Eight-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Nepali children: an observational follow-up of the TyVAC Nepal randomised controlled trial

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Abstract

Background

Typhoid remains a major public health problem in low- and middle-income countries, including Nepal. In high-burden settings, the WHO recommends the use of typhoid conjugate vaccines (TCVs). Here, we report vaccine effectiveness up to 8 years following a single dose of TCV.

Methods

TyVOID is a prospective cohort study extending follow-up of children enrolled in a phase 3, double-blind, randomised trial in Lalitpur, Nepal (TyVAC, Nov 2017–Oct 2021; ISRCTN43385161). Children aged 9 months to younger than 16 years were randomly assigned (1:1) to receive Vi-TT or a capsular group A meningococcal conjugate vaccine. After unmasking (2020–21) and cross-over vaccination, our study followed the trial participants until October 2025. Children who received Vi-TT were classified as previous (2017–18) or recent (2020–21) vaccinees. The primary outcome was the incidence of blood culture-confirmed typhoid identified through facility-based passive surveillance and medical record review. Adjusted incidence rate ratios (IRRs) were estimated using Poisson regression adjusted for age and sex. Vaccine effectiveness at 1 to 5 years and 4 to 8 years post-vaccination was estimated using a test-negative design among febrile children presenting to surveillance clinics (2021–25), comparing odds of Vi-TT vaccination between culture-confirmed typhoid cases with negative controls.

Findings

12,236 TyVAC participants were included. The primary analysis population included 4,941 previous and 4,856 recent Vi-TT vaccinees who attended the final trial visit. During a median follow-up of 3.7 years, typhoid incidence was 111 per 100,000 PYs (95% CI 64–177) among previous and 46 (18–94) among recent vaccinees (adjusted IRR 2.41, 95% CI 1.00–5.80). Vaccine effectiveness was 77% at 1 to 5 years (95% CI 46–90; p=0.0006) and 53% at 4 to 8 years (8–76; p=0.0267).

Interpretation

A single Vi-TT dose confers strong protection in the first 4 years among Nepali children, with evidence of waning by 8 years. These findings support consideration of a booster dose to sustain protection in children at school age when typhoid risk remains high.

Funding

TyVAC- Gates Foundation (grant number OPP1151153); TyVOID- Wellcome Trust (projects number 221438/Z/20/Z; 221348/Z/20/Z).

Research in context

Evidence before this study

Typhoid fever remains a major cause of morbidity and mortality in low- and middle-income countries, particularly in South Asia and sub-Saharan Africa. To review previous studies on TCV vaccine efficacy, we searched PubMed using the terms “typhoid conjugate vaccine” AND (“efficacy” OR “protection”) with searching filters for clinical trials, randomised controlled trials, or systematic reviews, between 1st Jan 2018 and 23rd Feb 2026, with no language restrictions. We identified 21 research articles, including three phase 3 randomised clinical trials conducted in Malawi, Nepal, and Bangladesh. All three trials reported high short-term vaccine efficacy of a single TCV dose within the first 2 years after vaccination (81% at 18–24 months in Malawi, 79% at 24 months in Nepal, and 85% at 18 months in Bangladesh). However, evidence regarding the durability of protection beyond 2 years has been inconsistent. Extended follow-up of the Malawi trial, with a median follow-up of 4.3 years, showed sustained protection (cumulative vaccine efficacy 78%, 95% CI 66–86) without clear waning, while the Bangladesh trial demonstrated declining protection, with effectiveness of 55% (95% CI 36–68) during years 3 to 5 after vaccination.

Added value of this study

This study provides the longest follow-up to date of a single dose of TCV, extending protection estimates up to 8 years after vaccination in children from our original randomised controlled trial in Nepal. Using both cohort comparison and test-negative design analyses, we show evidence of waning protection over time. Children vaccinated in 2017/2018 had approximately twice the incidence of blood culture-confirmed typhoid between 2021 and 2025 compared with those vaccinated in 2020/2021 (adjusted incidence rate ratio 2.41, 95%CI 1.00-5.80), and vaccine effectiveness declined from 77% (95% CI 46-90) during 1 to 5 years to 53% (8-76) during 4 to 8 years after vaccination. These findings provide robust longitudinal evidence that protection following a single TCV dose decreases beyond 5 years.

Implications of all available evidence

Evidence from randomised trials in Malawi, Bangladesh, and Nepal shows that a single dose of typhoid conjugate vaccine provides strong short-term protection against typhoid fever. However, accumulating long-term follow-up data indicates that protection may start to decline from 4 to 5 years post-vaccination. Our findings extend available evidence to 8 years after vaccination and suggest that waning protection could have important implications for sustaining immunity into later childhood, particularly in countries where TCV is delivered at younger ages through routine immunisation programmes. These results highlight the need to optimise vaccination strategies to ensure durable protection and support sustained typhoid control in endemic settings.

Introduction

Typhoid fever remains a major cause of morbidity and mortality in low- and middle-income countries (LMICs), particularly among children (1). Although global incidence, mortality, and disability-adjusted life years (DALYs) from typhoid fever have declined substantially since 1990, based on the most recent Global Burden of Disease data the disease still caused an estimated 6.2 million cases, 71 955 deaths, and 5.4 million DALYs worldwide in 2023 (2). Recent systematic review evidence incorporating data up to 2024 indicates that typhoid incidence remains substantial, with pooled estimates exceeding 200 cases per 100 000 person-years in population-based studies and the highest incidence in South Asia, alongside a disproportionate burden among young children (3).

Emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Salmonella* Typhi requiring treatment with broader spectrum antibiotics has further complicated the control of typhoid and led to growing concerns around related antimicrobial resistance (4). Vaccination programmes, in conjunction with the provision of clean drinking water and improvement of sanitation, have proven to be cost-effective measures to reduce the typhoid burden (5). However, despite global progress in water, sanitation, and hygiene (WASH), such structural improvements are slow to scale in many endemic regions and vaccination currently represents a cornerstone of prevention strategies.

Following WHO prequalification of the first typhoid conjugate vaccine (TCV; Typbar-TCV®, Bharat Biotech International, India) in 2017, WHO issued a global recommendation in 2018 for a single-dose schedule from six months of age, with catch-up vaccination through 15 years in endemic settings (6). Evidence from multiple randomised controlled trials (RCTs) in Malawi, Bangladesh and Nepal, implemented through the Typhoid Vaccine Acceleration Consortium (TyVAC), demonstrated the high short-term efficacy of a single TCV dose (7–10). A recent Cochrane review further confirmed that TCV substantially reduces laboratory-confirmed typhoid fever (risk ratio 0.20, 95% CI: 0.12–0.32) (11).

However, uncertainty remains regarding the medium- and long-term persistence of protection after a single TCV dose, with emerging evidence suggesting heterogeneity across settings. In Bangladesh, a five-year follow-up of the TyVAC trial (TyVOID study) showed evidence of waning protection, with test-negative estimates declining from 84% (95% CI 74–90) at 1 to 3 years to 57% (39–70) at 3 to 5 years post-vaccination, alongside more rapid protection waning among children vaccinated before two years of age (12). By contrast, follow-up data from Malawi suggested more sustained protection over 5 years, with estimates of 83% (95% CI: 60-94) in year one, 68% (27–88) in year four, and 90% (31–100) in year five (up to 4.61 years), without evidence of a progressive annual decline (13).

Understanding the durability of protection and age-related patterns among children vaccinated at younger ages is therefore a critical priority for national immunisation programmes and global policy. High-quality longitudinal data are essential to inform decisions on booster strategies, catch-up campaigns, and programme timing, and to support transmission models projecting the long-term population-level impact of TCV introduction. To address this evidence gap, we extended follow-up of the TyVAC Nepal trial (TyVOID study) to assess protection up to 8 years after a single dose of Vi-TT.

Methods

Study design

TyVAC Nepal was a phase 3 double-blinded RCT conducted in Lalitpur Metropolitan City, an urban area of the Kathmandu Valley, Nepal, between November 2017 and September 2021 (10). Following trial completion, the TyVOID Nepal prospective cohort study was started to extend follow up the TyVAC trial participants, initially planned for 2 years, but extended to October 2025 due to pandemic-related changes in healthcare-seeking behaviour and reduced case detection. Follow-up was conducted through community surveillance, with healthcare facility-based passive surveillance for typhoid fever. In addition to trial participants, passive surveillance was expanded to all residents in the study area. The study received ethical approval from the Oxford Tropical Research Ethics Committee and the Nepal Health Research Council (OxTREC 15-17, OxTREC 11-21, NHRC 240/2021) and was conducted in accordance with the principles of the Declaration of Helsinki.

Participants

In TyVAC, 20,019 children aged 9 months to 15 years of age were randomised 1:1 to receive either Vi-TT (Typbar-TCV®, Bharat Biotech International, India) or a control (MenA; MenAfriVac, Serum Institute of India, India). Participants were followed for 2 years, with planned unmasking and crossover vaccination beginning in January 2020. This process was interrupted by the COVID-19-related restrictions and was completed in May 2021. Additionally, not all trial participants completed crossover vaccination. In May 2022, Vi-CRM_{197} (Typhibev®, Biological E Ltd) was introduced through a national campaign, and some participants received this additional TCV. The proportion of participants reported as receiving Vi-CRM197 should not be interpreted as representative of national campaign coverage, as TyVAC participants were advised not to receive additional typhoid vaccination in line with WHO recommendations.

The full inclusion and exclusion criteria can be found in the protocol (appendix).

Procedures

Written informed consent was obtained from participants aged ≥18 years or from a parent or legal guardian for participants aged <18 years. Assent was obtained from children aged ≥7 years. Baseline demographic information, including sex, was collected at enrolment. Sex, but not gender, was recorded by self-report for adult participants or by parent or guardian report for participants aged <18 years, and categorised as male or female. Surveillance was conducted at Patan Hospital (outpatient and emergency departments) and at community-based fever clinics integrated into existing government health services. All residents in the study area presenting with a fever lasting ≥ 2 days and/or a fever of ≥ 38°C were eligible for blood culture regardless of their vaccination status. Blood cultures were obtained from all such participants, with additional clinically indicated blood investigations performed at the discretion of the treating clinician; for

those providing consent, an extra 1–2 mL of blood was collected and stored for future host susceptibility analyses. Samples were processed by Patan Hospital Microbiology Laboratory, and participants were treated according to clinical guidelines.

The original trial participants were contacted every 3 months by phone or in-person to confirm residence and consent, collect information on febrile illness, healthcare use other than the study fever clinics, antibiotic use and Vi-CRM_{197} vaccination at national roll-out, and reinforce study care-seeking guidance.

Outcomes

The primary outcome was the incidence of blood-culture-confirmed typhoid fever. A typhoid fever episode was defined as a febrile illness with at least one blood culture for *S.* Typhi, occurring ≥ 1 day post baseline. Febrile visits with ≤ 14 days interval were grouped as a single episode. The secondary outcome was the incidence of blood-culture-confirmed paratyphoid fever.

Statistical analysis

Power calculation for TyVOID assumed an incidence of 80 typhoid cases per 100,000 person-years in the 2020/2021 cohort. With approximately 14,661 person-years of follow-up per cohort, the study had 87% power to detect a reduction in vaccine efficacy from 80% to 45% (equivalent to an IRR of 2.75, similar to the estimate from the Bangladesh study). All analyses of primary and secondary outcomes were pre-specified in the statistical analysis plan before data analysis.

Two complementary approaches assessed the durability of protection. First, the incidence of typhoid was compared between children vaccinated with Vi-TT in 2017/2018 (previous-Vi-TT cohort) and those vaccinated in 2020/2021 (recent-Vi-TT cohort). The primary analysis population was children who received both Vi-TT and MenA vaccines, with available Vi-CRM_{197} status to ensure comparability between cohorts. Follow-up began on 21st Oct, 2021 and continued until the last contact, receipt of Vi-CRM_{197} during the national campaign (to ensure that estimates reflected the effect of Vi-TT vaccination only), or 31st Oct, 2025. Incidence rates were calculated per person-years, and adjusted incidence rate ratios (aIRRs) were estimated using Poisson regression, adjusting for age at TyVAC baseline and sex. Overdispersion was assessed using both deviance-to-degrees-of-freedom ratios and Pearson dispersion statistics, and no evidence of substantial overdispersion was observed. Subgroup analyses by age at the initial vaccination (<5, 5–10, and ≥10 years) were conducted using stratified models fitted separately within each age group. Interaction between vaccination and age group was assessed using a likelihood ratio test. Three sensitivity analyses were conducted: 1) inclusion of self-reported typhoid during follow-up; 2) Inclusion of children who received only Vi-TT in 2017/2018 but not MenA at unmasking in the previous-Vi-TT cohort; and 3) inclusion

of participants with missing information on Vi-CRM_{197} receipt, assuming they have not received Vi-CRM_{197}, as our trial participants who received Vi-TT were advised not to receive Vi-CRM_{197} as a second TCV.

Second, a test-negative design (TND) was used to estimate VE during 1 to 5 years and 4 to 8 years post-vaccination. The TND was specimen-based, whereby each febrile episode with a blood culture was treated as a separate observation in the analysis. The analysis population was age-eligible children for initial 2017/2018 vaccination who presented with fever to surveillance clinics between 21st Oct 2021 and 31st October 2025. Participants were classified as non-vaccinees, previous-Vi-TT (2017/2018), or recent-Vi-TT (2020/2021). Fever episodes after receipt of Vi-CRM_{197} were excluded to avoid confounding from additional typhoid conjugate vaccination and to ensure that analyses reflect the durability of protection following a single dose of Vi-TT. Test-positives were blood-culture-positive for *S.* Typhi, while test-negative controls had negative cultures. Conditional logistic regression was used to estimate odds ratios (ORs) of vaccination, matched by calendar month and adjusted for age at fever visits and sex. VE was calculated as (1–OR) × 100%. Subgroup analyses at age at initial vaccination (<5, 5–10, ≥10 years) were conducted, similar to the cohort analysis. The study was not powered to detect sex-specific differences in outcomes, and therefore, we did not conduct sex-stratified analysis.

Because TCV does not protect against paratyphoid fever, analysis of paratyphoid fever served as a bias indicator, with no association with vaccination expected.

A one-sided 0.05 significance level was used for the primary aIRR analysis based on the prespecified hypothesis of waning protection over time, as seen in the Bangladesh study (12). This decision was made before the final analysis, which was documented in the statistical analysis plan (SAP). A two-sided 0.05 was used for other analyses. Analyses were done in R (version 4.2.2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 16,131 TyVAC participants were enrolled at TyVOID baseline (Figure 1). Among these, 14,850 participants provided information on Vi-CRM_{197}, while the 1,281 participants with missing data were excluded. The primary analysis included individuals who received both Vi-TT and MenA: 4,941 received Vi-TT in 2017/2018, and MenA in 2020/2021 (previous-Vi-TT vaccinees), and 4,856 received the vaccines in the reverse sequence as recent-Vi-TT vaccinees. Baseline demographic characteristics were balanced between previous-Vi-TT and recent-Vi-TT vaccinees in the primary analysis population (Table 1). Sex and ethnicity distributions were similar across groups, while age at Vi-TT vaccination differed as expected by vaccination timing. In the sensitivity analysis, we further included 2,263 participants who received Vi-TT in 2017/2018 but did not participate in the unmasking process, and 276 participants who received Vi-TT in 2017/2018 but did not receive MenA during unmasking, as previous Vi-TT vaccinees.

During a median follow-up of 3.7 years (2021–2025), 7 typhoid cases were identified among recent-Vi-TT vaccinees and 17 among previous-Vi-TT vaccinees (Table 2). Incidence rates were 46 per 100,000 person-years (95% CI: 18–94) and 111 (95% CI: 64–177), respectively. The adjusted incidence rate ratio (aIRR) was 2.41 (95%CI: 1.00–5.80, one-sided p=0.025) (Table 2, Figure 2), indicating reduced protection 4 to 8 years post-vaccination, compared with 1 to 5 years. Sensitivity analyses showed consistent findings. Expanding the previous Vi-TT group to include participants who only received Vi-TT in 2017/2018, but not MenA in 2020-2021 yielded an aIRR of 1.92 (95% CI: 0.81–4.53) (Supplementary Table 2; Appendix page 3; Supplementary Figure 1; Appendix page 11). When all typhoid cases were included, including self-reported unverified typhoid cases, the aIRR was 1.80 (95% CI: 0.98–3.31) (Table 2). Including participants with missing Vi-CRM197 status did not change results (aIRR 2.40, 95% CI 1.0–5.79) (Supplementary Table 7; Appendix page 10).

Age-subgroup analyses showed a higher IRR in the younger age group, although estimates had wide confidence intervals due to small numbers, and there was no significant heterogeneity (p for interaction = 0.32) (Supplementary Table 3; Appendix page 4). The aIRR was 6.99 (95%CI: 0.86–56.79, one-sided p=0.0345) among children under 5 years of age at baseline TyVAC vaccination in 2017/2018, 1.21 (95%CI: 0.33–4.52) among those vaccinated at 5-10 years of age, and 2.53 (95%CI: 0.49–13.03) among those vaccinated at ≥10 years of age.

Test positive cases were older compared with test negative controls, whereas sex distribution was similar (Supplementary Table 1; Appendix page 2). In the TND analysis (n=1,696), VE was 77% (95%CI: 46–90,

p=0.0006) among recent-Vi-TT vaccinees and 53% (95%CI: 8−76, p=0.027) among previous-Vi-TT vaccinees (Table 3), compared with unvaccinated children. In age-subgroup analysis, no statistically significant protection was observed among children younger than 10 years at initial TyVAC vaccination, whereas among children aged 10-15 years, both previous- or recent-Vi-TT vaccination was associated with statistically significant protection (Supplementary Table 4; Appendix page 6). However, there was no significant heterogeneity (p for interaction = 0.26).

As a bias-indicator analysis, no difference in the risk of paratyphoid fever was observed between recent-Vi-TT and previous-Vi-TT vaccinees, with an aIRR of 0.99 (95% CI 0.43−2.29) (Supplementary Table 5; Appendix page 8), supporting the validity of the findings. Similarly, the TND analysis detected no protective effect of TCV against paratyphoid fever (Supplementary Table 6; Appendix page 9).

Discussion

In this study, we extended the follow-up of the TyVAC Nepal trial by 4 years to evaluate the medium to long-term protection following a single dose of Vi-TT. Between 2021 and 2025, children vaccinated in 2017/2018 experienced approximately twice the incidence of typhoid fever compared with those vaccinated in 2020/2021, suggesting waning VE over time. The pattern was consistent across the age-stratified analyses and sensitivity analyses, although estimates from the age-stratified analyses did not reach statistical significance due to the small number of cases, and should be interpreted with caution.

These findings were supported by TND results, which showed a decline in VE from 77% in 1 to 5 years to 53% in 4 to 8 years post-vaccination. The TND analysis is particularly useful as it includes the unvaccinated population in the analysis to increase the study power. TND has been widely used to evaluate vaccine effectiveness, particularly in settings where healthcare-seeking behaviour may differ between vaccinated and unvaccinated individuals (14–17).

VE in recent-Vi-TT vaccinees during their first 1 to 5 years (77%) was comparable to the VE reported in Malawi over a median 4.3 years of follow-up (78%) and in Bangladesh (VE of 93% at year 1 and 77% at year 4), supporting evidence of sustained protection for at least 4 years (12,13). In contrast, VE among previous-Vi-TT vaccinees in Nepal (4 to 8 years post-vaccination) was lower than that of recent-Vi-TT vaccinees (53% vs 77%), suggesting protection waning. A similar decline was observed in Bangladesh, where VE decreased to 39% at year 5, whereas Malawi reported sustained protection at year 5 (90%). These differences are likely multifactorial. Higher force of infection in South Asia compared with Malawi may accelerate apparent waning (18), as greater exposure could overcome vaccine-induced protection (19). Population-based surveillance data showed that the incidence of typhoid fever in Nepal and Bangladesh (1000 per 100 000 person-years) is substantially higher than in Malawi (400 per 100 000 person-years) (18). Differences in study design are also relevant: Nepal and Bangladesh used comparisons between previous and recent vaccinees to estimate the relative waning with TND analyses for validation, while Malawi maintained a masked parallel-group comparison, allowing direct estimation against a concurrent control group. Notably, published data from both Bangladesh and Malawi are limited to approximately 5 years of follow-up, whereas the post-unblinding follow-up in the Nepal cohort allows evaluation of vaccine effectiveness up to 8 years after vaccination. This represents the longest population-based follow-up to date following a single dose of Vi-TT and provides important insights into the long-term durability of TCV-induced protection.

Our findings also suggest that age at vaccination influences vaccine protection durability. Protection declined more rapidly among children vaccinated at younger ages, whereas those vaccinated at 10 to 15 years retained significant protection at 4 to 8 years. This aligns with findings from Bangladesh (12). This

pattern is biologically plausible and consistent with immunogenicity data showing that younger children experienced more rapid antibody decay and lower long-term anti-Vi IgG concentrations. In Bangladesh, anti-Vi IgG levels at 4 and 5 years post-vaccination were not significantly different despite a marked decline in VE. While anti-Vi IgG has been used as a correlate of protection to support the licensure of new TCVs, it may not fully explain long-term protection, and other immune responses, including anti-Vi IgA and functional antibody activity, are likely to contribute (20,21).

This period of declining effectiveness overlaps with the transition into school age, when exposure risk is likely to increase, underscoring the importance of vaccine durability beyond early childhood. Evidence from booster studies supports the biological plausibility of extending protection. In Nepal, a second dose administered at short intervals (3 or 6 months) induced only modest responses, with peak antibody levels lower than those observed after the primary dose, suggesting that closely spaced dosing may limit immune responses (22). In contrast, a study in Malawi showed that children vaccinated in infancy and boosted at 5 years mounted strong responses, supporting consideration of booster strategies at school-entry age (23).

Vaccine composition might also influence immune responses and durability, although available evidence remains limited. Several TCVs using different carrier proteins are now WHO-prequalified, including Vi-CRM_{197} and Vi-DT formulations. Recently, a test-negative case-control study from Nepal evaluating the Vi-CRM_{197} following national introduction reported an estimated VE of 89% (95% CI: 65−97) in the first 2 years post-vaccination, providing emerging real-world effectiveness evidence beyond Vi-TT (17). However, long-term efficacy and real-world effectiveness data are derived predominantly from studies of Vi-TT, with little comparable data available for other TCVs. This highlights the importance of continued long-term surveillance that can ideally link campaign vaccination data with clinical outcomes, which will be critical to understanding real-world vaccine effectiveness and the waning of protection for all TCVs (24).

Several limitations should be considered when interpreting the study findings. First, typhoid case detection was reduced following the COVID-19 pandemic because of sustained declines in healthcare-seeking behaviour and fever clinic attendance. As a result, the incidence of typhoid was very low during the early follow-up period in this study, with few cases observed in both vaccination groups. This led to partial overlap in cumulative incidence curves during the first 1 to 2 years of follow-up, reflecting limited data rather than the absence of differences in protection. The prolonged period of low detection affected incidences but is unlikely to have biased comparisons between previous- and recent-Vi-TT vaccinees, as the surveillance procedures were applied in the same manner across cohorts. The use of a test-negative design, which restricts analyses to individuals presenting with febrile illness, helps mitigate potential bias due to differences in healthcare-seeking behaviour. The consistency of findings between the cohort and TND

analyses further supports the robustness of these findings. While TND analyses are also subject to potential biases, such as selection bias, collider bias, and misclassification bias (due to imperfect blood culture sensitivity), these are unlikely to substantially affect our conclusions (16,25,26). The absence of an association with paratyphoid fever provides reassurance.

Second, the small number of confirmed typhoid cases limited the statistical power of our study, particularly for age-stratified analyses, and resulted in wide confidence intervals. Although the original study protocol specified a two-sided significance level, a one-sided test was used for the primary aIRR analysis based on a pre-specified directional hypothesis of waning protection in the SAP. Therefore, although the two-sided 95% confidence interval includes the null value, the corresponding one-sided p value indicates statistical significance and should be interpreted accordingly.

Third, exclusion of participants with missing Vi-CRM197 data and censoring at receipt of Vi-CRM197 may introduce selection bias, but sensitivity analyses suggested minimal impact. In addition, household water, sanitation, and hygiene (WASH) variables were not included in the analysis because they were collected through separate census datasets, which led to a significant challenge in data linkage with our study participants. Adjusting for these factors would have substantially reduced the sample size, and therefore, residual confounding from these factors cannot be excluded. However, since the two cohorts were randomised in the original studies, we believe these factors were well-balanced between the two cohorts.

Finally, because the timing of vaccination defines the comparison groups, age at Vi-TT vaccination is intrinsically linked to cohort membership and cannot be fully disentangled from exposure. Therefore, residual confounding by age or cohort effects cannot be excluded. Nevertheless, the consistency of findings across sensitivity analyses and the independent test-negative design analysis is a strength of this study and supports the robustness of the observed waning in VE. This pattern of waning protection is further supported by findings from Bangladesh, providing external confirmation of our results.

In conclusion, TCV provided strong protection against typhoid fever during the first 4 years after vaccination in Nepal. Protection remained detectable up to 8 years following a single dose, with evidence suggesting declining effectiveness over time. The observed waning raises important questions about the durability of protection, especially when TCV is administered at younger ages through routine immunisation. These findings have direct implications for maintaining protection during later childhood and school age and underscore the importance to optimise vaccination strategies for sustained typhoid control.

Figure 1 Consort Diagram. Among 16,131 TyVAC participants at baseline, 14,850 provided information regarding receipt of Vi-CRM197 during the Nepal government campaign. The primary analysis population included participants who attended the final TyVAC visit and completed crossover vaccination (previous Vi-TT recipients who subsequently received MenA; previous MenA recipients who subsequently received Vi-TT). Sensitivity analyses additionally included participants who received Vi-TT at baseline but did not receive MenA at the unmasking visit. Boxes outlined in red indicate the main analysis population; boxes outlined in blue indicate additional participants included in sensitivity analyses.

Figure 2 The cumulative incidence of blood culture-confirmed typhoid fever among vaccinees by groups. Kaplan–Meier estimates of cumulative incidence of blood culture-confirmed typhoid fever in the primary analysis population by study group. The “Previous Vaccinees” group represents participants who received Vi-TT at the baseline TyVAC vaccination visit and MenA at unmasking, whereas the “Recent Vaccinees” group represents participants who received MenA at the baseline and subsequently received Vi-TT at unmasking. Shaded areas represent 95% confidence intervals. Numbers at risk at each time point are shown below the plot.

Contributors

AJP, BB, ShS, MV, and XL designed the study. DP, MS, and SuS led the implementation of this study. YZ and XL designed the analysis plan. YCK, SD, and AK provided laboratory oversight. MS, HS, SuS, NH, MJ, AM, AD, SuR, ShR, JN, and SG collected the data for this study in collaboration with the larger TyVAC Nepal study team. YZ and XL accessed and verified the data. YZ analysed the data. YFM designed and managed the study database. SK and BC managed the project. DP, YZ, and FWB prepared the first draft manuscript, which was reviewed and edited by all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

AJP was the chair of the UK Department of Health and Social Care's Joint Committee on Vaccination until 2025; was a member of the WHOs Strategic Advisory Group of Experts until 2022; was the chair of WHOs TAG on Salmonella vaccines until end of 2024; is a member of WHOs TAG on Salmonella vaccines; and is a member of the WHO Product Development for Vaccines Advisory Committee from August 2025. AJP declares grant funding for research on vaccines from the Wellcome Trust, Innovate UK, Medical Research Council, National Institute for Health Research, European Commission, Bill & Melinda Gates Foundation, Ellison Institute of Technology, Serum Institute of India, Shionogi, and AstraZeneca. AJP, XL and SK are contributors to intellectual property licensed by Oxford University Innovation to AstraZeneca. XL is a member of the WHO SAGE typhoid working group and a member of the WHO TAG on Salmonella vaccines. All other authors declare that they have no conflict of interest.

Data sharing

De-identified individual participant data from this study will be made available to researchers without restriction when the study is complete. Data can be obtained by contacting xinxue.liu@paediatrics.ox.ac.uk.

Acknowledgements

We sincerely thank our funders (Wellcome Trust and Gates Foundation); the trial participants and their families; Patan Hospital and the Patan Academy of Health Sciences; the Child Health Division and Nepal Immunization Advisory Committee for their support; representatives of Lalitpur Metropolitan City, including

the mayor, ward chairpersons and representatives, Tole health promoters, and ward health implementation committees; and our clinical and laboratory teams for their dedication and contributions.

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