Case–control evaluation of a school-age BCG vaccination programme in subtropical Australia

A. Patel,¹ F. Schofield,² V. Siskind,³ E. Abrahams,⁴ & J. Parker⁵

In 1956 a programme was initiated to vaccinate all children aged 12–14 years who were attending schools in Queensland, Australia. In view of the declining incidence of tuberculosis in Australia as a whole, there was a need to evaluate the effectiveness of the programme and its procedures. We therefore carried out a case–control study of Queensland’s population, excluding certain known high-risk groups. Cases were Queensland residents with notified tuberculosis and of the appropriate age; two controls per case were chosen from the electoral roll. Information on vaccination status was obtained mainly from questionnaires and school records, where available.

The results show that at best BCG vaccination had a modest protective effect, approximately 30% when the patients were diagnosed, which was on average 15 years after they had been vaccinated in the school programme. In the north the climate of Queensland is tropical, while in the more heavily populated south it is subtropical. A substantial proportion of the school records reported weak positive reactions to preliminary tuberculin testing, believed to be due largely to atypical mycobacteria. A similar phenomenon has been observed in other tropical regions, and may help to explain the apparent absence of a strongly protective effect for BCG vaccination.

Introduction
A controlled trial of BCG vaccination of schoolchildren in England that started in 1950 reported that the protection afforded was 59–78% over 15 years (1–3). As a result, a BCG vaccination programme directed at children aged 12–14 years was instituted in Queensland schools in 1956, and within a few years was being carried out in all appropriate schools throughout the state. In Queensland the incidence of tuberculosis has been steadily falling over the last 20 years (Fig. 1), as it has in many developed countries, including the other Australian states, some of which, such as New South Wales, have had no population-wide BCG programme.

The Queensland State Health Department required information on the effectiveness of this school programme against tuberculosis in adults to enable it to consolidate the decision made in 1986 to discontinue the vaccination programme for those at a low risk of infection. This need was subsequently recognized by the National Health and Medical Research Council, which recommended investigating the efficacy and applicability of BCG vaccination also in other Australian states and territories.⁶

Aboriginal people and refugees or other immigrants from south-east Asia are two groups that are at greater risk of tuberculosis than the general Australian population. These groups are routinely afforded special screening, vaccination, and surveillance services against tuberculosis. In consequence,

Fig. 1. Incidence of tuberculosis, Queensland, Australia, 1965–84.

¹ Director, Division of Specialized Health Services, Department of Health, Brisbane, Australia.
² Emeritus Professor, Department of Social and Preventive Medicine, University of Queensland Medical School, Brisbane, Australia.
³ Reader, Department of Social and Preventive Medicine, University of Queensland Medical School, Herston Road, Herston, Queensland 4006, Australia. Requests for reprints should be sent to this author.
⁴ Previously, Director of Tuberculosis, Department of Health, Brisbane, Australia.
⁵ Previously, Chief Nurse, Chest Clinic, Department of Health, Brisbane, Australia.

they were excluded from this study. The study was therefore carried out on the relatively low-risk general population in Queensland, who were aged 15-44 years in 1985, and who could have been vaccinated in the secondary school programme.

**The vaccination procedure**

During the early years of the programme, children in the age group concerned (12-14-year-olds) were in the final year of primary school; however, following a change in 1962, this age group became the first year of secondary school. Subsequently, all schools were visited annually—beforehand some remotely situated schools had been visited only once every 2 years. All children in the target age group were eligible, except for a small number in remote rural areas who received their education at home through the “school of the air” radio broadcasts.

At the vaccinator’s first visit, an individual record card was prepared for each child attending, and all were tuberculin tested. Two days later, at the second visit the test was read and the result recorded on the card. If written parental agreement had been obtained, the negative reactors (Heaf grade 0) and a small proportion (about 10%) of the weak positive reactors (Heaf grade I) were BCG vaccinated. No subsequent examination was made to determine whether the vaccine had “taken”, i.e., had produced a local lesion. Intermediate positive (Heaf grade II) and strong positive reactors (Heaf grades III and IV) were not vaccinated, but the latter were put under clinical surveillance for tuberculosis. The record cards were stored alphabetically in the regional tuberculosis control offices.

**Methods**

**Epidemiological approach**

A retrospective cohort study was considered initially on the basis of the existing school card system. After exclusion of high-risk population groups, the rates of tuberculosis notification in Queensland were, however, extremely low. A cohort design would therefore have required the processing of an impractically large number of cards to ensure that enough cases were found to make credible estimates of the value of the programme. A case–control methodology, using the obligatory tuberculosis notifications to identify cases, was therefore chosen. Smith has pointed out the advantages of this method for developing countries and for the vaccination of newborn infants (4). In such situations, BCG scars, and not vaccination records, are the more usual indicators of vaccination status. On this basis, anyone whose vaccination has not taken is counted as unvaccinated. In the present study, however, the efficacy of both the programme and the vaccination procedure, rather than of the vaccine itself, has been estimated. Also, routine preliminary tuberculin testing is not carried out in developing countries.

In Queensland the criteria for notifying tuberculosis are a bacteriological confirmation of the causative organism in the sputum or a histologically diagnosed tuberculous lesion, including “surgical” tuberculosis. Also active tuberculosis diagnosed on strong clinical grounds is notifiable, and such cases comprised 20% of the total notifications. Every case in the study satisfied one of these criteria. Official notification of tuberculosis is compulsory and known to have been very close to complete. The cases enrolled were born in 1939–67, and all were diagnosed between 1964 and 1985.

Two controls per case were randomly selected from the list of voters’ names in the electoral division or subdivision where a case lived (electoral registration is compulsory in Australia from 18 years of age). Matching by area of residence results in matching also for some important environmental risk indicators for tuberculosis, in particular the generally greater risk in urban than rural environments and, in Australia, at latitudes further from the equator (5, 6). The controls were also matched with cases by sex and date of birth ± 36 months.

**Information collected**

An identical questionnaire was sent to every case and control, requesting his/her full name, maiden name of married women, main occupation, ethnic group, date and place of birth, and locations and names of primary and secondary schools attended. All participants were asked whether they had been given a tuberculin skin test at school, whether they had received BCG vaccine at school or elsewhere (and if so, for what reason), and whether they had ever been a contact of someone with tuberculosis. The answers provided by those who received their secondary schooling in Queensland were checked against the data on their record cards, if available. In addition, 13 cases and 28 controls were examined by trained nurses to determine whether they had a BCG scar. As a result, 32 “don’t knows” were reclassified.

**Statistical methods**

The results are presented in the form of odds ratios (matched and unmatched) and their 95% confidence intervals (CI). Since tuberculosis is rare in the target population, odds ratios are good estimates of relative risk—the complement of efficiency. Confidence limits for the unmatched odds or cross-product ratio were calculated using Cornfield’s method (7). The
Evaluation of a BCG programme in Australia

Table 1: Distribution of cases and matched controls by the place of birth and location of secondary schools

<table>
<thead>
<tr>
<th>No. of cases by:</th>
<th>Place of birth</th>
<th>Secondary school</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queensland</td>
<td>97 (53)*</td>
<td>113 (62)</td>
</tr>
<tr>
<td>Rest of Australia/New Zealand</td>
<td>43 (23)</td>
<td>43 (23)</td>
</tr>
<tr>
<td>Elsewhere</td>
<td>43 (23)</td>
<td>27 (15)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>183</strong></td>
<td><strong>183</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of controls by:</th>
<th>Place of birth</th>
<th>Secondary school</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queensland</td>
<td>236 (64)</td>
<td>255 (70)</td>
</tr>
<tr>
<td>Rest of Australia/New Zealand</td>
<td>86 (23)</td>
<td>82 (22)</td>
</tr>
<tr>
<td>Elsewhere</td>
<td>44 (12)</td>
<td>29 (8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>366</strong></td>
<td><strong>366</strong></td>
</tr>
</tbody>
</table>

* Figures in parentheses are percentages.

matched analysis used only those cases who shared certain characteristics with at least one matched control. Point estimates of the odds ratio were derived by maximum likelihood, and their confidence limits from the exact convolution distribution of the sufficient statistic (8).

We identified 290 eligible persons with notified tuberculosis who were believed still to be resident in Queensland. Four (1.4%) had died, and 14 (4.8%) had moved out of the state; 33 (11.4%) could not be traced; and 56 (19.3%) refused to participate or did not respond. After two mailings, 183 (63.1%) returned usable questionnaires (91 males and 92 females). To obtain two matched controls per case, we selected 603 names from the electoral rolls; 60.7% responded after two mailings. The distributions of the places of birth and secondary schools of the enrolled subjects are shown in Table 1. Proportionately more cases than controls were born or educated outside Australia/New Zealand.

Results

Record cards containing information on skin tests and BCG vaccination could be found for only 30% of the 368 study subjects who attended secondary schools in Queensland (28% of cases and 31% of controls)—the remainder had apparently been discarded or destroyed for lack of storage space. Where available, school records were used, but most of the results are based on subjects’ recall. Taking the school record card as authoritative for vaccination status, we estimated misclassification rates for the 95 individuals with both a school card and a definite self-reported BCG vaccination status. Of 54 (13 cases, 41 controls) who stated that they had been vaccinated, one case was in error (1.9%); and of 15 cases and 26 controls who claimed not to have been vaccinated, three cases and seven controls (overall, 24.4%) had received BCG vaccine at school according to their record card. In terms of the accuracy of recall, differences between cases and controls were small and not statistically significant. Similarly, of 110 respondents recorded as having received a tuberculin skin test, with or without subsequent vaccination, only five (1 case, and 4 controls) erroneously stated otherwise.

Programme effectiveness

To estimate the effectiveness, i.e., the “overall protective effect” (4), of the programme, not just of the vaccine, we compared cases and controls with respect to the proportions who reported that they had been tuberculin tested at a Queensland school. The results of matched and unmatched analyses are shown in Table 2, which also shows the proportions of Queensland-educated cases and controls who were vaccinated, as established by documentation, self-report, or scar examination. Both analyses show at best a modest protective effect (approximately 30%).

Efficacy of the BCG vaccination procedure

A total of 72 individuals (27 (15%) cases and 45 (12%) controls) whose vaccination status could not

Table 2: Self-reported history of tuberculin skin testing and BCG vaccination status of cases and controls who attended secondary school in Queensland

<table>
<thead>
<tr>
<th>No. of study subjects:</th>
<th>Positive</th>
<th>Negative</th>
<th>Total, known</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin testing</strong>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>80</td>
<td>25</td>
<td>105</td>
<td>8</td>
</tr>
<tr>
<td>Controls</td>
<td>179</td>
<td>39</td>
<td>218</td>
<td>37</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>259</td>
<td>64</td>
<td>323</td>
<td>45</td>
</tr>
<tr>
<td><strong>BCG status</strong>b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>45</td>
<td>62</td>
<td>107</td>
<td>6</td>
</tr>
<tr>
<td>Controls</td>
<td>114</td>
<td>111</td>
<td>225</td>
<td>30</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>159</td>
<td>173</td>
<td>332</td>
<td>36</td>
</tr>
</tbody>
</table>

a Odds ratio (OR) = 0.70; 95% confidence interval (CI) = 0.38–1.28. Matched analysis, 206 subjects: OR = 0.63; 95% CI = 0.26–1.43.

b OR = 0.71: 95% CI = 0.43–1.15. Matched analysis, 229 subjects: OR = 0.59; 95% CI = 0.29–1.19.

Table 3: BCG vaccination status of all cases and controls *

<table>
<thead>
<tr>
<th></th>
<th>No. of study subjects:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total, known</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cases</td>
<td>64</td>
<td>92</td>
<td>156</td>
<td>27</td>
</tr>
<tr>
<td>Controls</td>
<td>156</td>
<td>165</td>
<td>321</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>220</td>
<td>257</td>
<td>477</td>
<td>72</td>
</tr>
</tbody>
</table>

* Odds ratio (OR) = 0.74; 95% confidence interval (CI) = 0.49–1.10. Matched analysis, 434 subjects: OR = 0.67; 95% CI = 0.42–1.05.

be checked either from a school record card or by examining them for a BCG scar reported that they did not know whether they had received BCG vaccine. Data for these individuals have been excluded from the majority of analyses, but some have been included in Table 5.

Inclusion of all subjects of known BCG vaccination status in the analysis gives odds ratios of 0.74 (unmatched) and 0.67 (matched). These correspond to estimates of vaccination efficacy of 26% and 33%, respectively, with corresponding upper 95% confidence bounds of 51% and 58% (Table 3). Both confidence intervals include zero vaccination efficacy.

Omission of every case and control who did not attend a secondary school in Australia or New Zealand (42 individuals) from the unmatched analysis yielded an odds ratio of 0.77; the corresponding value in the matched analysis was 0.79 (Table 4). Exclusion of all cases and controls who were born outside Australia/New Zealand gave similar results: for 404 subjects the unmatched analysis resulted in an odds ratio of 0.85 (95% CI, 0.54–1.34); and the matched analysis on 308 subjects produced an odds ratio of 0.88 (95% CI, 0.50–1.56). Proportionally twice as many migrants to Queensland from New Zealand and elsewhere in Australia were unsure about their BCG vaccination status as those educated in Queensland; this may have shifted the odds ratios closer to unity.

These results, which are confined to subjects of known BCG vaccination status, are shifted towards a lower odds ratio, and thus a higher estimate of effectiveness, by making certain assumptions about the probability that subjects of unknown BCG vaccination status who went to secondary school in Queensland, Victoria, or New South Wales had actually been vaccinated. Of those who went to school in Queensland, 15 individuals (4 cases and 11 controls) whose school cards could be found answered “don’t know” to the question about their BCG vaccination status. All of these individuals had, however, been vaccinated at school. It was therefore assumed that 36 other people (6 cases and 30 controls) who attended Queensland secondary schools and whose BCG vaccination status was unknown had also been vaccinated at school, even though their cards could not be found.

A statewide secondary school BCG vaccination programme also existed in Victoria, although no vaccination cards were available; we therefore assumed that the three individuals schooled there (1 case and 2 controls) who had answered “don’t know” about their status had been vaccinated. On the other hand, since New South Wales had no school BCG vaccination programme, we assumed that the 13 people (9 cases and 4 controls) schooled there who had replied “don’t know” had not been vaccinated. (A small number of individuals who had been educated in New South Wales had later joined the armed forces, and if tuberculin-negative on recruitment, were routinely BCG vaccinated, usually aged 18–20 years). Such individuals have been included as “BCG positive” in the present analyses (Table 5).

Data on a further 20 individuals who replied “don’t know” to their BCG vaccination status, and for whom no other check was available, are not shown in Table 5 and were excluded from the other analyses. These individuals had been educated in states or countries that have BCG vaccination programmes in selected schools only. For those individuals who were included, the unmatched and matched analyses gave odds ratios of 0.63 and 0.61 for 529 and 509 subjects, respectively. Both upper confidence bounds were less than 1.0. These analyses, which included 50 additional subjects of uncertain BCG vaccination status, are the only ones to produce odds ratios that suggest a significant protective effect for BCG vaccination (about 40%).

Table 4: BCG vaccination status of cases and controls who received their secondary education in Australia or New Zealand *

<table>
<thead>
<tr>
<th></th>
<th>No. of study subjects:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total, known</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cases</td>
<td>57</td>
<td>82</td>
<td>139</td>
<td>17</td>
</tr>
<tr>
<td>Controls</td>
<td>140</td>
<td>156</td>
<td>296</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>197</td>
<td>238</td>
<td>435</td>
<td>58</td>
</tr>
</tbody>
</table>

* Odds ratio (OR) = 0.77; 95% confidence interval (CI) = 0.51–1.19. Matched analysis, 361 subjects: OR = 0.79, 95% CI = 0.47–1.32.
Table 5: BCG vaccination status of cases and controls, after inclusion of some subjects of unknown status

<table>
<thead>
<tr>
<th></th>
<th>No. of study subjects:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Cases</td>
<td>71</td>
<td>101</td>
</tr>
<tr>
<td>Controls</td>
<td>188</td>
<td>169</td>
</tr>
<tr>
<td>Total</td>
<td>259</td>
<td>270</td>
</tr>
</tbody>
</table>

* Those educated in Queensland or Victoria were assumed to be positive, those educated in New South Wales, negative, while all others whose vaccination status was unknown were excluded. Odds ratio (OR) = 0.63; 95% confidence interval (CI) = 0.43–40.92. Matched analysis, 509 subjects: OR = 0.61; 95% CI = 0.41–0.92.

However, because of the assumptions made in assigning vaccination status to the “don’t knows”, this significance may be illusory.

**Types of tuberculosis**

It has been suggested that BCG vaccination may give better protection against haematogenous forms of tuberculosis than other forms of the disease. Overall, 85% of the cases were notified as presenting with pulmonary tuberculosis, 12% were haematogenous (urinary, genital, bone, miliary, or meningitis), while 3% involved lymph node or alimentary tuberculosis (3 cases only were diagnosed as pulmonary plus haematogenous tuberculosis—they were included with the haematogenous group in this analysis). Among cases who had received BCG vaccine, 15% had the haematogenous form, while among those not vaccinated the proportion was 10%; these proportions increased to 19% and 12%, respectively, when the lymph node and alimentary cases were also included. (Among the small number of individuals who had participated in a BCG programme but were deliberately not vaccinated because their tuberculin tests were positive, the proportion of haematogenous plus lymphatic cases was 16%). Therefore, this series of cases provides no evidence that the BCG vaccine used in Australia had a differential protective effect against any particular form of tuberculosis.

**Discussion**

The results shown in Table 2, which refer to the public health effects of the programme, should be interpreted in the light of any possible bias in the methodology used. Firstly, children who did not receive BCG vaccine at school because of parental refusal or because they did not attend screening or vaccination sessions are perhaps more susceptible to tuberculosis than those who were vaccinated. Vaccination refusals were uncommon (about 1%), but nonattendance at sessions may have been as high as 15%. On balance, any bias from this source would tend to enhance estimates of the programme's effectiveness.

Secondly, selection bias could have resulted from the tuberculin skin testing of every schoolchild who attended the BCG vaccination programme. As in the United Kingdom (J), and in accord with practices in other developed countries, children who had strongly positive reactions were deliberately not given BCG vaccine. Since these children are probably at the highest risk of subsequently developing notifiable tuberculosis, the screening procedure could have produced an apparent association between nonvaccination and later notification of tuberculosis, thus falsely increasing any apparent protective effect of vaccination. However, when those who were tuberculin tested (included in the programme) were compared with those not tuberculin tested (not included in the programme), the odds ratio was little different (see Table 2).

In Queensland, and in some other low latitude areas of the world, positive tuberculin skin tests are also produced by infection with mycobacteria of nonhuman, nonbovine origin (10, 11). These generally cause weaker positive tuberculin reactions than those caused by tuberculosis organisms that are pathogenic to humans.

According to instructions given by the organizers of the programme, persons who exhibited weakly positive reactions were also to be vaccinated. Nevertheless, the available school cards show that in practice 90% of such children were excluded by the vaccinators.

Using data on the natural positivity rates in the various regions of Queensland over the last 30 years, we calculated that the odds ratios reported here are likely to be overestimates of the real protective effect of BCG vaccination in the study population (see Annex).

Nondifferential misclassification weakens observed epidemiological associations (I2), and misclassification of (self-reported) BCG vaccination status certainly occurred in this study, apparently to the same extent among cases and controls. However, application of estimated correction factors (I2) to the self-reported portion of the data in the unmatched analyses produced virtually the same odds ratios.

The results of the study gave further weight to the decision, already taken because of the markedly declining risk (Fig. 1), to discontinue the BCG
vaccination programme throughout Queensland's secondary schools. Special screening and vaccination programmes for groups excluded from this study (aboriginal people, refugees, and other immigrants from south-east Asia) are, however, continuing because they are at much greater risk of tuberculosis than the general population.

Our results need to be discussed with respect to recently proposed hypotheses about the apparent failure of BCG vaccination in other tropical populations. One such hypothesis is that the strain of BCG vaccine employed in Australia since 1946 is not protective. Although the vaccine's potency and laboratory stability according to WHO reference standards have been repeatedly confirmed (13), our study is the first to estimate its protective effect in human populations.

The second hypothesis, which results from a study of South American children aged 0–14 years, is that the protective effect of BCG vaccine takes some years to develop, with no protective effect in the first 3 years following vaccination, but with the relative risk being greatly reduced to 0.18 after 11–14 years (14). Also a long-term follow-up study in south India supports this conclusion (15–17). In contrast, in our study, the median and mean intervals between vaccination and tuberculosis notification were 15 years. Clearly any protection that might appear after a longer interval than this has a public health significance that is too small to justify continuing the vaccination programme.

The immunity conferred by BCG vaccine under the epidemiological conditions that prevail in Australia could decline with time. To examine this proposition, we included only individuals who had received their secondary education in Queensland, and whose age at vaccination could be reasonably assumed to be 13 years, the midpoint of the target ages. Notifications of tuberculosis were then classified in terms of the time since vaccination, as follows: early (<12 years); intermediate (12–21 years) and late (>21 years). Using a common pool of controls and stratifying by year of birth, we estimated that the odds ratio for early notifications was 0.53, that for intermediate, 0.83, and that for late, 1.64; all these estimates had wide confidence intervals. The observed trend, though not statistically significant, suggests that in Queensland, if any immunity is produced by BCG vaccine, it could gradually fade with time.

For both the vaccinated and unvaccinated cases who had been tuberculin negative or weakly positive at school, the mean and median ages at notification were 28 years. BCG vaccine therefore seems to have neither delayed nor reduced the risk of subsequent tuberculosis among the vaccinees. (As expected, the mean age at notification of cases who had been strongly tuberculin positive at school, and were thus unvaccinated, was significantly younger (22 years)).

These results are also consistent with a change in the pathogenesis of tuberculosis in Queensland over the 30 years of the BCG vaccination programme—from disease upon recent infection to disease from endogenous reactivation after past infection. Possibly, BCG vaccination protects less well against the latter type of infection than against the former. Primary infection of the study population (<45 years of age in 1985) may have occurred at quite a young age; upon starting employment, for instance. It could then have remained clinically dormant (on average, for 15 years after skin testing and BCG vaccination) until clinical disease appeared as a result of endogenous reactivation rather than reinfection. Our data provide some support for this hypothesis: the odds ratio for vaccination status among the 92 cases diagnosed before 1978, compared with their matched controls, is 0.46, compared with 1.19 among those diagnosed subsequently (P < 0.05).

A further hypothesis is that, in some subtropical and tropical climates such as Queensland's, the expected protective effect of BCG vaccination is anticipated by a naturally acquired protection against tuberculosis derived from human exposure to the nonhuman, nonbovine mycobacteria in the environment (18). Because of such prior exposure, there can therefore be no unvaccinated group against which the BCG-vaccinated can be compared. This hypothesis has been forwarded to account for the comparative failure of BCG vaccine to protect against adult tuberculosis in controlled cohort studies in south India. A recent animal experiment, however, does not support the alternative suggestion that environmental mycobacteria induce a suppressive effect such that later response to BCG vaccination would be inhibited (19).

We therefore suggest that BCG vaccination does not augment any acquired immunity that exposure to environmental mycobacteria might confer upon the population of Queensland (20, 21). In Victoria, in contrast, the prevalence of positive tuberculin tests that can be ascribed to such mycobacteria is low (6). A case–control study in Victoria could therefore test much less equivocally the first of the above-mentioned hypotheses, i.e., that the Australian BCG vaccine strain is not protective. Also a case–control study of the effect in young adults of mass BCG vaccination campaigns against pulmonary tuberculosis in Cameroon (where the sensitivity to mycobacteria other than Mycobacterium tuberculosis was low) reported that the protective effect was 66% and the duration of
Evaluation of a BCG programme in Australia

It should be emphasized that the reason for the failure of the secondary school BCG vaccination programme to protect young adults in Queensland is still not known, and that it occurred in tropical and subtropical conditions over a period of 20 years of steeply declining notification rate. The public health relevance and the epidemiological applicability of these findings in other countries may therefore be limited. In particular, this study is not relevant to BCG vaccination programmes against childhood forms of tuberculosis.

Our results nevertheless highlight the need for reliable ongoing epidemiological surveillance of all BCG vaccination programmes. Some programmes already carry out such activities but their effectiveness needs to be periodically assessed to guide policy. The case–control method is the most economical and feasible for this purpose (4). The results also show that there is a public health need for further research to identify the specific immunological processes whereby humans acquire protection against tuberculosis, and also to identify the immunogenic centres in mycobacteria that could be used to develop future vaccines.

Acknowledgements

We gratefully acknowledge financial support from the Queensland Chest and Lung Association Inc. Mrs S. Webb and the Queensland Department of Health are thanked for their assistance in the field work.

Résumé

Evaluation cas-témoins d’un programme de vaccination par le BCG d’enfants d’âge scolaire en Australie subtropicale


Chez les sujets scolarisés dans le Queensland, l’effet protecteur du programme a été estimé à environ 30% (non significativement différent de zéro dans l’étude statistique), que l’évaluation soit faite par une anamnèse de la vaccination ou par un test tuberculine. L’efficacité de la vaccination a été évaluée pour la totalité de l’échantillon de l’étude, quel que soit le lieu où les sujets avaient suivi leurs études secondaires—Queensland, ailleurs en Australie ou étranger. Les estimations de l’effet protecteur du programme vont de 23% à 39%, suivant les groupes qui avaient été inclus dans l’analyse et la classification des sujets dont l’état vaccinal était inconnu. L’intervalle de confiance contient la valeur zéro dans toutes les analyses sauf une, qui classait de façon optimiste les sujets dont l’état vaccinal était inconnu. A l’opposé des résultats d’une étude colombienne, nous avons trouvé qu’il n’y avait aucune preuve d’un effet retardé pour la protection conférée par la vaccination par le BCG, mais plutôt que la protection pouvait au mieux être temporaire.

Une mauvaise classification de l’état vaccinal ne semble pas avoir affecté nos résultats, alors que les biais dus à l’absentéisme ou au refus au moment de la séance de vaccination seraient plutôt en faveur de l’efficacité du programme. Un modèle statistique qui prenait en compte l’influence possible d’une “positivité naturelle”, avec des estimations de la prévalence de différents taux de réactivité à la tuberculine, indiquait que l’effet protecteur était surestimé. Trois autres explications aux résultats observés sont discutées. Parmi celles-ci, la première est que la souche de vaccin BCG employé peut ne pas être protectrice, bien qu’il soit prouvé qu’elle entraîne une sensibilité satisfaisante à la tuberculine. La seconde est que le BCG peut être moins efficace contre des réactivations endogènes que contre la maladie due à une infection récente, et que les premières soient devenues le type dominant de tuberculose dans le Queensland ces dernières années. Enfin, les mycobactéries non humaines et non bovines prévalentes dans les milieux tropicaux et subtropicaux, y compris le Queensland, peuvent conférer un certain degré non cumulatif de protection contre la tuberculose, semblable à celui dû à la vaccination.

References


**Annex**

**Effect of natural positivity**

The following assumptions were made in the statistical analysis of the data.

1) All Heaf grade I tuberculin positives (Mantoux 3–6 mm) at the time of vaccination and half the Heaf grade II positives (Mantoux 7–11 mm) were infected with environmental mycobacteria, whereas the remaining grade II positives and all those of higher grade were infected with human *Mycobacterium tuberculosis*. (The effect of modifying this assumption is also examined).

2) A proportion, $q$, of grade I positives, but none of those with higher grades, then received BCG vaccine.

In the population from which the sample was drawn, the component subgroups, with their specific risks of developing notified tuberculosis over the period of the study, area shown in the Table.

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Specific risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated negatives</td>
<td>$\rho_0$</td>
<td>$\pi$</td>
</tr>
<tr>
<td>Vaccinated negatives</td>
<td>$\rho_0$</td>
<td>$\psi \pi$</td>
</tr>
<tr>
<td>Positives, Heaf grade I</td>
<td>$\rho_1$</td>
<td>$\psi \pi$; with probability, $q$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\phi \pi$; with probability, $1 - q$</td>
</tr>
<tr>
<td>Positives, Heaf grade II</td>
<td>$\rho_2$</td>
<td>$\phi \pi$; with probability, 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\zeta \pi$; with probability, 0.5</td>
</tr>
<tr>
<td>Positives, Heaf grades III and IV</td>
<td>$\rho_3$</td>
<td>$\zeta \pi$</td>
</tr>
</tbody>
</table>

Thus in the reference population (size, $N$), there are the following groups:

- unvaccinated tuberculosis cases:
  $N(p_U \pi + p_A \phi \pi + p_B \zeta \pi)$;
- unvaccinated persons free of the disease (controls): $N[p_U(1 - \pi) + p_A(1 - \phi \pi) + p_B(1 - \zeta \pi)]$;
- vaccinated cases: $N(p_V + q \pi) \psi \pi$; and
- vaccinated controls: $N(p_V + q \pi)(1 - \psi \pi)$. 

432
Here the frequency of unvaccinated atypical infections \((p_A)\) equals \(p_1(1-q) + 0.5p_2\), and the frequency of typical infection \((p_B)\) equals \(0.5p_2 + p_3\).

Since the base risk in the unvaccinated tuberculin negatives, \(\pi\), is very small, the estimate of the odds ratio, i.e., \((\text{number of vaccinated cases} \times \text{number of unvaccinated controls})/\text{(number of unvaccinated cases} \times \text{number of vaccinated controls})\), tends to

\[
\psi[1 + (p_A(1-\phi) - p_B(\xi - 1))/(p_U + p_A\phi + p_B\xi)]
\]

Thus the odds ratio will be biased downward if \(\xi > 1 + p_A(1-\phi)/p_B\).

**Estimating the frequencies**

It should be noted first that the mean and median year of birth of both cases and controls was 1947, which corresponds to secondary school vaccination in approximately 1960. The observed frequencies of tuberculin positives in all grades are available for various cities and towns in Queensland from a survey conducted in 1959 (9), while the distribution of the population into various regions of the state can be obtained from the 1961 national census. Here we have divided the state into the following regions:

- south-east (roughly the current Brisbane and Moreton statistical divisions), which had 53% of the population in 1961;
- coastal (the area east of the Great Dividing Range, excluding the south-east), with 31% of the population; and
- the remaining inland area, with 16% of the population.

The frequencies of positivity in the south-east can be estimated from the corresponding data for Brisbane in the 1959 survey (21%), and those for the coastal and inland regions from the results for Ayr and Cairns (40%), and Roma (29%), respectively. Combining these estimates according to the corresponding population weights yields the following estimates: total positivity, 28%; grade I, 12.9%; grade II, 10.4%; and grades III and IV, 4.7%. This is in good agreement with the observed distribution of positivity among the 78 controls in the present study who had documented reactions to tuberculin testing, i.e., 20 positives (26%), 10 with Heaf grade I (13%), 8 with grade II (10%), and 2 with grade III (3%).

A total of 30% of the controls had their secondary school education outside Queensland; surveys carried out in 1959 in other Australian states suggest that a reasonable estimate of total positivity in this group would be 5% (10), and we assume the same distribution into grades as in Queensland. The final estimate for the frequency of positives in the reference population is then grade I (10%), grade II (8%), and grades III and IV (3%) combined, i.e., a total positivity of 27%.

From the available school cards, a reasonable value for \(q\), the proportion of grade I positives who were vaccinated, is 10%. Thus, \(p_A = 0.13\), \(p_B = 0.07\), and the bias is downward if \(\xi > 1 + 1.86(1 - \phi)\).

The direction of the bias in the estimate of the odds ratio therefore depends on the magnitude of \(\phi\) (the degree of protection afforded by non-human infection), and \(\xi\) (the extent to which the risk of developing notifiable tuberculosis in strongly positive reactors infected by human disease is elevated relative to unvaccinated negative reactors). If environmental mycobacteria confer no protection, i.e., \(1 - \phi = 0\), any increase in risk among the strongly positive reactors implies a downward bias. A more realistic, if conservative, value of \(\phi\) would be 0.7 (the initial estimate for \(\psi\), i.e., one minus the vaccine efficiency); in this instance the vaccine efficiency would be overestimated if \(\xi\) (the relative risk of human infection) were greater than 1.56.

Assumption 1) mentioned above can be modified to include all Heaf grade II positives, either with the Heaf grade I positives (nonhuman infection) or with the Heaf grades III and IV positives (human infection), rather than dividing them between two groups. The estimated frequencies and the parameter, \(q\), remain unaltered. If the first of these possibilities is taken, the ratio \(p_A/p_B\) increases from 1.86 to 5.7, and the condition for downward bias with \(\phi = 0.7\) is now \(\xi > 1.70\). In the second case, \(p_A/p_B = 0.82\), and the condition is \(\xi > 1.25\). In practice, it seems likely that all the above-mentioned conditions for the parameter, \(\xi\), would be fulfilled.