Cost benefit analysis of *Haemophilus influenzae* type b vaccination programme in Israel

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**Abstract**

Study objective—The recent availability of *Haemophilus influenzae* type b (HIB) conjugate vaccines prompted an examination of the costs and benefits of four and three dose HIB prevention programmes targeting all newborns in Israel.

Measurements and main results—A four dose programme would reduce the number of childhood (aged 0-13) HIB cases from 184-2 to 3 per year, yielding a benefit (51-03 million) to cost ($3-55 million) ratio of just 0-29/ for health services only, based on a vaccine price of $7-74 per dose. When benefits resulting from a reduction in mild handicaps and severe neurological sequelae are included, the benefit ($4-48 million) to cost ratio rises to 1-26/ and it reaches 1-45/ when the $0-66 million indirect benefits of reduced work absences and mortality are also included. Break even vaccine costs are $2-24 when health service benefits only are considered and $1-17 when all the benefits are included.

Conclusion—In the absence of other projects with higher benefit to cost ratios, Israel should start to provide a nationwide HIB vaccination programme since the monetary benefits to society of such a programme will exceed the costs to society. A barrier to implementation may occur, however, because the costs of the programme exceed the benefits to the health services alone.

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Between October 1988 and September 1990, 344 cases of *Haemophilus influenzae* type b (HIB) infection proved by positive blood culture or spinal fluid (CSF) culture occurred in Israel (population around 5 million), 750 000 of whom were children under 5 years old. Around 61-5% of cases were male and 72-09% occurred in Jews.1 Age specific incidence rates were 117, 41, 5-2, 2 and 0-4 per 100 000 for age groups 0-1, 1-2, 2-3, 3-4, 4-5, and 5-13 years respectively. Cases in persons over 13 years old are exceedingly rare.

The case fatality rate for blood culture or CSF culture positive HIB was 2-03%.1 About 53% of these HIB cases had meningitis1; the case fatality rate from HIB meningitis fell from 8-43% in 1970-79 to 3-77% in 1980-84 and to 2-96% in 1985-90.2

Around one in 588 of all children under 5 years acquires the disease and one in 1110 contracts meningitis.1 HIB not only has neurological sequelae; other systemic forms such as pneumonia, sepsis, and cellulitis also occur.1 In Israel, cases of HIB associated with epiglottitis are relatively rare events.1

The recent collaborative study in Israel1 collected data from HIB patients (with positive blood or CSF culture) who received care in emergency rooms of hospitals or were admitted to hospital pediatric departments. The study found that the duration of hospital stay ranged from 0 days (for those who only received care in the emergency room) to 90 days. The overall mean (SD) stay was 11-8 (5-7) days, with 64% of cases spending ≥ 10 days in hospital. Cases with meningitis spent a mean (SD) of 14-1 (6-6) days in hospital and 93% were there for ≥ 10 days.

The clinical efficacy of existing conjugate HIB programmes starting with children aged 2,3 5 3,6 and 4 months7 8 has been established in the USA and Finland. In Israel, the public has become aware of such a vaccine through various media sources and has to some extent decided to purchase the vaccines on the free market from pharmacists. In some cases, vaccines are purchased for children well over the “danger” age for HIB infections; 93% and 98% of cases occurring in children under 2 years and 5 years old respectively.1

In March 1992, the Israel Pediatric Association recommended HIB vaccination of all children between the ages of 2 and 23 months. Licencing and recommendations alone, however, are unlikely to have a major impact on the disease incidence in the community.9

Israel has a strong public health tradition via its network of family health centres. In the past three years, the Infectious Disease Committee of the Ministry of Health, aided by information from ex-ante cost-benefit analyses, have added nationwide vaccinations against hepatitis B for newborns10 and a second measles vaccination for schoolchildren11 to the traditional diphtheria, tetanus, and pertussis (DTP); polio; and measles, mumps, and rubella (MMR) vaccination schedules.

Cost-benefit studies of HIB vaccination programmes have been undertaken in the USA. These analyses, however, were based on single dose inoculation of children aged 18 or 24 months old.12 14 To help decide whether HIB vaccinations should be provided via the public health services in Israel, this paper provides a cost-benefit analysis of a nationwide four or three dose HIB immunisation programme in which conjugate vaccine is given to children at 2, 4, 6, and 15 months, or 2, 4, and 12 months of age.

**Methods**

Demographic, epidemiological (HIB age specific incidence and transitory probabilities of handicaps
and severe neurological sequelae), health service (type and amount of care required for HIB cases), and economic (costs of inoculation, costs of caring for HIB cases and vaccinating contacts, labour force participation rates) data were entered into a computerised spreadsheet model.

The basic formula used is as follows: Benefit to cost ratio = benefits of programme/costs of programme, where:

Cost of programme = costs of vaccine + additional labour costs of giving inoculation + training and health education costs + transportation costs of vaccine and nurses + cold-chain costs + costs of adverse reactions.

**Benefits of programme** = costs of HIB without vaccination programme – costs of HIB vaccination programme

where the costs of HIB include costs of ambulatory care, emergency room care, hospitalisation, as well as costs of prophylactic antibiotic treatments for contacts at home or in day-care situations. The costs also include costs of special education for children handicapped as a result of HIB and long term care costs for those with severe neurological sequelae.

Three different benefit to cost ratios were calculated using a discounted cash flow of 5.0% a year.

(i) The direct "health services" benefit to cost ratio, which includes only costs and benefits relating to health services (for example, costs of vaccine, ambulatory care, hospital stay, etc.).

(ii) The direct "welfare services" benefit to cost ratio, which includes only those costs and benefits relating to health services and the ministries of education (special education costs), labour and welfare (long term care for severe neurological sequelae).

(iii) The total "social" benefit to cost ratio (that is, to society as a whole). This includes the direct welfare services cost and benefits in addition to indirect benefits related to the reductions in parental time off work for caring for their children and reductions in mortality which will be achieved by implementing the programme.

**Results**

**COST OF VACCINATION PROGRAMMES**

Table I lists the unit and total costs of programmes aiming to provide four pediatric doses of conjugate type HIB vaccine to the estimated 100 000 in an annual birth cohort. The total cost of a four dose programme is $3.55 million based on a unit cost of $7.74 per dose. This was somewhat pessimistically estimated as being 50% higher than the federal contract prices in the USA, since the Ministry of Health in Israel has far less bargaining power with the pharmaceutical companies because of Israel's far lower absolute number of annual births. The total cost includes a provision of 18% for vaccine wastage and a compliance rate of 88% based on compliance with the DTP immunisation schedule in Israel.

Since the HIB immunisation would be administered within the current DTP and MMR at 15 months inoculation schedules in mother and child health clinics, we assumed the following: an estimate of only five minutes extra public health nurses' time per vaccination (costing $8.00 per hour); no extra parental time off work; no extra transportation costs of the inoculated persons or their parents; and no extra-marginal costs resulting from short term vaccination side effects. The vaccine has not been shown to be associated with any serious or long term sequelae. It is envisaged that the present cold-chain capacity is sufficient to handle an increased annual load of around 300 000–400 000 vaccine doses nationally (personal communication, Dr Matas, National Public Health Laboratories).

An allocation of $0–80 per targeted person per annum was estimated for additional health education and training costs relating to the HIB vaccine. The health education component will be aimed at raising compliance levels through public service media broadcasts. The training component will be aimed at increasing the public health nurses abilities to explain to parents and children the reasons for HIB immunisation and also the nurses own awareness of the importance of following an amended immunization schedule that includes HIB.

**COSTS OF TREATING HIB** (table II)

The total costs of $32 183 per case comprised the following elements:

**Hospital admission**

We assumed that 75% of cases had a 15 minute ambulatory care visit (costing $4.67) before arriving at the hospital and that all cases had a 15 minute follow up visit after discharge from hospital, also costing $4.67. Hospital stay costs for HIB were obtained by costing the treatments recorded in the case notes of a sample of "easy, moderate, and severe" cases of HIB treated at the Soroka Medical Centre. The costs of laboratory tests were obtained from the Ministry of Health pricing lists and the costs of pharmaceutical supplies from the chief pharmacist of a large Jerusalem teaching hospital (Alan Greenberg, personal communication 1992). Based on an average length of stay of 11.8 days, the average cost per case admitted to hospital was $6424. This figure included ambulatory and outpatient visits costing $8 and emergency room costs of $433. Hospital staff costs were based on the average cost of treatment in pediatric intensive care units and pediatric departments of $805 and $259 per day respectively for medical care, tests, and drugs, which included a general overhead of 46-84% and 35-14% respectively for cleaning, laundry and food, maintenance, heating, electricity, administration, depreciation, etc. Additional costs were also incurred through parents taking time off work to care for their child in hospital, based on mothers needing to be with their children for 20-8

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**Table I**

<table>
<thead>
<tr>
<th>HIB vaccine costs for the one year cohort</th>
<th>Unit cost ($)</th>
<th>No.</th>
<th>Total cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 doses</td>
<td>3 doses</td>
<td>4 doses</td>
</tr>
<tr>
<td>Vaccine doses</td>
<td>7.74</td>
<td>12.38</td>
<td>311 520</td>
</tr>
<tr>
<td>Swab</td>
<td>0.0083</td>
<td>0.0083</td>
<td>352 000</td>
</tr>
<tr>
<td>Disposable syringe</td>
<td>0.0434</td>
<td>0.0434</td>
<td>352 000</td>
</tr>
<tr>
<td>Needle</td>
<td>0.0020</td>
<td>0.0062</td>
<td>352 000</td>
</tr>
<tr>
<td>Labour</td>
<td>0.0080</td>
<td>0.0080</td>
<td>352 000</td>
</tr>
<tr>
<td>Side effects</td>
<td>0.0050</td>
<td>0.0050</td>
<td>352 000</td>
</tr>
<tr>
<td>Health education</td>
<td>0.0080</td>
<td>0.0080</td>
<td>100 000</td>
</tr>
<tr>
<td></td>
<td>3 549 934</td>
<td>4 126 346</td>
<td></td>
</tr>
</tbody>
</table>
days per case (including two days before hospital admission and seven days after discharge). After adjustment for the 5-5 day working week in Israel, annual holidays, and the female labour force participation rates of 42.3% (for those with children under a year old) and 63.7% (for those with children aged 1-5 years old), it is estimated that 6.81 net working days were lost at a cost of $37.98 per day,21 costing $259 per case. Finally, additional travelling costs of around $6 were incurred by the parents taking 75% of the children for pre- and all of the children for a post-hospitalisation ambulatory visits, each visit costing around $4.67 in physicians and medical secretary's wages.

Mortality
Mortality costs of $225 218 per deceased, or $4165 per case based on the 2.03% case fatality rate, were estimated for HIB deaths at a mean age of 1 year old, using the gross national product (GNP) per head method of valuing life, which assigns an equal value to everyone in society equivalent to the GNP per head of the population of $10 989 in 1991.17 Every child, irrespective of gender and whether they would have been a doctor, musician, farmer, unemployed, student or housewife received the same valuation, based on discounting the value of the deceased’s 76-4 expected years of life lost at the average case age of 13-8 months old.

Special education
We assumed that 13.4% of children would require special education because of HIB infection, based on Taylor’s study22 which found that 26.8% of children who had HIB needed special educational compared with 13.4% of a control group who had not contracted HIB. Special educational costs amounted to $11.958 per case of HIB, based on discounted costs of $89.228 per person requiring special education, under the assumption that each person requires special care for 16 years at a cost of $7841 per annum in excess of the costs of normal education.23

Severe neurological sequelae
We assumed that 7% of survivors of an HIB meningitis episode (3.67% of all HIB cases in Israel) have severe long term neurological sequelae requiring long term care.24 26 Costs of caring for children with severe neurological sequelae amount to $11.095 per case of HIB, based on discounted costs of $300 801 per case with severe neurological sequelae, assuming that each case requires special care for the rest of his or her lifetime at a cost of $14 764 per year.23

Following up contacts
The current practice in Israel is to provide anti-biotic prophylaxis to the household and child care contacts of HIB cases, who are at considerably higher risk of contracting HIB than the general population.29 30 Prophylactic treatment is based on each contact taking a four day course of Rifampin in doses of 20mg/kg to children, with a 600mg limit per dose.

Based on records in the Jerusalem district for 1991 and 1992 (Anita Bashiri, nurse epidemiologist, personal communication, 1992), each case has an average 2.79 adult contacts (immediate family plus child minder in 36% of the cases) and 5.50 child contacts (immediate family plus 9-8 day care contacts in 36% of the cases). In about 90% of cases, the parents of the HIB child visit the district health office to receive the Rifampin for all their household members. Conversely, in 90% of all cases (all districts except Jerusalem) the district health nurse visited the day care centre in order to explain the situation to the child minder and parents of the children and to distribute the Rifampin. In addition, each case generated about five telephone queries of 10 minutes duration from concerned neighbours for advice from the public health nurse.

Total contact costs per case amount to $427, including $376 for rifampin, $32 for the 4-04 hours of nurses’ time required (at $8-00 per hour), $8 for nurses’ travel costs, $7 for parents and child minders for time off work and $5 for their traveling costs to the district health office.

TOTAL BENEFITS
We assumed a vaccine efficacy of 26%, 97%, 100%, and 100% for the four conjugate doses given at 2, 4, 6, and 15 months respectively based on trials in the USA21 and Finland.2 We also assumed a compliance rate of 88% with the programme27 and that vaccine protection would last for five years,31 although it is possible that the vaccine efficacy could be even greater. We assumed there would be no reported vaccine associated cases since no increased incidence of HIB has been found during the first two weeks after immunization with HbOC.28 32

We assumed conservatively that the true national incidence rate of HIB is 10% higher than the rates found in Dagan’s study,1 since for some HIB patients blood cultures were either lost, negative, or were not obtained.

The implementation of a nationwide vaccination policy, with children receiving vaccinations at average age of 2.5, 4.5, 6.5, and 15-5 months, based on estimates of the true age-specific incidence rates of HIB, would reduce the number of HIB cases in the cohort’s lifetime from around 184.2 to 31.3 cases (table III).

The treatment modal costs per case (table II) were then multiplied by the estimated age-specific cohort incidence of HIB (table III), using a discount rate of 5.0%. If a four dose vaccination policy is adopted, treatment costs will fall by

<table>
<thead>
<tr>
<th>Status</th>
<th>Age (y)</th>
<th>0-1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccination</td>
<td>184.20</td>
<td>128.70</td>
<td>45.10</td>
<td>5.50</td>
<td>2.20</td>
<td>2.20</td>
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<tr>
<td>3 Dose vaccination</td>
<td>37.27</td>
<td>30.23</td>
<td>5.41</td>
<td>0.66</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>Reduction</td>
<td>145.93</td>
<td>98.47</td>
<td>39.69</td>
<td>4.84</td>
<td>1.94</td>
<td>1.94</td>
</tr>
<tr>
<td>4 Dose vaccination</td>
<td>31.33</td>
<td>24.29</td>
<td>5.41</td>
<td>0.66</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>Reduction</td>
<td>152.87</td>
<td>104.41</td>
<td>39.69</td>
<td>4.84</td>
<td>1.94</td>
<td>1.94</td>
</tr>
</tbody>
</table>
Table IV  Benefits of HIB vaccination programme for 100 000 babies

<table>
<thead>
<tr>
<th>Treatment costs ($)</th>
<th>4 dose vaccination</th>
<th>Benefit</th>
<th>3 dose vaccination</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccination</td>
<td>210 581</td>
<td>1 025 248</td>
<td>251 213</td>
<td>984 616</td>
</tr>
<tr>
<td>Work</td>
<td>70 665</td>
<td>3 450 345</td>
<td>845 426</td>
<td>3 113 604</td>
</tr>
<tr>
<td>Mortality</td>
<td>8 515</td>
<td>41 458</td>
<td>10 158</td>
<td>39 815</td>
</tr>
<tr>
<td>Total</td>
<td>1 259 440</td>
<td>5 141 582</td>
<td>1 359 824</td>
<td>4 073 816</td>
</tr>
</tbody>
</table>

Table V  Sensitivity analysis: benefit to cost ratios

<table>
<thead>
<tr>
<th>4 dose schedule</th>
<th>3 dose schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health services only</td>
<td>Health services plus sequelae</td>
</tr>
<tr>
<td>$1-00</td>
<td>0-24</td>
</tr>
<tr>
<td>$2-00</td>
<td>1-12</td>
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<td>$3-00</td>
<td>0-90</td>
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<td>$4-00</td>
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<td>0-45</td>
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<tr>
<td>$6-00</td>
<td>0-37</td>
</tr>
<tr>
<td>$7-00</td>
<td>0-32</td>
</tr>
<tr>
<td>$7-74</td>
<td>0-29</td>
</tr>
<tr>
<td>$8-00</td>
<td>0-28</td>
</tr>
</tbody>
</table>

Discussion

A four dose programme that aims to vaccinate all children at ages 2, 4, 6, and 12 months, will reduced the incidence of HIB in an annual cohort of 100 000 persons from 184-2 to 31-3 cases (table III). The number of HIB cases requiring special education as a result of sequelae would fall from 24-7 to 4-2, and the number of cases requiring long term neurological care would decrease from 6-8 to 1-2 cases. Mortality associated with HIB would decrease from 3-4 to 0-58 cases in an annual cohort of newborns.

The $3-55 million costs of such a programme (at a vaccine cost of $7-74 per dose), are exceeded by the benefits from the reduction in morbidity to the welfare services ($4-48 million) or to society as a whole ($5-14 million). However, the costs of the programme are over three times as large as the benefits to just the health services alone ($1-03 million).

The biggest component of costs per case was that of special education and care for long term severe neurological sequelae, accounting for around 67.1% of the $34 300 costs per case. Previous cost-benefit studies of HIB in the USA showed considerable variation in estimating special education costs and care costs for persons with severe neurological sequelae. Even if we underestimate the long term costs by 30%, benefits still exceed costs, with a social benefit to cost ratio of 1-16/1. Variation of other parameters (except for vaccine costs and discount rates) had little impact on the benefit to cost ratios.

If HIB vaccine is provided as a “cocktail” with DPT or MMR in the same syringe, the extra-marginal labour, syringe, needle, and swab costs of the programme would approach zero, reducing total costs to $3-29 million, giving a benefit to cost ratio of 2-6/1.

If the Ministry of Health manages to negotiate a four dose vaccine price equivalent to the $5-16 paid by federal contract in the USA, the benefit to cost ratios to society, welfare, and the health services will rise to 2-04/1, 1-76/1, and 0-43/1 respectively.

Assuming a vaccine cost of $12-38 per dose (also 50% higher than the federal contract costs in the USA), a three dose regimen using PRP type vaccines given at ages 2, 4, and 12 months and with vaccine efficacy of 60%, 89-3%, and 100-0%, would cost $5-85 million more (table I) and would prevent only six more cases (table III) than the four dose regimen. The total costs of $4-13 million exceed the benefits from the reduction in morbidity to the health services ($0-98 million), but are exceeded by the benefits to the welfare services ($4-30 million) or to society as a whole ($4-93 million). Any relative advantage in cost effectiveness of the four dose regimen over a three dose regimen depends almost entirely on the cost per dose differential, since the efficacy of both regimens is similar.

When we reduced the annual discount rate to 2-5%, the “social” benefit to cost ratios rose to...
Table VI. Benefit to cost ratio for prophylactic care of contacts of HIB cases

<table>
<thead>
<tr>
<th>Secondary attack rate (%)</th>
<th>0-10</th>
<th>1-00</th>
<th>1-28</th>
<th>2-00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected secondary cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per primary case ($)</td>
<td>34-12</td>
<td>34-93</td>
<td>343-70</td>
<td>638-86</td>
</tr>
<tr>
<td>Expected secondary cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with prophylaxis ($)</td>
<td>1-71</td>
<td>17-04</td>
<td>21-89</td>
<td>34-19</td>
</tr>
<tr>
<td>Benefit from follow up contacts ($)</td>
<td>32-48</td>
<td>324-93</td>
<td>415-82</td>
<td>649-67</td>
</tr>
<tr>
<td>Benefit to cost ratio for follow up contact</td>
<td>0-08</td>
<td>0-78</td>
<td>1-00</td>
<td>1-56</td>
</tr>
</tbody>
</table>

Assumes 95% efficiency of contact inoculations
Cost per case (excluding child care contacts) = $34 193

1-99/1 and 1-65/1 respectively for the four and three dose regimens. Conversely, using a 7-5% discount rate, the benefit to cost ratios fell to 1-18/1 and 0-97/1 respectively for the four and three dose regimens.

To reach the break even point for society (where benefits equal costs), the costs of the vaccine need to be around $11-21 and $14-81 per dose for the four and three dose regimens respectively (table V). However, if we have overestimated the long term care costs by 30% then the break even costs fall to $8-95 and $11-83 per dose respectively for the three and four dose regimens. The vaccine costs need to fall as low as $2-24 per dose for health service costs to be covered using four doses, and to $2-95 per dose using three doses (table V).

The imposition of a user fee for the HIB vaccine, in addition to the current $50 charge levied for all current childhood vaccinations and developmental check ups carried out by the neighbourhood family health centres, might enable the health services to fund the HIB project.

While improving the health service benefit to cost ratio, however, this would have no effect on the “social” benefit to cost ratio, as the user charge is merely a transfer payment from the general population to the Ministry of Health.

The break even point for antibiotic prophylaxis of contacts occurs where the secondary attack rate is 1-28%. Since the true secondary attack rate is unknown in Israel, stopping prophylactic care for contacts cannot be recommended. In addition, prophylaxis of contacts serves to lower the considerable anxiety generated in parents and neighbours of children who were in close contact with a child suffering from HIB.

Our calculations did not attribute any monetary valuation to the following additional benefits from decreased mortality and morbidity as a result of an HIB inoculation programme:

(i) The lessening of parental anxiety over HIB;
(ii) Reduced pain, worry, or grief as a result of a child contracting HIB.

(iii) Reduction in work absences (as no data were available) in connection with HIB cases which required special education and/or long term institutional care;

(iv) In an external benefits that accrue to individuals who feel pleased that people in the society they live in are free from the risk of contracting HIB, not only because they cannot catch HIB themselves (egostical externality), but also because they care about the health of their fellow citizens (altruistic externality); and

(v) The benefits that some members of the medical community will feel because Israel will be providing vaccinations against HIB like other western developed countries instead of being grouped with the developing countries who do not provide their children with HIB vaccinations.

The herd immunity effect generated by a widespread national HIB vaccination campaign will provide external benefits to children who did not receive the HIB inoculation. The resultant efficiency of the programme over and above the expected from the vaccine efficacy assumptions of our model give us downwardly biased benefit to cost ratios.

In the absence of other projects with higher benefit to cost ratios, Israel should start to provide a nationwide vaccination programme against HIB since the monetary benefits to society of such a programme will exceed the costs to society, assuming a vaccine price of $11-21 is achieved in negotiations with the pharmaceutical companies.

A barrier to provision might occur, however, if the Ministry of Health were to take a narrow view of the benefits of the programme and consider only the benefits to the health services alone. The net cost to the health services alone of preventing a child and its parents suffering pain, worry, or grief as a result of contracting HIB is $16 516. The net cost to the health services per year of human life saved from HIB is $11 382. Failure to institute a nationwide HIB vaccination programme for infants would contradict our ethical heritage as expressed in the Talmudic maxim that “He who saves a single life, it is as if he has saved the whole world”.

Addendum

In January 1993, the Ministry of Health’s Infectious Disease Committee unanimously voted for the introduction of a routine neonatal HIB vaccination.

The authors acknowledge the assistance of Alan Greenberg, Chief Pharmacist of Shari Zedek Hospital, Jerusalem in providing help with pharmaceutical costs and to Anita Bashi, Nurse Epidemiologist of Jerusalem District Health Office in providing data on follow up of contacts.


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