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Cost-benefit analysis of a nationwide neonatal inoculation programme against hepatitis B in an area of intermediate endemicity

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Abstract

***Study objective*—The aim was to estimate the costs and benefits of a nationwide neonatal vaccination campaign against hepatitis B in Israel for the 1990–2034 period.**

***Design*—Using morbidity, mortality, utilisation, and cost data from Israeli and international sources, a spreadsheet model was constructed to carry out the cost-benefit analysis.**

***Setting*—The entire State of Israel, an area of intermediate endemicity.**

***Participants*—The population of Israel from 1990–2034.**

***Main results*—A policy of immunising all Israeli neonates would, for a cost of $13·8 million, reduce the number of cases of hepatitis B during the 1990–2035 period in the cohort from 359 000 to 166 000 and save the nation around $21·5 million in health resources alone, $16·6 million in averted work absences, and a further $0·6 million in averted premature mortality costs. Even when the savings to the health services ($0·6 million) arising from the reduction in hepatocellular carcinoma are excluded, the direct benefit to cost ratio is 1·51/1, still in excess of unity.**

***Conclusions*—The decision to adopt a nationwide neonatal inoculation policy, starting in January 1992, appears to be not only medically but also economically justifiable.**

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Hepatitis B virus (HBV) infection is a major health hazard worldwide. It is estimated that between 200 and 300 million people are hepatitis B surface antigen (HBsAg) carriers.[1–3] Persons at increased risk in industrialised nations are those whose occupation, illness, or behavioural habits bring them into frequent contact with blood, blood products,[4 5] or possibly other body fluids. Such persons include health service workers, homosexuals, parenteral drug misusers, and prisoners. The morbidity and mortality of acute and chronic hepatitis B virus infection generate not only considerable direct health care costs, but also substantial indirect costs in terms of premature mortality costs and costs of days lost from work.

Available hepatitis B vaccines are safe and effective in preventing infection in adults,[6 7] children,[8] and infants at risk.[9] A recent study reported the virtual elimination (a decrease in incidence of 99%) of hepatitis B transmission over a five year period in persons of all ages as the result of widespread use of hepatitis B vaccine in remote Alaskan Eskimo villages.[10 11] Arevalo and Washington[12] found that routine screening of pregnant women (with subsequent inoculation) in the USA would be cost-effective at a disease prevalence rate of 0·06%, well below the national prevalence rate in the USA of 0·2%. A national policy of routine screening for all pregnant women would result in net savings in excess of $105 million per annum.

By November 1989, 23 of the 35 countries and areas in the WHO's Western Pacific region had started hepatitis B immunisation of newborn children[13]; nine more were expected to start in 1990.

Up to January 1991 in Israel, hepatitis B vaccination has been offered only to hospital and laboratory workers. Screening and vaccination of neonates is carried out in only a few of the country's 36 general hospitals. The cost of hepatitis B vaccines has been declining rapidly since recombinant vaccines have replaced serum derived vaccines, falling from $100 for three paediatric doses (including cold chain and administration costs[14]) in 1980 to approximately $2·80 in 1989.[15] This huge decrease in costs prompts an examination of the feasibility of a nationwide neonatal vaccination campaign.

This paper will present a cost-benefit analysis of a nationwide neonatal immunisation programme against hepatitis B for the 1990–2035 period. The model analysed uses methodology developed by Mulley *et al*[14] and sometimes relies on data adapted from studies in other countries, as not all the relevant data are available from the Israeli population.

The incremental costs and benefits of the vaccination strategies will take into account changing needs for ambulatory care, hospital admissions, work absences, and mortality benefits from projected reductions in acute hepatitis and its sequelae: chronic active hepatitis, cirrhosis, and primary hepatocellular carcinoma.[16–23]

Methods

DATA

Notifications (reported cases)

Viral hepatitis cases are reported individually, based on clinical diagnosis with or without laboratory confirmation by the attending physician, clinic, hospital, or other health care institution. Data are collected in the epidemiology department and public health divisions of the Ministry of Health. In January 1992, cases began to be reported with classification given to the type of hepatitis (A, B, nonA–nonB), instead of under the general heading of hepatitis.

In Israel, an average of 3666 cases and 13·1 deaths from acute viral hepatitis were reported

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annually during the period 1971–1985.[24–26] However in reality the total number of hepatitis virus infections in general and hepatitis B in particular is underestimated. As with most infectious diseases, there is considerable underreporting. Estimates of the reporting rate include those by Reisler *et al*[27] (27%–39%), Schwartz *et al*[28] (27%–56%), Kark and Bar Shani[29] (33% to 50%), Green *et al*[30] (40%–60%), and Fattal (41·2%)[31], the latter estimate based solely on a Kibbutz population. In our calculations we used a figure of 33·33%, based on the results found by Eliakim[32] in a study using ambulatory records. A similar rate (33%) has been found in (west) Germany.[8]

During the period 1971–1985, seroepidemiological studies indicated wide variations in the rates of hepatitis B infection between sexes and differing ethnic groups in Israel.[32–37] During the period 1971–1985 the case fatality rate for hepatitis was 3·56/1000 notifications. The percentage of males in notified hepatitis cases ranged from 53·3% in 1985 to 58·8% in 1974, averaging 55·2% during this period, compared to the USA (60·8%)[38] and the United Kingdom (67·6% to 74·2%).[39–40]

Annual reported incidence rates per year ranged from 0·051% in 1953 to 0·139% in 1979, averaging 0·087% during the period 1971–1985. In different Israeli populations, Sandler[35] and Green[30] reported attack rates 0·119% and 0·125%. Eliakim[32] reported that annual incidence rates based on Ministry of Health data varied between 0·051% and 0·132% for the period 1953–1974. These rates were then adjusted to between 0·18% and 0·297% when data based on ambulatory records at the insuring sick fund were used, reflecting a far higher reporting rate.

Published reports indicate that acute hepatitis B infection accounts for less than 9% of all hepatitis among Jews in Israel, with a further 11% having "non-A non-B" (mainly hepatitis C) hepatitis infection.[41] Around 10% of acute viral hepatitis in Israeli Defence Force conscripts is of type B,[35] 15% in Ethiopian immigrants,[42] and as high as 29·4% in pregnant women.[43] Schwartz[28] estimated only 65% of cases to be type A; however, higher estimates approaching 80% for hepatitis A infection were found in other Israeli studies.[34 38 42] An estimate of 17·9% was used, based on the newly established system which began reporting hepatitis by type in January 1992; this is considerably lower than that reported in the USA (30·9% in 1987).[44]

Hospital admissions

The most recent available hospital admission data by diagnosis are those of 1979 when 1288 persons (55·4% male) or 24·4% of reported hepatitis cases were admitted with hepatitis as their primary diagnosis, with an average length of stay of 9·7 days[46] compared with 9·4 days in 1976.[47] A small meta-analysis, based on the combined information of various case studies between 1972 and 1982,[31 45 48] calculated the average length of stay for hepatitis B cases to be 12·5 days, compared with 12 days in the USA[49] and 12·8 days in England.[50] This was only 11·7% longer than that of non-type-B hepatitis stays (11·2 days). The percentage of all notifications admitted to hospital in Israel (44·6%) during the period 1971–1980[24 25] was similar to that found in west London (48%).[39] The percentage of all hospital admissions for type B hepatitis found in various Israeli case studies ranged between 12·2% and 28·9%.[35 45 48 51 52] Case studies have found a predominance (ranging from 65%[45] to 75%[53 54]) of males among persons admitted to hospital for hepatitis B.

STRATEGIES AND ASSUMPTIONS

There are four main vaccination strategies: (1) active vaccination of every newborn without prevaccination screening of mothers for hepatitis B virus; (2) screening pregnant women followed by passive-active vaccination of babies at risk; (3) screening pregnant women followed by active vaccination of babies at risk; (4) screening pregnant women followed by active vaccination of babies at risk whose mothers are surface antigen positive (HBsAg+) and e antigen negative (HBeAg−) and with active and passive vaccination of at-risk babies whose mothers are HBsAg+/HBeAg+.

Strategy 1

Instituting a policy of inoculating all newborns by active vaccination (strategy 1) would reduce horizontal and vertical transmissions. Such a programme should operate for 45 years from 1990 until 2034 to ensure the near elimination of vertical and horizontal transmission risk within families. This specific programme does not include the provision of any booster doses in future years.

Perinatal transmission from an infected mother to her newborn varies from 12·5% to 90% depending on the hepatitis E antigen (HBeAg) status of the carrier mother.[12 20 21 32 55–60] A recent study among children born in the USA to Southeast Asian refugees found higher hepatitis B rates among children whose mothers were HBsAg carriers at birth and among children who lived in households with carrier siblings, suggesting both perinatal and horizontal child to child transmission paths.[61] We assumed a sensitivity of 98% for the HBsAg test and a transmission rate of 16·5%, being the midpoint of an 8–25% range relevant to Israel where approximately 98% of HBsAg carriers have antibodies to the E antigen (anti-HBe+) and less than 10% of HBsAg+/anti-HBe+ mothers are also hepatitis B virus-DNA+.[60 62]

Projections of the numbers of newborns were based on the 100 757 births in 1989, and a crude birth rate of 22·1/1000, adjusted downwards by a factor of 0·1/1000 per year, to reflect expected demographic changes in the population.

Earlier studies reported a range of vaccine efficiency rates from 70% to 96·8% for different protocols of hepatitis B immunoglobulin (HBIG) and active hepatitis B virus inoculation.[64–68] We used a vaccine efficacy figure of 95%[69] for a three dose hepatitis B vaccine protocol. It is now believed that in areas where the majority of HBsAg+ mothers are anti-HBe positive there is no need also to provide HBIG.[70 71]

Approximately 10% of vaccinees are expected to report temporary soreness or erythrema at the injection site.[6 33 72] In total, minor reactions are expected to occur in 25% of vaccinees.[14] Approxi-

mately 10% of these reactions will result in a physician visit[73] costing $4·67 each (15 minutes at $16 per hour physician costs plus five minutes of secretarial or nurse costs at $8 per hour). Shaw *et al*[74] reported 41 neurological adverse events (including five convulsions, 10 Bell's palsy, and nine Guillain-Barré syndrome) in 850 000 persons who received hepatitis B vaccination (0·0048%). Approximately 0·001% of children are expected to have severe adverse reactions, assumed to require three days of care in a general hospital ward at $265 per day, and two days of intensive care at $794 per day for an acute reversible condition[75] costing $2383 per case.

The figure of 3·08 severe reactions in 1990 probably represents an overestimate, since babies reacting severely to the first vaccination are unlikely to be revaccinated. There are no known serious chronic side effects of the vaccination in neonates.[12 64 66 76] It was assumed that there would be no fatalities as a result of the vaccination campaign due to improvements in the vaccine incorporated since Mulley's study,[14] which assumed a fatality rate of one per million vaccinations.

Based on a cost of $2·30 per paediatric dose,[77] with a vaccine wastage rate of 6%, the cost of three doses (including syringes and swabs) for the estimated 102 514 newborns in 1990 is $799 415 (including $43 210 for adverse reactions). The net present value of costs to the health services (using a 7·5% discount rate) of a programme from 1990 to 2034 is $13·81 million (including $0·75 million for adverse reactions).

Strategy 2

An alternative strategy (number 2) would be to screen each mother for HBsAg at a cost of approximately $7·17 per test. Only children born to positive mothers would then be given an HBIG dose (costing $20) and three hepatitis B vaccine doses. Our calculation of the number of children born to positive mothers included adjustments for multiple births and stillbirths.[78] Total health service costs for 1990 are $741 165 including $705 602 for screening mothers, $25 970 for providing HBIG to neonates, $9704 for hepatitis B vaccinations, and $519 for adverse reactions.

Strategy 3

A protocol of screening mothers and using only three active hepatitis B vaccinations to neonates at risk (strategy 3) will cost $715 195 in 1990, representing a saving of $25 970 in HBIG costs over strategy 2. Since the total cost of strategies 2 or 3 using screening is virtually the same as that for inoculating all neonates, substantial savings will only occur if the percentage of HBsAg positive mothers is considerably lower than the 2·0% figure used in this paper, or the price of three child doses of hepatitis B vaccine rises relative to HBsAg test costs.

Strategy 4

Strategy 4 would involve screening not only for HBsAg but also for anti-HBe status. This would enable active hepatitis B vaccinations to be given to at-risk babies whose mothers are anti-HBe positive, and active-passive vaccinations to be given to the 2% of at-risk babies whose mothers are HBeAg positive. On account of the extra costs of the HBeAg screening tests the total cost of strategy 4 in 1990 will be around $1·42 million, making it the least cost-effective of all the screening options.

COSTS AND CHOICE OF STRATEGIES

Table I lists the costs in 1990 and the discounted costs for the period 1990–2034 of carrying out the four vaccination strategies. Screening strategy 4 is rejected as it is by far the most expensive. Strategies 2 and 3 are rejected in favour of strategy 1, which provides protection for all newborns, as there are not only economic cost-effectiveness considerations but also ethical considerations in favour of providing protection for the large number of babies whose mothers do not fall into the at-risk category. For example, vaccinating the entire newborn population would only increase costs by around 3·4 to 8·5%; in contrast, if we choose to prescreen mothers and vaccinate only babies at risk (strategies 2 or 3), only 2·0–2·5% of newborns will be covered instead of 100% (assuming full compliance). A disadvantage of both strategies 2 and 3 is that they provide no protection for the 98·0% of children born to hepatitis B surface antigen negative (HBsAg−) mothers and only represent small savings over the use of strategy 1. These children will be at risk for infection through horizontal transmission, for example from an HBsAg+ father or sibling. As a result the effectiveness of these strategies is likely to be lower than that of inoculating all neonates. Therefore the vaccination of all neonates (strategy 1) is likely to be more cost-beneficial than a strategy of universal screening with a passive-active or active immunisation. The remainder of this paper will consist of a cost-benefit analysis of strategy 1, the active vaccination of every newborn without prevaccination screening of mothers for hepatitis B virus.

The cost-benefit analysis is based on a vast array of demographic data (age structures and projections, labour force participation), epidemiological data (hepatitis incidence and transitory probabilities to hepatocellular carcinoma), health service data (type and amount of care required for hepatitis cases), and economic data (costs of inoculation, costs of caring for hepatitis cases). These were entered into a model using a LOTUS 1–2–3 spreadsheet. The major advantage of having the model on a spreadsheet (in comparison to writing the model in program form) was the relative ease of adding in new values as new information became available, changing the model specification and performing sensitivity analyses.

Table I Costs of screening strategies ($ millions) (including adverse reactions)

Strategy	*1990*	*1990–2034*[a]
1: Active vaccination of every newborn without prevaccination screening of mothers for HBV	0·80	13·81
2: Screening pregnant women followed by passive-active vaccination of babies at risk	0·74	13·17
3: Screening pregnant women followed by active vaccination of babies at risk	0·72	12·73
4: Screening pregnant women followed by active vaccination of babies at risk whose mothers are HBsAg+/HBeAg− and with active and passive vaccination of at risk babies whose mothers are HBsAg+/HBeAg+	1·42	25·30

[a]Net present value using a 7·5% discount rate
HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen

Results

COST OF TREATING HEPATITIS B CASES

Vaccination using strategy 1 will result in a considerable reduction in hepatitis B morbidity and mortality. The appendix lists the costs of visits, hospital admissions and laboratory tests, as obtained from the Ministry of Health and the General Sick Fund (which insures over 75% of the population).

The prices of many tests and assays exceed those reported in earlier papers based on European[50 79] and American data.[12 14] The higher Israeli costs could be due to a combination of higher imported equipment costs, discriminatory market differential pricing by drug suppliers, inefficient laboratory practices, and high price to real cost differentials in the price lists of the Ministry of Health and Sick Funds. Since outlays for medication and surgery are usually minimal in hepatitis B patients and outweigh any increased isolation costs, the hospital costs for hepatitis B are assumed to be only 85% of the average $265 per diem hospital admission fee.

The appendix also lists estimates based on current practice in Israel of the quantity of services applicable to various forms of hepatitis B. Table II shows the cost by type and stage of hepatitis B as well as the transitional probabilities of developing further stages of hepatitis B by vaccination status.[14] An annual discount rate of 7·5% was used over a 20 year time horizon in order to aggregate expenditures incurred by chronic, persistent, and carrier cases across time. Based on experience in Israel, only 1% of carriers were assumed to present themselves for examination. Chronic active hepatitis B encompasses 30–60% of cirrhosis cases during the first 20 years following acute infection.[80–82]

Rapid death from fulminant hepatitis (median age of 45 years[14]) incurs $8341 in health care costs during only seven days in an intensive care unit. Such intensive care was assumed to cost $1192 per day, 4·5 times the average per day hospital cost on account of such factors as intensive care and blood products.

The cost of each stage of hepatitis B was multiplied by its probability of occurrence in order to calculate the average cost of hepatitis B per case. Because of the assumed greater severity of hepatitis in an unvaccinated patient,[14] the average direct cost was nearly 3·5 times that of a non-responder vaccinee ($706 *v* $207).

BENEFITS

The proposed nationwide intervention programme is based on a three dose vaccine to all neonates from 1990 to 2034. The triple dose is expected to provide protection for at least five years. Estimates of vaccination efficiency have ranged between 70% and 95%.[4 6 13 17 41 43 54 61 64 83–86] We used the upper estimate of 95% reflecting improved developments in vaccination techniques. We assumed that the incidence rate of hepatitis B in vaccinees and the transmission rate from mothers to neonates would fall by the vaccine's efficacy rate of 95% during the first five years of life. As no data are available on the effectiveness of the vaccine for longer periods, we assumed that vaccine efficiency would fall by 15% every five years thereafter, being 80·75% (95% × 85%) after 10 years, 68·64% (95% × 85% × 85%) after 15 years, etc. Assuming full compliance, this will reduce the number of cases in the cohort of persons who received a vaccination as neonates from 203 to 10 in 1990 and from 25 867 to 13 772 in 2035. An alternative option is to revaccinate every five years with a single booster injection until the age of 40 years. This would add an additional cost of around $11 million to the project during the period 1990–2035.

In addition to an absolute decrease in the number of cases, the case mix of hepatitis B and its complications will become less severe as a result of vaccination[14] (see table II).

The main monetary benefits of vaccination are the costs averted in caring for a reduced number of cases of hepatitis B. Reductions in incidence rate were multiplied by population estimates (assuming a 2% annual geometric growth rate in addition to an estimated immigration of 900 000 from the former USSR and 25 000 from Ethiopia during the 1990s) multiplied by the relevant unit cost per case depending on vaccination status (table II).

Benefits also occurred due to the reduction in numbers of neonates expected to develop hepatocellular carcinoma, since in the absence of a neonatal vaccination programme, 2·5% of neonates who acquire hepatitis B from their mothers are expected to develop hepatocellular carcinoma, and are expected to die from this condition[67] at a mean age of either 45 or 64 years, depending on whether their mothers were HBe+ or HBe− respectively.[69] Calculations earlier in this paper found chronic hepatitis costs to be 11·1% higher than those reported by Arevalo. This differential

Table II Direct costs of hepatitis B by stage

	Outcome (% of cases)		*Direct costs*
	Unvaccinated	*Vaccinated*	
Subclinical	50·00	75·00	$0
Anicteric	30·00	13·00	$477
Icteric	19·90	11·99	$888
Non-fulminant	99·90	99·00	
Resolved	89·91	98·01	$0
Asymptomatic carrier	4·995	0·495	$59
Persistent	3·497	0·347	$2111
Chronic active	1·499	0·149	$20 176
Fulminant	0·10	0·01	
Resolved	0·0200	0·0020	$3672
Asymptomatic carrier	0·0050	0·0005	$59
Persistent	0·0035	0·0004	$2111
Active	0·0015	0·0002	$20 176
Fatal[a]	0·0700	0·0070	$8341

[a]In addition there are mortality costs of $40 304

Table III Benefit and cost of hepatitis B neonatal vaccinations ($US millions)

	Direct	*Direct and work*	*Direct and mortality and work*
Newborn shots + boosters	13·06	13·06	13·06
Adverse reactions	0·75	0·75	0·75
Total costs	13·8	13·8	13·8
Hepatitis costs without vaccination	23·5	60·77	61·7
Hepatitis costs with vaccination	2·7	23·33	23·7
Benefits	20·9	37·4	38·0
Benefit to cost ratio	1·51	2·71	2·75
HCC costs without vaccination	1·36	1·43	1·49
HCC costs without vaccination	0·73	0·77	0·80
Benefits	0·63	0·66	0·69
Total benefits	21·5	38·1	38·7
Benefit to cost ratio (incl HCC)	1·56	2·76	2·80

HCC = hepatocellular carcinoma

percentage was applied to Arevelo's hepatocellular carcinoma costing[12] resulting in an Israel care cost estimate of $41 048 per case (at 1990 price levels) for hepatocellular carcinoma in the 44th or 64th year of life.

COST-BENEFIT ANALYSES (table III)

Implementation of the neonatal vaccination policy would reduce the number of hepatitis B cases in the cohort from 359 343 to 166 224 during the period 1990–2035, and generate direct health service benefits of $21·5 million, which exceeds the direct programme costs of $13·8 million, yielding a benefit to cost ratio of 1·56/1.

Discussion

The present study was designed to estimate the costs and benefits of a hepatitis B prevention programme to neonates in an area of intermediate endemicity, where the majority of HBsAg carriers are anti-HBe positive.

Israel is located in the Middle East, a region considered to be one where there are intermediate risks of developing hepatitis B during a lifetime, compared to the high risk regions of the Far East and Africa or the low risk regions of Western Europe and the USA.

Israel's estimated carrier population of 2·0–2·5% (depending on the mix of ethnic backgrounds) means that every year about 2500 babies will be at risk of acquiring hepatitis B infection, due to vertical and horizontal transmission. In addition, according to current estimates there are at present 60 000–80 000 HBsAg carriers in the general population who may transmit the disease horizontally. Since 98% of Israeli carriers are anti-HBe positive (of whom 6–8% still have circulating hepatitis B virus DNA[86]) the magnitude of the problem is less than that in Asia or Africa, but is still larger than that in Western Europe or the USA.

By instituting a national neonatal vaccination policy, the net savings in direct health service costs (ie, benefits less vaccination costs) in the 1990–2034 period would be $7·8 million ($7·2 million if hepatocellular carcinoma costs are excluded). The cost calculations assumed that no extra transportation costs of parents, labour costs, administration costs, or work losses would occur, as the three doses could be integrated within existing infant inoculation schedules against polio. In any case, most previously employed mothers would still be on maternity leave (three months paid and up to one year unpaid).

Table IV Benefit-cost ratios by reporting, discount rate, adult vaccine cost: neonatal programme

Discount rate	Direct costs and benefits (vaccine decay rate)			Total cost and benefits (vaccine decay rate)		
	0%	15%	30%	0%	15%	30%
			Reporting rate 33·3%			
10%	1·11	0·99	0·92	2·78	1·79	1·30
7·5%	1·78	1·56	1·45	3·36	2·80	2·10
5·0%	3·21	2·69	2·42	5·66	4·61	3·43
0%	21·31	14·50	10·86	27·01	19·07	14·99
			Reporting rate 50·0%			
10%	0·76	0·68	0·64	1·45	1·23	0·95
7·5%	1·20	1·06	0·98	2·27	1·90	1·44
5·0%	2·16	1·82	1·64	3·81	3·11	2·32
0%	14·29	9·75	7·34	18·11	12·81	10·13

Averted mortality, or savings of life years, is an indirect benefit of the vaccination programme. Using the human capital method of valuing life, with the deceased's future lost earnings discounted at 7·5% per annum, mortality costs of $40 304 were estimated for mortality from hepatocellular carcinoma or fulminant hepatitis in those who died aged 45 years. This method only gives a valuation of $9677 to those who died from hepatocellular carcinoma at the age of 64.

A further indirect benefit is that resulting from a reduction in work losses as a result of decreased morbidity. Such work losses were calculated by multiplying the age and sex specific labour force participation rates by age and sex specific wage costs,[79] and the age specific notification rates[24–26] of hepatitis B cases. Data were adjusted by an estimated unemployment rate of 10·0% in 1991.

As no Israeli data were available on work absences due to hepatitis virus infections (in cohort members who have reached working age) regardless of aetiology, we used Adler's estimate from England[50] of 117·3 days per year, adjusted upward for the five and a half day Israeli work week, to 123·2 days per year. This estimate was applied to each stage of hepatitis B, except subclinical and fatal fulminant forms. The fatal fulminant form was estimated to cause 20 lost work days before death. An additional calculation was made of work losses incurred by working parents (assumed to be females aged between 18 and 34 years), who were estimated to be at home to care for their unwell children for 30 days, reflecting the shorter duration of the illness in children.

When indirect benefits from decreased work absences are included, the benefit ($38·1 million) to cost ratio rises to 2·76/1. Addition of averted mortality costs increases benefits to $38·7 million, and the benefit to cost ratio to 2·80/1 (table III), a saving to the country of around $25·4 million ($24·7 million excluding hepatocellular carcinoma costs).

Unfortunately data in Israel are unavailable for age specific hepatocellular carcinoma cases regarding the age at onset of the initial hepatitis B infection. If the average age of hepatocellular carcinoma has been overstated in the neonatal group (ie, it is considerably less than 64 years), then the benefit to cost ratios will be biased downwards.

A sensitivity analysis was performed using different discount, vaccine effectiveness decay, and reporting rates (table IV). This analysis found the benefit to cost ratio to be particularly sensitive to the choice of discount rate, the direct benefit to cost ratio rising to 2·69/1 using a 5% rate and to 14·50/1 using a zero discount rate. A zero discount rate was included to take into account the argument that using a positive discount rate in a health study with a long time horizon effectively gives very little value to net decreases in morbidity or mortality enjoyed in the distant future, harming intergenerational equity. This zero discount rate gives equal weight to any decreases in mortality and morbidity, even in the distant future.

It could be argued that, since the memory of the immune system has been programmed, if there is any further encounter with viruses there will be an anamnestic reaction, thus effectively reducing the

vaccine effectiveness decay rate to 0% (ie, remaining at 95% effective throughout the person's lifetime). The sensitivity analysis showed that with a 0% vaccine decay rate, the direct benefit to cost ratio increases to 1·78/1, with the total benefit to cost ratio rising to 3·36/1. If the reporting rate rose to 50%, the direct benefit to cost ratio (using a 7·5% discount rate and 85% vaccine efficiency rate) decreases to 1·06/1, the total benefit to cost ratio being 1·90/1.

In keeping with the conservative nature of our estimates, the cost of transport and time involved in visiting a child in hospital was omitted in the valuation of benefits. It was also assumed that parents will accompany children on ambulatory visits outside of their working hours. No valuation was given to the benefit of having an increased potential pool of blood donors in the population, since around 1·5% of all blood donations in Israel are disqualified on account of HBsAg positivity (S Bar-Shani, personal communication).

The benefit to cost ratios are biased downward by the fact that we have conservatively assumed there to be no reduction in the incidence of persons who had never been vaccinated. As a result of herd immunity, these people will also have a reduction in hepatitis B incidence, an external benefit of the vaccination programme. The omitted major costs of liver transplant operations, each costing around $44 000 if performed in Israel (and around $88 000 if performed in Europe), plus an additional $44 000 to cover antiviral drugs currently used on an experimental basis to prevent reinfections, would also contribute to a downward bias. No valuation was put on the intangible benefit of freedom from anxiety concerning contracting hepatitis B that members of Israeli society might experience. Finally, no attempt was made to monetarise the benefits in such important but intangible dimensions as reduced pain, worry, or grief as morbidity and mortality decrease.

The incidence estimates which underpinned the cost-benefit analysis took into account the fact that between 25% and 40% of the Soviet Jewish immigrants have been infected with hepatitis B prior to their arrival in Israel (D Shouval, personal communication). Consideration could also be given to inoculating all new immigrants from the USSR under a certain age against hepatitis B, like the high risk group strategy currently being implemented for recent immigrants from Ethiopia under the age of two years.[87]

Implementation of a neonatal vaccination programme would result in a decrease in almost 200 000 hepatitis B cases over the 1990–2035 period. This huge decrease in morbidity can be gained at no net cost to society; indeed a net savings of around $25·4 million would accrue to society. Approximately $7·7 million of this will be savings to the health services, sufficient to finance around 90 liver transplants or around 900 coronary bypass operations. The adoption of a nationwide policy of inoculating neonates appears to be not only medically but also economically justifiable.

Appendix

Costs of visits, hospital admissions, and laboratory tests for hepatitis B cases

		Icteric		Fulminant		Carrier		Persistent		Chronic active				
% Receiving care	Anicteric 100%	Hosp 100%	Non-hosp 100%	Fatal 100%	Non-fatal 100%	Yr 1 1%	Yrs 2–20 1%	Yr 1 100%	Yrs 2–20 100%	Yr 1 100%	Yrs 2–5 20%	Yrs 2–5 80%	Yrs 6–10 100%	Yrs 11–20 100%
Physician visit ($4·67 per 15 min)	1	1	1		1	7	1	4	4	1	10	3	3	3
Medication ($1825 per year)											1	1		
Hep A tests ($14·34)	1	1	1		1	1		1		1				
HBsAg test ($7·17)	1	1	1		1	1	1	1	1	1				
Anti-HB assay ($7.17)	1	1	1		1	1		1		1				
Tests: urine + bilirubin ($11·55)	1	1	1		1	1		1		1				
blood count ($12·65)	1	1	1		1	1		1		1			3	3
liver function incl bilirubin ($19)	1	0	1		1	1	1	4	4	1			3	3
PT/PTT tests ($17·60)	1	3	1		1	1	1	1		1			3	3
ultrasound ($109·50)							1 (aged 40+)	1	1	1	1	1	1	1
endoscopy ($217·00)										1	1	1	1	1
α fetoprotein ($14·50)							1 (aged 40+)	1	1	1	1	1	1	1
Convalescent visits ($4·67)	2	6	6		6					2				
Lab follow up: blood count	1	1	1		1					1	3	3		
liver function incl bilirubin	3	3	3		3					3	3	3		
PT/PTT tests	1	1	1		1					1		3		
Post-convalescent visit ($4·67)	1	1	1		1					1				
HBsAg test	1	1	1		1					1	1	1	1	1
ANTI-HB assay	1	1	1		1					1				
Liver biopsy ($265 a day: 2 days)								100%		100%	100%	0%	20%	40%
Hospital admission ($225 a day: 5 days)	10%	25%		70%	30%			100%		100%	100%			
Hepatitis LOS ($225 a day)	10·6	10·6			15								5	5
Biopsy LOS ($265 a day)						1	1	2	2	2	2			
Fulminant LOS ($1192 a day)				7										

Hosp = admitted to hospital; Non-hosp = not admitted to hospital; Hep A = hepatitis A; HBsAg = hepatitis B surface antigen; LOS = length of stay

Postscript

In May 1991, partly on the basis of information presented in earlier drafts of this paper, the infectious disease committee of the Ministry of Health unanimously proposed the adoption of neonatal vaccinations without screening (strategy 1). The vaccination of all newborns nationwide began in Israel in January 1992.

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