BCG Evidence to Recommendation Framework

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.

	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	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]

[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

					birth dose, BCG immunization is usually delayed until the DTP1 vaccine (around 6 weeks of age).	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	There is a paucity of evidence to assess the effectiveness and efficacy of BCG vaccination at birth and at 6 weeks.[5] In comparison to birth dose, <u>modelling</u> of BCG co-administration with DTP1 at 6 weeks of age was estimated to lead to 3,119 (95% UR: 125–7,643), or 1.8% (95% UR: 0.1%-4.5%), increase in TB deaths.[6]	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*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 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	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 very limited implementation.

[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 SAGE Background documents.
[7] Uthman et al. Systematic review on the safety of BCG against TB and leprosy, unpublished, see SAGE Background documents

			rapid ART initiation, occurrence of BCGemia and BCG IRIS is less likely.[1]	
	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 differences 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 population: Are the desirable effects large relative to undesirable effects?	*No*: ☐ *Probably No*: ☐ *Uncertain*: ☐ *Probably Yes*: ☐ *Yes*: ☒ *Varies*: ☐	No formal analysis of preferences of 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 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 receiving other maternal and child health (MCH) postnatal care packages.	
EQ	What would be	*Increa-sed*	*Un-certain*	*Re-duced*	*Varies*	Implementing a BCG birth dose,	

[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

	the impact on health inequities?	☐		☐		☒		☐	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*	*Neither*	*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.	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	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]

[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

	☐ ☐ ☐ ☐ ☒ ☐		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.		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 ☐ 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)	• 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. • As newborns are also recommended to receive their first dose of hepatitis B vaccine as soon as possible after birth, ideally within 24 hours, co-administration of BCG with the hepatitis B birth dose is strongly recommended as it is safe to do so. • 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 and 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

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: Is there the need for a BCG revaccination following primary BCG immunization?
Population: Immunocompetent individuals.
Intervention: BCG revaccination following primary BCG immunization.
Comparison(s): Primary BCG immunization.
Outcome: Prevention of TB infection and disease

Background:
Primary infant BCG vaccination offers consistent durable protection for up to 10 years. There is some evidence of longer protection.[2] Therefore, there is a potential need for BCG revaccination. BCG revaccination is safe in *Mycobacterium tuberculosis* infected and uninfected populations. There is a lack of evidence from randomized controlled trials and retrospective cohort and case-control studies demonstrating the efficacy and effectiveness of BCG revaccination in adolescents and adults after primary BCG vaccination in infancy for protection against TB disease. Due to absence of evidence, BCG revaccination is not considered cost-effective. Further research is warranted to explore whether certain sub-groups of age, geographic or *M. tuberculosis* exposure categories would benefit from revaccination.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	BCG vaccination offers consistent durable protection against TB for up to 10 years.[3] Data on protection beyond 15 years are limited.[2] If effective, BCG revaccination could be a low-cost tool for TB control, particularly with waning protection	WHO/UNICEF Joint Reporting Form (JRF) data from 2016 show that 6 countries have BCG revaccination in their routine immunization schedule.[5]

[1] SAGE Working Group report, available at http://www.who.int/immunization/sage/meetings/2017/october/en/, accessed September 2017.
[2] Mangtani et al. The duration of protection of school-aged BCG vaccination in England: a population -based case–control study. International Journal of Epidemiology, dyx141 2017. Available at: https://academic.oup.com/ije/article/doi/10.1093/ije/dyx141/4098108/The-duration-of-protection-of-school-aged-BCG.
[3] Abubakar et al., 2017. Protection by Bacillus Calmette-Guérin vaccination against tuberculosis beyond 10 years: Systematic Review and Meta-Analysis [Under review].
[5] WHO/UNICEF joint reporting process. Available at http://www.who.int/entity/immunization/monitoring_surveillance/data/schedule_data.xls?ua=1, accessed July 2017.

						in adolescents and adults vaccinated at birth.[4]	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☐	The body of evidence to evaluate BCG revaccination against *M. tuberculosis* indicates that BCG revaccination is not effective.	A double-blind RCT of BCG (Glaxo) in Malawi showed no protective benefit of revaccination compared to placebo against confirmed TB disease (IRR 1.43; 95% CI 0.88 – 2.35).[6] In the BCG-REVAC RCT in Brazil, [7,8,9,] using TB incidence as the primary outcome, the study found that among children aged 7-14 years initially vaccinated at birth and then revaccinated with BCG (Moreau) at school age, overall vaccine efficacy was 9% (95% CI: -16 - 29%) after 0-5 years of follow-up and 12% (95% CI: -2-24%) after extended follow-up for 9 years. **Error! Bookmark not defined.**
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	BCG revaccination is safe in *M. tuberculosis* unexposed and exposed / infected, and HIV uninfected people.	Adverse reactions to BCG (Moreau-Rio de Janeiro substrain) revaccination in 71,000 Brazilian schoolchildren were rare. No skin tests were carried out, but right upper arms of all children were inspected for a BCG scar. Children were not vaccinated if they had two scars or unclear scar readings. No significant difference in the rate of adverse reactions was observed between primary BCG vaccination and BCG revaccination.[10]

[4] Plotkin SA, Orenstein W, Offit PA. Vaccines, 6th Edition. 2013.p.789-811
[6] Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Lancet, 1996. 348(9019): p. 17-24.
[7] Rodrigues LC et al., Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. Lancet. 2005 Oct 8;366(9493):1290-5. Epub 2005 Aug 31.
[8] Barreto ML, Pereira SM, Pilger D, Cruz AA, Cunha SS, Sant'Anna C, et al. Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: Second report of the BCG-REVAC cluster-randomised trial. Vaccine [Internet]. Elsevier Ltd; 2011;29(31):4875–7. Available from: http://dx.doi.org/10.1016/j.vaccine.2011.05.023
[9] Barreto ML, Pilger D, Pereira SM, Genser B, Cruz AA, Cunha SS, et al. Causes of variation in BCG vaccine efficacy: Examining evidence from the BCG REVAC cluster randomized trial to explore the masking and the blocking hypotheses. Vaccine [Internet]. Elsevier Ltd; 2014;32(30):3759–64. Available from: http://dx.doi.org/10.1016/j.vaccine.2014.05.042
[10] Dourado I et al., Rates of adverse reactions to first and second doses of BCG vaccination: results of a large community trial in Brazilian schoolchildren. Int J Tuberc Lung Dis. 2003 Apr;7(4):399-402.

				In an observational study of BCG (Danish; Glaxo and Behringwerke) revaccination in 2,997 Swedish school children reported the reactogenicity profile was similar to that of primary BCG vaccination.[11]
	Balance between benefits and harms	*Favours inter-vention* ☐ | *Favours com-parison* ☒ | *Favours both* ☐ | *Favours neither* ☐ | *Unclear* ☐	The comparison is favored when balancing the benefits and harms.	
	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* ☐	The evidence has low quality.	
		Safety of the intervention: *No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Mod-erate* ☐ | *High* ☐	The evidence has low quality.	
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 available though it is assumed that in general, there is no important uncertainty or variability.	
	Values and preferences of the target	*No* | *Probably No* | *Uncertain* | *Probably Yes* | *Yes* | *Varies*	A review of literature retrieved no evidence on the values and preferences of the target population.	

[11] Böttiger M et al., A comparative study of Danish (Statens Serum Institut), Glaxo and Behringwerke vaccines--revaccination of schoolchildren. J Biol Stand. 1983 Jan;11(1):1-12.

	population: Are the desirable effects large relative to undesirable effects?	☐	☐	☒	☐	☐	☐	But it is assumed that the revaccination is not preferable by the target group. Assessment of the values and preferences is very context specific and, in case no data are available, countries are asked to conduct these assessments in their specific setting.	
RESOURCE USE	Are the resources required small?	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☐			Additional resources will be needed to administer/implement revaccination. If countries also choose to carry out tuberculin skin testing (TST) prior to revaccination, additional costs will be incurred.	
	Cost-effectiveness	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☐			There is a lack of evidence for the effectiveness of revaccination. Therefore it is uncertain if BCG revaccination is cost-effective. Dye (2013)[12] modelled vaccine efficacy and cost-effectiveness when offering BCG (any vaccine) revaccination to TST negative adolescents after primary vaccination. The incremental cost per year of health life recovered was 116-9237 USD, and this cost-effectiveness doubled if additional benefits of transmission prevention were considered. When allowing for	Convention of doing a TST prior to revaccination will add considerable costs. In addition, there are frequent tuberculin shortages.

[12] Dye C. Making wider use of the world's most widely used vaccine: Bacille Calmette–Guérin revaccination reconsidered J. R. Soc. Interface 2013 Jul 31;10(87).

					both direct effects and indirect reduction of transmission and assuming 80% BCG revaccination efficacy, the model suggests BCG revaccination of TST negative adolescents could avert 17% of TB cases.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☒	*Re-duced* ☐	*Varies* ☐	It is not expected that the intervention has a huge impact of the intervention on health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☐	*Com parison* ☒	*Both* ☐	*Neit her* ☐	*Un-clear* ☐	Revaccination is likely not acceptable to the key stakeholders given the increased costs and limited additional benefit for the target population.	
	Which option is acceptable to target group?	*Inter-vention* ☐	*Com parison* ☒	*Both* ☐	*Neit her* ☐	*Un-clear* ☐	Ensuring adequate protection with the least number of injections is likely the most acceptable option to the target population.	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably No*	*Un-certain*	*Probably Yes*	*Yes*	*Varies*	Revaccination is feasible to implement with little difficulty to add it in the schedule. However,given the limited benefit of	

		☐ ☐ ☐ ☐ ☐ ☒	the intervention, it is not advisable to implement the intervention but to focus resources on the administration of the primary BCG vaccination and conduct of contact tracing for contagious TB cases.			
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)	• There is little additional benefit of repeat BCG vaccination against TB or leprosy. Therefore, revaccination is not recommended even if the TST reaction or result of an IGRA is negative. The absence of a BCG scar after vaccination is not indicative of a lack of protection and is not an indication for revaccination.
Implementation considerations	n/a
Monitoring and evaluation	n/a
Research priorities	• Additional longer-term studies should be conducted to explore vaccine efficacy and effectiveness and the need of revaccination in different subgroups of the population. • Research required on the revaccination of TST positives.

[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

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: What is the incremental effectiveness of vaccinating infants universally versus selectively in low burden TB countries (annual TB notification rate of ≤100 cases of all TB forms per million population)?

Population: Immunocompetent infants in countries with low burden of TB
Intervention: Routine administration of a BCG vaccine to selective infants at increased risk of TB in low TB endemic countries.
Comparison(s): Routine administration of a BCG vaccine universally to all infants in low TB endemic countries.
Outcome: TB infection and disease

As the incidence of TB continues to decline in developed countries, selective vaccination strategies in high-risk populations are being considered as an alternative to universal BCG vaccination.[2,3,4,5] However, selective immunization programmes depend heavily on the ability to identify and reach the target population.[6] The target population could be newborns of parents (or with close contacts/relatives) with previous TB, leprosy, or Buruli ulcer disease, newborns from immigrant populations from countries with high incidence of TB or leprosy, newborns from any other locally identified risk group for TB, leprosy and Buruli ulcer disease.

[1] BCG working group Report, available at http://www.who.int/immunization/sage/meetings/2017/october/en/, accessed September 2017.
[2] BCG World Atlas, 2nd Edition. Available: http://www.bcgatlas.org/, accessed July 2017.
[3] Dierig A, Tebruegge M, Krivec U, Heininger U, Ritz N. Current status of Bacille Calmette Guerin (BCG) immunisation in Europe - A ptbnet survey and review of current guidelines. Vaccine [Internet]. Elsevier Ltd; 2015;33(38):4994–9. Available: http://dx.doi.org/10.1016/j.vaccine.2015.06.097
[4] Tu H-AT, Vu HD, Rozenbaum MH, Woerdenbag HJ, Postma MJ. A review of the literature on the economics of vaccination against TB. Expert Rev Vaccines. 2012;11(3):303–17.
[5] Hersh AL, Tala-Heikkilä M, Tala E, Tosteson ANA, Fordham von Reyn C. A cost-effectiveness analysis of universal versus selective immunization with Mycobacterium bovis bacille Calmette-Guérin in Finland. Int J Tuberc Lung Dis. 2003;7(1):22–9.
[6] Feiring B, Laake I, Molden T, Haberg SE, Nokleby H, Seterelv SS, et al. Do selective immunisation against tuberculosis and hepatitis B reach the targeted populations? A nationwide register-based study evaluating the recommendations in the Norwegian Childhood Immunisation Programme. Vaccine [Internet]. Elsevier Ltd; 2016;34(17):2015–20. Available from: http://dx.doi.org/10.1016/j.vaccine.2016.02.060

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	In countries with a low burden of TB, some limit BCG vaccination to neonates and infants of recognized high-risk groups for TB or to tuberculin-skin-test negative older Due to the current flow of refugees from high TB endemic countries to low TB endemic countries, there is an ongoing discussion about how best to prevent TB.	Based on data from the 2016 Joint Reporting Form (data from 194 member states), 143 member states recommend universal birth dose of BCG; 13 countries give universal vaccination later during childhood; 21 countries did not have BCG vaccination in their routine schedule and 17 countries recommend selective BCG vaccination.
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	The evidence of the benefits of universal BCG vaccination in low endemic settings is uncertain. While several meta-analyses of available data have shown that the BCG vaccines can prevent a significant proportion of the cases of meningeal and miliary TB, the incidence of both of these conditions is very low in low burden countries, even without BCG vaccination.[1] Nevertheless, universal vaccination might prevent the few TB cases but leads to adverse events.	Studies report that the comparison of vaccination of specific groups in combination with active case finding is effective as well. [7,8] However, the amount of programmatic evidence for the latter is low, as few countries have fully reported the comparison results when they have changed to selective BCG vaccination.
	<u>Harms of the intervention</u>	*No*	*Un-certain*	*Yes*	*Varies*	There are no studies comparing the safety of routine administration of a	Rates of adverse events following immunization (AEFI) would be fewer if selective vaccination is chosen.

[7] Romanus V, Selective BCG vaccination in a country with low incidence of tuberculosis. Euro Surveill. 2006;11(3):14-7.
[8] Trnka L et al., Six years' experience with the discontinuation of BCG vaccination. 1. Risk of tuberculosis infection and disease. Tuber Lung Dis. 1993 Jun;74(3):167-72.

	Are the undesirable anticipated effects small?	☐ ☐ ☒ ☐	BCG to all infants or to selective infants at increased risk of TB. The harms of the intervention (selective strategy) include missing some high risk individuals. In general, universal BCG vaccination in low TB endemic countries is safe.	
	Balance between benefits and harms	*Favours inter-vention* ☐ *Favours com-parison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☒	The comparison of routine administration of a BCG vaccine to all infants in low TB endemic countries to BCG vaccination of selective infants at increased risk of TB in low endemic countries is unclear when balancing the benefits and harms. Either option relies on reaching groups who may not participate fully in the health care system.	
	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 are no published randomized control trials or case-control studies of the results - effectiveness or safety - of selective BCG vaccination in low burden countries.	
VALUES & PREFEREN	How certain is the relative importance of the desirable and undesirable	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	Based on a rapid review, no evidence was available though it is assumed that, in general, there is no important uncertainty or variability.	The possible effect of stigma must be considered; even though providing the vaccine to high-risk groups can be seen as a benefit, some members of the target group may consider it to be TB discriminatory and produce stigma, especially as BCG vaccination leaves a

	outcomes?	☐	☐	☐	☒	☐					scar in most cases. However, there is a need to balance the stigma of selective BCG vaccination and the risk of contracting TB.
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☒	*Probably Yes* ☐	*Yes* ☐	*Varies* ☐			Based on a rapid review, no evidence was available though it is assumed that, in general, there is no important desirable effect.	
RESOURCE USE	Are the resources required small?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒					Intervention: There will be costs associated with the identification of infants at increased risk of TB and providing the vaccine to them in a timely fashion. Comparison: Although no additional health care visits are needed, additional resources in respect to costs will be required for administration of universal BCG vaccination in low endemic countries.	BCG vaccine shortages could particularly impact countries that retain universal vaccination, and universal vaccination could inadvertently contribute to cause or contribute to shortages.
	Cost-	*No*	*Un-certain*	*Yes*	*Varies*					Although universal BCG vaccination	Reviews by Trunz et al. (2006)[9] and Tu et al. (2012)[4] provided a worldwide perspective on

[9] Trunz BB et al. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet. 2006 Apr 8;367(9517):1173-80.

	effectiveness	☐	☐	☐	☒			in countries with low TB incidence does offer protection in paediatric populations, the additional protection conferred by universal strategies is comparatively small and less cost-effective when compared to targeted vaccination of infants at increased risk of TB.	the costs and benefits of the BCG vaccine and concluded that vaccination remained cost-effective in high TB incidence settings.
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐ *No impact* ☐	*Re-duced* ☒	*Varies* ☐			The possible effect of stigma must be considered as some members considered at increased risk of TB may deem it to be discriminatory and actually produce stigma, even though providing the vaccine can be seen as a benefit, particularly as it provides an opportunity for a health visit contact.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒	*Com parison* ☐	*Both* ☐	*Neit her* ☐	*Un-clear* ☐		In low TB countries, universal BCG vaccination is not cost effective. Therefore, the intervention is likely to be more acceptable to key stakeholders.	
	Which option is acceptable to target group?	*Inter-vention*	*Com parison*	*Both*	*Neit her*	*Un-clear*		Ensuring adequate protection is likely the most acceptable option to the target population.	

		☐	☐	☒	☐	☐		
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	The feasibility will depend, in part, on the nature of the country's health care system and how they offer health care to immigrants, refugees, and those living in poverty. In low TB endemic countries, BCG should be given selectively to infants at increased risk of TB. However, infants at increased risk of TB are often immigrants and refugees who may have very limited access to health care in their new country.	

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)	Countries with a low incidence of TB or leprosy may choose to selectively vaccinate neonates in recognized risk groups for developing disease. High-risk groups to be considered for vaccination include the following: • Neonates to parents (or other close contacts/relatives) with previous TB or leprosy • Neonates in immigrant populations from countries with high incidence of TB and/or leprosy. • Neonates in any other locally identified risk group for TB and/or leprosy. In a few countries with low TB incidence, BCG vaccination is largely replaced by intensified case detection, contact tracing and supervised early treatment.			

Implementation considerations	<u>Switching from universal to selective risk group vaccination at birth</u> • Countries with declining rates of TB are encouraged to periodically evaluate the epidemiology of TB and consider if a switch from universal vaccination to selective risk group vaccination would be appropriate. • Before switching to selective BCG vaccination, countries should consider the impact of a switch on prevention of leprosy. Consideration may be given also to other mycobacterial infections, as well as any potential NSE of BCG vaccination on all-cause infant mortality. • When considering switching from universal to selective risk group vaccination, an efficient disease surveillance system capable of showing the current average annual rate of smear-positive pulmonary TB cases is a pre-requisite. Additional data shall be taken into consideration, in particular the average annual rate of tuberculous meningitis in children aged under five years and/or the average annual risk of tuberculous infection in children and should be monitored. Finally the epidemiological situation for leprosy should be assessed through both routine notification data and especially active screening activities. The burden of other mycobacterial infections such as Buruli ulcer disease in the country could be also reviewed.
Monitoring and evaluation	• The actual epidemiology of TB in country, particularly meningeal and miliary TB among children and adolescents • Cost data according to the structure of the health care system
Research priorities	• Feasibility studies by health care system and structure • Cost-benefit studies

[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

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 BCG be recommended, over no vaccination, to immunocompetent individuals to mitigate the burden of leprosy in leprosy-endemic countries?

Population: Immunocompetent individuals.
Intervention: BCG vaccination for infants.
Comparison(s): No vaccination in the context of routine leprosy control interventions.
Outcome: Leprosy disease.

Background:
Although the fight against leprosy has gained considerable success, with an elimination target set in 2000, more than 200,000 cases were notified in 2015. The detection rate of the disease (a proxy of incidence rate) is only slightly declining at a rate of about 4% per year.[2] Early diagnosis and complete treatment with multi-drug therapy (MDT) remain the key strategies for reducing disease burden. Although not specifically indicated for prevention of leprosy, there is strong evidence that BCG vaccination has contributed to the decline in the incidence of the disease[3]. Despite known evidence on the effectiveness of BCG to prevent leprosy, there are no WHO recommendations for use of BCG for the prevention of leprosy. Several studies from high burden countries have examined the efficacy/ effectiveness of other vaccines and the combination of post-exposure prophylaxis with BCG at birth and/or with BCG revaccination.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Leprosy is an infectious disease with important clinical, social, and public health consequences. BCG vaccination has been associated with reductions in the incidence of	With only partial efficacy of a chemoprophylaxis regimen, the availability of a vaccine becomes an important tool. The efficacy of BCG is variable (20-90%) taking into account different factors (e.g. age at vaccination, clinical form, number of doses, type of study, the latitude of study area).[4]

[1] http://www.who.int/immunization/sage/meetings/2017/october/en/ accessed September 2017.
[2] Weekly Epidemiological Record 2012, http://www.who.int/wer/2012/wer8734.pdf?ua=1
[3] Setia et al, The role of BCG in prevention of leprosy: a meta-analysis. Lancet Infect Dis. 2006 Mar;6(3):162-70.
[4] Merle CS1, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. Expert Rev Vaccines. 2010 Feb

					leprosy.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	In 5 trials, the efficacy of BCG vaccine against leprosy was 20-80% and the effectiveness in 6 cohort studies was 41-62% and 20-90% in 17 case-control studies, respectively.[5] Evidence indicates BCG at birth is effective for preventing future leprosy infection. One RCT found effects of a single dose rifampicin (SDR) greater in persons who also received childhood BCG (OR 0.20 (95% CI 0.08-0.49)).[6]	The evidence for BCG re-vaccination (two RCTs) is inconsistent and data on adverse events are limited.[7]
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Evidence does not support an increased safety risk for BCG vaccination in a population with a high leprosy burden. Infants known to be HIV-infected with or without symptoms of HIV infection should not receive BCG vaccination.	
	Balance between benefits and harms	***Favours inter-vention*** ☒	***Favours com-parison*** ☐	***Favours both*** ☐	***Favours neither*** ☐	***Unclear*** ☐	Evidence of the protective efficacy and effectiveness for BCG vaccine given in infancy is given. In contrast, evidence on adverse	There is limited evidence of protective efficacy of revaccination of BCG against leprosy.

[5] Smith and Saunderson. 2010. Leprosy. BMJ Clin Evid. Jun 28;2010. pii: 0915.
[6] Shuring *et al.*, 2009. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. Vaccine. 2009 Nov 23;27(50):7125-8
[7] Cunha SS et al. BCG Revaccination Does Not Protect Against Leprosy in the Brazilian Amazon: A Cluster Randomised Trial. PLoS Negl Trop Dis. 2008 Feb 13;2(2):e167.

<table>
<tr><td></td><td></td><td></td><td>events is limited.</td><td></td></tr>
<tr><td></td><td>What is the overall quality of this evidence for the critical outcomes?</td><td>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 ☐</td><td>Effects of vaccination on risk of leprosy
Comparison | Findings | Quality
BCG at birth vs. no BCG or placebo | Pooled OR 0.45 (0.34-0.56) from Syst.Review [8] | Moderate</td><td>BCG at birth plus killed M. leprae vs. placebo[9] | RRR 64% (50-74%) | Moderate
BCG plus killed M. leprae vs. BCG alone[10] | RR 1.06 (0.62 to 1.82) and RRR 56% (27-74%) | Low
BCG revaccination in contacts vs. no BCG revaccination[7] | RR 0.51 (0.26-0.99), RR 0.99 (0.69-1.43), | Low
ICRC vaccine vs. placebo[11] | RRR 66% (48-77%) | Moderate
Mycobacterium w vaccine vs placebo[12] | OR 0.61 (0.46-0.80) and RRR 26% (1.9-44%) | Moderate</td></tr>
<tr><td>VALUES & PREFERENCES</td><td>How certain is the relative importance of the desirable and undesirable outcomes?</td><td>Importa nt uncertai nty or variabili ty ☐ Possibly importa nt uncertai nty or variabili ty ☐ Probabl y no importa nt uncertai nty or variabili ty ☒ No importa nt uncertai nty or variabili ty ☐ No known undesir able outcom es ☐</td><td>No evidence available although it is assumed that, in general, there is no important uncertainty or variability.</td><td>In the context of implementation, communication strategies of BCG vaccination against TB could be used.
Whether some individuals are concerned about the theoretical risk of disseminated BCG disease or systemic BCG-itis to such an extent as to refuse vaccination is unknown.</td></tr>
</table>

8 Richardus JH and Oskam L. Protectig people against leprosy: chemoprophylaxis and immunoprophylaxis. Clin Dermatol. 2015 Jan-Feb;33(1):19-25.
9 Convit J, et al. Immunoprophylactic trial with combined Mycobacterium leprae/BCG vaccine against leprosy: preliminary results. Lancet 1992; 339:446-450
10 Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Lancet 1996:348:446-450.
11 Deo MG, et al. Antileprosy potentials of ICRC vaccine. A study in patients and healthy volunteers. Intl. J. Lrpr. Other Mycobact. Dis. 1983; 51: 540-549.
12 Sharma P, et al. Immunoprophylactic effects of the anti-leprosy Mw vaccine in household contacts of leprosy patients: clinical field trials with a follow up of 8-10 years. Lepr. Rev. 2005; 76: 127-143.

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐		
RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	No research evidence was identified. Costs of BCG at birth are likely to be mainly related to the cost of the vaccine.	In countries with high TB endemicity, there is no need for extra resources for BCG as a tool to prevent leprosy. However, if BCG vaccination discontinues, there may be additional costs.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	No research evidence was identified.	Given the affordability of the BCG vaccine, countries will need to consider whether the BCG vaccine is a priority intervention to fund. However, there is an additional benefit of the BCG vaccine being effective in the prevention of two diseases.
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ *Varies* ☐	Implementing BCG vaccine, in particular in resource-constrained settings, is expected to reduce health inequities related to prevention of leprosy.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health,	*Intervention* *Comparison* *Both* *Neither* *Unclear*	No research evidence was identified. Administering of the BCG vaccine against leprosy is assumed to be an acceptable option to key stakeholders.	

	Immunization Managers)?	☒	☐	☐	☐	☐				
	Which option is acceptable to target group?	*Inter-vention*	*Com-parison*	*Both*	*Neither*	*Un-clear*	No research evidence was identified. However, in some settings vaccination programs are already performed and appear acceptable. Increasing protection of the population against leprosy by BCG vaccination is likely to be acceptable to the target group.			
		☒	☐	☐	☐	☐				
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably No*	*Un-certain*	*Probably Yes*	*Yes*	*Varies*	The intervention is feasible if coordinated between maternal child health and EPI national immunization programmes.		
		☐	☐	☐	☐	☒	☐			
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)	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. As newborns are also recommended to receive their first dose of hepatitis B vaccine as soon as possible after birth, ideally within 24 hours, co-administration of BCG with the hepatitis B birth dose is strongly recommended as it is safe to do so. 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	• BCG vaccination relies on the assumption of BCG availability and that it is already routinely administered as part of the national immunization programme.			
Monitoring and evaluation	• There might be the need to implement a monitoring system for adverse events if other vaccines will be used (BCG adverse events monitoring already part of the EPI)			

Research priorities	• Trials on new and existing vaccines including studies on LepVax, a new sub-unit vaccine are needed. Any novel TB vaccines should also be evaluated for leprosy prevention and vice versa.

[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

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 BCG be recommended at birth, over no vaccination, to immunocompetent infants based on the evidence for BCG efficacy and effectiveness to mitigate against various forms of tuberculosis (TB)?

Population: Immunocompetent infants.
Intervention: BCG vaccination at birth.
Comparison(s): No vaccination.
Outcome: Protection against various forms of TB.

Background:
The BCG vaccine is one of the most widely used vaccines and based on previous available evidence, it prevents severe forms of tuberculosis (TB) in children, known to be most prone to disseminated TB. BCG vaccination is recommended by the WHO for all infants, as soon as possible after birth, in countries with a high burden of TB.[2] Additional TB prevention strategies include treatment of latent TB Infection in HIV infected persons and chemoprophylaxis for young child contacts of adults with pulmonary TB (PTB).[3] Recent research has extensively evaluated the efficacy and effectiveness of BCG vaccine against various forms of TB (TB infection, PTB, severe disease), and this evidence is important to guide current policy and practice regarding use of BCG vaccine for the mitigation of various forms of TB."

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The incidence of TB has fallen by an average of 1.5% per year since 2000. Decline in TB incidence is slow, falling on average by ~1.5% per year since 2000, and TB continues to be one of the top 10 causes of morbidity and mortality globally	In 2015, 87% of new TB cases occurred in the 30 high TB burden countries, however TB is reported in all regions and countries. Six countries accounted for 60% of the new TB cases: India, Indonesia, China, Nigeria, Pakistan, and South Africa.

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

						(10.4 million new cases and 1.8 million deaths in 2015), with little likelihood of achieving the SDG at current rate of decline in incidence.[4]	An estimated 25% of the global population today has latent TB infection, which pose a big challenge to the control or elimination of TB in this generation.
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Recent evidence of the additional protective effects of BCG vaccination against TB infection, progression to active TB disease, pulmonary TB and death has implications on its overall effect on the control of TB.A systematic review and meta-analysis of 18 RCTs comparing vaccinated with unvaccinated participants, provided evidence on BCG vaccine efficacy (VE) against severe forms of TB, and against PTB as follows[5]. ***Efficacy against miliary & meningeal TB (severe disseminated TB):*** Pooled VE was 85% overall (95% CI 69 – 92%); efficacy was higher with neonatal BCG (VE 90%), and for BCG given to TST negative school age children (VE 92%); VE was low in older children and adults. ***Efficacy against Pulmonary TB:***	In Mangtani et al meta-analysis of 18 RCTs, the effect of latitude on BCG efficacy/effectiveness was evaluated. Protection against PTB, efficacy appeared to be higher in settings further from the equator (latitude > 40^{o} RR 0.32, 95% CI 0.22-0.46 versus latitude 0^{o} - $<20^{o}$ RR 0.78, 95% CI 0.58 – 1.05), however closer examination of the specific populations included in different latitudes varied by age at vaccination and by stringency of TST testing for older children and adults, as such this finding is interpreted with caution.[5] Findings of higher VE at high latitude settings may be related to inclusion of individuals who were not already mycobacteria exposed. The 5 studies from latitude 20^{o} – 40^{o} were a mixture of school age or older participants, with mixture of stringent TST testing (3

[4] WHO. http://www.who.int/mediacentre/factsheets/fs104/en/

[5] Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: A systematic review of randomized controlled trials. Clin Infect Dis. 2014;58(4):470–80.

				Pooled VE for birth BCG across 5 RCTs was 59% (95% CI 42-71%) VE for BCG given to TST negative school age children across 4 RCTs was 74% (95% CI 63-82%) Protection in school age children not stringently TST tested, and in older persons with or without stringent testing protection was weaker (VE 41% and VE <20% respectively).ref 5 ***Prevention of Primary M.Tb infection:*** A systematic review and meta-analysis of 14 observational studies in which 3,855 child contacts (age <18 years) of adults with PTB underwent interferon gamma release assay (IGRA) to determine M.Tb infection status, and prevalence of IGRA positivity was compared among those with and without previous BCG vaccination. Prior BCG vaccination was associated with 19 – 27% lower prevalence in TB infection in the child contacts. In 6 of those studies with follow up for disease progression among those already infected (IGRA+) at	studies) and non-stringent testing (2 studies), most studies of low bias. A multivariable analysis of efficacy by latitude that included age, tuberculin testing and diagnostic bias, did not show a statistically significant difference between 20-40 degrees (RR 1.17; 95%CI 0.58-2.36) or 0-20 degrees (RR 1.73; 95%CI 0.93-3.25), compared to >40 degrees latitude.[5]

			enrolment, BCG vaccinated children had 58% (95% CI 23-77%) less progression to any active TB compared to unvaccinated children.[6]	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ *Un-certain* ☐ *Yes* ☒ *Varies* ☐	BCG vaccination in immunocompetent infants is considered as safe.[1]	A systematic review analyzed adverse events following BCG immunization. There was substantial variation in the reported rate of lymphadenitis across countries and across periods, ranging from as low as 0.41 per 1,000 vaccinated children in Saudi Arabia in 2012 to as much as 308 per 1,000 in HIV positive vaccinated children in Haiti in 1994. There was substantial variation in the reported rate of disseminated BCG across countries and across periods, ranging from 1.81 per 1,000 in South Africa to 167 per 1,000 in France. [7]
	Balance between benefits and harms	*Favours inter-vention* ☒ *Favours com-parison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	BCG is safe and reduces various forms of TB in children and young adults.	
	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* ☐	The quality of the evidence for the efficacy against TB disease was moderate. The quality evidence for the efficacy against primary TB infection was low. The evidence was low to moderate quality due to estimates from	There is a paucity of evidence comparing the effectiveness of different BCG products.

[6] Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. BMJ. 2014;349(aug04_5):g4643. Available http://www.bmj.com/content/349/bmj.g4643, accessed September 2017.

[7] Uthman et al. Systematic review on safety of BCG vaccination. available at http://www.who.int/immunization/sage/meetings/2017/october/en/, accessed September 2017.

							observational and RCTs.	
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 available, though it is assumed that in general, there is no important uncertainty or variability.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	There is no evidence on the values and preferences of the target population.
RESOURCE USE	Are the resources required small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐		BCG vaccination is part of the routine immunization programme in many countries; therefore, additional resources will not be needed.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐		Formal cost-effectiveness analyses have not been conducted, but given the emerging evidence of BCG vaccine protection against various forms of TB and a possibly longer duration than previously assumed, the benefits override the cost of the vaccine.	

EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐ | *Un-certain* ☐ | *Re-duced* ☒ | *Varies* ☐	Due to protection by BCG from various forms of TB, particularly in resource-constrained settings, BCG vaccination is expected to reduce health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ | *Com-parison* ☐ | *Both* ☐ | *Neither* ☐ | *Un-clear* ☐	Given the protection by BCG from various forms of TB, administering BCG 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 against various forms of TB is likely to be acceptable to the target group.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Un-certain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | *Varies* ☐	BCG vaccination is part of the routine immunization programme in many countries; therefore, continuation and improvements in BCG delivery are required.	

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)	• 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. 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. • 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	• BCG vaccination relies on the assumption of BCG availability and that it is already routinely administered as part of the national immunization programme.
Monitoring and evaluation	• Continued monitoring of BCG vaccination coverage at birth or soon after is important to ensure that infants are protected early in life.
Research priorities	• Research on the effect of latitude on BCG vaccine efficacy and effectiveness is required by conducting case-control and prospective cohort studies performed within low latitudes in particular. Prior infection or sensitisation to environmental mycobacteria is avoided if given BCG is given soon after birth. Studies on BCG vaccine efficacy and effectiveness should be carefully assessed when BCG is not given soon after birth or after stringent testing if given in childhood.

[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