SAGE Evidence to recommendations framework[i]

Detailed evidence related to the evidence to recommendation table can be found in the background papers presented to the Strategic Advisory Group of Experts (SAGE) on Immunization in October 2017[1]

Question: Should the BCG vaccine be given universally to all neonates at birth in a population with high prevalence for HIV to mitigate the risk of severe TB disease or should vaccination be delayed until HIV status is known?
Population: Neonates in a population with high prevalence of HIV
Intervention: One dose of BCG vaccine given at birth.
Comparison(s): Delaying BCG vaccination.
Outcome: Prevention of severe TB disease

Background:

Prevention of TB relies on two strategies: childhood vaccination with BCG, preferably at birth[2] and treatment of latent TB Infection[3] in people living with HIV, adult and child contacts of pulmonary TB cases.

The retrieved evidence shows that there is a substantially higher risk of disseminated BCG disease developing in HIV-infected children vaccinated at birth, which was addressed in the position paper's supplementary note in 2007.[4] HIV-testing and treatment is therefore highly relevant for the BCG recommendation in light of the need to identify individuals in this high risk group. The major conflict remains that although BCG vaccination is recommended at birth for optimizing protective efficacy, the unknown HIV status of HIV-exposed infants at this time point can lead to safety issues.

Success in scaling up ART in pregnant and breastfeeding women has resulted in remarkable reduction of HIV infections in infants. Around 76% of pregnant women living with HIV had access to antiretroviral medicines in 2016, up from 47% in 2010. New HIV infections among children globally have halved, from 300 000 [230 000–370 000] in 2010 to 160 000 [100 000–220 000] in 2016. Five-high burden countries—Botswana, Namibia, South Africa, Swaziland and Uganda—have already met the milestone of diagnosing and providing lifelong antiretroviral therapy to 95% of pregnant and breastfeeding women living with HIV.[5]

The risk for infants who are HIV status unknown and immunologically stable was assessed by considering how frequent BCGemia and BCG IRIS occurs in HIV-infected infants that received BCG. The analysis considered the context of earlier identification and ART initiation and what the implications for "delaying" or "missing" BCG vaccination for HIV-infected children would be.[1]

[1] BCG Working Group report, available at http://www.who.int/immunization/sage/meetings/2017/october/en/ , accessed September 2017.
[2] BCG atlas. Available at http://www.bcgatlas.org/contact.php, accessed July 2016.
[3] WHO. Latent TB infections. Available at http://www.who.int/tb/publications/ltbi_document_page/en/, accessed July 2016.
[4] WHO. Revised BCG vaccination guidelines for infants at risk for HIV infection. Wkly Epidemiol Rec. 2007 May 25;82(21):193-6.
[5] UNAIDS. GLOBAL AIDS UPDATE. 2017. Available at http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf, accessed February 2018.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	New HIV infections among children globally have halved, from 300 000 [230 000–370 000] in 2010 to 160 000 [100 000–220 000] in 2016, nevertheless those HIV-infected children, if they are not on ART, have a higher risk of disseminated BCG disease when they receive BCG vaccination. About 43% of infants born to women living with HIV receiving a virological test within two months of age.[5]	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	BCG vaccination at birth can prevent severe forms of TB. It has been estimated that high global coverage (90%) and widespread use of BCG in routine infant vaccination programmes could prevent over 115 000 TB deaths per birth cohort in the first 15 years of life.[Error! Bookmark not defined.] In some countries, delays in diagnosis of HIV infection in exposed children results in delays in BCG vaccination. The impact of such delays on HIV positive children and also on the incidence of TB is yet to be determined. HIV uninfected infants would be at a disadvantage by delaying BCG vaccination since they would have a higher risk of severe TB infection until HIV status is confirmed.	
	<u>Harms of the intervention</u>	*No*	*Un-certain*	*Yes*	*Varies*	HIV infected children are at high risk of BCG disease after BCG vaccination.[4] A	Overall, 88% of 144 low and middle income countries (LMICs) have adopted the WHO HIV recommendation[9] of

	Are the undesirable anticipated effects small?	☐	☐	☒	☐	recent study showed that early ART initiation before immunological and/or clinical HIV progression substantially reduced the risk of BCG-IRIS regional adenitis.[6] Observational data from a cohort in South Africa confirms a low risk: 0.6% of the 12 748 children who were vaccinated with BCG and receiving ART developed lymphadenitis.[7] A study protocol for a trial was designed, which will be conducted in HIV1-exposed infants in Uganda, to detemine the differences of early versus late BCG vaccination.[8] But data are not available yet. Anecdotally reports from physicians in high HIV-endemic countries reveal that BCG adenitis is a rare event and BCG IRIS might only occur in children receiving late treatment when immunological suppression has become severe. Additionally, global efforts to stop new HIV infections among children has led to substantial change. Diagnosis (infant diagnosis, particularly early infant diagnosis (EID)) and providing lifelong antiretroviral therapy to at least 95% of pregnant and breastfeeding women living	Option B+ to provide lifelong antiretroviral therapy (ART) to pregnant and breastfeeding women. Five-high burden countries—Botswana, Namibia, South Africa, Swaziland and Uganda—have already met the milestone of diagnosing and providing lifelong antiretroviral therapy to 95% of pregnant and breastfeeding women living with HIV. Treatment for pregnant and breastfeeding women has prevented an estimated 1.6 million infants from acquiring HIV – almost half of them in the last 5 years of the Global Plan. South Africa appears to be taking the lead on reducing not only the number of HIV-infected infants, but also the severity of the disease. Early identification of HIV-infected infants remains the key intervention to prevent AIDS related deaths (in 2015 80,000 children under the age of 5 died as consequence of HIV infection). West and Central African countries provide EID to less than a third of exposed infants. WHO has tried to address this with its 2016 policy[10] on antiretroviral drugs for treating and preventing HIV infection to promote an earlier testing provided to the point of care. Combination of a virological test

[6] Rabie H et al. Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis. Int J Tuberc Lung Dis. 2011 Sep;15(9):1194-200.
[7] Gupte MD et al. Comparative leprosy vaccine trial in south India. Indian J Lepr. 1998 Oct-Dec;70(4):369-88.
[8] Nankabirwa V et al. Early versus late BCG vaccination in HIV-1-exposed infants in Uganda: study protocol for a randomized controlled trial. Trials201718:152.
[10] WHO. Guidelines: HIV available at HIV http://www.who.int/hiv/pub/guidelines/en/, accessed February 2018.

			with HIV are the milestones for MTCT elimination. Around 76% of pregnant women living with HIV had access to antiretroviral medicines in 2016, up from 47% in 2010.	at birth and the use of point of care testing (POC) would enable a much more rapid identification of HIV infected infants (not available everywhere), as testing in laboratories requires much more time for the turnaround of the result. National-level programme data are limited in their ability to capture true maternal and infant outcomes due to loss to follow-up or data quality issues. As a result, current global models are likely to underestimate the numbers of new infections in children as well as the true extent of paediatric HIV-related mortality.
	Balance between benefits and harms	*Favours intervention* ☒ / *Favours comparison* ☐ / *Favours both* ☐ / *Favours neither* ☐ / Unclear ☐	Balance between benefit and harms favor the intervention (universal vaccination at birth). All elements point towards keeping the current policy of providing BCG vaccination to infants who are not HIV-infected or to those whose status is unknown. With the current HIV policy BCGemia and BCG IRIS are expected to be minimized.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ / *Very low* ☐ / *Low* ☐ / *Moderate* ☐ / *High* ☐ Safety of the intervention *No included studies* / *Very low* / *Low* / *Moderate* / *High*	No studies to assess the quality of evidence have been included. The study protocol for a trial which has been designed, for conduction in HIV1-exposed infants in Uganda, will generate more evidence.[8]	

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VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐ ***Possibly important uncertainty or variability*** ☐ ***Probably no important uncertainty or variability*** ☐ ***No important uncertainty or variability*** ☐ ***No known undesirable outcomes*** ☒	Ensuring early protection of infants against severe forms of TB is more important than delaying BCG vaccination to wait for HIV diagnostic.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	No formal analysis of preferences of the target group been done, but it's assumed that intervention (birth vaccine) is more preferable to the target group. Vaccination at birth is an opportune time for BCG administration as the infant is within the health system. If an infant is delivered at home, BCG vaccination forms part of an integrated visit to the health centre for both infant and mother e.g. postnatal care of the mother and newborn.	
RESOURCE USE	Are the resources required small?	*No* ☐ *Un-certain* ☐ *Yes* ☒ *Varies* ☐	Infants delivered in a health care facility can receive BCG vaccination at birth from trained nurses/midwives. For infants delivered at home, they can receive a BCG vaccination from trained nurses during	BCG vaccination at birth should be promoted as per existing WHO guidelines[11] or during the postnatal care visit for the mother and newborn.[12]

[11] WHO. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice. 2015. Available at http://apps.who.int/iris/bitstream/10665/249580/1/9789241549356-eng.pdf?ua=1, accessed February 2018.

[12] WHO. WHO recommendations on postnatal care of the mother and newborn. 2013 Available at http://apps.who.int/iris/bitstream/10665/97603/1/9789241506649_eng.pdf,accessed February 2018.

					their postnatal care visit for the mother and newborn or by outreach workers.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Formal cost-effectiveness analyses have not been conducted, but BCG at birth reduces more disease and death. Therefore, the benefit overrides the cost of the vaccine. For those born at home, attending clinic immediately after birth to receive BCG would not be considered an additional visit but, is a recommended contact for receiving other maternal and child health (MCH) postnatal care packages.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	Implementing a BCG birth dose, particularly in resource-constrained settings, is expected to reduce health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-venti on* ☒	*Com paris on* ☐	*Both* ☐	*Neit her* ☐	*Un-clear* ☐	Administering BCG at birth is an acceptable option to key stakeholders as it requires no change to the current immunization schedule.	

	Which option is acceptable to target group?	*Inter-vention* ☒ / *Com parison* ☐ / *Both* ☐ / *Neither* ☐ / *Un-clear* ☐	Ensuring early protection of infants is likely to be acceptable to the target group.	Delaying BCG vaccination e.g. to 6 weeks would result in as many as 5-6 vaccinations in one visit, which could be challenging to implement.
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☒ / *Varies* ☐	The intervention is feasible if linked with HIV policy implementation of ART, POD and EID. Additionally, important opportunities exist to integrate HepB birth dose; conduct birth registration; provide a vaccination card and key messages about vaccination to the caregiver.	BCG vaccination at birth should be promoted as per existing WHO guidelines[11] or during the postnatal care visit for the mother and newborn.[12]

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings

	☐	☐	☐	☐	☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Children who are HIV-infected when vaccinated with BCG at birth are at increased risk of developing disseminated BCG disease. However, if HIV-infected individuals, including children, are receiving ART, are clinically well and immunologically stable (CD4 % >25% for children aged <5 years or CD4 count ≥200 if aged >5 years) they should be vaccinated with BCG. • In general, populations with high prevalence of HIV infection also have the greatest burden of TB; in such populations the benefits of potentially preventing severe TB through vaccination at birth are outweighed by the risks associated with the use of BCG vaccine. Therefore, it is recommended that in such populations: • Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks. • Neonates of unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART. • Although evidence is limited, for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant confirmed to be clinically and immunologically stable (CD4% >25%).				

Implementation considerations	• Implementation of this policy will need to happen in the context of national HIV testing policies. Countries adopting HIV testing at birth with POC technologies may be able to identify HIV infected children early enough to guide BCG administration. • Health care workers providing BCG will need to be trained and mentored to be able to assess signs and symptoms suggestive of HIV • Appropriate and timely follow up of HIV exposed infants will ensure that infected children are identified as soon as possible and treatment and care provided (including management of any BCG related adverse event). • As ART is scaled up and coverage in pregnant women increases the likelihood of BCG related adverse effects due to HIV infection is expected to decrease
Monitoring and evaluation	The implementation of BCG vaccination of HIV-infected children, including those receiving ART, should be monitored in order to generate more data on safety and effectiveness.
Research priorities	The development of new vaccines is a high research priority. There is a need for vaccines that would provide greater protection than BCG, preventing all forms of TB including drug-resistant TB, as well as reactivation of TB, and that would be effective in all age groups including HIV-infected persons and perform consistently in all populations.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework