BCG REVACCINATION

HEALTH TECHNOLOGY ASSESSMENT SECTION

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DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

Tuberculosis (TB) is a contagious airborne disease posing major public health problem worldwide and has been declared as a global emergency by the WHO in 1993. Control of this disease relies upon prevention through Bacillus Calmette-Guérin (BCG) vaccination or chemoprophylaxis, ascertainment and treatment of the cases by employing the "directly observed therapy short course" (DOTS) approach. BCG vaccine has been used worldwide as a neonatal vaccination against severe forms of TB for around 80 years. The efficacy of BCG vaccination in newborns (primary BCG vaccination) is well recognized against disseminated TB. BCG revaccination is frequently given to children between six to fourteen years of age. However, there is considerable uncertainty as to the efficacy and extent of protection offered by booster of BCG vaccine (revaccination) against TB in these older children. This review was requested by the Director of Disease Control Division, Ministry of Health Malaysia to review the evidence on BCG revaccination against TB, to assist in revising the current vaccination policy.

Aims/Objectives

To assess the safety,effectiveness and cost effectiveness of BCG revaccination for the prevention of tuberculosis occurrence.

Results and conclusion

In terms of efficacy, there was fair to good level of evidence to show that BCG revaccination did not provide additional protection when given to children with scar. There was insufficient evidence on safety but it showed that occurrence of adverse event following second dose of BCG vaccination was rare. There was only one fair level of evidence on cost effectiveness, which showed that BCG revaccination was not cost effective in low incidence TB country given the lack of protection provided by the second dose.

Methods

Literature were searched through electronic databases which included PubMed, Medline, Cochrane Database of Systematic Reviews, Cochrane Database of Controlled Trial, Health Technology Assessment, National Horizon Scanning, other websites; INAHTA, ASERNIP-S, CADTH and FDA and general databases such as Google and Yahoo. The search strategy used the terms, which were either used singly or in various combinations: "BCG", "vaccination", "revaccination", "booster", "second dose", "tuberculosis", "prevention", "control" and "treatment". The search was limited to articles on human. There was no language limitation in the search. Systematic reviews, meta-analysis and randomised clinical trials pertaining to effectiveness, safety and cost effectiveness of BCG revaccination were included.

A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Programme (CASP) checklists and the evidence graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001).

BCG REVACCINATION

1. INTRODUCTION

Tuberculosis (TB) is a contagious airborne disease imposing major public health problem worldwide and was declared as a global emergency by the WHO in 1993.[1] One third of the world's population is believed to be infected with *Mycobacterium tuberculosis* .[1] The vast majority of TB cases (95%) and deaths (98%) are in the developing world, affecting mostly (75%) young adults in their most productive years. Annually, approximately 8.8 million new cases of TB are notified around the world. Of these, 1.7 million die from TB, with nearly two billion people have latent TB infection, and a small number develops clinical TB, depending on factors such as the development of immunodeficiency or other unknown conditions. Pulmonary TB is the most frequent clinical form, and is responsible for the transmission of the TB bacillus.[1]

Poverty, poorer healthcare and migration affect the effective TB control in the developing countries.[3] Control of this disease relies upon prevention through Bacillus Calmette-Guérin (BCG) vaccination or chemoprophylaxis, ascertainment and treatment of the cases by employing the "directly observed therapy short course" (DOTS) approach.[4] BCG vaccine is among the most widely used vaccine in the world and has been used since 1921 to prevent TB. BCG vaccination has been used worldwide as a neonatal vaccination against severe forms of tuberculosis.[1] The efficacy of BCG vaccination in newborns (primary BCG vaccination) is well recognized, as reviewed by Colditz *et al*.[4] It is particularly useful in giving protection against disseminated tuberculosis such as tuberculous meningitis and military TB.[5] BCG revaccination is frequently given to children between six to fourteen years of age. However, there is considerable uncertainty as to the efficacy and extent of protection offered by booster of BCG vaccine (revaccination) against TB in these older children.[6]

In the absence of scientific evidence that revaccination confers protection, World Health Organization (WHO) Global Programmes on Tuberculosis and on Vaccines in 1995 did not recommend repeat BCG schemes, but recommended a single dose of the BCG vaccine at or soon after birth in all countries with a high incidence of TB infection.[1] However policies for their use vary widely between countries, whereby some intermediate and high TB incidence countries are still giving multiple BCG vaccine as a part of their standard TB control programs.[7]

In Malaysia, the National BCG Vaccination Program was initiated in 1961. Routine BCG vaccination is given to newborns at birth (primary BCG vaccination). Thereafter, an additional booster dose is given to children at the age of seven (Sabah) and twelve years (other states) administered by the school health team who visited primary schools every year. The program was modified in July 2002 by which the additional booster dose was discontinued. The revaccination, however is still given to those children without BCG scar or with no BCG vaccination history, without prior Tuberculin Skin Test.[7] This review was requested by the Director of Disease Control Division, Ministry of Health Malaysia to review

the evidence on BCG revaccination against TB to assist in revising the current vaccination policy.

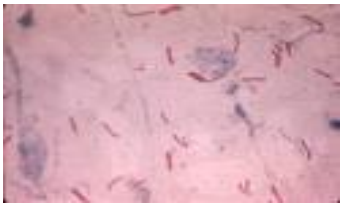
2. OBJECTIVES

To assess the safety, effectiveness, cost effectiveness of BCG revaccination for the prevention of tuberculosis occurrence.

3. TECHNICAL FEATURES

Bacillus Calmette-Guerin or Bacille Calmette-Guerin (BCG) is a live attenuated vaccine against tuberculosis that is prepared from a strain of the attenuated live bovine tuberculosis bacillus, *Mycobacterium bovis* which has lost its virulence in humans by being specially cultured in an artificial medium for years. It was first developed by Albert Calmette and Camille Guerin in 1921 at the Pasteur Institute.[8] The BCG vaccine was derived from *M. Bovis.* It elicited host response by delayed hypersensitivity reaction, which is related to the role of different proteins of the bacillus in the host response; particularly a 15100 molecular weight polypeptide called MPB70, a breakdown product of the secreted protein, methoxymycolate. [9]

Figure 1 : Microscopic diagram of *Mycobaterium spp* (left) and three dimensional view under electron microscope (right)



Immunological response to BCG vaccination

Administration of BCG produces artificial infection which spreads from the inoculation site via the lymphatic system to local lymph nodes. It produces an immunity equivalent to that produced by natural primary infection with virulent bacilli. BCG-induced immunity develops about six (6) weeks after vaccination. [9]

The mechanism of protection by BCG vaccination as indicated by experimental studies, consists of reduction in the hematogenous spread of bacilli from the site of primary infection, mediated by memory T lymphocytes induced by the first exposure to BCG. [9]

There is no evidence that BCG reduces the risk of becoming infected with tuberculosis bacilli, but it prevents forms of tuberculosis depending on hematogenous spread of the bacillus. This inhibition of the hematogenous spread of bacilli thus reduces the risk of

immediate disease and of disease due to reactivation. Since there is reduction in risk of immediate disease, but not of infection, there is a difference in the protective effect of BCG, depending on the type of tuberculosis infection (Table 1). [9]

Table 1: Protective efficacy of BCG against various clinical forms of tuberculosis [9]

Clinical form of tuberculosis	Protective efficacy of BCG (%)
Primary complex formed in the lung	20
Primary complex with local extension	32
Lymphadenitis	32
Tuberculosis of the bone	39
Tubercular meningitis	52
Disseminated tuberculosis	80

BCG strains

BCG vaccines are currently produced [redacted][6] There are several different BCG seed strains (substrains) used in BCG manufacturing (refer Table 2), and several different methods of BCG culture.[8] Among the most widely used strains are derivatives of the Pasteur-1173P2, Tokyo-172, Copenhagen-1331, and Glaxo-1077 strains. Some of these substrains, derived from the original strain by additional culture passages, lost residual invasiveness and were devoid of efficacy. Any strain used for vaccine production should be approved by WHO. WHO Expert Committee on Biological Standardization in 1987 has outlined procedures for BCG vaccine production to ensure its potency, safety, and efficacy and to reduce variability among BCG strains.[9]

Table 2: Substrains currently used in BCG manufacture, by doses produced per year

Substrain	Number of reported manufacturers	Doses used/year (x10 ^{6}, 1996 data)
Pasteur-1173 P2	5	28.5
Copenhagen- 1331	13	127
Glaxo – 1077	2	65
Tokyo – 172	2	43
Russian	2	40
Morreau	3	32
Other or unknown	11	42.5
Total	38	378

Genetic differences have developed between the various commercially used strains (antigenic drift), since BCG has never been cloned and has been grown under different condition and in

different laboratories.[8] Biological variability of BCG vaccine due to different strains occurs due to possible mutations and immunogenic differences between the strains cultured in different laboratories and in successive cultures for years.[8]

Nearly all of today's BCG vaccines are provided in freeze-dried form, except for small quantities of liquid BCG produced for local use.The freeze-drying process, in addition to the particular culture methods employed by different manufacturers, leads to considerable differences in the numbers and proportions of viable and dead organisms per dose of vaccine (refer Table 3). It is recognized that this has implications both for reactogenicity (measured in terms of the size of the local lesion) and for the induction of delayed type hypersensitivity (DTH, tuberculin sensitivity).[6]

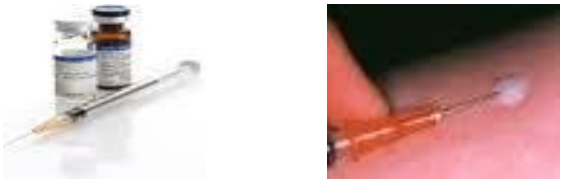
Table 3: Some characteristics of the major BCG subtrains in current use

Substrain	Number of manufacturers	Culturable particles per dose
Pasteur-1173 P2	5	37 500 – 500 000
Copenhagen - 1131	13	150 000 – 300 000
Glaxo - 1077	2	200 000 – 1 000 000
Tokyo - 172	2	3 000 000
Russian	2	Unknown
Moreau	3	Unknown

Route and method of administration

BCG is given as a single intradermal injection using a 25 or 26 gauge needle at the insertion of the deltoid (lower deltoid area). Intradermal injection is the method of choice, so as to involve the axillary instead of the upper clavicular lymph nodes. This is to minimize complications from postvaccination lymphadenopathy. [9]

Figure 2: BCG vaccine in vials (left) and intradermal injection technique (right)



Multiple puncture is an alternative technique for BCG administration, however it is not recommended by WHO. Several drops of BCG are rubbed on the same site as for intradermal injection, and an appropriate device with multiple points is used to introduce the vaccine under the skin. To obtain a result similar to intradermal injection, 40 punctures are needed which requires a large volume of vaccine and operationally difficult. [9]

If BCG is accidentally given subcutaneously, a local abscess may form (a BCG-oma) that may ulcerate, and often requires treatment with antibiotics.[7] Subcutaneous injection may reduce protective efficacy, particularly if the replication of the BCG bacilli is decreased in the deep subcutaneous tissue.[9]

Historically, BCG vaccination was first administered orally. However, intradermal or percutaneous administration was ultimately favoured following these reasons:[6]

- Oral vaccination required much larger doses of BCG for conversion (e.g. from 10 to 300mg, compared with 0.1mg for intradermal injection) and hence more expensive;
- It was difficult to control the effective dose with oral administration, as some viable bacilli were inactivated in the stomach and many passed right through the intestinal tract;
- Intradermal administration has been proven to be much more efficient at inducing tuberculin conversion;
- There were reports of cervical lymphadenopathy attributed to oral administration of vaccine.

Other techniques were found inferior either because of inconsistent dose delivery or adverse reactions (e.g. with jet injectors) or low tuberculin conversion rates (bifurcated needle). Percutaneous administration methods are generally simpler than intradermal methods, but are less consistent in terms of the amount of vaccine delivered. Some countries (e.g. Japan, South Africa) have employed percutaneous administration with special multipuncture devices (Figure 3).[9]

Figure 3: Ampules of BCG and saline with an apparatus
(4-5 cm length, with nine short needles) used for BCG vaccination in Japan

Dose

Most manufacturers (including all who provide vaccine for UNICEF) recommend a 0.05 ml dose for infants. Children and adults generally receive twice this amount (0.1 ml). Once reconstituted, the vaccine should not be kept more than one vaccination session due to the risk of contamination and loss of potency.[6]

Tuberculin skin test

The general test for quantitation of the delayed hypersensitivity reaction is the Mantoux or Tuberculin skin test. Other puncture tests, such as the Heaf test, are useful for screening patients for evidence of prior exposure to tuberculosis. The tests differ in the concentration of

tuberculin used, the method of introducing it into the patient, and the method of reading results.[9]

In the Mantoux test, 0.1 ml containing 5 TU (tuberculin units) of Purified Protein Derivative (PPD) solution is injected intradermally on the volar surface of the upper third of the forearm. PPD may be a purified product of tuberculin or may be derived from other Mycobacteria, such as *M. Bovis*. The results are read 48 to 72 hours later as the area of induration, with at least 5 mm in diameter is the threshold indicating a positive reaction. In Heaf test, Grades 2 to 4 are interpreted as positive. This Heaf test however uses quite a lot of tuberculin and does not give quantitative results.[9]

The tuberculin reaction follows a simple dose response, as does scar size. The dose-dependence of the tuberculin reaction however does not correlate with that for scar formation. This is probably explained because the scar (assuming standard administration technique) reflects the total bacillus mass (living or dead), while the tuberculin reaction measures viable bacilli.[9] Except in neonates, a tuberculin skin test should always be done before administering BCG. A reactive tuberculin skin test is a contraindication to BCG. Those with a positive tuberculin reaction is not given BCG, because there is a high risk of severe local inflammation and scarring. People found to have reactive tuberculin skin tests should be screened for active tuberculosis.[7]

Efficacy

The efficacy of a vaccine is a measure of its activity on individuals given the vaccine. It can be defined as the proportion of those vaccinated who gain protective immunity from the vaccination. Huge variation in the estimates of efficacy against pulmonary TB has been reported, ranging from 0% to more than 80% have been shown for different BCG vaccines in various geographical settings.[8] However, its efficacy in preventing tuberculous meningitis ranges from 52% to 84%. [11]

The protective response to BCG vaccine against infection by *M. tuberculosis* depends on a number of factors. Biological variability of BCG vaccine due to different substrains or exposure to environmental mycobacteria may influence the recipient's immune response, and hence interfere with the efficacy of BCG vaccine.[9] Other factors affecting variability of protective efficacy are related to firstly; the use of the vaccine, such as viability, dose used, route of vaccine administration; and secondly host related factors, such as nutritional status, age, concomitant illnesses, nutritional status and genetic aspects which may interfere with the estimates of vaccine efficacy.[1]

Length of protection

There is uncertainty about the duration of protection in addition to the uncertainty over efficacy.[1] BCG protection can wane with time since vaccination. There is no good evidence that BCG provides protection more than 10 years after vaccination. The average efficacy more than 10 years after vaccination was 14%.[9] Many controlled trials have followed efficacy for 15 years and have shown some decline over time, but the total duration of any

benefit was not known and could only be expressed as efficacy lasting for 15 years.[8] If observable protection does decline, it is unclear to what extent this might be attributable to waning of an active protective response (in which case booster doses might be effective), or to progressive exposure of the population to other immunizing infections, thereby diluting out the differential effect of BCG (in which case booster doses of BCG might not be warranted).[1]

Adverse event and contraindication

Since BCG is a live attenuated vaccine, occasionally its use will result in complications. Systemic effects have been observed following administration of BCG vaccine, including regional lymphadenitis, systemic BCG infection, and bone tuberculosis.[9]

Host characteristics will affect the incidence of adverse events. The major host characteristics which may affect adverse reactions to BCG immunization are age (higher incidence of adenitis in neonates as compared to older infants and children) and the increased risk of disseminated reactions (and possibly local reactions) in recipients with serious immune deficiency involving the T-cell-mediated system. [9]

The WHO recommended BCG not to be given to infants with symptomatic AIDS *(Special Programme on AIDS and Expanded Programme on Immunization 1987).*[9] It is also contraindicated in immunocompromised conditions, particularly if the person is known or suspected to be HIV positive.[8] Contraindication to BCG vaccination is categorized as either relative or temporary in these cases; weight less than 2 kg, skin reactions at the vaccination site, severe diseases, use of immunosuppressants; or absolute; in acquired or congenital immunodeficiencies.[2]

Scar

Following intradermal injection of live BCG vaccine into humans, a papule with induration appears within two to three weeks. The papule ulcerates at six to eight weeks, followed by a scar at the end of three months.[9]

The presence of such a scar in the appropriate place (generally just below the insertion of the deltoid on the right arm) has been used as evidence for prior BCG vaccination. However, with multiple puncture inoculation, there are many small papules which disappear more quickly and often without scarring. [9]

Although the size of the scar follows a simple dose-response, various other factors have been shown to influence the size and shape of the scar, including the technique of administration of vaccine (intradermal administration is more likely to leave a uniform scar, while improper, i.e. subcutaneous, administration may not); the characteristics of the recipient (keloid formation may be associated with race); loss of vaccine integrity and the strain of BCG used.[9] Some country (Brazil) do vaccinate children who do not have a scar, even if they have a positive history of BCG vaccination due to the theoretical possibility that unviable units of the vaccine might have been used, resulting in lack of a skin test response. [2]

Fine *et al.* found that of children vaccinated in infancy, fewer than 60% retained a recognizable scar after two years. Thus, scars are poor indicators of BCG vaccination in infancy.[9] Baretto ML et al (2006) stated that the presence of a vaccine scar indicates previous BCG vaccination; however there is no evidence in the literature revealing an association between vaccine scar and protection or immunity against TB.[2] Sanjoy et al (2007) also found no significant association between BCG scar size and its effectiveness against TB or leprosy.[13]

Agreement between a documented history of receipt of BCG vaccine and the presence of a BCG scar at one to two years after immunization has been reported. However, misclassification of vaccination status because of lack of scar formation would tend to reduce the apparent vaccine efficacy. For this reason, studies on BCG vaccine efficacy should rely on documentation of immunization by immunization card. [9]

Other uses of BCG vaccine

BCG vaccine is also employed as non-specific stimulants in the treatment of certain conditions, in particular bladder cancer (cancer immunotherapy), interstitial cystitis or painful bladder syndrome. Its use in other mycobacterial infection such as leprosy and Buruli ulcer has also been documented.[6]

A criterion has been set up by the International Union against Tuberculosis and Lung Disease, and it has to be met before a country stops or modify their BCG program. The criterion specifies these parameters:

- There is a well functioning TB program
- There has been a reliable monitoring system over the previous five years, or more enabling the estimation of annual incidence of TB by age and risk group
- Due consideration has been given to the possibility of increase in the incidence of TB resulting from HIV infection [8]

4. METHODOLOGY

4.1 SEARCH METHODS

Literature were searched through electronic databases which included PubMed, Medline, Cochrane Database of Systematic Reviews, Cochrane Database of Controlled Trial, Health Technology Assessment, National Horizon Scanning, other websites; INAHTA, ASERNIP-S, CADTH and FDA and general databases such as Google and Yahoo. The search strategy used the terms, which were either used singly or in various combinations: “BCG”, “BCG vaccination”, “BCG immunisation”, “BCG revaccination”, “children”, “adolescent”, “tuberculosis”, “prevention”, and “control”. The search was limited to articles on human. There was no language limitation in the search.

4.2 SELECTION OF STUDIES INCLUDED /EXCLUDED

Systematic reviews, meta-analysis, randomised clinical trials and observational studies pertaining to effectiveness, safety, and cost effectiveness of BCG revaccination conducted in human were included.

A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Programme (CASP) checklists and the evidence graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001).

Data were extracted and summarized in evidence table as in Appendix 3. The data were not pooled and only qualitative analysis was carried out.

Inclusion criteria:
Studies on primary BCG vaccination and revaccination conducted to children and adolescent were included.

Exclusion criteria:
Studies on BCG vaccination conducted to healthcare workers or other specific group of adults such as contacts of active TB patients were not included.

5. RESULTS AND DISCUSSION

There seven articles on BCG revaccination were retrieved. Three of the articles were randomized clinical trials, the other two were cohort studies, and one article each was on case control and cost effectiveness study.

5.1 EFFICACY/EFFECTIVENESS

Rodrigues LC *et al.* conducted a cluster randomized clinical trial in two Brazilian cities (Salvador and Manaus) to estimate the efficacy of BCG revaccination against tuberculosis. The study involved school aged children between the age 7 to 14 years who had one BCG vaccination as infants, recruited between 1996 and 1998. The final study population consisted of 103 718 children (386 schools) who were assigned BCG revaccination and 97 087 children (375 schools) no revaccination, after exclusion on the basis of age, BCG scar readings and absence from school on the day of study visit. Cases of tuberculosis were identified through record linkage to the Tuberculosis Control Programme Surveillance System who was assessed at 48 to 63 months later. Result demonstrated that there were 279 cases of tuberculosis (pulmonary and non pulmonary) in the study; 144 in the intervention group and 135 in the control group. They also found that the crude incidence of tuberculosis in the intervention group was 29.3 per 100,000 person years, and 30.2 per 100,000 person years in the control group (crude rate ratio 0.97; 95% CI 0.76 to 1.15). The efficacy of BCG revaccination against all types of tuberculosis is 9% (-16 to 29). The author concluded that revaccination given to children aged 7 to 14 years old does not confer additional protection.[14]
level 1

Karonga Prevention Trial Group also conducted a double blind randomized controlled trial of a single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Karonga District, northern Malawi. This study involved 121,020 individuals recruited between 1986 and 1989, in which 66,155 subjects without BCG scar were randomly allocated to scar negative vaccine group (BCG alone, BCG plus 5 x10 ^{7} killed *M leprae* or BCG plus 6 x10 ^{8} killed *M leprae*) and 54,865 subjects with BCG scar in scar positive vaccine group (received Placebo, BCG alone, or BCG plus 6 x10 ^{8} killed *M leprae*). Incident cases of leprosy and tuberculosis were ascertained over the subsequent 5 to 9 years. They found 376 cases of post-vaccination pulmonary tuberculosis and 31 of glandular tuberculosis by 1995. The result demonstrated that the incidence rate ratio (IRR) of diagnostically certain tuberculosis was higher among scar-positive individuals who had received a second BCG (IRR 1.69; 95% CI 0.99 to 2.99) than among those who had received placebo. There was no evidence that any of the trial vaccines contributed to protection against pulmonary tuberculosis. The author concluded that in a population in which a single BCG vaccination affords 50% or more protection against leprosy but none against tuberculosis, a second vaccination can add appreciably to the protection against leprosy, however without providing any protection against tuberculosis. [15 level 1]

Tala-Heikkila *et al*. in a prospective longitudinal study carried out in Finland assessed the impact of BCG revaccination of tuberculin negative school children in the prevention of tuberculosis. In Finland, BCG revaccination was given to schoolchildren at the age of 11 to 13 years if they were tuberculin negative (induration under 5mm) after two step Mantoux testing, using 0.1ml British (Glaxo 1077) BCG vaccine. The BCG revaccination was officially discontinued in 1989. This study involved six birth cohorts born between 1979 to 1984 who were vaccinated at birth (388,089 children), no longer covered by BCG revaccination program, and was followed up for the tuberculosis cases in 1990 to 1995 when the cohort reached 11 years. Corresponding data were collected for comparison from the period of revaccination in 1980 to 1985 among age cohort born in 1969 to 1974. Data from the National Tuberculosis Register was reviewed to observe tuberculosis trend. The result demonstrated three cases of tuberculosis registered among non-BCG-revaccinated children during 6 years after discontinuation of the program with incidence rate of 2.23 per million person year (95% CI 0.72 to 6.90), and control group revealed five cases with incidence rate of 3.78 per million person year (95% CI 1.57 to 9.07). Relative risk of tuberculosis in non-BCG-revaccinated children is 0.59 (95% CI 0.14 to 2.47). The author concluded that the cessation of BCG revaccination program had no effect on continuing overall TB decline in Finland, and efficacy of BCG revaccination seemed to be low or nonexistent in countries with low TB incidence. [16 level II-2]

Leung *et al.* conducted a cohort study in Hong Kong to assess the efficacy of BCG revaccination guided by tuberculin skin testing. Revaccination of tuberculin-negative aged 6 to 9 schoolchildren is a regular practice in Hong Kong. This study involved a cohort of 258,700 children participated in the BCG revaccination program during primary school, born between 1978 to 1982. The Glaxo BCG vaccine strain was used throughout the study period. They were followed up for 7 years until 1998 (mean duration of follow up, at or after the age of 11) for the development of active disease through the Tuberculosis Notification Register.

The BCG revaccination history of identified cases was ascertained through vaccination cards and clinic records. The study demonstrated that 85.2% of the cohort (258 700 out of 303 692 children) participated in the BCG revaccination programme and 79.7% of the participants were tuberculin-negative and revaccinated. Of these 343 developed tuberculosis after the age of 11 (302 were among the participants in the programme, while 41 were not). They reported that the BCG revaccination programme participants had an overall relative risk for developing tuberculosis of 1.28 (95% CI 0.92 to 1.77, p = 0.14) in comparison with non-participants; with the tuberculosis incidence of 16.5 and 12.9 per 100 000 person-years for participants and non-participants, respectively. Among those who participated, the tuberculin-negative/revaccinated group had a relative risk for developing tuberculosis of 0.39 (95%CI 0.31 to 0.49, p <0.001) in comparison with the tuberculin-positive/non revaccinated group, with respective tuberculosis incidence of 12.5 and 32.0 per 100 000 person-years. The study reported no significant difference in the incidence rates of tuberculosis among participants and non-participants in a school BCG revaccination programme. The increased risk for tuberculosis in the tuberculin-positive group did not support the use of the tuberculin testing for detection of immunity conferred by neonatal BCG vaccination.[17] level II-2

Sepulduva *et al.* in a case control study conducted in Santiago, Chile assessed the efficacy of BCG vaccination against pulmonary tuberculosis in young adults. The study determined if repeated BCG immunization increased its protective effect and determined factors that could explain the failure of BCG immunization in patients with tuberculosis. The study population consisted of 68 young adults (15- to 35-year-old) with recently diagnosed pulmonary tuberculosis and 188 controls without pulmonary tuberculosis who sought medical care for other ailments. The BCG immunization status of each patient was determined by recording the presence of BCG scars from immunization at birth, at age 6 and/or 14 years. They found that 13.2% among cases and 12.2% among controls were non-immunized. The vaccine efficacy calculated was 10% (confidence limits: 0 to 61%). They also demonstrated no significant difference in the percentage of individuals with 1, 2 and 3 BCG scars between cases and controls. Vaccine efficacy for the subgroup of individuals with multiple BCG scars was also low (10%). The study finding of patients with 2 and 3 BCG scars who developed tuberculosis suggested the presence of genetic and/or acquired predisposing factors capable of overriding protective immunity induced by BCG vaccination. The study failed to demonstrate an important protective effect of BCG vaccination against pulmonary tuberculosis as shown by the low efficacy of BCG immunization in young adults. [18] level II-2

5.2 SAFETY

Dourado I *et al* evaluated the rates of adverse reactions to first and second doses of BCG vaccination from the results of a large community trial conducted in Brazilian schoolchildren. The study population consisted of the vaccinated arm of children residing in one of the BCG-REVAC trial sites in Salvador, Brazil. The BCG-REVAC is an ongoing randomised controlled trial with no placebo conducted in children aged 7 to14 years enrolled in state schools. 0.1ml BCG vaccine of Moreau-Rio de Janeiro substrain was given intradermally by trained nurses to each study subject during September 1996 to September 1997. Adverse reaction was ascertained by enhanced routine passive surveillance. Data on suspected reactions were collected by a visiting nurse on a completed standardised form

used by the National Immunisation Programme for surveillance of adverse reactions. Demographic, clinical and vaccination status data obtained was linked to those from the trial database. They found that among 71,341 schoolchildren studied, 33 reactions were reported. Of these 25 fulfilled both study criteria (Brazilian National Immunisation Programme criteria and a standard classification of adverse reactions to BCG defined by Lotte *et al*.); resulting in incidence of 35/100,000 corresponding to a rate of one adverse reaction per 2854 vaccination. They found no deaths, permanent injuries or disseminated infections (BCG-osis). Most reactions (60%) were local cutaneous lesions (such as ulcers more than 1 cm) and 28% had axillary lymph node enlargement without suppuration. Other less frequent reactions were local dissemination of lesion (four cases), suppurating lymphadenitis (two cases), tuberculosis-like cutaneous lesions (two cases) and dissemination of the lesion to the left arm and left leg (one case). They also found four children had acute cutaneous eruptions with no other cause, which was known as Lotte's 'post-BCG syndrome'. Five cases required hospitalisation for less than 48 hours but none reported further complications. All events occurred within 1 to 70 days after vaccination. They had demonstrated reactions to second doses were more common than to first BCG vaccinations; 23 adverse reactions occurred in those with one scar (1 in 2580 applied doses, 95% CI 1/1692 to 1/3984) and two adverse reactions occurred in students with no scar (1 in 5990 applied doses, 95% CI 1/1485 to1/34 482). However, this difference was not statistically significant. The relative risk of adverse reactions in students with scar is twice compared to those without scar (RR 2.3; 95%CI 0.69–7.80). The author concluded that adverse reactions to a second dose of BCG are rare and do not represent an important hindrance to the policy of revaccination. [19] level I

5.3 COST EFFECTIVENESS

Rahman *et al* conducted a cost effectiveness and cost benefit analysis in Japan for a cohort of schoolchildren who underwent revaccination during 1996. The study aimed to estimate number and cost of immunizations required to prevent a case of TB and to determine the benefit-cost ratio of the BCG revaccination program in low incidence tuberculosis children in Japan. Revaccination is being practiced in Japan for decades among the tuberculin-negative schoolchildren of first grade primary and first grade junior high schools. The study population consisted of a hypothetical cohort comprising 1.35 million first grade primary school and 1.51 million first grade junior high school students enrolled in 1996 at locations throughout Japan. Assumptions of 50% vaccine efficacy for revaccination, a 10 year duration of protection, and a 5% annual discount rate were made in this study. The results demonstrated that the revaccination programme for 1996 schoolchildren would prevent 296 TB cases for a 10 year period at a cost of USD 108,378 per case averted. About 4,963 immunizations would be required to prevent one child from developing TB, and the benefit-cost ratio was 0.13. Benefits of the revaccination programme calculated revealed about USD2.7 million would be saved as treatment costs by averting 296 TB cases. The cost of treating a pulmonary TB in a 10 year old child is estimated to be around USD 11,576 which is much less than estimated cost for prevention (USD 108,378). The author concluded that the economic costs of revaccination far exceeded the benefits and hence current BCG revaccination policy should be re-examined. [20] level II-2

6. CONCLUSION

In terms of efficacy, there was fair to good level of evidence to show that BCG revaccination did not provide additional protection when given to children. There was insufficient evidence on safety but it showed that occurrence of adverse event following second dose of BCG vaccination was rare. There was only one fair level of evidence on cost effectiveness, which showed that BCG revaccination was not cost effective in low incidence TB country given the lack of protection provided by the second dose.

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