active CHB can clear the infection or progress to cirrhosis or HCC. Treatment is indicated for those diagnosed.
3. Inactive chronic HBV infection, undiagnosed (Y_{3i}) or diagnosed (W_{3i}): This phase is asymptomatic and is characterised by the presence of serum antibodies to HBeAg (anti-HBe), undetectable or low HBV DNA levels, and normal ALT. Individuals in this phase can clear the infection, but they also have a low probability of progression to CHB or HCC.
4. Compensated cirrhosis, undiagnosed (Y_{4i}) or diagnosed (W_{4i}): In this phase, the liver is scarred but is still mostly able to perform its basic functions. Individuals often have no symptoms. Treatment is indicated for this phase.
5. Decompensated cirrhosis (W_{5i}): In this phase, there is severe damage of the liver that can range up to liver failure. Individuals have clear clinical symptoms that lead to diagnosis and treatment is indicated in this phase.
6. Hepatocellular carcinoma (HCC) (W_{6i}): This is a type of primary liver cancer. Individuals have clear clinical symptoms that lead to diagnosis. Treatment is indicated in this phase.

These classes and phases are further divided into three activity groups, based on sexual activity, denoted with the subscript $i = 1,2,3$ (see details in section about the activity groups). Due to clinical symptoms with decompensated cirrhosis and HCC, we assumed that individuals in these phases are diagnosed. The other phases of acute and chronic HBV infection were distinguished into undiagnosed and diagnosed. All phases of chronic infection and cirrhosis can progress directly to HCC. Individuals with cirrhosis or HCC have an extra death rate (μ_4, μ_5, μ_6) due to HBV infection. All individuals with acute or

chronic infection or compensated cirrhosis have a probability to clear the infection and become immune.

S4. Transmission of HBV

Inactive chronic HBV infection is characterised by low levels of HBV DNA, therefore we assumed that the probability of HBV transmission per act of CAI is the lowest during inactive chronic infection. During active CHB and compensated cirrhosis, the level of infectivity is higher than that during inactive chronic HBV, while the level of infectivity is the highest during acute infection (Tables 1, S1). We assumed that individuals with decompensated cirrhosis or HCC do not engage in sexual practices that enable HBV transmission due to the severity of their health condition.

S5. Transmission rate

The rate λ_i at which men in activity group $i = 1,2,3$ get infected with HBV is defined by the equation:

$$\lambda_i = \alpha_{si} \sum_{j=1}^{4} m_{sij} \frac{\sum_{k=1}^{4} p_{skj}\left(Y_{kj} + W_{kj}\right) + p_{sTj} T_j}{N_j} + \alpha_{ci} \sum_{j=1}^{4} m_{cij} \frac{\sum_{k=1}^{4} p_{ckj}\left(Y_{kj} + W_{kj}\right) + p_{cTj} T_j}{N_j}$$

In these equations,

- $p_{skj} = 1 - \left(1 - \omega_j \beta_k\right)^{u_{sj}}$ and $p_{ckj} = 1 - \left(1 - \omega_j \beta_k\right)^{u_{cj}}$ are the probabilities of HBV transmission per steady and per casual partner, respectively, per year, if the infected partner is in state $k = 1,2,3,4$ of infection and from activity group $j = 1,2,3$; $p_{sTj} = 1 - \left(1 - \omega_j \beta_T\right)^{u_{sj}}$ and $p_{cTj} = 1 - \left(1 - \omega_j \beta_T\right)^{u_{cj}}$ are the respective probabilities of transmission from an infected partner under treatment.
- β_k is the probability of HBV transmission per act of CAI if the infected partner is in state $k = 1,2,3,4$ of infection.
- ω_j is a factor decreasing the probability to acquire HBV due to antiretroviral agents that reduce HBV acquisition. This reduction is due to antiretroviral treatment for HIV infection: $\omega_j = h_j c_j \psi_c + 1 - h_j c_j$, where h_j is the HIV prevalence in activity group j; c_j is

the fraction of HIV-infected MSM that is diagnosed and receives cART containing lamivudine, emtricitabine, and/or tenofovir, and ψ_c is the reduction in the probability to acquire HBV infection due to these antiretroviral agents [15, 16].

- u_{sj}, u_{cj} are the frequencies of CAI with steady and casual partners, respectively, if the infected individual is from activity group $j = 1,2,3$.
- α_{sj} and α_{cj} are the numbers of steady and casual partners per year, respectively, of men in activity group $j = 1,2,3$.
- N_j is the total size of activity group $j = 1,2,3$: $N_j = X_j + V_j + Z_j + T_j + \sum_{k=1}^{4} Y_{kj} + \sum_{k=1}^{6} W_{kj}$.
- m_{sij} and m_{cij} are parameters that define the level of mixing between activity groups $i, j = 1,2,3$, when forming steady and casual partnerships, respectively. These are defined by the equations:

$$m_{sij} = \varepsilon_s \delta_{ij} + (1 - \varepsilon_s) \frac{\alpha_{sj} N_j}{\sum_{v=1}^{3} \alpha_{sv} N_v} \quad \text{and} \quad m_{cij} = \varepsilon_c \delta_{ij} + (1 - \varepsilon_c) \frac{\alpha_{cj} N_j}{\sum_{v=1}^{3} \alpha_{cv} N_v},$$

where δ_{ij} is the Kronecker delta (being equal to 1, if $i = j$; and equal to 0, otherwise) and the parameters ε_s, ε_c determine the level of assortativeness in mixing of activity groups when forming steady and casual partnerships, respectively (if $\varepsilon_i = 1$, then mixing is assortative; if $\varepsilon_i = 0$, then mixing is proportionate).

S6. Sexual behaviour and sexual activity groups

We assumed that MSM can form steady relationships and have sex contacts with casual partners. Based on their number of partners, MSM were divided into three sexual activity groups: low, moderately high, and very high activity. MSM in the moderately and very high activity groups are referred to as high-activity MSM. MSM in each sexual activity group have different frequency of condomless anal intercourse (CAI) with their steady and casual partners, different rates of HBV testing, and different vaccination rates. Input parameters for the three sexual activity groups are shown in Table S1. Earlier studies have indicated that there must have been a decrease in sexual risk behaviour around the years 2002-2005 [17, 18]. To accommodate for such a change, we included in the model a decline in the frequency of CAI in 2002. CAI frequency from 2002 onwards was

obtained from ACS data. The frequency before 2002 was obtained by multiplying the frequency after 2002 by a factor (greater than 1) that was obtained from the fitting procedure.

S7. Size of MSM population

The total number of MSM in the Netherlands (size of the MSM population) was used in our calculations because the numbers of HBV infections, diagnoses, and vaccinations from the model and from the data have to be both divided by the total number of MSM to be comparable. Estimates of the size of the MSM population vary from 111,072 [19] to 392,000 [20]. The differences in the estimates depend on the year the estimate was made, the ages included (for example, 15-65 or 15-70 years), and the definition of MSM (men who had sex with men in the previous six/twelve months; or ever had sex with men; or men who identify themselves as homosexual/bisexual). We use the range 144,521 – 263,309 for the total number of MSM in the Netherlands [21]. We present results as % of the population or as numbers per 100,000 MSM per year.

S8. Vaccination via National HBV Vaccination Programme of Risk Groups

Individuals not yet infected with HBV can be vaccinated at a rate ζ_i, that was estimated based on data from the National HBV Vaccination Programme of Risk Groups [1, 6, 22]. This was zero up to 2002. From 2003 onwards, the vaccination rates ζ_i for activity group $i = 1,2,3$, were calculated from the following equations:

$$\zeta_i(t) = f_v(t) * v, \quad i = 1,$$

$$\zeta_i(t) = f_v(t) * v * h\ , \quad i = 2,3.$$

The value of v was sampled from the Uniform distribution between 1% and 2%. The factor h increases the vaccination rate of men in the moderately and very high activity groups compared to that of men in the low activity group [23]. The function $f_v(t) = 1.28 + 0.03t$ expresses the annual increase in the vaccination rate in year t, necessary to mimic

the increase in the actual number of vaccinations obtained from data. The values of these parameters are given in Tables S1-S2. For example, in the first year, the vaccination rate in the low-activity group was $1.28 * v$, in the second year it was $(1.28 + 0.03) * v$, etc. The vaccination rate ζ_i is applied to the susceptible (unvaccinated and uninfected) population, not the whole MSM population. Since the size of the susceptible population declines in time (as more and more MSM get vaccinated every year), if we had used a constant vaccination rate (2%, for example), that would have resulted in a declining number of MSM getting vaccinated every year. Since the data show an increasing number of vaccinations among MSM in time (Figure S2b and Table S2), we used an increasing vaccination rate to mimic the increase in the number of vaccinations from the data. Data on the number of MSM vaccinated annually were obtained from the National HBV Vaccination Programme of Risk Groups. We used only the number of MSM who had completed the three-dose HBV vaccination in each calendar year. These numbers were divided by the estimate of the size of the MSM population, to obtain the number of vaccinations expressed as number of MSM vaccinated against HBV per 100,000 MSM per year (Table A2). It was assumed that those vaccinated are completely protected against HBV infection and immunity lasts for life [24-28].

S9. Testing, diagnosis, and treatment of HBV infection

The rate of diagnosis of HBV infection depends on the presence of symptoms, but also on rates of opportunistic testing for STIs in general. Nowadays, most STI clinics in the Netherlands offer an “STI test” that includes tests for HIV, HBV, chlamydia, gonorrhoea, and syphilis. Some MSM seeking testing may have symptoms (possibly for an infection other than HBV), while others seek testing because regular STI testing every six months is recommended for MSM. We calculated rates of HBV testing based on data from the National Database of STI clinics. The reason for testing was not recorded in these data. Therefore, we used a “general” testing rate without distinguishing for reasons for testing. The testing rate γ_i depends on the sexual activity group of the man i=1,2,3. Since the number of HBV tests among MSM has increased in the recent years [8], we assumed an

increase in HBV testing starting in 2002 (Table S1). Furthermore, we assumed that a fraction f_s of individuals with acute HBV infection has clear clinical symptoms, seek testing, and are reported as acute infections. Due to the severity of decompensated cirrhosis and HCC, we assumed that individuals in these phases are all under some form of treatment or therapy, including chemotherapy, radiation therapy, and/or liver transplantation for HCC.

Antiviral treatment is indicated for individuals diagnosed with active CHB or compensated cirrhosis and most treated individuals achieve viral suppression. In the model, these individuals "progress" to the state T that includes those under antiviral treatment and virally suppressed. This occurs at a treatment rate τ, that depends on the fraction of diagnosed engaged in care, the fraction of those engaged in care who do start treatment, and the fraction of those treated who achieve viral suppression. Treatment has the following three effects for those achieving viral suppression: (a) the probability that they transmit HBV per act of CAI is reduced; (b) the rate of progressing to cirrhosis and HCC is reduced; and (c) the additional mortality rate due to HBV infection is reduced (compared to the respective probability and rates for those untreated). Guidelines for the treatment of HBV infection have been updated through the years: the indications (which patients should be treated) have become less restrictive and more effective antiviral agents are recommended as first-line therapy. The current treatment guidelines in the Netherlands were updated in 2012 by the Dutch Association of Gastrointestinal Liver Physicians [29]. According to these guidelines, all individuals with active CHB or cirrhosis are eligible for treatment; tenofovir, peginterferon, and entecavir are the recommended antiviral agents. Since the use of third generation antiviral agents has been increasing in the recent years in the Netherlands [30], we included in our analyses two treatment rates: the "old" treatment rates for the years up to and including 2011 and the "new" treatment rates from year 2012 onwards (Table 1).

S10. The impact of HIV treatment on acquisition of HBV

The prevalence of HIV infection was assumed to be 3-7%, 6-14%, and 9-21% in the low, moderately high, and very high activity groups, respectively. These were based on the estimates of HIV prevalence of 15% among MSM attending STI clinics and 5-10% among MSM not attending STI clinics in the Netherlands [21]. Among HIV infected MSM, the percentage diagnosed was assumed to be 75%, 82%, and 90% in the low, moderately high, and very high activity groups, respectively. These estimates were based on the estimates of the percentage undiagnosed of 10% (95% credible interval, 5-30%) among STI-clinic attendees and 35% (95% credible interval, 15-55%) among non-STI clinic attendees [21]. We assumed that 75% of diagnosed HIV-infected MSM receives antiretroviral therapy containing HBV-related antiretroviral agents (lamivudine, emtricitabine, or tenofovir) and, for these individuals, the probability to acquire HBV per CAI act is only 0.1 times the probability for those not receiving such antiretroviral agents. This is based on the findings that antiretroviral regimens with anti-HBV activity can reduce HBV incident infections by 90% [15, 16].

S11. Model fitting and validation

Using Latin Hypercube Sampling [31], 5,000 combinations of values of model parameters were sampled. The model calculations for the years until and including 2019 were repeated with these parameter combinations and with rates of HBV vaccination, testing, and treatment as before the pandemic. The number of diagnoses of acute HBV infections per 100,000 MSM per year was calculated from the model (with each of the 5,000 parameter sets) and from the data (obtained from OSIRIS). To compare the numbers of diagnoses from the data and from the model, the numbers from the data were expressed in numbers per 100,000 MSM per year, by dividing the number of diagnoses in a specific year by the total number of MSM in the Netherlands. We used a range of 144,521-263,309 MSM [21], resulting in a low estimate (dividing by 263,309 MSM) and a high estimate (dividing by 144,521 MSM) of diagnoses per 100,000 MSM. The parameter combinations that resulted in number of diagnoses (from the model) within the range

306 determined by the data were selected (182 parameter combinations) and used in the
307 model calculations from 2020 onwards. For validation, the model results were compared
308 with data on: (a) the number of MSM that received three-dose HBV vaccination per year
309 in 2003-2018; these numbers were obtained from the National HBV Vaccination
310 Programme of Risk Groups (Figure S2b, Table S2) and were scaled to numbers of
311 vaccinations per 100,000 MSM per year, by dividing with the two estimates (144,521 and
312 263,309) of the size of the MSM population, as explained above; (b) estimates of the
313 percentage of MSM hepatitis B surface antigen (HBsAg) positive and the percentage
314 hepatitis B core antibody (anti-HBc) positive, obtained from different studies (Figure S3
315 and Table S3).
316

Table S1. Parameters that depend on the sexual activity group of individuals.

		Activity group		
		Low	**Moderately high**	**Very high**
Parameter for activity group $i = 1, 2, 3$		**1**	**2**	**3**
% of MSM in specific activity group[a]		58%	26%	16%
Number of new steady partners per year[b]	α_{si}	0.1	0.2	0.7
Number of casual partners per year[a]	α_{ci}	0.75	9.12	41.15
Number of CAI acts per steady partner per year[a]	u_{si}	28	17	30
Number of CAI acts per casual partner per year[a]	u_{ci}	0.01	0.04	0.38
Vaccination rates[c]	ζ_i	$f_v(t) * v$	$f_v(t) * v * h$	$f_v(t) * v * h$
Average interval between opportunistic HBV tests (outside PrEP programme), in years[d]				
Before 2002	$1/\gamma_i$	10	5	3
From 2002 onwards	$1/\gamma_i$	3-7	1.5-2	0.5-1
HIV prevalence (% of each activity group infected with HIV) [17]	h_i	3-7%	6-14%	9-21%
% of HIV-infected MSM being diagnosed and receiving antiretroviral therapy with HBV-related agents [17]	c_i	53-59%	59-65%	65-71%

[a] Based on data from the Amsterdam Cohort Study (ACS) among MSM in Amsterdam [4, 5].

[b] The number of steady partners per year was calculated as 1/d, where d was the duration (in years) of steady partnerships in each activity group. The durations were assumed and not estimated from ACS, because MSM without sexual partners and MSM with very long steady relationships are underrepresented in ACS.

[c] The value of v was sampled from the uniform distribution between 1% and 2%, based on an annual vaccination coverage of 2% until 2010 [22]. The rate of annual increase in vaccinations was $f_v(t) = 1.28 + 0.03t$. The factor h describes the increased vaccination rate of moderately high and very high activity groups compared to that of low activity group; its value was sampled from the uniform distribution between 10% and 20%.

[d] Based on data from the National Database of STI clinics [8, 9].

Table S2. Number of MSM vaccinated against HBV, as obtained from data from the National HBV Vaccination Programme of Risk Groups [1, 6, 22].

Year	Actual number of vaccinations[a]	Estimate of number of vaccinations per 100,000 MSM per year[a]	
		Low estimate	High estimate
2002	16		
2003	1392	535[b]	974[b]
2004	2617	994	1811
2005	2228	846	1542
2006	2423	920	1677
2007	2524	959	1746
2008	2657	1009	1838
2009	2776	1054	1921
2010	2525	959	1747
2011	2546	967	1762
2012	2355	894	1630
2013	2693	1023	1863
2014	2888	1097	1998
2015	2810	1067	1944
2016	3083	1171	2133
2017	3101	1178	2146
2018	3177	1207	2198
2019	3317	1260	2295

[a] The actual number of vaccinations is the number of MSM who had completed the three-dose HBV vaccination in the respective year. The number of vaccinations per 100,000 MSM per year was obtained by dividing the actual number of vaccinations by the number of MSM in the Netherlands, estimated in the range 144,521 – 263,309 MSM [21].

[b] Risk-group vaccination was initiated in 2002 and only 16 MSM had completed the three-dose vaccination in the first year of the programme. Therefore, we assumed that the vaccination rate was zero in 2002 and the vaccination rate in 2003 was obtained using as actual number of vaccinations in 2003 the number of vaccinations in 2003 plus that in 2002 (16+1392=1408).

341 **Table S3.** Data for model fitting.

Outcome	Value	Source
Diagnoses acute HBV infection	See Figure S2	National Database OSIRIS [7]
Number of MSM with 3-dose HBV vaccination	See Figure S2	National HBV Vaccination Programme of Risk Groups [1, 22]
% HBsAg		
Among MSM presenting for vaccination at the National HBV Vaccination Programme of Risk Groups, average over years 1998-2011	0.6-0.7%	[22]
Among MSM presenting for vaccination at National HBV Vaccination Programme of Risk Groups, average over years 2002-2005	0.7-1.3%	Data National HBV Vaccination Programme of Risk Groups [1, 22]
Among MSM reporting to initiate PrEP at the Amsterdam PrEP Demonstration Project, 2015	0.5%	[32]
Estimate for MSM in 2016, using a modified workbook method	0.46-1.58%	[33]
% anti-HBc positive		
Among MSM presenting for vaccination at the National HBV Vaccination Programme of Risk Groups, average over years 1998-2011	11%	[22]
Among MSM presenting for vaccination at the National HBV Vaccination Programme of Risk Groups, average over years 2002-2005:	13-16%	Data National HBV Vaccination Programme of Risk Groups [1, 22]
Among MSM participating at an online survey of Rutgers Group in 2014, % reporting every having had HBV infection	8%	[34]
Among ACS participants in 2017	11%	ACS data [5]

342 Abbreviations: HBV, hepatitis B virus; MSM, men who have sex with men; OSIRIS, Online National
343 System for Registration of Infectious Diseases; HBsAg, hepatitis B surface antigen; anti-HBc,
344 hepatitis B core antibody, PrEP, pre-exposure prophylaxis; ACS, Amsterdam Cohort Study.
345

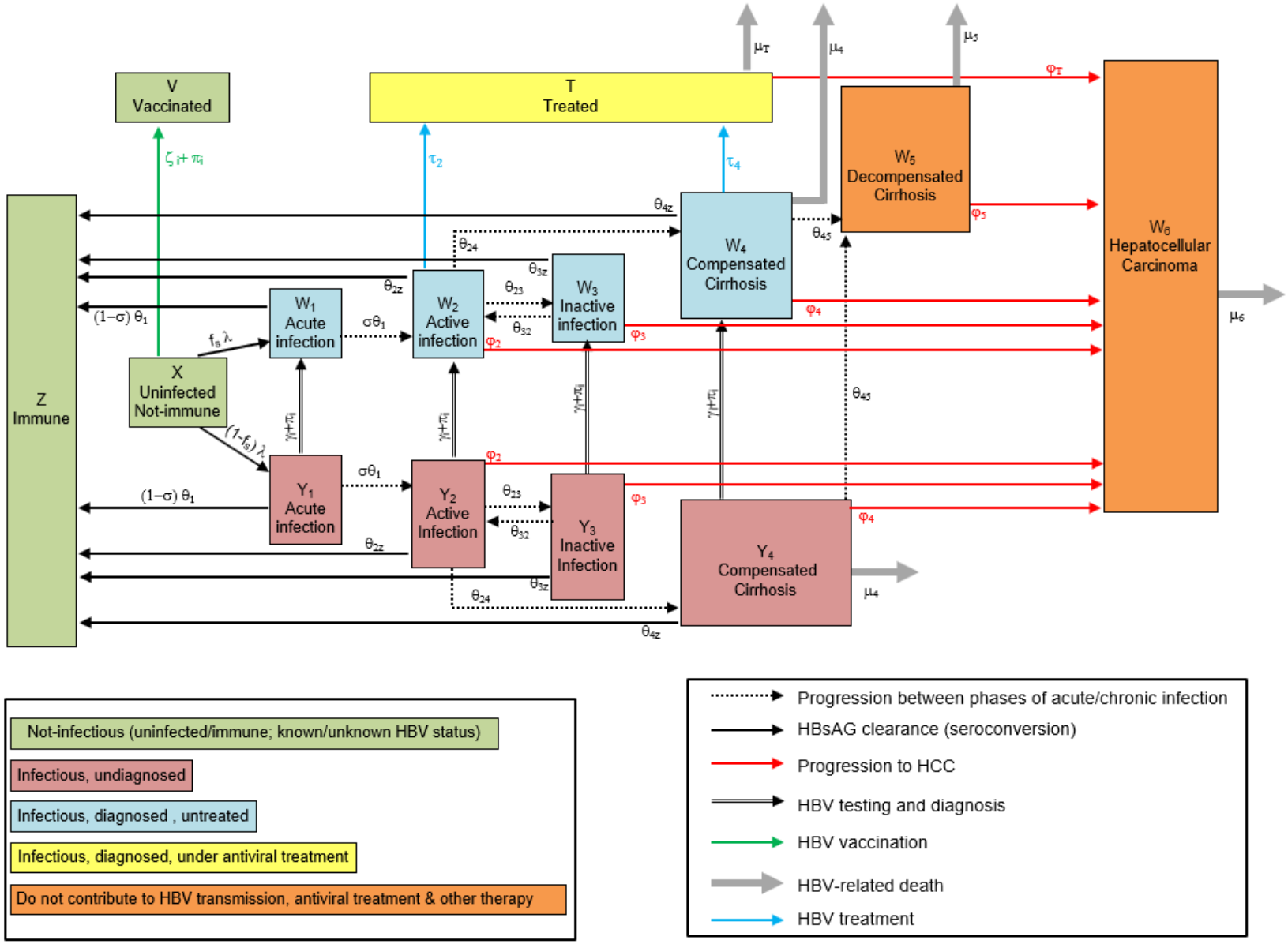

Figure S1. Flow diagram of the model of HBV transmission and progression.

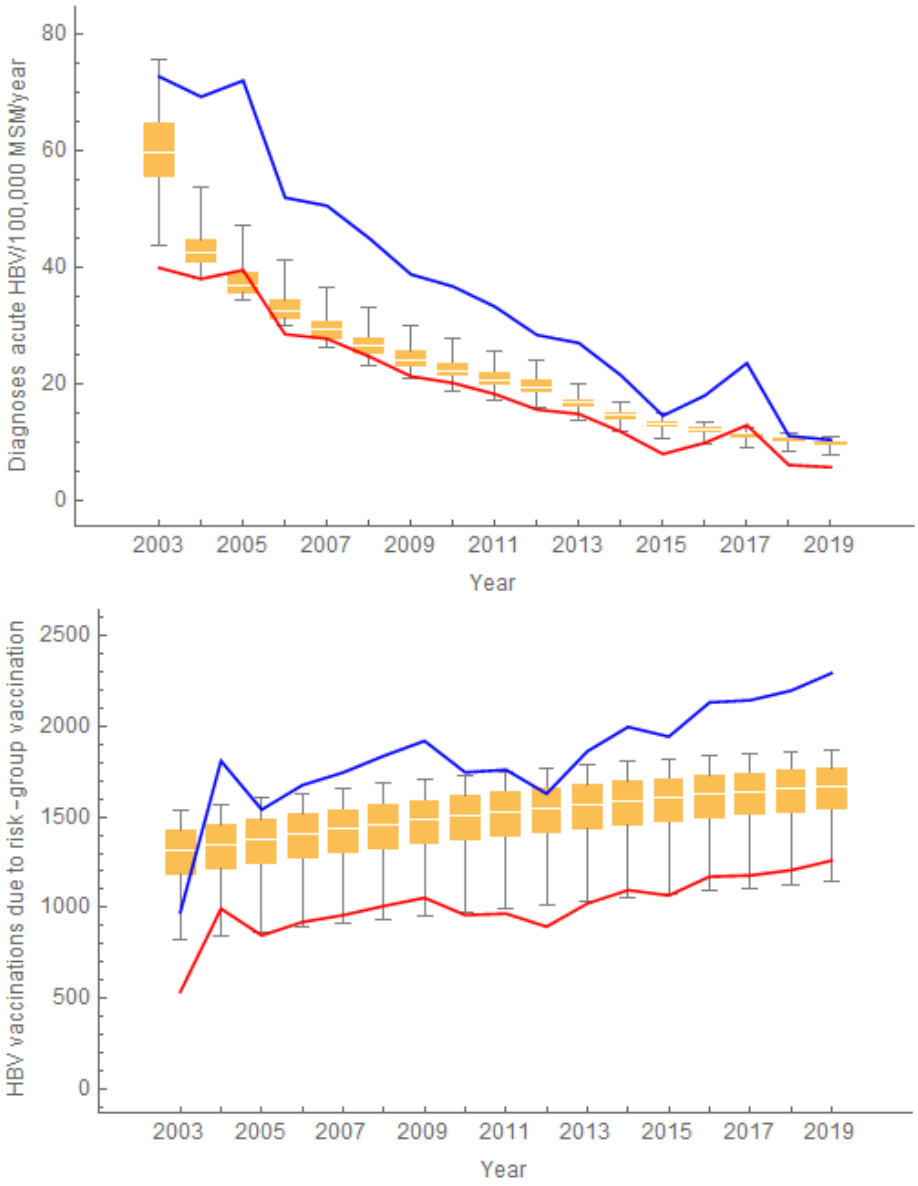

Figure S2. (a) Model fit to data on the number of diagnoses of acute HBV per 100,000 MSM per year. Data were obtained from the Online National System for Registration of Infectious Diseases (OSIRIS). (b) The number of HBV vaccinations among MSM per 100,000 MSM per year. Data from the National HBV Vaccination Programme of Risk Groups. In both plots: the red and blue lines show, respectively, the low and high estimates from the data, obtained by dividing the actual number (of diagnoses or vaccinations) by the high estimate (263,309) or the low estimate (144,521) of the total number of MSM in the Netherlands. The box plots show the respective numbers from the model; the white line shows the median, the orange box the interquartile range, and the black line segments show the whole range of the results with the selected parameters. MSM, men who have sex with men; HBV, hepatitis B virus.

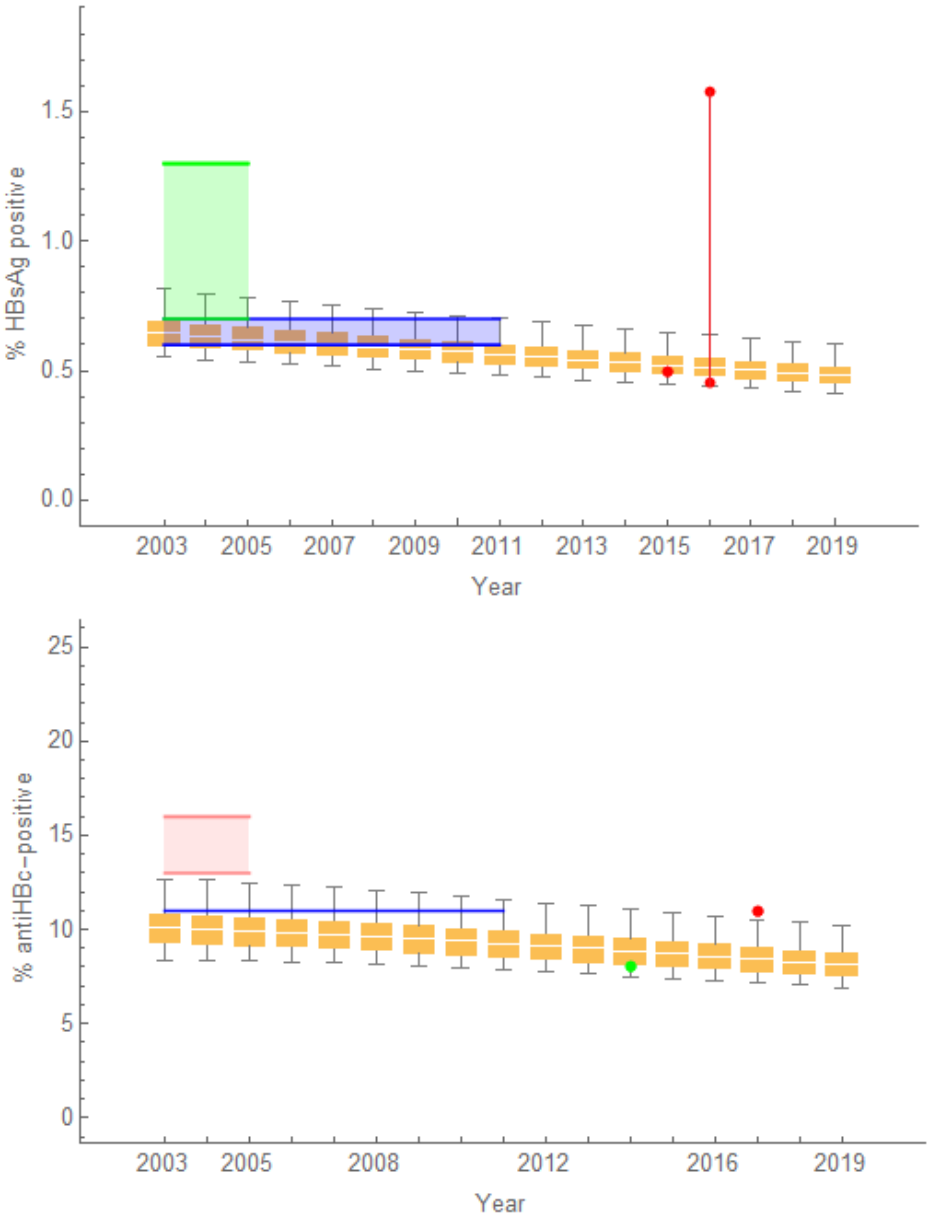

Figure S3. Results from the model and from data. (a) Percentage of MSM population being HBsAg positive. From the model, this is $\sum_{i,j}(Y_{ij} + W_{ij} + T_i)/N$. The data shown are: 0.6-0.7% in 2003-2011 (blue lines and blue shaded area); 0.7-1.3% in 2003-2005 (green lines and green shaded area); 0.5% in 2015; and 0.46-1.58% in 2016 (red points and line). (b) Percentage of MSM population being anti-HBc positive. From the model this is $\sum_{i,j}(Y_{ij} + W_{ij} + T_i + Z_i)/N$. The data shown are: 11% in 2003-2011 (blue line); 13-16% in 2003-2005 (pink lines and shaded area); 8% in 2014 (green point); and 11% in 2017 (red point). Data are explained in Table S3. In both plots, the orange box plots show the numbers from the model in each calendar year; the white line shows the median, the orange box the interquartile range, and the black line segments show the whole range of the results with the selected parameters. MSM, men who have sex with men; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody.

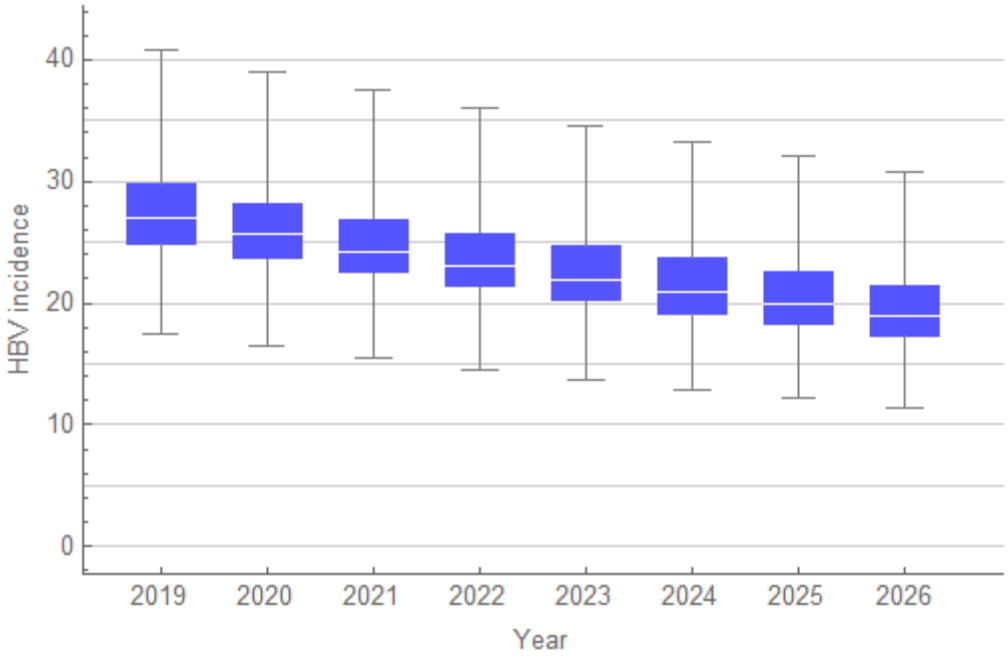

Figure S4. The incidence of hepatitis B virus (HBV) infections among men who have sex with men (MSM) in the Netherlands in 2019-2026 for the reference scenario showing the situation if the COVID-19 pandemic and related changes had not occurred. The incidence is presented as number of new HBV infections per 100,000 MSM per year. The white line segments show the median, the blue boxes show the interquartile range, and the black line segments show the whole range of model results with the selected parameters

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