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OFFICIAL STATEMENT

Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants

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A. C. Hesseling,*† M. F. Cotton,‡ C. Fordham von Reyn,§ S. M. Graham,¶ R. P. Gie,* G. D. Hussey#

*** Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Tygerberg, South Africa; † Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; ‡ Children's Infectious Diseases Clinical Research Unit, Department of Pediatrics and Child Health, Stellenbosch University, Tygerberg, South Africa; § DarDar International Programs, Section of Infectious Disease and International Health, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA; ¶ Centre for International Child Health, University of Melbourne Department of Paediatrics, Royal Children's Hospital Melbourne, Parkville, Victoria, Australia; # Institute of Infectious Diseases and Molecular Medicine and the School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa**

SUMMARY

This document outlines the consensus agreement from the Union's BCG Working Group regarding BCG vaccination in HIV-infected infants, in response to recently revised World Health Organization (WHO) guidelines, which make HIV infection in infants a full contraindication to bacille Calmette-Guérin (BCG) vaccination. BCG is one of the most widely given vaccines globally and is safe in immunocompetent individuals. Recent evidence shows that HIV-infected infants who were routinely vaccinated with BCG at birth, when asymptomatic, and who later developed AIDS, are at high risk of developing disseminated BCG disease (estimated incidence 407–1300 per 100 000). The document outlines requirements to implement selective BCG vaccination strategies in infants born to HIV-infected women and strategies to reduce the risk of vertical HIV transmission and disseminated BCG disease in infants.

KEY WORDS: BCG; HIV; disseminated disease; guidelines; PMTCT

THE BCG WORKING GROUP of the International Union Against Tuberculosis and Lung Disease (The Union), a Working Group of the Child Lung Health Section, welcomes the recently revised World Health Organization (WHO) recommendations regarding bacille Calmette-Guérin (BCG) vaccination in human immunodeficiency virus (HIV) infected infants. HIV infection in infants is now a full contraindication to BCG vaccination.[1]

BACKGROUND TO THE WHO POLICY CHANGE

BCG, a live attenuated *Mycobacterium bovis* vaccine, is almost universally given soon after birth in sub-Saharan African countries, where the brunt of the global paediatric HIV burden is concentrated. BCG coverage worldwide was estimated at over 100 million doses per year, resulting in the vaccination of 76% of the more than 130 million infants born globally in 2002.[2] Meta-analyses indicate a consistent BCG-induced protective efficacy in young non-HIV-infected children against disseminated forms of tuberculosis (TB) (tuberculous meningitis or miliary disease), with a summary estimate protective effect of 73% (67–79%) against tuberculous meningitis and 77% (58–87%) against miliary disease.[2] The protective effect of BCG against pulmonary disease in childhood is variable[3] and there is no evidence of any BCG-induced protective effect in HIV-infected children.[4] BCG is a safe vaccine in non-HIV-infected infants, with a reported incidence of disseminated BCG disease of less than 5 per million vaccinees.[5] Severe vaccine adverse events in non-HIV-infected infants are associated with rare congenital immunodeficiencies.

Until recently, the WHO recommended that in

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Correspondence to: A C Hesseling, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg 7505, South Africa. Tel: (+27) 21 9389173. Fax: (+27) 21 9389719. e- mail: annekeh@sun.ac.za or Anneke.Hesseling@lshtm.ac.uk

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countries with a high burden of TB, healthy infants should receive a single dose of BCG as soon as possible after birth, unless a child presented with symptomatic HIV infection. This recommendation was based on the low perceived risk of serious adverse events.[6] Identification of HIV infection at birth, when BCG is often administered, is not, however, possible in the vast majority of infants, as most HIV transmission in developing counties occurs peri- or postpartum and HIV-infected infants are usually not symptomatic at birth. Most Prevention of Mother-to-Child HIV Transmission (PMTCT) programmes recommend a diagnostic HIV-specific DNA polymerase chain reaction (PCR) at 6 weeks of age, with a minimum turnaround time for results of 1 week.

Recent evidence shows that HIV-infected infants who were routinely vaccinated with BCG at birth, when asymptomatic, and who later developed the acquired immune-deficiency syndrome (AIDS), were at increased risk of developing systemic or disseminated BCG disease, with an estimated incidence of 407–1300 per 100 000 infants documented in HIV-infected BCG-vaccinated infants from South Africa and Argentina.[7,8] Disseminated BCG is associated with all-cause mortality in excess of 75%.[8,9] Following a review of relevant data emerging over the last years, the Global Advisory Committee on Vaccine Safety (GACVS) and the Strategic Advisory Group of Experts (SAGE) therefore recommended revising previous WHO recommendations concerning BCG vaccination of HIV-infected infants, making HIV infection in infants a full contraindication for BCG vaccination, even in settings highly endemic for TB.[1, 10, 11] Among HIV-infected infants, the benefits of potentially preventing severe TB therefore appear to be outweighed by the risks associated with the use of BCG vaccine.

CHALLENGES TO THE IMPLEMENTATION OF THE REVISED BCG POLICY

Although clear data regarding the risk of BCG vaccination in HIV-infected infants are now emerging, the Working Group, along with the WHO, also recognises the challenges regarding practical implementation and safety considerations of this revised vaccination policy, especially in resource-limited settings. In its most recent document, the WHO rightly indicates that 'a number of factors need to be taken into consideration when assessing the risk for HIV infection and implementing the recommendations of GACVS. The lack of information about many of these factors in populations with limited resources makes this assessment, and therefore the implementation of the recommendations, particularly difficult'.[10]

Several considerations are listed by the WHO that pertain to national and local decision-making with regard to the revision and the implementation of the revised BCG vaccination policy, including the prevalence of TB in the general population, the potential for infant exposure to *M. tuberculosis*, the prevalence of HIV infection, the coverage and efficacy of interventions to prevent mother-to-child HIV transmission, rates of exclusive and mixed breastfeeding, and the capacity to conduct follow-up of immunised children and to perform early virological infant diagnosis. Other important considerations include good surveillance systems for TB and HIV, and good services for infant immunisation, child health and treatment of HIV-infected children.

A key implementation consideration is the ability of infant vaccination and PMTCT programmes to allow for strategies such as selectively delaying vaccination of HIV-exposed infants from birth until, for example, 10–14 weeks of age, following a negative HIV PCR testing result, e.g., at 4–6 weeks of age. This could be combined with alternative TB preventive strategies such as isoniazid preventive therapy in the intervening period. Such strategies will have to be implemented in close collaboration with other infant health programmes and will require fully functioning and integrated PMTCT and infant vaccination programmes with appropriate follow-up.

ENVISIONED IMPACT OF POLICY CHANGE

Apart from a reduction of the considerable risk of BCG vaccination in a small proportion of HIV-infected infants, there is a risk that non-vaccination at birth of a much larger proportion of infants born to HIV-infected women but who escape HIV infection themselves (HIV-exposed non-infected infants), will inadvertently lead to subsequent non-BCG vaccination of these infants. This is an important consideration in settings highly endemic for TB, where inadvertent non-vaccination of HIV-exposed non-infected infants may lead to an excess incidence of disseminated TB. As PMTCT programmes are strengthened and access to maternal HAART improves, the number of paediatric HIV infections will decline. This will result in an even smaller number of HIV-infected infants at risk of disseminated BCG compared to a much larger pool of HIV-exposed non-infected and non-HIV-exposed infants, who may benefit from BCG vaccination.

A further consideration is a potential reduced risk of disseminated BCG disease in HIV-infected infants who received BCG at birth and who are initiated early on highly active antiretroviral therapy (HAART). Although there are no published data, it is possible that the risk of disseminated BCG will decline with the restoration of cellular immunity as a result of institution of early HAART. Preliminary data suggest a reduced risk of BCG-related immune reconstitution inflammatory disease (IRIS) in infants initiated on HAART when under 12 weeks of age.[12] Early diagnosis of infant HIV infection linked to early initiation of HAART is also associated with reduced all-cause mortality,[13] a

further incentive for early infant HIV testing and referral.

CONDITIONS NECESSARY FOR IMPLEMENTATION

Successful implementation of a selective delayed BCG vaccination policy in HIV-exposed infants will require that all of the following conditions are met:

- High uptake of maternal HIV testing coupled with effective PMTCT strategies, including maternal HAART
- Early virological diagnosis of HIV infection in infants coupled with institution of HAART
- Coordination of PMTCT, vaccination and TB programmes to:
  - minimise loss to follow-up
  - implement alternative TB preventive strategies, and
  - deliver successful vaccination following selective non-vaccination at birth.

These conditions are currently not present in the overwhelming majority of countries highly endemic for HIV and TB. Current implementation of selective vaccination strategies is therefore not feasible in most settings. Even where such programmes exist, there are major operational problems.[14] In addition, surveillance systems for TB and HIV and follow-up services for children are often suboptimal. These include the lack of TB screening amongst HIV-infected pregnant women, who are at high risk of TB during the antenatal and postpartum periods.[15] This situation should improve with the roll-out and strengthening of PMTCT and HAART programmes and the integration of HIV and TB programmes. Progress should be periodically reviewed.

WORKING GROUP CONSENSUS AGREEMENT

The Working Group therefore supports the revised WHO BCG vaccination policy, but recommends that current universal BCG immunisation of infants continue in countries highly endemic for TB until countries have all programmes in place for implementing selective deferral of HIV-exposed infants. Selective deferred BCG vaccination of HIV-exposed infants should be done only in those settings with the necessary programmatic resources. The Working Group recommends regular review of programme implementation considerations and progress made.

The Working Group strongly supports:

- Improved PMTCT programmes, including early diagnosis, appropriate feeding options and appropriate management of HIV-infected infants
- Improved access to maternal HAART
- Improved TB screening amongst HIV-infected pregnant women
- Improved surveillance of BCG adverse events in settings highly endemic for TB and HIV
- Research on improved TB preventive strategies in HIV-exposed and -infected infants
- Research on the safety and feasibility of delayed BCG vaccination strategies
- Research on BCG benefits in HIV-exposed non-infected infants
- Research on the effects of HAART on the incidence of TB and BCG adverse events in HIV-infected infants
- Research regarding new vaccines that are effective and safe in immune-compromised children.

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RÉSUMÉ

Cette article décrit l'accord de consensus obtenu dans le Groupe de Travail BCG de L'Union au sujet de la vaccination des nourrissons infectés par le virus de l'immunodéficience humaine (VIH), en réponse à des directives récemment révisées de l'Organisation Mondiale de la Santé qui considèrent que l'infection VIH constitue une contre-indication complète à la vaccination par le bacille de Calmette et Guérin (BCG) chez les nourrissons. Le BCG est un des vaccins administrés le plus largement dans le monde et est dépourvu de risques chez les individus immunocompétents. Des observations récentes montrent que les nourrissons infectés par le VIH et vaccinés en routine par le BCG à la naissance au moment où ils étaient asymptomatiques, et qui ont développé ultérieurement un syndrome de l'immunodéficience acquise, encourent un risque élevé d'apparition d'une bécégite disséminée (incidence estimée entre 407 et 1300 pour 100 000). Cette article décrit les exigences de mise en œuvre de stratégies sélectives de vaccination par le BCG chez les enfants nés de mères infectées par le VIH ainsi que les stratégies visant à réduire le risque de transmission verticale du VIH et la bécégite disséminée chez les nourrissons.

RESUMEN

En el presente artículo se resume el acuerdo del grupo de trabajo de La Unión sobre la vacuna antituberculosa (BCG), con respecto a la vacunación con el BCG de lactantes infectados por el virus de la inmunodeficiencia humana (VIH). Este texto se preparó como respuesta a la reciente revisión de las recomendaciones de la Organización Mundial de la Salud, en la cual se establece que esta infección constituye una contraindicación formal a la vacunación con el BCG. Esta es una de las vacunas más ampliamente administradas en el mundo y su aplicación es segura en las personas inmunocompetentes. Pruebas científicas recientes han demostrado que los lactantes infectados por el VIH que se vacunaban en forma sistemática con el BCG al nacimiento cuando eran asintomáticos y que posteriormente contraían síndrome de inmunodeficiencia adquirida, presentaban un alto riesgo de becegeítis diseminada (incidencia calculada de 407 a 1300 por 100 000). El artículo resume los requisitos de aplicación de estrategias de vacunación selectivas con el BCG en los lactantes hijos de mujeres infectadas por el VIH y las estrategias destinadas a reducir el riesgo de transmisión vertical del VIH y de becegeítis diseminada en los lactantes.