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Typhoid fever vaccination strategies

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Abstract

Typhoid vaccination is an important component of typhoid fever prevention and control, and is recommended for public health programmatic use in both endemic and outbreak settings. We reviewed experiences with various vaccination strategies using the currently available typhoid vaccines (injectable Vi polysaccharide vaccine [ViPS], oral Ty21a vaccine, and injectable typhoid conjugate vaccine [TCV]). We assessed the rationale, acceptability, effectiveness, impact and implementation lessons of these strategies to inform effective typhoid vaccination strategies for the future. Vaccination strategies were categorized by vaccine disease control strategy (preemptive use for endemic disease or to prevent an outbreak, and reactive use for outbreak control) and vaccine delivery strategy (community-based routine, community-based campaign and school-based). Almost all public health typhoid vaccination programs used ViPS vaccine and have been in countries of Asia, with one example in the Pacific and one experience using the Ty21a vaccine in South America. All vaccination strategies were found to be acceptable, feasible and effective in the settings evaluated; evidence of impact, where available, was strongest in endemic settings and in the short- to medium-term. Vaccination was cost-effective in high-incidence but not low-incidence settings. Experience in disaster and outbreak settings remains limited. TCVs have recently become available and none are WHO-prequalified yet; no program experience with TCVs was found in published literature. Despite the demonstrated success of several typhoid vaccination strategies, typhoid vaccines remain underused. Implementation lessons should be applied to design

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Authors' contribution

All authors made substantial contributions to the drafting of the article or critical revising for intellectual content. All authors have approved the final article for submission.

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Conflict of interest statement

The authors report no conflicts of interest.

optimal vaccination strategies using TCVs which have several anticipated advantages, such as potential for use in infant immunization programs and longer duration of protection, over the ViPS and Ty21a vaccines for typhoid prevention and control.

Keywords

Typhoid fever; Typhoid vaccine; Vaccination strategies; Routine vaccination; Outbreak vaccination; School-based vaccination

1. Background

Typhoid fever, an acute, systemic infection caused by *Salmonella enterica* serovar Typhi, is estimated to cause over 21 million illnesses and 222,000 deaths globally each year [1]. Most cases and deaths occur among populations that lack safe water and adequate sanitation and hygiene infrastructure, primarily in Southern Asia and sub-Saharan Africa, with the highest burden estimated to be among young children [1,2]. Infection is transmitted by the fecal-oral route through contaminated food or water from persons who are acutely infected or from chronic carriers [3]. Typhoid most often manifests as an acute, non-specific febrile illness [4,5] and the most-used confirmatory test, blood culture, is only 40–60% sensitive [6]. Resistance to antibiotics commonly used for treatment is increasingly prevalent [7,8].

Recommended typhoid fever prevention and control measures involve case management with stool contact precautions, provision of safe water and proper sanitation, and ensuring safe food handling practices [9]. With available typhoid vaccines and promising new candidate vaccines in development, vaccination has emerged as a complementary strategy to control endemic disease or to interrupt transmission during outbreaks [10]. However, public health programmatic use (excluding research and private sector use) of typhoid vaccine has been limited, especially in high typhoid burden countries [1,11,12]. In this paper, we review experiences with typhoid vaccination strategies using available vaccines and describe the rationale, evidence for impact, acceptability and implementation lessons to inform effective vaccination strategies for the future.

2. Typhoid vaccines

Two typhoid fever vaccines have been licensed and available for use in several countries since the 1990s, replacing the earlier reactogenic, inactivated whole-cell vaccine, which is no longer recommended. The two include an injectable polysaccharide vaccine based on the purified Typhi Vi antigen (ViPS vaccine) and a live attenuated oral Ty21a vaccine, which have both been shown to be safe and effective in multiple settings. In 2008, the World Health Organization (WHO) recommended programmatic use of ViPS and Ty21a vaccines for endemic and epidemic disease control [10]. One ViPS vaccine (Sanofi Pasteur) was prequalified by WHO in 2011, enabling its procurement through United Nations agencies.

The ViPS vaccine is available as a single-dose, injectable vaccine for persons ≥2 years old. Similar to other polysaccharide vaccines, there is no booster effect (enhanced immunological response with repeat vaccine administration) and duration of immunity is

relatively short; revaccination is recommended every 2–3 years. Vaccine efficacy and field effectiveness range from 55 to 72% [13,14]. The live oral Ty21a vaccine is available in a capsule formulation, for administration in a 3–4 dose schedule on alternate days for persons ≥5 years old. It has protective efficacy and field effectiveness of 51–67% [15] and duration of protection of 5–7 years [10].

Typhoid conjugate vaccines (TCVs), subunit injectable vaccines in which Vi capsular polysaccharide antigen is linked to a protein carrier to enhance its immunogenicity [16], are in varying stages of development [17]. TCVs have several potential advantages over ViPS and Ty21a vaccines. Clinical trials of a lead TCV candidate demonstrated immunogenicity in children <2 years old, thereby having the potential for inclusion in routine childhood immunization schedules [18,19]. TCVs have a booster effect which is lacking in the ViPS vaccine [20] and a longer duration of protection [21]. Two TCVs are licensed in India and available in the private sector and a third vaccine candidate is undergoing licensure review in China.

Selected characteristics of available typhoid vaccines are detailed in Table 1.

3. Typhoid vaccination strategies

Implementation of typhoid vaccination involves selecting a disease control strategy and a vaccine delivery strategy. We categorize these strategies below.

3.1. Vaccine disease control strategies

A. **Preemptive**: vaccination for endemic disease control in the absence of an outbreak or in response to a disaster or crisis situation to prevent an outbreak (disaster response). Age groups or geographical areas at high risk may be targeted. A preemptive strategy requires knowledge of local typhoid epidemiology, collected through surveillance or special studies, so that high-risk groups or areas can be defined.

B. **Reactive (outbreak response)**: vaccination in response to an ongoing outbreak of typhoid fever. Age groups or geographical areas at high risk may be targeted. A reactive strategy requires knowledge of typhoid epidemiology during the outbreak so that affected groups or areas can be defined.

C. **Vaccination of food handlers**: vaccination of individuals determined to be food handlers. In general a food handler is any person who engages in the handling of food, or who handles surfaces likely to come into contact with food, for a food business [22]. Given the paucity of published data on vaccination of food handlers as a strategy to reduce typhoid incidence, we do not further consider this strategy in this report.

3.2. Vaccine delivery strategies

A. **Community-based routine**: vaccination offered as a routine service using existing health infrastructure such as health centers, immunization clinics or outreach systems.

B. **Community-based campaign**: vaccination offered as a supplemental immunization activity on single or multiple occasions or as a recurrent strategy at regular intervals (e.g., yearly campaigns in high-risk areas before the rainy season).

C. **School-based**: vaccination offered to school-aged children using schools as a delivery platform. This includes vaccination in the schools of children who are not enrolled, but excludes vaccination of the general population using schools as a venue only. Vaccination is often delivered to all eligible children at one point in time, as a campaign, for logistical convenience.

4. Literature review

We reviewed published English-language reports of country experiences with typhoid vaccination programs and pilot projects in the public sector, and grouped them according to vaccination strategy. We used the search terms “typhoid vaccine”, “typhoid vaccine programs”, “typhoid vaccination” and specific vaccines such as “Ty21a” and “Vi polysaccharide vaccine”. Clinical trials that examined vaccine safety and immunogenicity only, and studies of vaccination of travelers, were excluded.

5. Experiences with typhoid vaccination strategies

Except for the Chile Ty21a experience, all experiences have been with ViPS vaccine. When reported, impact data were noted though often the relative impact of vaccination versus improvements in water and sanitation cannot be determined. Typhoid vaccination strategy experiences are summarized in Table 2.

(1) Preemptive community-based routine vaccination

- China [23,24]

  A locally produced ViPS vaccine has been used in government-led programs in several provinces of China since 1995. During 1995–2006 in Guangxi province, vaccination was promoted for high-risk groups; students were vaccinated through schools, and residents of highly endemic areas were vaccinated at local public health facilities. In most cases, payment of around US$ 1 per dose was required. During 11 years of this combined community-based and school-based typhoid vaccination, coverages of 80–85% among residents of highly endemic areas and 60–70% among students were achieved. In the Guangxi city of Guilin, typhoid fever incidence decreased from 57/100,000 among students and 42/100,000 among non-students during 1991–1994 to <5/100,000 in both groups during 2006–2007. An increase in Paratyphi A during the same period suggests that the decline in typhoid fever may be attributable to vaccination rather than any concomitant improvements in water and sanitation. Similar programs were implemented in Guizhou, Yunnan and Sichuan provinces.

- Delhi State, India [23,25]

In 2004, the State Government of Delhi initiated a typhoid vaccination program targeting children 2–5 years old through routine immunization infrastructure. Each year, approximately 300,000–325,000 children have been vaccinated with a locally produced ViPS vaccine costing US$ 0.53/dose. The program is reported to be well accepted, but no formal evaluation has been conducted.

(2) Preemptive community-based vaccination campaign

- China, India and Pakistan [13,26–28]

  Typhoid ViPS vaccine demonstration projects were conducted in five countries as part of the Diseases of the Most Impoverished (DOMI) project during 2003–2006. Mass vaccination campaigns were conducted in high-risk communities in China, India, and Pakistan, targeting 92,476 persons, 37,686 persons and 27,236 respectively (total 157,398 persons). The programs incorporated social mobilization campaigns and were found to be feasible and acceptable in all three sites, with vaccination coverage rates of 68%, 69% and 78% in Pakistan, India and China respectively. The programs were estimated to be highly cost-effective based on a predictive, prospective cost-effectiveness analysis approach, and residents in low-income areas of the three sites indicated a willingness to pay US$ 2 to US$ 16 for ViPS vaccine for their children.

- Vietnam [23]

  Vietnam has had a government-led typhoid vaccination program since 1997, targeting children 3–10 years old in high-incidence districts based on enteric fever incidence during the previous year. Annual campaigns with a locally produced ViPS vaccine costing the government US$ 0.52/dose (2004) have reached selected districts in approximately half of Vietnam's provinces. In some districts with recent outbreaks, both children and adults were vaccinated. More than 500,000 children were vaccinated during the peak years of 2002–2004. Coverage was 70–90% among the target population, while only 0.1–4% of the general population was vaccinated. Reported enteric fever case numbers decreased substantially in Vietnam during this period; major improvements in water and sanitation infrastructure were also reported.

(3) Preemptive disaster-response community-based vaccination campaign

- Fiji [29]

  In March 2010, category 4 Cyclone Tomas caused extensive population displacement and damage to water and sanitation infrastructure in Fiji. A typhoid vaccination campaign during June–December 2010 delivered 64,015 doses of typhoid ViPS vaccine to persons ≥2 years old, primarily in cyclone-affected areas that were typhoid-

endemic. Annual typhoid fever incidence decreased during the post-campaign year (2011) relative to preceding years (2008–2009) in three subdivisions where a large proportion of the population was vaccinated (incidence rate ratios and 95% confidence intervals: 0.23, 0.13–0.41; 0.24, 0.14–0.41; 0.58, 0.40–0.86), and increased or remained unchanged in 12 subdivisions where little to no vaccination occurred.

- Pondicherry, India [30]

  About 17,000 doses of typhoid ViPS vaccine were administered to children <5 years old in Pondicherry, India following the 2004 Indian Ocean tsunami. No typhoid fever cases were reported in the tsunami-affected areas during the immediate post-campaign period.

- Pakistan [30]

  Following a 2005 earthquake in Pakistan, a typhoid ViPS vaccination campaign in internally displaced persons camps targeted about 50,000 children. No typhoid fever cases were reported during 4–6 months of routine surveillance following the campaign.

(4) Preemptive school-based vaccination

- Chile (Ty21a vaccine) [31]

  A field effectiveness trial comparing dosing schedules of the Ty21a oral vaccine was conducted among more than 200,000 school children in two areas in Chile. The trial demonstrated that a school-based strategy using multiple doses of the capsule formulation was logistically feasible in a relatively developed setting with good health and educational infrastructure, and resulted in a reduction in disease rates. Children younger than 8 years old had difficulty swallowing the capsules.

- China [23,24]

  School-based vaccination was implemented jointly with preemptive community-based routine vaccination, as described above.

- Nepal and Pakistan [32]

  As part of the Vi-based Vaccines for Asia (VIVA) initiative, school-based typhoid ViPS vaccination pilot projects were implemented in two areas each of Kathmandu, Nepal and Karachi, Pakistan. The projects vaccinated over 250,000 children in grades 1–10 in public and private schools, achieving coverage of 64–81% among the target population in Kathmandu and 39–60% in Karachi and demonstrating the feasibility of a school-based strategy in both settings. Written consent requirements may have affected participation in some schools. Extensive planning, advocacy to parents, multi-sectoral coordination

and collaboration with the local officials were crucial to the program's success.

- Indonesia and Vietnam [28,33,34]

  School-based typhoid ViPS vaccination was implemented as part of the DOMI project in North Jakarta, Indonesia and Hue, Vietnam. Vaccine was administered to 4828 children in grades 1–5 in North Jakarta and 32,267 children in grades 1–12 in Hue, achieving coverages of 91% (North Jakarta) and 58% (Hue). School-based typhoid vaccination was feasible with minimal disruption to regular school or health programs, and was highly cost-effective in both settings. A written consent requirement in Vietnam may have affected participation.

(5) Reactive (outbreak-response) community-based vaccination campaign

- Fiji [35]

  In May 2010, soon after Cyclone Tomas hit Fiji, a typhoid outbreak was reported from Fiji's Western Division. About 10,000 of the typhoid ViPS vaccine doses procured for disaster response were diverted to the outbreak-affected area. A decline in cases in the outbreak area was reported after the campaign, but no formal evaluation was conducted.

- Tajikistan [36]

  In March 1997, 18,362 Russian soldiers aged 18–21 years posted in Dushanbe, Tajikistan, were vaccinated with typhoid ViPS vaccine during a typhoid outbreak. Reported case numbers decreased from 174 cases in January–February 1997 to 51 cases during the 10-month period following the campaign.

(6) Reactive (outbreak-response) school-based vaccination

- China [37]

  During 1998–1999 in Xing-An county, Guangxi province, China, typhoid ViPS vaccines were administered to 1701 middle school students, including 441 who received vaccine after a typhoid outbreak began in the school. Vaccine effectiveness was similar among students vaccinated after the outbreak started (71%) and those vaccinated earlier (73%).

6. Discussion

A growing body of evidence supports the feasibility and effectiveness of community-based and school-based typhoid vaccination strategies, primarily using ViPS vaccines, for endemic disease control and outbreak response. Less is known about the effectiveness of preemptive use in disaster settings. Targeted vaccination achieving high coverage among populations at high risk of typhoid fever, even when these represent a small percentage of the

total population in an area, has been followed by substantial reductions in disease rates, though distinguishing the impact of vaccination from that of other interventions is often not possible. Vaccine effectiveness study design can address some of these limitations. Nonetheless, data on vaccine impact remain limited. Evidence for impact is strongest for preemptive use to control endemic disease, and for short-term and medium-term impact. Studies designed to assess long-term impact are needed.

All three described delivery strategies–community-based routine, community-based campaign, and school-based – were successfully used in programs. A combination of community- and school-based strategies may be most useful to reach both children and adults in high-incidence settings where all ages are at risk, as demonstrated in China [23,24,26]. Community-based routine vaccination is most likely to be successful where immunization infrastructure and service delivery are adequate to achieve high coverage in the high-risk target population.

Several programs and pilot projects chose delivery through a community- or school-based campaign to most effectively reach persons ≥2 years old [15,23,26–28,31–34]. Campaigns also provide the opportunity for integrated delivery of other age-appropriate services such as deworming or diphtheria-tetanus booster vaccination. Many countries are gaining experience with school-based vaccination programs for human papillomavirus (HPV) and other vaccines [38]. High rates of school enrolment, a relatively good school-based infrastructure, existing school health programs, and good coordination with school officials facilitated school-based delivery. However, successful disease control also requires strategies to reach non-enrolled children as these may be the most vulnerable to the disease.

For vaccines being added to an immunization program, community demand may play an important role in achieving high coverage in the target population. Social mobilization using communications messages designed on the basis of local formative research was a successful strategy in at least one pilot project [39]. Written consent procedures may have reduced participation in some school-based vaccination projects [32,33]; best practices for consent in this context should be further defined [40].

Nearly all public health typhoid vaccination programs have used ViPS vaccine and have been in countries of Asia and the Pacific. Notably, no experience was reported from sub-Saharan Africa despite the estimated and demonstrated high disease burden [1,12]. Program experience with the Ty21a vaccine is limited to a single field trial in Chile. The ViPS vaccine has several programmatic advantages over the Ty21a vaccine, including a single-dose schedule, indication for all ages 2 years and older, low cost, and low cold chain volume in the 20-dose vial. Ty21a has an advantage in longer duration of protection, and may be a suitable choice for some contexts such as school-based delivery where the multi-dose schedule can be accommodated. Ty21a also has potential cross-protection against Paratyphi A and B, and this could be important in areas where paratyphoid rates are increasing [41,42].

Development and availability of TCVs has been slow, and there is no public health program experience yet with TCVs. However, TCVs have known or expected characteristics

which could give them important programmatic advantages over ViPS and Ty21a vaccines: immunogenicity in adults and children as young as 6 months, high efficacy, expected long duration of immunity following a single dose, and booster response. These characteristics would facilitate use of TCVs in reactive or preemptive campaigns and could make integration into routine infant immunization schedules in endemic areas possible. To identify endemic areas for routine vaccination, the development of disease burden extrapolation models is necessary. Modeling of data suggests that a strategy combining routine vaccination and a catch-up campaign will have the highest impact on disease burden; using TCV would have the greatest impact among the three vaccine types [43]. Though additional implementation data are needed to document field effectiveness and long-term impact, TCVs may become the typhoid vaccine of choice. Identification of optimal vaccination strategies will be crucial for TCV implementation once prequalified vaccines become available with Gavi support.

In most published typhoid vaccination experiences, vaccine price has been low, often less than US$ 1 per dose. Low vaccine price has contributed to the findings of cost-effectiveness and willingness to pay. Vaccination was cost-effective in high-incidence but not low-incidence endemic settings [28]. Outbreak response immunization in a high-incidence and high-morbidity setting is also expected to be highly cost-effective [44]. Data on vaccine delivery cost, an important factor in cost-effectiveness, are limited. Costs for school-based delivery of HPV vaccine have been much higher than costs for delivery of vaccines in the routine infant immunization schedule [45]. Although cost data for TCVs are not currently available, delivery as part of a routine immunization schedule would be expected to minimize costs.

Typhoid vaccination is an important component of typhoid fever control, and several vaccination strategies have been demonstrated to be effective, cost-effective and feasible to implement in endemic and outbreak settings. Selection of a strategy depends on the local disease epidemiology, particularly age and geographic area, and the operational context. Disease incidence in the target population is an important determinant of cost-effectiveness so identification of the target high-risk group is a critical step. Establishment of robust surveillance systems and additional research is needed on vaccine impact, specifically the long-term impact of various vaccination strategies on disease incidence and epidemiology, including potential replacement by Paratyphi. Optimal strategies for use of TCV need to be defined. However, typhoid vaccination may be viewed as a short-term measure to control disease in areas where broad improvements in water and sanitation are not yet feasible [23]. Modeling suggests that vaccination alone cannot eliminate typhoid fever, whereas a combination of vaccination and improvements in water and sanitation may eliminate it [43]. In the long term, improvements in water and sanitation will bring broader benefits through the control of many diseases transmitted by contaminated food and water.

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Table 1

Selected characteristics of currently available typhoid vaccines.

Vaccine characteristics	Ty21a vaccine	Vi Polysaccharide vaccine	Vi Conjugate vaccine[a]
Type	Live, attenuated	Subunit	Subunit
Presentation	Enteric-coated capsules	Liquid, in single- and multi-dose vials	Liquid, in vials and pre-filled syringes
Storage and shelf-life	2–8° C to for 36 months; retains potency for ~14 days at 25° C	2–8° C for 36 months; stable for 6 months at 37° C and for 2 years at 22° C	2–8° C
Cold chain volume	Foil blister pack, volume not given	1.58 cm^3 per dose in 20-dose vial (WHO-prequalified vaccine)	Not available
Licensure status	Licensed in at least 56 countries	Licensed in at least 92 countries	Two vaccines licensed in India
WHO prequalification	No	Yes, TYPHIM-Vi (Sanofi Pasteur)	No
Age of vaccination	Capsules: ≥6 years per manufacturer, ≥5 years per WHO	≥2 years	≥6 months
Schedule	Capsules: 3–4 doses on alternate days;	Single dose	Single dose
Administration	Oral	0.5 ml injection	0.5 ml injection
Efficacy and effectiveness	33–77% (may be higher in some age groups)	55–72% (may be higher in some age groups)	To be determined
Earliest onset of protection	7 days after the last dose	7 days after injection	To be determined
Duration of protection	5–7 years	2–3 years	To be determined
Booster or revaccination recommended	After 5–7 years	Every 2–3 years	To be determined
Booster effect	Yes	No	Yes
Herd protection	Demonstrated	Demonstrated	Expected
Cross protection against *Salmonella* Paratyphi	Partial protection against Paratyphi B	No evidence of cross protection	Data not available

[a]For the currently licensed vaccines.

Table 2

Summary of reported experiences with typhoid vaccination strategies.

Vaccination strategy	Vaccine(s) used	Countries where used	Coverage achieved in target population	Acceptability and feasibility	Cost-effectiveness for use in target population	Demonstrated effectiveness or impact on disease burden
Preemptive community-based routine vaccination	ViPS	China, India [22–24]	23% (China). Not available (India).	Vaccination acceptable. Cost (US$ 1 per dose) acceptable (China).	Not studied	Large decrease in reported enteric fever cases in vaccination areas in China (implemented jointly with school-based vaccination).
Preemptive community-based vaccination campaign	ViPS	China, India, Pakistan, Vietnam [14,22,25–27]	68–78%	Vaccination acceptable. Across sites, parents willing to pay US$ 2 to US$ 16 per child vaccinated.	Very cost-effective in high incidence settings. Not cost-effective in low incidence setting. (predictive modeling)	Large decrease in reported enteric fever cases in vaccination area in Vietnam.
Preemptive disaster-response community-based vaccination campaign	ViPS	Fiji, India, Pakistan [28,29]	98% (Fiji). Not available (India, Pakistan).	Not studied	Not studied	Large decrease in typhoid incidences in vaccinated areas of Fiji while incidence increased or remained the same in other areas.
Preemptive school-based vaccination	Ty21a, ViPS,	Chile (Ty21a). China, Indonesia, Nepal, Pakistan, Vietnam (ViPS). [22,23,27,31–33]	91% (Ty21a). 39–81% (ViPS).	Vaccination feasible and minimally disruptive. Advocacy to parents important for acceptability. Written consent procedures may have affected participation.	Very cost-effective in high incidence settings but not in low-incidence settings (ViPS). Not studied (Ty21a).	Not studied except for China as part of combined school-based and community-based routine strategy.
Reactive (outbreak response) community-based vaccination campaign	ViPS	Fiji, Tajikistan [34,35]	98% (Fiji). Not available (Tajikistan).	Vaccination acceptable as an outbreak response strategy	High cost of campaign due to an island setting noted, cost effectiveness not determined (Fiji). Not studied (Tajikistan)	Number of reported cases dramatically declined among the vaccinated population post-vaccination (Tajikistan). Not evaluated (Fiji).
Reactive (outbreak response) school-based vaccination	ViPS	China [36]	81%	School-based vaccination acceptable in this school-based outbreak.	Not studied	Typhoid vaccination was equally effective when given before or after an outbreak started.