The estimated cost-effectiveness of vaccination in infants born to hepatitis B virus positive mothers

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Summary

An existing cohort model of hepatitis B virus (HBV) infection and disease was adapted to analyse the cost-effectiveness of targeted HBV vaccination in infants born to HBV surface antigen (HBsAg) positive mothers. The results suggest that vaccination of infants of HBsAg carrier mothers is cost-saving. It would be cost-effective to devote significant extra resources to ensuring high coverage in these children, particularly for doses given after birth (which are often given in the primary care setting). Improving the timeliness of vaccination, could save up to 14 lives, and could presumably be achieved at little extra cost.

Introduction

Hepatitis B virus (HBV) is blood-borne and can be transmitted between an infected mother and her child around the time of birth (cross-placental transmission is rare) [1]. The consequences of HBV infection can be grave. Infection can lead to acute hepatitis, which may occasionally result in liver failure and death, or chronic infection which eventually leads to cirrhosis, liver cancer and death in many individuals if left untreated [1]. The development of the carrier state is related to the age at infection [2]: infants infected within the first year of life have around a

90% chance of becoming carriers, whereas only about 5% of infected adults develop the carrier state.

The hepatitis B surface antigen (HBsAg) is a marker of infectiousness [1]. The “early antigen” (HBeAg) correlates with being highly infectious to others. Those HBsAg carriers who have antibody to the e-antigen (anti-HBe positive) tend to have lower viral loads and are therefore less infectious [1]. These markers can be detected in the serum of infected individuals using relatively inexpensive and highly sensitive and specific tests.

Safe and effective vaccines have been available against HBV since the 1980s. If given early after birth, they can prevent perinatal infection, particularly if combined with passive immunisation with hepatitis B immunoglobulin (HBIG) [1,3].

Although HBV infection is relatively rare in the UK [4], as infant infection can lead to serious health problems later in life [1], and there are highly sensitive tests and mechanisms to prevent infection (vaccines and immunoglobulin), antenatal screening and post-partum vaccination has been adopted. In 1998 the Government recommended that by 2000 all pregnant women should be offered screening for hepatitis B at each pregnancy and that infants born to HBsAg positive mothers receive a complete course of HBV immunisation (Health Service Circular 1998/127). The recommended schedule is currently that infants born to low-risk infected women (HBsAg positive, anti-HBe positive) receive four doses of HBV vaccine at birth and at, 1, 2 and 12 months of age, and that infants born to high risk mothers also receive a course of HBIG at birth [5].

Audits of the antenatal screening and targeted vaccination programme [6-8] and routine immunisation coverage data [9], suggest that the uptake of this programme is not ideal. Antenatal screening appears to be near universally adopted and coverage for the birth dose (with or without HBIG) also appears to be high. However, vaccination (particularly with the later doses, usually not administered in hospital) is often delayed beyond the point when efficacy can be assured, or never received. For instance, Bracebridge et al. [6] report an audit of the antenatal screening programme between 1996 and 2000 in North Essex (a period when some health authorities used a 0,1,6 month schedule). They report an uptake of 99.9% for antenatal screening, 100% (29/29) uptake of HBIG in high risk babies (90% within 24 hours, as recommended [5]). Whilst coverage of the second and third doses were 97% and 93%

respectively, only 72% and 79% of these were given on time. Sloan et al. [10] reviewed national data on high risk babies over a comparable period (1996-2001) and found a similar picture. They found that 92% of high-risk babies received HBIG and their first vaccine dose within 48 hours of birth, 92% received a second dose, and 86% a third dose. However, only 65% of infants received their second dose within 7 weeks and of those on the (now universally recommended) accelerated schedule only 65% received their third dose by 3 months of age [10]. Routine coverage data [9] (that is likely to be less reliable than local audits) suggest that the number of at-risk children receiving three doses of HBV vaccine by 12 months of age is 69%, which varies considerably by region. Notably, in London, which has the highest incidence of at-risk babies, the reported coverage at 12 months of age is only 54% (only 58% of London PCTs submitted data). No information on timeliness is available in this dataset.

This paper assesses the cost-effectiveness of vaccinating infants of HBsAg positive mothers compared with no vaccination from the perspective of the health care provider. A previously used Markov model is adapted for the purpose (Siddiqui et al., unpublished [11]). As hepatitis B infection is rare in the UK, the effect of prevention of onward transmission is ignored. Hence, other things being equal this model will underestimate the benefits of the programme.

Methods

A previously used cohort model of HBV infection and disease, and associated costs and consequences was adapted. The model follows a birth-cohort, born to HBsAg positive mothers, over their lifetime with or without vaccination and HBIG administration. Details of the original model are given in Siddiqui et al. (unpublished) [11]. The model assumes that infected individuals either develop acute disease, or become chronic carriers, or have a sub-clinical acute infection and become immune. The probability of these outcomes is dependent on age, the rates being based on reviews of the literature [2,12,4]. Acute cases may develop fulminant liver cancer which leads to either death or immunity, or may simply pass into the immune state. Chronic carriers can lose their infectiousness at a gradual rate and become immune, or can progress to compensated cirrhosis. From here they may develop liver cancer (hepatocellular carcinoma, HCC), which may lead to death, or they may develop decompensated cirrhosis, which in turn can lead to death, or liver cancer. Age-and gender-specific background mortality rates (based on current UK population) are applied to all states. If acute cases receive a liver transplant they are returned to the immune class, whereas HCC or decompensated cirrhosis cases who receive a transplant are returned to the chronic carrier state. Parameters describing

these transition rates were taken from the literature, with one notable exception. The parameters describing the progression from the carrier state to cirrhosis, were estimated by fitting the model to data on age-specific incidence of HCC from a cohort of Taiwanese men [13], and HBV-associated mortality from the US [14]. In contrast to previous models of HBV progression and disease [15-17], the model did not assume a constant rate at which individuals developed disease. Instead, a gamma-distributed waiting period was approximated by subdividing the carrier state into seven identical Markov states. Carriers progress sequentially through these states at a rate that was assumed to be equal between each state, and was estimated by fitting the model to data using least squares. This gave a much better fit to the data than a simple exponentially distributed waiting time (which derives from the use of a single transition rate from the healthy carrier state), as used by previous authors. Figure 1, which is taken from Siddiqui et al [11], shows the poor fit to HCC data for previously published HBV models, and the improvement in fit that can be gained by allowing for a gamma-distributed waiting time in the healthy carrier state. In addition, as women seem to be less likely to develop HBV-associated disease [18], separate progression rates were estimated for women. The model therefore follows males and females separately, with the sex ratio at birth assumed to be 50%.

Costs and quality of life detriments associated with acute and chronic disease were taken from the literature [11], and all costs are in £2007. Many of these costs and quality of life detriments were taken from studies of hepatitis C virus infected patients. Age-specific background quality of life adjustments were taken from the literature [19]. A discount rate of 3.5% per annum was assumed for both benefits and costs, as recommended by NICE [20].

The cost of a pre-filled syringe of EngerixB (infant dose) is £9.67 [21]. HBIG is distributed by the HPA Centre for Infections and costs £97.95 per ampoule. Allowing for distribution and administration costs, we assume that the cost per dose is £120. We assume that administration costs for the birth dose of HBV vaccine is similar to subsequent doses, at £10 per dose. This is based on the costs of a nurse consultation in general practice [22]. It is recommended that children are tested at 12 months of age (at the same time as the booster dose is given), at an assumed cost of £20. Therefore a completed course for a high-risk infant would cost £218.68, and a complete course for a low-risk infant £98.68.

As most of the historical data are in terms of eAg status we use this as our basis of classifying risk. In the base-case we assume that 12% are High risk, based on the proportion HBeAg positive in the samples sent to the National Health Service Blood and Transplant centres in England [23] (in 2007, 57 of the 481 HBsAg positives were also HBeAg positive). Edmunds et al. [24] reviewed the risk of perinatal infection in the absence of vaccination in different regions. They found that the mean risk from HBeAg positive (high risk) mothers was between 73 and 88% in most regions, though it appeared to be lower in sub-Saharan Africa (estimated mean risk of infection 28% 95%CI 9-60%). The mean risk from HBeAg negative (low risk) mothers varied between 7 and 14% by region. Based on this, in the absence of vaccination, we assume that 85% and 10% of high and low risk babies respectively will be infected perinatally, with 90% of them going on the develop the carrier state.

In a recent meta-analysis, Lee et al. [3] reported that the efficacy of neonatal vaccination with HBIG at preventing HBV infection was 92% (CI 83%-97%, where efficacy is 1-relative risk). The efficacy of HBV vaccination alone was estimated to be 72% (95%CI 60-80%), and the additional efficacy of HBIG was 50% (95% CI 40-59%), which would give a combined efficacy of 86%. There were no significant differences in efficacy by schedule, type of vaccine used (plasma-derived or yeast derived) or by dosage (high or low). This study did not, however, report on the efficacy in those who receive an incomplete course of vaccine. Data from the SPC for Engerix B suggests that in healthy subjects 11-15 years of age following the 0, 1, 2 and 12 month schedule 15% and 89% of vaccinees will have protective levels of antibody at one month and 3 months respectively, and 95.8% will have protective antibody titres after 13 months. We therefore assume that those who receive only the birth dose of vaccine are not protected, 15% of those receiving two doses are protected, and those receiving three or more doses are fully protected, with an efficacy of 72% if HBIG is not given at birth and 90% if HBIG is also given at birth (within 48 hours). Those who receive HBIG, and 2 or fewer doses of vaccine are assumed to have 50% protection (the protection afforded by HBIG, as estimated by Lee et al.[3]) over the first year of life. We assume that those successfully immunised will be protected for life.

In the base-case we assume that coverage for any dose is 92%, and that all of these (if they are high risk) receive HBIG. We assume that 92% of these will receive a second dose (at 1 month), and 86% will receive their third and fourth doses (based on the dta from Sloan et al. [10]). Those who receive these subsequent doses will be tested at one year, other infants will not. The

base-case assumptions imply that those who receive their vaccine doses late are protected. This may not be the case. Hence, we also take a pessimistic vaccine coverage assumption, in which we assume that doses given too late do not benefit the child. In the pessimistic coverage scenario, coverage of the birth dose and HBIG (when needed) remains at 92%, but coverage of the 2nd and subsequent doses is assumed to be 65% (based on the data on timeliness reported by Sloan et al. [10]).

Unimmunised infants born to HBsAg carrier mothers are at continued risk of infection from their mothers and potentially other household members, even after the perinatal period. One study from Taiwan suggested that 38% children born to HBsAg mothers and not infected perinatally were subsequently infected over an average 18 month follow-up period [25], a horizontal infection rate of 26% per year (11.3% in infants whose mothers were anti-HBe positive). It is unlikely that such high rates of transmission would occur in the UK [26], though what the risk might be is difficult to ascertain. There are reports of high rates of horizontal infection in Somalis living in Liverpool [27], but other studies suggest much lower rates of horizontal infection [26]. To account for a likely increased risk of infection in children with a carrier mother, we assume a high risk scenario in which children not infected perinatally have an annual 1% risk of infection for the first 15 years of life and then revert to the risk of infection estimated for those of South Asian origin in the UK [4] (surveillance of high risk infants suggested that only 10% were of white ethnicity, whereas 36% were of South Asian origin [10]), and a low-risk scenario where the age-specific risk of infection is taken to be the average risk for South Asians in the UK [4] (cumulative risk of horizontal infection over first 15 years ~1%). The low-risk scenario is taken as the base-case.

Results

Annual number of infants born to HBsAg mothers

There were 690,000 live births in England and Wales in 2007 (www.statistics.gov.uk). National screening data (www.hpa.org.uk) suggest that the prevalence of HBsAg in women giving birth is between 0.3 and 0.4%. Taking the midpoint of these values, gives an estimated 2,415 babies born to HBsAg positive mothers annually.

Lifetime risk of disease in the cohort

In the absence of immunisation, 17% of infants born to HBsAg positive mothers are expected to become chronic carriers of HBV. Under the low risk scenario (in which their risk of

acquiring HBV subsequently is equal to the average risk for South Asians in the UK) 131 of these would be expected to die of their HBV infection (100 of them males). This amounts to 8% of the male cohort, and 3% of the females. Many would be expected to develop disease over their lifetime (see Figure 2). Without vaccination the lifetime discounted cost of treating HBV in this cohort would be an estimated £296 per birth, or £1730 per carrier. A total of £715,000 (discounted) in the cohort as a whole. The cohort would be expected to lose a total of 162 discounted QALYs over their lifetime from HBV infection. Since most QALYs are lost due to death and disease in elderly individuals (Figure 2), discounting has a major impact on the estimated numbers of QALYs lost. There would be an estimated 1201 undiscounted QALYs lost in the cohort as a whole with the low-risk scenario.

Using the high risk scenario a total of 167 deaths from HBV would be expected in the cohort over their lifetime. There would be an estimated 206 discounted QALYs lost, and the discounted total cost of treating HBV in the cohort would be an estimated £1,047,000.

The vaccination programme at current level

Vaccination at the base-case (optimistic) level of coverage is expected to reduce the incidence of perinatal infection by about 60%. This would result in an estimated saving of 90 deaths and 169 discounted QALYs in the cohort as a whole, compared with no vaccination. The cost of the vaccination programme is estimated to be £229,000. However, the programme is estimated to result in net savings to the health service of approximately £288,000 (discounted) over the life-span of the cohort. Vaccination of children of HBsAg positive mothers is a dominant strategy resulting in health gains and cost savings, compared with no vaccination. If we assume the high risk scenario, then the net savings of the programme is expected to be £489,000, and the programme is expected to result in 206 QALYs gained in the cohort compared with no vaccination.

The effect of vaccination at pessimistic levels of coverage

At pessimistic levels of coverage (but base-line risk), the overall efficacy of the programme at preventing perinatal infection is estimated to be 46% (44% for infections later in life). An estimated 76 deaths would be averted compared with no vaccination (i.e. 14 fewer than with the base-case assumptions). Similarly 27 fewer QALYs would be gained from the vaccination programme. The net savings in health care costs (compared with no vaccination) at this lower level of coverage would be £260,000 (£28,000 less than at the base-case coverage).

Effect of improving coverage

Improving the birth dose coverage (and HBIG if indicated) to 100%, but leaving the other levels of coverage at the base-case has a modest effect. An extra 193 children would receive a birth dose of vaccine, 23 of them being high risk (and would receive HBIG). This results in an estimate of 5 additional QALYs gained. Extra net savings to the health service of £6000 are realised over the life-time of the cohort. This is assuming that administration costs do not increase. If administration for the additional children vaccinated increase to approximately £28 per dose of vaccine or HBIG, then this increase in coverage would remain cost-saving.

Increasing coverage of the second to fourth doses, so that every child who initiates a vaccine course (92% of the cohort) completes it is expected to have a much greater impact. This would result in an extra 800 doses of vaccine being given. This would result in an expected 16 discounted QALYs gained and extra net savings of £18,000 over the life-span of the cohort (again, assuming administration costs are unchanged). Administration costs for each extra dose could increase to £32.50 for such a change to be cost-saving, and approximately £600 for the change to be cost-effective (at 30,000 per QALY gained).

Discussion

Vaccination of infants born to HBsAg mothers is highly cost-effective. Indeed, it is likely to be cost-saving. This is hardly surprising as they are at high risk of becoming a carrier of HBV, with all the health costs associated with this. Indeed, the antenatal screening programme overall (including the costs of testing mothers) has been estimated to be cost-effective in the UK [28,29].

The model suggests that increasing birth dose coverage (of vaccine and HBIG, when needed) results in modest health gains compared with improving coverage of subsequent doses. This follows from our assumption that those receiving only the birth dose are not protected. The benefits therefore arise from the increase in HBIG coverage in high risk infants. The model results suggest that much greater benefits can be gained from increasing coverage of the subsequent doses. These are usually given in primary care, whereas the birth doses are usually given in hospital. Improving both areas of vaccine delivery should be regarded as a priority, but reducing the drop-off in coverage for doses given after birth should be particularly targeted.

Most mothers who are HBsAg positive were born outside the UK, and ensuring that their children are fully vaccinated can be difficult, due to language and cultural barriers [8], particularly after they have left hospital (i.e. for the second to fourth doses). However, the model suggests that all reasonable efforts should be made to vaccinate these children. Administration costs associated with increasing doses 2-4 could increase to around £600 per dose, and the increase in coverage would remain cost-effective. Put in context, this amounts to over half a week of a community nurse specialist's time [22].

Many infants receive their vaccines late. As the use of vaccine and immunoglobulin in this context is primarily as post-exposure prophylaxis and exposure appears to be concentrated at birth, it is important that infants receive the whole course in a timely manner. Sloan et al. [10] show that high risk infants who receive their second and third doses late are at increased risk of infection. Taking their cut-offs for timely vaccine administration as an indicator of a loss of effectiveness of vaccination, then an extra 14 deaths in each cohort might be expected because doses are given too late. Improving the timeliness of vaccination could presumably be achieved at little additional cost.

Antenatal screening for HBsAg is nearly universally accepted. However, by no means all at-risk infants identified via this process receive their full course of vaccine in a timely manner. Ensuring that they do so is highly likely to be effective and cost-effective.

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Figure 1 a). The predicted incidence of HCC in men, using previously published models (lines): Fenn et al. [17], Tilson et al. [16] and Goldstein et al. [15], and that observed in Taiwanese men [2](dots). (b) comparison of UK model [11] to data from Taiwan [2] (pink) and the US [14] (blue) by assumptions about carrier-cirrhosis progression (number of carrier states). The model was fitted to both Taiwan and USA data assuming different ages of acquisition. Both figures are from Siddiqui et al. (unpublished) [11].

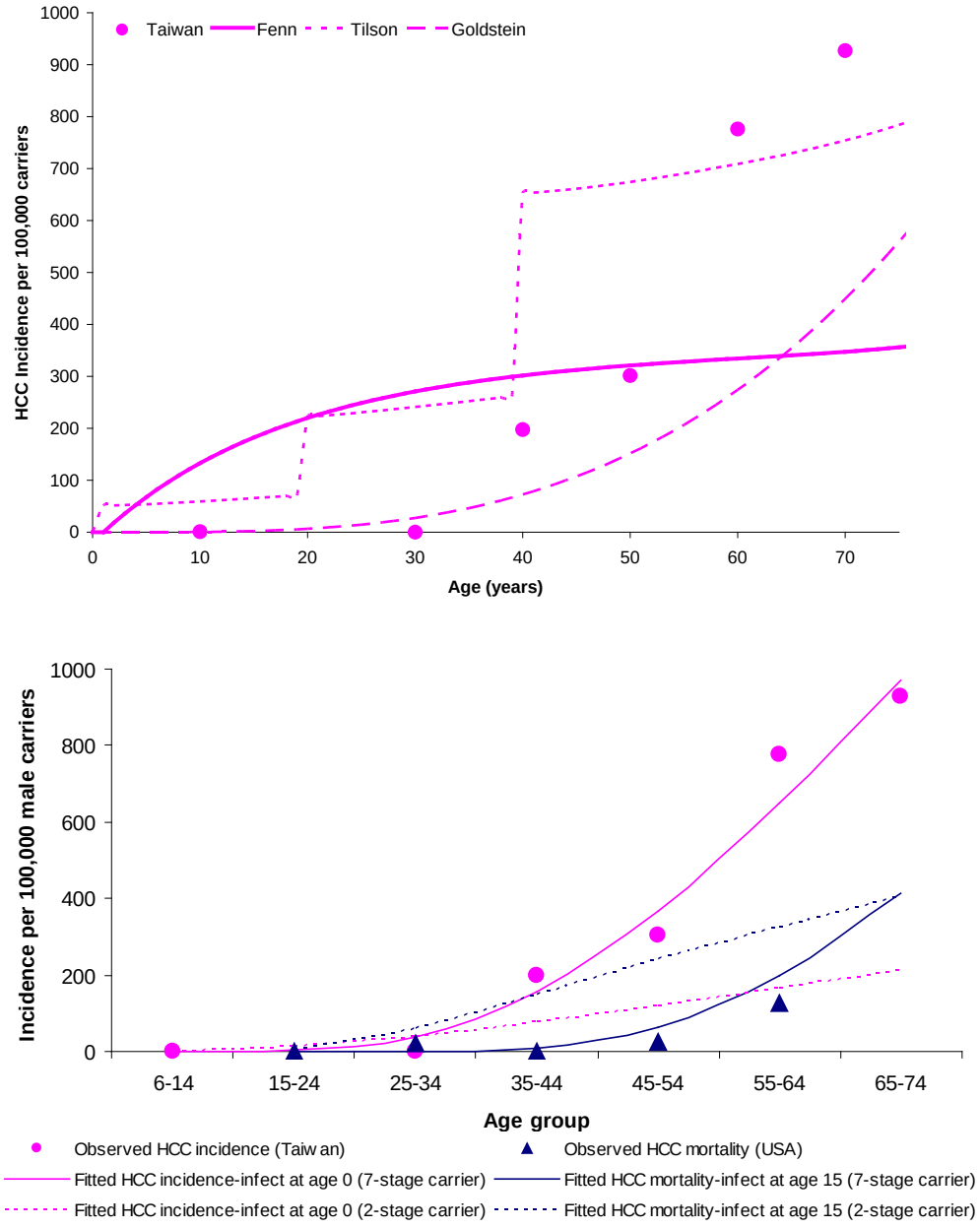

Figure 2. Progression to chronic HBV disease in the cohort, as predicted by the base-case model with the low-risk scenario. Left hand panels are for males, and right hand panels for females. Upper panels are without vaccination, lower panels with vaccination (both active and passive) at the base-line coverage levels.