# Concept note

## Title

## Key messages

* We updated global typhoid outbreak dataset.
* We assessed the impact of the typhoid conjugate vaccine for the outbreaks (n=XX) for which time series data are available while accounting for direct and indirect vaccine effectiveness using the dynamic and static modeling approaches.
* Vaccines could substantially reduce the expected number of cases. While introducing vaccines early in the outbreak would increase the impact of the vaccine, later introduction could still reduce the burden of the outbreak as the impact of the vaccine decreases almost linearly after the first few weeks during which the impact decreases exponentially.

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Title

The potential impact of outbreak-response vaccination against 35 outbreaks of typhoid fever reported 2000-2023

# Abstract

### Background

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# Main text

## Introduction

Typhoid fever, caused by the bacterium *Salmonella* *enterica* *serovar* Typhi (*S*. Typhi), remains a significant global public health concern, particularly in low- and middle-income countries (LMICs). *S*. Typhi is transmitted mainly through water and food contaminated with human feces; specially in LMICs where access to clean water and sanitation facilities is limited (1). Studies estimate that globally over 10,000,000 typhoid cases occur every year (2–5) with around 1% of those cases being potentially fatal.

In addition to improving water, sanitation, and hygiene, vaccines provide a nearer-term solution to typhoid fever, specifically with emergence of drug-resistant *S*. Typhi. Typhoid conjugate vaccines (TCVs) are suitable for children from six months and adults up to 45 years of age (6). They have been proven to be effective in randomized controlled trials (7–9) and during outbreaks by drug-resistant *S*. Typhi (10,11). As of February 2024, three TCVs—

Typbar-TCV (Bharat Biotech), TYPHIBEV (Biological E), and SKYTyphoid (SK Bioscience)—

have been prequalified by WHO and are therefore eligible for public procurement by UN organizations. Multiple LMICs including Pakistan, Nepal, Zimbabwe, Liberia, ana Samoa, with Gavi’s support, have introduced typhoid conjugate vaccines in their routine immunization programs along with catch-up campaigns (12).

While WHO recommends the use of TCVs during confirmed outbreaks of typhoid fever, data on their value in outbreak response is limited (6). Historically, typhoid outbreaks in LMICs, reported from 1989 to 2018, have been large and prolonged (13). This highlights ORVs can be particularly beneficial in these settings and necessitates the exploration of effective ORV strategies. Also, the presence of drug-resistant *S*. Typhi, wihch can lead to more severe and longer-lasting outbreaks, underscores the critical need for effective ORV strategies.

Effective ORV strategies will likely vary by setting and exploring various options can be facilitated by more detailed epidemiologic information. Few time series data are available for existing typhoid outbreaks. The striking difference between 45,215 cases from 25 countries reported during outbreak from 1989 to 2018 (13) and the estimated over 10,000,000 cases per year may imply that potentially many outbreaks are not detected.

Modeling can be useful in exploring the potential impact across various strategies, such as targeting high-risk populations and differing age groups. More contextualized strategies can be developed with added information. Modeling can also be used to examine longer-term and broader benefits on healthcare systems and communities and the impact on preventing future outbreaks, rather than focusing solely on the averted number of cases and deaths from the outbreak. The timing of vaccination will be critical in determining the impact of ORVs and therefore potential benefits of maintaining a stockpile may be explored.

## Methods

### Model for the transmission of typhoid fever

Model parameters for the natural history of infection are similar to the previous modeling studies and are based on the systematic review of the literature or observed studies. (**Table 1**).

**Table 1**. Model parameters.

|  |  |  |  |
| --- | --- | --- | --- |
| **Symbol** | **Description** | **Value** | **Reference** |
| γ | Relative infectiousness of chronic carriers | 0.25, Beta(a=6·34, b=19·4). | (*1*) |
| κ | Vaccine coverage | 0.8 [0.63-0.95] | (*2*) |
| ν | Vaccine efficacy (TCV) | 0.8 | 79·0% (61·9 to 88·5) at 2 yrs (*3*)  80.7% (64.2 to 89.6) (*4*)  95% (93 to 96) (*5*)  70·6% (6·4–93·0) for 9 mos to 2 yo; 79·6% (45·8–93·9) for 2–4 yo; and 79·3% (63·5–89·0) for 5-12 yo(*6*) |
|  | Duration of vaccine-induced immunity (TCV) | 4 years  (10 years, 70%) | At least 4 years (*6*) |
| 1 ∕ δ | Duration of infectiousness | 11. 8 days | 11.8 days of illness before visiting health facility (*7*), 4 weeks according the natural history of infection (*8*) |
| Θ | Percent cases resulting in carriers | 0.003 (<10y)  0.003(10-19y)  0.053 (>=20y) | 0.30 (<10 yo), 0.3 (10-19 yo), 2.14(20-29 yo), 4.4 (30-39 yo), 8.8 (40-49 yo), 10.1 (50-59), 7.8 (>60 yo) (*9*) |
| 1 ∕ω | Duration of natural immunity | 104 weeks | (*8*) |
| α | Disease-induced mortality | 0.025 | (*10*) |
| 1∕σ | Onset of protection from vaccine | 21 days [14 to 28] | The anti-Vi-IgG seroconversion rates at 4 weeks aftervaccination in all age strata were 98·0% (*11*) Seroconversion (≥four-fold rise in antibody titre 28 days after vaccination) was 100% in the Vi-TT group (*12*) |

### Static model

Vaccine impact in the static model was computed based on the definition of overall effectiveness as was done in our prior study.

### Model fitting

We modeled the time series of observed cases by assuming that the number of observed cases, , follows a Poisson or Negative Binomial distribution with its mean, , determined by the incidence of symptomatic cases (i.e., people in state *I*). For the case of Poisson distribution, the likelihood function, , of the model with parameters, , given the observations was maximized using the differential evolution method[ref].

#### Vaccine efficacy modeling

December 6, 2017, and March 9, 2019, blood culture–confirmed typhoid fever wasdiagnosed in 0.07% of the TCV group (7 of 10,005 of the participants) and 0.38% of theMenA vaccine group (38 of 10,013 participants). The protective efficacy of TCV was 81.6% (95%CI, 58.8 to 91.8; P<0.001) (*13*). The protective efficacy of TCV against blood culture-confirmed typhoid fever at 2 years was 79·0% (95% CI 61·9–88·5; p<0·0001). The incidence oftyphoid fever was 72 (95% CI 38–123) cases per 100000 person-years in the TCV group and 342 (95% CI 262–438) cases per 100,000 person-years in the MenA group.(*3*).

Also, in the clinical trial, cases that occurred within 2 weeks following immunization were excluded from the analysis (*13*).

The estimated efficacy of Vi-TCV was 84.6% (95% CI, 50.0 to 94.4) at 12 months, 82.9% (95% CI, 58.1 to 92.5) at 18 months, and 78.7% (95% CI, 52.8 to 91.7) at 24 months after vaccination.(*4*). After a median follow-up of 4·3 years (IQR 4·2–4·5), 24 (39·7 cases per100000 person-years) children in the Vi-TT group and 110 (182·7 cases per 100 000 person-years) children in the MenA group were diagnosed with a first episode of blood culture-confirmed typhoid fever. In the intention-to-treat population, efficacy of Vi-TT was 78·3% (95% CI 66·3–86·1), and 163 (129–222) children needed to be vaccinated to prevent one case.(*6*)

### Vaccination campaign

**Table 2**. TCV campaign settings

|  |  |  |
| --- | --- | --- |
| TCV campaign feature | Model settings that will be tested |  |
| Timing | Option 1: Vaccination begins within 1 - 6 months of outbreak start with an increment of two weeks (outbreak duration permitting)  We assume that the outbreak response can be quicker while observed delays may be quite long as shown in Harare, Zimbabwe, 6 mos (*14*). The reason behind this assumption is that processes involved in request for vaccine for Gavi and vaccine implementation can be streamlined over time and therefore the delay can be shorter in the future.  Option 2: Vaccination begins when the cumulative number of outbreak cases have been reached 100 -1,000 cases with an increment of 100 cases. |  |
| Campaign Coverage | Target population x assumed population coverage of 40-90% with an increment of 10%.  Based on 200,700 children (*15*) 85.4% (n= 318,698) (*14*) |  |
| Duration of a campaign | Vaccination campaign was completed within 2 weeks.  Based on 8 d (*14*), 42 d (*16*), 197 d (*17*) |  |
| Target age group | Option 1: 6 mo – 15 yo  Option 2: 6 mo – 45 yo  Based on campaigns conducted since Jan 3, 2018, when WHO announced the prequalification of a typhoid conjugate vaccine (TCV) manufactured by the Indian firm Bharat Biotech (*18*), 9 mo – 15 yo (*16*), 6 mo - 10 yo (*15*), 6 mo – 15 yo (*17*), 6 mo -15 yo, 16-45 yo (*14*) | (*14*) |
| Vaccination Rounds | One round of vaccination |  |

### 

## Results

# outbreaks including those without time series data,

# cases from # people that can be considered being at risk in the administrative unit

attack rates vary …

## Discussion

## Conclusion

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## Model equations

## Figure legends

**Figure 1**. Model schematic. S, E, I, A, R, and V represent susceptible, exposed, infectious, asymptomatic, recovered, and vaccinated states, respectively. Subscripts i, j for i, j = 1 or 2 represent the age group (<5 yo or >=5 yo) and the first or the second compartments for the state with Erlang-distributed residence time. Superscript k for k=1 or 2 of the V state represents the number of vaccine doses the person has received.

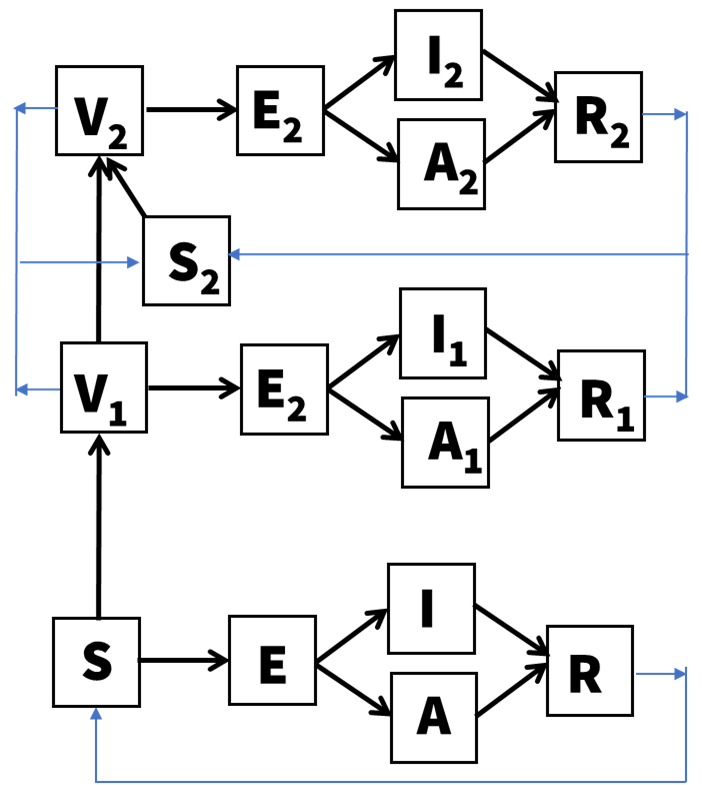


Figure 2. Comparison between model-predicted and observed values. Lines and dots represent model-predicted and observed values, respectively. Different colors represent model of different parameters regarding the fraction of asymptomatic infections and the distribution of case counts (Poisson vs. Negative Binomial)

