CURRENT TOPIC

BCG and tuberculosis

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Tuberculosis (TB) has represented a significant threat to children's health since antiquity. Far from being eradicated, conclusive evidence exists to suggest the presence of a global pandemic. It has been estimated that by the end of this decade 15 million children will have developed the disease worldwide, with five million deaths.[1] Various factors account for the resurgence of TB and these include the presence of pre-existing HIV infection,[2 3] migration of populations from areas with a relatively high prevalence of TB to developed countries,[4] adverse social conditions,[5] development of multidrug resistant strains of *Mycobacterium tuberculosis*,[6] inadequate medical management of individual cases,[7] and ineffective public health surveillance programmes.[8] Some industrialised countries have experienced a sustained decline in the incidence of childhood TB whereas others have observed that the rate of decline has either slowed or has even reversed.[9] In England and Wales the rate of notification for childhood TB declined from 7/100 000 in 1978 to 3.1/100 000 in 1988.[10] However, the number of notifications has steadily increased since then. This rise has been partly attributed to immigration of children and their families from the Indian subcontinent and increasing levels of deprivation.[11] The rate of notification for UK children of the Indian subcontinent and African-Caribbean ethnic origin continues to be significantly higher than for white children.[12] The precise impact of HIV infection and the development of multidrug resistance on the epidemiology of childhood TB in the UK has yet to be fully determined.

Strategies for TB control

In recognition of the re-emergence of TB as a significant international public health problem, the World Health Organisation has defined five key objectives as part of a TB control strategy: government commitment to effective control, effective case detection, supervised administration of short courses of chemotherapy at least for sputum positive cases, maintenance of regular supplies of drugs, and continued monitoring and evaluation.[13] Although no overall eradication strategy is in place within the UK, guidelines for the control and prevention of TB have been agreed by the Joint Tuberculosis Committee (JTC) of the British Thoracic Society.[14] Effective control is dependent on a combination of preventive, therapeutic, and surveillance measures. Known cases of TB must be notified and be adequately treated[15]; effective contact tracing of index cases should be undertaken by coordinated teams of nursing and support staff. Finally, definition and implementation of an appropriate bacille Calmette-Guérin (BCG) immunisation programme should be a prime objective for both health care providers and commissioners. Childhood diagnosis is often difficult as significant numbers of children with active disease who live in developed countries have few symptoms, and TB is legendary for presenting in a confusing myriad of different clinical scenarios.[16] Furthermore, overwhelming childhood infection has been documented to occur despite surveillance programmes.[17] Primary prevention of TB by means of BCG immunisation is a feasible strategy that may be both effective and cost effective.

Is BCG effective?

BCG is derived from an attenuated strain of *Mycobacterium bovis*, and since its introduction in 1921 over 3 billion doses of the vaccine have been given worldwide.[1] Although BCG remains the world's most popular vaccine with over 80% coverage of the world's population, there is considerable debate with respect to its effectiveness in the control of TB. A meta-analysis of over 1200 articles from international publications has concluded that the overall protective value of BCG against all forms of TB was of the order of just 50%, but that protection against more serious infection was greater, being 64% and 78% against tuberculous meningitis and disseminated infection, respectively.[18] It was also found that the reported efficacy of BCG varies considerably in different studies. This may result from various possible factors: variation in study validity; use of differing BCG preparations (several substrains of the vaccine are in current use); diverse population genetics and levels of nutrition; and environmental factors such as exposure to environmental (atypical) mycobacteria, climate, socioeconomic issues, and sunlight. For example, the reported efficacy of BCG in the prevention of pulmonary TB varies from 0% in South India to 77% in the UK Medical Research Council trial.[19] Evidence for the protective value of BCG in the UK is encouraging, with a reported overall value of 75% with greater levels of protection provided against TB meningitis and miliary infection.[20]

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Who should receive BCG and when should it be given?

Recommendations for BCG immunisation of children in the UK are to be found within *Immunisation against infectious disease*.[21] BCG is generally recommended for children who have not previously received the vaccine and who are found to have negative tuberculoprotein hypersensitivity on skin testing. Most districts implement an immunisation programme that is specifically directed towards high risk newborns, children who are recent immigrants from high risk areas, and schoolchildren aged 10–14 years. The value of neonatal BCG immunisation is accepted and tuberculin reactivity after neonatal intradermal BCG immunisation remains high and sustained at least until 4 years of age.[22] A selective rather than universal BCG immunisation policy is currently advised by the Department of Health, whereby BCG is offered to newborn infants whose parents are from areas with a high prevalence of TB—mainly Asia, Africa, Central and South America. Practical difficulties are inherent in the implementation of any selective immunisation programme in that the definition of what is considered to be "high risk" is not always straightforward and some children in need of immunisation may be missed for several reasons. It has been suggested that universal BCG immunisation should be undertaken in districts where the prevalence of TB is relatively high (that is, greater than 40 notifications/100 000 resident population each year).[23] This approach may be more practical to implement and be more acceptable politically to local populations.

With regard to the optimal time for giving BCG to infants, there is some evidence to suggest that later immunisation during infancy may confer a higher degree of immunity. BCG immunisation at 3 months of age was found in one study to provide a higher rate of tuberculin protein skin responses with fewer complications than when given during the first three days of life.[24]

School BCG programme

It was once thought that the school BCG programme should be stopped as a result of a falling incidence of TB in the UK during the 1970s, and at that time it was estimated that 4000 immunisations were required to prevent one case of active TB.[25] This view has been revised as a result of an increased notification rate since 1987. One of the difficulties inherent in the correct administration of BCG to schoolchildren has resulted from interpretation of tuberculin protein skin tests (most commonly, the Heaf test), and this is especially the case with older schoolchildren who have previously received BCG. Tuberculin protein skin tests are far from perfect in terms of screening. A positive test may result from infection with *M tuberculosis*, infection with atypical or non-tuberculous mycobacteria, or previous BCG immunisation. There is now some agreement that a highly positive reaction in a child who has previously received BCG is more likely to be indicative of infection with *M tuberculosis* and may represent a need for chemoprophylaxis.[26]

Despite the recommendations of the JTC, a survey in England and Wales in 1991 found wide variation in practice with respect to BCG immunisation of both newborns, schoolchildren, and children considered to be at high risk.[27] The need for cooperation between district immunisation coordinators, consultants in communicable disease control, and paediatricians was acknowledged. In light of an increase in the rate of notification of childhood TB since then and because of changes in health care delivery since recent NHS reforms, a repeat national survey of local BCG immunisation practice is probably warranted.

Is BCG safe?

BCG is considered to be a safe vaccine with a low incidence of adverse effects. Complications are more likely to occur in infants, where large doses of BCG are inadvertently given and if intradermal technique is faulty. Suppurative adenitis has been reported in 4% of infants who have received intradermal BCG and 0.3% of older children; osteomyelitis is an uncommon complication and disseminated BCG infection is extremely rare in normal children, occurring in about one to three cases per million doses.[26]

Most children after being given intradermal BCG develop a superficial ulcer that eventually heals within several months to form a small scar. It should be noted that a significant proportion of adolescents, particularly girls, consider a "normal" BCG scar to be cosmetically unacceptable.[28]

Among those UK children for whom BCG is not recommended are those who are immunocompromised and, in particular, those who have symptomatic HIV infection.[21] There is considerable debate about giving the BCG vaccine to newborn infants who are known to be at risk of HIV infection. Current advice within the UK is that BCG should be withheld if possible in this situation because the prevalence of both TB and HIV infection is still relatively low. A different view is held in most developing and some industrialised countries where both diseases are significantly more common. It is recommended that where the risk of childhood TB is high, BCG should be given to infants as early as possible, even if mothers are known to have HIV infection. It would be difficult, in any case, to identify and subsequently exclude those infants who are already HIV infected. A recent review has concluded that there may be a slight increase in minor adverse reactions after the administration of BCG to infants with asymptomatic HIV infection and that the benefits of immunisation outweigh the risk of complications.[29] A consensus view currently exists, however, that BCG should not be given to infants with active HIV disease and that the vaccine is contraindicated in older asymptomatic children who are found to be HIV positive.

Percutaneous BCG administration is increasingly used for infants as this technique is easier to learn and has a lower incidence of

complications compared with the intradermal method. In one study, however, just under 16% of infants immunised in this way were found to be tuberculin negative on skin testing three months later.[30] The significance of this finding is as yet unclear. One possible disadvantage of the percutaneous method is that the rate of BCG scar formation would appear to be lower, emphasising the importance of keeping good clinical records and recording all immunisations in the personal child health record. Further controlled research is therefore needed to determine the long term effectiveness of percutaneous BCG administration as a preventive measure.

Key messages

- BCG is a safe and effective vaccine for the prevention of childhood TB in the UK
- Percutaneous BCG administration may be an acceptable alternative to the intradermal method for infants, but requires further evaluation
- Districts with a high prevalence of TB should consider universal BCG immunisation of newborns
- New antituberculous vaccines are being developed, but their effectiveness needs to be determined

Future developments

A combination of frustration with the apparent failure of BCG to eradicate global TB and an enhanced understanding of the body's immunological response to *M tuberculosis* has resulted in searches for alternative primary preventive measures. The pathogenesis of TB and the precise protective mechanisms of BCG vaccine are still far from clear. Recent research has described the role of Th1 and Th2 cells as well as the possible regulatory function of certain adrenal steroid metabolites.[31] One experimental adjunct to treatment, based on immunotherapy, attempts to alter the immune response from one of tissue damage to that of bactericidal activity.[32] *Mycobacterium vaccae* is a relatively harmless environmental species that has been used in immunotherapy, with some encouraging results in patients with active TB. Other research is directed towards the development of new BCG vaccines, including subunit versions created from cell wall antigens, and the use of recombinant vaccine technology.[33] The superiority of these vaccines over standard BCG has yet to be determined.

Conclusions

An improved vaccine that would provide greater protection against *M tuberculosis*, although technically feasible, is still far from being an achievable goal. In the meantime, BCG remains an effective and safe vaccine when given in the UK, and paediatricians should ensure that all high risk children are immunised. Local BCG immunisation programmes should be defined in accordance with local need, coordinated and implemented by multidisciplinary groups, and evaluated by means of clinical audit. It must also be remembered that the use of BCG is just one important aspect of the overall process of TB control. Vigilance, early detection of children who have been infected with *M tuberculosis*, and effective treatment for those with active disease is also required. Paediatricians who are relatively unfamiliar with childhood TB may need to re-educate themselves in this area. Although the prevalence of TB may not have reached the alarming levels seen in other countries, there is no place for complacency.

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Commentary

Dr Bannon points out that TB is on the rise again, and that there is a worldwide need to try to gain control of this problem. This is certainly the message currently being directed at,[1] and emanating from,[2] the World Health Organisation.

In particular, Bannon advocates more standardised and perhaps widespread use of BCG as a means to this end. But as he points out, estimates of BCG efficacy vary widely, at best they are around 70–80%.[3–5] Many studies, however, show much less impressive results. If anything, the vaccine prevents severe disease in the young rather than reactivation and pulmonary disease in older age groups.[6]

Although paediatricians should be pleased and take encouragement that this vaccine protects children, they should also pause for thought. Children with TB pose a negligible infectious risk to others. They acquire TB not from each other but, for the most part, from adults with reactivated lung disease not preventable by BCG. Contact tracing of paediatric cases is about finding the source of the infection, not about finding other cases who have been infected by the child because there will not be any. Many of the vaccines we use routinely in children, such as measles vaccine and *Haemophilus influenzae* type b vaccine, induce herd immunity—breaking the transmission of infection from one individual to the next, protecting thereby the unimmunised as well as the immunised and resulting in dramatic reductions in incidence. But it seems we cannot expect this of BCG. The vaccine, given to infants and children, may protect the immunised individuals (somewhat unreliably) but will do little else to check the spread of the disease and thus can do little ultimately to control TB.

Bannon also mentions another problem with BCG, namely the fact that use of the vaccine complicates interpretation of the tuberculin skin test, still a mainstay in the diagnosis of TB. This has been one reason why the vaccine has not been used routinely in the United States. There, use of the skin test as a screening tool with prophylactic chemotherapy for positive cases, in children from high risk groups, or those living in areas of high prevalence has been a major strategic tool.[7]

A central plank of the WHO global strategy is now "directly observed treatment (short course)" ("DOTS").[2] This is relevant to developed as well as underdeveloped countries. In western Europe, many cases of TB occur in individuals and families who are:

- impoverished
- from ethnic minorities
- recently arrived in their country of residence
- have a poor understanding of the local language
- a combination of these.

Achieving a good level of understanding of the importance and practical aspects of a six month course of combination chemotherapy in such cases is extremely difficult. The shame and alienation associated with the diagnosis in some communities can make things worse. Most of us who manage children with TB in our clinics have a sense of unease as to whether the treatment is being reliably taken.

A major priority for public health services in Europe should be the provision of sufficient numbers of appropriately trained nursing staff or health workers to undertake directly observed treatment programmes, particularly in areas of high incidence. Such staff should, whenever possible, have cultural links with the communities they serve. They will also be able to undertake other vital parts of the strategy for controlling TB, namely case finding and education.

Finally, although vaccines and chemotherapy are the currency of doctors, who therefore feel it is legitimate to plan and discuss their use, it is not these tools but poverty which has dictated and continues to dictate the incidence of TB throughout recent history. TB peaked with the horrors of urban poverty and industrialisation in western Europe in the 19th century and started to fall as living standards rose, rising again in times of warfare and attendant social strife. Today, geographical and temporal differences in global incidence rates principally reflect poverty, while use of anti-TB drugs or of BCG are secondary factors. Although doctors and scientists have a part to play in this saga, the centre stage for the moment is occupied by politicians.[8]

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