13th INTERNATIONAL CONFERENCE TYPHOID & OTHER INVASIVE SALMONELLOSES
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Introduction of Typhoid Conjugate Vaccine –A successful implementation in strengthening National Immunization Program of Nepal

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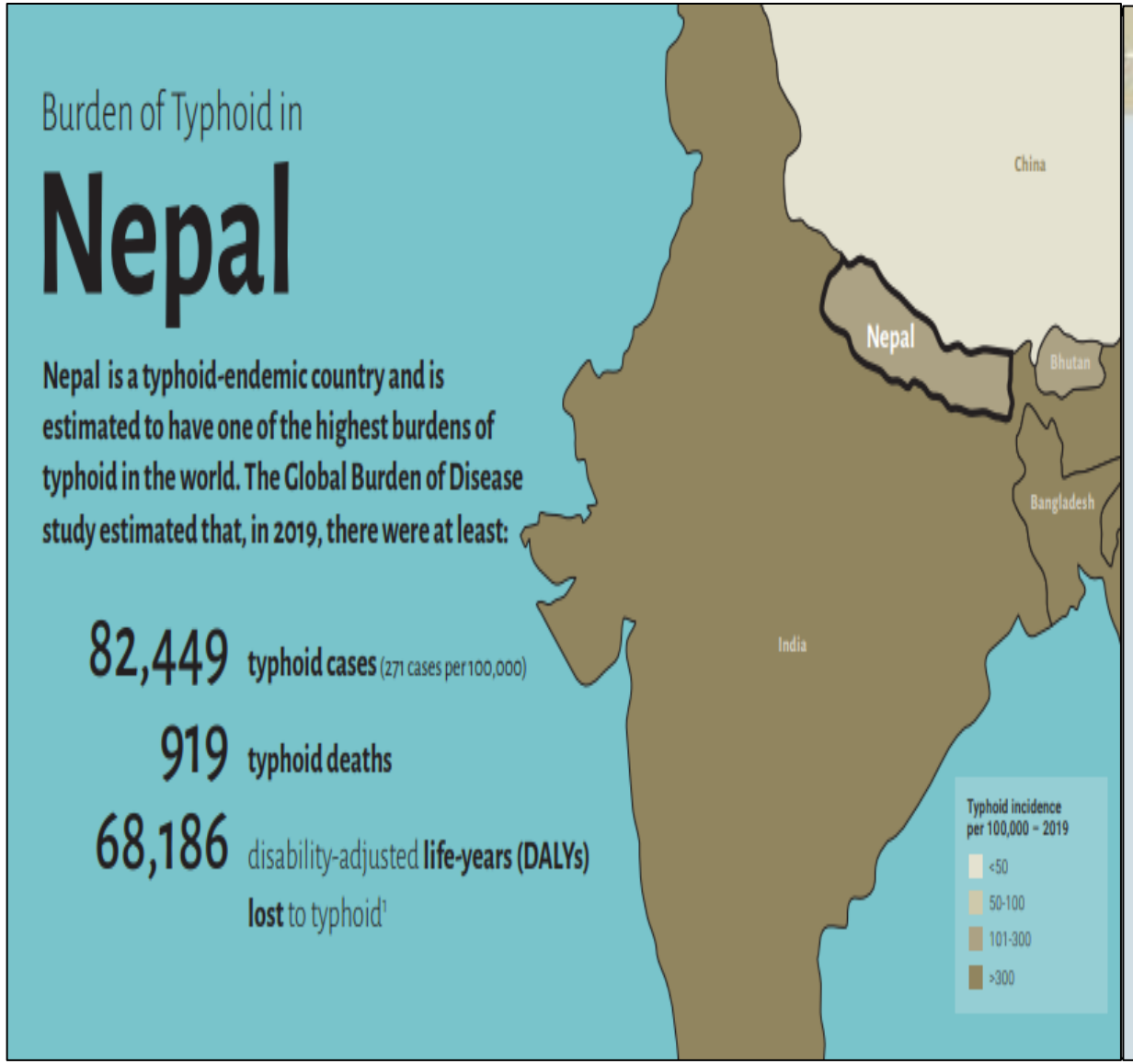
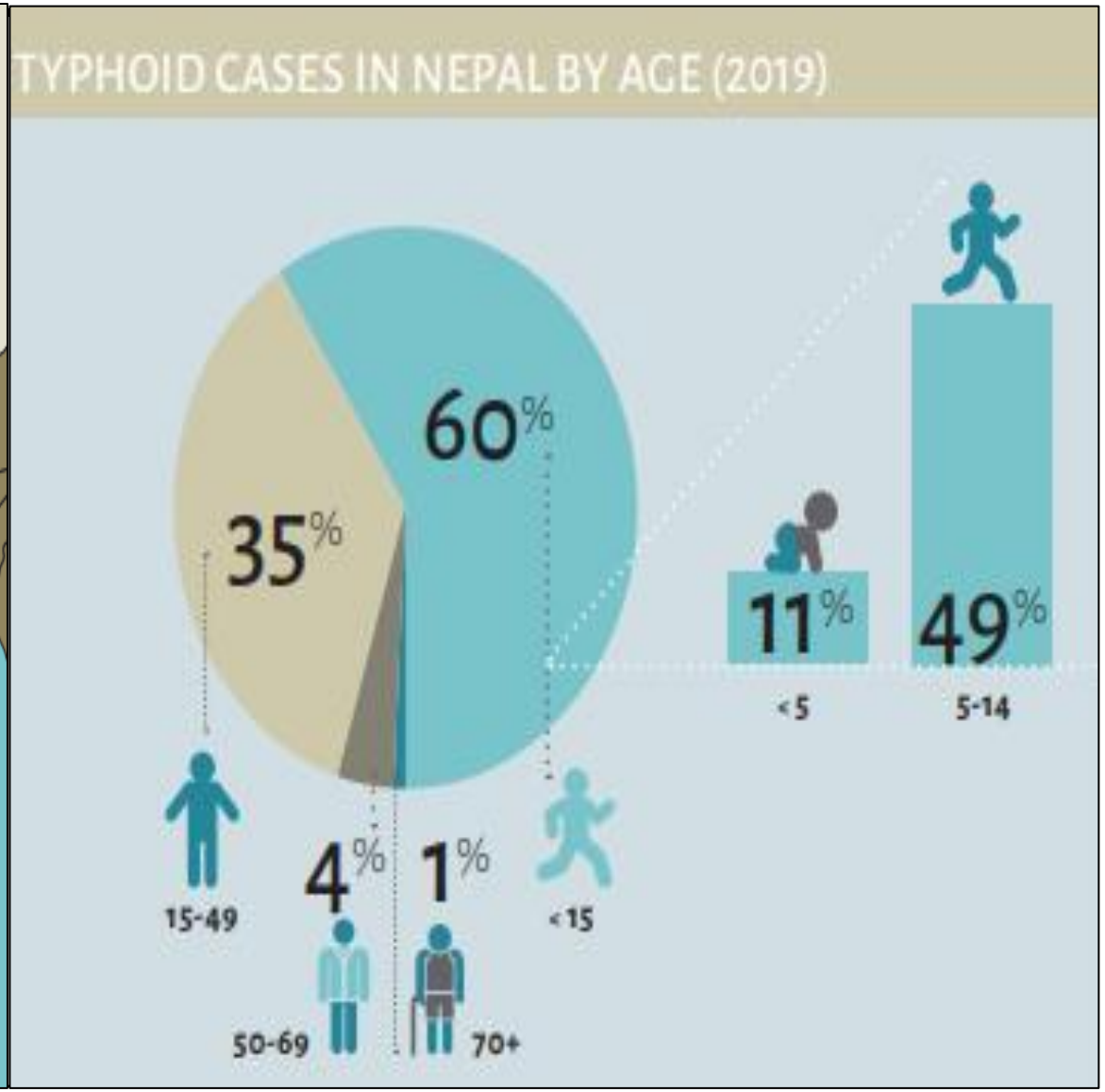
Background





(Institute for Health Metrics and Evaluation. Global Burden of Disease. 2019.)

Background

- 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).
(Kaljee LM, Pach A, Garrett D, et al. Social and economic burden associated with typhoid fever in Kathmandu and surrounding areas: A qualitative study. The Journal of Infectious Diseases. 2017)

- 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.
{Farah N Qamar, etal Antimicrobial Resistance in Typhoidal Salmonella: Surveillance for Enteric Fever in Asia Project, 2016–2019, Clinical Infectious Diseases, November 2020,)

- 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.
(Sahastrabuddhe, Sushant, etal. 2021. "Epidemiology of Typhoid in Nepal: Review of Literature to Identify High Burden Area for Potential Use of Typhoid Vaccine." Pediatric Infectious Disease)

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

The NEW ENGLAND JOURNAL of MEDICINE

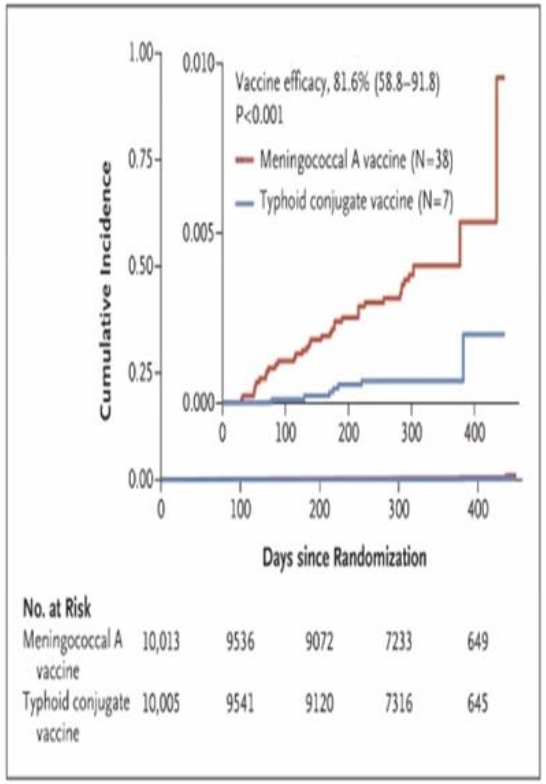
ORIGINAL ARTICLE

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

Mila Shakya, M.P.H., Rachel Colin-Jones, M.A., Katherine Theiss-Nyland, Ph.D., Merryn Voysey, D.Phil., Dikshya Pant, F.C.P.S., Nicola Smith, M.B., B.Chir., Xinxue Liu, Ph.D., Susan Tonks, B.Sc., Olga Mazur, B.Sc., Yama G. Farooq, M.Sc., Jenny Clarke, Ph.D., Jennifer Hill, Ph.D., Anup Adhikari, M.A., Sabina Dongol, D.Phil., Abhilasha Karkey, D.Phil., Binod Bajracharya, M.D., Sarah Kelly, M.Sc., Meeru Gurung, M.D., Stephen Baker, Ph.D., Kathleen M. Neuzil, M.D., Shrijana Shrestha, M.D., Buddha Basnyat, F.R.C.P.E., and Andrew J. Pollard, F.Med.Sci., for the TyVAC Nepal Study Team*

Vaccine efficacy: 81.6% (58.8% – 91.8%), p<0.001

Kaplan–Meier Estimates of the Cumulative Incidence of Blood Culture–Positive Typhoid Fever.

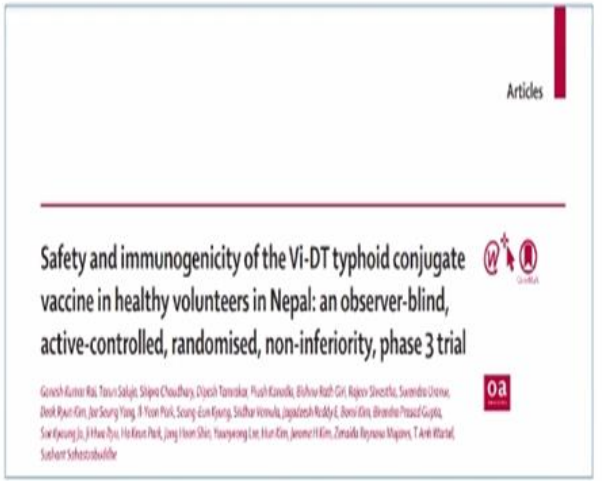


No. at Risk					
Meningococcal A vaccine	10,013	9536	9072	7233	649
Typhoid conjugate vaccine	10,005	9541	9120	7316	645

TYPHOID CONJUGATE VACCINE (VI-DT)

SK bioscience

- An alternate conjugate vaccine, Vi-DT using polysaccharide-diphtheria toxoid (SKYTyphoid) was tested for non-inferiority to Typbar 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
- SKYTyphoid has been approved for export, and is seeking WHO PQ


Articles

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


Articles

A Phase 3, Multicenter, Randomized, Controlled Trial to Evaluate Immune Equivalence and Safety of Multidose and Single-dose Formulations of Vi-DT Typhoid Conjugate Vaccine in Healthy Filipino Individuals 6 Months to 45 Years of Age

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

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 5, e2043103 (11 pages)
https://doi.org/10.1080/21645515.2022.2043103

Taylor & Francis
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RESEARCH PAPER

OPEN ACCESS

A multicenter, single-blind, randomized, phase-2/3 study to evaluate immunogenicity and safety of a single intramuscular dose of biological E's Vi-capsular polysaccharide-CRM_{197} conjugate typhoid vaccine (TyphiBEV™) in healthy infants, children, and adults in comparison with a licensed comparator

Subhash Thuluva, Vikram Paradkar, Ramesh Matur, Kishore T

Clinical Development Department, Biological E Limited, Hyderabad, India

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

Parameter (N=591/622)	Day 42 (Post Vaccination)	
	TyphiBEV™ (n=295)	Typbar-TCV (n=296)
≥4 Fold Rise	96.95% (286)	97.64% (289)
GMFR	223.38	260.81

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™ =Biological E's Typhoid ViCRM$_{197}$ conjugate vaccine.

Thuluva S et al. Hum Vaccin Immunother 2022; 18(5): 2043103

Methodology

Study Design	Crossectional Survey
Study Method	Mixed Method (Qualitative and Quantitative)
Study site	56,429 session sites at school for TCV campaign in 77 districts of Nepal.
Timeline	8th April – 1st May 2022.
Study Population	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.
Sample size and technique	WHO recommended Vaccination Coverage Cluster Surveys (n=78,37623 children).
Data Collection Methods	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 .

Number and Type of Human Resources and Vaccination Centers	
Vaccination centers	56,429
Vaccination staffs	10,000
Volunteers	112,858
AEFI management and Rapid Convenience Monitoring (RCM) staff	6,000
School health nurse or teacher as focal point	25,000
Teacher and student volunteers	50,000

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.

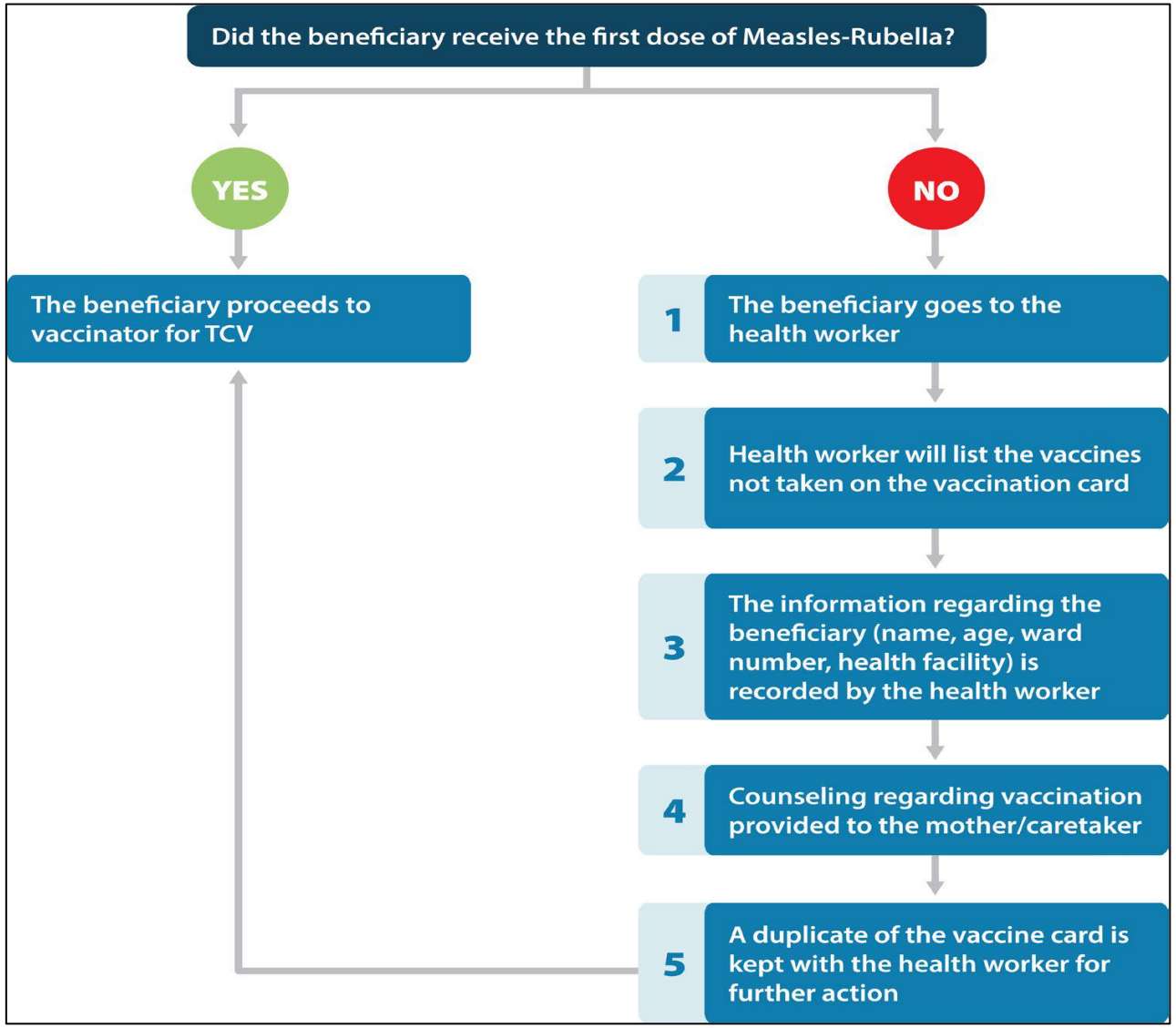
Implementation Strategies and Approach

- 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.

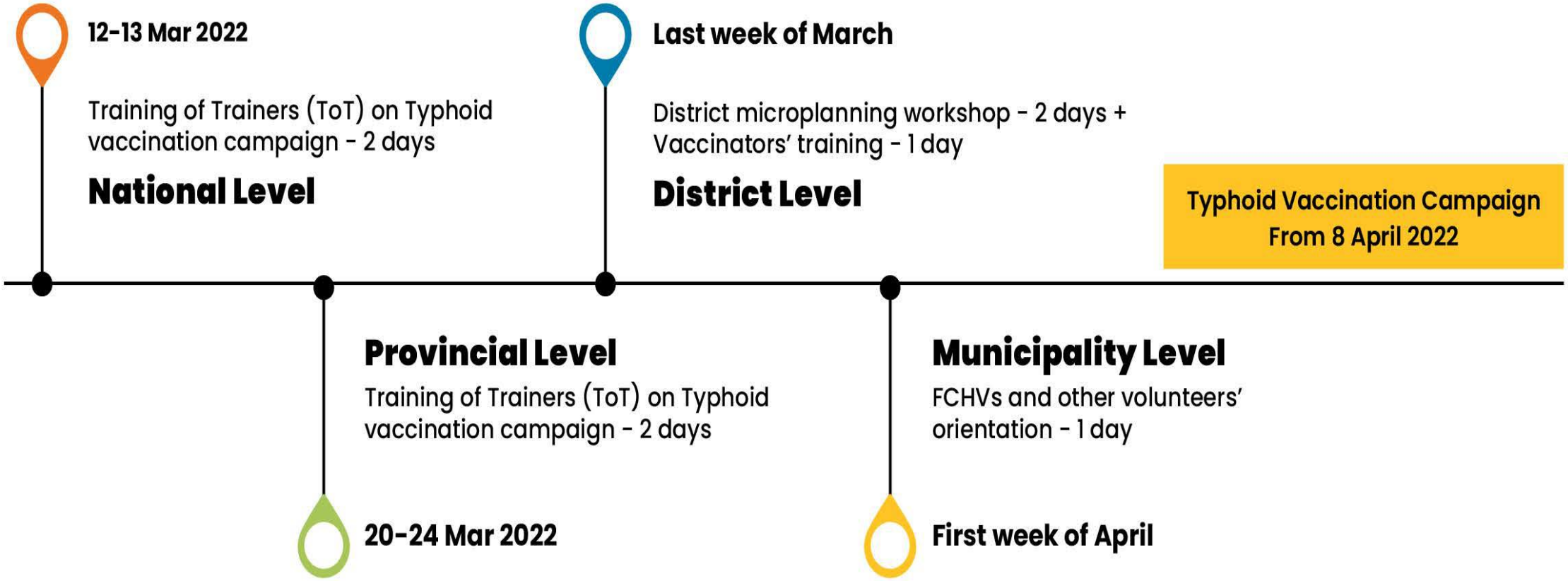
Implementation Strategies and Approach

- 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.

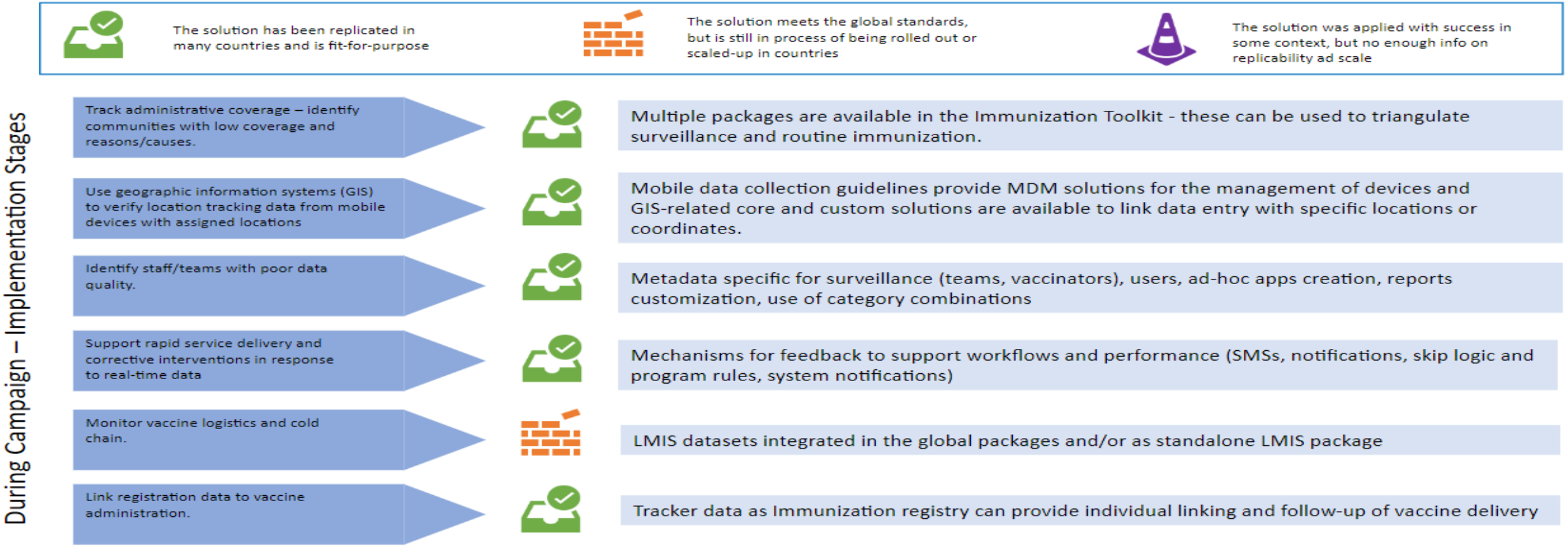


Implementation Strategies and Approach



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.



David H et al. "Real-Time Monitoring of Vaccination Campaign Performance Using Mobile Phones - Nepal, 2016." MMWR. Morbidity and mortality weekly report vol. 65,39 1072-1076. 7 Oct. 2016,

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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