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 to infants at birth or at the time of the first dose of the diphtheria tetanus and pertussis (DTP1) containing vaccine at 6 weeks of age to mitigate the risk of severe TB disease, with special focus on countries with a high burden of TB?

Population: Infants.
Intervention: One dose of BCG vaccine given at birth.
Comparison(s): One dose of BCG vaccine given at the same time as the first dose of DTP vaccine at the age of 6 weeks.
Outcome: Prevention of severe TB disease in childhood (miliary, meningeal form) and TB associated death

Background:

Prevention of TB relies on two strategies: worldwide vaccination with BCG, preferably at birth[2] and treatment of latent TB infection[3] in HIV infected persons and young children contacts of TB cases.

Despite its limitations, BCG remains an important tool for prevention of TB. WHO recommends that all infants in countries with a high burden of TB should receive the BCG vaccine as soon as possible after birth[4], yet in many countries, vaccination is delayed to be administered concomitantly with the first pentavalent vaccine at the age of 6 weeks. The BCG Working Group revisited this current recommendation considering the evidence base around the timing of BCG vaccination looking for any difference in terms of efficacy or safety between BCG vaccination at birth and at 6 weeks of age.

[1] BCG Working Group report, available at http://www.who.int/immunization/sage/meetings/2017/october/en/ , accessed September 2017.
[2] http://www.bcgatlas.org/contact.php, accessed July 2016
[3] http://www.who.int/tb/publications/ltbi_document_page/en/, accessed July 2016
[4] WHO BCG Position Paper. 2004. http://www.who.int/wer/2004/en/wer7904.pdf?ua=1

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The timing of BCG vaccinations varies between and within countries, with delayed vaccination (rather than at birth) extremely common in many countries. Although often officially reported as birth dose, BCG immunization is usually delayed until the DTP1 vaccine (around 6 weeks of age).	The median BCG coverage among infants across the 71 countries surveyed was 38% by 1 week of age; 75% by 6 weeks of age; 88% by 14 weeks of age and 93% by 52 weeks of age.[1]
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	There is a paucity of evidence comparing the effectiveness and efficacy of BCG vaccination at birth and at 6 weeks.[5] In comparison to birth dose, modelling of BCG co-administration with DTP1 at 6 weeks of age was estimated to lead to 5 556 (95% UR: 220–15 224), or 2.8% (95% UR: 0.1%-4.5%), increase in TB deaths.[6]	
	Harms of the intervention Are the undesirable anticipated	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	BCG vaccination in immunocompetent individuals is considered as safe.[7] Pediatric HIV infections are decreasing and the probability that a child is born to HIV- infected mother	A country example from South Africa, which has high HIV prevalence, is giving the priority to prevent TB and therefore vaccinates all children. Innovations such as HIV testing at birth and use of point-of-care (POC) technologies may allow more rapid identification of HIV-infected infants in the near future, but there is currently

[5] Uthman et al. Systematic review on the effectiveness and efficacy of BCG against TB, unpublished, see SAGE Background documents
[6] Roy et al. Mathematical modelling to estimate the impact of age of BCG vaccination on global paediatric TB mortality, unpublished, see http://www.who.int/immunization/sage/meetings/2017/october/presentations_background_docs/en/.
[7] Uthman et al. Systematic review on the safety of BCG against TB and leprosy, unpublished, see SAGE Background documents

	effects small?		and is HIV-infected at the time of BCG vaccination is now low. Early antiretroviral therapy (ART) initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis. As countries move to implement more rapid ART initiation, occurrence of BCGemia and BCG IRIS is less likely.[1]	very limited implementation.
	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | *Unclear* ☐	Balance between benefit & harms favor the intervention (vaccination at birth).	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention: *No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Mod-erate* ☐ | *High* ☐ Safety of the intervention: *No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Mod-erate* ☐ | *High* ☐	There is a paucity of evidence on the comparison of effectiveness and safety of BCG vaccination at birth and 6 weeks. [5,7]	
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* ☒	No evidence was available by conducting a rapid review.	
	Values and preferences of the target	*No* | *Probably No* | *Uncertain* | *Probably Yes* | *Yes* | *Varies*	No formal analysis of preferences of target group have been done, but it's assumed that intervention (birth	

	population: Are the desirable effects large relative to undesirable effects?	☐	☐	☐	☐	☒	☐	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 their postnatal care visit for the mother and newborn or by outreach workers.	BCG vaccination at birth should be promoted as per existing WHO guidelines[8] or during the postnatal care visit for the mother and newborn.[9]
	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	

[8] WHO. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice. 2015. http://apps.who.int/iris/bitstream/10665/249580/1/9789241549356-eng.pdf?ua=1
[9] WHO. WHO recommendations on postnatal care of the mother and newborn. 2013 http://apps.who.int/iris/bitstream/10665/97603/1/9789241506649_eng.pdf

			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-vention* ☒ *Com parison* ☐ *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* ☐ *Neit her* ☐ *Un-clear* ☐	Ensuring early protection of infants is likely to be acceptable to the target group.	Shifting BCG vaccination 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 postnatal care of the mother and newborn visit and if coordinated between MCH and EPI national immunization programmes. 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[10] or during the postnatal care visit for the mother and newborn.[11] Due to the large BCG vial size (10-20 doses), wastage is to be expected. However, the importance of giving the vaccine should override wastage concerns.
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		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐			

[10] WHO. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice. 2015. http://apps.who.int/iris/bitstream/10665/249580/1/9789241549356-eng.pdf?ua=1
[11] WHO. WHO recommendations on postnatal care of the mother and newborn. 2013 http://apps.who.int/iris/bitstream/10665/97603/1/9789241506649_eng.pdf

	☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations
Recommendation (text)	• In countries or settings with a high incidence of TB and/or leprosy, a single dose of BCG vaccine should be given to neonates at birth, or as soon as possible thereafter, for prevention of TB and leprosy disease. If it cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed. Any delay in vaccination may lead to opportunities for known or unknown exposure to TB or leprosy infected contacts. • Co-administration of BCG with the hepatitis B birth dose is safe and strongly recommended. In order to avoid missed opportunities for neonatal vaccination, BCG multi-dose vials should be opened and used despite any wastage of unused vaccine. • If the birth dose was missed, catch-up vaccination of unvaccinated older infants and children is recommended since evidence shows it is beneficial. Catch-up vaccination should be done at the earliest convenient encounter with the health-care system to minimize known or unknown exposure to TB or leprosy infected contacts.
Implementation considerations	• Ensure that health care workers have received the appropriate training for vaccine administration.
Monitoring and evaluation	• Programmes should monitor the timeliness of BCG vaccination.
Research priorities	• Studies on the effectiveness and safety of BCG vaccination at birth as compared to 6 weeks.

[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