Clinical Review

Evidence behind the WHO Guidelines: Hospital Care for Children: What is the Evidence that BCG Vaccination Should Not be Used in HIV-infected Children?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO’s recommendations. The WHO guidelines, and more reviews are available at: http://www.ichrc.org

This review addresses the question: What is the evidence that BCG vaccination should not be used in HIV-infected children?

The WHO Pocketbook of Hospital Care for Children recommends children who have or who are suspected to have human immunodeficiency virus (HIV) infection but are not yet symptomatic should be given all appropriate vaccines including Bacillus Calmette–Guerin (BCG). (Pocketbook chapter 8.3.1, p. 214). This guideline has been updated in 2007 as discussed below to withhold BCG in HIV-infected children regardless of symptomatology.

Introduction

The Bacillus Calmette–Guerin (BCG) vaccine was developed by Calmette and Guerin in 1908 and became widespread after its introduction into World Health Organization (WHO) Expanded Programme on Immunization (EPI) in 1974 [1, 2]. BCG is a live, attenuated vaccine.

There are several risks associated with the live attenuated BCG vaccine [3] including, regional, extra-regional, localized and disseminated disease [4]. In addition, different strains and methods of administration have been associated with varying levels of complications [5, 6]. BCG disease encompasses a range of adverse effects which can occur in those vaccinated. The most serious of these is disseminated BCG which can often prove fatal. Disseminated BCG almost exclusively occurs in children <5 years of age who are infected with human immunodeficiency virus (HIV) or otherwise immuno-compromised, and those whom are severely malnourished [7].

In general, populations with high prevalence of HIV infection also have the greatest burden of tuberculosis (TB). In such populations, HIV-uninfected children will particularly benefit from the use of BCG vaccine [8]. However, it is becoming increasingly unclear whether the vaccine is of any benefit to HIV-infected children; in areas of high TB prevalence the BCG vaccine has not resulted in a disproportionate increase in cases of severe TB among HIV-infected children. This suggests that it may be of benefit in these populations. On the other hand, there is the question of whether it actually poses a risk to immunocompromised children which this review aims to address.

In 1987, the WHO decided that the benefits of BCG immunization for all children outweighed the risks among those with HIV infection. Therefore, it was concluded that the BCG vaccination should only be withheld from symptomatic individuals [3]. However, in 2007 the guidelines were amended following advice from the Global Advisory Committee on Vaccine Safety (GACVS). The most significant change was that infants known to be HIV-infected should not receive BCG vaccination, regardless of the stage of their disease [8, 9].

The new guidelines pose the question of how to identify those infants with HIV infection in
resource-poor countries as signs and symptom of infection may not clinically manifest until 3 months of age or later, and where viral-specific diagnostic tests are unavailable. Postponing vaccination in order to identify infected individuals would have a deleterious effect in HIV-exposed infants who are uninfected [10, 11].

This review intends to answer the question: what is the evidence that BCG vaccination should not be used in HIV-infected children?

**Methodology**

A search of the Medline database of the US National library of medicine and the National Institutes of Health was performed. The Pubmed clinical search strategy used was [(BCG OR Bacille Calmette Guerin OR Bacillus Calmette Guerin) AND (HIV or Human Immunodeficiency Virus or AIDS or Acquired Immunodeficiency Syndrome) OR [(‘HIV Infections’ [MeSH] OR ‘Acquired Immunodeficiency Syndrome’ [MeSH] OR ‘HIV’ [MeSH]) AND (‘BCG Vaccine’ [MeSH])]]. Limits employed were humans, English language and All Child: 0–18 years. A time limit was not used. This resulted in 224 articles and 52 reviews.

The ISI Web of Knowledge was also searched. The Web of Science section was selected. The Science citation index was used and language was limited to English. The following search strategy was used; TS = [(BCG OR Bacille Calmette Guerin OR Bacillus Calmette Guerin) AND (HIV or Human Immunodeficiency Virus or AIDS or Acquired Immunodeficiency Syndrome) AND (Child OR babies OR baby OR infant)] AND Language = (English). This resulted in 183 articles.

The Cochrane Library was searched using the PubMed search terms but no results were found.

All titles of articles and reviews were read and those which were not relevant to the clinical question were excluded. If there was any doubt as to the relevance of an article, the full text was sourced. Articles were only used if they related specifically to the use of BCG vaccination in HIV-infected children, regardless of the mode of transmission. Methodological quality of the papers was assessed according to the criteria of the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001).

**Results**

Full text was retrieved of 57 articles. However, upon assessment it was decided that case studies were to be excluded as they were considered as level 4 quality, as defined by the Oxford criteria. Similarly, if the methodology was not well defined and follow up of >80% was not achieved these studies were excluded on the same basis. All the studies used were 2b studies, except for one study which was 2c [12], and therefore were all considered to be high quality. One study [13] which has not as yet been published has been presented at the International AIDS society meeting and is published on the WHO website. Its findings prompted a change in WHO policy, and consequently it was felt too important not to be included in this review.

It was noteworthy that in all of the papers, given the nature of the trials, the outcome assessment was not blinded as to whether BCG had been received, due to ethical considerations and adjustments for extraneous prognostic factors were rarely carried out. The studies differed in their methods of measuring the presence of BCG-induced complications. One study [14] was excluded because the authors determined the administration of a BCG vaccination on the basis of whether a scar was present or not. However in children infected with HIV, a BCG scar is less likely to develop therefore this method introduced exclusion bias. A second study [15] was excluded because it did not differentiate between blood transfusion and vertical transmission, thus offering a different exposure to the other studies used. Finally, a third study [16] was excluded due to a methodological flaw whereby children were injected with differing doses of the vaccine therefore introducing a large confounding factor. In total, four retrospective studies [5, 13, 17, 18], four prospective cohort studies [12, 19–21] and one cross-sectional study were identified [22].

All the studies were published between 1992 and 2008. All except two (in Argentina and Brazil) were undertaken in developing countries: Thailand, Zambia, South Africa, Rwanda and Haiti.

Two studies were undertaken using a similar methodology [17, 19]. First, infants were recruited following the administration of a BCG vaccination. These subjects had either been previously identified as being HIV positive or were then tested for HIV. Subjects were either followed prospectively or clinical records were examined retrospectively. Chokephaibulkit [17] reported 16 infants out of 1058 with mild complications, all of whom were HIV uninfected. The complications included 5 with a local abscess with drainage, 10 with axillary lymphadenopathy and 1 with a BCG cutaneous scar >1 cm in diameter. From analysis of 377 children, Msellati [19] reported one case of BCG adenitis in an HIV-positive infant. Suppuration at the injection site was found in six infants; one HIV-infected child and five HIV-uninfected children. This suggests that mild localized complications occur more commonly in children without HIV than with HIV.

The studies differed in their follow up time and size. The large Thai study [17] had 1202 eligible infants of whom 111 were HIV positive. In the Rwandan prospective cohort study [19], infants were checked every 2 weeks for regional adenitis and major side effects during the first 15 months of follow-up.
up, whereas in Thailand [17] infants were seen at 1, 2 and 4 months for physical exam.

These two studies [17, 19] both concluded that complications were uncommon in HIV-infected children. A study conducted by Waddell in Zambia [22] reached a similar conclusion, however this study was conducted differently. Rather than looking at individuals who had been vaccinated with BCG this study looked at 387 HIV-positive children hospitalized with suspected complications of HIV. The study determined that these individuals had been administered the BCG vaccination by immunization record or scar, or both. Of the 387 included in the study only 1 (0.26%) child had disseminated BCG. The authors concluded that disseminated BCG is not common among Zambian children with advanced HIV who had been immunized at birth; therefore the benefits of BCG vaccination outweighed the possible risks.

However, two studies [13, 18] that used a similar methodology reached a different conclusion to Waddell. In a 2006 study, Hessling et al. [18] evaluated 466 confirmed cases of any BCG complications seen at a tertiary hospital, finding 23.2% cases were among HIV-infected children and 40.7% were among children who were not HIV infected. BCG disease was diagnosed in 25 children. Of these, 17 (68%) were HIV infected and 2 (8%) were HIV uninfected but had other primary immune deficiencies. Eight of the 25 children had disseminated BCG disease, 6 were HIV infected. In 2007, Hessling et al. [20] used this data in combination with clinical surveillance data from a 2003 paper [6] to estimate that in South Africa in 2004, 417 per 100,000 per year were at risk of disseminated disease, assuming a vertical transmission risk of HIV of 5% [20].

A similar retrospective study was undertaken in Argentina [13] where 310 BCG-vaccinated patients of 374 perinatally HIV-infected children from 1992–2004 were followed. This study found 28 (9%) suffered complications; of these, 24 (86%) suffered from localized complications and 4 (14%) from disseminated complications. Fallo [13] compared the findings with data from a literature search which showed an incidence of 0.04 and 0.0001%, respectively, for the general population. TB was diagnosed in 14% of vaccinated and 11% of unvaccinated children, with no statistical difference found between these results.

These authors concluded that due to the high frequency of complications and increased risk of severe disease in perinatally HIV-infected children, BCG vaccination should be reconsidered in children at risk of HIV infection.

**HAART implementation**

Three studies [5, 12, 21] differed slightly from the rest. While still examining the effects of vaccinating an HIV-positive child with BCG vaccination, they were also specifically looking at evaluating Highly Active Antiretroviral Therapy (HAART) and its impact on an HIV-infected child with the BCG vaccine.

The first was a prospective observational study [12] that took place in Thailand where all children received BCG vaccination at birth. It found that out of the 150 HIV-positive children whom had received HAART, 4 patients were identified as having BCG-related complications due to immune reconstitution inflammatory syndrome (IRIS) within 10 weeks (one case of right axillary lymphadenitis, one case of abscess at the vaccination site and two cases of abscess at the vaccination site associated with ipsilateral axillary lymphadenopathy). In two of these children, the syndrome developed following a BCG booster which is a different exposure. The study therefore calculated the incidence rate as 2.7 cases/100 people (95% CI 0.7–6.7). This is similar to incidence rates of BCG complications in a non-HIV-infected population [12]. In all cases, with treatment the lesion markedly improved after 8 weeks.

The second was a retrospective study in South Africa between August 2002 and November 2004 [5] which reported a higher incidence of adverse events than that reported in the Thai study. In the study, 352 HIV-positive children were included, following enrolment in an antiretroviral treatment programme. They were then monitored at regular intervals over 6 months for signs of BCG disease. Of these children, 6% (21/352) developed BCG complications. Of these, 21 developed ipsilateral axillary lymphadenitis and 1 had suspected disseminated BCG infection. The authors note that the study was hospital-based and therefore may have overestimated the true incidence of adverse events in this population. Also, as it was a retrospective study, there was no standardized method for reporting and investigating adverse events, limiting the authors’ ability to analyse the outcomes. However overall, the study identified a high prevalence of BCG complications in children on HAART.

The third study disagreed with the results of the two studies discussed above. This was a prospective study [21] which reported the adverse reactions to BCG vaccine over a 7-year period in two groups of children; the first group (n = 141) were exposed to HIV via their mothers at birth but were uninfected as they were participating in a prevention of mother to child transmission (PMTCT) programme, the second group were infected with HIV (n = 66). Three cases of regional BCG disease were identified in the HIV-infected groups (3/66); one was associated with severe immunosuppression prior to HAART initiation. The other two cases developed as an IRIS in response to HAART therapy. No cases of adverse events were reported in the HIV-uninfected group and no cases of disseminated BCG disease occurred in either group. The authors of this study concluded that all
newborns should be vaccinated with BCG regardless of their HIV status due to the accrued benefits of this immunization.

Hessling et al. [18] whilst not focussing on HAART implementation also noted that HAART was started in four HIV-infected children before the onset of clinical BCG disease. In all of these children, BCG disease presented as acute ipsilateral adenopathy <3 months after the initiation of HAART. Nevertheless, the study recommended treating HIV-infected patients who had received BCG with HAART, as this was significantly associated with overall survival among HIV-infected children (OR 0.218; 95% CI 0.059–0.894; \( p = 0.35 \) by Fishers’ exact test).

Overall, the evidence appears to indicate a risk of increased adverse events as part of an IRIS in response to HAART in children previously immunized with the BCG vaccine. However, this is an area which needs more extensive research to reach a conclusion.

Discussion
Making comparisons between the studies is difficult. Although they were all considered high-quality studies, the methods were markedly different, particularly in terms of selection criteria. Waddell [22] was examining a cohort who had already been hospitalized with HIV-related complications. Hesseling [18] also acknowledges that their detection bias may have favoured the selection of HIV-infected children whom were more symptomatic. These studies are therefore difficult to compare with studies where a more generalized cohort of both symptomatic and non-symptomatic children was used.

The greatest limitation in the majority of these studies is the methods used to detect the presence of BCG infection. Only Hesseling [18] and Fallo [13] use microbiological techniques to confirm BCG disease. Studies using a clinical endpoint would have had a lower specificity. In addition, disseminated BCG disease in HIV-infected children may be misdiagnosed as TB. Therefore, the risk of disseminated BCG disease could be underestimated in the population.

The other main limitation of many of the studies is the poor measure of HIV infection. Hesseling [6, 18] used Elisa antibody testing, in infants <18 months. Without viral-specific testing, accuracy of HIV infection is not certain in infants under 18 months; this is a problem relevant not only to the studies, but the implementation of WHO’s current recommendation on BCG vaccination in HIV-infected infants.

Most studies agree that TB is still a very common cause of morbidity and mortality in developing countries, especially in those with a high incidence of HIV. The results of this limited research suggest that HIV-negative individuals are more likely to suffer complications than HIV-positive individuals; however HIV-positive individuals are more likely to suffer from the more serious complications such as disseminated BCG disease.

As more countries administer anti-retrovirals, and as childhood immunization with BCG is universal, there could be an increase in cases of immune reconstitution BCG disease, although with much better overall outcomes for HIV-infected children. Prospective studies are therefore needed to determine the rate of BCG-associated IRIS and to help assess whether antibiotic prophylaxis may be beneficial.

Conclusion
The limited evidence currently available has been the basis of the WHO recommendation that BCG vaccination should not be used in HIV-positive children, as severe complications appear more commonly in HIV-infected individuals [8]. This decision is supported by the findings from the Fallo [13] and Hesseling [18, 20] studies.

Although the WHO have suggested that HIV-infected infants should not be vaccinated this is obviously difficult in countries where BCG vaccination is administered before HIV status can be detected. Many high HIV-burden countries do not have viral-specific testing (such as PCR) routinely available to adequately assess the infection status of every new born infant.

More research needs to be undertaken in this area to clarify the situation, and treating clinicians need to be made aware of this issue with all its complexity. The WHO recommendation highlights the need for viral-specific testing to be widely available in developing countries. This will ensure HIV-infected infants are not exposed to BCG which may be potentially dangerous and HIV-exposed but uninfected infants are not denied this important vaccine.

References


