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<th>Description</th>
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<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>DOMI</td>
<td>Diseases of the Most Impoverished Programme</td>
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<tr>
<td>DTP</td>
<td>Diphtheria-Tetanus-Pertussis vaccine</td>
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<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<tr>
<td>GMT</td>
<td>Geometric mean titre</td>
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<tr>
<td>LMIC(s)</td>
<td>Low and middle income countries</td>
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<tr>
<td>MDR</td>
<td>Multi-drug resistant (in the context of typhoid fever, defined as resistance to the traditional first line antibiotics of ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole)</td>
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<tr>
<td>OLT</td>
<td>Open label trial</td>
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<tr>
<td>OPV</td>
<td>Oral polio vaccine</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SEAP</td>
<td>Surveillance of Enteric Fever in Asia Project</td>
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<tr>
<td>SETA</td>
<td>Severe Typhoid in Africa Program</td>
</tr>
<tr>
<td>STRATAA</td>
<td>Strategic Typhoid Alliance across Africa and Asia</td>
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<tr>
<td>TCV</td>
<td>Typhoid conjugate vaccine</td>
</tr>
<tr>
<td>TSAP</td>
<td>Typhoid Fever Surveillance in Africa Program</td>
</tr>
<tr>
<td>TyVAC</td>
<td>Typhoid Vaccine Acceleration Consortium</td>
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<tr>
<td>ViPS</td>
<td>Vi polysaccharide vaccine</td>
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<tr>
<td>Vi-rEPA</td>
<td>Vi polysaccharide antigen linked to the recombinant exoprotein A of <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>Vi-TT</td>
<td>Vi polysaccharide antigen linked to tetanus toxoid protein</td>
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<tr>
<td>WASH</td>
<td>Water Sanitation and Hygiene</td>
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EXECUTIVE SUMMARY

Typhoid fever remains an important cause of enteric disease in children in Low and middle income countries with global estimates of disease burden ranging between 11 and 21 million typhoid fever cases and approximately 145 000 to 161 000 deaths annually.

Transmission of Salmonella Typhi is by the feco-oral route through a short-cycle (contamination of food and water in the immediate environment through inadequate hygiene and sanitation measures, either by shedding from temporary or chronic carriers) or long-cycle transmission (defined as contamination of the broader environment, such as pollution of water supplies by sewage, inadequate treatment of piped water or use of raw human feces as a crop fertiliser).

The often non-specific symptoms of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide range of other febrile illnesses common in typhoid fever endemic regions. Laboratory confirmation of cases by blood culture (the most commonly used diagnostic test) has a limited sensitivity of approximately 50% and is further complicated by the common practice of pre-treatment with antibiotics or is often not performed for the majority of cases in LMICs.

A consistent finding of typhoid fever disease burden studies in the last two decades has been the high incidence of typhoid fever in South and South-East Asia with marked intra-country heterogeneity in both age-specific and geographic incidence. New data from sub-Saharan Africa have improved the understanding of the burden and risk factors in that region. Furthermore, new data confirm that 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 the age group 0-4 years; including 29.7% of typhoid fever episodes in the ≤2 year age group, 9.9% in the ≤1 year age group, and 2.9% in infants ≤6 months.

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination and appropriate antibiotic treatment are all effective strategies for prevention and control of typhoid fever. Multi-drug resistant (MDR) strains of S. Typhi emerged in the late 1980s leading to widespread use of fluoroquinolones, followed in the 1990s and 2000s by the appearance of fluoroquinolone resistant strains. More recently, MDR S. Typhi has caused large outbreaks in East Asia and Africa that are of significant concern. The S. Typhi H58 clade is responsible for much of the recent and current spread of resistant strains. AMR in typhoid fever 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.

Despite SAGE recommendations in 2008 for the use of Vi polysaccharide (ViPS) and Ty21a vaccines for the control of typhoid in endemic and epidemic settings, routine public health use has been very limited. The evidence review did not change the current recommendations for ViPS and Ty21a vaccines. Two Vi-tetanus toxoid (Vi-TT) conjugate vaccines are licensed in India. Based on the data available for review, the SAGE Working Group concluded that there is moderate-certainty evidence that at least one licensed Vi-TT vaccine (Typbar-TCV™ manufactured by Bharat Biotech International Limited) results in improved GMTs and seroconversion rates compared to ViPS vaccine (there are no comparative data with Ty21a). Further the data on co-administration of Typbar-TCV with measles-containing vaccines (measles and MMR) do not show evidence of interference with the immune responses to either vaccine. Data from a human challenge study using Typbar-TCV in a population of immunologically naïve adult volunteers produced an estimate of efficacy of 87.1% (95% CI 47.2-96.9%) based on an endpoint of persistent fever followed by positive blood culture. This was considered as good supporting evidence for the vaccine.

The available data from modelling indicate that routine immunization with TCV would lead to a gradual but sustained decrease in typhoid fever cases while routine vaccination with catch-up would lead to both an immediate and sustained decline in incidence. Further, cost-effectiveness analysis has shown that at a price of up to USD 2 per dose, routine vaccination with TCV is likely to be cost-effective in high incidence settings and in most medium incidence settings depending on the willingness to pay.

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.

**Draft recommendations:** The Working Group was tasked to address the following overall policy questions:
1. Should TCV be recommended in addition to the available ViPS and Ty21a vaccines for routine use in persons 2 years of age and older? (Critical question)

2. Should TCV be recommended for routine use in children less than 2 years of age? What should be the lower age limit for use in this group? (Critical question)

3. Should different recommendations be developed for use of the above vaccines in endemic settings versus outbreaks or humanitarian emergencies? (Non-critical question)

Based on its evidence review, the Working Group proposed the following draft recommendations for consideration by SAGE.

**Recommendation for individuals 2 years and above**

Given the continued high burden of typhoid fever and the increasing antimicrobial resistance of *S. Typhi*, and in view of the currently available evidence on safety, efficacy, feasibility, and affordability of at least one licensed typhoid conjugate vaccines and of the previously recommended ViPS and Ty21a vaccines, SAGE re-emphasizes the importance of the programmatic use of typhoid vaccines for controlling endemic disease.

Specifically, countries should consider the routine use of typhoid conjugate vaccine or ViPS vaccine or Ty21a vaccine in individuals aged 2 years and above. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. These vaccines should be given irrespective of the intensity of other control strategies.

**Recommendation for children below 2 years**

Given the high proportion of typhoid fever that is sufficiently severe to require outpatient or inpatient care in children <2 years in many areas, SAGE recommends the use of TCV in children <2 years of age, administered as a single dose at any time between 6 months to 23 months of age in endemic countries. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. The decision on the age of TCV administration should be based on the local epidemiology of typhoid fever, geographic heterogeneity, and taking into account programmatic considerations of the routine childhood immunization programme.

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*a* It should be noted that this question was worded to avoid any sense of prioritizing TCV over ViPS or Ty21a.

*b* Critical questions required an assessment of the quality of evidence.
There are opportunities to administer one dose of TCV at 9 months of age with MCV1, or at 15-18 months of age with MCV2, recognizing that in many places the appreciable burden of typhoid fever starts to appear at 12 months of age.

**Recommendation for vaccine use in outbreaks and humanitarian emergencies**

Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended for outbreak control. Typhoid vaccines may be considered in humanitarian emergencies depending on the risk assessment in the local setting. However, it should be emphasized that the mainstay of typhoid fever prevention in such settings is often the provision of clean water and chlorination of water supplies, along with promotion of hygiene measures. The WHO has published guidance for the risk assessment of typhoid and other vaccine-preventable diseases in humanitarian settings as a framework for decision making on the use of vaccines in those settings.

**Recommendations for special groups**

SAGE recommends vaccination of the following specific groups of epidemiological relevance, by virtue of being at high risk or important for transmission, in line with the above age-appropriate recommendations. When ViPS or Ty21a is used, SAGE emphasizes the current recommendations for revaccination.

- **Clinical microbiology laboratory staff** with a recognized risk of occupational exposure to S. Typhi.
- **Professional food handlers**: where possible, preference for use of a Vi negative vaccine, such as Ty21a should be considered in order to protect the possibility for serological identification of a chronic carrier status among vaccinated persons. However, professional food handlers should not go unvaccinated due to lack of Ty21a vaccine. The value of not vaccinating this group (where Ty21a is not available) needs to be carefully weighed within the existing national policies.
- **Travellers from non-endemic to endemic areas**: Typhoid vaccination may be offered to travellers to destinations where the risk of typhoid fever is high. Where available, licensed combination Typhoid-Hepatitis A vaccines may be used for travellers.

**General recommendations**

- All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.
- Ideally, cost-effectiveness analyses should be part of the decision-making and planning process to initiate programmatic use of typhoid vaccines.
- SAGE recommends post-licensure monitoring of effectiveness of TCV (including serological and clinical endpoints) and robust monitoring of safety in line with the GACVS recommendations.
- SAGE recommends that countries monitor the occurrence of AMR strains of S. Typhi in endemic and epidemic disease and contribute to the global database on antimicrobial resistance.
1. MAGNITUDE OF THE PROBLEM

1.1 Background on the pathogen, the disease and risk factors

Typhoid fever is an acute generalized infection, caused by the bacterium Salmonella enterica serovar Typhi (commonly referred to as S. Typhi), which remains an important public health problem in many low and middle income countries (LMICs). Salmonella enterica serovar Paratyphi A and Paratyphi B (and uncommonly Paratyphi C) cause a clinically indistinguishable disease, particularly in parts of Asia. Typhoid fever and paratyphoid fever are collectively referred to as enteric fever. Typhoid fever exhibits a wide range of clinical severity, including a broad spectrum of illness, with more severe forms being characterized by persisting high fever, abdominal discomfort, malaise, and headache.

<table>
<thead>
<tr>
<th>Key new data since 2008 SAGE recommendations</th>
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<tbody>
<tr>
<td>• Global estimates of disease burden ranging between 11 and 21 million typhoid fever cases and approximately 145 000 to 161 000 deaths annually.</td>
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<tr>
<td>• Improved overall understanding of the burden and risk factors in sub-Saharan Africa.</td>
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<tr>
<td>• New data on age-specific occurrence confirm that typhoid fever with severity sufficient to seek medical care is common in the 0-4 year age group, with a large proportion of disease occurring between 6 months and 2 years of age.</td>
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<tr>
<td>• An increasing record of major outbreaks, in some cases with antimicrobial resistant S. Typhi strains.</td>
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<tr>
<td>• Large population-based studies of the burden of typhoid fever are ongoing in Africa and Asia.</td>
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Humans are the only known reservoir of infection of S. Typhi and transmission is by the feco-oral route through consumption of contaminated water or food. Transmission may occur via short-cycle (defined as contamination of food and water in the immediate environment through inadequate hygiene and sanitation measures, either by shedding from temporary or chronic carriers) or by long-cycle transmission (defined as contamination of the broader environment, such as pollution of water supplies by sewage, inadequate treatment of piped water or use of raw human feces as a crop fertiliser) [1].

The incubation period of typhoid fever lasts 7 to 14 days on average, but can range from 3 to 60 days and the untreated illness often lasts several weeks and occasionally months. Complications are estimated to occur in 10 to 15% of hospitalized patients and are more common amongst untreated patients whose illness has persisted for ≥2 weeks, the most common life-threatening complications being intestinal haemorrhage, intestinal perforation and encephalopathy with haemodynamic shock [1]. Recent reports of typhoid fever epidemics in the Democratic Republic of Congo [2] and Uganda [3] described unexpectedly frequent rates of intestinal perforation (>40%) associated with high mortality (18 to 43%). Other less common complications include shock, typhoid hepatitis, empyema, osteomyelitis, and psychosis. In the
pre-antibiotic era, a case-fatality ratio of approximately 10 to 20% was reported however current estimates range from 1 to 4% in those who receive adequate therapy [4]. In approximately 2 to 5% of typhoid fever cases, depending on the individual’s age and whether there is pre-morbid disease of gallbladder mucosa, gallbladder infection during the acute illness persists to establish a chronic carrier state [4]. Chronic biliary carriers have an elevated risk of hepatobiliary cancers [5,6].

Variable hospitalization rates of 2 to 40% have been reported for typhoid fever indicating that the disease can be severe in a notable proportion of patients, while the majority of remaining cases either self-medicate or are treated on an outpatient basis [7,8]. In population-based studies in five Asian countries conducted by the Diseases of the Most Impoverished (DOMI) Programme, the average length of hospital stay was nearly 15 days in China and 9 days in India [8]. A more recent systematic review and meta-analysis of typhoid intestinal perforation in LMICs, covering the period 1991-2011 (23 studies), reported an overall mean length of hospital stay of 18.4 days (N = 2,542; 95% CI 15.6, 21.1) [9].

The often non-specific symptoms of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide range of other febrile illnesses including malaria, dengue fever, influenza and other infections that are common in typhoid fever endemic regions. Reliance on clinical diagnosis not only leads to inaccurate surveillance and a considerable mis-representation of the incidence of typhoid fever, but also can result in inappropriate treatment. In areas where malaria is perceived to be common, patients with typhoid fever may remain undiagnosed and receive inappropriate or delayed treatment, making them more likely to experience more complications and higher mortality. In most settings, confirmation of the diagnosis depends on isolation of S. Typhi in the laboratory through blood cultures. Unfortunately, blood culture is limited by modest sensitivity of approximately 50%. Sensitivity may be further diminished by the common practice of pre-treatment with antibiotics. Blood culture is not often performed for the majority of cases in LMICs, especially among those treated in non-hospital settings and in some countries may be underutilized in both infants and young children. The currently available serological tests are compromised by a variable antibody response to the pathogen that may persist for shorter or longer periods, and cross reactivity of S. Typhi and S. Paratyphi A with other enteric bacteria [10].

*Risk factors for typhoid fever*

The risk of transmission of typhoid fever is increased in populations that lack access to safe water and adequate sanitation, and in the context of poor hygiene among food handlers. Population density, elevation and overcrowding have been associated with an increased risk of enteric fever in surveillance studies in urban areas in India, [11]. However clustering of typhoid fever cases was not associated with population
density in other sites [12]. The risk of typhoid fever has also been associated with lower socioeconomic status, lower literacy rates, increased household size, and handling of *S. Typhi* by clinical microbiology laboratory staff [1,4].

The precise role of chronic carriers in transmission is not fully understood and is thought to vary between settings of high, medium and low disease incidence generally defined as >100 per 100 000, 10-100 per 100 000 and <10 per 100 000 cases per year respectively in typhoid fever endemic areas [13]. Published studies suggest that chronic carriers account for a limited proportion of within-household transmission of typhoid fever, primarily to children [12,14]. By contrast, chronic carriers represent a reservoir of infection, and contribute to the long-term persistence of typhoid fever through ongoing shedding of *S. Typhi* into the environment and possibly contaminating water supplies.

### 1.2 Epidemiological patterns

**The global burden of typhoid fever**

The evidence base [15] and sophistication of methods [16] for estimating the global burden of typhoid fever has grown markedly over the past decade. Estimates of the global burden of typhoid fever have been made by a number of groups with some updating their estimates periodically. The most recent estimate of the global burden of typhoid fever from the World Health Organization, in 2010, was 21.0 million illnesses and 144 890 deaths accounting for 10.3 million disability adjusted life years (DALYs) [17]. The Institute for Health Metrics and Evaluation (IHME) has estimated for 2013 and 2015, 11.0 and 12.5 million illnesses [18,19], 160 700 and 148 800 deaths [20,21], accounting for 11.1 and 10.6 million DALYS [22,23] respectively. A group from Yale University recently estimated that 17.8 million typhoid fever illnesses occurred in 2015 in LMICs [16].

A systematic review of global published and grey literature with mixed methods case studies in eight selected countries was recently performed for the time period 1990 to 2015, to examine trends in typhoid fever incidence and to evaluate contextual factors which could potentially be associated with reduction in incidence of typhoid fever over time at the national level or in large, representative sub-national populations [24]. Contextual factors examined included access to improved drinking water, hand washing, reduction of open defecation, consumption of raw vegetables and fruits or street foods, household size, literacy rates, and antimicrobial resistance (AMR) patterns. No clear pattern was observed in general population incidence trends nor in the reduction of typhoid fever incidence. In contrast to most areas studied, Nepal experienced a possible increase in national incidence between 2008 and 2013. There also
appeared to be no clear pattern in typhoid fever incidence by income level, however the authors reported a lack of adequate information on socio-economic strata. At the subnational level no substantial changes were seen over time, except during outbreaks. In the same project, the country case studies showed a mixed picture with evidence of consistent reduction in typhoid fever rates in some countries including Chile, Thailand and Viet Nam. There appeared to be no clear association with socio-economic development.

Together the data since 2000 show some evidence of a reduced burden of typhoid fever compared to the 1990s, but with little consistency in trends observed [24], and that typhoid fever incidence rates appear to have plateaued in recent years (Figure 1).

Figure 1. Trends in estimates of the global burden of typhoid
Crump et al: estimates are for typhoid + paratyphoid (hollow diamond) and typhoid only (solid diamond)
Buckle et al: estimates are adjusted for low diagnostic sensitivity (hollow circle) and unadjusted (solid circle)
Mogasale et al: estimates are adjusted for water-related risk (solid square) and unadjusted (hollow square)
Courtesy of JD Stanaway [25]

**Country-specific incidence rates and intra-country variations**

A consistent finding of typhoid fever disease burden studies in the last two decades is the high incidence of typhoid fever in South and South-East Asia. Within these regions, there is marked inter- and intra-country heterogeneity in typhoid fever incidence [8,26]. For example, data from the DOMI programme highlighted
incidence rates varying between 24.2 per 100,000 person years in Viet Nam to 493.5 per 100,000 person years in parts of India [8]. A systematic review and meta-analysis of published studies of typhoid and paratyphoid fever in India between 1950 and 2015 reported a statistically significant decline in laboratory-confirmed typhoid fever apparent since the early 1990s but still with a pooled estimate of typhoid fever incidence, based on three population-based studies, of 377 per 100,000 person years [27].

The heterogeneity of typhoid fever disease incidence may be even more pronounced in Africa. Recent data from the Typhoid Fever Surveillance in Africa Program (TSAP) highlighted marked differences between sites with adjusted incidence rates ranging from 0 per 100,000 person years at a site in Sudan to 383 per 100,000 person years at a site in Burkina Faso [15].

In both Asia and Africa, previous studies demonstrated marked intra-country variation suggesting that typhoid fever occurs predominantly in urban areas with high population density. Surveillance in two sites in Kenya between 2006 and 2009 found the incidence of blood-culture confirmed typhoid fever varied from 29 to 247 cases per 100,000 person years in rural and urban sites respectively [28]. However, recent studies have demonstrated high rates of typhoid fever in rural areas in both regions - for example Cambodia [29], Ghana [15] and Tanzania [30] - showing that the disease is not restricted to urban settings with poor sanitation systems. Although populations are small, many island nations of Oceania experience high typhoid fever incidence [16] and large outbreaks.

Seasonal trends in typhoid fever incidence in a given population have been described in some sites (Figure 2) [31] but not found in other sites [15].

**Typhoid fever in infants and children**

The incidence of enteric fever within the paediatric population has historically been an area of debate. Peak incidence has long been described in school-age children 5-19 years of age [4], however conflicting data on the burden of disease among infants and preschool children were published from the 1970s to 1990s. More recently, data from surveillance studies have emerged underlining the large burden of disease in preschool children. The prospect of typhoid vaccines that can be used in infants and young children has focused attention on the occurrence of typhoid fever early in life. A recent systematic review and meta-analysis of studies in Asia and Africa sought to compare the relative proportion of children with enteric fever in the age groups <5 years, 5-9 years, and 10-14 years [32]. This meta-analysis showed that in Africa a relatively smaller proportion of disease occurred in the youngest age group, whereas in Asia there was marked variation between studies in the proportion of disease <5 years of age with some studies showing considerable disease in this age group. Estimates of the proportion of typhoid fever cases in those aged <5
years ranged from 14 to 29%, compared with 30 to 44% in those 5–9 years of age and 28 to 52% in those 10–14 years of age. The review demonstrated that infants and preschool children experience a substantial proportion of disease that would be missed by school-based vaccination campaigns. A limitation of this review however was the lack of age stratification in published reports within the <5 years age group.

Figure 2. Monthly trends in bloodstream infections of invasive *Salmonella* diagnosed at the Queen Elizabeth Central Hospital, Blantyre, Malawi from November 2010-October 2014 [31].

To address the limitation of lack of age stratification in the published literature in the <5 years age group, the WHO SAGE Working Group on Typhoid Vaccines sought unpublished data from sites conducting typhoid fever surveillance and from ongoing studies of typhoid fever epidemiology\(^a\). Data were received from 15 sources from Africa, Asia, and the Americas that allowed typhoid fever occurrence to be calculated by month of age from 0 to 60 months, and in age intervals of 5 years. Available data were of inpatients, outpatients, or both, collected between 1998 and 2017 representing >10 000 blood culture confirmed

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\(^a\) Current disease burden studies are conducted by the following projects: SEAP (Surveillance of Enteric Fever in Asia Project) in Bangladesh, Nepal and Pakistan; SETA (Severe Typhoid in Africa Program) in Burkina Faso, Democratic Republic of Congo, Ethiopia, Ghana, Madagascar and Nigeria; STRATAA (Strategic Typhoid Alliance across Africa and Asia) in Malawi, Bangladesh and Nepal; and the Navi Mumbai TCV Introduction Program in India.
episodes of typhoid fever. These data showed that among studies of all age groups, 27% of typhoid fever occurred in the age group 0-4 years. Of typhoid fever cases in the age group 0-4 years, giving equal weighting to data collected in these studies, 29.7% of typhoid fever episodes occurred at age ≤2 years; 9.9% at age ≤1 year; and 2.9% at age ≤6 months. While the data sources likely reflect locations with high typhoid fever incidence, these data confirm that 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. Figure 3 illustrates the age distribution by month of typhoid fever in children <5 years of age; similar patterns were observed in some but not all of the unpublished datasets reviewed.

Figure 3. Age distribution in children <2 years
Frequency plots of aggregate age distribution data by month for S. Typhi in children <5 years of age.

Black bars represent cases where age in months is known and gray bars represent the cases where age is known in years evenly distributed across the year [33].

Typhoid fever outbreaks

Typhoid fever cases reported in outbreaks are mostly excluded from estimates of typhoid fever burden and there are currently no published estimates of the true burden of typhoid outbreaks in endemic or non-endemic settings. Nonetheless, typhoid fever outbreaks have been reported with increasing frequency in published literature and these substantially improve insights into the public health problem.

In the last decade, well characterized outbreaks of confirmed typhoid fever in sub-Saharan Africa have been
reported in Malawi [33], Mozambique [34], Uganda [3,35], Zambia [36], and Zimbabwe [37] among others.

The increased occurrence of outbreaks due to multi drug resistant S. Typhi is of particular concern (see Section 1.3 for discussion in the context of antimicrobial resistance).

Typhoid fever outbreaks can also reveal important epidemiological data that may not be observed with sporadic cases such as the increased frequency of perforations observed in Uganda and DRC [2,3]. A high frequency of neurological manifestations, including altered mental status, dysarthria, upper motor neurone syndromes, ataxia, tremors and Parkinsonism was described in an outbreak of typhoid fever in 2009 along the Malawi-Mozambique border [34].

Overcrowding, inadequate hygiene and disruption to water supplies following humanitarian disasters can lead to typhoid fever outbreaks. However, there are very few documented reports of typhoid fever outbreaks in humanitarian emergencies such as in Fiji in 2011 during the post-Cyclone Thomas response [38].

Recent work by WHO, US Centers for Disease Control and Prevention (CDC) and the International Vaccine Institute (IVI) to review typhoid fever outbreaks, published from 1990 to 2017 in endemic and non-endemic settings, has yielded preliminary descriptive data on the magnitude of the public health problem. Forty one published reports on typhoid fever outbreaks were considered to have enough epidemiological data to contribute to the initial descriptive analysis; approximately 95% (39/41) of these papers reported confirmation of the outbreak by blood culture isolation of S. Typhi cases, however data on the proportion of blood culture confirmed cases (among all cases reported in the outbreak) was only available for 41% of those (37/39). Not unexpectedly the majority of outbreaks have been reported in Asia and Africa. Among a total of 35 distinct outbreaks described, 10 (25.6%) and 8 (20.5%) were reported in the WHO South-East Asia Region and African Region respectively while the remaining where equally distributed across the other four WHO Regions. Two (of 9) outbreaks in the period 2010 to June 2017 and 2 (of 15) outbreaks in the period 2000 to 2009 were of substantial magnitude, based on the duration (from first to last case) and number of cases (suspected and confirmed) reported: in Lusaka, Zambia (989 days, 2 040 cases) [36], Kasese District, Uganda (875 days, 1 341 cases) [35], Kasese District, Uganda (551 days, 577 cases) [3] and on the Malawi-Mozambique border (252 days, 303 cases) [34]. Such large scale outbreaks point to the potential public health burden, particularly in low resource settings, for the appropriate management of outbreaks. The remaining outbreaks in this period (across all WHO Regions) ranged in duration from 6 to 219 days (mean of 70 days). Notably, some of these relatively shorter-lasting outbreaks had substantial numbers of cases (suspected and confirmed) reported; a range of 6 to 5 963 cases (with a mean of 896
cases) indicating that several epidemiological features - including the attack rate (when reported or possible to calculate), disease severity, fatality, frequency of antimicrobial resistance - are important to fully characterise the magnitude of the public health burden of typhoid outbreaks. Further work is ongoing to finalize this review.

1.3 Trends in antimicrobial resistance of S. Typhi and implications for control

<table>
<thead>
<tr>
<th>Key new data since 2008 SAGE recommendations</th>
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<tbody>
<tr>
<td>• A relentless increase in antimicrobial resistance (AMR) in some regions, including emergence of strains resistant to fluoroquinolones and extended spectrum cephalosporins.</td>
</tr>
<tr>
<td>• Spread of the drug-resistant S. Typhi H58 clade. New drug-resistant clades are emerging.</td>
</tr>
<tr>
<td>• Increasing frequency of outbreaks of multi drug resistant S. Typhi.</td>
</tr>
<tr>
<td>• AMR leading to increases in morbidity and possibly mortality, with an economic impact due to prolonged hospitalization and cost of antimicrobials.</td>
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<tr>
<td>• WHO published (February 2017) the Global Priority Pathogen List, including fluoroquinolone-resistant Salmonella spp. as a high priority pathogen, to guide the research, discovery and development (R&amp;D) of new and effective antibiotics.</td>
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As previously noted, typhoid fever mortality ranged between 10 and 20% in the pre-antibiotic era, and the introduction of effective antibiotics reduced this to 1 to 4%. Significant antibiotic resistance began to appear in S. Typhi in the 1970s in the form of resistance to chloramphenicol, then the antibiotic of choice for treatment. At this time resistance was sporadic in the sense that resistant S. Typhi would emerge in a particular region but not become fixed in the population for substantial lengths of time. Multi-drug resistant (MDR) strains of S. Typhi, defined in the typhoid fever literature as resistance to the traditional first line antibiotics of ampicillin, chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole, first appeared in the late 1980s in South Asia and the Middle East [39,40]. More recently, MDR S. Typhi has caused large outbreaks in East Asia and Africa [3,30,34-36,41]. The MDR phenotype is encoded by resistance genes that are carried on transferrable plasmids. The appearance of MDR strains led to widespread use of fluoroquinolones, but in turn was followed in the 1990s and 2000s by the appearance of strains with decreased susceptibility to fluoroquinolones, mediated by point mutations in the fluoroquinolone target genes, and associated with an impaired response to fluoroquinolone treatment [7, 39-42]. A Cochrane review of fluoroquinolone use conducted in 2011 found some evidence that gatifloxacin, the “newest fluoroquinolone” at the time, remained effective in some regions where resistance to older fluoroquinolones has developed [43]. Strains with full resistance to fluoroquinolones, such as ciprofloxacin and gatifloxacin, are now increasingly common in South Asia [44,45] and have been spreading into sub-Saharan Africa [46,47]. As resistance to fluoroquinolones has emerged in particular regions, other
antibiotics such as cephalosporins and azithromycin have become the drugs of choice. Sporadic reports of resistance to azithromycin has appeared but as yet has not become common [39,40,48,49]. Extended-spectrum cephalosporins such as cefixime, ceftriaxone have been reliably active until recently. Since 2010 there have been increasing reports of extended-spectrum cephalosporin resistant strains in Asia and Africa (often due to the CTX-M ESBL gene) [39,40]. A large outbreak in Pakistan of MDR typhoid resistant to fluoroquinolones and extended spectrum cephalosporins has recently been reported and is still ongoing [50]. These patients are needing treatment with oral azithromycin and intravenous meropenem, a drug class of last resort.

AMR in typhoid fever leads to an increased proportion of patients experiencing clinical treatment failure and complications, an increased proportion requiring hospital admission and prolonged hospital stay, and the need to use more expensive treatment options [39,40,51-53]. Mortality may increase depending on specific local AMR patterns and drug availability [39,40,51]. Acute faecal shedding of S. Typhi for the initial weeks after completion of treatment can be five-fold higher after treatment of more resistant strains, so that although patients are clinically cured, there is an increased transmission of such resistant strains [54]. AMR in typhoid fever could also lead to an increase in chronic carriers, through poorly effective therapy, and the prevalence of chronic carriers is associated with long-term risk of increased prevalence of hepatobiliary carcinoma [56]. AMR is associated with typhoid fever outbreaks. Recent outbreaks have occurred in Malawi [33], Mozambique [34], Uganda [3,35] and Zambia [36] due to the H58 multidrug resistant clade with a high proportion of patients developing complications. The ongoing outbreak in Hyderabad, Pakistan of MDR S. Typhi infections with additional resistance to fluoroquinolones and ceftriaxone is a cause for serious concern [50]. Although, at present ciprofloxacin and ceftriaxone resistance is found in less than 1% of all strains in Pakistan, historical parallels suggest that resistance rates can change quickly. In Ho Chi Minh City, Viet Nam in 1998, strains with decreased susceptibility to fluoroquinolones increased from less than 5% to 80% in a few months [55].

The global pattern of AMR is dynamic (Figure 4) and changing in each location and over time [56]. In a recent systematic review of published reports of antimicrobial resistance of S. Typhi over the last 20-30 years, a general decline in MDR strains as well as an increase in strains with decreased susceptibility to fluoroquinolones have been seen [56]. There are limitations in the data on AMR, in that typhoid rates based on hospitalized cases are generally biased towards more resistant strains and data from young children are often lacking because of the reluctance of clinicians to take blood from this group. Nevertheless, it is clear that antimicrobial resistant S. Typhi infections are common in many areas and that the introduction of a resistant strain in a new area can lead to large outbreaks. The S. Typhi H58 clade, with IncHI1 plasmids
carrying MDR genes and target site mutations causing fluoroquinolone resistance, is responsible for much of the recent and current spread of resistant strains. The clade is considered to have emerged on the Indian subcontinent 30 years ago, and then spread to South-East Asia and most recently to sub-Saharan Africa [57,58]. The H58 clade appears to remain fit and competitive and is able to rapidly reacquire the MDR phenotype, suggesting that it may be adapted to the MDR state in a manner we do not understand. Other recent studies indicate that H58 is also acquiring other new phenotypes such as increased bile resistance [56]. New clades are also appearing in Nigeria and Democratic Republic of Congo [59].

![Antimicrobial Resistance Trends](image)

**Figure 4.** Trends in antimicrobial susceptibility of S. Typhi over time [56]

Graphical representation of the proportion of S. Typhi isolates globally that are resistant to antimicrobials (indicated by coloured lines). Isolates represented in this graph were consolidated from published reports assembled systematically between 1973 and 2015 from endemic and epidemic sources. Note that Nalidixic acid susceptibility is sometimes used as an indirect indicator of fluoroquinolone resistance, although this is not a tight correlation. In addition the CLSI guidelines for ciprofloxacin have changed periodically and the more recent revisions are likely to be more accurate.

A febrile illness is one of the commonest reasons for individuals to seek healthcare and antibiotic treatment in LMICs [60]. This antibiotic usage is likely both directly (through targeted treatment) and indirectly (through general usage) to be driving the emergence of resistance in S. Typhi. In regions where typhoid fever is common, anyone presenting with a persistent fever is a suspect typhoid fever case once malaria has been excluded, and is likely to be treated with antibiotics [61,62]. As vaccination is not in routine use in almost all endemic countries, antibiotics are the treatment of choice even when a confident diagnosis of
Typhoid fever is lacking. Population and hospital based studies of febrile illness in children and healthcare utilization in LMICs have shown a high prevalence of antibiotic prescription for febrile illness [63-65] as well as a common practice of seeking healthcare in pharmacies [28,56,66]. Efficacious antibiotics can speed recovery (within days), reduce the risk of complications and can limit the shedding of S. Typhi. Where there is resistance to the antibiotic of choice recovery can be significantly delayed and relapse of the disease (even months later) may become more common [42]. Complicating things further is the risk in LMICs that antibiotics will be bought without prescription and without clinical supervision and the quality of the antibiotic is not guaranteed. The deployment of typhoid vaccines could therefore have a dual effect of reducing the levels of circulating S. Typhi that are resistant to the local treatment of choice, and also reducing the levels of patients presenting with a febrile syndrome who are currently being prescribed antibiotics. Over time this may change physician practices towards prescribing less antibiotics. The consequent reduction in antibiotic usage could reduce the antibiotic pressure that is driving the current emergence and spread of new resistant S. Typhi phenotypes.

2. TYPHOID FEVER PREVENTION AND CONTROL MEASURES

<table>
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<th>Key new data since 2008 recommendations</th>
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<td>• Despite SAGE recommendations almost a decade ago for use of Vi polysaccharide and Ty21a vaccines, their uptake has been limited and mostly implemented through short-term programmes or demonstration projects.</td>
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<td>• The UN Sustainable Development Goals (SDGs) provide a relevant framework within which control of typhoid and paratyphoid fever, through integration of vaccination with other intervention, should be leveraged and implemented by policy makers (most notably SDG #6: Ensure availability and sustainable management of water and sanitation for all).</td>
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Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination are all effective strategies for prevention and control of typhoid. Further, acute typhoid fever and S. Typhi chronic carriage can be effectively treated with antibiotics and thereby curtail faecal shedding. The growing prevalence of antibiotic resistance has made this treatment option increasingly difficult and costly.

Improvements to water supplies, including filtration and chlorination can reduce the burden of typhoid fever and have led to its virtual elimination in many high-income settings. Conversely, contamination of municipal water supplies and drinking un-boiled water have been implicated in several outbreaks of typhoid fever in diverse settings [1]. In one outbreak in Tajikistan in 1997, associated with inadequate treatment of
municipal water supplies, the re-introduction of chlorination of water supplies was effective in leading to a marked decline in typhoid fever cases [67].

There is evidence that typhoid immunization can substantially reduce typhoid fever burden, especially when targeted towards high-risk age groups and geographic areas, and when combined with improved sanitation. Unlike the significant investment required for major infrastructure development, vaccination is relatively more affordable to governments, does not require substantial behavioural change and has been shown to be cost-effective [68]. In general, most policymakers agree that routine public health use of typhoid vaccines should be integrated with other control strategies: access to safe water supply, sanitation improvements, hygiene education messages, community or national food hygiene measures, and appropriate case and chronic carrier detection and management.

3. POLICY QUESTIONS REVIEWED BY THE SAGE WORKING GROUP ON TYPHOID VACCINES

The Working Group reviewed and assessed the currently available evidence on typhoid fever and typhoid vaccines (including Ty21a and Vi polysaccharide (ViPS) vaccine, in addition to typhoid conjugate vaccine (TCV)), to inform policy recommendations to be submitted to SAGE for consideration in October 2017 and for the subsequent update of the current WHO Position Paper on Typhoid Vaccines [69]. The Working Group defined an overall set of policy questions on which recommendations would be based as well as a set of questions to guide the assessment of the quality of evidence and inform the assessment of the overall policy questions.

**Overall vaccine policy questions:**

4. Should TCV be recommended in addition to the available ViPS and Ty21a vaccines for routine use in persons 2 years of age and older? (Critical question)

5. Should TCV be recommended for routine use in children less than 2 years of age? What should be the lower age limit for use in this group? (Critical question)

6. Should different recommendations be developed for use of the above vaccines in endemic settings versus outbreaks or humanitarian emergencies? (Non-critical question)

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a It should be noted that this question was worded to avoid any sense of prioritizing TCV over ViPS or Ty21a.

b Critical questions required an assessment of the quality of evidence.
Specific (critical) questions on vaccine performance:

1. What is the effectiveness of ViPS and live attenuated oral Ty21a vaccines in preventing typhoid fever in the target age groups?
2. What is the effectiveness of TCV in preventing typhoid fever in persons aged 2 years and above, in children aged 12-23 months, and in infants less than 12 months of age?
3. What is the duration of protection following vaccination with TCV? Is there a need for a booster dose following primary immunization with typhoid conjugate vaccine?
4. What is the risk of serious adverse events (SAEs) following vaccination with ViPS, Ty21a and TCV?

In order to address these policy-related questions, the most recent available data and evidence on the following topics were reviewed: the epidemiology of typhoid fever; global and country trends of typhoid fever and its risk factors; antimicrobial resistance of S. Typhi and implications for typhoid fever control; and data on the composition and performance of licensed typhoid vaccines; mathematical modelling of typhoid fever transmission and vaccine impact; and a cost-effectiveness evaluation of TCV. For the assessment of the quality of evidence in relation to the critical questions, a systematic review and meta-analysis of immunogenicity, efficacy and safety data for typhoid vaccines was commissioned by WHO and performed by the Cochrane Response and the Cochrane Infectious Disease Group (see Annex C).

4. CHARACTERISTICS AND PERFORMANCE OF TYPHOID VACCINES

Key new data since 2008 recommendations

- Field effectiveness trials of ViPS in Kolkata, India and Karachi, Pakistan showed moderate protection (56-59%) of older children 5-16 years old while there was variable protection of preschool children 2-4 years of age in the 2 settings. Indirect protection was shown in the Kolkata trial but not in the Karachi trial.
- New data on typhoid conjugate vaccines; two products licensed in India (and other countries for one of the 2 products) and available in the private market.
- Large field effectiveness trials are planned under the Typhoid Vaccine Acceleration Consortium (TyVAC).

4.1 Vaccines currently recommended by WHO

Two currently licensed typhoid fever vaccines – a live oral Ty21a vaccine and a parenteral Vi polysaccharide (ViPS) vaccine - have been recommended by WHO for use since 2000. In 2007, SAGE endorsed updated recommendations for public health use of both vaccines for the control of endemic and epidemic disease [69]. The recommendations emphasized the immunization of school-age and/or preschool-age children in areas where typhoid fever in these age groups is shown to be a significant public health problem, particularly where antibiotic-resistant S. Typhi is prevalent. However, since the 2008 WHO Position Paper, a
low typhoid vaccine uptake in endemic countries has been observed. Multiple contributing factors have been reported, including challenges with (a) national level decision-making (e.g., lack of disease burden estimation and ascertainment of high-risk groups for a risk-based vaccination strategy); (b) financing (lack of national funds and donor support) and (c) implementation strategies, including integration with existing vaccination schedules.

**Vi polysaccharide vaccine**

This subunit vaccine was first licensed in the United States in 1994 and is recommended for use in individuals ≥2 years of age. It is composed of a purified Vi capsular polysaccharide from the Ty2 S. Typhi strain and elicits a T-cell independent IgG response. ViPS vaccine is given parenterally as a single dose (with a target value of about 25µg of Vi antigen) and is followed by high levels of seroconversion of serum IgG anti-Vi antibodies [70-73]. Administering a booster dose one or two months later is not helpful, since unconjugated ViPS is a T-independent antigen that does not confer immunological memory. In persons immunized with Vi who live in non-endemic areas the titres of serum anti-Vi drop rapidly after the second year [73]. Hypo-responsiveness upon subsequent re-vaccination with ViPS, as is seen with meningococcal C and pneumococcal polysaccharide vaccines, was suggested in some studies but was not observed in others [74-77]. In the pre-licensure trials in Nepal, South Africa and China, vaccine effectiveness was 72% (95% CI 42, 86) [70], 64% (95% CI 36, 79) [71], and 69% (95% CI 28, 87) [78] over 17 months, 21 months and 19 months of follow-up, respectively. In a post-licensure cluster randomized trial in Kolkata, vaccine effectiveness was 56% (95% CI, 18,77) in the older children 5-14 years of age, and 80% (95% CI 53, 91) in children under 5 years of age [79]. This finding of a higher level of protection in younger children was unusual among field trials of typhoid vaccines. Immunization of older age groups within the same community could have resulted in a possible herd immunity that may have influenced the estimate of protection in the young children. When the same Vi vaccine was evaluated in another cluster randomized trial in children in Karachi, Pakistan, no protection was seen in younger children <5 years of age, while the vaccine effectiveness in children 5-16 years of age was 57% (95% CI 6, 81) [80], and very similar to the protection observed in this age group in the Kolkata trial [79]. An outbreak of typhoid fever in a contingent of vaccinated French soldiers in Cote d’Ivoire showed that an interval since vaccination of greater than three years was a significant risk factor for development of typhoid fever [81]. In volunteers immunized with ViPS or placebo and challenged experimentally with virulent S. Typhi, the level of efficacy of Vi vaccine was 56%. Results of pre-licensure clinical trials of ViPS vaccine and the results of the post-licensure effectiveness trials in Kolkata and Karachi are summarized in Annex A.
Several Vi products have been licensed and marketed globally or locally; there is currently one WHO prequalified product, Typhim Vi\textsuperscript{TM} produced by Sanofi Pasteur.

**Vi combination vaccines**

Two Vi polysaccharide–hepatitis A combination vaccines are licensed mainly for use by travellers: Hepatyrix\textsuperscript{TM} produced by GSK Biologics and Viatim\textsuperscript{TM} produced by Sanofi Pasteur MSD. Each of these combination vaccines is described as stimulating seroconversion to the component vaccine antigens in a manner equivalent to monovalent Vi and hepatitis A vaccines [4].

**Ty21a vaccine**

This vaccine was first licensed in Europe in 1983 and in the USA in 1989, and is recommended for use in individuals aged ≥5 years of age. It is an orally administered, live attenuated Ty2 strain of *S. Typhi* which harbours a number of attenuating mutations among which the inactivation of galE (encoding an enzyme involved in lipopolysaccharide biosynthesis) and the inability to synthesize Vi polysaccharide capsule are of particular importance [82-84]. The Ty21a vaccine stimulates serum and mucosal antibodies to O, H and other surface antigens and elicits powerful, long-lived cell-mediated immune responses (including cytokine production and cytotoxic lymphocytes that recognize cellular targets expressing *S. Typhi* antigens) [85-86]. However, because the antigen is lacking, Ty21a cannot stimulate Vi antibodies.

One non-mechanistic correlate of protection is serum IgG anti-O seroconversion [87] and another is the magnitude of the IgA antibody secreting cell (ASC) response 7 days following oral immunization [88]. These responses correlated with immunization schedules and formulations that conferred the highest levels of efficacy during field trials of efficacy in Chile. The magnitude of cell-mediated immune responses is now considered to be the best predictor of protection.

Vaccine efficacy of Ty21a was 87% in early volunteer challenge studies in the early 1970s [89], and 96% (95% CI 77, 99) in the first cluster randomized efficacy trial in Alexandria, Egypt in school children 6-7 years of age who were followed for three years [90]. The formulation used in the Alexandria trial was not amenable to large-scale manufacture. Four additional trials of different formulations and immunization schedules of Ty21a were carried out in Santiago, Chile in the 1980s. Three doses of Ty21a in enteric-coated capsules, taken orally every other day conferred 67% (95% CI 47, 79) protection over three years [91] and 62% protection over seven years [92] of follow-up in a cluster randomized (by school classes), placebo-controlled field trial of efficacy. Vaccine efficacy increased with age and was 59% in 5-9 year old children, 67% in 10-14 year olds and 85% in teenagers >15 years of age [91]. A double sachet formulation that allowed
administration in a liquid cocktail amenable to reliably immunizing younger and older children conferred 77% protection over three years [93] and 78% protection over five years [92] of follow-up in another field trial in Santiago, Chile. In a large-scale effectiveness trial in which 216 692 Santiago school children were randomly allocated to receive two, three or four doses of vaccine in an every other day schedule, the incidence of typhoid fever diminished significantly with increasing number of doses administered [94]. Ty21a vaccine was also found to confer a moderate level of protection (49%) against S. Paratyphi B disease [95]. In a trial of children and adults in a very high incidence setting in Plaju, Indonesia, where vaccine or placebo was randomly allocated at the level of the individual, three doses (one week apart) of a double sachet “liquid” formulation conferred 53% efficacy, while three doses of enteric-coated capsules taken one week apart provided 42% efficacy over three years of follow-up [96]. In this trial, Ty21a did not confer protection against S. Paratyphi A, which was also circulating in the trial region. The previously marketed liquid formulation of Ty21a is no longer produced.

Results of pre-licensure clinical trials of the Ty21a vaccine are summarized in Annex A.

**Safety of ViPS and Ty21a vaccines**

No serious adverse events and a minimum of local adverse events were associated with ViPS vaccination of >11 000 children in South Africa, almost 7 000 individuals aged 5–44 years in Nepal, approximately 130 000 subjects aged 3–50 years in China and nearly 195 000 individuals in 5 Asian sites. The ViPS vaccine has also proved to be well tolerated and safe when co-administered with routine childhood vaccines. Furthermore, re-vaccination of children aged 9–14 years two years after the first dose of ViPS has been shown to be safe. Currently, WHO recommends no contraindications to the use of ViPS vaccine other than previous severe hypersensitivity reaction to vaccine components. Although the ViPS vaccine is safe for HIV-infected individuals, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells [69].

Ty21a is remarkably well tolerated and has low rates of adverse events. In 3 double-blinded, randomized placebo-controlled efficacy trials in Chile and Indonesia involving approximately 325 000 schoolchildren and both formulations of the vaccine, reactogenicity was assessed through active surveillance. The rates of diarrhoea, vomiting, fever and rash were not significantly different between the vaccinated and the control groups [4]. Proguanil and antibacterial drugs should be stopped from 3 days before until 3 days after giving Ty21a, as such drugs may harm live bacterial vaccines. The vaccine is unlikely to be efficacious if administrated at the time of ongoing diarrhoea. It is not known whether this live attenuated vaccine may
cause fetal harm when administered to pregnant women. Ty21a can be administered to HIV positive, asymptomatic individuals as long as the T-cell count (CD4) is >200/mm³.

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed data on the ViPS and Ty21a vaccines in December 2016 and concluded that both 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 [97].

The results of the Cochrane systematic review and meta-analysis of serious adverse events for ViPS and Ty21a vaccines are included in Annex C.

### 4.2 Typhoid conjugate vaccines

Covalently linking polysaccharides to carrier proteins to produce conjugate vaccines that are administered parenterally modifies fundamentally the manner in which the polysaccharides are seen by the immune system and the magnitude and quality of the immune responses that ensue. The practical consequence being that the T-independent antigen behaviour of unconjugated polysaccharides (characterized by limited affinity maturation and relatively short-lived production of antibody of low avidity, poor (or absent) immunogenicity in infants, and lack of immunologic memory) is replaced by more robust responses involving high avidity antibody and evidence of immunologic memory, including in young infants. A succession of safe, well tolerated, immunogenic and highly protective conjugate vaccines ensued to prevent invasive disease caused by *Haemophilus influenzae* type b, 13 serotypes of *Streptococcus pneumoniae*, and four serogroups of *Neisseria meningitidis*. Collectively, these conjugate vaccines constitute among the best tolerated, most immunogenic and most protective vaccines ever developed and have been amongst the most impactful public health tools for disease control.

Despite the extraordinary achievements of various conjugate vaccines, there are subtleties and complexities that influence their performance. Even within a broad category such as Hib conjugate vaccines, the immunogenicity and level and duration of protection can vary widely from one conjugate to another depending on the specific carrier protein, the length and structure of the polysaccharide and the method of conjugation [98]. This should be taken into account as one reviews the various new typhoid Vi conjugates that are already licensed or in clinical development.
**Development of Vi conjugate vaccines**

Recognizing that *S. Typhi* expresses a highly regulated Vi (for “virulence”) capsular polysaccharide on its surface and that purified Vi polysaccharide was immunogenic and moderately protective in adults and children >3 years of age, stimulated research to develop typhoid Vi conjugate vaccines that might enhance and extend protection and allow immunization of infants and toddlers, something that unconjugated Vi as a T-independent antigen cannot do successfully. This work, which began in the early 1980s, included the evaluation of multiple potential carrier proteins [99,100]. Substantial data on human immunogenicity and evidence of efficacy are available for two specific TCVs, one consisting of Vi linked to the recombinant exoprotein A of *Pseudomonas aeruginosa* (Vi-rEP<sub>A</sub>) and the other linked to tetanus toxoid protein (Vi-TT). Two Vi-TT products are licensed in India (Typbar-TCV™ manufactured by Bharat Biotech International Limited [or Bharat Biotech] and PedaTyph™ manufactured by Bio-Med Private Limited). Two additional products are undergoing licensure review by national regulatory authorities including a Vi-TT and a Vi-rEP<sub>A</sub> product in India and China, respectively.

**Vi-rEP<sub>A</sub> vaccine (US National Institutes of Health)**

Extensive clinical data exist for a prototype Vi-rEP<sub>A</sub> vaccine developed by the US National Institutes of Health (NIH) which demonstrated safety, immunogenicity and clinical efficacy in the course of trials in infants, children and young adults in Viet Nam. A Phase III efficacy study in 11 091 Vietnamese children 2-5 years old showed a two-dose efficacy (per protocol analysis) of 91.5% (95% CI 77.1, 96.6) during 27 months of active surveillance. During these 27 months there was 87.7% efficacy among 771 recipients of a single dose of vaccine (intent-to-treat analysis). Passive surveillance was continued for 19 additional months during which vaccine efficacy was 82.4% (95% CI 22.3, 9.1) (intent-to-treat analysis). The efficacy over the full 46 months of surveillance was 89.0% (95% CI 76.0, 96.9) (intent-to-treat analysis) [101]. When disease occurred among children vaccinated with Vi-rEP<sub>A</sub>, illness severity (determined by rate of hospitalization) was reduced. Vaccination with a full dose (25µg of Vi polysaccharide) and half dose (12.5 µg) elicited similar responses.

Vi-rEP<sub>A</sub> was demonstrated to be safe and immunogenic in infants when given on a primary schedule of 2, 4 and 6 months plus a booster dose at 12 months of age with concomitant administration of routine EPI vaccines (DTP, OPV and Hepatitis B) [102]. The Vi-rEP<sub>A</sub> trials in Viet Nam showed persistence of antibodies above putative protective levels for 8 years in 75 children who were given a single-dose of Vi-rEP<sub>A</sub> at 5-8 years of age upon completion of the efficacy trial and whose titres were followed for 8 years thereafter.
This experimental vaccine was not commercialized and remains the only conjugate candidate for which clinical efficacy data have been generated in the target population.

**Typbar-TCV® (Bharat Biotech): Clinical trials by the manufacturer**

Typbar-TCV consists of 25µg of Vi polysaccharide from *S. Typhi* conjugated to tetanus toxoid carrier protein in isotonic saline, licensed as a single intramuscular dose for use in children aged 6 months and above and in adults ≤ 45 years.

Four key clinical trials have been conducted by Bharat Biotech with their Vi-TT conjugate vaccine as outlined below (see Annexes B1 to B4 for flow charts):

1. A randomized controlled trial (RCT) comparing the clinical tolerability and relative immunogenicity of Typbar-TCV versus Typbar vaccine (unconjugated ViPS produced by Bharat Biotech, 25 µg Vi polysaccharide per 0.5ml dose) in subjects 2-45 years of age.

2. An open label trial (OLT) that assessed the safety and immunogenicity of Typbar-TCV in infants 6-11 months and toddlers 12-23 months of age. This trial represented the first use of Typbar-TCV in young children <2 years of age. A proportion of the infants and toddlers were given a booster dose of Typbar-TCV two years after primary immunization (day 720) which allowed the response to a booster to be assessed, as well as the magnitude and kinetics of the antibody titres up to 5 years after primary immunization in some boosted and unboosted children who were followed long-term.

3. A randomized controlled trial comparing the reactogenicity and immunogenicity of Typbar-TCV versus Sanofi Pasteur ViPS (Typhim Vi) in subjects 2-15 years of age. Typhim Vi is currently the only WHO pre-qualified typhoid vaccine.

4. A comparison of the reactogenicity and immunogenicity following co-administration of measles vaccine with Typbar-TCV at ~9 months of age versus either vaccine administered alone and of Typbar-TCV co-administered with measles-mumps-rubella (MMR) vaccine in subjects 2-15 years of age at 15 months of age to determine whether there is clinical or immunologic interference. One sub-group that received Typbar-TCV with measles got a booster with Typbar-TCV one month later. Another subgroup got a booster with Typbar-TCV 180 days later.

1. **RCT comparing the immunogenicity of Typbar-TCV versus Typbar**  
   (Annex B1, Table 1)

This trial was undertaken to compare directly, in randomly allocated groups of subjects 2-45 years of age, the relative immunogenicity and clinical tolerability of unconjugated ViPS (Typbar) versus conjugated Vi-TT
Serum specimens collected at day 0 and day 42 showed the rise in geometric mean titre (GMT) and the percent seroconversion (4-fold or greater) following administration of a single dose of either vaccine. While the rates of seroconversion of serum IgG anti-Vi antibody were similar in recipients of each vaccine (97.3% for Typbar-TCV and 93.1% for Typbar), the day 42 GMT of the Typbar-TCV group (1292.5 [95% CI 1153, 1449]) was significantly higher than for the recipients of the unconjugated ViPS (411.1 [95% CI 359, 471]) [104].

The clinical protocol was amended so that a homologous booster dose of Vi-TT or ViPS could be administered to a proportion of subjects 720 days after they had received their first dose of vaccine; serum was obtained on day 720 and 42 days later (day 762) to measure Vi antibody titres. Six weeks following receipt of the second immunization with Typbar-TCV or Typbar, the GMTs of subjects given either vaccine rose 19-fold (Typbar-TCV) and 9-fold (Typbar), with the Typbar-TCV GMT reaching a day 762 anti-Vi titre ~3.6-fold higher than the subjects boosted with Typbar [104]. The anti-Vi antibody responses to the ViPS and Vi-TT vaccines following the primary and the booster dose of ViPS or Vi-TT vaccines were previously reported [104]. Some of these results are also summarized in Figure 5A.

The clinical protocol for this trial was further amended to allow follow-up blood specimens to be obtained from any participants, boosted or unboosted, who were available on days 1095 and 1825, i.e., 3 years and 5 years after initial vaccination, and 2 years and 3 years after the day 720 booster for those who were boosted. This amendment allowed the longevity of the Vi antibody responses to be assessed. The serological data summarized as the GMT observed at different time points in the various groups are shown in Figure 5A. Light blue bars (solid and hatched) show the kinetics of anti-Vi antibody in a group of 84 compliant subjects, the “all specimens cohort”, who received primary immunization with Typbar-TCV on day 0 and a second immunization on day 720, and had serum specimens collected at all time points including days 0, 42, 720, 762, 1095 and 1825. The baseline day 0 GMT of this compliant “all specimens cohort” of individuals closely resembles the baseline GMT of the other groups. The GMT rose markedly on day 42 following primary immunization but fell ~10-fold by day 720. Following the booster dose of Typbar-TCV the GMT rose notably to reach a level slightly higher than day 42. Sera collected on days 1095 and 1825 from this highly compliant group of subjects showed that the GMT fell significantly from the day 762 GMT but nevertheless remained significantly higher than the day 720 GMT. Although the day 1825 GMT was somewhat lower than day 1095 GMT, the difference was not significant and the slope of the antibody decline between these last two time points two years apart was gradual.
For comparison, Figure 5A also shows the kinetics of the Vi antibody GMTs in a compliant “all specimens cohort” of 26 subjects who received primary immunization with Typbar ViPS vaccine (dark blue bars, solid and hatched) and provided serum specimens at all key time points including days 0, 42, 720, 762, 1095 and 1825. The GMT on day 42 was significantly lower in the Tybar ViPs subjects than for the recipients of Typbar-TCV, as was the day 762 GMT of Typbar ViPs recipients following a re-immunization with the same vaccine on day 720, when compared to the “all specimens” subjects who were boosted with Typbar-TCV (light blue hatched bars). However, by day 1095 and 1825 the GMTs of the compliant “all specimens cohort” who received a primary and a second immunization (day 720) with Tybar were not significantly lower than the “all specimens cohort” who received primary and booster doses of Typbar-TCV. Similar observations were made for less compliant “any available specimens” subjects who received primary immunization, were boosted on day 720 and had serum specimens collected on days 0 & 42 and at least one other time point (day 762, 1095 or 1825). Thus, the numbers of subjects on any given day were much larger. These subjects are represented by light orange (Typbar-TCV) and dark orange (Typbar) bars in Figure 5A. The kinetics of these larger groups which include subjects who did not provide specimens at all time points show parallel results as the smaller “all specimens cohorts” (light and dark blue). The GMT of Typbar-TCV recipients (light orange) was significantly higher than Typbar recipients (dark orange) on days 42 and 762 but was not so on days 1095 and 1825 (Figure 5A).

Importantly, significant differences were noted between Typbar-TCV and Typbar vaccinees who were not boosted at day 720 and had specimens collected at day 1095 and 1825. The small numbers of unboosted subjects among the compliant “all specimens cohorts” who provided specimens on days 0 and 42 as well as on both days 1095 and 1825 are seen in Figure 5A for unboosted Typbar-TCV recipients (light brown, N=38) and Typbar recipients (dark brown, N=83). The GMTs between these two groups (higher in Typbar-TCV) was not significantly different on day 1095 but it was significantly different on day 1825. In larger cohorts of unboosted individuals who provided sera on days 0 and 42 and either day 1095 or 1825 (but not both), the GMT of the Typbar-TCV group (white bars) was significantly higher on both days 1095 and 1825, versus the Typbar ViPS recipients (grey bars). These data indicate that an initial vaccination with Vi conjugate (Typbar-TCV) elicits a significantly longer-lived antibody responses in the absence of a booster than unconjugated ViPS (Typbar).

Figure 5B charts the longevity of antibody elevation among the different groups by tracking in boosted and non-boosted cohorts the percent of individuals on any given day post-vaccination whose titres remained at least four-fold above their day 0 baseline. Since there is not an agreed-upon threshold cut-off of serum IgG Vi antibody that designates protection, the cut-off of four-fold or greater over baseline as the common
measure of comparison was used. Analysing the data portrayed in Figure 5B, one notes that among the “all specimens cohorts” who received an initial dose of Typbar-TCV or Typbar vaccine, and a second vaccination on day 720, (light blue versus dark blue) and the “any available specimen” subjects (light versus dark orange) who received both an initial and a second dose of vaccine, there was a significantly higher prevalence of elevated titres observed among the Typbar-TCV recipients on day 720; there was borderline significance on day 762. In contrast, among the unboosted “all specimens cohorts” (light versus dark brown) and the “any available specimen” subjects (white versus grey), the Typbar-TCV recipients had significantly higher prevalence of elevated titres on both days 1095 and 1825. This analysis corroborates the GMT data demonstrating that a single dose of Typbar-TCV elicits higher titres of Vi antibody which remain elevated for longer than Vi antibody stimulated by Typbar.

Beyond demonstrating that Vi conjugate elicits a significantly higher magnitude and longevity of IgG anti-Vi antibodies than ViPS, comparisons were made of the quality of the antibodies elicited by each vaccine at various time points. The assays included measurement of antibody avidity and an analysis of IgG sub-classes. Data for sera collected from a subset of subjects on days 0, 42, 720 and 762 were previously reported [104]. An Avidity Index (AI) of 60 provided a useful cut-off for comparison [105], with significantly more Typbar-TCV recipients having an AI >60 than Typbar recipients. Figure 6 adds data for subjects whose sera from day 1825 were tested for persons who were boosted on day 720 as well as unboosted subjects. At day 42, six weeks following primary immunization, there was no difference in the avidity of anti-Vi in recipients of the two vaccines [104]. In contrast, by day 720 there was a notable increase in the proportion of Typbar-TCV recipients who had high avidity antibodies compared to Typbar-TCV recipients [104]. This difference in high avidity antibodies was even more striking at day 1825 in both boosted and non-boosted subjects.

Although the numbers of sera tested were small, the distribution of IgG subclasses of anti-Vi in recipients of Typbar-TCV was qualitatively different from that for Typbar recipients [104].

The anti-Vi antibody responses in children 2-4 years of age who received an initial immunization with Typbar-TCV closely resembles the responses observed among older children and adults.

In multi-dose vials (5 doses per vial), 2-phenoxyethanol serves as the preservative to maintain sterility. Mohan et al also compared anti-Vi responses in recipients of mono-dose versus multi-dose vials of Typbar-TCV and showed that the responses did not differ [104].
Table 1. GMTs of anti-Vi IgG antibodies at baseline and at various time points after administration of an initial dose of vaccine (Day 0) and after a second dose of the same vaccine (Day 720 after the initial immunization) – Randomized Controlled Trial (RCT) and Open Label Trial (OLT)

<table>
<thead>
<tr>
<th></th>
<th>RCT (subjects 2-45 years of age): Typbar-TCV</th>
<th>RCT (subjects 2-45 years of age): Typbar (ViPS)</th>
<th>OLT (subjects 6-23 months of age) Typbar-TCV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 42</td>
<td>Day 720</td>
</tr>
<tr>
<td>Subjects with serum specimens on days 0 &amp; 42 and at least one other time point on days 762, 1095 or 1825</td>
<td>332</td>
<td>332</td>
<td>243</td>
</tr>
<tr>
<td>GMT EU/mL (95% CI)</td>
<td>(10.4, 9.6, 11.3)</td>
<td>(1292.5, 1152.9, 1448.9)</td>
<td>(81.7, 72.6, 91.9)</td>
</tr>
<tr>
<td>Percent of subjects whose titres are &gt;4-fold above their day 0 baseline titre</td>
<td>97.3</td>
<td>97.3</td>
<td>74.1</td>
</tr>
<tr>
<td>Subjects with the full series of specimens on days 0, 42, 720, 762, 1095 and 1825</td>
<td>84</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>GMT EU/mL (95% CI)</td>
<td>(9.5, 8.3, 10.9)</td>
<td>(1305.4, 1069.6, 1593.2)</td>
<td>(94.1, 75.9, 116.6)</td>
</tr>
<tr>
<td>Percent of subjects whose titres are &gt;4-fold above their day 0 baseline titre</td>
<td>96.4</td>
<td>96.4</td>
<td>79.8</td>
</tr>
<tr>
<td>Subjects with serum specimens on days 0 &amp; 42 and at least one other time point on days 762, 1095 or 1825</td>
<td>305</td>
<td>305</td>
<td>196</td>
</tr>
<tr>
<td>GMT EU/mL (95% CI)</td>
<td>(11.6, 10.5, 12.9)</td>
<td>(411.1, 358.9, 470.9)</td>
<td>(45.7, 39.6, 52.6)</td>
</tr>
<tr>
<td>Percent of subjects whose titres are &gt;4-fold above their day 0 baseline titre</td>
<td>93.1</td>
<td>93.1</td>
<td>53.1</td>
</tr>
<tr>
<td>Subjects with the full series of specimens on days 0, 42, 720, 762, 1095 and 1825</td>
<td>26</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>GMT EU/mL (95% CI)</td>
<td>(15.6, 9.6, 25.4)</td>
<td>(513.9, 316.8, 833.6)</td>
<td>(58.8, 39.9, 86.6)</td>
</tr>
<tr>
<td>Percent of subjects whose titres are &gt;4-fold above their day 0 baseline titre</td>
<td>92.3</td>
<td>92.3</td>
<td>50</td>
</tr>
<tr>
<td>Subjects with serum specimens on days 0 &amp; 42 and at least one other time point on days 762, 1095 or 1825</td>
<td>307</td>
<td>307</td>
<td>220</td>
</tr>
<tr>
<td>GMT EU/mL (95% CI)</td>
<td>(9.4, 8.7, 10.3)</td>
<td>(1937.4, 1785.0, 2102.9)</td>
<td>(48.7, 42.4, 55.9)</td>
</tr>
<tr>
<td>Percent of subjects whose titres are &gt;4-fold above their day 0 baseline titre</td>
<td>98.1</td>
<td>98.1</td>
<td>59.5</td>
</tr>
<tr>
<td>Subjects with the full series of specimens on days 0, 42, 720, 762, 1095 and 1825</td>
<td>126</td>
<td>126</td>
<td>126</td>
</tr>
<tr>
<td>GMT EU/mL (95% CI)</td>
<td>(9.4, 8.2, 10.8)</td>
<td>(1902.7, 1670.0, 2167.8)</td>
<td>(53.8, 44.7, 64.7)</td>
</tr>
<tr>
<td>Percent of subjects whose titres are &gt;4-fold above their day 0 baseline titre</td>
<td>97.6</td>
<td>97.6</td>
<td>91.3</td>
</tr>
</tbody>
</table>

Anti-Vi IgG antibody titres estimated by VaccZyme ELISA kit

CI = confidence interval; ELISA= enzyme-linked immunosorbent assay; EU = enzyme-linked immunosorbent assay units; GMT = geometric mean titre; ViPs = Vi polysaccharide vaccine
For AS TCV Not Boosted, graphed values are from the group with N=64. Values from the N=54 group are Day 0 = 10.1 (8.4, 12.1); Day 42 = 1347.8 (933.2,1946.5); For AS ViPS Not Boosted, graphed values are from the group with N=129. Values from the N=122 group are Day 0 = 11.7 (10.1,13.7); Day 42 = 387.7 (308.4, 487.5)

Figure 5. Serum anti-Vi IgG responses in RCT of older children, adolescents and adults, 2-45 years of age, given a primary and booster immunizations with Typbar-TCV and Typbar vaccines*

TCV: Typhoid conjugate vaccine (Typbar-TCV); ViPS: Vi Polysaccharide vaccine (Typbar); *N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point
Data for unboosted subjects at Days 0 and 42 show the titres at baseline and post-Dose 1 for the subset of children who were subsequently not boosted (hatched bars), in comparison to those for the whole cohort at Days 0 and 42. This shows that relatively high titres observed for the non-booster group at Days 1095 and 1825 do not appear to correlate with significantly higher titres at baseline and Day 42.

Source: Bharat Biotech
Salient observations and conclusions from the randomized trial comparing Typbar-TCV and Typbar.

- The Typbar-TCV conjugate vaccine elicits significantly higher titres of IgG Vi antibody at 6 weeks after a primary immunization and 6 weeks after a second immunization than unconjugated Typbar.
- With respect to duration of elevated antibody titres at 3 and 5 years after a single immunization, the GMT of anti-Vi and the proportion of individuals with titres ≥4-fold over their baseline was significantly higher among recipients of the conjugate vaccine.
- The proportion of subjects with IgG antibody exhibiting an AI >60 was significantly higher in Typbar-TCV recipients compared to Typbar recipients.
- Among these subjects aged 2-45 years who were mainly adults and children >4 years of age, the GMT of anti-Vi IgG attained 42 days after administration of a second dose of Typbar-TCV closely resembled the GMT recorded at 42 days after the initial dose of conjugate vaccine.

2. Open Label Trial (OLT) (Annex B2, Table 1)
An open label trial was undertaken in which 327 infants and toddlers 6-23 months of age were administered Typbar-TCV, representing the first time that this conjugate vaccine was evaluated in children too young to receive unconjugated ViPS. Of these 327 children, 307 (93.9%) had serum specimens collected on day 0 and 42. On day 720, 193 of these young children were boosted with a second dose of Typbar-TCV.
Values for ACS Not Boosted used data from group with N=47. Values for group with N=41 (Day 0 = 97.7 (7.5, 12.7); Day 42 = 1610.4 (1170.1, 2212.7))

Values for ASC Not Boosted used data from group with N=47. Values for group with N=41 (Day 42 = 97.6% (99.9%, 87.1%))

Figure 7A & B. Serum anti-Vi IgG responses in Open-Label Trial of infants and toddlers, 6-23 months of age, given a primary and booster immunizations with Typbar-TCV*

*N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point
Data for AAS subjects at Days 0 and 42 (dark blue solid bar) show the titres at baseline and post-Dose 1 for the subset of children who were subsequently boosted while the (hatched bars) shows their titres at day 720 (pre-boost) and 3 and 5 years post-boost.
Source: Bharat Biotech
and 187 of these boosted children provided serum specimens on both day 720 and day 762 to assess the response to the booster. The strong serological responses of these young children to an initial and a booster dose of Typbar-TCV through day 762 have been published [104] and they are also summarized in Figures 7A and 7B. Serum specimens were obtained from available boosted and unboosted infants and toddlers at 3 years (day 1095) and 5 years (day 1825) following initial immunization.

Serological results involving specimens collected beyond day 762 are summarized in Figures 7A and 7B. Figure 7A shows that a cohort of fully compliant “all specimens” children (specimens on days 0, 42, 1095 and 1825) and a cohort of somewhat less compliant “any available specimen” children who provided specimens on days 0 and 42 and either 1095 or 1825 (but not both) and who were boosted (orange and blue hatched bars) exhibited very similar GMTs on days 1095 and 1825, with the latter GMTs being significantly lower than the former. Similarly, the “all specimens cohort” and “any available specimens subjects” who were not boosted at day 720 (white and gray bars) showed nearly identical GMTs that were significantly lower at day 1095 and 1825 than the GMTs of the boosted cohorts (Figure 7A); the day 1825 GMTs were somewhat lower than the day 1095 values.

Figure 7B displays the longevity of the elevated anti-Vi titres by displaying the proportion of subjects at each time point following initial immunization at day 0, whose titres were still >4-fold above their day 0 titre. The proportion of elevated titres was higher in boosted cohorts (orange and blue hatched bars) than the unboosted subjects (white and gray bars).

Figures 7C and D portray the data in the same way, albeit with the cohorts ages 6-11 months (dark orange and dark blue) displayed alongside the cohorts immunized at age 12-23 months. These figures show that, with respect to both GMTs and longevity of elevated titres (percent of subjects at each study day whose titres remain 4-fold or greater above their day 0 titre), the infants ages 6-11 months responded as robustly as the toddlers ages 12-23 months.

**Salient observations and conclusions from the Open Label Trial of Typbar-TCV in infants and toddlers.**

- Tested for the first time in infants 6-11 months and toddlers 12-23 months of age, Typbar-TCV was not only well tolerated but a single dose was impressively immunogenic eliciting high titres of IgG anti-Vi antibody that endured up to 5 years in a proportion of young children.
- Responses in infants 6-11 months were as robust as responses in toddlers age 12-23 months.
Figure 7C & D: Serum anti-Vi IgG responses in Open-Label Trial of infants and toddlers, 6-23 months of age, given a primary and booster immunizations with Typbar-TCV*

*N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point

Data for AAS subjects at Days 0 and 42 (dark blue solid bar) show the titres at baseline and post-Dose 1 for the subset of children who were subsequently boosted while the (hatched bars) shows their titres at day 720 (pre-boost) and 3 and 5 years post-boost.

Source: Bharat Biotech
3. **RCT comparing Typbar-TCV versus Sanofi Pasteur ViPS vaccine (Typhim Vi)** (Annex B3)

Although the reactogenicity and immunogenicity of Bharat Biotech Typbar-TCV was compared directly to unconjugged ViPS Typbar vaccine, it was important to undertake an analogous comparison using the WHO-prequalified ViPS (Typhim Vi, Sanofi Pasteur).

Figures 8A and 8B summarize the results of this study. On day 0, 340 subjects 2-15 years of age were randomly allocated to receive a single intramuscular dose of Typbar-TCV (N=170) or Typhim Vi (N=170). Serum specimens collected on day 28 were tested along with day 0 specimens to determine the rate of seroconversion stimulated by each vaccine and the GMT. Sera collected on day 90 and 180 allowed the longevity of the antibody responses to each vaccine (GMT and percent of subjects whose anti-Vi titre remained ≥4-fold above their day 0 baseline). On day 180, one-half of the Typbar-TCV cohort was allocated to receive a booster dose of Typbar-TCV and serum was obtained thirty days later (day 210) to assess the rate of seroconversion versus unboosted Typbar-TCV recipients and unboosted Typhim Vi recipients.

Figure 9A shows that the GMT on day 28 of the Typbar-TCV recipients was significantly (approximately one-half log) higher than the Typhim Vi recipients. On day 90 the GMT of the Typbar-TCV cohort remained significantly higher than the Typhim Vi recipients, although the GMTs of recipients of both vaccines had fallen from the day 28 titre. Administration of a booster dose of Typbar-TCV on day 180 raised the GMT recorded on day 210 over the unboosted Typbar-TCV and Typhim Vi groups. Interestingly, the GMT of the boosted Typbar-TCV subjects did not reach the level recorded on day 28. Whereas the GMT on day 210 of the unboosted Typbar-TCV vaccinees was higher than the Typhim Vi recipients, the difference was not significant (Figure 9A).

Figure 9B displays the percent of individuals in each group on the different study days whose titres remained ≥4-fold above their day 0 baseline. The Typbar-TCV recipients had a prevalence slightly higher than Typhim Vi recipients but the differences were not statistically significant except for the boosted Typbar-TCV group on day 210.

Analysis of the results with the subjects broken down by age into 2-4 year olds and 5-15 year old age groups showed similar patterns in the younger age group compared to the older age group, documenting that Typbar-TCV was as immunogenic in preschool children as in school age children (data not shown).

The results of the Typbar-TCV versus Typhim Vi randomized controlled trial corroborate the results of the earlier randomized trial comparing Typbar-TCV versus Typbar.
Figure 8. Serum anti-Vi IgG responses in subjects 2-15 yrs of age, given a primary and booster immunizations with Typbar-TCV and ViPS (Typhim Vi) vaccines* in a randomized open label study

TCV: Typhoid conjugate vaccine (Typbar-TCV); ViPS: Vi Polysaccharide vaccine (Typhim Vi); N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point. Data for TCV subjects at Days 0, 28 and 90 show baseline and post Dose-1 titres (dark blue solid bar) and for the 2 subgroups of subjects boosted and not boosted at day 210 (hatched bar for post-boost titres and light blue solid bar for unboosted subjects)
Salient observations and conclusions from the randomized trial of Typbar-TCV versus Typhim Vi in children 2-15 years of age.

- A single intramuscular dose of Typbar-TCV was significantly more immunogenic than Typhim Vi, the only WHO pre-qualified typhoid vaccine.
- A booster dose of Typbar-TCV administered to children 6 months after their primary immunization with Typbar-TCV raised Vi antibody titres but not as high as the peak that followed the primary immunization.

4. Co-administration of measles vaccine with Typbar-TCV at ~9 months of age versus either vaccine alone and of Typbar-TCV co-administered with measles-mumps-rubella vaccine at 15 months of age (Annex B4)

The ability of a single intramuscular dose of Typbar-TCV to elicit high rates of seroconversion and high GMTs of IgG anti-Vi antibody in infants 6-11 months and in toddlers 12-23 months of age stimulated interest in administering this conjugate vaccine at either 9 months of age, concomitant with measles containing vaccine 1 (MCV1) or with MCV2, which is administered at 15-18 months of age, or at both ages. Thus, a randomized controlled trial was designed to compare the immunogenicity of Typbar-TCV when co-administered with measles vaccine at 9 months of age compared to infants who received Typbar-TCV alone one month before (age 8 months) or one month after measles vaccine (age 10 months). Similarly, the effect of co-administration of Typbar-TCV and MCV1 on the measles antibody response was assessed by comparing IgG measles antibody in sera from infants who received both vaccines concomitantly versus measles vaccine alone. Six months after primary immunization (15 months of age), all children received measles-mumps-rubella (MMR) vaccine with one group receiving concomitantly administered Typbar-TCV along with MMR.

Co-administering two different vaccines such as TCV and measles at the same EPI visit should not produce an immune response that is inferior with respect to either anti-Vi or anti-measles antibodies. The concern is one-directional because there is no safety concern about whether the co-administration of the two vaccines is superior to each vaccine administered alone in the absence of the other. A non-interference (non-inferiority) trial aims to show that co-administration of two vaccines stimulates immune responses that are not inferior to the responses elicited by the individual vaccines by as much as a sufficiently small pre-specified non-inferiority margin. The two immune response end points that are commonly used for assessing non-inferiority are geometric mean titre (GMT) and the proportion of vaccine recipients who
reach a critical antibody threshold that is considered protective. Bharat Biotech did not pre-specify a non-inferiority margin or present a point estimate and 95% confidence interval for the ratio of GMTs or the difference in proportions reaching a threshold of protection. Rather, Bharat Biotech calculated 95% confidence intervals around the point estimates of GMT (Figure 9A) and around the percent of infants on a given study day whose titres of anti-Vi remained ≥4-fold above the day 0 value and looked for CIs that did not overlap. That analysis does not allow conclusions about non-interference.

**Effect of co-administration of measles vaccine on anti-Vi responses to Typbar-TCV.**

Figure 9A summarizes the anti-Vi antibody GMTs in the five different groups that were allocated to receive vaccine on day 0 as in the box below:

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine</th>
<th>N</th>
<th>Bar Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1A</td>
<td>Typbar-TCV + Measles</td>
<td>98</td>
<td>dark orange bars</td>
</tr>
<tr>
<td>Group 1B</td>
<td>Typbar-TCV + Measles</td>
<td>99</td>
<td>light orange bars</td>
</tr>
<tr>
<td>Group 2</td>
<td>Measles</td>
<td>98</td>
<td>dark blue bars</td>
</tr>
<tr>
<td>Group 3</td>
<td>Typbar-TCV</td>
<td>98</td>
<td>light blue bars</td>
</tr>
<tr>
<td>Group 4</td>
<td>Measles</td>
<td>100</td>
<td>white bars</td>
</tr>
</tbody>
</table>

The baseline (day 0) GMT of anti-Vi antibody did not differ among the five groups. The anti-Vi GMT on day 28 in infants of these five groups provides the evidence for or against interference between the two vaccines. Bharat Biotech calculated 95% confidence intervals around the point estimates of GMT (Figure 9A) and around the percent of infants on a given study day whose titres of anti-Vi remained ≥4-fold above the day 0 value (Figure 9B). The day 28 GMT of anti-Vi antibody in Group 3 constitutes the positive control, i.e., the GMT observed when Typbar-TCV is administered without measles vaccine. The day 28 anti-Vi GMT of Group 3 must then be compared with the day 28 GMTs of Groups 1A and 1B, both of whom were given Typbar-TCV concomitantly with measles vaccine. Interestingly, the 95% CIs overlap but the Group 1A and 1B GMTs were actually each higher than the Group 3 GMT (Figure 9A). The Group 3 infants received their Typbar-TCV alone at 8 months of age, whereas all the other groups received their day 0 vaccinations at 9 months of age. The somewhat lower (albeit non-significant) anti-Vi GMT of Group 3 may be consequent to their younger age. Nevertheless, the anti-Vi response of Group 3 infants was long-lived. They received no booster dose of Typbar-TCV through day 720, the termination of surveillance. Yet their GMT at day 720 was significantly higher than Group 4 who had received no Typbar-TCV and lower than Groups 1A (who received two doses of Typbar-TCV on days 0 & 28) and Group 1B (who received two doses of Typbar-TCV on days 0 and 180).
Figure 9B displays the longevity of the anti-Vi responses assessed as the percent of infants in each group on each study day who exhibit anti-Vi titres \( \geq 4 \)-fold above their pre-vaccination baseline. The only significant difference observed was on day 360 between Group 2 (dark blue bar) who received a dose of Typbar-TCV 338 days earlier at age 10 months and Group 3 (light blue bars) who had received their single dose of Typbar-TCV 360 days earlier at 8 months of age.

**Effect of co-administration of Typbar-TCV vaccine on IgG anti-measles antibody responses to monovalent measles (at 9 months of age) or MMR at 15 months of age.** (Figure 9C)

The baseline (day 0) GMT of anti-measles IgG antibody did not differ among the groups. The anti-measles GMT on day 28 in infants of these five groups provides the first piece of evidence for or against interference between the two vaccines. Bharat Biotech calculated 95% confidence intervals around the point estimates of GMT (Figure 9C) and around the percent of infants on a given study day whose titres of anti-measles virus IgG remained \( \geq 4 \)-fold above the day 0 value (Figure 9D). The day 28 GMT of anti-measles antibody in Group 2 and 4 constitute the positive controls, i.e., the GMT observed when measles vaccine is given in the absence of co-administered Typbar-TCV. Comparison of the day 28 and day 56 anti-measles titres of Group 3 give additional data on the response to measles vaccine in the absence of Typbar-TCV. The day 28 anti-measles GMT of Group 2 and 4 must then compared with the day 28 GMTs of Groups 1A and 1B, both of whom were given measles vaccine concomitantly with Typbar-TCV. Interestingly, the 95% CIs of these mentioned Groups all closely overlap implying no interference based on this method of analysis (Figure 9C). The anti-measles Vi responses of these groups were all near identical through day 180 when all groups received MMR, with Group 1B receiving Typbar-TCV co-administered with MMR. The measles antibody GMTs of all groups were similar on day 360 and 720 (Figure 9C).

Figure 9D displays the longevity of the anti-measles antibody responses assessed as the percent of infants in each group on each study day who exhibit anti-measles titres \( \geq 4 \)-fold above their pre-vaccination baseline. No significant differences were detected among the groups at any time relevant points including days 56, 180, 360 and 720.
Figure 9. Serum anti-Vi IgG & measles IgG titres and percentage of subjects with titres > 4-fold above Day 0 titre in infants given Typbar-TCV with or without measles-containing vaccine in an open label non-interference study*

*N = number of subjects for whom serum specimens were available for measurement of anti-Vi antibodies at each time point
**Typbar-TCV: Human challenge model**

The efficacy of Typbar-TCV vaccine was assessed recently in an observer-participant-blinded study using an established controlled human typhoid infection model in naïve adult volunteers (aged 18 to 60 years, n=103) in a non-endemic setting (the UK). Participants were randomized to receive a single parenteral dose of Typbar-TCV, Vi-PS (Typhim Vi, Sanofi-Pasteur) or a control (group ACWY meningococcal conjugate) vaccine. Both Vi vaccines contained 25µg of Vi-polysaccharide per 0.5ml dose [106]. Approximately one month post-vaccination, participants were orally challenged with 1-5x10^4 CFUs of S. Typhi Quailes strain (a wild-type strain originally isolated from a chronic carrier in Baltimore, USA), preceded by the ingestion of 120ml of sodium bicarbonate buffer [107].

Different vaccine efficacy estimates of Typbar-TCV were obtained using clinical or microbiological diagnostic endpoints. Vaccine efficacy was estimated as 87.1% (95% CI 47.2, 96.9%) against a persistent fever (defined as fever ≥38°C persisting for >12 hours) followed by positive blood culture for S. Typhi (Vi-TT attack rate 5% vs control attack rate was 42%) compared to vaccine effectiveness of 52.3% (95% CI -4.2, 78.2%) for the ViPS against the same endpoint (an attack rate of 20%). When other endpoints were used (varying fever thresholds, or the typhoid triad of fever ≥38.0 °C plus headache and abdominal pain), the effectiveness of Typbar-TCV ranged between 37.2% (95% CI, 11.8-64.7%) for bacteraemia alone and 89.5% (95% CI 20.8, 98.6%) for a clinical diagnosis.

Seroconversion was 100% in Typbar-TCV recipients and 88.6% in the ViPS recipients, with significantly higher GMTs detected one-month post-vaccination in Typbar-TCV vaccinees (GMT of 562.9 EU/ml [396.9, 798.4] versus 140.5 EU/ml [91.0, 216.9], P<0.001). An inverse straight-line relationship was demonstrable between the level of anti-Vi IgG titre and the probability of developing serologically defined typhoid, but with no apparent antibody titre threshold. Overall, Typbar-TCV induced satisfactory antibody response and memory, where higher levels of anti-Vi antibody correlated with increased protection. The model is limited in its generalizability in that a moderate dose of bacteria was used with neutralization of gastric acid and all volunteers were typhoid naïve and living in a non-endemic setting. The model is assumed to produce a higher attack rate than usual long-cycle transmission in an average endemic setting which may potentially overcome immune responses that might be protective in the endemic setting, and if so may underestimate vaccine efficacy. On the other hand, the inoculum size and use of bicarbonate may closely resemble the dose ingested in certain types of food vehicles contaminated by food handlers who are chronic typhoid carriers.
Vi vaccination appears not to prevent stool shedding of S. Typhi, with 71% shedding in the control group, 59% in the Vi-TT group and 60% in the ViPS group (non-significant difference), although the analysis was confounded by a high number of missing samples. It is unclear whether this observation would also be repeated outside of a moderate dose challenge study setting.

**PedaTyph™ (BioMed)**

This Vi-TT was the first TCV to be licensed in India but with limited publically available pre-licensure data to be assessed. It consists of 5µg of Vi polysaccharide from S. Typhi conjugated to 5µg of tetanus toxoid protein in isotonic saline.

Available evidence on the vaccine is provided by three published post-licensure studies:

- A randomized comparative trial of 400 healthy Indian children three months to five years of age who received one dose of PedaTyph (n=200) or two doses eight weeks apart (n=200). In 163 of the single dose recipients (101 children <2 years and 24< 1 year of age) who were available for follow up, a seroconversion rate (≥4fold increase over pre-immunization titre) of 83% was reported at eight weeks post-vaccination, with the highest seroconversion rate in infants (seroconversion rates of 73%, 89% and 96% for children >2 years, ≤2years and <1year respectively) [108].

- In a follow up of the first study cohort of 400 children [108], 40 children who received either one or two doses of PedaTyph were recalled 30 months after vaccination to assess the longevity of immune response [109]. (It is worth noting that the authors also report that 10 non-vaccinated children were “recalled”, however since the previous paper did not describe an unvaccinated control arm, the selection criteria used for these 10 children is unclear). Anti-Vi IgG titres were reported to be significantly higher in vaccinated subjects (one dose or 2 doses) at 30 months post-vaccination compared to non-vaccinated subjects, and the titres in the two-dose group were reported to be higher than the single-dose group but not significant.

- A quasi-randomized, open-label trial was conducted post-licensure in 905 Kolkata children aged 6 months to 12 years who received two doses of PedaTyph 6 weeks apart and were followed with active surveillance (weekly telephone calls plus monthly school visits) for 1 year, along with 860 unvaccinated control children [110]. Among the vaccinees, 61.8% were older than 5 years, 29.1% were 3 to 5 years, and 9.1% were 6 months to 2 years of age. The control children had a similar age distribution: 61.8% older than 5 years, 29.1% 3 to 5 years, and 12.7% 6 months to 2 years of age. Notably, no cases of blood culture–confirmed typhoid fever were recorded among the 905
vaccinees during one year of surveillance versus 11 confirmed cases among the 860 unvaccinated control children, indicating a vaccine efficacy of 100% (95% CI, 97.7, 100 [P < 0.001]).

In subjects older than 2 years of age, PedaTyph is recommended to be administered intramuscularly in a two-dose schedule with 4 to 8 weeks between the doses. A booster is recommended every 10 years by the manufacturer, although no data are available to support the booster recommendation. For children 3 to 23 months old, two doses of vaccine are recommended 4 to 8 weeks apart followed by a booster at 24 to 30 months of age. The manufacturer also recommends a booster every 10 years thereafter in persons immunized at this young age [4].

Recognizing the important limitations regarding information about the studies described above (and apparent non-rigorous study design) in the published papers, efforts were made to seek additional data for the SAGE Working Group’s evidence review. Despite WHO efforts, no additional data were obtained from the manufacturer to facilitate in-depth review of the trial data (including age-stratified data) for this vaccine. The available published data were included in the meta-analysis by Cochrane (see Annex C).

**Immunobridging of currently licensed TCVs to NIH Vi-rEPA vaccine**

The WHO regulatory guidelines on the quality, safety and efficacy of typhoid conjugate vaccines [111] notes that there is no established immunological correlate of protection for conjugated Vi vaccines, and that antibody persistence data may be viewed in terms of the percentages of vaccinees that have anti-Vi IgG concentrations above a predefined threshold for a specified period of time. These guidelines also noted that there are no established or standardized assays for assessing functional antibody responses to Vi-containing vaccines. Based on the assay used in the Vi-rEPA efficacy trial in Viet Nam, a threshold value of 4.3 μg/ml anti-Vi antibody measured by ELISA [112] was suggested to be associated with a high level of sustained protection lasting approximately 4 years after vaccination. The WHO guidelines therefore recommended that, in the absence of an international standard, TCV sponsors who wish to apply this threshold value to the results of their own assays should perform a calibration against the assay used in the Vi-rEPA efficacy trial.

An independent expert review was sought by the Working Group to perform an immunobridging of the licensed TCVs to the Vi-rEPA vaccine, the only TCV with efficacy established. A review of the history of establishing the proposed protective threshold and of the underlying serological methods concluded that, due to methodological and/or documentation gaps, it was impossible to bridge data generated with the new TCVs and analysed by the current NIH ELISA protocol to immunogenicity data generated in the original
Vi-rEPA trial in Vietnam. Thus no quantitative bridging to the Vi-rEPA vaccine could be conducted to support these recommendations. The general consensus is that efforts should now concentrate on generating efficacy data for new TCVs, with consideration for nested immunogenicity studies as an integral part, in order to help establish a correlate of protection. Further, ongoing efforts should be accelerated to develop approved international standards to permit comparisons between data generated by different laboratories as the pipeline of additional TCV candidates progresses.

**Safety of TCV**

In its December 2016 review of safety data for typhoid vaccines [97], the GACVS noted that the first Vi conjugated vaccine (US NIH Vi-rEPA) had a safety profile similar to that of the polysaccharide vaccine after evaluation in randomized control trials of >11 000 subjects in Viet Nam. In the available published data on PedaTyph, based on evaluation of safety in approximately 2 200 subjects (including 1 765 subjects in a Phase IV field effectiveness trial), the most frequent adverse events described were local, non-specific reactions and fever. No safety signals were reported.

More detailed data were presented to GACVS for Typbar-TCV based on evaluation of immunogenicity and safety in approximately 1 000 subjects drawn from pre-licensure and post-licensure studies of the co-administration with measles containing vaccines (MCV), and a comparator study with Typhim Vi (with a total of 470 vaccine recipients in the 2 studies). Post-marketing surveillance data collected in the private sector in India (with more than 3 million doses of the vaccine distributed up to that point in time) were also presented. Overall, GACVS found that the adverse event profile was similar to the specific comparator vaccines in respective age groups for each study, and no safety signals were reported. However, GACVS noted that safety follow-up was largely passive and the data available were limited. Post-marketing surveillance, based on approximately 3 000 reports only received from paediatricians in the private sector in India, showed fever, pain and swelling reported in approximately 1–10% of vaccinees in any age group; no serious adverse events were reported to the manufacturer.

Of note, GACVS concluded that while the safety profile of the licensed Vi-TT vaccines appeared similar to ViPS, there were limitations to the available data. GACVS therefore made recommendations for further safety monitoring of TCV including the need for a stronger post-marketing surveillance; 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); the use of Brighton Collaboration case definitions and active monitoring of SAEs of interest; and, where feasible, analysis of non-specific effects of vaccination.
The results of the Cochrane systematic review and meta-analysis of serious adverse events associated with TCV are included in Annex C.

5. MATHEMATICAL MODELLING OF THE IMPACT OF VACCINATION STRATEGIES ON THE TRANSMISSION OF TYPHOID

Researchers from Yale established a model describing the transmission dynamics of typhoid fever to evaluate the following vaccination strategies: a one-time campaign in 6 to 15-year old school children, routine vaccination at 6 years of age and routine vaccination at 6 years plus a catch-up campaign at 6–15 years [113]. Typhoid vaccination was incorporated into the model with the following assumptions: Ty21a VE 48%, with waning immunity comparable to that from natural infection, TCV VE 95% during 1st year, ViPS VE 68% during 1st year, duration of immunity of 19 years for TCV (with wide CI) and 3 years for ViPS vaccine. The dynamic model assumes loss of immunity to subclinical infection, differences in the risk of clinical disease for primary versus subsequent infection, a chronic carrier state, and a balance between a short cycle transmission and a long cycle transmission. The model provided a good fit to typhoid fever data from Vellore, India (2000-2011, derived from passive surveillance) and captures well both the level and age distribution of disease.

A one-time campaign is predicted to decrease the incidence of typhoid fever immediately, with a decrease greater than expected due to the direct effect of the vaccine alone. After a period of 5 to 10 years, the incidence of typhoid fever rebounds to the pre-campaign levels for the ViPS vaccine, with a slightly slower rebound for Ty21a and TCV. The model shows that routine vaccination would lead to a more gradual but sustained decline in typhoid fever incidence for the Ty21a and TCV vaccines, but a slight rebound in incidence is still predicted for ViPS. Routine vaccination with catch-up would lead to both an immediate and sustained decline in incidence with the Ty21a and TCV vaccines, but incidence would return to near pre-vaccination levels with the ViPS vaccine after a period of 10-15 years, even with routine vaccination continuing. In settings where incidence peaks in older age groups, the model shows that vaccination of school-aged children would be adequate, while in settings with an early peak in age distribution vaccination should start early.

Uncertainties in the model included prevalence and relative infectiousness of asymptomatic carriers, the rate of waning immunity to clinical disease, the reporting fraction of clinical cases, the importance of short cycle versus long cycle transmission, implications of AMR emergence for typhoid fever dynamics, and the strength, duration and nature of vaccine-induced immunity.
A model comparison exercise, involving four modelling groups, was recently initiated (under the TyVAC) and will help to address some of the current model uncertainties. It is expected that this model comparison will lead to guidance to country policy makers preparing for decisions on potential vaccination programs on an appropriate model to address questions in their specific settings.

6. COST-EFFECTIVENESS ANALYSIS OF TYPHOID CONJUGATE VACCINES

Researchers from Yale have conducted a cost-effectiveness analysis (CEA) comparing routine vaccination at 9 months of age to routine vaccination at 9 months with catch-up vaccination scenarios targeting individuals up to 5 years, 15 years, 25 years and for all ages [68]. This model was applied to different urban and rural settings with varying incidence, cost of illness, cost of vaccine delivery and found that routine vaccination is preferred over no vaccination at willingness-to-pay (WTP) thresholds per DALY of >=1$/DALY in Delhi, India and Dong Thap, Viet Nam; >=5000 I$/DALY (less than the GDP per capita) in Kolkata, India; >=3000 I$/DALY in Kibera, Kenya (slightly less than the GDP per capita), and >8000 I$/DALY in Lwak; Kenya. However routine vaccination alone was not the preferred strategy in any setting. The model was influenced by the number of doses required in children, and the probability of inpatient or outpatient treatment. However, the difference between settings was found to exert a major influence, due to differences in incidence, cost of illness, and cost of the vaccine. The researchers conclude that at a price of USD 2 or less per dose, routine vaccination with TCV is likely to be cost-effective in high incidence settings and in most medium incidence settings depending on the willingness to pay. Catch-up campaigns would be economically justified particularly in high incidence settings and at higher willingness-to-pay thresholds. Further details of this CEA model are available in the published paper provided on the SAGE website [68]. Further work is ongoing to develop CEAs for Gavi-eligible countries using vaccine prices between USD 2.5 and USD 5 per dose.

Another group of researchers in Stanford University, using a dynamic transmission model, showed that routine immunization of infants through EPI would be cost-effective in moderate incidence settings at a price of USD 2 per dose. In higher incidence settings (>110/100,000 person years) routine vaccination plus school-based catch-up campaigns would be required [114].
7. KEY WORKING GROUP CONCLUSIONS

7.1 Assessment of the potential benefits of the new generation typhoid conjugate vaccine

*Typbar-TCV*

Overall (across all ages) there is moderate-certainty evidence from clinical trials 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 at 6 weeks after a primary immunization and 6 weeks after a second immunization than unconjugated Typbar. With respect to the duration of elevated antibody titres at 3 and 5 years after a single immunization, the GMT of anti-Vi and the proportion of individuals with titres >4-fold over their baseline was significantly higher among recipients of the conjugate vaccine. The proportion of subjects with IgG antibody exhibiting an AI >60 was significantly higher in Typbar-TCV recipients compared to Typbar recipients. The anti-Vi IgG GMT attained 42 days after administration of a second dose of Typbar-TCV closely resembled the GMT recorded at 42 days after the initial dose of conjugate vaccine.

Tested for the first time in infants 6-11 months and toddlers 12-23 months of age, Typbar-TCV was not only well tolerated but a single dose was impressively immunogenic eliciting high titres of IgG anti-Vi antibody that endured up to 5 years in a proportion of young children. Responses in infants 6-11 months were as robust as responses in toddlers age 12-23 months.

Additional data on avidity and IgG subclasses provide further confidence in the quality of the antibody response and potential for a strong booster response.

The Oxford human challenge study using Typbar-TCV in a population of immunologically naïve adult volunteers produced an estimate of efficacy of 87.1% (95% CI 47.2-96.9%) based on an endpoint of persistent fever followed by positive blood culture, thus reflective of real life parameters under which a typhoid fever case would be confirmed. The challenge was seen as very stringent by the Working Group, and possibly in excess of that usually observed in the field, as measured by “attack rate”. While the human challenge study is seen as a proof-of-concept study rather than an efficacy trial, the results are similar to those of the non-commercialized Vi-rEPA vaccine from a well-designed efficacy trial. That trial provided strong evidence of long-term protection up to 46 months in children aged 2-5 years (for both anti-Vi IgG and a VE of 89% (95% CI 76, 97) over a follow up period comprised of 27 months of active surveillance and
19 months of passive surveillance, the latter being again closer to real-life conditions. Efficacy for the separate periods of follow up was estimated at 92% and 82% respectively.

**PedaTyph**

The quality of evidence for this vaccine was assessed as very low due to apparent methodological weaknesses in the trials and lack of additional data for in-depth review. While the Working Group recognises this is the only trial for which effectiveness data were reported for younger children, there are significant questions concerning the study design.

No conclusions can therefore be made about the potential use of this vaccine, unless further data are obtained for review to inform policy decisions.

In summary, the assessment of the quality of evidence for TXCV concluded that efficacy data are limited. However, the Vi-TT (Typbar-TCV) data from the Oxford human challenge study are compelling as is the evidence generated earlier with a Vi-rEPA vaccine in a high incidence setting in Viet Nam. A formal bridging of the data generated with the two licensed TCVs to immunogenicity data in the original Vi-rEPA trials in Viet Nam was not possible due to changes in assay standards established for the latter, which are impossible to reconcile because of the loss of the original serum samples.

There is moderate quality evidence on the effectiveness of TCV in persons >2 years of age in comparison to ViPS. There are no comparative data for any TCV versus Ty21a vaccine.

Additional data to be generated from planned field studies of effectiveness, including, (i) evaluation of a Typbar-TCV introduction programme in Navi Mumbai, India and (ii) studies in Africa and Asia by the Typhoid Vaccine Acceleration Consortium (TyVAC) [115] will likely change this assessment. These data are not expected to be available in the next 2-3 years. Experience with other conjugate vaccines points to a reasonable expectation of higher levels of clinical protection than the currently recommended ViPS and Ty21a vaccines.
7.2 Assessment of potential harms of typhoid vaccines

Taking into consideration the GACVS review of overall safety data for licensed typhoid vaccines with no signal of serious safety events, the human challenge study data on SAEs following Typbar-TCV and ViPS vaccine, and the GRADing of evidence on SAEs, the Working Group concluded that based on a limited amount of data, no safety concern has been identified for the licensed typhoid vaccines.

The Working Group took note that there is no evidence of a potential risk of hypo-responsiveness occurring with ViPS, although it has been reported for other polysaccharide vaccines.

Theoretically, a lower force of infection after vaccination could potentially lead to a shift of disease to older age groups and constitute a negative effect of vaccination if older individuals were more likely to become chronic carriers. There have been suggestions in the literature that older individuals previously not exposed may be more likely to develop severe disease, however this evidence is not considered robust.

In summary, the Working Group considered the evidence for safety of TCV as acceptable, taking into account all available evidence including the lack of safety signals from the TCV trials and the good safety profiles of the ViPS and Vi-rEPA vaccines. Nonetheless, the Working Group reiterates the GACVS recommendations for further safety evaluation.

7.3 Duration of protection

Available evidence on Typbar-TCV suggests protection may persist for 5 years or more after primary immunization, and there is some indication from the available data that natural boosting may occur with the Typbar-TCV. Following a single dose of Vi-rEPA, antibody persistence of up to 8 years in 2-5 year old children was observed. Serological data on PedaTyph are limited to 1 year follow up of subjects from a trial with a non-rigorous design. Evidence on the duration of protection from the Oxford human challenge study is limited to 1 month follow up in naïve adult volunteers.

7.4 Need for booster doses

The currently available data suggest no indication of a need for booster doses for children or adults residing in typhoid-endemic areas. However, the data indicate that the immune response is boostable through repeated vaccination, and possibly through natural exposure.

Data from the Vi-rEPA trial in infants (with doses given at 2, 4 and 6 months plus a “booster” dose 6 months later) were considered by the Working Group as weak immunological evidence of boosting. Further, there
are differences with each conjugate vaccine, and infants will respond differently from older children and adults.

### 7.5 Balance of benefits and harms

There are potential benefits of vaccination in view of the current AMR challenges which could change the dynamics of typhoid fever epidemiology and treatment. In this scenario, the potential for vaccination to reduce mortality and morbidity would be increased by reducing the typhoid fever AMR burden.

Mathematical modelling of the impact of vaccination on transmission predicts that a one-time campaign (modelled in 6-15 year old school children) could decrease the incidence of typhoid fever immediately, with a decrease greater than expected due to the direct effect of the vaccine alone, while routine vaccination would lead to a more gradual but sustained decline in incidence.

There is no evidence currently to suggest potential geographic or age shifts for typhoid fever infection after vaccination. The suggestion that older individuals who contract typhoid fever are at risk for increased severity of disease, or increased development of the carrier state, needs to be further explored.

### 7.6 Programmatic considerations for vaccination

**Typhoid vaccine product characteristics**

**Vi polysaccharide vaccine** is licensed for individuals aged ≥2 years to be administered subcutaneously or intramuscularly as a single dose; the target value for each single human dose is about 25μg of Vi antigen. It is stable for 6 months at 37 °C, and for 2 years at 22 °C. The recommended storage temperature is 2–8 °C. The WHO prequalified ViPS, Typhim Vi produced by Sanofi Pasteur, is marketed in a multi-dose vial (20 doses liquid formulation comprising 25 μg of Vi antigen with ≤1.250 mg phenol as preservative per 0.5 ml dose) with vaccine vial monitor (VVM) type 30 and estimated cold chain volume per dose of 1.58. As such it is noted as being prone to wastage and more suitable for campaign settings (http://www.who.int/immunization_standards/vaccine_quality/pq_238_typhoid_20dose_sanofi_pasteur/en/).

**Ty21a vaccine** is licensed for use in individuals aged ≥5 years of age. It is currently available in a formulation consisting of enteric coated capsules for oral administration every other day in a 3-dose regimen (4-dose regimen in Canada and the US). Ty21a requires storage at 2-8 °C and retains potency for approximately 14 days at 25 °C.
Typbar-TCV is licensed for intramuscular administration of a single dose in pre-school and school-age children and adults aged ≥6 months to ≤ 45 years of age. It is marketed as a single dose (0.5 ml) vial or pre-filled syringe and as multi-dose (2.5 ml) vials. Typbar-TCV consists of 25µg of Vi polysaccharide per 0.5 ml dose, and in its multi-dose presentation each 0.5 ml dose contains 5mg of 2-Phenoxyethanol. The manufacturer-recommended storage temperature is 2-8°C.

Vaccination of children <2 years of age

The evidence from unpublished data on typhoid fever occurrence in children <2 years of age provides strong considerations for implementation of TCV vaccination in that age group. In general, the available data confirm that in high incidence settings, typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the 0-4 years age group with a large proportion of disease occurring between 6 months and 2 years of age. About 10% of disease is considered to occur in children below 1 year of age.

Recommendations for one dose of TCV at 9 months of age with MCV1, or at 15-18 months of age with MCV2, are both valid, recognizing that in many places the appreciable burden of typhoid disease starts to appear at 12 months of age. The Working Group took note, however, that at both time points several other vaccines are already scheduled. A potential preference for TCV to be given in the first year of life should be considered.

TCV use in children <2 years of age should include requirements for robust post-licensure surveillance of effectiveness and safety.

Data on co-administration of TCV with measles-containing vaccines (measles and MMR) show no evidence of interference with the immune response to measles vaccine. At the time of report writing, the results of analysis on the immune response to mumps and rubella components of the MMR are not yet available.

Typhoid vaccine use in outbreaks

Previous evidence of the impact of Vi vaccination in controlling typhoid fever outbreaks (for example in China and Tajikistan) formed the basis for the current WHO recommendation on vaccine use for the control of outbreaks [69]. There is little additional documented experience on the use of vaccines for typhoid fever outbreak control or in humanitarian emergencies. Further, the impact of vaccination in the context of other control interventions such as improved water and sanitation services has not been studied systematically.

In Fiji, a mass typhoid vaccination campaign using ViPS vaccine was conducted in cyclone-affected and
high-risk areas in 2010; >64,000 ViPS doses were administered covering 7% of the total Fiji population and approximately 10,000 doses were used to respond to a concurrent outbreak [38]. Annual typhoid fever incidence was reported to have decreased during the post-campaign year (2011) relative to preceding years (2008–2009) in three subdivisions where a large proportion of the population was vaccinated while the incidence increased or remained unchanged in 12 subdivisions where little to no vaccination occurred.

7.7 Delivery strategies

The currently available data from modelling indicate that routine immunization with TCV would lead to a gradual but sustained decrease in typhoid fever cases while routine vaccination with catch-up would lead to both an immediate and sustained decline in incidence. Further, cost-effectiveness analysis has shown that at a price of up to USD 2 per dose, routine vaccination with TCV is likely to be cost-effective in high incidence settings and in most medium incidence settings depending on the willingness to pay. Catch-up campaigns would be economically justified (preferred) in high incidence settings and at higher willingness to pay thresholds. 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.

Currently, no reliable risk prediction tools are available to support implementation of typhoid vaccination programmes using a risk-based approach. However, efforts are under way to develop risk prediction models. Further support to accelerate the development of such tools is highly warranted. For typhoid fever endemic countries considering a risk-based approach, it should be noted that identification of high-risk groups is likely to be more feasible for most countries at the first sub-national level while implementation of a high-risk approach at the district (or similar) level is likely to be challenging for most countries. Equity issues and integration of vaccination with other typhoid fever control interventions will also need to be considered.

In summary, 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.

**Catch-up vaccination**

There is a potential case for catch-up vaccination at the time of introduction of the vaccine. With a high incidence in preschool and school aged children, routine introduction plus catch-up could possibly achieve an immediate impact and an indirect herd effect.

There is weak overall evidence currently of the additional benefits and impact on disease from catch-up vaccination beyond the obvious “the more immune individuals the better”. An indirect effect of TCV use has not yet been studied and it has been suggested that this effect might be outweighed by transmission via chronic carriers. However, available modelling data should be used to estimate the potential effect of catch-up vaccination. Ongoing work by Pitzer et al [68] extending the Yale model for the analysis of 54 Gavi-eligible countries will be valuable. Options to be evaluated include routine vaccination plus country-wide catch-up vaccination or routine vaccination plus catch-up vaccination in targeted (high-risk) areas.

In addition to the overall considerations for a delivery strategy (as discussed above), decisions on catch up vaccination will need to take into account vaccine supply, expected impact (e.g., reduction of incidence in a shorter time period with a possible indirect effect), cost (usually much higher than routine), and other operational issues, including transport, cold chain, and logistics. Further research is recommended to obtain empirical data to support decisions at country-level on catch-up vaccination, including target age ranges.

**8. DRAFT POLICY RECOMMENDATIONS**

**Recommendation for individuals 2 years and above**

Given the continued high burden of typhoid fever and the increasing antimicrobial resistance of *S. Typhi*, and in view of the currently available evidence on safety, efficacy, feasibility, and affordability of at least one licensed typhoid conjugate vaccines and of the previously recommended ViPS and Ty21a vaccines, SAGE re-emphasizes the importance of the programmatic use of typhoid vaccines for controlling endemic disease.

Specifically, countries should consider the routine use of typhoid conjugate vaccine or ViPS vaccine or Ty21a vaccine in individuals aged 2 years and above. The evidence reviewed for at least one licensed TCV
(Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. These vaccines should be given irrespective of the intensity of other control strategies.

**Recommendation for children below 2 years**

Given the high proportion of typhoid fever that is sufficiently severe to require outpatient or inpatient care in children <2 years in many areas, SAGE recommends the use of TCV in children <2 years of age, administered as a single dose at any time between 6 months to 23 months of age in endemic countries. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. The decision on the age of TCV administration should be based on the local epidemiology of typhoid fever, geographic heterogeneity, and taking into account programmatic considerations of the routine childhood immunization programme.

There are opportunities to administer one dose of TCV at 9 months of age with MCV1, or at 15-18 months of age with MCV2, recognizing that in many places the appreciable burden of typhoid fever starts to appear at 12 months of age.

**Recommendation for vaccine use in outbreaks and humanitarian emergencies**

Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended for outbreak control. Typhoid vaccines may be considered in humanitarian emergencies depending on the risk assessment in the local setting. However, it should be emphasized that the mainstay of typhoid fever prevention in such settings is often the provision of clean water and chlorination of water supplies, along with promotion of hygiene measures. The WHO has published guidance for the risk assessment of typhoid and other vaccine-preventable diseases in humanitarian settings as a framework for decision making on the use of vaccines in those settings [116].

**Recommendations for special groups**

SAGE recommends vaccination of the following specific groups of epidemiological relevance, by virtue of being at high risk or important for transmission, in line with the above age-appropriate recommendations. When ViPS or Ty21a is used, SAGE emphasizes the current recommendations for revaccination.

- **Clinical microbiology laboratory staff** with a recognized risk of occupational exposure to S. Typhi.
• **Professional food handlers**: where possible, preference for use of a Vi negative vaccine, such as Ty21a should be considered in order to protect the possibility for serological identification of a chronic carrier status among vaccinated persons. However, professional food handlers should not go unvaccinated due to lack of Ty21a vaccine. The value of not vaccinating this group (where Ty21a is not available) needs to be carefully weighed within the existing national policies.

• **Travellers from non-endemic to endemic areas**: Typhoid vaccination may be offered to travellers to destinations where the risk of typhoid fever is high. Where available, licensed combination Typhoid-Hepatitis A vaccines may be used for travellers.

**General recommendations**

• All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.

• Ideally, cost-effectiveness analyses should be part of the decision-making and planning process to initiate programmatic use of typhoid vaccines.

• SAGE recommends post-licensure monitoring of effectiveness of TCV (including serological and clinical endpoints) and robust monitoring of safety in line with the GACVS recommendations.

• SAGE recommends that countries monitor the occurrence of AMR strains of *S. Typhi* in endemic and epidemic disease and contribute to the global database on antimicrobial resistance.

### 9. TYPHOID CONJUGATE VACCINES UNDER DEVELOPMENT

A number of additional TCV candidates are currently in varying stages of clinical development as summarized in Table 2 based on the information available at time of writing this report. A review of these candidates was outside the terms of reference of this Working Group.

<table>
<thead>
<tr>
<th>Developer-Manufacturer</th>
<th>Type of TCV (carrier protein)</th>
<th>Target age and/or schedule (if known)</th>
<th>Clinical development stage</th>
<th>Licensure timeline</th>
<th>Plan to apply for PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanzhou Institute of Biological Products (China)³</td>
<td>Vi-rEPA</td>
<td>Phase III randomized double-blind controlled study (subjects 2-55 years) conducted in</td>
<td>Submitted to DCG(I) (China NRA) for marketing authorization for initial licensure in ≥ 2 years</td>
<td>Not confirmed</td>
<td></td>
</tr>
<tr>
<td>Company/Institute</td>
<td>Vaccine Formulation</td>
<td>Target Age Group</td>
<td>Trial Details</td>
<td>Marketing Authorization Status</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Zydus Cadila (India)(^1,^3)</td>
<td>Vi-TT</td>
<td>Single dose 25ug Vi; ≥ 6 months of age</td>
<td>Phase III non-inferiority trial with Typbar-TCV™ completed in India</td>
<td>Submitted to DCG(I) (India NRA) for marketing authorization Not confirmed</td>
<td></td>
</tr>
<tr>
<td>Biological E (India)(^1,^2)</td>
<td>Vi-CRM(_{197})</td>
<td>Single dose 25ug Vi; ≥ 6 months of age</td>
<td>Phase I (Q2 2017)</td>
<td>Target NRA licensure 2018 Yes</td>
<td></td>
</tr>
<tr>
<td>Eubiologics (Republic of Korea)(^1,^3)</td>
<td>Vi-CRM197</td>
<td>Children &lt; 2 years of age, and adults</td>
<td>Preclinical/Phase I</td>
<td>Not confirmed</td>
<td></td>
</tr>
<tr>
<td>Incepta (Bangladesh)(^1,^3)</td>
<td>Vi-DT</td>
<td>Children &lt; 2 years of age, and adults</td>
<td>Preclinical</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>PT Biofarma (Indonesia)(^1,^3)</td>
<td>Vi-DT</td>
<td>Children &lt; 2 years of age, and adults</td>
<td>Phase I trial (Q2 2017)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>SK Chemicals (Republic of Korea)(^1,^3)</td>
<td>Vi-DT</td>
<td>Children &lt; 2 years of age, and adults</td>
<td>Phase II (dose scheduling in children &lt;2 years) planned to start in Q4 2017</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>DAVAC (Viet Nam) and Finlay Institute (Cuba)(^1,^3)</td>
<td>Vi-DT</td>
<td>Preclinical</td>
<td></td>
<td>Not confirmed</td>
<td></td>
</tr>
<tr>
<td>Walvax (China)(^1,^3)</td>
<td>Vi-TT</td>
<td>Preclinical</td>
<td></td>
<td>Not confirmed</td>
<td></td>
</tr>
</tbody>
</table>

Vi-CRM197: Vi polysaccharide derived from *Citrobacter freundii* sensu lato (i.e., derived from a member of the *C. freundii* complex but not *C. freundii*) conjugated to cross-reactive material 197, a nontoxic mutated form of diphtheria toxin.
Vi-DT: Vi polysaccharide derived from *S. Typhi* conjugated to diphtheria toxoid
Vi-rEPA: Vi polysaccharide derived from *S. Typhi* conjugated to recombinant exoprotein A of *Pseudomonas aeruginosa*
Vi polysaccharide derived from *S. Typhi* conjugated to tetanus toxoid

Sources: \(^{1}\)Manufacturer information provided to WHO; \(^{2}\)Goel A. Progress in the development of a Vi-CRM197 conjugate vaccine. 10th International Conference on Typhoid and other Invasive Salmonellosis. April 4-6, 2017. Kampala, Uganda; \(^{3}\)Sahastrabuddhe S. Overview of typhoid conjugate vaccine pipeline: current status and future plans. 10th International Conference on Typhoid and other Invasive Salmonellosis. April 4-6, 2017. Kampala, Uganda

### Acknowledgments

The Working Group and WHO Secretariat gratefully acknowledge contributions of the following towards the evidence review and this report: researchers from CVD Chile, CVD Mali, GERMS-South Africa, icddr,b, Dhaka Shishu Hospital Bangladesh, the MAL055 RTS,S-AS01 Salmonella Ancillary Study Team, SEAP, SETA/TSAP and STRATAA for their invaluable collaboration in providing pre-publication/unpublished data to assist with review of the age-specific occurrence of typhoid fever in children < 2 years of age; researchers at the
University of Washington Strategic Analysis, Research & Training (START) Center for literature searches in selected areas; collaborators in the US Centers for Disease Control and Prevention (CDC) and the International Vaccine Institute for literature searches and review of data on typhoid fever outbreaks; Alex Chung (WHO intern) for assisting with literature review and synthesis; Amanda Buskirk (Postdoctoral Fellow, CVD Maryland) for plotting graphs; TyVAC and independent experts invited for their critical inputs in varying areas of expertise; and to Bharat Biotech for its openness in providing data on its TCV to the degree of granularity required.

References

22. GBD 2013 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet. 2015;386:2145-91
25. Stanaway, J.D. (2016, November). Considerations for extrapolating site-specific data (SETA|SEAP) to broader regional and global contexts. In Breiman, R., and Zaidi, A. (Chairs), Bridging the gap towards defining the burden of typhoid in sub-Saharan Africa and Southeast Asia. Symposium conducted at the American Society of Tropical Medicine and Hygiene, 65th Annual Meeting, Atlanta, GA.


50. Yousafzai MT, Qamar FN, Shakoor S, Saleem K, Kazi M, Garett D et al. Outbreak investigation of ceftriaxone resistant S.Typhi in Hyderabad, Pakistan. 10th International Conference on Typhoid and other Invasive Salmonellosis. April 4-6, 2017. Kampala, Uganda


### Annex A: Summary of clinical trials of Ty21a and ViPS vaccines

#### Table A1. Efficacy results of randomized controlled clinical trials of Vi polysaccharide vaccine

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Formulation</th>
<th>No. of study participants</th>
<th>Ages (Years)</th>
<th>Control vaccine</th>
<th>Follow-up period</th>
<th>Protective efficacy for blood culture confirmed typhoid fever (95% CIs)</th>
<th>Typhoid fever incidence rate in control group (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kathmandu Valley, Nepal (1986-1988)</td>
<td>1 dose of Vi (25 µg)</td>
<td>6,907</td>
<td>5-44</td>
<td>Pneumococcal polysaccharide</td>
<td>17 months</td>
<td>72% (42-86%)</td>
<td>926</td>
</tr>
<tr>
<td>E. Transvaal, South Africa (1985-1988)</td>
<td>1 dose of Vi (25 µg)</td>
<td>11,384</td>
<td>6-14</td>
<td>Meningococcal A/C polysaccharide</td>
<td>21 months 36 months</td>
<td>64% (36-79%) 55%</td>
<td>773</td>
</tr>
<tr>
<td>Quan County, Guangxi Province, China (1995-1997)*</td>
<td>1 dose of locally-produced Vi (30 µg)</td>
<td>131,271</td>
<td>3-50 (92% school-age)</td>
<td>Saline placebo</td>
<td>19 months</td>
<td>69% (28-87%) (72% in school children)</td>
<td>63-78</td>
</tr>
</tbody>
</table>

Sources: Levine 1999; Ivanoff et al, 1994; Simanjuntak, 1991; Hessel et al, 1999; Klugman et al. 1987; Acharya et al, 1987; Yang et al., 2001; Acosta et al., 2005

*Note: An earlier efficacy study of Vi in China (1994-95) was a double-blinded, randomized, saline placebo control study among 81,000 5-55 year olds in Boaying County in Jiangsu Province. The efficacy at 12 months was 71% (95% CI 33-88%) (published in Chinese: Wang ZG, Zhou WZ, Shi J. Efficacy and side effects following immunization with Salmonella typhi Vi capsular polysaccharide vaccine. Zhonghua Liu Xing Bing Xue Za Zhi 1997;18(1):26-9.).
### Table A2. Post licensure cluster-randomized effectiveness trials of Vi polysaccharide vaccine in children 2-16 years – Kolkata, India¹ and Karachi, Pakistan²

<table>
<thead>
<tr>
<th></th>
<th>ViPS</th>
<th>Hepatitis A</th>
<th>Adjusted vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kolkata</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of subjects (2-4 years)</td>
<td>1097</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>Typhoid fever cases</td>
<td>5</td>
<td>27</td>
<td>80% (53, 91)</td>
</tr>
<tr>
<td>Incidence/10⁵ person days</td>
<td>0.64</td>
<td>3.54</td>
<td></td>
</tr>
<tr>
<td># of subjects (5-14 years)</td>
<td>4282</td>
<td>4584</td>
<td></td>
</tr>
<tr>
<td>Typhoid fever cases</td>
<td>21</td>
<td>54</td>
<td>56% (18, 77)</td>
</tr>
<tr>
<td>Incidence/10⁵ person days</td>
<td>0.69</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td><strong>Karachi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of subjects (2-4 years)</td>
<td>3154</td>
<td>3324</td>
<td></td>
</tr>
<tr>
<td>Typhoid fever cases</td>
<td>16</td>
<td>13</td>
<td>-38% (-192, 35)</td>
</tr>
<tr>
<td>Incidence/10³ persons</td>
<td>3.0</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td># of subjects (5-16 years)</td>
<td>10,084</td>
<td>10,669</td>
<td>57% (6, 81)</td>
</tr>
<tr>
<td>Typhoid fever cases</td>
<td>14</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Incidence/10³ persons</td>
<td>0.8</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

¹Sur et al. NEJM 2009; ²MI Khan et al. Vaccine 2012
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Formulation</th>
<th>No. of study participants</th>
<th>Ages (Years)</th>
<th>Control vaccine</th>
<th>Follow- up period</th>
<th>Protective efficacy for blood culture confirmed typhoid fever (95% CIs)</th>
<th>Typhoid incidence rate in control group (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexandria, Egypt (1978-80)</td>
<td>Liquid given with tablet of NaHCO₃*</td>
<td>32,388</td>
<td>6-7</td>
<td>Placebo</td>
<td>36 months</td>
<td>96% (77-99%)</td>
<td>50</td>
</tr>
<tr>
<td>Area Occidente, Santiago, Chile (1983-86)</td>
<td>3 doses of enteric-coated capsules given (1-2 days between doses)</td>
<td>140,000</td>
<td>6-19</td>
<td>Placebo (plus 4 vaccine groups that varied in formulation and time interval between doses)</td>
<td>36 months</td>
<td>67% (47-79%)</td>
<td>110</td>
</tr>
<tr>
<td>Area Sur Oriente, Santiago, Chile (1986)</td>
<td>3 doses of enteric-coated capsules (1-2 days between doses)</td>
<td>81,321</td>
<td>6-19</td>
<td>Placebo</td>
<td>3 years</td>
<td>33% (0-57%)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>3 doses liquid suspension (1-2 days between doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 doses liquid suspension (7 days between doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Sumatra, Indonesia (1986-1989)</td>
<td>3 doses of enteric-coated capsules (7 days between doses)</td>
<td>20,543</td>
<td>3-44</td>
<td>Placebo</td>
<td>30 months</td>
<td>42% (23-57%)</td>
<td>810</td>
</tr>
<tr>
<td></td>
<td>3 doses liquid suspension (7 days between doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53% (36-66%)</td>
<td></td>
</tr>
</tbody>
</table>

* This formulation was not commercialized.
Annex B: Flowcharts of clinical trials of Typbar-TCV

B1: CONSORT diagram of Phase 3 Randomized Controlled Trial - Safety and immunogenicity of Typbar-TCV versus Typhbar vaccine in children and adults aged 2-45 years of age

* Could not follow-up: Subjects could not be reached for follow-up visits.
# Additional subjects reached for follow up as compared to day 1095 (3 years).
¥ Booster dose: Subjects received a second dose of the same vaccine that they received on day 0.

243 subjects “could be reached” for the scheduled visit at day 720. 183 subjects received a booster (Day 720) and had samples analyzed as the booster group (at subsequent time points). Remaining 60 subjects, together with 89 subjects not followed up, did not receive a booster and were analyzed as the non-booster group (at Days 1095 and 1825 only).

197 subjects “could be reached” for the scheduled visit at day 720. 62 subjects received a booster (Day 720) and had samples analyzed as the booster group (at subsequent time points). Remaining 135 subjects, together with 108 subjects not followed up, did not receive a booster and were analyzed as the non-booster group (at Days 1095 and 1825 only).

Source: Bharat Biotech International Limited
B2: Flowchart of Phase 3 Open Label Trial - Safety and immunogenicity of Typbar-TCV versus Typbar vaccine in infants aged 6-23 months

* Could not follow-up: Subjects could not be reached for follow-up visits.

# Additional subjects reached for follow up as compared to day 1095 (3 years).

¥ Booster dose: Subjects received a second dose of the same vaccine that they received on day 0.

220 subjects “could be reached” for the scheduled visit at day 720. 193 subjects received a booster (Day 720) and had samples analyzed as the booster group (at subsequent time points). Remaining 27 subjects, together with 87 subjects not followed up, did not receive a booster and were analyzed as the non-booster group (at Days 1095 and 1825 only).

Source: Bharat Biotech International Limited
B3: CONSORT diagram of co-administration of measles vaccine with Tybar-TCV at ~9 months of age versus either vaccine alone and of Tybar-TCV co-administered with measles-mumps-rubella vaccine at 15 months of age.

Source: Bharat Biotech International Limited
B4: CONSORT diagram of randomized controlled trial of the reactogenicity and immunogenicity of Typbar-TCV versus Sanofi Pasteur ViPS (Typhim Vi™) in subjects 2-15 years of age

Source: Bharat Biotech International Limited
Annex C: GRADE tables

C2: Systematic review and meta-analysis of immunogenicity, efficacy and safety data of Vi-TT typhoid conjugate vaccines
Source: Cochrane Response and Cochrane Infectious Diseases Group

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### Summary of Findings 1.2: Vi-TT typhoid conjugate vaccines (2 doses) versus placebo, no intervention or control vaccine in children and adults

**Patients:** 6 month to 12-year old children; 18-60 year old adults (efficacy and immunogenicity)

**Setting:** India, UK (efficacy), Vietnam, UK (immunogenicity)

**Comparison:** Vi-TT typhoid conjugate vaccine (PedTyph™, 2 doses (6 week interval) or Typhbar-TCV®, 1 dose) versus placebo, no intervention (normal vaccination course) or control vaccine (MENVEO®, 1 dose)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plain language summary</th>
<th>Vaccine type and doses</th>
<th>Absolute effect</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants &amp; studies</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Vi-TT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of typhoid fever in adults follow-up: &lt;1 month</td>
<td>We do not know about the effects of 1 dose Typhbar-TCV on incidence of typhoid fever compared with placebo at &lt;1 month follow-up, evidence was of very low certainty.</td>
<td>Typhbar-TCV</td>
<td>Mean: 7.8 EU</td>
<td>Mean: 57.9 EU</td>
<td>Ratio 73.91 (43.89 to 124.47)</td>
<td>72 participants in 1 RCT</td>
</tr>
<tr>
<td>Incidence of typhoid fever in children follow-up: Year 1</td>
<td>We do not know about the effects of 2 doses Pedatyph on incidence of typhoid fever compared with normal course of vaccination; evidence was of very low certainty.</td>
<td>Pedatyph</td>
<td>Mean: 7.8 EU</td>
<td>Mean: 57.9 EU</td>
<td>Ratio 73.91 (43.89 to 124.47)</td>
<td>72 participants in 1 RCT</td>
</tr>
<tr>
<td>Ratio of GMTs in adults follow-up: &lt;1 month</td>
<td>We do not know about the effects of 1 dose Typhbar-TCV on GMTs compared with placebo at &lt;1 month follow-up, evidence was of very low certainty.</td>
<td>Typhbar-TCV</td>
<td>Mean: 7.8 EU</td>
<td>Mean: 57.9 EU</td>
<td>Ratio 73.91 (43.89 to 124.47)</td>
<td>72 participants in 1 RCT</td>
</tr>
<tr>
<td>Seroconversion in adults follow-up: &lt;1 month</td>
<td>We do not know about the effects of 1 dose Typhbar-TCV on seroconversion compared with placebo at &lt;1 month follow-up, evidence was of very low certainty.</td>
<td>Typhbar-TCV</td>
<td>Mean: 7.8 EU</td>
<td>Mean: 57.9 EU</td>
<td>Ratio 73.91 (43.89 to 124.47)</td>
<td>72 participants in 1 RCT</td>
</tr>
<tr>
<td>SAEs (RCTs) in children follow-up: up to 1 month</td>
<td>Evidence from RCTs We do not know about the effect of 2 doses Pedatyph on SAEs compared with no treatment in children; evidence was of very low certainty.</td>
<td>Pedatyph</td>
<td>Mean: 7.8 EU</td>
<td>Mean: 57.9 EU</td>
<td>Ratio 73.91 (43.89 to 124.47)</td>
<td>72 participants in 1 RCT</td>
</tr>
<tr>
<td>SAEs (RCTs) in adults follow-up: up to 1 month</td>
<td>Evidence from RCTs We do not know about the effect of 1 dose Typhbar-TCV compared with control vaccine on SAEs in adults; evidence was of very low certainty.</td>
<td>Typhbar-TCV</td>
<td>Mean: 7.8 EU</td>
<td>Mean: 57.9 EU</td>
<td>Ratio 73.91 (43.89 to 124.47)</td>
<td>72 participants in 1 RCT</td>
</tr>
</tbody>
</table>

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Note: C2: VERY LOW* indicates that the evidence is of very low certainty due to serious indirectness and imprecision.
Background Paper on Typhoid Vaccines for SAGE (October 2017)

| SAEs (NRCS) in children and adults follow-up: 3 months | Evidence from non-randomised comparison: We do not know about the effect of 1 dose Typhbar-TCV on SAEs; evidence was of very low certainty. | Typhbar-TCV 1 dose | One SAE was reported among 327 participants in a non-randomised arm of an RCT.

---

Evidence quality: VERY LOW

- Effect could not be estimated because no events were reported.
- Primary trial is not cluster adjusted. This estimate uses a small assumed intra-cluster correlation co-efficient of 0.0015. (Alternatively, assuming a large intra-cluster correlation co-efficient of 0.1 would give RR 0.85, 95% CI 0.04 to 20.08).
- Downgraded two levels for serious indirectness: evaluated by only one trial in adults in the UK; human challenge study design uses high levels of bacterial inoculum and controls timing of infection relative to vaccination.
- Downgraded one level for imprecision: small sample size.
- Downgraded one level for risk of bias: unblinded, unadjusted cluster trial with baseline differences between intervention and control groups.
- Downgraded one level for imprecision: no events were reported.
- Non-randomised comparisons start at moderate level evidence.
- Downgraded one level for indirectness: evaluated by only one trial in one setting (India).
- One hospitalisation for per-rectum bleeding and altered bowel habit, diagnosed with inflammatory bowel disease. Deemed not related to vaccination - onset of symptoms occurred prior to vaccination.
- Lower respiratory tract infection in an 18-month-old girl, resolved upon treatment, assessed by trialists as unrelated to vaccination.
Forest plots 1.2: Vi-TT typhoid conjugate vaccine versus placebo, no intervention or control vaccine in children and adults

**Patients:** 6 month to 12-year old children (efficacy); 18-60 year old adults (immunogenicity)

**Setting:** India (efficacy), Vietnam (immunogenicity)

**Comparison:** Vi-TT typhoid conjugate vaccine (Pedia Typh™, 2 doses (6 week interval) or Typhbar-TCV™, 1 dose) versus placebo, no intervention (normal vaccination course) or control vaccine (MENVEO®, 1 dose)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of typhoid fever</td>
<td></td>
<td>VERY LOW</td>
</tr>
<tr>
<td>with 2 doses PedaTyph in infants and children (0.5 to 12 years) or 1 dose Typhbar-TCV in adults follow up: &lt;1 month (Pollard GBR); Year 1 (Mitra 2016 IND)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of GMTs</td>
<td></td>
<td>VERY LOW</td>
</tr>
<tr>
<td>with 1 dose Typhbar-TCV in adults follow up: &lt;1 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion</td>
<td></td>
<td>VERY LOW</td>
</tr>
<tr>
<td>with 1 dose Typhbar-TCV in adults follow up: &lt;1 month</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Incidence of typhoid fever

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VI-TT Events Total</th>
<th>Control Events Total</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Typbar-TCV</td>
<td>Pollard 2017 GBR*</td>
<td>2 37</td>
<td>13 31</td>
<td>0.13 [0.03, 0.53]</td>
</tr>
<tr>
<td>1.1.3 PedaTyph</td>
<td>Mitra 2016 IND</td>
<td>0 637</td>
<td>9 716</td>
<td>0.06 [0.00, 1.01]</td>
</tr>
</tbody>
</table>

### Ratio of GMTs

<table>
<thead>
<tr>
<th>Study name</th>
<th>Vaccine: Vi-TT vs. MENVEO</th>
<th>Ratio of GMT (95% CI)</th>
<th>Vi-TT Control</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollard 2017 GBR*</td>
<td>73.91 (43.89, 124.47) 39 15+ yrs*</td>
<td>1 124</td>
<td>Favor Vi-TT</td>
<td></td>
</tr>
</tbody>
</table>

### Seroconversion

<table>
<thead>
<tr>
<th>Study name</th>
<th>Vaccine: Vi-TT vs. MENVEO</th>
<th>MH RR (95% CI)</th>
<th>Events Vi-TT</th>
<th>Events Control</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollard 2017 GBR*</td>
<td>67.11 (4.28, 1051.36) 37/37 0/33 15+ yrs*</td>
<td>1 4 67</td>
<td>Favor Vi-TT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs (RCTs)</td>
<td>Vi-TT vs no treatment: only 1 study (Mitra 2016 IND) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.3)</td>
<td>Very Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vi-TT vs control vaccine: only 1 study (Pollard 2017 GBR) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.4)</td>
<td>Very Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs (NRCS)</td>
<td>Vi-TT: only 1 study (Mohan 2015 IND) included. Tabulated in Appendix 1.2 (A.1.2.5)</td>
<td>Very Low</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = 18-60 yrs, *human challenge study, unpublished data
### Summary of Findings 1.4: Vi-TT typhoid conjugate vaccines versus typhoid Vi-polysaccharide vaccine (ViPS) in children and adults

**Patients:** 2 to 60-year old children and adults  
**Setting:** India, United Kingdom  
**Comparison:** Vi-TT typhoid conjugate vaccine (Tybar-TCV<sup>®</sup>, 1 dose) versus typhoid ViPS vaccine (Typhim Vi<sup>®</sup> or Tybar<sup>®</sup>, 1 dose)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plain language summary</th>
<th>Absolute effect</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
</table>
| **Incidence of typhoid fever**  
in adults  
follow-up: <1 month | We do not know about the effect of 1 dose Tybar-TCV on the incidence of typhoid fever in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low. | 200 per 1000  
54 per 1000 (1.2 to 24.2) | RR 0.27 (0.06 to 1.21)  
72 participants in 1 RCT | VERY LOW<sup>12</sup>  
due to serious indirectness and imprecision |
| **Ratio of GMTs**  
in adults  
follow-up: 0–<1 month | We do not know about the effect of 1 dose Tybar-TCV on GMTs in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low. | Mean: 140.5 EU  
Mean: 579.7 EU | Ratio 4.12 (2.38 to 7.12)  
74 participants in 1 RCT | VERY LOW<sup>12</sup>  
due to serious indirectness and imprecision |
| **Ratio of GMTs**  
in children and adults  
follow-up: 1–<2 months | There probably is higher GMTs with 1 dose Tybar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1 to <2 months’ follow-up in children and adults. | Mean: 411 EU/mL  
Mean: 1203 EU/mL | Ratio 3.15 (2.70 to 3.61)  
637 participants in 1 RCT | MODERATE<sup>3</sup>  
due to indirectness |
| **Ratio of GMTs**  
in children and adults  
follow-up: 1–<2 years | There probably is higher GMTs with 1 dose Tybar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1 to <2 years’ follow-up in children and adults. | Mean: 45.8 EU/mL  
Mean: 81.7 EU/mL | Ratio 1.78 (1.53 to 2.08)  
440 participants in 1 RCT | MODERATE<sup>3</sup>  
due to indirectness |
| **Seroconversion**  
in adults  
follow-up: 0–<1 month | We do not know about the effect of 1 dose Tybar-TCV on seroconversion rate in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low. | 886 per 1000  
1000 per 1000 (877 to 1000) | RR 1.13 (0.99 to 1.28)  
72 participants in 1 RCT | VERY LOW<sup>12</sup>  
due to serious indirectness and imprecision |
| **Seroconversion**  
in children and adults  
follow-up: 1–<2 months | There probably is a slightly better seroconversion rate for 1 dose Tybar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1–<2 months follow-up in children and adults. | 931 per 1000  
968 per 1000 (940 to 1000) | RR 1.04 (1.01 to 1.08)  
637 participants in 1 RCT | MODERATE<sup>3</sup>  
due to indirectness |
| **Seroconversion**  
in children and adults  
follow-up: 1–<2 years | There probably is a better seroconversion rate for 1 dose Tybar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1–<2 years follow-up in children and adults. | 533 per 1000  
741 per 1000 (640 to 863) | RR 1.39 (1.20 to 1.62)  
440 participants in 1 RCT | MODERATE<sup>3</sup>  
due to indirectness |
**SAEs (RCTs)**  
*in children and adults follow up: up to 3 months*  

**Evidence from RCTs:**  
There probably is little or no difference in SAE rate for 1 dose Typhbar-TCV typhoid conjugate vaccine compared with VIPS typhoid vaccine in children and adults at up to 3 months follow-up.  

<table>
<thead>
<tr>
<th>114, per 10,000</th>
<th>4.1 per 10,000 (8 to 20)</th>
<th>RR 0.36 (0.07 to 1.82) 732 participants in 2 RCTs</th>
<th>MODERATE due to imprecision</th>
</tr>
</thead>
</table>

**SAEs (NRCS)**  
*in children 22 years follow up: 2 days*  

**Evidence from non-randomised comparative studies:**  
We do not know about the effect of 1 or 2 doses Pedatyph typhoid conjugate vaccine compared with VIPS typhoid vaccine on SAEs; certainty of evidence was very low.  

| 0 / 37 | 0 / 169 | RR not estimable 206 participants in 1 non-randomised comparative study | VERY LOW due to no randomisation, indirectness, and imprecision |

CI= confidence interval; ELISA= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; NRCS= non-randomised comparative study; RCT= randomised controlled trial; RR= risk ratio; VIPS= typhoid Vi-polysaccharide vaccine; Vi-TT= typhoid Vi antigen coupled to tetanus toxin carrier protein

* Effect could not be estimated because no events were reported  
1 Downgraded two levels for serious indirectness: evaluated by only one trial in adults in the UK; human challenge study design uses high levels of bacterial inoculum and controls timing of infection relative to vaccination.  
2 Downgraded one level for imprecision: small sample size.  
3 Downgraded one level for indirectness: evaluated by only one trial in 8 sites in India.  
4 Downgraded one level for imprecision: wide 95% CI that include both no effect and benefit for VIPS.  
5 Non-randomised comparative studies start at moderate certainty evidence.  
6 Downgraded one level for indirectness: evaluated by only one trial in 3 sites in India.  
7 Downgraded one level for imprecision: no events were reported.  
8 Four hospitalisations in VIPS groups, none assessed to be related to vaccine: polyarthritis following typhoid challenge and antibiotic use, requiring ongoing rheumatological input; urinary retention secondary to vaginal ulceration; semi-elective tonsillecetomy for investigation of tonsillar lesion; febrile convulsions in a 3 year-old, resolved.  
9 One hospitalisation in Vi-TT group: per-rectum bleeding and altered bowel habit, diagnosed with inflammatory bowel disease. Not related to vaccination - onset of symptoms occurred prior to vaccination.
### Forest plots 1.4: Vi-TT typhoid conjugate vaccines versus typhoid Vi-polysaccharide vaccine (ViPS) in children and adults

**Patients:** 2 to 60-year old children and adults  
**Setting:** India, United Kingdom  
**Comparison:** Vi-TT typhoid conjugate vaccine (Typhbar-TCV®, 1 dose) versus typhoid ViPS vaccine (Typhim Vi® or Typhbar®, 1 dose)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of typhoid fever with 1 dose Typhbar-TCV in adults follow-up &lt;3 month</td>
<td></td>
<td>💯₀₀₀₀ VERY LOW</td>
</tr>
<tr>
<td>Ratio of GMTs with 1 dose Typhbar-TCV in children and adults follow-up 0 months to &lt;2 years</td>
<td></td>
<td>💯₀₀₀₀ VERY LOW</td>
</tr>
</tbody>
</table>
### Seroconversion/seroprotection

with 1 dose Tybar-TCV
in children and adults
follow up: 0 months to <2 years

<table>
<thead>
<tr>
<th>Time points</th>
<th>Study name</th>
<th>Vaccine: Vi-TT vs. VIPS</th>
<th>MH RR (95% CI)</th>
<th>Events Vi-TT</th>
<th>Events VIPS</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 mths</td>
<td>Pollard 2017 GBR*</td>
<td>Tybar-TCV vs. Typhim Vi</td>
<td>1.13 (0.99, 1.28)</td>
<td>37/37</td>
<td>31/35</td>
<td>15+ yrs*</td>
</tr>
<tr>
<td>1-2 mths</td>
<td>Mohan 2015 IND</td>
<td>Tybar-TCV vs. Tybar</td>
<td>1.04 (1.01, 1.08)</td>
<td>323/322</td>
<td>284/305</td>
<td>2.15 yrs*</td>
</tr>
<tr>
<td>1-2 yrs</td>
<td>Mohan 2015 IND</td>
<td>Tybar-TCV vs. Tybar</td>
<td>1.39 (1.20, 1.62)</td>
<td>180/243</td>
<td>105/197</td>
<td>2.15 yrs*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup name</th>
<th>Study name</th>
<th>Vaccine: Vi-TT vs. VIPS</th>
<th>MH RR (95% CI)</th>
<th>Events Vi-TT</th>
<th>Events VIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human challenge</td>
<td>Pollard 2017 GBR*</td>
<td></td>
<td>0.39 (0.06, 2.50)</td>
<td>1/41</td>
<td>3/37</td>
</tr>
<tr>
<td>Not human challenge</td>
<td>Mohan 2015 IND</td>
<td></td>
<td>0.31 (0.01, 7.53)</td>
<td>0/340</td>
<td>1/1314</td>
</tr>
</tbody>
</table>

Overall (I-squared = 0.0%, p = 0.903) | | 0.36 (0.07, 1.82) | 1/381 | 4/351 |

Vi-TT vs VIPS NCRS: only 1 study (Garg 2014 IND) included for this comparison. Tabulated in Appendix 1.2 (A1.2.5).

* Human challenge study, unpublished data

1 A 0.5 continuity correction was added to all cells of the 2x2 table

2 1 hospitalisation for per-rectum bleeding and altered bowel habit. Diagnosed with inflammatory bowel disease. Not related to vaccination - onset of symptoms occurred prior to vaccination

3 3 Hospitalisations, none assessed to be related to vaccine. Polychromatophasia following typhoid challenge and antibiotic use, requiring ongoing rheumatological input. Hospitalisation for urinary retention secondary to vaginal ulceration. Hospitalisation for semi-elective tonsilllectomy for investigation of tonsillar lesion.

4 1 Hospitalisation for febrile convulsions in a 3 year old, resolved and assessed to be unrelated to vaccination.
Summary of Findings 1.6: Booster versus no booster Vi-TT in infants, children and adults

**Patients:** infants, children and adults  
**Setting:** India  
**Comparison:** Booster dose of Tybar-TCV at 720 days after one initial dose, versus no booster (one initial dose of Tybar-TCV only)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plain language summary</th>
<th>Absolute effect</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of typhoid fever</td>
<td>No studies were identified for this outcome.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of GMTs (aged 2-45 years) follow up: 42 days after booster dose (approx. 762 days after 1st dose) versus 720 days after 1st dose</td>
<td>We do not know about the effect of a booster dose of Tybar-TCV on GMTs in children and adults because the certainty of evidence is very low.</td>
<td>Mean: 81.7 EU/mL Mean: 1685.3 EU/mL</td>
<td>Ratio 20.63 (19.05 to 22.03) 183 participants in 1 non-random cohort*</td>
<td>O OO O VERY LOW/12 due to risk of bias and indirectness</td>
</tr>
<tr>
<td>Ratio of GMTs (aged 6-23 months) follow up: 42 days after booster dose (approx. 762 days after 1st dose) versus 720 days after 1st dose</td>
<td>We do not know about the effect of a booster dose of Tybar-TCV on GMTs in infants because the certainty of evidence is very low.</td>
<td>Mean: 48.7 EU/mL Mean: 1721.9 EU/mL</td>
<td>Ratio 35.36 (32.18 to 38.84) 193 participants in 1 open-label trial**</td>
<td>O OO O VERY LOW/12 due to risk of bias and indirectness</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>No studies were identified for this outcome.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td>No studies were identified for this outcome.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI= confidence interval; EU= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; RCT=randomised controlled trial; RR= risk ratio  
*Three-hundred and forty participants aged 2 to 45 years received one dose of Tybar-TCV in a single arm of an RCT, and a non-random sample of 183 of these participants went on to receive a booster dose at 720 days. The comparison is between 243 of the 340 participants who received one dose with serum samples available at 720 days, and 175 of the 183 participants who received the initial dose plus a booster, with serum samples available at approximately 762 days. All 175 participants analysed in the booster dose group are also included within the non-booster dose groups. Correlation equal to 0 (no adjustment for matching), and 0.5 and 0.75 were applied; correlation to 0.5 shown in summary of findings table.

**Three-hundred and twenty-seven participants aged 6 to 23 months received one dose of Tybar-TCV in an open-label trial, and a non-random sample of 193 of these participants went on to receive a booster dose at 720 days. The comparison is between 220 of the 327 participants who received one dose with serum samples available at 720 days, and 187 of the 193 participants who received the initial dose plus a booster, with serum samples available at approximately 762 days. All 187 participants analysed in the booster dose group are also included within the non-booster dose groups. Correlation equal to 0 (no adjustment for matching), and 0.5 and 0.75 were applied; correlation to 0.5 shown in summary of findings table.

1 Downgraded two levels for risk of bias: non-randomised comparison: analysis of the same sample participants before and after booster dose; age is a serious confounder, not controlled across groups.

2 Downgraded one level for indirectness: evaluated by only one trial in India.
### Forest plots 1.6: Booster versus no booster Vi-TT in infants, children and adults

**Patients:** infants, children and adults  
**Setting:** India  
**Comparison:** Booster dose of Typhbar-TCV at 720 days after one initial dose, versus no booster (one initial dose of Typhbar-TCV only)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of typhoid fever</td>
<td>No studies were identified for this outcome.</td>
<td></td>
</tr>
<tr>
<td><strong>Ratio of GMTs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>follow up: 1 month after booster dose versus 6 months after 3rd dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study or Subgroup</td>
<td>Booster</td>
<td>No booster</td>
</tr>
<tr>
<td>1.1.1 Age 2-45 years</td>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td>Mohan 2015 (correlation 0)</td>
<td>175</td>
<td>243</td>
</tr>
<tr>
<td>Mohan 2015 (correlation 0.5)</td>
<td>175</td>
<td>243</td>
</tr>
<tr>
<td>Mohan 2015 (correlation 0.75)</td>
<td>175</td>
<td>243</td>
</tr>
<tr>
<td>1.1.2 Age 6-23 months</td>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td>Mohan 2015 (correlation 0)</td>
<td>187</td>
<td>220</td>
</tr>
<tr>
<td>Mohan 2015 (correlation 0.5)</td>
<td>187</td>
<td>220</td>
</tr>
<tr>
<td>Mohan 2015 (correlation 0.75)</td>
<td>187</td>
<td>220</td>
</tr>
</tbody>
</table>

Seroconversion: No studies were identified for this outcome.  
SAEs: No studies were identified for this outcome.
### Summary of findings 1.8: 1 dose versus 2 doses Vi-TT typhoid conjugate vaccine in children

**Patients:** children (mean age: 4.5 years)  
**Setting:** India  
**Comparison:** 1 dose versus 2 doses (2 month interval) Vi-TT (Peda Typh™️) typhoid conjugate vaccine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plain language summary</th>
<th>Absolute effect</th>
<th>Relative effect (95% CI)</th>
<th>Nº of participants &amp; studies</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of typhoid fever</td>
<td>No studies were identified for this outcome.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of GMTs in 2 to &lt;5 year olds follow-up: 2 to &lt;5 years</td>
<td>We do not know about the effect of 1 dose compared with 2 doses PedaTyph typhoid conjugated vaccine on ratio of GMTs at 2 to &lt;5 years follow-up in children; evidence is of very low certainty.</td>
<td>Mean: 17 µg/mL</td>
<td>Mean: 14 µg/mL</td>
<td>Ratio 0.82 (0.25 to 2.68)</td>
<td>40 participants in 1 RCT</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>No studies were identified for this outcome.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SAEs (RCTs)**  
in infants and children (≤5 years) follow-up: up to 7 days  
Evidence from RCTs  
We do not know about the effect of 2 doses compared with 1 dose PedaTyph typhoid conjugated vaccine on SAEs in children; evidence is of very low certainty.  
0/200 | 0/200 | RR not estimable**  
400 participants in 1 RCT  
☐☐☐☐ VERY LOW!⁴⁴⁴⁴ due to risk of bias, indirectness, and imprecision

CI= confidence interval; GMT= Geometric mean titre; RCT= randomised controlled trial; RR= risk ratio; Vi-TT= typhoid Vi antigen coupled to tetanus toxoid carrier protein

³³³³ Downgraded one level for risk of bias: high risk of performance and attrition bias, and non-random comparison (a non-random subsample of children from an RCT were included in follow-up).

³⁴⁴⁴ Downgraded one level for indirectness:  evaluated by only one trial in children in one setting (India).

**Downgraded one level for imprecision: small sample size.

**Downgraded one level for risk of bias: high risk of performance and detection bias, and unclear randomisation methods.

**Downgraded one level for imprecision: no events were reported among relatively few participants, effect could not be estimated.
Forest plots 1.8: 1 dose versus 2 doses Vi-TT typhoid conjugate vaccine in children

Patients: children (mean age: 4.5 years)
Setting: India
Comparison: 1 dose versus 2 doses (2 month interval) Vi-TT (Pedia Typhim®) typhoid conjugate vaccine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Forest plot</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of typhoid fever</td>
<td>No studies were identified for this outcome.</td>
<td></td>
</tr>
<tr>
<td>Ratio of GMTs follow-up 2 to &lt;5 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time point</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study name</td>
<td>Vi-TT: 1 dose vs. 2 doses</td>
<td></td>
</tr>
<tr>
<td><strong>2-5 yrs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinnasami 2013 IND</td>
<td>0.82 (0.25, 2.08)</td>
<td>20 20 2-5 yrsA</td>
</tr>
<tr>
<td>Favors Vi-TT 2 doses</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>Favors Vi-TT 1 dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion</td>
<td>No studies were identified for this outcome.</td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = range not reported; mean age 4.5 years at 30 months follow-up.
Annex D: List of Working Group members and Declaration of interests

SAGE members
- Ilesh Jani (Chair of Working Group), Instituto Nacional de Saúde (National Institute for Health), Mozambique
- Kari Johansen, European Centre for Disease Prevention and Control, Sweden.

Experts
- Narendra Arora, International Clinical Epidemiology Network (INCLEN), India
- Zulfiqar A. Bhutta (SickKids Center for Global Child Health, The Hospital for Sick Children, Canada; Center of Excellence in Women and Child Health, Aga Khan University, Pakistan)
- John A. Crump (Centre for International Health, Department of Preventive and Social Medicine, University of Otago, New Zealand)
- Myron M. Levine (Center for Vaccine Development, University of Maryland School of Medicine, USA)
- Dafrossa Lyimo (National EPI Manager (Dar es Salaam), Tanzania)
- Florian Marks (Department of Epidemiology, International Vaccine Institute, Republic of Korea)
- Mark A. Miller (Office of the Director; and Division of International Epidemiology and Population Studies, National Institutes of Health, USA)
- Christopher M. Parry (Liverpool School of Tropical Medicine, UK; School of Tropical Medicine and Global Health, University of Nagasaki, Japan)
- Richard A. Strugnell (Department of Microbiology and Immunology, University of Melbourne, Australia)
- Dipika Sur (Consultant, Translational Health Science and Technology Institute, India)

WHO Secretariat
- Adwoa Bentsi-Enchill (Primary focal point)
- Joachim Hombach

Declaration of interests
All members completed a declaration of interests. The reported relevant interests (at any time throughout the work of the Working Group) are summarized below:

Zulfiqar A. Bhutta
- His institution (the Aga Khan University) received a grant from the former Novartis Vaccines Institute for Global Health (NVGH) to undertake a typhoid conjugate vaccine trial, for which he was Principal Investigator. This grant ceased in Sept 2012. This interest was assessed as non-personal, specific and financially significant.*
- His institution (The Hospital for Sick Children, Toronto) received a grant from the Bill and Melinda Gates Foundation (BMGF) for research on global trends in typhoid fever. This interest was assessed as non-personal, specific and financially significant.*

Myron M. Levine
- Has provided scientific advice, with no financial compensation, to a typhoid vaccine developer (Bharat Biotech) for the analysis and presentation of data on its licensed typhoid conjugate vaccine. This interest was assessed as non-personal, specific and financially insignificant.*
• His institution (the University of Maryland) has a license agreement with Bharat Biotech for a bivalent typhoid/paratyphoid vaccine (in early preclinical development) for which M Levine is a co-inventor. This interest was assessed as personal, specific and financially significant.*

• Through a Wellcome Trust grant to his institution (the University of Maryland), he is the Principal Investigator to develop and perform early clinical trials of a non-typhoidal Salmonella (NTS) conjugate vaccine for which he is a co-inventor. The University of Maryland has a technology transfer agreement with Bharat Biotech for this NTS vaccine candidate. This interest was assessed as personal, non-specific and financially significant.*

• His institution (the University of Maryland) has a license agreement with PaxVax to commercialize an oral cholera vaccine for which he is a co-inventor. Paxvax is also the current manufacturer of the live oral typhoid vaccine Ty21a. This interest was assessed as personal, non-specific and financially significant.*

Florian Marks
• His institution, the International Vaccine Institute (IVI), has a typhoid vaccine development program. IVI has technology transfer agreements and provides ongoing scientific and technical advice to three current developers of typhoid conjugate vaccines. F Marks is employed in the Epidemiology Department of IVI and this interest was assessed as non-personal, specific, and financially significant.*

• His institution (IVI) has received research grants from the BMGF to conduct a multi-country typhoid fever burden studies in Africa (the Typhoid Fever Surveillance in Africa Program and the Severe Typhoid in Africa Program), for which he is Principal Investigator. This interest was assessed as non-personal, specific and financially significant.*

Mark A. Miller
• His institution (the US National Institutes of Health) received a BMGF grant for the development of a biological reference standard for typhoid vaccines. This interest was assessed as non-personal, specific and financially significant.*

Richard Strugnell
• He is a consultant to a planned efficacy trial for the Typbar-TCV conjugate vaccine (expected to start in mid-late 2018). This potential interest was assessed as non-personal and specific, however the financial significance could not be determined at the time of assessment as the trial was not yet funded.*

* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

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