Informal Consultation of experts on Typhoid Fever, South East Asia Region

28-29 September, 2016 New Delhi, India
## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>API</td>
<td>Association of Physicians of India</td>
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<tr>
<td>BEIV</td>
<td>Broader economic impact of vaccines</td>
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<tr>
<td>CE</td>
<td>Cost effectiveness</td>
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<td>CEA</td>
<td>Cost effectiveness analysis</td>
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<td>COI</td>
<td>Cost of illness</td>
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<td>EPI</td>
<td>Expanded programme on immunization</td>
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<td>IB-VPD</td>
<td>Invasive bacterial vaccine preventable diseases</td>
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<td>MDG</td>
<td>Millennium development goals</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts on immunization</td>
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<td>SEAP</td>
<td>Surveillance of Enteric Fever in Asia Project</td>
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<td>SEAR</td>
<td>South East-Asia Region</td>
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<td>SETA</td>
<td>Severe Typhoid in Africa Program</td>
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<td>STRATAA</td>
<td>Strategic Typhoid Alliance across Africa and Asia</td>
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<td>TSAP</td>
<td>Typhoid Surveillance in Africa Project</td>
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<td>TCV</td>
<td>Typhoid conjugate vaccine</td>
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<tr>
<td>Vi-rEPA</td>
<td>Vi antigen conjugated with recombinant exoprotein A from <em>Pseudomonas aeruginosa</em></td>
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<tr>
<td>Vi-CRM\textsubscript{197}</td>
<td>Vi antigen conjugated with cross-reactive material \textsubscript{197}, a non-toxic mutated form of diphtheria toxin</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Executive summary

Typhoid fever continues to be an important public health problem, affecting many low-income and middle-income countries with over 21 million typhoid cases and 200 000 deaths estimated globally each year. The majority of the morbidity and mortality associated with typhoid fever is reported in Asia and Africa.

The existing challenges to combat typhoid fever include non-availability of rapid diagnostic tests, inadequate use of standard treatment practices, emerging antimicrobial resistance, lack of safe water, inadequate sanitary facilities and poor hygienic standards. All of these underscore the importance of expanding efforts to prevent typhoid infection.

Currently, a number of important research studies or projects are ongoing in a variety of settings to examine a broad range of issues such as further understanding of the disease burden including risk factors, disease severity and long-term sequelae; the importance of long-term carriers in disease transmission; antimicrobial resistance; economic burden; and approaches to strengthening surveillance systems including the feasibility of integrating typhoid and other invasive salmonellosis in the WHO-coordinated Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) surveillance network.

Vaccination has emerged as an effective strategy to control endemic disease or to interrupt transmission during outbreaks. However despite the demonstrated safety and efficacy of the available parenteral Vi polysaccharide and oral, live attenuated Ty21a typhoid vaccines for enteric fever prevention and control, the public health programmatic use and private sector use of typhoid vaccines has been limited in high burden countries.

In 2008, WHO issued updated global policy recommendations for the use of the Vi polysaccharide and Ty21a vaccines in areas where typhoid remains a significant public health problem and where antibiotic resistance is prevalent. Since then significant progress has been achieved in the development of typhoid conjugate vaccines (TCVs). WHO’s Strategic Advisory Group of Experts on Immunization (SAGE) will be requested to consider the updated evidence for typhoid vaccines in general and TCVs in particular in 2017 for recommendations on use.

It is the need of the hour to review the evidence on the immunogenicity of typhoid conjugate vaccines, their potential effectiveness and to consider future vaccine introduction within a framework for typhoid control in the Region.
Background
The global enteric fever burden reported by World Health Organization (WHO) in 2004 was estimated over 21 million cases and 222,000 deaths per year, predominantly in pre-school and school aged children. Further estimates of the disease burden have been reported in intervening years ranging between 12 to 21 million cases per year when varying risk factor adjustments are applied. The majority of this burden occurs in Asia, including 90% of the fatal outcomes of globally estimated case fatality rates.

In recent years, considerable knowledge has been generated on typhoid fever (and related paratyphoid fever) disease burden estimates; typhoid vaccine use through experience in a number of demonstration projects as well as modelling studies; and on projections for vaccine demand to guide investment decisions by potential donors. With available typhoid vaccines and promising new candidate vaccines in development, it is imperative to assess the measures to effectively reduce the burden of typhoid through vaccination and/or other control strategies. Many countries have controlled typhoid without vaccination, but investments in safe drinking water and better sanitation are long-term solutions for typhoid, while vaccination has the potential for rapid control of disease as well as for reduction in the unnecessary usage of antibiotics.

To further understand the disease and economic burden of typhoid, further efforts are required to establish and strengthen surveillance systems for enteric fever. The development and use of reliable and appropriate diagnostic methods for Salmonella Typhi in developing countries needs further attention.

The focus on vaccine preventable diseases in the South East Asia Region (SEAR) of WHO has led to remarkable achievements such as maintaining a polio-free status and attaining maternal and neonatal tetanus elimination. With the availability of antibiotics, typhoid is neglected by policy makers and there is a need now to focus attention on this important cause of illness in the SEAR and consider what strategies might be most appropriate in different settings.

The current need is to strengthen surveillance to advance typhoid prevention and control in the SEAR through appropriate strategies for typhoid vaccination in parallel with other control strategies.
Objectives
The meeting was convened with regional and international typhoid experts with the following specific objectives:

• To review global and regional enteric fever disease burden, ongoing studies to further improve understanding of the disease and economic burden, surveillance challenges including diagnostics, and the feasibility and effectiveness of control strategies.

• To review the status of typhoid conjugate vaccine development and current knowledge on vaccine performance, as well as expected timelines for global typhoid vaccine policy revision and activities to support future vaccine introduction.

• To share global activities to accelerate prevention and control of typhoid and other invasive salmonellosis, and discuss considerations for development of a regional plan aimed at (a) ensuring visibility of typhoid and paratyphoid fever as a priority public health problem; and (b) an agreed program for typhoid control in general and typhoid vaccine introduction specifically.
Global and regional updates on typhoid and paratyphoid disease burden

The estimated burden of typhoid fever in Asia has been well documented ranging between 6.9 and 10.1 million cases annually with incidence rates up to 274 per 100,000 cases per year in some parts of the region.

While the global burden of enteric fever is primarily in Asia and Africa, the burden in Africa had been less well established. However, increasing efforts were made in recent years to estimate the burden of invasive Salmonella disease in sub-Saharan Africa, in particular infections caused by *Salmonella* enterica serovar Typhi (*S. Typhi*), through a number of epidemiological studies including the Typhoid Surveillance in Africa Project (TSAP) established in 2009. An important finding from TSAP was that of remarkably high incidence rates in Africa (in at least 3 of 13 African sites) similar to rates previously described in Asia. Other significant new findings included high incidence rates among children less than 15 years old; incidence rates in many rural populations that were similar to or higher than urban locations; and a substantial prevalence of antimicrobial resistance overall and multidrug resistant strains of invasive *Salmonella* species circulating in sub-Saharan Africa.

The emergence of multidrug resistant (MDR) typhoid is a major global health threat affecting many endemic countries. A single dominant MDR lineage of *S. Typhi*, the H58 lineage, has emerged and spread throughout Asia and Africa over the last 30 years. The H58 lineage is reported to be displacing antibiotic-sensitive isolates and transforming the global genotypic distribution of *S. Typhi*. Further, the multidrug resistant H58 lineage is linked to severe disease and therefore emphasizes an urgent need for timely preventive measures.

A comparison of the estimates of typhoid disease burden in Asia with the global estimates is shown in Table 1.

Table 1: An overview of typhoid disease burden estimates from 1986 to 2014

<table>
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<tr>
<th>Year</th>
<th>World</th>
<th>Asia</th>
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<tr>
<td>1986</td>
<td>12.5 million</td>
<td>6.98 million</td>
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<tr>
<td>2004</td>
<td>21.65 million typhoid, 5.41 million paratyphoid, 216,500 typhoid deaths</td>
<td>10.1 million typhoid, 1.35 million paratyphoid, 101,000 typhoid deaths</td>
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<tr>
<td>2010</td>
<td>13 million enteric fever episodes</td>
<td>6.9 million enteric fever episodes</td>
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<tr>
<td>2014</td>
<td>11.8 million typhoid cases, 128,000 typhoid deaths</td>
<td>8.6 million typhoid cases, 93,000 typhoid deaths</td>
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The current enteric fever burden in selected SEAR countries was reviewed based on published and unpublished estimates. Most of the studies reporting typhoid and/or paratyphoid fever burden estimates in the SEAR are over a decade old and there is significant heterogeneity among them.

Though the data in most cases are not denominator-based there is evidence of a large burden of laboratory-confirmed typhoid in India, based on both culture and serological tests. In a multicentre hospital-based surveillance for invasive bacterial diseases in Bangladesh, *S. Typhi* is the commonest organism isolated. The disease estimates from Nepal indicate a continuous high burden of enteric fever over the last two decades. All the estimates indicate high incidence in the younger age group of pre-school children. There are unpublished data from the region that indicate equal prevalence of typhoid in urban and rural settings suggesting that geographic differences in urban versus rural disease burden may not be a significant epidemiological consideration for typhoid prevention and control, at least in some settings. The results of ongoing studies in the Region (see under “Key discussions” below) are expected to shed more light on the current situation in Asia.

Progress towards the Millennium Development Goals (MDGs) and projected urbanization put a huge burden on resources for maintaining safe water and improving hygiene standards in each of the Member States in SEAR. The available data in the Region also highlight a need for well-coordinated efforts for effective WASH interventions.

The emergence of antimicrobial resistance in *Salmonella* species in the SEAR indicates significant resistance to floroquinolones and rising resistance to the first line of available drugs and this makes tackling the disease even more challenging. The local epidemiological data are crucial for developing strategies and policies.

The evidence indicates a strong need for strengthening surveillance, strengthening health systems, exploring latest diagnostic methods and developing vaccine strategies along with guidelines for antimicrobial treatment in a SEAR regional plan for typhoid prevention and control in endemic, outbreak and emergency settings.
Key discussions

1. Overview of studies/activities to generate further data to guide vaccination policy and vaccine introduction

Several key studies - recent, ongoing and planned - are anticipated to provide results globally and in the SEAR by 2018/2019. These include studies characterizing the burden and epidemiology of enteric fever as well as potential studies on typhoid conjugate vaccine effectiveness: the Surveillance of Enteric Fever in Asia Project (SEAP), Severe Typhoid in Africa Program (SETA), a National Typhoid Surveillance System in India, a Typhoid Conjugate Vaccine Demonstration Project in Navi Mumbai, India and the Strategic Typhoid Alliance across Africa and Asia (STRATAA) study all with sites in SEAR, and the Typhoid Surveillance in Africa Project (TSAP) and Severe Typhoid in Africa Program (SETA) in Africa. In addition, a pilot is ongoing to assess the feasibility of including enteric fever in the IB-VPD surveillance network.

These recent and ongoing studies aim to generate data collectively on a variety of issues, mainly burden, transmission and antimicrobial resistance patterns, modelling of typhoid dynamics, vaccine impact and economic analyses. It is worth noting that these studies are occurring against a background of several gaps identified in the information countries will need to consider for vaccine introduction such as:

- data to support (potential) risk-based vaccination strategy;
- data to support the optimum vaccination schedule in children < 2 years old;
- a need to understand the impact of long-term carriers on disease burden (through serologic or microbiological studies);
- evidence of individual and herd protection from vaccination;
- data on the feasibility and acceptance of multiple injections;
- cost effectiveness data for different vaccine delivery strategies; and
- evidence on the impact of vaccination in the context of other control strategies.

Data are needed to support the development of global policy including the SAGE recommendations and the WHO position paper on typhoid vaccines which will further support vaccine introduction decisions at the regional and country levels and facilitate funding decisions by donors for support on typhoid vaccine use.

Past experience has shown that the lack of robust epidemiological data to map out high-risk populations to be targeted for vaccination contributed to low typhoid vaccine uptake. Further, experience with introduction of new vaccines in general indicates that availability of data to support vaccine introduction, as outlined above, will be a major driver of vaccine demand and acceptability by countries.
2. Studies on epidemiology of enteric fever in SEAR

2. a) Surveillance of Enteric fever in Asia Project (SEAP)

SEAP is a multi-site project in Bangladesh, Nepal, India and Pakistan designed to collect and analyse enteric fever information (clinical and laboratory-confirmed cases) in two phases. Phase I included retrospective review of existing data to assess the health facilities with potential to participate in Phase II and to inform the design of that phase. Phase II (in three sites excluding India) is planned to be a prospective population-based surveillance to feed into policy recommendations on enteric fever prevention and control including vaccine implementation, and to facilitate assessments of the impact of vaccines and other interventions.

Data in Phase I from India is not yet available. It may reflect only the tip of the iceberg as many agents responsible for febrile diseases such as scrub typhus, dengue all coexist in India. Further, because of the use of non-specific serological tests, enteric fever in India is not always confirmed using appropriate laboratory methods.

In Bangladesh, the high enteric fever incidence in infants and in pre-school aged children is quite worrisome as currently no conjugate vaccine is licensed for use in less than two year olds. The number of laboratory confirmed cases of typhoid fever is very low in the various sites assessed and there are limited data on typhoid complications. The emergence of antimicrobial resistance to ciprofloxacin is posing a challenge in the treatment of typhoid fever.

The Nepal findings from Phase I indicate that data on empirical typhoid diagnosis is an unreliable marker of disease burden. Data currently available do not provide estimates of disease burden particularly outside the urban areas. In an era of emerging antimicrobial resistance, information on clinical outcomes is critical and current data available do not provide follow up details. Laboratory supported surveillance is essential as blood cultures are not available for all suspected cases and treatment is started based on strong clinical suspicion. The laboratory-confirmed cases indicate young adults, 18-25 years of age, bear the maximum brunt of the disease burden in Nepal.

Summary of the preliminary findings from Phase I of SEAP:

- The data support a continued burden of typhoid fever in SEAR, however there is a need to better understand heterogeneity of the disease and the drivers of typhoid transmission.
- There are incomplete surveillance data and differing case definitions among the study sites.
- There is a need for
  - thoughtfully-designed prospective studies to standardize and better quantify the true burden of typhoid illness and severity
sustainable surveillance to guide public health decisions and to measure the impact of prevention and control efforts.

- The lack of data on complications due to typhoid in SEAR countries needs to be addressed.
- Phase I does not provide information on the economic impact of typhoid.

The primary objective for the prospective studies during SEAP Phase II is to characterize the burden of enteric fever in the selected countries including:

- population-based adjusted incidence of enteric fever;
- hospital and population-based incidence of complications, specifically intestinal perforations;
- current status and evolving patterns of antimicrobial susceptibility for *S. s Typhi* and *S. Paratyphi*;
- long-term impact of enteric fever;
- case fatality rate; and
- clinical spectrum, including long-term sequelae.

Secondary objectives are to:

- characterize the risk factors for severe illness;
- explore the relationship, if any, between antimicrobial resistance, antimicrobials prescribed, and outcomes;
- determine the cost of illness from a health care, patient and societal perspective; and
- bio-bank *Salmonella* bacterial strains isolated during the study period.

### 2. b) Surveillance for typhoid fever in India

In India, studies published during the decade from 1996-2006 have been analysed with the objective of estimating the incidence of severe typhoid fever and characterizing the burden of severe disease. Patterns in antimicrobial use and antimicrobial resistance in patients with enteric fever were analysed in publications from India over the last three decades. The characteristic findings of these studies include:

- The outcome of cohort studies show high incidence of typhoid especially in young children.
- The incidence and prevalence estimates reveal heterogeneity.
- Decline in typhoid isolation and complications at tertiary care facilities, over the past decade, has led to the perception of declining disease burden.
- Hospital surveillance is likely biased and underestimates incidence as antibiotic practices confound disease burden.
- Antimicrobial resistance might unmask the disease burden in future.
• The rural and peri-urban setting do not have well established disease prevalence.
• There is no clarity regarding case fatality and complication rates.
• The cost associated with typhoid is not explicitly calculated.

2. c) Proposed Typhoid Conjugate Vaccine Demonstration Project, Navi Mumbai, India

The objective of this project is to understand the burden of enteric fever in Navi Mumbai and evaluate the acceptability, effectiveness, impact on disease burden and economic impact of typhoid conjugate vaccine introduction through an existing government infrastructure. The disease burden is proposed to be estimated at two sites, one in Mumbai (urban slum served by the Grant Medical College, a tertiary care government hospital) and another in Pune (the KEM hospital rural surveillance site, Vadu). The proposed components are:

• prospective hospital-based surveillance over two years from 2017-2018;
• vaccine coverage survey (potentially to be combined with a health care utilization survey);
• vaccine effectiveness study through a nested case control design;
• vaccine impact analysis based on surveillance data and health care utilization; and
• economic evaluation (cost of illness, costing of vaccination, cost effectiveness).

The key considerations identified in discussion were:

• A step wedge design with selection of health system administrative clusters is to be used for vaccine introduction.
• The study plans to use the government infrastructure to cover the entire birth cohort, and consider catch up campaigns and expansion to private clinics.
• Incidence of S. Typhi and S. Paratyphi should be estimated before and during use of typhoid conjugate vaccine.
• Available Salmonella isolates will be identified for further characterization in addition to prospective surveillance.
• Use polio field surveillance staff to support vaccination delivery during the demonstration project.
• Although 10% typhoid vaccine coverage is reported in the proposed intervention area, this should be estimated prior to vaccine introduction to understand whether prior coverage may have already impacted disease.

2. d) S. Typhi antimicrobial susceptibility pattern in Indonesia

The following studies from Indonesia contribute to understanding the typhoid disease burden in Indonesia.
A paper on the clinical picture, treatment and post-treatment status of typhoid fever cases in Indonesia, published in 1998*, reported a high disease burden in adults. The estimation of complications including intestinal bleeding, perforation, septic shock, hepatitis and pancreatitis was feasible because it was a study conducted at five hospitals in Surabaya, Jakarta, Medan and Palembang in Indonesia. Another publication in 2013 on passive surveillance of enteric fever in all age groups in North Jakarta indicated no multidrug resistant S. Typhi in circulation.

Several studies** in Indonesia have assessed the risk factors for typhoid in endemic disease and in emergency situations. Poor food hygiene, lack of handwashing and housing/environmental conditions were highlighted as risk factors for typhoid fever. After the December 2004 tsunami, close contact with typhoid patients and non-availability of clean water and drugs, were identified as key risk factors for spread of typhoid fever in emergency situations.

Emergence of drug resistance to fluoroquinolone in adults has been documented in Indonesia in 2009, using molecular methods and sequencing. A cross-sectional hospital-based laboratory-supported descriptive study in outpatients and inpatients was carried out in 2012-2013 in multiple hospitals and public health clinics in Jakarta to assess the antimicrobial susceptibility pattern in children 1-18 years old with typhoid fever.

The highest prevalence was seen in the age group 5-9 years and majority of the subjects had received antibiotics prior to admission. The findings indicated the susceptibility of all isolates to first line drugs and second line drugs used for treatment in Indonesia, no multi-drug resistance found (in progress to publish)

Another study designed (Personal communication with the CDC MOH in Indonesia) to examine the role of typhoid carriers in disease transmission was conducted in 6 provinces to sample 600 food vendors outside elementary and junior high schools. The culture of rectal swab specimens from the food vendors showed all negative results. The study offered typhoid vaccination to responders who have screened negative for S. Typhi carriage.

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**refer to the following studies:


The following gaps have been identified as contributing factors to typhoid fever remaining a public health concern in Indonesia:

- lack of an effective diagnostic test;
- lack of antimicrobial guidelines for treatment and the emergence of drug resistance that together complicate the management of patients;
- difficulties in treatment of carriers; and
- non-availability of typhoid vaccines in the public sector.

The following were outlined as efforts required to reduce the burden of typhoid fever:

- national guideline on treatment of typhoid fever to minimize antibiotic resistance;
- further study on typhoid carriers to guide appropriate measures to interrupt transmission; and
- typhoid vaccines to be effectively used in targeted areas or populations.

3. Economic evaluation of typhoid and typhoid conjugate vaccine use

3. a) Global and regional studies to generate economic data

Health economic studies to forecast vaccine demands include studies on the cost of illness (COI), intervention costs, (vaccine delivery cost estimation) and cost effectiveness analysis (economic evaluation of interventions).

COI studies generally provide three types of information – out of pocket costs for a typhoid fever case and their family, productivity loss due to illness and health system costs for treating fever cases. The published data on cost of typhoid illness are more than a decade old and from a limited number of countries (India, Zanzibar and Vietnam). Thus the current efforts to include COI analyses in typhoid fever surveillance or burden studies (e.g., the Navi Mumbai project and SETA project) will be of significant value. Some of the ongoing studies also include long-term follow-up for socio-economic impact and quality of life components. Additional COI studies are under consideration as a part of new BMGF grants.

Cost of intervention differs by vaccine strategy, vaccine formulation and health systems so the costs collected from different studies are not comparable. The use of standardized tools will however help to generate uniform data in order to compare the costs across countries and regions. Through new coordinated efforts, harmonization of data is being attempted in the SETA and SEAP projects.

Economic evaluation helps in understanding the value of money invested in vaccination and compares some intervention to no intervention with a specified perspective. The cost effectiveness is a ratio of incremental costs of the vaccination program to program effectiveness as measured by DALYs averted:

\[
\text{Cost of vaccination program - Healthcare costs saved} = \frac{\text{Incremental cost of the vaccination program}}{\text{DALYs without vaccination - DALYs with vaccination}} = \text{DALYs averted}
\]
Other economic studies/analyses, such as estimating private demand for the vaccine, budget impact analysis and an analysis of vaccine financing options, can contribute evidence for a comprehensive analysis before vaccine implementation plans are rolled out.

These economic analyses and supporting tools are good for advocacy with Member States as they can facilitate evidence-based decision at the national level. In the regional context it was opined that improvements in water and sanitation services will result in very small pockets of typhoid disease, therefore economic analyses should include the benefits of investments in water and sanitation.

3. b) Preparation for WHO guidance and technical support for economic evaluation of typhoid and TCV use

In countries with limited resources, economic considerations are increasingly relevant as additional arguments in decision-making and planning to introduce vaccines. The WHO is making efforts to strengthen the capacity to assess public health, economic and other implications of health interventions and technologies in developing countries by providing countries with the necessary guidance and tools to support strong and efficient processes for decision-making on immunization.

A variety of studies and analyses are important to help the decision-making for vaccine introduction:

- understand the economic burden of disease: broader economic impact of vaccines (BEIV);
- assess cost effectiveness of vaccine: cost effectiveness analysis (CEA);
- support planning and costing of nationwide vaccine introductions: budget impact analysis; and
- assess affordability, value for money and return on investments.

To ensure rational practices and policies at the country level, WHO in collaboration with other key partners and stakeholders, provides technical support and guidance for decision making on introduction of vaccines and their impact evaluation. WHO has developed an “economic value chain” framework that provides a toolbox to close information gaps across the continuum of decision-making, implementation and evaluation of the introduction efforts (refer to Fig 1). Countries are encouraged to use these tools to increase standardization of economic evidence that will in turn guide global, regional and country level policies.

WHO plans to develop, pilot and eventually roll out typhoid-specific tools within the economic value chain from 2017 and collaborations will be explored with the ongoing typhoid burden study groups for inputs into these tools as needed. Currently water and
sanitation costs are not included in the economic value chain, however these parameters were highlighted as important for the typhoid tools and will be considered.

FIG 1: WHO's proposed economic value chain for Typhoid Vaccines

4. Control strategies: Vaccines

4. a) Update on typhoid vaccines

Two typhoid vaccines are currently recommended by WHO and licensed widely for use: (a) a parenteral Vi polysaccharide vaccine (ViPS) with minimum age of vaccination of two years and (b) an oral live attenuated Ty21a vaccine with a minimum age of vaccination of five years. The ViPS is administered as a single dose and offers protection against blood culture-confirmed typhoid fever in about 55-72% of vaccinees for 3 years while the Ty21a vaccine is administered in 3-4 doses and has a protective efficacy of approximately 33-67% for up to 7 years. Only one ViPS vaccine is currently WHO prequalified. There is strong evidence of the lack of widespread uptake of both vaccines.
Newer generation typhoid conjugate vaccines (TCVs) have been designed to be effective in infants. Among the conjugated vaccines, the Vi polysaccharide is linked to one of several possible carrier proteins to convert a T-independent immune response to a T-dependent response, thus increasing the immunogenic response including memory response. A prototype Vi-rEPA conjugate vaccine developed by the US National Institutes of Health and extensively evaluated from the mid-1990s, was based on conjugation with a recombinant exoprotein A from *Pseudomonas aeruginosa* carrier protein, and provides the most extensive data from clinical trials on the safety, immunogenicity and effectiveness of a TCV. Although this vaccine did not progress to licensure and marketing, the data on it have been highly relevant for the understanding and evaluation of additional TCV candidates. Potential differences in TCVs based on different carrier proteins and conjugation methods is a key consideration for regulatory evaluation.

Two TCVs have been licensed in India for parenteral use in infants, older children and adults and are currently used in the private sector. Several other TCV vaccine candidates are in varying stages of development (see Figure 2). The most commonly used TCV platforms are Vi-TT which uses tetanus toxoid as a carrier protein, Vi-DT using diphtheria toxoid and Vi-CRM197 which is conjugated to cross-reactive material 197, a non-toxic mutated form of diphtheria toxin.

*Figure 2: Typhoid conjugate vaccine pipeline (data available as at September 2016)*

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<th>Typhoid conjugate vaccine pipeline*</th>
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<tr>
<td><strong>1994-2010</strong></td>
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<tr>
<td>Preclinical stage</td>
</tr>
<tr>
<td>Biological E (B)</td>
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<tr>
<td>PT Biofarma (A)</td>
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<tr>
<td>SK Chemicals (A)</td>
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<td>Incepta (A)</td>
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**NH-Vi-EPA development - not commercialized (Phase I-Phase I efficacy, infant co-admin)**

- EuBiologics**
- DAVAC**
- Walvax**

(A) VI technology transfer
(B) NVGH technology transfer

Vi-CRM197 | Vi-DT | Vi-TT | Vi-EPA | Under review

*Information available as of Sept 2016*
Clinical trials with the NIH Vi-rEPA vaccine showed that administration of a single dose to school-aged children 5-11 years, conferred protection in 97% of vaccinees for up to 8 years and 1-2 doses resulted in 89% efficacy in children aged 2-5 years for 4 years (the data suggested waning immune response in the latter age group).

An early Vi-CRM$_{197}$ vaccine candidate was shown, in Phase I and II trials in European adults, to be as immunogenic as ViPS. Phase II trials in adults, children and infants in India, Pakistan and the Philippines also indicated that Vi-CRM was as immunogenic as ViPS however, antibody titers were reported to be short-lived.

In India, the Biomed Vi-TT vaccine (Pedatyp) and the Vi-TT vaccine manufactured by Bharat Biotech (Typbar TCV) were licensed in 2008 and 2013 respectively on immunogenicity data (refer to figure 2). A multicentre, double-blind, randomised controlled Phase III study for safety and immunogenicity of Typbar TCV in healthy infants, children and adults provided evidence of four-fold rise of anti-Vi IgG response, 6 weeks post vaccination in controlled trial settings. Pedatyp has been reported to be safe and effective in a post-licensure school-based cluster randomized study in children 6 months to 12 years old, published in 2016.

The Indian Academy of Paediatrics recommends: single dose vaccination of Typbar TCV at 9-12 months of age with an interval of at least 4 weeks with measles/MMR vaccine and a booster dose of either ViPS or TCV at 2 years of age. Further studies with Typbar TCV are underway to establish evidence for co-administration with measles-containing vaccine and additional safety data through post-marketing surveillance.

A human challenge study by the Oxford Vaccine Group, University of Oxford will assess the clinical efficacy of Typbar TCV and provide critical data for SAGE policy review.

4. b) SAGE pathway and expected timelines for update of vaccine policy and WHO position paper & vaccine introduction

Regional and country immunization policy decisions, immunization strategies and monitoring are guided by the SAGE recommendations for a particular vaccine. Although the evidence for SAGE recommendations may be based on data generated in a limited set of countries, evaluation of the evidence by SAGE and other WHO advisory committees enables the development of guidance for the use of a vaccine more broadly by other target countries.

A SAGE Working Group on Typhoid Vaccines was established in 2016 to review the scientific evidence and relevant programmatic considerations to formulate updated recommendations on the use of typhoid vaccines, with a focus on TCVs. As yet
unpublished data from the studies highlighted at this consultation may be helpful to address specific data gaps in the evidence review.

The SAGE is scheduled to review the evidence for updated typhoid recommendations in October 2017, and an updated WHO Position Paper on typhoid vaccines is expected to be published in 2018. The pathway for WHO recommendations on vaccine use is as depicted in Figure 3.

Figure 3: Pathway for WHO recommendations on vaccine use

5. Other control strategies: key issues and considerations

5. a) Water, Sanitation & Hygiene interventions
Data from the SEAR regarding trends in access to improved drinking water sources indicate that over the last three decades there has been a significant increase in drinking water coverage. There is strong evidence that the SEAR met the MDG target for drinking water with 93% coverage. However, improved water does not mean the water is clean or uncontaminated. There are data indicating that despite improved drinking water sources, a substantial number of people did not benefit in terms of health outcomes.
In the Southern Asian region, trends in the number of people using improved, shared or unimproved sanitation facilities indicate a marked reduction in the number of people practising open defecation. However, although a significant reduction was noted in overall open defecation during the last two decades, regional and national averages mask the existing inequalities in sanitation coverage. Clean water and improved sanitation are effective in prevention and control of typhoid when coverage is uniformly high, but data from the region indicates that partial improvement in sanitation does not necessarily translate to health benefits.

5. b) Early diagnosis and treatment
The Association of Physicians of India has issued recommendations for the management of typhoid fever in India. These treatment guidelines also detail the appropriate diagnostic tests for different stages of illness, but challenges remain in early diagnosis due to non-uniform availability of appropriate laboratory tests, such as blood culture.

The requirement of paired serological samples is difficult to meet within the Region and thus lowers the number of laboratory-confirmed cases. The high-specificity PCR tests involve infrastructure investments and are not available in periurban and rural settings. Further challenges remain as available point of care tests (POCT) are not reliable.

5. c) Antimicrobial resistance
Early administration of antibiotics has advantages in that it aborts bacteraemia and shortens illness along with prevention of complications. However disadvantages of early antibiotic administration are that it impairs diagnosis and promotes emergence of antimicrobial resistance in Salmonella. Inappropriate antibiotic prescribing practices in India is high and antibiotics are widely available over the counter. Studies suggest that people are prescribed antibiotics with a high number of combinations. However information regarding antibiotics used specifically for typhoid cases is not available by class. Antimicrobial resistance has already resulted in challenges in the treatment of typhoid, and further emergence of resistance to currently used antibiotics will amplify the cost burden and health consequences.

Key considerations for designing typhoid control strategies in SEAR
The continued high burden of typhoid fever and challenges of - reliable diagnostics, timely evidence based treatment, emerging antimicrobial resistance, poor hygiene standards, limitations in data analysis to understand local epidemiological situations and lack of research on vaccine effectiveness data harmonization; underscore the importance of following considerations for designing typhoid control strategies:

1. Needs in endemic, outbreaks and emergency settings
It is important to evaluate the relevant data and understand the disease burden in a variety of settings with varying levels of transmission in order to achieve effective reduction in the disease burden.
In endemic settings, defining the geography of disease, access to healthcare and water and sanitation are important to ensure promotion of equity by addressing population needs.

The population at risk of outbreaks needs to be identified with an appropriate surveillance system. Issues related to safe water, rapid diagnostics, sample transport to sites with diagnostic capacity and drug availability need to be addressed in a well-formulated outbreak management plan.

SAGE has developed guidelines for the use of vaccines in emergencies and Member States should make the best use of this guidance. Further, Member States are encouraged to provide feedback to SEARO on the use of the guidelines to assist with improvements where needed.

Geography

The available data indicate that typhoid and paratyphoid fever are prevalent in SEAR across national boundaries. There can be benefits in highlighting the epidemiological data to emphasize typhoid (and paratyphoid fever) as a regional public health problem and not only a problem for individual countries. This would also give greater weight to the need for a regional approach to enteric fever control.

Population density/slums

Poor personal hygiene has far reaching consequences beyond health and needs to be addressed as a societal problem and not only in the public health context. The potential solutions to tackle poor hygiene are often resource intensive and there is a need to advocate for change in societal standards and norms. Active participation of the community is essential and there is a need for continuous emphasis on issues such as improvements in education that can have a long-term impact on socio-economic indicators.

Water & Sanitation

Currently the progress of WASH interventions in SEAR is not uniform. Inequity in coverage of interventions puts the health of those in areas of low coverage at higher risk. Definitions of access to safe water and improved sanitation do not necessarily correlate with better health outcomes. Increasing urbanisation and scarcity of water pose a huge challenge against addressing the need for safe water and sanitation services. Personal hygiene especially of food handlers needs augmented focus. Strong integration will need to be built between Ministries of Health and ministries and other governmental bodies responsible for sanitation and water distribution.

Health care access

The access to health care facilities is essential to support early diagnosis and initiate evidence based treatment in case of enteric fever. The lack of diagnostics complicates
case management and contributes to resistance to commonly used antibiotics which is a growing challenge. Access to affordable, specific and rapid diagnostics needs urgent attention. Another challenging area is the diagnosis and treatment of carriers/asymptomatic individuals and guidelines should be developed on this.

. Emergence of antimicrobial resistance in Salmonella species clearly indicates the urgency for developing solutions at the earliest to rationalize antimicrobial usage. It is also evident that widespread use of antimicrobials alters the gut microbial flora and may increase susceptibility to infection, thus further worsening the situation.

Strengthening laboratory supported surveillance will prevent over-reliance on clinical diagnosis and support evidence-based treatment options thereby helping to address antimicrobial resistance.

2. Potential vaccine delivery strategies and supply issues

Typhoid vaccination is the fastest and most effective way to prevent typhoid fever and lower the disease burden. Typhoid vaccines have been demonstrated to be effective in programmatic use and also have a potential significant role in outbreak response or managing the risk of infection in humanitarian emergencies.

The availability of typhoid vaccine is not uniform at both sub–national and national levels in the Region. The private sector remains the key provider of typhoid vaccine as affordability and financial sustainability remain a problem for public sector delivery in most countries.

Development and evaluation of strategies to reach high-risk populations are critical. There is a need to enhance data comparability to provide the best evidence to support introduction of typhoid vaccines in the Region, therefore efforts should be made to harmonize study methods and tools for data collection.

3. Vaccine acceptability and programmatic consideration

There is no evidence of significant vaccine hesitancy in the Region. Data provided by SEAR countries indicate acceptability of typhoid vaccine, but currently vaccine is available only with the private sector. Policy makers need cost effectiveness data and adequate funding sources to ensure sustainable vaccine supply post-introduction.

Typhoid incidence is very low in countries such as Sri Lanka due to strengthened health systems and WASH strategies, so an integrated approach for effective typhoid management is important. It is essential to work on communication strategies to promote desired changes in the community as a long-term solution for typhoid control.

In the short-term, effective surveillance ensuring meaningful indicators are monitored is important to measure disease burden, detect outbreaks, track antimicrobial resistance patterns and evaluate progress towards control.
4. Limitations in using burden data for revising typhoid vaccine policy

- Availability of disease burden data in SEAR is varied and limited in some countries. In most countries burden data are primarily from the health management information systems or notification of communicable diseases with or without laboratory confirmation of typhoid fever or paratyphoid fever.
- A standard uniform case definition has not been used in generating evidence, thus making data non-comparable.
- Visits to general physicians are rarely reported and thus there are no mechanisms to review case management.
- Patients are often treated based on clinical diagnosis prior to laboratory confirmation.
- A low cost diagnostic test of adequate specificity for laboratory confirmation is not available.

Uncertainties with local disease burden

- The available data from hospital records are often unreliable to estimate the true typhoid disease burden, as many cases are labelled as fever of unknown origin without laboratory diagnosis, resulting in potential under-reporting of typhoid cases.
- Most reports are from passive hospital-based reporting primarily from government facilities.
- The reporting is not usually targeted to identify cases among high-risk groups.
- The collected data are often not analysed adequately to understand the epidemiology of the disease.
- Mortality data are not usually reported.
- No country in the Region has a comprehensive action plan for control of typhoid fever.

Vaccines

- There is limited use of available vaccines in the Region confined only to the private sector.
- Data from ongoing studies and projects will be required for decision-making and advocacy for typhoid vaccine introduction in routine public health programmes such as school-health programmes or in the EPI schedule.
- Evidence of typhoid vaccine co-administration with other vaccines in EPI schedule is required.
- The Medical/Paediatric Associations have varied or no recommendations for typhoid vaccine use. No guidance exists for typhoid vaccine use in Bangladesh and Bhutan whereas national Medical/Paediatric Associations in India, Indonesia and Myanmar have recommended use of typhoid vaccines in their populations. The Nepal NITAG
proposed vaccination for food handlers and persons in high-risk areas whereas in Sri Lanka vaccination is confined to high-risk populations.

- The potential role of vaccine in lowering typhoid transmission by lowering the faecal shedding of *S. Typhi* is unknown.
- There is currently no conclusive evidence on the duration of protection offered by the licensed TCVs and the need for booster doses.

### 5. Challenges

- Obtaining geographically representative data on typhoid fever including
  - cases, deaths and case fatality ratio
  - identification of clustering of cases and pattern of antibiotics use
  - limited information on complications and antimicrobial resistance.
- Addressing competing priorities including other vaccine preventable diseases
- Not enough evidence on cost of morbidity due to typhoid fever to guide decision-making.
Way forward

There is a need to strengthen intersectoral coordination to enhance cost effectiveness of preventive measures, vaccine introduction and WASH interventions. Developing guidelines regarding antimicrobial treatment for enteric fever in each member state of SEAR, WHO, is likely to prevent further emergence of antimicrobial resistance. To support the innovative, rapid and specific diagnostics a meticulous analysis of data from different studies and other sources is crucial. There is a need to embark on harmonization efforts for comparability of data and for appropriate use of the data (epidemiological and economic) on typhoid fever in Southern Asia.

Data and surveillance

- Defining the data sources to improve the availability and quality of data and establish systems for data collection, analysis, interpretation and dissemination.
  - Indicators to monitor the progress of typhoid disease burden including data from rural areas, age-specific morbidity & mortality, asymptomatic/chronic carriers at the regional, national and sub-national levels.
  - Sentinel surveillance for high-risk areas/populations in selected countries; screening high-risk groups (e.g. food handlers) to determine the magnitude of the problem.
  - Review rates of complication due to typhoid and paratyphoid fever to capture both immediate and longer-term outcomes as part of the evidence on disease burden.
  - Monitoring antimicrobial resistance and tracking the incidence of paratyphoid fever with a decline in S. Typhi incidence.

Vaccine studies and strategies

- Active engagement with endemic countries in SEAR to ensure and support a robust plan for typhoid vaccine introduction including establishing the relevant baseline/pre-vaccination data to assist in vaccine impact evaluation. (SAGE recommendations on typhoid vaccines and an updated WHO position paper are anticipated in 2017-2018. In addition, there is anticipation for at least 1 prequalified vaccine by end of 2018 to inform a vaccine investment strategy by Gavi for eligible countries. Additional data on safety and co-administration of Typbar TCV with measles-containing vaccines are expected to be available by 2018-2019 to inform decision-making on TCV introduction.)
- Assessment of the potential value of existing ViPS and Ty21a vaccines in the short-to medium-term or in specific situations (such as humanitarian emergencies) needs based on country demand and to ensure adequacy of vaccine supply and pilot projects to demonstrate effectiveness of vaccine use along with other interventions.
- Sharing evidence to support potential recommendations for vaccination of food handlers and frequent travellers visiting high-risk areas.
• Inclusion of measures such as WASH interventions for control and prevention of enteric fever and developing cost evaluation tools including measurement of productivity loss and gains, including through herd effects.
  Projection of vaccine supply needs, both for routine vaccination and for campaigns in collaboration with vaccine manufacturers.
• Exploring domestic funding opportunities to ensure sustainable funding for introduction of vaccines following externally funded pilot studies and develop guidelines on when typhoid vaccination can potentially be stopped.
• Requesting NITAGs to review country disease burden status and adequacy of control measures including national consultations targeting appropriate stakeholders.

WASH interventions and other control measures
• Improving sanitation and provision of clean safe water as the long term sustainable measures along with vaccine introduction for prevention and control of typhoid fever.
• Re-enforcement of medical and para-medical services teaching curricula with current knowledge on disease transmission and the importance of the environment and behavioural changes to prevention and control of typhoid.
• Implement approaches that target effective behaviour change for the appropriate use of available safe water and sanitary facilities, and development of communication strategies for improving hygiene standards.
• More cohesive engagement across governmental and non-governmental institutions responsible for water supply and sanitation and with professional bodies or other relevant areas to improve standards of personal hygiene.
• Ensuring commitment from the highest levels of government and strong political engagement to ensure the sustainability of measures embarked upon by Member States for the prevention and control of typhoid.

Typhoid case management
• Thorough assessment of causes of fever of unknown origin to more accurately determine the burden of typhoid and of other febrile illnesses.
• Developing and using affordable diagnostics to strengthen laboratory confirmation of typhoid fever cases to improve clinical diagnosis and appropriate use of antibiotics preventing further emergence of antimicrobial resistance.
Annex 1: Agenda

- Update on current knowledge about typhoid and paratyphoid disease burden – global and regional (15 mins)
- Landscape of relevant studies/activities (recent, ongoing and planned) to generate further data to guide policy and vaccine introduction (10 min)
- Reports on enteric fever studies in SEAR countries
- Global and regional studies/activities (recent, ongoing and planned) to generate further economic data (15 mins)
- Preparation for WHO guidance and technical support for economic evaluation of typhoid and TCV use (15 mins)
- Limitations/challenges in SEAR to understand disease and economic burden and/or using burden data to design and implement effective vaccination strategies (as well as other control strategies)
- What have been the key issues with the use of ViPS and Ty21a vaccines?
- Are there gaps in knowledge at country level?
- What are the potential solutions addressing those challenges?
- SAGE pathway and expected timelines for update of vaccine policy and WHO position paper & vaccine introduction
- WASH, Antimicrobial resistance, Case management: Review of key issues for typhoid control in SEAR (Presentations followed by open (moderated) discussion)
  - Overview and perspectives from India (J John)
  - Serotype Salmonella typhi and antimicrobial susceptibility pattern in children in Jakarta (Karyanti)
  - Roundtable – perspectives form other SEAR countries (status, strengths, gaps)
  - What would be the key considerations for SEAR regional plan for typhoid prevention and control (objectives and targets in context of integrated control strategies ….) strategies for endemic, outbreak and emergency settings research agenda
- The next steps towards development of a regional plan?
- Meeting conclusions and wrap up
# Annex2: List of participants

## List of participants:

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