EVIDENCE TO RECOMMENDATIONS TABLE[i] - TYPHOID VACCINES

Question 1: Should typhoid conjugate vaccine be recommended in addition to the available ViPS and Ty21a vaccines for routine use in persons 2 years of age and older?

Population: Individuals 2 years of age and older

Intervention: One dose of TCV (irrespective of other control strategies)

Comparison: (a) One dose ViPS, or (b) 3-dose primary series of Ty21a

Outcome: Typhoid fever (blood culture confirmed)

Question 2: Should typhoid conjugate vaccine be recommended for routine use in children less than 2 years of age?

Population: Children less than 2 years of age

Intervention: One dose of TCV (irrespective of other control strategies)

Comparison: (a) Other vaccine, (b) placebo or (c) no vaccine

Outcome: Typhoid fever (blood culture confirmed)

Background:

Typhoid fever remains a major cause of morbidity and mortality, affecting populations within many low-income and middle-income countries (LMICs). Global estimates of the disease burden range between 11 and 21 million typhoid fever cases and approximately 145 000 to 161 000 deaths annually.

In 2008, SAGE recommended the use of Vi polysaccharide (ViPS) and live attenuated Ty21a vaccines for the control of typhoid in endemic and epidemic settings. Two newer generation Vi-tetanus toxoid conjugate vaccines are currently licensed (Typbar-TCV and PedaTyph™ vaccines) and others are in clinical development or undergoing licensure review by national regulatory authorities.

Decision-makers considering the use of typhoid vaccines in public health immunization programs must take into account the potential added benefits of typhoid conjugate vaccine (TCV) vis-à-vis the currently recommended ViPS and Ty21a vaccines (in persons $\geq$2 years and $\geq$ 5years respectively), the disease burden in the <2 year age group, and the overall public health and socioeconomic impact of typhoid fever in their settings.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☒	Typhoid fever remains a public health problem in many low-income and middle-income countries. In particular disease burden studies in the last two decades have demonstrated high typhoid incidence in South and South-East Asia with marked intra-country heterogeneity in both age-specific and geographic incidence. More recent data from sub-Saharan Africa have also demonstrated substantially high incidence, with evidence of heterogeneity. Past studies suggested that typhoid fever occurs predominantly in urban areas with high population density. However, recent data show equally high or higher incidence rates in some rural sites as in urban sites, underlining that typhoid is not restricted to urban settings with high population density. Typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the 0-4 year age group with a large proportion of disease occurring between 6 months and 2 years of age. Among all age groups 27% of typhoid fever episodes are estimated to occur in children 0-4 years; including 29.7% of typhoid fever episodes in the ≤2 year age	The continued increase in antimicrobial resistance (AMR) of S. Typhi, including the emergence of strains resistant to fluoroquinolones and extended spectrum cephalosporins, as well as the occurrence of large outbreaks caused by multi-drug resistant strains of *S.* Typhi are of significant concern. AMR leads to increased clinical treatment failure and complications, an increased frequency of hospital admission and prolonged hospital stay, and more expensive treatment options not affordable in many endemic settings.

			group, 9.9% in the ≤1 year age group, and 2.9% in infants ≤6 months.[1]	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention *Are the desirable anticipated effects large?*	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	There is moderate-certainty evidence that Typbar-TCV results in improved GMTs and seroconversion rates compared to ViPS vaccine. Among subjects 2-45 years of age, Typbar-TCV elicits significantly higher titres of IgG Vi antibody than unconjugated Typbar at 6 weeks after a primary immunization (1292.5 [95%CI 1152.9, 1448.9], N=332 versus 411.1 [95%CI 358.9, 470.9], N=305) and 6 weeks after a second immunization (1680.6 [95%CI 1498.3, 1885.1], N=174 versus 475.0 [95%CI 339.9, 663.6]) N=50). At 3 and 5 years after a single immunization, the anti-Vi GMTs and the proportion of individuals with titres >4-fold over their baseline were significantly higher among recipients of the TCV.[1] In infants 6-11 months old and toddlers 12-23 months old, a single dose of Typbar-TCV elicited high titres of IgG anti-Vi antibody (1937.4 [95%CI 1785.0, 2102.9], N=307) that endured up to 5 years in a proportion of young children. Data on antibody avidity and IgG subclasses provide further confidence in	Further supporting evidence is provided from an efficacy trial of the first Vi conjugate vaccine (NIH Vi-rEPA, non-commercialized) which demonstrated long-term protection up to 46 months in children aged 2-5 years (VE of 89% [95% CI 76, 97]). The SAGE Working Group on Typhoid Vaccines was unable to conclude on the potential benefits for PedaTyph in order to make a policy recommendation (See Background Paper). There are no comparative data for any TCV versus Ty21a vaccine. An indirect (herd) effect of TCV has not yet been studied. Data to be generated from planned field studies of effectiveness, in Asia and Africa will provide additional evidence for licensed TCVs in the future; these data are not expected to be available in the next years.

[1] WHO. Background paper to SAGE on Typhoid Policy Recommendations. 2017. Available at http://www.who.int/immunization/sage/meetings/2017/october/1_Typhoid_SAGE_background_paper_Final_v3B.pdf?ua=1, accessed December 2017.

			the quality of the antibody response, and that the vaccine-induced immune response is boostable.[1] When Typbar-TCV was evaluated in a human challenge model in a population of immunologically naïve adult volunteers (16 to 80 years of age), efficacy of 87.1% (95% CI 47.2-96.9%) was estimated based on an endpoint of persistent fever followed by positive blood culture, thus reflecting clinical and surveillance parameters under which a typhoid fever case would be confirmed.[1]	
	Harms of the intervention *Are the undesirable anticipated effects small?*	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	The Global Advisory Committee on Vaccine Safety (GACVS) assessed, in December 2016, the safety of the three classes of typhoid vaccines and concluded that ViPS and Ty21a vaccines have a good safety profile, with the most common adverse events being fever, erythema and localized pain, and gastrointestinal events (latter primarily with Ty21a), and that other adverse events are generally rare. GACVS also concluded that the safety profile of the licensed TCV vaccines appeared similar to that of ViPS and no safety signals were reported to date, however there were limitations to the available data. GACVS therefore made recommendations for more robust safety	Supporting evidence on safety is provided by results from the NIH Vi-rEPA vaccine trials, evaluated in >11 000 subjects in Viet Nam, which showed a safety profile similar to that of the ViPS control vaccine, the most common adverse events being fever, erythema and pain at the injection site. Further safety data have been generated by the manufacturer for Typbar-TCV. Additional safety data are planned to be generated in upcoming public sector introduction of TCV in Navi Mumbai, India and in vaccine effectiveness studies planned by the Typhoid Vaccine Acceleration

			monitoring of TCVs (see Background Paper). The human challenge study cited above reported the following frequency of serious adverse events (SAEs): 1/41 (2.4%) in Typbar–TCV recipients (following 1 dose) versus 3/37 (8.1%) in the ViPS group (1 dose) and 0/34 (0%) in the control (ACWY meningococcal conjugate) vaccine group. The SAEs in both the Typbar-TCV and ViPS groups were assessed by the Data Safety and Monitoring Committee within this study and determined to be unrelated to vaccination.[1]	Consortium (TyVAC) in Asia and Africa. The GACVS will maintain a regular review of safety data from multiple sources.
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	The balance favours the intervention in relation to both the <2 year and ≥2 year populations. In the population ≥2 years of age, TCV appears to have a favourable benefit (judged on the immunogenicity profile) over ViPS. The favourable balance is further increased in view of the current AMR trends and their impact on the dynamics of typhoid fever epidemiology and treatment.[1]	A potential herd effect of TCV has not yet been studied (but was demonstrated with ViPS in a randomised controlled trial in Kolkata, India) and not part of the current assessment of balance. A herd effect would ultimately increase the benefit-to-harm ratio.

	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐	<u>Effectiveness (including immunogenicity):</u> Moderate certainty evidence for Typbar-TCV. <u>Safety:</u> Moderate certainty evidence for Typbar-TCV.	Note: The overall assessment on certainty of the evidence takes into account all of the data review (including both the GRADE scores and the expert opinions of the evidence by the Working Group).
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* ☐	Possible desirable outcomes on an individual or population level are a reduction in the occurrence of typhoid fever (reduction of febrile episodes overall) and potential reduction in the consumption of antibiotics A potential undesirable outcome at an individual and programmatic level may be the addition of another vaccine to the routine immunization schedule for children.	

	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 direct evidence is available on the values and preferences of the target population, however, it is expected that these would be positive given the benefits of the intervention to reduce illness, hospitalization and treatment costs. Protection against typhoid fever is likely to outweigh any rare SAEs.	In September 2016, an *Informal Consultation of Experts on Typhoid Fever, South East Asia Region*, hosted by the WHO Regional Office for South-East Asia, expressed the need to review the evidence on the immunogenicity and potential effectiveness of TCV, and to consider vaccine introduction within a framework for typhoid control in the Region.
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	Programmatic use of typhoid vaccines does not currently exist in the majority of endemic countries. Therefore it is likely that as a *de novo* vaccine introduction, substantial resources would be required for vaccine purchase and delivery.	Costs related to the programmatic use of TCV should be balanced against resources/costs for other typhoid control strategies; currently there are no conclusive data from modelling on resources or other studies.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Modelling studies have shown that at approximately USD 2 per dose, routine vaccination with TCV is likely to be cost effective in high incidence settings (Yale model) and most medium incidence settings (Yale and Stanford models). The Stanford model found that in high incidence settings routine vaccination plus school-based catch-up campaigns could be justified.	Countries should conduct cost-effectiveness analyses as part of the decision-making and planning process to initiate programmatic use of typhoid vaccines. Further work is ongoing on the modelling of cost-effectiveness, including a model comparison exercise, and should be used to address current model uncertainties and provide guidance to country decision makers in this area.

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	TCV is currently only available to high income populations through the private sector in India. Public sector introduction of TCV would therefore contribute towards reducing inequities as typhoid is largely associated with underserved populations.	At least one TCV has been licensed in other countries (other than the country of original marketing authorization) and is likely also to be limited to the private sector in those countries although complete data are currently not available to WHO and the Working Group.
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	Countries should assess whether adequate resources can be allocated to implement and sustain typhoid vaccination in the routine immunization schedule. This especially applies to low and middle income countries with limited resources, where typhoid vaccination might be competing with other important public health interventions.	Data on acceptability of TCV (to both the target population and decision makers) are expected to be generated through upcoming studies, notably a study to evaluate the public sector introduction of TCV in Navi Mumbai, India as well as in the vaccine effectiveness studies planned by TyVAC.

	Which option is acceptable to target group?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	Against an option of no vaccine (in children <2 years) it is presumed that the option of TCV would be acceptable to the target group because of the anticipated benefits. Against an option of the currently recommended ViPS or TY21a, the greater benefits of TCV, including the favourable benefit-to-harm ratio, and feasibility of administration in a routine programme (compared to repeated doses parenterally every 3 years for ViPS and 3-dose schedule administered orally every other day for Ty21a) are likely to make TCV more acceptable.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *<u>Varies</u>* ☐	Administration of TCV is similar to other parenteral vaccines in routine childhood immunization (i.e., requires no additional specific skills or equipment), and can be linked to existing EPI contacts	

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)	Among the available typhoid vaccines, TCV is preferred at all ages in view of its improved immunological properties, use in younger children and expected longer duration of protection. Countries may also consider the routine use of ViPS vaccine in individuals aged 2 years and older, and Ty21a vaccine for individuals aged more than 6 years. Choice of vaccination should consider costs, programmatic issues and duration of protection. WHO recommends the introduction of TCV to be prioritized in countries with the highest burden of typhoid disease or a high burden of antimicrobial resistant *S.* Typhi. Decisions on the age of TCV administration, target population and delivery strategy for routine and catch-up vaccination should be based on the local epidemiology of typhoid fever, including antimicrobial resistance patterns, and programmatic considerations of the routine childhood immunization programme. National decisions on the preferred vaccination strategy (universal, risk-based, or phased) should be based on an analysis of the disease burden and risk factors for transmission, availability and quality of surveillance data, cost-effectiveness, affordability, and operational feasibility. The experiences and impact of different vaccination strategies, as well as integration with water, sanitation and hygiene (WASH) or other interventions, should be monitored and documented in order to support further improvement in typhoid control.

Implementation considerations	Currently, no reliable risk prediction tools are available to support implementation of typhoid vaccination programmes using a risk-based approach. Where reliable data are available to assess the level of typhoid fever incidence with confidence, the vaccine delivery strategy should take into account the local epidemiological and programmatic considerations. In particular, in countries with reliable epidemiological evidence of high incidence in well-defined sub-populations, a vaccination strategy based on risk assessment (high incidence population groups) should be considered. This may be particularly important for large countries where resources are limited. In countries with substantial typhoid fever burden but where surveillance does not allow characterisation of typhoid fever incidence among sub-populations, a universal (country-wide) strategy should be considered, and may prove more feasible and cost-effective. In the short-term to medium-term the indication for, and feasibility of, specific delivery strategies – for routine and catch up vaccination - will need to be carefully weighed by national authorities in each country. Decisions on catch up vaccination will need to take into account vaccine supply, expected impact, cost (usually much higher than routine), and other operational issues, including transport, cold chain, and logistics.

Monitoring and evaluation	Introduction of TCV should include post-licensure monitoring of effectiveness and vaccine safety. This should include monitoring of any potential safety risks in special population groups (e.g. malnourished children, immunocompromised individuals and, where applicable, pregnant women). WHO recommends (i) further safety monitoring of all TCVs through strengthening post-marketing surveillance and ensuring robust safety evaluation of TCV in planned effectiveness studies, including any potential safety risks in special population groups (e.g. malnourished children, immunocompromised individuals and, where applicable, pregnant women); (ii) the use of Brighton Collaboration case definitions and active monitoring of serious adverse events of interest; and (iii) analysis of non-specific effects of vaccination, where feasible. Information on antimicrobial resistance patterns will be valuable in informing vaccine introduction decisions, measuring the impact of the vaccine, and adjusting antibiotic treatment recommendations in specific settings. WHO recommends that endemic countries strengthen the surveillance of typhoid fever in all age groups, and monitor the presence of antimicrobial resistant strains of *S.* Typhi in endemic and epidemic disease, before and after introduction of typhoid vaccines.[2] (See also under *General recommendations* in the Background Paper.)
Research priorities	Priority should be given to generating data that will further support typhoid vaccination policy and immunization programmes, particularly through research in the following areas: development of tools or methods to identify populations and individuals at risk of typhoid fever; the risk of transmission from chronic carriers of *S.* Typhi and strategies to identify and treat carriers; correlate(s) of protection for typhoid vaccines; co-administration with other childhood vaccines (where not yet studied); safety and immunogenicity in special populations, including malnourished children, immunocompromised persons, and pregnant women; duration of protection for a single dose of TCV and the potential need for revaccination; whether the tetanus toxoid carrier protein of the licensed TCVs provides protection equivalent to a booster dose of tetanus vaccine; and the impact of different TCV strategies including target age ranges for routine and catch-up vaccination as well as vaccination for outbreak control. (See also summary of research priorities in the *TyVAC Executive Summary* on the SAGE Website

[2] WHO. Surveillance standards for typhoid and other invasive Samonellosis. In: WHO Vaccine Preventable Diseases Surveillance Standards. (In press)

[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/