ORIGINAL ARTICLE

Safety and Efficacy of a Typhoid Conjugate Vaccine in Malawian Children

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ABSTRACT

BACKGROUND

Typhoid fever caused by multidrug-resistant H58 *Salmonella* Typhi is an increasing public health threat in sub-Saharan Africa.

METHODS

We conducted a phase 3, double-blind trial in Blantyre, Malawi, to assess the efficacy of Vi polysaccharide typhoid conjugate vaccine (Vi-TCV). We randomly assigned children who were between 9 months and 12 years of age, in a 1:1 ratio, to receive a single dose of Vi-TCV or meningococcal capsular group A conjugate (MenA) vaccine. The primary outcome was typhoid fever confirmed by blood culture. We report vaccine efficacy and safety outcomes after 18 to 24 months of follow-up.

RESULTS

The intention-to-treat analysis included 28,130 children, of whom 14,069 were assigned to receive Vi-TCV and 14,061 were assigned to receive the MenA vaccine. Blood culture–confirmed typhoid fever occurred in 12 children in the Vi-TCV group (46.9 cases per 100,000 person-years) and in 62 children in the MenA group (243.2 cases per 100,000 person-years). Overall, the efficacy of Vi-TCV was 80.7% (95% confidence interval [CI], 64.2 to 89.6) in the intention-to-treat analysis and 83.7% (95% CI, 68.1 to 91.6) in the per-protocol analysis. In total, 130 serious adverse events occurred in the first 6 months after vaccination (52 in the Vi-TCV group and 78 in the MenA group), including 6 deaths (all in the MenA group). No serious adverse events were considered by the investigators to be related to vaccination.

CONCLUSIONS

Among Malawian children 9 months to 12 years of age, administration of Vi-TCV resulted in a lower incidence of blood culture–confirmed typhoid fever than the MenA vaccine. (Funded by the Bill and Melinda Gates Foundation; ClinicalTrials.gov number, NCT03299426.)

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This article was updated on September 16, 2021, at NEJM.org.

N Engl J Med 2021;385:1104-15.
DOI: 10.1056/NEJMoa2035916

CME at NEJM.org

Typhoid fever, a systemic febrile illness caused by *Salmonella enterica* serovar Typhi, is responsible for more than 9 million infections and more than 110,000 deaths globally each year, and the highest disease burden is observed among school-age and preschool children.[1,2] An estimated 1.2 million cases of typhoid and 18,703 deaths attributed to typhoid occur annually in sub-Saharan Africa, with 383 to 843 cases per 100,000 person-years being reported in some urban settings.[3-5]

The increasing public health challenge posed by typhoid fever across sub-Saharan Africa over the past decade is due in part to the emergence and spread of several multidrug-resistant (MDR [i.e., resistant to the first-line agents chloramphenicol, ampicillin, and cotrimoxazole]) *Salmonella* Typhi lineages, particularly H58 (clade 4.3.1) and H56 (clade 3.1.1).[6-8] In Malawi and other countries in East Africa and southern Africa, MDR H58 *S.* Typhi emerged in 2010 after its introduction from Asia.[7,9] Specifically, it became the predominant bloodstream infection among adults and children in Malawi, with a 21% incidence of complications among children (including a 3.6% incidence of small-bowel perforation) and a 2.1% case fatality rate.[9-12] Emerging antimicrobial resistance to fluoroquinolones has been documented in East Africa,[7,13] Nigeria,[6] and the Democratic Republic of Congo.[14] Extensively drug-resistant (XDR) typhoid, which is resistant to fluoroquinolones and third-generation cephalosporins, is established in Pakistan.[15] The dual threat in Africa of local emergence and introduction of untreatable XDR typhoid from Asia underscores the need for typhoid fever prevention.[15]

In 2018, the World Health Organization (WHO) recommended typhoid conjugate vaccine (TCV) for use in all countries in which typhoid is endemic, prioritizing countries with the highest burden of typhoid disease or antimicrobial resistance.[16] The Typhoid Vaccine Acceleration Consortium (TyVAC) was launched in 2017 with the aim of accelerating the introduction of TCV in low-income settings. The consortium is a partnership of 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. TyVAC is conducting large, randomized, controlled efficacy trials of Vi polysaccharide TCV (Vi-TCV) in diverse epidemiologic settings in Malawi, Nepal, and Bangladesh.[17-20] Here, we present the efficacy results and safety outcomes from a clinical trial in Malawi of a single dose of Vi-TCV[21,22] through 18 to 24 months of follow-up.[23]

METHODS

TRIAL OVERSIGHT

The trial was approved by the Malawi National Health Sciences Research Committee; the Malawi Pharmacy, Medicines, and Regulatory Authority; the institutional review board at the University of Maryland, Baltimore; and the research ethics committee at the University of Liverpool. Bharat Biotech International supplied Vi-TCV free of charge. The sponsors had no role in the design of the trial; the collection, analysis, or interpretation of the data; or the writing of the manuscript.

TRIAL DESIGN AND PARTICIPANTS

This single-center, phase 3, double-blind, individually randomized, active-controlled trial was conducted in two urban townships (Ndirande and Zingwangwa) in Blantyre, Malawi. Detailed methods have been published previously.[23,24] In brief, we planned to enroll approximately 28,000 healthy children 9 months to 12 years of age who were residing in the trial areas. Eligible children had no previous typhoid vaccination and no acute illness or history of allergy or hypersensitivity. Parents or guardians provided written informed consent, and assent was obtained from children who were 8 years of age or older. Human immunodeficiency virus (HIV) status was solicited verbally; positive status was confirmed by the participant's health passport, where possible. Participants were recruited through government health centers and primary schools. Safety data (adverse events and serious adverse events) were recorded prospectively.

RANDOMIZATION AND MASKING

Participants were randomly assigned in a 1:1 ratio to receive a single dose of Vi-TCV or a

control vaccine (meningococcal capsular group A conjugate [MenA] vaccine), with the use of block randomization, with block sizes varying from 6 to 12. The randomization sequence was generated with the use of the blockrand package (version 1.3) in R Software, version 3.4.1 (R Foundation for Statistical Computing), and was concealed before randomization (which occurred immediately before vaccination). Parents, guardians, participants, and trial staff involved in screening, eligibility assessment, and follow-up were unaware of the trial-group assignments. Nurses who were aware of the trial-group assignments prepared and administered vaccines in a private area and had no further role in the trial.

PROCEDURES AND VACCINES

The trial vaccine was Typbar-TCV (Bharat Biotech International), a WHO-prequalified tetanus-toxoid conjugated Vi-TCV containing 25 μg of Vi polysaccharide per 0.5-ml dose. MenA (MenAfriVac, Serum Institute of India) was used as the control vaccine and was administered at a dose of 10 μg per 0.5 ml to children 1 year of age or older and at a dose of 5 μg per 0.5 ml to children younger than 1 year of age. Vaccines were administered intramuscularly in the left thigh (in children <1 year of age) or in the left arm (in children ≥1 year of age). Both Vi-TCV and the MenA vaccine were administered with routine measles–rubella vaccine (in the right thigh) in children 9 to 11 months of age (according to the Malawi Expanded Program on Immunization guidelines).

ENHANCED FEVER AND SAFETY SURVEILLANCE

All participants were monitored for 30 minutes after vaccination for immediate adverse events. Enhanced passive surveillance for fever and serious adverse events was conducted at four primary health centers (in Ndirande and Zingwangwa and at Gateway Clinic and Nancholi Youth Organization Clinic) and at Queen Elizabeth Central Hospital, a government referral hospital, where parents and guardians were instructed to bring unwell children at any time. Usual provision of health service was enhanced by telephone calls and community messaging. If children presented with febrile illness (subjective fever for ≥72 hours, an axillary temperature of ≥38°C, or hospitalization with a history of fever of any duration), a blood culture was obtained (5 ml [in children <5 years of age] or 10 ml [in children ≥5 years of age]) and a rapid diagnostic test for malaria was performed. Antimicrobial resistance of *S.* Typhi isolates was tested by means of disk diffusion.[25] Isolates that showed pefloxacin resistance underwent confirmatory testing for ciprofloxacin resistance with the use of Etest (bioMérieux), with a minimum inhibitory concentration of more than 0.06 mg per liter indicating resistance. Hospital admission and antimicrobial treatment were at the discretion of the facility clinician. Participants with blood culture–confirmed *S.* Typhi were contacted every 2 weeks until they were asymptomatic to monitor treatment response and outcomes.

OUTCOMES

The primary outcome was blood culture–confirmed typhoid fever occurring at any time after vaccination. Secondary outcomes were the safety profiles of Vi-TCV and the MenA vaccine (assessed according to the number of adverse events detected in the first 30 minutes after vaccination), the number of serious adverse events within 28 days after vaccination, and the number of adverse events within 6 months after vaccination. For the primary evaluation of vaccine efficacy, all children were under enhanced passive surveillance for at least 18 months (from February 21, 2018, to April 3, 2020).

STATISTICAL ANALYSIS

Details regarding the sample-size and power calculations have been reported previously.[23] In brief, assuming a vaccine efficacy of 75%, we calculated that a minimum of 30 cases of typhoid fever would be needed to test the null hypothesis of no protective efficacy (i.e., vaccine efficacy ≤0%). The primary analysis was performed in the intention-to-treat population, which included all children who underwent randomization and received a dose of a vaccine. The first episode of blood culture–

confirmed typhoid fever occurring after vaccination was used for the primary analysis. In the intention-to-treat analysis, the vaccine group was defined according to the vaccine that was assigned, not the vaccine that was received. The per-protocol analysis of vaccine efficacy included children who completed the trial without any protocol deviations, received the vaccine to which they were assigned, and had the first episode of blood culture–confirmed typhoid fever at least 14 days after vaccination.

Because of the interruption of surveillance (starting on April 3, 2020) as a result of coronavirus disease 2019, the protocol was amended to allow the primary efficacy analysis to be conducted as of April 3, 2020, encompassing 18 to 24 months of follow-up per participant. The data and safety monitoring board approved the amendment because the trial had reached the prespecified number of typhoid cases, and a prolonged disruption in surveillance would affect evaluations of incidence, cases prevented, and the number needed to vaccinate. Surveillance of the full cohort, conducted in a blinded manner, is planned to continue until September 30, 2021 (a minimum of 36 months of follow-up) for secondary longer-term efficacy and subgroup analyses.

The incidence rate was calculated as the number of first episodes of blood culture–confirmed typhoid fever divided by the total follow-up time. Individual follow-up time was the smallest of the following: time to the first episode of typhoid fever; time to withdrawal from the trial, loss to follow-up, death, or relocation out of the trial area; or the time to the end of the analysis period. The incidence rate ratio was calculated as the ratio of the incidence rate in the Vi-TCV group to that in the MenA group. The vaccine efficacy was calculated as (1 − incidence rate ratio) × 100%. Subgroup analyses were conducted to evaluate vaccine efficacy according to sex, trial site (Ndirande or Zingwangwa), and age at the time of vaccination (<5 years or ≥5 years). Poisson regression with the interaction term between each prespecified subgroup of interest and the vaccine group was used to compare vaccine efficacy across subgroups.

The absolute risk reduction was calculated as the risk of blood culture–confirmed typhoid fever in the MenA group minus that in the Vi-TCV group. The number needed to vaccinate was calculated as 1 ÷ absolute risk reduction, representing the number of children who would need to be vaccinated to prevent one case of blood culture–confirmed typhoid fever. The cumulative incidence of typhoid fever for each vaccine group was calculated with the use of the Kaplan–Meier method, and vaccine efficacy was estimated at 12, 18, and 24 months after vaccination with the use of the life-table method. All analyses were performed according to the prespecified statistical analysis plan with the use of Stata software, version 16 (StataCorp). Full details of the trial design and conduct are provided in the protocol, available with the full text of this article at NEJM.org.

RESULTS

TRIAL PARTICIPANTS

From February 21, 2018, to September 27, 2018, a total of 29,949 children underwent screening, and 28,212 were randomly assigned to receive Vi-TCV or the MenA vaccine (Fig. 1). The intention-to-treat population included 28,130 children who had received a dose of a vaccine (14,069 in the Vi-TCV group and 14,061 in the MenA group), and the per-protocol population included 27,882 children who had received the assigned vaccine (13,945 in the Vi-TCV group and 13,937 in the MenA group) (Fig. 1). The median age of the participants was 6.0 years (range, 0.8 to 12.0), and the baseline characteristics were similar in the two groups (Table 1).

VACCINE EFFICACY

Between February 21, 2018, and April 3, 2020, a total of 7776 children presented to a passive surveillance center and met the criteria for having blood-culture assessment performed. Blood cultures were obtained from 7314 children (94.1%). A total of 75 samples were positive for *S.* Typhi; 2 samples were from a 9-year-old child who had had two episodes of typhoid fever, at 24 weeks and at 49 weeks after vaccination; the

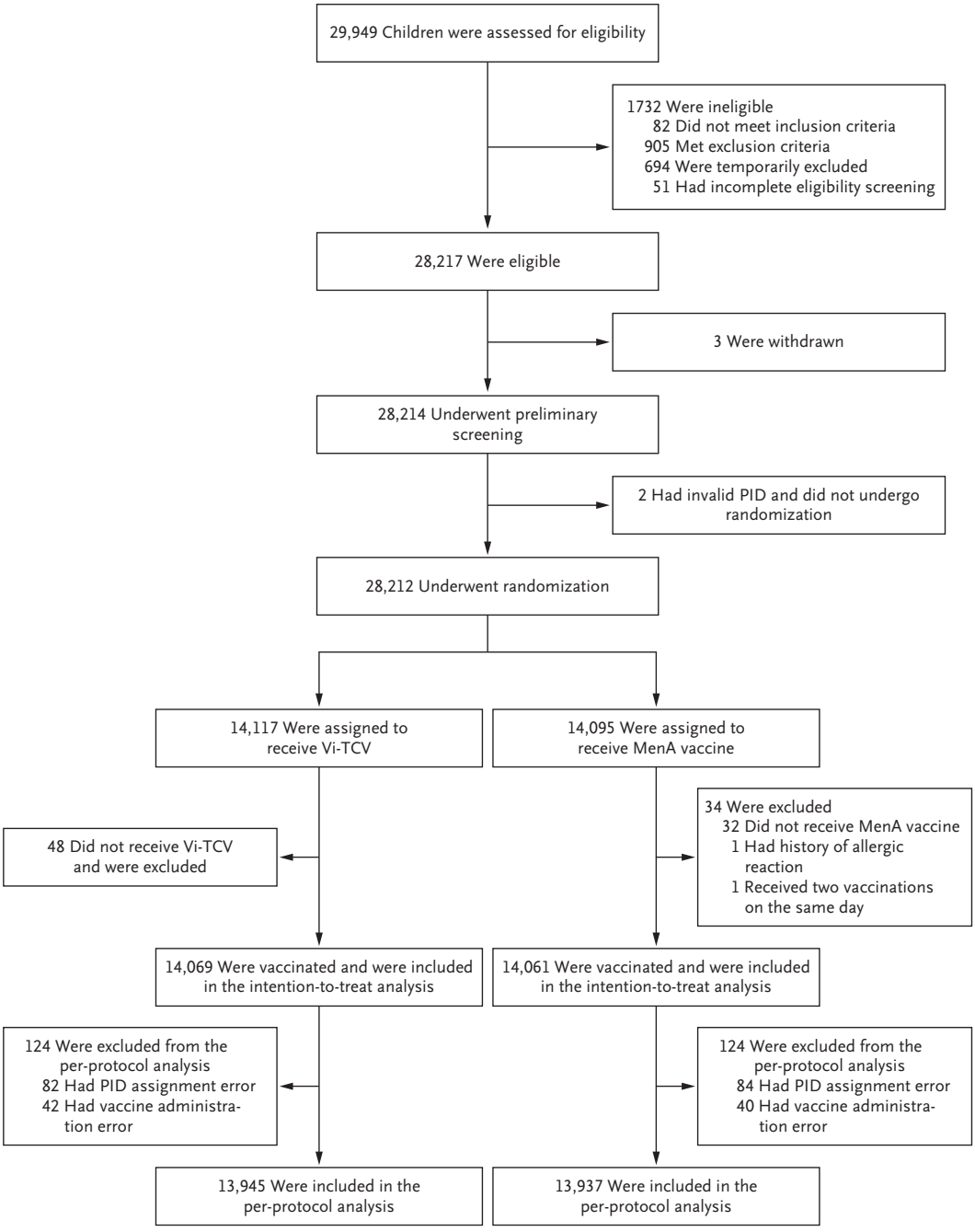

Figure 1. Enrollment and Randomization.

MenA denotes meningococcal capsular group A conjugate, PID participant identification number, and Vi-TCV Vi polysaccharide typhoid conjugate vaccine.

Table 1. Baseline Characteristics of the Children in the Intention-to-Treat Population.*

Characteristic	Vi-TCV (N = 14,069)	MenA Vaccine (N = 14,061)	Overall (N = 28,130)
Sex — no. (%)			
Female	7065 (50.2)	7231 (51.4)	14,296 (50.8)
Male	7004 (49.8)	6830 (48.6)	13,834 (49.2)
Age at enrollment — yr			
Mean	6.1±3.3	6.2±3.3	6.1±3.3
Median (range)	6.0 (0.8–12.0)	6.0 (0.8–12.0)	6.0 (0.8–12.0)
Age group — no. (%)			
<2 yr	1552 (11.0)	1598 (11.4)	3,150 (11.2)
≥2 to <5 yr	3506 (24.9)	3581 (25.5)	7,087 (25.2)
≥5 yr	9011 (64.0)	8882 (63.2)	17,893 (63.6)
Trial site — no. (%)			
Ndirande	8863 (63.0)	8832 (62.8)	17,695 (62.9)
Zingwangwa	5206 (37.0)	5229 (37.2)	10,435 (37.1)

* Plus–minus values are means ±SD. The intention-to-treat population included all participants who underwent randomization and received a dose of a vaccine. Percentages may not total 100 because of rounding. MenA denotes meningococcal capsular group A conjugate, and Vi-TCV Vi polysaccharide typhoid conjugate vaccine.

second episode was therefore excluded from the efficacy analyses. All 75 isolates were MDR, and 4 (5.3%) were resistant to ciprofloxacin (Table S1 in the Supplementary Appendix, available at NEJM.org).

In the intention-to-treat analysis (Table 2), there were 74 blood culture–confirmed cases of typhoid fever: in 12 children in the Vi-TCV group (incidence rate, 46.9 cases per 100,000 person-years) and in 62 children in the MenA group (incidence rate, 243.2 cases per 100,000 person-years). One participant in the MenA group died from severe typhoid 7 months after vaccination. The protective efficacy of Vi-TCV against blood culture–confirmed typhoid fever at any time after vaccination was 80.7% (95% confidence interval [CI], 64.2 to 89.6). The Kaplan–Meier curves show separation in the cumulative incidence between the Vi-TCV and MenA groups (P<0.001) (Fig. 2). 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. The absolute risk reduction was 3.6 cases per 1000 vaccinated children, corresponding to a number needed to vaccinate of 277.8. Three episodes of blood culture–confirmed typhoid fever that occurred in the 14 days after vaccination were excluded from the per-protocol analysis, yielding an overall efficacy of 83.7% (95% CI, 68.1 to 91.6) in the per-protocol analysis (Table 2).

In the intention-to-treat analysis, the incidence of blood culture–confirmed typhoid fever in the MenA group was similar in children who were younger than 5 years of age and children who were 5 years of age or older (Table 2 and Fig. S1). The protective efficacy of Vi-TCV was 81.2% (95% CI, 54.8 to 92.1) among boys, 80.3% (95% CI, 52.8 to 91.8) among girls, 77.9% (95%

Table 2. Blood Culture–Confirmed Typhoid Fever and Vaccine Efficacy.

Variable	Vi-TCV			MenA Vaccine			Protective Efficacy of Vi-TCV (95% CI)	Absolute Risk Reduction (95% CI)*	Number Needed to Vaccinate (95% CI)†
	Children (total follow-up time)	Cases of Typhoid	Incidence of Typhoid	Children (total follow-up time)	Cases of Typhoid	Incidence of Typhoid			
	no. (person-yr)	*no.*	*cases/100,000 person-yr (95% CI)*	*no. (person-yr)*	*no.*	*cases/100,000 person-yr (95% CI)*	*percent*	*cases/1000 children*	
Intention-to-treat population‡	14,069 (25,577)	12	46.9 (24.2–82.0)	14,061 (25,493)	62	243.2 (186.5–311.8)	80.7 (64.2–89.6)§	3.6 (2.4–4.8)§	277.8 (208.3–416.7)
Age <5 yr	5,058 (9086)	5	55.0 (17.9–128.4)	5,179 (9305)	20	215.0 (131.3–332.0)	74.4 (31.7–90.4)	2.9 (1.0–4.8)	344.8 (208.3–1000.0)
Age ≥5 yr	9,011 (16,491)	7	42.5 (17.1–87.5)	8,882 (16,188)	42	259.5 (187.0–350.7)	83.7 (63.6–92.7)	4.0 (2.4–5.5)	250.0 (181.8–416.7)
Per-protocol population¶	13,945 (25,323)	10	39.5 (18.9–72.6)	13,937 (25,239)	61	241.7 (184.9–310.5)	83.7 (68.1–91.6)§	3.7 (2.5–4.8)§	270.3 (208.3–400.0)
Age <5 yr	5,044 (9057)	5	55.2 (17.9–128.8)	5,158 (9261)	20	216.0 (131.9–333.5)	74.4 (31.8–90.4)	2.9 (1.0–4.8)	344.8 (208.3–1000.0)
Age ≥5 yr	8,901 (16,267)	5	30.7 (10.0–71.7)	8,779 (15,978)	41	256.6 (184.1–348.1)	88.0 (69.7–95.3)	4.1 (2.6–5.6)	243.9 (178.6–384.6)

* The absolute risk reduction (the risk in the MenA group minus the risk in the Vi-TCV group) is the total reduction in the risk of blood culture–confirmed typhoid fever that resulted from vaccination with Vi-TCV.
† The number needed to vaccinate is the number of children that would be needed to be vaccinated to prevent one case of blood culture–confirmed typhoid fever.
‡ Shown are data in the intention-to-treat population from the time of randomization.
§ P<0.001.
¶ Shown are data in the per-protocol population beginning 14 days after randomization.

Table 3. Safety Outcomes in the Intention-to-Treat Population.*

Variable	Vi-TCV (N=14,069)	MenA Vaccine (N=14,061)	Total (N=28,130)
No. of participants with serious adverse events within 28 days after vaccination	4	10	14
No. of participants with serious adverse events within 6 mo after vaccination	47	71	118
No. of serious adverse events within 28 days after vaccination	4	10	14
Infections and infestations	3	8	11
Other	1	2	3
No. of serious adverse events within 6 mo after vaccination	52	78	130
Infections and infestations	34	55	89
Respiratory tract infection	16	21	37
Gastroenteritis	11	8	19
Malaria	4	10	14
Other infections	3	16	19
Nervous system disorders†	6	9	15
Injury, poisoning, and procedural complications‡	7	6	13
Other	5	8	13
No. of deaths within 6 mo after vaccination	0	6§	6

* For the data reported in this table, the assigned vaccine group is the same as the received vaccine group.
† Nervous system disorders included febrile convulsion and seizure.
‡ Injury, poisoning, and procedural complications included fractures and road traffic accidents.
§ The causes of death were acute kidney injury secondary to hypovolemia, intraabdominal infection resulting from shunt infection, death in the community from unknown cause, tracheoesophageal fistula after ingestion of a foreign body, massive trauma, and blood culture–negative sepsis and unknown chronic illness (i.e., malnutrition, tuberculosis, or a malignant condition).

CI, 46.5 to 90.9) among children in Ndirande, and 82.9% (95% CI, 59.2 to 92.8) among children in Zingwangwa.

SAFETY

Three boys in the MenA group had directly observed adverse events, all mild in severity, within 30 minutes after vaccination. Two events (rash and syncope) were considered to be related to vaccination, and one (diarrhea) was determined to be unrelated to the trial regimen.

Within 28 days after vaccination, 14 serious adverse events occurred in 14 participants: 4 events in the Vi-TCV group (in 3 girls and 1 boy) and 10 events in the MenA group (in 9 girls and 1 boy) (Table 3). Within 6 months after vaccination, 130 serious adverse events (52 in the Vi-TCV group and 78 in the MenA group) occurred in 118 participants (47 in the Vi-TCV group and 71 in the MenA group). Although more serious adverse events were ob-

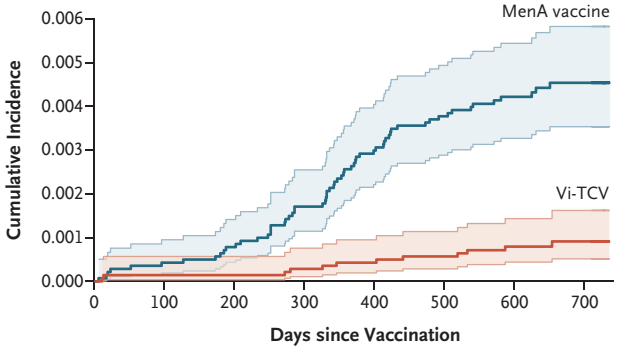

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Blood Culture–Positive Typhoid Fever in the Intention-to-Treat Population.

The intention-to-treat population included all participants who underwent randomization and received a dose of a vaccine. Shaded areas indicate 95% confidence intervals. Blood culture–confirmed typhoid fever occurred in 62 children in the MenA group and in 12 children in the Vi-TCV group.

DISCUSSION

In this field trial in Africa, a single dose of Vi-TCV was effective in preventing typhoid fever among children 9 months to 12 years of age. Overall, the incidence of typhoid was 243.2 per 100,000 person-years in the MenA group and was similarly high in school-age and preschool children. An intention-to-treat analysis comparing this incidence with that in the Vi-TCV group yielded a protective efficacy of Vi-TCV of 80.7%. The efficacy of Vi-TCV was similar in children who were younger than 5 years of age and children who were 5 years of age or older at the time of vaccination, and this efficacy remained consistent throughout the observation period. It is encouraging that the efficacy of Vi-TCV (80.7% in the intention-to-treat analysis and 83.7% in the per-protocol analysis) in Malawi after 18 to 24 months is consistent with a previously reported efficacy of 81.6% after 12 months of follow-up among Nepalese children 9 months to 16 years of age.[17] The safety profile of Vi-TCV was reassuring, with no excess serious adverse events in the Vi-TCV group and no adverse or serious adverse events considered to be related to the vaccine. The six children who died within the first 6 months after vaccination were in the MenA group. One death from typhoid in the MenA group occurred 7 months after vaccination.

Previous trials of typhoid vaccines have been performed in Africa. In a randomized, controlled trial involving 23,075 South African children 5 to 16 years of age, a single dose of unconjugated Vi capsular polysaccharide vaccine was 55 to 60% effective over a period of 3 years.[26,27] A systematic review and meta-analysis of randomized, controlled trials, including trials in Africa, showed that at 3 years the cumulative efficacy of the oral Ty21a vaccine and the polysaccharide Vi vaccine were similar, at 51% (95% CI, 36 to 62) and 55% (95% CI, 30 to 70), respectively.[28] Despite a 2008 WHO recommendation for programmatic use of existing vaccines in countries in which typhoid is endemic,[29] no African country integrated these vaccines into routine schedules, largely because of the unsuitability of their use in the youngest children and the need for repeated doses. The burden of typhoid in Malawi, and elsewhere in Africa, is high among school-age and preschool children.[11] Although earlier typhoid vaccines were shown to be effective in school-age children, our trial showed that the incidence of typhoid was similar in preschool and school-age children and that a single dose of Vi-TCV was also effective among African children younger than 5 years of age. Vi-TCV efficacy was consistent throughout the trial period, and ongoing typhoid surveillance (36 to 42 months) of this cohort will provide further data on the durability of protection and will enable further age-stratified analyses in younger children. Analysis of a subgroup of this trial population is under way and will provide data on age-stratified immunogenicity.

Routine introduction of Vi-TCV among infants, coupled with catch-up campaigns targeting children up to the age of 15 years, offers a strategy for typhoid control.[30] The WHO recommends vaccine introduction in countries with a high incidence of typhoid or with emerging antimicrobial resistance. In February 2019, Zimbabwe[31] deployed Vi-TCV programmatically as a local, targeted, mass-vaccination campaign among children 6 months to 15 years of age in response to an antimicrobial-resistant typhoid outbreak. Routine introduction of Vi-TCV paired with catch-up campaigns is planned in Zimbabwe, Liberia, and Malawi.

Prevention of mother-to-child HIV transmission and successful national rollout of antiretroviral treatment have dramatically reduced the prevalence of HIV among children in Malawi. In the period from 2015 to 2016, the prevalence was 1% among children 4 years of age or younger and 1.5% among children 14 years of age or younger.[32] It is nonetheless reassuring that among the 196 HIV-infected children identified and included in this trial, there was no excess of serious adverse events observed among those in the Vi-TCV group, and no serious adverse events were considered to be related to vaccination. Globally, across all age groups, HIV infection is associated with greatly reduced odds of diagnosis of blood culture–

confirmed typhoid (odds ratio, 0.04; 95% CI, 0.01 to 0.11).[33] Several explanations for this counterintuitive finding have been proposed.[34] The continued surveillance in this trial, along with an ongoing substudy assessing the immunogenicity of a one-dose or two-dose schedule of Vi-TCV among HIV-exposed children at 9-month and 15-month immunization visits, will provide additional information in this vulnerable population.

MDR *S.* Typhi remains prevalent in sub-Saharan Africa,[8] which is reflected in our finding that 100% of samples were resistant to first-line agents for suspected bloodstream infection. In the context of the rise in fluoroquinolone-resistant strains of *S.* Typhi across Asia,[8] it is particularly worrisome that four *S.* Typhi strains among participants enrolled in this trial showed reduced susceptibility to fluoroquinolones. The threat of the independent emergence of azithromycin-resistant typhoid, as seen in several Asian countries,[35] adds urgency and relevance to efforts to introduce a safe and efficacious Vi-TCV vaccine across the African continent and globally.

Supported by a grant (OPP1151153, to the Typhoid Vaccine Acceleration Consortium) from the Bill and Melinda Gates Foundation. The Malawi–Liverpool–Wellcome Program is funded by a grant (206545/Z/17/Z) from the Wellcome Trust. Dr. Gordon was supported by a Research Professorship (NIHR300039) from the National Institute for Health Research, U.K. Department of Health and Social Care. Dr. Birkhold was supported by a grant (T32 DK067872) from the National Institutes of Health.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial participants and their parents and guardians; the staff of the Malawi Ministries of Health and Education; the Blantyre District Health Officer; the staff of the Paediatric Department of the Queen Elizabeth Central Hospital; the staff of the health centers in Ndirande and Zingwangwa, the Gateway Health Clinic, and the Nancholi Youth Organization Clinic; the director and the staff of the departments of the Malawi–Liverpool–Wellcome Program; the Malawi trial team (John Ndaferankhande, Nedson Chasweka, Lucky Somanje, Chrissy Banda, Josophine Chilongo, Patricia Phula, Georgina Makuta, Monica Kamwana, and Moses Kamzati); Victoria Mapemba (Blantyre Malaria Project); the University of Maryland team (Leslie Jamka, Shrimati Datta, Ian Woods, Christina Scheele, and Tamar Pair); the members of the data and safety monitoring board (Roma Chilengi [chair], Prakash Ghimire, A.K.M. Nurul Anwar [deceased], S.M. Shamsuzzaman, Jalaluddin Ashraful Haq, Nur Haque Alam, Tisungane Knox Titus Mvalo, and Mary E. Putt); and Bharat Biotech International for supplying the investigational vaccine free of charge.

APPENDIX

The authors' affiliations are as follows: the Malawi–Liverpool–Wellcome Program (P.D.P., P.P., J.E.M., T.M., F.M., C.M., H.M., D.B., M.M., M.H., M.G., M.A.G.), the Blantyre Malaria Project (N.N., O.M.N.), the Department of Paediatrics, Queen Elizabeth Central Hospital (Q.D.), the District Health Office, Blantyre District Council (G.K.), and Kamuzu University of Health Sciences (M.A.G.) — all in Blantyre, Malawi; the Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore (Y.L., J.K.T., F.A., K.S., E.R., M.B., K.K., M.B.L., K.M.N.); and Oxford Vaccine Group, the Department of Paediatrics, Oxford University, Oxford (J.E.M.), Liverpool School of Tropical Medicine (C.M., M.H., M.G.), and the Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool (M.A.G.), and the Division of Infection and Immunity, University College London, London (R.S.H.) — all in the United Kingdom.

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