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.
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 a target for elimination as a public health problem set in 2000, more than 200,000 cases were reported in 2016. The detection rate of the disease (a proxy of incidence rate) is only slightly declining at a rate of about 3% 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 is effective to prevent leprosy and that it 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. A current study is assessing the effect of BCG revaccination among a large cohort of contacts.

[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.

	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 leprosy.	With only limited 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]
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> 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 sub-study from a large 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. Limited data on efficacy among different age groups
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	The limited Evidence available does not support an increased safety risk for BCG vaccination in a population with a high leprosy burden.	

[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

[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

<table>
<tr><td rowspan="4"></td><td>Balance between benefits and harms</td><td>Favours inter-vention: ☒ | Favours com-parison: ☐ | Favours both: ☐ | Favours neither: ☐ | Unclear: ☐</td><td>Evidence of the protective efficacy and effectiveness for BCG vaccine given in infancy is given.
In contrast, evidence on adverse events is limited.</td><td>There is limited evidence of protective efficacy of revaccination of BCG against leprosy.</td></tr>
<tr><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
<table><tr><th>Comparison</th><th>Findings</th><th>Quality</th></tr><tr><td>BCG at birth vs. no BCG or placebo</td><td>Pooled OR 0.45 (0.34-0.56) from Syst.Review[1]</td><td>Moderate</td></tr></table>7</td><td><table><tr><th>Outcome: Leprosy diagnosis</th><th>Number of studies and study design</th><th>Effect estimates</th><th>Quality</th></tr><tr><td>BCG plus killed M. Leprae vs. placebo</td><td>1 RCT</td><td>RR 0.36 (0.26-0.50)</td><td>Modera te</td></tr><tr><td>BCG plus killed M. Leprae vs. BCG alone</td><td>3 RCT</td><td>RR 1.06 (0.62-1.82)
RR 0.89 (0.53-1.47)
RR 0.50 (0.40-0.63)</td><td>Low</td></tr><tr><td>ICRC vaccine vs. placebo</td><td>1 RCT</td><td>RR 0.34 (0.23-0.52)</td><td>Modera te</td></tr><tr><td>Mycobacterium w vaccine vs. placebo</td><td>2 RCT</td><td>RR 0.61 (0.46-0.80)
RR 0.74 (0.56-0.98)</td><td>Modera te</td></tr></table></td></tr>
<tr><td rowspan="3">VALUES & PREFERENCES</td><td>How certain is the relative importance of the desirable and undesirable outcomes?</td><td>Important uncertainty or variability: ☐ | Possibly important uncertainty or variability: ☐ | Probably no important uncertainty or variability: ☒ | No important uncertainty or variability: ☐ | No known undesirable outcomes: ☐</td><td rowspan="2">No evidence available although it is assumed that, in general, there is no important uncertainty or variability.</td><td rowspan="2">In the context of implementation, same 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>
<tr><td>Values and preferences of the target</td><td>No | Probably No | Uncertain | Probably Yes | Yes | Varies</td></tr>
</table>

7 Richardus JH and Oskam L. Protectig people against leprosy: chemoprophylaxis and immunoprophylaxis. Clin Dermatol. 2015 Jan-Feb;33(1):19-25.

	population: Are the desirable effects large relative to undesirable effects?	☐ ☐ ☐ ☒ ☐ ☐		
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, Immunization Managers)?	*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.	

	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 also leprosy by BCG vaccination is likely to increase acceptability 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, EPI and TB.	
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		We recommend the comparison	We recommend against the intervention and the comparison			

	☒ ☐ Only in the context of rigorous research ☐ ☐ ☐ 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 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	• 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