Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal


BACKGROUND
Salmonella Typhi is a major cause of fever in children in low- and middle-income countries. A typhoid conjugate vaccine (TCV) that was recently prequalified by the World Health Organization was shown to be efficacious in a human challenge model, but data from efficacy trials in areas where typhoid is endemic are lacking.

METHODS
In this phase 3, randomized, controlled trial in Lalitpur, Nepal, in which both the participants and observers were unaware of the trial-group assignments, we randomly assigned children who were between 9 months and 16 years of age, in a 1:1 ratio, to receive either a TCV or a capsular group A meningococcal conjugate vaccine (MenA) as a control. The primary outcome was typhoid fever confirmed by blood culture. We present the prespecified analysis of the primary and main secondary outcomes (including an immunogenicity subgroup); the 2-year trial follow-up is ongoing.

RESULTS
A total of 10,005 participants received the TCV and 10,014 received the MenA vaccine. Blood culture–confirmed typhoid fever occurred in 7 participants who received TCV (79 cases per 100,000 person-years) and in 38 who received MenA vaccine (428 cases per 100,000 person-years) (vaccine efficacy, 81.6%; 95% confidence interval, 58.8 to 91.8; P<0.001). A total of 132 serious adverse events (61 in the TCV group and 71 in the MenA vaccine group) occurred in the first 6 months, and 1 event (pyrexia) was identified as being vaccine-related; the participant remained unaware of the trial-group assignment. Similar rates of adverse events were noted in the two trial groups; fever developed in 5.0% of participants in the TCV group and 7.1% in the MenA vaccine group in the first week after vaccination. In the immunogenicity subgroup, seroconversion (a Vi IgG level that at least quadrupled 28 days after vaccination) was 99% in the TCV group (677 of 683 participants) and 2% in the MenA vaccine group (8 of 380 participants).

CONCLUSIONS
A single dose of TCV was immunogenic and effective in reducing S. Typhi bacteremia in children 9 months to 16 years of age. (Funded by the Bill and Melinda Gates Foundation; Current Controlled Trials number, ISRCTN43385161.)
Typhoid fever is a systemic illness caused by Salmonella enterica serovar Typhi. An estimated 11 million to 21 million cases of febrile illness and 117,000 to 161,000 deaths are attributed to the disease each year.\textsuperscript{12,13}

Typhoid fever is a major public health problem in Kathmandu, Nepal,\textsuperscript{6,7} where S. Typhi accounts for up to 45% of all positive blood cultures and is the leading cause of bloodstream infections among pediatric patients.\textsuperscript{8,10} Typhoid is seasonal in Kathmandu, with a high incidence in July and August and a lower incidence in winter. Estimates of the annual population incidence of typhoid vary from 297 (95% confidence interval [CI], 128 to 472)\textsuperscript{11} to 449 (95% CI, 383 to 521) per 100,000.\textsuperscript{2} Antibiotic-resistant S. Typhi is increasingly common in South Asia. Extensively drug-resistant (XDR) variants of S. Typhi have recently emerged in other nearby South Asian countries such as India and Bangladesh, and a large outbreak is ongoing in Pakistan. The disease in South Asian populations is becoming increasingly difficult to treat.\textsuperscript{12,13}

The World Health Organization (WHO) recommended the use of vaccines against typhoid in 2008,\textsuperscript{14} but vaccine-based control programs have not been widely implemented. Oral live attenuated Ty21a vaccine and Vi polysaccharide vaccine were available, but the capsules could not be swallowed by young children (Ty21a vaccine) or the vaccine was poorly immunogenic in young children (Vi polysaccharide vaccine) and therefore these vaccines were deemed to be unsuitable for widespread use. In clinical trials conducted in 2001, a prototype typhoid conjugate vaccine (TCV), Vi-rEPA (Vi conjugated to recombinant Pseudomonas aeruginosa exotoxin A) had greater than 90% efficacy in children between the ages of 2 and 5 years, but this vaccine is not currently available.

More recently, new-generation TCVs containing Vi polysaccharide conjugated to a tetanus-toxoid protein carrier have become available. A phase 3 safety and immunogenicity study showed that a TCV was highly immunogenic and safe in young children.\textsuperscript{15} Furthermore, in a stringent typhoid challenge model involving adults in an area where typhoid fever is not endemic, a TCV had a protective efficacy of 54.6% (95% CI, 26.8 to 71.8).\textsuperscript{16}

In October 2017, on the basis of these results of immunogenicity and human challenge studies, the WHO Strategic Advisory Group of Experts recommended the use of TCV over other available vaccines against typhoid in view of its improved immunologic properties, suitability for use in infants and young children, and expected longer duration of protection.\textsuperscript{14} Gavi, the Vaccine Alliance also approved a funding window for 2019–2020 to support the introduction of TCVs in developing countries. To aid Gavi-eligible countries in accelerating the introduction of these vaccines, the Typhoid Vaccine Acceleration Consortium was formed.\textsuperscript{17} This consortium is a partnership between the Center for Vaccine Development and Global Health at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH, an international nonprofit organization.

We conducted a phase 3, individually randomized trial of the efficacy of a TCV in a population in an area where typhoid is endemic. Herein, we report the prespecified efficacy results of this trial after 1 year of follow-up.

\section*{Methods}

\textbf{Trial Design, Participants, and Oversight}

We conducted this phase 3, double-blind, randomized, controlled trial in Lalitpur Metropolitan City, Kathmandu Valley, Nepal. The methods have been described previously.\textsuperscript{18,19} Briefly, children between the ages of 9 months and 16 years who were living in the trial catchment area, who were in good health at the time of enrollment, and whose parents or legal guardians were willing and competent to provide written informed consent were eligible to participate. The lower age limit of 9 months was chosen to align with the potential future program of administration of TCV with measles vaccine at 9 months of age.

The trial was approved by the Oxford Tropical Research Ethics Committee and the Nepal Health Research Council. The Wellcome Trust funded the development of the typhoid human challenge model that supported the rationale for this trial. An initial donation of investigational vaccine was received from Bharat Biotech International, and the remaining doses were purchased by the Typhoid Vaccine Acceleration Consortium. Bharat Biotech International had no other role in the trial.
Typhoid Conjugate Vaccine Trial in Nepal

VACCINES
A tetanus-toxoid conjugated Vi polysaccharide typhoid vaccine (Typbar-TCV; Bharat Biotech International) containing 25 μg of Vi polysaccharide per 0.5-ml dose was used as the trial vaccine. Meningococcal capsular group A conjugate vaccine (MenA; MenAfriVac, Serum Institute of India) was the control vaccine (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

RANDOMIZATION AND BLINDING
Participants were assigned to receive either the TCV or the MenA vaccine with the use of 1:1 stratified block randomization, with block sizes randomly varying from 2 to 6. Stratification was performed according to age (9 months to <5 years or ≥5 years to <16 years). After provision of written informed consent and a general examination, participants were randomly assigned with the use of a trial-specific randomization application loaded on an electronic tablet device. A subgroup of children were further randomly selected in a ratio of 2 to 1 (1000 participants in the TCV group and 500 participants in the MenA vaccine group) to have blood drawn for the immunogenicity analysis.

Parents, guardians, participants, clinicians, and trial staff were unaware of the trial-group assignments. Only the staff members who administered the vaccine were aware of the vaccine given; they were not subsequently involved in participant follow-up.

OUTCOMES
Assessment of Vaccine Efficacy
Blood cultures were obtained from any trial participant who presented to Patan Hospital or 18 community-based trial clinics and reported having a fever for 2 or more days, a current temperature of at least 38°C, or both. Follow-up telephone calls were made once every 3 months to capture additional possible cases of typhoid fever in participants who presented to nontrial facilities. Available medical records were reviewed to capture blood culture–confirmed typhoid diagnoses made at nontrial hospitals and clinics. Persons with typhoid who did not receive treatment from a hospital or clinic, those who received treatment but from whom a blood culture was not obtained, and those who were not reported to the trial team were not captured in these trial data.

The primary outcome was typhoid fever confirmed by blood culture. Secondary outcomes included adverse events within the first 7 days after vaccination, serious adverse events within 6 months after vaccination, febrile illness of any duration, the length of hospital stay, and clinical typhoid diagnoses.

Assessment of Safety
Participants were observed in the clinic for at least 20 minutes after the vaccine was administered. All participants received a diary in which to record local and systemic adverse events (sample questions and answer choices used in the diary are provided in Table S2 in the Supplementary Appendix). On day 7, the parents and guardians of the participants were contacted by telephone, and any vaccine-related adverse events and all serious adverse events were recorded. Follow-up calls and visits every 3 months are ongoing to capture serious adverse events.

Immunogenicity
Anti-Vi IgG titers were measured in plasma samples obtained on day 0 and day 28 at the Oxford Vaccine Group Laboratory, University of Oxford, with the use of a commercial enzyme-linked immunosorbent assay (ELISA) kit (VaccZyme, Binding Site) according to the manufacturer’s instructions. Additional blood-sample collections were planned at follow-up at 18 months and 2 years.

PLANNED INTERIM EFFICACY ANALYSIS
The target sample for the trial was 20,000 children, and over the 2-year trial follow-up period, 45 cases of typhoid fever were expected if the assumptions underlying the sample size held true (see the Supplementary Appendix). Although this was originally designed as a 2-year trial, given the importance of the results for public health, an interim analysis was planned after at least 1 year of follow-up had been completed, if 45 cases of typhoid fever were observed by this time. The interim analysis therefore has the full statistical power for the primary outcome that was planned in the protocol (power of 80% and alpha level of 5%). The protocol, available at NEJM.org, was amended to include the interim analysis when it became clear that the 45 cases...
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could be reached before 2 years of follow-up. On August 1, 2018, approximately 9 months into the trial, the international data safety and monitoring board agreed to the interim analysis and this analysis received ethical approval. As part of the interim analysis, the trial participants and staff remained unaware of the trial-group assignments, and follow-up is ongoing.

STATISTICAL ANALYSIS

The primary analysis of blood culture–confirmed typhoid fever included only cases that occurred at least 14 days after vaccination. In addition, secondary outcomes reported in this interim analysis include adverse events within the first 7 days after vaccination, serious adverse events within 6 months after vaccination, and immunogenicity in the first 28 days.

For the interim analysis of the primary outcome, the incidence of typhoid fever was estimated as the number of cases divided by the total number of person-years of follow-up. Vaccine efficacy was calculated as (1 – IRR) × 100%, where IRR is the incidence rate ratio (the ratio of the incidence in the TCV group as compared with the MenA vaccine group).

All P values are two-sided; a P value of less than 0.05 was considered to indicate statistical significance in the efficacy assessment. Serious adverse events, local and systemic reactions to vaccine, and baseline characteristics were not compared statistically.

The cumulative incidence of typhoid fever is presented with the use of the Kaplan–Meier method. The investigators agreed to and signed a detailed statistical analysis plan (available with the full protocol) covering all analyses before unblinding of trial data for analysis. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

RESULTS

TRIAL PARTICIPANTS

From November 20, 2017, to April 9, 2018, a total of 20,119 children underwent screening, and 20,019 participants were randomly assigned to receive TCV or MenA vaccine (Fig. S1). The baseline characteristics were similar between the two groups (Table S1).

VACCINE EFFICACY

Between December 6, 2017, and March 9, 2019, a total of 46 cases of blood culture–confirmed typhoid fever were recorded. One case occurred within 2 weeks after vaccination and was excluded from the analyses. All participants recovered; five participants (two in the TCV group and three in the MenA vaccine group) were admitted to the hospital.

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) (Fig. 1 and Table 1). Among the 41 isolates available for antimicrobial susceptibility testing, no multidrug-resistant (MDR) strains (i.e., those with resistance to amoxicillin, chloramphenicol, and trimethoprim–sulfamethoxazole) were identified. Most of the strains were not susceptible to ciprofloxacin, and 2 isolates had reduced susceptibility to azithromycin (Table S5).

Blood culture–confirmed typhoid fever occurred in 23 participants who presented to clinics with at least 3 days of fever before their blood was drawn for culture (the threshold recommended by the WHO for blood cultures in typhoid surveillance programs).20 Vaccine efficacy
in participants who had at least 3 days of fever was 85.1% (95% CI, 49.7 to 95.6) (Table 1).

**IMMUNOGENICITY**
A total of 1343 participants provided at least one sample for the immunogenicity analysis. At baseline, 268 of 849 participants in the TCV group (31.6%) and 122 of 460 participants in the MenA vaccine group (26.5%) had detectable Vi IgG antibody levels (Table 2). Anti-Vi antibodies were measured with the use of an ELISA. The geometric mean titer for these antibodies at day 28 was 2038 ELISA units (EU) per milliliter (95% CI, 1905 to 2180) in the TCV group and 7.0 EU per milliliter (95% CI, 6.2 to 7.9) in the MenA vaccine group (P<0.001). Seroconversion (an antibody titer that more than quadrupled 28 days after vaccination) was 99.1% in the TCV group and 2.1% in the MenA vaccine group (Table 2).

**REACTOGENICITY**
Adverse reactions in the first 7 days after vaccination were assessed in 18,743 of the children (93.6%). A total of 5.9% of the children had pain at the vaccination site (5.1% in the TCV group and 6.7% in the MenA vaccine group); among children with pain, the pain was mild in 92.5%. A total of 6.7% of the children were reported to be generally unwell (6.4% in the TCV group and 7.1% in the MenA vaccine group), and 5.2% of the children had a fever (reported by their parents or guardians) in the first 7 days after vaccination (5.0% in the TCV group and 5.4% in the MenA vaccine group). Vomiting and diarrhea occurred in 1.4% and 1.8% of the children, respectively (vomiting in 1.2% of the TCV group and 1.6% of the MenA vaccine group, and diarrhea in 1.7% of the TCV group and 1.8% of the MenA vaccine group), and in children who were reported to have these symptoms, 20.5% of the symptoms were moderate and 25.9% were severe. A total of 1.8% of the children were eating less than usual (1.8% of the TCV group and 1.9% of the MenA vaccine group). All other reactions were rare, occurring in fewer than 1% of the children (Table 3).

### Table 1. Occurrence of Blood Culture–Confirmed Typhoid Fever and Protective Efficacy of Typhoid Conjugate Vaccine (TCV).*

<table>
<thead>
<tr>
<th>Variable</th>
<th>TCV (N = 10,005)</th>
<th>MenA Vaccine (N = 10,014)</th>
<th>Efficacy of TCV (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases Incidence no. of cases/100,000 person-yr (95% CI);‡</td>
<td>Cases Incidence no. of cases/100,000 person-yr (95% CI);‡</td>
<td>percent</td>
<td></td>
</tr>
<tr>
<td>Confirmation of typhoid fever on blood culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 14 days after vaccination</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 14 days§</td>
<td>7 (79 (37–165))</td>
<td>38 (428 (311–588))</td>
<td>81.6 (58.8–91.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Detection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At clinic</td>
<td>5 (27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through active follow-up and medical-record review</td>
<td>2 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture–confirmed typhoid fever in participants with at least 3 days of fever before blood culture¶</td>
<td>3 (34 (11–105))</td>
<td>20 (226 (146–350))</td>
<td>85.1 (49.7–95.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval, and MenA group A meningococcal.
† P values for the comparison of the TCV group and the MenA vaccine group were calculated with the use of the log-rank test.
‡ In the TCV group, there were 8903 person-years of follow-up, and in the MenA vaccine group there were 8885 person-years of follow-up. Participants with no follow-up contact contributed half a day of follow-up in calculations. Participants who moved away from Lalitpur no longer contributed to person-years of follow-up time.
§ In all reported cases of culture-positive typhoid fever reported from a medical-record review, isolates were checked, when available, to re-confirm diagnostic results.
¶ Cases of typhoid fever shown are from clinics only. Data were not available from cases detected through medical-record review.
Table 2. Vi IgG Levels at Baseline and 28 Days after Randomization in the Immunogenicity Cohort.*

<table>
<thead>
<tr>
<th>Trial Group and Vi IgG Level</th>
<th>Day 0</th>
<th>Day 28</th>
<th>Period from Day 0– Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level above lower limit of quantification of the assay — no. of participants/total no. (%)†</td>
<td>268/849 (31.6)</td>
<td>708/709 (99.9)</td>
<td></td>
</tr>
<tr>
<td>Geometric mean concentration (95% CI) — EU/ml</td>
<td>7.2 (6.7–7.8)</td>
<td>2038 (1905–2180)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.7 (3.7–13.4)</td>
<td>2221 (1297–3726)</td>
<td></td>
</tr>
<tr>
<td>Level at least quadrupled from day 0 — no. of participants/total no. (%)</td>
<td>677/683 (99.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MenA vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level above lower limit of quantification of the assay — no. of participants/total no. (%)†</td>
<td>122/460 (26.5)</td>
<td>112/388 (28.9)</td>
<td></td>
</tr>
<tr>
<td>Geometric mean concentration (95% CI) — EU/ml</td>
<td>6.5 (5.9–7.1)</td>
<td>7.0 (6.2–7.9)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.7 (3.7–8.9)</td>
<td>3.7 (3.7–10.5)</td>
<td></td>
</tr>
<tr>
<td>Level at least quadrupled from day 0 — no. of participants/total no. (%)</td>
<td>8/380 (2.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P = 0.07 for the comparison between the two trial groups at day 0, and P<0.001 for the comparison between the two trial groups at day 28. P values were calculated with the use of the nonparametric two-sided Wilcoxon rank-sum test. EU denotes enzyme-linked immunosorbent assay units, and IQR interquartile range.
† The lower limit of quantification of the assay was 7.4 EU per milliliter. Values below this limit were substituted with 3.7 EU per milliliter for the analysis.

Table 3. Solicited Adverse Reactions within 7 Days after Vaccination (Reported and Classified by the Participants).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TCV (N=9380)</th>
<th>MenA Vaccine (N=9363)</th>
<th>All Participants (N=18,743)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8898 (94.9)</td>
<td>8732 (93.3)</td>
<td>17,630 (94.1)</td>
</tr>
<tr>
<td>Mild</td>
<td>455 (4.9)</td>
<td>575 (6.1)</td>
<td>1,030 (5.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>26 (0.3)</td>
<td>53 (0.6)</td>
<td>79 (0.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (&lt;0.1)</td>
<td>3 (&lt;0.1)</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Swelling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9322 (99.4)</td>
<td>9273 (99.0)</td>
<td>18,595 (99.2)</td>
</tr>
<tr>
<td>Mild</td>
<td>53 (0.6)</td>
<td>81 (0.9)</td>
<td>134 (0.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (0.1)</td>
<td>9 (0.1)</td>
<td>14 (0.1)</td>
</tr>
<tr>
<td><strong>Redness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9369 (99.9)</td>
<td>9345 (99.8)</td>
<td>18,714 (99.8)</td>
</tr>
<tr>
<td>Mild</td>
<td>10 (0.1)</td>
<td>14 (0.1)</td>
<td>24 (0.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (&lt;0.1)</td>
<td>4 (&lt;0.1)</td>
<td>5 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8907 (95.0)</td>
<td>8861 (94.6)</td>
<td>17,768 (94.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>473 (5.0)</td>
<td>502 (5.4)</td>
<td>975 (5.2)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9272 (98.8)</td>
<td>9213 (98.4)</td>
<td>18,485 (98.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>84 (0.9)</td>
<td>121 (1.3)</td>
<td>205 (1.1)</td>
</tr>
</tbody>
</table>
Serious Adverse Events

In the first 28 days after vaccination, 18 serious adverse events were reported in 17 participants (7 participants in the TCV group and 10 in the MenA vaccine group) (Table 4 and Table S3). One serious adverse event, a high-grade fever within 24 hours after vaccination, was considered by the investigators to be vaccine-related. The participant was admitted to the local hospital, and antipyretic agents were administered. The fever subsided after 12 hours, the results of laboratory tests were within normal limits, and the participant was discharged without an alternative diagnosis. The participant remained unaware of the trial-group assignment.

A total of 132 serious adverse events that oc-
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The efficacy of the WHO-prequalified TCV was assessed in children in an area where typhoid fever was endemic, a single dose of TCV was immunogenic and efficacious. The incidence of typhoid fever (428 cases per 100,000 person-years in our MenA vaccine group) showed the high burden of disease in children in this geographic setting.

Although most isolates in this trial were ciprofloxacin-resistant, no MDR strains were identified. However, the increase in cases of XDR typhoid in other geographic areas severely limits treatment options. More than 5000 cases of XDR typhoid have been reported in Pakistan since 2016, and cases have also been reported in travelers returning from Pakistan. It will be interesting to see whether the current use of the TCV in Pakistan will curb the spread of the drug-resistant strain through immunologic mechanisms.

A single dose of TCV was associated with a reduction of 81.6% in the incidence of typhoid fever among the children in our trial. This protection is higher than that of Vi polysaccharide vaccine, which was estimated to have 65% efficacy in a trial in India and 35% efficacy in a trial in Pakistan, and it is higher than that associated with live attenuated oral typhoid vaccines. The results are similar to the 91.5% efficacy (95% CI, 77.1 to 96.6) seen with two doses of Vi-rEPA in Vietnam in 1997. The results are also consistent with the seroeficacy estimate of 85% (95% CI, 80 to 88) with TCV (according to data extrapolated from serologic responses in a phase 3 trial in India). The vaccine efficacy was
54.6% (95% CI, 26.8 to 71.8) in a human challenge trial conducted in Oxford.\textsuperscript{16} However, the challenge model used a composite definition of typhoid fever that potentially included self-limiting asymptomatic bacteremia that was not detected in the field, adults rather than children, and a probable high challenge dose (after neutralization of gastric acid), which may explain why the vaccine efficacy was low.

TCV is immunogenic, eliciting an antibody response 1 month after vaccination. This is consistent with previous findings in immunogenicity trials.\textsuperscript{15,16,24} Immunogenicity trials involving children and adults in India showed seroconversion rates of more than 90% across different age strata at day 42 after vaccination as compared with baseline titers and a quadrupling of the anti–Vi-antibody titer occurred 2 to 5 times more often in the TCV group than in the Vi polysaccharide vaccine group.\textsuperscript{15} The Vi-rEPA trial showed that Vi IgG increased by a factor of more than 575 (P<0.001) 4 weeks after administration of the conjugate Vi-rEPA vaccine, although a different assay was used.\textsuperscript{24} Conjugate vaccines such as the Vi-rEPA vaccine are T-cell–dependent and are expected to provide longer-term protection, unlike the protection provided by polysaccharide vaccines, which generally lasts for only 2 to 3 years.\textsuperscript{26}

Our data on reactogenicity to the vaccine are consistent with those from the phase 3 trial in India\textsuperscript{15} and the human challenge model trial.\textsuperscript{16} In our trial, one serious adverse event was deemed by the investigators to be a vaccine-related fever without any alternative diagnosis, but the data remain blinded to the trial-group assignments. Reported adverse events were similar in both groups, indicating an acceptable safety profile that was comparable to that of another widely used conjugate vaccine. These data were part of a package reviewed by the WHO Global Advisory Committee on Vaccine Safety in December 2018; this review led to an endorsement of the safety of this vaccine.\textsuperscript{27}

Further data are required to show vaccine efficacy in the medium term and long term, the indirect effect and herd immunity achieved from large-scale vaccination, and the effectiveness in age groups and populations that are different from those in this trial. Follow-up of our trial in Nepal is ongoing, and further trials in Malawi and Bangladesh are under way to address some of these questions.\textsuperscript{28,29} Our findings uphold the recent recommendations of the WHO to use TCV in high-burden settings and to immunize children who are 9 months to 15 years of age.\textsuperscript{3}

The views expressed in this article do not necessarily represent the views of the U.K. Department of Health and Social Care, the Joint Committee on Vaccination and Immunization, the European Medicines Agency, or the World Health Organization. A data sharing statement provided by the authors is available with the full text of this article at NEJM.org. Supported by a grant (OP1151153, to the Typhoid Vaccine Acceleration Consortium) from the Bill and Melinda Gates Foundation.

No potential conflict interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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