

## Executive summary

### Introduction

The Typhoid Vaccine Acceleration Consortium (TyVAC), a partnership between the Center for Vaccine Development at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH, an international nonprofit, aims to accelerate the introduction of new typhoid conjugate vaccines (TCVs) as part of an integrated approach to reduce the burden of typhoid in countries eligible for support from Gavi, the Vaccine Alliance (Gavi). This five-year project began in October 2016 and ends in October 2021.

### Approach

TyVAC's goal of accelerating the introduction of new TCVs requires 1) Supportive global policies, financing, and vaccine supply and 2) A supportive local environment in countries that have the necessary information, infrastructure, and financing to introduce and sustain age-specific vaccines using appropriate strategy. This goal is based on the overall assumptions that a TCV manufacturer maintains World Health Organization prequalification, an adequate supply of TCV is available during the project period, and no unforeseeable events (natural disasters, epidemics, political strife) occur that disrupt project activities or vaccine supply.

Core project activities address challenges posed by typhoid fever and demonstrate TCV introduction for optimal impact in select and varying epidemiologic and geographic settings. The overall approach is to engage local and global stakeholders to design and execute a vaccine introduction strategy based on prior successful new vaccine introductions.

### Project objectives

1. Serve as a coordinating body for typhoid-related research and control activities
2. Foster supportive global policies
3. Ensure typhoid and TCVs are recognized as global, regional, and national health priorities
4. Provide data on impact, effectiveness, appropriate vaccination strategies, and associated costs
5. Support countries in decision-making and preparation for sustained TCV introduction

### Research activities

To achieve its objectives, TyVAC is engaged in research activities to assess existing data and generate new evidence related to typhoid disease burden, antimicrobial resistance (AMR), disease modeling, demand forecasting, cost-effectiveness, health impact analyses, and regional data on TCVs. We are conducting country-level analyses to understand cost and economic value of vaccines and inform decision-makers at the national level as well as assess country preparedness and interest in TCV vaccine introduction.

## Progress to date

- **Typhoid disease burden:** John Crump leads the team collecting all existing information that describes typhoid epidemiology and typhoid vaccines. Data that has been collected has been presented to the SAGE working group.
- **Antimicrobial resistance (AMR):** Work to document AMR globally is ongoing. The development of an AMR database continues through sequencing of new *S.Typhi* isolates. A new typhoid/AMR website will soon be publically available. Gordon Dougan presented a draft paper on to the SAGE working group.
- **Disease modeling:** Systematic reviews of case fatality rates for typhoid fever, seasonal patterns of typhoid fever, and associations between climatic factors and typhoid fever incidence, that began under a pilot grant from the Yale Climate Change and Health Initiative, were completed. Manuscripts are underway.
- **Demand forecasting:** Development of the first version of a vaccine demand forecast model is complete. The model will be compared to demand forecast models prepared by Linksbridge, a consulting firm hired by the Bill & Melinda Gates Foundation to develop a demand forecast model and models prepared by the Gavi TCV sub-team.
- **Cost effectiveness:** There is ongoing work to extend cost-effectiveness modeling across all Gavi-eligible countries. Efforts to link predictions from burden (incidence) models to the dynamic model are underway. There are continuing efforts to collate data on the probability of hospitalization and costs of illness and vaccination. As requested by the SAGE working group, the team has provided evidence compiled from published studies relating to cost of illness, cost effectiveness, cost of delivery, and demand forecasting.
- **Country preparedness:** TyVAC has selected ten countries for scoping visits to determine their appropriateness and interest in TCV introduction. In six of these countries, TyVAC will assess acceptability and feasibility of TCV introduction.
- **Health impact analysis; vaccine impact studies:** Clinical trials in Nepal, Bangladesh, and Malawi will generate evidence on the impact of Vi-TCV vaccines. Table 1 below summarizes trial designs and anticipated timelines. Sites were selected because of their on-going typhoid surveillance activities, and diverse sociodemographic and typhoid epidemiology. These proposed studies are designed to complement each other and related efforts, such as data available from the vaccine manufacturer and from the Centers for Disease Control and Prevention and its partners through the planned evaluation of a programmatic introduction of the vaccine by the Indian government.
- **Cost of illness:** Completed a literature review of cost of illness and cost of vaccine delivery. Detailed work plan for cost of illness studies in Nepal and Malawi is under development.

**Table 1: Summary of TyVAC vaccine effectiveness trials**

Site	Nepal (Kathmandu)	Malawi (Blantyre)	Bangladesh (Dhaka)
Trial design	Individually randomized controlled trial	Individually randomized controlled trial	Cluster randomized controlled trial
Comparator (control) vaccine	Serogroup A meningococcal conjugate vaccine	Serogroup A meningococcal conjugate vaccine	Live attenuated Japanese Encephalitis
Sample size targets	20,000	24,000	43,350
Participant age	9 months to <16 years	9 months through 12 years	9 months to <16 years
Anticipated start date	Quarter 1 2017	Quarter 1 2018	Quarter 2 2018
Primary outcome	Determine efficacy and rate reduction of Vi-TCV in preventing blood culture-confirmed symptomatic infection by <i>S. Typhi</i>		
Study duration	30 months	36 months	30 months
Follow-up duration, post vaccination	24 months, for each participant	24-30 months, for each participant until the number of verified cases is reached	24 months, for each participant
Safety follow-up	<ul style="list-style-type: none"> <li>• Immediate reactogenicity</li> <li>• SAEs</li> <li>• A subset for reactogenicity in first 7 days</li> </ul>	<ul style="list-style-type: none"> <li>• Immediate reactogenicity</li> <li>• SAEs</li> <li>• A subset for reactogenicity in first 7 days</li> </ul>	Protocol development ongoing
Immunogenicity data	Anti-Vi antibodies on Day 0 and at 1 month (Day 28): (1000 in vaccine arm; 500 in control arm)	Anti-Vi antibodies on Day 0, 1 month (Day 28), and day 730 (600 children, 200 in each of 3 age groups: 9-11 months, 1-5 years, and 6-12 years)	Protocol development ongoing
Co-administration with other vaccines (Measles-Rubella)	N/A	Measles and Rubella antibody response in 200 children aged 9-11 months	N/A

**Research and program gaps**

Research and program gaps out of scope or not funded within the TyVAC project include:

- Studies on co-administration of TCV vaccine: There have been no studies on the immunogenicity of co-administration of TCV vaccine with vaccines commonly used in routine Expanded Programme on Immunization programs in many Gavi-eligible countries in sub-Saharan Africa, most notably yellow fever and Meningitis A conjugate vaccine
- Impact of TCV vaccine use during outbreaks
- Impact of TCV vaccine in other African countries with different epidemiology and socio-demographics than Malawi
- New typhoid surveillance studies, environmental surveillance
- Development and testing of new diagnostics

- Technical assistance or support to existing or new manufacturers
- Technical support to countries for implementation
- Post-introduction monitoring

### **Other activities**

#### **Policy and advocacy**

Building on extensive experience in advocacy and communication for vaccine introductions, TyVAC is implementing a collaborative communications strategy to raise awareness and ensure typhoid control and TCVs are recognized as global, regional, and national health priorities. Leveraging and expanding existing efforts, TyVAC partnered with the Coalition against Typhoid (CAT) to create a broad call to action, to Take on Typhoid that draws stakeholders from multiple sectors, including typhoid, vaccines, water, sanitation, and hygiene (WASH), and child health. Take on Typhoid will engage a diverse group of partners across the health and WASH sectors to promote action to reduce the burden and social impact of typhoid. The TyVAC/CAT website, nearing completion, will provide a resource with advocacy tools, data, and relevant information to promote integrated typhoid prevention and control solutions.