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Epidemiological patterns of hepatitis B virus (HBV) in highly endemic areas

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SUMMARY

This paper uses meta-analysis of published data and a deterministic mathematical model of hepatitis B virus (HBV) transmission to describe the patterns of HBV infection in high endemicity areas. We describe the association between the prevalence of carriers and a simple measure of the rate of infection, the age at which half the population have been infected (A_{50}), and assess the contribution of horizontal and perinatal transmission to this association. We found that the two main hyper-endemic areas of sub-Saharan Africa and east Asia have similar prevalences of carriers and values of A_{50}, and that there is a negative nonlinear relationship between A_{50} and the prevalence of carriers in high endemicity areas (Spearman's Rank, $P = 0.0086$). We quantified the risk of perinatal transmission and the age-dependent rate of infection to allow a comparison between the main hyper-endemic areas. East Asia was found to have higher prevalences of HBeAg positive mothers and a greater risk of perinatal transmission from HBeAg positive mothers than sub-Saharan Africa, though the differences were not statistically significant. However, the two areas have similar magnitudes and age-dependent rates of horizontal transmission. Results of a simple compartmental model suggest that similar rates of horizontal transmission are sufficient to generate the similar patterns between A_{50} and the prevalences of carriers. Interrupting horizontal transmission by mass immunization is expected to have a significant, nonlinear impact on the rate of acquisition of new carriers.

INTRODUCTION

Infection with hepatitis B virus (HBV) poses a significant public health problem in many parts of the world, particularly in developing countries [1]. It has been estimated that over 1 billion individuals have evidence of exposure to HBV [2] and there are approximately 300 million carriers of the virus, most of whom come from east Asia and sub-Saharan Africa [1]. Carriers of HBV have a high risk of developing chronic liver disease such as cirrhosis or hepatocellular carcinoma [3]. As many as 30% of carriers who survive for 30 years or more may subsequently die of the chronic sequelae of HBV infection [4]. Infection by HBV can therefore be a major cause of morbidity and mortality in areas, such as east Asia and sub-Saharan Africa, that have high prevalences of carriers. Whilst there is no currently available treatment for carriers, infection can be prevented by immunization with plasma-derived or recombinant vaccine. Both vaccines are safe and effective [5], however they are expensive compared to other vaccines commonly given in childhood [1], they require multiple doses, and vaccine induced specific antibody titres decline over time [6–8]. To optimize the use of vaccination as a means of controlling HBV a thorough under-

standing of the epidemiology of the virus is required as a prerequisite to assessing the direct and indirect consequences of mass immunization.

The epidemiology of HBV varies greatly among different areas of the world. It is, however, possible to broadly classify geographical areas according to the prevalence of HBV infection [4]. In areas with low endemicity of the virus, such as North America and northern Europe, transmission of HBV typically occurs between adults via parenteral exposure or sexual contact, and groups with high risk behaviours, such as intra-venous drug users or homosexual men, can be identified. In areas of high endemicity on the other hand, such as east Asia and sub-Saharan Africa, infection with HBV is not restricted to those with high risk behaviours and infection primarily occurs during childhood. This study focuses on the epidemiology of HBV in highly endemic areas, which we define as a region in which more than 75% of the adult population has serological evidence of past or current infection with HBV. Worldwide the two principal areas of high endemicity, in terms of the numbers of people infected, are east Asia and sub-Saharan Africa [1], and this paper concentrates on the epidemiology of HBV in these areas.

There are two main features of HBV epidemiology in highly endemic areas: a low average age at infection and a high prevalence of carriers. These two variables are dependent on one another as numerous studies [9–11] have clearly shown a rapid decline in the probability of developing the carrier state with increasing age at infection. Approximately 90% of infants become carriers if infected [12–14], whereas 10%, or less, of adults develop the carrier state if infected [15–17]. This decline in the risk of developing the carrier state with increasing age at infection is highly nonlinear and appears to be remarkably consistent for a wide range of communities and geographical settings [18]. Childhood infection by HBV occurs principally via 2 routes in developing countries namely, perinatal transmission, which is infection from an infectious mother to her infant around the time of birth (within the first year), and horizontal transmission which can be defined as infection resulting from close contact which is not perinatal and not sexual in nature. The definition of horizontal transmission is vague and the mechanisms by which the virus is transmitted are poorly understood, though infection is thought to occur primarily within the household and most frequently between siblings [19, 20].

This paper reviews the patterns of HBV infection in highly endemic countries and attempts to define the epidemiological relationships between the routes of infection, the age at infection and the prevalence of carriers. This study aims to highlight those factors which influence the pattern of HBV infection in highly endemic zones, aid future data collection, and assist further studies that aim to quantitatively predict the impact of different control programmes.

The present study makes extensive use of published serological surveys. A variety of host sub-populations which differ in their HBV infection status can be distinguished on the basis of specific serological markers. Consequently, these markers are invaluable for epidemiological research. The following is a resume of the interpretation of serological markers used throughout the text. The hepatitis B surface antigen (HBsAg) is indicative of viral replication and infectiousness. In acute patients who are able to mount an effective response to HBV the levels of HBsAg decline in the late convalescent period and disappear after about 3 months [21, 22]. In carriers, however, HBsAg remains detectable for long periods of time and perhaps indefinitely (see later). Individuals positive for HBsAg for greater than 6 months are defined as carriers of the virus [23]. Antibody produced against HBsAg due to either natural infection or vaccination is termed anti-HBs. This protective antibody is passively transferred from an immune mother to her infant. Antibody to the viral core antigen (anti-HBc) develops during the acute phase of infection and seems to persist for the lifetime of the individual [21, 24], it is therefore used as a marker of past or present infection. The presence of anti-HBc is sometimes the only detectable marker of exposure to HBV [21, 24]. Anti-HBc is passed across the placenta and is present in breast-milk, but it is not a protective antibody. The early or e-antigen (HBeAg) can be detected in the early phase of infection and is rapidly cleared in acute infections. HBeAg may persist in the serum of chronic HBsAg carriers for several years. The presence of HBeAg correlates with high infectivity and it is used as a marker of rapid viral replication [25].

METHODS

Selection of surveys and interpretation of data

Data presented in this paper were obtained from an extensive survey of the published literature. Surveys

were selected for inclusion in this study based primarily on the serological markers investigated.

Cross-sectional, serological surveys for HBV markers, finely stratified by age yield estimates of age-dependent forces of infection and the magnitude of HBV transmission within a community. Surveys were included only if the proportion HBsAg positive and anti-HBc positive had been recorded. Some 5–20% of individuals previously infected with HBV are positive for anti-HBc alone [24], therefore absence of this marker from a study could lead to a significant underestimate of infection rates. Hence those surveys which did not measure anti-HBc were excluded from the analysis. Twelve surveys covering 16 different communities fitted the selection criteria. They included surveys from The Gambia [26], Zambia [27], Nairobi [28], Senegal [30], South Africa [31], Taiwan [32], four surveys from the Philippines [33] and one from Shanghai [34]. In addition to the surveys from sub-Saharan Africa and east Asia, three more studies from other highly endemic populations were included, from French Polynesia [35], Solomon Islands [36] and Venezuela [37]. A variety of serological tests were used in the surveys for detection of serological markers. However, the tests do not differ appreciably in sensitivity and specificity for a particular marker [38, 39], and this is therefore unlikely to be a significant source of bias.

Hospital based surveys of pregnant women and mother-infant pairs were used to estimate the prevalence of serological markers in pregnant women and the risk of perinatal transmission according to the infection status of the mother. Note that we take perinatal transmission to be infection of the infant by the mother in the first year of life. Many of the perinatal transmission studies pre-date the practice of immunization of infants at risk of HBV infection, and, as a result, the serological tests used may have been older and less reliable than those used in the cross-sectional surveys.

Statistical methods

The age at which half the sample population has evidence of past or present infection, hereafter termed A_{50}, was chosen as a simple measure of the overall magnitude or rate of infection within a community. The value of A_{50} approximates to the median age at infection if the proportion of the population with at least one marker approaches 100% in the upper age groups. The A_{50} value was preferred to the mean age

at infection as a marker of the rate of infection as it can be interpolated directly from age-serological profiles, whereas calculation of the mean age at infection requires prior estimation of the underlying forces of infection. A test for linearity in the relationship between the value of A_{50} and the prevalence of carriers, recorded in the surveys, was performed in two ways. First, by residual analysis of a linear regression model (Bartlett's three group regression, which does not weight by sample size, was chosen, as the independent variable, A_{50}, was estimated [40]). Second, the likelihood ratio test was used to compare the fit of a linear and quadratic model to the data. These models were fitted by maximum likelihood which automatically weights by sample size.

Differences in the prevalence of HBsAg and HBeAg positive pregnant mothers and the risk of transmission to infants over the first year of life amongst different geographical areas were investigated using multilevel mixed effect models (MLn: Institute of Education, University of London). Data on individuals' status for each outcome measure was derived from several studies. Based on location, studies were grouped into broad geographical areas: sub-Saharan Africa, east Asia, other developing countries and developed countries. For each binary outcome, a multi-level version of the logistic model was fitted. In the models, the geographical area in which each study was performed was treated as a fixed effect parameter, while a single study-level random effect parameter was incorporated to account for clustering of responses within study location, i.e. the within area variation. For the case in which data from three geographical areas were used the full model can be written as:

$$\text{logit } y_{ijk} = \log\left(\frac{\pi_{ijk}}{1-\pi_{ijk}}\right) + e_{ijk}$$
$$= b_1(\text{Africa})_k + b_2(\text{Develop})_k$$
$$+ b_3(\text{Asia})_k + u_{jk} + e_{ijk},$$

where: y_{ijk} is binary and denotes the observed value of the response variable for the ith individual in the jth study location in the kth geographical area; π_{ijk} is the probability of an individual's outcome measure being positive; b_1, b_2 and b_3 are the fixed effect estimates for sub-Saharan Africa, other developing countries and east Asia respectively; u_{jk} denotes the departure of the jth study mean from its corresponding kth area mean estimate. The distribution of the us is assumed to be Normal with mean 0 and variances independent of j. The model provides an estimate of the variance; e_{ijk}

are the residual error terms and are assumed to follow a binomial distribution with variance equivalent to:

$$\frac{\pi_{ijk}(1-\pi_{ijk})}{N_{ijk}};$$

$N_{ijk} = 1$ since individual responses are being modelled.

The possibility that the distribution of the error terms was extra-binomial was assessed by estimating a variance inflation factor, σ_1^2 such that, when $\sigma_1^2 = 1$, the distribution is indeed binomial. In all models with variance estimates not constrained to the binomial distribution, when σ_1^2 was estimated to be less than 1, the model was re-run with variance constrained to the binomial assumption. In addition, normal probability plots of the study-level standardized residuals were used to assess whether the assumption of normality of the us was acceptable, 95% confidence intervals on the resulting mean prevalence estimates for each area were reported.

The force of infection, λ, is the *per capita* rate at which susceptibles become infected and may vary with the age of the susceptible [41]. Age-specific forces of infection were estimated from serological data in two ways to counter any shortcomings in either technique. Both methods assume that the incidence of infection is unchanging through time. The first method assumes that the force of infection is constant over discrete age classes and a change in the rate at which susceptibles become infected between age groups (revealed in a change in the rate of acquisition of serological markers) is assumed to reflect a change in the force of infection. The force of infection in age group i, λ_i, is calculated from the difference in the fraction susceptible between adjoining age groups using the following expression.

$$\lambda_i = \frac{-\ln[x_{i+1}/x_i]}{\Delta a_i},\tag{1}$$

where x_i is the proportion susceptible in age-group i and Δa_i is the difference between the midpoints of age classes i and $i+1$ [42]. If seroprevalence falls with increasing age (due to random or temporal factors), then the estimate of the force of infection by this technique will be negative. This is epidemiologically untenable and in these instances the force of infection was set to zero over that age difference. The second technique, developed by Grenfell and Anderson [43], overcomes this problem by fitting a continuous function which can be constrained to be equal or greater than zero to the force of infection by maximum

likelihood. The expected age-serological profile is simply $1-x(a)$ where $x(a)$ is given by the following expression [43]

$$x(a) = \exp\left[-\int_0^a \lambda(a')\,da'\right],\tag{2}$$

where $\lambda(a)$ takes the form of a polynomial of order 0–4. As the proportion with evidence of previous or current infection is binomial then the polynomial form of $\lambda(a)$ providing the best fit to the observed age-serological profile can be estimated by maximum likelihood.

Simple model of HBV transmission patterns

We propose a simple compartmental, deterministic model to describe the transmission dynamics of HBV similar to that proposed by Anderson and May [41]. Incidence of HBV infection is assumed to be at endemic equilibrium with respect to time. The rates of change with respect to age of the proportion of individuals in a closed population who are susceptible, x, acutely infected, y, and carriers, c, are described by the following equations

$$\frac{dx}{da} = -\lambda(a)\,x,\tag{3}$$

$$\frac{dy}{da} = \lambda(a)\,x - \sigma y,\tag{4}$$

$$\frac{dc}{da} = p(a)\,\sigma y - \gamma c.\tag{5}$$

Susceptibles are infected at an age-specific, *per capita* rate $\lambda(a)$ and move directly into an acute phase. A proportion of these highly infectious individuals, $p(a)$, then pass into the carrier class at a rate σ. The remainder recover and develop immunity to reinfection at the same rate. Carriers eventually lose infectiousness and become immune at a rate γ. Immunity is assumed to be lifelong. The above equations have the initial condition that at birth $y(0) = c(0) = 0$ and $x(0) = 1$, that is, all individuals are born susceptible. Equations 3–5 can be solved by assuming that σ is large relative to the other parameters and consequently that equation 4 is zero, and an expression for the prevalence of carriers in the population at age $a, c(a)$ is derived:

$$c(a) \approx \int_0^a \lambda(s)\,x(s)\,p(s)\,f(a-s)\,ds,\tag{6}$$

where $f(t)$ is the proportion of carriers who retain the carrier state t years after infection. For a constant rate of loss of carriage $f(t)$ is

$$f(t) = \exp[-\gamma t].\tag{7}$$

Although it is likely that the rate of loss of carriage is not constant, but dependent on a variety of factors such as age and time since infection. However, there are not sufficient data to determine this dependency, and a constant rate is used as a guide to the order of magnitude of this parameter.

The probability of developing the carrier state, $p(a)$, declines nonlinearly with increasing age at infection. This relationship is well described by

$$p(a) = \exp(-0.645\,a^{0.455})\tag{8}$$

and appears to hold for a wide range of countries, both developed and developing [18]. With an appropriate function for $\lambda(a)$ the proportion of susceptibles at age a can be calculated from equation 2 and hence equation 6 can be evaluated given an estimate of the rate of loss of carriage. The prevalence of carriers in the population (C) is simply

$$C = \frac{\int_0^L c(a)\,n(a)\,\mathrm{d}a}{\int_0^L n(a)\,\mathrm{d}a},\tag{9}$$

where L is the maximum lifespan and $n(a)$ is the proportion surviving to age a. Assuming a constant, *per capita* natural mortality rate, μ, the proportion surviving to age a is $\exp(-\mu a)$. It follows from equation 2 that

$$\ln(0.5) = -\int_0^{A_{50}} \lambda(a)\,\mathrm{d}a,\tag{10}$$

where A_{50} is, as before, the age at which half the population have evidence of infection. The model was solved numberically to yield the prevalence of carriers (equation 9) for a range of A_{50} values (equation 10) and for different functions for the age dependent force of infection (i.e. exponential decline and constant). To generate different values of A_{50} for the exponential model ($y = b_0\,\exp(b_1 a)$), the slope (b_1) was held constant and the intercept (b_0) was calculated to achieve the necessary value of A_{50}. The value of b_1 was estimated from the median line for the force of infection (Figure 2d) by least squares.

RESULTS

Relationship between the rate of infection and the prevalence of carriers

The areas studied all had high prevalences of carriers (prevalence of HBsAg ranged from 3·5–37·3%) and had high rates of transmission in childhood (the age at which half the population was infected ranged from 1·5–18 years). A plot of A_{50} against the prevalence of carriers for 16 surveys from areas of high HBV endemicity revealed a consistent pattern (Fig. 1). Areas with low values of A_{50} (high transmission) had, on average a greater proportion of carriers in the population than areas with higher values of A_{50} (low transmission). This correlation was found to be statistically significant (Spearmans's Rank Order Correlation $\rho = -0.6325$, $t(14) = -3.0558$, $P < 0.0086$). Furthermore, the relationship appears to be consistent, irrespective of geographical area though the number of studies is too few to allow a formal comparison. Residual analysis of a linear regression model (Bartlett's three group regression [40]) fitted to the data revealed that the associaton was non-linear and was further confirmed by comparing the fit of a linear and a quadratic function to the data by maximum likelihood. The quadratic model gave a significantly better fit to the data (likehood ratio test $G = 21.73$, χ^2 test with 1 D.F. $P < 0.0005$). It is of interest, that studies from east Asia did not record higher prevalences of carriers, nor lower values of A_{50} than surveys from sub-Saharan Africa. We repeated the analysis using different measures of the prevalence of carriers, i.e. the prevalence of carriers younger than 20, 15 and 10 years, to avoid possible biases due to differences between surveys in the upper age limit. The results were very similar to those presented in Figure 1 for the overall prevalence of carriers and are therefore not shown.

Incidence of perinatal transmission

The incidence of perinatal transmission depends primarily on the prevalence of carrier mothers and the risk of transmission of the virus from a carrier mother to her infant; acute infections are rare in adults from high endemicity areas [44].

The prevalence of carrier mothers appears to be somewhat greater in sub-Saharan Africa and east Asia than in other developing countries (data summarized in Table 1), although these differences may be an artifact of biases in the selection of study sites. A
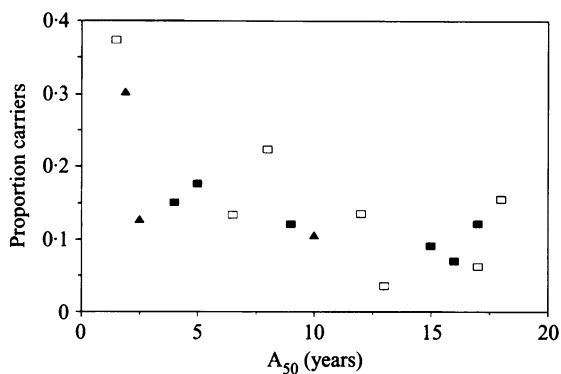
Fig. 1. The correlation between the overall prevalence of carriers and the estimated age at which 50% of individuals have evidence of infection, A_{50}, from 16 surveys from highly endemic areas [26–29, 31–37]. Data from African countries is denoted by □, south-east Asian counties by ■, and other high endenicity areas by ▲.

greater proportion of carrier mothers in east Asia appear to be HBeAg positive (and therefore highly infectious) compared with sub-Saharan African mothers, although the differences are only on the margins of being statistically significant (Table 2). As expected, the risk of perinatal transmission is far greater from HBeAg positive mothers than from HBeAg negative mothers (comparing Tables 3 and 4). There appears, however, to be some geographical variation in the risk of perinatal transmission, most markedly for HBeAg positive mothers (Table 3). In east Asia and other countries (the latter are identified as Developed and Developing in Table 3), the risk of perinatal transmission from HBeAg positive carrier mothers is approximately 70–85% whereas the corresponding risk to infants in sub-Saharan Africa appears to be lower (Table 3). This study provides no evidence of significant geographical differences in the risk to infants from HBeAg negative, carrier mothers (Table 4).

Age-specific rates of horizontal transmission

Childhood infection by HBV is primarily due to horizontal transmission in developing countries, therefore the rate or force of infection is a measure of the rate of horizontal transmission. Age-specific force of infection patterns estimated from a large number of surveys from developing countries are summarized in Figure 2. Figure 2a records the best-fit polynomial forms of $\lambda(a)$ for seven surveys in sub-Saharan Africa, and Figure 2b shows similar results for six surveys from east Asia. In most cases the general pattern of

the force of infection in childhood (under 15) is for it to decline with increasing age. There appears to be no substantial differences between the two regions described in Figures 2a, b. Estimates of the force of infection from 16 surveys from highly endemic developing countries (including the 13 illustrated in Figs 2a, b), using two different methods are summarized in Figures 2c, d. In Figure 2c, forces of infection have been estimated for each distinct age-class, whereas in Figure 2d, for the same data sets, the forces of infection were described by polynomial functions (as in Figs 2a, b). The results from the 16 surveys have been summarized by plotting the median and upper and lower estimates of the force of infection for each yearly age class. It is clear that the methods provide very similar results, with a clear trend for the force of infection to be greatest in infants and young children followed by a steady decline throughout childhood.

Modelling HBV infection patterns

We employed a simple model of the horizontal transmission of HBV to investigate the importance of the magnitude and the age-dependent nature of the force of infection in determining the prevalence of carriers in a population. The model could capture the relationship between the age at which half the population has evidence of infection by HBV and the overall prevalence of carriers in the community (Fig. 3a), reproducing the patterns in the observed data for both a constant and an exponentially decreasing force of infection.

The model was also used to investigate the influence of the rate of loss of carriage on HBV infection patterns. Figure 3b demonstrates that for a constant force of infection, an average duration of the carrier state of approximately 30–40 years provides the best fit to the data.

DISCUSSION

This study clearly shows that in areas of high HBV endemicity a large proportion of the population is infected during childhood (i.e. they have low values of A_{50}), and that there is a nonlinear, inverse relationship between the age at which half the population has evidence of HBV infection and the overall prevalence of carriers in the population. As transmission of HBV primarily occurs in childhood we have attempted to

Table 1. *Summary of the prevalence of HBsAg amongst pregnant women by region**

	Sub-Saharan Africa	East Asia	Developing
Overall sample size†	5861	43047	12330
Range of sample sizes	94–3000	1343–17570	300–8575
Mean prevalence‡ (%)	10·6	9·5	3·6
95% confidence interval (%)	7·4–15·0	5·8–15·0	2·1–6·3

* Sub-Saharan Africa includes 2 studies from Senegal [60, 61], 1 each from Ethiopia, Namibia, Kenya and Tanzania [58, 62–64] respectively. East Asia includes 3 studies from Taiwan [13 48 49], 2 studies from Hong Kong [65, 66], 1 from Japan [67] and 1 from Thailand [68]. Developing refers to data from developing countries which are not in east Asia or sub-Saharan Africa (this term is also used in Tables 2–4) and includes 2 studies from India [69, 70], and 1 each from Egypt [71], Indonesia [72] and Kuwait [73].

† The overall sample size is the sum of the sample size from each of the individual surveys within a geographical region. The same term is used in Tables 2–4.

‡ The mean prevalence is derived from the model parameter estimate, and the 95% confidence intervals are calculated from the standard errors of these estimates. This also applies to Tables 2–4. Study level variance estimate equals 0·204; σ_1^2 (extra-binomial variation) estimated to equal 1·04, unconstrained binomial variance used.

Table 2. *Summary of the prevalence of HBeAg amongst HBsAg positive pregnant women in different regions**

	Sub-Saharan Africa	East Asia	Developing
Overall sample size	243	3774	429
Range of sample sizes	25–116	14–1026	23–322
Mean prevalence‡ (%)	11·6	45·8	10·5
95% confidence interval (%)	4·9–24·8	22·2–71·5	3·1–30·4

* Data as Table 1, excluding studies not reporting HBeAg. Sub-Saharan Africa includes 2 studies from Senegal [60, 74], and 1 each from Ethiopia [62] and Kenya [58]. East Asia includes 3 studies from Taiwan [48, 49, 75], 2 from Hong Kong [65, 66], and 1 each from Thailand [68], and Japan [76]. Developing includes 2 studies from India [69, 70], and 1 each from Egypt [71] and Kuwait [73].

† Study level variance estimate equals 0·623; σ_1^2 estimated to equal 0·999, constrained binomial variance used, i.e. $\sigma_1^2 = 1·0$.

Table 3. *Summary of the risk to the infant of perinatal infection over the first year of life from HBeAg positive mothers by region**

	Sub-Saharan Africa	East Asia	Developing	Developed
Overall sample size	17	352	49	11
Range of sample sizes	4–13	17–94	1–19	4–7
Mean (%) infected†	27·9	87·5	81·6	73·0
95% confidence interval (%)	9·2–59·6	62·6–96·7	46·7–95·8	25·0–95·5

* Sub-Saharan Africa includes 2 surveys, 1 from Kenya [58] and 1 from Senegal [74]. East Asia includes 5 surveys from Taiwan [14, 48, 49, 75, 77], 2 from Hong Kong [66, 78], and 1 each from Japan [76] and Thailand [68]. Developed includes 4 surveys from India [69, 70, 79, 80], and 1 each from Egypt [71], and Kuwait [73]. Developed refers to developed countries and includes 1 survey each from UK [81] and Italy [82].

† The percentage of infants infected (core antibody and/or surface antigen positive) during their first year calculated from model estimates. Study level variance estimates equals 0·293; σ_1^2 estimated to equal 0·949, constrained binomial variance used, i.e. $\sigma_1^2 = 1·0$.

quantify the magnitude of perinatal and horizontal infection. By quantifying these epidemiological variables we are able to compare the transmission of HBV between the main highly endemic areas of east Asia and sub-Saharan Africa.

Comparing estimates of the age-dependent forces

Table 4. *Summary of the risk to the infant of perinatal infection over the first year of life from HBeAg negative, HBsAg positive mothers by region***

	Sub-Saharan Africa	East Asia	Developing	Developed
Overall sample size	85	259	356	116
Range of sample sizes	38–47	15–108	11–186	24–92
Overall % infected†	8·0	13·2	13·6	7·2
95% confidence interval (%)	1·8–28·7	2·6–46·2	2·6–48·1	10·8–40·8

* Sub-Saharan Africa includes 1 survey from Kenya [58] and 1 from Senegal [74]. East Asia includes 4 surveys from Taiwan [14, 48, 75, 77], and 1 survey each from Hong Kong [78], Thailand [68] and Japan [76]. Developing includes 4 surveys from India [69, 70, 79, 80], and 1 each from Egypt [71] and Kuwait [73]. Developed includes 1 survey from UK [81] and Italy [82].
† The percentage of infants infected (core antibody and/or surface antigen positive) during their first year calculated from model estimates. Study level variance estimates equals 0·810; σ_1^2 estimated to equal 0·953, constrained binomial variance used, i.e. $\sigma_1^2 = 1·0$.
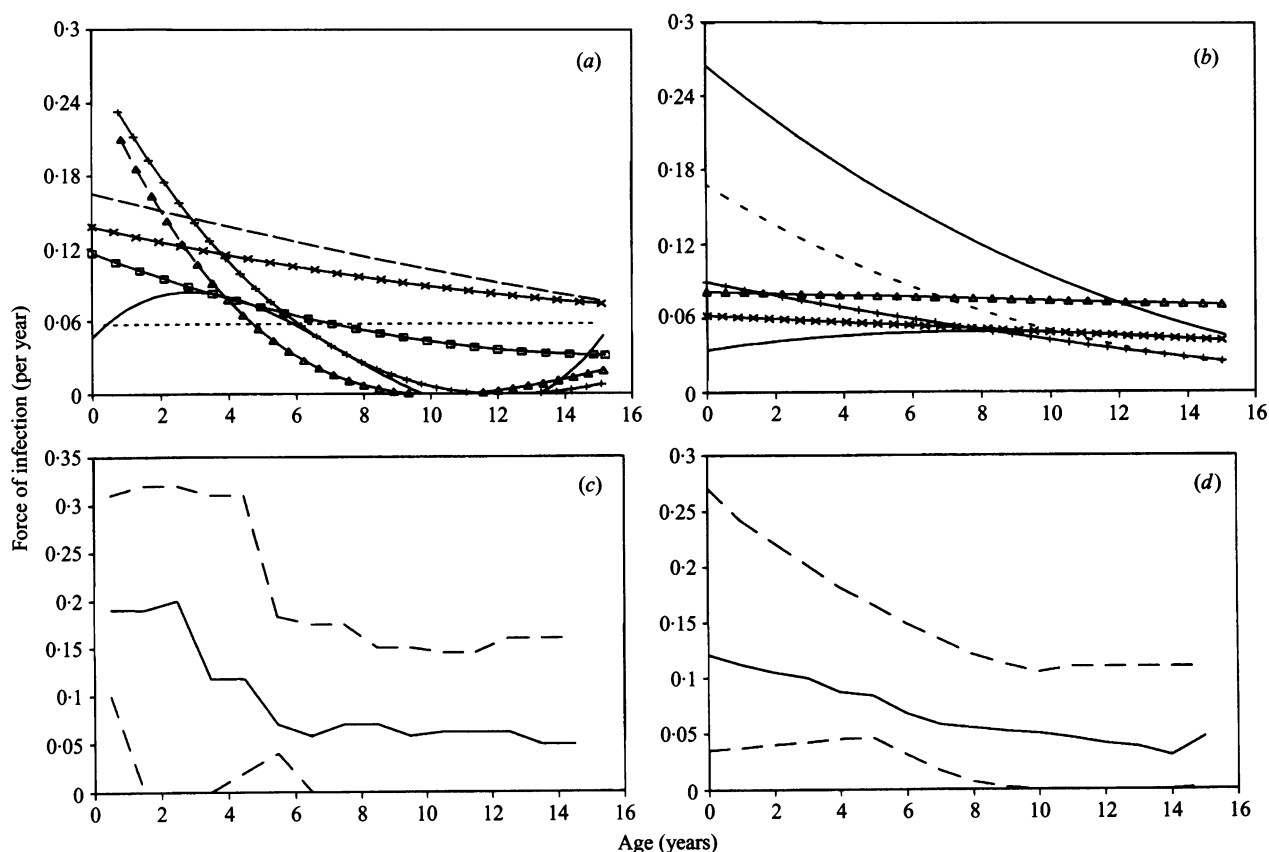

Fig. 2. Age dependence in the force of HBV infection in highly endemic communities. (*a*) Maximum-likelihood estimates are based on 7 surveys from sub-Saharan Africa, see text and [43] for details (solid line, Zambia [27]; dotted line, Nairobi [28]; dashed line, The Gambia [26]; +, Khalawaat, Sudan [29]; △, Saleim, Sudan [29]; ×, Senegal [30]; and □, South Africa [31]). (*b*) Maximum-likelihood estimates from 6 surveys in east Asia (solid line, Taiwan [32]; dotted line, Kinalaglagan, Philippines [33]; dashed line, Tagumpay, Philippines [33]; +, Santa Rosa, Philippines [33]; △, Agoho, Philippines [33]; and ×, Shanghai [34]). (*c, d*) Summarizes age dependent patterns in the force of infection from 16 different surveys, estimated by two methods (see text for details): discrete age-class (*c*) [42], and continuous age (*d*) [43]. In addition to the 13 surveys shown in (*a*) and (*b*), 3 more surveys from other highly endemic populations [35–37] were included. The median (solid line) and upper and lower bounds (dashed lines) were calculated for each year age group.

of infection in childhood revealed that similar patterns of HBV infection exist in highly endemic areas. Typically the force of infection is highest in young children and declines throughout childhood. The force of infection is therefore highest in those age groups that have a high probability of becoming a
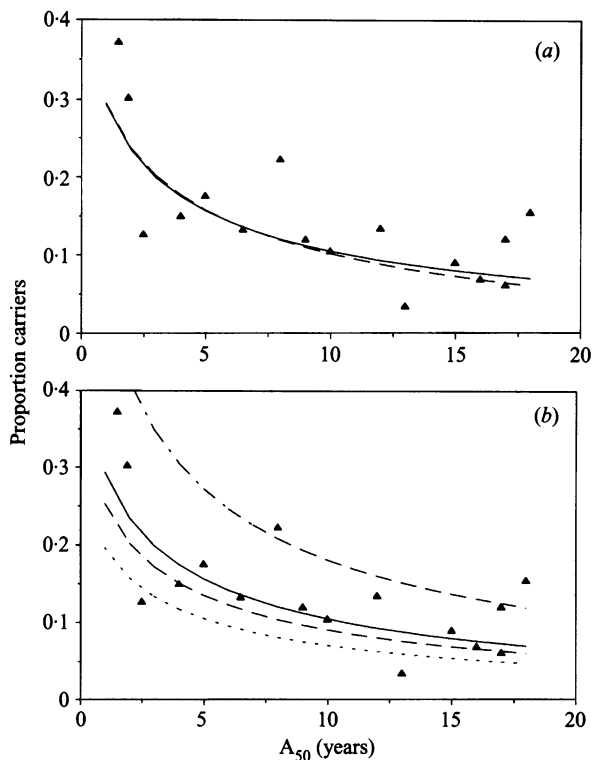
Fig. 3. Model results of the expected proportion of carriers in the population for a range of A_{50} values. The data points (▲) are the same as in Figure 1. (a) The model was solved for a constant (solid line) and a force of infection which decreases exponentially by age (dotted line). The rate of loss of carriage, γ, and the natural mortality rate, μ, was assumed to be constant ($1/40$ year^{-1} and $1/50$ year^{-1} respectively). In (b) the model was solved for different rates of loss of carriage, the half-life of carriage was 40 years (solid line), 30 years (dashed), 20 years (dotted) and no loss of carrier state (dot-dash). The foce of infection was held constant by age.

carrier. This common pattern suggests that highly endemic areas share common features that allow the efficient horizontal spread of the virus. The decline in the force of infection with age may be associated with the commonly observed decline in the prevalence of HBeAg positive carriers with age [32, 45, 46] or a change in the patterns of mixing between children. Alternatively, this apparent decline in the force of infection with age may be due to common temporal factors, such as population growth. However, there is no evidence that increasing population density increases the rate of infection for HBV [47], and it is difficult to envisage alternative time-dependent factors common to all areas studied. The results of the simple model suggest that this decline in the force of infection over the childhood years is not a necessary condition for generating the observed decline, between surveys, in the prevalence of carriers with increasing values of A_{50}. This suggests that the relationship between the

prevalence of carriers and the value of A_{50} is primarily the result of higher average ages at infection in lower transmission areas resulting in a decrease in the proportion who become carriers.

The major difference in the epidemiology by HBV between sub-Saharan Africa and east Asia appears to be in the incidence of perinatal transmission. A greater proportion of HBsAg positive carriers mothers appear to be highly infectious (positive for HBeAg) in east Asia than in sub-Saharan Africa, and there may be a lower risk of perinatal infection from HBeAg positive mothers in Africa than in east Asia. The difference in prevalence of HBeAg among carrier mothers might be explained by environmental or genetic differences, or perhaps as a consequence of perinatal transmission, i.e., infection during the perinatal period may be associated with a slower rate of loss of HBeAg. The apparent lower risk of perinatal transmission from HBeAg positive mothers in Africa may be due to differences in perinatal practices, though the statistically significant difference may be an artifact of the small number of studies with small sample sizes. The point needs to be clarified as it would have important implications from the prevention of perinatal transmission in other parts of the world.

Although east Asian countries appear to have a higher incidence of perinatal transmission they do not have lower values of A_{50} nor greater prevalences of carriers than sub-Saharan African countries. This may be because horizontal transmission appears to be the main route by which carriers are infected, even in east Asia. In pre-vaccination Taiwan, which appears to have the highest known incidence of perinatal transmission, we can estimate that 60%, or more, of carriers were probably infected horizontally (from [18, 32, 48, 49]); in sub-Saharan Africa over 90% of carriers would be expected to be infected via horizontal transmission (from [18] and Tables 1–4). The relative importance of horizontal transmission is supported by the results of the model which showed that the observed patterns of infection could be generated by a model of the horizontal spread of HBV. Although a higher incidence of perinatal infection does not seem to influence the overall prevalence of carriers or the rate of infection to any large extent, it may have important implications for the control of HBV, as perinatal infection is more difficult to prevent by immunization than horizontal transmission.

The importance of carriers to the transmission of HBV can be roughly estimated by comparing the duration of the carrier state and the infectiousness of

carriers with the longevity of the acute stage and the infectiousness of the acutely infected individuals. Serological data from longitudinal studies of carriers suggests that HBsAg is lost from a proportion of carriers, and that the mean duration of the carrier state (in all carriers) is somewhere in the range of 20–200 years [10, 50–53]. The results of the model provide an alternative method for estimating the rate of loss of carriage, and suggest that the mean duration of the carrier state is 30–40 years. The relative infectiousness of carriers can be estimated from perinatal transmission studies of acutely and chronically infected mothers. Serological data, mainly from developed countries, suggest that acutely infected mothers transmit HBV to 70–75% of their infants within 3 months of birth [39, 54, 55], whereas only 0–27% of carrier mothers infect their infants in a similar time period [55–58]. Comparing the mean proportion of infants infected from acutely and chronically infected mothers suggests that on average (i.e. including both HBeAg positive and negative mothers) mothers in the acute phase are approximately 7 times as infectious as chronically infected mothers. Hence, the lower infectiousness of carriers is more than offset by the longer periods of infectiousness of carriers compared to acutes (30–40 years compared to about 3 months [22]), and they are therefore more important to the spread of HBV.

Areas with a low average age at infection, irrespective of the route of transmission, will, on average, have high prevalences of carriers because of the age-dependent nature of becoming a carrier. These areas can therefore be expected to have a higher force of infection (as carriers are responsible for the majority of transmission) and hence a lower average age at infection. This positive feedback probably accounts for the very high variation in endemicity among different localities and will tend to produce hyper-endemic regions if the conditions for childhood infection are met. If, however, childhood infection is prevented by mass immunization of infants, the decrease in the rate of generation of new carriers will be greater than linear because of the decline with increasing age in the risk of a carrier. Mass immunization will reduce the circulation of virus in the community such that the average age at infection in those not successfully immunized will increase (as seen in other childhood infections [59]), hence reducing their chances of becoming infected (Fig. 2), and, if infected, of becoming carriers. In addition, even if vaccination does not induce life-long immunity,

delaying infection in young children will itself reduce the numbers of carriers in a population. As many countries are considering, or have already begun, mass immunization programmes, the quantitative aspects of these programmes on the transmission dynamics of HBV require urgent attention.

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