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The transmission dynamics of hepatitis B in the UK: a mathematical model for evaluating costs and effectiveness of immunization programmes

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SUMMARY

Complex hepatitis B (HBV) epidemiology makes it difficult to evaluate and compare effectiveness of different immunization policies. A method for doing so is presented using a mathematical model of HBV transmission dynamics which can represent universal infant and adolescent vaccination strategies and those targeted at genito-urinary (GU) clinic attenders and infants born to infectious mothers. Model structure, epidemiological underpinning, and parameterization, are described. Data from the UK National Survey of Sexual Attitudes and Lifestyles is used to define patterns of sexual activity and GU clinic attendance; data deficiencies are discussed, in particular that of UK seroprevalence of HBV markers stratified by age, sex, and risk factors. General model predictions of endemic HBV marker prevalence in homosexual and heterosexual populations seem consistent with published UK data. The simulations exhibit non-linearities in the impact of different vaccination strategies. Estimated number of carriers prevented per vaccine dose for each strategy provides a measure of costs and benefits, varying temporally over the course of a programme, and with level of vaccine coverage. Screening before vaccination markedly increases payback per dose in homosexuals but not in heterosexuals; mass infant vaccination gives the poorest effectiveness ratio and vaccination of infants after antenatal screening the best; in general, increasing vaccine coverage yields lower pay-back per dose. The model provides a useful framework for evaluating costs and benefits of immunization programmes, but for precise quantitative comparison more UK epidemiological data is urgently needed.

INTRODUCTION

The epidemiology of hepatitis B (HBV) is made complex by a variety of factors including the presence of multiple risk groups and routes of transmission, heterogeneity in behaviour, such as sexual contact patterns, and processes, such as the probability of developing chronic carriage following infection, which are age-dependent [1, 2]. In the UK for example, HBV transmission appears to be predominantly via sexual contact, the sharing of unsterilized hypodermic needles (leading to contact with contaminated blood), from hazards associated with occupation and, in the case of children born to carrier mothers, from the intimacy of maternal and neonatal blood at parturition [3]. Thus, in the UK, HBV infection is associated with specific risk groups. In particular, these are intravenous drug users (IVUs), homosexual men, and heterosexuals with high rates of sexual partner change. The Communicable Disease Sur-

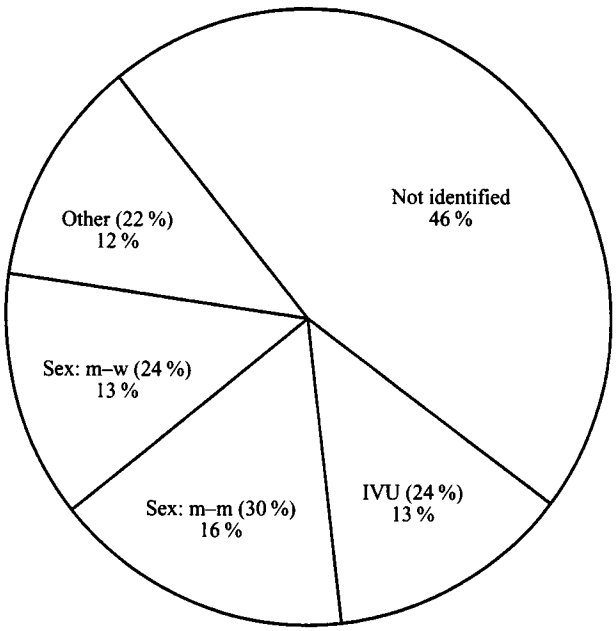

Fig. 1. Pie chart showing categorization of cases of HBV reported to the UK Communicable Disease Surveillance Centre (CDSC) (Fairley CK, Heptonstall J, personal communication); the percentage breakdown of those cases for which a risk was identified is shown in brackets.

veillance Centre (CDSC) of the Public Health Laboratory Service (PHLS) receives reports of cases of acute HBV in England and Wales. Over the period 1990–4, of reports for which an exposure risk was identified, 24% were associated with IVU, 24% with sex between men and women and 30% with sex between men (Fig. 1) (Fairley CK, Heptonstall J, personal communication). Other risk groups include ethnic minorities originating from high HBV endemicity countries (particularly from SE Asia) [4], and occupational groups such as dentists, surgeons and laboratory workers [5]. The role of perinatal transmission in the endemic spread of HBV may be disproportionately large in relation to the incidence of infection via this route because infants thus infected are at much higher risk of becoming chronic carriers [2]. The complexity of the situation is amplified by virtue of interactions between these risk groups.

In the UK where the prevalence of HBV in the general population is low (in comparison with southern European countries, the present immunization policy recognizes the risk group nature of transmission, and the importance of targeting particular sections of the community who are not only most likely to become infected but also to transmit infection to others. Immunization may be offered selectively to individuals who are deemed to be at heightened risk of exposure as a result of occupation (e.g. laboratory workers), lifestyle characteristics (e.g. intravenous drug use or homosexuality), or close contact with a case or carrier. The latter would include babies at risk of infection by being born to mothers who have acute infection during pregnancy or are chronic carriers; to ensure effective immunization in these circumstances administration of hepatitis B immunoglobulin (HBIG) is also recommended [6]. These are, however, only recommendations and no co-ordinated national programme of HBV vaccination is in force at present.

The World Health Organization has recommended that universal hepatitis B vaccination should be integrated into national immunization programmes in all countries by 1997 [7]. Within Europe a number of countries such as Spain and Italy, known to have relatively high endemic HBV prevalence for the region, have initiated adolescent or combined adolescent and infant vaccination programmes [8, 9]. There is clearly a need at present to reassess HBV immunization policy in the UK.

The options which might be considered in the UK are: (i) to maintain the present policy only; (ii) to adopt a universal infant or adolescent vaccination programme; (iii) to implement a national programme of antenatal screening to identify carrier mothers whose infants would be followed up; (iv) to increase the effort put into targeting those most at risk or (v) some combination of (i) to (iv). The choice of strategy might best be made on the basis of an assessment of the relative effectiveness of each option in relation to costs and benefits in the UK setting. However, this requires the making of quantitative predictions about the impact of different vaccination regimens on the incidence of infection and disease.

Simple linear models, applying a direct relationship between number of vaccine doses given and projected overall incidence or number of cases prevented for any level of vaccine coverage (e.g. [10]), provide some insights, but are not sufficient to capture the subtleties of the transmission dynamics of HBV plus the associated risks of serious disease (11). The complexities of HBV epidemiology outlined above make it difficult to predict the impact on incidence of a particular control strategy with such models. Vaccination affects not only the individual concerned but feeds back into the dynamics of the system by eliminating the possibility of that individual infecting another. Thus, immunisation reduces the force of infection for all individuals (the so-called 'herd

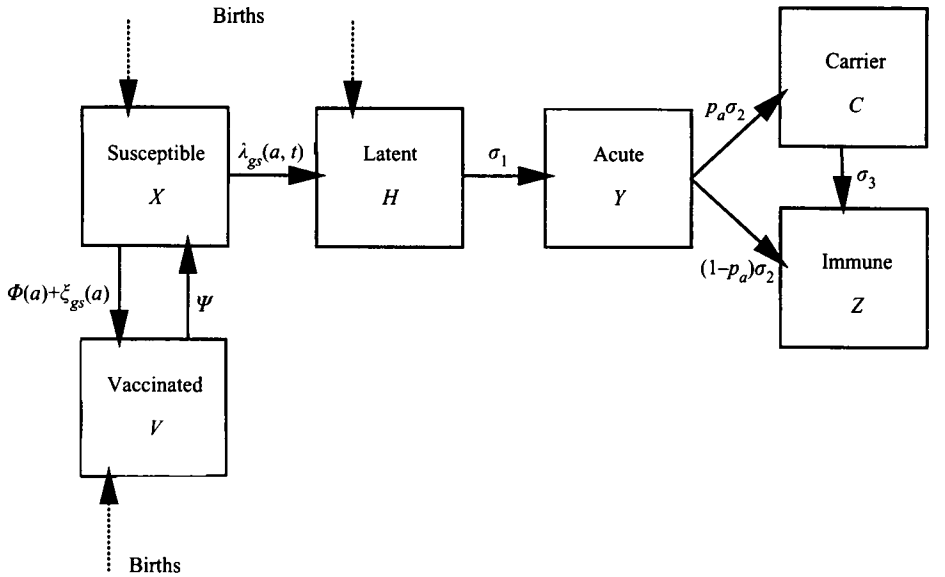

Fig. 2. Flow chart showing the six compartments of the model of HBV transmission dynamics. Births into the system are indicated by broken arrows. Other arrows indicate epidemiological and vaccine-associated transitions. See text and Appendix for details.

immunity' effect) [12, 13]. The more heterogeneous the population, for example in the context of rates of sexual partner change and the form of mixing between different activity and risk groups, the more complex will be the consequences of this herd immunity effect. Mathematical models of the transmission dynamics of HBV have the capacity to mimic such complexity, and are able to simulate temporal changes brought about by any given vaccination programme [12].

In this paper we consider an enhanced version of a previous model used to evaluate the effectiveness of different immunisation programmes in the UK [14]. The present version includes all options for immunisation listed above and both sexual and perinatal transmission routes, and considers separately, as before, heterosexuals and homosexuals, two of the three main groups involved in HBV transmission in the community. We make use of data on rates of acquisition of sexual partners stratified by age from the recent National Survey of Sexual Attitudes and Lifestyles (NATSSAL) in the UK [15]. In the absence of detailed data for the UK, other parameters which are less dependent on national behaviour patterns are obtained from a variety of sources, in particular from studies in the USA. Published data on the prevalence of HBV markers has been reviewed and used to provide a check on the model predictions of endemic prevalence of infection. A summary of these data is shown in the results section (Table 3) [16–27], illustrating the wide range in marker prevalence for different risk groups in the population. The available serological data is, however, very coarsely stratified by age, if at all, and is often not representative of the wider heterosexual or homosexual populations. There is clearly an urgent need to increase the quality of epidemiological data on HBV in the UK, particularly in the form of age-stratified seroprevalence of different markers in different risk groups.

This model is used to obtain epidemiological insight into the implications of different vaccination options, highlighting the interplay between instances of specific costs (doses of vaccine delivered) and effectiveness (numbers of carrier cases prevented), and illustrating the nature of non-linearities that exist in the effectiveness of different levels of coverage of vaccine for a particular strategy. Although of a preliminary nature, the comparison of model projections under different vaccination regimens affords a basis by which to begin the quantitative assessment of the comparative effectiveness of these regimens.

METHODS AND MATERIALS

Mathematical model

The compartmental model of sexual transmission dynamics of HBV originally described by Anderson and colleagues [14] is a partial differential equation model whose numerical solution provides the required projections of the incidence and prevalence of infection. The present model also incorporates age-

Table 1. *Parameters relating to infection, fertility and vaccination*

Transmission risk (/year/partnership) [14, 28]		
	Heterosexual	Homosexuals
Acute infection (β_1)	0·33	0·46
Carrier (β_2)	0·25	0·30
Rates of leaving compartments (/person/year) [14, 29]		
Incubation (σ_1)	8·667	
Acute infection (σ_2)	3·467	
Carrier state (σ_3)	0·015	
Proportion of acutes becoming carriers [2]		
Adult (p_1)	0·1	
Infant (p_2)	0·885	
Proportion of babies born infected		
Acute mother (b_1)	0·724	
Carrier mother (b_2)	0·115	

Age-dependent fertility*

Age class (yr)	Fertility (/person/year)
15–20	0·031
20–25	0·093
25–30	0·123
30–35	0·081
35–40	0·028
40–45	0·005

Vaccination of adolescents and GU clinic attenders

Doses received (i)	Proportion given i doses (100% compliance)	Proportion receiving i doses who are effectively immunized	Proportion effectively immunized under i dose schedule
1	1·0	0·4	0·16
2	0·6	0·7	0·23
3	0·5	0·9	0·68

Proportion of adolescents/clinic attenders receiving at least the first dose of a three dose schedule who go on to become effectively vaccinated (Q) [14]: 0·68.

* Source: 1983–92 Office of Population Censuses and Surveys data for England and Wales; the rate for each age class has been scaled by the same amount to ensure constant model population size whilst retaining the relationship between the rates for the different age classes.

dependent fertility and vertical (perinatal) transmission, and includes options to allow for the mass vaccination of neonates and vaccination targeted at infants identified as being at risk of perinatal infection. Following birth the model includes no risk of infection until the onset of sexual activity. The formulation of the model allows vaccine based immunity to wane at a constant rate, but here vaccine immunity is assumed to be lifelong. Heterosexual and homosexual segments of the population are modelled separately, exhibiting contrasting rates of sexual partner change and transmission risk, and, as a result, different profiles of incidence and prevalence of carriers.

The model has six infection and immunity related population compartments, namely, those susceptible to infection (X), latently infected (H), acutely infected (Y), immune following infection (Z), chronic carriers (C), and immune following vaccination (V) (Fig. 2). A proportion, p_a of acutely infected individuals in age class a become carriers, the remainder recovering to the immune class. The population is fully age-structured with 12 age groups (each spanning 5 years) each having six classes with differing rates of acquisition of sexual partners. Births occur into three compartments: susceptible, vaccinated immune (following vaccination after antenatal screening or mass

Table 2. *Parameters relating to sexual behaviour [14, 15]*

Heterosexuals						
Activity class	1	2	3	4	5	6
Proportion in class	0·273	0·286	0·303	0·132	0·005	0·001
Age range	Rate of acquisition of new partners (/year)					
15–20	0·035	0·295	1·155	3·514	8·589	12·549
20–25	0·036	0·305	1·193	3·631	8·875	12·967
25–45	0·026	0·221	0·865	2·631	6·431	9·397
45–50	0·019	0·157	0·616	1·874	4·581	6·693
50–60	0·014	0·116	0·456	1·388	3·391	4·955
Homosexuals						
Activity class	1	2	3	4	5	6
Proportion in class	0·451	0·353	0·125	0·06	0·01	0·001
Age range	Rate of acquisition of new partners (/year)					
15–20	0·045	0·434	1·285	2·547	4·725	7·819
20–30	0·210	2·034	6·029	11·951	22·168	36·686
30–40	0·234	2·263	6·708	13·297	24·663	40·815
40–50	0·212	2·058	6·100	12·091	22·427	37·115
50–60	0·046	0·443	1·313	2·603	4·828	7·991

infant vaccination) or latent (as a result of perinatal infection). For heterosexuals the proportion born into each is governed by the age distributions of healthy and infectious mothers; the proportion, ω_s born into each sexual activity class s is constant. For homosexuals the proportion of births into each compartment was maintained at the equilibrium levels for births into the different heterosexual compartments (although this is computationally convenient, it does lead to some underestimation in the homosexual model of the effects of mass vaccination programmes on the level of perinatal transmission). Sexual contacts are considered to begin at age 15 and continue until age 60. Beyond this age individuals are assumed to make no further contribution to HBV transmission. Additional mortality from acute infection and long term additional mortality in carriers is omitted since it is not likely to be significant for transmission. It may of course be highly significant for cost/effectiveness analysis and will be included in subsequent versions of the model. The partial differential equations (PDEs) of which the heterosexual model is comprised (the homosexual model being a simpler variant), and the initial conditions, are set out in the Appendix.

Parameter assignments

Parameter assignments are set out in Tables 1 and 2 and are based on those in the previous paper [14] with a number of important revisions. Rates of acquisition of new partners have been estimated by use of unpublished data from the National Survey of Sexual Attitudes and Lifestyles (NATSSAL) [15]. Numbers of partners over the last year were subtracted from numbers over the last 5 years and divided by four to provide an indication of the yearly rate of loss of partners. This was in turn used as a proxy for the rate of acquisition. Model rates of partner acquisition for each age band were estimated by fitting gamma distributions to this data, retaining the same population distribution into the six activity classes as in the previous paper [14]. The NATSSAL does not report on individuals under age 16 so here the rates for the 10–15 year age group have been set to zero. It should be noted from Table 2 that around 80% of the heterosexual population (grouped into classes 1–3) have yearly rates of sexual partner change of around one or less, and about the same proportion of the homosexual population have new partnership rates of around two or less per year. Using published raw data [28] a revised estimate was made of the risk of transmission from an acutely infected individual in a heterosexual partnership. The ratio of this value to the risks of transmission from a heterosexual carrier, and from acutely infected and carrier homosexuals were kept the same as in the previous paper [14]. Published estimates for the rate of transition from the carrier state to the recovered immune state, σ_3, vary widely. Edmunds (unpublished observations) estimates a mean duration of the carrier state of 30–40 years (but

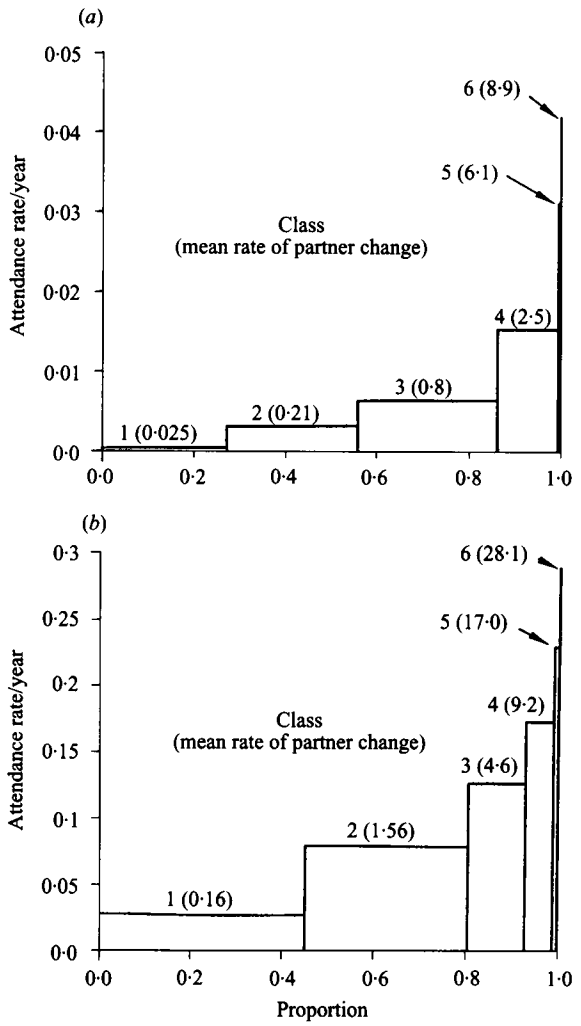

Fig. 3. Rate of GU clinic attendance according to sexual activity class (and, in brackets, the mean annual rate of partner change for the class). The width of the bars correspond to the proportion of the population in each class. Graph (*a*) represents the heterosexual population and graph (*b*) the homosexual population.

this estimate was produced using data from areas of high endemicity where most infection occurs in childhood); on the other hand Alward [29] suggests a rate of transition out of the carrier state of about 1% per year, a mean duration of about 100 years. Here we have chosen a figure of 65 years which is not inconsistent with either estimate, bearing in mind the uncertainties involved. The percentage of infected babies born to infected mothers has been set at 72·4% for acutely infected mothers and 11·5% for carrier mothers (Edmunds, unpublished observations). The risk for adults of becoming a carrier after acute infection remains at the 10% used in the earlier paper; the higher risk following perinatal infection was set at 88·5% [2].

Vaccination strategies

Vaccination programmes were applied singly for a variety of coverage levels for a period of 50 years starting from the equilibrium state reached in the absence of vaccination.

Mass vaccination

Under mass infant vaccination a fixed proportion was vaccinated at birth with a full course of vaccine, with 90% of those receiving vaccine then removed to the immune compartment [14]. However, for children infected perinatally, immunization delivered as part of the routine vaccination programme is assumed to be ineffective (this assumes vaccination is not within the first 24 h after birth [6]). With mass vaccination of adolescents a fixed proportion is vaccinated at age 10 years. There is little information on compliance rates in general for adolescent vaccination, and even less in the case where vaccination is against a sexually transmitted disease, so the working assumption has been made that compliance would be the same as for GU clinic attenders (Table 1); the overall proportion gaining immunity from the specified compliance and seroconversion rates for one, two and three doses was 0·68 (Table 1) [14].

Targeted vaccination

For infant immunization following antenatal screening, all who are identified as being at risk are assumed to have been given vaccine and HBIG and 90% of these are assumed to be effectively vaccinated [14]. The nominal level of vaccination corresponds to the proportion of potentially infectious mothers who are scheduled for screening; this is reduced arbitrarily by 15% to allow for some seropositive mothers nonetheless remaining unidentified.

In GU clinics vaccination coverage is related to the likelihood of clinic attendance, which, in turn, is assumed to be functionally related to the rate of sexual partner change [15]. In the previous paper [14] coverage was governed by sexual activity class alone. Here survival analysis is used with data from the NATSSAL to consider the relationship between individuals' rates of partner acquisition (see above) and their rates of attendance at GU clinics. Exponential regression models were fitted to the data giving a rate of attendance for heterosexuals of:

$$\exp[0{\cdot}801 \ln(c_{gs}(a)) - 4{\cdot}923]$$

and for homosexuals of:

$$\exp[0{\cdot}455 \ln(c_{gs}(a)) - 2{\cdot}755]$$

where c_{gs}(a) is the rate of partner acquisition (see Appendix). The specified level of vaccination is applied to all those attending. This analysis suggests that, for many, rates of attendance at GU clinics are very low, with the 80% of heterosexuals found in activity classes 1–3 attending at a rate much less than once in a lifetime, and the 80% of homosexuals in classes 1–2 attending less than once in 12 years (Fig. 3). Numbers of doses of vaccine administered in GU clinics are calculated under two simplifying assumptions, where prior screening is undertaken (hence vaccine is given only to susceptibles, i.e. class X) and where vaccination is given without screening. In the latter case, vaccine is given to individuals of any class excepting those with previous vaccination history; these are assumed to have been screened to establish that they have responded to vaccine and belong in the vaccine immune class (i.e. class V); if not they are vaccinated again and are assumed to respond in the same way as vaccine naive individuals. As in the previous paper, in GU vaccination only a proportion of those given the first or second vaccination in a course return for second or final doses. A much smaller proportion of those receiving only one or two doses are effectively immunized [14] (Table 1).

RESULTS

Infection at endemic equilibrium

The model was run to endemic equilibrium, i.e. until stability was achieved in the distribution of infection by age and activity class. Figure 4 shows the resultant age-prevalence of carriers and acutes (graph *a*) and individuals with evidence of past exposure (graph *b*) for heterosexuals and homosexuals. Here the prevalence of carriers in the entire heterosexual population is about 0·22% (graph *a*), with between 1·5 and 5% of adults (depending on age) having some history of infection (graph *b*). For homosexuals carrier prevalence is an order of magnitude greater than for heterosexuals, and between about 5% (at 15–20 years) and 55% (at 55–60 years) show history of infection.

Table 3 provides an indication from published sources [16–27] of the prevalence of specific markers in the UK stratified where possible by age and risk group (data for IVUs are not included). If we assume the prevalence of anti-HBc reflects the proportion ever infected, comparison with Figure 4 suggests that the model results are, in general, consistent with levels observed in the UK population.

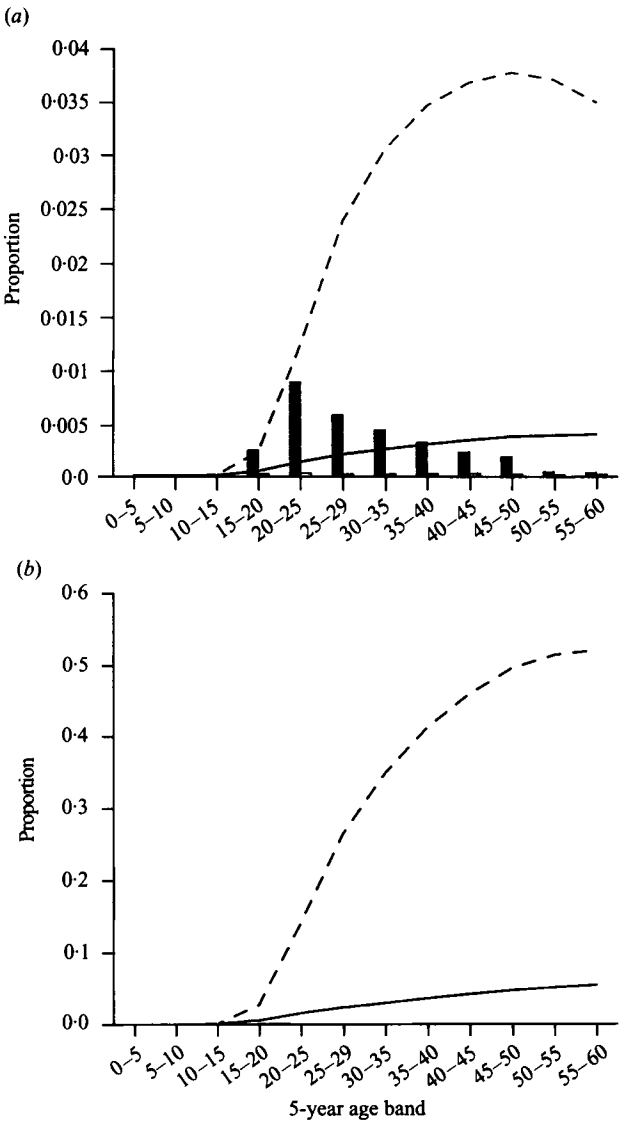

Fig. 4. Equilibrium proportion, distributed by age, of heterosexuals (solid lines and light bars) and homosexuals (dashed lines and dark bars), who are chronic carriers (graph (*a*), lines), acutely infected (bars), or have any marker of HBV infection past or present (graph (*b*)).

Figure 5 shows the predicted proportion of individuals who are chronic carriers of HBV stratified by sexual activity class (1 is lowest, 6 is highest), for heterosexuals (light bars) and homosexuals (dark bars). Noting again that about 80% of heterosexual individuals are grouped into classes 1–3 and a similar proportion of homosexuals into classes 1–2, the distribution of prevalence in Figure 5 emphasizes the importance of individuals in the higher sexual activity classes to the spread of HBV infection and, therefore HBV control.

Table 3. *Prevalence of hepatitis B markers in the UK*

Ref.	Sample size	Age range	HBsAg	Other marker	Population
16	3760	—	38 (1%)	—	Inner London antenatal
17	440	—	17 (4%)	Anti-HBc/anti-HBs 140 (31·8%)	Homosexual/bisexual men: London GU clinic
18				Anti-HBc	Homosexual men: bars,
	568	All	—	94 (16·5%)	clubs, gay groups, GU
	143	< 26	—	10 (7%)	clinics
	425	26+	—	84 (19·8%)	
19				Anti-HBc	Homosexual men: GU
	177	All	—	100 (56·5%)	clinic
	12	16–20	—	4 (33%)	
	31	21–25	—	11 (35%)	
	46	26–30	—	27 (58%)	
	43	31–35	—	31 (72%)	
	21	36–40	—	12 (57%)	
	8	41–45	—	5 (62%)	
	10	46–50	—	7 (70%)	
	—	51–55	—	—	
	4	56–60	—	1 (25%)	
	2	61–65	—	2 (100%)	
20	6226	—	33 (0·5%)		N London antenatal
21		—	—	Anti-HBc	Women: London GU
	647	—	—	27 (4·2%)	clinic
				No known risk: 6 (0·9%))	
22	7300 (all)	—	72 (1·0%)	—	London GU clinic
	2500 (female)	—	2 (0·08%)	—	
	2800 (male hetero.)	—	17 (0·6%)	—	
	2000 (male homo.)	—	53 (2·6%)	—	
23	~ 13550 (male)	—	(0·28%)		Blood donors
	~ 13550 (female)	—	(0·12%)		
24				Any marker	London general practice
	1002 (all)	—	10 (1%)	10·1%	patients
	691 (female)	—	5 (0·7%)	(4·3% UK born to UK	
	311 (male)	—	5 (1·6%)	born parents)	
25	Year 1987			Anti-HBc	Female London GU
	412 (female)	17–67	—	40 (9·7%)	clinic
	318 (female UK)		—	19 (4·6%)	
	Year 1989–90				
	850 (female)	15–70	—	36 (4·0%)	
	640 (female UK)		—	24 (3·7%)	
26	—	—	—	Any marker	SE London GU clinic
	1481 (all)	—	52 (3·5%)	406 (27·4%)	(includes some IVUs)
	162 (female)	—	6 (3·7%)	36 (22·2%)	
27	1893	—	(1·85%)	—	Blood donors

The basic reproductive rate, R_0, of HBV is a measure of the potential of the infection to spread in the community and, thereby an indicator of the difficulty expected in attempting to prevent transmission. The relationship between R_0 and the equilibrium prevalence of acute infection is plotted in

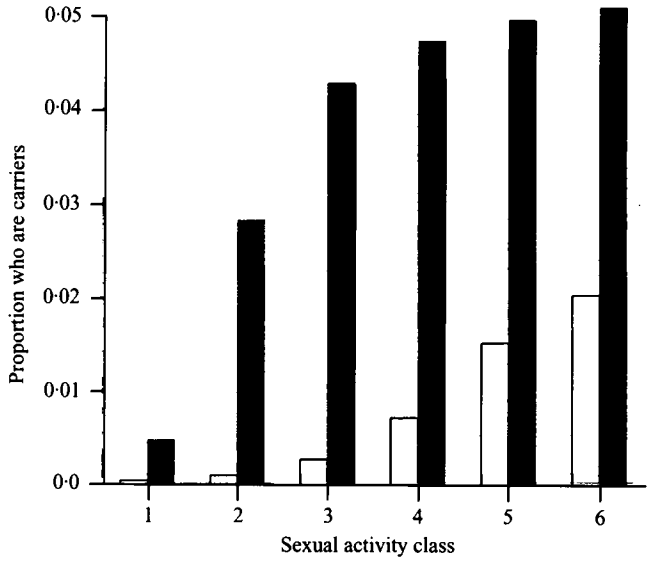

Fig. 5. Equilibrium distributions, by sexual activity classes (Table 3), of heterosexuals (light shaded bars) and homosexuals (dark shaded bars) who are chronic carriers.

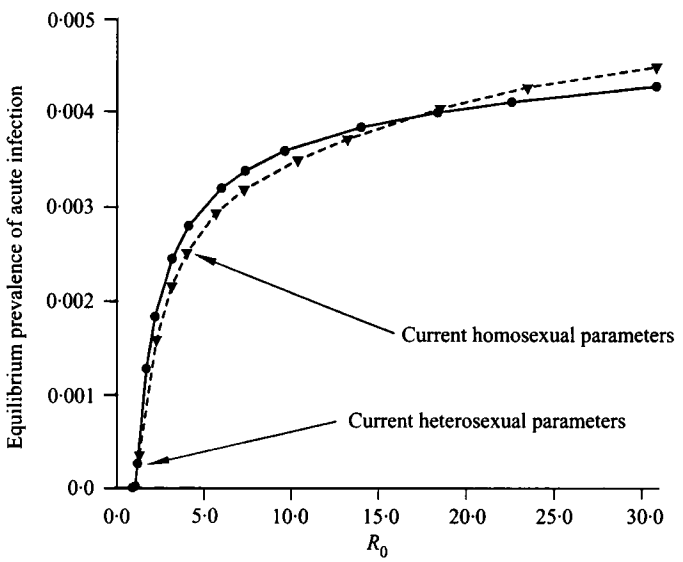

Fig. 6. Relationship between the predicted equilibrium proportion of acutely infected individuals and the basic reproductive rate (R_0) for heterosexuals (——) and homosexuals (– – –). Arrows indicate the estimated R_0 values using the parameter sets of Tables 1 and 2.

Figure 6, for the heterosexual (solid line) and homosexual (dashed line) sections of the population. The model was run to endemic equilibrium for a range of parameter values, yielding a series of values of R_0 and endemic prevalence of infection. Details of the derivation of R_0 are given in the Appendix. As R_0 increases (here the result of changing by the same proportion the rate of acquisition of new sexual partners and the fertility rate) the model will tend asymptotically towards a maximum equilibrium proportion of acutely infected individuals. For heterosexuals the original parameter set (Tables 1 and 2) gives an R_0 of 1·2. This is near to the threshold level of 1, below which there is no endemic stability and the disease would be expected to die out under the assumption of random (i.e. proportionate) mixing within the population. For homosexuals the relationship is of similar form although the original R_0 of 4·0 lies further towards the maximum of the curve.

The differences in the estimated R_0 values for the two sub-populations (1·2 for heterosexuals and 4·0 for homosexuals) is attributable to differences in the rates of change of sexual partnerships and transmission risks detailed in Table 1 and 2. The form of each curve in Figure 6 and the positions of the current R_0 values

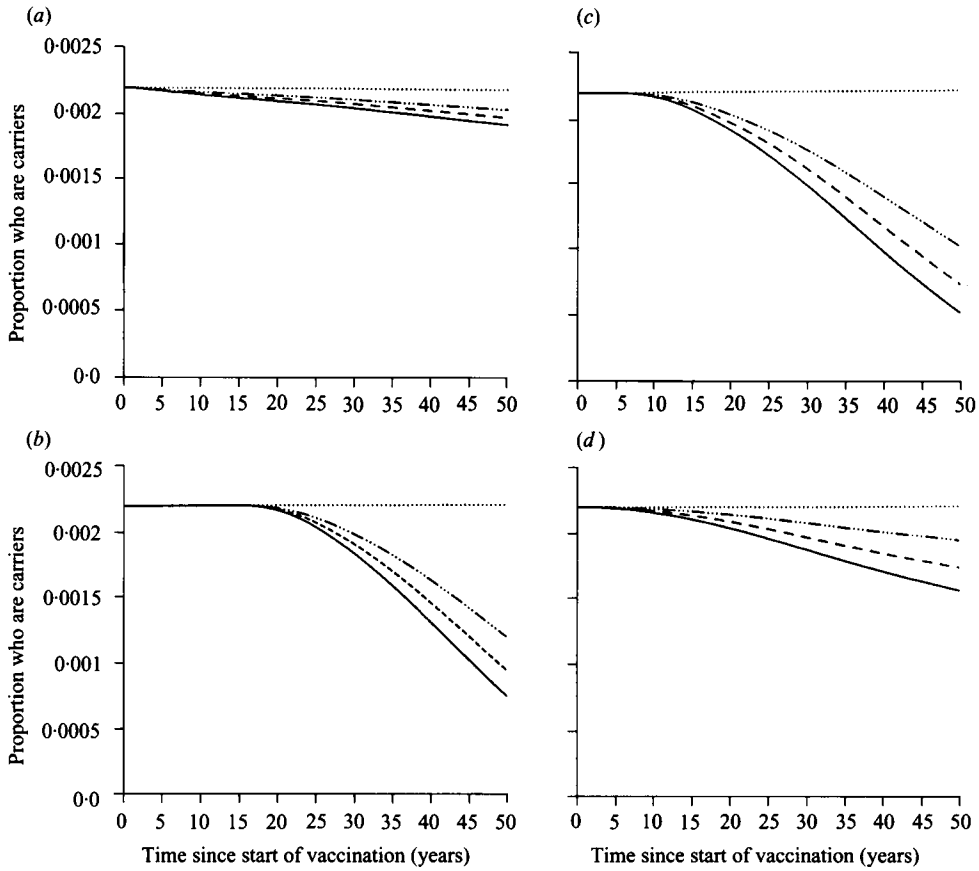

Fig. 7. Predicted impact of different HBV mass vaccination programmes on the proportion of carriers in the heterosexual population over a 50-year period. Graphs (*a–c*) illustrate the effects of antenatal screening, mass infant and adolescent vaccination programmes, respectively, with coverage of 50% (—···—), 70% (– – –) or 90% (——). Graph (*d*) is for vaccination targeted at GU clinic attenders with coverage of 30% (—···—), 60% (– – –), and 90% (——). In all graphs the endemic proportion who are carriers (in the absence of vaccination) is shown by the dotted line (.....). (See text for further details of the immunization schedule).

suggest that heterosexual transmission should be highly responsive to any slight changes in the reproductive rate brought about by mass vaccination (having a R_0 value on the steepest part of the curve), whereas transmission among homosexuals should be somewhat less sensitive to such change as R_0 lies on a part of the curve where greater changes in the reproductive rate (induced by immunization) are required to yield a specified reduction in prevalence compared with that of heterosexuals.

The impact of vaccination

Figures 7 and 8 illustrate the temporal impact of different mass vaccination options on the prevalence of heterosexual and homosexual carriers, respectively. Although, quantitatively the impact of different policies is not directly comparable because for example compliance over a course of vaccination (three doses) has been only crudely estimated the general trends can be related. The delay in the impact of infant immunization (Figs. 7*b*, 8*a*) compared with adolescent or GU targeted (Figs. 7*c*, 7*d*, 8*b*) is clearly illustrated. Mass infant immunization affects heterosexuals (Fig. 7*b*) and homosexuals (Fig. 8*a*) to a similar degree (and similarly for mass adolescent vaccination, results for homosexuals not shown). Antenatal screening and subsequent follow up of infants born to carrier mothers is of little apparent effect (Fig. 7*a*) because only a very small proportion of mothers are chronic carriers. The effect is, however, non-negligible since each perinatal infection prevented approximates to the prevention of a chronic carrier, as a result of the higher probability of infected infants developing the carrier state [2].

Vaccination targeted at GU clinic attendees has the potential to induce a significant reduction in carrier prevalence, particularly so for the homosexual community (Fig. 7*d*, 8*b*). This is even though vaccination is targeted at a relatively small proportion of the

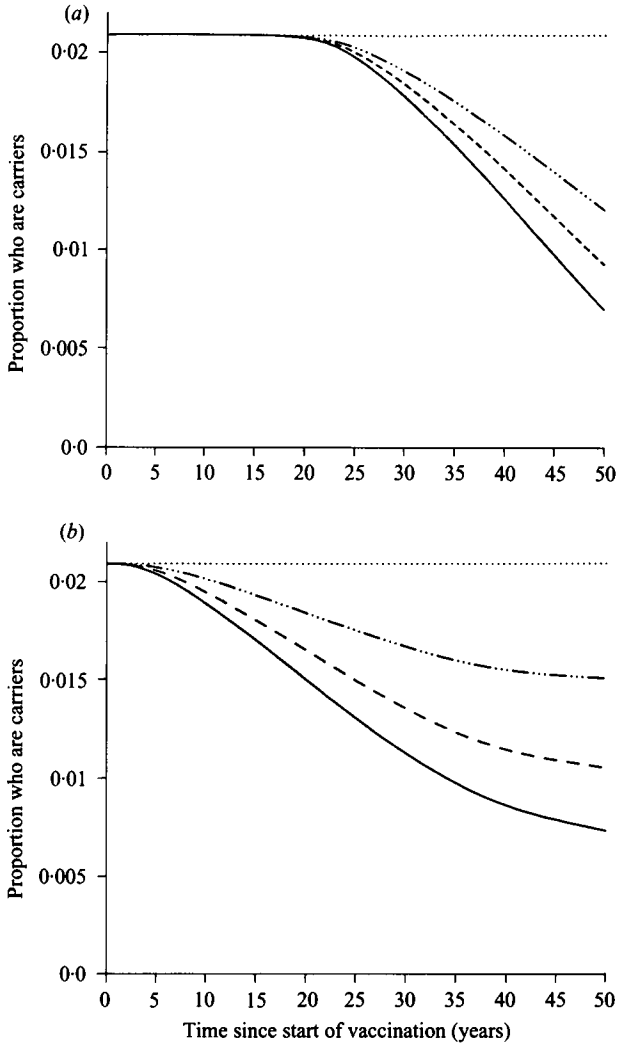

Fig. 8. Predicted impact of different HBV mass vaccination programmes on the proportion of chronic carriers in the homosexual population over a 50-year period. Graph (*a*) records the results under a mass infant schedule, and graph (*b*) for a targeted GU clinic schedule, with details as for Figure 7*b*, *d*, respectively.

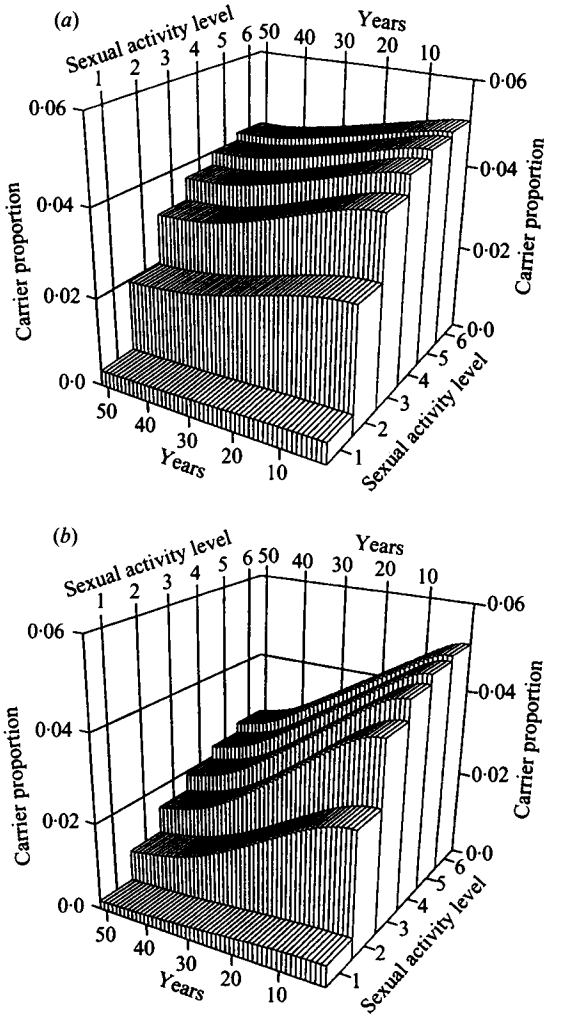

Fig. 9. Temporal changes in the proportion of each sexual activity class (1, low; 6, high) who are chronic HBV carriers, for homosexuals, following the initiation of a targeted GU vaccination programme with 30% (graph (*a*)) and 90% (graph (*b*)) coverage (details of the schedule are as for Fig. 7*d*).

community, i.e. those with high rates of partner change and most likely to attend GU clinics (Fig. 3). The mechanism underlying this result is that it preferentially removes from the pool of susceptibles those most at risk of acquiring, and subsequently transmitting infection (see Fig. 5). This preferential vaccination of individuals who otherwise would have most potential for transmission, reduces the transmission risk to all individuals (a herd immunity effect), and will act to reduce R_0 by a degree which is disproportionate to the numbers receiving vaccine. The effect may be seen most clearly in Figure 9 which reveals a significant reduction in carrier prevalence for homosexuals in the lower activity classes (the majority of individuals). This results from the indirect protection afforded to individuals in all activity classes generated by targeting vaccination predominately at the higher activity classes. The factors limiting the impact of GU clinic vaccination are: (i) of every 100 individuals who begin a course of vaccination only an estimated 68% here derive protection (far less than for infant immunization) (see Table 1) and (ii) the rate at which individuals attend GU clinics. The latter is reflected in the difference in vaccination impact between homosexuals (Fig. 8*b*) and heterosexuals (Fig. 7*d*), since homosexuals have higher rates of partner change and for a given rate of partner change homosexuals will attend clinics more frequently (Fig. 3). There is therefore for the homosexual population a greater force acting to decrease R_0, which outweighs

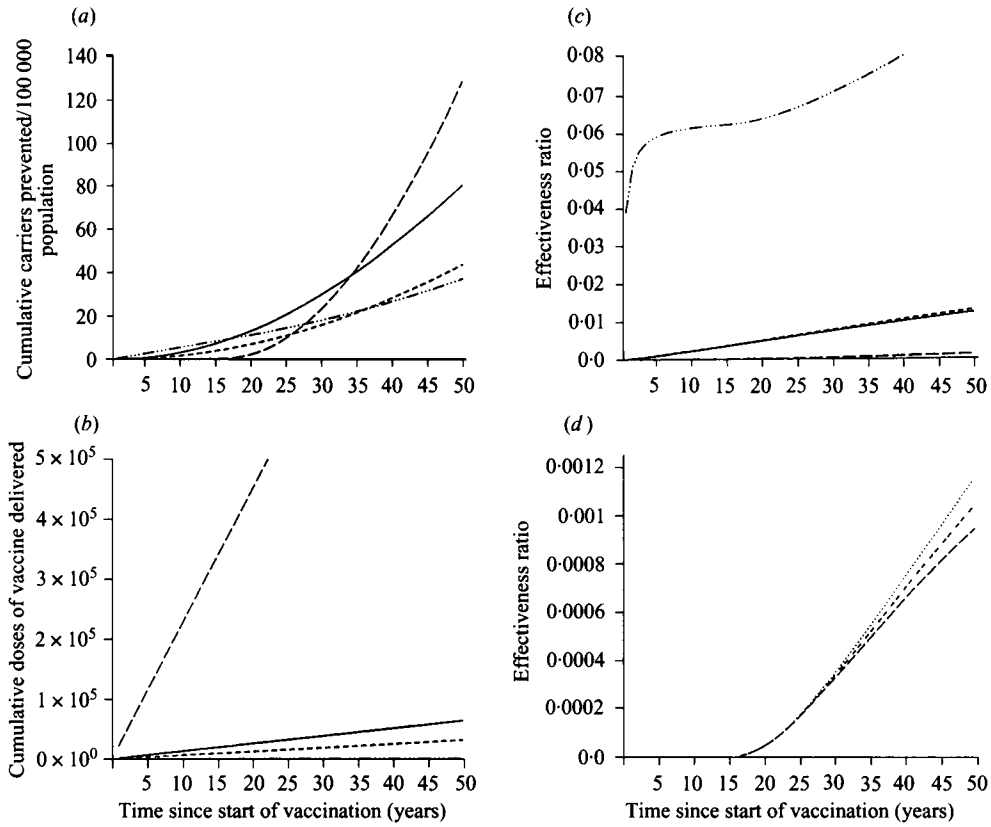

Fig. 10. Temporal changes in a measure of effectiveness and cost for HBV vaccination in heterosexuals for a variety of different mass immunization schedules. Graph (*a*) shows the accumulated numbers of carriers prevented over a 50-year period under an antenatal policy with 90% cover (—· · ·—), a policy of targeting GU clinic attendees with coverage of 30% (– – –) or 60% (——) (schedule details as for Fig. 7*d*), and a mass infant programme with 50% cover (— —). The associated cumulative numbers of doses of vaccine delivered for each programme, and the ratio of accumulated carriers over cumulative doses (a measure of effectiveness per dose of vaccine), are shown in graphs (*b*) and (*c*), respectively. Graph (*d*), illustrates the number of carriers prevented per dose of vaccine for three levels of infant immunization; 50% (… …), 70% (– – –) and 90% (— —).

the greater sensitivity to changes of R_0 for heterosexuals, which was observed in Figure 6.

A further point to draw out of these projections (Figs. 7–9) is the non-linearity of the impact of vaccination. An increase in infant mass vaccination from 50 to 70 to 90% does not induce equivalent successive decreases in carrier prevalence (Figs 7*b*, 8*a*). Similarly for GU targeted vaccination (in particular for homosexuals, Fig. 8*b*) where an additional 30% coverage from 0 to 30%, from 30 to 60%, and from 60 to 90%, yields, successively diminishing impact on carrier prevalence.

Estimating a relative measure of effectiveness

As an example of an output measurement useful for comparing the costs and effectiveness of different vaccination strategies (e.g. GU targeting compared with mass infant) or of different levels of coverage of a particular policy, we calculate the cumulative number of carriers prevented per cumulative dose of vaccine delivered. The derivation of this measure is illustrated in Figure 10, for the heterosexual model for a variety of vaccination schedules. Figure 10*a* records the cumulative effectiveness resulting from the implementation of a variety of different policies, over a period of 50 years. Effectiveness is measured as the number of carriers prevented compared with the 'no vaccination' situation, accumulated over time. In other words this equates to the area between the appropriate carrier incidence curve from the start of vaccination for a particular policy, and the endemic equilibrium line. These results are then scaled by the cumulative number of doses of vaccine delivered for each regimen (Fig. 10*b*) to give the results in Figures 10*c* and *d*, recording the cumulative number of carriers prevented per dose (a cost-effectiveness measure).

Some general points emerge from the results shown in Figures 10*c* and *d*. First, it is clear that different policies are markedly different in the amount of effect per dose of vaccine delivered. For example, each dose

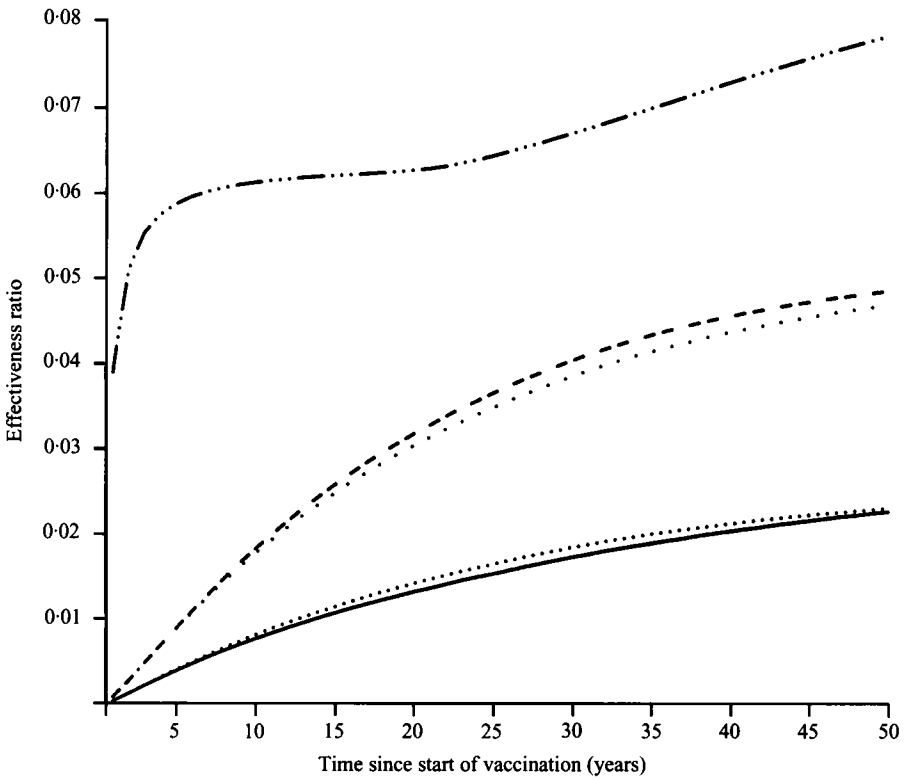

Fig. 11. Changes, over time, in a measure of effectiveness and cost, for homosexuals, under different immunization schedules. The relative effects of an antenatal screening programme (90% cover, —···—) are compared with those of targeting GU clinics, with 30% coverage with prior screening (– – –) or without (. . . . .), or 60% coverage, with (. . . . .) or without (——) prior screening (for details of schedules see text).

of vaccine given to an infant of an infectious mother has a high probability of preventing a chronic carrier (see Table 1), unlike mass infant vaccination, where the vast majority of those receiving vaccine are very unlikely to be exposed to infection. Note, however, that the monetary cost of delivering a dose of vaccine would be very different for each type of policy. Secondly, that the effectiveness per dose changes over time, resulting, for example, from the lag between an individual receiving a vaccine (e.g. in infancy) and that individual being exposed to infection (when sexually active). Thirdly, that the non-linearity in impact of vaccination at different levels of coverage referred to earlier, in relation to Figures 7–9, may be reflected in a decrease in effectiveness per dose with increasing coverage, e.g. for infant immunization effectiveness per dose for 50 > 70 > 90% (Fig. 10*d*) and, more marginally, GU targeted vaccination at 30% coverage has greater effectiveness/dose than 60% (Fig. 10*c*).

Similarly to Figures 10*c* and *d*, the temporal change in cumulative effectiveness/cumulative dose of vaccine for various policies for vaccination of homosexuals are illustrated in Figure 11. These examples are chosen to illustrate differences compared with the heterosexual results. First, compared with a policy without screening, Figure 11 reveals a marked increase in effectiveness per dose in a GU targeted policy if vaccine is given only to those who, following screening, are found to be seronegative. This was not the case with heterosexuals, where very little increase in effectiveness was accrued (results not shown). The difference lies in the fact that whereas a high proportion of homosexuals will have evidence of previous infections, for heterosexuals the proportion with markers of infection will be so small as to make screening an almost worthless operation. A further complication to this picture, is that unlike mass vaccination where all are vaccinated regardless of serological status and doses *per capita* stay constant over time, doses delivered in a programme involving prior screening will change over time. Vaccination lowers the number of susceptibles, which in turn lowers the numbers of doses given. However, as incidence falls, levels of immunity arising from infection decline so there is a countervailing tendency towards increasing numbers of susceptibles and hence numbers of doses (results not shown). Secondly, Figure 11 illustrates the potential for the relationship between the effectiveness/dose profile for different

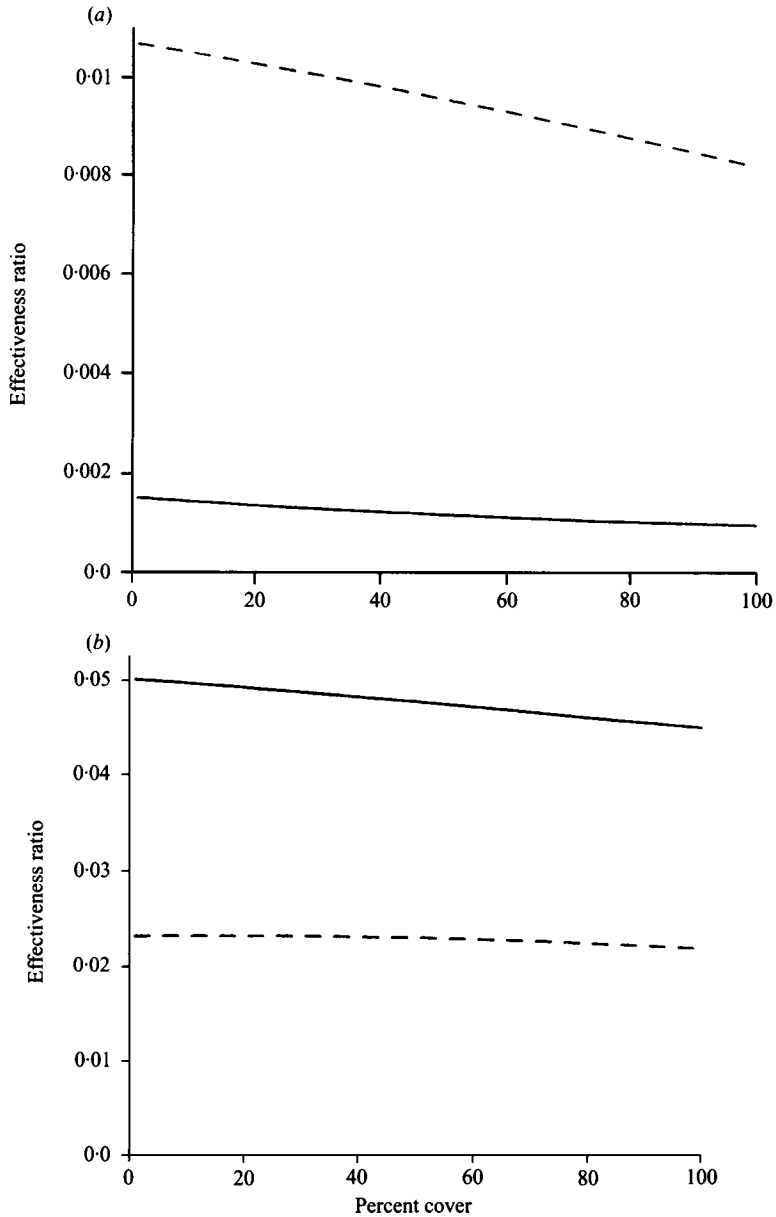

Fig. 12. Effectiveness per dose of vaccine after 50 years of different immunization programmes, in relation to vaccination coverage. Graph (*a*) shows the result of mass infant immunization of heterosexuals (——) and homosexuals (— —). Graph (*b*) compares targeted vaccination of homosexual GU clinic attendees, with (——) or without (— —) prior screening.

vaccination strategies to alter quantitatively as time progresses from the start of vaccination. This is simply a result of a combination of differences in time lags in the development of effect and the relative potential for a particular type of policy to control infection.

The relationship between vaccination effectiveness and coverage

Figure 12 describes the relationship between the cumulative effectiveness per cumulative dose of vaccine and level of vaccine coverage after 50 years of vaccination for a number of different vaccination regimens applied to heterosexuals or homosexuals. In general the trend is for effectiveness per dose to decrease with increasing vaccine coverage, although the decrease may be quite small. The interpretation is simply that as vaccination coverage increases there are proportionally fewer individuals who can derive indirect protection from the lowering of the force of infection, i.e. the herd immunity effect per vaccinated individual diminishes as the vaccinated proportion increases. Differences between the heterosexual and homosexual groups in the form of the relationship and the magnitude of the effectiveness:dose ratio

result from differences in the rates of sexual partnership change (and therefore the relative magnitude of the basic reproductive rates for the two populations).

DISCUSSION

Compared with childhood viral infections, such as rubella and measles, the predicted rate of spread of HBV in the heterosexual and homosexual populations modelled in this study is low [12], determined largely by those in the higher activity classes. Whereas estimates of R_0 for rubella and measles in the UK are around 7 and 16, respectively (in the absence of mass vaccination), estimates for HBV from this study are significantly less (around 4 and just over 1 for the homosexual and heterosexual populations respectively. Given the relationship between R_0 and the prevalence of infection in the model (Fig. 6), the predicted marked impact of even moderate levels of vaccination coverage on prevalence is not unexpected.

Measured by numbers of carriers prevented per dose, mass infant vaccination appears to be least cost effective. Selecting for vaccination infants born to infectious mothers results in a very high effectiveness to cost ratio because of the high probability both of infection, and becoming a carrier; however, there are additional screening costs, and benefits for the population as a whole will be delayed because of the time taken to reach sexual maturity. Mass vaccination of adolescents is much more effective in the shorter term than of infants because of its immediate effect, and at early stages of the programme the impact of vaccination at GU clinics is more rapid still as there is no lag effect and it is targeted at those most important to the spread of the virus.

The disproportionate importance of a small fraction of individuals with high rates of partner change to endemic persistence of HBV infection in both heterosexual and homosexual communities has been clearly illustrated. However, the way in which this translates into effectiveness of a programme of vaccination whose goal is to target vaccination at such individuals (i.e. through GU clinic attendance) is not simple. In particular, this effectiveness depends on how frequently those with the highest rates of new partnerships actually attend clinics. Analysis of data from the NATSSAL suggests that for heterosexuals this frequency is low (particularly compared with homosexuals), and our projections show that, although heterosexual transmission is potentially highly sensitive to control measures (R_0 is low), GU clinic vaccination may have only a moderate effect. A far greater impact could be expected amongst homosexuals, as a result of a relatively high rate of GU clinic attendance by those at highest risk of HBV infection. However, all these results are sensitive to the nature of the relationship between rates of partnership turnover and of clinic attendance. Although excellent in many ways, the NATSSAL data are not ideal for this purpose, providing only coarsely stratified time of last attendance. Until the relationship is more firmly established, the true cost effectiveness of a targeted strategy will be difficult to estimate. It is clear, nevertheless that in contrast to heterosexuals, screening of homosexuals before vaccination results in a much better pay-back per vaccine dose because of relatively high infection-based immunity, and though some potential vaccinees may not return for screening results, reducing numbers vaccinated, pay-back per dose of vaccine would not be significantly affected.

The level of the cost-effectiveness ratio varies non-linearly through time because there are lags, sometimes of many years, before different strategies give their full impact; the cost-effectiveness ratios for different strategies also vary relative to one another over time. Additional non-linearities arise from indirect protection afforded to unvaccinated individuals by vaccinating others in the population, and this further complicates estimation of cost effectiveness; the stimulations suggest that as vaccination cover increases, the incremental increase in this herd immunity effect will become smaller (to a varying degree depending on individual programmes). Thus the net effect of herd immunity decreases with increasing coverage because the proportion of those able to benefit from indirect protection is much smaller; increasing coverage therefore may not yield proportionately increased pay-back.

We have considered only numbers of carriers prevented per dose of vaccine as a crude measure of cost effectiveness. Clearly a more sophisticated analysis would consider also costs of setting up and administering possible programmes. For example it may be possible to incorporate an HBV programme into existing mass infant vaccination programmes without significant additional cost other than for vaccine. For a screening based programme the costs of administration and of screening itself may be significant. Administration costs are also a factor in mass adolescent HBV vaccination, as, at the time of writing, the continuation of possible parallel mass adolescent programmes such as for rubella are in

question. On the effectiveness (and cost saving) side of the equation there are many factors to be considered. Clearly the impact on people's lives of reduction in disease and mortality are of utmost importance, but is notoriously difficult to quantify and often avoided for this reason. Encouragingly, a recent World Bank report [30] has taken some steps in this direction. Ill health and premature mortality also impact on the economy in terms of reduced production, loss of investment in education and training, increases in social security costs and consequent higher burden of taxation, as well as higher social costs in terms of families under stress as a result of long term ill health or premature mortality of a parent. Benefits of vaccination are clearly widespread, but decision makers may only consider effectiveness on a much narrower basis. Even looking at savings in health care costs alone there are many factors to consider: primary care costs for acute cases, high costs of hospitalization and intensive care of fulminant liver disease (1% of symptomatic acute cases develop fulminant disease), long-term cost of treatment of carriers (e.g. interferon therapy), high costs of care for cirrhosis and primary liver cancer. The work reported here outlines a tool for producing quantitative projections of incidence and prevalence, which in turn allow more sophisticated and thorough cost-effectiveness analyses of differing vaccination programme options. The model facilitates consideration of which vaccination strategy is likely to prove most cost effective. However it can also show where improved levels of compliance are most likely to be rewarded by reduced incidence when vaccination strategies are combined. Because of the non-linearities involved, the results may not be those that are expected on intuitive grounds alone.

The present paper demonstrates the potential of a mathematical model of HBV transmission as a predictive tool providing valuable insights with which to inform decision making. However, a number of model enhancements are also desirable such as the incorporation of transmission between heterosexuals, homosexuals, and intravenous drug users in a single model. This in turn requires further consideration of the way the pattern of contact between the groups is modelled, as proportionate mixing will no longer be adequate to represent possible mixing patterns [31]; a more assortative (or like-with-like) pattern is appropriate. This also applies to the pattern of mixing between different age groups [15] which may affect the impact of vaccination occurring at particular life stages such as infancy or at the onset of adolescence. Clearly, also, before the model can be used for accurate prediction of the impact of HBV vaccination in the UK more relevant data are needed; the absence of national data for HBV based on seroprevalence survey (stratified by age, sex, ethnic origin, sexual lifestyle and risk behaviour, and sexual activity class) is a particular shortcoming that needs urgent attention. Nevertheless the paper does give weight to the view that costs involved in collecting such data would be justified. The idea that more and better data is needed for better estimation of model parameters and validation of model predictions is perhaps rather familiar. However this does not detract from its force; nor does an insufficiency of good data negate the potential of such models to provide valuable insights with which to inform decision making.

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APPENDIX

Partial differential equations

The model's six partial differential equations are:

$$\frac{\partial X_{gs}}{\partial t}+\frac{\partial X_{gs}}{\partial a}=\Psi V_{gs}(a,t)-[\lambda_{gs}(a,t)+\Phi(a)+\zeta_{gs}(a)]\,X_{gs}(a,t),$$

$$\frac{\partial H_{gs}}{\partial t}+\frac{\partial H_{gs}}{\partial a}=\lambda_{gs}(a,t)\,X_{gs}(a,t)-\sigma_1 H_{gs}(a,t),$$

$$\frac{\partial Y_{gs}}{\partial t}+\frac{\partial Y_{gs}}{\partial a}=r_1 H_{gs}(a,t)-\sigma_2 Y_{gs}(a,t),$$

$$\frac{\partial Z_{gs}}{\partial t}+\frac{\partial Z_{gs}}{\partial a}=(1-p_a)\sigma_2 Y_{gs}(a,t)+\sigma_3 C_{gs}(a,t),$$

$$\frac{\partial C_{gs}}{\partial t}+\frac{\partial C_{gs}}{\partial a}=p_a\sigma_2 Y_{gs}(a,t)-\sigma_3 C_{gs}(a,t),$$

$$\frac{\partial V_{gs}}{\partial t}+\frac{\partial V_{gs}}{\partial a}=[\Phi(a)+\zeta_{gs}(a)]\,X_{gs}(a,t)-\Psi V_{gs}(a,t),$$

where

$$\Phi(a) = \int_{\alpha}^{\alpha+\delta\alpha} u\delta(a-P)\,da$$

(δ representing the Dirac delta function), the force of infection λ is:

$$\lambda_{gs}(a,t) = c_{gs}(a)\frac{\sum_r \int_{\alpha_1}^{\alpha_2} c_{hr}(\alpha)[\beta_1 Y_{hr}(t,a)+\beta_2 C_{hr}(t,\alpha)]\mathrm{d}\alpha}{\sum_r \int_{\alpha_1}^{\alpha_2} c_{hr}(\alpha) N_{hr}(t,\alpha)\mathrm{d}\alpha}$$

(g and h representing opposite sexes and α_1 and α_2 the ages of starting and ceasing sexual activity), and $\zeta_{gs}(a) = i\exp[k_1 \ln(c_{gs}(a)) - k_2]$ (k_1 and k_2 being constants and i being the proportion of GU clinic attenders receiving vaccine).

The appropriate boundary conditions are:

$$\begin{aligned}
X_{gs}(0,t) = \omega_{gs}\sum_r \int_{\alpha_4}^{\alpha_3} \nu(a)(1-q)\{[X_{Fr}(a,t) \\
+ V_{Fr}(a,t) + Z_{Fr}(a,t) + H_{Fr}(a,t)] \\
+ (1-mn)[(1-b_1)\,Y_{Fr}(a,t) \\
+ (1-b_2)\,C_{Fr}(a,t)]\}\,\mathrm{d}a,
\end{aligned}$$

$$\begin{aligned}
H_{gs}(0,t) = \omega_{gs}\sum_r \int_{\alpha_4}^{\alpha_3} \nu(a)(1-mn)[b_1\,Y_{Fr}(a,t) \\
+ b_2\,C_{Fr}(a,t)]\,\mathrm{d}a,
\end{aligned}$$

$$\begin{aligned}
V_{gs}(0,t) = \omega_{gs}\sum_r \int_{\alpha_4}^{\alpha_3} \nu(a)q[X_{Fr}(a,t) + V_{Fr}(a,t) \\
+ Z_{Fr}(a,t) + H_{Fr}(a,t)] \\
+ [\{mn + q(1-mn)(1-b_1)\}\,Y_{Fr}(a,t) \\
+ \{mn + q(1-mn)(1-b_2)\}C_{Fr}(a,t)]\,\mathrm{d}a,
\end{aligned}$$

(where α_3 and α_4 are the ages of onset and cessation of childbearing)

$$Y_{gs}(0,t) = 0, \quad C_{gs}(0,t) = 0, \quad Z_{gs}(0,t) = 0.$$

Key:

$X_{gs}(a,t)$	susceptibles of sex g in activity class s at age a and time t;
H	individuals infected but not yet infectious (latent);
Y	acutely infectious individuals;
Z	individuals who have recovered from infection and are now immune;
C	carrier individuals;
V	vaccinated immune individuals;
N	all individuals (i.e. $X+H+Y+Z+C+V$);
$\lambda_{gs}(a,t)$	force of infection acting on susceptibles of age a at time t, who are of sex g in activity class s;
$\zeta_{gs}(a)$	vaccination rate of individuals of age a, sex g, activity class s as a result of GU clinic attendance;
m	proportion of infected (C, Y and H) mothers identified in screening;
n	proportion of new born babies vaccinated who are born to infected mothers;
q	proportion of babies vaccinated as a result of mass vaccination;
u	proportion of recruits to sexually active population who are vaccinated;
Ψ	rate of waning vaccine-induced immunity;
$\nu(a)$	fertility at age a;
$c_{gs}(a)$	rate of formation of new partnerships by those of sex g, age a, in activity class s;
β_1	probability of transmission from partnership with acutely infected individual;
β_2	probability of transmission from partnership with carrier individual;
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;
p_a	proportion of acutes of age class a who progress to become carriers;
b_1	proportion of babies, born to acutely infected mothers, infected perinatally;
b_2	proportion of babies, born to carrier mothers, infected perinatally;
ω_{gs}	distribution of recruits of sex g amongst sexual activity classes;
P	age of vaccination at puberty;
$\Phi(a)$	function for instantaneous vaccination at puberty;
s, r	sexual activity class;
g, h	sex (F is female);
a, α	age.

Calculation R_0

R_0 the basic reproductive rate (more accurately, the basic reproductive number) represents the average number of secondary infections produced when a single infected individual is introduced into a population where all are susceptible [12]. In this paper we consider a population which is heterogeneous in age and rates of sexual activity. We therefore assume that a single infected individual is distributed over all age groups and sexual activity classes in accordance with the age and activity class distribution of acutely infected individuals at model equilibrium. Each

component of this 'distributed' individual produces secondary infections through sexual partnerships and, in the case of females, births. The number of these infections are summed to give the overall number of secondary infections produced by the distributed single infected individual. The expression for R_0 is accordingly:

$$R_0 = \sum_g \sum_r \int_0^L (y^*_{gr}(a,0)) \left\{ \int_0^{L-\alpha} c_{gr}(a+t) \left[\beta_1 e^{-\sigma_2 t} + p_a \beta_2 (e^{\sigma_3 t} - e^{-\sigma_2 t}) \left(\frac{\sigma_2}{\sigma_2 - \sigma_3} \right) \right] + \nu_{gr}(a+t) \left[b_1 e^{-\sigma_2 t} + p_i b_2 \left(\frac{\sigma_2}{\sigma_2 - \sigma_3} \right) \right] dt \right\} da,$$

where L is the lifespan. With current values of σ and p this expression approximates to:

$$R_0 \approx \sum_g \sum_r \int_0^L y^*_{gr}(a,0) \left(\int_0^{L-\alpha} e^{-\sigma_3 t} [p_a c_{gr}(a+t) \beta_2 + p_a \nu_{gr}(a+t) b_2] dt \right) da.$$

The calculation of R_0 values was implemented in the same program as the numerical solution to the PDE equations of the model.