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REVIEW OF THE ROLE OF TYPHOID FEVER VACCINE FOR TRAVELERS IN TROPICAL AREAS

REVIEW PERAN VAKSIN DEMAM TIFOID UNTUK WISATAWAN DI DAERAH TROPIS

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ABSTRACT

Typhoid fever is a systemic infectious disease caused by *Salmonella enterica* subspecies *enterica* serovar Typhi (*S. Typhi*). Transmission commonly occurs through food or drinks contaminated with the feces or urine of infected individuals. Travelers to endemic areas, particularly tropical regions, are at high risk of infection. Symptoms include high fever, nausea, and abdominal pain. Improvements in sanitation and hygiene have contributed to a decline in typhoid incidence; however, the effectiveness of antibiotic treatment is decreasing due to rising resistance. Vaccination has become a highly recommended preventive measure for both local populations and travelers. This study is a literature review of English-language articles published between 2014 and 2024, sourced from PubMed (106 articles), Google Scholar (915), and ProQuest (14), using the keywords “typhoid fever” and “vaccine.” A total of 49 relevant articles were analyzed. The results show that the World Health Organization (WHO) recommends typhoid vaccination in endemic areas. In conclusion, vaccination is effective in reducing morbidity and mortality rates and in preventing antibiotic resistance. Well-planned preventive strategies are essential for protecting public health.

A. INTRODUCTION

Typhoid fever is caused by infection with gram-negative bacteria, namely *Salmonella enterica* subspecies enterica serovar Typhi (S. Typhi). Travelers who visit tropical areas, especially in tropical areas, are at high risk of being infected with this disease. Transmission of typhoid fever generally occurs through food and drink contaminated with feces or urine from other sufferers.

Symptoms that usually appear include high fever, nausea, abdominal pain, and discomfort in the abdominal area.(Manesh *et al.*, 2021)

To reduce the incidence of typhoid fever, it is important to maintain clean water and adequate sewage systems. However, the success of typhoid fever treatment with antibiotics is currently decreasing, which is caused by increasing drug resistance. Therefore, vaccination is urgently needed to prevent the spread of typhoid fever, and the use of this vaccine is recommended not only for local residents in endemic areas, but also for tourists who will visit the area.(Masuet-Aumatell and Atouguia, 2021)

Apart from typhoid fever, paratyphoid disease can also attack tourists who visit endemic areas.(Manesh *et al.*, 2021). Transmission of this disease is similar to typhoid fever, namely through contaminated food, drink, or water. It is very important to create good sanitation, so that the incidence of typhoid fever can be minimized.(Masuet-Aumatell and Atouguia, 2021). Typhoid fever and cholera have similarities in terms of transmission, which generally occurs in developing countries with inadequate sanitation.(Amicizia *et al.*, 2019)

It is estimated that there are around 26.9 million cases of typhoid fever worldwide. However, this figure is difficult to ascertain because the symptoms are non-specific, many cases are not reported, and many patients are not properly diagnosed with typhoid fever.(Masuet-Aumatell and Atouguia, 2021). Currently, the global burden of typhoid fever is significant, necessitating broader vaccination efforts.(Balasubramanian *et al.*, 2019). Vaccines should be one of the main foundations in efforts to maintain global health.(Hajj Hussein *et al.*, 2015)

B. METHOD

This study employed a systematic literature review design to examine the global recommendations and research trends regarding typhoid fever vaccination from 2014 to 2024. The review focused on peer-reviewed journal articles published in English and indexed in three prominent databases: PubMed, Google Scholar, and ProQuest. The search was conducted using the keywords "typhoid fever" and "vaccine" to capture articles that discussed both disease characteristics and vaccine-related strategies or interventions. The inclusion criteria covered original research, review articles, and policy statements that focused on vaccination as a method for preventing typhoid fever in endemic regions or among travelers.

The literature search yielded a total of 1,035 articles, with 106 retrieved from PubMed, 915 from Google Scholar, and 14 from ProQuest. After removing duplicates and screening titles and abstracts based on relevance and inclusion criteria, 49 articles were deemed eligible for full-text review and data extraction. Articles were excluded if they focused solely on diagnostic techniques, treatment regimens, or epidemiology without linking to vaccine-related content. Quality assessment of the selected articles was conducted

using appropriate appraisal tools for both observational and experimental studies to ensure reliability and relevance of findings.

The synthesis of the literature revealed that the World Health Organization (WHO) consistently recommends typhoid vaccination for residents and tourists traveling to endemic and tropical regions, particularly in South and Southeast Asia, sub-Saharan Africa, and parts of Latin America. The articles also discussed the effectiveness of various typhoid vaccines, including the Ty21a live oral vaccine, Vi capsular polysaccharide vaccine, and newer conjugate vaccines. Several studies highlighted the benefits of incorporating typhoid vaccines into national immunization programs, especially for children and high-risk populations, to reduce disease burden and antibiotic resistance.

C. RESULT AND DISCUSSION

Typhoid fever has three stages of infection, namely recovery, temporary recovery, and carrier. About 10% of patients who have recovered still show Salmonella typhi bacteria in their feces up to three months after infection. About 1-4% of sufferers can turn into carriers for more than a year, which contributes to the presence of Salmonella bacteria in the population. These bacteria multiply in the intestinal lining and can survive in the bile ducts, therefore 90% of carriers experience gallstones.(Masuet-Aumatell and Atouguia, 2021)

In the body there are mechanisms against Salmonella. The first line of defense is the stomach, which uses gastric acid to neutralize the pathogen before Salmonella reaches the ileum. Commensal microbes in the intestine also help suppress the growth of S. Typhi. On the surface of the intestinal mucosa, there is a layer of mucin (glycosylated) in the form of MUC2 and MUC5B, as well as antimicrobial molecules such as α-HD5, HD6, human β-defensins 1 and 2, and immunoglobulin A (IgA) which function to protect the intestinal lining by blocking germs from entering and blocking the movement of flagella. To attach to enterocytes, Salmonella Typhi uses fimbriae, as well as a type III secretion system (T3SS-1 or STIV). These germs can avoid the immune response by stimulating Rho-family GTPase or TLR-5, osmolarity changes, T3SS-1 decreases and flagellin, and Vi capsules increase which are immunomodulatory.(Barton *et al.*, 2021)

The process of Salmonella invasion through phagocytes in the bacteremia stage, increases the levels of protective proteins H2O2 and Vi capsules, protects lipopolysaccharide (LPS) from the TLR-4 receptor and inhibits iNOS which functions against the intestinal barrier. Reducing the expression of Salmonella flagellin can prevent pyroptosis, thereby reducing inflammation that usually occurs in the neutrophil response. Although S. Typhi can stimulate the immune system, the response is not completely effective, making it a candidate for the development of a vaccine that reduces the incidence and mortality of typhoid fever. (Barton *et al.*, 2021)

Research related to typhoid fever, including the mechanism in the intestinal mucosa, as well as the relationship between the immune system and tryptophan metabolism, has been conducted. The role of CD4 T cells is very important in the immune response during the first and second infections. Gene sequencing in Salmonella Typhi aimed at eliminating typhoid fever has also been conducted in 2017.(Yap and Thong, 2017)

Antibiotic therapy has been shown to shorten the duration of illness, reduce complications, and reduce mortality from typhoid fever, but the problem of antibiotic resistance is currently increasing.(Masuet-Aumatell and Atouguia, 2021). In 2015, there was data on antibiotic resistance in sub-Saharan Africa, especially in children under five years of age.(Gessner, Halloran and Khan, 2015)

Typhoid fever vaccines have been available since 1896, but their implementation has faced several obstacles, such as lack of data, limited vaccine quantities, short duration of protection, limited effectiveness in young adults, high costs, and lack of infrastructure.(Khan *et al.*, 2017)

Table 1. Typhoid fever vaccine journals

Data	**Information**
Global vaccine	2015. (Kariuki *et al.*, 2015)
Human vaccine trials	Vaccine M01ZH09 2016. (Darton *et al.*, 2016)
Typhoid, paratyphoid fever vaccine	2017. (Zuckerman, Hatz and Kantele, 2017)
Typhoid fever vaccine	2018. (Milligan *et al.*, 2018)
Intestinal mucosal vaccine	2017. (Gayetfile:///C:/Users/James/Documents/Atelier de recherche/Rotavirus_vaccines_past_present_and_futu.pdf, 2017)
Salmonella, Shigella, Vibrio Cholerae, S.Paratyphi A and S.Typhi vaccines	Tahun 2020. (Gibani *et al.*, 2020)

Prevention of typhoid fever can be done through health promotion, improving hygiene, providing sanitation, and clean food, and vaccination in tropical areas. WHO is expected to recommend a vaccine in order to control typhoid fever. There are two types of vaccines available, namely Vivotif®, which is an enteric-coated capsule of the attenuated Ty21a vaccine, and TYPHIM Vi® (Sanofi Pasteur), which is a liquid taken from the unconjugated Vi polysaccharide (ViPS) vaccine.

Table 2. Types of typhoid fever vaccines

Vaccine Name	Information
Phase 1 capsular protein vaccine (Typhax)	2020. (Cartee *et al.*, 2020)
Ty21a vaccine	(Masuet-Aumatell and Atouguia, 2021)
Vi polysaccharide vaccine (ViPS vaccines)	Salmonella Typhi Vi antigen polysaccharide capsule. (Masuet-Aumatell and Atouguia, 2021)
ViCPS vaccine	Specifically for (IGRT) immunoglobulin replacement therapy. (Parker *et al.*, 2018)
Vi-tetanus conjugated (PedaTyph)	Efficacy and safety studies. (Mitra *et al.*, 2016)
	Phase 2b study of the efficacy and immunogenicity of Vi-tetanus toxoid.(Jin *et al.*, 2017)
	Phase 3 trial in Blantyre, Malawi 28,000 children 12 months to 12 years.(Meiring *et al.*, 2019)
	Phase 3 in children aged 9-12 months, the results of the Vi-TCV vaccine reduced the results of typhoid fever blood cultures.(Patel *et al.*, 2021)
	Articles with double-blind, randomized controlled trials, the results are the same.(Nampota-Nkomba *et al.*, 2022)
Vi-TT is related to genes and molecules	The vaccine enhances the humoral immune system. (Zhu *et al.*, 2023)
	Phase 3 efficacy trial of typhoid conjugate vaccine over 4 years in Malawian children, results were highly effective with a single dose of Vi-TT. (Patel *et al.*, 2024)
Single dose Vi-DT is safe, immunogenic. (Mitra *et al.*, 2016)	In 2018, a phase 1 trial was conducted in adults and children in the Philippines, and the results showed that Vi-DT was safe, well tolerated and effective in increasing immunity in participants aged 2-45 years..(Capeding *et al.*, 2018)
Vi-DT	Phase 2 trial study for Vi-DT vaccine in Filipino infants and children. (Capeding *et al.*, 2020)
	Indonesia, phase 2 trials were conducted for children aged 6 to <24 months.(Medise *et al.*, 2020)
	In 2023, a phase 3 clinical trial was reported on healthy volunteers, 15-25 years old, with the same results.(Tamrakar *et al.*, 2024)

The combination of typhoid and hepatitis A vaccines can be done using VIVAXIM® vaccine (Sanofi Pasteur), as well as ViPS vaccines and tetanus toxoid conjugates (typhoid conjugate vaccines [TCVs]) such as Typbar-TCV™ (Bharat Biotech) and Ped aTyph™ (Bio-Med). The Ty21a vaccine, which is a genetic mutation of the salmonella strain Ty21, cannot express the Vi polysaccharide antigen. However, the Ty21a vaccine is able to induce both humoral and systemic immune responses, and increase serum IgG and IgA levels against O salmonella polysaccharides.(Masuet-Aumatell and Atouguia, 2021)

Vaccination programs are more effective when implemented in both vaccinated and unvaccinated groups. Vaccination in one group can reduce infections in another group that has not received the vaccine. For example, a study conducted in Santiago, Chile showed that with one or two doses of vaccine during a typhoid fever epidemic in the control group, it can provide positive results in two observation periods. The implementation of a widespread vaccination program will lead to the formation of herd immunity, which indirectly provides protection to those who are not vaccinated.(Masuet-Aumatell and Atouguia, 2021)

TCV vaccine contains Vi-polysaccharide capsule combined with carrier protein. Each dose of PediTyph contains 5 µg of Vi polysaccharide from S. Typhi combined with 5 µg of tetanus toxoid produced from inactivated tetanus toxin (Clostridium tetani), making it safe for use in children.(Masuet-Aumatell and Atouguia, 2021)

The phase 3 clinical trial, conducted at four hospitals, involved healthy individuals aged 6 months to 45 years. It also explored the effectiveness of salmonella and shigella vaccines in travelers and residents of endemic areas. Another study tested the Vi-conjugate vaccine and MMR (measles-mumps-rubella) and meningococcal type A vaccines in children aged 15-23 months in Burkina Faso, showing that TCV was safe when used in combination with MCV-A for 15 months. A study involving Vi-TT (typbar-TCV) and MMR vaccines in infants aged 8-9 months in India also showed safe results.(Vadrevu *et al.*, 2022)

Phase 2 trials of the Vi-DT vaccine were conducted from October to December 2018 in 200 subjects aged 2-11 years, showing an increase in antibodies after 28 days post-vaccination. Common side effects include pain at the injection site, fever, and muscle pain. The Vi polysaccharide vaccine bound to CRM 197 (a non-toxic mutant of diphtheria toxin) has undergone phase 2 clinical trials for infants, children, and adults. The Vi-DT vaccine, bound to diphtheria toxoid, has passed phase 2 clinical trials in children aged 3-23 months, while phase 3 trials for children and adults were completed in January 2020. The Vi-DT vaccine showed good tolerance with high immunogenicity.(Masuet-Aumatell and Atouguia, 2021).

Vaccination strategies that can be implemented include a combination of using various types of vaccines, as well as attention to environmental

cleanliness. Vaccination has the potential to reduce antibiotic therapy and reduce the incidence of drug resistance, and can lead to immunity. Vaccination is recommended for travelers who will come to endemic areas. WHO recommends the Ty21a, TCV or ViPS vaccines, as a control measure in endemic areas of typhoid fever and to prevent outbreaks. The TCV vaccine can be given to all ages, increases immunity and provides long-term protection. The ViPS vaccine is recommended for children over 2 years of age, while the Ty21 vaccine is intended for children over 6 years of age.(Masuet-Aumatell and Atouguia, 2021)

D. CONCLUSION

Antibiotic therapy for typhoid fever can cause drug resistance and that is the biggest threat to, by therapy is not successful, then there needs to be another way, namely vaccination, to prevent typhoid fever infection in endemic areas. Research and information on resistant salmonella strains are very useful for making government policies in order to implement vaccination. The government's decision on typhoid fever vaccines is also based on an analysis of the cost burden of typhoid fever and the risk of spreading the disease, the existing data is very necessary for the safety and health of tourists.

The purpose of writing this literature review is to provide information that typhoid fever vaccine is very important and has been done a lot of research. In order to maintain global health, it is hoped that mass vaccination can be carried out.

REFERENCE

Amicizia, D. *et al.* (2019) 'Burden of typhoid fever and cholera: Similarities and differences. Prevention strategies for European travelers to endemic/epidemic areas', *Journal of Preventive Medicine and Hygiene*, 60(4), pp. E271–E285. doi: 10.15167/2421-4248/jpmh2019.60.4.1333.

Balasubramanian, R. *et al.* (2019) 'The global burden and epidemiology of invasive non-typhoidal Salmonella infections', *Human Vaccines and Immunotherapeutics*, 15(6), pp. 1421–1426. doi: 10.1080/21645515.2018.1504717.

Barton, A. J. *et al.* (2021) 'Host restriction, pathogenesis and chronic carriage of typhoidal Salmonella', *FEMS Microbiology Reviews*, 45(5), pp. 1–12. doi: 10.1093/femsre/fuab014.

Capeding, M. R. *et al.* (2018) 'Safety and immunogenicity of a Vi-DT typhoid conjugate vaccine: Phase I trial in Healthy Filipino adults and children', *Vaccine*, 36(26), pp. 3794–3801. doi: 10.1016/j.vaccine.2018.05.038.

Capeding, M. R. *et al.* (2020) 'Immunogenicity, safety and reactogenicity of a Phase II trial of Vi-DT typhoid conjugate vaccine in healthy Filipino infants and toddlers: A preliminary report', *Vaccine*, 38(28), pp. 4476–4483. doi:

10.1016/j.vaccine.2019.09.074.

Cartee, R. T. *et al.* (2020) 'A phase 1 randomized safety, reactogenicity, and immunogenicity study of typhax: A novel protein capsular matrix vaccine candidate for the prevention of typhoid fever', *PLoS Neglected Tropical Diseases*, 14(1), pp. 1–15. doi: 10.1371/journal.pntd.0007912.

Darton, T. C. *et al.* (2016) 'Using a Human Challenge Model of Infection to Measure Vaccine Efficacy: A Randomised, Controlled Trial Comparing the Typhoid Vaccines M01ZH09 with Placebo and Ty21a', *PLoS Neglected Tropical Diseases*, 10(8), pp. 1–27. doi: 10.1371/journal.pntd.0004926.

Gayetfile:///C:/Users/James/Documents/Atelier de recherche/Rotavirus_vaccines_past_present_and_futu.pdf (2017) 'crossm Vaccination against Salmonella Infection ':, *Microbiology and Moleculer, Biologi Reviews*, 81(3), pp. 1–26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28615285.

Gessner, B. D., Halloran, M. E. and Khan, I. (2015) 'The case for a typhoid vaccine probe study and overview of design elements', *Vaccine*, 33(S3), pp. C30–C35. doi: 10.1016/j.vaccine.2015.03.085.

Gibani, M. M. *et al.* (2020) 'Homologous and heterologous re-challenge with salmonella typhi and salmonella paratyphi a in a randomised controlled human infection model', *PLoS Neglected Tropical Diseases*, 14(10), pp. 1–25. doi: 10.1371/journal.pntd.0008783.

Hajj Hussein, I. *et al.* (2015) 'Vaccines Through Centuries: Major Cornerstones of Global Health', *Frontiers in Public Health*, 3(November), pp. 1–16. doi: 10.3389/fpubh.2015.00269.

Jin, C. *et al.* (2017) 'Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial', *The Lancet*, 390(10111), pp. 2472–2480. doi: 10.1016/S0140-6736(17)32149-9.

Kariuki, S. *et al.* (2015) 'Antimicrobial resistance and management of invasive Salmonella disease', *Vaccine*, 33(S3), pp. C21–C29. doi: 10.1016/j.vaccine.2015.03.102.

Khan, M. I. *et al.* (2017) 'Barriers to typhoid fever vaccine access in endemic countries', *Research and Reports in Tropical Medicine*, Volume 8, pp. 37–44. doi: 10.2147/rrtm.s97309.

Manesh, A. *et al.* (2021) 'Typhoid and paratyphoid fever: A clinical seminar', *Journal of Travel Medicine*, 28(3), pp. 1–13. doi: 10.1093/jtm/taab012.

Masuet-Aumatell, C. and Atouguia, J. (2021) 'Typhoid fever infection – Antibiotic resistance and vaccination strategies: A narrative review', *Travel Medicine and Infectious Disease*, 40(December 2020), p. 101946. doi: 10.1016/j.tmaid.2020.101946.

Medise, B. E. *et al.* (2020) 'A novel Vi-diphtheria toxoid typhoid conjugate vaccine is safe and can induce immunogenicity in healthy Indonesian children 2–11 years: a phase II preliminary report', *BMC Pediatrics*, 20(1), pp. 1–8. doi:

10.1186/s12887-020-02375-4.

Meiring, J. E. *et al.* (2019) 'Typhoid vaccine acceleration consortium Malawi: A Phase III, randomized, double-blind, controlled trial of the clinical efficacy of typhoid conjugate vaccine among children in Blantyre, Malawi', *Clinical Infectious Diseases*, 68(Suppl 2), pp. S50–S58. doi: 10.1093/cid/ciy1103.

Milligan, R. *et al.* (2018) 'Vaccines for preventing typhoid fever', *Cochrane Database of Systematic Reviews*, 2018(5). doi: 10.1002/14651858.CD001261.pub4.

Mitra, M. *et al.* (2016) 'Efficacy and safety of vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study', *Human Vaccines and Immunotherapeutics*, 12(4), pp. 939–945. doi: 10.1080/21645515.2015.1117715.

Nampota-Nkomba, N. *et al.* (2022) 'Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months to 12 years in Malawi: a nested substudy of a double-blind, randomised controlled trial', *The Lancet Global Health*, 10(9), pp. e1326–e1335. doi: 10.1016/S2214-109X(22)00275-3.

Parker, A. R. *et al.* (2018) 'Measurement and interpretation of Salmonella typhi Vi IgG antibodies for the assessment of adaptive immunity', *Journal of Immunological Methods*, 459(April), pp. 1–10. doi: 10.1016/j.jim.2018.05.013.

Patel, P. D. *et al.* (2021) 'Safety and Efficacy of a Typhoid Conjugate Vaccine in Malawian Children', *New England Journal of Medicine*, 385(12), pp. 1104–1115. doi: 10.1056/nejmoa2035916.

Patel, P. D. *et al.* (2024) 'Efficacy of typhoid conjugate vaccine: final analysis of a 4-year, phase 3, randomised controlled trial in Malawian children', *The Lancet*, 403(10425), pp. 459–468. doi: 10.1016/S0140-6736(23)02031-7.

Tamrakar, D. *et al.* (2024) 'Safety and immunogenicity of conjugate vaccine for typhoid (Vi-DT): Finding from an observer-blind, active-controlled, randomized, non-inferiority, phase III clinical trial among healthy volunteers', *Human Vaccines and Immunotherapeutics*, 20(1), pp. 1–9. doi: 10.1080/21645515.2023.2301631.

Vadrevu, K. M. *et al.* (2022) 'Safety, immunogenicity and non-interference of concomitant Typhoid Vi capsular polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV®) and measles or measles-mumps-rubella vaccines in 8–9 months-old Indian children', *Human Vaccines and Immunotherapeutics*, 18(7). doi: 10.1080/21645515.2022.2150030.

Yap, K. P. and Thong, K. L. (2017) 'Salmonella Typhi genomics: envisaging the future of typhoid eradication', *Tropical Medicine and International Health*, 22(8), pp. 918–925. doi: 10.1111/tmi.12899.

Zhu, H. *et al.* (2023) 'Molecular correlates of vaccine-induced protection against typhoid fever', *Journal of Clinical Investigation*, 133(16), pp. 1–17. doi: 10.1172/JCI169676.

Zuckerman, J. N., Hatz, C. and Kantele, A. (2017) ‘Review of current typhoid fever vaccines, cross-protection against paratyphoid fever, and the European guidelines’, *Expert Review of Vaccines*, 16(10), pp. 1029–1043. doi: 10.1080/14760584.2017.1374861.