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

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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 a high burden of tuberculosis and HIV infection coupled with a well-functioning programme for the prevention of HIV infection in 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 per 100 000 BCG-vaccinated, HIV-infected infants were as follows: 778 (95% confidence interval, CI: 361–1319) in 2004 (vertical HIV transmission rate: 10.4%); 1300 (95% CI: 587–2290) in 2005 (transmission rate: 6.1%); and 1013 (95% CI: 377–1895) in 2006 (transmission rate: 5.4%). The pooled incidence over the study period was 992 (95% CI: 567–1495) per 100 000.

Conclusion Multicentre surveillance data showed that the risk of disseminated BCG disease in HIV-infected infants is considerably higher than previously estimated, although likely to be under-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.

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

Introduction

Vaccination with bacille Calmette-Guérin (BCG), a live at-tenuated 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 United Nations 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 has shown 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] In South Africa, the reported incidence of culture-confirmed tuberculosis among HIV-infected infants is 1596 per 100 000 (95% CI: 115–2132), a rate 24.2 times higher than among infants not infected with HIV.[5] It is pos-

sible 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 con-firmed in one or more anatomical sites far from both the site of injection and regional lymph nodes.[6] Disseminated BCG disease is associated with a case-fatality rate of > 70% in infants.[6,7] By comparison, the background mortality rate among South African HIV-infected infants is 12.2 per 100 person-years (95% CI: 8.2–17.4).[8]

Systemic or disseminated BCG disease may be clini-cally indistinguishable from tuberculosis and can only be confirmed through positive mycobacterial culture species identification, preferably by polymerase chain reaction (PCR) for the RD1 genetic region that is lost during attenuation of BCG.[9]

While the documented risk of disseminated BCG disease in non-HIV-infected infants is < 5 per 1 million vaccinees and is associated with rare congenital immune deficiencies,[10] it has been shown to be 1100 to 4170 per 1 million in HIV-

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infected infants routinely vaccinated at birth.[3,11] Consequently, in 2007 the WHO Global Advisory Committee on Vaccine Safety and the Strategic Advisory Group of Experts recommended revising BCG vaccination policy for HIV-infected infants.[12,13] This milestone recommendation and the ensuing change in policy[14] 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* 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 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 province[16] 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/mm^3 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, a reflection of 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.[19]

Incidence of disseminated BCG disease

As disseminated BCG disease 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.[11]

Case definitions and data collection

Systemic or disseminated BCG disease was defined as the isolation of *M. bovis* BCG from one or more clinical samples – regional lymph nodes, respiratory secretions, blood, bone marrow or cerebrospinal fluid – taken at sites distant from the vaccination site, in the presence of a clinical syndrome consistent with disseminated BCG disease.[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 culture system (Becton-Dickinson, Hunt Valley, MD, 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.

Incidence

The numerator for calculating the incidence of disseminated BCG disease was the total estimated number of HIV-infected infants diagnosed with such disease at the three study hospitals during the study period. Those with disease caused by *M. tuberculosis* or nontuberculous mycobacteria were excluded. The denominator was the estimated annual number of HIV-infected BCG-vaccinated infants in Western Cape Province, which was obtained from different data sources in the absence of reliable population data on infants in the province. Data for the Western Cape from the Actuarial

Table 1. **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[a], assuming 98–99% BCG vaccination coverage (no. and 95% CI)	778 (361–1319)	1300 (587–2290)	1013 (377–1895)

BCG, bacille Calmette-Guérin; CI, confidence interval.

[a] Per 100 000 HIV-infected vaccinated infants. The pooled estimate for the incidence of disseminated BCG disease over the entire study period was 992 per 100 000 HIV-infected, BCG-vaccinated infants (95% CI: 567–1495).

Society of South Africa's 2003 AIDS and demographic model 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 effect 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 disseminated BCG disease.

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. Values for the number of cases of disseminated BCG disease 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 disseminated BCG disease 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 HIV infection or with unknown HIV status. Of HIV-infected infants, 53 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 disseminated BCG disease, the estimated number of infants with HIV infection, and the estimated incidence of disseminated BCG disease in these infants. Figures are for the Western Cape Province for the years 2004–2006. The estimated incidence per 100 000 HIV-infected, BCG-vaccinated infants was as follows: 778 (95% CI: 361–1319) in 2004 (estimated vertical HIV transmission rate: 10.4%); 1300 (95% CI: 587–2290) in 2005 (estimated transmission rate: 6.1%); and 1013 (95% CI: 377–1895) in 2006 (estimated transmission rate: 5.4%). The pooled estimate for the incidence of disseminated BCG disease over the entire 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, which resulted in an all-cause mortality rate of 78.1%. The median time to death following a diagnosis of disseminated BCG disease 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 risk of disseminated BCG disease that is approximately 3- to 4-fold higher than the earlier preliminary estimates of 110–417 cases per 100 000 infants.[11] The difference in risk estimates is most likely due to the inclusion in the present study of all three provincial referral hospitals instead of just one, as in the earlier study, while the denominator for the incidence calculation was derived by 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 disseminated BCG disease found in infants without HIV infection 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 burdens of HIV and tuberculosis. The risk of disseminated BCG disease 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 infection, the efficacy of programmes for PMTCT of HIV, breastfeeding patterns, and the ability to follow up immunized children and 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. WHO outlined four specific scenarios that affect the balance of risks and benefits of BCG vaccination in a setting with high tuberculosis and HIV infection burdens and these scenarios are listed in Box 1.

Implementation of the revised BCG vaccination guidelines is likely to be challenging, even with 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 selectively delay the BCG vaccination of HIV-exposed infants until 10–14 weeks after birth, for example, until a negative HIV-DNA PCR test result is obtained at a routine vaccination visit. 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

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Box 1. **Four scenarios, outlined by WHO, that affect the balance of risks and benefits of BCG vaccination in settings with high burdens of tuberculosis and HIV infection**[14]

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 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.

BCG, bacille Calmette-Guérin.

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likely to reduce the infant population at risk of disseminated BCG disease 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 infection and tuberculosis are highly prevalent.[25]

Although data on the risk of disseminated BCG disease in infants on HAART are lacking, a recent study demonstrated that giving HAART to HIV-infected infants ≤ 12 weeks of age reduced all-cause mortality and tuberculosis in the first year of life, unlike deferring HAART until standard HIV symptomatic or CD4 criteria were met.[8] In addition, the incidence of regional 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 such infants. In contrast, most infants without 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 or who may be at high risk of tuberculosis because of immunological factors or a high maternal risk of tuberculosis.[27,28,29] BCG vaccination should be offered to HIV-unexposed infants once HIV infection has been ruled out.

The study has several limitations. Firstly, it is likely that numerator data were considerably underestimated, as not all HIV-infected infants with disseminated BCG disease in the province would have been referred to and investigated in the three study hospitals. In addition, cases may have been missed because mycobacterial disease in children is usually paucibacillary. Secondly, the denominator – the number of BCG-vaccinated 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, among whom vertical transmission will also be lower 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, disseminated BCG disease 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 routine vaccination coverage was almost universal.

In conclusion, the risk of disseminated BCG disease was high in HIV-infected infants routinely vaccinated at birth in a setting with high tuberculosis and HIV burdens and a well-functioning PMTCT programme. However, there are operational obstacles to selectively deferring 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. ■

Résumé

Infection disséminée par le bacille de Calmette-Guérin chez les nourrissons infectés par le VIH d'Afrique du Sud

Objectif Déterminer l'incidence en population de l'infection disséminée par le bacille de Calmette-Guérin (BCG) chez les nourrissons infectés par le VIH (âge ≤ 1 an) dans une situation caractérisée par une forte charge de tuberculose et d'infections à VIH, mais aussi par un bon fonctionnement du programme de prévention de l'infection par le VIH chez les nourrissons.

Méthodes Le numérateur, ou nombre de nouveaux cas d'infection disséminée par le BCG, a été déterminé à partir des données de surveillance multicentrique, collectées prospectivement au sujet des nourrissons présentant une infection à VIH confirmée au cours de la période 2004-2006. Le dénominateur, ou nombre total de nourrissons infectés par le VIH et vaccinés par le BCG, a été obtenu à partir d'estimations en population du nombre de nourrissons vivants et à partir de la prévalence rapportée des infections à VIH maternelles, des taux de transmission verticale du VIH et des taux de vaccination par le BCG.

Résultats L'incidence de l'infection disséminée par le BCG pour 100 000 nourrissons vaccinés par le BCG a été estimée à : 778

cas (intervalle de confiance à 95 %, IC : 361-1319) en 2004 (taux de transmission verticale du VIH : 10,4 %) ; 1300 cas (IC à 95 % : 587-2290) en 2005 (taux de transmission : 6,1 %) ; et 1013 cas (IC à 95 % : 377-1895) en 2006 (taux de transmission : 5,4 %). L'incidence globale sur l'ensemble de la période étudiée était de 992 (IC à 95 % : 567-1495) pour 100 000.

Conclusion Les données de surveillance multicentrique ont montré que le risque d'infection disséminée par le BCG chez les nourrissons infectés par le VIH était considérablement plus élevé qu'on ne l'avait estimé auparavant, bien que probablement encore sous-estimé. On a besoin d'urgence de données sur le rapport risque/bénéfice de la vaccination par le BCG chez les nourrissons infectés par le VIH pour étayer la prise de décisions dans des contextes où les charges d'infection à VIH et de tuberculose sont importantes. Des stratégies sûres et efficaces de prévention de la tuberculose sont nécessaires pour les nourrissons infectés par le VIH.

Resumen

Infección diseminada por el bacilo de Calmette–Guérin en lactantes infectados por el VIH en Sudáfrica

Objetivo Determinar la incidencia poblacional de la infección diseminada por el bacilo de Calmette-Guérin (BCG) en lactantes (niños ≤ 1 años) en un entorno de alta carga de tuberculosis e infección por VIH y de aplicación satisfactoria de un programa de prevención de la infección por VIH en los lactantes.

Métodos El numerador, o número de nuevos casos de infección diseminada por BCG, se calculó a partir de datos de vigilancia multicéntricos reunidos prospectivamente sobre lactantes con infección confirmada por VIH durante 2004-2006. El denominador, o número total de lactantes infectados por el VIH y vacunados con la BCG, se calculó a partir de estimaciones poblacionales

del número de lactantes vivos y de la prevalencia de infección materna por VIH, de las tasas de transmisión vertical del VIH y de las tasas de vacunación con BCG.

Resultados Las incidencias estimadas de infección diseminada por BCG por 100 000 lactantes infectados por el VIH y vacunados con BCG fueron las siguientes: 778 (intervalo de confianza del 95%, IC95%: 361–1319) en 2004 (transmisión vertical del VIH: 10,4%); 1300 (IC95%: 587–2290) en 2005 (tasa de transmisión: 6,1%); y 1013 (IC95%: 377–1895) en 2006 (tasa de transmisión: 5,4%). La incidencia combinada a lo largo del periodo estudiado fue de 992 (IC95%: 567–1495) por 100 000.

Conclusión Los datos de la vigilancia multicéntrica revelaron que el riesgo de infección diseminada por BCG en los lactantes infectados por el VIH era considerablemente superior al estimado anteriormente. Urge disponer de datos sobre la relación riesgo-beneficio de la vacunación con BCG en los lactantes infectados por el VIH a fin de fundamentar la adopción de decisiones en los entornos con alta carga de infección por VIH y de tuberculosis. Es preciso formular estrategias seguras y eficaces de prevención de la tuberculosis para los lactantes infectados por el VIH.

ملخص

المرض الناجم عن عصيات كالميت – غيران المنتشر لدى الأطفال المصابين بفيروس الإيدز في جنوب أفريقيا

الغرض: تحديد معدل الوقوع السكاني المرتكز للمرض الناجم عن عصيات كالميت – غيران لدى الأطفال (الذين تقل أعمارهم عن سنة) المصابين بفيروس الإيدز في أحد المواقع التي تعاني من عبء ثقيل من السل والعدوى بفيروس الإيدز معاً في ظل برامج جيدة الأداء للوقاية من عدوى الأطفال بفيروس الإيدز.

الطريقة: استمد الباحثون العدد المقسوم (البسط) أو عدد الحالات الجديدة للمرض الناجم عن عصيات كالميت – غيران المنتشر، من معطيات ترصُّد في مراكز متعددة جمعت استباقياً عن الأطفال الذين تأكدت إصابتهم بفيروس الإيدز خلال المدة 2004 – 2006. أما المقام (المخرج) أو عدد حالات الأطفال المصابين بفيروس الإيدز الذين تلقوا تلقيحاً بعصيات كالميت – غيران، فقد استمد من تقديرات سكانية المرتكز لعدد الأطفال الأحياء ومن معدل انتشار عدوى الأمهات بفيروس الإيدز المبلَّغ عنه ومن معدلات السراية العمودية بفيروس الإيدز ومعدلات التلقيح بالبي سي جي.

الموجودات: بلغ المعدل المقدَّر لوقوع المرض الناجم عن عصيات كالميت – غيران لكل مئة ألف من الأطفال المصابين بفيروس الإيدز وتلقوا لقاح البي سي جي 778، بفاصلة ثقة 95% تراوحت بين 361 و1319) وذلك في عام 2004، وفي عام 2005 بلغ 1300 (بفاصلة ثقة 95% تراوحت بين 587 – 2290)، وعام 2006 بلغ 1013 (بفاصلة ثقة 95%، تراوحت بين 337 و1895)، فيما بلغ معدل السراية العمودية لفيروس الإيدز في عام 2004 (10.4%) وفي عام 2005 (6.1%)، وفي عام 2006 (5.4%). وكان المعدل التجميعي للوقوعات طيلة فترة الدراسة 992 لكل مئة ألف (بفاصلة ثقة 95%، إذ تراوح بين 567 – 1495).

الاستنتاج: لقد أظهرت معطيات الترصُّد المستمدة من مراكز متعددة أن خطر المرض الناجم عن عصيات كالميت – غيران المنتشر لدى الأطفال المصابين بفيروس الإيدز يعتبر مرتفعاً بشكل أكبر مما كان مقدَّراً من قبل. وتمس الحاجة للمعطيات حول نسبة المخاطر مقابل المنافع للتطعيم بلقاح البي سي جي للأطفال المصابين بفيروس الإيدز، وذلك لتزويد أصحاب القرار السياسي بمعلومات عن المواقع التي يرتفع فيها عبء كل من العدوى بالسل وبفيروس الإيدز. كما تمس الحاجة إلى وجود استراتيجيات مأمونة وفعالة للوقاية من السل لدى الأطفال المصابين بفيروس الإيدز.

References

1. Joint United Nations Programme on HIV/AIDS. *AIDS epidemic update.* Geneva: UNAIDS; 2007. Available from: http://www.unaids.org [accessed on 10 October 2008].

2. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006;367:1173-80. PMID:16616560 doi:10.1016/S0140-6736(06)68507-3

3. Fallo A, Torrado L, Sánchez A, Cerqueiro C, Schargrodsky L, López EL. Delayed complications of Bacillus Calmette-Guérin (BCG) vaccination in HIV-infected children. In: *International AIDS Society Conference, Rio de Janeiro, 24–27 July 2005.* Available from: http://www.ias-2005.org/planner/Presentations/ppt/749.ppt [accessed on 10 October 2008].

4. Bhat GJ, Diwan VK, Chintu C, Kabika M, Masona J. HIV, BCG and TB in children: a case control study in Lusaka, Zambia. *J Trop Pediatr* 1993;39:219-23. PMID:8411315

5. Hesseling AC, Cotton MF, Jennings TM, Whitelaw A, Johnson LF, Eley B, et al. High incidence of tuberculosis among HIV-infected infants: evidence from a South African, population-based study highlights the need for improved tuberculosis control strategies. *Clin Infect Dis* 2009;48:108-14. PMID:19049436 doi:10.1086/595012

6. Hesseling AC, Rabie H, Marais BJ, Manders M, Lips M, Schaaf HS, et al. Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis* 2006;42:548-58. PMID:16421800 doi:10.1086/499953

7. Talbot EA, Perkins MD, Silva SF, Frothingham R. Disseminated bacille Calmette-Guérin disease after vaccination: case report and review. *Clin Infect Dis* 1997;24:1139-46. PMID:9195072 doi:10.1086/513642

8. Violari A, Cotton M, Gibb D, Babiker A, Steyn J, Jean-Phillip P, et al. Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study. In: *4th International AIDS Society Conference, Sydney, Australia, 22–25 July 2007.* Available from: http://www.ias2007.org/pag/PSession.aspx?s=150 [accessed on 10 October 2008].

9. Talbot EA, Williams D, Frothingham R. PCR identification of *Mycobacterium bovis* BCG. *J Clin Microbiol* 1997;35:566-9. PMID:9041390

10. Lotte A, Wasz-Hockert O, Poisson N, Engbaek H, Landmann H, Quast U, et al. Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bull Int Union Tuberc Lung Dis* 1988;63:47-59. PMID:3066422

11. Hesseling AC, Marais BJ, Gie RP, Schaaf HS, Fine PEM, et al. The risk of disseminated Bacille Calmette-Guérin (BCG) disease in HIV-infected children. *Vaccine* 2007;25:14-8. PMID:16959383 doi:10.1016/j.vaccine.2006.07.020

12. Global Advisory Committee on Vaccine Safety. Revised BCG vaccination guidelines for infants at risk for HIV infection. 25 May 2007. *Wkly Epidemiol Rec* 2007;82:181-96. PMID:17526120

13. Strategic Advisory Group of Experts. Meeting of the immunization Strategic Advisory Group of Experts, April 2007: conclusions and recommendations. *Wkly Epidemiol Rec* 2007;82:181-96. PMID:17526120

14. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Wkly Epidemiol Rec* 2007;82:193-6. PMID:17526121

15. Casanueva E. Adverse events after Bacille Calmette-Guérin (BCG) vaccination in HIV infected children. In: *3rd World Congress of Pediatric Infectious Disease, Santiago, Chile, 19-23 November 2002.*

16. Corrigal J. Western Cape provincial EPI vaccination survey. 2005. Available from: http://www.capegateway.gov.za/Text/2007/6/cd_volume_7_childhood_diseases_overview.pdf [accessed on 10 October 2008].

17. *City of Cape Town/metropole region TB control programme progress.* Cape Town: Durban: South Africa Department of Health, Provincial Government of the Western Cape; 2005. Available from: http://www.hst.org.za/publications/618 [accessed on 10 October 2008].

18. Dorrington R, Bourne D. Re-estimated provincial HIV antenatal survey prevalence for 2007 and a reinterpretation of the national trend. *S Afr Med J* 2008;98.

19. *STROBE statement: strengthening the reporting of observational studies in epidemiology.* Bern: STROBE Initiative; 2008. Available from: http://www.strobe-statement.org [accessed on 10 October 2008].

20. Actuarial Society of South Africa. ASSA 2003 AIDS and Demographic Model. Cape Town: ASSA; 2005. Available from: http://www.actuarialsociety.org.za/ [accessed on 10 October 2008].

21. Dorrington RE, Johnson LF, Bradshaw D, Daniel T. *The demographic impact of HIV/AIDS in South Africa. National and provincial indicators for 2006.* Cape Town: Centre for Actuarial Research, South African Medical Research Council & Actuarial Society of South Africa; 2006. Available from: http://www. commerce.uct.ac.za/Research_Units/CARE/ [accessed on 10 October 2008].

22. Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci* 1986;1:54-75. doi:10.1214/ss/1177013815

23. Mak TK, Hesseling AC, Hussey GD, Cotton MF. Making BCG vaccination programmes safer in the HIV era. *Lancet* 2008;372:786-7. PMID:18774406 doi:10.1016/S0140-6736(08)61318-5

24. Pugatch D. Testing infants for human immunodeficiency virus infection. *Pediatr Infect Dis J* 2002;21:711-2. PMID:12237612

25. Hesseling AC, Cotton MF, Fordham von Reyn C, Graham SM, Gie RP, Hussey GD. Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants. *Int J Tuberc Lung Dis* 2008;12:1376-9. PMID:19017445

26. Rabie H, Violari A, Madhi S, Gibb D, Steyn A, van Niekerk R, et al. Complications of BCG vaccination in HIV-infected and uninfected children: CHER Study [Abstract #600]. In:*15th Conference on Retroviruses and Opportunistic Infections, Boston, United states of America, 3-6 February 2008.* Available from: http://www.retroconference.org/2008/ Abstracts/33235.htm [accessed on 10 October 2008].

27. Kouakoussui A, Fassinou P, Anaky MF, Elenga N, Laguide R, Wemin ML, et al. Respiratory manifestations in HIV-infected children pre- and post-HAART in Abidjan, the Ivory Coast. *Paediatr Respir Rev* 2004;5:311-5. PMID:15531256 doi:10.1016/j.prrv.2004.07.008

28. Gupta A, Nayak U, Ram M, Bhosale R, Patil S, Basavraj A, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005. *Clin Infect Dis* 2007;45:241-9. PMID:17578786 doi:10.1086/518974

29. Kali PB, Gray GE, Violari A, Chaisson RE, McIntyre JA, Martinson NA. Combining PMTCT with active case finding for tuberculosis. *J Acquir Immune Defic Syndr* 2006;42:379-81. PMID:16645548 doi:10.1097/01. qai.0000218434.20404.9c

30. Kröger L, Brander E, Korppi M, Wasz-Höckert O, Backman A, Kröger H, et al. Osteitis after newborn vaccination with three different Bacillus Calmette-Guérin vaccines: twenty-nine years of experience. *Pediatr Infect Dis J* 1994;13:113-6. PMID:8190535

31. Waddell RD, Lishimpi K, von Reyn CF, Chintu C, Baboo KS, Kreiswirth B, et al. Bacteremia due to *Mycobacterium tuberculosis* or *M. bovis*, Bacille Calmette-Guérin (BCG) among HIV- positive children and adults in Zambia. *AIDS* 2001;15:55-60. PMID:11192868 doi:10.1097/00002030-200101050-00009