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.
	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 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)	• Studies show minimal or no evidence of any 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