Safety of the intradermal Copenhagen 1331 BCG vaccine in neonates in Durban, South Africa

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Objective To evaluate the safety of the intradermal Copenhagen BCG vaccine in neonates at different levels of delivery and neonatal units of the Durban Functional Region and surrounding regions.
Methods A prospective study was carried out over a two-year period between July 1997 and June 1999. All neonates who had been vaccinated with the intradermal vaccine were evaluated at immunization clinics six weeks after immunization, or earlier if adverse effects occurred.
Findings In total, 9763 neonates were examined: in 95.4% the vaccination scar had healed and 1.5% had no visible scar. Adverse events occurred in 3.1%. The proportion of neonates with no visible vaccination scars decreased over the study period, as did the number with adverse events. The lowest rate of adverse events and the highest rates of healed vaccination scars were seen in the tertiary hospital and regional and district hospitals that were in close proximity to the academic centre involved in this study.
Conclusions In the study sites, the transition from the percutaneous to intradermal route of administration of BCG vaccine was successful and took place without incurring unacceptably high rates of adverse events. To minimize adverse events, however, it is essential to continue training health personnel involved in implementing intradermal BCG vaccination programmes.

Keywords: Tuberculosis, Pulmonary/prevention and control; BCG vaccine/administration and dosage/adverse effects; Injections, Intradermal/adverse effects; Infant, Newborn; Prospective studies; South Africa (*source: MeSH*).

Mots clés: Tuberculose pulmonaire/prévention et contrôle; Vaccin BCG/administration et posologie/effets indésirables; Injection intradermique/effets indésirables; Nouveau-né; Etude prospective; Afrique du Sud (*source: INSERM*).

Palabras clave: Tuberculosis pulmonar/prevención y control; Vacuna BCG/administración y dosificación/efectos adversos; Inyecciones intradérmicas/efectos adversos; Recién nacido; Estudios prospectivos; Sudáfrica (*fuente: BIREME*).

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Introduction

Tuberculosis (TB) is one of the most important public health issues worldwide. It is thought that in the 1990s there were 90 million new cases of TB infection, one-sixth of whom were children (*1*), and that 5 million of these infected children died from the disease (*2*). South Africa currently has some of the highest TB incidence rates in the world, with 67 000 new pulmonary TB cases and 2500 TB-related deaths reported annually (*3*). The nationwide incidence of pulmonary TB is 310 cases per 100 000 people, with KwaZulu Natal having an even higher incidence of 413 cases per 100 000 people (*4*).

TB control

Four major approaches to TB control have been advocated globally: improving socioeconomic conditions; identifying and treating infectious cases; chemoprophylaxis of exposed individuals; and BCG (Bacillus Calmette–Guérin) vaccination. However, the role of the BCG vaccine in controlling the TB pandemic remains controversial. A meta-analysis of large numbers of BCG vaccine efficacy trials revealed a protection rate against pulmonary TB of only 86% in randomized controlled trials and of 75% in case-controlled studies, despite extensive use of the vaccine (*5*). Colditz et al. found an overall protective efficacy of 50% for the prevention of pulmonary TB (*6*). There are many reasons for this variable efficacy, including vaccine quality; vaccine strain; host genetics and

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nutrition; exposure of the vaccine to ultraviolet light; latitude where the study was conducted; prevalence of other environmental mycobacteria; infection incidence; and the study design. A 15-year follow-up trial of BCG-vaccine recipients in South India showed no protection against TB in adults and a low level of protection (27%) in children (*7*). Despite this variation, major trials worldwide — including another recent Indian study — have demonstrated the efficacy of BCG vaccine against disseminated TB, especially tuberculous meningitis and miliary TB (*8*). However, South Africa has reported high rates of tuberculous meningitis over the last two decades, particularly in the Western Cape, a region with high BCG vaccination coverage of more than 90% of the population (*9*).

BCG vaccination policies in South Africa

Policies relating to BCG vaccination have not changed in South Africa since 1973, when this vaccination became compulsory by law (*10*). Since then, the multiple-puncture, percutaneous method of administration by the "Japanese tool" was adopted, using the 172 Tokyo strain of BCG (TBCG). This tool consists of a hollow plastic cylinder with nine stainless-steel needles implanted at one end, and a rectangular flange around the cylinder and needle end. The flange is used to spread the vaccine and control the depth of penetration of the needles. Due to the cost of the tool, it is often reused, although it is intended to be disposable.

The decision to adopt the percutaneous method and the TBCG vaccine was based on two studies of post-vaccination Mantoux tests, the ease of administration to infants, and lower rates of adverse events than with the intradermal method (*11, 12*). The decision to use a percutaneous route was at variance with the recommendations of WHO and UNICEF, which advocate an intradermal route. In 1982, Glatthar & Kleeberg evaluated the Japanese tool for BCG vaccinations and found it deficient in many respects, such as the difficulty of sterilizing the tool (*13*). Despite these findings, the tool continues to be a component of TB control programmes.

WHO and UNICEF recommendations

The recommendation of WHO and UNICEF to use the intradermal route was based on several studies showing better efficacy than the percutaneous route, and many countries have adopted this policy (*14*). A recent collaboration between the Statens Serum Institute, Denmark, and the Lithuanian Department of Health found enhanced levels of tuberculin reactivity and scar formation, and very few side-effects with intradermal dosing of Copenhagen strain 1331 BCG vaccine (CBCG) (*15*). Other studies, comparing the percutaneous TBCG and intradermal TBCG vaccination, found more adverse events with the intradermal vaccine (*16, 17*). Following use of intradermal vaccines, however, several countries have seen a decline in the number of tuberculous meningitis cases. In Harare, Zimbabwe, for example, analysis of 300 consecutive cases of bacterial meningitis found no tuberculous meningitis (*18*); and in São Paulo, Brazil, a case-controlled study indicated a protective efficacy of greater than 80% against tuberculous meningitis in matched neighbourhood and hospital controls (*19*). A few neonatal studies have found that administering the vaccine intradermally provided 100% protection against miliary TB (*20, 21*). We therefore undertook a study to evaluate the safety of the CBCG vaccine using the intradermal route of administration.

Methods

Prospective study

A two-year prospective study was conducted between July 1997 and June 1999, in the delivery and neonatal units of the Durban Functional Region (DFR) and surrounding regions (see Table 1). The centres were chosen because they represent different tiers of the health care system. A total of approximately 40 000 deliveries take place annually in all these centres.

As the routinely used TBCG vaccine was not available at the concentration needed for intradermal injection, the CBCG vaccine was chosen instead. Beginning in September 1996, the new CBCG vaccine was introduced in four sectors in the DFR at six-week intervals using a stepped, sequential enrolment. Simultaneously, any remaining stocks of the old TBCG vaccine were removed prior to the start of the study, to prevent adverse events (especially abscess formation) that could result from inadvertent use of the old percutaneous TBCG vaccine for intradermal vaccinations. This process was completed in February 1997, but data collection did not begin until July 1997 to ensure unbiased sampling.

Vaccination procedures. To facilitate introduction of the new vaccine, a workshop for primary care nurses and trainers, and midwives was arranged prior to the study. The workshop covered methods for storing and reconstituting the vaccine, the correct dosage, and the sites and techniques for administering the vaccine. A dose of 0.05 ml of vaccine injected into the middle of the deltoid muscle of the right arm was chosen as the most appropriate dose and site for vaccination. A short, bevelled 25–26-gauge disposable needle and a 1 ml disposable syringe were used for the injection. After cleaning and stretching the skin with the fingers, the bevel of needle was placed upwards and the needle inserted 2 mm into the skin parallel to the long axis of the arm. The contents were injected at high pressure to induce a 7 mm bleb. If the needle was accidentally inserted deep into the skin, or if there was failure to induce a bleb, the entire process was started ab initio. The nursing staff and primary care trainers were also trained to recognize adverse events. Data were entered on a simple form, which was circulated to all the participating sites. Forms were completed at each routine follow-up six weeks

after vaccination, and were sent to the academic centre (Department of Paediatrics and Child Health, University of Natal) at regular intervals.

Additional studies

To determine the risk of inducing disseminated TB by BCG vaccination, we also performed a detailed evaluation of a small subset (n = 10) of symptomatic HIV-infected neonates with adverse events and other systemic manifestations following intradermal CBCG vaccination. This study was undertaken at King Edward VIII hospital, a tertiary facility in the DFR.

We also undertook a crude analysis of the efficacy of BCG vaccines delivered by the percutaneous and intradermal routes by reviewing the incidence of tuberculous meningitis and miliary TB during the period 1995–99 at King George V hospital, a designated TB isolation facility serving the DFR.

The entire project received ethical approval from the Medicines Control Council and the University of Natal and was supported by the South African Department of Health.

Results

Prospective study

During the two-year period, we evaluated the safety of the intradermal CBCG vaccine in 9763 six-week-old neonates. As shown in Table 2, the percentage of healed vaccination scars during the last six months of the study was higher than that seen during the first six months (96.5% and 93.4%, respectively), and the percentage of adverse events decreased (2.2% and 3.8%, respectively). Overall, visible healed vaccination scars were seen in 95.4% of the neonates, while 1.5% had no visible vaccine-related scar.

Adverse events occurred in 300 (3.1%) of the neonates, and 41.0% of these presented with extranodal injection-site abscesses; 36.3% had oozing (median duration 3 days, range 1–42 days); 18.0% had lymphadenopathy (with lymph nodes greater than 1.5 cm; a third of these cases had suppuration); and 6.7% had other adverse effects, such as swelling, erythema, keloid formation, and ulcers (Table 3). Throughout the study, the prevalence of abscesses in the neonates remained constant, while that of lymphadenopathy increased.

In evaluating the results from different locations (Table 4), regional and district hospitals outside the DFR, and primary care centres in the DFR, had the lowest rates of visible, healed vaccination scars (87.1% regional and district and 89% primary care) and the highest rates of absence of vaccination scars (8.5% regional and district, and 7.6% primary care). In contrast, the tertiary hospital and regional and district hospitals in the DFR had higher rates of healed vaccination scars (96.4% tertiary, and 96.2% regional and district) and lower rates of adverse events (2.7% tertiary, and 2.8% regional and district hospitals). Private hospitals had a high adverse event rate of 4.7%. A high proportion of the neonates vaccinated at St Aidans, a private hospital, had no scar formation (6.2%).

Table 1. **Institutions selected for the two-year prospective study**

Type of institution	In or outside the Durban Functional Region	Name of institution
Academic centre	In	Department of Paediatrics and Child Health, University of Natal
Tertiary hospital	In	King Edward VIII
Regional hospitals	In	Addington
	In	RK Khans
	In	Prince Mshiyeni
	Outside	Stanger
District hospitals	In	St. Mary's Marianhill Osindisweni
	In	Mahatma Gandhi
	Outside	CJ Crookes
Primary centres	In	Tongaat Health Centre
	In	Phoenix Health Centre
	In	Kwa Mashu Polyclinic
	In	Kwadabeka Clinic
Private hospitals	In	McCords
	In	St Aidans

Table 2. **Visible vaccination status and frequency of adverse events in neonates receiving intradermal Copenhagen 1331 BCG vaccine**

Period of evaluation	No. of vaccine recipients			
	followed up	with healed vaccination scar	with no vaccination scar	with adverse events[a]
July–Dec. 1997	2763	2580 (93.4)[b]	79 (2.9)	104 (3.8)
Jan.–Dec. 1998	4859	4666 (96.0)	45 (0.9)	148 (3.0)
Jan.–June 1999	2141	2067 (96.5)	26 (1.2)	48 (2.2)
Total	**9763**	**9313 (95.4)**	**150 (1.5)**	**300 (3.1)**

[a] Six vaccine recipients had two adverse events, e.g. an abscess and regional lymphadenopathy.

[b] Figures in parentheses are percentages.

Additional studies

BCG-induced disseminated TB. Post-vaccination disseminated TB could not be confirmed in any of the 10 cases that underwent detailed evaluation (tested by tissue biopsy), although both acid-fast bacilli and *Mycobacterium tuberculosis* were detected in aspirates from extranodal injection-site abscesses. Regardless of whether the abscesses were left untreated, or aspirated by needle with or without isoniazid prophylaxis, all the abscesses healed, although the duration of the adverse events was as long as 42 days in some cases.

Comparison of percutaneous and intradermal routes. A crude assessment suggests that the intradermal BCG vaccine method has very little impact on the rates of disseminated childhood TB,

Table 3. **Types of adverse events in neonates receiving intradermal Copenhagen 1331 BCG vaccine**

Period of evaluation	No. of vaccine recipients[a]			
	with oozing	with lympha-denopathy[b]	with injection-site abscesses	with other adverse events[c]
July–Dec. 1997	39 (37.5)[d]	18 (17.3)	44 (42.3)	4 (3.8)
Jan.–Dec. 1998	61 (41.2)	23 (15.5)	59 (39.9)	10 (6.7)
Jan.–June 1999	9 (18.7)	13 (27.1)	20 (41.7)	6 (12.5)
Total	**109 (36.3)**	**54 (18.0)**	**123 (41.0)**	**20 (6.7)**

[a] Six vaccine recipients had two adverse events, e.g. an abscess and regional lymphadenopathy.

[b] Lymph nodes > 1.5 cm.

[c] Other adverse events included erythema, swelling, ulcers, and keloid formation.

[d] Figures in parentheses are percentages.

Table 4. **Visible vaccination status and frequency of adverse events associated with neonatal intradermal Copenhagen 1331 BCG vaccinations at different types of institutions**

Type of institution	No. of vaccine recipients			
	followed up	with healed vaccination scar	with no vaccination scar	with adverse events[a]
Tertiary hospital in the DFR[b]	2194	2112 (96.4)[c]	22 (1.0)	60 (2.7)
Regional and district hospitals in the DFR	5738	5518 (96.2)	59 (1.0)	161 (2.8)
Regional and district hospitals outside the DFR	389	339 (87.1)	33 (8.5)	17 (4.4)
Primary care centres in the DFR	437	389 (89.0)	33 (7.6)	15 (3.4)
Private hospitals in the DFR	1005	955 (95.1)	3 (0.3)	47 (4.7)

[a] Six vaccine recipients had two adverse events.

[b] DFR = Durban Functional Region.

[c] Figures in parentheses are percentages.

because the number of tuberculous meningitis and miliary TB cases at the TB isolation site did not change significantly over a five-year evaluation — which included periods before and after the change to the intradermal method (Table 5).

Discussion

WHO and UNICEF have recommended the intradermal injection of BCG vaccine by needle and syringe as the standard method for vaccinating neonates against TB. In most countries this is the standard method, but South Africa is one of the remaining countries to administer the vaccine by percutaneous route using the Japanese tool, despite having one of the highest incidences of TB worldwide and an increasing prevalence of tuberculous meningitis in the Western Cape. Concerns about the percutaneous method include the risks associated with inadequate sterilization of the tool in the face of an HIV/AIDS epidemic, and the fact that this method has not been evaluated in the last 25 years in South Africa. As a result, the South African Department of Health, under the guidance of the directorate of the National Expanded Programme on Immunization, is being pressured to re-evaluate the current programme of percutaneous vaccination and to replace it with the intradermal method.

Our study of 9763 neonates in the DFR and surrounding regions demonstrated that 95.4% of the neonates vaccinated intradermally with the CBCG vaccine had healed vaccination scars, confirming adequate vaccination. Only 1.5% lacked visible scars. Despite this success, care is required when implementing the change of method, because 3.1% of the neonates experienced adverse events to the vaccination, despite a programme to educate health care professionals before starting the study.

Adverse events

The most common adverse events were injection-site abscesses. These did not result from inadvertent use of the TBCG vaccine, in place of the CBCG vaccine, or from repeated use of the CBCG vaccine, since care was taken to the remove all the old TBCG vaccines from the study sites, and repeated vaccinations were neither reported nor observed. Instead, it is likely that the adverse events were primarily related to the undetected, erroneous, deep subcutaneous administration of the CBCG vaccine. A large, prospective, multicentre European study has reported the frequency of adverse events to be between 0.01 and 17.2 per 1000 vaccine recipients (*22*).

The incidence of significant lymphadenopathy in this study was similar to reports from other centres, where a range of 0–38% has been recorded (*13*). A high incidence of adverse events was observed in similar studies in the West Indies, but it was concluded that this was related to increased susceptibility of the subjects to the Pasteur strain used in the vaccinations (*23, 24*).

Oozing was probably related to a local, transient response to vaccination, but in a few cases the duration was prolonged. This could be part of the natural immune response to the vaccine, or it could be related to the incorrect use of waterproof dressings which were initially applied. Keloid formation and ulcers occurred very infrequently, suggesting that the correct site for vaccination was used. BCG osteitis following intradermal vaccination, seen in Finland at a rate of 300 per 100 000 people (*25*), was not identified in our study.

Detailed evaluation of a subset of patients at risk for disseminated TB showed that there were no

serious adverse events. Disseminated TB following BCG vaccincation, which is rare (*26*), also did not occur despite the likely prevalence of HIV coinfection in some neonates. In a study in Kigali, Rwanda, where the prevalence of HIV infection was approximately 30% in women of reproductive age, no case of BCG-induced disseminated TB was identified in a cohort of 404 neonatal BCG-vaccine recipients. Of this group, 37 HIV-infected neonates were followed up for 15 months (*27*).

A study of a small group of patients from Harare, Zimbabwe, in 1986 revealed a 5% incidence of suppurative lymphadenopathy, which was attributed mainly to incorrect site of vaccination and poor reconstitution of the vaccine (*28*). The management of these and other adverse events in the Zimbabwean study and our study was similar. Needle aspiration directed away from the site of the abscess, as advocated by Banani & Alborzi (*29*), allowed healing and prevented the development of sinuses. Isoniazid prophylaxis for two months was rarely indicated in our study.

Comparison of percutaneous and intradermal vaccination routes

A comparison of the adverse events resulting from the new intradermal and the old percutaneous BCG vaccine is warranted. In 1939, Rosenthal investigated the possibility of giving BCG by multiple punctures because of the high incidence of adverse reactions with the intradermal route (*30*). He found that they could be reduced with the percutaneous route of administration.

Other factors that influence the frequency of adverse events include the age at vaccination. In a Jamaican study, BCG-related adenitis and abscess formation occurred in 1.9% of infants aged 0–6 weeks; in 0.6% aged 7–52 weeks; and there were no cases reported in children aged over 52 weeks (*23*). In TB-endemic areas, however, the recommendation that BCG vaccination should take place at birth should not be altered — even though the likelihood of adverse events is higher at this stage — because the risk of acquiring TB is high.

The stable incidence of tuberculous meningitis and miliary TB in South Africa in the face of an HIV/AIDS epidemic also suggests that the new intradermal route of vaccination is at least as effective as the percutaneous method in preventing disseminated TB.

Vaccination status

The high rate of healed scar formation was reassuring and supports the findings of Marchant et al., who found that CBCG vaccine given at birth induced a memory T-helper 1 response similar in magnitude to that induced later in life (*31*). Prematurity also does not prevent an adequate response to BCG vaccination (*32, 33*). The lack of scar formation in infants vaccinated in some peripheral health centres may be related to the incorrect handling of vaccine; lack of protection of vaccine stocks from light (UV exposure produces breaks in the cold chain); or to incorrect vaccination technique. A study by Rani et al. showed that scar failure occurred in up to 10% of vaccine recipients, but the incidence was even higher in neonates vaccinated in the first 48 hours after birth (*34*). However, an in vitro evaluation of leukocyte migration inhibitory responses in these neonates indicated an adequate vaccination status, despite no scar formation. Overall, it appears that the ability to induce tuberculin reactivity with BCG vaccine is similar with either the intradermal or percutaneous method, but this ability is reduced with repeated use of the disposable tool for percutaneous vaccination (*35, 36*).

Table 5. **Number of children with tuberculous meningitis and miliary tuberculosis at King George V Hospital, a tuberculosis isolation facility, before and after change of vaccination policy (July 1997)**

Period of evaluation	Average no. of tuberculous meningitis cases annually in children aged		Average no. of miliary TB cases annually in children aged	
	0–6 yrs	over 6 yrs	0–6 yrs	over 6 yrs
Before policy change (Jan. 95–June 97)	13.6	6.3	8.0	2.7
After policy change (Jan. 98–Dec. 99)	12.5	8.5	4.5	1.0

Policy implications

A decision to use the new intradermal CBCG vaccine needs to be considered carefully. In our study, the incidence of adverse events decreased as health workers became more familiar with the new method of administration. Institutions with different medical educational programmes performed differently, as measured in terms of rates of visible vaccination scars and adverse events. There were fewer adverse events and higher rates of healed vaccination scars in the tertiary hospital and regional and district hospitals in close proximity to academic centre, when compared to outlying services. In contrast, primary care centres in the DFR, and district and regional hospitals outside the DFR had lower rates of healed vaccination scars and higher rates of adverse events. Different levels of proficiency among health care workers could also contribute to the variation in success rates. This would suggest that a more intensive educational programme directed to all health professionals would be required in the more remote areas; and continued re-evaluation would be essential following implementation of the programme. It is hoped that the incidence of adverse events will decrease as more health workers become familiar with the intradermal vaccination method.

Overall, this study supports the transition from percutaneous, multiple-puncture BCG vacci-

nation to intradermal BCG vaccination, even though there are potential risks associated with the change. The benefits of the intradermal method include lowering the total cost of vaccination, leaving a clear scar that indicates an adequate immunological response, and better safety and sterility. These advantages clearly outweigh the disadvantages of the adverse events observed in this study. In any case, the number of adverse events could be minimized by providing training before, during, and after implementation of the new vaccination method; such training could also help to guide managers of vaccination programmes. Consequently, it would be wise to re-evaluate the efficacy of the intradermal CBCG vaccine in South Africa. ■

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Conflict of interests: none declared.

Résumé

Innocuité du vaccin BCG intradermique de souche Copenhagen 1331 chez le nouveau-né à Durban (Afrique du Sud)

Objectif Evaluer l'innocuité du vaccin BCG intradermique de souche Copenhagen 1331 chez le nouveau-né dans des maternités et des services de néonatologie de différents niveaux, dans la région de Durban (Durban Functional Region et environs).

Méthodes Une étude prospective a été réalisée sur une période de deux ans entre juillet 1997 et juin 1999. Tous les nouveau-nés qui avaient reçu le vaccin intradermique ont été examinés dans des services de vaccination au bout de six semaines, ou plus tôt en cas d'effets indésirables.

Résultats Au total, 9763 nouveau-nés ont été examinés : chez 95,4 % d'entre eux, la lésion vaccinale était cicatrisée, et dans 1,5 % des cas il n'y avait pas de cicatrice visible. Des effets indésirables ont été observés chez 3,1 % des nouveau-nés vaccinés. La proportion de nouveau-nés ne présentant pas de cicatrice vaccinale visible diminuait au cours de l'étude, de même que le nombre de cas d'effets indésirables. Le taux le plus faible d'effets indésirables et le taux le plus élevé de lésions vaccinales cicatrisées ont été observés à l'hôpital tertiaire ainsi que dans les hôpitaux régionaux et de district proches du centre universitaire participant à l'étude.

Conclusion Sur les sites d'étude, le passage de la voie percutanée à la voie intradermique d'administration du vaccin BCG a été une réussite et n'a pas donné lieu à un taux inacceptable de manifestations indésirables. Il est toutefois indispensable, pour réduire encore ces manifestations, de poursuivre la formation du personnel de santé participant à la mise en œuvre des programmes de vaccination BCG par voie intradermique.

Resumen

Inocuidad de la vacuna BCG intracutánea, cepa Copenhague 1331, en los recién nacidos en Durban (Sudáfrica)

Objetivo Evaluar la inocuidad de la vacuna BCG intracutánea, cepa Copenhague 1331, en los recién nacidos en diferentes niveles de las maternidades y los servicios de neonatología de la Región Funcional de Durban y alrededores.

Métodos Se llevó a cabo un estudio prospectivo durante dos años, de julio de 1997 a junio de 1999. Todos los recién nacidos que habían recibido la vacuna intracutánea fueron evaluados en consultorios de inmunización seis semanas después de la vacunación, o antes si aparecían efectos adversos.

Resultados Se examinó en total a 9763 recién nacidos: en el 95,4% de los casos la marca de la vacunación había cicatrizado, y un 1,5% de los niños no presentaban cicatriz visible. El 3,1% de los neonatos sufrieron reacciones adversas. La proporción de recién nacidos sin cicatrices de vacunación visibles disminuyó a lo largo del periodo de estudio, al igual que el número de los afectados por reacciones adversas. En el hospital terciario y en los hospitales regionales y distritales próximos al centro universitario que participó en este estudio se observaron la tasa más baja de acontecimientos adversos y las tasas más altas de cicatrización de las marcas de vacunación.

Conclusión En los sitios estudiados, la transición de la vía percutánea a la intracutánea como opciones de administración de la vacuna BCG se hizo de manera satisfactoria y no se acompañó de tasas inadmisiblemente altas de reacciones adversas. A fin de reducir éstas al mínimo, sin embargo, es esencial proseguir la formación del personal de salud implicado en la ejecución de los programas de administración intracutánea de la vacuna BCG.

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