References for Typhoid Vaccines: WHO Position Paper, March 2018

Acharya VI et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of Salmonella typhi. A preliminary report. N Engl J Med. 1987;317:1101-1104.
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.

Als D et al. Global trends in typhoidal salmonellosis: A systematic review. (Submitted 2017).
No Abstract Available.

Antillon M et al. Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low- and middle-income settings. Vaccine. 2017;35:3506-3514.
Background: Typhoid fever remains endemic in low- and middle-income countries. Programmatic use of existing vaccines is limited, but upcoming typhoid conjugate vaccines (TCVs) could warrant wider use. We evaluated the cost-effectiveness of five TCV delivery strategies in three urban areas (Delhi and Kolkata, India and Nairobi, Kenya) and two rural settings (Lwak, Kenya and Dong Thap, Vietnam) with varying incidence. **Methods and findings:** We evaluated routine infant vaccination with and without catch-up campaigns among older individuals. We used a dynamic model of typhoid transmission to simulate cases, hospitalizations, deaths, disability-adjusted life-years (DALY) lost, treatment and intervention costs. We estimated cost-effectiveness (in terms of cost in international dollars (I$) per DALY averted) from the healthcare payer perspective, and assessed how it was influenced by uncertain model parameters. Compared to no vaccination, routine infant vaccination at I$1/dose was cost-saving in Delhi and Dong Thap, “very cost-effective” in Kolkata and Nairobi, and “cost-effective” in Lwak according to World Health Organization thresholds. However, routine vaccination was not the optimal strategy compared to strategies that included a catch-up campaign, which yielded the highest probability of being cost-saving in Delhi and Dong Thap and were most likely to provide a return on investment above a willingness-to-pay threshold of I$1440 in Kolkata, I$2300 in Nairobi, and I$5360 in Lwak. Vaccine price impacted the optimal strategy, and the number of doses required and rate of hospitalization were the primary sources of uncertainty. **Conclusion**: Routine vaccination with TCV would be cost-effective in most settings, and additional one-time catch-up campaigns would also be economically justified.

Arjyal A et al. Gatifloxcain versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial. Lancet Infect Dis. 2016;16:535-545.

Background: Because treatment with third-generation cephalosporins is associated with slow clinical improvement and high relapse burden for enteric fever, whereas the fluoroquinolone gatifloxacin is associated with rapid fever clearance and low relapse burden, we postulated that gatifloxacin would be superior to the cephalosporin ceftriaxone in treating enteric fever. **Methods :** We did an open-label, randomised, controlled, superiority trial at two hospitals in the Kathmandu valley, Nepal. Eligible participants were children (aged 2–13 years) and adult (aged 14–45 years) with criteria for suspected enteric fever (body temperature ⩾38 • 0° C for ⩾4 days without a focus of infection). We randomly assigned eligible patients (1:1) without stratification to 7 days of either oral gatifloxacin (10 mg/kg per day) or intravenous ceftriaxone (60 mg/kg up to 2 g per day for patients aged 2 – 13 years, or 2 g per day for patients aged ⩾14 years). The randomisation list was computer-generated using blocks of four and six. The primary outcome was a composite of treatment failure, defined as the occurrence of at least one of the following: fever clearance time of more than 7 days after treatment initiation; the need for rescue treatment on day 8; microbiological failure (ie, blood cultures positive for Salmonella enterica serotype Typhi, or Paratyphi A, B, or C) on day 8; or relapse or disease-related complications within 28 days of treatment initiation. We did the analyses in the modified intention-to-treat population, and subpopulations with either confirmed blood-culture positivity, or blood-culture negativity. The trial was powered to detect an increase of 20% in the risk of failure. This trial was registered at ClinicalTrials.gov , number NCT01421693 , and is now closed. **Findings:** Between Sept 18, 2011, and July 14, 2014, we screened 725 patients for eligibility. On July 14, 2014, the trial was stopped early by the data safety and monitoring board because S Typhi strains with high-level resistance to ciprofloxacin and gatifloxacin had emerged. At this point, 239 were in the modified intention-to-treat population (120 assigned to gatifloxacin, 119 to ceftriaxone). 18 (15%) patients who received gatifloxacin had treatment failure, compared with 19 (16%) who received ceftriaxone (hazard ratio [HR] 1·04 [95% CI 0·55–1·98]; p=0·91). In the culture-confirmed population, 16 (26%) of 62 patients who received gatifloxacin failed treatment, compared with four (7%) of 54 who received ceftriaxone (HR 0·24 [95% CI 0·08–0·73]; p=0·01). Treatment failure was associated with the emergence of S Typhi exhibiting resistance against fluoroquinolones, requiring the trial to be stopped. By contrast, in patients with a negative blood culture, only two (3%) of 58 who received gatifloxacin failed treatment versus 15 (23%) of 65 who received ceftriaxone (HR 7·50 [95% CI 1·71–32·80]; p=0·01). A similar number of non-serious adverse events occurred in each treatment group, and no serious events were reported. **Interpretation:** Our results suggest that fluoroquinolones should no longer be used for treatment of enteric fever in Nepal. Additionally, under our study conditions, ceftriaxone was suboptimum in a high proportion of patients with culture-negative enteric fever. Since antimicrobials, specifically fluoroquinolones, are one of the only routinely used control measures for enteric fever, the assessment of novel diagnostics, new treatment options, and use of existing vaccines and development of next-generation vaccines are now a high priority.

Azmatullah A et al. Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever. J Glob Health. 2015;5:020407.

Children suffer the highest burden of enteric fever among populations in South Asian countries. The clinical features are non–specific, vary in populations, and are often difficult to distinguish clinically from other febrile illnesses, leading to delayed or inappropriate diagnosis and treatment. We undertook a systematic review to assess the clinical profile and laboratory features of enteric fever across age groups, economic regions, level of care and antibiotic susceptibility patterns.

Baker S et al. Combined high-resolution genotyping and geospatial analysis reveals modes of endemic urban typhoid fever transmission. Open Biol. 2011;1:110008.

Typhoid is a systemic infection caused by Salmonella Typhi and Salmonella Paratyphi A, human-restricted bacteria that are transmitted faeco-orally. Salmonella Typhi and S. Paratyphi A are clonal, and their limited genetic diversity has precluded the identification of long-term transmission networks in areas with a high disease burden. To improve our understanding of typhoid transmission we have taken a novel approach, performing a longitudinal spatial case–control study for typhoid in Nepal, combining single-nucleotide polymorphism genotyping and case localization via global positioning. We show extensive clustering of typhoid occurring independent of population size and density. For the first time, we demonstrate an extensive range of genotypes existing within typhoid clusters, and even within individual households, including some resulting from clonal expansion. Furthermore, although the data provide evidence for direct human-to-human transmission, we demonstrate an overwhelming contribution of indirect transmission, potentially via contaminated water. Consistent with this, we detected S. Typhi and S. Paratyphi A in water supplies and found that typhoid was spatially associated with public water sources and low elevation. These findings have implications for typhoid-control strategies, and our innovative approach may be applied to other diseases caused by other monophyletic or emerging pathogens.

Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. Arch Dis Child. 1996;75:214–217.

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.

Breiman RF et al. Population-based incidence of typhoid fever in an urban informal settlement, Nairobi, Kenya: implications for typhoid vaccine use in Africa. PLoS One. 2012;7:e29119.

Background: High rates of typhoid fever in children in urban settings in Asia have led to focus on childhood immunization in Asian cities, but not in Africa, where data, mostly from rural areas, have shown low disease incidence. We set out to compare incidence of typhoid fever in a densely populated urban slum and a rural community in Kenya, hypothesizing higher rates in the urban area, given crowding and suboptimal access to safe water, sanitation and hygiene. **Methods**: During 2007-9, we conducted population-based surveillance in Kibera, an urban informal settlement in Nairobi, and in Lwak, a rural area in western Kenya. Participants had free access to study clinics; field workers visited their homes biweekly to collect information about acute illnesses. In clinic, blood cultures were processed from patients with fever or pneumonia. Crude and adjusted incidence rates were calculated. **Results**: In the urban site, the overall crude incidence of Salmonella enterica serovar Typhi (S. Typhi) bacteremia was 247 cases per 100,000 person-years of observation (pyo) with highest rates in children 5-9 years old (596 per 100,000 pyo) and 2-4 years old (521 per 100,000 pyo). Crude overall incidence in Lwak was 29 cases per 100,000 pyo with low rates in children 2-4 and 5-9 years old (28 and 18 cases per 100,000 pyo,

respectively). Adjusted incidence rates were highest in 2-4 year old urban children (2,243 per 100,000 pyo) which were >15-fold higher than rates in the rural site for the same age group. Nearly 75% of S. Typhi isolates were multi-drug resistant. **Conclusions**: This systematic urban slum and rural comparison showed dramatically higher typhoid incidence among urban children <10 years old with rates similar to those from Asian urban slums. The findings have potential policy implications for use of typhoid vaccines in increasingly urban Africa.

Britto C et al. An appraisal of the clinical features of pediatric enteric fever: systematic review and meta-analysis of the age-stratified disease occurrence. Clin Infect Dis. 2017;64:1604-1611.
Children bear a substantial proportion of the enteric fever disease burden in endemic areas. Controversy persists regarding which age groups are most affected, leading to uncertainty about optimal intervention strategies. We performed a systematic review and meta-analysis of studies in Asia and Africa to compare the relative proportion of children with enteric fever in the age groups <5 years, 5–9 years, and 10–14 years. Overall, studies conducted in Africa showed a relatively smaller occurrence of disease in the youngest age group, whereas in Asia the picture was more mixed with a very large degree of heterogeneity in estimates. The clinical features of enteric fever reviewed here differ between younger and older children and adults, likely leading to further uncertainty over disease burden. It is evident from our review that preschool children and infants also contribute a significant proportion of disease burden but have not been adequately targeted via vaccination programs, which have been focusing primarily on school-based vaccination campaigns.

Carias C. et al. Economic evaluation of typhoid vaccination in a prolonged typhoid outbreak setting: the case of Kasese district in Uganda. Vaccine 2015;33:2079-2085.
Background:Vaccination has been increasingly promoted to help control epidemic and endemic typhoid fever in high-incidence areas. Despite growing recognition that typhoid incidence in some areas of sub-Saharan Africa is similar to high-incidence areas of Asia, no large-scale typhoid vaccination campaigns have been conducted there. We performed an economic evaluation of a hypothetical one-time, fixed-post typhoid vaccination campaign in Kasese, a rural district in Uganda where a large, multi-year outbreak of typhoid fever has been reported. **Methods:** We used medical cost and epidemiological data retrieved on-site and campaign costs from previous fixed-post vaccination campaigns in Kasese to account for costs from a public sector health care delivery perspective. We calculated program costs and averted disability-adjusted life years (DALYs) and medical costs as a result of vaccination, to calculate the cost of the intervention per DALY and case averted. **Results:** Over the 3 years of projected vaccine efficacy, a one-time vaccination campaign was estimated to avert 1768 (90%CI: 684–4431) typhoid fever cases per year and a total of 3868 (90%CI: 1353–9807) DALYs over the duration of the immunity conferred by the vaccine. The cost of the intervention per DALY averted was US$ 484 (90%CI: 18–1292) and per case averted US$ 341 (90%CI: 13–883). **Conclusion:** We estimated the vaccination campaign in this setting to be highly cost-effective, according to WHO's cost-effective guidelines. Results may be applicable to other African settings with similar high disease incidence estimates.

Carles G et al. Typhoid fever and pregnancy. J Gynecol Obstet Biol Reprod. 2002;31:495–499.
Typhoid fever is rare in Europe, but well-recognized endemic disease in tropical zones. We report our findings in a series of 25 cases of typhoid fever during pregnancy observed in French Guiana and reviewed the literature on clinical signs, diagnosis and treatment. Salmonellea typhi causes septicemia of digestive origin that can cross the placenta resulting in chorioamniotitis. Maternal-fetal infection with S. typhi can lead to miscarriage, fetal death, neonatal infection, as well as diverse maternal complications. In order to avoid maternal complications and possible fetal transmission, treatment with ceftriaxone should be initiated as early as possible.

Cook J. et al. The cost-effectiveness of typhoid Vi vaccination programs: calculations for four urban sites in four Asian countries. Vaccine. 2008;26:6305-6316.
The burden of typhoid fever remains high in impoverished settings, and increasing antibiotic resistance is making treatment costly. One strategy for reducing the typhoid morbidity and mortality is vaccination with the Vi polysaccharide vaccine. We use a wealth of new economic and epidemiological data to evaluate the cost-effectiveness of Vi vaccination against typhoid in sites in four Asian cities: Kolkata (India), Karachi (Pakistan), North Jakarta (Indonesia), and Hue (Vietnam). We report results from both a societal as well as a public sector financial perspective. Baseline disease burden estimates in the four areas are: 750 cases per year in two Kolkata neighborhoods (pop 185,000); 84 cases per year in the city of Hue (pop 280,000); 298 cases per year in two sub-districts in North Jakarta (pop 161,000), and 538 cases per year in three squatter settlements in Karachi (pop 102,000). We estimate that a vaccination program targeting all children (2–14.9) would prevent 456, 158, and 258 typhoid cases (and 4.6, 1.6, and 2.6 deaths), and avert 126, 44, and 72 disability-adjusted life years (DALYs) over 3 years in Kolkata, North Jakarta and Karachi, respectively. The net social costs would be US$160 and US$549, per DALY averted in Kolkata and North Jakarta, respectively. These programs, along with a similar program in Karachi, would be considered “very cost-effective” (e.g. costs per DALY averted less than per capita gross national income (GNI)) under a wide range of assumptions. Community-based vaccination programs that also target adults in Kolkata and Jakarta are less cost-effective because incidence is lower in adults than children, but are also likely to be “very cost-effective”. A program targeting school-aged children in Hue, Vietnam would prevent 21 cases, avert 6 DALYs, and not be cost-effective (US$3779 per DALY averted) because of the low typhoid incidence there.

Crump JA et al. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance and antimicrobial management of invasive Salmonella infections. Clin Microbiol Rev. 2015;28:901-937.
Summary> Salmonella enterica infections are common causes of bloodstream infection in low-resource areas, where they may be difficult to distinguish from other febrile illnesses and may be associated with a high case fatality ratio. Microbiologic culture of blood or bone marrow remains the mainstay of laboratory diagnosis. Antimicrobial resistance has emerged in Salmonella enterica, initially to the traditional first-line drugs chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. Decreased fluoroquinolone susceptibility and then fluoroquinolone resistance have developed in association with chromosomal mutations in the quinolone resistance-determining region of genes encoding DNA gyrase and topoisomerase IV and also by plasmid-mediated resistance mechanisms. Resistance to extended-spectrum cephalosporins has occurred more often in nontyphoidal than in typhoidal Salmonella strains. Azithromycin is effective for the management of uncomplicated typhoid fever and may serve as an alternative oral drug in areas where fluoroquinolone resistance is common. In 2013, CLSI lowered the ciprofloxacin susceptibility breakpoints to account for accumulating clinical, microbiologic, and pharmacokinetic-pharmacodynamic data suggesting that revision was needed for contemporary invasive Salmonella infections. Newly established CLSI guidelines for azithromycin and Salmonella enterica serovar Typhi were published in CLSI document M100 in 2015.

Darton TC et al. 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 Negl Trop Dis. 2016;10:e0004926.
Typhoid persists as a major cause of global morbidity. While several licensed vaccines to prevent typhoid are available, they are of only moderate efficacy and unsuitable for use in children less than two years of age. Development of new efficacious vaccines is complicated by the human host-restriction of Salmonella enterica serovar Typhi (S. Typhi) and lack of clear correlates of protection. In this study, we

aimed to evaluate the protective efficacy of a single dose of the oral vaccine candidate, M01ZH09, in susceptible volunteers by direct typhoid challenge.We performed a randomised, double-blind, placebo-controlled trial in healthy adult participants at a single centre in Oxford (UK). Participants were allocated to receive one dose of double-blinded M01ZH09 or placebo or 3-doses of open-label Ty21a. Twenty-eight days after vaccination, participants were challenged with 104CFU S. Typhi Quailes strain. The efficacy of M01ZH09 compared with placebo (primary outcome) was assessed as the percentage of participants reaching pre-defined endpoints constituting typhoid diagnosis (fever and/or bacteraemia) during the 14 days after challenge. Ninety-nine participants were randomised to receive M01ZH09 (n = 33), placebo (n = 33) or 3-doses of Ty21a (n = 33). After challenge, typhoid was diagnosed in 18/31 (58.1% [95% CI 39.1 to 75.5]) M01ZH09, 20/30 (66.7% [47.2 to 87.2]) placebo, and 13/30 (43.3% [25.5 to 62.6]) Ty21a vaccine recipients. Vaccine efficacy (VE) for one dose of M01ZH09 was 13% [95% CI -29 to 41] and 35% [-5 to 60] for 3-doses of Ty21a. Retrospective multivariable analyses demonstrated that pre-existing anti-Vi antibody significantly reduced susceptibility to infection after challenge; a 1 log increase in anti-Vi IgG resulting in a 71% decrease in the hazard ratio of typhoid diagnosis ([95% CI 30 to 88%], p = 0.006) during the 14 day challenge period. Limitations to the study included the requirement to limit the challenge period prior to treatment to 2 weeks, the intensity of the study procedures and the high challenge dose used resulting in a stringent model.Despite successfully demonstrating the use of a human challenge study to directly evaluate vaccine efficacy, a single-dose M01ZH09 failed to demonstrate significant protection after challenge with virulent Salmonella Typhi in this model. Anti-Vi antibody detected prior to vaccination played a major role in outcome after challenge.ClinicalTrials.gov (NCT01405521) and EudraCT (number 2011-000381-35).

Feasey NA et al. Rapid emergence of multidrug resistant, H58 lineage Salmonella Typhi in Blantyre, Malawi. PLoS Negl Trop Dis. 2015 ;9:e0003748.

Between 1998 and 2010, S. Typhi was an uncommon cause of bloodstream infection (BSI) in Blantyre, Malawi and it was usually susceptible to first-line antimicrobial therapy. In 2011 an increase in a multidrug resistant (MDR) strain was detected through routine bacteriological surveillance conducted at Queen Elizabeth Central Hospital (QECH).Longitudinal trends in culture-confirmed Typhoid admissions at QECH were described between 1998-2014. A retrospective review of patient cases notes was conducted, focusing on clinical presentation, prevalence of HIV and case-fatality. Isolates of S. Typhi were sequenced and the phylogeny of Typhoid in Blantyre was reconstructed and placed in a global context.Between 1998-2010, there were a mean of 14 microbiological diagnoses of Typhoid/year at QECH, of which 6.8% were MDR. This increased to 67 in 2011 and 782 in 2014 at which time 97% were MDR. The disease predominantly affected children and young adults (median age 11 [IQR 6-21] in 2014). The prevalence of HIV in adult patients was 16.7% [8/48], similar to that of the general population (17.8%). Overall, the case fatality rate was 2.5% (3/94). Complications included anaemia, myocarditis, pneumonia and intestinal perforation. 112 isolates were sequenced and the phylogeny demonstrated the introduction and clonal expansion of the H58 lineage of S. Typhi.Since 2011, there has been a rapid increase in the incidence of multidrug resistant, H58-lineage Typhoid in Blantyre. This is one of a number of reports of the re-emergence of Typhoid in Southern and Eastern Africa. There is an urgent need to understand the reservoirs and transmission of disease and how to arrest this regional increase.

Froeschle JE et al. Duration of Vi antibodies in participants vaccinated with Typhim Vi (Typhoid Vi polysaccharide vaccine) in an area not endemic for typhoid fever. Vaccine. 2009;28:1451-1453.

After a single injection of Typhim Vi® (typhoid Vi polysaccharide vaccine), serum antibody concentrations were monitored for 3 years in 37 adults who resided where typhoid fever was not endemic. Anti-Vi antibody concentrations declined progressively during the study, to levels that support the current US recommendation for revaccination every 2 years.

Gaind et al. Molecular characterization of ciprofloxacin-resistant Salmonella enterica serovar Typhi and Paratyphi A causing enteric fever in India. J Antimicrob Chemother. 2006;58:1139–1144.
Objectives: To define the genetic characteristics and resistance mechanisms of clinical isolates of Salmonella enterica serovar Typhi (S. Typhi) and S. enterica serovar Paratyphi A (S. Paratyphi A) exhibiting high-level fluoroquinolones resistance. **Methods**: Three S. Typhi and two S. Paratyphi A ciprofloxacin-resistant isolates (MICs > 4 mg/L) were compared with isolates with reduced susceptibility to ciprofloxacin (MICs 0.125–1 mg/L) by PFGE, plasmid analysis, presence of integrons and nucleotide changes in topoisomerase genes. **Results**: In S. Typhi and Paratyphi A, a single gyrA mutation (Ser-83→Phe or Ser-83→Tyr) was associated with reduced susceptibility to ciprofloxacin (MICs 0.125 – 1 mg/L); an additional mutation in parC (Ser-80→Ile, Ser-80→Arg, Asp-69→Glu or Gly-78→Asp) was accompanied by an increase in ciprofloxacin MIC (≥ 0.5 mg/L). Three mutations conferred ciprofloxacin resistance: two in gyrA (Ser-83→Phe and Asp-87→Asn or Asp-87→Gly) and one in parC. This is the first report of parC mutations in S. Typhi. Ciprofloxacin-resistant S. Typhi and S. Paratyphi A differed in their MICs and mutations in gyrA and parC. Moreover S. Typhi harboured a 50 kb transferable plasmid carrying a class 1 integron (dfrA15/aadA1) that confers resistance to co-trimoxazole and tetracycline but not to ciprofloxacin. PFGE revealed undistinguishable XbaI fragment patterns in ciprofloxacin-resistant S. Typhi as well as in S. Paratyphi A isolates and showed that ciprofloxacin-resistant S. Typhi have emerged from a clonally related isolate with reduced susceptibility to ciprofloxacin after sequential acquisition of a second mutation in gyrA. **Conclusions**: To our knowledge this is the first report of molecular characterization of S. Typhi with full resistance to ciprofloxacin. Notably, the presence of a plasmid-borne integron in ciprofloxacin-resistant S. Typhi may lead to a situation of untreatable enteric fever.

Gilman RH et al. Evaluation of a UDP-glucose-4-epimeraseless mutant of Salmonella typhi as a live oral vaccine. J Infect Dis. 1977;136:717-723.
A mutant (Ty21a) of Salmonella typhi, which lacks the enzyme uridine 5'-diphosphate-glucose-4-epimerase, was evaluated in volunteers for use as a live attenuated oral typhoid vaccine. Five to eight doses of vaccine (containing 3-10(10) viable organisms per dose) were given to 155 men without significant side effects. The rate of excretion of the vaccine strain in stools was low, and the majority of isolations occurred on day 1 after vaccination. Revertants able to fement galactose were not found in any of 958 stool isolates tested. The mutant, strain Ty21a, grown in brain-heart infusion broth (BHIB) with 0.1% galactose, produces more O side chain than the same vaccine strain cultivated without galactose. Volunteers vaccinated with strain Ty21a grown in galactose and then challenged with 10(5) virulen S. typhi were significantly protected from disease and also had decreased stool carriage of S. typhi as compared with controls. Strain Ty21a grown without galactose did not provide vaccinees significant protection nor decrease fecal excretion of S. typhi as compared with controls. Strain Ty21a, when grown in BHIB with 0.1% galactose, results in a safe, stable and protective oral vaccine that warrants further study in field trials.

Gonzalez-Escobedo G et al. Chronic and acute infection of the gall bladder by Salmonella Typhi: understanding the carrier state. Nat Rev Microbiol. 2011;9:9-14.
Despite major treatment and prevention efforts, millions of new typhoid infections occur worldwide each year. For a subset of infected individuals, Salmonella enterica subsp. enterica serovar Typhi colonizes the gall bladder and remains there long after symptoms subside, serving as a reservoir for the further spread of the disease. In this Progress article, we explore recent advances in our understanding of the mechanisms by which Salmonella spp. — predominantly S. Typhi — colonize and persist in the human gall bladder.

International Typhoid Consortium et al. Molecular surveillance identifies multiple transmissions of typhoid in West Africa. PLoS Negl Trop Dis. 2016;10:e0004781.

The burden of typhoid in sub-Saharan African (SSA) countries has been difficult to estimate, in part, due to suboptimal laboratory diagnostics. However, surveillance blood cultures at two sites in Nigeria have identified typhoid associated with Salmonella enterica serovar Typhi (S. Typhi) as an important cause of bacteremia in children.A total of 128 S. Typhi isolates from these studies in Nigeria were whole-genome sequenced, and the resulting data was used to place these Nigerian isolates into a worldwide context based on their phylogeny and carriage of molecular determinants of antibiotic resistance.Several distinct S. Typhi genotypes were identified in Nigeria that were related to other clusters of S. Typhi isolates from north, west and central regions of Africa. The rapidly expanding S. Typhi clade 4.3.1 (H58) previously associated with multiple antimicrobial resistances in Asia and in east, central and southern Africa, was not detected in this study. However, antimicrobial resistance was common amongst the Nigerian isolates and was associated with several plasmids, including the IncHI1 plasmid commonly associated with S. Typhi.These data indicate that typhoid in Nigeria was established through multiple independent introductions into the country, with evidence of regional spread. MDR typhoid appears to be evolving independently of the haplotype H58 found in other typhoid endemic countries. This study highlights an urgent need for routine surveillance to monitor the epidemiology of typhoid and evolution of antimicrobial resistance within the bacterial population as a means to facilitate public health interventions to reduce the substantial morbidity and mortality of typhoid.

Jin C et al. 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. Lancet. 2017;390:2472–2480.

Background: Salmonella enterica serovar Typhi (S Typhi) is responsible for an estimated 20 million infections and 200 000 deaths each year in resource poor regions of the world. Capsular Vi-polysaccharide-protein conjugate vaccines (Vi-conjugate vaccines) are immunogenic and can be used from infancy but there are no efficacy data for the leading candidate vaccine being considered for widespread use. To address this knowledge gap, we assessed the efficacy of a Vi-tetanus toxoid conjugate vaccine using an established human infection model of S Typhi. **Methods:** In this single-centre, randomised controlled, phase 2b study, using an established outpatient-based human typhoid infection model, we recruited healthy adult volunteers aged between 18 and 60 years, with no previous history of typhoid vaccination, infection, or prolonged residency in a typhoid-endemic region. Participants were randomly assigned (1:1:1) to receive a single dose of Vi-conjugate (Vi-TT), Vi-polysaccharide (Vi-PS), or control meningococcal vaccine with a computer-generated randomisation schedule (block size 6). Investigators and participants were masked to treatment allocation, and an unmasked team of nurses administered the vaccines. Following oral ingestion of S Typhi, participants were assessed with daily blood culture over a 2-week period and diagnosed with typhoid infection when meeting pre-defined criteria. The primary endpoint was the proportion of participants diagnosed with typhoid infection (ie, attack rate), defined as persistent fever of 38°C or higher for 12 h or longer or S Typhi bacteraemia, following oral challenge administered 1 month after Vi-vaccination (Vi-TT or Vi-PS) compared with control vaccination. Analysis was per protocol. This trial is registered with ClinicalTrials.gov , number NCT02324751 , and is ongoing. **Findings**: Between Aug 18, 2015, and Nov 4, 2016, 112 participants were enrolled and randomly assigned; 34 to the control group, 37 to the Vi-PS group, and 41 to the Vi-TT group. 103 participants completed challenge (31 in the control group, 35 in the Vi-PS group, and 37 in the Vi-TT group) and were included in the per-protocol population. The composite criteria for typhoid diagnosis was met in 24 (77%) of 31 participants in the control group, 13 (35%) of 37 participants in the Vi-TT group, and 13 (35%) of 35 participants in the Vi-PS group to give

vaccine efficacies of 54·6% (95% CI 26·8–71·8) for Vi-TT and 52·0% (23·2–70·0) for Vi-PS. Seroconversion was 100% in Vi-TT and 88·6% in Vi-PS participants, with significantly higher geometric mean titres detected 1-month post-vaccination in Vi-TT vaccinees. Four serious adverse events were reported during the conduct of the study, none of which were related to vaccination (one in the Vi-TT group and three in the Vi-PS group). **Interpretation** : Vi-TT is a highly immunogenic vaccine that significantly reduces typhoid fever cases when assessed using a stringent controlled model of typhoid infection. Vi-TT use has the potential to reduce both the burden of typhoid fever and associated health inequality.

Kantele A. Antibody-secreting cells in the evaluation of the immunogenicity of an oral vaccine. Vaccine. 1990;8:321-326.
The immune response to different dosage schedules of oral live Salmonella typhi Ty21a vaccines was studied by enumeration of specific antibody-secreting cells (ASC) in the peripheral blood believed to have been stimulated by the vaccine antigen on mucosal surfaces and to be on their way back to those sites for local antibody secretion. Four groups of subjects were vaccinated with either three (3 × S), two (2 × S) or one (1 × S) dose of a suspension-formulated vaccine, or with three doses of vaccine in enteric-coated capsules (3 × E). The ASC-responses were highest in group 3 × S, followed by 3 × E, 2 × S and 1 × S, in this order. These differences parallel differences in protection from disease as observed in field trails with these regimens. This assay might therefore be useful for presumptive assessment of the protective ability of new vaccines or vaccine regimens. It certainly can be used to measure the immunogenicity of an oral vaccine.

Kariuki S et al. Typhoid in Kenya is associated with a dominant multidrug-resistant salmonella enterica serovar typhi haplotype that is also widespread in Southeast Asia. J Clin Microbiol. 2010;48:2171–2176.
In sub-Saharan Africa, the burden of typhoid fever, caused by Salmonella enterica serovar Typhi, remains largely unknown, in part because of a lack of blood or bone marrow culture facilities. We characterized a total of 323 S. Typhi isolates from outbreaks in Kenya over the period 1988 to 2008 for antimicrobial susceptibilities and phylogenetic relationships using single-nucleotide polymorphism (SNP) analysis. There was a dramatic increase in the number and percentage of multidrug-resistant (MDR) S. Typhi isolates over the study period. Overall, only 54 (16.7%) S. Typhi isolates were fully sensitive, while the majority, 195 (60.4%), were multiply resistant to most commonly available drugs—ampicillin, chloramphenicol, tetracycline, and cotrimoxazole; 74 (22.9%) isolates were resistant to a single antimicrobial, usually ampicillin, cotrimoxazole, or tetracycline. Resistance to these antibiotics was encoded on self-transferrable IncHI1 plasmids of the ST6 sequence type. Of the 94 representative S. Typhi isolates selected for genome-wide haplotype analysis, sensitive isolates fell into several phylogenetically different groups, whereas MDR isolates all belonged to a single haplotype, H58, associated with MDR and decreased ciprofloxacin susceptibility, which is also dominant in many parts of Southeast Asia. Derivatives of the same S. Typhi lineage, H58, are responsible for multidrug resistance in Kenya and parts of Southeast Asia, suggesting intercontinental spread of a single MDR clone. Given the emergence of this aggressive MDR haplotype, careful selection and monitoring of antibiotic usage will be required in Kenya, and potentially other regions of sub-Saharan Africa.

Keddy KH et al. Fluoroquinolone-resistant typhoid, South Africa. Emerg Infect Dis. 2010;16:879-880.
No Abstract Available.

Keddy KH et al. Persistence of antibodies to Salmonella typhi Vi capsular polysaccharide vaccine in South African school children ten years after immunization. Vaccine. 1999;17:110–113.

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 μg 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.

Keitel WA et al. Clinical and serological responses following primary and booster immunization with Salmonella typhi Vi capsular polysaccharide vaccines. Vaccine. 1994;12:195-199.

Clinical and serum antibody responses following intramuscular injection of two formulations of Salmonella typhi Vi capsular polysaccharide (Vi) were assessed in a double-blind evaluation. Healthy adults were randomly assigned to receive a 25 micrograms dose of liquid (Vi-Liq; n = 182) or freeze-dried Vi vaccine (Vi-Lyoph; n = 55), or placebo (n = 86). Erythema and/or induration > or = 1 cm in diameter at the injection site developed in 13/182 (7%) of Vi-Liq and 3/55 (5%) of Vi-Lyoph recipients (not significant, n.s.). Fever (oral temperature > or = 100 degrees F (37.8 degrees C)) occurred in < 2% of vaccinees. The frequencies of rises of fourfold or greater and of maximal Vi antibody levels were similar in the two vaccine groups. Fourfold or greater rises in serum Vi antibody levels (RIA) developed in 53% of Vi-Lyoph and 60% of Vi-Liq recipients by 1 week (n.s.), and 98 and 93%, respectively, by 1 month (n.s.). The frequencies of adverse reactions and mean Vi antibody levels following booster immunization with Vi-Liq 27 to 34 months after primary immunization (n = 55) were similar to those observed following primary immunization, although subjects given a booster dose were more likely to develop local reactions > or = 1 cm in diameter than those given a first dose (10/55 versus 13/182, p = 0.013 by the chi 2 test). Primary and booster immunizations with the Vi vaccines are well tolerated in healthy adults; mean Vi antibody levels remain significantly elevated for up to 34 months after primary immunization.

Khan MI et al. Effectiveness of Vi capsular polysaccharide typhoid vaccine among children: a cluster randomized trial in Karachi, Pakistan. Vaccine. 2012;30:5389-5395.

Abstract

BACKGROUND:

Typhoid fever is endemic in Karachi, with an incidence among children ranging from 170 to 450 per 100,000 child-years. Vaccination strategies are important for prevention, and the Vi capsular polysaccharide (ViCPS) vaccine has been shown to be effective in reducing the burden of typhoid fever.

METHODS:

A cluster randomized trial was conducted in three low socioeconomic urban squatter settlements in Karachi, Pakistan between 2002 and 2007. Subsamples were followed up for assessment of immune response and adverse events after vaccination.

RESULTS:

The study participants were similar in a wide variety of socio-demographic and economic characteristics at baseline. A total of 27,231 individuals of the total target population of 51,965 in 120 clusters either

received a ViCPS vaccine (13,238 [52% coverage]) or the control Hepatitis A vaccine (13,993 [53%]). Typhoid fever was diagnosed in 30 ViCPS vaccine recipients and 49 Hepatitis A vaccine recipients with an adjusted total protective effectiveness of 31% (95%CI: -28%, 63%). The adjusted total vaccine protective effectiveness was -38% (95%CI: -192%, 35%) for children aged 2-5 years and 57% (95%CI: 6%, 81%) for children 5-16 years old.

CONCLUSION:
The ViCPS vaccine did not confer statistically significant protection to children in the study areas, and there was a decline in antibody response 2 years post-vaccination. However, the ViCPS vaccine showed significant total protection in children 5-16 years of age, which is consistent with other studies of ViCPS vaccine conducted in India, Nepal, China and South Africa. These findings suggest that ViCPS vaccination of school-aged children will protect the children of urban, typhoid endemic areas against typhoid fever.

Klugman K et al. Protective activity of Vi polysaccharide vaccine against typhoid fever. Lancet. 1987;2:1165-1169.

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.

Koshiol J et al. Salmonella enterica serovar Typhi and gallbladder cancer: a case–control study and meta-analysis. Cancer Med. 2016;5:3310–3325.

In Chile, where gallbladder cancer (GBC) rates are high and typhoid fever was endemic until the 1990s, we evaluated the association between Salmonella enterica serovar Typhi (S. Typhi) antibodies and GBC. We tested 39 GBC cases, 40 gallstone controls, and 39 population-based controls for S. Typhi Vi antibodies and performed culture and quantitative polymerase chain reaction for the subset with bile, gallstone, tissue, and stool samples available. We calculated gender and education-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association with GBC. We also conducted a meta-analysis of >1000 GBC cases by combining our results with previous studies. GBC cases were more likely to have high Vi antibody titer levels than combined controls (OR: 4.0, 95% CI: 0.9–18.3), although S. Typhi was not recovered from bile, gallstone, tissue, or stool samples. In our meta-analysis, the summary relative risk was 4.6 (95% CI: 3.1–6.8, Pheterogeneity=0.6) for anti-Vi and 5.0 (95% CI: 2.7–9.3, Pheterogeneity = 0.2) for bile or stool culture. Our results are consistent with the meta-analysis. Despite differences in study methods (e.g., S. Typhi detection assay), most studies found a positive association between S. Typhi and GBC. However, the mechanism underlying this association requires further investigation

Kroon FP et al. Impaired antibody response after immunization of HIV-infected individuals with the polysaccharide vaccine against Salmonella typhi (Typhim-Vi). Vaccine. 1999;17:2941–2945.

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 <200×106/l CD4+ T lymphocytes was significantly lower compared with patients with ⩾200×106/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.

Levine MM. Chapter 61: Typhoid fever vaccines. In: Plotkin's Vaccines, 2017;Seventh Edition:1114–1144.
No abstract available.

Levine MM et al. Duration of efficacy of Ty21a, attenuated salmonella typhi live oral vaccine. Vaccine. 1999;17:S22-S27.
Currently, two different formulations of Ty21a live oral typhoid vaccine are commercialized. The enteric-coated capsule formulation was licensed based on results of three years of follow-up of a randomized, placebo-controlled, double-blind field trial in Area Occidente, Santiago, Chile, which demonstrated that three doses of this formulation, given on an every other day immunization schedule, conferred the best protection among several options evaluated. Subsequently, a liquid formulation (lyophilized vaccine organisms reconstituted with buffer and water into a vaccine cocktail) was commercialized after it was shown to provide superior protection than enteric-coated capsules over three years of follow-up in a randomized, placebo-controlled field trial in Area Sur Oriente and Area Norte, Santiago. Surveillance in the Area Occidente trial was continued for four additional years (i.e., total seven years of follow-up) and in the Area Sur Oriente/Area Norte trial for two additional years (i.e., a total of five years of follow-up). These additional surveillance data, which were analyzed to ascertain the longevity of protection conferred by these formulations of Ty21a, revealed that three doses of Ty21a in enteric-coated capsules (every other day schedule) conferred 67% protection over three years and 62% protection over seven years of follow-up, whereas three doses of liquid formulation (every other day schedule) elicited 77% protection over three years and 78% over five years of follow-up. Based on its excellent clinical acceptability, ease of oral administration, proven practicality in school-based mass immunization, and long-term efficacy enduring at least seven years, it is proposed that school-based immunization with Ty21a be utilized as a control measure in areas where the incidence of typhoid fever is high and Salmonella typhi are antibiotic-resistant.

Levine MM et al. Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. Lancet. 1987;1:1049-1052.
Three doses, given within one week, of Ty21a attenuated Salmonella typhi oral vaccine in an enteric-coated formulation provided 67% efficacy for at least 3 years in a randomised, placebo-controlled field trial involving 109,000 schoolchildren in Santiago, Chile. Increasing the interval between doses to twenty-one days did not enhance protection. Significantly less protection followed administration of vaccine in gelatin capsules with sodium bicarbonate. Ty21a provides the same level of protection as the heat/phenol-inactivated whole cell parenteral vaccine but differs in not causing adverse reactions. Ty21a may now be regarded as a practical public health tool.

Levine MM et al. Progress in vaccines against typhoid fever. Rev Infect Dis 1989;11:S552-S567.
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.

Levine MM et al. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by Salmonella enterica Serovar Paratyphi B. Clin Infect Dis. 2007;45:S24-S28.

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 = .019).

Lin FYC et al. The efficacy of a Salmonella Typhi Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med. 2001;344:1263-9.

Background: Typhoid fever is common in developing countries. The licensed typhoid vaccines confer only about 70 percent immunity, do not protect young children, and are not used for routine vaccination. A newly devised conjugate of the capsular polysaccharide of Salmonella typhi, Vi, bound to nontoxic recombinant Pseudomonas aeruginosa exotoxin A (rEPA), has enhanced immunogenicity in adults and in children 5 to 14 years old and has elicited a booster response in children 2 to 4 years old. **Methods:** In a double-blind, randomized trial, we evaluated the safety, immunogenicity, and efficacy of the Vi-rEPA vaccine in children two to five years old in 16 communes in Dong Thap Province, Vietnam. Each of the 11,091 children received two injections six weeks apart of either Vi-rEPA or a saline placebo. Cases of typhoid, diagnosed by the isolation of S. typhi from blood cultures after 3 or more days of fever (a temperature of 37.5°C or higher), were identified by active surveillance over a period of 27 months. We estimated efficacy by comparing the attack rate of typhoid in the vaccine group with that in the placebo group. **Results**: S. typhi was isolated from 4 of the 5525 children who were fully vaccinated with Vi-rEPA and from 47 of the 5566 children who received both injections of placebo (efficacy, 91.5 percent; 95 percent confidence interval, 77.1 to 96.6 percent; P<0.001). Among the 771 children who received only one injection, there was 1 case of typhoidin the vaccine group and 8 cases in the placebo group. Cases were distributed evenly among all age groups and throughout the study period. No serious adverse reactions were observed. In all 36 children studied four weeks after the second injection of the vaccine, levels of serum IgG Vi antibodies had increased by a factor of 10 or more. **Conclusions** : The Vi-rEPA conjugate typhoid vaccine is safe and immunogenic and has more than 90 percent efficacy in children two to five years old. The antibody responses and the efficacy suggest that this vaccine should be at least as protective in persons who are more than five years old.

Lo NC et al. Comparison of strategies and incidence thresholds for Vi conjugate vaccines against typhoid fever: A cost- effectiveness modeling study. J Infect Dis. 2018;doi:10.1093/infdis/jix598.
Background: Typhoid fever remains a major public health problem globally. While new Vi conjugate vaccines hold promise for averting disease, the optimal programmatic delivery remains unclear. We aimed to identify the strategies and associated epidemiologic conditions under which Vi conjugate vaccines would be cost-effective. **Methods**: We developed a dynamic, age-structured transmission and cost-effectiveness model that simulated multiple vaccination strategies with a typhoid Vi conjugate vaccine from a societal perspective. We simulated 10-year vaccination programs with (1) routine immunization of infants (aged <1 year) through the Expanded Program on Immunization (EPI) and (2) routine immunization of infants through the EPI plus a 1-time catch-up campaign in school-aged children (aged 5-14 years). In the base case analysis, we assumed a 0.5% case-fatality rate for all cases of clinically symptomatic typhoid fever and defined strategies as highly cost-effective by using the definition of a low-income country (defined as a country with a gross domestic product of $1045 per capita). We defined incidence as the true number of clinically symptomatic people in the population per year. **Results**: Vi conjugate typhoid vaccines were highly cost-effective when administered by routine immunization activities through the EPI in settings with an annual incidence of >50 cases/100000 (95% uncertainty interval, 40-75 cases) and when administered through the EPI plus a catch-up campaign in settings with an annual incidence of >130 cases/100000 (95% uncertainty interval, 50-395 cases). The incidence threshold was sensitive to the typhoid-related case-fatality rate, carrier contribution to transmission, vaccine characteristics, and country-specific economic threshold for cost-effectiveness. **Conclusions**: Typhoid Vi conjugate vaccines would be highly cost-effective in low-income countries in settings of moderate typhoid incidence (50 cases/100000 annually). These results were sensitive to case-fatality rates, underscoring the need to consider factors contributing to typhoid mortality (eg, healthcare access and antimicrobial resistance) in the global vaccination strategy.

Lunguya O et al. Salmonella Typhi in the Democratic Republic of the Congo: fluoroquinolone decreased susceptibility on the rise. PLoS Negl Trop Dis. 2012;6:e1921.
Background: Drug resistance of Salmonella enterica serovar Typhi (Salmonella Typhi) to first-line antibiotics is emerging in Central Africa. Although increased use of fluoroquinolones is associated with spread of resistance, Salmonella Typhi with decreased ciprofloxacin susceptibility (DCS) has rarely been reported in Central Africa. **Methodology/Principal Findings**: As part of a microbiological surveillance study in the Democratic Republic of the Congo (DR Congo), Salmonella Typhi isolates from bloodstream infections were collected prospectively between 2007 and 2011. The genetic relationship of the Salmonella Typhi isolates was assessed by pulsed-field gel electrophoresis (PFGE). The antimicrobial resistance profile of the isolates was determined and mutations associated with DCS were studied. In total, 201 Salmonella Typhi isolates were collected. More than half of the Salmonella Typhi isolates originated from children and young adults aged 5-19. Thirty different PFGE profiles were identified, with 72% of the isolates showing a single profile. Multidrug resistance, DCS and azithromycin resistance were 30.3%, 15.4% and 1.0%, respectively. DCS was associated with point mutations in the gyrA gene at codons 83 and 87. **Conclusions/Significance**: Our study describes the first report of widespread multidrug resistance and DCS among Salmonella Typhi isolates from DR Congo. Our findings highlight the need for increased microbiological diagnosis and surveillance in DR Congo, being a prerequisite for rational use of antimicrobials and the development of standard treatment guidelines.

Marks F et al. Incidence of invasive Salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. Lancet Glob Health. 2017;5:e310-323.
Background: Available incidence data for invasive salmonella disease in sub-Saharan Africa are scarce. Standardised, multicountry data are required to better understand the nature and burden of disease in

Africa. We aimed to measure the adjusted incidence estimates of typhoid fever and invasive non-typhoidal salmonella (iNTS) disease in sub-Saharan Africa, and the antimicrobial susceptibility profiles of the causative agents. **Methods**: We established a systematic, standardised surveillance of blood culture-based febrile illness in 13 African sentinel sites with previous reports of typhoid fever: Burkina Faso (two sites), Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar (two sites), Senegal, South Africa, Sudan, and Tanzania (two sites). We used census data and health-care records to define study catchment areas and populations. Eligible participants were either inpatients or outpatients who resided within the catchment area and presented with tympanic (≥38 • 0° C) or axillary temperature (≥37 • 5° C). Inpatients with a reported history of fever for 72 h or longer were excluded. We also implemented a health-care utilisation survey in a sample of households randomly selected from each study area to investigate health-seeking behaviour in cases of self-reported fever lasting less than 3 days. Typhoid fever and iNTS disease incidences were corrected for health-care-seeking behaviour and recruitment. **Findings**: Between March 1, 2010, and Jan 31, 2014, 135 Salmonella enterica serotype Typhi (S Typhi) and 94 iNTS isolates were cultured from the blood of 13 431 febrile patients. Salmonella spp accounted for 33% or more of all bacterial pathogens at nine sites. The adjusted incidence rate (AIR) of S Typhi per 100 000 person-years of observation ranged from 0 (95% CI 0–0) in Sudan to 383 (274–535) at one site in Burkina Faso; the AIR of iNTS ranged from 0 in Sudan, Ethiopia, Madagascar (Isotry site), and South Africa to 237 (178–316) at the second site in Burkina Faso. The AIR of iNTS and typhoid fever in individuals younger than 15 years old was typically higher than in those aged 15 years or older. Multidrug-resistant S Typhi was isolated in Ghana, Kenya, and Tanzania (both sites combined), and multidrug-resistant iNTS was isolated in Burkina Faso (both sites combined), Ghana, Kenya, and Guinea-Bissau. **Interpretation**: Typhoid fever and iNTS disease are major causes of invasive bacterial febrile illness in the sampled locations, most commonly affecting children in both low and high population density settings. The development of iNTS vaccines and the introduction of S Typhi conjugate vaccines should be considered for high-incidence settings, such as those identified in this study. Funding: Bill & Melinda Gates Foundation.

Mermin JH et al. A massive epidemic of multidrug-resistant typhoid fever in Tajikistan associated with consumption of municipal water. J Infect Dis. 1999;179:1416–1422.

From 1 January through 30 June 1997, 8901 cases of typhoid fever and 95 associated deaths were reported in Dushanbe, Tajikistan. Of 29 Salmonella serotype Typhi isolates tested, 27 (93%) were resistant to ampicillin, chloramphenicol, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole. In a case-control study of 45 patients and 123 controls, Salmonella Typhi infection was associated with drinking unboiled water (matched odds ratio, 7; 95% confidence interval, 3–24; P < .001). Of tap water samples, 97% showed fecal coliform contamination (mean level, 175 cfu/100 mL). Samples taken from water treatment plants revealed that fecal coliform contamination occurred both before and after treatment. Lack of chlorination, equipment failure, and back-siphonage in the water distribution system led to contamination of drinking water. After chlorination and coagulation were begun at the treatment plants and a water conservation campaign was initiated to improve water pressure, the incidence of typhoid fever declined dramatically.

Michel R et al. Outbreak of typhoid fever in vaccinated members of the French Armed Forces in the Ivory Coast. Eur J Epidemiol. 2005;20:635-642.

In 2001, an outbreak of typhoid fever occurred among the members of the French Armed Forces. All had received a typhoid vaccination as per the immunization schedule practiced in the Armed Forces (every 5 years). A retrospective cohort study was conducted in 94 personnel. The objectives were to confirm the diagnosis, determine the source of contamination and identify the factors associated with defective vaccinal efficacy. Twenty-four cases were clinically identified. A cucumber salad was identified as the

contaminating dish (Risk Ratio=3.6; 95%CI 1.5–8.9). Only one factor was related to defective vaccinal efficacy; the risk of typhoid fever was twofold higher in people vaccinated more than 3 years previously (Risk Ratio = 2.2; 95%CI, 1.1–4.2). Compliance with food hygiene rules could have prevented 24 cases of typhoid fever. Nevertheless, repeat vaccination against typhoid fever is now conducted every 3 years in the French Forces, in compliance with the manufacturers' recommendations.

Mohan VK et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. Clin Infect Dis. 2015;61:393-402.
Background: Enteric fever caused by Salmonella Typhi remains a major public health problem in developing countries. Typbar-TCV is a single-dose typhoid Vi polysaccharide–tetanus toxoid conjugate vaccine for persons ⩾6 months of age. **Methods**: Six hundred fifty-four healthy subjects aged 2–45 years enrolled in a double-blind, randomized controlled trial (RCT) received a single dose of Typbar-TCV or comparator "Vi polysaccharide" (Typbar), and 327 healthy subjects aged 6–23 months received a single dose of Typbar-TCV in an open-label trial (OLT); both received single- or multidose presentations from different lots. After 2 years, subsets in each group received a booster dose. The primary objective included analysis of geometric mean titer (GMTs) and 4-fold rise of anti-Vi serum immunoglobulin G (IgG) enzyme-linked immunosorbent assay titers over baseline (seroconversion [SCN]) 42 days after immunization. **Results**: Typbar-TCV recipients in the RCT attained higher anti-Vi IgG GMTs 42 days after immunization (SCN, 97%; GMT, 1293 [95% confidence interval {CI}, 1153–1449]) than recipients of Typbar (SCN, 93%; GMT, 411 [95% CI, 359–471]) (P < .001). Typbar-TCV was highly immunogenic in the OLT (SCN, 98%; GMT, 1937 [95% CI, 1785–2103]). Two years after vaccination, anti-Vi titers remained higher in Typbar-TCV subjects (GMT, 82 [95% CI, 73–92]); and exhibited higher avidity (geometric mean avidity index [GMAI], 60%) than in Typbar recipients (GMT, 46 [95% CI, 40–53]; GMAI 46%) in the RCT (P < .001). OLT Typbar-TCV recipients achieved GMT of 48 (95% CI, 42–55) and GMAI of 57%. Typbar-TCV induced multiple IgG subclasses and strong booster responses in all ages. No serious vaccine-attributable adverse events were observed. **Conclusions**: Single-dose Typbar-TCV is well tolerated and induces robust and long-lasting serum anti-Vi IgG across age groups.

Muyembe-Tamfum JJ et al. An outbreak of peritonitis caused by multidrug-resistant Salmonella Typhi in Kinshasa, Democratic Republic of Congo. Travel Med Infect Dis. 2009;7:40–43.
Between October 2004 and January 2005, 144 patients with peritonitis were admitted to the surgical wards of Kinshasa General Hospital and a few private city clinics. 63 patients (44%) underwent surgical intervention because of intestinal perforation consistent with typhoid fever; the case fatality rate was 53%. The majority of patients had received a course of first-line antibiotics such as chloramphenicol, ampicillin or co-trimoxazole before admission. On bacteriological investigation, Salmonella Typhi was isolated from the blood of 11 patients with peritonitis. The isolates were all resistant to ampicillin, chloramphenicol, tetracycline and co-trimoxazole, but sensitive to third-generation cephalosporins, quinolone (nalidixic acid, ciprofloxacine) and amoxicillin-clavulanic acid. Several factors contributed to the poor outcome of this disease including a) the use of inappropriate antibiotics, b) long delay in diagnosis, c) difficult access to health facilities. This is the first documented outbreak of typhoid fever caused by a multidrug-resistant S. Typhi in Kinshasa.

Neil KP et al. A large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese District, Uganda, 2008-2009. Clin Infect Dis. 2012;54:1091–1099.
Background: Salmonella enterica serovar Typhi (Salmonella Typhi) causes an estimated 22 million typhoid fever cases and 216 000 deaths annually worldwide. In Africa, the lack of laboratory diagnostic capacity limits the ability to recognize endemic typhoid fever and to detect outbreaks. We report a large

laboratory-confirmed outbreak of typhoid fever in Uganda with a high proportion of intestinal perforations (IPs). **Methods**: A suspected case of typhoid fever was defined as fever and abdominal pain in a person with either vomiting, diarrhea, constipation, headache, weakness, arthralgia, poor response to antimalarial medications, or IP. From March 4, 2009 to April 17, 2009, specimens for blood and stool cultures and serology were collected from suspected cases. Antimicrobial susceptibility testing and pulsed-field gel electrophoresis (PFGE) were performed on Salmonella Typhi isolates. Surgical specimens from patients with IP were examined. A community survey was conducted to characterize the extent of the outbreak. **Results**: From December 27, 2007 to July 30, 2009, 577 cases, 289 hospitalizations, 249 IPs, and 47 deaths from typhoid fever occurred; Salmonella Typhi was isolated from 27 (33%) of 81 patients. Isolates demonstrated multiple PFGE patterns and uniform susceptibility to ciprofloxacin. Surgical specimens from 30 patients were consistent with typhoid fever. Estimated typhoid fever incidence in the community survey was 8092 cases per 100 000 persons. **Conclusions**: This typhoid fever outbreak was detected because of an elevated number of IPs. Underreporting of milder illnesses and delayed and inadequate antimicrobial treatment contributed to the high perforation rate. Enhancing laboratory capacity for detection is critical to improving typhoid fever control.

Overbosch D et al. Combined typhoid fever and hepatitis A vaccine: comparison of immunogenicity and safety to concomitant monovalent vaccine over 3 years. J Travel Med. 2005;12:319-326.
Background: The safety and immunogenicity of Viatim, a combined hepatitis A (HA) and typhoid fever (Vi) vaccine, were compared with the monovalent component vaccines up to and 1 month after a booster dose at 3 years. **Methods:** Healthy, adult volunteers were randomized to receive Viatim (group A, n = 179) or separate HA and Vi vaccines (group B, n = 181); subgroups were boosted after 3 years with Viatim (groups C and D, n = 56 and 46, respectively). Local and systemic reactions were recorded for 28 days postvaccination. Seroconversion and seroprotection rates and geometric mean antibody concentrations were measured at 14 and 28 days, 1, 2, and 3 years postvaccination, and 28 days after the booster dose. **Results:** Local and systemic safety profiles were equivalent between the two groups. Immediate local reactions were infrequent (1 in group A and 2 in group B). Local reactions, consisting mostly of mild or moderate pain, were least frequent with monovalent HA. Antibody concentrations to both antigens were similar in groups A and B, in which HA seroprotection rates ($\geqslant$ 20 mIU/mL) were respectively, 98.7% and 100% at day 28, and 99.1% and 99.0% after 3 years, achieving 100% after the booster. Vi seroprotection rates ($\geqslant$ 1 μg/mL) of 85.2% and 84.9% after 28 days fell to 32.1% and 35.6% after 3 years, increasing to 67.3% and 69.8% after the booster dose. **Conclusions:** The combined HA/Vi vaccine, Viatim, had equivalent tolerability and safety and was as rapidly immunogenic as its component monovalent vaccines when given concurrently. A booster dose after 3 years significantly increased antibody levels with some evidence of relative hyporesponsiveness of the typhoid response.

Parry CM et al. Risk factors for the development of severe typhoid fever in Vietnam. BMC Infect Dis. 2014;14:73.
Background: Typhoid fever is a systemic infection caused by the bacterium Salmonella enterica serovar Typhi. Age, sex, prolonged duration of illness, and infection with an antimicrobial resistant organism have been proposed risk factors for the development of severe disease or fatality in typhoid fever. **Methods:** We analysed clinical data from 581 patients consecutively admitted with culture confirmed typhoid fever to two hospitals in Vietnam during two periods in 1993–1995 and 1997–1999. These periods spanned a change in the antimicrobial resistance phenotypes of the infecting organisms i.e. fully susceptible to standard antimicrobials, resistance to chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole (multidrug resistant, MDR), and intermediate susceptibility to ciprofloxacin (nalidixic acid resistant). Age, sex, duration of illness prior to admission, hospital location and the presence of MDR or intermediate ciprofloxacin susceptibility in the infecting organism were examined by logistic

regression analysis to identify factors independently associated with severe typhoid at the time of hospital admission. **Results**: The prevalence of severe typhoid was 15.5% (90/581) and included: gastrointestinal bleeding (43; 7.4%); hepatitis (29; 5.0%); encephalopathy (16; 2.8%); myocarditis (12; 2.1%); intestinal perforation (6; 1.0%); haemodynamic shock (5; 0.9%), and death (3; 0.5%). Severe disease was more common with increasing age, in those with a longer duration of illness and in patients infected with an organism exhibiting intermediate susceptibility to ciprofloxacin. Notably an MDR phenotype was not associated with severe disease. Severe disease was independently associated with infection with an organism with an intermediate susceptibility to ciprofloxacin (AOR 1.90; 95% CI 1.18-3.07; p = 0.009) and male sex (AOR 1.61 (1.00-2.57; p = 0.035). **Conclusions:** In this group of patients hospitalised with typhoid fever infection with an organism with intermediate susceptibility to ciprofloxacin was independently associated with disease severity. During this period many patients were being treated with fluoroquinolones prior to hospital admission. Ciprofloxacin and ofloxacin should be used with caution in patients infected with S. Typhi that have intermediate susceptibility to ciprofloxacin.

Plotkin SA et al. A new typhoid vaccine composed of the Vi capsular polysaccharide. Arch Intern Med. 1995;155:2293-2299.

Typhoid is still prevalent in many parts of the world. We reviewed all published and unpublished studies of a newly licensed vaccine composed of the Vi capsular polysaccharide of Salmonella typhi, the causative agent of the disease, which had been licensed previously outside the United States. These included observational studies and double-blind randomized studies done in the United States, Europe, and the developing world in which children and adults unexposed to typhoid or those living in endemic areas were enrolled. A single dose of 25 µg of the purified polysaccharide was given by intramuscular injection. The vaccine was well tolerated, inducing only minor reactions in fewer than 10% of subjects. An antibody response occurred in about 90% of subjects and lasted about 3 years. Seroconversion was shown in children as young as 2 years. Protective efficacy was evaluated in two studies conducted in areas in which typhoid is endemic; the efficacy was 55% and 75%, respectively, in adults and in children older than 5 years. The Vi vaccine compares favorably with other typhoid vaccines in regard to safety, patient compliance, immunogenicity, and efficacy. Vi polysaccharide is a well-standardized antigen that is effective in a single parenteral dose, is safer than whole-cell vaccine, and may be used in children 2 years of age or older.

Roggelin L et al. Serological response following re-vaccination with Salmonella typhi Vi-capsular polysaccharide vaccines in healthy adult travellers. Vaccine. 2015;33:4141-4145.

An injectable Vi-capsular polysaccharide vaccine against typhoid fever is available but vaccine-induced immunity tends to wane over time. The phenomenon of immunotolerance or hyporesponsiveness has earlier been described for polysaccharide vaccines such as pneumococcal capsular polysaccharide vaccine and some publications also suggest a possible immunotolerance after revaccination with Vi-capsular polysaccharide vaccines. In this study, post-immunisation antibody concentrations in adult travellers first vaccinated with a Salmonella typhi Vi-capsular polysaccharide vaccine (primary vaccination group) were compared with those having received one or more vaccinations previously (multiple vaccinations group). Vaccines administered were Typherix® (GlaxoSmithKline), Typhim Vi® (Sanofi Pasteur MSD) or Hepatyrix® (GlaxoSmithKline). Blood samples were obtained prior to vaccination (day 0) and on day 28 (−1/+14) after vaccination. Serum Vi-Antigen IgG concentrations were measured by ELISA. Of the 85 subjects included in the per protocol data set, 45 (53%) belonged to the multiple vaccinations group. In both groups, geometric mean antibody concentrations (GMCs) were significantly higher after vaccination than before vaccination. Pre-vaccination GMCs were lower in the primary vaccination group than in the multiple vaccinations group (3.40 µg/ml versus 6.13 µg/ml, P = 0.005), while there was no significant difference in the post vaccination GMCs between groups (11.34 µg/ml

versus 14.58 μg/ml, P = 0.4). In the multiple vaccinations group, vaccination was performed 18 to 57 months after the last vaccination (median 38 months) and there was a negative correlation between time since last vaccination and antibody concentration on day 0. In conclusion, we were not able to demonstrate a relevant immunotolerance after multiple versus primary vaccination with S. typhi Vi-capsular polysaccharide vaccines.

Salerno-Goncalves R et al. Characterization of CD8(+) effector T cell responses in volunteers immunized with Salmonella enterica serovar Typhi strain Ty21a typhoid vaccine. J Immunol. 2002;169:2196-2203.

Salmonella enterica serovar Typhi (S. typhi) strain Ty21a remains the only licensed attenuated typhoid vaccine. Despite years of research, the identity of the protective immunological mechanisms elicited by immunization with the Ty21a typhoid vaccine remains elusive. The present study was designed to characterize effector T cell responses in volunteers immunized with S. typhi strain Ty21a typhoid vaccine. We determined whether immunization with Ty21a induced specific CTL able to lyse S. typhi-infected cells and secrete IFN-γ, a key effector molecule against intracellular pathogens. We measured the functional activity of these CTL by a 51Cr-release assay using 8-day restimulated PBMC from Ty21a vaccinees as effector cells and S. Typhi-infected autologous PHA-activated PBMC as target cells. Most vaccinees exhibited consistently increased CD8-mediated lysis of targets by postimmunization PBMC when compared with preimmunization levels. We also developed an IFN-γ ELISPOT assay to quantify the frequency of IFN-γ spot-forming cells (SFC) in PBMC from Ty21a vaccinees using an ex vivo system. Significant increases in the frequency of IFN-γ SFC following immunization (mean ± SD, 393 ± 172; range 185–548 SFC/106 PBMC; p = 0.010), as compared with preimmunization levels, were observed. IFN-γ was secreted predominantly by CD8+ T cells. A strong correlation was recorded between the cytolytic activity of CTL lines and the frequency of IFN-γ SFC (r2 = 0.910, p < 0.001). In conclusion, this work constitutes the first evidence that immunization of volunteers with Ty21a elicits specific CD8+ CTL and provides an estimate of the frequency of CD8+ IFN-γ-secreting cells induced by vaccination. Salmonella enterica serovar Typhi (S. typhi), the causative agent of typhoid fever, is a human-restricted intracellular Gram-negative bacterium that infects both phagocytic and nonphagocytic cells (1, 2). Worldwide, typhoid fever affects ∼16 million individuals annually with 600,000 deaths (3). In Asia and northeast Africa, the appearance of S. typhi showing resistance to many antibiotics has become an important public-health problem (4). Therefore, an improved prophylactic vaccine to prevent typhoid fever is urgently needed. Although much is known regarding the immune responses elicited by Salmonella typhimurium in the murine model (1, 5), which results in a typhoid-like disease, little is known about the protective immune responses to S. typhi infection in humans. Because of the narrow restriction of S. typhi for human hosts, definitive studies in humans are desirable3 (6). Results from studies in typhoid patients and vaccine trials with attenuated S. typhi indicate that Abs appear to be involved in protection against S. typhi (2, 6, 7). However, the role of cell-mediated immunity (CMI)4 in protectionfrom S. typhi infection remains unclear. There is considerable evidence that host resistance to many intracellular bacteria such as Listeria monocytogenes (8, 9), and Mycobacteria (10, 11) is strongly influenced by CMI responses. We have previously demonstrated the presence of specific CTL and IFN-γ production to S. typhi Ags in volunteers immunized with attenuated S. typhi strain CVD 908 and suggested that these might be important effector mechanisms in resistance to S. typhi infection (12, 13). Despite years of research, there is little information on the protective immunological mechanisms elicited by oral immunization with S. typhi strain Ty21a typhoid vaccine (the only licensed attenuated live vaccine) which has been shown to have a variable rate of protection depending on the formulation used and the number and spacing of the doses administered (2). The purpose of this study was to determine whether immunization with Ty21a typhoid vaccine elicited two key T cell-mediated effector mechanisms, i.e.,

specific CTL able to lyse S. typhi-infected targets and production of IFN-γ in response to stimulation with S. typhi-infected cells.

Simanjuntak C et al. Oral immunisation against typhoid fever in Indonesia with Ty21a vaccine. Lancet. 1991;338:1055-1059.

When tested under conditions of moderate transmission of typhoid fever, a liquid formulation of the oral typhoid fever vaccine Ty21a had a protective efficacy of 96% in Egypt, and an enteric coated capsule formulation had an efficacy of 67% in Chile. We compared the two formulations under conditions of intense transmission of typhoid fever in Indonesia in a randomised, double-blind trial. 20,543 subjects (age range 3-44 years) received either three doses of enteric coated capsules containing placebo or live Ty21a, or three doses of lyophilised placebo or live Ty21a reconstituted with phosphate buffer. During 30 months of follow-up, the rate of blood-culture-positive typhoid fever among controls was 810/100,000 per year. Rates of typhoid fever were 379/100,000 per year for subjects who received the liquid formulation of vaccine and 468/100,000 per year for subjects who received enteric coated capsules. The protective efficacies of the liquid and enteric coated formulations were 53% and 42%, respectively. Neither formulation protected against infection with Salmonella paratyphi A. No major side-effects were noted, but the overall incidence of side-effects was greater in the vaccine groups. Under conditions of intense transmission, Ty21a protected against typhoid fever; however, because Ty21a will not protect all individuals, there is a need for additional approaches to prevent the disease. PIP: When tested under conditions of moderate transmission of typhoid fever, a liquid formulation of the oral typhoid fever vaccine, Ty21a, had a protective efficacy of 96% in Egypt, and an enteric coated capsule formulation had an efficacy of 67% in Chile. The authors compared the 2 formulations under conditions of intense transmission of typhoid fever in Indonesia in a randomized, double blind trial. 20,543 subjects (age range 3-44 years) received either 3 doses of enteric-coated capsules containing placebo or live Ty21a, or 3 doses of lyophilized placebo or live Ty21a reconstituted with phosphate buffer. During 30 months of followup, the rate of blood-culture-positive typhoid fever among controls was 810/100,000/year. Rates of typhoid fever were 379/100,000/year for subjects who received the liquid formulation of vaccine and 468/100,000/year for subjects who received enteric coated capsules. The protective efficacies of the liquid and enteric coated formulations were 53% and 42%, respectively. Neither formulation protected against infection with Salmonella paratyphi A. No major side effects were noted, but the overall incidence of side effects was greater in the vaccine groups. Under conditions of intense transmission, Ty21a protected against typhoid fever; however since it will not protect all individuals, there is a need for additional approaches in prevention of the disease.

Sulaiman K et al. Culture-confirmed typhoid fever and pregnancy. Int J Infect Dis. 2007;11:337–341

Background : The relationship between pregnancy and typhoid fever is not well defined. The objective of this study was twofold: to assess the effect of the pregnant and postpartum host on typhoid disease expression, and to explore the relationship between typhoid fever and pregnancy outcome. **Methods:** Over an 11-year period, all 181 adult women with blood culture-confirmed typhoid fever admitted to a university hospital in Karachi, Pakistan were studied; those with pregnancy-related disease were compared to the non-pregnant women. The relationship between typhoid fever and pregnancy outcome was evaluated by comparing 80 pregnant women with typhoid, with 194 randomly selected pregnant women without typhoid who were matched for age and study year. **Results:** In adult females with bacteremic typhoid disease, a significant proportion was pregnancy-related (47%). These women were less likely to have other co-morbid illnesses (2% vs. 27%, $p < 0.001$) and were almost exclusively treated with ampicillin/amoxicillin or third-generation cephalosporins, while the non-pregnant women with typhoid fever preferentially received quinolones. The mean duration of antimicrobial therapy was similar in both groups (14 days) but the non-pregnant group defervesced earlier (4.2 days vs. 5.6 days, p

= 0.011). Complications of typhoid fever were significantly more likely in the non-pregnant group (23% vs. 8%, p = 0.005) and primarily involved lower gastrointestinal bleeding. On comparing the pregnant women with typhoid with randomly selected age-matched pregnant women without typhoid, there were no apparent effects of typhoid fever on pregnancy outcome as measured by gestational age at delivery, pregnancy complications, modes of delivery, neonate gender, birth weight, or birth Apgar scores. **Conclusions:** While pregnancy is a risk factor for and effects typhoid disease expression, typhoid fever does not appear to affect pregnancy outcome.

Sur D et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. N Eng J Med. 2009;361:335-344.

Background: Typhoid fever remains an important cause of illness and death in the developing world. Uncertainties about the protective effect of Vi polysaccharide vaccine in children under the age of 5 years and about the vaccine's effect under programmatic conditions have inhibited its use in developing countries. **Methods:** We conducted a phase 4 effectiveness trial in which slum-dwelling residents of Kolkata, India, who were 2 years of age or older were randomly assigned to receive a single dose of either Vi vaccine or inactivated hepatitis A vaccine, according to geographic clusters, with 40 clusters in each study group. The subjects were then followed for 2 years. **Results**: A total of 37,673 subjects received a dose of a study vaccine. The mean rate of vaccine coverage was 61% for the Vi vaccine clusters and 60% for the hepatitis A vaccine clusters. Typhoid fever was diagnosed in 96 subjects in the hepatitis A vaccine group, as compared with 34 in the Vi vaccine group, with no subject having more than one episode. The level of protective effectiveness for the Vi vaccine was 61% (95% confidence interval [CI], 41 to 75; P<0.001 for the comparison with the hepatitis A vaccine group). Children who were vaccinated between the ages of 2 and 5 years had a level of protection of 80% (95% CI, 53 to 91). Among unvaccinated members of the Vi vaccine clusters, the level of protection was 44% (95% CI, 2 to 69). The overall level of protection among all residents of Vi vaccine clusters was 57% (95% CI, 37 to 71). No serious adverse events that were attributed to either vaccine were observed during the month after vaccination. **Conclusions**: The Vi vaccine was effective in young children and protected unvaccinated neighbors of Vi vaccinees. The potential for combined direct and indirect protection by Vi vaccine should be considered in future deliberations about introducing this vaccine in areas where typhoid fever is endemic.

Thompson CN et al. Typhoid fever in Fiji: a reversible plague? Trop Med Int Health. 2014;19:1284–1292.

The country of Fiji, with a population of approximately 870 000 people, faces a growing burden of several communicable diseases including the bacterial infection typhoid fever. Surveillance data suggest that typhoid has become increasingly common in rural areas of Fiji and is more frequent amongst young adults. Transmission of the organisms that cause typhoid is facilitated by faecal contamination of food or water and may be influenced by local behavioural practices in Fiji. The Fijian Ministry of Health, with support from Australian Aid, hosted a meeting in August 2012 to develop comprehensive control and prevention strategies for typhoid fever in Fiji. International and local specialists were invited to share relevant data and discuss typhoid control options. The resultant recommendations focused on generating a clearer sense of the epidemiology of typhoid in Fiji and exploring the contribution of potential transmission pathways. Additionally, the panel suggested steps such as ensuring that recommended ciprofloxacin doses are appropriate to reduce the potential for relapse and reinfection in clinical cases, encouraging proper hand hygiene of food and drink handlers, working with water and sanitation agencies to review current sanitation practices and considering a vaccination policy targeting epidemiologically relevant populations.

UNAIDS. GLOBAL AIDS UPDATE. 2017. Available at http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf, accessed February 2018.
No Abstract Available.

Voysey M and Pollard AJ. Sero-efficacy of Vi-polysaccharide tetanus-toxoid typhoid conjugate vaccine (Typbar-TCV). Clin Infect Dis. 2018;doi:10.1093/cid/cix1145.
Background: Salmonella Typhi is the major cause of enteric fever in lower income countries. New conjugate vaccines show promise as public health interventions, however there are no efficacy data available from endemic areas. **Methods**: Data were obtained from a previously published phase 3 randomised controlled trial comparing Vi-polysaccharide tetanus-toxoid conjugate vaccine (Typbar-TCV; Bharat Biotech Intl Ltd, India): (Vi-TT) with Vi-polysaccharide (Typbar; Bharat Biotech Intl Ltd, India): (Vi-PS) in participants aged 2- 45 years. An additional open-label arm administered Vi-TT to children aged 6 months to 23 months. The proportion of participants with presumed clinical or subclinical infection ('seroincidence'), was determined using mixture models and compared using relative risks. **Results:** 81/387 (21%) participants were classified as having presumed typhoid infection during the 2 year period post-vaccination. Seroincidence was lower in those randomised to Vi-TT than Vi-PS in those aged 2-45 years; 21/155 (13.5%) vs 47/129 (36.4%); RR 0.372 (95%CI 0.235-0.588), p<0.0001 and in those aged 2-15 years RR 0.424 (95%CI 0.231-0.778), p=0.0039. There was no difference in seroincidence in those receiving Vi-TT aged 2-45 years and those aged 6-23 months; 21/155 (13.5%) vs 13/103 (12.6%); RR 1.073 (0.563, 2.046), p=0.8293. Vaccine seroefficacy was 85% (95%CI 80-88%). **Conclusion**: This is the first field estimate of the seroefficacy of a Vi-TT vaccine and shows that Typbar TCV substantially reduces the number of serologically defined (sub)clinical infections in infants, children and adults. These results support the recent World Health Organisation recommendations for deployment of typhoid conjugate vaccines in high burden areas.

Wahdan MH et al. A controlled field trial of live Salmonella typhi strain Ty21a oral vaccine against typhoid: Three year results. J Infect Dis. 1982;145:292-296.
A controlled field trial of Salmonella typhi strain Ty 21a oral vaccine against typhoid was carried out in Alexandria, Egypt, from March 1978 to March 1981. A total of 32,388 children was included in the study. The children were divided in two comparable groups, one given three doses of vaccine and the other three doses of placebo. Each dose of vaccine contained 1-8 X 10(9) live Ty 21a bacteria. The population was monitored, and each suspected case of typhoid was investigated bacteriologically and serologically. The effectiveness of the vaccine was assessed by analyzing the number of confirmed cases of typhoid fever in the two groups. The incidence of typhoid fever was 4.9 cases per 10,000 children per year in the control group and 0.2 cases per 10,000 children per year in the vaccine group. The results indicate that, in the dose schedule used, the Ty 21a mutant strain, which is stable and safe, is protective for a period of at least three years.

Wahid et al. Immunization with Ty21a live oral typhoid vaccine elicits crossreactive multifunctional CD8+ T-cell responses against Salmonella enterica serovar Typhi, S. Paratyphi A, and S. Paratyphi B in humans. Mucosal Immunol. 2015:10.
Previously we have extensively characterized Salmonella enterica serovar Typhi (S. Typhi)-specific cell-mediated immune (CMI) responses in volunteers orally immunized with the licensed Ty21a typhoid vaccine. In this study we measured Salmonella-specific multifunctional (MF) CD8+ T-cell responses to further investigate whether Ty21a elicits crossreactive CMI against S. Paratyphi A and S. Paratyphi B that also cause enteric fever. Ty21a-elicited crossreactive CMI responses against all three Salmonella serotypes were predominantly observed in CD8+ T effector/memory (TEM) and, to a lesser extent, in

CD8+CD45RA+ TEM (TEMRA) subsets. These CD8+ T-cell responses were largely mediated by MF cells coproducing interferon-γ and macrophage inflammatory protein-1β and expressing CD107a with or without tumor necrosis factor-α. Significant proportions of Salmonella-specific MF cells expressed the gut-homing molecule integrin α4β7. In most subjects, similar MF responses were observed to S. Typhi and S. Paratyphi B, but not to S. Paratyphi A. These results suggest that Ty21a elicits MF CMI responses against Salmonella that could be critical in clearing the infection. Moreover, because S. Paratyphi A is a major public concern and Ty21a was shown in field studies not to afford cross-protection to S. Paratyphi A, these results will be important in developing a S. Typhi/S. Paratyphi A bivalent vaccine against enteric fevers.

Wain J et al. Typhoid fever. Lancet. 2014;385:1136-1145.
Control of typhoid fever relies on clinical information, diagnosis, and an understanding for the epidemiology of the disease. Despite the breadth of work done so far, much is not known about the biology of this human-adapted bacterial pathogen and the complexity of the disease in endemic areas, especially those in Africa. The main barriers to control are vaccines that are not immunogenic in very young children and the development of multidrug resistance, which threatens efficacy of antimicrobial chemotherapy. Clinicians, microbiologists, and epidemiologists worldwide need to be familiar with shifting trends in enteric fever. This knowledge is crucial, both to control the disease and to manage cases. Additionally, salmonella serovars that cause human infection can change over time and location. In areas of Asia, multidrug-resistant Salmonella enterica serovar Typhi (S Typhi) has been the main cause of enteric fever, but now S Typhi is being displaced by infections with drug-resistant S enterica serovar Paratyphi A. New conjugate vaccines are imminent and new treatments have been promised, but the engagement of local medical and public health institutions in endemic areas is needed to allow surveillance and to implement control measures.

Watson HC et al. A cross-sectional seroepidemiological survey of typhoid fever in Fiji. PLoS Negl Trop Dis. 2017;11: e0005786.
Fiji, an upper-middle income state in the Pacific Ocean, has experienced an increase in confirmed case notifications of enteric fever caused by Salmonella enterica serovar Typhi (S. Typhi). To characterize the epidemiology of typhoid exposure, we conducted a cross-sectional sero-epidemiological survey measuring IgG against the Vi antigen of S. Typhi to estimate the effect of age, ethnicity, and other variables on seroprevalence. Epidemiologically relevant cut-off titres were established using a mixed model analysis of data from recovering culture-confirmed typhoid cases. We enrolled and assayed plasma of 1787 participants for anti-Vi IgG; 1,531 of these were resident in mainland areas that had not been previously vaccinated against S. Typhi (seropositivity 32.3% (95%CI 28.2 to 36.3%)), 256 were resident on Taveuni island, which had been previously vaccinated (seropositivity 71.5% (95%CI 62.1 to 80.9%)). The seroprevalence on the Fijian mainland is one to two orders of magnitude higher than expected from confirmed case surveillance incidence, suggesting substantial subclinical or otherwise unreported typhoid. We found no significant differences in seropositivity prevalences by ethnicity, which is in contrast to disease surveillance data in which the indigenous iTaukei Fijian population are disproportionately affected. Using multivariable logistic regression, seropositivity was associated with increased age (odds ratio 1.3 (95% CI 1.2 to 1.4) per 10 years), the presence of a pit latrine (OR 1.6, 95%CI 1.1 to 2.3) as opposed to a septic tank or piped sewer, and residence in settlements rather than residential housing or villages (OR 1.6, 95% CI 1.0 to 2.7). Increasing seropositivity with age is suggestive of low-level endemic transmission in Fiji. Improved sanitation where pit latrines are used and addressing potential transmission routes in settlements may reduce exposure to S. Typhi. Widespread unreported infection suggests there may be a role for typhoid vaccination in Fiji, in addition to public health management of cases and outbreaks.

WER No. 2, 2017 pp. 13-20.
No Abstract Available.

WER No. 6, 2008, pp. 49–59.
No Abstract Available.

WER No. 39, 2015, pp. 505–510.
No Abstract Available.

WER No. 48, 2017, pp.729-747.
No Abstract Available.

WHO. Background paper to SAGE on Typhoid Policy Recommendations. 2017. Available at http://www.who.int/immunization/sage/meetings/2017/october/1_Typhoid_SAGE_background_paper_Final_v3B.pdf?ua=1, accessed February 2018.

Typhoid fever remains an important cause of enteric disease in children in Low and middle income countries with global estimates of disease burden ranging between 11 and 21 million typhoid fever cases and approximately 145 000 to 161 000 deaths annually.

Transmission of *Salmonella* Typhi is by the feco-oral route through a short-cycle (contamination of food and water in the immediate environment through inadequate hygiene and sanitation measures, either by shedding from temporary or chronic carriers) or long-cycle transmission (defined as contamination of the broader environment, such as pollution of water supplies by sewage, inadequate treatment of piped water or use of raw human feces as a crop fertiliser).

The often non-specific symptoms of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide range of other febrile illnesses common in typhoid fever endemic regions. Laboratory confirmation of cases by blood culture (the most commonly used diagnostic test) has a limited sensitivity of approximately 50% and is further complicated by the common practice of pre-treatment with antibiotics or is often not performed for the majority of cases in LMICs.

A consistent finding of typhoid fever disease burden studies in the last two decades has been the high incidence of typhoid fever in South and South-East Asia with marked intra-country heterogeneity in both age-specific and geographic incidence. New data from sub-Saharan Africa have improved the understanding of the burden and risk factors in that region. Furthermore, new data confirm that typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the 0-4 year age group with a large proportion of disease occurring between 6 months and 2 years of age. Among all age groups, 27% of typhoid fever episodes are estimated to occur in the age group 0-4 years; including 29.7% of typhoid fever episodes in the <2 year age group, 9.9% in the <1 year age group, and 2.9% in infants <6 months.

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination and appropriate antibiotic treatment are all effective strategies for prevention and control of typhoid fever. Multi-drug resistant (MDR) strains of *S.* Typhi emerged in the late 1980s leading to widespread use of fluoroquinolones, followed in the 1990s and 2000s by the appearance of fluoroquinolone resistant strains. More recently, MDR *S.* Typhi has caused large outbreaks in East Asia and Africa that are of significant concern. The *S.* Typhi H58 clade is responsible for much of the recent and current spread of resistant strains. AMR in typhoid fever leads to increased clinical treatment failure and complications, an increased frequency of hospital admission and prolonged hospital stay, and more expensive treatment options not affordable in many endemic settings.

Despite SAGE recommendations in 2008 for the use of Vi polysaccharide (ViPS) and Ty21a vaccines for the control of typhoid in endemic and epidemic settings, routine public health use has been very limited. The evidence review did not change the current recommendations for ViPS and Ty21a vaccines. Two Vi-tetanus toxoid (Vi-TT) conjugate vaccines are licensed in India. Based on the data available for review, the SAGE Working Group concluded that there is moderate-certainty evidence that at least one licensed Vi-TT vaccine (Typbar-TCV™ manufactured by Bharat Biotech International Limited) results in improved GMTs and seroconversion rates compared to ViPS vaccine (there are no comparative data with Ty21a). Further the data on co-administration of Typbar-TCV with measles-containing vaccines (measles and MMR) do not show evidence of interference with the immune responses to either vaccine. Data from a human challenge study using Typbar-TCV in a population of immunologically naïve adult volunteers produced an estimate of efficacy of 87.1% (95% CI 47.2-96.9%) based on an endpoint of persistent fever followed by positive blood culture. This was considered as good supporting evidence for the vaccine.

The available data from modelling indicate that routine immunization with TCV would lead to a gradual but sustained decrease in typhoid fever cases while routine vaccination with catch-up would lead to both an immediate and sustained decline in incidence. Further, cost-effectiveness analysis has shown that at a price of up to USD 2 per dose, routine vaccination with TCV is likely to be cost-effective in high incidence settings and in most medium incidence settings depending on the willingness to pay.

Currently, no reliable risk prediction tools are available to support implementation of typhoid vaccination programmes using a risk-based approach. Where reliable data are available to assess the level of typhoid fever incidence with confidence, the vaccine delivery strategy should take into account the local epidemiological and programmatic considerations. In particular, in countries with reliable epidemiological evidence of high incidence in well-defined sub-populations, a vaccination strategy based on risk assessment (high incidence population groups) should be considered. This may be particularly important for large countries where resources are limited. In countries with substantial typhoid fever burden but where surveillance does not allow characterisation of typhoid fever incidence among sub-populations, a universal (country-wide) strategy should be considered, and may prove more feasible and cost-effective.

Draft recommendations: The Working Group was tasked to address the following overall policy questions:

1. Should TCV be recommended in addition to the available ViPS and Ty21a vaccines for routine use in persons 2 years of age and older? (Critical question)

2. Should TCV be recommended for routine use in children less than 2 years of age? What should be the lower age limit for use in this group? (Critical question)

3. Should different recommendations be developed for use of the above vaccines in endemic settings versus outbreaks or humanitarian emergencies? (Non-critical question)

Based on its evidence review, the Working Group proposed the following draft recommendations for consideration by SAGE.

Recommendation for individuals 2 years and above

Given the continued high burden of typhoid fever and the increasing antimicrobial resistance of *S.* Typhi, and in view of the currently available evidence on safety, efficacy, feasibility, and affordability of at least one licensed typhoid conjugate vaccines and of the previously recommended ViPS and Ty21a vaccines, SAGE re-emphasizes the importance of the programmatic use of typhoid vaccines for controlling endemic disease.

Specifically, countries should consider the routine use of typhoid conjugate vaccine or ViPS vaccine or Ty21a vaccine in individuals aged 2 years and above. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS

and Ty21a, and supports a recommendation for its public health use. These vaccines should be given irrespective of the intensity of other control strategies.

Recommendation for children below 2 years

Given the high proportion of typhoid fever that is sufficiently severe to require outpatient or inpatient care in children <2 years in many areas, SAGE recommends the use of TCV in children <2 years of age, administered as a single dose at any time between 6 months to 23 months of age in endemic countries. The evidence reviewed for at least one licensed TCV (Typbar-TCV) demonstrate that it is likely offering longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use. The decision on the age of TCV administration should be based on the local epidemiology of typhoid fever, geographic heterogeneity, and taking into account programmatic considerations of the routine childhood immunization programme.

There are opportunities to administer one dose of TCV at 9 months of age with MCV1, or at 15-18 months of age with MCV2, recognizing that in many places the appreciable burden of typhoid fever starts to appear at 12 months of age.

Recommendation for vaccine use in outbreaks and humanitarian emergencies

Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended for outbreak control. Typhoid vaccines may be considered in humanitarian emergencies depending on the risk assessment in the local setting. However, it should be emphasized that the mainstay of typhoid fever prevention in such settings is often the provision of clean water and chlorination of water supplies, along with promotion of hygiene measures. The WHO has published guidance for the risk assessment of typhoid and other vaccine-preventable diseases in humanitarian settings as a framework for decision making on the use of vaccines in those settings.

Recommendations for special groups

SAGE recommends vaccination of the following specific groups of epidemiological relevance, by virtue of being at high risk or important for transmission, in line with the above age-appropriate recommendations. When ViPS or Ty21a is used, SAGE emphasizes the current recommendations for revaccination.

- **Clinical microbiology laboratory staff** with a recognized risk of occupational exposure to S. Typhi.

- **Professional food handlers**: where possible, preference for use of a Vi negative vaccine, such as Ty21a should be considered in order to protect the possibility for serological identification of a chronic carrier status among vaccinated persons. However, professional food handlers should not go unvaccinated due to lack of Ty21a vaccine. The value of not vaccinating this group (where Ty21a is not available) needs to be carefully weighed within the existing national policies.

- **Travellers from non-endemic to endemic areas**: Typhoid vaccination may be offered to travellers to destinations where the risk of typhoid fever is high. Where available, licensed combination Typhoid-Hepatitis A vaccines may be used for travellers.

General recommendations

- All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.

- Ideally, cost-effectiveness analyses should be part of the decision-making and planning process to initiate programmatic use of typhoid vaccines.

- SAGE recommends post-licensure monitoring of effectiveness of TCV (including serological and clinical endpoints) and robust monitoring of safety in line with the GACVS recommendations.
- SAGE recommends that countries monitor the occurrence of AMR strains of *S.* Typhi in endemic and epidemic disease and contribute to the global database on antimicrobial resistance.

WHO. Evidence to Recommendation Table: Typhoid Vaccines. Available at http://www.who.int/immunization/sage/meetings/2017/october/6_SAGE_Typhoid_E2R_Final.pdf?ua=1, accessed February 2018.
No Abstract Available.

WHO. List of prequalified vaccines. Available at https://extranet.who.int/gavi/PQ_Web/, accessed February 2018.
No Abstract Available.

WHO. Surveillance standards for typhoid and other invasive Samonellosis. In: WHO Vaccine Preventable Diseases Surveillance Standards. (In press).
No Abstract Available.

WHO. Typhoid Vaccine Standardization. 2013. Available at http://www.who.int/biologicals/vaccines/typhoid/en/, accessed February 2018.
No Abstract Available.

WHO. Vaccination in acute humanitarian emergencies. A Framework for decision making. 2017. Available at http://apps.who.int/iris/bitstream/10665/255575/1/WHO-IVB-17.03-eng.pdf, accessed February 2018.
Humanitarian emergencies, regardless of type and cause, have a number of common risk factors for communicable diseases inextricably linked to excess risk of morbidity and mortality which can come from vaccine–preventable diseases (VPDs). The reduction of VPDs is a significant aim of public-health interventions during crises. The WHO Strategic Advisory Group of Experts (SAGE) on Immunization carried out a comprehensive review of evidence on vaccination decision-making processes and considerations in humanitarian emergencies. This review resulted with decision-making framework which provides a transparent, evidence-based, and rigorous methodology for deciding on vaccination options in acute humanitarian emergencies. It consists of three essential steps: 1) assessing the local epidemiological risks of VPDs among the affected population, 2) vaccine selection and characteristics to consider, and 3) local contextual constraints that further assist in effective and timely decisions. The diagram below provides a schematic representation of this three-step approach in decision-making process. This framework is intended to guide decision making on vaccination interventions immediately after the onset or during planning in anticipation of a possible or likely acute emergency. It may be applied in emerging humanitarian emergencies, or crisis of short duration, and in long-standing crisis and conflicts resulting in protracted humanitarian emergencies. The concept of “acute” emergency does not imply that the emergency in itself is short-lived, as in a protracted crisis situations can emerge and be considered as “acute”. An acute emergency signifies a situation meeting one or more of the following conditions: sudden unplanned displacement of a large proportion of the population, direct exposure of the civilian population to new or exacerbated and sustained episodes of armed conflict, impending or already occurred sudden deterioration of nutritional status, natural or industrial disasters, and/or sudden breakdown of critical administrative and management functions which result in large-scale disruption of public health and related services. This decision-making framework is intended for senior-

level government and partner organization officials who are expected to work together to reach a decision regarding the need of vaccine antigen(s) in a given humanitarian emergency. It makes part of a package which also includes “Vaccination in Humanitarian Emergencies Implementation Guide”. Both documents are supported with electronic versions to ensure that the most up-to-date vaccine and disease-specific data, and references to additional information and
guidance are provided.

Wijedoru L et al. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD008892.

Background: Differentiating both typhoid (Salmonella Typhi) and paratyphoid (Salmonella Paratyphi A) infection from other causes of fever in endemic areas is a diagnostic challenge. Although commercial point-of-care rapid diagnostic tests (RDTs) for enteric fever are available as alternatives to the current reference standard test of blood or bone marrow culture, or to the widely used Widal Test, their diagnostic accuracy is unclear. If accurate, they could potentially replace blood culture as the World Health Organization (WHO)-recommended main diagnostic test for enteric fever. **Objectives:** To assess the diagnostic accuracy of commercially available rapid diagnostic tests (RDTs) and prototypes for detecting Salmonella Typhi or Paratyphi A infection in symptomatic persons living in endemic areas. **Search methods:** We searched the Cochrane Infectious Diseases Group Specialized Register, MEDLINE, Embase, Science Citation Index, IndMED, African Index Medicus, LILACS, ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) up to 4 March 2016. We manually searched WHO reports, and papers from international conferences on Salmonella infections. We also contacted test manufacturers to identify studies. **Selection criteria:** We included diagnostic accuracy studies of enteric fever RDTs in patients with fever or with symptoms suggestive of enteric fever living in endemic areas. We classified the reference standard used as either Grade 1 (result from a blood culture and a bone marrow culture) or Grade 2 (result from blood culture and blood polymerase chain reaction, or from blood culture alone). **Data collection and analysis**: Two review authors independently extracted the test result data. We used a modified QUADAS-2 extraction form to assess methodological quality. We performed a meta-analysis when there were sufficient studies for the test and heterogeneity was reasonable. **Main results**: Thirty-seven studies met the inclusion criteria and included a total of 5080 participants (range 50 to 1732). Enteric fever prevalence rates in the study populations ranged from 1% to 75% (median prevalence 24%, interquartile range (IQR) 11% to 46%). The included studies evaluated 16 different RDTs, and 16 studies compared two or more different RDTs. Only three studies used the Grade 1 reference standard, and only 11 studies recruited unselected febrile patients. Most included studies were from Asia, with five studies from sub-Saharan Africa. All of the RDTs were designed to detect S.Typhi infection only. Most studies evaluated three RDTs and their variants: TUBEX in 14 studies; Typhidot (Typhidot, Typhidot-M, and TyphiRapid-Tr02) in 22 studies; and the Test-It Typhoid immunochromatographic lateral flow assay, and its earlier prototypes (dipstick, latex agglutination) developed by the Royal Tropical Institute, Amsterdam (KIT) in nine studies. Meta-analyses showed an average sensitivity of 78% (95% confidence interval (CI) 71% to 85%) and specificity of 87% (95% CI 82% to 91%) for TUBEX; and an average sensitivity of 69% (95% CI 59% to 78%) and specificity of 90% (95% CI 78% to 93%) for all Test-It Typhoid and prototype tests (KIT). Across all forms of the Typhidot test, the average sensitivity was 84% (95% CI 73% to 91%) and specificity was 79% (95% CI 70% to 87%). When we based the analysis on the 13 studies of the Typhidot test that either reported indeterminate test results or where the test format means there are no indeterminate results, the average sensitivity was 78% (95% CI 65% to 87%) and specificity was 77% (95% CI 66% to 86%). We did not identify any difference in either sensitivity or specificity between TUBEX, Typhidot, and Test-it Typhoid tests when based on comparison to the 13 Typhidot studies where indeterminate results are either reported or not applicable. If TUBEX and Test-it Typhoid are compared to all Typhidot studies, the

sensitivity of Typhidot was higher than Test-it Typhoid (15% (95% CI 2% to 28%), but other comparisons did not show a difference at the 95% level of CIs. In a hypothetical cohort of 1000 patients presenting with fever where 30% (300 patients) have enteric fever, on average Typhidot tests reporting indeterminate results or where tests do not produce indeterminate results will miss the diagnosis in 66 patients with enteric fever, TUBEX will miss 66, and Test-It Typhoid and prototype (KIT) tests will miss 93. In the 700 people without enteric fever, the number of people incorrectly diagnosed with enteric fever would be 161 with Typhidot tests, 91 with TUBEX, and 70 with Test-It Typhoid and prototype (KIT) tests. The CIs around these estimates were wide, with no difference in false positive results shown between tests. The quality of the data for each study was evaluated using a standardized checklist called QUADAS-2. Overall, the certainty of the evidence in the studies that evaluated enteric fever RDTs was low. **Authors' conclusions**: In 37 studies that evaluated the diagnostic accuracy of RDTs for enteric fever, few studies were at a low risk of bias. The three main RDT tests and variants had moderate diagnostic accuracy. There was no evidence of a difference between the average sensitivity and specificity of the three main RDT tests. More robust evaluations of alternative RDTs for enteric fever are needed.

Wong VK et al. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events. Nat Genet. 2015;47:632–639.

The emergence of multidrug-resistant (MDR) typhoid is a major global health threat affecting many countries where the disease is endemic. Here whole-genome sequence analysis of 1,832 Salmonella enterica serovar Typhi (S. Typhi) identifies a single dominant MDR lineage, H58, that has emerged and spread throughout Asia and Africa over the last 30 years. Our analysis identifies numerous transmissions of H58, including multiple transfers from Asia to Africa and an ongoing, unrecognized MDR epidemic within Africa itself. Notably, our analysis indicates that H58 lineages are displacing antibiotic-sensitive isolates, transforming the global population structure of this pathogen. H58 isolates can harbor a complex MDR element residing either on transmissible IncHI1 plasmids or within multiple chromosomal integration sites. We also identify new mutations that define the H58 lineage. This phylogeographical analysis provides a framework to facilitate global management of MDR typhoid and is applicable to similar MDR lineages emerging in other bacterial species.

Wong VK et al. An extended genotyping framework for Salmonella enterica serovar Typhi, the cause of human typhoid. Nat Commun. 2016;7:12827.

The population of Salmonella enterica serovar Typhi (S. Typhi), the causative agent of typhoid fever, exhibits limited DNA sequence variation, which complicates efforts to rationally discriminate individual isolates. Here we utilize data from whole-genome sequences (WGS) of nearly 2,000 isolates sourced from over 60 countries to generate a robust genotyping scheme that is phylogenetically informative and compatible with a range of assays. These data show that, with the exception of the rapidly disseminating H58 subclade (now designated genotype 4.3.1), the global S. Typhi population is highly structured and includes dozens of subclades that display geographical restriction. The genotyping approach presented here can be used to interrogate local S. Typhi populations and help identify recent introductions of S. Typhi into new or previously endemic locations, providing information on their likely geographical source. This approach can be used to classify clinical isolates and provides a universal framework for further experimental investigations.

Yang HH et al. Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. Bull World Health Organ. 2001;79:625-631.

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 significantly in China.

Yousafzai MT et al. Outbreak investigation of cefriaxone resistant S. Typhi in Hyderabad, Pakistan. 10th International Conference on Typhoid and other Invasive Salmonellosis. April 4-6,2017. Kampala, Uganda.
No Abstract Available.

Zhou WZ et al. Revaccination with locally-produced Vi typhoid polysaccharide vaccine among Chinese school-aged children: safety and immunogenicity findings. Pediatr Infect Dis J. 2007;26:1001-1005.
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 μg 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.