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Risk of disseminated BCG disease and HIV infection

Disseminated bacille Calmette–Guérin disease in HIV-infected South African infants

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. المقالة لهذه الكامل النص نهاية في الخلاصة لهذه العربية الترجمة.

Abstract

Objective To determine the population-based incidence of disseminated bacille Calmette–Guérin (BCG) disease in HIV-infected infants (aged ≤ 1 year) in a setting with high burden of tuberculosis and HIV infection coupled with a well-functioning programme for the prevention of HIV infection to infants.

Methods The numerator, or number of new cases of disseminated BCG disease, was derived from multicentre surveillance data collected prospectively on infants with a confirmed HIV infection during 2004–2006. The denominator, or total number of HIV-infected infants who were BCG-vaccinated, was derived from population-based estimates of the number of live infants and from reported maternal HIV infection prevalence, vertical HIV transmission rates and BCG vaccination rates.

Findings The estimated incidences of disseminated BCG disease in HIV-infected infants were as follows: 778 per 100 000 (95% confidence interval, CI: 361–1319) in 2004 (vertical HIV transmission rate: 10.4%); 1300 per 100 000 (95% CI: 587–2290) in 2005 (transmission rate: 6.1%); and 1013 per 100 000 (95% CI: 377–1895) in 2006 (transmission rate: 5.4%). The pooled incidence over the study period was 992 per 100 000 (95% CI: 567–1495).

Conclusion Multicentre surveillance data showed that the risk of disseminated BCG disease in HIV-infected infants was considerably higher than previously estimated. There is an urgent need for data on the risk–benefit ratio of BCG vaccination in HIV-infected infants to inform decision-making in settings where HIV infection and tuberculosis burdens are high. Safe and effective tuberculosis prevention strategies are needed for HIV-infected infants.

Background

Vaccination with bacille Calmette–Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, is almost universally given in sub-Saharan African countries where the brunt of the global burden of paediatric infection with type-1 HIV is concentrated. The Joint UN Programme on HIV/AIDS (UNAIDS) estimates that 390 000–420 000 children <15 years of age acquire HIV infection each year.¹ BCG vaccination is usually given at birth or in the perinatal period. In 2002, an estimated 75% of the 130 million children born worldwide were vaccinated with BCG.²

BCG has consistent efficacy for the prevention of disseminated tuberculosis in young children without HIV infection.. A recent meta-analysis indicates a summary

protective BCG effect of 73% (95% confidence interval, CI: 67–79) against tuberculous meningitis and 77% (95% CI: 58–87) against miliary tuberculosis.²

In contrast, there is limited evidence that BCG has a protective effect in HIV-infected infants and children.^{3,4} Moreover, a high incidence of tuberculosis, in whom a high incidence of culture-confirmed has been reported (1596 per 100 000; 95% CI: 115–2132 amongst South African HIV-infected infants), a rate 24.2-fold higher than observed in HIV-uninfected infants.⁵ It is possible that HIV-related suppression of T cells compromises specific T-cell mediated immune responses and reduces BCG efficacy in infants.

Adverse events linked to BCG vaccination range from mild, localized complications to more serious, systemic or disseminated BCG disease, in which *M. bovis* BCG is confirmed from at one or more anatomical sites distant from both the injection site and regional lymph nodes.⁶ Disseminated BCG disease is associated with a case fatality rate of > 70% in infants.^{6,7} compared to a background mortality amongst South African HIV-infected infants of 12.2 per 100 person-years (95% CI: 8.2–17.4).⁸

Systemic or disseminated BCG disease (dBCG) may be clinically indistinguishable from tuberculosis and can only be confirmed by obtaining positive mycobacterial cultures species identification, preferably by polymerase chain reaction (PCR) for the RD1 genetic region, lost during attenuation of BCG.⁹

While the documented risk of dBCG in non-HIV-infected infants is < 5 per 1 million vaccinees and is associated with rare congenital immune deficiencies,¹⁰ the risk of dBCG was previously shown to be 110 to 417 per 100,000 in HIV-infected infants routinely vaccinated at birth.^{3,11} Consequently, in 2007 the WHO Global Advisory Committee on Vaccine Safety (GACVS) and the Strategic Advisory Group of Experts (SAGE) recommended revising BCG vaccination policy for HIV-infected infants.^{12,13} This milestone recommendation and the ensuing change in policy¹⁴ have resulted in HIV infection becoming a full contraindication for BCG vaccination in infants, even in those who are asymptomatic at birth and at risk of *Mycobacterium tuberculosis* (*M.tuberculosis*) infection early in life. In preceding years, WHO advised increasing caution on the use of BCG in HIV-infected children, following case reports of disseminated BCG disease.^{3,6,7,15} WHO also called for more

epidemiological data on the true impact of serious BCG adverse events and for closer monitoring of these events in areas of high HIV infection prevalence, with a specific focus on distinguishing BCG infection from disease caused by *M. tuberculosis*.^{12,13} In light of the limited data available to inform the discussion of BCG risks and benefits in HIV-infected infants, we conducted a multicentre surveillance study to estimate more accurately the population incidence of disseminated BCG disease in HIV-infected infants in a setting where tuberculosis and HIV infection are highly endemic and universal neonatal BCG vaccination is practiced.

Methods

Study setting and design

This multicentre prospective hospital-based surveillance study was conducted between 1 January 2004 and 31 December 2006 in the three paediatric referral hospitals that service the Western Cape Province, South Africa: Tygerberg Children's Hospital, Red Cross Children's Hospital and Groote Schuur Hospital. These hospitals have specialist paediatric HIV services and routinely perform mycobacterial culture in children with suspected mycobacterial disease at in conjunction with speciation of *M. tuberculosis* complex isolates. Routine prospective laboratory surveillance for BCG-related adverse events was initiated following earlier case reports of serious BCG complications in HIV-infected infants.⁶

In South Africa, universal BCG vaccination of infants at birth was implemented in 1973. Most infants are born in health-care centres. Since 2000, intradermal vaccination with the *M. bovis* Danish strain 1331 (Statens Serum Institute, Copenhagen, Denmark) is administered in the right deltoid region. In 2005, neonatal vaccination coverage was 98–99% in the province¹⁶ and the overall tuberculosis incidence was 917 per 100 000 total population.¹⁷ In 2006, the HIV infection prevalence among pregnant women in the public health sector was 15.1% (95% CI: 11.6–18.7).¹⁸ There is a well-established public programme for the prevention of mother-to-child transmission (PMTCT) of HIV. HIV testing is offered universally to women at their first antenatal visit. During 2004–2005, dual therapy with zidovudine and nevirapine was used for PMTCT in both mothers and infants. From 2006 onwards, zidovudine was initiated at 28 weeks of pregnancy rather

than 34 weeks. Currently, women whose CD4+ T-lymphocyte (CD4) count is ≤ 200 cells/mm³ are fast-tracked for highly active antiretroviral therapy (HAART). All HIV-infected women are provided with free milk powder for 6 months if they choose to formula-feed. Infant HIV testing was offered at 14 weeks of age with a single HIV-DNA PCR test and infants were followed for 6 months until discharged from the PMTCT programme. The reported vertical HIV transmission rate varied from 5.4% to 10.4% during the study period, reflecting variations in the introduction, uptake and performance of PMTCT regimens. The uptake of maternal antenatal HIV testing during 2006 was 93.0%; around 90% of women exclusively fed their infants using formula (data from Western Cape Department of Health).

This study was approved by the research ethics committees of Stellenbosch University and the University of Cape Town. Study implementation and reporting adhered to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for the reporting of cross-sectional studies.¹⁹

Incidence of disseminated BCG disease

As dBCG is predominantly seen in HIV-infected children ≤ 1 year of age and who exhibit rapid progression to advanced HIV disease,^{3,6,7} all HIV-infected children ≤ 1 year of age (infants) diagnosed with disseminated BCG disease during the study period were eligible for inclusion. The incidence of disseminated BCG disease was calculated as previously described.¹¹ In addition CIs were derived from multiple sources of uncertainty and actual reported, rather than estimated rates of vertical HIV transmission were used. Two cases were included in a previous report from Tygerberg Children's Hospital (2004).¹¹

Case definitions and data collection

Systemic or disseminated BCG disease (dBCG) was defined as the isolation of *M. bovis* BCG from ≥ 1 clinical samples taken at sites distant from the vaccination site and regional lymph nodes, including respiratory secretions, blood, bone marrow or cerebrospinal fluid, and in the presence of a clinical syndrome consistent with dBCG.⁶ Patient data were obtained from hospital and laboratory records. Mycobacterial culture and HIV testing were routinely performed at the discretion of attending physicians. The

automated Middlebrook 7H9 broth-based Mycobacterial Growth Indicator Tube (MGIT) culture system (Becton-Dickinson, Maryland, United States) was used for mycobacterial culture; the identification of an isolate as *M. bovis* BCG was confirmed using a multiplex PCR assay that distinguishes *M. bovis* BCG from other members of the *M. tuberculosis* complex.⁹ The date on which the mycobacterial culture sample was obtained was used to calculate patient age. Infant HIV infection status was determined using HIV-DNA PCR.

Numerator

The numerator for calculating the incidence of dBCG was the total estimated number of HIV-infected infants diagnosed each year with dBCG at the three study hospitals during the study period. Those with mycobacterial disease caused by *M. tuberculosis* or nontuberculous mycobacteria, were excluded.

Denominator

In the absence of reliable population data on infants in Western Cape Province, a number of different data sources were used to determine the denominator for the incidence of disseminated BCG disease: i.e. the estimated annual number of HIV-infected BCG-vaccinated infants in the province. Data from the Actuarial Society of South Africa (ASSA) 2003 AIDS and Demographic Model for the Western Cape were used to estimate the total number of person-years of observation for all infants.^{20,21} This model provides a projection of the population of South Africa by age, sex, race, province and HIV status, and allows for the impact of AIDS on mortality and fertility rates. It is calibrated to census data, demographic and health survey data, and data on recorded deaths and HIV infection prevalence in national surveys. The proportion of the total number of person-years of observation that corresponded to HIV-infected infants was estimated using the prevalence of maternal HIV infection in the province in conjunction with vertical HIV transmission rates reported by the PMTCT programme. Finally, the reported BCG vaccination coverage rate was used to estimate the number of HIV-infected BCG-vaccinated infants at risk of dBCG.

Confidence intervals

The CIs for the incidence rates were estimated through a bootstrap approach in which the three key quantities used to calculate the incidence rate were treated as independent

random variables, as follows. Values for the number of cases of dBCG were sampled from a Poisson distribution that had the same mean as the observed number of cases; values for the HIV prevalence were sampled from β distributions based on means and standard deviations determined from published antenatal prevalence estimates and associated CIs; and values for mother-to-child transmission rates were sampled from β distributions based on reported mother-to-child transmission rates and associated sample sizes. The sampling procedure was repeated 10 000 times for each incidence estimate and bootstrap CIs were obtained using the percentile method.²²

Results

In total, 32 cases of dBCG were confirmed in HIV-infected infants during the study period: 12 in 2004, 12 in 2005 and 8 in 2006. All were included in the study analysis. No cases were observed in infants without or with unknown HIV infection. 53 HIV-infected infants had disease due to *M. tuberculosis* and 11 had disease due to nontuberculous mycobacteria; these were excluded from analysis.

Table 1 shows the number of infants with dBCG disease, the estimated number of infants with HIV infection, and the estimated incidence of dBCG in these infants. Figures are for the Western Cape Province for the years 2004–2006. The estimated incidence was as follows: 778 per 100 000 (95% CI: 361–1319) in 2004, with an estimated vertical HIV transmission rate of 10.4%; 1300 per 100 000 (95% CI: 587–2290) in 2005, with an estimated transmission rate of 6.1%; and 1013 per 100 000 (95% CI: 377–1895) in 2006, with an estimated transmission rate of 5.4%. The pooled estimate for the incidence of dBCG over the total study period was 992 per 100 000 (95% CI: 567–1495). The infants' mean age at presentation was 9 months (range: 1–12 months); 25 of the 32 infants died, resulting in an all-cause mortality rate of 78.1%. The median time to death following a diagnosis of dBCG was 75 days (range: 0–359 days).

Discussion

We present population estimates of disseminated BCG disease in routinely vaccinated HIV-infected infants obtained through multicentre prospective surveillance. These data confirm that BCG vaccination in HIV-infected infants poses a significant risk of

disseminated BCG disease, approximately 3- to 4-fold higher than earlier preliminary estimates of 110–417 per 100 000 infants.¹¹ The difference in risk estimates most likely occurred because the present study included all three provincial referral hospitals, whereas the earlier study included only one hospital, while the denominator for the incidence calculation was derived using the same method. In addition, we used reported rates for vertical HIV transmission in the study period rather than assumed rates of 5%, 10% and 15% in different scenarios.¹¹ Our calculation of the CIs for the incidence rates was based on three known sources of uncertainty. Thus, the result is more likely to reflect the true uncertainty of the incidence estimates. The low incidence of dBCG disease found in HIV-uninfected infants is consistent with other reports. (10, 11)

Our data support recently revised WHO recommendations against vaccinating HIV-infected infants with BCG. However, it is difficult to decide how to defer BCG vaccination selectively in all infants born to HIV-infected women in settings with high burden of HIV and tuberculosis. The risk of dBCG in the relatively small number of HIV-infected infants must be balanced against the risk of not vaccinating infants without HIV infection, who remain the vast majority of infants.²³

Recently, WHO has emphasized that application of the revised BCG vaccination guidelines will depend on local factors,¹⁴ including the risk of exposure to *M. tuberculosis*, the prevalence of tuberculosis and HIV infections, the efficacy of PMTCT programmes for HIV, breastfeeding patterns, and the ability to follow up immunized children and to perform early virological testing. Other requirements include a good tuberculosis surveillance system for pregnant women and their infants and well-functioning integrated services for infant immunization and the treatment of HIV-infected children. The four specific scenarios outlined by WHO affecting the balance of risks and benefits of BCG vaccination in a setting with high tuberculosis and HIV infection burdens are listed in Figure 1.

Implementation of the revised BCG vaccination guidelines is likely to be challenging, even with a well-functioning PMTCT programmes and good diagnostic facilities, as most HIV transmission occurs peripartum or postpartum. The sensitivity of a

single HIV-DNA PCR test performed < 48 hours after birth is < 40% but increases to > 90% at 2–4 weeks.²⁴ In South Africa and many other developing countries, HIV PCR testing is performed only after 6 weeks, if at all. A key consideration is therefore, whether infant vaccination and PMTCT programmes are able to accommodate selectively delaying the BCG vaccination of HIV-exposed infants until 10–14 weeks after birth, for example, at a routine vaccination visit after a negative HIV-DNA PCR test result. Delayed vaccination could be combined with an alternative tuberculosis prevention strategy, such as isoniazid treatment. Such an approach would require close collaboration with other health programmes and an integrated PMTCT and infant vaccination programme with adequate follow-up.

Better prevention of maternal and infant HIV infection and more rapid access to HAART for those infected is likely to reduce the infant population at risk of dBCG as well as the risk of severe vaccine complications in HIV-infected infants. The International Union against Tuberculosis and Lung Disease BCG Working Group has recently issued a consensus statement on the use of BCG vaccination in countries where HIV and tuberculosis are highly prevalent.²⁵

Although data on the risk of dBCG in infants on HAART are lacking, a recent study demonstrated that giving HAART to HIV-infected infants \leq 12 weeks of age reduced all-cause mortality and tuberculosis in the first year of life compared with deferring HAART until standard HIV symptomatic or CD4 criteria were met.⁸ In addition, the incidence of BCG complications was lower.²⁶

The available data therefore indicate a considerable risk of both tuberculosis and serious BCG complications in HIV-infected infants, while there is little evidence that BCG vaccination is beneficial in HIV-infected infants. In contrast, most infants without an HIV infection benefit from BCG vaccination and are at a low risk of serious vaccine complications. Little is known about the protective efficacy of BCG vaccination in infants exposed to HIV but not HIV-infected, and who may be at high risk of tuberculosis because of immunological factors or a high maternal risk of tuberculosis.^{28,29} BCG vaccination should be offered to HIV-unexposed infants once HIV infection has been excluded.

The study has several limitations. Firstly, it is likely that numerator data were underestimated as not all HIV-infected infants with dBCG in the province would have been referred to and investigated in these three study hospitals. In addition, cases may have been missed because mycobacterial disease in children is usually paucibacillary. Secondly, the denominator – the number of HIV-infected infants – may have been overestimated. In particular, HIV infection prevalence estimates were obtained only for pregnant women attending public health facilities; the prevalence is likely to be lower in those attending private health facilities, who will also have a lower rate of vertical transmission due to better access to treatment. On the other hand, the denominator may have been underestimated, as it was derived using vertical HIV transmission rates reported by the provincial PMTCT programme, which may have been biased by incomplete uptake of maternal HIV testing and PMTCT, loss to follow-up, inadequate testing of HIV-exposed infants or missing data. In 2006, an estimated 93% of mothers were tested for HIV and 74.7% of infants were tested at or after 14 weeks. The large CIs reported in the present study reflect uncertainties in the vertical HIV transmission rate and maternal HIV infection prevalence. Our survey should also be replicated in other settings with different levels of mycobacterial exposure and susceptibility to tuberculosis and HIV infection. In our study, dBCG was due to Danish strain 1331 BCG. Vaccine strain may influence BCG-related adverse events and should be considered when these are monitored and reported.^{30,31} We did not have data available on the incidence of tuberculosis among non-vaccinated HIV-infected infants since the routine vaccination coverage was almost universal.

In conclusion, the risk of dBCG was high in HIV-infected infants routinely vaccinated at birth in a setting with high tuberculosis and HIV burden and a well-functioning PMTCT programme. However, there are operational obstacles to selectively defer BCG vaccination in infants born to HIV-infected women. Since not vaccinating an infant who is exposed to HIV but remains uninfected may increase the risk of disseminated tuberculosis, BCG vaccination should continue in settings where HIV infection and tuberculosis are both highly endemic until it is feasible to implement a policy of selective vaccination. Clear goals should be established for the implementation of safe vaccination practices in HIV-infected infants and for reducing the burden of

maternal and infant tuberculosis. More data are needed on the protective effect of BCG vaccination in HIV-infected infants and in HIV-exposed uninfected infants, as well as on the operational feasibility of deferred BCG vaccination in HIV-exposed infants. Safe and effective antituberculosis preventive strategies, including effective vaccines, are urgently needed for HIV-infected infants.

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Competing interests

None declared.

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Figure 1. Four scenarios outlined by WHO that affect the balance of risks and benefits of BCG vaccination in settings with high burden of tuberculosis and HIV infection¹⁴

- 1. Infants born to women of unknown HIV status.** The benefits of BCG vaccination outweigh the risks, and infants should be vaccinated.
- 2. Infants whose HIV infection status is unknown and who demonstrate no sign or symptom of HIV infection, but who are born to women known to be HIV-infected.** The benefits of BCG vaccination usually outweigh the risks, and infants should receive the vaccine after consideration of local factors.
- 3. Infants who are known to be HIV-infected, with or without signs or symptoms of HIV infection.** The risks of BCG vaccination outweigh the benefits and infants should not receive the vaccine, but they should receive other routine vaccines.
- 4. Infants whose HIV infection status is unknown but who have signs or symptoms of HIV infection and who were born to HIV-infected mothers.** Infants with unknown HIV infection status but who have signs or symptoms of HIV infection and were born to HIV-infected mothers. The risks of BCG vaccination usually outweigh the benefits, and children should not be vaccinated during the first few weeks of life, since clinical symptoms of HIV infection typically occur after 3 months of age. However, the vaccine can be given if HIV infection is ruled out by early virological testing.

Table 1. The estimated incidence of disseminated BCG disease in HIV-infected infants (aged ≤ 1 year) vaccinated at birth with BCG, Western Cape Province, South Africa

Year	2004	2005	2006
No. of cases of disseminated BCG disease in HIV-infected infants ≤ 1 year of age	12	12	8
Estimated total no. of infants ≤ 1 year of age	98 236	98 339	98 137
Provincial maternal HIV prevalence (% and 95% CI)	15.4 (12.5–18.2)	15.7 (11.3–20.1)	15.2 (11.6–18.7)
Reported vertical HIV transmission rate (%)	10.4	6.1	5.4
Estimated total no. of HIV-infected infants	1573	942	806
Estimated incidence of disseminated BCG disease per 100 000 HIV-infected vaccinated infants (no. and 95% CI), assuming 98-99% BCG vaccination coverage	778 (361–1319)	1300 (587–2290)	1013 (377–1895)

BCG, bacille Calmette-Guérin; CI, confidence interval. The pooled estimate for the incidence of disseminated BCG over the total study period was 992 per 100 000 (95% CI: 567–1495).