# Concept note

## Title

Impact of outbreak-response immunization against typhoid outbreaks: analysis of 39 typhoid outbreaks reported from 2000-2023

## Key messages

* We updated global typhoid outbreak dataset for those time series of incidence is available.
* We introduced the impact of
* 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 by week 9 would increase the impact of the vaccine, later introduction by week 20 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.
* Introducing vaccines in these area, burdens may reduce the burde, let’s assume that the vaccine are given pre-emptive and outbreak-response vaccination.

## List of Figures

**Figure 1**. PRISMA diagram

**Figure 2**. Geographical and temporal distribution

**Figure 3**. Illustration of the outbreak and vaccine impact computation

**Figure 4**. Summary of vaccine impact

1. Case reduction (%) by campaign timing since the outbreak began: box plot showing ~30 outbreaks at three different vaccine coverages
2. Case reduction (%) by cumulative cases at vaccination

**Figure S1**. Indirect vaccine effectiveness against vaccine coverage rates, population immunity in the beginning of an outbreak

## 

## List of Tables

**Table 1**. Study characteristics

**Table 2.** Model parameters

**Table 3**. Vaccination campaign settings

**Table 4**. Vaccine impact applied to the burden of sub-Saharan Africa, but maybe globally using GBD estimates.

## Overall analysis framework

1. Total outbreaks to model: 39
2. We used the static model that incorporate the indirect as well as direct effect of the vaccine.
3. Indirect effects were modeled based on the observations in the field and the predictions from the dynamic model
4. Outcome metrics include: (precent) cases/deaths/DALYs averted, vaccine efficiency (cases/deaths/DALYs averted per 1,000 doses), cost per case/death/DALY averted

## Research in Context

### Evidence before this study

We searched PubMed on December 19, 2024, with no language or date restrictions, using the search terms ((typhoid fever[Title/Abstract]) OR (typhoid[Title/Abstract])) AND (vaccin\*[Title/Abstract]) AND (model\*[Title/Abstract]) AND ((impact\*[Title/Abstract]) OR (effect\*[Title/Abstract]) OR (predict\*[Title/Abstract])). This resulted in 161 articles for screening. Studies that focused on typhoid fever transmission modeling to investigate the impact of vaccine scenarios were included, which identified a total of X studies. Most studies modeled vaccine scenarios in single geographic areas (). Antillon et al. modeled the impact of TCV on five individual endemic settings. One study by Birger et al. estimated the effect of vaccination in 73 countries, but focused on the effect on antimicrobrial-resistant typhoid fever and did not perform a cost-effectiveness analysis.

### Added value of this study

### 

### Implications of the available evidence

Title

Impact of outbreak-response immunization against typhoid outbreaks: analysis of 39 typhoid outbreaks reported from 2000-2023

# Abstract

# Main text

## Introduction

Typhoid fever is caused by the bacterium *Salmonella* *enterica* *serovar* Typhi, transmitted through water and food contaminated with human feces (1). It remains a significant global public health concern, particularly in low- and middle-income countries (LMICs), where access to clean water and sanitation facilities is limited. 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 shorter-term solution to typhoid fever, specifically with the 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, and Samoa, with Gavi’s support, have introduced typhoid conjugate vaccines in their routine immunization programs along with catch-up campaigns (12).

The WHO recommends the use of TCVs during confirmed typhoid fever outbreaks; however, data on their effectiveness in outbreak response remain limited (6). Historically, typhoid outbreaks in LMICs, reported between 1989 and 2018, have been extensive and prolonged (13). This underscores the potential value of ORVs in such settings and highlights the need to develop effective ORV strategies. Additionally, the emergence of drug-resistant S. Typhi, which can result in more severe and persistent outbreaks, further emphasizes the urgency of implementing effective ORV approaches.

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 significant discrepancy between one study reporting 45,215 cases from 25 countries during outbreaks between 1989 and 2018 (13) and the estimated annual incidence of over 10,000,000 cases suggests that many outbreaks may go undetected.

Modeling can be useful in exploring the potential public health impact across various vaccination strategies, such as targeting high-risk populations and differing age groups. Modeling can also be used to examine longer-term benefits on healthcare systems and communities and the impact on preventing future outbreaks. Therefore, this study aims to

## 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 2**. 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) | 0.3 0 (<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 after vaccination 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 was  
diagnosed in 0.07% of the TCV group (7 of 10,005 of the participants) and 0.38% of the  
MenA 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 of  
typhoid 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 per  
100000 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

c

|  |  |  |
| --- | --- | --- |
| 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 to 6 months.  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

## Reference

1. J. Bilcke, M. Antillón, Z. Pieters, E. Kuylen, L. Abboud, K. M. Neuzil, A. J. Pollard, A. D. Paltiel, V. E. Pitzer, Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. *Lancet Infect Dis* **19**, 728–739 (2019).

2. M. Hancuh, J. Walldorf, A. A. Minta, C. Tevi-Benissan, K. A. Christian, Y. Nedelec, K. Heitzinger, M. Mikoleit, A. Tiffany, A. D. Bentsi-Enchill, L. Breakwell, Typhoid Fever Surveillance, Incidence Estimates, and Progress Toward Typhoid Conjugate Vaccine Introduction - Worldwide, 2018-2022. *MMWR Morb Mortal Wkly Rep* **72**, 171–176 (2023).

3. M. Shakya, M. Voysey, K. Theiss-Nyland, R. Colin-Jones, D. Pant, A. Adhikari, S. Tonks, Y. F. Mujadidi, P. O’Reilly, O. Mazur, S. Kelly, X. Liu, A. Maharjan, A. Dahal, N. Haque, A. Pradhan, S. Shrestha, M. Joshi, N. Smith, J. Hill, J. Clarke, L. Stockdale, E. Jones, T. Lubinda, B. Bajracharya, S. Dongol, A. Karkey, S. Baker, G. Dougan, V. E. Pitzer, K. M. Neuzil, S. Shrestha, B. Basnyat, A. J. Pollard, Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial. *Lancet Glob Health* **9**, e1561–e1568 (2021).

4. P. D. Patel, P. Patel, Y. Liang, J. E. Meiring, T. Misiri, F. Mwakiseghile, J. K. Tracy, C. Masesa, H. Msuku, D. Banda, M. Mbewe, M. Henrion, F. Adetunji, K. Simiyu, E. Rotrosen, M. Birkhold, N. Nampota, O. M. Nyirenda, K. Kotloff, M. Gmeiner, Q. Dube, G. Kawalazira, M. B. Laurens, R. S. Heyderman, M. A. Gordon, K. M. Neuzil, Safety and Efficacy of a Typhoid Conjugate Vaccine in Malawian Children. *N Engl J Med* **385**, 1104–1115 (2021).

5. M. T. Yousafzai, S. Karim, S. Qureshi, M. Kazi, H. Memon, A. Junejo, Z. Khawaja, N. Ur Rehman, M. S. Ansari, R. Ali, I. U. Ujjan, H. M. Lohana, N. M. Memon, M. Hussain, R. Nigar, N. Bar-Zeev, F. N. Qamar, Effectiveness of typhoid conjugate vaccine against culture-confirmed Salmonella enterica serotype Typhi in an extensively drug-resistant outbreak setting of Hyderabad, Pakistan: a cohort study. *Lancet Glob Health* **9**, e1154–e1162 (2021).

6. P. D. Patel, Y. Liang, J. E. Meiring, N. Chasweka, P. Patel, T. Misiri, F. Mwakiseghile, R. Wachepa, H. C. Banda, F. Shumba, G. Kawalazira, Q. Dube, N. Nampota-Nkomba, O. M. Nyirenda, T. Girmay, S. Datta, L. P. Jamka, J. K. Tracy, M. B. Laurens, R. S. Heyderman, K. M. Neuzil, M. A. Gordon, P. D. Patel, Y. Liang, J. E. Meiring, N. Chasweka, P. Patel, T. Misiri, F. Mwakiseghile, R. Wachepa, H. C. Banda, F. Shumba, G. Kawalazira, Q. Dube, N. Nampota-Nkomba, O. M. Nyirenda, T. Girmay, S. Datta, L. P. Jamka, J. K. Tracy, M. B. Laurens, R. S. Heyderman, K. M. Neuzil, M. A. Gordon, C. Banda, D. Banda, J. Chilongo, A. Chisale, M. Haward, H. Msuku, J. Ndaferankhande, C. Nyirongo, P. Phula, J. Tamani, V. Mapemba, F. Hubbard, M. Myers, T. Pair, Efficacy of typhoid conjugate vaccine: final analysis of a 4-year, phase 3, randomised controlled trial in Malawian children. *The Lancet* **403**, 459–468 (2024).

7. Z. D. Mamo, A. Addisu, T. Marama, Typhoid fever outbreak investigation in Ofla Woreda, Southern Zone of Tigray Region, Ethiopia, 2016: An unmatched 1:2 case-control. *JIDI* **10**, 27–35 (2018).

8. R. B. Hornick, S. E. Greisman, T. E. Woodward, H. L. DuPont, A. T. Dawkins, M. J. Snyder, Typhoid fever: pathogenesis and immunologic control. *N Engl J Med* **283**, 686–691 (1970).

9. W. R. Ames, M. Robins, Age and Sex as Factors in the Development of the Typhoid Carrier State, and a Method for Estimating Carrier Prevalence. *Am J Public Health Nations Health* **33**, 221–230 (1943).

10. Z. Pieters, N. J. Saad, M. Antillón, V. E. Pitzer, J. Bilcke, Case Fatality Rate of Enteric Fever in Endemic Countries: A Systematic Review and Meta-analysis. *Clin Infect Dis* **67**, 628–638 (2018).

11. G. K. Rai, T. Saluja, S. Chaudhary, D. Tamrakar, P. Kanodia, B. R. Giri, R. Shrestha, S. Uranw, D. R. Kim, J. S. Yang, I.-Y. Park, S.-E. Kyung, S. Vemula, J. R. E, B. Kim, B. P. Gupta, S. K. Jo, J. H. Ryu, H. K. Park, J. H. Shin, Y. Lee, H. Kim, J. H. Kim, Z. R. Mojares, T. A. Wartel, S. Sahastrabuddhe, Safety and immunogenicity of the Vi-DT typhoid conjugate vaccine in healthy volunteers in Nepal: an observer-blind, active-controlled, randomised, non-inferiority, phase 3 trial. *Lancet Infect Dis* **22**, 529–540 (2022).

12. C. Jin, M. M. Gibani, M. Moore, H. B. Juel, E. Jones, J. Meiring, V. Harris, J. Gardner, A. Nebykova, S. A. Kerridge, J. Hill, H. Thomaides-Brears, C. J. Blohmke, L.-M. Yu, B. Angus, A. J. Pollard, Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *The Lancet* **390**, 2472–2480 (2017).

13. M. Shakya, R. Colin-Jones, K. Theiss-Nyland, M. Voysey, D. Pant, N. Smith, X. Liu, S. Tonks, O. Mazur, Y. G. Farooq, J. Clarke, J. Hill, A. Adhikari, S. Dongol, A. Karkey, B. Bajracharya, S. Kelly, M. Gurung, S. Baker, K. M. Neuzil, S. Shrestha, B. Basnyat, A. J. Pollard, Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal. *N Engl J Med* **381**, 2209–2218 (2019).

14. M. Poncin, J. Marembo, P. Chitando, N. Sreenivasan, I. Makwara, Z. Machekanyanga, W. Nyabyenda, I. Mukeredzi, M. Munyanyi, A. Hidle, F. Chingwena, C. Chigwena, P. Atuhebwe, H. Matzger, R. Chigerwe, A. Shaum, K. Date, D. Garone, P. Chonzi, J. Barak, I. Phiri, M. Rupfutse, K. Masunda, A. Gasasira, P. Manangazira, Implementation of an outbreak response vaccination campaign with typhoid conjugate vaccine - Harare, Zimbabwe, 2019. *Vaccine X* **12**, 100201 (2022).

15. F. N. Qamar, M. T. Yousafzai, A. Khaliq, S. Karim, H. memon, A. Junejo, I. Baig, N. Rahman, S. Bhurgry, H. Afroz, U. Sami, Adverse events following immunization with typhoid conjugate vaccine in an outbreak setting in Hyderabad, Pakistan. *Vaccine* **38**, 3518–3523 (2020).

16. K. Date, R. Shimpi, S. Luby, R. N, P. Haldar, A. Katkar, K. Wannemuehler, V. Mogasale, S. Pallas, D. Song, A. Kunwar, A. Loharikar, V. Yewale, D. Ahmed, L. Horng, E. Wilhelm, S. Bahl, P. Harvey, S. Dutta, P. Bhatnagar, Decision Making and Implementation of the First Public Sector Introduction of Typhoid Conjugate Vaccine-Navi Mumbai, India, 2018. *Clin Infect Dis* **71**, S172–S178 (2020).

17. F. N. Qamar, R. Batool, S. Qureshi, M. Ali, T. Sadaf, J. Mehmood, K. Iqbal, A. Sultan, N. Duff, M. T. Yousafzai, Strategies to Improve Coverage of Typhoid Conjugate Vaccine (TCV) Immunization Campaign in Karachi, Pakistan. *Vaccines (Basel)* **8**, 697 (2020).

18. T. Burki, Typhoid conjugate vaccine gets WHO prequalification. *The Lancet Infectious Diseases* **18**, 258 (2018).

## 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.

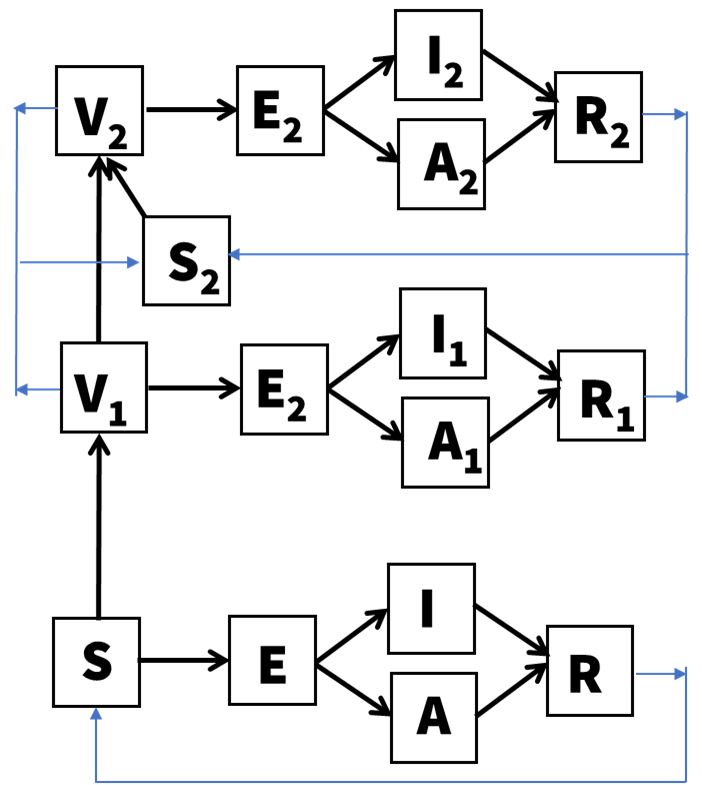


Figure 2. Comparison between model-predicted and observed values. Lines and dots represent model-predicted and observed values, respectively. Different colors represent model of different parameters regarding the fraction of asymptomatic infections and the distribution of case counts (Poisson vs. Negative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

