Safety of BCG vaccination and implications for HIV-exposed and infected children

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SAGE meeting, 17-19 October 2017

Background

- BCG is a live attenuated vaccine (*M. bovis*);
- BCG reduces the risk of pulmonary and extra-pulmonary disease by approximately 50%, with a higher efficacy against TB meningitis and disseminated TB disease;
- BCG vaccines also provide some protection against leprosy and non-tuberculous mycobacterial infections;
- Vaccine strain/product differences for effectiveness not demonstrated in the scientific literature while it is well recognized for reactogenicity and complications*.

*Pasteur 1173 P2 and Danish 1331 most reactogenic

Lotte et al BCG Complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics Adv Tuberc Res 1984:21:107-193

AEFIs listed in SPCs

Classification	AEFI	Occurrence
Local	injection site reaction/local ulceration with ipsilateral regional lymph node swelling < 10 mm/scar	Expected
Regional	ipsilateral regional lymph node swelling > 10 mm that can suppurate/form fistulae	0.1-1 per 1 000
Distant	any single site beyond regional lymph nodes incl. skin, gut, osteitis (bone) or osteomyelitis (bone marrow)	0.1-1 per 10 000 Can occur >12 months after BCG
Disseminated	Generalized BCG infection in im-munocompromised, potentially fatal	< 0.1 per 100 000

Contraindications

- Individuals receiving systemic corticosteroids or other immunosuppressiv treatment incl radiotherapy;
- Infants exposed to immunosuppressive treatment while *in utero* (e.g. TNF-α inhibitor);
- Individuals with primary or secondary immuno-deficiencies (incl HIV-infected and infants born to HIV+);
- Individuals receiving prophylactic treatment against tuberculosis.

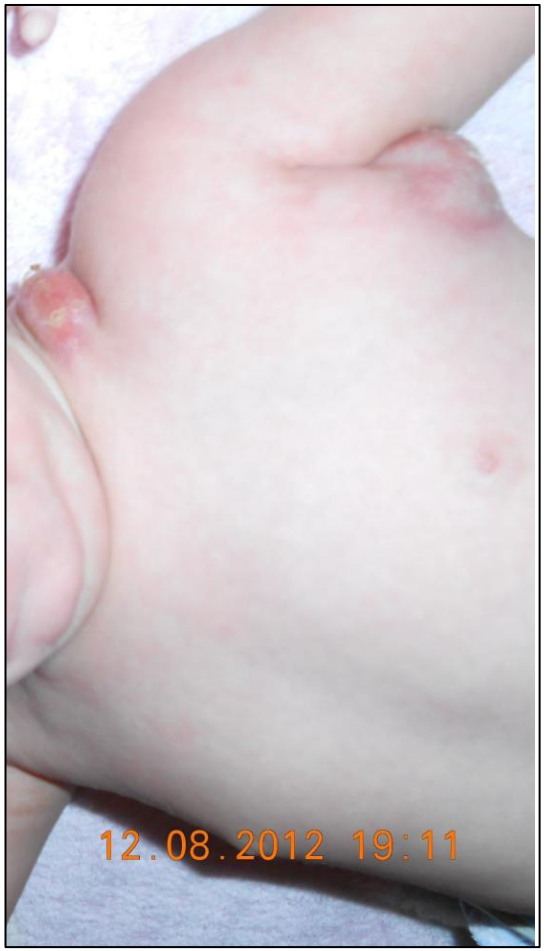
Overview of existing literature reviews

Author	Year of publication	Populations
Lotte et al	1984	Worldwide
Lotte et al	1988	Six European countries
Bannister et al	2009	Healthy children worldwide
Azzopardi et al	2009	HIV-infected infants worldwide
Mak Report to WHO	2005	Worldwide incl HIV
Cuello-Garcia et al	2013	Treating BCG-induced disease

Lotte et al A bibliography of the complications of BCG vaccination. A comprehensive list of the world literature since the introduction of BCG up to July 1982, supplemented by over 100 personal communications. Adv Tuberc Res. 1984;21:194-245. Lotte et al BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. Adv Tuberc Res. 1984;21:107-93. Azzopardi et al. Bacille Calmette-Guérin vaccine-related disease in HIV-infected children: a systematic review. Int J Tuberc Lung Dis. 2009 Nov;13(11):1331-44. Review. Mak Review of management of BCG vaccine-related adverse evens Final report 2005 Cuello-Garcia et al Treating BCG-induced disease in children Cochrane database syst rev 2013

Lymphadenitis 1962 – 1978 following use of different BCG vaccine products*

Europe	Number of cases per 1,000 vaccinated	Africa, Asia and Oceania	Number of cases per 1,000 vaccinated
Austria	1.0	Algeria	5
Denmark	0.5	Cameroon	18
Finland	1.1	Hong Kong	0.1
France	4.0	India	3.3
West Germany	0.2	Morocco	11
USSR	0.11	Tunisia	5
		Thailand	5
		Turkey (Tokyo)	0.3
		Turkey (national)	1.3

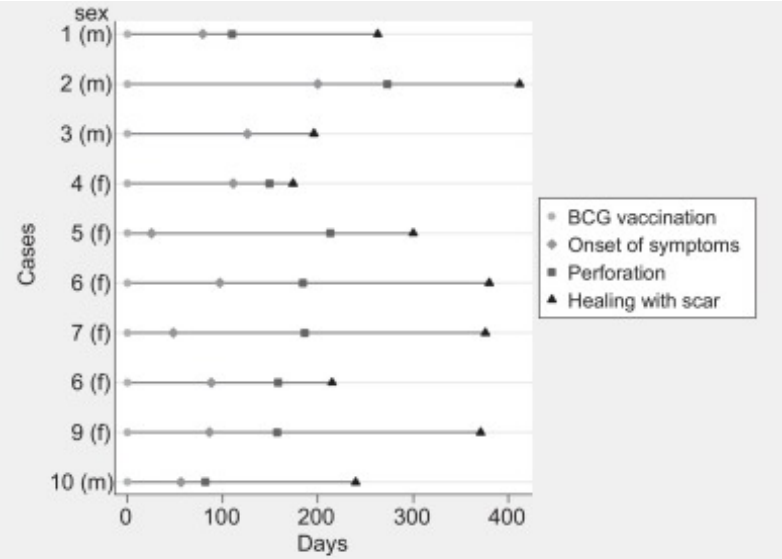


*Lotte et al, 1984 A bibliography of the complications of BCG vaccination. A comprehensive list of the world literature since the introduction of BCG up to July 1982, supplemented by over 100 personal communications. Adv Tuberc Res. 1984;21:194-245.

World Health Organization

Lymphadenitis in recent RCT (2012-2015)*

Adverse reaction	n/N	Risk (95%CI
Regional lymphadenitis	13/2118	6.1 per 1000 (3.3 – 10/1000)
Suppurated lymphadenitis	10/2118	4.7 per 1000 (2.3 – 8.7 per 1000)



In case 3 it was not possible to determine the exact time of perforation

5-fold increase compared to SPC

Age at vaccination 0 (0-6) days

Age at onset of symptoms 87 (25-200) days

Time course of 10 cases of suppurative lymphadenitis

All children in this study recovered without sequelae within 4 - 6 mo with conservative treatment, but aspiration and surgery may occasionally be indicated

*Nissen et al Adverse reactions to the Bacillus Calmette–Guérin (BCG) vaccine in new-born infants—an evaluation of the Danish strain 1331 SSI in a randomized clinical trial Vaccine Volume 34, Issue 22, 11 May 2016, Pages 2477-2482

Lymphadenitis – batch-related variation over time

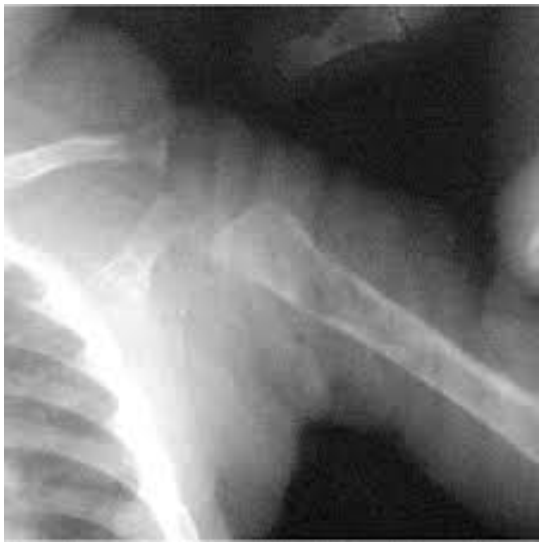
- Saudi Arabia (BCG SSI Danish 1331)
  - 2002 – 2007* A rate of 1.96 cases per 1000 vaccinated
  - 2007 – 2010 A rate increase to 10.14 per 1000 vaccinated
- Latvia (BCG SSI Danish 1331)
  - 2005 – 2010 A rate of 0.5 per 1000 vaccinated observed
  - 2011 - 2012 A rate increase to 3.6 per 1000 vaccinated
  - 2013 - A rate decrease to 0.9 per 1000 vaccinated
- Singapore (BCG SSI Danish 1331)
  - 2009 – 2010 A rate of 0.71 - 0.85 per 1000 vaccinated
  - 2011 A rate increase to 3.16 per 1000 vaccinated
  - 2012 A rate decrease to 0.77 per 1000 vaccinated

Batch variation has been reported for many other BCG vaccine strains/products

*Abdulkarim Abdullah Alrabiaah et al Outbreak of Bacille Calmette-Guérin-related lymphadenitis in Saudi children at a university hospital after a change in the strain of vaccine Annals of Saudi Medicine 2012; 32:1
Engelis et al BCG-SSI(®) vaccine-associated lymphadenitis: Incidence and management Medicina (Kaunas). 2016;52(3):187-91. doi: 10.1016/j.medici.2016.05.001. Epub 2016 May 30.*Soh et al Investigations into an outbreak of suppurative lymphadenitis with BCG vaccine SSI(®) in Singapore.Vaccine. 2014 Oct 7;32(44):5809-15

Distant BCG-induced osteitis/osteomyelitis

- Often affecting the long bones and can occur 4 - 24 months post vaccination;
- Incidence of osteitis/ osteomyelitis has been reported as 0.01-30 per million vaccinated and seems to vary with vaccine strain*, however batch-related variation up to 700 per million**;
- Prognosis of osteitis/ osteomyelitis is generally good without any sequelae.



*Lotte et al A bibliography of the complications of BCG vaccination. A comprehensive list of the world literature since the introduction of BCG up to July 1982, supplemented by over 100 personal communications. Adv Tuberc Res. 1984;21:194-245.

**Swedish outbreak: 333 cases per million doses, Finnish outbreak: 729 per million doses Romanus et al First experience with BCG discontinuation in Europe. Experience in Sweden 15 years after stopping general BCG vaccination at birth Bull Int Union Tuberc Lung Dis 1997;1 (5):417-421

Disseminated BCG infection

- Occurs within 6-12 months of vaccination and are mostly seen in children with underlying primary immunodeficiences (SCID, CGD, disorders of the gamma-IFN/IL-12 pathway, MSMD) or HIV**;
- Incidence is estimated to 2-3.4 per million vaccinated*, although one Canadian study of First Nations and Inuit populations reported a rate of 205 (95%CI 42-600) per million vaccinated;
- Case fatality rates of 80-85%, in spite of treatment;
- Consider not to vaccinate infants with siblings that developed disseminated BCG infection and if possible investigate for PID.

*Lotte et al BCG Complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics Adv Tuberc Res 1984:21:107-193
Talbot et al Disseinated BCG disease after vaccination: case report and review. Clin Infect Dis 1997;24(6):1139-46

Age differences in AEFI rates

Age at vaccination and BCG vaccine-related AEFI rate per 100,000 doses (includes any passive reports following BCG including reactogenicity seen after most BCG vaccinations)

Age	BCG AEFI rate	95% CI
0 - <3 m	56	(37-81)
3 - <6 m	204	(132-300)
6 - <9 m	459	(251-769)
9 -<12 m	520	(224-1024)
1-<7 yrs	706	(492-981)
Total	153	(126-184)

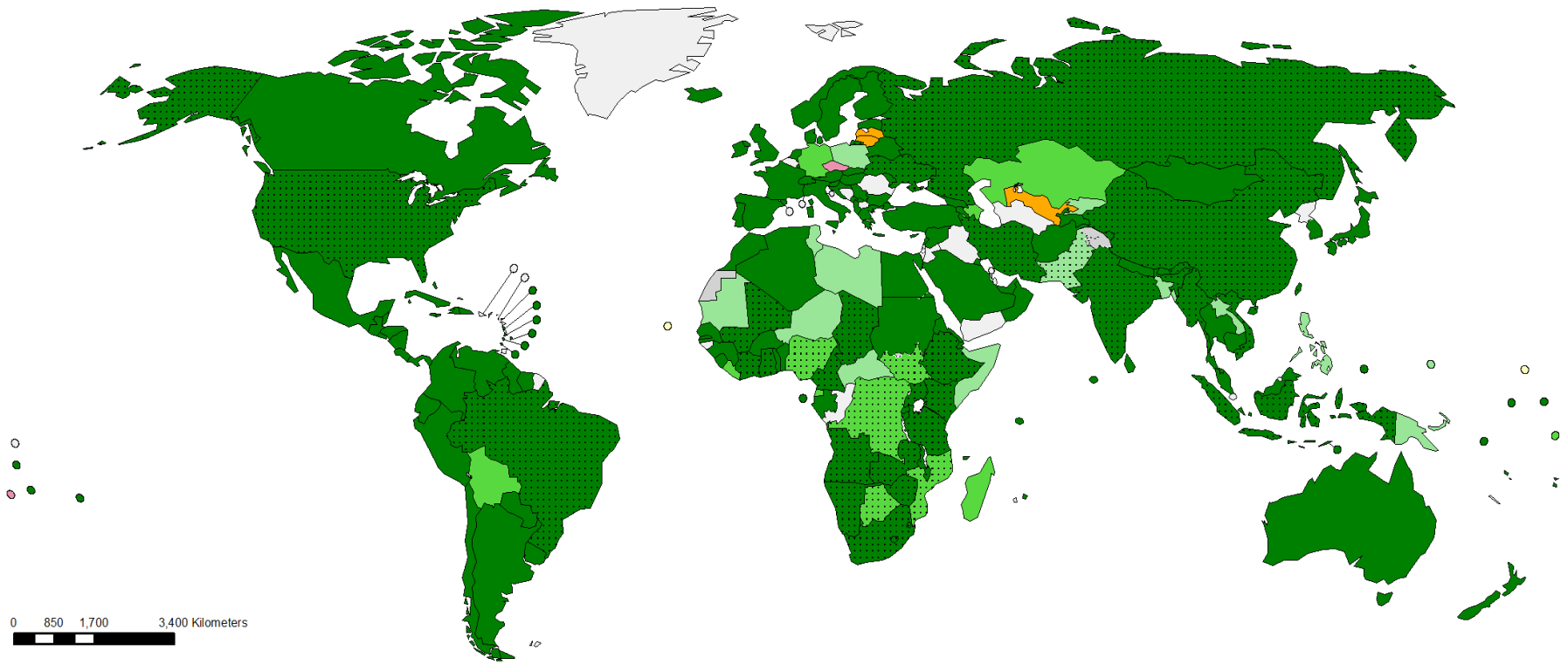
A short report on adverse events following immunisation with BCG vaccine was made available to the BCG safety subgroup from the Therapeutic Goods Administration Australia for vaccinations between 1 January 2009 – 31 December 2014 in children aged less than 7 years. Adverse events following immunisation with Bacille Calmette-Guérin vaccination: baseline data to inform monitoring in Australia following introduction of new unregistered BCG vaccine. Alexandra Hendry, Aditi Dey, Frank Beard, Gulam Khandaker, Richard Hill and Kristine Macartney. CDI 2016; 40(4):E470-E474.

WHO Policy Recommendation (2007) Infants at risk of HIV infection*

- Evidence showed that children who were HIV-infected when vaccinated with BCG at birth, and who later developed AIDS, were at increased risk of developing disseminated BCG disease
- → Children known to be HIV+, even if asymptomatic, should **NOT** be immunized with BCG
- **Challenges**
  - Unfortunately, accurate diagnosis of HIV infection relies upon direct demonstration of the HIV virus, as maternal HIV antibody is passively transferred to the infant in utero.
  - Signs of HIV are uncommon in the first weeks of life when BCG is usually offered
  - Since not all women are offered HIV testing during pregnancy, the status of HIV infection of children born to HIV-infected mothers is not always recognized at or around the time of birth.

*http://www.who.int/vaccine_safety/committee/topics/bcg/immunocompromised/Dec_2006/en/

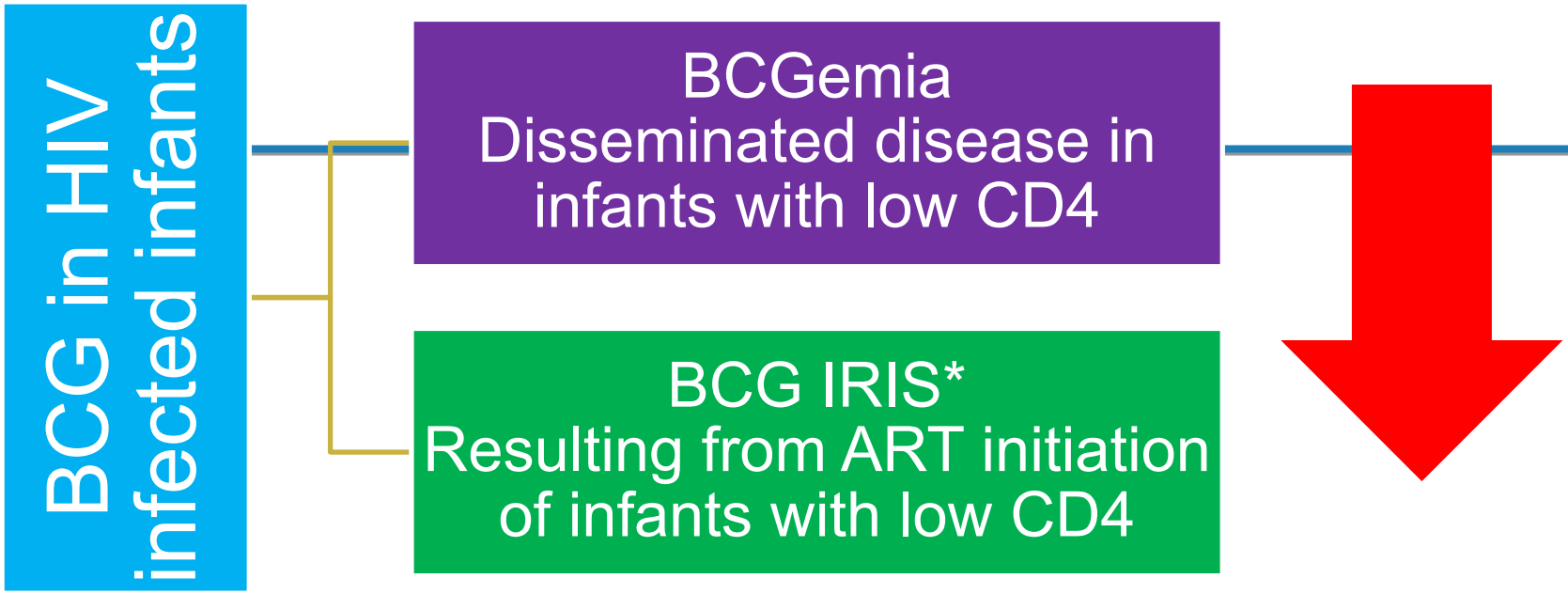
Implementation of Treat All policy for pregnant and breastfeeding women living with HIV (situation as of July 2017)



- Implemented countrywide
- Implemented in a large number (>50%) of MCH sites
- Implemented in a small number (<50%) of MCH sites
- Policy adopted, not yet implemented
- ART during pregnancy and breastfeeding only
- Other
- Data not reported
- Fast-Track countries
- Not applicable

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

World Health Organization



As a result of effective Prevention of Mother-to-Child Transmission interventions and more rapid Antiretroviral treatment initiation the clinical syndromes associated to BCG in HIV infected infants are decreasing remarkably so

with the current HIV policy BCGemia and BCG IRIS are expected to be minimized

*Immune reconstitution inflammatory syndrome

**Smith et al Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. AIDS. 2009 Jun 1;23(9):1097-107

Early antiretroviral treatment reduces risk of BCG immune reconstitution adenitis*

- Incidence of BCG-IRIS was 10.9 and 54.3 per 100 person years (py) among infants with CD4 count ⩾25% at enrolment receiving early (at median age 7.4 weeks) vs. deferred (23.2 weeks) ART, respectively (HR 0.24, 95%CI 0.11–0.53, P < 0.001);
- Low CD4 counts and high HIV-1 RNA at initiation were the strongest independent risk factors for BCG-IRIS;
- Early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis.

*H. Rabie et al Early antiretroviral treatment reduces risk of BCG immune reconstitution adenitis Int J Tuberc Lung Dis 2011 15(9):1194–1200

Summary safety profile – prophylaxis against tuberculosis

- Review of the literature has not revealed any new safety signals following vaccination with BCG vaccines;
- Many BCG strains/products have occasionally triggered batch-related ‘outbreaks’ of lymphadenitis or osteitis/osteomyelitis;
- Disseminated BCG disease serious but mainly occurs in children with primary immunodeficiency or untreated HIV infection;
- Although HIV infection continues to be a contraindication, BCG vaccination may be considered in ART treated and immunologically stable infants in high endemic settings;
- Increased incidence of AEFI with increased age >3 months. Vaccination at birth or 6 weeks of age will likely differ little since time to onset of AEFI often >1-2 months.

Thank you