10.1093/heapol/czi006
HEALTH POLICY AND PLANNING; **20**(1): 50–59

The cost-effectiveness of introducing hepatitis B vaccine into infant immunization services in Mozambique

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Objective: To estimate the cost-effectiveness of introducing hepatitis B vaccine into routine infant immunization services in Mozambique, which took place in the year 2001.

Methods: A decision analytic model was used to estimate the impact of hepatitis B vaccination. This model was developed for the WHO to estimate the global burden of disease from hepatitis B. Cost data of vaccine delivery and medical treatment related to hepatitis B infection were collected for the analysis.

Findings: The introduction of hepatitis B vaccine has increased the annual budget for immunization services by approximately 56%. It is predicted that more than 4000 future deaths are averted annually by the intervention. In the base case scenario, the incremental costs per undiscounted deaths averted amount to US$436, and the costs per undiscounted DALY averted amount to US$36. Since the major impact of hepatitis B vaccination will not start to be evident for at least another 40 years (deaths from hepatitis B mainly occur between 40–60 years of age), the cost per DALY averted rises to US$47, when using a discount rate of 3% on health effects. We found that the monovalent hepatitis B vaccine was considerably more cost-effective than the hepatitis B vaccine in combination with DTP.

Interpretation: If policy makers value future health benefits equal to current benefits, the cost-effectiveness of infant hepatitis B vaccination is in the range of other primary health care interventions for which similar analysis has been undertaken.

Key words: hepatitis B, vaccines, modelling, cost-effectiveness, economics, costs, Mozambique

Introduction

Hepatitis B vaccine introduction in Mozambique

The Global Alliance for Vaccines and Immunization (GAVI), launched in 1999, is an alliance between the private and public sector committed to saving children's lives and improving health through the widespread use of vaccines. GAVI collaborates closely with the Vaccine Fund, which provides financing for immunization services and for purchasing new and under-utilized vaccines against diseases such as hepatitis B, yellow fever and *haemophilus influenzae* type b (Hib). By March 2004, GAVI and the Vaccine Fund have helped finance the introduction of hepatitis B vaccine into routine childhood immunization services in 53 developing countries, of which 23 are in sub-Saharan Africa (http://www.vaccinealliance.org).

Mozambique was among the first 13 countries to receive awards for new vaccines granted by the Vaccine Fund. In a proposal to GAVI and the Vaccine Fund, the Vice Minister of Health in Mozambique requested support for introduction of hepatitis B vaccine in combination with diphtheria, tetanus and pertussis (DTP) vaccine. This proposal was endorsed by all members of the Inter-Agency Coordinating Committee for immunization services in Mozambique (Government of Mozambique 2000). The proposal was approved by GAVI in September 2000 and the first shipment of vaccines was received in Mozambique in April 2001. The vaccine, a DNA recombinant vaccine derived from hepatitis B surface antigen (HBsAg), is procured through UNICEF's supply division (http://www.supply.unicef.dk).

The financial support received from the Vaccine Fund for hepatitis B vaccine is currently planned to cease after 5 years. Hence, by 2005 the Government of Mozambique must have identified other funds to use for purchasing the vaccine, if the decision is made to keep the vaccine in the schedule. To prepare for this transition it is requested by GAVI that all countries receiving support submit a 'Financial Sustainability Plan' at the mid-point in funding (Financing Task Force of the Global Alliance for Vaccines and Immunization, 2003). Hence, the Ministry of Health in Mozambique submitted a Financial Sustainability Plan in 2002 (Ministry of Health 2002). According to the plan, the main strategy to be adopted to ensure continued funding for hepatitis B vaccine is increased advocacy for resources from the State budget as

well as from bilateral and multinational partners. A cost-effectiveness analysis of the hepatitis B vaccine is likely to be a useful tool for this strategy.

Evidence on cost-effectiveness and cost-benefit of hepatitis B vaccine worldwide

The global literature is relatively rich in economic evaluations of immunization against hepatitis B, especially studies from industrialized countries. Several reviews have been written that summarise the published economic literature to date (Jefferson and Demicheli 1994; Beutels et al. 2002; Aggarwal 2002; Sadykova 2002). Beutel's review covering economic evaluations after 1994 reports five studies from very low endemic countries, eight studies from low endemic countries, four studies from intermediate endemic countries, and two studies from highly endemic countries (Beutels 2001). These studies build on the 90 economic evaluation studies reviewed by Jefferson and Demicheli until 1994, of which 12 were from developing countries (Jefferson and Demicheli 1994). The overwhelming conclusion of these reviews is that the introduction of the hepatitis B vaccine can be fully justified on economic grounds, 'economic' grounds meaning either that the cost-benefit ratio is positive or that the cost-effectiveness ratio suggests the vaccine to be a good 'buy' for the public health services, or both. A consensus statement in 2001 concluded that universal hepatitis B vaccination (of infants or adolescents) is the most optimal strategy worldwide, except for a few areas of lowest endemicity. In general, the higher the endemicity, the more cost-effective it becomes to vaccinate in the earlier years of life (Beutels 2001).

Study aims

The objective of the study was to estimate the costs per death and Disability Adjusted Life Years (DALYs) averted from introducing hepatitis B vaccine into routine, infant immunization services in Mozambique. The analysis was undertaken from the point of view of society. We disregarded costs due to adverse events of the vaccine, as these events are reported to be minor (WHO 2000).

The type of analysis conducted was an incremental cost-effectiveness analysis, being the most relevant when deciding whether to keep hepatitis B vaccine within the national immunization schedule. This is because the immunization system already exists, and the intervention only involves adding the hepatitis B vaccine to the schedule. In practice, this means estimating the incremental costs associated with introducing the hepatitis B vaccine, while at the same time excluding all those costs that would have been incurred anyway (Gold et al. 1996; Drummond et al. 1997).

Methods

Effectiveness estimation

Hepatitis B virus (HBV) infection leads to one of three outcomes in an infected person: death from fulminant hepatitis within days or weeks of clinical onset of disease, recovery following asymptomatic or symptomatic acute HBV infection, or the development of a chronic carrier state which may or may not progress to clinical chronic liver disease, mainly cirrhosis or hepatocellular carcinoma (HCC), also called primary liver cancer (Kane et al. 1993).

A static model developed for WHO to estimate the global burden of disease from HBV was used to estimate deaths averted by introducing the vaccine in Mozambique (Gay et al. 2001). The model includes age- and sex-specific mortality that hepatitis B surface antigen (HBsAg) carriers

Table 1. Variables and values used in the epidemiological model when estimating deaths averted from hepatitis B vaccine in Mozambique

Variable	Base case values	Range used in uncertainty analysis	Distribution used in uncertainty analysis	Data source(s)
2001 birth cohort	794 650	–	–	Lopez et al. (2002)
Carrier rate	14% nationwide	12, 16%	Normal	7 published studies and expert opinion
Annual relative risk of carriers dying of HBV vs. other causes	1.05%	0.88%, 1.22%	Triangular	Data from Gambia, Taiwan, Alaska (Beasley 1981; McMahan 1990; Whittle et al. 2002)
Rate of loss of surface antigen after 25 years	1%	0.3%, 2.5%	Triangular	Literature review Gay et al. (2001)
Acute deaths as % of total deaths from HBV	10%	8%, 11%	Triangular	Goldstein et al. (2003)
Coverage rate of the third dose of DTP–hepatitis B vaccine	80%	70, 85%	Triangular	Base case is official country estimates (WHO 2002b). Range is based on PriceWaterhouseCoopers (2002).
Vaccine efficacy (3 doses)	95%	90, 99%	Triangular	WHO hepatitis B management guidelines (WHO 2001b) for base case and upper range. Lower range based on assumption about vaccine storage quality.
Vaccine wastage	25%	None	–	MOH in Mozambique
Discount rate	0% and 3%	–	Alternative scenarios	Gold et al. (1996)

experience due to HBV associated hepatocellular carcinoma (HCC) and cirrhosis. Deaths from other chronic sequelae of HBV infection, such as chronic active hepatitis, are assumed to be relatively small and ignored in the model (Gay et al. 2001).

Generally, the model operates by assuming that at any given age, the number of chronic hepatitis B related deaths is modelled by the following relationship:

$$Deaths_{\text{Age j,Sex i}} = Survivors_{\text{Age j,Sex i}} \times P_{\substack{\text{HBsAG Carriage} \\ \text{at Age j, Sex i}}} \times R_{\substack{\text{Risk of Death from Hepatocellular carcinoma} \\ \text{or Cirrhosis for Age j, Sex i}}}$$

The main advantage of this model is the limited data inputs needed to estimate deaths. The model could be improved if the incidence of acute infection could be predicted, as well as the proportion of acute infections that transition to chronic infections. However, little if any data are available from developing countries on the incidence of acute infections.

Risk of death from hepatocellular carcinoma (HCC) and cirrhosis in HBsAg carriers

The value for the risk of death in HBsAg carriers was the same as used in the WHO estimation of the burden of hepatitis for the year 2000 (Gay et al. 2001; WHO 2002a). As explained by Gay et al. (2001) this estimate is based on incidence data of HCC and cirrhosis recorded between 1988 and 1997 by the National Cancer Registry of The Gambia as well as prospective studies from Taiwan and Alaska (Beasley et al. 1981; McMahon et al. 1990). The age- and sex-specific mortality rates for HCC and cirrhosis were assumed to equal the incidence of these conditions, as the life expectancy of most cases is short. In the base case, where the average of the rates derived for Taiwan and The Gambia is used, 27% of male carriers and 9% of female carriers would be expected to die from hepatitis before the age of 75 years, in the absence of death from other causes. In the uncertainty analysis we attach a distribution to this variable with a likely range (see Table 1).

Prevalence of carriage

A key input parameter of the model is the prevalence of carriage at 25 years. Above this age the prevalence is estimated by the following relationship:

$$P_{\substack{\text{Age i, Sex} \\ \text{Prevalence of carriage} \\ \text{at Age i, for given Sex}}} = P_{\substack{\text{Age 25} \\ \text{Prevalence of carriage} \\ \text{at Age 25, both sexes} \\ \text{combined}}} \times \underbrace{\exp\{-\alpha(i-25)\}}_{\substack{\text{Probability of remaining} \\ \text{HBsAg Positive}}} \times \underbrace{\exp\{-\beta_{Sex} i^{n+1}/(n+1)\}}_{\substack{\text{Probability of not dying} \\ \text{from Hepatitis B related} \\ \text{liver disease}}}$$

The following parameter values were used, derived from a literature review (Gay et al. 2001): $\alpha = 1\%$, $\beta_M = 0.0133/100\,000$, $\beta_F = 0.0038/100\,000$, $n = 2.71$.

A range is attached to α in the sensitivity analysis. Unfortunately, there are no published studies available from Mozambique on HBsAg carriage, not for individuals around 25 years old or for any other age groups. However, by interviewing hepatitis B experts in Mozambique, the following information was gathered:

- The main transmission route is believed to be horizontal between young children under 5 years of age. The carrier rate is believed to be around 20% for 3–4 year old children. However, a proportion of these children clear carriage and for 25 year olds the carriage is believed to be around 15%.
- Evidence is emerging that carriage rates decrease as people move from rural to urban areas. Although this effect is not entirely understood, it is hypothesized that this may be due in part to changes in living conditions and reductions in family sizes, as well as later age of mothers at the birth of their first child, thereby reducing vertical transmission.

Based on this information and on a review of published evidence from other sub-Saharan African countries, including Madagascar, Nigeria, Zaire and Zimbabwe (Kew et al. 1977; Jager et al. 1990; Kiire et al. 1990; Harry et al. 1994; Jacobs et al. 1994; Boisier et al. 1996; Madzime et al. 1999), the best estimates of carriage rates of 25 year olds in Mozambique are the following:

- 15% carrier rate in rural areas, where 80% of the Mozambican population lives;
- 10% carrier rate in urban areas, where 20% of the Mozambican population lives.

In the base case we use an adjusted rate of 14% for 25 year olds.

Deaths from acute hepatitis B

The model does not estimate deaths from acute hepatitis B. Instead, we assume that acute deaths amount to 10% of the deaths from chronic hepatitis. This assumption is based on findings from Goldstein et al. (2003) when estimating the global reduction in hepatitis B burden from vaccination. As with deaths from chronic hepatitis B, the risk of death from acute disease is dependent on the age of infection. When using the age structure of infection from sub-Saharan Africa, Goldstein et al. (2003) finds that deaths from acute disease amount to approximately 10% of all deaths from hepatitis B. This assumption is varied in the uncertainty analysis.

Population data

Data on 2001 births in Mozambique were derived from the United Nations Population Division (United Nations 2001). When estimating the future population numbers for the 2001 birth cohort, we used country- and sex-specific life tables from the WHO (Lopez et al. 2002). This ensures that co-morbidity is taken into account in the model.

DALY estimation

DALYs were estimated according to the formula published in the 1996 Global Burden of Disease series (Murray and Lopez 1996b). As suggested by Murray and Lopez, DALYs were calculated both with and without discounting the value of future life years with a 3% discount rate. Separate DALY estimates were calculated for acute disease, cirrhosis and HCC. The disability weight for an episode of acute hepatitis varies according to age and is reported between 0.170 and 0.212 on a scale from 0 to 1 (0 being the least 'damaging' and 1 being the most 'damaging'). The disability weight is quoted as 0.33 for cirrhosis and 0.239 for HCC (Murray and Lopez 1996b). The duration of disability for acute disease was assumed to be 0.17 years (Murray and Lopez 1996a). For cirrhosis and HCC the duration of disease varies according to age and sex. For cirrhosis the duration is between 5–10 years, and for HCC it is 0.7–2 years (Murray and Lopez 1996a).

Programme cost estimation

It was decided to do a full cost analysis of the immunization services, instead of only an incremental cost analysis of hepatitis B vaccine delivery. This enabled us to estimate the percentage change in costs due to the new vaccine. The ingredient approach for costing was used. We identified all resource items used for vaccine delivery along with their respective quantities and unit costs (Kou 2002).

Data were to a large extent collected from the Expanded Programme on Immunization (EPI) central offices. Approximations and assumptions were required to estimate the allocation of staff time and vehicles to immunization services, as these resources are shared with other health services. Capital items were annualized using a 3% discount rate.

We estimated the incremental costs of introducing the DTP-hepatitis B combination vaccine as well as hepatitis B vaccine in monovalent form. Hepatitis B vaccine in combination with other antigens already in the schedule does not involve any additional injections and is therefore considerably simpler to introduce than a vaccine in a separate vial (Kou 2002). Furthermore, since the combination vaccine was introduced in the same vial size as before (10 dose vial), it does not take up more space in the cold chain either. However, these advantages might be outweighed by the relatively large price difference between the two types of vaccines. Presently, the price of DTP-HepB combination vaccine is around US$1.2 per dose (DTP vaccine alone is only around US$0.12), but monovalent hepatitis B vaccine can be procured from UNICEF for only around US$0.27 per dose (UNICEF 2004). Delivery costs of the monovalent vaccine include syringes, safety boxes, waste management of used syringes, transport and storage in addition to the vaccine. We assessed the impact on the cold chain of introducing a monovalent vaccine by using the WHO 'vaccine volume calculator' (WHO 2001a).

Future costs saved

Future health service costs saved from the avoidance of treating complications of hepatitis B include the acute morbidity associated with the initial infection as well as chronic liver disease due to HBV, such as chronic active hepatitis, chronic persistent hepatitis, cirrhosis and hepatocellular carcinoma. All these conditions involve outpatient visits where either treatment takes place or patients are referred to a higher level of care, which in some cases will lead to inpatient admission.

We estimated the annual number of acute and chronic morbidity cases by using a model similar to the one used for the effectiveness estimates (Gay et al. 2001). The model estimates were compared to available surveillance and hospital inpatient data from Maputo for verification. Since the numbers were in similar ranges, we concluded that our model estimates were robust. Data on resource utilization and unit costs of treatment were collected from the government health sector as well as from traditional healers. We did not collect data from the formal, private health sector as these facilities still cover only a very small proportion of the Mozambican population. Instead, we assumed that the traditional healer costs covered all out-of-pocket costs of the patients.

The assumptions made when estimating treatment costs are summarised in Table 2. Cost data for inpatient care were collected at Maputo Central Hospital, which is a regional and national referral hospital with 1500 beds. The population served by the hospital from Maputo is about 1.1 million. There are no figures on the number of referrals from other districts.

Costs of treatment consist of hospital overhead costs as well as patient-specific costs related to drugs and laboratory tests. Due to resource constraints, it is not possible for the hospital to provide optimal treatment to patients with acute or chronic hepatitis and the drugs used are considerably less expensive than those that comply with international treatment standards (Core Working Party 2000). For patients with cirrhosis and hepatocellular carcinoma, there is essentially no treatment available in Mozambique.

Generalized unit costs for outpatient care in African settings were used to approximate government outpatient costs in Mozambique (Goodman et al. 2000). Treatment costs from traditional healers were collected from the Traditional Medicines Unit at the National Institute of Health in Mozambique. The costs of receiving treatment from a traditional healer essentially consist of the consultation fee as well as the cost of a traditional herbal tea, which is usually prescribed for HBV-related symptoms.

After estimating the approximate annual treatment costs due to HBV, we estimated the proportion of treatment costs that will be saved in the future due to vaccination by multiplying these costs by the vaccination coverage rate and the vaccine efficacy. Finally, we discounted future cost savings to their present value using a 3% discount rate and assuming that the costs will be incurred on average 40 years into the future.

Table 2. Variables and input values used to calculate treatment costs saved from preventing HBV-related disease in Mozambique (2001 US$[a])

	Variable	Base case	Range used in uncertainty analysis	Distribution used in uncertainty analysis	Data source
Annual no. of morbidity cases due to hepatitis B virus (HBV):					
Acute HBV infections	No. of patients	22 869	Point estimate		Model estimate
Chronic morbidity	No. of patients	2 058	Point estimate		Model estimate
Government health service costs:					
Hospital inpatient	No. of admissions in whole country	12 000	Standard deviation of 2000	Normal	Maputo Quarternary Hospital, assumption about limited access to care
	Average length of stay (days)	8	5, 11	Triangular	Maputo Quarternary Hospital
	Cost per day, including drugs	US$5	3, 7	Triangular	Maputo Quarternary Hospital
Hospital outpatient facility	% of outpatient visits at hospital	0.32	Point estimate		Goodman et al. (2000)
	No. of visits	3 840	Standard deviation of 500	Normal	Assumption that 50% of patients use government facilities
	Cost per visit	US$3	2, 4	Triangular	Goodman et al. (2000)
Health centre outpatient	No. of visits	8 160	Standard deviation of 1000	Normal	Assumption that 50% of patients use government facilities
	Cost per visit	US$1	Point estimate		
Laboratory tests	% patients who have laboratory test	5%	Point estimate		Maputo Quarternary Hospital
	Cost per laboratory test	US$4	Point estimate		Maputo Quarternary Hospital
Out-of-pocket/private costs to traditional healers:					
Visits to traditional healer	% patients seeking care	80%	70%, 90%	Triangular	Assumption
Visits to traditional healer	No. of visits per patient	3	2, 5	Triangular	Assumption
Cost of treatment	Costs per consultation	Maputo: US$3 Other urban: US$0.63 Rural: US$0.21	Maputo: US$2, 4 Other urban: US$0.56, 0.69 Rural: US$0.15, 0.27	Triangular	Traditional Medicines Unit, National Institute of Health, Mozambique
	Cost of traditional tea per person	US$0.40	Point estimate		Traditional Medicines Unit, National Institute of Health, Mozambique

*The exchange rate used when calculating the values was 24 000 MTS for US$1.

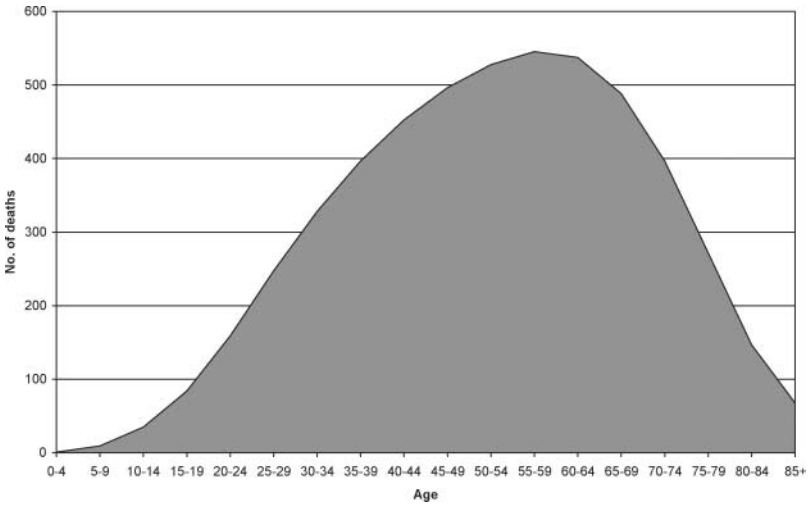

Figure 1. Predicted deaths from chronic hepatitis for 2001 birth cohort in a scenario with no vaccination

Cost-effectiveness

Cost-effectiveness ratios were calculated by subtracting the predicted, discounted, annual treatment costs savings from the annual vaccine delivery costs and dividing this number by the predicted number of hepatitis B deaths and DALYs averted from vaccination. Cost-effectiveness ratios were calculated with and without discounting future health effects by 3% per year. Future costs were always discounted by 3% per annum.

Uncertainty analysis

Based on assumed ranges and distributions of the uncertain variables used in the model, a probabilistic uncertainty analysis was done by a Monte Carlo simulation (2000 simulations) using Crystal Ball©, giving prediction intervals around the mean cost-effectiveness ratios (Decisioneering Inc. 2003). The input values used in the model for the base case, as well as the ranges and distributions used for the uncertainty analyses, are summarised in Tables 1 and 2.

Table 3. Total annual immunization services costs in Mozambique and incremental costs of hepatitis B vaccine introduction (2001 US$)[a]

Cost category	Without hepatitis B vaccine	% of total	Incremental costs of DTP–hepB vaccine[c]	Incremental costs of hepatitis B monovalent[d]
Capital costs				
Vehicles	221 230	5.8	0	0
Storage	223 188	5.8	0	0
Social mobilization		0.0	7 580	7 580
Training		0.0	49 605	49 605
Total capital costs	444 418	11.6	57 185	57 185
Recurrent costs				
Personnel	1 090 340	28.5	0	0
Vaccines	868 047	22.7	2 106 843	616 761
Auto disposable syringes	171 500	4.5	0	212 357
Disposable syringes	21 150	0.6	0	0
Safety boxes	35 420	0.9	0	11 869
Surveillance	226 266	5.9	0	0
Transport operating & maintenance	485 970	12.7	0	24 299
Cold chain storage	487 513	12.7	0	24 376
Total recurrent costs	3 386 207	88.4	2 106 843	889 661
TOTAL COSTS	3 830 625	100.0	2 164 028	946 846
Percentage increase			56%	25%
Costs per fully immunized child[b]	6.60		10.34	8.24

[a] The exchange rate used when calculating the values was 24 000 MTS for US$1.
[b] Assuming a target population of 725 000 and vaccine coverage rate of 80%.
[c] Assumed price of DTP–hepB vaccine: US$1.078 per dose.
[d] Assumed price of hepatitis B vaccine: US$0.2862 per dose.

Results

Effectiveness

Figure 1 illustrates the deaths from chronic hepatitis B predicted by the model with base case parameters in a situation with no hepatitis B vaccine introduced for the 2001 birth cohort. A total of 5767 deaths from acute and chronic disease are predicted in the base case scenario, with the majority occurring in the age group 35–56 years. With a birth cohort of 794 650 children, it is thus predicted that 0.73% of the cohort will die from HBV-related disease in the absence of vaccination.

In the base case scenario it is predicted that 4383 deaths and 53 275 DALYs are averted by the introduction of hepatitis B vaccine, and once these are discounted, taking into account that the deaths are averted on average 40 years into the future, this reduces to the equivalent of 1043 deaths and 40 752 DALYs annually.

Programme costs

Table 3 presents the annual costs of immunization services and the incremental costs of introducing hepatitis B vaccine, in combination with DTP or as monovalent vaccine. In 2001, total immunization services costs would have been approximately US$3.83 million without hepatitis B vaccine introduction, or around US$6.6 per fully immunized child. When assuming that hepatitis B vaccine was delivered for the full financial year, the costs increased to US$5.99 million or US$10.3 per fully immunized child. This is a 56% increase in total costs. It can be seen that the large majority of incremental costs, US$2.1 million, were due to the costs of vaccines. While Mozambique used to pay US$0.079 per dose of DTP vaccine, the price per dose of the vaccine combined with hepatitis B is US$1.08. Other additional costs incurred were social mobilization and training of staff, together making up 2.6% of the incremental costs.

Introduction of the monovalent vaccine would only result in a 25% increase in total costs. With the vaccine volume calculator we estimated that introduction of the monovalent vaccine would increase the vaccine storage volume by 29%. According to the Ministry of Health logistician, this increase can be accommodated at national and provincial level with the present cold chain capacity. However, at district and health facility level the cold chain capacity might present some limitations, even though these could perhaps be accommodated with better space management. We assumed a 5% increase in cold chain and transport costs to cover for the additional work load in logistics.

Future costs saved

We estimate that total treatment costs from HBV-related illnesses amounted to US$540 509 in 2001. Out-of-pocket costs amount to 7% of the total. When discounted by 3% per year for 40 years, annual treatment costs reduce to US$165 697. Total potential discounted savings are US$125 930 per year. When using the assumptions summarised in Table 2, the probabilistic uncertainty analysis shows that the treatment costs saved lives in a 95% prediction interval of US$73 880–200 607. Hence, a fairly wide prediction interval due to the uncertainty about these costs.

Cost-effectiveness

Table 4 presents the cost-effectiveness ratios in the base case scenario. At zero discount rate, the incremental cost for combination vaccine is US$436 per death averted and US$36 per DALY averted. When discounting future health effects at 3% per year, the incremental cost-effectiveness ratio increases to US$1833 per death averted and US$47 per DALY averted. The cost-effectiveness results for the monovalent vaccine are considerably more favourable. At zero discount rate, the incremental cost for the monovalent vaccine is US$178 per death averted and US$15 per DALY averted. When discounting future health effects at 3% per year, the

Table 4. Incremental cost-effectiveness of hepatitis B vaccine in Mozambique: base case scenario (2001 US$)

Intervention	Net costs	Total deaths	Total DALYs	Incremental costs	Incremental deaths	Incremental DALYs	Cost-effectiveness ratio (deaths)	Cost-effectiveness ratio (DALYs)
Combination vaccine								
Undiscounted results								
No hepatitis B vaccination	165 697	5 767	70 099					
Hepatitis B vaccination	2 077 866	1 384	16 824	1 912 169	4 383	53 275	436	36
Discounted results (3%)								
No hepatitis B vaccination	165 697	1 373	53 621					
Hepatitis B vaccination	2 077 866	329	12 869	1 912 169	1 043	40 752	1 833	47
Monovalent vaccine								
Undiscounted results								
No hepatitis B vaccination	165 697	5 767	70 099					
Hepatitis B vaccination	946 846	1 384	16 824	781 149	4 383	53 275	178	15
Discounted results (3%)								
No hepatitis B vaccination	165 697	1 373	53 621					
Hepatitis B vaccination	946 846	329	12 869	781 149	1 043	40 752	749	19

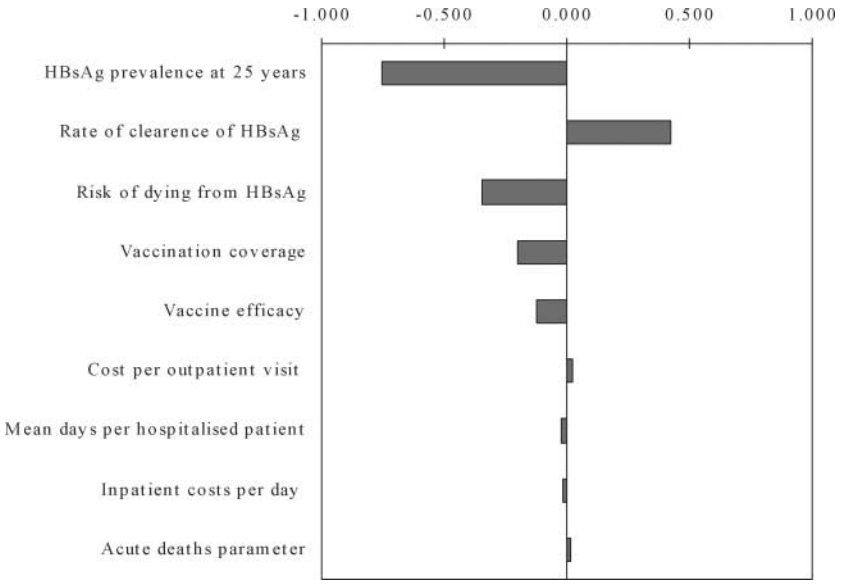

Figure 2. Costs per DALYs averted: sensitivity chart

incremental cost-effectiveness ratio increases to US$749 per death and US$19 per DALY averted.

Uncertainty analysis

The probabilistic uncertainty analysis reveals that the cost-effectiveness ratios are located in wide prediction intervals. The 95% prediction intervals are summarised in Table 5. The uncertainty chart is illustrated in Figure 2 for costs per discounted DALY averted. The uncertainty chart shows to what extent the cost-effectiveness ratio is sensitive to uncertain variables, as defined in Tables 1 and 2. The overall uncertainty is a combination of the ratio's uncertainty to the uncertain variables as defined in the model, and the uncertainty of the variables. It can be seen that the cost-effectiveness result is most sensitive to HBsAg prevalence at 25 years of age and to the rate of clearance of HBsAg. These are thus the most important assumptions in the model. This is not surprising, as these are the variables that determine the predicted number of deaths from hepatitis B. In order to narrow the prediction interval, more accurate information on these two variables needs to be generated.

Discussion

This study has found that more than 4000 premature deaths will be averted in Mozambique through routine hepatitis B vaccination of infants in the 2001 birth cohort. However, most of these benefits will not take place for around 40–50 years, when the major long-term complications would otherwise take place. The cost-effectiveness of introducing the hepatitis B vaccine into routine vaccination services costs US$15 per discounted DALY for monovalent vaccine and US$36 per discounted DALY for combination vaccine. When health effects are discounted, the cost per DALY averted increases to US$19 and US$47 for monovalent and combination vaccine, respectively.

Table 5. Uncertainty analysis of cost-effectiveness of DTP–hepatitis B combination vaccine

Outcome measure	Mean value	95% interval
C/E (discounted deaths)	2034	(1404, 3067)
C/E (discounted DALYs)	52	(36, 78)
C/E (non-discounted deaths)	496	(329, 777)
C/E (non-discounted DALYs)	40	(27, 59)

The relatively large difference between the discounted and non-discounted estimates illustrates that, in the case of hepatitis B vaccine, it is crucial to report both approximations. When both results are reported, it can be left to policy makers to determine to what extent they value a future life as much as a present, thereby deciding which result to use when comparing the cost-effectiveness ratios of different health interventions.

Comparison with cost-effectiveness evidence of hepatitis B vaccine from other countries has several problems: different cost base years, different methodologies and different units of effect. For example, in the only published economic evaluation to date based on real experience of introduction of hepatitis B vaccine in a highly endemic country, Hall et al. (1993) estimate the cost of averting a death from liver cancer in The Gambia to be in the range US$150–200, but this is at 1993 prices, and the study does not discount the future health effects. Other studies have modelled hypothetical cost-effectiveness ratios in developing country settings, ranging from US$16 per life year gained in India (Aggarwal et al. 2003), to US$21 per Quality-Adjusted Life Year gained in a group of developing countries (Shepard et al. 1995), to US$58 per life year saved in Israel (Sadykova 2002). Therefore, while comparison is difficult due to different outcome measures and different cost base years, it can be concluded that the cost-effectiveness of the monovalent vaccine in Mozambique has around the same, or more favourable, cost-effectiveness ratio

compared with other developing country settings. Clearly the combination vaccine in Mozambique has a less favourable cost-effectiveness ratio, due to the considerably higher unit cost of the vaccine.

The most pressing question faced by health policy makers in Mozambique is whether the hepatitis B vaccine should be financed from public funds, based on the vaccine delivery costs and the estimated cost-effectiveness of the vaccine. However, there is very limited cost-effectiveness information on other health interventions in Mozambique to compare with the results in this study, in order to make resource allocation decisions based on comprehensive and up-to-date cost-effectiveness evidence. To our knowledge, this is the first cost-effectiveness study of a health intervention in Mozambique.

When comparing the cost per DALY averted with other cost-effectiveness studies of health interventions in sub-Saharan Africa, and in comparison with the annual gross national income per capita in Mozambique of US$210, the intervention can be considered moderately cost-effective. Goodman et al. (2000) illustrated that preventive interventions against malaria in a very low income country were in the range of US$4–85 per discounted DALY averted. Hence, the cost-effectiveness of the monovalent hepatitis B vaccine is in the lower range of interventions to prevent malaria, and the combination hepatitis B vaccine in the middle range.

In the absence of AIDS-related deaths in Mozambique, the cost-effectiveness of hepatitis B vaccine would in no doubt be more favourable. Deaths from hepatitis B mainly occur between the ages of 40–60 years. However, due to the AIDS epidemic, many people have died before this age.

One of the weaknesses of our analysis is that herd immunity is not taken into account when estimating the long-term effect of the vaccine. This means that we are likely to overestimate the cost-effectiveness ratio. Another weakness is that the data on treatment costs are only based on data collection from one health care institution. Moreover, we have not included treatment costs of formal, private health institutions, such as private hospitals, and we have not tried to estimate the proportion of patients who seek higher quality health care overseas. Another major weakness with regard to treatment costs is that it is impossible to predict what type of technologies for treatment will be available for hepatitis B related illnesses in Mozambique in 40 years time. In our analysis we have assumed that the costs of future treatment will be similar to today, but this assumption is very uncertain. If the Mozambican health sector were to invest in improved and more expensive treatment of hepatitis B, the cost-effectiveness of the vaccine would improve.

Given these economic arguments, and given the greatly increased but short-term financial support available for funding new and under-utilized vaccines, this study comes at an important time. With some early experiences of the first phase of GAVI already reported from the field, with data on coverage, implementation success and vaccine costs, cost-effectiveness ratios will reflect the reality more closely than previous studies that cover generalized groups of countries and contain major data assumptions. Therefore, the improved accuracy and certainty of the cost-effectiveness results will add to the debate on financing and vaccine sustainability. Also, the cost-effectiveness model developed for this study can be readily applied to other countries.

References

Aggarwal R. 2002. Inclusion of Hepatitis B vaccine in national immunization program in India: A review of economic analyses. Report undertaken for the World Health Organization Regional Office for South-East Asia.

Beasley RP, Hwang LY, Lin CC, Chien CS. 1981. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22 707 men in Taiwan. *The Lancet* **2**: 1129–33.

Beutels P. 1994. Economic evaluations of Hepatitis B immunization: a global review of recent studies 2000. *Health Economics* **10**: 751–74.

Beutels P, Edmunds WJ, Antonanzas F et al. 2002. Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. *Pharmacoeconomics* **20**: 1–7.

Boisier P, Rabarijaona L, Piollet M, Roux JF, Zeller HG. 1996. Hepatitis B virus infection in general population in Madagascar: evidence for different epidemiological patterns in urban and in rural areas. *Epidemiology and Infection* **117**: 133–7.

Core Working Party for Asia-Pacific Consensus on Hepatitis B and C. 2000. Consensus statements on the prevention and management of hepatitis B and hepatitis C in the Asia-Pacific region. *Journal of Gastroenterology and Hepatology* **15**: 825–41.

Decisioneering Inc. 2003. Crystal Ball 2000.2. Denver, Colorado.

Drummond MF, O'Brien B, Stoddart GL, Torrance GW. 1997. *Methods for the economic evaluation of health care programmes*. Second edition. Oxford: Oxford University Press.

Financing Task Force of the Global Alliance for Vaccines and Immunization. 2003. Guidelines for preparing a national immunization program financial sustainability plan, July 2003. Available from [http://www.gaviftf.org].

Gay N, Edmunds JW, Bah E, Nelson CB. 2001. Estimating the global burden of hepatitis B. Department of Vaccines and Biologicals. Geneva: World Health Organization. Unpublished work.

Gold MR, Siegel JE, Weinstein MC. 1996. *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press.

Goldstein ST, Zhou F, Hadler SC. 2003. The global reduction in Hepatitis B disease burden from vaccination. Abstract from International Viral Hepatitis Conference 2003, Sydney, and personal communication with S Goldstein, Center for Disease Control, Atlana, USA, October 2003.

Goodman C, Coleman P, Mills A. 2000. *Economic analysis of malaria control in Sub-Saharan Africa*. Geneva: Global Forum for Health Research.

Government of Mozambique. 2000. Proposal for support submitted to GAVI and The Fund. September 2000. Available from [http://www.vaccinealliance.org].

Hall A, Robertson R, Crivelli P et al. 1993. Cost-effectiveness of Hepatitis B vaccine in The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **87**: 333–6.

Harry TO, Bajani MD, Moses AE. 1994. Hepatitis B virus infection among blood donors and pregnant women in Maiduguri. *Nigeria. East African Medical Journal* **71**: 596–7.

Jacobs B, Berege ZA, Schalula PJ, Klokke AH. 1994. Secondary school students: a safer blood donor population in an urban area with high HIV prevalence in East Africa. *East African Medical Journal* **71**: 720–3.

Jager H, Goussard B, Kabeya CM et al. 1990. Voluntary blood donor recruitment: a strategy to reduce transmission of HIV-1, hepatitis-B and syphilis in Kinshasa, Zaire. *Infusionstherapie* **17**: 224–6.

Jefferson T, Demicheli V. 1994. Is vaccination against Hepatitis B efficient: a review of world literature. *Health Economics* **3**: 25–37.
Kane M, Clements J, Hu D. 1993. Hepatitis B. In: Jamison DT, Bobadilla J-L, Mosley WH, Measham AR (eds). *Disease control priorities in developing countries*. New York: Oxford University Press for the World Bank, 321–30.
Kew M, Marcus R, Geddes E. 1977. Some characteristics of Mozambican Shangaans with primary hepatocellular cancer. *South African Medical Journal* **51**: 306–9.
Kiire C and African Regional Study Group. 1990. Hepatitis B infection in sub-Saharan Africa. *Vaccine* (supplement) **8**: s107–12.
Kou UK. 2002. *Guidelines for estimating costs of introducing new vaccines into the national immunization system. WHO/V&B/02.11*. Geneva: World Health Organization, Department of Vaccines and Biologicals.
Lopez AD, Ahmad OB, Guillot M et al. 2002. *World mortality in 2000. Life tables for 191 countries*. Geneva: World Health Organization.
Madzime S, Adem M, Mahomed K et al. 1996. Hepatitis B virus infection among pregnant women delivering at Harare Maternity Hospital, Harare Zimbabwe, to 1997. *Central African Journal of Medicine* **45**: 195–8.
McMahon BJ, Alberts SR, Wainwright RB, Bulkow L, Lanier AP. 1990. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. *Archives of Internal Medicine* **150**: 1051–4.
Ministry of Health. 2002. Plano de Sustentabilidade Financeira do Programa Alargado de Vacinacao. Maputo: Mozambique Ministry of Health. Available from [http://www.vaccinealliance.org].
Murray CJL, Lopez AD. 1996a. *Global health statistics*. Geneva: World Health Organization.
Murray CJL, Lopez AD. 1996b. *The global burden of disease*. Geneva: World Health Organization.
PriceWaterhouseCoopers. 2002. Report on the immunization data quality audit (DQA) for the year 2001–Mozambique. Study undertaken for the Global Alliance for Vaccines and Immunization.
Sadykova D. 2002. Cost-effectiveness analysis of vaccination against Hepatitis B in Kahzakstan. Master of Public Health thesis. Jerusalem: Hadassah Hospital-Hebrew University School of Public Health.
Shepard DD, Walsh JA, Kleiau E, Stansfield S, Bhalotra S. 1995. Setting priorities for the Children's Vaccine Initiative: a cost-effectiveness approach. *Vaccine* **13**: 707–14.
UNICEF. 2004. Supply division, at [http://www.supply.unicef.dk], accessed 8 April 2004.
United Nations. 2001. World population prospects: The 2000 revision file 4: Births by major area, region, and country, 2001-2050. Estimates 2001-2050. POP/DB/WPP/Rev.2000/1/F5. New York: United Nations.
Whittle H, Jaffar S, Wansbrough M et al. 2002. Observational study of vaccine efficacy 14 years after trial of hepatitis B vaccination in Gambian children. *British Medical Journal* **325**: 569.
WHO. 2000. *Supplementary information on vaccine safety. Part 2: Background rates of adverse events following immunization*. Department of Vaccines and Biologicals. WHO/V&B/00.36. Geneva: World Health Organization.
WHO. 2001a. Vaccine volume calculator: An aid for the introduction of new vaccines. Available at [http://www.who.int/vaccines-documents].
WHO. 2001b. *Introduction of hepatitis B vaccine into childhood immunization services. Management guidelines, including information for health workers and parents. WHO/V&B/01.31*. Geneva: World Health Organization.
WHO. 2002a. *The World Health Report 2002: Reducing risks, promoting healthy life*. Geneva: World Health Organization.
WHO. 2002b. *WHO, Vaccines and Biologicals. WHO vaccine-preventable diseases: Monitoring system. 2002 global summary*. Geneva: World Health Organization.

Acknowledgements

In Mozambique, there were several people who provided important information to help validate the model input values: Dr Joao Manuel Fumane (Director, National Institute of Health), Mr Sergio Skateas (National Institute of Health), Dr Jorge Barreto (Immunologist, National Institute of Health), Dr Iacubo Omar (Clinical Director at Maputo Central Hospital), Dr Ratiba Omar (Maputo Central Hospital, Medicine Ward), Dra Lina Cunha (Maputo Central Hospital, Medicine Ward), Dra Ana Charles (EPI Manager), Dr Manuel Novela (Advisor to EPI Manager) and Mrs Balbina Mario (EPI Logistics). In WHO Geneva, Dr Lara Wolfson assisted with the effectiveness estimates. The opinions in this paper are those of the authors and not necessarily those of the institutions they represent.

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