

Position Paper on Typhoid fever vaccines

Selected references

Epidemiology

Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ. 2004 May;82(5):346-53.

OBJECTIVE: To use new data to make a revised estimate of the global burden of typhoid fever, an accurate understanding of which is necessary to guide public health decisions for disease control and prevention efforts. **METHODS:** Population-based studies using confirmation by blood culture of typhoid fever cases were sought by computer search of the multilingual scientific literature. Where there were no eligible studies, data were extrapolated from neighbouring countries and regions. Age-incidence curves were used to model rates measured among narrow age cohorts to the general population. One-way sensitivity analysis was performed to explore the sensitivity of the estimate to the assumptions. The burden of paratyphoid fever was derived by a proportional method. **FINDINGS:** A total of 22 eligible studies were identified. Regions with high incidence of typhoid fever (>100/100,000 cases/year) include south-central Asia and south-east Asia. Regions of medium incidence (10-100/100,000 cases/year) include the rest of Asia, Africa, Latin America and the Caribbean, and Oceania, except for Australia and New Zealand. Europe, North America, and the rest of the developed world have low incidence of typhoid fever (<10/100,000 cases/year). We estimate that typhoid fever caused 21,650,974 illnesses and 216,510 deaths during 2000 and that paratyphoid fever caused 5,412,744 illnesses. **CONCLUSION:** New data and improved understanding of typhoid fever epidemiology enabled us to refine the global typhoid burden estimate, which remains considerable. More detailed incidence studies in selected countries and regions, particularly Africa, are needed to further improve the estimate.

Vollaard AM, Ali S, van Asten HA, Widjaja S, Visser LG, Surjadi C, van Dissel JT. Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia. JAMA. 2004 Jun 2;291(21):2607-15.

CONTEXT: The proportion of paratyphoid fever cases to typhoid fever cases may change due to urbanization and increased dependency on food purchased from street vendors. For containment of paratyphoid a different strategy may be needed than for typhoid, because risk factors for disease may not coincide and current typhoid vaccines do not protect against paratyphoid fever. **OBJECTIVE:** To determine risk factors for typhoid and paratyphoid fever in an endemic area. **DESIGN, SETTING, AND PARTICIPANTS:** Community-based case-control study conducted from June 2001 to February 2003 in hospitals and outpatient health centers in Jatinegara district, Jakarta, Indonesia. Enrolled participants were 1019 consecutive patients with fever lasting 3 or more days, from which 69 blood culture-confirmed typhoid cases, 24

confirmed paratyphoid cases, and 289 control patients with fever but without Salmonella bacteremia were interviewed, plus 378 randomly selected community controls. MAIN OUTCOME MEASURES: Blood culture-confirmed typhoid or paratyphoid fever; risk factors for both diseases. RESULTS: In 1019 fever patients we identified 88 (9%) Salmonella typhi and 26 (3%) Salmonella paratyphi A infections. Paratyphoid fever among cases was independently associated with consumption of food from street vendors (comparison with community controls: odds ratio [OR], 3.34; 95% confidence interval [CI], 1.41-7.91; with fever controls: OR, 5.17; 95% CI, 2.12-12.60) and flooding (comparison with community controls: OR, 4.52; 95% CI, 1.90-10.73; with fever controls: OR, 3.25; 95% CI, 1.31-8.02). By contrast, independent risk factors for typhoid fever using the community control group were mostly related to the household, ie, to recent typhoid fever in the household (OR, 2.38; 95% CI, 1.03-5.48); no use of soap for handwashing (OR, 1.91; 95% CI, 1.06-3.46); sharing food from the same plate (OR, 1.93; 95% CI, 1.10-3.37), and no toilet in the household (OR, 2.20; 95% CI, 1.06-4.55). Also, typhoid fever was associated with young age in years (OR, 0.96; 95% CI, 0.94-0.98). In comparison with fever controls, risk factors for typhoid fever were use of ice cubes (OR, 2.27; 95% CI, 1.31-3.93) and female sex (OR, 1.79; 95% CI, 1.04-3.06). Fecal contamination of drinking water was not associated with typhoid or paratyphoid fever. We did not detect fecal carriers among food handlers in the households. CONCLUSIONS: In Jakarta, typhoid and paratyphoid fever are associated with distinct routes of transmission, with the risk factors for disease either mainly within the household (typhoid) or outside the household (paratyphoid).

Meltzer E, Sadik C, Schwartz E. Enteric fever in Israeli travelers: a nationwide study. J Travel Med. 2005 Sep-Oct;12(5):275-81.

BACKGROUND: Enteric fever (EF) has become a travel-related disease in industrialized countries. The possible effects of vaccination on typhoid epidemiology in travelers are unknown. We compared the incidence and clinical and microbiologic findings in travelers returning with EF, according to pretravel vaccination status and vaccine type. METHODS: We performed a nationwide descriptive analysis of EF incidence in Israeli travelers; EF is a notified disease in Israel. Data from 1995 through 2003 were evaluated; all cases of EF acquired during recent travel (6 wk) were included. From 1995 to 1999, the Ty21a oral vaccine was used exclusively in Israel. It was replaced with the Vi vaccine from 2000 to 2003. Patients with pretravel typhoid vaccination were compared with unvaccinated patients, and according to vaccine type. RESULTS: Seventy-eight cases met our criteria. The causative agents were Salmonella typhi in 79.5% and Salmonella paratyphi A in 20.5%; 74.4% were acquired by travelers to the Indian Subcontinent. S. paratyphi A accounted for 10.5% of cases among Ty21a vaccinees as compared with 47.4% among Vi vaccinees ($p = .02$). For the Indian Subcontinent, the general attack rate of S. typhi and S. paratyphi A during the period of vaccination with Ty21a was 2.37 in 10,000 and 0.26 in 10,000 travelers, respectively, whereas during the period of vaccination with Vi, the attack rate was 1.40 in 10,000 and 0.79 in 10,000. There were no deaths; however, more complications and relapses occurred in the S. paratyphi A group. CONCLUSIONS: Among Israeli travelers S. typhi infection is declining whereas S. paratyphi A is increasing, with most cases occurring in vaccinated travelers. Prior typhoid

vaccination did not modify the course of the disease. *S. paratyphi A* infection in travelers is not milder than *S. typhi* infection. Although this is not a prospective, controlled, randomized trial, it appears that the Ty21a vaccine may be less effective for *S. typhi* but may offer some protection against *S. paratyphi A*. Sequential vaccination with the available oral and Vi vaccine may merit consideration. A more effective vaccine for *S. typhi* and *S. paratyphi A* is urgently needed.

Sur D, von Seidlein L, Manna B, Dutta S, Deb AK, Sarkar BL, Kanungo S, Deen JL, Ali M, Kim DR, Gupta VK, Ochiai RL, Tsuzuki A, Acosta CJ, Clemens JD, Bhattacharya SK. The malaria and typhoid fever burden in the slums of Kolkata, India: data from a prospective community-based study. *Trans R Soc Trop Med Hyg.* 2006 Aug;100(8):725-33.

Recent research has indicated that the malaria burden in Asia may have been vastly underestimated. We conducted a prospective community-based study in an impoverished urban site in Kolkata, India, to estimate the burden of malaria and typhoid fever and to identify risk factors for these diseases. In a population of 60452 people, 3605 fever episodes were detected over a 12-month period. The blood films of 93 febrile patients contained Plasmodium (90 *P. vivax*, 2 *P. falciparum* and 1 *P. malariae*). Blood cultures from 95 patients grew *Salmonella enterica* serotype Typhi. Malaria patients were found to be significantly older (mean age 29 years) compared with patients with typhoid fever (15 years; $P < 0.001$) but had similar clinical features on presentation. Having a household member with malaria, illiteracy, low household income and living in a structure not built of bricks were associated with an increased risk for malaria. Having a household member with typhoid fever and poor hygiene were associated with typhoid fever. A geographic analysis of the spatial distribution of malaria and typhoid fever cases detected high-risk neighbourhoods for each disease. Focal interventions to minimise human-vector contact and improved personal hygiene and targeted vaccination campaigns could help to prevent malaria and typhoid fever in this site.

Ram PK, Naheed A, Brooks WA, Hossain MA, Mintz ED, Breiman RF, Luby SP. Risk factors for typhoid fever in a slum in Dhaka, Bangladesh. *Epidemiol Infect.* 2007 Apr;135(3):458-65.

We systematically investigated risk factors for typhoid fever in Kamalapur, a poor urban area of Bangladesh, to inform targeted public health measures for its control. We interviewed patients with typhoid fever and two age-matched controls per case about exposures during the 14 days before the onset of illness. The municipal water supply was used by all 41 cases and 81 of 82 controls. In multivariate analysis, drinking unboiled water at home was a significant risk factor [adjusted odds ratio (aOR) 12.1, 95% CI 2.2-65.6]. Twenty-three (56%) cases and 21 (26%) controls reported that water from the primary source was foul-smelling (aOR 7.4, 95% CI 2.1-25.4). Eating papaya was associated with illness (aOR 5.2, 95% CI 1.2-22.2). Using a latrine for defecation was significantly protective (aOR 0.1, 95% CI 0.02-0.9). Improved chlorination of the municipal water supply or disinfecting drinking water at

the household level may dramatically reduce the risk of typhoid fever in Kamalapur. The protective effect of using latrines, particularly among young children, should be investigated further.

Microbiology/disease/drug resistance

Parry CM. The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Viet Nam. *Trans R Soc Trop Med Hyg.* 2004 Jul;98(7):413-22.

Multidrug-resistant (MDR) *Salmonella* Typhi (resistant to chloramphenicol, ampicillin, and trimethoprim-sulphamethoxazole) and isolates with reduced susceptibility to fluoroquinolones (indicated by resistance to nalidixic acid, NaR) have caused epidemics and become endemic in southern Viet Nam during the 1990s. Short courses of ofloxacin have proved acceptable for treating MDR/NaS isolates of *S. Typhi* (ofloxacin MIC₉₀ = 0.06 mg/l) causing uncomplicated disease. Ofloxacin (10-15 mg/kg/d) given for 2, 3, or 5 d cured >90% of patients with an average fever clearance time (FCT) of 4 d. Less than 3% of patients relapsed or had a positive post-treatment stool culture. In contrast, the response of NaR isolates (ofloxacin MIC₉₀ = 0.5 mg/l) to such regimens is poor. For example, ofloxacin (20 mg/kg/d) given for 7 d cured only 75% of patients, with an FCT of 7 d, and 19% of patients had positive post-treatment faecal cultures. Currently available alternatives for NaR infections include ceftriaxone, cefixime, and azithromycin. These antimicrobials are reasonably effective but expensive. New, effective, and affordable regimens are needed to treat these NaR infections. Short courses of the new generation fluoroquinolones or combinations of the available antimicrobials are possible options.

Chau TT, Campbell JI, Galindo CM, Van Minh Hoang N, Diep TS, Nga TT, Van Vinh Chau N, Tuan PQ, Page AL, Ochiai RL, Schultsz C, Wain J, Bhutta ZA, Parry CM, Bhattacharya SK, Dutta S, Agtini M, Dong B, Honghui Y, Anh DD, Canh do G, Naheed A, Albert MJ, Phetsouvanh R, Newton PN, Basnyat B, Arjyal A, La TT, Rang NN, Phuong le T, Van Be Bay P, von Seidlein L, Dougan G, Clemens JD, Vinh H, Hien TT, Chinh NT, Acosta CJ, Farrar J, Dolecek C. Antimicrobial drug resistance of *Salmonella enterica* serovar typhi in Asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. *Antimicrob Agents Chemother.* 2007 Dec;51(12):4315-23.

This study describes the pattern and extent of drug resistance in 1,774 strains of *Salmonella enterica* serovar Typhi isolated across Asia between 1993 and 2005 and characterizes the molecular mechanisms underlying the reduced susceptibilities to fluoroquinolones of these strains. For 1,393 serovar Typhi strains collected in southern Vietnam, the proportion of multidrug resistance has remained high since 1993 (50% in 2004) and there was a dramatic increase in nalidixic acid resistance between 1993 (4%) and 2005 (97%). In a cross-sectional sample of 381 serovar Typhi strains from 8 Asian countries, Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan, and central Vietnam, collected in 2002 to 2004, various rates of multidrug resistance (16 to

37%) and nalidixic acid resistance (5 to 51%) were found. The eight Asian countries involved in this study are home to approximately 80% of the world's typhoid fever cases. These results document the scale of drug resistance across Asia. The Ser83-->Phe substitution in GyrA was the predominant alteration in serovar Typhi strains from Vietnam (117/127 isolates; 92.1%). No mutations in gyrB, parC, or parE were detected in 55 of these strains. In vitro time-kill experiments showed a reduction in the efficacy of ofloxacin against strains harboring a single-amino-acid substitution at codon 83 or 87 of GyrA; this effect was more marked against a strain with a double substitution. The 8-methoxy fluoroquinolone gatifloxacin showed rapid killing of serovar Typhi harboring both the single- and double-amino-acid substitutions.

Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. Arch Dis Child. 1996 Sep;75(3):214-7

The risk factors for mortality were analysed in a consecutive group of 1158 children presenting to the Aga Khan University Medical Center, Karachi, with multidrug resistant typhoid fever that had been proved on culture. There were 19 deaths, representing an overall case fatality rate of 1.6%. Multidrug resistant typhoid was associated with a more severe clinical illness and higher rates of toxicity, hepatomegaly, hypotensive shock, and death. Irrespective of drug resistance status, typhoid fever was found to be a more severe illness in young infants with significantly higher rates of diarrhoea, hypotensive shock, and mortality. Univariate analysis of admission characteristics associated with increased risk for mortality revealed significant association with younger age ($p < 0.05$), hypotensive shock or hypothermia ($p < 0.001$), obtundation ($p < 0.001$), seizures ($p < 0.05$), anaemia at admission ($p < 0.005$), and leucocytosis ($p < 0.001$). Logistic regression analysis of risk factors for mortality showed persistent association of hypothermia, toxicity, and anaemia with mortality. The data provides evidence that multidrug resistant typhoid in childhood is associated with increased risk of mortality, especially in infancy and closer attention to several risk factors for increased morbidity and case fatality rates may lead to improved outcome of treatment.

Baker S, Sarwar Y, Aziz H, Haque A, Ali A, Dougan G, Wain J, Haque A. Detection of Vi-negative Salmonella enterica serovar typhi in the peripheral blood of patients with typhoid fever in the Faisalabad region of Pakistan. J Clin Microbiol. 2005 Sep;43(9):4418-25.

The synthesis and transportation proteins of the Vi capsular polysaccharide of Salmonella enterica serovar Typhi (serovar Typhi) are encoded by the *viaB* operon, which resides on a 134-kb pathogenicity island known as SPI-7. In recent years, Vi-negative strains of serovar Typhi have been reported in regions where typhoid fever is endemic. However, because Vi negativity can arise during in vitro passage, the clinical significance of Vi-negative serovar Typhi is not clear. To investigate the loss of Vi expression at the genetic level, 60 stored strains of serovar Typhi from the Faisalabad region of Pakistan were analyzed by PCR for the presence of SPI-7 and two genes essential for Vi production: *tviA* and *tviB*. Nine of the sixty strains analyzed (15%)

tested negative for both *tviA* and *tviB*; only two of these strains lacked SPI-7. In order to investigate whether this phenomenon occurred *in vivo*, blood samples from patients with the clinical symptoms of typhoid fever were also investigated. Of 48 blood samples tested, 42 tested positive by *fliC* PCR for serovar Typhi; 4 of these were negative for *tviA* and *tviB*. Three of these samples tested positive for SPI-7. These results demonstrate that *viaB*-negative, SPI-7-positive serovar Typhi is naturally occurring and can be detected by PCR in the peripheral blood of typhoid patients in this region. The method described here can be used to monitor the incidence of Vi-negative serovar Typhi in regions where the Vi vaccine is used.

Typhoid vaccines

Acharya IL, Lowe CU, Thapa R, Gurubacharya VL, Shrestha MB, Cadoz M, Schulz D, Armand J, Bryla DA, Trollfors B, et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella typhi*. A preliminary report. *N Engl J Med*. 1987 Oct 29;317(18):1101-4.

We conducted a pilot study followed by a large clinical trial in Nepal of the use of the capsular polysaccharide of *Salmonella typhi* (Vi) as a vaccine to prevent typhoid fever. In the pilot study, involving 274 Nepalese, there were no significant side effects of the Vi vaccine; about 75 percent responded with a rise in serum antibodies of fourfold or more. In the clinical trial, residents of five villages were given intramuscular injections of either Vi or, as a control, pneumococcus vaccine dispensed in coded, randomly arranged, single-dose syringes. There were 6907 participants, of whom 6438 were members of the target population (5 to 44 years of age); each was visited every two days. Those with temperatures of 37.8 degrees C or higher for three consecutive days were examined and asked to give blood for culture. Typhoid was diagnosed as either blood culture-positive or clinically suspected on the basis of bradycardia, splenomegaly, and fever, with a negative blood culture. Seventeen months after vaccination, the codes were broken for the 71 patients meeting the criteria for either culture-positive or clinically suspected typhoid. The attack rate of typhoid was 16.2 per 1000 among the controls and 4.1 per 1000 among those immunized with Vi (P less than 0.00001). The efficacy of Vi was 72 percent in the culture-positive cases, 80 percent in the clinically suspected cases, and 75 percent in the two groups combined. These data provide evidence that Vi antibodies confer protection against typhoid. Surveillance continues to determine the duration of Vi-induced immunity.

Klugman KP, Gilbertson IT, Koornhof HJ, Robbins JB, Schneerson R, Schulz D, Cadoz M, Armand J. Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. *Lancet*. 1987 Nov 21;2(8569):1165-9.

The protective efficacy against typhoid fever of a single intramuscular injection of 25 micrograms of the Vi capsular polysaccharide (CPS) was assessed in a randomised double-blind controlled trial. Vaccination of 11,384 children was followed by 21 months' surveillance. 47 blood-culture-proven cases of typhoid occurred in children

who received meningococcal A + C CPS vaccine and 19 cases in those vaccinated with Vi CPS. Protective efficacy was 60% calculated from the day of vaccination and 64% from 6 weeks after vaccination. Surveillance also included 11,691 unvaccinated children; 173 cases occurred in this group. Protective efficacy in relation to the unvaccinated group was 77.4% and 81.0% after 21 months, calculated immediately and 6 weeks after vaccination, respectively. Vaccination was associated with minimum local side-effects, and an increase in anti-Vi antibodies occurred, as measured by radioimmunoassay and enzyme-linked immunosorbent assay. Antibody levels remained significantly raised at 6 and 12 months post vaccination. Vi CPS is thus a safe and effective means of typhoid vaccination.

Levine MM, Ferreccio C, Black RE, Tacket CO, Germanier R. Progress in vaccines against typhoid fever. Rev Infect Dis. 1989 May-Jun;11 Suppl 3: S552-67.

The widely available heat-phenol-inactivated whole cell typhoid vaccine, which provides approximately 65% protection, has limited usefulness because of the adverse reactions it evokes. In contrast, several new typhoid vaccines promise protection without reactogenicity. Attenuated oral vaccine Ty21a has been evaluated in three field trials of efficacy in Santiago, Chile, involving 530,000 schoolchildren. Three doses of Ty21a in an enteric-coated formulation given within one week provided 69% efficacy for at least four years. Fewer doses conferred less protection, while adding a fourth dose significantly enhanced protection; increasing the interval between doses did not improve protection. Large-scale vaccination with Ty21a appeared to cause a herd-immunity effect. Ty21a has reached the stage of being a practical tool for public health. With respect to other vaccines, the safety and immunogenicity of an auxotrophic (Aro-,Pur-) *Salmonella typhi* mutant (strain 541Ty) has recently been evaluated. Lastly, parenteral purified Vi polysaccharide of *S. typhi* was safe and immunogenic and provided 64%-72% protection (for at least 17-21 months) in controlled field trials in Nepal and South Africa.

Black RE, Levine MM, Ferreccio C, Clements ML, Lanata C, Rooney J, Germanier R. Efficacy of one or two doses of Ty21a *Salmonella typhi* vaccine in enteric-coated capsules in a controlled field trial. Chilean Typhoid Committee. Vaccine. 1990 Feb;8(1):81-4.

Typhoid fever remains an important public health problem in many areas of the world and an effective, non-reactogenic vaccine would be useful to control this disease. An attenuated *Salmonella typhi* strain (Ty21a), which has shown promise in previous trials, was evaluated in a controlled field trial in Santiago, Chile. In this trial, 82,543 schoolchildren were randomly assigned to receive one or two doses of Ty21a vaccine in enteric-coated capsules or placebo. The enteric-coated vaccine formulation was well tolerated and practical for mass oral immunization. In the first two years of surveillance, 213 cases of bacteriologically-confirmed typhoid fever were found in schoolchildren participating in the trial; annual rates in the placebo group were 139 and 227 per 100,000. Vaccine efficacy in the first two years after vaccination was 59% for two doses and 29% for one dose; no efficacy was found 3-5 years after vaccination. These results indicate that it will be necessary to identify a vaccine

formulation and schedule for Ty21a *S. typhi* that is practical and provides high level protection for greater than 2 years.

Keddy KH, Klugman KP, Hansford CF, Blondeau C, Bouveret le Cam NN. Persistence of antibodies to the Salmonella typhi Vi capsular polysaccharide vaccine in South African school children ten years after immunization. Vaccine. 1999 Jan;17(2):110-3.

Between 10 and 11 years after children were vaccinated with Vi capsular polysaccharide of *Salmonella typhi* or meningococcal A + C control vaccine in a double blind randomized trial, we traced 83 subjects, aged 16-20 years. A blood sample was taken for determination of Vi antibody titres in both groups by radioimmunoassay. TO and TH titres were also done to assess if the participants had had recent exposure to typhoid fever. Fifty-eight percent of subjects in both groups had protective levels of Vi antibody against *Salmonella typhi* (a titre greater than 1 microgram ml⁻¹). There was no significant difference in the levels of Vi antibodies in the cases versus the controls ($p = 0.5$). Two of the children who had received meningococcal A + C vaccine had recently had typhoid fever. Our data show that adolescents in typhoid endemic areas have high levels of Vi antibodies regardless of previous vaccination status, suggesting that Vi antibodies are acquired in adolescence by a large percentage of the population in this area. Moreover, Vi vaccination has led to ongoing antibody production in greater than 50% of Vi vaccinated children in an endemic area for a period of 10 years. Ongoing antigenic exposure may have contributed to these antibody levels.

Klugman KP, Koornhof HJ, Robbins JB, Le Cam NN. Immunogenicity, efficacy and serological correlate of protection of Salmonella typhi Vi capsular polysaccharide vaccine three years after immunization. Vaccine. 1996 Apr;14(5):435-8.

The protective efficacy and immunogenicity of Vi capsular polysaccharide vaccine against typhoid fever was measured 3 years after its administration in a double-blind randomized trial. Vaccine efficacy was not significantly different during each year of the trial and was 55% (95% CI: 30-71%) over the 3 year period. In a case-control study at 3 years after vaccination, recipients of Vi had higher levels of Vi antibodies than controls, as measured by radio-immunoassay (GMT 1.28 vs 0.76 microgram ml⁻¹, $P = 0.0004$) and by passive haemagglutination assay (GMT 10.46 vs 3.52, $P = 0.0001$). The serological correlate of protection has been estimated using the relative risks of typhoid fever in the 2 groups and the relative ratio of antibody levels. The estimated protective level is 1 microgram ml⁻¹ suggesting that at a mean age of 9 years, 64% of vaccinates and 40% of controls had protective antibody against typhoid fever in this endemic area.

Tarr PE, Kuppens L, Jones TC, Ivanoff B, Aparin PG, Heymann DL. Considerations regarding mass vaccination against typhoid fever as an adjunct to

sanitation and public health measures: potential use in an epidemic in Tajikistan. Am J Trop Med Hyg. 1999 Jul;61(1):163-70.

We report on the ongoing epidemic of typhoid fever in Tajikistan that started in 1996. It has involved more than 24,000 cases to date, and is characterized by multiple point sources, overflow of sewage, contaminated municipal water, and person-to-person spread. Of the *Salmonella typhi* isolates available for testing in western laboratories, more than 90% are multidrug-resistant (MDR). Most recently, 28 (82%) of 34 isolates are resistant to ciprofloxacin, representing the first reported epidemic of quinolone-resistant typhoid fever. In the past, mass immunization during typhoid fever epidemics has been discouraged. A review of this policy is recommended in light of the alarming emergence of quinolone-resistant strains of *S. typhi*, the availability of improved vaccines, and the ongoing epidemic in Tajikistan. Mass immunization may be a useful measure for the control of prolonged MDR typhoid fever epidemics, as an adjunct to correction of municipal infrastructure and public health intervention.

Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. Impaired antibody response after immunization of HIV-infected individuals with the polysaccharide vaccine against *Salmonella typhi* (Typhim-Vi). Vaccine. 1999 Aug 6;17(23-24):2941-5.

Infections with *Salmonella* species, including *Salmonella typhi*, are more frequently observed in HIV-infected individuals than in healthy individuals. HIV-infected individuals were vaccinated with polysaccharide vaccine against *Salmonella typhi* (Typhim-Vi) which is assumed to be a T-cell-independent antigen. We found that the antibody response in patients with $< 200 \times 10^6/l$ CD4+ T lymphocytes was significantly lower compared with patients with $> \text{or} = 200 \times 10^6/l$ CD4+ T lymphocytes and healthy controls. The antibody response after vaccination with the polysaccharide salmonella Vi-antigen was correlated with the number of CD4+ T lymphocytes and therefore Typhim-Vi can be considered to be a T-cell-independent type 2 antigen. The results of this study indicate that after vaccination the proportion of HIV-infected individuals with protective antibody concentrations against *Salmonella typhi* will be lower than in healthy controls.

Hessel L, Debois H, Fletcher M, Dumas R. Experience with *Salmonella typhi* Vi capsular polysaccharide vaccine. Eur J Clin Microbiol Infect Dis. 1999 Sep;18(9):609-20.

Typhoid fever remains an important health threat in many parts of the world, with an estimated 16 million cases and 600,000 deaths occurring each year. The emergence of *Salmonella typhi* strains multiply resistant to antibiotics has complicated the treatment of this disease. Field experience of 8 years shows that a vaccine composed of purified Vi capsular polysaccharide of *Salmonella typhi*, given as a single intramuscular or deep subcutaneous injection, has consistent immunogenicity and efficacy. Side effects, based on reports since 1989, are infrequent and mild. Furthermore, the Vi vaccine may be administered simultaneously with other common "travel" vaccines, at two different sites of injection, without affecting immunogenicity and tolerability. This review

presents an update of the development and clinical experience with the Salmonella typhi Vi polysaccharide vaccine (Typhim Vi; Pasteur Mérieux Connaught, France).

Yang HH, Kilgore PE, Yang LH, Park JK, Pan YF, Kim Y, Lee YJ, Xu ZY, Clemens JD. An outbreak of typhoid fever, Xing-An County, People's Republic of China, 1999: estimation of the field effectiveness of Vi polysaccharide typhoid vaccine. J Infect Dis. 2001 Jun 15;183(12):1775-80.

To evaluate the effectiveness of Vi polysaccharide vaccine (Vi vaccine) in preventing typhoid fever, an analysis was done of an outbreak of typhoid fever among students attending a middle school in the People's Republic of China, where Vi vaccine is licensed for use. Vi vaccine effectiveness was analyzed by using Cox proportional hazards modeling to account for the time-dependent nature of vaccination and illness status during the outbreak. Among 1260 students who had been immunized before the outbreak, receipt of Vi vaccine was associated with 73% (95% confidence interval [CI], 32%-89%) protection. Among the additional 441 students immunized during the outbreak, receipt of Vi vaccine was associated with 71% (95% CI, -9% to 92%) protection. These results provide the first evidence about the effectiveness of Vi vaccine when deployed routinely in a typhoid-endemic area and support the use of Vi vaccine as a public health tool to control typhoid fever.

Yang HH, Wu CG, Xie GZ, Gu QW, Wang BR, Wang LY, Wang HF, Ding ZS, Yang Y, Tan WS, Wang WY, Wang XC, Qin M, Wang JH, Tang HA, Jiang XM, Li YH, Wang ML, Zhang SL, Li GL. Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. Bull World Health Organ. 2001;79(7):625-31.

OBJECTIVE: To test the efficacy of locally produced Vi vaccine over a time period of longer than one year. **METHODS:** A double-blinded, randomized field trial was performed in Guangxi Zhuang Autonomous Region in south-western China, using 30 micrograms doses of locally produced Vi. Enrolled subjects were 3-50 years of age, although the majority (92%) were school-aged children, who have the highest rate of typhoid fever in this setting. A total of 131,271 people were systematically allocated a single dose of 30 micrograms of Vi polysaccharide or saline placebo. The study population was followed for 19 months, with passive surveillance conducted in the Ministry of Health and the Regional Health and Anti-epidemic Centre (HAEC). Clinically suspected cases of typhoid fever were confirmed by blood culture, or by serological reaction with O-antigen (Widal tests). **FINDINGS:** After 19 months, there were 23 culture-confirmed cases of typhoid fever in the placebo group versus 7 cases in the Vi group (Protective efficacy (PE) = 69%; 95% CI = 28%, 87%). Most of the isolates were from school-aged children: 22 cases in the placebo group versus 6 in the Vi group (PE = 72%; 95% CI = 32%, 82%). No serious post-injection reactions were observed. The locally produced Vi polysaccharide vaccine showed levels of protective efficacy similar to those for Vi vaccine produced in industrial countries. **CONCLUSION:** The slightly higher dose of vaccine did not seem to alter efficacy.

Levine MM. Typhoid fever vaccines. In: Plotkin AS, Orenstein WA, editors. Vaccines. 4th edition. Philadelphia: W.B. Saunders Company; 2004, pp. 1057-1093. (No summary available).

Acosta CJ, Hong-Hui Y, Ning W, Qion G, Qun D, Xiaolei M, Baode Z, Liu W, Danovaro-Holliday MC, Ochiai RL, Wang XY, Kim DR, Zhi-Yi X, Bai-Qing D, Galindo CM, Clemens JD. Efficacy of a locally produced, Chinese Vi polysaccharide typhoid fever vaccine during six years of follow-up. *Vaccine*. 2005 Dec 1;23(48-49):5618-23.

A locally produced Vi polysaccharide vaccine against typhoid fever was licensed in China following two placebo-controlled, efficacy trials conducted in the early 1990s in Baoying, Jiangsu Province, and Quan-zhou, Guangxi Province. The two trials each enrolled over 80,000 participants and followed participants for 12 and 19 months post-vaccination, respectively. To define the long-term efficacy of this vaccine, we retrospectively assessed the occurrence of typhoid fever, diagnosed with clinical and serological criteria, in the two study populations for 6 years following vaccination. During the second year following vaccination, vaccine efficacy was 100% (95% CI: 17%, 100%) in Baoying and 85% (95% CI: 49%, 96%) in Quan-zhou. There was suggestive protection (51%; PE: -95%, 88%) during the third year in Baoying, nearly identical to the level observed in the third year of an earlier trial in South Africa. These results confirm that this vaccine protects for at least 2 years, and are consistent with the assertion that the vaccine protects for at least 3 years.

Zhou WZ, Koo HW, Wang XY, Zhang J, Park JK, Zhu F, Deen J, Acosta CJ, Chen Y, Wang H, Galindo CM, Ochiai L, Park T, von Seidlein L, Xu ZY, Clemens JD. Revaccination with locally-produced vi typhoid polysaccharide vaccine among chinese school-aged children: safety and immunogenicity findings. significantly in China. *Pediatr Infect Dis J*. 2007 Nov;26(11):1001-5.

OBJECTIVE: To evaluate the safety and immunogenicity of revaccination with locally-produced Vi polysaccharide vaccine 3 years after the first dose in Chinese children aged 9 to 14 years. **METHODS:** A randomized, placebo-controlled trial was conducted in Suzhou, Jiangsu, China. Six hundred and sixty-seven eligible children who had previously received a primary dose of Vi vaccine were randomly assigned to receive 1 dose of 30 mug Vi vaccine or placebo. In addition, 331 eligible children received 1 dose of Vi polysaccharide vaccine as a primary vaccination. Adverse events were followed for 28 days after vaccination. Serum samples were collected from a subgroup of participants on day 0 and day 28, and Vi antibodies were analyzed using a passive hemagglutination method. **RESULTS:** Revaccination was found to be safe and immunogenic. No severe adverse events were observed. A significant increase in antibody titers after vaccination was observed among children who had and had not been previously vaccinated. Twenty-eight days after injection, the seropositive rate was 79% in both revaccination and primary injection groups; the geometric mean antibody titer was 1:40 in the primary injection group and 1:29 in the revaccination

group ($P = 0.24$). Although the difference of attained geometric mean titers in follow-up sera was not significantly different in these 2 groups, the fold-rise of these titers from baseline was significantly higher in the primary injection group than in the revaccination group (7.7 versus 3.1, $P < 0.001$). **CONCLUSION:** We found that revaccination using the locally produced Vi polysaccharide vaccine among Chinese school-aged children was safe and increased antibody titers. Revaccination can be used to extend the duration of protection provided by Vi polysaccharide vaccine.

Levine MM, Ferreccio C, Black RE, Lagos R, San Martin O, Blackwelder WC. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by Salmonella enterica Serovar Paratyphi B. Clin Infect Dis. 2007 Jul 15;45 Suppl 1:S24-8.

In randomized, controlled field trials in Area Norte and Area Occidente of Santiago, Chile, 2 (Norte) or 3 (Occidente) doses of live oral typhoid vaccine Ty21a in enteric-coated capsules conferred protection against confirmed Salmonella enterica serovar Typhi disease (53% efficacy in Norte; 67% efficacy in Occidente) during 3 years of follow-up. There was also a trend in each trial showing protection against S. enterica serovar Paratyphi B disease (56% efficacy in Norte; 42% efficacy in Occidente). To enhance statistical power, an analysis was performed using pooled data from the 2 trials; this pooling of data was justified by the following facts: epidemiologic surveillance and microbiological methods were identical, the trials overlapped during 22 of the 36 months of follow-up in each trial, the estimates of efficacy against paratyphoid B fever in the 2 trials were roughly similar, and the ratio of follow-up of vaccine recipients to control subjects in both trials was ~1 : 1. In the pooled analysis, Ty21a conferred significant protection against paratyphoid B fever (efficacy, 49%; 95% confidence interval, 8%-73%; $P=0.019$).

Fraser A, Paul M, Goldberg E, Acosta CJ, Leibovici L. Typhoid fever vaccines: systematic review and meta-analysis of randomised controlled trials. Vaccine. 2007 Nov 7;25(45):7848-57.

We undertook a systematic review and meta-analysis of randomised controlled trials comparing a typhoid fever vaccine with any alternative typhoid fever vaccine or inactive agent. Trials evaluating killed whole-cell vaccines were excluded. The cumulative efficacy at 3 years for the Ty21a and the polysaccharide Vi vaccine were similar: 51% (95%CI 36%, 62%), and 55% (95%CI 30%, 70%), respectively. The cumulative efficacy of the Vi-rEPA vaccine at 3.8 years was higher, 89% (95%CI 76%, 97%), but this vaccine has not yet been licensed for use and was evaluated in only one trial. Adverse events were mild in nature and for most, not significantly more frequent in any of the vaccine groups when compared with placebo. Both the currently licensed Ty21a and Vi vaccine, are safe and efficacious for preventing typhoid fever. Neither vaccine is currently registered for administration to children below 2 years of age. Given the recent finding that typhoid fever also affects infants, development of a conjugate vaccine is warranted.

WHO documents

Background document: The diagnosis, treatment and prevention of typhoid fever. Communicable Diseases Surveillance and Response. Vaccines and Biologicals. World Health Organization. WHO/V&B/03.07