Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness

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Summary

Background BCG vaccine has shown consistently high efficacy against childhood tuberculous meningitis and miliary tuberculosis, but variable efficacy against adult pulmonary tuberculosis and other mycobacterial diseases. We assess and compare the costs and effects of BCG as an intervention against severe childhood tuberculosis in different regions of the world.

Methods We calculated the number of tuberculous meningitis and miliary tuberculosis cases that have been and will be prevented in all children born in 2002, by combining estimates of the annual risk of tuberculosis infection, the proportion of infections that lead to either of these diseases in unvaccinated children, the number of children vaccinated, and BCG efficacy.

Findings We estimated that the 100·5 million BCG vaccinations given to infants in 2002 will have prevented 29 729 cases of tuberculous meningitis (5th–95th centiles, 24 063–36 192) in children during their first 5 years of life, or one case for every 3435 vaccinations (2771–4177), and 11 486 cases of miliary tuberculosis (7304–16 280), or one case for every 9314 vaccinations (6172–13 729). The numbers of cases prevented would be highest in South East Asia (46%), sub-Saharan Africa (27%), the western Pacific region (15%), and where the risk of tuberculosis infection and vaccine coverage are also highest. At US$2–3 per dose, BCG vaccination costs US$206 (150–272) per year of healthy life gained.

Interpretation BCG vaccination is a highly cost-effective intervention against severe childhood tuberculosis; it should be retained in high-incidence countries as a strategy to supplement the chemotherapy of active tuberculosis.

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Introduction

Randomised controlled trials and case-control studies have shown consistently high efficacy of BCG vaccination against severe forms of childhood tuberculosis, principally miliary disease and meningitis, but variable efficacy against pulmonary tuberculosis in adults.[1–5] Increases in tuberculous meningitis and mycobacterial glandular disease were reported after BCG vaccination was discontinued in Sweden and the former Czechoslovakia.[6–8] BCG also prevents leprosy.[9] More controversially, it might reduce childhood mortality from other causes, perhaps because BCG promotes a T-helper-1 immune response.[10,11] The studies whose results showed high efficacy against severe childhood tuberculosis have lent support to the view that BCG should continue to be used in countries where the disease remains a substantial public-health problem, and roughly 100 million doses are given to infants every year.

However, the evidence for efficacy from trials is not, on its own, sufficient to justify BCG vaccination on its present large scale. That argument needs an assessment of the number of cases and deaths prevented in relation to effort and cost. We have used information about efficacy together with data for risk of severe childhood tuberculosis to assess, for all countries and territories where BCG vaccine is routinely administered to infants, the number of cases of tuberculous meningitis and miliary tuberculosis expected, with and without BCG vaccination, in children born in 2002. This analysis leads to estimates of the numbers of cases prevented by country, by region, and for the whole world.

Methods

We assessed the annual risk of infection for tuberculosis by country and the risk of tuberculous meningitis and miliary tuberculosis in children after infection, and we have updated earlier meta-analyses of BCG efficacy. To see whether BCG vaccination is good value for money in comparison with other health programmes, we have calculated the cost of vaccination per case and death prevented, and the cost per year of healthy life gained.

Study design

The method to calculate the effect of BCG vaccination is based on that of Fine and colleagues,[12] but has been refined for the present study. The expected number of cases of tuberculous meningitis after infection acquired by children for the 5 years of peak risk after birth can be obtained from $5B\lambda\rho_{men}$, where B is the number of children born in 2002, λ is the annual tuberculosis infection rate per head of population (annual risk of infection), and ρ_{men} is the proportion of these infections that leads to tuberculous meningitis in unvaccinated children aged 0–4 years. By extension, the number of such cases prevented in this cohort of children is $5B\lambda\rho_{men}\rho_v\varepsilon_{men}$, in which ρ_v is the proportion vaccinated and ε_{men} is the vaccine efficacy. The

	Estimated annual risk of infection (%)
Africa (high HIV)	0·57–2·16†
Africa (low HIV)	0·13–1·95
Central Europe	0·07–0·20‡
Established market economies	0·01–0·12
Eastern Mediterranean	0·01–1·07§
Former Soviet Union	0·19–0·66
Latin America	0·02–0·74¶
Southeast Asia	0·13–1·87||
Western Pacific	0·08–1·21**

*Countries in the regions are similar to the classification by WHO,[14] but have been adapted for this analysis (a full list is available from the authors on request). †Does not include Djibouti and Swaziland (which had values of 2·87 and 2·80, respectively). ‡Does not include Romania (0·53). §Does not include Afghanistan (1·81). ¶Does not include Haiti (1·12). ||Does not include Timor-Leste (2·11). **Does not include Cambodia (2002 tuberculin test survey[15] provides 2·06, and Papua New Guinea (1·62).

Table 1: **Estimated yearly risk of infection by region of the world***

number of vaccinations needed to prevent one case of meningitis is therefore $1/(5\lambda\rho_{men}\varepsilon_{men})$, and the cost per case prevented is $C/(5\lambda\rho_{men}\varepsilon_{men})$, where C is the monetary cost in US$. The same approach can be used for miliary tuberculosis by substituting ρ_{mil} and ε_{mil} as appropriate. The components of these formulae were estimated as follows.

Estimated numbers of births (B) in 2002 have been obtained from the UN Population Division for all 194 countries and territories included in the study.[13] To explore the effect of BCG in different parts of the world, we grouped these countries into nine regions, on the basis of previous WHO analyses of tuberculosis epidemiology and control (table 1).[14]

Annual risk of infection (λ) for all countries was calculated from WHO 2002 estimates of the prevalence rate of smear-positive pulmonary tuberculosis (ρ_{s+}),[16,17] multiplied by the per capita contact rate for each smear-positive case (β). To apply this method to all countries requires an estimate of the contact rate (β), which was derived as follows. According to a widely used rule of thumb in tuberculosis epidemiology, an untreated smear-positive case transmits about ten infections per year, but this rule was derived from just six sets of observations made on incidence, prevalence, and mortality during the prechemotherapy era.[18,19] The rate of transmission could be lower on average than this estimate if cases are diagnosed and treated promptly, before development of heavy bacterial loads, as in the established market economies. It could also be substantially less than ten per year in African countries, because patients with smear-positive tuberculosis tend to be less infectious when coinfected with HIV.[20] We have therefore re-evaluated the magnitude of the contact rate, and examined the data for any evidence of regional variation in the contact rate.

Table 2[21–34] summarises data from 11 countries where annual risk of infection has been measured by tuberculin surveys in children (21 surveys). Four of these countries (Cambodia, China, the Philippines, South Korea) also did surveys of the prevalence of sputum smear-positive disease among adults in the same populations at the same time

	Annual risk of infection from tuberculin test surveys*		Prevalence smear-positive tuberculosis per 100 000 population (ρ_{s+})		Estimated contact rate per head of population per year (β)	Reference
Cambodia	2002	2·06% (1·77, 2·40)	2002 (survey)	269	7·8	21
China	1979	1·1%	1979 (survey)	187	5·7	22
China	1990	1·0%	1990 (survey)	134	7·2	22
China	2000	0·7 %	2000 (survey)	110	6·5	23
The Philippines	1981–83	2·5%	1981–83 (survey)	660	3·8	24,25
The Philippines	1997	2·3%	1997 (survey)	310	7·4	24,25
South Korea†	1965	5·3%	1965 (survey)	668	7·9	26
South Korea†	1970	3·9%	1970 (survey)	559	7·0	26
South Korea†	1975	2·3%	1975 (survey)	480	4·8	26
South Korea†	1980	1·8%	1980 (survey)	309	5·8	26
South Korea†	1985	1·2%	1985 (survey)	239	5·0	26
South Korea†	1990	1·1%	1990 (survey)	143	7·7	26
South Korea†	1995	0·5%	1995 (survey)	93	5·4	26
Kenya	1994–96	1·1%	1995 (WHO estimate)	132	8·3	27
Tanzania	1993–98	0·9%	1996 (WHO estimate)	172	5·2	28
Tanzania	2000	0·68% (0·55, 0·81)	2000 (WHO estimate)	214	3·1	29
Malawi	1994	1·0%	1995 (WHO estimate)	248	4·0	30
Madagascar	1991–94	1·2%	1995 (WHO estimate)	145	8·4	31
Egypt	1995–97	0·3%	1996 (WHO estimate)	24	13·2	32
Laos	1996	1·1%	1996 (WHO estimate)	165	6·7	33
India	2000–2003	1·5% (1·3, 1·7)	2002 (WHO estimate)	155	9·6	34

*Year of survey and % (95% CI). †Data from South Korea are from six surveys of infection and disease carried out at 5-year intervals.

Table 2: **Average contact numbers for smear-positive tuberculosis cases calculated from the ratio of the annual risk of infection and smear-positive tuberculosis prevalence by country**

(13 surveys). For the remaining seven countries, measures of annual risk of infection can be matched only with published WHO estimates of smear-positive prevalence.[16,17] Despite difficulties in measuring the prevalence of infection[35] and disease,[36] we used the available data and estimates to calculate β from the ratio of annual risk of infection/prevalence (λ/ρ_{s+}), in two ways. The simpler method treats all observations as independent, within and between countries (n=21). The alternative method considers only the countries to be independent variables (n=11), first calculating the mean value of β within each country, and then taking the mean across countries. Although some sputum smear-negative tuberculosis patients will contribute to transmission in any population[37] their exclusion from this analysis leads to higher estimates of β in compensation.

For Cambodia, China, the Philippines, and South Korea, where estimates of β would not be affected by HIV, the two methods provide β=6·3 (95% CI 5·6–7·0) and β=6·5 (5·6–7·4). For the four African countries (Kenya, Tanzania, Malawi, and Madagascar), using a combination of annual risk of infection from tuberculin surveys and WHO estimates of prevalence, we get β=5·8 (3·7–7·9) and β=6·2 (3·8–8·6). Taking the results of all the studies listed in table 2, including the last three from Egypt, Laos, and India, gives β=6·7 (5·7–7·7) when all observations are treated independently and β=7·4 (5·8–9·0) when only the countries are treated independently. Average values of β are about the same whether expressed as the median or the mean. In these estimates there is no evidence of any systematic difference by region or method of calculation. We therefore used a point estimate of β=6 for all regions of the world, with a range of 3–9 to specify the lower and upper limits of triangular distributions in uncertainty analyses.

With this estimate of β and WHO estimates of smear-positive prevalence (ρ_{s+}), calculations of $\lambda=\beta\rho_{s+}$ for the individual countries in each region provide the ranges for ARI in table 1. For Cambodia, India, and Tanzania, where the annual risk of infection has been measured from tuberculin surveys, the measured values and reported 95% CIs have been used instead of estimates. For China, we used the measured value of annual risk of infection, but no CIs were reported. To assess the number of children exposed to infection, we assumed that annual risk of infection remains constant during the period 2002–07, and made no allowance for any variation in the risk of infection with age.

The proportion of infections in children less than 5 years of age that lead to tuberculous meningitis (ρ_{men}) is calculated from the ratio of tuberculous meningitis incidence to annual risk of infection, if both have been measured together. Findings in the Netherlands on the relation between annual risk of infection and tuberculous meningitis deaths in children aged 0–4 years between 1921 and 1940, in 5-year groups, provide four estimates for ρ_{men} in the range 0·7–1·0%.[38,39] This calculation assumes that the case fatality before anti-tuberculosis drugs became available was 100%. A linear regression of tuberculous meningitis incidence against annual risk of infection, as recorded in Barcelona between 1975 and 1991,[40] provides an estimate for ρ_{men} of 0·96% (SE 0·067%). On the basis of the data, we have assumed, for the calculations that follow, a uniform distribution of ρ_{men} with lower and upper bounds at 0·7% and 1·0%. The risk of miliary tuberculosis has been quantified in relation to tuberculous meningitis, and four studies show ratios of miliary to meningitis cases of between 0·25 and 0·5.[41–44] We have used these values as lower and upper bounds of a uniform distribution.

BCG vaccination coverage and efficacy

WHO recommends that BCG is given at birth, or shortly after birth, and provides estimates of coverage (ρ_v) for almost all countries where such vaccination is done.[45,46] In 2002, BCG was administered at birth or shortly after birth in 157 countries and territories. Coverage was greater than 90% in 101 countries and less than 60% in only nine countries. BCG coverage worldwide was estimated as 100·5 million (76%) of the 132·8 million children born in 2002. We assumed that there was no coverage in countries where BCG vaccination is not used at all (eg, Netherlands, USA), where BCG is given only to school age or older children (five countries including Norway), and where BCG is administered to risk groups only (five countries including UK, Sweden, and Switzerland). There were no estimates for Bahrain, North Korea (official country estimate 97%), Jordan (where immunisation has recently begun), and for West Bank and Gaza, so these were excluded from the analysis. WHO has not assessed BCG coverage in Japan, where it is recommended that vaccination takes place before age 4 years; we therefore used the official country estimate of 96%.

We re-evaluated BCG efficacy against childhood tuberculous meningitis and miliary tuberculosis by adding seven more published investigations to earlier meta-analyses of published case-control studies.[1,5] BCG efficacy (ε_i) was estimated in each study (i) from the odds ratio (OR), $\varepsilon=1-OR_i$, and the overall efficacy against either meningitis or miliary disease was calculated with Woolf's method.[47] This method uses the weighted average of the logarithm of the odds ratio.

$\Sigma log(OR_i)w_i/\Sigma w_i$, where each weight ($w_i$) is the reciprocal of the variance reconstructed from reported or calculated 95% CIs, and the variance of the weighted average efficacy is $1/\Sigma w_i$. We also did χ^2 tests for statistical heterogeneity in all of the studies included in this new meta-analysis.

The total of 18 case-control studies listed in table 3[48–61] provides revised estimates of efficacy for tuberculous meningitis of 73% and for miliary tuberculosis of 77%, which are similar to earlier published estimates.[1,2,5] There was marginal evidence of statistical heterogeneity in 13 of 14 meningitis studies (χ^2 test, p=0·04), and less

	Publication date	Efficacy (%, 95% CI)	Reference
Tuberculous meningitis			
Buenos Aires, Argentina	1988	98% (70 to 100)	48
Bahia, Brazil	1991	91% (78 to 97)	49
São Paulo, Brazil	1990/93	87% (72 to 94)	50,51
São Paulo, Brazil	1990/93	92% (65 to 98)	50,51
Belo Horizonte, Brazil	1988	81% (47 to 93)	52
Belo Horizonte, Brazil	1988	65% (17 to 86)	52
Yangon, Burma	1987	52% (13 to 73)	53
Nagpur, India	1996	87% (70 to 94)	54
Chennai, India	1996	77% (63 to 86)	55
Delhi, India	1996	64% (30 to 81)	56
Delhi, India	1989	84% (69 to 97)	57
Lucknow, India	1999	47% (–6 to 74)	58
Papua New Guinea*	1980	58% (–36 to 87)	59
Delhi, India	1993	56% (–49 to 87)	60
Summary efficacy		73% (67 to 79)	
Miliary tuberculosis			
Buenos Aires, Argentina	1988	78% (28 to 93)	48
Yangon, Burma	1987	80% (45 to 92)	53
Papua New Guinea*	1980	70% (0 to 91)	59
Djakarta, Indonesia	1983	75% (5 to 94)	61
Summary efficacy		77% (58 to 87)	

*Not designed as a case-control study.

Table 3: **Meta-analysis of BCG efficacy against tuberculous meningitis and miliary tuberculosis from case–control studies**

heterogeneity in the full set of 18 studies (including four studies of miliary tuberculosis; p=0·07). The heterogeneity in the meningitis studies increased substantially when we included the study from Lucknow, India.[58] However, we have not excluded it from the meta-analysis for two reasons. First, the variation around the point estimate of efficacy is large (95%CI–6%, 74%), so this study contributes little to the weighted average. Second, the point estimate of 47% is low, so, in as much as it does contribute to the analysis, it tends to yield more conservative estimates of BCG effect.

We assumed that these revised average estimates of efficacy apply for the 5 years after vaccination in 2002, the period covered by our calculations, and the 95% CI were used to define normal distributions about the point estimates. We have also assumed that BCG vaccination provides the same protection everywhere against childhood tuberculosis. Although our meta-analysis points to a lower level of protection against childhood tuberculous meningitis in Asia (efficacy 69%, 95% CI 60–76%, from eight case-control studies) than in Latin America (87%, 78–92%, from six case-control studies), these are barely distinguishable from each other in view of the CIs, and neither differs from the global average.

Although around 20% of all cases of tuberculous meningitis and miliary tuberculosis occurs in children aged 5 years and older, the annual risk of developing severe tuberculosis in older children and adults is greatly reduced, and here we have conservatively discounted any protective effect of BCG for more than 5 years after the vaccine has been given during infancy.

Cost-effectiveness

An investigation in Indonesia showed that the cost per vaccinated infant was US$1·80 (1978 dollars), but only US$0·40 if BCG were added to an existing vaccination programme.[62] A second study in the Czech Republic costed BCG revaccination at about US$1·75 per child, including Mantoux testing.[63] Because such studies are scarce we have priced stand-alone BCG vaccination, in consultation with the WHO department of vaccines, immunisation and biologicals, at $2–3 per inoculation, taking a uniform distribution between lower and upper limits for uncertainty analysis. In the absence of better data than those available, we have used this range of costs for all nine regions of the world, irrespective of the coverage in each country.

The costs per case and death prevented are regarded as the same, on the assumption of a case fatality rate of 100% as in the pre-antibiotic era,[64] and in the absence of any more recent data for the outcomes of treatment. By calculating the cost per year of healthy life gained, we can compare BCG with other health interventions, and this cost is shown by $C/(5\lambda\rho_{men}\varepsilon_{men}DALY)$, where *DALY* is the number of disability-adjusted life-years lost for every childhood tuberculosis death, age-weighted and discounted at 3% per year. A boy or girl who dies aged 2·6 years on average loses 30·2 *DALY*s on the WHO standard life table.[65]

Uncertainty analysis

The analyses described above yield estimates of (a) the annual risk of infection, (b) the probability of developing tuberculous meningitis or miliary tuberculosis for those who are infected but unvaccinated, (c) BCG vaccination coverage, (d) the protective efficacy of BCG against meningitis and miliary tuberculosis, (e) the cost of vaccination, and (f) the number of *DALY*s lost for the death of each child, as well as the forms of error distributions and error estimates for each of these six groups of variables. The data provided a total of 17 inputs for each of 194 countries. Multivariate uncertainty analysis was used to compute best estimates of the numbers of cases, deaths, and *DALY*s gained, and to assess the magnitude of errors surrounding these estimates. We did 1500 iterations using the program @Risk 4.5 Professional choosing, for each run, values for the above distributions by Latin hypercube sampling. The results are expressed as means with 5th and 95th centiles.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, or writing of the report. The

	Africa (high HIV)	Africa (low HIV)	Central Europe	Established market economies	Eastern Mediterranean	Former Soviet Union	Latin America	Southeast Asia	Western Pacific	World
Number of cases of tuberculous meningitis prevented in children born in 2002 up to age 5 years										
Mean	4480	3592	112	55	2030	415	855	13 771	4419	29 729
5th centile	2899	2250	71	35	1293	265	545	10 923	3579	24 063
95th centile	6200	5066	157	76	2880	595	1197	17 028	5338	36 192
Number of vaccinations per case prevented										
Mean	2443	2993	20 989	40 605	5861	8109	13 560	2294	4439	3435
5th centile	1672	2003	14 074	27 639	3880	5331	9141	1820	3619	2771
95th centile	3572	4511	31 263	59 905	8639	11 943	20 096	2835	5398	4177
Cost per case or death prevented (US$)										
Mean	6113	7491	52 511	101 628	14 656	20 287	33 885	5738	11 103	8592
5th centile	3899	4733	33 461	64 436	9236	12 467	21 477	4218	8232	6320
95th centile	9321	11 567	81 306	155 981	22 369	31 028	52 232	7602	14 616	11 311
Cost per DALY gained (US$)										
Mean	202	248	1739	3365	485	672	1 122	190	368	285
5th centile	129	157	1108	2134	306	413	711	140	273	209
95th centile	309	383	2692	5165	741	1027	1 730	252	484	375
Number of cases of miliary tuberculosis prevented in children born in 2002 up to age 5 years										
Mean	1730	1387	43	21	784	161	330	5322	1708	11 486
5th centile	966	743	23	11	426	85	176	3313	1066	7304
95th centile	2717	2184	68	33	1 217	252	513	7582	2421	16 280
Number of vaccinations per case prevented										
Mean	6620	8108	56 978	110 161	15 891	22 029	36 758	6223	12 046	9314
5th centile	3819	4639	32 419	63 930	9208	12 599	21 221	4087	7974	6172
95th centile	10 732	13 651	95 766	184 515	26 254	37 423	61 516	9359	18 107	13 729
Cost per case or death prevented (US$)										
Mean	16 561	20 286	142 550	275 646	39 732	55 097	91 821	15 563	30 126	23 294
5fifth centile	9 227	11 013	77 969	152 222	21 886	29 917	50 822	9 577	18 827	14 518
95th centile	27 502	35 265	245 986	463 166	66 927	96 779	154 192	24 288	46 734	36 001
Cost per DALY gained (US$)										
Mean	548	672	4720	9127	1316	1824	3040	515	998	771
5th centile	306	365	2582	5040	725	991	1683	317	623	481
95th centile	911	1168	8145	15 337	2216	3205	5106	804	1547	1192

Table 4: **Effectiveness and cost of BCG for the prevention of tuberculous meningitis and miliary tuberculosis, by region and for the world**

corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

According to the methods described, the BCG vaccinations given to 100·5 million of the 132·8 million children born in 2002 would have prevented almost 30 000 cases of tuberculous meningitis, or one case for roughly every 3500 inoculations (table 4). These vaccinations will also have prevented nearly 11 500 cases of miliary tuberculosis, or one case for roughly every 9300 inoculations. Most of the cases would have been prevented in southeast Asia (46%), Africa (27%, both African regions combined), and the western Pacific region (15%). These are also the regions in which fewest inoculations are required to prevent one case. Only eight of the 30 countries in the established market economies use BCG routinely, preventing less than 60 cases of tuberculous meningitis, or one case for about every 40 000 inoculations (table 4). The numbers of cases prevented in individual countries within the regions are recorded in a supplementary report available from the authors on request.

At US$2–3 per dose, BCG vaccination costs around US$8600 per case of tuberculous meningitis prevented worldwide, about $24 000 per case of miliary tuberculosis prevented, and $6212 (95% CI 4530–8217) to prevent any case of severe tuberculosis (table 4). Because we have assumed costs to be the same in different parts of the world, the cost-effectiveness by region varies in proportion with the number of inoculations needed to prevent one case. The cost per tuberculous meningitis case prevented was therefore lowest in southeast Asia and highest in the established market economies. The average costs per *DALY* gained globally were roughly $300 for meningitis, $800 for miliary disease, and $206 (150–272) for any case of severe tuberculosis, with the variation between regions again proportional to the number of inoculations needed to prevent one case (table 4).

Discussion

The 100 million doses of BCG vaccine given to children every year prevent about 40 000 cases of tuberculous meningitis and miliary tuberculosis before these children reach their fifth birthdays, or roughly one case prevented for every 2500 inoculations. Worldwide, the cost of vaccination is US$200 or less per year of healthy life gained. The cost per *DALY* gained in every region of the world is much less than the average annual income per head (eg, gross national income ≤US$735 in low income countries). On the basis of the guideline that health interventions are good value up to a cost per *DALY* gained of twice annual income,[66,67] BCG is a cost-effective intervention against severe childhood tuberculosis. BCG vaccination is only a little less cost effective than the treatment of active disease by short-course chemotherapy, which is typically less than US$50 per *DALY* gained in low-income and middle-income countries, and widely thought to be good value for money.[68–70]

BCG has its biggest effect, and is most cost effective, in southeast Asia, Africa, and the western Pacific region, where tuberculosis infection rates and BCG coverage are highest. Cost-effectiveness ratios are least favourable in the few developed countries where BCG vaccination is still routine, but where the risk of infection is now fairly low. Here, the cost per *DALY* gained runs into thousands of dollars, which should prompt further discussion about whether BCG can be withdrawn from routine use in these richer countries, and reserved for groups of people at high risk, such as health-care workers, and infants born to migrants from high-incidence countries.[46,71] Discontinuation of BCG also eliminates the difficulty of confusing infection with vaccination when tuberculin testing is used for contact tracing in local tuberculosis control efforts. The International Union Against Tuberculosis and Lung Disease has suggested that routine BCG vaccination should be discontinued when the notification rate of pulmonary tuberculosis reaches less than five per 100 000 per year (among other criteria), but this threshold was not based on cost-effectiveness analysis.[72]

There are at least five reasons why our investigation of the cost-effectiveness of BCG programmes is likely to be conservative. First, we have not allowed for the protection provided against pulmonary or extrapulmonary tuberculosis and leprosy in children aged 5 years and older.[9] In this context, Aronson and colleagues[73] showed that BCG protected a population of Native Americans against pulmonary and extrapulmonary tuberculosis with an average efficacy of 52% in 60 years. Second, we have assumed that only smear-positive patients are infectious, which tends to an underestimate of annual risk of infection.[19,37] Third, we have not accounted for any non-specific effects of BCG on child mortality.[11,74] Fourth, our meta-analysis includes a study[58] from Lucknow, India, with a low estimate of BCG efficacy against meningitis, which might have been excluded on grounds of statistical heterogeneity. And fifth, our costing of BCG vaccination, if inaccurate, errs on the high side.

On the other hand, we have implicitly assumed that the risk of infection and BCG coverage are uniformly distributed in populations. These assumptions are almost certainly not true, and would lead to an overestimate of BCG effect if, in less deprived communities where the risk of tuberculosis is low, vaccine coverage is higher than in more deprived communities for reasons other than the BCG programme. Furthermore, we have taken the best estimate of BCG efficacy against meningitis as 73% in all regions, although the data indicate that protection could be less than this figure in Asia where most vaccine is administered. This high efficacy would also tend to overestimate the effect of BCG globally. Finally, if the case fatality rate of tuberculous meningitis and miliary tuberculosis is less than 100%, we have overestimated the effectiveness of BCG, as measured by the number of *DALY*s gained. However, case fatality rates somewhat less than 100% would not invalidate our general conclusion that BCG is a cost-effective intervention.

There are several additional, potentially important sources of uncertainty that are hard to assess, especially in deriving estimates of the annual risk of infection. The annual risk of infection for every country is calculated from an estimate of the transmission or contact rate per case per unit time and the smear-positive prevalence. We have used one universal estimate of the contact rate, on the basis of studies done in only 11 countries. The CI surrounding the average contact rate is wide, and the uncertainty may conceal systematic variation among different regions of the world. The estimated prevalence of smear-positive disease for each country is a consensus figure published by WHO;[17] for the many countries where prevalence has not been measured directly in population-based surveys, the accuracy of these estimates is not known.

Thus, we have quantified the global effect of BCG, one of the world's most widely used vaccines. Notwithstanding the uncertainties, and since decisions about cost-effectiveness are typically based on order-of-magnitude differences,[68,70] our results lend support to the continued use of BCG in countries where tuberculosis incidence remains well above the threshold set by the International Union Against Tuberculosis and Lung Disease. These are typically low-income and middle-income countries where BCG is used as an adjunct to the principal method of tuberculosis control—the treatment of active disease by short-course chemotherapy.

Contributors

C Dye and P Fine conceived the project and developed the methods in outline. B Bourdin Trunz refined the methods, undertook the background research and the analysis of effect, and submitted an interim report on the work as an unpublished MSc thesis at the London School of Hygiene and Tropical Medicine. C Dye drafted the journal paper, which was finalised with input from all authors.

Conflict of interest statement

C Dye works for WHO, which recommends BCG vaccination for infants. B Bourdin Trunz was partly funded by WHO to carry out this study. P Fine is a member of the BCG Panel of the United Kingdom Joint Committee on Vaccination and Immunisation (JCVI), which also advocates the use of BCG. However, the opinions expressed in this paper are those of the authors; they are not the official views of WHO or JCVI.

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