Introduction of Typhoid Conjugate Vaccine – A successful implementation in strengthening National Immunization Program of Nepal

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Background

Burden of Typhoid in Nepal

Nepal is a typhoid-endemic country and is estimated to have one of the highest burdens of typhoid in the world. The Global Burden of Disease study estimated that, in 2019, there were at least:

- 82,449 typhoid cases (27 cases per 100,000)
- 919 typhoid deaths
- 68,186 disability-adjusted life-years (DALYs)

• Typhoid also imposes an **economic burden** in Nepal. One study in Kathmandu found that the combined direct and indirect mean costs for hospitalized typhoid patient were US$233, one third of the average Nepali family’s annual income (US$730 annually).


• Nepal is also grappling with a significant burden of **antimicrobial resistance** due to the widespread misuse of antibiotics, inadequate healthcare systems, and poor infection control measures. Multiple studies in the country have highlighted the prevalence of prescribing multiple antibiotics without proper bacterial confirmation or susceptibility testing, leading to unnecessary antibiotic use.


• To combat the growing threat, **vaccination** against diseases like typhoid fever is crucial in preventing the transmission of resistant infections and reducing the reliance on antibiotics.

Objectives

• The school based TCV campaign was implemented as a catch-up strategy prior to introducing TCV into the routine immunization program in Nepal.

Specific objectives:

• To provide population immunity/protection through one dose of TCV to all children aged 15 months to 14 years to reduce the incidence of typhoid disease and its complications.

• To utilize the opportunity to strengthen and promote routine immunization and identify children with zero dose and those who have missed full immunization, including measles-rubella.

• To introduce TCV in the routine immunization schedule to be given at 15 months of age.
TCV efficacy trials in Nepal

**Phase 3 Vaccine Efficacy Study of TCV in Nepal**


- Vaccine efficacy: 81.6% (95.8%–91.8%), p<0.001
  - Meningococcal A vaccine: 10.013
  - Typhoid conjugate vaccine: 10.005

**Typhoid Conjugate Vaccine (VI-DT)**

- An alternate conjugate vaccine, VI-DT using polysaccharide-diphtheria toxoid (SKTyphoid) was tested for non-inferiority to Tybar TCV
- Developed at IVI, transferred to SK Bioscience in 2013
- Phase 3 multi-center study in Nepal showed non-inferiority measured by anti-Vi IgG seroconversion rate at 4 weeks post-vaccination (n=1800)
- Phase 3 multi-center study in the Philippines to evaluate multi-dose and single dose formulations
- SKTyphoid has been approved for export, and is seeking WHO PQ

Safety and immunogenicity of the VI-DT typhoid conjugate vaccine in healthy volunteers in Nepal: an observer-blind, active-controlled, randomised, non-inferiority phase 3 trial

- Safety and immunogenicity of the VI-DT typhoid conjugate vaccine in healthy volunteers in Nepal: an observer-blind, active-controlled, randomised, non-inferiority phase 3 trial
TYPHOID CONJUGATE VACCINE (VI-CRM)

- Developed by GSK Vaccines Institute for Global Health (GVGH), then transferred to Biological E, India
- Achieved WHO PQ in December 2020 - TyphiBEV
- Conjugated to CRM$_{197}$ protein, a variant of diphtheria toxin
- A phase 4 clinical trial (VEVACT, NCT05500482) is ongoing to examine the impact of introduction in South India
- Multiple WHO PQ vaccines allows for a more secure vaccine supply

Table 4. Fold increase of IgG antibody concentrations from baseline to Day 42 by vaccine group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 42 (Post Vaccination)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TyphiBEV$^{TM}$ (n=295)</td>
</tr>
<tr>
<td></td>
<td>Typbar-TCV (n=296)</td>
</tr>
<tr>
<td>Geometric Mean Fold Rise (n=296)</td>
<td>56.95%</td>
</tr>
<tr>
<td>GMFR</td>
<td>223.38</td>
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</tbody>
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GMFR = geometric mean fold rise, n = subject count, IgG = Immunoglobulin G, N = sample size, PP = per protocol, Typbar-TCV = Bharat Biotech’s Typbar-Typhoid Vi-TT conjugate vaccine, TyphiBEV$^{TM}$ = Biological E’s Typhoid ViCRM$_{197}$ conjugate vaccine.
# Methodology

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Crossectional Survey</th>
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<tbody>
<tr>
<td>Study Method</td>
<td>Mixed Method (Qualitative and Quantitative)</td>
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<tr>
<td>Study site</td>
<td>56,429 session sites at school for TCV campaign in 77 districts of Nepal.</td>
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<tr>
<td>Timeline</td>
<td>8th April – 1st May 2022.</td>
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<tr>
<td>Study Population</td>
<td>Quantitative: All children from 15 months – 14 years of age. Qualitative: stakeholders who were actively engaged in the TCV immunization campaign, as well as representatives of the Government and international partners.</td>
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<tr>
<td>Sample size and technique</td>
<td>WHO recommended Vaccination Coverage Cluster Surveys (n=78,37623 children).</td>
</tr>
<tr>
<td>Data Collection Methods</td>
<td>Quantitative: Immunization Information were recorded and collected during the campaign session. Qualitative: eight in depth interviews were done with stakeholders who were actively engaged in the TCV immunization campaign, as well as representatives of the Government and international partners.</td>
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<tr>
<td>Human Resources and Vaccination Centers</td>
<td>Number</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Vaccination centers</td>
<td>56,429</td>
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<tr>
<td>Vaccination staffs</td>
<td>10,000</td>
</tr>
<tr>
<td>Volunteers</td>
<td>112,858</td>
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<tr>
<td>AEFI management and RCM staff</td>
<td>6,000</td>
</tr>
<tr>
<td>School health nurse or teacher as focal point</td>
<td>25,000</td>
</tr>
<tr>
<td>Teacher and student volunteers</td>
<td>50,000</td>
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Implementation Strategies and Approach

The TCV campaign adopted several approaches to strengthen routine immunization practices.

- **Invitation card** which provides the full immunization schedule on the reverse side. These cards were distributed to all households with children in the eligible age range.
Implementation Strategies and Approach

- A unique campaign **vaccination card** with two versions: one for children aged 15 to 24 months and the other for children aged 2 to 14 years. The card includes a detachable counterfoil that was designed to be torn off and kept at the health facility for tracking children with missed doses.
Implementation Strategies and Approach

• Health workers at vaccination sessions provided **counseling** to caregivers of children under 24 months on the importance of routine immunization at given the specific age group.

• **Assessment** for measles-rubella vaccine status (provided at 15 months) along with other routine vaccines.
Implementation Strategies and Approach

12–13 Mar 2022
Training of Trainers (ToT) on Typhoid vaccination campaign – 2 days
National Level

Last week of March
District microplanning workshop – 2 days + Vaccinators’ training – 1 day
District Level

20–24 Mar 2022
Training of Trainers (ToT) on Typhoid vaccination campaign – 2 days
Provincial Level

First week of April
FCHVs and other volunteers’ orientation – 1 day
Municipality Level

Typhoid Vaccination Campaign
From 8 April 2022
Implementation Strategies and Approach

- Door-to-door **rapid convenience monitoring** (RCM) during the TCV campaign in Nepal was used to identify and reach children who were missed by the initial vaccination campaign efforts and to increase coverage. In the campaign, RCM was conducted on all levels.

Results

• A national achievement of 95% coverage with all seven provinces exceeding 90% coverage was seen with the implementation of Typhoid conjugate Vaccine in Nepal.

• Concurrent monitoring conducted alongside the TCV campaign helped in identifying 8000 children who had missed vaccine doses (mainly measles-rubella 1st or 2nd dose but also DPT/Penta 3), including 200 zero dose children.

• High level of political commitment at all level, good stakeholder engagement and advocacy, and high community participation were the main facilitators of this successful implementation.

• Timely release of the funds, municipal elections at the time of campaign, migration of eligible children from high altitudes to low altitudes or neighboring countries, difficult geographical terrain, managing logistics, training and mobilization across the country were major challenges seen during the implementation.

“It was difficult to find suppliers for IEC material during that phase as most suppliers were busy printing voter lists and ballot paper.”

1. Gavi defines “zero-dose” as a child under 2 years old who has not received any dose of diphtheria, pertussis, tetanus vaccine (DPT) and “partially immunized” not received at least DPT 2.
2. GAVI 5.0 Goal to reduce zero dose by 25%
3. IA2030 to reduce zero dose by 50%
Conclusion

• Nepal is the first country in the WHO southeast Asia region and the fourth country in the world to introduce the Typhoid Conjugate vaccine in its routine immunization program in 2022 with the support from Gavi.

• This survey provided the accurate vaccination coverage estimates to assess the program performance, monitoring and planning and evidence-based decision-making capacity.

• TCV catchup campaign was a catalyst to identify zero dose children and partially immunized children who missed their routine immunization schedule through the learnings from past vaccination campaigns, including COVID-19 vaccine to recover and reestablish the routine immunization.

• This survey also helped in understanding the effectiveness of supplementary immunization activity mechanism to strengthen routine immunization in Nepal.

• Unique vaccination card and electronic app-based monitoring were innovations that helped to identify missed TCV and zero-children.

• Exemplary teamwork and efficient use of human resources helped to brave challenges of terrain, mobility of population and climatic difficulties, despite budgetary constraints.
Children line up to receive TCV at their school, April 2022.

A mom waits with her daughter to receive TCV during Nepal’s introduction campaign in April 2022. PATH/Rocky Prajapati.
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