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BCG vaccination status of children with tuberculous meningitis and the use of unsupervised isoniazid prophylaxis

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From 1985 to 1992, 193 children with tuberculous meningitis (TBM) with a median age of 26 months were admitted to the Department of Paediatrics and Child Health, Tygerberg Hospital. Of these children 143 (74%) were documented to have received BCG, either by reference to 'Road to Health' cards or by contact with local authority clinic staff. In a further 18 children a BCG scar was visible. Therefore at least 161 of the children (83%) had received BCG vaccination. As the Western Cape has also been shown to have the highest incidence of TBM in South Africa, there is concern that BCG as currently used does not have a significant protective effect against disseminated tuberculosis.

Seventy-seven children (40%) were also reported to have a close household contact who had been treated for pulmonary tuberculosis within the previous 24 months. Only 17 of these children (22%), however, were prescribed prophylactic isoniazid and only 7 of these completed 3 months or more prophylaxis.

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Since its introduction in 1921, BCG has been the subject of considerable controversy and acrimonious debate.[1,2] Controlled trials of BCG vaccination have produced results varying from an efficacy of 80% to a negative influence in some instances, and these trials have been dogged by variation in the epidemiological situation, the dose and strain of BCG used, the manner of vaccination and age at vaccination.[3] Despite the above problems, recent assessments, usually by case control studies, of the use of neonatal BCG vaccination in developing countries have consistently shown an efficacy of between 60% and 80% in the prevention of disseminated forms of tuberculosis.[4-7]

Neonatal BCG vaccination has been carried out on a large scale in South Africa since 1973 and is now given to more than 90% of neonates in the area served by the Western Cape Regional Services Council.[8]

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Isoniazid chemoprophylaxis given to infected individuals for at least 6 months is known to reduce the incidence of subsequent tuberculous disease; this has been substantiated in a number of clinical trials.[9] However, non-compliance is a recognised problem[10] that considerably reduces the efficacy of this measure.[11,12]

In this paper we describe our further experience with the BCG status of children presenting with tuberculous meningitis (TBM) in the Western Cape and the failure to implement isoniazid prophylaxis to prevent TBM in the close contacts of adults with pulmonary tuberculosis.

Methods

From 1985 to 1992, 193 children aged from 3 months to 154 months (median 26 months) with TBM were admitted to the Department of Paediatrics and Child Health, Tygerberg Hospital, for the management of raised intracranial pressure and other complications.[13] Aspects of the clinical presentation and BCG status of 88 of the children seen between 1985 and 1988 have been presented previously.[14] In 26 children (13%) the diagnosis of TBM was confirmed by culture of *Mycobacterium tuberculosis* from cerebrospinal fluid. In the remainder the diagnosis of probable TBM was accepted and supported by one or more of the following: (*i*) culture of *M. tuberculosis* from gastric aspirate in 15 children; (*ii*) a chest radiograph compatible with the diagnosis of primary tuberculosis in 91 children (47%); and (*iii*) a Mantoux test that gave an induration of more than 15 mm in 87 children (45%).

The severity of neurological involvement on admission was classified on the basis of the British Medical Research Council report of 1948.[15] (*i*) stage I — these children were fully conscious with signs of meningeal irritation only; (*ii*) stage II — these children were mentally confused and had, in addition, cranial nerve palsies or hemiparesis; (*iii*) stage III — these children were comatose or had complete hemiplegia or, more rarely, quadriplegia.

The BCG status of the children was confirmed by reference to 'Road to Health' cards or, when these were not available, by the local authority clinic closest to the patients' home address. In addition, children were examined for the presence of a BCG scar on the right upper arm.

Parents or caretakers were questioned as to the presence of close adult contacts with pulmonary tuberculosis in the household and whether the children had been offered chemoprophylaxis. Staff at the clinic nearest to the patients' homes were again contacted to confirm that chemoprophylaxis had indeed been given and to comment on the degree of compliance achieved.

This study was approved by the Ethical Committee of the Faculty of Medicine of the University of Stellenbosch.

Results

Eighty-five (44%) of the children were at stage III of the disease on admission, 104 (54%) stage II and 4 (2%) at stage I. In Fig. 1 the percentage of children presenting with stage III TBM is illustrated in relation to age. Whereas 60%

of children under 12 months of age were at stage III TBM, 44% of those aged 24-36 months and only 19% of those over 60 months of age were at stage III TBM on admission.

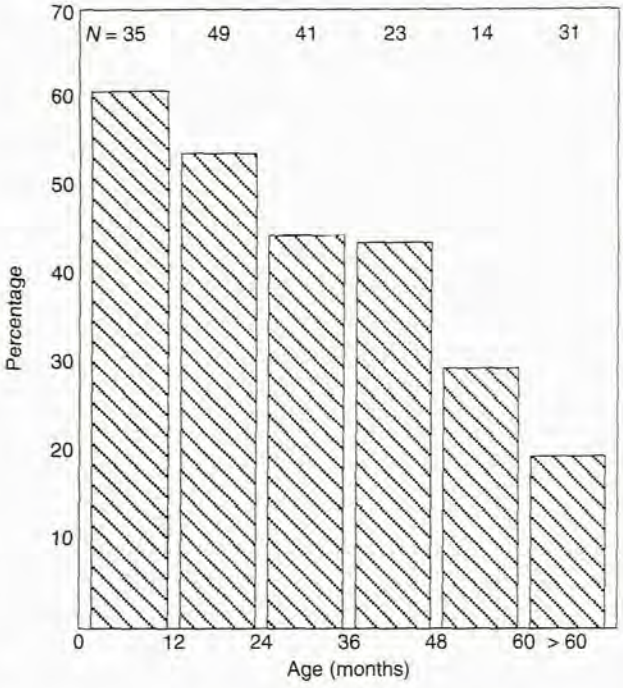

Fig. 1. Percentage of children at stage III of tuberculous meningitis relative to age at presentation.

The assessment of the BCG status of the children is summarised in Table I. In 143 children (74%) BCG vaccination was confirmed either by annotation thereof on a 'Road to Health' card or by contact with the relevant local authority clinic. In a further 18 children a BCG scar was visible. BCG vaccination had therefore been given to at least 161 (83%) children. A BCG scar could be detected in only 54 (38%) of the 143 children confirmed to have received BCG and who were evaluated for the presence of a scar. Evidence for the fading of the BCG scar is provided by the fact that of the 59 children under 24 months of age at the time of admission who were confirmed to have received BCG, 32 (54%) had a scar still visible, as opposed to only 22 (32%) of the 67 children who were 24 months or older at the time of admission.

Table I. BCG status of children with tuberculous meningitis

BCG vaccination confirmed (*N* = 143)			BCG vaccination not confirmed (*N* = 50)		
Scar assessed	Scar present	Scar absent	Scar assessed	Scar present	Scar absent
133 (93%)	54 (41%)	79 (59%)	39 (78%)	18 (46%)	21 (54%)

Seventy-seven children (40%) had had close household contact with at least one adult who had been treated for pulmonary tuberculosis within the previous 2 years. Of the 84 children aged less than 24 months, 40 (48%) had had a close household contact compared with 37 (34%) of the 109 children aged 24 months or more. In 19 instances (25%) the contact was a grandparent, and in 38 (49%) a parent; 7 of the latter were said to have died of pulmonary tuberculosis. Other family members or lodgers constituted the remaining 20 contacts several of whom had had contact with the child in the capacity of 'child-minder', while the mother worked. Eleven children had been in contact with more than one adult with pulmonary tuberculosis.

Only 17 (22%) of the children reported to be a close household contact of an adult with pulmonary tuberculosis were placed on isoniazid prophylactic therapy and 7 of these children were said to have completed 3 months of prophylactic therapy. One child, on completion of 3 months' isoniazid therapy, was tuberculin tested and given a repeat BCG vaccination.

Discussion

BCG vaccination

In South Africa BCG vaccination of newborns was made compulsory in 1973 when Japanese BCG strain 172 (Tokyo) was introduced, administered by multiple puncture percutaneous device. This BCG strain is derived from Pasteur Institute seed culture taken to Japan by Kyoshi Shiga in 1925 and maintained there by serial subculture on a potato bile medium. After the 172nd transfer, a freeze-dried lot now known as strain 172 was prepared, and the first WHO reference preparation of BCG was obtained from this freeze-dried lot.[16]

Evaluated in South Africa shortly after its introduction, this strain gave satisfactory levels of tuberculin conversion in 53% of individuals compared with 45% with the previously used Glaxo BCG, also administered by multiple puncture. Intradermal injection of the Japanese vaccine, however, gave better tuberculin conversion results in 77% of those evaluated.[17]

Unfortunately tuberculin hypersensitivity does not necessarily reflect protection against disease and in a British Medical Research Council trial equal degrees of protection resulted from two vole vaccines, only one of which induced tuberculin hypersensitivity.[18]

Evaluation of records at Boksburg-Benoni Hospital between 1971 and 1976, during which period neonatal BCG vaccination with the Japanese strain was introduced, noted a marked decline in deaths from TBM and miliary tuberculosis; this decline was associated with the introduction of neonatal vaccination.[19] When the presence of a BCG scar was accepted as evidence of efficacious vaccination, a subsequent study in the Pretoria area also found a considerable protective effect.[20] No formal controlled trial of the currently used vaccine administered by multiple puncture device has, however, been carried out. Retrospective analysis of the use of strain 172 (Tokyo) in Indonesia and Colombia did suggest a significant protective effect.[21]

In addition to the above studies, BCG vaccination by percutaneous multiple puncture gave satisfactory tuberculin conversion when evaluated in the UK,[22] while formal trials of

percutaneous BCG vaccination in the USA showed a protective effect in Chicago, but no protection in the southern states.[3] It should be noted that the 'immediate households' of children studied in Chicago were, in accordance with Calmette's suggestions, free of tuberculosis at the time of vaccination.[23] Many children in the Western Cape may be exposed to tuberculous infection of varying intensity shortly after vaccination.

Very few complications, in particular regional lymphadenitis, are experienced in South Africa after BCG vaccination. While this is welcomed and may be the result of ease of administration by the percutaneous puncture method, it has been suggested that the absence of complications in the neonate may reflect an inadequately protective dose.[24] Again this factor has never been assessed in formal controlled trials.

Prevention of disseminated forms of tuberculosis such as TBM and miliary tuberculosis is one of the main aims of neonatal BCG vaccination. It is thus disappointing that the majority of children with TBM seen at our hospital did in fact receive BCG at birth or shortly afterwards. Furthermore despite BCG vaccination being one of the most successfully administered vaccines in the Western Cape, the incidence of TBM was recently found to be 24,3/100 000, one of the highest in the world,[25] and when 75 children from the Western Cape with miliary tuberculosis were evaluated recently 88% had evidence confirming BCG vaccination.[26]

While our findings cannot be taken to indicate that BCG vaccination failed to influence the incidence of TBM they do suggest reason for concern and a need for controlled trials to evaluate alternative forms of BCG administration and the possible value of different strains of BCG.

Isoniazid chemoprophylaxis

There is no reason to doubt the efficacy of isoniazid chemoprophylaxis if given for at least 6 months. The debate is rather about its place in a national tuberculosis control programme. It has therefore been stated that it is the conventional wisdom that chemoprophylaxis has no role in developing or high prevalence countries. Certainly a preventive programme should have a very low priority in such a country's overall tuberculosis control strategy. Nevertheless it might be considered, if only for infected, young, close contacts of infectious cases.[8]

Until recently it was recommended that close contacts of adult pulmonary tuberculosis patients be placed on isoniazid prophylaxis and that after 3 months a tuberculin test be performed. If negative it was assumed that the child was uninfected and that BCG vaccination should be administered. If positive, 'treatment' would be continued for a further 3 months. These recommendations are similar to those of the American Thoracic Society.[27]

Of the 77 children (40%) who had a close household contact with pulmonary tuberculosis only 17 (22%) were prescribed prophylaxis and only 4 actually completed 3 months of *unsupervised* therapy. Only 1 child appears to have received a second BCG at this point.

Although there is no way of knowing in how many children unsupervised isoniazid chemoprophylaxis did prevent TBM and miliary tuberculosis, our data and those relating to the occurrence of TBM and miliary tuberculosis in the Western Cape referred to above, suggest that even when unsupervised chemoprophylaxis *is* applied it is not particularly successful. As approximately 17% of adult pulmonary tuberculosis patients in the Western Cape health region[28] are not completing their prescribed course of therapy it should come as no surprise that isoniazid chemoprophylaxis is not enthusiastically pursued by hard-pressed local authority health personnel.

Given several established epidemiological facts and our own data, a stepwise approach to supervised childhood chemoprophylaxis might be considered.

Mortality from childhood tuberculosis is highest in children under 1 year of age and declines rapidly thereafter. Arnold Rich,[29] before the availability of chemotherapy, quoted a mortality rate from tuberculosis infection of 4 920/100 000 in those under 1 year of age, this fell to 123/100 000 in those over 1 year. In South Africa between 1970 and 1980 the case fatality ratio as a result of tuberculosis was 7,1% in those under 1 year, 2,8% in those 1 - 2 years and 1,1% in those 2 - 3 years of age.[30]

More than half of our TBM patients under 2 years of age were at stage III disease and this proportion declined progressively with age. Of those 5 years or older less than 20% were at stage III on admission.

Adults with 'smear-positive' cavitating pulmonary tuberculosis are more likely to infect close contacts, and infection in these contacts is more likely to proceed to disease than is the case with those 'positive' for *M. tuberculosis* on culture only.[31]

With the above in mind, and considering the enormous workload imposed by adult pulmonary tuberculosis on the local authority clinic system, a better targeted, incremental approach to chemoprophylaxis for close child contacts of adults with pulmonary tuberculosis might be considered; supervised chemoprophylaxis should be prescribed for all children under 1 year of age in close household contact with an adult pulmonary tuberculosis patient whose sputum is 'smear positive' for acid-fast bacilli. Older children and those in contact with pulmonary tuberculosis sufferers whose sputum is not 'smear positive' should be offered unsupervised isoniazid chemoprophylaxis as is frequently the case at present.

Only when more than 75% of infants who qualify for prophylaxis as set out above are being successfully 'treated' would the scheme be extended to an older group or those whose index cases are producing smear-negative but culture-positive sputum.

This approach would help ensure that children most in need of chemoprophylaxis did, in fact, receive it and permit local authorities with sufficient resources to offer supervised prophylaxis to older children where appropriate, without depriving other child contacts of the possible benefits of unsupervised isoniazid chemoprophylaxis.

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