Economic evaluation of universal BCG vaccination of Japanese infants

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Background	The international controversy surrounding the use and effectiveness of the Bacillus Calmette-Guérin (BCG) vaccine and the low incidence of tuberculosis (TB) among Japanese children prompted this study.
Methods	We compared 'universal BCG vaccination' with 'no vaccination at all' using a cost-effectiveness analysis. The study population was a hypothetical cohort comprising a total of 1.2 million infants born in 1996 at locations all over Japan. A model was developed to calculate the number of TB cases prevented by the vaccination programme. Assuming 40–80% overall vaccine efficacy (64–86% for TB-meningitis) and 10 years of protection, we calculated the cost and number of immunizations required to prevent one child from developing TB, the total number of TB cases averted by vaccination and total costs required for the programme.
Results	Based on an assumption of flexible vaccine efficacy (40–80%), we estimated that 111–542 TB cases including 10–27 of TB-meningitis would be prevented during the 10 years after BCG vaccination among the cohort of infants born in 1996. About US$35 950–175 862 or 2125–10 399 immunizations would be required to prevent one child from developing TB. Sensitivity analyses covering a wide duration of protection, incidence of TB, vaccine coverage and discount rate, revealed that other than vaccine efficacy, the cost of preventing a single case of TB is highly sensitive to the duration of BCG protection and TB incidence.
Conclusion	The cost per case of TB prevented is heavily dependent on vaccine efficacy and the duration of protection, and is high compared with the cost of treating one child who has developed TB.
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Efficacy of Bacillus Calmette-Guérin (BCG) vaccination is a matter of international debate.[1,2] It varies from detrimental to over a 90% protective benefit in prospective trials and case-control studies;[3] and 50% in a meta-analysis of the literature.[4] The efficacy was lowest in the Madras trial, in which BCG vaccination failed to protect against pulmonary tuberculosis.[5]

Japan has had a policy of universal BCG vaccination of infants against tuberculosis (TB) since 1951.[6] Children aged 6 and 12 also undergo BCG revaccination, although the effectiveness of this practice is not well-established. The average incidence of TB has decreased from 698 per 100 000 in 1951 to 33.7 per 100 000 in 1996.[7] Improved social and economic circumstances since

World War II have played an important role in reducing the incidence of TB in Japan. Universal vaccination is not practised in regions where the incidence of TB is low, such as the USA and some western European countries. These countries target high-risk groups. Although the overall incidence of TB is much higher in Japan than in other developed countries, the paediatric incidence is much lower, at 2.1 per 100 000 compared with 3.1 per 100 000 in the USA.[6] This situation reflects the fact that individuals infected before the 1940s and the ageing population are mostly responsible for the persistent incidence of TB in Japan.[8] The criteria established by the International Union Against Tuberculosis and Lung Disease (IUATLD)[9] to discontinue universal

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Table 1 International Union Against Tuberculosis and Lung Disease (IUATLD) criteria for discontinuing Bacillus Calmette-Guérin (BCG) vaccination and Japanese status

Criteria for terminating BCG vaccination[9]	[a] Japanese status[6,7]
1. The average annual notification rate of sputum smear-positive pulmonary tuberculosis should be 5/100 000 population or less during the previous 3 years. OR:	1. 18.9, 18.8, and 18.4 per 100 000 population during 1994, 1995, and 1996 in Japan
2. The average annual notification rate of tuberculous meningitis in children under 5 years old should be less than one per 10 million general population over the previous 5 years. OR:	2. 0.5–0.7 per 10 million general population over the previous 5 years (1992–1996)
3. The average annual risk of tuberculous infection should be 0.1% or less	3. 0.06% in Japan during 1992

[a] Among the three criteria, satisfying one is sufficient to discontinue universal BCG vaccination programme. Japan has already met two of them.

BCG vaccination have already been met in Japan (Table 1). Fulfilment of these criteria, along with the low paediatric TB incidence in Japan, has stimulated a debate in Japan as to whether or not universal vaccination should be retained. The analysis reported here was designed to compare the cost and number of immunizations required to prevent a single case of TB by the universal BCG vaccination programme with the alternative of no vaccination.

Materials and Methods

Costs of universal vaccination programme

Since universal vaccination in Japan is a national government-run programme, the analysis was conducted from the perspective of actual cost incurred by this programme and estimated from the data on expenditure on the BCG vaccination programme in Kyoto city. The cost of this programme includes the cost of the purified protein derivative (PPD) testing kit, the cost of BCG vaccines together with injection materials (multiple puncture discs) and personnel costs. Other costs were estimated according to the third party payer's viewpoint.[10] The costs of treating side effects caused by BCG and follow-up of PPD positive infants were based on published reports and expert opinion.[7,11,12] Indirect costs, such as loss of work for parents accompanying children to health centres either for vaccination or for treating side effects incurred by BCG, were not included in this analysis. The relevant cost and epidemiological parameters are listed in Table 2. Using the notations in Table 2, cost is expressed as follows:

$$\text{Cost of universal vaccination programme} =$$
$$N \times PV \times C_{BCG} \times 100\,000 +$$
$$N(PV + PP)C_{PPD} \times 100\,000 + C_{SE} + C_{fu} \quad (1)$$

Effectiveness of universal vaccination programme

Effectiveness of this programme is assessed by the number of TB cases averted by vaccination. We developed a model with which to calculate the total number of TB cases prevented by vaccinating a given cohort based on the population number in the cohort (in 100 000), vaccine efficacy, duration of protection, current TB incidence, vaccine coverage and discount rate. Because discounting health benefits in cost-effectiveness analysis is a controversial issue, we performed discounted and undiscounted analyses. All infants born in 1996 in Japan were considered a hypothetical cohort with which to compare 'universal vaccination' with 'no universal vaccination at all' to estimate the number

of TB cases prevented (P_{tb}) by the vaccination programme. We developed the following formula to calculate the numbers of averted TB cases (P_{tb}).

$$P_{tb} = \frac{N \times PV \times VE}{(1 - PV \times VE)} \times \sum_{k=1}^{d} \frac{I_{tk}}{(1+r)^{k-1}}$$

The same formula was used to estimate the number of averted TB-meningitis (TBM) cases, using different values for vaccine efficacy and incidence of TBM. Since the efficacy of the vaccine against overall TB and TBM differs (usually higher in preventing TBM), extra TBM (P_{extb}) averted were added to P_{tb}. In addition to cases directly averted by the vaccination programme, some were averted by a break in the transmission chain. We assumed that the prevalence of TB would be 0.65% among contacts of TB patients and that the average number of contacts per TB patient would be three until identified as TB case.[17] Therefore, the number of cases averted by breaking the transmission chain would be equal to $P_{ttb} = (P_{tb} + P_{extb}) \times 3 \times 0.0065$. Thus the net TB number averted by the vaccination (P_{ntb}) programme was equal to $P_{tb} + P_{extb} + P_{ttb}$.

The number of immunizations (V_n) required to prevent one case of TB will be:

$$V_n = \frac{\text{Total number of immunizations } (PV \times N \times 100\,000)}{\text{Net total number of TB averted } (T_{ntb} = P_{tb} + P_{extb} + P_{ttb})}$$

Data acquisition and assumptions

Vaccine efficacy

Because of wide-ranging uncertainty, we analysed our data using values for overall BCG vaccine efficacy of 40%, 60%, and 80%. Separate calculations also used 64%[4] and 86%[13] efficacy against TBM.

Duration of protection

We assumed that after vaccinating the 1996 infant cohort, protection against TB would continue for up to 10 years since there is no good evidence that the BCG vaccine provides protection beyond this time frame.[14]

Number of infants in a cohort

There were 1.207 million infants born in 1996 in Japan.[15] This is considered a hypothetical cohort with which to calculate the number of TB cases averted by the vaccination programme.

Incidence of TB among vaccinated cohort (I_{tk})

Since the universal vaccination programme for infants has continued in Japan for years, the future incidence of TB among the infants born in 1996 is considered the same as that among infants born before 1996 and vaccinated. The present study

Table 2 Parameters of cost-effectiveness analysis of Bacillus Calmette-Guérin (BCG) vaccination programme against tuberculosis (TB) and cited baseline values

Symbol	Parameter	Baseline value
VE	Vaccine efficacy against TB	40–80%
	Vaccine efficacy against TB-meningitis	64–86%[4,13]
d	Duration of BCG vaccine effectiveness	10 years[14]
N (in 100 000)	No. of infants born in 1996 in Japan	12.07[15]
	No. of BCG vaccinations against infants in 1996	11.53[7]
PV	Proportion of vaccinated infants	0.955[7,15]
PP	Proportion of PPD-positive infants	0.0134[7]
I_{tk}	TB incidence among the cohort in Japan	–[7]
	0–4 years old	2.2 per 100 000
	5–9 years old	1.1 per 100 000
I_{uk}	Hypothetical incidence of TB among the unvaccinated per 100 000	–
I_{vk}	Hypothetical incidence of TB among the vaccinated per 100 000	–
C_{BCG}	Cost per BCG vaccination (including personnel costs)[a]	US$11.8
C_{PPD}	Cost per PPD injection (including personnel costs)[a]	US$3.7
C_{SE}	Costs for treating patient having BCG side effects[b]	–
C_{fu}	Costs for follow-up of PPD positive patients[b]	–
P_{ntb}	Total no. of TB cases averted by vaccination of 1996 infant cohort	–
V_n	No. of immunizations required to prevent one case of TB	–
r	Discount rate	5%

[a] Costs estimated based on information provided by Kyoto City Municipality office, Kyoto, Japan.

[b] Costs estimated based on published studies and expert opinion.[7,11,12]

Exchange rate, 110 Yen = 1 US$.

assumes that the future TB incidence of the 1996 cohort would be equal to that in the age groups 0–4 and 5–9 years old in 1996.

Incidence of TB among unvaccinated cohort (I_{uk})

A hypothetical incidence of TB (I_{uk}) among a cohort of the same size if unvaccinated, can be calculated using the incidence of TB among the vaccinated cohort (I_{tk}), vaccine efficacy (VE), and proportion of the vaccinated infants (PV). Logically, the incidence of TB among unvaccinated infants (about 5% in Japan) within the universal vaccination cohort would also be the same as that of the hypothetical unvaccinated cohort.

Proportion of cohort being vaccinated

The proportion of infants born in 1996 who underwent BCG vaccination was 0.955.[7,15] One report indicates that PPD-positive infants, an estimated 1.4% of the total cohort,[7] were not vaccinated. We assumed that 95% of the cohort was vaccinated and that the TB incidence among PPD-positive infants would be the same as that in the unvaccinated cohort.

TB mortality

We assumed that TB-related death would not occur for 10 years after vaccinating the cohort because no such event has been identified among the population of the 0–9-year-olds in recent years in Japan.

BCG side effects

Information on the side effects of BCG vaccination in Japan was extracted from the report by Mori *et al*.[11] Prevalence of overall lymph node swelling was 1.06%, while the estimated rates of lymphadenopathy, suppurative adenitis and surgical treatment for lymphadenitis after BCG vaccination were 0.73%, 0.02%

and 0.006%, respectively. The incidence of other extremely rare but severe side effects such as BCG osteomyelitis or disseminated BCG infection were not included in this analysis since no relevant data are available.

Results

Cost of vaccination programme

The total cost associated with the vaccination programme was US$19.5 million. The major components of costs were in declining order, personnel (US$10.0 million), BCG vaccines with multiple puncture discs (US$6.98 million) and PPD test kits (US$0.98 million). Cost for treating side effects of BCG vaccinations was US$1.18 million (about US$1 per immunization) and that for follow-up of PPD-positive patients was US$0.46 million.

Number of TB cases averted

The estimated total number of TB cases averted by vaccinating 1.2 million infants born in 1996 would be 111–542 including 10–27 cases of TBM and 2–10 cases averted by breaking the chain of transmission (Table 3). Of the 111–542 cases, 80–387 would be averted in the first 5 years after BCG vaccination with the remaining 31–155 in the last 5 years.

Number of immunizations and cost of preventing a single case of TB

The calculated cost and total number of immunizations required to prevent one case of TB were US$35 950–175 862 and 2125–10 399 injections, respectively (Table 3). In other words, 10–47 TB cases would be prevented by vaccinating 100 000 infants.

Table 3 Total number of averted tuberculosis (TB) cases, cost and number of immunizations required to prevent one case of TB after vaccinating 1996 infant cohort in Japan

Vaccine efficacy	Cost of preventing one case of TB (US$)	No. of immunizations required to prevent a single case	Total no. of averted TB cases
40%	175 862	10 399	111
60%	85 348	5047	228
80%	35 950	2125	542

Based on exchange rate, 110 yen = 1 US$.

Table 4 Sensitivity analyses of cost (in US$) of preventing a single case of tuberculosis (TB)

	Vaccine efficacy		
	40%	60%	80%
Duration of BCG[a] protection (years)			
5	241 786	118 615	50 034
20	69 907	33 225	13 957
TB incidence (% baseline)			
50	351 723	170 697	71 900
200	87 931	42 674	17 995
Vaccine coverage			
75%	254 838	134 489	75 895
100%	160 918	75 383	28 460
Discount rate (%)			
Nil	148 609	72 018	30 327
3	164 982	79 988	33 689
10	203 222	98 796	41 624

[a] Bacillus Calmette-Guérin.

Based on exchange rate, 110 yen = 1 US$.

Sensitivity analyses

Sensitivity analyses tested the robustness of the estimates based on the underlying assumptions (Table 4). The major uncertainty was vaccine efficacy, which was included as a flexible range (40–80%) in the baseline estimates. Other than that, variations in the duration of BCG protection and TB incidence affect the cost and number of immunizations required to prevent a single case of TB. Changing the duration of BCG protection from 10 to 5 years increased the cost and number of immunizations to 37–39% above baseline values. The average TB incidence rate, although recently stable among Japanese children, shows marked regional variation. If it is half of the baseline value, the costs and number of immunizations required to prevent a single TB case would be doubled (Table 4). Cost effectiveness was improved by higher vaccine coverage and when discounting was omitted (Table 4).

Discussion

The cost of preventing a single case of TB is determined by vaccine efficacy, duration of BCG protection, TB incidence and vaccine coverage. However, BCG vaccine efficacy itself is a highly controversial issue. If the BCG vaccine was ineffective, there would be no reason to continue the vaccination programme. Even with flexible vaccine efficacy (40–80%), as used in this analysis as a baseline estimate, the cost of preventing a single case of TB (US$35 950–175 862) appears to be high. That cost is likely to exceed that required to treat a single patient with TB.

Based on some published parameters[17] and experts' opinion, the cost of treating a 2-year-old child with pulmonary TB would be around US$10 500, which is considerably less than our estimated cost of preventing that child contracting TB. The costs of preventing a single case of TB and of treating an infected patient become comparable only when vaccine efficacy is 80% and associated with either 20 years of protection or a doubled TB incidence rate (Table 4). Since only 10–27 of the averted cases would be TBM, they contribute only a small amount to the ratio of the cost of treatment compared with that of prevention.

It is known that BCG side effects can occasionally be life-threatening. Two patients with severe-combined-immunodeficiency syndrome have been identified among BCG vaccinees during the last 10 years in Japan.[18,19] The cost required to control and compensate adverse outcomes could be very high and are not included in the analysis. Similarly, the cost associated with the treatment of other occasional side effects of BCG vaccinations (e.g. BCG osteomyelitis and disseminated BCG infection) are not included in our analysis because of their rarity and inadequate data. If those costs were included, the cost of preventing a single case of TB would be higher than baseline values.

The limitations of this study are those attributable to the veracity of the data sources and to the manner of interpreting the results. We used data derived mostly from meta-analyses of multiple studies conducted in countries other than Japan. In addition, since TB-related mortality has not been recently identified among the 0–9 years age group in Japan, conventional

indices of cost effectiveness, such as cost per life year gained, are not appropriate. Therefore, the study results are described as the cost of preventing one case of TB.

The efficacy of the BCG vaccine in Japan could be different from that determined from meta-analyses of studies conducted in other countries. In fact BCG efficacy varies widely within and between countries. The inter-country variation in BCG efficacy is statistically explainable by the latitude of countries.[20] Atypical mycobacteria that accrue natural protection against TB are highly prevalent at lower latitudes, therefore BCG could do little to protect against TB in countries at such geographical locations. The reverse is true for countries at higher latitudes. Considering the latitude of Japan (35°) actual vaccine efficacy could be around 40–60%, which represents a cost of US$85 348–175 862 to prevent a single case of TB, which is 8 to 16 times higher than the cost required to treat one patient who has developed TB.

Universal BCG vaccination of newborns or infants is no longer practised in most low-risk countries. In fact, BCG is only recommended for high-risk groups in the USA, and universal vaccination was discontinued in Sweden, Austria, Switzerland, Israel, as well as in selected areas of the Czech Republic and Germany many years ago.[21–24] Australia and New Zealand do not have a general BCG vaccination programme.[25] However, in France, UK and Norway general BCG vaccination is recommended at 6, 11 and 13 years of age, respectively.[26] In a recent study, universal BCG vaccination of neonates in the UK was recommended in areas where the average incidence of TB is over 40 per 100 000 population.[27]

The incidence of TB is an important determinant of the cost of preventing a single case of TB. The paediatric TB incidence varies by region in Japan.[7] Nineteen of 47 administrative units (prefectures) have a TB incidence that is about 50% or less than the national average, that of 11 units is 150–200% and that of the remaining 17 units is almost equal to the national average. Therefore, the cost of preventing a single case of TB would be double in prefectures where the incidence is 50% or less of the national average, while it would be half in those prefectures where the incidence is double. Thus, a BCG vaccination programme could be formulated for each prefecture based on incidence data.

The high overall average TB incidence in Japan is due to high incidence among the elderly. Epidemics of TB in eastern Japan between 1910 and 1920 and in western Japan during the 1940s,

the high risk of TB infection (4%) up to World War II,[6] and lower socioeconomic conditions before the war, were responsible for the high infection rates of the past. However, the incidence of TB declined rapidly until 1982, and then plateaued and remained at 33–40 per 100 000 in the last few years.[7] The paediatric TB incidence in Japan is comparable to that of the USA or most western European countries where universal BCG vaccination is no longer practised. Almost 75% of the paediatric TB cases in Japan are thought to have been contracted from individuals with active TB.[28] Such paediatric patients are amenable to appropriate preventive measures such as contact examination and chemoprophylaxis, which could further decrease the current rate. Thus the cost effectiveness of universal vaccination would also decline. Therefore, a high average incidence of TB in Japan does not necessarily justify continuing the universal vaccination programme.

Universal BCG vaccination in Japan does not appear to be cost effective from an economic viewpoint. The cost effectiveness of selective BCG vaccination for high-risk groups (e.g. contacts of TB cases, homeless people, and immigrants from countries with a high prevalence of TB) should be analysed and compared with that of the universal vaccination programme.

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Contributors

MR initiated the research, gathered data, conducted data analysis, and wrote the paper. TF participated in all processes and is guarantor for this paper. MS and KH participated in data analysis and discussion. IT, KT, and TS participated in design and discussion.

KEY MESSAGES

- Estimates of the efficacy of BCG vaccine are highly variable.
- Japan has already met the International Union Against Tuberculosis and Lung Disease criteria to discontinue the universal BCG vaccination programme.
- Paediatric TB incidence in Japan is similar or comparable to other low-risk countries where universal vaccination is discontinued.
- Based on 40–80% vaccine efficacy, 2125–10 399 BCG immunizations or US$35 950–US$175 862 are required to prevent one child from developing TB, whereas the cost of treating one child with pulmonary TB is about US$10 500.
- Cost of preventing one child from developing TB is highly sensitive to vaccine efficacy and duration of BCG protection.

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Appendix

In a cohort where the incidences of TB among the vaccinated and unvaccinated cohorts are I_{vk} and I_{uk}, vaccine efficacy (VE) for that cohort would be:

$$VE = (I_{uk} - I_{vk})/I_{uk} \times 100 \qquad (1) \text{ (percentage)}$$

$$VE = (I_{uk} - I_{vk})/I_{uk} \qquad (2) \text{ (proportion)}$$

Where the proportion of vaccinated is PV and number of population is N (in 100 000), the total number of individuals who develop TB in that cohort in a given year (Kth year) would be equal to the total number who developed TB among the vaccinated plus the total number of the same among the unvaccinated. Let us assume I_{tk} is the average TB incidence.

So $N \times I_{tk} = I_{vk} \times PV \times N + I_{uk} \times (1 - PV) \times N$
  or, $I_{tk} = I_{vk} \times PV + I_{uk} \times (1 - PV)$
    $= (1 - VE) \, I_{uk} \times PV + (1 - PV) \, I_{uk} \qquad \text{(from eqn 2)}$
    $= I_{uk} \, (1 - PV \times VE)$
  or, $I_{uk} = I_{tk}/(1 - PV \times VE) \qquad\qquad\qquad (3)$

If a BCG vaccination programme does not exist, then the incidence of TB would be I_{uk} among the cohort. The number of TB averted (P_{tbk}) in a given year would then be:

$P_{tbk} = N(I_{uk} - I_{tk})$
    $= N\{I_{tk}/(1 - PV \times VE) - I_{tk}\} \qquad\qquad \text{(from eqn 3)}$
    $= (N \times I_{tk} \times PV \times VE)/(1 - PV \times VE)$
    $= (N \times I_{tk} \times PV \times VE)/(1 - PV \times VE) \qquad (4)$

During 10 years (duration of BCG protection) the total number of TB averted would be equal to:

$P_{tb} = (N \times I_{t1} \times PV \times VE)/(1 - PV \times VE) + (N \times I_{t2} \times PV \times VE)/(1 - PV \times VE) + \ldots (N \times I_{t10} \times PV \times VE)/(1 - PV \times VE)$

$$= \frac{N \times PV \times VE}{(1 - PV \times VE)} \times \sum_{k=1}^{k=10} \frac{I_{tk}}{(1+r)^{k-1}} \qquad (5)$$

(while 'r' is annual discount rate)