Epidemiol. Infect. (2002), **128**, 229–244. © 2002 Cambridge University Press
DOI: 10.1017/S0950268801006562 Printed in the United Kingdom

Vaccination against hepatitis B in low endemic countries

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(*Accepted 19 October 2001*)

SUMMARY

A mathematical model that takes transmission by sexual contact and vertical transmission into account was employed to describe the transmission dynamics of hepatitis B virus (HBV) and vaccination against it. The model is an extension of a model by Williams et al. (*Epidemiol Infect* 1996; **116**; 71–89) in that it takes immigration of hepatitis B carriers from countries with higher prevalence into account. Model parameters were estimated from data from The Netherlands where available. The main results were that, given the estimates for the parameters describing sexual behaviour in The Netherlands, the basic reproduction number R_0 is smaller than 1 in the heterosexual population. As a consequence, the immigration of carriers into the population largely determines the prevalence of HBV carriage and therefore limits the possible success of universal vaccination. Taking into account the prevalence of hepatitis B carriage among immigrants and an age-dependent probability of becoming a carrier after infection, we estimate that a fraction of between 5 and 10% of carrier states could be prevented by universal vaccination.

INTRODUCTION

In 1992 the WHO advised all countries with a hepatitis B prevalence higher than 5% to start universal vaccination of infants in 1995 and all countries with a lower prevalence to start universal vaccination in 1997. A number of Western European countries with very low prevalence of hepatitis B have been reluctant to do so (United Kingdom, The Netherlands, Scandinavian countries). The reason is that it is unclear how effective such a universal vaccination programme would be in a situation where prevalence is low and a substantial fraction of all cases can be attributed to import from countries with a higher prevalence. In The Netherlands a cost-effectiveness study was performed recently to study the effects of universal vaccination and estimate the costs and long term benefits [1]. This study consisted of several parts: (1) a collection of all available surveillance data concerning HBV infection in The Netherlands, (2) a case-control study to estimate the contributions of different transmission routes to the spread of HBV in The Netherlands, (3) the use of a mathematical model to describe the transmission dynamics of HBV, and (4) a Markov chain model to describe states of infection, their health care costs and health losses.

In this paper we report on the third part of the study, namely the mathematical modelling and the results obtained for the Dutch situation. The model

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we used is based on earlier work by Williams et al. [2]. The model describes the transmission of HBV in an age-structured population with six sexual activity classes. Transmission takes place via sexual contact or vertically, i.e. from a mother to her newborn baby. We modified the model to account for immigration of hepatitis B carriers into the population. Also, in contrast to Williams et al. [2] we assumed that the probability of becoming carrier after infection by sexual contact is age dependent. These modifications have a major impact on the disease dynamics and therefore implications for vaccination strategies in low endemic countries. Using the modified model, we investigated the effect of vaccination on the incidence and prevalence of HBV infection.

METHODS

Model structure

First, we give a short summary of the model characteristics. For more details we refer to [2]. The model population is structured by sex (male, female), age (between 0 and 60 years), and sexual activity (six activity classes). It is assumed that the male to female ratio is 1:1. The age distribution is uniform on the interval [0,60], i.e. mortality is assumed to be zero up to age 60, and infinite above that. It is assumed that births balance deaths, so that the population size is constant. Births are attributed to the age of the mothers according to a fertility distribution. Individuals are born into a sexual activity class and stay there throughout their lives. The distribution over the activity classes is constant over time. It is assumed that sexual mixing between and among activity and age classes is proportionate, i.e. it is random mixing weighted by the activity level. Sexual activity starts at the age of 15, and for every activity class there is a given level of sexual activity (defined as rate of partner change) per age class. In other words, sexual activity for all activity classes first rises up to the age 25, then decreases again, only the absolute levels are different in the different activity classes. In first instance the model is designed to describe a purely heterosexual population. The population of homosexual men is then modelled as a separate population as described below.

The infection can be transmitted by sexual contact or vertically, i.e. from mother to newborn child. This means that new infections in the model occur either in 0-years olds, or in age classes from 15 years onwards; in between the incidence is 0. An infected individual goes through a latent stage (H), in which he is not yet infectious. Then he moves on to develop acute infection (Y), after which he either becomes a carrier (C), or immune (Z) (Fig. 1). If there is vaccination, an individual can move into the vaccinated class (V).

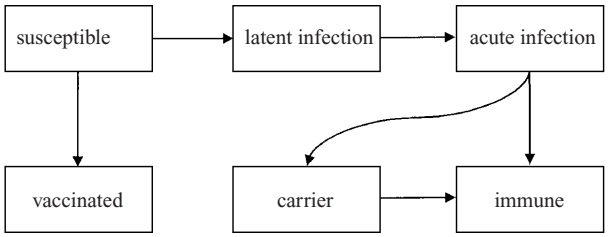

Fig. 1. Flow diagram of the hepatitis B model.

The spread of HBV in a homosexual population is modelled independently, i.e. there is assumed to be no sexual contact between homo- and heterosexual populations. For a homosexual population there is no distinction between male and female, i.e. the entire population is assumed to be male. The main difference with the heterosexual model is in the parameter values describing the sexual activity rates. As homosexual men can also become carriers at birth, the model also assumes an inflow of infected individuals at birth. Those rates are coupled to the steady state values of the heterosexual model. This is somewhat artificial, as it means that vaccination programmes do not have an impact on the inflow of infected homosexual males at birth. But the effect is too small to justify putting effort into a dynamic description of this inflow at birth.

The model as described by Williams et al. [2] has been modified in some points to accommodate for our specific needs. Most importantly, we incorporated immigration into the population in the model. The original model describes a closed population. In our modified version immigration occurs with a constant annual net per capita rate, a fixed age distribution, and a constant prevalence of carriers and immunes. Immigrants are assumed to mix homogeneously with the resident population. To keep population size constant we apply a rescaling that keeps the fractions in the different population subgroups unchanged. Another change in the model is the incorporation of an age-dependent probability of becoming a carrier after infection with HBV. We used a functional form proposed by Edmunds et al. [3]. Also, we took into account that immunity after vaccination might not last lifelong. Although there is currently no evidence that immunity wanes [4], the vaccine is not available

https://doi.org/10.1017/S0950268801006562 Published online by Cambridge University Press

long enough yet to positively exclude the loss of immunity long after vaccination. Based on the assumption that the average duration of immunity is 50 years, we set the rate of losing immunity (ψ) to 0·02/year.

We derived an explicit formula for computing the basic reproduction number R_0 following the methods of Heesterbeek [5] and Diekmann et al. [6] (see Appendix). Our formula differs from the one given by Williams et al. [2], but is in accordance with the generally accepted theory in mathematical epidemiology.

Parameter values

We consider The Netherlands as a typical example of a low prevalence country and therefore as far as possible we used parameter values that describe the specific situation in that country. Those values differ in some aspects from the parameter values used in [2] for the United Kingdom situation. The largest difference is in the estimates for the sexual activity parameters. On the basis of a sex survey in The Netherlands our estimates are considerably lower than those for the United Kingdom (see below). Possible reasons for this difference are discussed in the discussion section. Sensitivity analysis shows, however, that the qualitative results remain unchanged, as we will show in the results section.

Heterosexual population

To estimate the rates of partner change for the heterosexual population we used data from a survey conducted in The Netherlands in 1989 [7]. In this survey 1001 persons aged between 15 and 49 years were interviewed about their sexual behaviour. Of this group, 979 persons reported mainly heterosexual behaviour. On the basis of those data we estimated the rate of partner change for every individual in the sample. Then we fitted a gamma distribution to the data for every 5 year age class [2, 8]. Those gamma distributions were then used to calculate average rates of partner change for the different activity classes as described below.

The subdivision of the population into activity classes is arbitrary. We chose to use the same subdivision as Williams et al. [2] so that results can be more easily compared. The fractions in the different activity classes are 0·273, 0·286, 0·303, 0·132, 0·005 and 0·001 for the activity classes 1–6, respectively. On the basis of this subdivision into fractions we computed average rates of partner change per activity and age class from the gamma distributions fitted to the data. In Table 1*a* the rates for the United Kingdom are given (from [2]), and in Table 1*b* the rates as estimated for The Netherlands.

Although a sample of the size as in the Dutch survey can represent the sexual behaviour of the majority of the population quite well, small subgroups such as highly sexually active core groups will hardly be represented. As a consequence, the estimates based on those data are probably an underestimate of the true rate of partner change in the heterosexual population of The Netherlands. Also, the numbers in the different age classes are small, resulting in uncertain estimates. We therefore performed a sensitivity analysis to see how the model outcomes depend on the sexual behaviour data.

Homosexual men

For homosexual men there was no representative sample available (the survey of the general population included only 17 homosexual men). Because the estimates from the United Kingdom are based on a sample size of 18876 respondents we expect those estimates to be much more certain [9]. Therefore, we chose parameter values based on the estimates given in [2] for the United Kingdom (see Table 1*c*) and the estimates for the heterosexual populations as follows. As we found the rates of partner change to be lower for the heterosexual population in The Netherlands than in the United Kingdom, we assumed a same relationship for the rates of partner change in the homosexual population. We achieved this in the following way: for every age and activity class we computed the ratio of rates of partner change of the Dutch and the English heterosexual populations (from Table 1*a*, *b*). Then we multiplied the parameters for the English homosexual population with these ratios. The resulting parameters are given in Table 1*d*. So, those rates are not based on data from homosexual men in The Netherlands and are in that sense arbitrary. Our argument for this procedure is that it is based on data describing sexual behaviour of homosexual men in a Western European country in a representative sample [9], and that the parameter values of homosexual and heterosexual populations have the same quantitative relationship as observed in the United Kingdom.

For all simulations described in the results section, except for the sensitivity analyses, we used the

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Table 1. *Estimates for the age-specific rates of partner change* (*numbers of new sex partners per year*) *for* (*a*) *the heterosexual population in the UK* [2], (*b*) *the heterosexual population in The Netherlands* (n = *979*) *on the basis of survey data from 1989* [7], (*c*) *the homosexual population in the UK* [2]. (*d*) *Parameter values for the age specific rates of partner change* (*numbers of new sex partners per year*) *of homosexual men in The Netherlands* (*computed as described in the text*)

	Sexual activity class						
Age	1	2	3	4	5	6	Average
(a) United Kingdom (heterosexual population)							
15–19	0·035	0·295	1·155	3·514	8·589	12·549	0·963
20–24	0·036	0·305	1·193	3·631	8·875	12·967	0·995
25–44	0·026	0·221	0·865	2·631	6·431	9·397	0·721
45–49	0·019	0·157	0·616	1·874	4·581	6·693	0·514
50–59	0·014	0·116	0·456	1·388	3·391	4·955	0·380
(b) The Netherlands (heterosexual population)							
15–19	0·004	0·059	0·334	1·250	3·382	5·096	0·306
20–24	0·001	0·032	0·417	2·357	7·604	12·029	0·497
25–29	0·0	0·008	0·170	1·234	4·385	7·113	0·245
30–34	0·0	0·002	0·119	1·276	5·204	8·731	0·240
35–39	0·0	0·0	0·016	0·438	2·391	4·291	0·079
40–44	0·0	0·0	0·013	0·516	3·140	5·773	0·094
45–59	0·0	0·0	0·009	0·253	1·223	2·272	0·035
(c) United Kingdom (homosexual population)							
15–19	0·045	0·434	1·285	2·547	4·725	7·819	0·542
20–29	0·21	2·034	6·029	11·951	22·168	36·686	2·542
30–39	0·234	2·263	6·708	13·297	24·663	40·815	2·828
40–49	0·212	2·058	6·1	12·091	22·427	37·115	2·571
50–59	0·046	0·443	1·313	2·603	4·828	7·991	0·554
(d) The Netherlands (homosexual population)							
15–19	0·005	0·086	0·371	0·906	1·861	3·175	0·155
20–24	0·003	0·214	2·109	7·757	18·993	34·032	1·030
25–29	0·000	0·069	1·183	5·604	15·116	27·768	0·688
30–34	0·000	0·022	0·923	6·448	19·957	37·922	0·747
35–39	0·000	0·000	0·125	2·216	9·171	18·638	0·259
40–44	0·000	0·000	0·091	2·373	10·949	22·800	0·286
45–49	0·000	0·000	0·094	1·635	5·990	12·597	0·182
50–59	0·000	0·000	0·027	0·475	1·742	3·663	0·053

parameter values given in 1 *b*, *d*. The estimates based on the United Kingdom data (Tables 1 *a*, *c*) were used in the sensitivity analysis for the sexual behaviour parameters.

Transmission and probability of becoming a carrier

For the transmission probabilities per partnership and other disease specific parameters we used the same values as Williams et al. [2] with one exception, namely the probability of becoming a carrier after infection. While Williams et al. [2] assume that the probability of becoming a carrier after infection by sexual transmission is constant at 0·1, we follow Edmunds et al. [3] in assuming that this probability can be described by an age dependent function (*a* denotes age)

$$p(a) = \exp(-\gamma_1 a^{\gamma_2})$$

with constants $\gamma_1 > 0$ and $\gamma_2 > 0$. In Edmunds et al. [3] the values of γ_1 and γ_2 were estimated with maximum likelihood methods as $\gamma_1 = 0{\cdot}645$ and $\gamma_2 = 0{\cdot}455$ based on 21 studies in which the ratio of carriers and infecteds was known (Fig. 2). The probability of becoming carrier is around 0·1 at the age of starting sexual activity and decreases with increasing age. The

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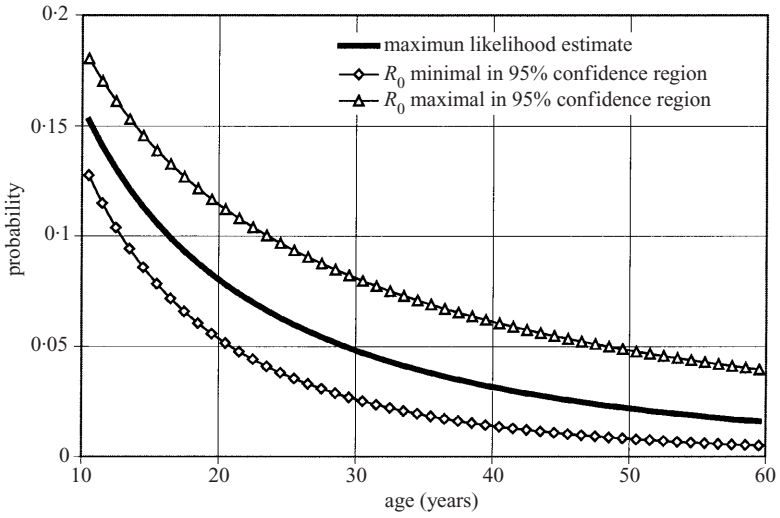

Fig. 2. The age dependent probability of becoming a carrier after infection with hepatitis B. The figure shows the maximum likelihood estimate from Edmunds et al. [3], and an upper and lower bound for which R_0 for the heterosexual population is maximal and minimal, respectively, within the 95% confidence region.

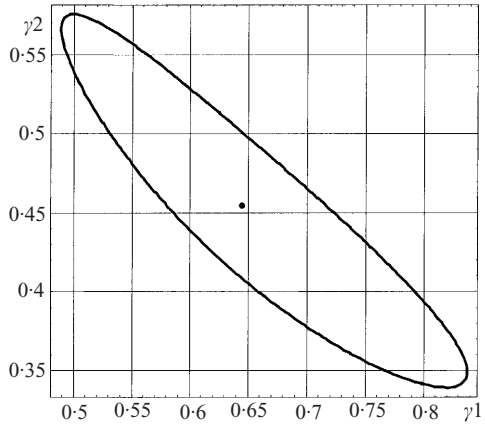

Fig. 3. The 95% confidence region for the estimate of the parameters γ_1 and γ_2. The dot represents the point estimate of Edmunds et al. [3].

probability of becoming a carrier after vertical infection is estimated at 0·885 by Edmunds et al. [3].

In order to conduct a sensitivity analysis for the influence of the age specific probability of becoming carrier we extended the statistical analysis of the data set used in Edmunds et al. [3] by computing a 95% confidence region around the point estimate for γ_1 and γ_2 (Fig. 3). On the boundary of the confidence region we chose those two pairs of parameters γ_1 and γ_2, that respectively maximize and minimize the basic reproduction ratio R_0. The maximum value of R_0 is reached for $\gamma_1 = 0{\cdot}724$ and $\gamma_2 = 0{\cdot}366$. The minimum value of R_0 is reached for $\gamma_1 = 0{\cdot}57$ and $\gamma_2 = 0{\cdot}546$. Using those two pairs of values for γ_1 and γ_2 in the above function for $p(a)$ yields the upper and lower estimates for $p(a)$ shown in Figure 2. In general, the values of γ_1 and γ_2, for which R_0 takes its extremes depend also on other age-dependent model parameters, especially on the rates of partner change. We found, however, that there is no difference between those values of γ_1 and γ_2 whether they are based on the rates of partner change from the United Kingdom or The Netherlands. The reason is that in both populations the age distributions of sexual activity are similar.

Table 2. *Age-specific fertility in The Netherlands*, 1996 [11]

Age	Live births/woman/year
15–19	0·0041
20–24	0·0332
25–29	0·0969
30–34	0·1197
35–39	0·0465
40–44	0·0066
45–49	0·0003

Population size and fertility

When it was necessary to use absolute population sizes we assumed a population of 12·9 million people aged between 0 and 60 years. Furthermore we assumed that 2% of the population are homosexual men [10]. Table 2 shows the yearly birth rates in 5-year age classes in The Netherlands in 1996 [11]. In comparison with the United Kingdom rates the mean age at giving birth is somewhat higher.

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Table 3. *Upper estimates for the prevalence of HBV carriers and immune immigrants* [11]

Prevalence of HBV in country of origin	Fraction immigrants	Carriers (%)	Immune (%)
Low	0·127	1	4
Medium	0·677	5	35
High	0·196	14	66

Immigration

We estimated the per capita immigration rate at 0·004/year. This amounts to (net) immigration of 51 600 persons per year in a population of 12·9 million. This estimate excludes asylum seekers, because they are relatively isolated from the rest of the population, and once they are permitted to stay, are registered as immigrants. The prevalence of HBV carriers in immigrants was assumed to be 1–6%, based on different estimates.

The lower estimate was chosen arbitrarily based on opinions formed in a seroprevalence study [12]. The upper estimate was computed as follows. Based on actual data of countries of origin of immigrants, we estimated the fraction of immigrants from countries with low, medium, and high endemic prevalence of HBV as 0·127, 0·677 and 0·196, respectively. Furthermore, we assumed that 1% of immigrants from low prevalence countries, 5% of immigrants from medium prevalence countries, and 14% of immigrants from high prevalence countries are carriers. These are averages of the prevalence ranges according to the definitions of low, medium, and high prevalence as defined by the WHO [13]. We also assumed that 4% of immigrants from low endemic countries are immune but not carriers, and the same holds for 35% of immigrants from medium endemic countries and 66% of immigrants from high endemic countries (Table 3) [11, 14].

In total this amounts to a yearly immigration of between 4 (lower estimate) and 25 (upper estimate) HBV carriers per 100 000 inhabitants. The age distribution of immigrants that was used in the model is given in Table 4 [11].

Table 4. *Age-distribution of immigrants aged 0–60 years as used in the model* [11]

Age	Fraction
0–4	0·074
5–9	0·069
10–14	0·058
15–19	0·090
20–24	0·152
25–29	0·177
30–34	0·142
35–39	0·096
40–44	0·060
45–49	0·037
50–54	0·028
55–59	0·018

Three epidemiological scenarios

Based on the range of prevalence of HBV carriers among immigrants, we considered three different scenarios: a lower bound scenario (1% carriers and 5% immune), a medium scenario (1·7% carriers and 11·9% immune), and an upper bound scenario (6% carriers and 37% immune). The prevalences in the medium scenario were chosen, so that the prevalence of carriers and immunes in the total population in equilibrium equal those measured in The Netherlands in a population based seroprevalence study [15]. In this study it was found that 0·2% of the general population in The Netherlands are carriers of HBV and 2·1% had ever been infected. For each of these three scenarios the endemic steady state can be computed, which is then used as an initial state for different vaccination programmes. We assumed that before the start of universal vaccination the only prevention programme implemented is a routine screening programme for pregnant women, in effect in The Netherlands since 1989. We assumed, that 87% of all infected pregnant women are identified by screening ($M = 0{\cdot}87$), and that 90% of their babies are effectively immunized ($n = 0{\cdot}9$).

Basic reproduction number

The model computes prevalence and yearly incidence of HBV infections based on the above parameter values. Also, the basic reproduction ratio R_0 is computed for the heterosexual and the homosexual population. This quantity describes how many secondary infections an infected individual causes during his entire infectious period in a completely susceptible population. If $R_0 > 1$, the infection can circulate in the population without import of new cases. If $R_0 < 1$, the infection would become extinct without continuous import of new cases from outside. Therefore, the knowledge whether R_0 is larger or smaller than 1 is essential for assessing the effects of prevention

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measures [16]. We derived a new formula for R_0 following methods introduced by Heesterbeek [5] and Diekmann et al. [6] (see Appendix).

RESULTS

Endemic equilibrium before vaccination

For all three scenarios we get $R_0 = 0{\cdot}53$ for the heterosexual population and $R_0 = 2{\cdot}66$ for the homosexual population. This implies that in the heterosexual population the endemic presence of HBV is kept up by continuous immigration of new HBV carriers. Without immigration the virus would die out. In the homosexual population the virus can circulate without import from outside.

In the low prevalence scenario (i.e. a low HBV prevalence among immigrants) the prevalence of carriers in the total population in endemic equilibrium is 0·12%, and the prevalence of immunes is 1·02%. The yearly incidence is 6·75 per 100000 (compare Table 5). In absolute numbers this means for a population of 12·9 million: there is a yearly immigration of 516 carriers; there are 411 new infections in the heterosexual population and 460 new infections in the male homosexual population. Those 871 new infections will result in 56 new carriers (based on the maximum likelihood curve as shown in Fig. 2). The latter are 9·8% of all incoming carriers in the total population. This is the fraction of carriers that can be prevented by universal vaccination (Table 6).

Similarly, for the high prevalence scenario the prevalence of carriers in the total population is 0·67%, the prevalence of immunes is 6·06%, and the yearly incidence is 19·03 per 100000 (see Table 5). Again, in absolute numbers this means for a population of 12·9 million: there is a yearly immigration of 3096 carriers; there are 1989 new infections in the heterosexual population and 466 new infections in the male homosexual population. Those 2455 new infections will result in 169 new carriers (based on the maximum likelihood curve as shown in Fig. 2). The latter are 5·2% of all incoming carriers in the total population. This is the fraction of carriers that can be prevented by universal vaccination (Table 6).

Finally, for the medium prevalence scenario the prevalence of carriers is 0·2% in the total population, the prevalence of immunes is 2·08% and the yearly incidence is 8·76 per 100000 (see Table 5). Translated to a population of 12·9 million this means that there is a yearly immigration of 877 carriers; there are 671 new infections in the heterosexual population and 459 new infections in the male homosexual population. Those 1129 new infections will result in 74 new carriers (based on the maximum likelihood curve as shown in Fig. 2). The latter are 7·8% of all incoming carriers in the total population. This is the fraction of carriers that can be prevented by universal vaccination (Table 6).

Sensitivity analysis

In sensitivity analyses we investigated how the endemic equilibrium depends on model parameters (other than the prevalence of carriers among immigrants). The two most influential sets of parameters were found to be the rates of partner change and the age dependent probability of becoming a carrier after infection. Therefore, we want to present the results of those sensitivity analyses here.

There is large uncertainty in the estimates for the rates of partner change. Not only are the data itself uncertain due to the unreliability of sex survey data in general, also the sample size of the survey in The Netherlands was relatively small (979 heterosexual respondents). This means that the number of respondents per age class and the numbers in high activity core groups are small resulting in uncertain estimates of the parameters.

We computed the endemic equilibrium based on the United Kingdom estimates for the rates of partner change (Tables 1*a*, *c*) and assuming a prevalence of carriers of 1·7% among immigrants. The results are summarized in Table 7*a*. The number of new infections in the population is now 6435 as opposed to 1129 in the simulations based on the estimates from the Dutch data. The number of carriers resulting from transmission within the population is in this case 334, as opposed to 74 in the calculations with the estimates based on Dutch data. Also, the basic reproduction number is somewhat higher at 0·79 for the heterosexual population and 2·92 for the homosexual population. So in general, one can say that the qualitative behaviour of the model is the same for both sets of sexual behaviour parameters (Dutch and UK), but the quantitative results depends sensitively on R_0. Note, that the immigration rate does not influence the values of R_0, so the prevalence of carriers among immigrants will not change the qualitative behaviour of the model.

We also performed a sensitivity analysis to investigate the influence of the age specific rate of becoming carrier on the model dynamics. A first and important result was that replacing the constant value

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Table 5. *Prevalence and incidence in endemic steady state for three scenarios*

	Heterosexual population	Homosexual men	Total population
Low prevalence scenario			
Carriers (%)	0·116	0·405	0·12
Immune (%)	0·906	6·4	1·02
Yearly incidence (per 100000)	3·25	178·3	6·75
R_0	0·53	2·66	—*
No. new infections	411	460	871
Medium prevalence scenario			
Carriers (%)	0·195	0·48	0·2
Immune (%)	1·98	7·3	2·08
Yearly incidence (per 100000)	5·3	177·8	8·76
R_0	0·53	2·66	—*
No. new infections	671	459	1129
High prevalence scenario			
Carriers (%)	0·66	0·91	0·67
Immune (%)	5·97	10·67	6·06
Yearly incidence (per 100000)	15·73	180·6	19·03
R_0	0·53	2·66	—*
No. new infections	1989	466	2455

* As there is no interaction between hetero- and homosexual populations in the model, it does not make sense to compute R_0 for the total population.

Table 6. *Yearly inflow of carriers for the three epidemiological scenarios*

	Low prevalence	Medium prevalence	High prevalence
No. carriers following transmission in The Netherlands	56	74	169
No. carriers immigrating	516	877	3096
% preventable by vaccination in The Netherlands	9·8	7·8	5·2

Table 7. *Sensitivity analysis for* (*a*) *rates of partner change*, (*b*) *the probability of becoming carrier after infection*

	Heterosexual population	Homosexual men	Total population
(a) Rates of partner change			
Carriers (%)	0·27	1·1	0·29
Immune (%)	3·5	21·1	3·85
Yearly incidence (per 100000)	36·4	711·9	49·9
R_0	0·79	2·92	—
No. new infections	4598	1837	6435
(b) Probability of becoming a carrier			
Carriers (%)	0·21	0·77	0·23
Immune (%)	2·09	8·67	2·22
Yearly incidence (per 100000)	7·3	221	11·6
R_0	0·70	3·59	—
No. new infections	927	570	1497

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Table 8. R_0 *values for the heterosexual population for different assumptions about the probability of becoming carrier after infection. The results in the first row are based on the UK sexual behaviour parameters* (*Table 1a*), *in the second row on those of The Netherlands* (*Table 1b*)

	Constant	Maximum likelihood	Upper bound	Lower bound
United Kingdom	1·11	0·79	1·07	0·60
The Netherlands	0·69	0·53	0·70	0·41

of 0·1 for the rate of becoming carrier by an age-dependent function as described in the Methods section, had a major impact on the disease dynamics, because the value of R_0 for the heterosexual population shifted from above 1 to below 1. We therefore performed a sensitivity analysis with respect to the parameters γ_1 and γ_2 in the function $p(a)$. For both the United Kingdom and the Dutch sexual behaviour parameters we computed four values of R_0, namely for a constant probability of becoming carrier of 0·1, for the age-dependent probability given by the maximum likelihood estimate for $p(a)$ ($\gamma_1 = 0{\cdot}645$ and $\gamma_2 = 0{\cdot}455$), and for upper and lower bounds of $p(a)$ based on the 95% confidence region for γ_1 and γ_2 (upper bound $\gamma_1 = 0{\cdot}724$ and $\gamma_2 = 0{\cdot}366$, lower bound $\gamma_1 = 0{\cdot}570$ and $\gamma_2 = 0{\cdot}546$). The resulting values are summarized in Table 8. We conclude that we cannot rule out the possibility that R_0 is larger than 1 for the United Kingdom sexual parameter estimates; for the Dutch estimates the conclusion that $R_0 < 1$ seems robust. In any case, taking a constant probability of 0·1 for becoming carrier after sexual transmission produced an overestimate of R_0 and therefore an overestimate of the incidence of hepatitis B infections. To see what the consequences would be of a higher R_0 for the Dutch population, we did a full simulation (heterosexual and homosexual populations) on the basis of the upper bound estimates. For the heterosexual population R_0 is then 0·7 and for the homosexual population R_0 is 3·59. In Table 7*b* the simulation results for this set of parameters is summarized (again with the assumption of 1·7% prevalence of carriers among immigrants).

Effects of vaccination

Subsequently, we introduced universal vaccination of newborns in the model population. In the model, the parameter Q denotes the fraction of all newborns, that is effectively immunized by universal vaccination. This parameter describes a product of vaccination coverage and vaccine efficacy (after 1, 2, or 3 doses of vaccine). We investigated for different values of Q (0·8, 0·9, 0·95) the effect of vaccination on the prevalence of carriers and on the incidence of new infections in the 50 years after the start of the vaccination programme.

As shown in Figure 4 it takes about 20 years for the first effects to be apparent after introduction of universal vaccination. After 50 years of vaccination the prevalence of carriers is reduced by around 7·5% in the lower bound scenario and by 4·5% in the upper bound scenario. The reason that the effect is so small lies in the fact that the prevalence of carriers is mainly determined by the immigration of new carriers into the population, and this cannot be influenced by vaccination within the population.

In Figure 5 the effect is shown of universal vaccination on the yearly incidence of new infections. In the lower bound scenario incidence drops after 50 years of universal vaccination from 6·8 to 1·8 per 100000, if 95% of all newborns are effectively immunized each year. In the upper bound scenario, incidence drops from 19·0 to 6·3 per 100000. So we see a reduction by 74% in the lower bound scenario and a reduction of around 67% in the upper bound scenario. The age-distribution of new infections shifts somewhat towards older age classes, and there is a slight increase of the percentage of infections that are caused by vertical transmission. The latter, however, remains below 3% in all cases. The shift in the age distribution towards older age classes can be attributed to our assumption that immunity after vaccination does not last lifelong, implying that vaccinated individuals can become susceptible again with increasing age.

In summary, we conclude that the effect of universal vaccination on the prevalence of carriers is small, and therefore also the impact on prevention of long-term complications such as liver cirrhosis and liver cancer. It also means that the force of infection will not decrease substantially with vaccination, and therefore that the indirect effects of vaccination via herd immunity are small. Here we assume that the prevalence of carriers among immigrants stays constant over the 50 years after start of the vaccination programme. The effects on incidence are larger than the effects on prevalence, because vaccination can prevent transmission of infection within the popu-

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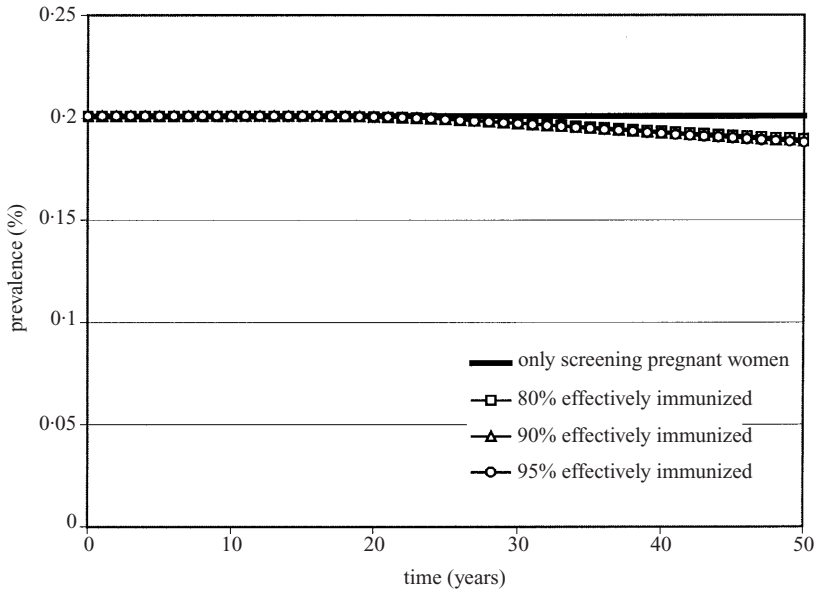

Fig. 4. The prevalence of hepatitis B carriers over time after introduction of universal infant vaccination in year 0 for the medium prevalence scenario.

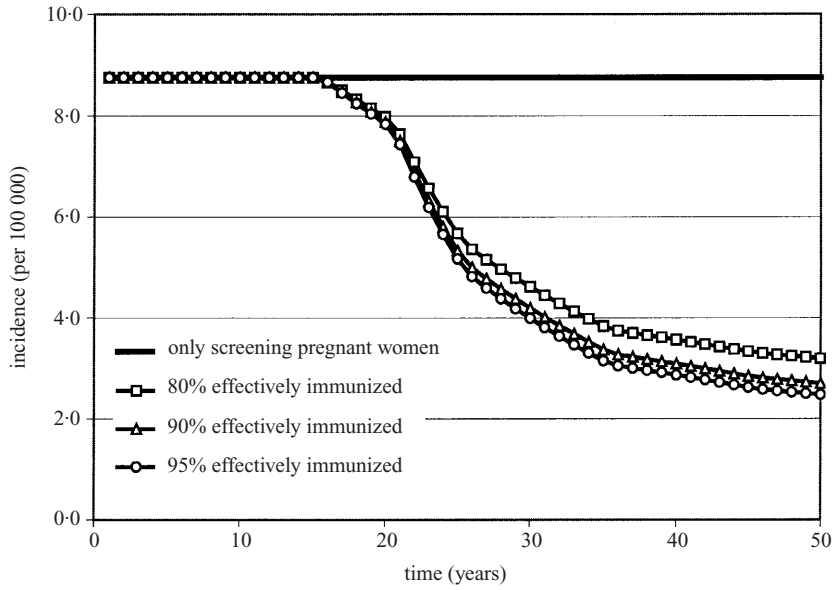

Fig. 5. The yearly incidence of hepatitis B infection over time after introduction of universal infant vaccination in year 0 for the medium prevalence scenario.

lation. But again, this only has a minor influence on the force of infection, because the force of infection is mainly determined by the prevalence of carriers in the population.

DISCUSSION

We conclude that the present situation in the Netherlands is as follows: In the heterosexual population R_0 is smaller than 1, in the homosexual population it is larger than 1. There is a yearly incidence of between 6 and 19 per 100 000 attributable to sexual and vertical transmission. This implies that there are between 56 and 169 new carriers per year due to transmission within the country. At the same time immigration of carriers takes place with a rate of 4 to 25 per 100 000 per year. Consequently, a fraction of less than 10% of all carriers can be prevented by the introduction of universal infant vaccination in The Netherlands.

To get some idea about how reliable those conclu-

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sions are, we have to compare the simulation results for the endemic equilibrium before the start of vaccination with epidemiological data from The Netherlands. Based on the notification of around 250 cases of acute hepatitis B infection per year, one can estimate that there are between 750 and 1250 new infections per year, depending on what fraction of all infections are assumed to be subclinical. This amounts to an incidence of between 4·7 and 8·1 per 100000 per year. While this estimate accounts for the large fraction of infections that go unnoticed because they are subclinical, it does not take underreporting and underdiagnosis into account, so it is plausible that it is still an underestimate of the true incidence. Also, these figures are somewhat lower than the incidence that our model computes for the endemic steady state in the medium prevalence scenario. In a seroprevalence study of a representative sample of the general population in The Netherlands, the prevalence of carriers was estimated to be 0·2%, and the prevalence of anti-HBc positives 2·1% [15]. Those figures lie in the range covered by our lower and upper bound scenarios. That fact supports our choice of model parameters, because those bounds were derived without making use of the data from the seroprevalence study, but are based solely on the parameter estimates for sexual behaviour, immigration, age-specific probability of becoming a carrier, and transmission of infection. Our medium scenario was chosen, so that the prevalence of carriers equalled 0·2%. For this medium scenario the incidence in endemic equilibrium is 8·8 per 100000, possibly indicating an underreporting of up to 50%.

In the screening of pregnant women it was found that 88% of all HBV carriers have a background relating to medium or high endemic countries [17]. This confirms the conclusion from our model that the prevalence of HBV carriers is determined mainly by immigration from endemic countries. Furthermore, in a study conducted recently in The Netherlands, in which sources of acute hepatitis B infections were investigated, it was found that around 60% of sex partners of heterosexual cases and only around 18% of sex partners of infected homosexual men were from high or medium endemic countries (unpublished observations). This would support our hypothesis that transmission chains are short in the heterosexual population, and importation of new cases plays a major role, while in the population of homosexual men HBV can circulate and therefore transmission chains are longer.

Below we discuss possible reasons for uncertainty in our model results that should be kept in mind in interpreting our quantitative results.

Risk groups and transmission routes

The model describes only transmission via sexual contact and vertical transmission from mother to newborn child. It does not incorporate horizontal transmission within families, or infection of persons travelling to highly endemic areas. Furthermore, the model does not explicitly describe risk groups other than core groups of highly sexually active heterosexual and homosexual persons, such as injecting drug users, certain groups of patients and health care workers. Therefore, the prevalences and incidences found in the model could be lower than found in reality. In preliminary results from a case-control study in The Netherlands [18] it was found that approximately 60% of all new infections can be attributed to sexual transmission.

R_0 *and small core groups*

The structure of the model with respect to its description of sexual behaviour is in many aspects an abstraction of reality based on some arbitrary choices of how to quantify this reality. These choices obviously have some influence on the simulation results. One of those choices is the subdivision of the population in six activity classes. The fractions of the population in each of those classes can in principle be chosen freely, and then the parameters can be estimated based on that choice. A subdivision into six classes is relatively coarse and leads in our case to a value of R_0 that is smaller than 1 for the heterosexual population. This does not exclude the possibility, however, that there are small subgroups in the heterosexual population for which R_0 is larger than 1, and where continued circulation of the virus can occur. The subgroup with the highest level of sexual activity in the model contains 0·1% of the population. For the population of The Netherlands this amounts to a group of around 10000 sexually active persons aged between 15 and 60 years. By choosing a subdivision into more than six activity classes one might obtain better quantitative simulation results, but this requires larger data sets to get good estimates of the model parameters.

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Uncertainty in sexual behaviour parameters

Besides the uncertainties related to model abstractions there are problems with the data on which the parameter estimates are based. One problem is that there are hardly any data about sexual behaviour in The Netherlands based on representative samples from the population. The only larger survey was conducted in 1989 and included 1001 respondents [7]. The number is clearly much too small to (a) include a sufficiently large group of homosexual men, and (b) include enough persons from highly sexually active core groups. From two cohort studies in Amsterdam there are data about sexual behaviour of homosexual men [19, 20]. It is reasonable to expect that highly sexually active men are overrepresented in those studies. Another problem in estimating the parameters is that the estimation method relies on the assumption that the rates of partner change are constant over time intervals of 5 years. Furthermore, a gamma distribution was fitted to the data per age class, also in some respects an arbitrary choice.

Sexual behaviour of immigrants

In the model as it is implemented now, it is assumed that sexual behaviour of immigrants does not differ from that of the resident population. There are indications, however, that immigrants might have higher rates of partner change on average than the resident population [21]. If this is true in general (up to now only specific ethnic groups in some parts of Amsterdam have been studied), the incidence of new infections in The Netherlands could be higher than is now computed by the model. Also, within certain groups of immigrants R_0 might be larger than 1. Furthermore, the model assumes homogeneous mixing of immigrants with the resident population, which is most certainly not the case in reality. The homogeneous mixing assumption could result in an overestimation of the prevalence and especially the incidence by the model.

Sensitivity analyses

We have presented sensitivity analyses with respect to the parameters for sexual behaviour and for the probability of becoming a carrier after infection. Those two sets of parameters seemed to have the largest influence on R_0 and on the transmission dynamics. In the first sensitivity analysis it turns out that the sexual behaviour parameters have a large influence on the incidence (Table 7*a*). The increase of incidence for higher sexual activity parameters can be explained by the increase of R_0 in both hetero- and homosexual populations. The prevalence of carriers remains in the range of the confidence interval of the estimate obtained in the seroprevalence study of the Dutch population, but the incidence would now suggest an underreporting of around 90%.

In the second sensitivity analysis we compared a constant probability of becoming carrier after infection with various age-dependent functions in their impact on the value of the basic reproduction ratio R_0. We did this for both the United Kingdom and the Dutch sexual behaviour parameters. Our conclusions are that (a) taking a constant probability of becoming carrier after sexual tranmission of 0·1 results in an overestimate of R_0 and the incidence of hepatitis B infections; (b) for the Dutch sexual behaviour parameters the conclusion that R_0 is smaller than one seems to be robust; (c) for a worst case scenario (United Kingdom sexual behaviour parameters in combination with an upper bound estimate for the age-dependent probability of becoming carrier) we cannot rule out that R_0 is just above 1. For both sensitivity analyses summarized in Table 7, R_0 for the heterosexual population remains below 1, which is the reason for the large influence of immigration on the prevalence of carriers in the population. The results of the sensitivity analyses supports our view that the model describes well the qualitative dynamics of hepatitis B transmission in a low prevalence country like The Netherlands.

It is interesting in this respect to note the difference between our results and those in the original paper by Williams et al. [2]. Using a constant probability of 10% of becoming carrier after being infected by sexual transmission those authors found that R_0 in the heterosexual population is larger than 1. This is also the case with our improved formula for R_0 (see appendix) that yields a value of $R_0 = 1{\cdot}11$ for the heterosexual population and $R_0 = 4{\cdot}67$ for the homosexual population. The difference between those values and the ones given in [2] is only due to the different ways of calculating R_0.

Conclusions and future research

In The Netherlands HBV circulates only in high risk groups such as homosexual men and small groups of sexually very active heterosexuals. In a large part of the general population the virus cannot maintain itself

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without import of new cases from outside. As a consequence, the prevalence of HBV carriers in the heterosexual population is determined mainly by immigration of carriers from highly endemic countries and/or transmission in those countries. In the homosexual population importation of new cases plays a minor role in determining prevalence.

After introduction of universal infant vaccination it takes 15–20 years before effects on prevalence and incidence are noticeable. Universal vaccination can have a considerable impact on the incidence of new infections within the population, but the prevalence of HBV carriers will not decrease much as long as the prevalence in those highly endemic countries where immigrants come from, does not change. Therefore also the force of infection will hardly decrease after vaccination. This implies that vaccination has to be kept up over many decades, to keep up the protection of the population. The percentage of new carriers that can be prevented by vaccination is small. This implies that a large part of the costs for health care that are a consequence of HBV carriage will remain in the future.

In currently ongoing research we are investigating the importance of horizontal transmission among young children for the effectiveness of vaccination programmes. A large fraction of all infections in young children are subclinical [22], and, in addition, a large fraction become carriers once they are infected. Therefore the impact of this age group on the cost-effectiveness may be larger than one would expect on the basis of the number of notified cases in these age groups. We expect, however, that including horizontal transmission will not change the conclusions of this paper, because persons infected by horizontal transmission will, in general, be part of the population with low sexual activity, and therefore cause few secondary transmissions.

ACKNOWLEDGEMENTS

We would like to thank Irene Veldhuijzen, Maarten Postma, Jeroen Struijs, John Williams, Hans Jager and André de Roos for their contributions to the work presented in this paper.

APPENDIX

Calculation of R_0 for the hepatitis B model

We follow the notation used by Williams et al. [2]. The parameters used in the calculation of R_0 are

σ_1 rate of moving from latent to acute state
σ_2 rate of moving from acute to carrier state
σ_3 rate of moving from carrier to immune state
$c_k(a)$ rate of partner change for individuals of age a in activity class k
β_1 probability of transmission from partnership with acutely infected individual
β_2 probability of transmission from partnership with carrier individual
b_1 proportion of babies, born to acutely infected mothers, infected perinatally
b_2 proportion of babies, born to carrier mothers, infected perinatally
$\nu_g(a)$ fertility rate at age a for sex g

Population structure and basic reproduction ratio

The population is structured by three variables: sex, age and activity class.

(1) Sex g takes the values 'female' and 'male'; a sex ratio of 1 to 1 is assumed and complete symmetry of male and female heterosexual subpopulations, i.e this variable can be neglected except for computing the fertility.
(2) Age a takes values in $[0, L]$ with $L = 60$. The population is uniformly distributed on that age interval.
(3) Activity class k takes values in $\{1, \ldots, 6\}$ with constant fractions in the different activity classes denoted by ω_k (with $\Sigma_k \omega_k = 1$).

R_0 for the heterosexual population is computed as the dominant eigenvalue of a 2×2-matrix consisting of the elements R^a_{0s} (secondary infections produced by sexual transmission by an individual infected as an adult), R^a_{0v} (secondary infections produced by vertical transmission by an individual infected as an adult), R^b_{0s} (secondary infections produced by sexual transmission by an individual infected as an infant), and R^b_{0v} (secondary infections produced by vertical transmission by an individual infected as an infant). The matrix is given by

$$\begin{pmatrix} R^a_{0s} & R^a_{0v} \\ R^b_{0s} & R^b_{0v} \end{pmatrix}.$$

So we get

$$R_0 = \tfrac{1}{2}\left((R^a_{0s} + R^b_{0v}) + \sqrt{(R^a_{0s} - R^b_{0v})^2 + 4R^a_{0v}R^b_{0s}}\right). \qquad (1)$$

For the population of homosexual men the basic reproduction ratio simply equals R^a_{0s}, because there is no vertical infection. Those homosexual men who were themselves infected by infected mothers at birth are

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neglected for this analysis, because we are interested in the possible persistence of the infectious disease in the population independent of transmission from external sources.

We need to know the probability distribution for an individual who was infected τ time units ago, to be in state Y (acutely infected) or in state C (carrier) now. This distribution can be computed from the model equations by integrating the appropriate equations under the assumption that the individuals is in state H (latent) at $\tau = 0$ with probability 1. If we denote with $P_Y(\tau)$ and $P_C(\tau, a)$ the probabilities to be in Y and C, respectively, we get

$$P_Y(\tau) = \frac{\sigma_1}{\sigma_2 - \sigma_1}(e^{-\sigma_1\tau} - e^{-\sigma_2\tau})$$

$$P_C(\tau, a) = p(a)\frac{\sigma_1\sigma_2}{\sigma_2 - \sigma_1}\left(\frac{1}{\sigma_2 - \sigma_3}(e^{-\sigma_2\tau} - e^{-\sigma_3\tau}) - \frac{1}{\sigma_1 - \sigma_3}(e^{-\sigma_1\tau} - e^{-\sigma_3\tau})\right).$$

The function $p(a)$ denotes the age-dependent fraction of individuals who become a carrier after being acutely infected. This is given as

$$p(a) = \begin{cases} \gamma_0 & \text{for } a = 0 \\ \exp(-\gamma_1 a^{\gamma_2}) & \text{for } a > 0 \end{cases}$$

with parameters $\gamma_0, \gamma_1, \gamma_2 > 0$.

Sexual transmission

The model assumes separable mixing with respect to sexual activity, i.e. the infectivity function $A(\tau, \xi, \eta)$ relating to that transmission route can be written as a product of a function $f(\xi)$ that only depends on the state of the susceptible individual, and a function $B(\tau, \eta)$ that only depends on the state of the infected individual

$$A(\tau, \xi, \eta) = f(\xi)B(\tau, \eta).$$

The function $A(\tau, \xi, \eta)$ describes the rate of transmission between a susceptible individual of type ξ and an infectious individual of type η, who was infected τ time units ago, where $\xi = (g, a, k)$ is the state of the susceptible and $\eta = (g, a, k)$ the state of the infected individual. The separable mixing property of the model, that follows from the formulation of the model equations in [2], allows us to apply the methods described in Heesterbeek [5] for computing the basic reproduction rate in age structured populations. Based on those methods, R^a_{0s} can be computed as (sex is neglected because the model is symmetric)

$$R^a_{0s} = \sum_k \int_0^L f(k, \alpha)N(k, \alpha) \times \int_0^{L-a} B(\tau, k, \alpha + \tau)\mathrm{d}\tau\, \mathrm{d}\alpha,$$

where $N(k, a)$ denotes the distribution of the population over the activity classes and age. So we get

$$R^a_{0s} = \sum_{k=1}^{6} \int_0^L \frac{\omega_k}{L}\frac{c_k(\alpha)}{K}\int_0^{L-\alpha} c_k(\alpha + \tau) \times (\beta_1 P_Y(\tau) + \beta_2 P_C(\tau, \alpha))\mathrm{d}\tau\, \mathrm{d}\alpha \quad (2)$$

with

$$K = \frac{1}{L}\sum_{k=1}^{6}\int_0^L \omega_k c_k(\alpha)\mathrm{d}\alpha.$$

This formula does not depend on the total population size, because the model assumes that transmission depends on the fraction of infected individuals and not on their absolute number. In other words, the model does not assume mass action, but assumes a density dependent force of infection. So then it is not the number of susceptible individuals in the formula for R_0, but only the distribution over the possible states that matters.

Similarly we can compute

$$R^b_{0s} = \sum_{k=1}^{6} \omega_k \int_0^L c_k(\tau)(\beta_1 P_Y(\tau) + \beta_2 P_C(\tau, 0))\mathrm{d}\tau \quad (3)$$

for those individuals infected at birth.

Vertical transmission

We get

$$R^a_{0v} = \sum_{k=1}^{6} \int_0^L \frac{\omega_k}{L}\frac{c_k(\alpha)}{K}\int_0^{L-\alpha} \nu_g(\alpha + \tau) \times (b_1 P_Y(\tau) + b_2 P_C(\tau, \alpha))\mathrm{d}\tau\, \mathrm{d}\alpha \quad (4)$$

and

$$R^b_{0v} = \int_0^L \nu_g(\tau)(b_1 P_Y(\tau) + b_2 P_C(\tau, 0))\mathrm{d}\tau. \quad (5)$$

Explicit calculation of the integrals

As the functions in all integrals consist of step-functions defined over age classes and exponentials, all integrals can be evaluated explicitly. (For this

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purpose we interpret $p(a)$ as a stepfunction given on yearly intervals and taking the value of p in the midpoint of the interval.) First, the integrals of $P_Y(\tau)$ and $P_C(\tau, a)$ are given by

$$\begin{aligned} Q_Y(\tau) &= \int P_Y(s)\mathrm{d}s \\ &= \frac{\sigma_1}{\sigma_2-\sigma_1}\left(\frac{1}{\sigma_2}\mathrm{e}^{-\sigma_2\tau}-\frac{1}{\sigma_1}\mathrm{e}^{-\sigma_1\tau}\right) \\ Q_C(\tau, a) &= \int P_C(s, a)\mathrm{d}s \\ &= p(a)\frac{\sigma_1\sigma_2}{\sigma_2-\sigma_1}\left(\frac{1}{\sigma_2-\sigma_3}\left(\frac{1}{\sigma_3}\mathrm{e}^{-\sigma_3\tau}-\frac{1}{\sigma_2}\mathrm{e}^{-\sigma_2\tau}\right)\right. \\ &\quad \left.-\frac{1}{(\sigma_1-\sigma_3)}\left(\frac{1}{\sigma_3}\mathrm{e}^{-\sigma_3\tau}-\frac{1}{\sigma_1}\mathrm{e}^{-\sigma_1\tau}\right)\right). \end{aligned}$$

We get

$$\begin{aligned} R^a_{0s} &= \sum_{k=1}^{6}\sum_{i=0}^{L-1}\frac{\omega_k}{L}\frac{c_k(i)}{K} \\ &\quad \times\int_0^1(-1)\left(\sum_{j=0}^{L-1-i}c_k(i+j)(\beta_1 P_Y(1-s+j)\right. \\ &\quad \left.+\beta_2 P_C(1-s+j, i))\right)\mathrm{d}s \\ &= \sum_{k=1}^{6}\sum_{i=0}^{L-1}\frac{\omega_k}{L}\frac{c_k(i)}{K} \\ &\quad \times\sum_{j=0}^{L-1-i}c_k(i+j)(\beta_1(Q_Y(1+j)-Q_Y(j)) \\ &\quad +\beta_2(Q_C(1+j, i)-Q_C(j, i))) \end{aligned}$$

and

$$\begin{aligned} R^a_{0v} &= \sum_{k=1}^{6}\sum_{i=0}^{L-1}\frac{\omega_k}{L}\frac{c_k(i)}{K} \\ &\quad \times\int_0^1(-1)\left(\sum_{j=0}^{L-1-i}\nu_g(i+j)(b_1 P_Y(1-s+j)\right. \\ &\quad \left.+b_2 P_C(1-s+j, i))\right)\mathrm{d}s \\ &= \sum_{k=1}^{6}\sum_{i=0}^{L-1}\frac{\omega_k}{L}\frac{c_k(i)}{K} \\ &\quad \times\sum_{j=0}^{L-1-i}\nu_g(i+j)\,(b_1(Q_Y(1+j)-Q_Y(j)) \\ &\quad +b_2(Q_C(1+j, i)-Q_C(j, i))). \end{aligned}$$

Furthermore

$$\begin{aligned} R^b_{0s} &= \sum_{k=1}^{6}\omega_k\sum_{i=0}^{L-1}c_k(i)(\beta_1(Q_Y(i+1)-Q_Y(i)) \\ &\quad +\beta_2(Q_C(i+1, 0)-Q_C(i, 0))) \\ R^b_{0v} &= \sum_{i=0}^{L-1}\nu_g(i)(b_1(Q_Y(i+1)-Q_Y(i)) \\ &\quad +b_2(Q_C(i+1, 0)-Q_C(i, 0))). \end{aligned}$$

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