REVIEW

Does BCG have a role in tuberculosis control and prevention in the United Kingdom?

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The United Kingdom has recently changed its BCG vaccination policy in response to the changing epidemiology of tuberculosis (TB) in children. One of the changes has been the abandonment of the long standing school's BCG programme because of the low risk of TB in that population. The other change has been the targeting of those infants and children at increased risk of TB, particularly in populations with increased rates of TB. However, there remain questions as to what role BCG plays in TB control and prevention in the UK.

The Medical Research Council BCG trial from 1950 studied over 50 000 schoolchildren aged 14–15½ years. The Danish strain of vaccine was administered intradermally and *Mycobacterium microti*, the vole bacillus, was administered percutaneously. Follow up was comprehensive[1–4] and cases suggestive of TB were assessed by an independent researcher.[1 2 4] After 15 years the protective efficacy was 78.4% (99% CI 69% to 86%) and 80.8% (99% CI 68% to 91%) for the BCG and vole bacillus vaccines, respectively. There were 10 cases of tuberculous meningitis and miliary pulmonary TB: all occurred in non-vaccinated subjects.[4] Despite a large study population there were not enough cases of TB to draw a conclusion regarding efficacy of the two vaccines between 15 and 20 years, although average efficacy over the 20 year period was 77% for both.[5]

The efficacy of BCG vaccine administered to newborns in Manchester between 1965 and 1980 was estimated at more than 75%.[6] Subsequently, two case-control studies showed a protective efficacy of BCG vaccine given to newborn Asian children of 64% (95% CI 43% to 77%) and 49% (95% CI 14% to 62%), respectively.[7 8]

BCG POLICY IN THE UK

Children who were recent home contacts of a case of pulmonary TB became eligible for the BCG vaccine in 1949.[1] A national programme for the vaccination of 14 year old schoolchildren began in 1953 due to the high rates of TB in school leavers. In the 1960s a selective BCG vaccination programme was introduced. This was based on declining TB rates in the indigenous population and higher rates in new immigrants from countries with a high prevalence of TB and targeted infants whose parents were new entrants to the UK from countries with a high incidence of TB.[9]

The TB Action Plan for stopping TB in England, published in October 2004, highlighted the need to review the BCG vaccination programme.[10] In July 2005 the Joint Committee on Vaccination and Immunisation introduced new guidelines for BCG vaccination in the UK, including discontinuation of the schools' BCG programme. New recommendations in the updated version of the Green Book include vaccination of the following:

- Infants (0–12 months) living in areas where the annual incidence of TB is 40 per 100 000 or greater
- Infants (0–12 months) with a parent or grandparent who was born in a country where the annual TB incidence is 40 per 100 000 or greater
- Previously unvaccinated children aged 1–5 years with a parent or grandparent who was born in a country where the annual TB incidence is 40 per 100 000 or greater. These children should be identified at suitable opportunities and could be vaccinated without prior tuberculin testing
- Previously unvaccinated, tuberculin negative children aged 6–16 years with a parent or grandparent who was born in a country where the annual TB incidence is 40 per 100 000 or greater. These children should be identified at suitable opportunities, tuberculin tested, and vaccinated if negative
- Previously unvaccinated, tuberculin negative contacts of cases of respiratory TB
- Previously unvaccinated, tuberculin negative new entrants under 16 years of age who were born in or lived for at least three months in a country with an annual TB incidence of 40 per 100 000 or greater
- Others deemed to be at risk:
  - Unvaccinated, tuberculin negative individuals aged under 35 years at occupational risk
  - Unvaccinated, tuberculin negative individuals aged under 35 years who are going to live or work for more than one month in a country where the annual incidence of TB is 40 per 100 000 or greater.[9]

Furthermore, the schools' BCG programme has recently been discontinued[11] as economic analysis has shown that due to a low and falling incidence of active TB in school age children this policy was no longer cost effective.[12] The other major policy change has been the recommendation to vaccinate all children under the age of

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12 months who live in high prevalence areas in the UK.[9] However, the cost effectiveness of the neonatal BCG vaccination programmes in the UK, selective and universal, is unknown.[12]

UNIVERSAL OR SELECTIVE NEONATAL BCG VACCINATION POLICY?

It has been recognised that there are logistic difficulties in identifying at risk infants, not only for BCG but other selective procedures. These include language barriers, the time involved in assessment of risk status and the difficulty in assessment of risk status, for example, for children of mixed ethnicity and when reliable information on TB prevalence is not available.[13–15] Furthermore, the definition of 'area' is ill defined and prone to variation. For example, the rate of TB notifications in London is now 41.3 per 100 000.[16] Does this suggest that there should be a universal BCG policy for all infants in London? Notification rates in London boroughs vary from less than 10 per 100 000 to over 100 per 100 000,[17] and some London boroughs have already adopted a universal neonatal BCG vaccination contrary to previous recommended policy. It remains unclear at what incidence threshold a universal programme should be adopted, especially in areas where TB notification rates are increasing.[13]

BCG AND GLOBAL TB CONTROL AND PREVENTION

The World Health Organisation (WHO) recommends neonatal BCG vaccination in countries with a ''high prevalence'' of TB, even in those with a high prevalence of HIV. However, WHO does not recommend BCG vaccination for ''older infants or children'' suspected of HIV positivity who are symptomatic or immunosuppressed. BCG vaccine is also recommended for children at particular risk of TB exposure in low endemic countries and for those exposed to multiresistant *M tuberculosis*.[18] BCG vaccine is not recommended for those over 1 year old.[19] BCG is used in over 150 countries and is mainly given in the neonatal period.[19 20] However, some countries, such as the USA, do not routinely vaccinate with BCG, based on the uncertain efficacy against pulmonary TB in adolescents and adults, as well as the need to maintain the utility of tuberculin testing as a diagnostic test in the population.[21]

META-ANALYSES OF BCG EFFICACY

The protective efficacy of BCG remains controversial, varying from 0% to 80% in different populations and geographic regions.[22] Meta-analysis of prospective trials has shown a combined relative risk (RR) for TB of 0.49 (95% CI 0.34 to 0.70)—that is, a protective effect of 51%.[23] Another meta-analysis has shown that the combined protection against meningeal and miliary TB was 86%.[24]

A meta-analysis of BCG efficacy in newborns and infants showed a combined protective efficacy of 0.74 (95% CI 0.62 to 0.83) against mainly pulmonary TB. The combined RR for death from TB was 0.35 (95% CI 0.14 to 0.88) and the combined odds ratio for TB meningitis was 0.36 (95% CI 0.18 to 0.70).[25] The three afore-mentioned meta-analyses were published over 10 years ago, and a more contemporary Cochrane systematic review examining the effects of BCG vaccination on TB is expected shortly.[26]

Various explanations for the variability of BCG efficacy in different trials and study populations have been suggested, including latitude variation, vaccine strain, and methodological differences.[22 27 28] Studies conducted further from the equator appear to show a higher BCG efficacy; however, latitude may be a proxy for other factors.[22] Exposure to cross-reacting environmental mycobacteria may also impact on the observed efficacy of BCG by either masking or inhibiting the protection induced by BCG.[22]

SAFETY OF BCG VACCINE

Available data suggest that BCG is a safe vaccine. The risk of local complications has been estimated at less than 0.4 per 1000 vaccinees under the age of 1 year and less than 0.03 per 1000 vaccinees 1–20 years of age. Local complications include ulceration, abscess formation, and regional suppurative lymphadenitis. Disseminated BCG has been estimated to occur at less than 1 per 10 000 vaccinated neonates[29] and is associated with immune defects including HIV infection, severe combined immunodeficiency, and chronic granulomatous disease.[30]

ALTERNATIVE TB VACCINES

For the first time, after 80 years of widespread use of BCG, evaluations of new vaccine candidates in humans are available. Alternative approaches in vaccine development include subunit vaccines based on *M tuberculosis* antigens, recombinant BCG vaccines and attenuated *M tuberculosis* vaccines. Another approach has been a prime-boost strategy which may be relevant in populations already heavily vaccinated with BCG.[31] While vaccines are in different stages of development and use in humans, BCG remains the only vaccine available for the prevention of TB.

WHAT ROLE DOES BCG PLAY IN TB CONTROL AND PREVENTION?

There have been several changes to BCG vaccination policy in the UK recently. However, there remain unanswered questions regarding the optimal BCG strategy in the UK. While a better vaccine for TB prevention is awaited, BCG remains at present the only vaccine available, particularly for severe forms of TB in children. While the new policy aims to identify and vaccinate those at highest risk of TB, it does not address all difficulties in implementation. There must also be mechanisms whereby changing local and overseas epidemiological data can be efficiently translated into effective public policy. Neither does this policy address issues of who identifies high risk infants and how. There are also concerns that, in the absence of a school's BCG programme, opportunistic screening and ''targeted vaccination'' of high risk children may not occur. Furthermore, there also needs to be better documentation of BCG vaccination, which would allow more effective monitoring of this programme.

In addition to BCG vaccination, other components of TB control need to be in place, particularly the early diagnosis and treatment of infectious individuals, as well as improved services for surveillance, contact tracing, and new entrant screening.[10]

CONCLUSION

BCG remains the only vaccine available for TB prevention. Continued TB surveillance and contemporary data on BCG efficacy in Britain is required to inform further decisions on BCG policy. Monitoring of the implementation of the new BCG policy will be necessary to identify and resolve logistic difficulties at the local level.

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