

SAGE evidence to recommendations frameworkⁱ

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 2017¹

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.

¹BCG working group Report, available at <http://www.who.int/immunization/sage/meetings/2017/october/en/>, accessed September 2017.

²BCG World Atlas, 2nd Edition. Available: <http://www.bcgatlas.org/>, accessed July 2017.

³Dierig 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>

⁴Tu 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.

⁵Hersh 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.

⁶Feiring 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>

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	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.
		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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 meningial 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.
		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

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.

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VALUES & PREFERENCE	Are the undesirable anticipated effects small?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<i>Favours intervention</i>	<i>Favours comparison</i>	<i>Favours both</i>	<i>Favours neither</i>	<i>Unclear</i>	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					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.	
		<i>No included studies</i>	<i>Very low</i>	<i>Low</i>	<i>Moderate</i>	<i>High</i>		
	Safety of the intervention							
	<i>No included studies</i>	<i>Very low</i>	<i>Low</i>	<i>Moderate</i>	<i>High</i>			
	<i>Important uncertainty or variability</i>	<i>Possibly important uncertainty or variability</i>	<i>Probably no important uncertainty or variability</i>	<i>No important uncertainty or variability</i>	<i>No known undesirable outcomes</i>	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	

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	outcomes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		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 <input type="checkbox"/>	Probably No <input type="checkbox"/>	Uncertain <input checked="" type="checkbox"/>	Probably Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input type="checkbox"/>	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 <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input checked="" type="checkbox"/>		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 <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input type="checkbox"/>		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 military tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet. 2006 Apr 8;367(9517):1173-80.

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	effectiveness	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input checked="" type="checkbox"/>	<p>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.</p>	<p>the costs and benefits of the BCG vaccine and concluded that vaccination remained cost-effective in high TB incidence settings.</p>
EQUITY	What would be the impact on health inequities?	<p><i>Increased</i></p> <input type="checkbox"/> <p><i>Uncertain</i></p> <input type="checkbox"/> <p><i>No impact</i></p> <input type="checkbox"/> <p><i>Reduced</i></p> <input checked="" type="checkbox"/>	<p><i>Varies</i></p> <input type="checkbox"/>	<p>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.</p>	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	<p><i>Intervention</i></p> <input checked="" type="checkbox"/> <p><i>Comparison</i></p> <input type="checkbox"/> <p><i>Both</i></p> <input type="checkbox"/> <p><i>Neither</i></p> <input type="checkbox"/> <p><i>Unclear</i></p> <input type="checkbox"/>		<p>In low TB countries, universal BCG vaccination is not cost effective. Therefore, the intervention is likely to be more acceptable to key stakeholders.</p>	
	Which option is acceptable to target group?	<p><i>Intervention</i></p> <input type="checkbox"/> <p><i>Comparison</i></p> <input type="checkbox"/> <p><i>Both</i></p> <input type="checkbox"/> <p><i>Neither</i></p> <input type="checkbox"/> <p><i>Unclear</i></p> <input type="checkbox"/>		<p>Ensuring adequate protection is likely the most acceptable option to the target population.</p>	

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		<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>			
FEASIBILITY	<p>Is the intervention feasible to implement?</p>	<p><i>No</i> <i>Probably No</i> <i>Uncertain</i> <i>Probably Yes</i> <i>Yes</i> <i>Varies</i></p> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<p>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.</p>		
Balance of consequences	<p>Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings</p> <input type="checkbox"/>	<p>Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings</p> <input type="checkbox"/>	<p>The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i></p> <input type="checkbox"/>	<p>Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings</p> <input type="checkbox"/>	<p>Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings</p> <input checked="" type="checkbox"/>

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<p style="text-align: center;">Type of recommendation</p>	<p style="text-align: center;">We recommend the intervention</p>	<p style="text-align: center;">We suggest considering recommendation of the intervention</p>	<p style="text-align: center;">We recommend the comparison</p>	<p style="text-align: center;">We recommend against the intervention and the comparison</p>
<p style="text-align: center;">Recommendation (text)</p>	<p style="text-align: center;"><input type="checkbox"/></p>	<p style="text-align: center;"><input type="checkbox"/> Only in the context of rigorous research</p> <p style="text-align: center;"><input checked="" type="checkbox"/> Only with targeted monitoring and evaluation</p> <p style="text-align: center;"><input checked="" type="checkbox"/> Only in specific contexts or specific (sub)populations</p>	<p style="text-align: center;"><input type="checkbox"/></p>	<p style="text-align: center;"><input type="checkbox"/></p>
<p>Countries with a low incidence of TB or leprosy may choose to selectively vaccinate neonates in recognized risk groups for developing disease.</p> <p>High-risk groups to be considered for vaccination include the following:</p> <ul style="list-style-type: none"> • Neonates to parents (or other close contacts/relatives) with previous TB or leprosy • Neonates in households with contacts to countries with high incidence of TB and/or leprosy. • Neonates in any other locally identified risk group for TB and/or leprosy. <p>In a few countries with low TB incidence, BCG vaccination is largely replaced by intensified case detection, contact tracing and supervised early treatment.</p>				

Implementation considerations	<p><u>Switching from universal to selective risk group vaccination at birth</u></p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Feasibility studies by health care system and structure • Cost-benefit studies

¹ 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>