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REVIEW ARTICLE

Bacille Calmette-Guérin vaccine-related disease in HIV-infected children: a systematic review

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SUMMARY

OBJECTIVE: To describe the characteristics and risk of bacille Calmette-Guérin (BCG) vaccine related disease in human immunodeficiency virus (HIV) infected infants.

METHODS: Systematic literature review of articles published from 1950 to April 2009 in the English language. We identified all microbiologically confirmed cases of disseminated BCG disease in vertically HIV-infected children reported in the literature.

RESULTS: Sixteen observational studies and 11 case reports/series were included. Observational studies suffered from high rates of loss to follow-up and death. Loco-regional BCG disease was reported in both HIV-infected and non-infected children. Disseminated BCG disease was reported only in children with immunodeficiency and only in studies employing sophisticated laboratory techniques. Sixty-nine cases of disseminated BCG were identified in the literature: 47 cases were reported in six observational studies, the majority (41/47) from the Western Cape of South Africa. A Brazilian cohort study reported no cases of disseminated BCG amongst 66 HIV-infected children observed over a 7-year period. A recent South African surveillance study reported 32 cases of disseminated BCG over a 3-year period, estimating the risk of disseminated BCG to be 992 per 100 000 vaccinations in HIV-infected children. Few cases of severe disseminated TB were reported in the cohort studies among HIV-infected children vaccinated with BCG.

CONCLUSION: Data on the risk of BCG vaccination in HIV-infected children are limited. Targeted surveillance for BCG complications employing sophisticated diagnostic techniques is required to inform vaccination policy.

KEY WORDS: BCG; HIV; disseminated; review

FOR MORE THAN 30 YEARS, bacille Calmette-Guérin (BCG) vaccinations have been administered to newborns in settings where tuberculosis (TB) is endemic.[1] BCG is the only vaccine currently available for TB, and it is efficacious, cost-effective and requires only one encounter with the infant.[2,3] It is also considered safe in healthy infants.[1] Vaccine site ulceration and scar formation are common and accepted to be a normal response to vaccination.[4] Loco-regional adverse reactions such as large ulcers (>10 mm diameter) and regional adenitis are usually self-limiting and occur in 100–400 per million vaccinations, with the risk varying with vaccine strain, dose, bacillary load, route of administration and population characteristics.[1,4,5] Disseminated BCG disease from the live attenuated vaccine is a rare but potentially fatal complication, reported in less than 5 per million vaccinations, almost exclusively in immunocompromised hosts.[6] Previously, those considered at risk were children with rare congenital immunodeficiency, but there has been growing concern that human immunodeficiency virus (HIV) infection would increase the risk of disseminated BCG disease.[7] As countries now experiencing the greatest burden of TB also have high rates of HIV infection,[8] the safety of BCG vaccination programmes in high-prevalence HIV countries is being reconsidered.

The World Health Organization (WHO) first addressed the safety of BCG in HIV-infected children in 1987, and recommended until recently that asymptomatic (presumed immunocompetent) HIV-infected children should receive the vaccine.[6,9,10] In 2007, the WHO revised this policy to recommend that HIV-infected infants should not receive BCG even if asymptomatic.[11] This major policy reversal was prompted by data from South Africa and Argentina that suggested that the risk of disseminated BCG disease was markedly increased in children with asymptomatic HIV infection at the time of vaccination.[12,13] However, the risks associated with BCG vaccine in HIV-infected

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children have not been established, and disparate findings have been published for many other at-risk populations.[14–16]

The implementation of the current WHO policy has important public health implications and major programmatic challenges, especially in resource-poor communities that are endemic for TB-HIV. These challenges are recognised by the WHO and have recently been outlined by the BCG Working Group of the International Union Against Tuberculosis and Lung Disease (The Union).[11,17] It is difficult to identify asymptomatic HIV-infected infants for selective withholding of BCG vaccination from the much larger group of HIV-exposed but non-infected infants for whom BCG is still indicated. Indeed, this is often impossible in the context of Expanded Programme on Immunization (EPI) activities in resource-limited settings, where the greatest burden of mother-to-child transmission of HIV and TB exist. Delaying BCG vaccination until HIV infection status is known, however, increases the risk of severe disease due to *Mycobacterium tuberculosis* for the HIV-exposed but non-infected infant, and possibly for the HIV-infected infant as well. Prospective data on the protective efficacy of BCG against TB are lacking in HIV-infected infants but will be critical to informing policy, including in settings where early antiretroviral treatment (ART) is available.

In the present review, we describe the characteristics of all reported cases of disseminated BCG disease in HIV-infected children, and evaluate if it is possible to arrive at a valid estimate of the risk of BCG disease in HIV-infected infants.

METHODS

Search strategy

PubMed, MEDLINE and publications on the WHO website were searched for articles published between 1950 and April 2009 in English. EMBase (1980–April 2009) and The Cochrane Library were also subsequently searched using the same strategy. Broad search terms were used to maximise the sensitivity of the search, as BCG disease in HIV is a rare outcome: '(bacille Calmette Guerin OR BCG) AND HIV' and '(bacille Calmette Guerin OR BCG) AND disseminated'. Bibliographies of retrieved publications were also reviewed for relevant citations. Endnote X was used to manage citations and Stata 10 (Stata Corp, College Station, TX, USA) to calculate summary statistics.

Inclusion criteria

Original data published in English language were included. Case reports and series of microbiologically confirmed disseminated BCG in HIV-infected infants were identified and included to inform the clinical presentation and prognosis of disseminated BCG disease in HIV-infected children. To estimate risk, experimental and observational studies that measured both the exposure to HIV infection and BCG vaccination and the outcome of BCG disease were included. Studies were only included if the infant's HIV infection was reported to be the result of mother-to-child transmission, and BCG vaccination was given as a single dose in the newborn period. Observational studies that measured BCG vaccination status solely by scar were excluded because of the possibility of ascertainment bias (HIV-infected children are less likely to form a scar from vaccination).[18]

Given that many studies have been published from a few geographic areas, it was possible that a case of disseminated BCG disease might have been reported by more than one publication; possible duplicate data were identified by reviewing the population sampled, sampling period and contributing authors.

Exposure and outcome definitions

Infants born to mothers with HIV infection were considered HIV-exposed. Infants born to mothers without HIV infection were considered non-HIV-exposed. Confirmation of HIV status for infants aged $<$18 months required antigen-based testing such as polymerase chain reaction (PCR). Infants were considered BCG-vaccinated if they received BCG (either subcutaneous or intradermal) in the newborn period, confirmed by scar or vaccination record.

We aimed to standardise the definition of BCG disease using the Revised Paediatric Classification for BCG disease:[19]

Local disease: an abscess $>$10 mm diameter or severe scar ulceration.

Regional disease: involvement of the ipsilateral lymph node.

Distant disease: involvement of any site beyond the ipsilateral node.

Disseminated disease: demonstration of BCG at a distant site (and/or demonstration of BCG in blood or bone marrow by culture/PCR) combined with a systemic syndrome compatible with mycobacterial disease (fever, weight loss, anaemia, death).

BCG immune reconstitution inflammatory syndrome (IRIS) was defined as BCG disease (local, regional, distant or disseminated) occurring within 3 months of commencing ART. The measure of BCG disease used by each study was classified as clinical, mycobacterial culture with biochemical speciation, or BCG-specific PCR.

Cases of TB disease were reported, as these may represent missed BCG disease without mycobacterial speciation. The rate of microbiologically confirmed severe TB (TB meningitis or disseminated TB) in BCG-vaccinated children also informs efficacy estimates.

RESULTS

A total of 1035 publications were identified using the broad search strategy in PubMed, MEDLINE and the WHO website. No further studies were identified in a subsequent search of EMBase or The Cochrane Library. All abstracts were read, and 215 full-text publications were sourced and reviewed, identifying 88 original studies or reports. Sixteen limited reviews were identified, but these were not systematic and included studies of poor quality with exposures other than HIV from vertical transmission.[9,20–34]

Microbiologically confirmed cases of disseminated BCG are shown in Table 1. Sixteen observational studies met the inclusion criteria (Figure), including 10 cohort studies (Tables 2 and 3) and six cross-sectional and surveillance studies (Table 4).[12–14,18,19,36,37,39,49–56] Studies with longitudinal follow-up demonstrated high rates of death and loss to follow-up, especially among the HIV-exposed/infected infants (see footnote to Table 3). Two publications authored by Hesseling et al. reported the same six cases of disseminated BCG: the 2006 report included loco-regional disease, while the 2007 report allowed for a population-based estimate of risk; both are included in the review.[13,19]

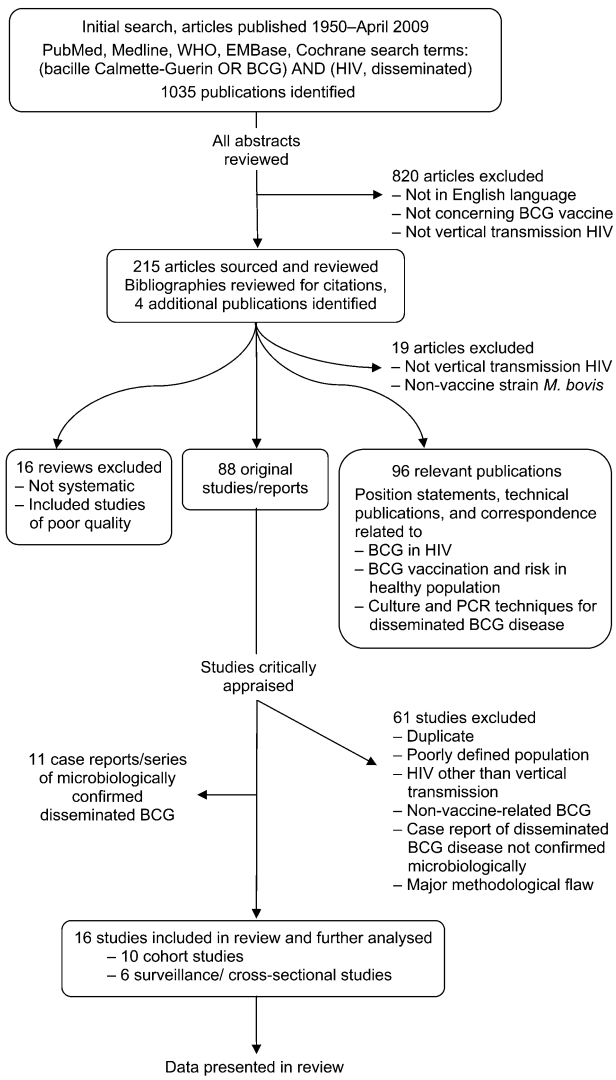

Figure Results of the search and review process. WHO = World Health Organization; BCG = bacille Calmette-Guérin; HIV = human immunodeficiency virus; PCR = polymerase chain reaction.

Clinical features of disseminated BCG disease in HIV-infected children

Sixty-nine cases of disseminated BCG disease confirmed by culture or PCR were reported in HIV-infected children; 47 in six observational studies,[12,19,36,37,39,56] 15 in four case series[35,40,42,43] and seven in single-case reports.[21,22,44–48] Clinical details are summarised in Table 1; clinical details were not available for the 32 cases reported by Hesseling et al.[56] All children received BCG in the neonatal period. The BCG strain varied depending on national policy, with the Danish strain being the most commonly reported. At least two cases of disseminated disease presented after commencing ART.[36,57] The median age at onset of BCG disease was 8 months (range 3–35) in the 22 cases in whom this was reported. Of the 36 cases with reported outcome, 29 (81%) died. Time to death from diagnosis of BCG disease was reported in 17 of the 29 deaths, and ranged from a few days to 18 months. Among the 17 deaths where time to death was reported, those receiving antimycobacterial treatment (12/17) had a mean survival of 5.9 months compared to 0.18 months for those untreated ($P = 0.05$). Seven children with disseminated BCG survived. The treatment of five survivors reported by Bologna et al. is unclear, with 'survival improving with the use of highly active antiretroviral treatment' (HAART).[42] The other two survivors received antimycobacterial treatment and ART.[19,36]

Risk of loco-regional BCG disease in HIV-infected children

Loco-regional BCG complications were observed in both HIV-infected and non-HIV-infected children. In total, the 15 observational studies (Tables 2, 3 and 4) reported 235 cases of loco-regional disease; 103 cases of loco-regional disease occurred in HIV-infected infants (61 cases of loco-regional IRIS), 45 among HIV-exposed but non-infected infants and 87 among non-HIV-exposed and non-infected infants. A pooled risk was not calculated owing to the different vaccine strains used in these studies. De Souza et al.[14] and Rabie et al.[50] both reported complications exclusively in HIV-infected children, while Chokephailbulikt et al.[49] reported complications only in HIV-exposed non-infected children. Hesseling et al. reported two children with loco-regional BCG disease who also had *M. tuberculosis* isolated from gastric aspirate (combined disease).[37] Of note, the Zairian cohort study of Ryder et al. reported a large number of local

Table 1 Presentation, treatment and outcome of HIV-infected children with disseminated BCG disease

First author, year, reference	Case label in published report *n*	BCG strain, timing	Age at presentation of BCG disease	Clinical presentation	Isolates	CD4 count %	ART	Antimycobacterial treatment	Outcome (hospital diagnosis)	Time to death
Rezai, 2008[35]	1	? Strain ? Route Within 3 days	5 months	Hepatosplenomegaly, lymphadenopathy, osteomyelitis, macular rash, fever, weight loss	? (demonstration of AFB at 2 or more sites)	Not reported	Not reported	INH, RMP, EMB, SM	Died	Not reported
Nuttall, 2008[36]	1	Danish ID First weeks	Not reported	Failure to thrive, hepatosplenomegaly, axillary adenitis	Pus from LN, x 2 gastric aspirates	Not reported	✓ (pre-BCG disease)	Antimycobacterial	Survived	
Hesseling, 2006[19]*	2	Danish ID Birth	10 months	Scar ulceration, axillary suppurative adenitis CXR perihilar opacification	FNA axillary LN, gastric aspirate	7	✓ (post-BCG disease)	I&D LN, RMP, INH, PZA, EMB, OFX	Died 18 months (sepsis and dysentery)	8 months
	4	Danish ID Birth	5 months	Scar abscess/ulceration CXR lobar consolidation	Gastric aspirate	29	×	Nil	Died (PJP)	8 days
	12	Danish ID Birth	20 months	CXR lobar opacification, mediastinal adenopathy	Gastric aspirate	12	✓ (post-BCG disease)	RMP, INH, PZA, EMB	Survived	
	13	Danish ID Birth	8 months	Scar ulceration Axillary adenitis CXR: bronchopneumonia	FNA and biopsy LN, gastric aspirate	7	×	I&D, biopsy RMP, INH, EMB	Died (CMV, neurological disease)	2 months
	15	Danish ID Birth	8 months	Scar ulceration CXR: mediastinal adenopathy	Gastric aspirate	6	×	RMP, INH, PZA, ETH	Died (gastroenteritis)	1 month
	17	Danish ID Birth	17 months	CXR: miliary opacification	Gastric aspirate	5	×	RMP, INH, PZA, ETH	Died (marasmus, ? disseminated BCG)	19 days
		Danish ID Birth	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Died	Not reported
Hesseling, 2003[37]	A	Danish ID	6 months	Axillary adenitis, hepatosplenomegaly CXR: mediastinal nodes, lobar consolidation	FNA and biopsy LN, gastric aspirate	1	×	INH, RMP, EMB, ETH, OFX, AMK	Died at 2 years	18 months
	D	Danish ID	3 months	Sepsis, hepatosplenomegaly, generalised adenopathy CXR: diffuse alveolar opacity	Gastric aspirate	18	×	Nil	Died	4 days
Fallo, 2005[12]	1[38]	? Strain ID	29 months	Osteomyelitis, splenomegaly CXR: mediastinal adenitis	Bone	1	✓ (pre-BCG disease)	INH, EMB, PZA, AMK	Died (disseminated BCG, CNS lymphoma)	2 months
	2	? Strain ID	10 months	Cervical and mediastinal adenopathy	Cervical LN	10	Not reported	INH, EMB, PZA	Initial improvement, died ('not BCG')	Not reported

Fallo, 2005[12] (*continued*)	3	? Strain ID	5 months	Suppurative adenitis Pneumonitis	Lymph node Gastric aspirate	9	Not reported	INH, EMB, PZA	Initial improvement, died ('not BCG')	Not reported
	4	? Strain ID	5 months	Suppurative adenitis Pneumonitis	Lymph node Gastric aspirate	21	Not reported	INH, EMB, PZA	Improvement then relapse, died ('not BCG')	Not reported
Waddell, 2001[39]	1	Not reported	6 months	Clinical AIDS Pneumonia	Blood	Not reported	Not reported	Not reported	Died 2 days later	2 days
Deeks, 2005[40] Sheifele, 1998[41]	2	Pasteur ID Day 3	3 months	Ulcerated BCG site Axillary adenitis Pneumonia	BCG site Axillary LN (granulomas in lung)	Not reported	×	INH, RMP, clarithromyicn	Died 5 months later (sepsis)	5 months
Bologna, 2000[42†]	1–12	Not reported	Not reported	Pulmonary involvement ($n = 9$) Hepatosplenomegaly ($n = 2$) PUO ($n = 1$)	Gastric aspirate ($n = 9$) Bone ($n = 2$) Ear swab ($n = 1$)	All >15	Some ? Timing	? Survival improved with HAART	7/12 died	Not reported
Alexander, 2007[43]		Danish ID Birth	Not reported	Severe adenitis referred to surgical unit	Gastric washing	Not reported	✓	Not reported	Not reported	
Rosenfeldt, 1997[44]		? Strain Day 5	8 months	Tachycardia Low grade fever Neurological impairment	CSF Blood Bone marrow	Not reported	Not reported	INH, RMP, ETH	Died (PJP pneumonia, no granuloma/AFB at autopsy)	2 months
Raton, 1997[45]		? Strain 1st month	8 months	Axillary adenitis Respiratory failure Skin papules	Axillary node Blood (AFB skin)	355/ml	×	Nil	Died No autopsy (culture-positive after death)	10 days
Edwards, 1996[21]		? Strain Birth	35 months	Cardiac-respiratory failure Generalised adenopathy	Blood culture	Not reported	×	Nil	Died (culture-positive after death)	Days
Campos, 1996[22]		Rio de Janeiro ID 1 month	23 months	Pneumonia Abdominal distension	Mesenteric nodes Peritoneal fluid	5%	×	INH, RMP, PZA, EMB	Died (PJP pneumonia, no AFB at autopsy)	2 months
Sirisanthana, 1995[46]		? Strain Birth	21 months	Supra-clavicular draining abscess, generalised adenopathy, right lung infiltrate with effusion	Supra-clavicular abscess	Not reported	×	INH, RMP, PZA	Improvement in adenitis Died 2 months later (respiratory illness)	2 months
Ninane, 1988[47]		? Strain Day 10	4 months	Lethargy, diarrhoea Axillary adenopathy Hepatosplenomeagly	CSF	Not reported	×	RMP, INH, EMB	Died (bacterial sepsis)	3 months
Houde, 1988[48]		? Strain Week 3	3½ months	Failure to thrive, HSM Ulcerated BCG site Pneumonia	Blood Gastric aspirate Tracheal aspirate Lung biopsy	Not reported	×	INH, RMP	Initial improvement, died at 22 months (PJP pneumonia)	18½ months

*These 6 cases are also reported in Hesseling et al., 2007[13] (full details of the seventh case were not available).
†12 cases presented.
HIV = human immunodeficiency virus; BCG = bacille Calmette-Guérin; ART = antiretroviral treatment; AFB = acid-fast bacilli; INH = isoniazid; RMP = rifampicin; EMB = ethambutol; SM = streptomycin; ID = intradermal; LN = lymph node; ✓ = yes; CXR = chest X-ray; FNA = fine-needle aspiration; I&D = incision and drainage; PZA = pyrazinamide; OFX = ofloxacin; × = no; PJP = *Pneumocystis jirovecii* pneumonia; CMV = cytomegalovirus; ETH = ethionamide; AMK = amikacin; CNS = central nervous system; AIDS = acquired immune-deficiency syndrome; PUO = pyrexia of unknown origin; HAART = highly active antiretroviral treatment; CSF = cerebrospinal fluid.

Table 2 Cohort studies of HIV-exposed infants, comparing HIV-positive with HIV-negative children

First author, year, reference	Setting	BCG strain, timing	Study sample	Study design and follow-up	Deaths/lost	BCG disease measure	BCG disease		TB (severe)	Comments
							Local	Disseminated		
De Souza, 2008[14]	Brazil	Brazilian ID Birth	207 HIVE 66 HIV+ 141 HIV−	Prospective Monthly, follow-up 2–7 years	9 deaths (all HIV+) ? lost	Culture	1* + 2 IRIS (all HIV+)	0	0	HIV+ aged 15 days–10 years at recruitment
Chokephaibulkit, 2007[49]	Bangkok, Thailand	Tokyo ID Birth	1202 HIVE 111 HIV+ 1091 HIV−	Retrospective 0, 1, 2, 4 months	4 deaths (all HIV+) 120 lost	Clinical	16 in HIV− (1 local, 15 regional)	0	0	Retrospective, short follow-up. All BCG complications in HIV− Some received ART (? number)
Thaithumyanon, 2000[18]	Bangkok, Thailand	Tokyo ID Birth	223 HIVE 26 HIV+ 89 HIV−	Prospective 3, 6, 9, 12, 15, 18, 24 months	2 deaths 108 lost	Clinical	0	0	0	Many lost to follow-up 1 death at 4 months due to pneumonia
Studies of children receiving ART										
Rabie/CHER, 2008[50]	South Africa	Danish ID Birth	542 HIVE 292 HIV+ ARTe 125 HIV+ ARTd 125 HIV−	Prospective Median 40 weeks (IQR 25-58)	3 deaths (? lost)	Culture	2 (HIV+) 33 IRIS	0	1 (? 6 more)	Of HIV-infected children, 292 received ART early from 6–12 weeks (ARTe) and 125 delayed when CD4 < 20% (ARTd), 373 HIV+ in total received ART
Nuttal, 2008[36]	South Africa	Danish ID 1st week	352 symptomatic HIV+ on ART (no control)	Retrospective Monthly	? deaths 3 lost	PCR	20 IRIS	1 IRIS	0	1 child with local disease had fever, clinical sepsis—BCG isolated from gastric aspirate—likely disseminated disease
Puthanakit, 2006[51]	Northern Thailand	Tokyo ID Birth	153 symptomatic HIV+ on ART	Prospective Monthly to 11 months	5 deaths ? lost	PCR	2 IRIS	0	0	2 further cases in children who had boosters

*Local BCG disease aggressively treated with ART and antimycobacterial drugs.
HIV = human immunodeficiency virus; HIVE = HIV exposed; HIV+ = HIV-positive; HIV− = HIV-negative; BCG = bacille Calmette-Guérin; TB = tuberculosis; ID = intradermal; IRIS = immune reconstitution inflammatory syndrome; ART = anti-retroviral treatment; CHER = Children with HIV Early AntiRetroviral Therapy; IQR = interquartile range; PCR = polymerase chain reaction.

Table 3 Cohort studies comparing HIV-exposed with non-HIV-exposed children

First author, year, reference	Setting	BCG strain, timing	Study sample	Study design and follow-up	Deaths/lost*	BCG disease measure	BCG disease		TB (severe)	Comments
							Local	Disseminated		
Ryder, 1993[52]	Zaire	Pasteur ? SC Day 2	474 HIVE 616 HIVNE	Prospective Monthly until 12 months	116 died (88 HIVE), 284 lost (136 HIVE)	Clinical	69 (30 HIVE)	0	0	In 38 HIVE children who died, 15 had BCG fistulas- ? missed disseminated BCG
Msellati, 1991[53]	Rwanda	? Strain ? Route Birth	209 HIVE 213 HIVNE	Prospective Twice a month for 15 months	14 died (all HIVE), 33 lost (26 HIVE) 6 excluded (all HIVNE)	Clinical	1 (HIV+)	0	0	6 HIVNE infants who tested HIV+ excluded- ? problem with assay
Lallemant-Le Couer, 1991[54]	Congo	Pasteur ID Birth	64 HIVE 130 HIVNE	Prospective 3rd monthly until 36 months	21 died (18 HIVE) 2 lost (1 HIVE)	Clinical	34 (11 HIVE)	0	0	18 HIVE died, 5 from pneumonia ? missed disseminated BCG/TB
Hira, 1989[55]	Zambia	? Strain ? Route Birth	109 HIVE 40 HIVNE	Prospective 6 monthly for 24 months	23 died (all HIVE) 96 lost (all HIVE)	Clinical	7 (4 HIVE)	0	? 4 (all HIVE)	Cases of TB not confirmed by culture ? missed BCG

*Pooled risk of death (HIVE vs. HIVNE; RR 4.8, 95%CI 3.3–7.1, $P < 0.001$); pooled risk of being lost to follow-up (RR 1.7, 95%CI 1.5–2.1, $P < 0.001$); pooled risk of being lost to follow-up of dying (RR 2.3, 95%CI 1.9–2.6, $P < 0.001$).
HIV = human immunodeficiency virus; HIVE = HIV-exposed; HIVNE = non-HIV-exposed; BCG = bacille Calmette-Guérin; TB = tuberculosis; SC = subcutaneous; HIV+ = HIV-positive; ID = intradermal; RR = relative risk; CI = confidence interval.

Table 4 Surveillance and cross-sectional studies measuring risk of BCG in HIV-exposed and HIV-positive children

First author, year, reference	Setting	BCG strain, timing	Study population	Study sample	Study sampling	BCG disease measure	BCG disease		TB (severe)	Comments
							Local	Disseminated		
Hesseling, 2009[56]	South Africa	Danish ID Birth	Estimated population of HIV-infected children vaccinated with BCG	3226 estimated	Prospective January 2004–December 2006	PCR	NA	32	NA	Active surveillance for disseminated BCG in 3 hospitals servicing Western Cape Province Denominator data (HIV+ vaccinated with BCG) estimated using measured vertical transmission rate
Hesseling, 2007[13]	South Africa	Danish ID Birth	Estimated population of HIV-infected children vaccinated with BCG	3798 estimated*	Prospective January 2002–December 2004	PCR	NA	9 (7 HIV+)	NA	Similar to 2009 study, however based mainly at Tygerberg hospital Denominator data estimated using estimated vertical transmission rates
Hesseling, 2006[19]	South Africa	Danish ID Birth	Children with *M. tuberculosis* isolates on culture	466, 108 HIV+	Retrospective August 2002–January 2005	PCR	17 (11 HIV+)	8 (6 HIV+)	NA	Local cases include 4 cases of local IRIS Disseminated cases overlap with the 7 cases presented in the 2007 study
Fallo, 2005[12]	Argentina	? Strain ID ? Timing	HIV-infected infants vaccinated with BCG	310	Retrospective 1992–2004	Culture	28	4	10	In total, 44 cases of TB were reported, of which up to 10 may have been disseminated TB or TB meningitis (this data is a subset of a larger study which included children not vaccinated). Not all cases of TB were confirmed by culture or PCR
Hesseling, 2003[37]	South Africa	Danish ID Birth	HIV+ children with *M. tuberculosis* isolates	49	Retrospective January 1992–August 2002	PCR	3 (all HIV+)	2 (all HIV+)	NA	Only those with available samples included. ? bias. Unclear if all BCG vaccinated
Waddell, 2001[39]	Zambia	? Strain ? Route ? Timing	Children (and adults) admitted with clinical AIDS	736 children (488 HIV confirmed)	Prospective 1996–1998	PCR	NA	1	6	Small volume of blood used in culture (1.5 ml) and transported to US—may have affected sensitivity

*Corresponds to 10% vertical transmission.
BCG = bacille Calmette-Guérin; HIV = human immunodeficiency virus; HIVE = HIV-exposed; HIV+ = HIV-positive; TB = tuberculosis; ID = intradermal; PCR = polymerase chain reaction; NA = not available; AIDS = acquired immune-deficiency syndrome.

complications, with an overall rate of 6%.[52] Twenty-five cases of regional adenitis (12/474 HIV-exposed infants, 13/616 non-HIV-exposed, relative risk [RR] 1.2, 95% confidence interval (CI) 0.6–2.6) and 44 cases of fistulisation (18 in HIV-exposed infants, RR 0.9, 95%CI 0.5–1.6) were reported, with no statistical difference by HIV exposure status. Data are limited on outcome for loco-regional BCG disease in HIV-infected children. Hesseling et al. reported 11 cases of loco-regional BCG complications, of which six died.[19] They reported that ART for infants with local and disseminated disease was associated with significantly improved survival.

Risk of disseminated BCG disease in HIV-infected children

A total of 49 cases of disseminated BCG were reported in the observational studies (Tables 2, 3 and 4), 47 in HIV-infected infants and two cases in children with other immunodeficiencies. Table 5 summarises the risk of disseminated BCG for various exposure groups.

Of the 47 cases of disseminated BCG disease in HIV-infected children reported in observational studies, 41 (87%) were reported by Hesseling et al. from the Western Cape Province of South Africa. In their earliest study, they speciated 183 mycobacterial isolates from 49 HIV-infected children using PCR.[37] *M. bovis* BCG was identified in five children, with three having loco-regional disease and two disseminated disease. The 2006 study similarly involved laboratory surveillance, enrolling 466 children with mycobacterial isolates, of which 108 were HIV-infected.[19] Eight children were identified to have disseminated disease (six HIV-infected, two with other immunodeficiencies). The 2007 prospective study included data

Table 5 Rates of disseminated BCG in studies with well-defined denominator populations and microbiologically confirmed BCG disease

First author, year, reference	Setting	Denominator: Population	Denominator: *n*	Cases *n*	Rate (95%CI) per 100 000*
ART-naïve HIV-infected children					
Hesseling, 2009[56]	South Africa	Estimated number of HIV+ children vaccinated with Danish BCG (using measured vertical transmission rates)	3226	32	992 (567–1495)
Hesseling, 2007[13]	South Africa	Estimated number of HIV+ children vaccinated with Danish BCG, assuming:			
		5% vertical transmission	1898	7	369 (148–758)
		10% vertical transmission	3798	7	184 (74–379)
		15% vertical transmission	5696	7	122 (49–253)
De Souza, 2008[14]	Brazil	Infants with vertically acquired HIV infection immunised with Rio de Janerio BCG	66	0	0 (0–5435)
Fallo, 2005[38]	Argentina	Infants with vertically acquired HIV infection immunised with BCG	310	4	1290 (352–3270)
HIV+ receiving ART					
Rabie, 2008[50]	South Africa	HIV-infected infants commenced on ART early (asymptomatic) or delayed (symptomatic)	417	0	0 (0–881)
Nuttal, 2008[36]	South Africa	Symptomatic HIV-infected infants commenced on ART	352	1	284 (7–1573)
Puthanakit, 2006[51]	Northern Thailand	Symptomatic HIV-infected children admitted to hospital commenced on ART	153	0	0 (0–2382)
Special clinical situations					
Waddell, 2001[39]	Zambia	Children admitted with clinical AIDS, confirmed HIV+	488	1	0.2% (0–1%)
Hesseling, 2006[19]	South Africa	Children investigated for mycobacterial disease with mycobacterial isolates			
		All children	466	8	1.7% (1–3%)
		HIV+ children	108	6	5.5% (2–12%)
Hesseling, 2003[37]	South Africa	HIV+ children with mycobacterial isolates	49	2	4% (0.5–14%)

*95% binomial proportion CIs are reported, with one-sided estimates (97.5%CI) reported if numerator was 0.
BCG = bacille Calmette-Guérin; CI = confidence interval; ART = antiretroviral treatment; HIV = human immunodeficiency virus; HIV+ = HIV-positive; AIDS = acquired immune-deficiency syndrome.

from the 2006 study (laboratory surveillance), and also employed clinical surveillance, reporting a further case of disseminated disease.[13] The denominator (HIV-infected children immunised with BCG) was estimated using population data. Rates of HIV infection among children were estimated using data on maternal HIV status and estimated HIV vertical transmission rates (5–15%); the BCG vaccine coverage rate was assumed to be 95%. The estimated risk of disseminated BCG was calculated for each year of observation, and ranged from 110–417 per 100 000 HIV-infected children vaccinated with BCG. Pooled data for the 3 years of observation and calculated confidence intervals are shown in Table 5. A recent study by the same authors expanded the surveillance for disseminated BCG to three hospitals servicing the Western Cape Province, and included measured (rather than estimated) vertical transmission rates to estimate the denominator.[56] BCG vaccine coverage was based on census and health survey data and taken to be 98–99%. In total, 32 cases of disseminated BCG were reported, with a pooled risk of 992 per 100 000 (95% CI 567–1495).

The Argentinean study of Fallo et al. reported four cases of disseminated BCG amongst 310 HIV-infected, BCG-vaccinated children (Table 4, clinical details in Table 1).[12] Details of recruitment, duration of observation and numbers of lost to follow-up or deaths were not available for this retrospective study. These data are a subset of a larger study which included 64 non-BCG-vaccinated HIV-infected children; however, measure of BCG vaccination status was unclear. Fifty-one cases of TB (44 in those considered vaccinated) were reported, including 10 cases of disseminated TB or TB meningitis, with no difference in the rate between those considered vaccinated or not.[58] TB was diagnosed clinically in most cases, and confirmed by culture or PCR in 19 (37%) children.

In a Zambian study, Waddell et al. collected mycobacterial blood cultures from 736 children with clinical AIDS.[39] Mycobacteraemia was measured by culture and speciation using PCR. Of the 736 children with clinical acquired immune-deficiency syndrome (AIDS), 488 (66%) were confirmed to be HIV-infected and 387 of these had evaluable blood cultures and clinical histories (cultures were not evaluable in 101 HIV-infected children, as they were blood culture-positive for other bacteria or fungi). Ninety-eight per cent (378/387) were BCG-vaccinated (68 had been immunised by record but did not have a scar). Six HIV-infected children had positive blood cultures for mycobacteria, with one of these speciated to *M. bovis* BCG.

BCG disease in HIV-infected children receiving ART

Three cohort studies reported BCG complications in children receiving ART.[36,50,51] The 'Children with HIV Early anti-Retroviral' (CHER) study recruited 415 BCG-vaccinated (Danish ID) HIV-infected infants, allocating 292 to receive ART 'early' from week 6 to week 12 (regardless of CD4 count), and 125 to receive ART 'deferred' when CD4 $< 20\%$.[50] In total, 373 received ART, with 33 children developing regional adenitis (rate 9%, incidence 11.2 per 100 person-years). The risk of regional adenitis was much higher in those in the deferred arm (13/83, 16%) compared to the early treatment arm (13/250, 5%, odds ratio [ORs] 3.4, 95%CI 1.5–7.7, $P = 0.004$). Two children not receiving ART developed regional adenitis, with dissemination suspected but not proven in these children. In this study, BCG disease was measured clinically and was not microbiologically confirmed. Three children died (BCG disease possibly contributing to two deaths) and seven children had clinical pulmonary TB (one case of TB was confirmed by culture). Nuttal et al. reported 20 cases of regional adenitis and one case of disseminated disease among 352 BCG-vaccinated (Danish strain intradermal) children with symptomatic HIV-infected receiving ART (rate 6%, 95%CI 3.7–8.0).[36] Of 21 children with clinical BCG disease, 10 had microbiological assessment, with seven of these confirmed *M. bovis* BCG (including the child with disseminated disease). A Thai study reported two cases of loco-regional BCG disease among 153 children receiving ART (two further cases were reported among children who received booster vaccination).[51,59] These cases of BCG disease were confirmed by PCR (isolated from regional node in one child and vaccine site ulcer in another child with associated regional adenitis).

Few data were available on the management and outcome of BCG complications in HIV-infected children receiving ART. Of the 21 cases of BCG disease reported by Nuttal (20 local, one disseminated), 10 received antimycobacterial treatment, 15 had incision and drainage (some had both medical and surgical treatment), with eight managed conservatively.

DISCUSSION

The recommendation to withhold vaccination from HIV-infected children is based on concerns about disseminated BCG disease. In 2007, an estimated 420 000 children became HIV-infected, most living in sub-Saharan Africa and acquiring infection vertically.[57] If HIV-infected infants continue to receive BCG vaccine and the risk of disseminated disease is 417 per 100 000 vaccinations, about 1700 would develop disseminated BCG globally every year.[15] If the risk of disseminated BCG in HIV-infected infants is 992/100 000, then 4000 would develop disseminated BCG disease annually. Our review found only 69 confirmed cases of disseminated BCG disease in HIV-infected children reported in the literature. BCG disease is likely to be under-reported in resource-limited settings. Clinical suspicion is low, as it is traditionally considered a

rare complication, with the clinical presentation of disseminated BCG disease similar to that of disseminated TB or severe sepsis. Studies demonstrating cases of disseminated BCG disease used either culture with biochemical speciation or PCR. Studies reporting no cases of disseminated disease had significant limitations: poor measures of exposure and outcome, short periods of observation, and high (or unknown) rates of death and loss to follow-up.

The South African surveillance studies reported by Hesseling et al. have refocused attention on BCG vaccine policy, identifying a serious complication that has remained largely hidden among children with clinical TB or those who have died. The accuracy of estimated risk reported by these surveillance studies may be limited by study design. In the earlier study, several assumptions were made to estimate the number of HIV-infected children vaccinated (and at risk of complications), including vaccine coverage and vertical transmission rate.[13] The more recent study used measured population rates of vertical transmission and vaccination and included a larger population base.[56] Both studies were conducted in the same region, but the estimates of risk obtained were significantly different. These studies also employed PCR testing to identify BCG disease. While likely to be very sensitive, it may also be that the demonstration of BCG at distant sites in the severely immunosuppressed child with AIDS (likely to have a systemic syndrome of fever, anaemia, weight loss and death) does not necessarily represent disseminated BCG disease; a transient 'BCGaemia' may be part of the normal vaccination process.[59] The risk of disseminated BCG calculated from the Argentinean study is similar to Hesseling et al.'s recent estimate.[12,56] The Argentinean study was retrospective, and details of recruitment, measure of BCG vaccination status and number lost to follow-up were unclear for this cohort study. The study also reported a large number of cases of TB that were microbiologically confirmed and may have included missed cases of BCG disease.

Based on Hesseling et al.'s recent estimate, at least 100 HIV-infected infants would have to be followed to observe one case of disseminated BCG. The small sample (66 HIV-infected children) may explain why De Souza et al. reported no cases of disseminated BCG in the recent Brazilian study.[14] HIV-infected children were aged 15 days to 10 years at recruitment, which may have introduced bias, and local disease was aggressively treated with HAART and antimycobacterial treatment, which may have halted progression to disseminated BCG disease. Nine children died, and these may have included missed cases of disseminated disease. Among the causes of death attributed, one child died with gastroenteritis and clinical sepsis, one with pneumonia (unclear pathogen) and a further two of unclear aetiology. The strain of BCG used in Brazil is Moreau Rio de Janeiro, which may carry a different risk of disseminated disease than the Danish strain used in South Africa. There may also be population differences in disease susceptibility. Children from the Western Cape region of South Africa, for example, including those with HIV infection, may be more susceptible to mycobacterial disease than populations in Brazil or elsewhere. This region reported very high childhood TB incidence, even before the HIV epidemic.[60] Large cohort studies from other African populations in Zimbabwe, Malawi and Rwanda have not reported any cases of disseminated BCG disease amongst HIV-infected children who died.[61–63] While these studies were not specifically designed to measure complications of BCG, they had large sample sizes (559 deaths among 1147 HIV-infected infants were observed in the Zimbabwe Vitamin A for Mothers and Babies Project [the ZVITAMBO cohort])[64] and were conducted in settings highly endemic for TB-HIV, with high rates of BCG coverage. Differing results and contextual factors have important implications for generalising the findings of Hesseling et al.'s study and informing vaccination policy on a global scale.

Disseminated BCG is a catastrophic complication of vaccinating HIV-infected infants with a high case fatality rate. However, the cause of death in these children may not always be attributable to disseminated BCG disease. Several case reports describe children with disseminated BCG disease who received antimycobacterial treatment and died several months later with *Pneumocystis jirovecii* pneumonia (PJP) or sepsis.[22,44,46–48] In healthy children, BCG vaccination suppresses T-cell counts for up to 2 months.[61,65] This reduction in T-cell count may cause rapid progression of immunosuppression in HIV-infected infants receiving BCG, increasing the risk of opportunistic infection and mortality. Disseminated BCG disease is part of a continuum of BCG-related complications. While loco-regional disease in immunocompetent children is usually self-limiting, 6 of the 11 cases of loco-regional disease reported by Hesseling et al. died.[19] Loco-regional disease in HIV-infected children may represent disseminated disease, or be associated with overwhelming immunodeficiency and associated poor prognosis. Few studies report the outcome of loco-regional BCG disease in HIV-infected children.

Risk of death from BCG disease appears to be modified by antimycobacterial treatment and ART. This has important implications, as the WHO now recommends that all HIV-infected infants aged <12 months, irrespective of clinical or immunological status, should receive ART.[62,63] On the one hand, ART introduces the risk of IRIS (although the risk of IRIS is reduced with early ART).[50] On the other hand, preservation of immune function in children receiving ART may modify the immune response to vaccinations and may reduce the risk of disseminated BCG. The early use of HAART will probably change not only the profile of

disseminated BCG disease risk in HIV-infected infants, but also the risk of TB and, possibly, BCG efficacy.[66]

Measuring the efficacy of BCG in HIV-infected children is complex and beyond the scope of this review. These studies were not designed to measure the efficacy of BCG in HIV-infected children, although some observations can be made. BCG is most protective of TB meningitis and disseminated TB, both of which have recognisable clinical presentation.[3] Few cases of severe TB were reported in the longitudinal cohort studies, suggesting that BCG may still afford some protection in HIV-infected children. A recent study from South Africa found that HIV-infected infants were at increased risk for all types of TB but did not find a disproportionate increased risk of disseminated TB or TB meningitis.[67] While BCG-induced T-cell immune responses are much lower in HIV-infected compared to HIV-exposed non-infected and non-HIV-exposed infants in the absence of HAART, the correlation with in vivo immunity remains unclear.[68] Measured response to BCG varies between populations and between seasons.[69] Vitamin D status also affects in vitro response to BCG, and vitamin D deficiency may contribute to susceptibility to TB and BCG disease among children living in the Western Cape.[70] The WHO has now directed that recording and reporting of childhood TB cases should be routine and should include HIV status whenever possible.[71] This may provide an opportunity to examine the incidence of TB meningitis or miliary TB over time as a possible surrogate for BCG efficacy in different settings of BCG coverage and HIV prevalence.

The present review has several important limitations. Only studies published in English were included. Inclusion criteria were strict and only cases of disseminated BCG confirmed microbiologically were included. While this ensured specificity, sensitivity may have suffered. The definitions of HIV and BCG exposure were also strict to reflect current vaccination policy, and they allow for an estimate of risk that relates to vaccination of infants in areas endemic for TB and HIV. A French study in which some children acquired HIV infection from blood transfusion was excluded.[72] A Haitian cohort study was excluded as it reported children who received an inconsistent dose of BCG due to error.[20] An Argentinean study including children who received two doses of BCG was also excluded.[73] Duplicate data may have also introduced error, especially as a large number of cases of disseminated BCG was reported from the Western Cape Province. A surgical case series that reported two cases of disseminated BCG was excluded as it was based at the same hospital and had the same sampling period as Hesseling et al.'s 2007 report.[74]

The review could also not fully take into account the different vaccine strain, bacillary load and route of administration which, in combination with population differences and other therapies (such as ART), modify the risk of complications. It does, however, highlight issues for consideration in surveillance for BCG complications. Disseminated BCG has an onset between 3 and 36 months after vaccination. This has important implications for study design and clinical follow-up in settings where attendance usually drops after vaccinations are completed at 9 months. Clinical surveillance alone is unlikely to be sensitive or specific for disseminated BCG. The work of Hesseling et al. supports that active laboratory-based surveillance with appropriate speciation is essential to detect disseminated BCG disease. While widespread use of laboratory surveillance is unlikely to be cost-effective, targeted surveillance of 'at risk' groups may be. In the ZVITAMBO cohort, 63% of HIV-infected children died before their second birthday compared to 9% of HIV-exposed non-infected infants and 3% of non-exposed infants.[64] Eighty per cent of these deaths occurred in the first 6 months of life, making the accurate ascertainment of the cause of these deaths difficult.

HIV-infected infants are at risk of BCG disease, but the degree of increased risk remains uncertain. Improved laboratory-based surveillance and more incidence data of confirmed cases are urgently needed. Improved population-based studies in areas outside sub-Saharan Africa are also required to inform vaccination policy. BCG disease is associated with a high mortality in HIV-infected children, and early ART has a potential role in management and prevention. Most infants with HIV infection will continue to be vaccinated with BCG in the neonatal period, despite the current WHO recommendations. Early HIV diagnosis would facilitate implementation of the current WHO recommendations of withholding BCG from HIV-infected infants, but wider implementation of other, more readily available, recommendations, such as prevention of mother-to-child transmission of HIV, would also have a significant impact on the burden of BCG disease. Improved knowledge of the potential efficacy of BCG for HIV-infected and HIV-exposed infants in TB-endemic communities is critical to the risk-benefit analysis needed to inform policy.

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RÉSUMÉ

OBJECTIF : Décrire les caractéristiques et les risques des maladies liées au vaccin bacille Calmette-Guérin (BCG) chez les nourrissons infectés par le virus de l'immunodéficience humaine (VIH).

MÉTHODES : Revue systématique des articles publiés dans la littérature entre 1950 et avril 2009 en langue anglaise. Nous avons identifié tous les cas de bécégite disséminée confirmés par examen microbiologique signalés dans la littérature chez les enfants ayant subi une infection verticale par le VIH.

RÉSULTATS : On a pu inclure 16 études observationnelles et 11 rapports de cas ou de séries. Les études observationnelles souffrent de taux élevés de pertes de suivi et de décès. La bécégite locorégionale a été signalée à la fois chez les enfants infectés ou non par le VIH. La bécégite disséminée n'a été signalée que chez les enfants atteints d'immunodéficience et uniquement dans les études utilisant des techniques sophistiquées de laboratoire. On a pu identifier dans la littérature 69 cas de bécégite disséminée ; 47 cas ont été signalés dans six études

observationnelles, la majorité (41/47) provenant du Cap de l'Ouest en Afrique du Sud. Une étude brésilienne de cohorte n'a pas signalé de cas de bécégite disséminée chez les 66 enfants infectés par le VIH et suivis pendant une période de 7 ans. Une étude de surveillance récente en Afrique du Sud a signalé 32 cas de bécégite disséminée sur une période de 3 ans et estime le risque de bécégite disséminée à 992 pour 100 000 vaccinations d'enfants infectés par le VIH. Un petit nombre de cas de tuberculose grave disséminée ont été signalés dans les études de cohorte parmi les enfants infectés par le VIH et vaccinés par le BCG.

CONCLUSION : Les données concernant les risques de la vaccination par le BCG chez les enfants infectés par le VIH sont limitées. Une surveillance ciblée des complications du BCG utilisant des techniques sophistiquées de diagnostic est nécessaire pour orienter la politique de vaccination.

RESUMEN

OBJETIVO : Describir las características la enfermedad causada por la vacuna BCG en lactantes infectados por el virus de la inmunodeficiencia humana (VIH) y calcular su riesgo de padecerla.

MÉTODOS : Se llevó a cabo un análisis sistemático de los artículos científicos publicados en inglés entre 1950 y abril del 2009. Se detectaron todos los casos publicados de enfermedad diseminada causada por la BCG, confirmada bacteriológicamente, en niños con infección por el VIH adquirida por transmisión materno-fetal.

RESULTADOS : Se incluyeron 16 estudios de observación y 11 informes o series de casos. En los estudios de observación se encontró un alto índice de casos perdidos durante el seguimiento y de defunciones. Se observaron informes de enfermedad locorregional causada por la BCG en niños con infección por el VIH y en niños que no padecían esta infección. La becegeítis generalizada solo se comunicó en niños con inmunodeficiencia y exclusivamente en estudios donde se utilizaban técnicas sofisticadas de laboratorio. En las publicaciones se comunicaron 69 casos de enfermedad diseminada, 47 notificados en seis estudios de observación, la mayoría (41 de 47) provenientes del Cabo Occidental de Sudáfrica. En un estudio de cohortes de 66 niños infectados por el VIH en el Brasil no se informó ningún caso de becegeítis generalizada durante un período de observación de 7 años. En un reciente estudio de vigilancia en Sudáfrica, se notificaron 32 casos de becegeítis diseminada en un lapso de 3 años y se calculó que el riesgo de padecer la enfermedad era de 992 por 100 000 vacunaciones de niños infectados por el VIH. Se comunicaron pocos casos de tuberculosis diseminada en los estudios de cohortes de niños con infección por el VIH que recibieron la vacuna antituberculosa.

CONCLUSIÓN : Existen pocos datos sobre el riesgo de la vacuna antituberculosa en niños infectados por el VIH. Se precisa instaurar una vigilancia dirigida de las complicaciones de la BCG, con técnicas diagnósticas sofisticadas, a fin de fundamentar las políticas sobre vacunación.