



START CENTER
STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

TYPHOID FEVER LITERATURE SEARCH

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER

REPORT TO THE BILL AND MELINDA GATES FOUNDATION

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INTRODUCTION

The Vaccine Delivery Team at the Bill & Melinda Gates Foundation engaged the Strategic Analysis, Research & Training (START) Center at the University of Washington to identify peer-reviewed and grey literature that contributed to the current scientific knowledge of typhoid fever since 2007. The literature search was conducted with the goal of sharing the results with the World Health Organization (WHO) to potentially contribute to the review of evidence in support of typhoid fever vaccination policy and future development of technical resources and guidance on typhoid fever and typhoid fever vaccines.

The START team conducted a primary search in PubMed and a secondary validation search with Google Scholar using a combination of search terms including *typhoid*, *typhoid fever*, *S typhi*, *S paratyphi*, **typhi*, **paratyphi*, *salmonella typhi* and *salmonella paratyphi*. The search was restricted to human subject studies published between January 2007 and the date of search (July 2016), and focused on the following five areas:

1. Epidemiological patterns and global burden of typhoid fever (including incidence rates, age distribution patterns, risk factors for infection, severity and complications), including typhoid fever outbreaks
2. Disease and environmental surveillance
3. Economic burden of typhoid fever, economic evaluation of vaccination and other control strategies.
4. Recent trends in antibiotic resistance of *Salmonella typhi*
5. Challenge models and vaccine trials

The START team excluded lab studies, non-typhoid fever-related studies, typhoid fever diagnostic studies, and studies on traveler's preparedness through a title, abstract, and two consensus reviews.

The content of this document consists of the abstract, reference, and hyperlink to the articles identified and selected through the START team's literature search and review. Articles are organized by the five areas. Some articles contain information relevant to more than one area, and they are listed under each category section of the document (additional categories are indicated along with reference for each article).



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EPIDEMIOLOGICAL PATTERNS AND GLOBAL BURDEN OF TYPHOID FEVER

Enteric fever in Karachi: current antibiotic susceptibility of *Salmonellae* isolates.

Author	Abdullah FE, Haider F, Fatima K, Irfan S, Iqbal MS.
Publication	J Coll Physicians Surg Pak. 2012 Mar;22(3):147-50.
URL	Not publically available
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

OBJECTIVE: To determine the current sensitivity and resistance profile of *Salmonellae* (S.) isolates in a laboratory setting. **STUDY DESIGN:** An observational study. **PLACE AND DURATION OF STUDY:** Dr. Essa's Laboratory and Diagnostic Centre, Karachi, Pakistan, from November 2008 - October 2010. **METHODOLOGY:** Isolates from blood culture specimens of 481 bacteraemic patients were identified using conventional biochemical tests. *Salmonellae* was confirmed with specific antisera and their antibiograms determined by Kirby-Bauer Disc Diffusion method using 12 relevant antibiotics. Inclusions of the study were bacteraemia documented in all blood samples positive for *S. typhi*, *S. paratyphi-A* and *B*. Exclusions were all samples other than blood and blood samples negative for *S. typhi* and *S. paratyphi-A* and *B* during the same period. Multidrug resistance (MDR) of isolates was defined as the isolates showing resistance to all conventional anti-typhoid medicines i.e., Chloramphenicol, Ampicillin and Co-trimoxazole. **RESULTS:** Specimens (n=217) yielded 131 *Salmonellae typhi* (60.36%), 71 *S. paratyphi-A* (32.71%), and 15 *S. paratyphi-B* (6.9%); these were sensitive to the Quinolones [Enoxacin: 94.96% (n=91), Ciprofloxacin, 96.47% (n=182), Ofloxacin: 95.74% (n=203)], and Cephalosporins [Cefixime: 96.62% (n=202), Cefotaxime: 99.17% (n=206), Ceftriaxone: 98.79% (n=208)]. Resistance to Amoxicillin was 96.48% (n=128) and 29.91% (n=78) to Co-trimoxazole. About 62.64% (n=136) of the isolates were MDR strains. **CONCLUSION:** Ciprofloxacin is currently a suitable empirical choice in presumed enteric fever cases, but culture and sensitivity analysis should be encouraged and results incorporated in prescription strategy. Increasing frequency of *S. paratyphi-A* isolates possibly suggests incomplete coverage employing monovalent vaccine.

Public health management of *Salmonella Typhi*/Paratyphi case and contact screening: lessons from North London.

Author	Addiman S, Maimaris W, Thomas HL, White G, Lawrence J, Balasegaram S.
Publication	Public Health. 2013 Mar;127(3):207-13.
URL	http://ac.els-cdn.com/S0033350612004647/1-s2.0-S0033350612004647-main.pdf?_tid=2bcd0950-6a4c-11e6-a284-00000aacb361&acdnat=1472078786_09da3568a5ad544c4e9554f9d4ac82a2

OBJECTIVES: To evaluate the public health management *Salmonella enterica* serovar Typhi (typhoid) and *Salmonella enterica* serovar Paratyphi (paratyphoid) cases and their contacts to assess the outcome of screening. **STUDY DESIGN:** Retrospective case note review. **METHODS:** 329 cases and 1153 contacts from North London over a four year period were reviewed. Structured questionnaires were developed to capture travel history, relationship between case/contact and the number, timing and documented results of faecal specimens. Evaluation of compliance with the clearance/screening schedule was examined and the positive yield of faecal samples for cases and contacts was calculated. **RESULTS:** 1% (3/329) of cases had a positive clearance sample; all were identified on their first faecal specimen. Of the 645 contacts who were screened, only 10 (1.5%), all of whom had travelled with the index case, were

positive. Person-to-person transmission was only identified for two UK acquired cases, where possible carrier sources were identified outside the screening schedule. **CONCLUSION:** The lack of evidence of secondary transmission from acute cases, coupled with the low positive yield from clearance samples support the revision of the national guidance for the public health management of cases of enteric fever and their contacts.

Factors associated with typhoid relapse in the era of multiple drug resistant strains.	
Author	Ahmad KA, Khan LH, Roshan B, Bhutta ZA.
Publication	J Infect Dev Ctries. 2011 Oct 13;5(10):727-31.
URL	http://www.jidc.org/index.php/journal/article/view/21997942/615
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

INTRODUCTION: Typhoid has an estimated global burden of greater than 27 million cases per annum with a clinical relapse rate of 5% to 20%. Despite the large relapse burden, the factors associated with relapse are largely unknown. **METHODOLOGY:** We have followed a protocol for the diagnosis and management of pediatric typhoid since 1988. We report factors associated with relapse of culture-proven enteric fever in 1,650 children presenting to the Aga Khan University Medical Center, Karachi, Pakistan, over a 15-year period. **RESULTS:** In those infected with multiple drug resistant (MDR) strains, factors associated with subsequent relapse include constipation at presentation and presentation within 14 days of fever onset. Diarrhoea in those children infected with drug sensitive strains had an association with decreased subsequent relapse, as was quinolone therapy. **CONCLUSIONS:** Multiple clinical factors at presentation are associated with subsequent typhoid fever relapse. These factors may be postulated to be associated with subsequent relapse due to alterations in the reticuloendothelial system organism load. These data will be valuable in developing algorithms for clinical follow-up in children infected with MDR enteric fever.

Investigation of the outbreak of typhoid in a village of Thar Desert Rajasthan, India.	
Author	Anand PK, Ramakrishnan R.
Publication	Indian J Med Res. 2010 Jun;131:799-803.
URL	http://www.ijmr.org.in/downloadpdf.asp?issn=0971-5916;year=2010;volume=131;issue=6;spage=799;epage=803;aulast=Anand;type=2
Additional Categories	Disease and environmental surveillance

BACKGROUND & OBJECTIVES: Outbreaks of typhoid have been reported from Maharashtra, Bangalore, West Bengal and Pondicherry in India but rarely from Rajasthan. We investigated an outbreak of typhoid in a village of Thar Desert of Rajasthan. **METHODS:** A retrospective cohort study was carried out during May-July 2007 in Varkana village, Pali district, Rajasthan, to identify the risk factor for disease. The information on outbreak was collected and then described in time, place and person characteristics to arrive at aetiological hypotheses. **RESULTS:** There were 219 cases of typhoid in village. Attack rate was 104 cases per 1000 population. Maximum attack rate of 276 cases per 1000 population was noted in persons of 10-14 yr age group. Forty three serum samples were reported positive for Widal agglutination test out of 70 tested. Drinking of water from government overhead tanks was associated with disease significantly (RR= 11.1, 95% CI= 3.7-33). Two of the three water samples from government tanks were found positive for faecal contamination. **INTERPRETATION & CONCLUSION:** The outbreak of



typhoid in a village affected >200 persons of all age groups and both gender. Exposure to the drinking water from government tanks was found significantly associated with the disease. Preventive and control measures undertaken after analytical epidemiological study helped in terminating the outbreak.

Risk factors for typhoid outbreak in Sungai Congkak Recreational Park, Selangor 2009.

Author	Anita S, Amir KM, Fadzilah K, Ahamad J, Noorhaida U, Marina K, Paid MY, Hanif Z.
Publication	Med J Malaysia. 2012 Feb;67(1):12-6.
URL	http://www.e-mjm.org/2012/v67n1/Typhoid_Outbreak.pdf
Additional Categories	Disease and environmental surveillance

Typhoid fever continues to pose public health problems in Selangor where cases are found sporadically with occasional outbreaks reported. In February 2009, Hospital Tengku Ampuan Rahimah (HTAR) reported a cluster of typhoid fever among four children in the pediatric ward. We investigated the source of the outbreak, risk factors for the infection to propose control measures. We conducted a case-control study to identify the risk factors for the outbreak. A case was defined as a person with *S. typhi* isolated from blood, urine or stool and had visited Sungai Congkak recreational park on 27th January 2010. Controls were healthy household members of cases who have similar exposure but no isolation of *S. typhi* in blood, urine or stool. Cases were identified from routine surveillance system, medical record searching from the nearest clinic and contact tracing other than family members including food handlers and construction workers in the recreational park. Immediate control measures were initiated and followed up. Twelve (12) cases were identified from routine surveillance with 75 household controls. The Case-control study showed cases were 17 times more likely to be 12 years or younger (95% CI: 2.10, 137.86) and 13 times more likely to have ingested river water accidentally during swimming (95% CI: 3.07, 58.71). River water was found contaminated with sewage disposal from two public toilets which effluent grew salmonella spp. The typhoid outbreak in Sungai Congkak recreational park resulted from contaminated river water due to poor sanitation. Children who accidentally ingested river water were highly susceptible. Immediate closure and upgrading of public toilet has stopped the outbreak.

Epidemiological characteristics and molecular typing of *Salmonella enterica* serovar Typhi during a waterborne outbreak in Eastern Anatolia.

Author	Bayram Y, Gdcođlu H, Otl B, Aypak C, Grsoy NC, Uluç H, Berktaş M.
Publication	Ann Trop Med Parasitol. 2011 Jul;105(5):359-65.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4089787/pdf/atm-105-05-359.pdf
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

In this study, we aimed to study the molecular and epidemiological characteristics of *Salmonella enterica* serovar Typhi (*S. Typhi*) outbreak in Eastern Anatolia. Six hundred and thirty-seven patients from the same county with clinical diagnosis of typhoid fever were investigated with conventional methods from stool, urine and blood specimens. Antibiotic susceptibility tests and identifications were performed for positive specimens. Clonal relationships between the isolates were investigated using pulsed field gel electrophoresis (PFGE) method. A questionnaire was completed for the water consumption habits of patients. Of 91 culture positive specimens, 76 were blood, 13 were stool and 2 were urine. The isolates were resistant to ampicillin, ampicillin/sulbactam, chloramphenicol, cefuroxime,



amikacin, gentamicin and trimethoprim-sulfamethoxazole. Although there was a single band difference in some isolates, PFGE results indicated that this was an outbreak caused by single strain according to the Tenover criteria. This outbreak thought to be associated with the consumption of tap water contaminated with sewage represents a breakdown of the basic public health and civil engineering infrastructure. Appropriate public health measures should be taken in order to avoid such outbreaks in the future.

Cluster of indigenous typhoid fever cases in a French city.	
Author	Baclet N, Haeghebaert S, Legout L, Caillaux M, Moreau-Crepeaux S, Vachée A, Senneville E, Chaud P, Yazdanpanah Y, Poissy J.
Publication	Med Mal Infect. 2011 May;41(5):248-52.
URL	Not publically available
Additional Categories	Disease and environmental surveillance

[Article in French]

BACKGROUND: A cluster of indigenous typhoid fever cases in the greater Lille area, in January 2009, triggered investigations to identify the contamination source and to optimize care for infected individuals. **METHODS:** A case was defined as a person, living in the greater Lille area of, having presented with symptoms of typhoid fever, from January to March 2009. **RESULTS:** Sixteen cases of typhoid fever were identified between January 23 and March 22, 2009. Patients, none of whom had travelled, had all participated in a common meal on January 10, 2009. A woman, who helped prepare the meal and who had previously stayed in an endemic zone, was detected as the asymptomatic carrier of *Salmonella typhi*. **CONCLUSION:** In France, although typhoid fever remains essentially an imported disease, there is a risk of indigenous epidemic and its diagnosis can be suggested for individuals who have not travelled. The features of this cluster illustrate the importance of respecting basic rules of hygiene in catering.

A typhoid fever outbreak in a slum of South Dumdum municipality, West Bengal, India, 2007: evidence for foodborne and waterborne transmission.	
Author	Bhunia R, Hutin Y, Ramakrishnan R, Pal N, Sen T, Murhekar M.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683821/
Publication	BMC Public Health. 2009 Apr 27;9:115.

BACKGROUND: In April 2007, a slum of South Dumdum municipality, West Bengal reported an increase in fever cases. We investigated to identify the agent, the source and to propose recommendations. **METHODS:** We defined a suspected case of typhoid fever as occurrence of fever for $\geq$ one week among residents of ward 1 of South Dumdum during February – May 2007. We searched for suspected cases in health care facilities and collected blood specimens. We described the outbreak by time, place and person. We compared probable cases (Widal positive $\geq$ 1:80) with neighbourhood-matched controls. We assessed the environment and collected water specimens. **RESULTS:** We identified 103 suspected cases (Attack rate: 74/10,000, highest among 5-14 years old group, no deaths). *Salmonella* (enterica) Typhi was isolated from one of four blood specimens and 65 of 103 sera were $\geq$ 1:80 Widal positive. The outbreak started on 13 February, peaked twice during the last week of March and second week of April and lasted till 27 April. Suspected cases clustered around three public taps. Among 65 probable cases and 65 controls, eating milk products from a sweet shop (Matched odds ratio [MOR]: 6.2, 95%



confidence interval [CI]: 2.4-16, population attributable fraction [PAF]: 53%) and drinking piped water (MOR: 7.3, 95% CI: 2.5-21, PAF-52%) were associated with illness. The sweet shop food handler suffered from typhoid in January. The pipelines of intermittent non-chlorinated water supply ran next to an open drain connected with sewerage system and water specimens showed faecal contamination. CONCLUSION: The investigation suggested that an initial foodborne outbreak of typhoid led to the contamination of the water supply resulting in a secondary, waterborne wave. We educated the food handler, repaired the pipelines and ensured chlorination of the water.

Typhoid fever and paratyphoid fever: Systematic review of estimate global morbidity and mortality for 2010.

Author	Buckle GC, Fischer-Walker CL, Black R.
Publication	J Glob Health. 2012 June; 2(1): 010401.
URL	http://pubmedcentralcanada.ca/pmcc/articles/PMC3484760/pdf/jogh-02-010401.pdf

BACKGROUND: Typhoid and paratyphoid fever remain important causes of morbidity worldwide. Accurate disease burden estimates are needed to guide policy decisions and prevention and control strategies. **METHODS:** We conducted a systematic literature review of the PubMed and Scopus databases using pre-defined criteria to identify population-based studies with typhoid fever incidence data published between 1980 and 2009. We also abstracted data from annual reports of notifiable diseases in countries with advanced surveillance systems. Typhoid and paratyphoid fever input data were grouped into regions and regional incidence and mortality rates were estimated. Incidence data were extrapolated across regions for those lacking data. Age-specific incidence rates were derived for regions where age-specific data were available. Crude and adjusted estimates of the global typhoid fever burden were calculated. **RESULTS:** Twenty-five studies were identified, all of which contained incidence data on typhoid fever and 12 on paratyphoid fever. Five advanced surveillance systems contributed data on typhoid fever; 2 on paratyphoid fever. Regional typhoid fever incidence rates ranged from <1/100,000 in Central and Eastern Europe and Central Asia to 724.6/100000 in Sub-Saharan Africa. Regional paratyphoid incidence rates ranged from 0.8/100000 in North Africa/Middle East to 77.4/100000 in Sub-Saharan Africa and South Asia. The estimated total number of typhoid fever episodes in 2010 was 13.5 million (interquartile range 9.1–17.8 million). The adjusted estimate accounting for the low sensitivity of blood cultures for isolation of the bacteria was 26.9 million (interquartile range 18.3–35.7 million) episodes. These findings are comparable to the most recent analysis of global typhoid fever morbidity, which reported crude and adjusted estimates of 10.8 million and 21.7 million typhoid fever episodes globally in 2000. **CONCLUSION:** Typhoid fever remains a significant health burden, especially in low- and middle-income countries. Despite the availability of more recent data on both enteric fevers, additional research is needed in many regions, particularly Africa, Latin America and other developing countries.



Economic evaluation of typhoid vaccination in a prolonged typhoid outbreak setting: the case of Kasese district in Uganda.

Author	Carias C, Walters MS, Wefula E, Date KA, Swerdlow DL, Vijayaraghavan M, Mintz E
Publication	Vaccine. 2015 Apr 21;33(17):2079-85.
URL	Not publically available
Additional Categories	Economic burden of typhoid, economic evaluation of vaccination

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.

The contribution of neighbours to an individual's risk of typhoid outcome.

Author	Chao DL, Park JK, Marks F, Ochiai RL, Longini IM, Halloran ME.
Publication	Epidemiol Infect. 2015 Dec;143(16):3520-7.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619120/

An individual's risk of infection from an infectious agent can depend on both the individual's own risk and protective factors and those of individuals in the same community. We hypothesize that an individual's exposure to an infectious agent is associated with the risks of infection of those living nearby, whether their risks are modified by pharmaceutical interventions or by other factors, because of the potential for transmission from them. For example, unvaccinated individuals living in a highly vaccinated community can benefit from indirect protection, or living near more children in a typhoid-endemic region (where children are at highest risk) might result in more exposure to typhoid. We tested this hypothesis using data from a cluster-randomized typhoid vaccine trial. We first estimated each individual's relative risk of confirmed typhoid outcome using their vaccination status and age. We defined a new covariate, potential exposure, to be the sum of the relative risks of all who live within 100 m of each person. We found that potential exposure was significantly associated with an individual's typhoid outcome, and adjusting for potential exposure affected estimates of vaccine efficacy. We suggest that it is useful and feasible to adjust for spatially heterogeneous distributions of individual-level risk factors, but further work is required to develop and test such approaches.



Spatial analyses of typhoid fever in Jiangsu province, People's Republic of China.

Author	Cheng YJ, Tang FY, Bao CJ, Zhu YF, Liang Q, Hu JL, Liu WD, Wu Y, Reilly KH, Shen TQ, Zhao Y, Peng ZH, Yu RB, Wang H, Shen HB, Chen F.
Publication	Geospat Health. 2013 May;7(2):279-88.
URL	http://geospatialhealth.net/index.php/gh/article/view/86/86

An analysis of the geographical distribution of typhoid incidence rates, based on various statistical approaches such as trend surface, spatial autocorrelation, spatial correlation and spatial regression, was carried out at the county level in Jiangsu province, People's Republic of China. Temperature, moisture content, proximity to water bodies and the normalized difference vegetation index in the autumn were the four underlying factors found to contribute the most to the development of the epidemic. Typhoid infection was most severe in the south-eastern region of Jiangsu and a significant hotspot with high positive autocorrelation was detected in Taicang county in the south-east of the province. To improve the typhoid situation, intervention efforts should be concentrated in the south-eastern region of the province, targeting the hotspot and include reduction of lake pollution.

Modelling typhoid risk in Dhaka metropolitan area of Bangladesh: the role of socio-economic and environmental factors.

Author	Corner RJ, Dewan AM, Hashizume M.
Publication	Int J Health Geogr. 2013 Mar 16;12:13.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3610306/pdf/1476-072X-12-13.pdf

BACKGROUND: Developing countries in South Asia, such as Bangladesh, bear a disproportionate burden of diarrhoeal diseases such as cholera, typhoid and paratyphoid. These seem to be aggravated by a number of social and environmental factors such as lack of access to safe drinking water, overcrowdedness and poor hygiene brought about by poverty. Some socioeconomic data can be obtained from census data whilst others are more difficult to elucidate. This study considers a range of both census data and spatial data from other sources, including remote sensing, as potential predictors of typhoid risk. Typhoid data are aggregated from hospital admission records for the period from 2005 to 2009. The spatial and statistical structures of the data are analysed and principal axis factoring is used to reduce the degree of co-linearity in the data. The resulting factors are combined into a quality of life index, which in turn is used in a regression model of typhoid occurrence and risk. **RESULTS:** The three principal factors used together explain 87% of the variance in the initial candidate predictors, which eminently qualifies them for use as a set of uncorrelated explanatory variables in a linear regression model. Initial regression result using ordinary least squares (OLS) were disappointing, this was explainable by analysis of the spatial autocorrelation inherent in the principal factors. The use of geographically weighted regression caused a considerable increase in the predictive power of regressions based on these factors. The best prediction, determined by analysis of the Akaike information criterion (AIC) was found when the three factors were combined into a quality of life index, using a method previously published by others, and had a coefficient of determination of 73%. **CONCLUSIONS:** The typhoid occurrence/risk prediction equation was used to develop the first risk map showing areas of Dhaka metropolitan area whose inhabitants are at greater or lesser risk of typhoid infection. This, coupled with seasonal information on typhoid incidence also reported in this paper, has the potential to advise public health professionals on developing prevention strategies such as targeted vaccination.



Global trends in typhoid and paratyphoid fever.

Author	Crump JA. Mintz ED.
Publication	Clin Infect Dis. 2010 Jan 15;50(2):241-6.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2798017/
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and Southeast Asia, where enteric fever is associated with poor sanitation and unsafe food and water. High-quality incidence data from Asia are underpinning efforts to expand access to typhoid vaccines. Efforts are underway to develop vaccines that are immunogenic in infants after a single dose and that can be produced locally in countries of endemicity. The growing importance of *Salmonella enterica* serotype Paratyphi A in Asia is concerning. Antimicrobial resistance has sequentially emerged to traditional first-line drugs, fluoroquinolones, and third-generation cephalosporins, posing patient treatment challenges. Azithromycin has proven to be an effective alternative for treatment of uncomplicated typhoid fever. The availability of full genome sequences for *S. enterica* serotype Typhi and *S. enterica* serotype Paratyphi A confirms their place as monomorphic, human-adapted pathogens vulnerable to control measures if international efforts can be redoubled.

Typhoid fever vaccination strategies.

Author	Date KA, Bentsi-Enchill A, Marks F, Fox K.
Publication	Vaccine. 2015 Jun 19;33 Suppl 3:C55-61.
URL	Not publically available
Additional Categories	Challenge models and vaccine trials

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



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

Typhoid fever and its association with environmental factors in the Dhaka Metropolitan Area of Bangladesh: a spatial and time-series approach.

Author	Dewan AM, Corner R, Hashizume M, Ongee ET.
Publication	PLoS Negl Trop Dis. 2013;7(1):e1998.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3554574/pdf/pntd.0001998.pdf

Typhoid fever is a major cause of death worldwide with a major part of the disease burden in developing regions such as the Indian sub-continent. Bangladesh is part of this highly endemic region, yet little is known about the spatial and temporal distribution of the disease at a regional scale. This research used a Geographic Information System to explore, spatially and temporally, the prevalence of typhoid in Dhaka Metropolitan Area (DMA) of Bangladesh over the period 2005-9. This paper provides the first study of the spatio-temporal epidemiology of typhoid for this region. The aims of the study were: (i) to analyse the epidemiology of cases from 2005 to 2009; (ii) to identify spatial patterns of infection based on two spatial hypotheses; and (iii) to determine the hydro-climatological factors associated with typhoid prevalence. Case occurrences data were collected from 11 major hospitals in DMA, geocoded to census tract level, and used in a spatio-temporal analysis with a range of demographic, environmental and meteorological variables. Analyses revealed distinct seasonality as well as age and gender differences, with males and very young children being disproportionately infected. The male-female ratio of typhoid cases was found to be 1.36, and the median age of the cases was 14 years. Typhoid incidence was higher in male population than female ($\chi^2 = 5.88$, $p < 0.05$). The age-specific incidence rate was highest for the 0-4 years age group (277 cases), followed by the 60+ years age group (51 cases), then there were 45 cases for 15-17 years, 37 cases for 18-34 years, 34 cases for 35-39 years and 11 cases for 10-14 years per 100,000 people. Monsoon months had the highest disease occurrences (44.62%) followed by the pre-monsoon (30.54%) and post-monsoon (24.85%) season. The Student's t test revealed that there is no significant difference on the occurrence of typhoid between urban and rural environments ($p > 0.05$). A statistically significant inverse association was found between typhoid incidence and distance to major waterbodies. Spatial pattern analysis showed that there was a significant clustering of typhoid distribution in the study area. Moran's I was highest (0.879; $p < 0.01$) in 2008 and lowest (0.075; $p < 0.05$) in 2009. Incidence rates were found to form three large, multi-centred, spatial clusters with no significant difference between urban and rural rates. Temporally, typhoid incidence was seen to increase with temperature, rainfall and river level at time lags ranging from three to five weeks. For example, for a 0.1 metre rise in river levels, the number of typhoid cases increased by 4.6% (95% CI: 2.4-2.8) above the threshold of 4.0 metres (95% CI: 2.4-4.3). On the other hand, with a 1 °C rise in temperature, the number of typhoid cases could increase by 14.2% (95% CI: 4.4-25.0).



Trends and disease burden of enteric fever in Guangxi province, China, 1994-2004.

Author	Dong BQ, Yang J, Wang XY, Gong J, von Seidlein L, Wang ML, Lin M, Liao HZ, Ochiai RL, Xu ZY, Jodar L, Clemens JD.
Publication	Bull World Health Organ. 2010 Sep 1;88(9):689-96.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2930361/
Additional Categories	Disease and environmental surveillance

OBJECTIVE: To determine the burden of enteric fever through trends in morbidity and mortality, bacterial species and antimicrobial resistance in Guangxi, a southern, subtropical, coastal province of China with a disproportionally large burden of enteric fever. **METHODS:** Data on morbidity and mortality caused by enteric fever between 1994 and 2004 were extracted from the Guangxi Center for Disease Control and Prevention. Laboratory-based surveillance and outbreak investigations were integrated with reports of notifiable infectious diseases to estimate the bacterial species-specific incidence of enteric fever. To adjust for underreporting, survey data were collected from three prefectures that represent the hyper-, moderate-and low-endemic regions of Guangxi province. **FINDINGS:** In Guangxi province, enteric fever incidence rate varied over the study period, with a peak of 13.5 cases per 100 000 population in 1995 and a low of 6.5 in 2003. The disease occurred most frequently during the summer and autumn months and in the group aged 10-49 years. The incidence of enteric fever varied by region within Guangxi province. During the 11-year period covered by the study, 61 outbreaks of enteric fever were reported, and *Salmonella paratyphi A* (SPA) became the predominant causative agent in the province. **CONCLUSION:** Prospective studies may provide a better understanding of the reason for the shifting epidemiology of enteric fever in Guangxi province. Given the emergence of resistance to first- and second-line antimicrobials for the treatment of enteric fever, a bivalent vaccine against both SPA and *S. typhi* would facilitate for disease control.

Burden of typhoid fever in Sulaimania, Iraqi Kurdistan.

Author	Dworkin J, Saeed R, Mykhan H, Kanan S, Farhad D, Ali KO, Abdulwahab RH, Palardy J, Neill MA.
Publication	Int J Infect Dis. 2014 Oct;27:70-3.
URL	http://www.sciencedirect.com/science/article/pii/S1201971214015896

BACKGROUND: Typhoid fever imposes a high disease burden worldwide, but resource limitations mean that the burden of typhoid fever in many countries is poorly understood. **METHODS:** The authors conducted a prospective surveillance study at the adult and pediatric teaching hospitals in Sulaimania, Iraqi Kurdistan. All patients presenting with an undifferentiated febrile illness consistent with typhoid were eligible for enrollment. Enrolled patients had blood cultures and *Brucella* serologies performed. Incidence was calculated with reference to census data. **RESULTS:** Both typhoid fever and brucellosis were common, and the incidence of typhoid fever was 21 cases/100 000 patient-years. Classic disease symptoms were uncommonly observed. **DISCUSSION:** Cost-effective surveillance projects to calculate disease burden of typhoid fever are practical and replicable. Typhoid has successfully adapted to the healthcare environment in Sulaimania. Additional work in the region should focus on antibiotic resistance and other enteric pathogens such as *Brucella* spp.



Enteric fever in Cambodian children is dominated by multidrug-resistant H58 *Salmonella enterica* serovar Typhi with intermediate susceptibility to ciprofloxacin.

Author	Emary K, Moore CE, Chanpheaktra N, An KP, Chheng K, Sona S, Duy PT, Nga TV, Wuthiekanun V, Amornchai P, Kumar V, Wijedoru L, Stoesser NE, Carter MJ, Baker S, Day NP, Parry CM.
Publication	Trans R Soc Trop Med Hyg. 2012 Dec;106(12):718-24.
URL	http://www.sciencedirect.com/science/article/pii/S0035920312001745
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

Infections with *Salmonella enterica* serovar Typhi isolates that are multidrug resistant (MDR: resistant to chloramphenicol, ampicillin, trimethoprim-sulphamethoxazole) with intermediate ciprofloxacin susceptibility are widespread in Asia but there is little information from Cambodia. We studied invasive salmonellosis in children at a paediatric hospital in Siem Reap, Cambodia. Between 2007 and 2011 *Salmonella* was isolated from a blood culture in 162 children. There were 151 children with enteric fever, including 148 serovar Typhi and three serovar Paratyphi A infections, and 11 children with a non-typhoidal *Salmonella* infection. Of the 148 serovar Typhi isolates 126 (85%) were MDR and 133 (90%) had intermediate ciprofloxacin susceptibility. Inpatient antimicrobial treatment was ceftriaxone alone or initial ceftriaxone followed by a step-down to oral ciprofloxacin or azithromycin. Complications developed in 37/128 (29%) children admitted with enteric fever and two (1.6%) died. There was one confirmed relapse. In a sample of 102 serovar Typhi strains genotyped by investigation of a subset of single nucleotide polymorphisms, 98 (96%) were the H58 haplotype, the majority of which had the common serine to phenylalanine substitution at codon 83 in the DNA gyrase. We conclude that antimicrobial-resistant enteric fever is common in Cambodian children and therapeutic options are limited.

Investigation of a community outbreak of typhoid fever associated with drinking water.

Author	Farooqui A, Khan A, Kazmi SU.
Publication	BMC Public Health. 2009 Dec 20;9:476.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2804617/
Additional Categories	Disease and environmental surveillance

BACKGROUND: This report is about the investigation of an outbreak of typhoid fever claimed three human lives and left more than 300 people suffered within one week. The aim of this report is to draw the attention of global health community towards the areas that are still far from basic human essentialities. **METHODS:** A total of 250 suspected cases of typhoid fever were interviewed, out of which 100 were selected for sample collection on the basis of criteria included temperature >38 degrees °C since the onset of outbreak, abdominal discomfort, diarrhea, vomiting and weakness. Food and water samples were also collected and analyzed microbiologically. **RESULTS:** Inhabitants of village lived in poor and unhygienic conditions with no proper water supply or sewage disposal facilities and other basic necessities of life. They consumed water from a nearby well which was the only available source of drinking water. Epidemiological evidences revealed the gross contamination of well with dead and decaying animal bodies, their fecal material and garbage. Microbiological analysis of household and well water samples revealed the presence of heavy bacterial load with an average total aerobic count 106-109 CFU/ml. A number of Gram positive and Gram negative bacteria including *Escherichia coli*, *Klebsiella*,



Bacillus species, Staphylococcus species, Enterobacter species, and Pseudomonas aeruginosa were isolated. Lab investigations confirmed the presence of multidrug resistant strain of Salmonella enterica serovar Typhi in 100% well water, 65% household water samples and 2% food items. 22% of clinical stool samples were tested positive with Salmonella enterica serovar Typhi. **CONCLUSIONS:** This study indicated the possible involvement of well water in outbreaks. In order to avoid such outbreaks in future, we contacted the local health authorities and urged them to immediately make arrangements for safe drinking water supply.

Typhoid fever acquired in the United States, 1999-2010: epidemiology, microbiology, and use of a space-time scan statistic for outbreak detection.

Author	Imanishi M, Newton AE, Vieira AR, Gonzalez-Aviles G, Kendall Scott ME, Manikonda K, Maxwell TN, Halpin JL, Freeman MM, Medalla F, Ayers TL, Derado G, Mahon BE, Mintz ED.
Publication	Epidemiol Infect. 2015 Aug;143(11):2343-54.
URL	Not publically available
Additional Categories	Disease and environmental surveillance

Although rare, typhoid fever cases acquired in the United States continue to be reported. Detection and investigation of outbreaks in these domestically acquired cases offer opportunities to identify chronic carriers. We searched surveillance and laboratory databases for domestically acquired typhoid fever cases, used a space-time scan statistic to identify clusters, and classified clusters as outbreaks or non-outbreaks. From 1999 to 2010, domestically acquired cases accounted for 18% of 3373 reported typhoid fever cases; their isolates were less often multidrug-resistant (2% vs. 15%) compared to isolates from travel-associated cases. We identified 28 outbreaks and two possible outbreaks within 45 space-time clusters of ≥ 2 domestically acquired cases, including three outbreaks involving ≥ 2 molecular subtypes. The approach detected seven of the ten outbreaks published in the literature or reported to CDC. Although this approach did not definitively identify any previously unrecognized outbreaks, it showed the potential to detect outbreaks of typhoid fever that may escape detection by routine analysis of surveillance data. Sixteen outbreaks had been linked to a carrier. Every case of typhoid fever acquired in a non-endemic country warrants thorough investigation. Space-time scan statistics, together with shoe-leather epidemiology and molecular subtyping, may improve outbreak detection.

A review of the disease burden, impact and prevention of typhoid fever in Nigeria.

Author	Iperepolu OH, Entonu PE, Agwale SM.
Publication	West Afr J Med. 2008 Jul;27(3):127-33.
URL	Not publically available
Additional Categories	Disease and environmental surveillance

BACKGROUND: Typhoid fever is still a common infection in many parts of the world, especially in developing countries where sanitation and water supply are a common problem. A recent study placed the disease burden at 21650 974 illnesses and 216510 deaths during 2000. The infection is a major cause of morbidity and mortality in Nigeria. **OBJECTIVE:** This review set out to present in one concise volume a review of the major findings from published articles on the burden and impact of typhoid fever in Nigeria to aid easy reference for researchers. It highlights the disease burden, the different diagnostic



methods and their sensitivities, complications, treatment methods as well as the various preventive measures including the use of typhoid vaccine in the control of the disease. **METHODS:** Several published articles covering a period of 40 years were accessed different journals and reviewed, and their major findings presented in this review. **RESULTS:** The disease burden from typhoid fever in Nigeria is still high with associated serious complications, which in most cases have been managed effectively with the use of potent antibiotics and surgical intervention. However, the typhoid problem has been compounded by the emergence and circulation of multi-drug resistant strains of the organism being sensitive only to the newer generation antibiotics. **CONCLUSION:** Typhoid fever remains a major public health problem in Nigeria. The infection however can be prevented by good sanitation, improving good water supply, the provision of proper sewage disposal system, as well as the effective use of the available typhoid vaccines. The government and people of Nigeria should rise up to the challenge of stamping out this ugly trend.

Epidemiology, clinical manifestations, and molecular typing of <i>Salmonella typhi</i> isolated from patients with typhoid fever in Lebanon.	
Author	Kanj SS, Kanafani ZA, Shehab M, Sidani N, Baban T, Baltajian K, Dakdouki GK, Zaatari M, Araj GF, Wakim RH, Dbaibo G, Matar GM.
Publication	J Epidemiol Glob Health. 2015 Jun;5(2):159-65.
URL	http://www.sciencedirect.com/science/article/pii/S2210600614000744
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

The objective of this study was to examine the epidemiology and the clinical manifestations of typhoid fever as well as the susceptibility and strain relatedness of *Salmonella typhi* isolates in Lebanon from 2006 to 2007. A total of 120 patients with typhoid fever were initially identified from various areas of the country based on positive culture results for *S. typhi* from blood, urine, stools, bone marrow and/or positive serology. Clinical, microbiological and molecular analysis was performed on cases with complete data available. These results indicated that drinking water was an unlikely mode of transmission of the infection. Despite increasing reports of antimicrobial resistance among *S. typhi* isolates, the vast majority of these isolates were susceptible to various antibiotic agents, including ampicillin, cephalosporins, quinolones, and trimethoprim/sulfamethoxazole. Molecular analysis of the isolates revealed a predominance of one single genotype with no variation in distribution across the geographical regions.

Epidemiology of typhoid and paratyphoid fever in India.	
Author	Kanungo S, Dutta S, Sur D.
Publication	J Infect Dev Ctries. 2008 Dec 1;2(6):454-60.
URL	http://www.jidc.org/index.php/journal/article/view/19745523/79
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

Enteric fever (typhoid and paratyphoid fever) is a major human bacterial infection. Although the disease is not common in industrialised countries, it remains an important and persistent health problem in developing nations. Hospital-based studies and outbreak reports from India indicate that enteric fever is a major public health problem in this country, with *Salmonella enterica* serovar Typhi (*S. Typhi*) the most



common aetiologic agent but with an apparently increasing number of cases due to *S. Paratyphi A* (SPA). Because risk factors such as poor sanitation, lack of a safe drinking water supply and low socio economic conditions in resource-poor countries are amplified by the evolution of multidrug resistant salmonellae with reduced susceptibility to fluoroquinolone, treatment failure cases have been reported in India, which is associated with increased mortality and morbidity. Vaccination, which requires strict planning and proper targeting of the vulnerable age groups, is considered to be an effective tool in controlling this disease in endemic areas, given there is development of a conjugate vaccine against both serovars (*S. Typhi* and *S. Para A*).

Differential epidemiology of <i>Salmonella Typhi</i> and <i>Paratyphi A</i> in Kathmandu, Nepal: a matched case control investigation in a highly endemic enteric fever setting.	
Author	Karkey A, Thompson CN, Tran Vu Thieu N, Dongol S, Le Thi Phuong T, Voong Vinh P, Arjyal A, Martin LB, Rondini S, Farrar JJ, Dolecek C, Basnyat B, Baker S.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749961/pdf/pntd.0002391.pdf
Publication	PLoS Negl Trop Dis. 2013 Aug 22;7(8):e2391.
Additional Categories	Disease and environmental surveillance

BACKGROUND: Enteric fever, a systemic infection caused by the bacteria *Salmonella typhi* and *Salmonella Paratyphi A*, is endemic in Kathmandu, Nepal. Previous work identified proximity to poor quality water sources as a community-level risk for infection. Here, we sought to examine individual-level risk factors related to hygiene and sanitation to improve our understanding of the epidemiology of enteric fever in this setting. **METHODOLOGY AND PRINCIPAL FINDINGS:** A matched case-control analysis was performed through enrollment of 103 blood culture positive enteric fever patients and 294 afebrile community-based age and gender-matched controls. A detailed questionnaire was administered to both cases and controls and the association between enteric fever infection and potential exposures were examined through conditional logistic regression. Several behavioral practices were identified as protective against infection with enteric fever, including water storage and hygienic habits. Additionally, we found that exposures related to poor water and socioeconomic status are more influential in the risk of infection with *S. Typhi*, whereas food consumption habits and migration play more of a role in risk of *S. Paratyphi A* infection. **CONCLUSIONS AND SIGNIFICANCE:** Our work suggests that *S. Typhi* and *S. Paratyphi A* follow different routes of infection in this highly endemic setting and that sustained exposure to both serovars probably leads to the development of passive immunity. In the absence of a polyvalent vaccine against *S. Typhi* and *S. Paratyphi A*, we advocate better systems for water treatment and storage, improvements in the quality of street food, and vaccination with currently available *S. Typhi* vaccines.

The Ecological Dynamics of Fecal Contamination and <i>Salmonella Typhi</i> and <i>Salmonella Paratyphi A</i> in Municipal Kathmandu Drinking Water.	
Author	Karkey A, Jombart T, Walker AW, Thompson CN, Torres A, Dongol S, Tran Vu Thieu N, Pham Thanh D, Tran Thi Ngoc D, Voong Vinh P, Singer AC, Parkhill J, Thwaites G, Basnyat B, Ferguson N, Baker S.
Publication	PLoS Negl Trop Dis. 2016 Jan 6;10(1):e0004346.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749961/pdf/pntd.0002391.pdf

One of the UN sustainable development goals is to achieve universal access to safe and affordable drinking water by 2030. It is locations like Kathmandu, Nepal, a densely populated city in South Asia with



endemic typhoid fever, where this goal is most pertinent. Aiming to understand the public health implications of water quality in Kathmandu we subjected weekly water samples from 10 sources for one year to a range of chemical and bacteriological analyses. We additionally aimed to detect the etiological agents of typhoid fever and longitudinally assess microbial diversity by 16S rRNA gene surveying. We found that the majority of water sources exhibited chemical and bacterial contamination exceeding WHO guidelines. Further analysis of the chemical and bacterial data indicated site-specific pollution, symptomatic of highly localized fecal contamination. Rainfall was found to be a key driver of this fecal contamination, correlating with nitrates and evidence of *S. Typhi* and *S. Paratyphi A*, for which DNA was detectable in 333 (77%) and 303 (70%) of 432 water samples, respectively. 16S rRNA gene surveying outlined a spectrum of fecal bacteria in the contaminated water, forming complex communities again displaying location-specific temporal signatures. Our data signify that the municipal water in Kathmandu is a predominant vehicle for the transmission of *S. Typhi* and *S. Paratyphi A*. This study represents the first extensive spatiotemporal investigation of water pollution in an endemic typhoid fever setting and implicates highly localized human waste as the major contributor to poor water quality in the Kathmandu Valley.

Molecular epidemiological investigation of a typhoid fever outbreak in South Africa, 2005: the relationship to a previous epidemic in 1993.

Author	Keddy KH, Sooka A, Ismail H, Smith AM, Weber I, Letsoalo ME, Harris BN.
Publication	Epidemiol Infect. 2011 Aug;139(8):1239-45.
URL	Not publically available
Additional Categories	Disease and environmental surveillance

In 2005, over 600 clinically diagnosed typhoid fever cases occurred in South Africa, where an outbreak had been previously described in 1993. Case-control and molecular investigations, including *Salmonella enterica* serovar Typhi (*S. Typhi*) isolates from that area from 1993, 2005 and later, were undertaken. Controls were significantly older than cases ($P=0.003$), possibly due to immunity from previous infection, and a significantly larger proportion had attended a gathering ($P=0.035$). Exposure to commercial food outlets and person-to-person transmission was not significant. Pulsed-field gel electrophoresis and multi-locus tandem repeat analysis revealed common clusters of *S. Typhi* strains identified in 1993 and 2005 as well as in 2007 and 2009. This outbreak probably occurred in a non-immune population due to faecally contaminated water. *S. Typhi* strains appeared to be related to strains from 1993; failure to address unsafe water may lead to further outbreaks in the area if the current population immunity wanes or is lost.

The burden of enteric fever.

Author	Kothari A, Pruthi A, Chugh TD.
Publication	J Infect Dev Ctries. 2008 Aug 30;2(4):253-9.
URL	http://www.jidc.org/index.php/journal/article/view/19741285

Enteric fever is a disease of developing countries associated with poor public health and low socio-economic indices. Cases of enteric fever occurring in travelers returning to the United States and the UK suggest that it is present across the developing world but that the Indian subcontinent represents a hotspot of disease activity. The best figures available for the global burden of enteric fever support this and suggest that Africa (50/ 100,000) has a far lower burden of disease than Asia (274/100,000).



However these figures are based mainly on data for typhoid fever in Asia and the data for returning travelers is biased by preferred travel destinations. Given that most socio-economic indices, including known risk factors for enteric fever, such as provision of safe drinking water and sanitation, are much lower in most parts of Africa than in South-East and South-Central Asia it seems remarkable that Africa has such a low burden of disease. In such a scenario, rather than comparing whole continents, it may be more relevant to estimate region-specific burden of disease. It is clear is that there is an urgent need for more population-based studies of typhoid fever incidence in different parts of Africa to clarify the typhoid fever situation for the continent and so guide public health intervention.

Typhoid outbreak in Songkhla, Thailand 2009-2011: clinical outcomes, susceptibility patterns, and reliability of serology tests.	
Author	Limpitikul W, Henpraserttae N, Saksawad R, Laoprasopwattana K.
Publication	PLoS One. 2014 Nov 6;9(11):e111768.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4222948/
Additional Categories	Disease and environmental surveillance

OBJECTIVE: To determine the clinical manifestations and outcomes, the reliability of *Salmonella enterica* serotype Typhi (S ser. Typhi) IgM and IgG rapid tests, and the susceptibility patterns and the response to treatment during the 2009-2011 typhoid outbreak in Songkhla province in Thailand. **METHOD:** The medical records of children aged <15 years with S ser. Typhi bacteremia were analysed. The efficacy of the typhoid IgM and IgG rapid tests and susceptibility of the S ser. Typhi to the current main antibiotics used for typhoid (amoxicillin, ampicillin, cefotaxime, ceftriaxone, co-trimoxazole, and ciprofloxacin), were evaluated. **RESULTS:** S ser. Typhi bacteremia was found in 368 patients, and all isolated strains were susceptible to all 6 antimicrobials tested. Most of the patients were treated with ciprofloxacin for 7-14 days. The median time (IQR) of fever before treatment and duration of fever after treatment were 5 (4, 7) days and 4 (3, 5) days, respectively. Complications of ascites, lower respiratory symptoms, anemia (Hct <30%), and ileal perforation were found in 7, 7, 22, and 1 patients, respectively. None of the patients had recurrent infection or died. The sensitivities of the typhoid IgM and IgG tests were 58.3% and 25.6% respectively, and specificities were 74.1% and 50.5%, respectively. **CONCLUSION:** Most of the patients were diagnosed at an early stage and treated with a good outcome. All S ser. Typhi strains were susceptible to standard first line antibiotic typhoid treatment. The typhoid IgM and IgG rapid tests had low sensitivity and moderate specificity.

Typhoid fever among children, Ghana.	
Author	Marks F, Adu-Sarkodie Y, Hüngrer F, Sarpong N, Ekuban S, Agyekum A, Nkrumah B, Schwarz NG, Favorov MO, Meyer CG, May J.
Publication	Emerg Infect Dis. 2010 Nov;16(11):1796-7.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294512/pdf/10-0388_finalL.pdf
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

[START Summary]

This letter to the editor describes a study that examined *S. enterica* serovar Typhi incidence in Ghanaian children under 15 years of age. Typhoid fever incidences were calculated for September 2007 through November 2008. Incidence in children younger than five years of age was about 190 cases/100,000



population and highest in children 2-5 years of age (290/100,000 per year) and 5-8 years of age (200/100,000 per year). In children older than eight years of age, incidence decreased continuously, and the number of cases was too low to enable precise age-stratified incidence estimates.

A first step in bringing typhoid fever out of the closet.

Author	Maurice J.
Publication	Lancet. 2012 Feb 25;379(9817):699-700.
URL	Not publically available

[START Summary]

This commentary notes that typhoid fever has become under-prioritized by the international health community, as well as by many of the health officials of the low-and-middle income countries where the disease is most prevalent. It goes onto to describe some ways to help bring the disease into the spotlight, as discussed during a Coalition against Typhoid (CaT) meeting held in WHO's Geneva headquarters in January 2012. The main focus of the meeting was on modelling the epidemiology of the disease and on identifying the best ways of combating it. This commentary gives some examples of how mathematical models of typhoid fever might tackle the main cause of this neglect.

Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment.

Author	Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, Kim YE, Park JK, Wierzba TF.
Publication	Lancet Glob Health. 2014 Oct;2(10):e570-80.
URL	http://www.sciencedirect.com/science/article/pii/S2214109X14703018

BACKGROUND: No access to safe water is an important risk factor for typhoid fever, yet risk-level heterogeneity is unaccounted for in previous global burden estimates. Since WHO has recommended risk-based use of typhoid polysaccharide vaccine, we revisited the burden of typhoid fever in low-income and middle-income countries (LMICs) after adjusting for water-related risk. **METHODS:** We estimated the typhoid disease burden from studies done in LMICs based on blood-culture-confirmed incidence rates applied to the 2010 population, after correcting for operational issues related to surveillance, limitations of diagnostic tests, and water-related risk. We derived incidence estimates, correction factors, and mortality estimates from systematic literature reviews. We did scenario analyses for risk factors, diagnostic sensitivity, and case fatality rates, accounting for the uncertainty in these estimates and we compared them with previous disease burden estimates. **FINDINGS:** The estimated number of typhoid fever cases in LMICs in 2010 after adjusting for water-related risk was 11.9 million (95% CI 9.9-14.7) cases with 129 000 (75 000-208 000) deaths. By comparison, the estimated risk-unadjusted burden was 20.6 million (17.5-24.2) cases and 223 000 (131 000-344 000) deaths. Scenario analyses indicated that the risk-factor adjustment and updated diagnostic test correction factor derived from systematic literature reviews were the drivers of differences between the current estimate and past estimates. **INTERPRETATION:** The risk-adjusted typhoid fever burden estimate was more conservative than previous estimates. However, by distinguishing the risk differences, it will allow assessment of the effect at the population level and will facilitate cost-effectiveness calculations for risk-based vaccination strategies for future typhoid conjugate vaccine.



Burden of typhoid and paratyphoid fever in a densely populated urban community, Dhaka, Bangladesh.

Author	Naheed A, Ram PK, Brooks WA, Hossain MA, Parsons MB, Talukder KA, Mintz E, Luby S, Breiman RF.
Publication	Int J Infect Dis. 2010 Sep;14 Suppl 3:e93-9.
URL	http://www.sciencedirect.com/science/article/pii/S1201971210022800
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

BACKGROUND: We conducted blood culture surveillance to estimate the incidence of typhoid and paratyphoid fever among urban slum residents in Dhaka, Bangladesh. **METHODS:** Between January 7, 2003 and January 6, 2004, participants were visited weekly to detect febrile illnesses. Blood cultures were obtained at the clinic from patients with fever ($\geq 38^{\circ}\text{C}$). *Salmonella* isolates were assayed for antimicrobial susceptibility. **RESULTS:** Forty *Salmonella* Typhi and eight *Salmonella* Paratyphi A were isolated from 961 blood cultures. The incidence of typhoid fever was 2.0 episodes/1000 person-years, with a higher incidence in children aged <5 years (10.5/1000 person-years) than in older persons (0.9/1000 person-years) (relative risk=12, 95% confidence interval (CI) 6.3-22.6). The incidence of paratyphoid fever was 0.4/1000 person-years without variation by age group. Sixteen *S. Typhi* isolates were multidrug-resistant (MDR). All *S. Paratyphi* isolates were pan-susceptible. The duration of fever among patients with an MDR *S. Typhi* infection was longer than among patients with non-MDR *S. Typhi* (16 ± 8 vs. 11 ± 4 days, $p=0.02$) and *S. Paratyphi* (10 ± 2 days, $p=0.04$) infections. **CONCLUSIONS:** Typhoid fever is more common than paratyphoid fever in the urban Bangladeshi slum; children <5 years old have the highest incidence. Multidrug resistance is common in *S. Typhi* isolates and is associated with prolonged illness. Strategies for typhoid fever prevention in children aged <5 years in Bangladesh, including immunization, are needed.

A study of typhoid fever in five Asian countries: disease burden and implications for controls.

Author	Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, Bhutta ZA, Canh DG, Ali M, Shin S, Wain J, Page AL, Albert MJ, Farrar J, Abu-Elyazeed R, Pang T, Galindo CM, von Seidlein L, Clemens JD; Domic Typhoid Study Group.
Publication	Bull World Health Organ. 2008 Apr;86(4):260-8. Erratum in Bull World Health Organ. 2015 Apr 1;93(4):284. Bull World Health Organ. 2015 Jun 1;93(6):440.
URL	http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/18438514/
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

OBJECTIVE: To inform policy-makers about introduction of preventive interventions against typhoid, including vaccination. **METHODS:** A population-based prospective surveillance design was used. Study sites where typhoid was considered a problem by local authorities were established in China, India, Indonesia, Pakistan and Vietnam. Standardized clinical, laboratory, and surveillance methods were used to investigate cases of fever of ≥ 3 days' duration for a one-year period. A total of 441,435 persons were under surveillance, 159,856 of whom were aged 5-15 years. **FINDINGS:** A total of 21,874 episodes of fever were detected. *Salmonella typhi* was isolated from 475 (2%) blood cultures, 57% (273/475) of



which were from 5-15 year-olds. The annual typhoid incidence (per 100,000 person years) among this age group varied from 24.2 and 29.3 in sites in Vietnam and China, respectively, to 180.3 in the site in Indonesia; and to 412.9 and 493.5 in sites in Pakistan and India, respectively. Altogether, 23% (96/413) of isolates were multidrug resistant (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole). **CONCLUSION:** The incidence of typhoid varied substantially between sites, being high in India and Pakistan, intermediate in Indonesia, and low in China and Vietnam. These findings highlight the considerable, but geographically heterogeneous, burden of typhoid fever in endemic areas of Asia, and underscore the importance of evidence on disease burden in making policy decisions about interventions to control this disease.

Incidence of typhoid bacteremia in infants and young children in southern coastal Pakistan.

Author	Owais A, Sultana S, Zaman U, Rizvi A, Zaidi AK.
Publication	Pediatr Infect Dis J. 2010 Nov;29(11):1035-9.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3073093/
Additional Categories	Disease and environmental surveillance

INTRODUCTION: The burden of typhoid fever in preschool children is not well recognized. The purpose of this study was to estimate the incidence of typhoid bacteremia in Pakistani children <5 years of age, with a focus on children younger than 2 years of age. This will help to inform prevention policies in highly endemic countries. **METHODS:** Household surveillance from February 1, 2007 to May 12, 2008, was carried out by community health workers in 2 low-income, coastal communities of Karachi. Workers referred each sick child <5 years old to the local clinic. Blood for culture was obtained from those who gave consent, and inoculated in BACTEC Peds Plus bottles (Becton Dickinson, Sparks, MD) and processed per manufacturer's guidelines. **RESULTS:** Overall, 5570 children contributed 3949 observation years. Blood culture was obtained from 1165 cases, yielding 36 pathogens. *Salmonella* Typhi was isolated in 16 cases, *Salmonella* Paratyphi A in 2 cases, and *Salmonella* Paratyphi B in 1 case. The incidence of typhoid bacteremia in children <2 years of age was 443.1 (95% confidence interval, 193.8-876.5) per 100,000 child years. The overall incidence rate of typhoid for children <5 years was 405.1 (95% confidence interval, 239.8-643.9) per 100,000 child years. **CONCLUSION:** Typhoid is a common and significant cause of morbidity among young children in Pakistan, including children less than 2 years of age. Vaccines that provide protection to preschool children should be included in typhoid control efforts.

Risk factors for the development of severe typhoid fever in Vietnam.

Author	Parry CM, Thompson C, Vinh H, Chinh NT, Phuong le T, Ho VA, Hien TT, Wain J, Farrar JJ, Baker S.
Publication	BMC Infect Dis. 2014 Feb 10;14:73.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3923984/pdf/1471-2334-14-73.pdf

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.

Descriptive epidemiology of typhoid fever during an epidemic in Harare, Zimbabwe, 2012.

Author	Polonsky JA, Martínez-Pino I, Nackers F, Chonzi P, Manangazira P, Van Herp M, Maes P, Porten K, Luquero FJ.
Publication	Pediatr Infect Dis J. 2010 Nov;29(11):1035-9.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4259398/pdf/pone.0114702.pdf
Additional Categories	Disease and environmental surveillance

BACKGROUND: Typhoid fever remains a significant public health problem in developing countries. In October 2011, a typhoid fever epidemic was declared in Harare, Zimbabwe - the fourth enteric infection epidemic since 2008. To orient control activities, we described the epidemiology and spatiotemporal clustering of the epidemic in Dzivaresekwa and Kuwadzana, the two most affected suburbs of Harare. METHODS: A typhoid fever case-patient register was analysed to describe the epidemic. To explore clustering, we constructed a dataset comprising GPS coordinates of case-patient residences and randomly sampled residential locations (spatial controls). The scale and significance of clustering was explored with Ripley K functions. Cluster locations were determined by a random labelling technique and confirmed using Kulldorff's spatial scan statistic. PRINCIPAL FINDINGS: We analysed data from 2570 confirmed and suspected case-patients, and found significant spatiotemporal clustering of typhoid fever in two non-overlapping areas, which appeared to be linked to environmental sources. Peak relative risk was more than six times greater than in areas lying outside the cluster ranges. Clusters were identified in similar geographical ranges by both random labelling and Kulldorff's spatial scan statistic. The spatial scale at which typhoid fever clustered was highly localised, with significant clustering at distances up to 4.5 km and peak levels at approximately 3.5 km. The epicentre of infection transmission shifted from one cluster to the other during the course of the epidemic. CONCLUSIONS: This study demonstrated highly localised clustering of typhoid fever during an epidemic in an urban African setting, and highlights the importance of spatiotemporal analysis for making timely decisions about targeting prevention and



control activities and reinforcing treatment during epidemics. This approach should be integrated into existing surveillance systems to facilitate early detection of epidemics and identify their spatial range.

Enteric fever burden in North Jakarta, Indonesia: a prospective, community-based study.

Author	Punjabi NH, Agtini MD, Ochiai RL, Simanjuntak CH, Lesmana M, Subekti D, Oyofa BA, von Seidlein L, Deen J, Shin S, Acosta C, Wangsasaputra F, Pulungsih SP, Saroso S, Suyeti S, R S, Sudarmono P, Syarurachman A, Suwandono A, Arjoso S, Beecham HJ 3rd, Corwin AL, Clemens JD.
Publication	J Infect Dev Ctries. 2013 Nov 15;7(11):781-7.
URL	http://www.jidc.org/index.php/journal/article/view/24240034/936
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

INTRODUCTION: We undertook a prospective community-based study in North Jakarta, Indonesia, to determine the incidence, clinical characteristics, seasonality, etiologic agent, and antimicrobial susceptibility pattern of enteric fever. **METHODOLOGY:** Following a census, treatment centre-based surveillance for febrile illness was conducted for two-years. Clinical data and a blood culture were obtained from each patient. **RESULTS:** In a population of 160,261, we detected 296 laboratory-confirmed enteric fever cases during the surveillance period, of which 221 (75%) were typhoid fever and 75 (25%) were paratyphoid fever. The overall incidence of typhoid and paratyphoid cases was 1.4, and 0.5 per thousand populations per year, respectively. Although the incidence of febrile episodes evaluated was highest among children under 5 years of age at 92.6 per thousand persons per year, we found that the burden of typhoid fever was greatest among children between 5 and 20 years of age. Paratyphoid fever occurred most commonly in children and was infrequent in adults. **CONCLUSION:** Enteric fever is a public health problem in North Jakarta with a substantial proportion due to paratyphoid fever. The results highlight the need for control strategies against enteric fever.

Challenges in measuring complications and death due to invasive *Salmonella* infections.

Author	Qamar FN, Azmatullah A, Bhutta ZA.
Publication	Vaccine. 2015 Jun 19;33 Suppl 3:C16-20.
URL	Not publically available

Despite the highest burden of Typhoid fever in children globally, exact estimates of morbidity and mortality are lacking due to scarcity of published data. Despite a high prevalence and a socioeconomic burden in developing countries, published data with morbidity and mortality figures are limited especially Africa and South American regions. Data from the community is insufficient and most case fatality estimates are extrapolations from hospital based studies that do not cover all geographical regions, and include cases which may or not be culture confirmed, MDR resistant or sensitive cases, or from mixed populations of age (adults and children). Complications of typhoid such as intestinal perforation, bone marrow suppression, and encephalopathy are dependent on MDR/Fluoroquinolone resistant *Salmonella* infection, comorbidities such as malnutrition, and health-care access. Data is again insufficient to estimate the true burden of Typhoid Fever in different regions and groups of populations. Although there has been a rapid decline in cases in developed countries with the advent of improved sanitization, timely and easy access to health care and laboratories, this is still not the case in the developing countries where Typhoid deaths are still occurring. The way forward is to develop rapid and cost effective point of care diagnostic tests, put in place validated clinical algorithms for suspected



clinical cases, and design prospective, and community based studies in different groups, implement maintenance of electronic health records in large public sector hospitals and regions to identify populations that will benefit most from the implementation of vaccine. Policies on public health education and typhoid vaccine may help to reduce morbidity and mortality due to the disease.

Risk factors for typhoid fever in a slum in Dhaka, Bangladesh.

Author	Ram PK, Naheed A, Brooks WA, Hossain MA, Mintz ED, Breiman RF, Luby SP.
Publication	Epidemiol Infect. 2007 Apr;135(3):458-65.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2870597/

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

Salmonella infections: an update on epidemiology, management, and prevention.

Author	Sánchez-Vargas FM, Abu-El-Haija MA, Gómez-Duarte OG.
Publication	Epidemiol Infect. 2007 Apr;135(3):458-65.
URL	Not publically available

Salmonella species are a group of Gram-negative enterobacteria and known human pathogens in developing as well as industrialized countries. Despite significant advances in sanitation, provision of potable water, and highly controlled food chain surveillance, transmission of Salmonella spp. continues to affect communities, preferentially children, worldwide. This review summarizes updated concepts on typhoidal and non-typhoidal Salmonella infections, starting with a historical perspective that implicates typhoid Salmonella as a significant human pathogen since ancient times. We describe the epidemiology of this pathogen with emphasis on the most recent non-typhoidal Salmonella outbreaks in industrialized countries and continued outbreaks of typhoid Salmonella in underserved countries. An overview of clinical aspects of typhoid and non-typhoid infections in developing and industrialized countries, respectively, is provided, followed by a description on current treatment concepts and challenges treating multidrug-resistant Salmonella infections. We conclude with prevention recommendations, and recent research studies on vaccine prevention.



Stochastic simulation of endemic *Salmonella enterica* serovar Typhi: the importance of long lasting immunity and the carrier state.

Author	Saul A, Smith T, Maire N.
Publication	PLoS One. 2013 Sep 10;8(9):e74097.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3769365/pdf/pone.0074097.pdf

BACKGROUND: Typhoid fever caused by *Salmonella enterica* serovar Typhi (*S. Typhi*) remains a serious burden of disease, especially in developing countries of Asia and Africa. It is estimated that it causes 200,000 deaths per year, mainly in children. *S. Typhi* is an obligate pathogen of humans and although it has a relatively complex life cycle with a long lived carrier state, the absence of non-human hosts suggests that well targeted control methods should have a major impact on disease. Newer control methods including new generations of vaccines offer hope but their implementation would benefit from quantitative models to guide the most cost effective strategies. This paper presents a quantitative model of Typhoid disease, immunity and transmission as a first step in that process. **METHODOLOGY/PRINCIPAL FINDINGS:** A stochastic agent-based model has been developed that incorporates known features of the biology of typhoid including probability of infection, the consequences of infection, treatment options, acquisition and loss of immunity as a result of infection and vaccination, the development of the carrier state and the impact of environmental or behavioral factors on transmission. The model has been parameterized with values derived where possible from the literature and where this was not possible, feasible parameters space has been determined by sensitivity analyses, fitting the simulations to age distribution of field data. The model is able to adequately predict the age distribution of typhoid in two settings. **CONCLUSIONS/SIGNIFICANCE:** The modeling highlights the importance of variations in the exposure/resistance of infants and young children to infection in different settings, especially as this impacts on design of control programs; it predicts that naturally induced clinical and sterile immunity to typhoid is long lived and highlights the importance of the carrier state especially in areas of low transmission.

Risk factors for typhoid in Darjeeling, West Bengal, India: evidence for practical action.

Author	Sharma PK, Ramakrishnan R, Hutin Y, Manickam P, Gupte MD.
Publication	Trop Med Int Health. 2009 Jun;14(6):696-702.
URL	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2009.02283.x/epdf

OBJECTIVE: To identify risk factors for typhoid and propose prevention measures. **METHODS:** Case-control study; we compared hospital-based typhoid cases defined as fever $>38^{\circ}\text{C}$ for ≥ 3 days with four-fold rise in 'O' antibodies on paired sera (Widal) with community, age and neighbourhood matched controls. We obtained information on drinking water, fruits, vegetables, milk products and sanitation; and calculated matched odds ratios (MOR) and attributable fractions in the population (AFP) for the risk factors or failure to use prevention measures. **RESULTS:** The 123 typhoid cases (median age: 25 years, 47% female) and 123 controls did not differ with respect to baseline characteristics. Cases were less likely to store drinking water in narrow-mouthed containers (MOR: 0.4, 95% CI: 0.2-0.7, AFP 29%), tip containers to draw water (MOR: 0.4, 95% CI: 0.2-0.7, AFP 33%) and have home latrines (MOR: 0.5, 95% CI: 0.3-0.8, AFP 23%). Cases were more likely to consume butter (OR: 2.3, 95% CI: 1.3-4.1, AFP 28%), yoghurt (OR: 2.3, 95% CI: 1.4-3.7, AFP 34%) and raw fruits and vegetables, including onions (MOR: 2.1, 95% CI: 1.2-3.9, AFP 34%), cabbages (OR: 2.8, 95% CI: 1.7-4.8, AFP 44%) and unwashed guavas (OR: 1.9, 95% CI: 1.2-3, AFP 25%). **CONCLUSION:** Typhoid was associated with unsafe water and sanitation



practices as well as with consumption of milk products, fruits and vegetables. We propose to chlorinate drinking water at the point of use, wash/cook raw fruits and vegetables and ensure safer preparation/storage of local milk products.

Effects of habitat characteristics on the growth of carrier population leading to increased spread of typhoid fever: a model.

Author Shukla JB, Goyal A, Singh S, Chandra P.

Publication J Epidemiol Glob Health. 2014 Jun;4(2):107-14.

URL <http://www.sciencedirect.com/science/article/pii/S2210600613001184>

In this paper, a non-linear model is proposed and analyzed to study the effects of habitat characteristics favoring logistically growing carrier population leading to increased spread of typhoid fever. It is assumed that the cumulative density of habitat characteristics and the density of carrier population are governed by logistic models; the growth rate of the former increases as the density of human population increases. The model is analyzed by stability theory of differential equations and computer simulation. The analysis shows that as the density of the infective carrier population increases due to habitat characteristics, the spread of typhoid fever increases in comparison with the case without such factors.

Risk factors for typhoid fever in children in squatter settlements of Karachi: a nested case-control study.

Author Siddiqui FJ, Haider SR, Bhutta ZA.

Publication J Infect Public Health. 2008;1(2):113-20.

URL http://ac.els-cdn.com/S1876034108000312/1-s2.0-S1876034108000312-main.pdf?_tid=7456d1c6-6b0d-11e6-b0c8-00000aacb361&acdnat=1472161801_dcc08fee813e84dca088acd086e19e94

Typhoid fever remains a major public health problem in developing countries such as Pakistan. A great majority of cases occur in children living in poor sanitary conditions in squatter settlements in large cities. We conducted a case-control study to identify risk factor for typhoid fever in children under the age of 16 years residing in squatter settlements of Karachi. We enrolled 88 typhoid fever patients, diagnosed by positive blood culture or Typhidot test, between June 1999 and December 2001. Simultaneously, we enrolled 165 age-matched neighborhood controls. Multivariate analysis done through conditional binary logistic regression analysis technique showed that increasing number of persons in the household (odds ratio [OR]=1.9; 95% confidence interval [CI] 1.2-3.1), non-availability of soap near hand washing facility (OR=2.6; 95% CI 1.1-6.3), non-use of medicated soap (OR=11.2; 95% CI 1.3-97.6) and lack of awareness about contact with a known case of typhoid fever (OR=3.7; 95% CI 1.6-8.4) were independent risk factors of the disease. Health education with emphasis on hand washing may help decrease the burden of typhoid fever in developing countries.



Outbreak of Salmonella Typhi enteric fever in sub-urban area of North India: a public health perspective.**Author** Singla N, Bansal N, Gupta V, Chander J.**Publication** Asian Pac J Trop Med. 2013 Feb;6(2):167-8.**URL** <http://www.sciencedirect.com/science/article/pii/S1995764513600176>

Outbreaks of enteric fever are a major health concern not only due to significant human morbidity and mortality but also fear of spread of multidrug resistant strains. We report an outbreak of enteric fever caused by *Salmonella enterica* serotype Typhi in a suburban area, in city Chandigarh of North India. Twenty-seven strains of *S. typhi* were isolated from blood cultures over a period of two weeks with 18 of these 27 patients residing in the same area. Maximum cases were in the age group 5-14 years (10 patients, 55.5%) while 4 (22.2%) cases were children under 5 years. All the strains showed similar resistogram being resistant to ampicillin and nalidixic acid, intermediate to ciprofloxacin and sensitive to chloramphenicol, ceftriaxone, cefotaxime, cotrimoxazole and azithromycin on disc diffusion testing. Minimum inhibitory concentration of ciprofloxacin was determined by agar dilution method and was found to be raised ($\geq 2 \mu\text{g/mL}$). This nalidixic acid resistant *S. typhi* outbreak report warrants the necessity of implementing stringent sanitation practices in public health interest.

Epidemiology and risk factors for endemic typhoid fever in Uzbekistan.**Author** Srikantiah P, Vafokulov S, Luby SP, Ishmail T, Earhart K, Khodjaev N, Jennings G, Crump JA, Mahoney FJ.**Publication** Trop Med Int Health. 2007 Jul;12(7):838-47.**URL** <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2007.01853.x/epdf>**Additional Categories** Disease and environmental surveillance
Trends in antibiotic resistance of *Salmonella typhi*

BACKGROUND: To investigate the risk factors for infection with endemic typhoid fever in the Samarkand region of Uzbekistan. **METHODS:** Case-control study of culture-confirmed bloodstream infection with *Salmonella Typhi*. Patients were compared to age-matched community controls. *Salmonella Typhi* isolates were tested for antimicrobial susceptibility. **RESULTS:** We enrolled 97 patients and 192 controls. The median age of patients was 19 years. In a conditional regression model, consumption of unboiled surface water outside the home [adjusted odds ratio (aOR)=3.0, 95% confidence interval (CI)=1.1-8.2], use of antimicrobials in the 2 weeks preceding onset of symptoms (aOR=12.2, 95% CI 4.0-37.0), and being a student (aOR=4.0, 95% CI 1.4-11.3) were independently associated with typhoid fever. Routinely washing vegetables (aOR 0.06, 95% CI 0.02-0.2) and dining at a tea-house (aOR 0.4, 95% CI 0.2-1.0) were associated with protection against illness. *Salmonella Typhi* resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole was identified in 6 (15%) of 41 isolates tested. **CONCLUSIONS:** Endemic typhoid fever in Uzbekistan is transmitted by contaminated water. Recent use of antimicrobials also increased risk of infection. Targeted efforts at improving drinking water quality, especially for students and young adults, are likely to decrease transmission of typhoid fever. Measures to decrease the unnecessary use of antimicrobials would be expected to reduce the risk of typhoid fever and decrease the spread of multiple drug-resistant *Salmonella Typhi*.



Epidemiological features of typhoid/paratyphoid fever in provinces with high incidence rate and in the whole country, in 2012.	
Author	Sun JL, Zhang J, Ma HL, Chang ZR.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2013 Dec;34(12):1183-8.
URL	http://zhlxboxzz.yiigle.com/CN112338201312/594787.htm?locale=zh_CN
Additional Categories	Disease and environmental surveillance

[Article in Chinese]

OBJECTIVE: Through analyzing the national statutory reporting data on typhoid, paratyphoid fever in 2012, we were trying to understand the whole picture of typhoid, paratyphoid fever at the national level as well as to understand the trends and characteristics of typhoid and paratyphoid fever in provinces with high incidence rate, so as to the development of prevention and control strategies of the diseases in those high-incidence rate provinces. **METHODS:** We descriptively analyzed the national typhoid and paratyphoid fever statutory reporting data which was reported through disease surveillance information reporting system in 2012. **RESULTS:** 11 998 cases with typhoid and paratyphoid fever were reported with 3 fatal ones, in 2012 in the whole country. The incidence rate was 0.89 per 100,000. Compared to the data gathered in 2011, the incidence rates of typhoid/ paratyphoid fever increased by 1.20%. The total number of the confirmed cases on typhoid and paratyphoid fever was 6522 and was accounted for 54.36% of the total cases, in which paratyphoid fever accounted for 36.86%. Cases were mainly involved farmers and followed by students and children. Incidence rates of typhoid and paratyphoid fever in children aged 0-4 years old appeared the highest (respectively 1.31/100 000 and 0.46/100 000). Yunnan, Guizhou, Guangdong, Guangxi, Zhejiang, Hunan and Xinjiang provinces (autonomous regions) were identified as provinces with high-incidence rates of typhoid and paratyphoid fever. During 2005-2012, the incidence rates in most of the above high-incidence provinces showed a downward trend, except for in Guangdong which had only showed a slight change. There were variations on peak period and highly-hit population in seven high-incidence provinces. **CONCLUSION:** The incidence rate of typhoid/paratyphoid fever was in a relatively low level in China. Prevention and control strategies on the diseases in children under 5 years old remained a challenge, warranted more work to be done. The epidemiological situation is still severe in some high-incidence rate provinces.

Comparisons of predictors for typhoid and paratyphoid fever in Kolkata, India.	
Author	Sur D, Ali M, von Seidlein L, Manna B, Deen JL, Acosta CJ, Clemens JD, Bhattacharya SK.
Publication	BMC Public Health. 2007 Oct 12;7:289.
URL	http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/17935611/

BACKGROUND: Exposure of the individual to contaminated food or water correlates closely with the risk for enteric fever. Since public health interventions such as water improvement or vaccination campaigns are implemented for groups of individuals we were interested whether risk factors not only for the individual but for households, neighbourhoods and larger areas can be recognised? **METHODS:** We conducted a large enteric fever surveillance study and analyzed factors which correlate with enteric fever on an individual level and factors associated with high and low risk areas with enteric fever incidence. Individual level data were linked to a population based geographic information systems. Individual and household level variables were fitted in Generalized Estimating Equations (GEE) with the logit link function to take into account the likelihood that household factors correlated within household



members. RESULTS: Over a 12-month period 80 typhoid fever cases and 47 paratyphoid fever cases were detected among 56,946 residents in two bustees (slums) of Kolkata, India. The incidence of paratyphoid fever was lower (0.8/1000/year), and the mean age of paratyphoid patients was older (17.1 years) than for typhoid fever (incidence 1.4/1000/year, mean age 14.7 years). Residents in areas with a high risk for typhoid fever had lower literacy rates and economic status, bigger household size, and resided closer to waterbodies and study treatment centers than residents in low risk areas. CONCLUSION: There was a close correlation between the characteristics detected based on individual cases and characteristics associated with high incidence areas. Because the comparison of risk factors of populations living in high versus low risk areas is statistically very powerful this methodology holds promise to detect risk factors associated with diseases using geographic information systems.

Salmonella spp. in patients suffering from enteric fever and food poisoning in Tamar city, Yemen.

Author	Taha RR, Alghalibi SM, Saeedsaleh MG.
Publication	East Mediterr Health J. 2013 Jan;19(1):88-93.
URL	Not publically available

Salmonella remains a public health concern around the world, including Yemen although data on its incidence are few. This study determined the incidence of Salmonella infection in 250 enteric fever and 210 food poisoning cases attending Tamar general hospital and Dar Alshafaa medical clinic in 2008. In total, 773 clinical specimens were taken: 250 blood, 187 urine and 336 stool samples. Of the patients with enteric fever and food poisoning, 16.4% and 15.2% respectively were infected with Salmonella. The serovars isolated were: Salmonella Typhi (45.6%), Salmonella Enteritidis (24.4%), Salmonella Paratyphi B (14.4%), Salmonella Typhimurium (13.3%) and Salmonella Paratyphi A (2.2%). The distribution of somatic groups was: D (70%), B (27.7%) and A (2.2%). None of the isolates was resistant to ciprofloxacin, sparfloxacin, ceftriaxone or moxifloxacin, while 71.1% were resistant to co-trimoxazole, 62.2% to gentamicin, 56.6% to ampicillin and 35.5% to nalidixic acid.

Azithromycin and ciprofloxacin resistance in Salmonella bloodstream infections in Cambodian adults.

Author	Vlieghe ER, Phe T, De Smet B, Veng CH, Kham C, Bertrand S, Vanhoof R, Lynen L, Peetermans WE, Jacobs JA.
Publication	PLoS Negl Trop Dis. 2012;6(12):e1933.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3521708/pdf/pntd.0001933.pdf
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

BACKGROUND: Salmonella enterica is a frequent cause of bloodstream infection (BSI) in Asia but few data are available from Cambodia. We describe Salmonella BSI isolates recovered from patients presenting at Sihanouk Hospital Centre of Hope, Phnom Penh, Cambodia (July 2007-December 2010). METHODOLOGY: Blood was cultured as part of a microbiological prospective surveillance study. Identification of Salmonella isolates was performed by conventional methods and serotyping. Antibiotic susceptibilities were assessed using disk diffusion, MicroScan and E-test macromethod. Clonal relationships were assessed by Pulsed Field Gel Electrophoresis; PCR and sequencing for detection of mutations in Gyrase and Topoisomerase IV and presence of qnr genes. PRINCIPAL FINDINGS: Seventy-two Salmonella isolates grew from 58 patients (mean age 34.2 years, range 8-71). Twenty isolates were



identified as *Salmonella* Typhi, 2 as *Salmonella* Paratyphi A, 37 as *Salmonella* Choleraesuis and 13 as other non-typhoid *Salmonella* spp. Infection with human immunodeficiency virus (HIV) was present in 21 of 24 (87.5%) patients with *S. Choleraesuis* BSI. Five patients (8.7%) had at least one recurrent infection, all with *S. Choleraesuis*; five patients died. Overall, multi drug resistance (i.e., co-resistance to ampicillin, sulphamethoxazole-trimethoprim and chloramphenicol) was high (42/59 isolates, 71.2%). *S. Typhi* displayed high rates of decreased ciprofloxacin susceptibility (18/20 isolates, 90.0%), while azithromycin resistance was very common in *S. Choleraesuis* (17/24 isolates, 70.8%). Two *S. Choleraesuis* isolates were extended spectrum beta-lactamase producer. **CONCLUSIONS AND SIGNIFICANCE:** Resistance rates in *Salmonella* spp. in Cambodia are alarming, in particular for azithromycin and ciprofloxacin. This warrants nationwide surveillance and revision of treatment guidelines.

Typhoid fever.	
Author	Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL.
Publication	Lancet. 2015 Mar 21;385(9973):1136-45.
URL	Not publically available
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

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.

Shifts in geographic distribution and antimicrobial resistance during a prolonged typhoid fever outbreak--Bundibugyo and Kasese Districts, Uganda, 2009-2011.	
Author	Walters MS, Routh J, Mikoleit M, Kadivane S, Ouma C, Mubiru D, Mbusa B, Murangi A, Ejoku E, Rwantangle A, Kule U, Lule J, Garrett N, Halpin J, Maxwell N, Kagirita A, Mulabya F, Makumbi I, Freeman M, Joyce K, Hill V, Downing R, Mintz E.
Publication	PLoS Negl Trop Dis. 2014 Mar 6;8(3):e2726.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945727/
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

BACKGROUND: *Salmonella enterica* serovar Typhi is transmitted by fecally contaminated food and water and causes approximately 22 million typhoid fever infections worldwide each year. Most cases occur in



developing countries, where approximately 4% of patients develop intestinal perforation (IP). In Kasese District, Uganda, a typhoid fever outbreak notable for a high IP rate began in 2008. We report that this outbreak continued through 2011, when it spread to the neighboring district of Bundibugyo. **METHODOLOGY/PRINCIPAL FINDINGS:** A suspected typhoid fever case was defined as IP or symptoms of fever, abdominal pain, and ≥ 1 of the following: gastrointestinal disruptions, body weakness, joint pain, headache, clinically suspected IP, or non-responsiveness to antimalarial medications. Cases were identified retrospectively via medical record reviews and prospectively through laboratory-enhanced case finding. Among Kasese residents, 709 cases were identified from August 1, 2009–December 31, 2011; of these, 149 were identified during the prospective period beginning November 1, 2011. Among Bundibugyo residents, 333 cases were identified from January 1–December 31, 2011, including 128 cases identified during the prospective period beginning October 28, 2011. IP was reported for 507 (82%) and 59 (20%) of Kasese and Bundibugyo cases, respectively. Blood and stool cultures performed for 154 patients during the prospective period yielded isolates from 24 (16%) patients. Three pulsed-field gel electrophoresis pattern combinations, including one observed in a Kasese isolate in 2009, were shared among Kasese and Bundibugyo isolates. Antimicrobial susceptibility was assessed for 18 isolates; among these 15 (83%) were multidrug-resistant (MDR), compared to 5% of 2009 isolates. **CONCLUSIONS/SIGNIFICANCE:** Molecular and epidemiological evidence suggest that during a prolonged outbreak, typhoid spread from Kasese to Bundibugyo. MDR strains became prevalent. Lasting interventions, such as typhoid vaccination and improvements in drinking water infrastructure, should be considered to minimize the risk of prolonged outbreaks in the future.

Spatiotemporal transmission and determinants of typhoid and paratyphoid fever in Hongta District, Yunnan Province, China.

Author	Wang JF, Wang Y, Zhang J, Christakos G, Sun JL, Liu X, Lu L, Fu XQ, Shi YQ, Li XM.
Publication	PLoS Negl Trop Dis. 2013;7(3):e2112. Erratum in PLoS Negl Trop Dis. 2013 Mar;7(3).
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597484/pdf/pntd.0002112.pdf
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

BACKGROUND: Typhoid and paratyphoid fever are endemic in Hongta District and their prevalence, at 113 per 100,000 individuals, remains the highest in China. However, the exact sources of the disease and its main epidemiological characteristics have not yet been clearly identified. **METHODS AND FINDINGS:** Numbers of typhoid and paratyphoid cases per day during the period 2006 to 2010 were obtained from the Chinese Center of Disease Control (CDC). A number of suspected disease determinants (or their proxies), were considered for use in spatiotemporal analysis: these included locations of discharge canals and food markets, as well as socio-economic and environmental factors. Results showed that disease prevalence was spatially clustered with clusters decreasing with increasing distance from markets and discharge canals. More than half of the spatial variance could be explained by a combination of economic conditions and availability of health facilities. Temporal prevalence fluctuations were positively associated with the monthly precipitation series. Polluted hospital and residential wastewater was being discharged into rainwater canals. *Salmonella* bacteria were found in canal water, on farmland and on vegetables sold in markets. **CONCLUSION:** Disease transmission in Hongta District is driven principally by two spatiotemporally coupled cycles: one involving seasonal



variations and the other the distribution of polluted farmland (where vegetables are grown and sold in markets). Disease transmission was exacerbated by the fact that rainwater canals were being used for disposal of polluted waste from hospitals and residential areas. Social factors and their interactions also played a significant role in disease transmission.

Epidemiological characteristics of typhoid fever and antibiotic susceptibility testing of <i>Salmonella</i> Typhi isolates in Guangxi, 1994-2013.	
Author	Wang M, Kan B, Yang J, Lin M, Yan M, Zeng J, Quan Y, Liao H, Zhou L, Jiang Z, Huang D.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2014 Aug;35(8):930-4.
URL	Not publically available
Additional Categories	Disease and environmental surveillance Trends in antibiotic resistance of <i>Salmonella typhi</i>

[Article in Chinese]

OBJECTIVE: Through analyzing the typhoid epidemics and to determine and monitor regional resistance characteristics of the shift of drug resistant profile on *Salmonella* (S.) Typhi, to understand the related epidemiological characteristics of typhoid fever and to provide evidence for the development of strategies, in Guangxi. **METHODS:** Data of typhoid fever from surveillance and reporting system between 1994 to 2013 was collected and statistically analyzed epidemiologically. The susceptibility of 475 S. Typhi isolates from patients on ten antibiotics was tested by broth micro-dilution method and minimum inhibition concentration was obtained and interpreted based on the CLSI standard. **RESULTS:** From 1994 to 2013, a total of 57 928 cases of typhoid fever were reported in Guangxi province with an annual incidence of 6.29/100 000 and mortality as 0.03%. The higher incidence was observed in the population under 20 years of age. There was no significant difference on incidence between male and female, but farmers and students were among the hardest hit groups. More cases were seen from the northern part of the province. Cases appeared all year round with the peak from May to October. A total of 13 major outbreaks during 2001 to 2013 were reported and the main transmission route was water-borne. All the strains were sensitive to third generation cephalosporins cefotaxime and fluoroquinolones norfloxacin. The susceptibility rates to tetracycline, chloramphenicol, ampicillin and gentamicin was around 98% but relative lower susceptible rate to ciprofloxacin was seen as 89.89% . The lowest susceptibility was found for streptomycin and sulfamethoxazole agents, with the rates as 67.73% and 65.89% , respectively. One strain was found to have been resistant to ciprofloxacin and another 47 isolates with reduced susceptibility to ciprofloxacin. Twenty eight isolates were found to be resistant to multiple antibiotics and one displayed ampicillin, chloramphenicol, streptomycin, sulfamethoxazole tetracycline and nalidixic acid (ACSSxT-NAL) resistance profile. This was the first report in China. Multi-drug resistant strains were frequently isolated from small scale outbreaks of typhoid fever. **CONCLUSION:** The incidence of typhoid fever in Guangxi was still high and some strains showed multi-drug resistance and reduced susceptibility to ciprofloxacin, indicating that the surveillance and monitor programs on drug resistance of S. Typhi should be strengthened, to prevent large scale outbreaks of typhoid fever in this province.



Typhoid and paratyphoid fever in Yunnan province: distributional patterns and the related meteorological factors.

Author	Wang LX, Yan MY, Fang LQ, Fu XQ, Wang DC, Sun JL, Cao WC, Zhang J, Kan B.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2011 May;32(5):485-9.
URL	http://zhlxboxzz.yiigle.com/CN112338201105/593807.htm?locale=zh_CN
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

[Article in Chinese]

OBJECTIVE: To characterize the spatial distribution of typhoid and paratyphoid fever (TPF) in Yunnan province, China and to determine the effectiveness of meteorological factors on the epidemics of TPF. **METHODS:** Data of reported TPF cases in Yunnan province (2001 - 2007) from the China Information System for Diseases Control and Prevention was applied to GIS-based spatial analyses to detect their spatial distribution and clustering of TPF incidence at the county level. Panel data analysis was used to identify the relationships between the TPF incidence and meteorological factors including monthly average temperature, monthly cumulative precipitation and monthly average relative humidity. **RESULTS:** During the study period, the average incidence of TPF in Yunnan province was 23.11/100 000, with majority of the TPF cases emerged in summer and autumn. Although widely distributed, two TPF clusters were detected in Yunnan province based on the spatial analysis: one area around Yuxi city with the average annual incidence as 207.45/100 000 and another at the junctions of Yunnan province with Burma and Laos. Based on results from panel data analysis, the incidence of TPF was shown to be associated with meteorological factors such as temperature, precipitation, relative humidity and one month lag of temperature increase [10°C increase in the monthly average temperature: IRR = 1.30 (95%CI: 1.24 - 1.36); 10% increase in monthly average relative humidity: IRR = 1.07 (95%CI: 1.05 - 1.09); 100 mm rise in monthly cumulative precipitation: IRR = 1.02 (95%CI: 1.00 - 1.03); and 10°C average temperature increase, the last month: IRR = 1.73 (95%CI: 1.64 - 1.82)]. **CONCLUSION:** Areas with high TPF incidence were detected in this study, which indicated the key areas for TPF control in Yunnan province. Meteorological factors such as temperature, precipitation and humidity played a role in the incidence of TPF.

Rethinking typhoid fever vaccines: implications for travelers and people living in highly endemic areas.

Author	Whitaker JA, Franco-Paredes C, del Rio C, Edupuganti S.
Publication	J Travel Med. 2009 Jan-Feb;16(1):46-52.
URL	http://jtm.oxfordjournals.org/content/16/1/46.long

[START Summary]

This letter to the editor describes a study that examined *S. enterica* serovar Typhi incidence in Ghanaian children under 15 years of age. Typhoid fever incidences were calculated for September 2007 through November 2008. Incidence in children younger than five years of age was about 190 cases/100,000 population and highest in children 2-5 years of age (290/100,000 per year) and 5-8 years of age (200/100,000 per year). In children older than eight years of age, incidence decreased continuously, and the number of cases was too low to enable precise age-stratified incidence estimates.



DISEASE AND ENVIRONMENTAL SURVEILLANCE

Environmental Transmission of Typhoid Fever in an Urban Slum.

Author	Akullian A, Ng'eno E, Matheson AI, Cosmas L, Macharia D, Fields B, Bigogo G, Mugoh M, John-Stewart G, Walson JL, Wakefield J, Montgomery JM.
Publication	PLoS Negl Trop Dis. 2015 Dec 3;9(12):e0004212.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4669139/

BACKGROUND: Enteric fever due to *Salmonella Typhi* (typhoid fever) occurs in urban areas with poor sanitation. While direct fecal-oral transmission is thought to be the predominant mode of transmission, recent evidence suggests that indirect environmental transmission may also contribute to disease spread. **METHODS:** Data from a population-based infectious disease surveillance system (28,000 individuals followed biweekly) were used to map the spatial pattern of typhoid fever in Kibera, an urban informal settlement in Nairobi Kenya, between 2010-2011. Spatial modeling was used to test whether variations in topography and accumulation of surface water explain the geographic patterns of risk. **RESULTS:** Among children less than ten years of age, risk of typhoid fever was geographically heterogeneous across the study area ($p = 0.016$) and was positively associated with lower elevation, OR = 1.87, 95% CI (1.36-2.57), $p < 0.001$. In contrast, the risk of typhoid fever did not vary geographically or with elevation among individuals more than ten years of age [corrected]. **CONCLUSIONS:** Our results provide evidence of indirect, environmental transmission of typhoid fever among children, a group with high exposure to fecal pathogens in the environment. Spatially targeting sanitation interventions may decrease enteric fever transmission.

Investigation of the outbreak of typhoid in a village of Thar Desert Rajasthan, India

Author	Anand PK, Ramakrishnan R.
Publication	Indian J Med Res. 2010 Jun;131:799-803.
URL	http://www.ijmr.org.in/downloadpdf.asp?issn=0971-5916;year=2010;volume=131;issue=6;spage=799;epage=803;aulast=Anand;type=2
Additional Categories	Epidemiological patterns and global burden of typhoid fever

BACKGROUND & OBJECTIVES: Outbreaks of typhoid have been reported from Maharashtra, Bangalore, West Bengal and Pondicherry in India but rarely from Rajasthan. We investigated an outbreak of typhoid in a village of Thar Desert of Rajasthan. **METHODS:** A retrospective cohort study was carried out during May-July 2007 in Varkana village, Pali district, Rajasthan, to identify the risk factor for disease. The information on outbreak was collected and then described in time, place and person characteristics to arrive at aetiological hypotheses. **RESULTS:** There were 219 cases of typhoid in village. Attack rate was 104 cases per 1000 population. Maximum attack rate of 276 cases per 1000 population was noted in persons of 10-14 yr age group. Forty three serum samples were reported positive for Widal agglutination test out of 70 tested. Drinking of water from government overhead tanks was associated with disease significantly (RR= 11.1, 95% CI= 3.7-33). Two of the three water samples from government tanks were found positive for faecal contamination. **INTERPRETATION & CONCLUSION:** The outbreak of typhoid in a village affected >200 persons of all age groups and both gender. Exposure to the drinking water from government tanks was found significantly associated with the disease. Preventive and control measures undertaken after analytical epidemiological study helped in terminating the outbreak.

Risk factors for typhoid outbreak in Sungai Congkak Recreational Park, Selangor 2009.

Author	Anita S, Amir KM, Fadzilah K, Ahamad J, Noorhaida U, Marina K, Paid MY, Hanif Z.
Publication	Med J Malaysia. 2012 Feb;67(1):12-6.
URL	http://www.e-mjm.org/2012/v67n1/Typhoid_Outbreak.pdf
Additional Categories	Epidemiological patterns and global burden of typhoid fever

Typhoid fever continues to pose public health problems in Selangor where cases are found sporadically with occasional outbreaks reported. In February 2009, Hospital Tengku Ampuan Rahimah (HTAR) reported a cluster of typhoid fever among four children in the pediatric ward. We investigated the source of the outbreak, risk factors for the infection to propose control measures. We conducted a case-control study to identify the risk factors for the outbreak. A case was defined as a person with *S. typhi* isolated from blood, urine or stool and had visited Sungai Congkak recreational park on 27th January 2010. Controls were healthy household members of cases who have similar exposure but no isolation of *S. typhi* in blood, urine or stool. Cases were identified from routine surveillance system, medical record searching from the nearest clinic and contact tracing other than family members including food handlers and construction workers in the recreational park. Immediate control measures were initiated and followed up. Twelve (12) cases were identified from routine surveillance with 75 household controls. The case-control study showed cases were 17 times more likely to be 12 years or younger (95% CI: 2.10, 137.86) and 13 times more likely to have ingested river water accidentally during swimming (95% CI: 3.07, 58.71). River water was found contaminated with sewage disposal from two public toilets which effluent grew salmonella spp. The typhoid outbreak in Sungai Congkak recreational park resulted from contaminated river water due to poor sanitation. Children who accidentally ingested river water were highly susceptible. Immediate closure and upgrading of public toilet has stopped the outbreak.

Cluster of indigenous typhoid fever cases in a French city.

Author	Baclet N, Haeghebaert S, Legout L, Caillaux M, Moreau-Crepeaux S, Vachée A, Senneville E, Chaud P, Yazdanpanah Y, Poissy J.
Publication	Med Mal Infect. 2011 May;41(5):248-52.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

[Article in French]

BACKGROUND: A cluster of indigenous typhoid fever cases in the greater Lille area, in January 2009, triggered investigations to identify the contamination source and to optimize care for infected individuals. **METHODS:** A case was defined as a person, living in the greater Lille area of, having presented with symptoms of typhoid fever, from January to March 2009. **RESULTS:** Sixteen cases of typhoid fever were identified between January 23 and March 22, 2009. Patients, none of whom had travelled, had all participated in a common meal on January 10, 2009. A woman, who helped prepare the meal and who had previously stayed in an endemic zone, was detected as the asymptomatic carrier of *Salmonella Typhi*. **CONCLUSION:** In France, although typhoid fever remains essentially an imported disease, there is a risk of indigenous epidemic and its diagnosis can be suggested for individuals who have not travelled. The features of this cluster illustrate the importance of respecting basic rules of hygiene in catering.



Epidemiological characteristics and molecular typing of *Salmonella enterica* serovar Typhi during a waterborne outbreak in Eastern Anatolia.

Author	Bayram Y, G H, Otl B, Aypak C, Gsoy NC, Ulu H, Berkta M.
Publication	Ann Trop Med Parasitol. 2011 Jul;105(5):359-65.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4089787/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i>

In this study, we aimed to study the molecular and epidemiological characteristics of *Salmonella enterica* serovar Typhi (*S. Typhi*) outbreak in Eastern Anatolia. Six hundred and thirty-seven patients from the same county with clinical diagnosis of typhoid fever were investigated with conventional methods from stool, urine and blood specimens. Antibiotic susceptibility tests and identifications were performed for positive specimens. Clonal relationships between the isolates were investigated using pulsed field gel electrophoresis (PFGE) method. A questionnaire was completed for the water consumption habits of patients. Of 91 culture positive specimens, 76 were blood, 13 were stool and 2 were urine. The isolates were resistant to ampicillin, ampicillin/sulbactam, chloramphenicol, cefuroxime, amikacin, gentamicin and trimethoprim-sulfamethoxazole. Although there was a single band difference in some isolates, PFGE results indicated that this was an outbreak caused by single strain according to the Tenover criteria. This outbreak thought to be associated with the consumption of tap water contaminated with sewage represents a breakdown of the basic public health and civil engineering infrastructure. Appropriate public health measures should be taken in order to avoid such outbreaks in the future.

Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: implications for typhoid vaccine use in Africa.

Author	Breiman RF, Cosmas L, Njuguna H, Audi A, Olack B, Ochieng JB, Wamola N, Bigogo GM, Awiti G, Tabu CW, Burke H, Williamson J, Oundo JO, Mintz ED, Feikin DR.
Publication	PLoS One. 2012;7(1):e29119.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3261857/pdf/pone.0029119.pdf

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 2007-2009, 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.

Differential epidemiology of *Salmonella* Typhi and Paratyphi A in Kathmandu, Nepal: a matched case control investigation in a highly endemic enteric fever setting.

Author	Karkey A, Thompson CN, Tran Vu Thieu N, Dongol S, Le Thi Phuong T, Voong Vinh P, Arjyal A, Martin LB, Rondini S, Farrar JJ, Dolecek C, Basnyat B, Baker S.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749961/pdf/pntd.0002391.pdf
Publication	PLoS Negl Trop Dis. 2013 Aug 22;7(8):e2391.
Additional Categories	Epidemiological patterns and global burden of typhoid

BACKGROUND: Enteric fever, a systemic infection caused by the bacteria *Salmonella typhi* and *Salmonella Paratyphi A*, is endemic in Kathmandu, Nepal. Previous work identified proximity to poor quality water sources as a community-level risk for infection. Here, we sought to examine individual-level risk factors related to hygiene and sanitation to improve our understanding of the epidemiology of enteric fever in this setting. **METHODOLOGY AND PRINCIPAL FINDINGS:** A matched case-control analysis was performed through enrollment of 103 blood culture positive enteric fever patients and 294 afebrile community-based age and gender-matched controls. A detailed questionnaire was administered to both cases and controls and the association between enteric fever infection and potential exposures were examined through conditional logistic regression. Several behavioral practices were identified as protective against infection with enteric fever, including water storage and hygienic habits. Additionally, we found that exposures related to poor water and socioeconomic status are more influential in the risk of infection with *S. Typhi*, whereas food consumption habits and migration play more of a role in risk of *S. Paratyphi A* infection. **CONCLUSIONS AND SIGNIFICANCE:** Our work suggests that *S. Typhi* and *S. Paratyphi A* follow different routes of infection in this highly endemic setting and that sustained exposure to both serovars probably leads to the development of passive immunity. In the absence of a polyvalent vaccine against *S. Typhi* and *S. Paratyphi A*, we advocate better systems for water treatment and storage, improvements in the quality of street food, and vaccination with currently available *S. Typhi* vaccines.

Re-emergence of susceptibility to conventional first line drugs in *Salmonella* isolates from enteric fever patients in Nepal.

Author	Chand HJ, Rijal KR, Neupane B, Sharma VK, Jha B.
Publication	J Infect Dev Ctries. 2014 Nov 13;8(11):1483-7.
URL	http://www.jidc.org/index.php/journal/article/view/25390062/1197
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

INTRODUCTION: Enteric fever is endemic in Nepal and poses a significant public health burden. The first-line drugs ampicillin, chloramphenicol, and cotrimoxazole have not been part of empirical therapy for two decades due to the development of multidrug-resistant *Salmonella* strains. The objective of this study was to determine the antibiogram pattern of *Salmonella* serovars isolated from the blood of clinically suspected enteric fever patients. **METHODOLOGY:** A cross sectional study was carried out in a tertiary care hospital in Lalitpur, Nepal, between July 2011 and February 2012. Standard microbiological



procedures were followed during collection and processing of blood samples, isolation and identification of *Salmonella* serotypes. The antimicrobial sensitivity of ampicillin, chloramphenicol, cotrimoxazole, nalidixic acid, and ciprofloxacin was determined using a modified Kirby-Bauer disk diffusion method as per the guidelines of the Clinical and Laboratory Standards Institute. **RESULTS:** Out of 86 *Salmonella* isolates, 56 (65.1%) were *Salmonella* Typhi and 30 (34.9%) were *Salmonella* Paratyphi A. *Salmonella* Typhi were 100% sensitive to chloramphenicol, cotrimoxazole, and ciprofloxacin and 98.2% sensitive to ampicillin. Similarly, *Salmonella* Paratyphi A isolates were 100% sensitive to ampicillin and cotrimoxazole and 96.7% sensitive to chloramphenicol and ciprofloxacin. More than 90.0% of isolates were nalidixic acid resistant and none of the *Salmonella* isolates were multi-drug resistant. **CONCLUSIONS:** This study revealed the increasing frequency of nalidixic acid-resistant *Salmonella* isolates, indicating the possibility of fluoroquinolone resistance in near future. Furthermore, re-emergence of susceptibility to conventional first-line drugs ampicillin, chloramphenicol, and cotrimoxazole supports the possibility of using these drugs in empirical therapy.

Twenty-six years of enteric fever in Australia: an epidemiological analysis of antibiotic resistance.

Author	Commons RJ, McBryde E, Valcanis M, Powling J, Street A, Hogg G.
Publication	Med J Aust. 2012 Mar 19;196(5):332-6.
URL	https://www.mja.com.au/journal/2012/196/5/twenty-six-years-enteric-fever-australia-epidemiological-analysis-antibiotic

OBJECTIVES: To determine incidence and trends in antibiotic resistance in Australian *Salmonella enterica* subspecies *enterica* serovars Typhi (*S. Typhi*) and Paratyphi (*S. Paratyphi*) isolates over the past 26 years. **DESIGN:** A retrospective analysis of consecutive microbiologically confirmed enteric fever isolates. **PARTICIPANTS AND SETTING:** All *S. Typhi* and *S. Paratyphi* isolates from patients diagnosed with enteric fever in Australia between 1985 and 2010. **MAIN OUTCOME MEASURES:** Incidence and variation in antibiotic resistance over time and according to country of origin. **RESULTS:** We analysed 2551 isolates, which originated from 74 countries or regions, mainly India (33%) and Indonesia (22%). The incidence among Australian residents increased from four to five before 2003 to seven cases per million person-years after 2003. Multidrug resistance (chloramphenicol, ampicillin, trimethoprim) and nalidixic acid resistance emerged rapidly from the early 1990s, with nalidixic acid resistance increasing to 70% in 2009-2010, while multidrug resistance was relatively stable at between 4% and 11%. Nalidixic acid and multidrug resistance rates are highest in isolates from the Indian subcontinent. Some countries in South-East Asia, such as Indonesia, had very low rates of resistance; however, this varied across the region. **CONCLUSIONS:** Nalidixic acid resistance has become widespread in enteric fever isolates from the Indian subcontinent and some parts of South-East Asia, justifying the use of ceftriaxone or azithromycin rather than ciprofloxacin as first-line treatment. However, resistance in some countries remains rare, potentially allowing treatment to be adjusted according to country of origin.



Global trends in typhoid and paratyphoid fever.

Author	Crump JA. Mintz ED.
Publication	Clin Infect Dis. 2010 Jan 15;50(2):241-6.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2798017/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and Southeast Asia, where enteric fever is associated with poor sanitation and unsafe food and water. High-quality incidence data from Asia are underpinning efforts to expand access to typhoid vaccines. Efforts are underway to develop vaccines that are immunogenic in infants after a single dose and that can be produced locally in countries of endemicity. The growing importance of *Salmonella enterica* serotype Paratyphi A in Asia is concerning. Antimicrobial resistance has sequentially emerged to traditional first-line drugs, fluoroquinolones, and third-generation cephalosporins, posing patient treatment challenges. Azithromycin has proven to be an effective alternative for treatment of uncomplicated typhoid fever. The availability of full genome sequences for *S. enterica* serotype Typhi and *S. enterica* serotype Paratyphi A confirms their place as monomorphic, human-adapted pathogens vulnerable to control measures if international efforts can be redoubled.

Typhoid fever surveillance and vaccine use - South-East Asia and Western Pacific regions, 2009-2013.

Author	Date KA, Bentsi-Enchill AD, Fox KK, Abeyasinghe N, Mintz ED, Khan MI, Sahastrabuddhe S, Hyde TB; Centers for Disease Control and Prevention (CDC).
Publication	MMWR Morb Mortal Wkly Rep. 2014 Oct 3;63(39):855-60.
URL	http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6339a2.htm
Additional Categories	Challenge models and vaccine trials

Typhoid fever is a serious, systemic infection resulting in nearly 22 million cases and 216,500 deaths annually, primarily in Asia. Safe water, adequate sanitation, appropriate personal and food hygiene, and vaccination are the most effective strategies for prevention and control. In 2008, the World Health Organization (WHO) recommended use of available typhoid vaccines to control endemic disease and outbreaks and strengthening of typhoid surveillance to improve disease estimates and identify high-risk populations (e.g., persons without access to potable water and adequate sanitation). This report summarizes the status of typhoid surveillance and vaccination programs in the WHO South-East Asia (SEAR) and Western Pacific regions (WPR) during 2009-2013, after the revised WHO recommendations. Data were obtained from the WHO/United Nations Children's Fund (UNICEF) Joint Reporting Form on Immunization, a supplemental survey of surveillance and immunization program managers, and published literature. During 2009-2013, 23 (48%) of 48 countries and areas of SEAR (11) and WPR (37) collected surveillance or notifiable disease data on typhoid cases, with most surveillance activities established before 2008. Nine (19%) countries reported implementation of typhoid vaccination programs or recommended vaccine use during 2009-2013. Despite the high incidence, typhoid surveillance is weak in these two regions, and vaccination efforts have been limited. Further progress toward typhoid fever prevention and control in SEAR and WPR will require country commitment and



international support for enhanced surveillance, targeted use of existing vaccines and availability of newer vaccines integrated within routine immunization programs, and integration of vaccination with safe water, sanitation, and hygiene measures.

Trends and disease burden of enteric fever in Guangxi province, China, 1994-2004.

Author	Dong BQ, Yang J, Wang XY, Gong J, von Seidlein L, Wang ML, Lin M, Liao HZ, Ochiai RL, Xu ZY, Jodar L, Clemens JD.
Publication	Bull World Health Organ. 2010 Sep 1;88(9):689-96.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2930361/
Additional Categories	Epidemiological patterns and global burden of typhoid fever

OBJECTIVE: To determine the burden of enteric fever through trends in morbidity and mortality, bacterial species and antimicrobial resistance in Guangxi, a southern, subtropical, coastal province of China with a disproportionately large burden of enteric fever. **METHODS:** Data on morbidity and mortality caused by enteric fever between 1994 and 2004 were extracted from the Guangxi Center for Disease Control and Prevention. Laboratory-based surveillance and outbreak investigations were integrated with reports of notifiable infectious diseases to estimate the bacterial species-specific incidence of enteric fever. To adjust for underreporting, survey data were collected from three prefectures that represent the hyper-, moderate-and low-endemic regions of Guangxi province. **FINDINGS:** In Guangxi province, enteric fever incidence rate varied over the study period, with a peak of 13.5 cases per 100 000 population in 1995 and a low of 6.5 in 2003. The disease occurred most frequently during the summer and autumn months and in the group aged 10-49 years. The incidence of enteric fever varied by region within Guangxi province. During the 11-year period covered by the study, 61 outbreaks of enteric fever were reported, and *Salmonella paratyphi A* (SPA) became the predominant causative agent in the province. **CONCLUSION:** Prospective studies may provide a better understanding of the reason for the shifting epidemiology of enteric fever in Guangxi province. Given the emergence of resistance to first- and second-line antimicrobials for the treatment of enteric fever, a bivalent vaccine against both SPA and *S. typhi* would facilitate for disease control.

Investigation of a community outbreak of typhoid fever associated with drinking water.

Author	Farooqui A, Khan A, Kazmi SU.
Publication	BMC Public Health. 2009 Dec 20;9:476.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2804617/
Additional Categories	Epidemiological patterns and global burden of typhoid fever

BACKGROUND: This report is about the investigation of an outbreak of typhoid fever claimed three human lives and left more than 300 people suffered within one week. The aim of this report is to draw the attention of global health community towards the areas that are still far from basic human essentialities. **METHODS:** A total of 250 suspected cases of typhoid fever were interviewed, out of which 100 were selected for sample collection on the basis of criteria included temperature >38 degrees °C since the onset of outbreak, abdominal discomfort, diarrhea, vomiting and weakness. Food and water samples were also collected and analyzed microbiologically. **RESULTS:** Inhabitants of village lived in poor and unhygienic conditions with no proper water supply or sewage disposal facilities and other basic necessities of life. They consumed water from a nearby well which was the only available source of



drinking water. Epidemiological evidences revealed the gross contamination of well with dead and decaying animal bodies, their fecal material and garbage. Microbiological analysis of household and well water samples revealed the presence of heavy bacterial load with an average total aerobic count 106-109 CFU/ml. A number of Gram positive and Gram negative bacteria including *Escherichia coli*, *Klebsiella*, *Bacillus* species, *Staphylococcus* species, *Enterobacter* species, and *Pseudomonas aeruginosa* were isolated. Lab investigations confirmed the presence of multidrug resistant strain of *Salmonella enterica* serovar Typhi in 100% well water, 65% household water samples and 2% food items. 22% of clinical stool samples were tested positive with *Salmonella enterica* serovar Typhi. CONCLUSIONS: This study indicated the possible involvement of well water in outbreaks. In order to avoid such outbreaks in future, we contacted the local health authorities and urged them to immediately make arrangements for safe drinking water supply.

Rapid emergence of multidrug resistant, H58-lineage *Salmonella typhi* in Blantyre, Malawi.

Author	Feasey NA, Gaskell K, Wong V, Msefula C, Selemani G, Kumwenda S, Allain TJ, Mallewa J, Kennedy N, Bennett A, Nyirongo JO, Nyondo PA, Zulu MD, Parkhill J, Dougan G(3), Gordon MA, Heyderman RS.
Publication	PLoS Negl Trop Dis. 2015 Apr 24;9(4):e0003748.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4409211/
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

INTRODUCTION: 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). METHODS: 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. RESULTS: 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*. CONCLUSIONS: 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.



Typhoid fever acquired in the United States, 1999-2010: epidemiology, microbiology, and use of a space-time scan statistic for outbreak detection.

Author	Imanishi M, Newton AE, Vieira AR, Gonzalez-Aviles G, Kendall Scott ME, Manikonda K, Maxwell TN, Halpin JL, Freeman MM, Medalla F, Ayers TL, Derado G, Mahon BE, Mintz ED.
Publication	Epidemiol Infect. 2015 Aug;143(11):2343-54.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

Although rare, typhoid fever cases acquired in the United States continue to be reported. Detection and investigation of outbreaks in these domestically acquired cases offer opportunities to identify chronic carriers. We searched surveillance and laboratory databases for domestically acquired typhoid fever cases, used a space-time scan statistic to identify clusters, and classified clusters as outbreaks or non-outbreaks. From 1999 to 2010, domestically acquired cases accounted for 18% of 3373 reported typhoid fever cases; their isolates were less often multidrug-resistant (2% vs. 15%) compared to isolates from travel-associated cases. We identified 28 outbreaks and two possible outbreaks within 45 space-time clusters of ≥ 2 domestically acquired cases, including three outbreaks involving ≥ 2 molecular subtypes. The approach detected seven of the ten outbreaks published in the literature or reported to CDC. Although this approach did not definitively identify any previously unrecognized outbreaks, it showed the potential to detect outbreaks of typhoid fever that may escape detection by routine analysis of surveillance data. Sixteen outbreaks had been linked to a carrier. Every case of typhoid fever acquired in a non-endemic country warrants thorough investigation. Space-time scan statistics, together with shoe-leather epidemiology and molecular subtyping, may improve outbreak detection.

A review of the disease burden, impact and prevention of typhoid fever in Nigeria.

Author	Iperepolu OH, Entonu PE, Agwale SM.
Publication	West Afr J Med. 2008 Jul;27(3):127-33.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

BACKGROUND: Typhoid fever is still a common infection in many parts of the world, especially in developing countries where sanitation and water supply are a common problem. A recent study placed the disease burden at 21650 974 illnesses and 216510 deaths during 2000. The infection is a major cause of morbidity and mortality in Nigeria. **OBJECTIVE:** This review set out to present in one concise volume a review of the major findings from published articles on the burden and impact of typhoid fever in Nigeria to aid easy reference for researchers. It highlights the disease burden, the different diagnostic methods and their sensitivities, complications, treatment methods as well as the various preventive measures including the use of typhoid vaccine in the control of the disease. **METHODS:** Several published articles covering a period of 40 years were accessed different journals and reviewed, and their major findings presented in this review. **RESULTS:** The disease burden from typhoid fever in Nigeria is still high with associated serious complications, which in most cases have been managed effectively with the use of potent antibiotics and surgical intervention. However, the typhoid problem has been compounded by the emergence and circulation of multi-drug resistant strains of the organism being sensitive only to the newer generation antibiotics. **CONCLUSION:** Typhoid fever remains a major public



health problem in Nigeria. The infection however can be prevented by good sanitation, improving good water supply, the provision of proper sewage disposal system, as well as the effective use of the available typhoid vaccines. The government and people of Nigeria should rise up to the challenge of stamping out this ugly trend.

Antimicrobial resistance among blood culture isolates of *Salmonella enterica* in New Delhi.

Author	Jain S, Das Chugh T.
Publication	J Infect Dev Ctries. 2013 Nov 15;7(11):788-95.
URL	http://www.jidc.org/index.php/journal/article/view/24240035/937
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

INTRODUCTION: Enteric fever is a global public health problem, especially in developing countries. Antimicrobial resistance is a major issue enteric fever management. This study examined current pattern of antimicrobial susceptibility among *Salmonella enterica* isolates from enteric fever cases at a tertiary care centre in New Delhi, India. **METHODOLOGY:** Blood cultures from patients with enteric fever during January 2010-July 2012 were processed using the BACTEC automated system. Antimicrobial susceptibility was tested using Kirby Bauer's disc diffusion method and/or Phoenix 100 automated system. **RESULTS:** Of 344 isolates of *Salmonella enterica*, 266 (77.3%) were *S. Typhi*, 77 (22.4%) were *S. Paratyphi A*, and one (0.3%) was *S. Paratyphi B*. Resistance to nalidixic acid (NA(R)) (96.7%) was most common, followed by ciprofloxacin (37.9%), and azithromycin (7.3%). Multi-drug resistance was observed only in *S. Typhi* (3.4%). Among NA(R) strains, 61.8% were sensitive, 11.1% were moderately sensitive, and 23.9% were resistant to ciprofloxacin (0.8%, 57.4%, and 37.9% respectively according to revised CLSI breakpoint criteria for ciprofloxacin). Resistance to third-generation cephalosporin was found in seven (2%) strains of *S. enterica*. **CONCLUSION:** Increasing rates of nalidixic acid, fluoroquinolone and azithromycin resistance among *S. enterica*, particularly in *S. Paratyphi A* strains, is of concern, as *S. Paratyphi A* infection is becoming increasingly common and is not prevented by current vaccinations. Our results favour use of cefexime or possibly chloramphenicol as first choice for uncomplicated enteric fever. MICs for third-generation cephalosporins and susceptibility pattern must be closely monitored in view of its emerging resistance among *Salmonella enterica*.

Epidemiology of typhoid and paratyphoid fever in India.

Author	Kanungo S, Dutta S, Sur D.
Publication	J Infect Dev Ctries. 2008 Dec 1;2(6):454-60.
URL	http://www.jidc.org/index.php/journal/article/view/19745523/79
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

Enteric fever (typhoid and paratyphoid fever) is a major human bacterial infection. Although the disease is not common in industrialised countries, it remains an important and persistent health problem in developing nations. Hospital-based studies and outbreak reports from India indicate that enteric fever is a major public health problem in this country, with *Salmonella enterica* serovar *Typhi* (*S. Typhi*) the most common aetiological agent but with an apparently increasing number of cases due to *S. Paratyphi A* (SPA). Because risk factors such as poor sanitation, lack of a safe drinking water supply and low socio economic conditions in resource-poor countries are amplified by the evolution of multidrug resistant salmonellae



with reduced susceptibility to fluoroquinolone, treatment failure cases have been reported in India, which is associated with increased mortality and morbidity. Vaccination, which requires strict planning and proper targeting of the vulnerable age groups, is considered to be an effective tool in controlling this disease in endemic areas, given there is development of a conjugate vaccine against both serovars (S. Typhi and S. Para A).

The Ecological Dynamics of Fecal Contamination and Salmonella Typhi and Salmonella Paratyphi A in Municipal Kathmandu Drinking Water.	
Author	Karkey A, Jombart T, Walker AW, Thompson CN, Torres A, Dongol S, Tran Vu Thieu N, Pham Thanh D, Tran Thi Ngoc D, Voong Vinh P, Singer AC, Parkhill J, Thwaites G, Basnyat B, Ferguson N, Baker S.
Publication	PLoS Negl Trop Dis. 2016 Jan 6;10(1):e0004346.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4703202/
Additional Categories	Epidemiological patterns and global burden of typhoid fever

One of the UN sustainable development goals is to achieve universal access to safe and affordable drinking water by 2030. It is locations like Kathmandu, Nepal, a densely populated city in South Asia with endemic typhoid fever, where this goal is most pertinent. Aiming to understand the public health implications of water quality in Kathmandu we subjected weekly water samples from 10 sources for one year to a range of chemical and bacteriological analyses. We additionally aimed to detect the etiological agents of typhoid fever and longitudinally assess microbial diversity by 16S rRNA gene surveying. We found that the majority of water sources exhibited chemical and bacterial contamination exceeding WHO guidelines. Further analysis of the chemical and bacterial data indicated site-specific pollution, symptomatic of highly localized fecal contamination. Rainfall was found to be a key driver of this fecal contamination, correlating with nitrates and evidence of S. Typhi and S. Paratyphi A, for which DNA was detectable in 333 (77%) and 303 (70%) of 432 water samples, respectively. 16S rRNA gene surveying outlined a spectrum of fecal bacteria in the contaminated water, forming complex communities again displaying location-specific temporal signatures. Our data signify that the municipal water in Kathmandu is a predominant vehicle for the transmission of S. Typhi and S. Paratyphi A. This study represents the first extensive spatiotemporal investigation of water pollution in an endemic typhoid fever setting and implicates highly localized human waste as the major contributor to poor water quality in the Kathmandu Valley.

Molecular epidemiological investigation of a typhoid fever outbreak in South Africa, 2005: the relationship to a previous epidemic in 1993.

Author	Keddy KH, Sooka A, Ismail H, Smith AM, Weber I, Letsoalo ME, Harris BN.
Publication	Epidemiol Infect. 2011 Aug;139(8):1239-45.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

In 2005, over 600 clinically diagnosed typhoid fever cases occurred in South Africa, where an outbreak had been previously described in 1993. Case-control and molecular investigations, including Salmonella enterica serovar Typhi (S. Typhi) isolates from that area from 1993, 2005 and later, were undertaken. Controls were significantly older than cases ($P=0.003$), possibly due to immunity from previous infection,



and a significantly larger proportion had attended a gathering ($P=0.035$). Exposure to commercial food outlets and person-to-person transmission was not significant. Pulsed-field gel electrophoresis and multi-locus tandem repeat analysis revealed common clusters of *S. Typhi* strains identified in 1993 and 2005 as well as in 2007 and 2009. This outbreak probably occurred in a non-immune population due to faecally contaminated water. *S. Typhi* strains appeared to be related to strains from 1993; failure to address unsafe water may lead to further outbreaks in the area if the current population immunity wanes or is lost.

Risk factors associated with typhoid fever in children aged 2-16 years in Karachi, Pakistan.

Author	Khan MI, Ochiai RL, Soofi SB, Von-Seidlein L, Khan MJ, Sahito SM, Habib MA, Puri MK, Park JK, You YA, Ali M, Nizami SQ, Acosta CJ, Bradley-Sack R, Clemens JD, Bhutta ZA.
Publication	Epidemiol Infect. 2012 Apr;140(4):665-72.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

We analysed the data from the control group in a typhoid vaccine trial in Karachi to assess the differences in individual-, household- and cluster-level characteristics for developing typhoid fever. The annual incidence of typhoid in children aged 2-16 years in the control arm of the vaccine trial was 151/100 000 population. After adjustment, the risk of typhoid was lower with increasing age [risk ratio (RR) 0.89, 95% confidence interval (CI) 0.83-0.95], was higher with an increase in population density (RR 1.13, 95% CI 1.05-1.21) and was lower in the households using a safe drinking-water source (RR 0.63, 95% CI 0.41-0.99). Typhoid fever affects younger children living in areas of high population density and lack of access to safe water in Pakistan. A combination of environmental and biological interventions is required to prevent the continued epidemiological and economic impact of typhoid fever in high-risk areas of Pakistan.

Typhoid outbreak in Songkhla, Thailand 2009-2011: clinical outcomes, susceptibility patterns, and reliability of serology tests.

Author	Limpitikul W, Henpraserttae N, Saksawad R, Laoprasopwattana K.
Publication	PLoS One. 2014 Nov 6;9(11):e111768.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4222948/
Additional Categories	Epidemiological patterns and global burden of typhoid fever

OBJECTIVE: To determine the clinical manifestations and outcomes, the reliability of *Salmonella enterica* serotype Typhi (S ser. Typhi) IgM and IgG rapid tests, and the susceptibility patterns and the response to treatment during the 2009-2011 typhoid outbreak in Songkhla province in Thailand. **METHOD:** The medical records of children aged <15 years with S ser. Typhi bacteremia were analysed. The efficacy of the typhoid IgM and IgG rapid tests and susceptibility of the S ser. Typhi to the current main antibiotics used for typhoid (amoxicillin, ampicillin, cefotaxime, ceftriaxone, co-trimoxazole, and ciprofloxacin), were evaluated. **RESULTS:** S ser. Typhi bacteremia was found in 368 patients, and all isolated strains were susceptible to all 6 antimicrobials tested. Most of the patients were treated with ciprofloxacin for 7-14 days. The median time (IQR) of fever before treatment and duration of fever after treatment were 5 (4, 7) days and 4 (3, 5) days, respectively. Complications of ascites, lower respiratory symptoms, anemia (Hct <30%), and ileal perforation were found in 7, 7, 22, and 1 patients, respectively. None of the



patients had recurrent infection or died. The sensitivities of the typhoid IgM and IgG tests were 58.3% and 25.6% respectively, and specificities were 74.1% and 50.5%, respectively. **CONCLUSION:** Most of the patients were diagnosed at an early stage and treated with a good outcome. All S ser. Typhi strains were susceptible to standard first line antibiotic typhoid treatment. The typhoid IgM and IgG rapid tests had low sensitivity and moderate specificity.

Towards sustainable public health surveillance for enteric fever.

Author	Luby SP, Saha S, Andrews JR.
Publication	Vaccine. 2015 Jun 19;33 Suppl 3:C3-7.
URL	Not publically available

Enteric fever that results from infection by the typhoidal Salmonellas (Salmonella Typhi and Salmonella Paratyphi A, B and C) is a life-threatening preventable illness. Surveillance of enteric fever is important to understand current burden of disease, to track changes in human health burden from increasing antimicrobial resistance and to assess the impact of efforts to reduce disease burden. Since enteric fever occurs predominantly in low income communities, expensive surveillance is not sustainable. Traditional hospital-based surveillance does not estimate population burden and intensive community-based cohort studies do not capture the severe disease that is crucial to policy decisions. While cohort studies have been considered the gold standard for incidence estimates, the resources required to conduct them are great; as a consequence, estimates of enteric fever burden have been highly geographically and temporally restricted. A hybrid approach combining laboratory diagnosis that is already being conducted in healthcare centers with community-based surveillance of health care facility use offers a low-cost, sustainable approach to generate policy relevant data.

Typhoid outbreak investigation in Dzivaresekwa, suburb of Harare City, Zimbabwe, 2011.

Author	Muti M, Gombe N, Tshimanga M, Takundwa L, Bangure D, Mungofa S, Chonzi P.
Publication	Pan Afr Med J. 2014 Aug 18;18:309.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4247891/

INTRODUCTION: Typhoid fever is a systemic infection caused by a Gram negative bacterium, Salmonella typhi. Harare City reported 1078 cases of suspected typhoid fever cases from October 2011 to January 2012. We initiated an investigation to identify possible source of transmission so as to institute control measures. **METHODS:** An unmatched 1:1 case-control study was conducted. A questionnaire was administered to study participants to identify risk factors for contracting typhoid. A case was a resident of Dzivaresekwa who presented with signs and symptoms of typhoid between October and December 2011. Water samples were collected for microbiological analysis. **RESULTS:** 115 cases and 115 controls were enrolled. Drinking water from a well (OR=6.2 95% CI (2.01-18.7)), attending a gathering (OR=11.3 95% CI (4.3-29.95)), boiling drinking water (OR=0.21 95% CI (0.06-0.76)) and burst sewer pipe at home (OR=1.19 95% CI (0.67-2.14)) were factors associated with contracting typhoid. Independent risk factors for contracting typhoid were drinking water from a well (AOR=5.8; 95% CI (1.90-17.78)), and burst sewer pipe at home (AOR=1.20; 95% CI (1.10-2.19)). Faecal coli forms and E. coli were isolated from 8/8 well water samples. Stool, urine and blood specimens were cultured and serotyped for Salmonella typhi and 24 cases were confirmed positive. Shigella, Giardia and E coli were also isolated. Ciprofloxacin, X-pen and Rocephin were used for case management. No complications were reported. **CONCLUSION:**



Contaminated water from unprotected water sources was the probable source of the outbreak. Harare City Engineer must invest in repairing water and sewage reticulation systems in the city.

Burden of typhoid and paratyphoid fever in a densely populated urban community, Dhaka, Bangladesh.

Author	Naheed A, Ram PK, Brooks WA, Hossain MA, Parsons MB, Talukder KA, Mintz E, Luby S, Breiman RF.
Publication	Int J Infect Dis. 2010 Sep;14 Suppl 3:e93-9.
URL	http://www.sciencedirect.com/science/article/pii/S1201971210022800
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i>

BACKGROUND: We conducted blood culture surveillance to estimate the incidence of typhoid and paratyphoid fever among urban slum residents in Dhaka, Bangladesh. **METHODS:** Between January 7, 2003 and January 6, 2004, participants were visited weekly to detect febrile illnesses. Blood cultures were obtained at the clinic from patients with fever ($\geq 38^{\circ}\text{C}$). *Salmonella* isolates were assayed for antimicrobial susceptibility. **RESULTS:** Forty *Salmonella typhi* and eight *Salmonella Paratyphi A* were isolated from 961 blood cultures. The incidence of typhoid fever was 2.0 episodes/1000 person-years, with a higher incidence in children aged <5 years (10.5/1000 person-years) than in older persons (0.9/1000 person-years) (relative risk=12, 95% confidence interval (CI) 6.3-22.6). The incidence of paratyphoid fever was 0.4/1000 person-years without variation by age group. Sixteen *S. Typhi* isolates were multidrug-resistant (MDR). All *S. Paratyphi* isolates were pan-susceptible. The duration of fever among patients with an MDR *S. Typhi* infection was longer than among patients with non-MDR *S. Typhi* (16 ± 8 vs. 11 ± 4 days, $p=0.02$) and *S. Paratyphi* (10 ± 2 days, $p=0.04$) infections. **CONCLUSIONS:** Typhoid fever is more common than paratyphoid fever in the urban Bangladeshi slum; children <5 years old have the highest incidence. Multidrug resistance is common in *S. Typhi* isolates and is associated with prolonged illness. Strategies for typhoid fever prevention in children aged <5 years in Bangladesh, including immunization, are needed.

Typhoid fever in Lebanon: epidemiological study.

Author	Naji-Rammal S, Bedrossian N.
Publication	Sante. 2010 Apr-Jun;20(2):81-6.
URL	http://www.jle.com/fr/revues/san/e-docs/la_fievre_typhoide_au_liban_etude_epidemiologique_285738/article.phtml

[Article in French]

Typhoid fever is a major public health problem, especially in developing countries. From 2000 through 2008, the infectious disease surveillance unit at the Lebanese Ministry of Public Health received 6148 reports of typhoid cases. A case is considered positive for typhoid or paratyphoid fever when fever of at least 38 degrees C persists for three days, and *Salmonella enterica* serovar Typhi or Paratyphi is isolated from blood, bone marrow, or stool. Statistical analysis was performed with STATA v.10 software. The most cases were recorded in 2003 ($n=891$), followed by 2007 ($n=879$), while the fewest were recorded in 2005 ($n=461$). The distribution of typhoid was not homogeneous between age groups: the age group most affected were those aged 20-39 years, followed by those from 10-19 years; those older than 60 years were least affected. Nor was the geographic distribution, by district (combining Nabatieh and the South together), homogeneous. The most affected individuals were in the North ($n=2,192$), followed by



Bekaa (n=1,651) and Mount Lebanon (n= 1,094). Beirut was the least affected, with 210 cases. The results indicate that typhoid fever remains endemic in Lebanon and that the risk of epidemic episodes is still present.

A study of typhoid fever in five Asian countries: disease burden and implications for controls.	
Author	Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, Bhutta ZA, Canh DG, Ali M, Shin S, Wain J, Page AL, Albert MJ, Farrar J, Abu-Elyazeed R, Pang T, Galindo CM, von Seidlein L, Clemens JD; Domi Typhoid Study Group.
Publication	Bull World Health Organ. 2008 Apr;86(4):260-8. Erratum in Bull World Health Organ. 2015 Apr 1;93(4):284. Bull World Health Organ. 2015 Jun 1;93(6):440.
URL	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC18438514/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i>

OBJECTIVE: To inform policy-makers about introduction of preventive interventions against typhoid, including vaccination. **METHODS:** A population-based prospective surveillance design was used. Study sites where typhoid was considered a problem by local authorities were established in China, India, Indonesia, Pakistan and Viet Nam. Standardized clinical, laboratory, and surveillance methods were used to investigate cases of fever of ≥ 3 days' duration for a one-year period. A total of 441,435 persons were under surveillance, 159,856 of whom were aged 5-15 years. **FINDINGS:** A total of 21,874 episodes of fever were detected. *Salmonella typhi* was isolated from 475 (2%) blood cultures, 57% (273/475) of which were from 5-15 year-olds. The annual typhoid incidence (per 100,000 person years) among this age group varied from 24.2 and 29.3 in sites in Viet Nam and China, respectively, to 180.3 in the site in Indonesia; and to 412.9 and 493.5 in sites in Pakistan and India, respectively. Altogether, 23% (96/413) of isolates were multidrug resistant (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole). **CONCLUSION:** The incidence of typhoid varied substantially between sites, being high in India and Pakistan, intermediate in Indonesia, and low in China and Viet Nam. These findings highlight the considerable, but geographically heterogeneous, burden of typhoid fever in endemic areas of Asia, and underscore the importance of evidence on disease burden in making policy decisions about interventions to control this disease.

Incidence of typhoid bacteremia in infants and young children in southern coastal Pakistan.	
Author	Owais A, Sultana S, Zaman U, Rizvi A, Zaidi AK.
Publication	Pediatr Infect Dis J. 2010 Nov;29(11):1035-9.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3073093/
Additional Categories	Epidemiological patterns and global burden of typhoid fever

INTRODUCTION: The burden of typhoid fever in preschool children is not well recognized. The purpose of this study was to estimate the incidence of typhoid bacteremia in Pakistani children <5 years of age, with a focus on children younger than 2 years of age. This will help to inform prevention policies in highly endemic countries. **METHODS:** Household surveillance from February 1, 2007 to May 12, 2008, was carried out by community health workers in 2 low-income, coastal communities of Karachi. Workers



referred each sick child <5 years old to the local clinic. Blood for culture was obtained from those who gave consent, and inoculated in BACTEC Peds Plus bottles (Becton Dickinson, Sparks, MD) and processed per manufacturer's guidelines. RESULTS: Overall, 5570 children contributed 3949 observation years. Blood culture was obtained from 1165 cases, yielding 36 pathogens. Salmonella Typhi was isolated in 16 cases, Salmonella Paratyphi A in 2 cases, and Salmonella Paratyphi B in 1 case. The incidence of typhoid bacteremia in children <2 years of age was 443.1 (95% confidence interval, 193.8-876.5) per 100,000 child years. The overall incidence rate of typhoid for children <5 years was 405.1 (95% confidence interval, 239.8-643.9) per 100,000 child years. CONCLUSION: Typhoid is a common and significant cause of morbidity among young children in Pakistan, including children less than 2 years of age. Vaccines that provide protection to preschool children should be included in typhoid control efforts.

Descriptive epidemiology of typhoid fever during an epidemic in Harare, Zimbabwe, 2012.	
Author	Polonsky JA, Martínez-Pino I, Nackers F, Chonzi P, Manangazira P, Van Herp M, Maes P, Porten K, Luquero FJ.
Publication	Pediatr Infect Dis J. 2010 Nov;29(11):1035-9.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4259398/pdf/pone.0114702.pdf
Additional Categories	Epidemiological patterns and global burden of typhoid fever

BACKGROUND: Typhoid fever remains a significant public health problem in developing countries. In October 2011, a typhoid fever epidemic was declared in Harare, Zimbabwe - the fourth enteric infection epidemic since 2008. To orient control activities, we described the epidemiology and spatiotemporal clustering of the epidemic in Dzivaresekwa and Kuwadzana, the two most affected suburbs of Harare. METHODS: A typhoid fever case-patient register was analysed to describe the epidemic. To explore clustering, we constructed a dataset comprising GPS coordinates of case-patient residences and randomly sampled residential locations (spatial controls). The scale and significance of clustering was explored with Ripley K functions. Cluster locations were determined by a random labelling technique and confirmed using Kulldorff's spatial scan statistic. PRINCIPAL FINDINGS: We analysed data from 2570 confirmed and suspected case-patients, and found significant spatiotemporal clustering of typhoid fever in two non-overlapping areas, which appeared to be linked to environmental sources. Peak relative risk was more than six times greater than in areas lying outside the cluster ranges. Clusters were identified in similar geographical ranges by both random labelling and Kulldorff's spatial scan statistic. The spatial scale at which typhoid fever clustered was highly localised, with significant clustering at distances up to 4.5 km and peak levels at approximately 3.5 km. The epicentre of infection transmission shifted from one cluster to the other during the course of the epidemic. CONCLUSIONS: This study demonstrated highly localised clustering of typhoid fever during an epidemic in an urban African setting, and highlights the importance of spatiotemporal analysis for making timely decisions about targetting prevention and control activities and reinforcing treatment during epidemics. This approach should be integrated into existing surveillance systems to facilitate early detection of epidemics and identify their spatial range.



Enteric fever burden in North Jakarta, Indonesia: a prospective, community-based study.

Author	Punjabi NH, Agtini MD, Ochiai RL, Simanjuntak CH, Lesmana M, Subekti D, Oyofo BA, von Seidlein L, Deen J, Shin S, Acosta C, Wangsasaputra F, Pulungsih SP, Saroso S, Suyeti S, R S, Sudarmono P, Syarurachman A, Suwandono A, Arjoso S, Beecham HJ 3rd, Corwin AL, Clemens JD.
Publication	J Infect Dev Ctries. 2013 Nov 15;7(11):781-7.
URL	http://www.jidc.org/index.php/journal/article/view/24240034/936
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i>

INTRODUCTION: We undertook a prospective community-based study in North Jakarta, Indonesia, to determine the incidence, clinical characteristics, seasonality, etiologic agent, and antimicrobial susceptibility pattern of enteric fever. **METHODOLOGY:** Following a census, treatment centre-based surveillance for febrile illness was conducted for two-years. Clinical data and a blood culture were obtained from each patient. **RESULTS:** In a population of 160,261, we detected 296 laboratory-confirmed enteric fever cases during the surveillance period, of which 221 (75%) were typhoid fever and 75 (25%) were paratyphoid fever. The overall incidence of typhoid and paratyphoid cases was 1.4, and 0.5 per thousand populations per year, respectively. Although the incidence of febrile episodes evaluated was highest among children under 5 years of age at 92.6 per thousand persons per year, we found that the burden of typhoid fever was greatest among children between 5 and 20 years of age. Paratyphoid fever occurred most commonly in children and was infrequent in adults. **CONCLUSION:** Enteric fever is a public health problem in North Jakarta with a substantial proportion due to paratyphoid fever. The results highlight the need for control strategies against enteric fever.

Trends in antimicrobial susceptibility of Salmonella Typhi from North India (2001-2012).

Author	Singhal L, Gupta PK, Kale P, Gautam V, Ray P.
Publication	Indian J Med Microbiol. 2014 Apr-Jun;32(2):149-52.
URL	http://www.ijmm.org/article.asp?issn=0255-0857;year=2014;volume=32;issue=2;spage=149;epage=152;aualast=Singhal
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

PURPOSE: Enteric fever is endemic in India with *Salmonella Typhi* being the major causative agent. Antibiotic therapy constitutes the mainstay of management. The present study was undertaken to find the susceptibility profile of *Salmonella enterica* var *Typhi* (*S. Typhi*) blood isolates in a tertiary care hospital between January 2001 and December 2012. **MATERIALS AND METHODS:** A retrospective analysis of laboratory records was carried out. Conventional blood culture method was used until 2009; from January 2010 onwards BACTEC 9240 system has been in use. *Salmonella* were confirmed by serotyping using group and type specific antisera. Antibiotic susceptibility was performed using the disk diffusion method. In addition, 116 isolates were subjected to minimum inhibitory concentration testing for chloramphenicol, ciprofloxacin, amoxicillin and nalidixic acid (NA) using agar dilution and for ceftriaxone and azithromycin using E-strips (Biomérieux). **RESULT:** A total of 1016 typhoidal salmonellae were obtained. The predominant serotype obtained was *S. Typhi* (852, 83.8%) followed by *Salmonella enterica* var *Paratyphi A* (164, 16.2%). We observed a re-emergence of susceptibility to first line antibiotics and a notable decline in multidrug resistant (MDR) strains. We also found all recent isolates



resistant to NA and susceptible to third generation cephalosporins and 84.5% of isolates having decreasing ciprofloxacin susceptibility using revised criteria as per Clinical and Laboratory Standards Institute 2012 guidelines. CONCLUSION: There has been re-emergence of susceptibility to first line antibiotics and a notable decline in MDR strains of *S. Typhi*. We have a very high resistance to NA and decreasing susceptibility to ciprofloxacin. Third generation cephalosporins and azithromycin seem to be effective therapeutic options. Judicious use of these antibiotics is mandatory to prevent emergence of resistant strains.

Epidemiology and risk factors for endemic typhoid fever in Uzbekistan.

Author	Srikantiah P, Vafokulov S, Luby SP, Ishmail T, Earhart K, Khodjaev N, Jennings G, Crump JA, Mahoney FJ.
Publication	Trop Med Int Health. 2007 Jul;12(7):838-47.
URL	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2007.01853.x/epdf
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i>

BACKGROUND: To investigate the risk factors for infection with endemic typhoid fever in the Samarkand region of Uzbekistan. METHODS: Case-control study of culture-confirmed bloodstream infection with *Salmonella Typhi*. Patients were compared to age-matched community controls. *Salmonella Typhi* isolates were tested for antimicrobial susceptibility. RESULTS: We enrolled 97 patients and 192 controls. The median age of patients was 19 years. In a conditional regression model, consumption of unboiled surface water outside the home [adjusted odds ratio (aOR)=3.0, 95% confidence interval (CI)=1.1-8.2], use of antimicrobials in the 2 weeks preceding onset of symptoms (aOR=12.2, 95% CI 4.0-37.0), and being a student (aOR=4.0, 95% CI 1.4-11.3) were independently associated with typhoid fever. Routinely washing vegetables (aOR 0.06, 95% CI 0.02-0.2) and dining at a tea-house (aOR 0.4, 95% CI 0.2-1.0) were associated with protection against illness. *Salmonella Typhi* resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole was identified in 6 (15%) of 41 isolates tested. CONCLUSIONS: Endemic typhoid fever in Uzbekistan is transmitted by contaminated water. Recent use of antimicrobials also increased risk of infection. Targeted efforts at improving drinking water quality, especially for students and young adults, are likely to decrease transmission of typhoid fever. Measures to decrease the unnecessary use of antimicrobials would be expected to reduce the risk of typhoid fever and decrease the spread of multiple drug-resistant *Salmonella Typhi*.

Epidemiological features of typhoid/paratyphoid fever in provinces with high incidence rate and in the whole country, in 2012.

Author	Sun JL, Zhang J, Ma HL, Chang ZR.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2013 Dec;34(12):1183-8.
URL	http://zhlxboxzz.yiigle.com/CN112338201312/594787.htm?locale=zh_CN
Additional Categories	Epidemiological patterns and global burden of typhoid fever

[Article in Chinese]

OBJECTIVE: Through analyzing the national statutory reporting data on typhoid, paratyphoid fever in 2012, we were trying to understand the whole picture of typhoid, paratyphoid fever at the national level as well as to understand the trends and characteristics of typhoid and paratyphoid fever in provinces with high incidence rate, so as to the development of prevention and control strategies of the diseases



in those high-incidence rate provinces. **METHODS:** We descriptively analyzed the national typhoid and paratyphoid fever statutory reporting data which was reported through disease surveillance information reporting system in 2012. **RESULTS:** 11 998 cases with typhoid and paratyphoid fever were reported with 3 fatal ones, in 2012 in the whole country. The incidence rate was 0.89 per 100,000. Compared to the data gathered in 2011, the incidence rates of typhoid/ paratyphoid fever increased by 1.20%. The total number of the confirmed cases on typhoid and paratyphoid fever was 6522 and was accounted for 54.36% of the total cases, in which paratyphoid fever accounted for 36.86%. Cases were mainly involved farmers and followed by students and children. Incidence rates of typhoid and paratyphoid fever in children aged 0-4 years old appeared the highest (respectively 1.31/100 000 and 0.46/100 000). Yunnan, Guizhou, Guangdong, Guangxi, Zhejiang, Hunan and Xinjiang provinces (autonomous regions) were identified as provinces with high-incidence rates of typhoid and paratyphoid fever. During 2005-2012, the incidence rates in most of the above high-incidence provinces showed a downward trend, except for in Guangdong which had only showed a slight change. There were variations on peak period and highly-hit population in seven high-incidence provinces. **CONCLUSION:** The incidence rate of typhoid/paratyphoid fever was in a relatively low level in China. Prevention and control strategies on the diseases in children under 5 years old remained a challenge, warranted more work to be done. The epidemiological situation is still severe in some high-incidence rate provinces.

Azithromycin and ciprofloxacin resistance in *Salmonella* bloodstream infections in Cambodian adults.

Author	Vlieghe ER, Phe T, De Smet B, Veng CH, Kham C, Bertrand S, Vanhoof R, Lynen L, Peetermans WE, Jacobs JA.
Publication	PLoS Negl Trop Dis. 2012;6(12):e1933.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3521708/pdf/pntd.0001933.pdf
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i>

BACKGROUND: *Salmonella enterica* is a frequent cause of bloodstream infection (BSI) in Asia but few data are available from Cambodia. We describe *Salmonella* BSI isolates recovered from patients presenting at Sihanouk Hospital Centre of Hope, Phnom Penh, Cambodia (July 2007-December 2010). **METHODOLOGY:** Blood was cultured as part of a microbiological prospective surveillance study. Identification of *Salmonella* isolates was performed by conventional methods and serotyping. Antibiotic susceptibilities were assessed using disk diffusion, MicroScan and E-test macromethod. Clonal relationships were assessed by Pulsed Field Gel Electrophoresis; PCR and sequencing for detection of mutations in Gyrase and Topoisomerase IV and presence of *qnr* genes. **PRINCIPAL FINDINGS:** Seventy-two *Salmonella* isolates grew from 58 patients (mean age 34.2 years, range 8-71). Twenty isolates were identified as *Salmonella* Typhi, 2 as *Salmonella* Paratyphi A, 37 as *Salmonella* Choleraesuis and 13 as other non-typhoid *Salmonella* spp. Infection with human immunodeficiency virus (HIV) was present in 21 of 24 (87.5%) patients with *S. Choleraesuis* BSI. Five patients (8.7%) had at least one recurrent infection, all with *S. Choleraesuis*; five patients died. Overall, multi drug resistance (i.e., co-resistance to ampicillin, sulphamethoxazole-trimethoprim and chloramphenicol) was high (42/59 isolates, 71.2%). *S. Typhi* displayed high rates of decreased ciprofloxacin susceptibility (18/20 isolates, 90.0%), while azithromycin resistance was very common in *S. Choleraesuis* (17/24 isolates, 70.8%). Two *S. Choleraesuis* isolates were extended spectrum beta-lactamase producer. **CONCLUSIONS AND SIGNIFICANCE:** Resistance rates in *Salmonella* spp. in Cambodia are alarming, in particular for



azithromycin and ciprofloxacin. This warrants nationwide surveillance and revision of treatment guidelines.

Typhoid fever.	
Author	Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL.
Publication	Lancet. 2015 Mar 21;385(9973):1136-45.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

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.

Shifts in geographic distribution and antimicrobial resistance during a prolonged typhoid fever outbreak--Bundibugyo and Kasese Districts, Uganda, 2009-2011.	
Author	Walters MS, Routh J, Mikoleit M, Kadivane S, Ouma C, Mubiru D, Mbusa B, Murangi A, Ejoku E, Rwantangle A, Kule U, Lule J, Garrett N, Halpin J, Maxwell N, Kagirita A, Mulabya F, Makumbi I, Freeman M, Joyce K, Hill V, Downing R, Mintz E.
Publication	PLoS Negl Trop Dis. 2014 Mar 6;8(3):e2726.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945727/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Trends in antibiotic resistance of <i>Salmonella typhi</i> Challenge models and vaccine trials

BACKGROUND: *Salmonella enterica* serovar Typhi is transmitted by fecally contaminated food and water and causes approximately 22 million typhoid fever infections worldwide each year. Most cases occur in developing countries, where approximately 4% of patients develop intestinal perforation (IP). In Kasese District, Uganda, a typhoid fever outbreak notable for a high IP rate began in 2008. We report that this outbreak continued through 2011, when it spread to the neighboring district of Bundibugyo. **METHODOLOGY/PRINCIPAL FINDINGS:** A suspected typhoid fever case was defined as IP or symptoms of fever, abdominal pain, and ≥ 1 of the following: gastrointestinal disruptions, body weakness, joint pain, headache, clinically suspected IP, or non-responsiveness to antimalarial medications. Cases were identified retrospectively via medical record reviews and prospectively through laboratory-enhanced case finding. Among Kasese residents, 709 cases were identified from August 1, 2009-December 31, 2011; of these, 149 were identified during the prospective period beginning November 1, 2011. Among



Bundibugyo residents, 333 cases were identified from January 1-December 31, 2011, including 128 cases identified during the prospective period beginning October 28, 2011. IP was reported for 507 (82%) and 59 (20%) of Kasese and Bundibugyo cases, respectively. Blood and stool cultures performed for 154 patients during the prospective period yielded isolates from 24 (16%) patients. Three pulsed-field gel electrophoresis pattern combinations, including one observed in a Kasese isolate in 2009, were shared among Kasese and Bundibugyo isolates. Antimicrobial susceptibility was assessed for 18 isolates; among these 15 (83%) were multidrug-resistant (MDR), compared to 5% of 2009 isolates. CONCLUSIONS/SIGNIFICANCE: Molecular and epidemiological evidence suggest that during a prolonged outbreak, typhoid spread from Kasese to Bundibugyo. MDR strains became prevalent. Lasting interventions, such as typhoid vaccination and improvements in drinking water infrastructure, should be

Spatiotemporal transmission and determinants of typhoid and paratyphoid fever in Hongta District, Yunnan Province, China.

Author	Wang JF, Wang Y, Zhang J, Christakos G, Sun JL, Liu X, Lu L, Fu XQ, Shi YQ, Li XM.
Publication	PLoS Negl Trop Dis. 2013;7(3):e2112. Erratum in PLoS Negl Trop Dis. 2013 Mar;7(3).
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597484/pdf/pntd.0002112.pdf
Additional Categories	Epidemiological patterns and global burden of typhoid fever

BACKGROUND: Typhoid and paratyphoid fever are endemic in Hongta District and their prevalence, at 113 per 100,000 individuals, remains the highest in China. However, the exact sources of the disease and its main epidemiological characteristics have not yet been clearly identified. METHODS AND FINDINGS: Numbers of typhoid and paratyphoid cases per day during the period 2006 to 2010 were obtained from the Chinese Center of Disease Control (CDC). A number of suspected disease determinants (or their proxies), were considered for use in spatiotemporal analysis: these included locations of discharge canals and food markets, as well as socio-economic and environmental factors. Results showed that disease prevalence was spatially clustered with clusters decreasing with increasing distance from markets and discharge canals. More than half of the spatial variance could be explained by a combination of economic conditions and availability of health facilities. Temporal prevalence fluctuations were positively associated with the monthly precipitation series. Polluted hospital and residential wastewater was being discharged into rainwater canals. Salmonella bacteria were found in canal water, on farmland and on vegetables sold in markets. CONCLUSION: Disease transmission in Hongta District is driven principally by two spatiotemporally coupled cycles: one involving seasonal variations and the other the distribution of polluted farmland (where vegetables are grown and sold in markets). Disease transmission was exacerbated by the fact that rainwater canals were being used for disposal of polluted waste from hospitals and residential areas. Social factors and their interactions also played a significant role in disease transmission.



Epidemiological characteristics of typhoid fever and antibiotic susceptibility testing of *Salmonella* Typhi isolates in Guangxi, 1994-2013.

Author	Wang M, Kan B, Yang J, Lin M, Yan M, Zeng J, Quan Y, Liao H, Zhou L, Jiang Z, Huang D.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2014 Aug;35(8):930-4.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

[Article in Chinese]

OBJECTIVE: Through analyzing the typhoid epidemics and to determine and monitor regional resistance characteristics of the shift of drug resistant profile on *Salmonella* (S.) Typhi, to understand the related epidemiological characteristics of typhoid fever and to provide evidence for the development of strategies, in Guangxi. **METHODS:** Data of typhoid fever from surveillance and reporting system between 1994 to 2013 was collected and statistically analyzed epidemiologically. The susceptibility of 475 S. Typhi isolates from patients on ten antibiotics was tested by broth micro-dilution method and minimum inhibition concentration was obtained and interpreted based on the CLSI standard. **RESULTS:** From 1994 to 2013, a total of 57 928 cases of typhoid fever were reported in Guangxi province with an annual incidence of 6.29/100 000 and mortality as 0.03%. The higher incidence was observed in the population under 20 years of age. There was no significant difference on incidence between male and female, but farmers and students were among the hardest hit groups. More cases were seen from the northern part of the province. Cases appeared all year round with the peak from May to October. A total of 13 major outbreaks during 2001 to 2013 were reported and the main transmission route was water-borne. All the strains were sensitive to third generation cephalosporins cefotaxime and fluoroquinolones norfloxacin. The susceptibility rates to tetracycline, chloramphenicol, ampicillin and gentamicin was around 98% but relative lower susceptible rate to ciprofloxacin was seen as 89.89% . The lowest susceptibility was found for streptomycin and sulfamethoxazole agents, with the rates as 67.73% and 65.89% , respectively. One strain was found to have been resistant to ciprofloxacin and another 47 isolates with reduced susceptibility to ciprofloxacin. Twenty eight isolates were found to be resistant to multiple antibiotics and one displayed ampicillin, chloramphenicol, streptomycin, sulfamethoxazole tetracycline and nalidixic acid (ACSSxT-NAL) resistance profile. This was the first report in China. Multi-drug resistant strains were frequently isolated from small scale outbreaks of typhoid fever. **CONCLUSION:** The incidence of typhoid fever in Guangxi was still high and some strains showed multi-drug resistance and reduced susceptibility to ciprofloxacin, indicating that the surveillance and monitor programs on drug resistance of S. Typhi should be strengthened, to prevent large scale outbreaks of typhoid fever in this province.



Typhoid fever surveillance and vaccine use, South-East Asia and Western Pacific Regions, 2009–2013.

Author	World Health Organization
Publication	Wkly Epidemiol Rec. 2014 Oct 3;89(40):429-39.
URL	http://www.who.int/wer/2014/wer8940.pdf
Additional Categories	Challenge models and vaccine trials

[START Summary] This report summarizes the status of typhoid surveillance and vaccination programmes in the WHO South-East Asia and Western Pacific Regions during the 5 years (2009–2013) following the revised WHO recommendations. Data were obtained from 3 sources: the WHO/United Nations Children's Fund (UNICEF) Joint Reporting Form on Immunization (JRF), a supplemental survey of surveillance and immunization programme managers, and published reports. During 2009–2013, 23 (48%) of 48 countries and areas of the South East Asia (11) and Western Pacific (37) Regions collected surveillance or notifiable disease data on typhoid cases, with most surveillance activities established before 2008. Implementation of typhoid vaccination programmes or recommended vaccine use during 2009–2013 was reported by 9 (19%) countries. Despite the high recognized disease burden, typhoid surveillance is weak in both of these Regions and vaccine uptake has been limited. Further progress towards typhoid fever prevention and control in the South-East Asia and Western Pacific Regions will require country commitment and international support for enhanced surveillance to assess disease burden at national and subnational levels, targeted use of existing vaccines, availability of WHO-prequalified conjugate vaccines integrated in routine immunization programmes, and integration of vaccination with water, sanitation and hygiene measures.

Antimicrobial resistance surveillance of Salmonella isolates from the First People's Hospital of Yunnan Province, China.

Author	Yaxian J, Hui Z, Hua N, Xiaoqin M, Fengliang L, Ning X, Jiajia L, Jie J, Rui Z.
Publication	J Infect Dev Ctries. 2015 Apr 15;9(4):333-7.
URL	http://www.jidc.org/index.php/journal/article/view/25881520/1277
Additional Categories	Trends in antibiotic resistance of <i>Salmonella typhi</i>

INTRODUCTION: Typhoid fever is a common disease in Yunnan province; however, the resistant phenotype and epidemic characteristics of *Salmonella* in this area are still unclear. In this study, a 15-year surveillance of antimicrobial susceptibility of *Salmonella* is reported. **METHODOLOGY:** From January 1999 to December 2013, *Salmonella* isolates were recovered from patients in the First People's Hospital of Yunnan Province. Antimicrobial susceptibility was detected and data were analyzed using WHONET5.6. **RESULTS:** A total of 845 *Salmonella* isolates were recovered between 1999 and 2013. The most frequently isolated *Salmonella* serovar was *S. Paratyphi A* (93%), and 75.1% (635/845) of the isolates were from the young and middle-aged population. The resistance rates of *Salmonella* spp. to ciprofloxacin, ampicillin, and ceftriaxone increased dramatically during the 15 years. Carbapenems retained the highest and most stable activity against isolates. The resistance rates of all *Salmonella* isolates to chloramphenicol and sulfamethoxazole were 0.4% (3/845) and 1.8% (15/845), respectively. **CONCLUSIONS:** As *Salmonella* isolates have been observed to be resistant to first-line antibiotics, antimicrobial agents should be used rationally and prescriptions should be based on case-by-case susceptibility testing.



ECONOMIC BURDEN OF TYPHOID FEVER, ECONOMIC EVALUATION OF VACCINATION

Economic evaluation of typhoid vaccination in a prolonged typhoid outbreak setting: the case of Kasese district in Uganda.

Author	Carias C, Walters MS, Wefula E, Date KA, Swerdlow DL, Vijayaraghavan M, Mintz E
Publication	Vaccine. 2015 Apr 21;33(17):2079-85.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

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.

Evaluating investments in typhoid vaccines in two slums in Kolkata, India.

Author	Cook J, Sur D, Clemens J, Whittington D.
Publication	J Health Popul Nutr. 2009 Dec;27(6):711-24. Comment in J Health Popul Nutr. 2009 Dec;27(6):709-10.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2928108/

New-generation vaccines against typhoid fever have the potential to reduce the burden of disease in areas where the disease is endemic. The case for public expenditure on typhoid Vi polysaccharide vaccines for two low-income, high-incidence slums (Narkeldanga and Tiljala) in Kolkata, India, was examined. Three measures of the economic benefits of the vaccines were used: private and public cost-of-illness (COI) avoided; avoided COI plus mortality risk-reduction benefits; and willingness-to-pay (WTP) derived from stated preference (contingent valuation) studies conducted in Tiljala in 2004. Benefits and costs were examined from a social perspective. The study represents a unique opportunity to evaluate typhoid-vaccine programmes using a wealth of new site-specific epidemiological and economic data. Three typhoid-vaccination strategies (targeting only enrolled school children, targeting all children, and targeting adults and children) would most likely pass a social cost-benefit test, unless benefits are restricted to include only avoided COI. All three strategies would be considered 'very cost-effective'

using the standard comparisons of cost per disability-adjusted life-year avoided with per-capita gross domestic product. However, at an average total cost per immunized person of approximately US\$ 1.1, a typhoid-vaccination programme would absorb a sixth of existing public-sector spending on health (on a per-capita basis) in India. Because there appears to be significant private economic demand for typhoid vaccines, the Government could design a financially-sustainable programme with user-fees. The results show that a programme where adults pay a higher fee to subsidize vaccines for children (who have higher incidence) would avoid more cases than a uniform user-fee and still achieve revenue-neutrality.

The cost-effectiveness of typhoid Vi vaccination programs: calculations for four urban sites in four Asian countries.

Author	Cook J, Jeuland M, Whittington D, Poulos C, Clemens J, Sur D, Anh DD, Agtini M, Bhutta Z; DOMI Typhoid Economics Study Group.
Publication	Vaccine. 2008 Nov 25;26(50):6305-16.
URL	Not publically available

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.

An optimization model for reducing typhoid cases in developing countries without increasing public spending.

Author	Lauria DT, Maskery B, Poulos C, Whittington D.
Publication	Vaccine. 2009 Mar 4;27(10):1609-21.
URL	Not publically available

This article considers the investment case for using the Vi polysaccharide vaccine in developing countries from two perspectives: reducing typhoid cases and limiting new health care spending. A case study is presented using data from South and Southeast Asia. The purpose of the paper, however, is to draw broad implications that may apply to developing countries in general. Typical consumer demand functions developed from stated preference household surveys in South and Southeast Asia are used to



predict probabilities of adults and children purchasing typhoid vaccinations at different prices. These functions are incorporated in a formal mathematical model. Using data from the recent literature for South and Southeast Asia for typhoid incidence, Vi vaccine effectiveness, public cost of illness, and vaccination program cost, three mass vaccination policy alternatives are evaluated: charging adults and children different (optimal) prices, charging uniform prices, and providing free vaccines. Assuming differential pricing is politically feasible, different vaccine prices for children and adults would maximize the number of typhoid cases avoided from a mass vaccination program if the public sector faces a budget constraint on spending for the vaccination program. However, equal prices for children and adults produce very similar results, and they might be more readily accepted by the community. Alternatively, if vaccines are free, the number of cases is not significantly reduced compared to either pricing policy, but a large external financial contribution from government or donors would be required. A Monte Carlo simulation explores the effects of uncertain parameters on vaccination program outcomes.

Cost of illness due to typhoid fever in five Asian countries.

Author	Poulos C, Riewpaiboon A, Stewart JF, Clemens J, Guh S, Agtini M, Anh DD, Baiqing D, Bhutta Z, Sur D, Whittington D; DOMI Typhoid COI Study Group.
Publication	Trop Med Int Health. 2011 Mar;16(3):314-23.
URL	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2010.02711.x/epdf

OBJECTIVE: To generate community-based estimates of the public (paid by the government) and private (paid by households) costs of blood culture-confirmed typhoid fever in Hechi, China; North Jakarta, Indonesia; Kolkata, India; Karachi, Pakistan and Hue, Vietnam. **METHODS:** To measure out-of-pocket costs of illness and lost earnings, families with culture-proven cases were surveyed 7, 14 and 90 days after onset of illness. Public costs of treatment were measured at local health facilities using a micro costing (bottom-up) method. **RESULTS:** The costs of hospitalized cases ranged from USD 129 in Kolkata to USD 432 in North Jakarta (hospitalization rates varied from 2% in Kolkata to 40% in Hechi) and the costs of non-hospitalized cases ranged from USD 13 in Kolkata to USD 67 in Hechi. Where costs were highest (Hechi, North Jakarta and Karachi), the bulk of the costs of hospitalized cases was borne by families, comprising up to 15% of annual household income. **CONCLUSION:** Although these estimates may understate true costs due to the fact that higher quality treatment may have been provided earlier-than-usual, this multi-country community-based study contributes to evidence on the public and private costs of typhoid fever in developing countries. These cost estimates were used in a cost-effectiveness analysis of typhoid vaccines and will help policymakers respond to World Health Organization's updated typhoid fever immunization recommendations.

Treatment cost for typhoid fever at two hospitals in Kolkata, India.

Author	Sur D, Chatterjee S, Riewpaiboon A, Manna B, Kanungo S, Bhattacharya SK.
Publication	J Health Popul Nutr. 2009 Dec;27(6):725-32.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2928117/

The purpose of this study was to estimate treatment cost for typhoid fever at two hospitals in Kolkata, India. This study was an incidence-based cost-of-illness analysis from the providers' perspective. Micro-costing approach was employed for calculating patient-specific data. Unit costs of medical services used in the calculation were directly measured from the study hospital by standard method. The study hospitals were selected based on accessibility to data and cooperation. Eighty-three Widal-positive



and/or culture-confirmed patients with typhoid fever during November 2003-April 2006 were included in the study. Most (93%) patients were children. Eighty-one percent was treated at the outpatient department. The average duration of hospitalization for child and adult patients was 8.4 and 4.2 days respectively. The average cost of treating children, adults, and all patients was US\$ 16.72, 72.71, and 20.77 respectively (in 2004 prices). Recalculation based on 80% occupancy rate in inpatient wards (following the recommendation of the World Health Organization) found that the cost of treating children, adults, and all patients was US\$ 14.53, 36.44, and 16.11 respectively.

A review of typhoid fever transmission dynamic models and economic evaluations of vaccination.

Author	Watson CH, Edmunds WJ.
Publication	Vaccine. 2015 Jun 19;33 Suppl 3:C42-54.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504000/

Despite a recommendation by the World Health Organization (WHO) that typhoid vaccines be considered for the control of endemic disease and outbreaks, programmatic use remains limited. Transmission models and economic evaluation may be informative in decision making about vaccine programme introductions and their role alongside other control measures. A literature search found few typhoid transmission models or economic evaluations relative to analyses of other infectious diseases of similar or lower health burden. Modelling suggests vaccines alone are unlikely to eliminate endemic disease in the short to medium term without measures to reduce transmission from asymptomatic carriage. The single identified data-fitted transmission model of typhoid vaccination suggests vaccines can reduce disease burden substantially when introduced programmatically but that indirect protection depends on the relative contribution of carriage to transmission in a given setting. This is an important source of epidemiological uncertainty, alongside the extent and nature of natural immunity. Economic evaluations suggest that typhoid vaccination can be cost-saving to health services if incidence is extremely high and cost-effective in other high-incidence situations, when compared to WHO norms. Targeting vaccination to the highest incidence age-groups is likely to improve cost-effectiveness substantially. Economic perspective and vaccine costs substantially affect estimates, with disease incidence, case-fatality rates, and vaccine efficacy over time also important determinants of cost-effectiveness and sources of uncertainty. Static economic models may under-estimate benefits of typhoid vaccination by omitting indirect protection. Typhoid fever transmission models currently require per-setting epidemiological parameterisation to inform their use in economic evaluation, which may limit their generalisability. We found no economic evaluation based on transmission dynamic modelling, and no economic evaluation of typhoid vaccination against interventions such as improvements in sanitation or hygiene.



TRENDS IN ANTIBIOTIC RESISTANCE OF *SALMONELLA* TYPHI

Enteric fever in Karachi: current antibiotic susceptibility of *Salmonellae* isolates.

Author	Abdullah FE, Haider F, Fatima K, Irfan S, Iqbal MS.
Publication	J Coll Physicians Surg Pak. 2012 Mar;22(3):147-50.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

OBJECTIVE: To determine the current sensitivity and resistance profile of *Salmonellae* (S.) isolates in a laboratory setting. **STUDY DESIGN:** An observational study. **PLACE AND DURATION OF STUDY:** Dr. Essa's Laboratory and Diagnostic Centre, Karachi, Pakistan, from November 2008 - October 2010. **METHODOLOGY:** Isolates from blood culture specimens of 481 bacteraemic patients were identified using conventional biochemical tests. *Salmonellae* was confirmed with specific antisera and their antibiograms determined by Kirby-Bauer Disc Diffusion method using 12 relevant antibiotics. Inclusions of the study were bacteraemia documented in all blood samples positive for *S. typhi*, *S. paratyphi*-A and B. Exclusions were all samples other than blood and blood samples negative for *S. typhi* and *S. paratyphi*-A and B during the same period. Multidrug resistance (MDR) of isolates was defined as the isolates showing resistance to all conventional anti-typhoid medicines i.e., Chloramphenicol, Ampicillin and Co-trimoxazole. **RESULTS:** Specimens (n=217) yielded 131 *Salmonellae typhi* (60.36%), 71 *S. paratyphi*-A (32.71%), and 15 *S. paratyphi*-B (6.9%); these were sensitive to the Quinolones [Enoxacin: 94.96% (n=91), Ciprofloxacin, 96.47% (n=182), Ofloxacin: 95.74% (n=203)], and Cephalosporins [Cefixime: 96.62% (n=202), Cefotaxime: 99.17% (n=206), Ceftriaxone: 98.79% (n=208)]. Resistance to Amoxicillin was 96.48% (n=128) and 29.91% (n=78) to Co-trimoxazole. About 62.64% (n=136) of the isolates were MDR strains. **CONCLUSION:** Ciprofloxacin is currently a suitable empirical choice in presumed enteric fever cases, but culture and sensitivity analysis should be encouraged and results incorporated in prescription strategy. Increasing frequency of *S. paratyphi*-A isolates possibly suggests incomplete coverage employing monovalent vaccine.

Antibiotic susceptibility pattern and the indicator of decreased ciprofloxacin susceptibility of *Salmonella enterica* serovar Typhi isolated from Dhulikhel Hospital, Nepal.

Author	Acharya D, Trakulsomboon S, Madhup SK, Korbsrisate S.
Publication	Jpn J Infect Dis. 2012;65(3):264-7.
URL	https://www.istage.jst.go.jp/article/yoken/65/3/65_264/_pdf

Monitoring the antibiotic susceptibility pattern of *Salmonella enterica* serovar Typhi (*S. Typhi*) is important for efficiently managing cases of typhoid fever. In this study, the antimicrobial susceptibility patterns of 114 *S. Typhi* isolates, which were collected from a university hospital in Nepal during July 2009-December 2010, were investigated by disc diffusion assays. All of the *S. Typhi* isolates were sensitive to amoxycillin-clavulanic acid. More than 95% of the isolates were sensitive to chloramphenicol, ceftazidime, ceftriaxone, and cotrimoxazole. In addition, 1.7% of the studied isolates showed multiple drug resistance patterns. Of the 40 *S. Typhi* isolates, 32 strains (80%) showed nalidixic acid (NA) resistance with decreased susceptibility to ciprofloxacin (CIP). Importantly, we found the simultaneous presence of NA resistance and decreased susceptibility to CIP, suggesting that the resistance to NA is a reliable indicator of decreased CIP susceptibility (sensitivity, 97.5%; specificity, 100.0%). Furthermore, the sequencing of NA-resistant *S. Typhi* isolates showed a predominant amino acid alteration in the

quinolone resistance-determining region (QRDR) of *gyrA* gene at position 83 from Ser→Phe. Two isolates with resistance to both CIP and NA had a double-mutation (Ser83→Phe and Asp87→Asn) in the QRDR of the *gyrA* gene, of which one had an additional amino acid mutation (Ser80→Ilu) in the QRDR of the *parC* gene.

Molecular evaluation of drug resistance in clinical isolates of *Salmonella enterica* serovar Typhi from Pakistan.

Author	Afzal A, Sarwar Y, Ali A, Maqbool A, Salman M, Habeeb MA, Haque A.
Publication	J Infect Dev Ctries. 2013 Dec 15;7(12):929-40.
URL	http://www.jidc.org/index.php/journal/article/view/24334939/958

INTRODUCTION: This study aimed to determine the drug susceptibility patterns and genetic elements related to drug resistance in isolates of *Salmonella enterica* serovar Typhi (*S. Typhi*) from the Faisalabad region of Pakistan. **METHODOLOGY:** The drug resistance status of 80 isolates were evaluated by determining antimicrobial susceptibility, MICs, drug resistance genes involved, and the presence of integrons. Nalidixic acid resistance and reduced susceptibility to ciprofloxacin were also investigated by mutation screening of the *gyrA*, *gyrB*, *parC*, and *parE* genes. **RESULTS:** Forty-seven (58.7%) isolates were multidrug resistant (MDR). Among the different resistance (R) types, the most commonly observed (13/80) was AmChStrTeSxtSmzTnp, which is the most frequent type observed in India and Pakistan. The most common drug resistant genes were blaTEM-1, cat, strA-strB, tetB, sul1, sul2, and dfrA7. Among the detected genes, only dfrA7 was found to be associated in the form of a single gene cassette within the class 1 integrons. **CONCLUSIONS:** MIC determination of currently used drugs revealed fourth-generation gatifloxacin as an effective drug against multidrug-resistant *S. Typhi*, but its clinical use is controversial. The Ser83→Phe substitution in *gyrA* was the predominant alteration in nalidixic acid-resistant isolates, exhibiting reduced susceptibility and increased MICs against ciprofloxacin. No mutations in *gyrB*, *parC*, or *parE* were detected in any isolate.

Factors associated with typhoid relapse in the era of multiple drug resistant strains.

Author	Ahmad KA, Khan LH, Roshan B, Bhutta ZA.
Publication	J Infect Dev Ctries. 2011 Oct 13;5(10):727-31.
URL	http://www.jidc.org/index.php/journal/article/view/21997942/615
Additional Categories	Epidemiological patterns and global burden of typhoid fever

INTRODUCTION: Typhoid has an estimated global burden of greater than 27 million cases per annum with a clinical relapse rate of 5% to 20%. Despite the large relapse burden, the factors associated with relapse are largely unknown. **METHODOLOGY:** We have followed a protocol for the diagnosis and management of pediatric typhoid since 1988. We report factors associated with relapse of culture-proven enteric fever in 1,650 children presenting to the Aga Khan University Medical Center, Karachi, Pakistan, over a 15-year period. **RESULTS:** In those infected with multiple drug resistant (MDR) strains, factors associated with subsequent relapse include constipation at presentation and presentation within 14 days of fever onset. Diarrhoea in those children infected with drug sensitive strains had an association with decreased subsequent relapse, as was quinolone therapy. **CONCLUSIONS:** Multiple clinical factors at presentation are associated with subsequent typhoid fever relapse. These factors may be postulated to be associated with subsequent relapse due to alterations in the reticuloendothelial



system organism load. These data will be valuable in developing algorithms for clinical follow-up in children infected with MDR enteric fever.

Epidemiological characteristics and molecular typing of *Salmonella enterica* serovar Typhi during a waterborne outbreak in Eastern Anatolia.

Author	Bayram Y, Gdcođlu H, Otl B, Aypak C, Grsoy NC, Uluç H, Berktař M.
Publication	Ann Trop Med Parasitol. 2011 Jul;105(5):359-65.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4089787/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

In this study, we aimed to study the molecular and epidemiological characteristics of *Salmonella enterica* serovar Typhi (*S. Typhi*) outbreak in Eastern Anatolia. Six hundred and thirty-seven patients from the same county with clinical diagnosis of typhoid fever were investigated with conventional methods from stool, urine and blood specimens. Antibiotic susceptibility tests and identifications were performed for positive specimens. Clonal relationships between the isolates were investigated using pulsed field gel electrophoresis (PFGE) method. A questionnaire was completed for the water consumption habits of patients. Of 91 culture positive specimens, 76 were blood, 13 were stool and 2 were urine. The isolates were resistant to ampicillin, ampicillin/sulbactam, chloramphenicol, cefuroxime, amikacin, gentamicin and trimethoprim-sulfamethoxazole. Although there was a single band difference in some isolates, PFGE results indicated that this was an outbreak caused by single strain according to the Tenover criteria. This outbreak thought to be associated with the consumption of tap water contaminated with sewage represents a breakdown of the basic public health and civil engineering infrastructure. Appropriate public health measures should be taken in order to avoid such outbreaks in the future.

Changing antibiotic sensitivity pattern and scope of chloramphenicol in the management of hospitalised patients of typhoid fever.

Author	Beig FK, Ahmad F, Abqari S.
Publication	J Indian Med Assoc. 2009 Dec;107(12):862-5.
URL	Not publically available

Enteric fever is a global health problem and there is emerging drug resistance with some reports of re-emerging sensitivity to previously used antibiotics eg, chloramphenicol. This study was done to compare the drug sensitivity pattern of enteric fever over a decade period. Twenty-five culture positive patients for *S typhi* from one study done between October 1993 to February 1995 and 35 positive patients from another study done between September 2005 and August 2006 in the same hospital were taken into account and their sensitivity pattern was compared. A total of 36% of cases were sensitive to all the drugs and equal number were multidrug resistant in the study in 1995, while in 2006 only 14.2% ($p < 0.05$) were sensitive to all drugs and percentage of multidrug resistance has increased to 42% ($p > 0.05$). Sensitivity to chloramphenicol had decreased from 68.00% to 54.30% ($p > 0.05$). With the emergence of resistant strains there is significant decline in overall sensitivity to all first line drugs. However, there is no change in chloramphenicol sensitivity of *Salmonella enterica* serovar typhi 10 years back and now, this alone is not the sufficient reason for reintroduction of this drug especially in younger patients.



Re-emergence of susceptibility to conventional first line drugs in Salmonella isolates from enteric fever patients in Nepal.**Author** Chand HJ, Rijal KR, Neupane B, Sharma VK, Jha B.**Publication** J Infect Dev Ctries. 2014 Nov 13;8(11):1483-7.**URL** <http://www.jidc.org/index.php/journal/article/view/25390062/1197>**Additional Categories** Disease and environmental surveillance

INTRODUCTION: Enteric fever is endemic in Nepal and poses a significant public health burden. The first-line drugs ampicillin, chloramphenicol, and cotrimoxazole have not been part of empirical therapy for two decades due to the development of multidrug-resistant *Salmonella* strains. The objective of this study was to determine the antibiogram pattern of *Salmonella* serovars isolated from the blood of clinically suspected enteric fever patients. **METHODOLOGY:** A cross sectional study was carried out in a tertiary care hospital in Lalitpur, Nepal, between July 2011 and February 2012. Standard microbiological procedures were followed during collection and processing of blood samples, isolation and identification of *Salmonella* serotypes. The antimicrobial sensitivity of ampicillin, chloramphenicol, cotrimoxazole, nalidixic acid, and ciprofloxacin was determined using a modified Kirby-Bauer disk diffusion method as per the guidelines of the Clinical and Laboratory Standards Institute. **RESULTS:** Out of 86 *Salmonella* isolates, 56 (65.1%) were *Salmonella* Typhi and 30 (34.9%) were *Salmonella* Paratyphi A. *Salmonella* Typhi were 100% sensitive to chloramphenicol, cotrimoxazole, and ciprofloxacin and 98.2% sensitive to ampicillin. Similarly, *Salmonella* Paratyphi A isolates were 100% sensitive to ampicillin and cotrimoxazole and 96.7% sensitive to chloramphenicol and ciprofloxacin. More than 90.0% of isolates were nalidixic acid resistant and none of the *Salmonella* isolates were multi-drug resistant. **CONCLUSIONS:** This study revealed the increasing frequency of nalidixic acid-resistant *Salmonella* isolates, indicating the possibility of fluoroquinolone resistance in near future. Furthermore, re-emergence of susceptibility to conventional first-line drugs ampicillin, chloramphenicol, and cotrimoxazole supports the possibility of using these drugs in empirical therapy.

Rapid emergence of multidrug resistant, H58-lineage Salmonella typhi in Blantyre, Malawi.**Author** Feasey NA, Gaskell K, Wong V, Msefula C, Selemani G, Kumwenda S, Allain TJ, Mallewa J, Kennedy N, Bennett A, Nyirongo JO, Nyondo PA, Zulu MD, Parkhill J, Dougan G(3), Gordon MA, Heyderman RS.**Publication** PLoS Negl Trop Dis. 2015 Apr 24;9(4):e0003748.**URL** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4409211/>**Additional Categories** Disease and environmental surveillance

INTRODUCTION: 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). **METHODS:** 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. **RESULTS:** 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*. CONCLUSIONS: 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.

Screening, phylogenetic analysis and antibiotic sensitivity pattern of *Salmonella enterica* serovar Typhi isolates from typhoid asymptomatic carriers.

Author Chandrasekaran B, Balakrishnan S.

Publication Asian Pac J Trop Med. 2011 Oct;4(10):769-72.

URL <http://www.sciencedirect.com/science/article/pii/S1995764511601910>

OBJECTIVE: To isolate the *Salmonella enterica* serovar Typhi (*S. typhi*) from asymptomatic typhoid carriers in the local population. To assess the antibiotic sensitivity and resistant pattern of *S. typhi* isolates against viable antibiotics and phylogenetic analysis of *S. typhi* isolates on the basis of 16S rDNA gene. **METHODS:** *S. typhi* was isolated and identified based on the cultural characteristics on BSA (Bismuth Sulphite Agar), MacConkey agar, agglutination test with specific antiserum and phylogenetic analysis. *S. typhi* isolates were tested for sensitivity and resistant pattern with a number of viable antibiotics by disc diffusion method. **RESULT:** A total of 15 bile samples were collected from the food handlers to screen the typhoid asymptomatic carriers. Positive result was yielded for 3 out of 15 samples. *S. typhi* isolates showed resistant to ampicillin (100%), tetracyclin (100%), rifampicin (66.5%), ofloxacin (33.5%), cloxacillin (33.5%) and susceptibility to gentamycin (100%), amikacin (100%), chloramphenicol (100%), streptomycin (100%), kanamycin (100%), ciprofloxacin (100%), amoxycillin (66.5%) and ofloxacin (66.5%). **CONCLUSIONS:** This study demonstrates the outbreak of typhoid fever occurs through asymptomatic carrier. In addition, this study also reveals the occurrence of considerable drug resistant among the *S. typhi* isolates.

Antimicrobial susceptibility of *Salmonella enterica* serovars in a tertiary care hospital in southern India.

Author Choudhary A, Gopalakrishnan R, Nambi PS, Ramasubramanian V, Ghafur KA, Thirunarayan MA.

Publication Indian J Med Res. 2013 Apr;137(4):800-2.

URL <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3724263/>

BACKGROUND & OBJECTIVES: *Salmonella enterica* serovars Typhi and Paratyphi are predominantly known to cause enteric fever. Multidrug resistance in *S. Typhi* and *S. Paratyphi* has emerged as a cause of concern. This study was done to evaluate status in antimicrobial susceptibility patterns of *Salmonella enterica* serovar Typhi (*S. Typhi*) and *S. Paratyphi* obtained from blood culture in a tertiary care hospital in south India. **METHODS:** Blood isolates of *Salmonella* species over a two year period between May 2009 and June 2011 were studied. A total of 322 isolates of *Salmonella* species were tested for antimicrobial susceptibility by Kirby-Bauer disc diffusion method. The MIC of ciprofloxacin was obtained by E-test, and azithromycin MIC was confirmed by agar dilution method for a limited number of isolates.



TRENDS IN ANTIBIOTIC RESISTANCE OF *SALMONELLA* TYPHI

RESULTS: Of the total of 322 isolates studied, 186 (57.8%) were *S. Typhi*, 134 (41.6%) were *S. Paratyphi A*, and two were *S. Paratyphi B*. Of these, 44(13.66%) were resistant to ciprofloxacin (MIC <0.50 µg/ml) and 296 (91.9%) were nalidixic acid resistant. Of these 296 nalidixic acid resistant isolates, 278 (94%) were susceptible to ciprofloxacin by MIC criteria (<0.5 µg/ml). Of the 262 isolates tested for azithromycin sensitivity, only 120 (46%) were susceptible, whereas 81 (31%) were resistant and 55 (21%) showed intermediate susceptibility. Of the isolates, 322 (90%) were susceptible to ampicillin and (95%) were susceptible to co-trimoxazole. However, all the isolates were susceptible to chloramphenicol and ceftriaxone. **INTERPRETATION & CONCLUSIONS:** Nalidixic acid resistance screening is not a reliable surrogate indicator of ciprofloxacin resistance. Ciprofloxacin MIC should to be routinely done. Azithromycin resistance appears to be emerging. However, isolates showed a high degree of susceptibility to ampicillin, co-trimoxazole and chloramphenicol. Thus, antibiotics like ampicillin and co-trimoxazole may once again be useful for the management of enteric fever in southern India.

Global trends in typhoid and paratyphoid fever.

Author	Crump JA. Mintz ED.
Publication	Clin Infect Dis. 2010 Jan 15;50(2):241-6.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2798017/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance Challenge models and vaccine trials

Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and Southeast Asia, where enteric fever is associated with poor sanitation and unsafe food and water. High-quality incidence data from Asia are underpinning efforts to expand access to typhoid vaccines. Efforts are underway to develop vaccines that are immunogenic in infants after a single dose and that can be produced locally in countries of endemicity. The growing importance of *Salmonella enterica* serotype Paratyphi A in Asia is concerning. Antimicrobial resistance has sequentially emerged to traditional first-line drugs, fluoroquinolones, and third-generation cephalosporins, posing patient treatment challenges. Azithromycin has proven to be an effective alternative for treatment of uncomplicated typhoid fever. The availability of full genome sequences for *S. enterica* serotype Typhi and *S. enterica* serotype Paratyphi A confirms their place as monomorphic, human-adapted pathogens vulnerable to control measures if international efforts can be redoubled.

Trends in antibiotic susceptibility of enteric fever isolates in East London.

Author	Dave J, Sefton A, de Pinna E, Woodford N, Meade R, Jordan M, Grant K, Holliman R, Millar M.
Publication	Travel Med Infect Dis. 2015 May-Jun;13(3):230-4.
URL	https://www.researchgate.net/publication/276164684_Trends_in_antibiotic_susceptibility_of_enteric_fever_isolates_in_East_London

BACKGROUND: The study sought evidence for changes in the proportions of antibiotic resistant strains among isolates of *Salmonella enterica* serovar Typhi (*S. typhi*) and *Salmonella enterica* serovar Paratyphi (*S. paratyphi*) between 2005 and 2012. **METHODS:** Blood culture isolates of *S. typhi* and *S. paratyphi* from patients attending Newham and The Royal London Hospitals were included in the study. The organisms were cultured on selective media and identified by Maldi-ToF, API 20E and serology.



Minimum inhibitory concentrations (MICs) of augmentin, chloramphenicol, co-trimoxazole, ceftriaxone, ciprofloxacin and azithromycin were determined by E tests for 194 isolates. RESULTS: Median MICs of ciprofloxacin and ceftriaxone were stable at 0.5 mg/L and 0.125 mg/L, respectively. Chloramphenicol, azithromycin, co-trimoxazole and augmentin median MICs were 4 mg/L, 8 mg/L, 0.064 mg/L and 0.5 mg/L, respectively. MIC90 values were lower than the resistant breakpoint for ceftriaxone, azithromycin and augmentin, but were >256 mg/L for chloramphenicol, 32 mg/L for co-trimoxazole and 1 mg/L for ciprofloxacin. CONCLUSIONS: Antibiotic resistance remained stable for enteric fever isolates between 2005 and 2012. The isolates remained susceptible to augmentin, ceftriaxone and azithromycin over this period, but the MIC90 was greater than the resistant breakpoint for chloramphenicol, cotrimoxazole and ciprofloxacin. The implications for clinical practice are that isolates of *S. typhi* and *S. paratyphi* from East London remain sensitive to ceftriaxone and azithromycin.

Antimicrobial resistance, virulence profiles and molecular subtypes of *Salmonella enterica* serovars Typhi and Paratyphi A blood isolates from Kolkata, India during 2009-2013.

Author Dutta S, Das S, Mitra U, Jain P, Roy I, Ganguly SS, Ray U, Dutta P, Paul DK.

Publication PLoS One. 2014 Aug 6;9(8):e101347.

URL <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123848/>

Enteric fever, caused by *Salmonella enterica*, remains an unresolved public health problem in India and antimicrobial therapy is the main mode of treatment. The objective of this study was to characterize the *Salmonella enterica* isolates from Kolkata with respect to their antimicrobial resistance (AMR), virulence profiles and molecular subtypes. *Salmonella enterica* blood isolates were collected from clinically suspected enteric fever patients attending various hospitals in Kolkata, India from January 2009 to June 2013 and were tested for AMR profiles by standard protocols; for resistance gene transfer by conjugation; for resistance and virulence genes profiles by PCR; and for molecular subtypes by Pulsed Field Gel Electrophoresis (PFGE). A total of 77 *Salmonella enterica* serovar Typhi (*S. Typhi*) and 25 *Salmonella enterica* serovar Paratyphi A (*S. Paratyphi A*) from Kolkata were included in this study. Although multidrug resistance (resistance to chloramphenicol, ampicillin, co-trimoxazole) was decreasing in *S. Typhi* (18.2%) and absent in *S. Paratyphi A*, increased resistance to fluoroquinolone, the current drug of choice, caused growing concern for typhoid treatment. A single, non-conjugative non-IncHI1 plasmid of 180 kb was found in 71.4% multidrug resistant (MDR) *S. Typhi*; the remaining 28.6% isolates were without plasmid. Various AMR markers (*bla*TEM-1, *catA*, *sul1*, *sul2*, *dfrA15*, *strA-strB*) and class 1 integron with *dfrA7* gene were detected in MDR *S. Typhi* by PCR and sequencing. Most of the study isolates were likely to be virulent due to the presence of virulence markers. Major diversity was not noticed among *S. Typhi* and *S. Paratyphi A* from Kolkata by PFGE. The observed association between AMR profiles and *S. Typhi* pulsotypes might be useful in controlling the spread of the organism by appropriate intervention. The study reiterated the importance of continuous monitoring of AMR and molecular subtypes of *Salmonella* isolates from endemic regions for better understanding of the disease epidemiology.



Enteric fever in Cambodian children is dominated by multidrug-resistant H58 *Salmonella* enterica serovar Typhi with intermediate susceptibility to ciprofloxacin.

Author	Emary K, Moore CE, Chanpheaktra N, An KP, Chheng K, Sona S, Duy PT, Nga TV, Wuthiekanun V, Amornchai P, Kumar V, Wijedoru L, Stoesser NE, Carter MJ, Baker S, Day NP, Parry CM.
Publication	Trans R Soc Trop Med Hyg. 2012 Dec;106(12):718-24.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123848/
Additional Categories	Epidemiological patterns and global burden of typhoid fever

Infections with *Salmonella* enterica serovar Typhi isolates that are multidrug resistant (MDR: resistant to chloramphenicol, ampicillin, trimethoprim-sulphamethoxazole) with intermediate ciprofloxacin susceptibility are widespread in Asia but there is little information from Cambodia. We studied invasive salmonellosis in children at a paediatric hospital in Siem Reap, Cambodia. Between 2007 and 2011 *Salmonella* was isolated from a blood culture in 162 children. There were 151 children with enteric fever, including 148 serovar Typhi and three serovar Paratyphi A infections, and 11 children with a non-typhoidal *Salmonella* infection. Of the 148 serovar Typhi isolates 126 (85%) were MDR and 133 (90%) had intermediate ciprofloxacin susceptibility. Inpatient antimicrobial treatment was ceftriaxone alone or initial ceftriaxone followed by a step-down to oral ciprofloxacin or azithromycin. Complications developed in 37/128 (29%) children admitted with enteric fever and two (1.6%) died. There was one confirmed relapse. In a sample of 102 serovar Typhi strains genotyped by investigation of a subset of single nucleotide polymorphisms, 98 (96%) were the H58 haplotype, the majority of which had the common serine to phenylalanine substitution at codon 83 in the DNA gyrase. We conclude that antimicrobial-resistant enteric fever is common in Cambodian children and therapeutic options are limited.

Rapid emergence of multidrug resistant, H58-lineage *Salmonella* typhi in Blantyre, Malawi.

Author	Feasey NA, Gaskell K, Wong V, Msefula C, Selemani G, Kumwenda S, Allain TJ, Mallewa J, Kennedy N, Bennett A, Nyirongo JO, Nyondo PA, Zulu MD, Parkhill J, Dougan G, Gordon MA, Heyderman RS.
Publication	PLoS Negl Trop Dis. 2015 Apr 24;9(4):e0003748.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4409211/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

INTRODUCTION: 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). **METHODS:** 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. **RESULTS:** 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*. CONCLUSIONS: 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.

Antimicrobial resistance in typhoidal salmonellae.

Author	Harish BN, Menezes GA.
Publication	Indian J Med Microbiol. 2011 Jul-Sep;29(3):223-9.
URL	Not publically available

Infections with *Salmonella* are an important public health problem worldwide. On a global scale, it has been appraised that *Salmonella* is responsible for an estimated 3 billion human infections each year. The World Health Organization (WHO) has estimated that annually typhoid fever accounts for 21.7 million illnesses (217,000 deaths) and paratyphoid fever accounts for 5.4 million of these cases. Infants, children, and adolescents in south-central and South-eastern Asia experience the greatest burden of illness. In cases of enteric fever, including infections with *S. Typhi* and *S. Paratyphi* A and B, it is often necessary to commence treatment before the results of laboratory sensitivity tests are available. Hence, it is important to be aware of options and possible problems before beginning treatment. Ciprofloxacin has become the first-line drug of choice since the widespread emergence and spread of strains resistant to chloramphenicol, ampicillin, and trimethoprim. There is increase in the occurrence of strains resistant to ciprofloxacin. Reports of typhoidal salmonellae with increasing minimum inhibitory concentration (MIC) and resistance to newer quinolones raise the fear of potential treatment failures and necessitate the need for new, alternative antimicrobials. Extended-spectrum cephalosporins and azithromycin are the options available for the treatment of enteric fever. The emergence of broad spectrum β -lactamases in typhoidal salmonellae constitutes a new challenge. Already there are rare reports of azithromycin resistance in typhoidal salmonellae leading to treatment failure. This review is based on published research from our centre and literature from elsewhere in the world. This brief review tries to summarize the history and recent trends in antimicrobial resistance in typhoidal salmonellae.

Antimicrobial resistance among blood culture isolates of *Salmonella enterica* in New Delhi.

Author	Jain S, Das Chugh T.
Publication	J Infect Dev Ctries. 2013 Nov 15;7(11):788-95.
URL	http://www.jidc.org/index.php/journal/article/view/24240035/937
Additional Categories	Disease and environmental surveillance

INTRODUCTION: Enteric fever is a global public health problem, especially in developing countries. Antimicrobial resistance is a major issue enteric fever management. This study examined current pattern of antimicrobial susceptibility among *Salmonella enterica* isolates from enteric fever cases at a tertiary care centre in New Delhi, India. METHODOLOGY: Blood cultures from patients with enteric fever during January 2010-July 2012 were processed using the BACTEC automated system. Antimicrobial susceptibility was tested using Kirby Bauer's disc diffusion method and/or Phoenix 100 automated system. RESULTS: Of 344 isolates of *Salmonella enterica*, 266 (77.3%) were *S. Typhi*, 77 (22.4%) were *S.*



Paratyphi A, and one (0.3%) was *S. Paratyphi B*. Resistance to nalidixic acid (NA(R)) (96.7%) was most common, followed by ciprofloxacin (37.9%), and azithromycin (7.3%). Multi-drug resistance was observed only in *S. Typhi* (3.4%). Among NA(R) strains, 61.8% were sensitive, 11.1% were moderately sensitive, and 23.9% were resistant to ciprofloxacin (0.8%, 57.4%, and 37.9% respectively according to revised CLSI breakpoint criteria for ciprofloxacin). Resistance to third-generation cephalosporin was found in seven (2%) strains of *S. enterica*. CONCLUSION: Increasing rates of nalidixic acid, fluoroquinolone and azithromycin resistance among *S. enterica*, particularly in *S. Paratyphi A* strains, is of concern, as *S. Paratyphi A* infection is becoming increasingly common and is not prevented by current vaccinations. Our results favour use of cefexime or possibly chloramphenicol as first choice for uncomplicated enteric fever. MICs for third-generation cephalosporins and susceptibility pattern must be closely monitored in view of its emerging resistance among *Salmonella enterica*.

Epidemiology, clinical manifestations, and molecular typing of salmonella typhi isolated from patients with typhoid fever in Lebanon.

Author	Kanj SS, Kanafani ZA, Shehab M, Sidani N, Baban T, Baltajian K, Dakdouki GK, Zaatari M, Araj GF, Wakim RH, Dbaiibo G, Matar GM.
Publication	J Epidemiol Glob Health. 2015 Jun;5(2):159-65.
URL	http://www.sciencedirect.com/science/article/pii/S2210600614000744
Additional Categories	Epidemiological patterns and global burden of typhoid fever

The objective of this study was to examine the epidemiology and the clinical manifestations of typhoid fever as well as the susceptibility and strain relatedness of *Salmonella typhi* isolates in Lebanon from 2006 to 2007. A total of 120 patients with typhoid fever were initially identified from various areas of the country based on positive culture results for *S. typhi* from blood, urine, stools, bone marrow and/or positive serology. Clinical, microbiological and molecular analysis was performed on cases with complete data available. These results indicated that drinking water was an unlikely mode of transmission of the infection. Despite increasing reports of antimicrobial resistance among *S. typhi* isolates, the vast majority of these isolates were susceptible to various antibiotic agents, including ampicillin, cephalosporins, quinolones, and trimethoprim/sulfamethoxazole. Molecular analysis of the isolates revealed a predominance of one single genotype with no variation in distribution across the geographical regions.

Epidemiology of typhoid and paratyphoid fever in India.

Author	Kanungo S, Dutta S, Sur D.
Publication	J Infect Dev Ctries. 2008 Dec 1;2(6):454-60.
URL	http://www.jidc.org/index.php/journal/article/view/19745523/79
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance Challenge models and vaccine trials

Enteric fever (typhoid and paratyphoid fever) is a major human bacterial infection. Although the disease is not common in industrialised countries, it remains an important and persistent health problem in developing nations. Hospital-based studies and outbreak reports from India indicate that enteric fever is a major public health problem in this country, with *Salmonella enterica* serovar Typhi (*S. Typhi*) the most common aetiologic agent but with an apparently increasing number of cases due to *S. Paratyphi A* (SPA).



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Because risk factors such as poor sanitation, lack of a safe drinking water supply and low socio economic conditions in resource-poor countries are amplified by the evolution of multidrug resistant salmonellae with reduced susceptibility to fluoroquinolone, treatment failure cases have been reported in India, which is associated with increased mortality and morbidity. Vaccination, which requires strict planning and proper targeting of the vulnerable age groups, is considered to be an effective tool in controlling this disease in endemic areas, given there is development of a conjugate vaccine against both serovars (S. Typhi and S. Para A).

Antimicrobial resistance and management of invasive Salmonella disease.

Author	Kariuki S, Gordon MA, Feasey N, Parry CM.
Publication	Vaccine. 2015 Jun 19;33 Suppl 3:C21-9.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

Invasive Salmonella infections (typhoidal and non-typhoidal) cause a huge burden of illness estimated at nearly 3.4 million cases and over 600,000 deaths annually especially in resource-limited settings. Invasive non-typhoidal Salmonella (iNTS) infections are particularly important in immunosuppressed populations especially in sub-Saharan Africa, causing a mortality of 20-30% in vulnerable children below 5 years of age. In these settings, where routine surveillance for antimicrobial resistance is rare or non-existent, reports of 50-75% multidrug resistance (MDR) in NTS are common, including strains of NTS also resistant to fluoroquinolones and 3rd generation cephalosporins. Typhoid (enteric) fever caused by Salmonella Typhi and Salmonella Paratyphi A remains a major public health problem in many parts of Asia and Africa. Currently over a third of isolates in many endemic areas are MDR, and diminished susceptibility or resistance to fluoroquinolones, the drugs of choice for MDR cases over the last decade is an increasing problem. The situation is particularly worrying in resource-limited settings where the few remaining effective antimicrobials are either unavailable or altogether too expensive to be afforded by either the general public or by public health services. Although the prudent use of effective antimicrobials, improved hygiene and sanitation and the discovery of new antimicrobial agents may offer hope for the management of invasive salmonella infections, it is essential to consider other interventions including the wider use of WHO recommended typhoid vaccines and the acceleration of trials for novel iNTS vaccines. The main objective of this review is to describe existing data on the prevalence and epidemiology of antimicrobial resistant invasive Salmonella infections and how this affects the management of these infections, especially in endemic developing countries.

Trends of etiology and drug resistance in enteric fever in the last two decades in Nepal: a systematic review and meta-analysis.

Author	Karki S, Shakya P, Cheng AC, Dumre SP, Leder K.
Publication	Clin Infect Dis. 2013 Nov;57(10):e167-76.
URL	http://cid.oxfordjournals.org/content/57/10/e167.long
Additional Categories	Epidemiological patterns and global burden of typhoid fever

Prospective time-trend analyses on shifting etiology and trends of drug resistance in enteric fever are scarce. Using published and unpublished datasets from Nepal, we performed a systematic review and meta-analysis to understand the trends in etiology and resistance to antimicrobials that have occurred



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since 1993. Thirty-two studies involving 21 067 *Salmonella enterica* serotype Typhi (ST) and *S. enterica* serotype Paratyphi A (SPA) isolates were included. There was an increasing trend in enteric fever caused by SPA during the last 2 decades ($P < .01$). We observed sharply increasing trends in resistance to nalidixic acid and ciprofloxacin for both ST and SPA. In contrast, multi-drug resistance (MDR), resistance to traditional first-line antibiotics such as chloramphenicol and co-trimoxazole have significantly decreased for both organisms. The resistance to ceftriaxone has remained low, suggesting it is likely to remain useful as a reserve antibiotic for treatment. Trends in decreasing resistance to traditional first-line antibiotics and decreasing MDR provide an opportunity to reconsider these first-line antimicrobials as therapeutic options.

Emergence of multidrug-resistant *Salmonella enterica* serovar Typhi with reduced susceptibility to fluoroquinolones in Cambodia.

Author Kasper MR, Sokhal B, Blair PJ, Wierzb TF, Putnam SD.

Publication Diagn Microbiol Infect Dis. 2010 Feb;66(2):207-9.

URL Not publically available

From December 2006 to April 2009, we conducted an etiology study among Cambodian patients presenting with acute fever of unknown origin. *Salmonella enterica* serovar Typhi was detected in 0.9% (41/4985) blood cultures. Antimicrobial susceptibility testing showed decreased susceptibility to ampicillin (56% resistant; MIC(90), >256 microg/mL), chloramphenicol (56% resistant; MIC(90), >256 microg/mL), trimethoprim/sulfamethoxazole (56% resistant; MIC(90), >256 microg/mL), nalidixic acid (81% resistant; MIC(90), not defined), ciprofloxacin (0% resistant; MIC(90), 0.5 microg/mL), and ceftriaxone (0% resistant; MIC(90), 0.094 microg/mL). Multidrug resistance, defined as antimicrobial resistance to ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole, was found in 56% of the isolates, and 80% had reduced susceptibility to ciprofloxacin (defined as MIC $\geq$ 0.12 microg/mL).

Epidemiology, clinical presentation, and patterns of drug resistance of *Salmonella* Typhi in Karachi, Pakistan.

Author Khan MI, Soofi SB, Ochiai RL, Khan MJ, Sahito SM, Habib MA, Puri MK, Von Seidlein L, Park JK, You YA, Ali M, Nizami SQ, Acosta CJ, Sack RB, Clemens JD, Bhutta ZA.

Publication J Infect Dev Ctries. 2012 Oct 19;6(10):704-14.

URL <http://www.jidc.org/index.php/journal/article/view/23103892/780>

INTRODUCTION: Enteric fever remains a major public health problem in Asia. Planning appropriate preventive measures such as immunization requires a clear understanding of disease burden. We conducted a community-based surveillance for *Salmonella* Typhi infection in children in Karachi, Pakistan. **METHODOLOGY:** A de jure household census was conducted at baseline in the study setting to enumerate all individuals. A health-care facility-based passive surveillance system was used to capture episodes of fever lasting three or more 3 days in children 2 to 16 years old. **RESULTS:** A total of 7,401 blood samples were collected for microbiological confirmation, out of which 189 *S. Typhi* and 32 *S. Paratyphi A* isolates were identified with estimated annual incidences of 451/100,000 (95% CI: 446 - 457) and 76/100,000 (95% CI: 74 - 78) respectively. At the time of presentation, after adjusting for age, there was an association between the duration of fever and temperature at presentation, and being infected with multidrug-resistant *S. Typhi*. Of 189 isolates 83 were found to be resistant to first-line antimicrobial therapy. There was no statistically significant difference in clinical presentation of blood culture sensitive and resistant *S. Typhi* isolates. **CONCLUSION:** Incidence of *S. Typhi* in children is high in urban squatter



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settlements of Karachi, Pakistan. Findings from this study identified duration of fever and temperature at the time of presentation as important symptoms associated with blood culture-confirmed typhoid fever. Preventive strategies such as immunization and improvements in water and sanitation conditions should be the focus of typhoid control in urban settlements of Pakistan.

Changing trends in antimicrobial resistance of *Salmonella enterica* serovar typhi and *salmonella enterica* serovar paratyphi A in Chennai.

Author	Krishnan P, Stalin M, Balasubramanian S.
Publication	Indian J Pathol Microbiol. 2009 Oct-Dec;52(4):505-8.
URL	Not publically available

BACKGROUND AND OBJECTIVES: Chloramphenicol was considered the anti-microbial gold standard for typhoid treatment but, following the increasing worldwide frequency of antibiotic resistance, ciprofloxacin has been the mainstay of therapy since 1980. Recent studies have shown a shifting of susceptibility to conventional drugs like chloramphenicol, ampicillin and cotrimoxazole. The primary objective of the study was to evaluate the in vitro activity of chloramphenicol and other first-line drugs in comparison with cephalosporins and quinolones. **MATERIALS AND METHODS:** Fifty isolates of *Salmonella* obtained from blood culture were subjected to serotyping at the Central Research Institute, Kasauli. Phage typing and biotyping was performed at the National Phage Typing Centre, New Delhi. Antibiotic sensitivity testing was carried out for 10 drugs by the Kirby-Bauer disc diffusion method and minimum inhibitory concentration by broth microdilution for nalidixic acid, chloramphenicol, ciprofloxacin, ceftriaxone, cefixime and ofloxacin. Multi-drug-resistant (MDR) strains were checked for plasmid. **RESULTS:** In the present study, 70 and 30% of the isolates were *Salmonella enterica* serovar typhi and paratyphi A, respectively. They were highly sensitive to chloramphenicol (86%), ampicillin (84%) and cotrimoxazole (88%). Highest sensitivity was seen for cephalosporins, followed by quinolones. Seventeen/21 (81%) and 100% of the *Salmonella enterica* serovar typhi strains belonged to E1 phage type and biotype 1, respectively. Antibigram showed 2% of the strains to be sensitive to all the drugs tested and 12% were MDR and showed the presence of plasmids. **CONCLUSION:** The study indicates reemergence of chloramphenicol-susceptible *Salmonella enterica* serovar typhi and paratyphi A isolates, a significant decline in MDR strains and high resistance to nalidixic acid. E1 phage type and biotype 1 are found to be most prevalent in Chennai, India.

Rising prevalence of enteric fever due to multidrug-resistant *Salmonella*: an epidemiological study.

Author	Kumar S, Rizvi M, Berry N.
Publication	J Med Microbiol. 2008 Oct;57(Pt 10):1247-50.
URL	http://www.microbiologyresearch.org/docserver/fulltext/jmm/57/10/1247.pdf?expires=1472162360&id=id&accname=sgid025940&checksum=AF56EA458B21D9DF50101B35BF6D0099

A prospective study of the prevalent aetiology of enteric fever was undertaken at a tertiary care hospital in North India at intervals of every 3 years. *Salmonella* spp. were isolated from 174 (7%) patients. Amongst these, 140 (80%) patients were infected by *Salmonella enterica* subspecies enterica serovar Typhi (*S. Typhi*) and 16 (9%) by *S. enterica* serovar Paratyphi A; the remaining 11% were infected by other *S. enterica* serogroups, Typhimurium, Paratyphi C and Senftenberg, and other group E salmonella. A significantly greater number of *S. Typhi* were isolated in the summer and monsoon months. Multidrug



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resistance (resistance to chloramphenicol, ampicillin and co-trimoxazole) sequentially increased from 34% in 1999 to 66% in 2005. Increasing resistance was also noticed to the other antibiotics, especially to the cephalosporins. Moreover 8% of the *S. Typhi* isolates were found to be presumptive extended spectrum beta-lactamase producers. There was a gradual development of resistance to fluoroquinolones over the 7 years. No resistance was observed to fluoroquinolones in 1999, while in 2005 4.4% resistance was observed to sparfloxacin, 8.8% resistance to ofloxacin and a high resistance, 13%, to ciprofloxacin. This is an alarming development and it is of paramount importance to limit unnecessary use of fluoroquinolones and third generation cephalosporins so that their efficacy against salmonella is not jeopardized further.

Multidrug-resistant typhoid fever.

Author	Kumar R, Gupta N; Shalini.
Publication	Indian J Pediatr. 2007 Jan;74(1):39-42.
URL	Not publically available

OBJECTIVE: To study the epidemiological pattern, clinical picture, the recent trends of multidrug-resistant typhoid fever (MDRTF), and therapeutic response of ofloxacin and ceftriaxone in MDRTF. **METHODS:** The present prospective randomized controlled parallel study was conducted on 93 blood culture-proven *Salmonella typhi* children. All MDRTF cases were randomized to treatment with ofloxacin or ceftriaxone. **RESULTS:** Of 93 children, 62 (66.6%) were MDRTF. 24 cases were below 5 years, 26 between 5-10 years and 12 were above 10 years. Male to female ratio was 1.85: 1. Majority of cases came from lower middle socio-economic classes with poor personal hygiene. Fever was the main presenting symptom. Hepatomegaly and splenomegaly was present in 88% and 46% cases respectively. 19 (30.6%) cases developed complications. Mean defervescence time with ceftriaxone and ofloxacin was 4.258 and 4.968 days respectively. **CONCLUSION:** MDRTF is still emerging as serious public and therapeutic challenge. Ceftriaxone is well-tolerated and effective drug but expensive whereas ofloxacin is safe, cost-effective and therapeutic alternative in treatment of MDRTF in children with comparable efficacy to ceftriaxone.

Trends in *Salmonella* enteric serovar Typhi in Nairobi, Kenya from 2004 to 2006.

Author	Mengo DM, Kariuki S, Muigai A, Revathi G.
Publication	J Infect Dev Ctries. 2010 Jun 30;4(6):393-6.
URL	http://www.jidc.org/index.php/journal/article/view/20601792

BACKGROUND: Typhoid fever is a global health problem. The World Health Organization (WHO) estimates that the current annual global burden of typhoid is approximately 22 million new cases, 5% of which are fatal. **METHODOLOGY:** To assess the trends in antibiotic resistance in 100 *Salmonella enterica* serovar Typhi strains were isolated from the blood of patients in Nairobi, Kenya, from 2004 to 2006. All isolates were tested against ampicillin, chloramphenicol, nalidixic acid, ciprofloxacin, cotrimoxazole, cefuroxime, ceftriaxone, amoxycillin/clavulanic acid, tetracycline and gentamycin. Susceptibility and resistance were determined using MIC and disk diffusion tests. **RESULTS:** From 2004 to 2006 a total of 100 strains were studied; 70% of the isolates were multidrug resistant (MDR) while 15% of the isolates were sensitive to all drugs tested. Of 13 isolates that were resistant to ciprofloxacin and nalidixic acid by disk diffusion, 11 had an MIC of 0.25 microg/ml while two isolates had an MIC of 1.00 microg/ml. Resistance in ampicillin decreased from 88% in 2004 to 64% in 2005; this increased to 76% in 2006. Similar trends were observed for four other antibiotics tested. **CONCLUSION:** The prescription of first-



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line antibiotics used in the treatment of *S. Typhi* should be stopped temporarily. Drugs such as ciprofloxacin would be useful in the treatment of typhoid caused by MDR *S. Typhi*. There is need to monitor the resistance in fluoroquinolones as resistance to these drugs has been observed and they are the current drugs used to treat typhoid.

Absence of multidrug resistance in *Salmonella enterica* serotypes Typhi and Paratyphi A isolates with intermediate susceptibility to ciprofloxacin.

Author	Misra R, Prasad KN, Amrin N, Kapoor P, Singh S, Ghar M.
Publication	Trans R Soc Trop Med Hyg. 2015 Aug;109(8):538-40.
URL	Not publically available

BACKGROUND: We describe the antimicrobial susceptibility pattern of 64 blood stream isolates of *Salmonella enterica* serotypes Typhi and Paratyphi A studied from January 2013 to December 2014 at a tertiary care centre in North India. **METHODS:** Isolates were identified by standard biochemical reactions and confirmed by slide agglutination using specific antisera. Antimicrobial susceptibility testing was performed by Kirby-Bauer disc diffusion method and by E-test. **RESULTS:** In this study, 92% (46/50) of *Salmonella Typhi* and all Paratyphi A (n=14) isolates were susceptible to ampicillin, chloramphenicol and cotrimoxazole. Eighty percent of Typhi (40/50) and 64% (9/14) of Paratyphi A were intermediately susceptible to ciprofloxacin. Nineteen percent (12/64) of isolates were resistant to ciprofloxacin. No resistance to ceftriaxone and azithromycin was detected. **CONCLUSIONS:** Our study adds to the current knowledge of world-wide reports of multidrug resistance in *S. Typhi*.

Burden of typhoid and paratyphoid fever in a densely populated urban community, Dhaka, Bangladesh.

Author	Naheed A, Ram PK, Brooks WA, Hossain MA, Parsons MB, Talukder KA, Mintz E, Luby S, Breiman RF.
Publication	Int J Infect Dis. 2010 Sep;14 Suppl 3:e93-9.
URL	http://www.sciencedirect.com/science/article/pii/S1201971210022800
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

BACKGROUND: We conducted blood culture surveillance to estimate the incidence of typhoid and paratyphoid fever among urban slum residents in Dhaka, Bangladesh. **METHODS:** Between January 7, 2003 and January 6, 2004, participants were visited weekly to detect febrile illnesses. Blood cultures were obtained at the clinic from patients with fever ($\geq 38^{\circ}\text{C}$). *Salmonella* isolates were assayed for antimicrobial susceptibility. **RESULTS:** Forty *Salmonella Typhi* and eight *Salmonella Paratyphi A* were isolated from 961 blood cultures. The incidence of typhoid fever was 2.0 episodes/1000 person-years, with a higher incidence in children aged <5 years (10.5/1000 person-years) than in older persons (0.9/1000 person-years) (relative risk=12, 95% confidence interval (CI) 6.3-22.6). The incidence of paratyphoid fever was 0.4/1000 person-years without variation by age group. Sixteen *S. Typhi* isolates were multidrug-resistant (MDR). All *S. Paratyphi* isolates were pan-susceptible. The duration of fever among patients with an MDR *S. Typhi* infection was longer than among patients with non-MDR *S. Typhi* (16 ± 8 vs. 11 ± 4 days, $p=0.02$) and *S. Paratyphi* (10 ± 2 days, $p=0.04$) infections. **CONCLUSIONS:** Typhoid fever is more common than paratyphoid fever in the urban Bangladeshi slum; children <5 years old have the highest incidence. Multidrug resistance is common in *S. Typhi* isolates and is associated with



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prolonged illness. Strategies for typhoid fever prevention in children aged <5 years in Bangladesh, including immunization, are needed.

Antimicrobial susceptibility of *Salmonella* Typhi in India.

Author	Nagshetty K, Channappa ST, Gaddad SM.
Publication	J Infect Dev Ctries. 2010 Mar 8;4(2):70-3.
URL	http://www.jidc.org/index.php/journal/article/view/20212336

BACKGROUND: Typhoid fever continues to remain a major public health problem, especially in regions such as Gulbarga, due to poor sanitation and personal hygiene. Gulbarga region is often prone to enteric fever outbreaks and is an endemic region of typhoid fever. Enteric fever caused by *Salmonella* Typhi has not been adequately explored in this region. **METHODOLOGY:** A total of 95 isolates of *S. Typhi* collected from different clinical and environmental sources were tested for antimicrobial susceptibility according to the CLSI guidelines. MIC of resistant isolates to various antibiotics was performed by agar dilution method. **RESULTS:** Of the total isolates studied, 10% were found to be multidrug resistant (MDR) (defined as resistance to ampicillin, chloramphenicol and co-trimoxazole). There was a decrease in the susceptibility to ciprofloxacin of *S. Typhi* with MIC showing an upward trend (0.125-4 microg/mL). Concurrently, there has been an increase in the number of isolates sensitive to all antibiotics except nalidixic acid. **CONCLUSION:** MDR *S. Typhi* continues to be an important public health issue in Gulbarga. Presence of quinolone resistance and associated low-level ciprofloxacin resistance is a concern and requires further study.

A study of typhoid fever in five Asian countries: disease burden and implications for controls.

Author	Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, Bhutta ZA, Canh DG, Ali M, Shin S, Wain J, Page AL, Albert MJ, Farrar J, Abu-Elyazeed R, Pang T, Galindo CM, von Seidlein L, Clemens JD; Domi Typhoid Study Group.
Publication	Bull World Health Organ. 2008 Apr;86(4):260-8. Erratum in Bull World Health Organ. 2015 Apr 1;93(4):284. Bull World Health Organ. 2015 Jun 1;93(6):440.
URL	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC18438514/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

OBJECTIVE: To inform policy-makers about introduction of preventive interventions against typhoid, including vaccination. **METHODS:** A population-based prospective surveillance design was used. Study sites where typhoid was considered a problem by local authorities were established in China, India, Indonesia, Pakistan and Viet Nam. Standardized clinical, laboratory, and surveillance methods were used to investigate cases of fever of ≥ 3 days' duration for a one-year period. A total of 441,435 persons were under surveillance, 159,856 of whom were aged 5-15 years. **FINDINGS:** A total of 21,874 episodes of fever were detected. *Salmonella typhi* was isolated from 475 (2%) blood cultures, 57% (273/475) of which were from 5-15 year-olds. The annual typhoid incidence (per 100,000 person years) among this age group varied from 24.2 and 29.3 in sites in Viet Nam and China, respectively, to 180.3 in the site in Indonesia; and to 412.9 and 493.5 in sites in Pakistan and India, respectively. Altogether, 23% (96/413) of isolates were multidrug resistant (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole). **CONCLUSION:** The incidence of typhoid varied substantially between sites, being high in India and



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Pakistan, intermediate in Indonesia, and low in China and Viet Nam. These findings highlight the considerable, but geographically heterogeneous, burden of typhoid fever in endemic areas of Asia, and underscore the importance of evidence on disease burden in making policy decisions about interventions to control this disease.

Emergence of resistance in community-acquired enteric fever.

Author	Narain U, Gupta R.
Publication	Indian Pediatr. 2015 Aug;52(8):709.
URL	http://www.indianpediatrics.net/aug2015/709.pdf

We present a retrospective analysis of 225 blood culture-proven pediatric patients with the sensitivity pattern represented in the Antibigram obtained by Vitek-2 Systems. Resistance to typhoid fever with commonly used oral antibiotics (Ciprofloxacin 41.4%, Amoxy-clavulonic acid 44.1% and Cotrimoxazole 32.7%) was common.

Antimicrobial resistance in typhoidal and nontyphoidal salmonellae.

Author	Parry CM, Threlfall EJ.
Publication	Curr Opin Infect Dis. 2008 Oct;21(5):531-8.
URL	Not publically available

PURPOSE OF REVIEW: Increasing occurrence of antimicrobial resistance in both typhoidal and nontyphoidal salmonellae is a major public health problem. Recent studies documenting the occurrence and types of resistance, with particular reference to quinolones and extended spectrum cephalosporins, and new approaches to treatment are reviewed. **RECENT FINDINGS:** Community and hospital-based studies in different Asian and African countries show widely variable rates of resistance in *Salmonella enterica* serovars Typhi and Paratyphi A. Occurrence of multidrug resistance has declined in some areas, but the incidence of decreased ciprofloxacin susceptibility has reached high levels, particularly in the Indian subcontinent, and isolates with full resistance to this antimicrobial are increasingly reported. Similar variability in resistance rates occurs among nontyphoidal salmonellae, with variation between serovars and by region. There are reports of plasmid-mediated qnr genes and a variety of extended spectrum cephalosporin resistance genes in nontyphoidal serovars. Two randomized controlled trials report gatifloxacin as a potential treatment option in enteric fever caused by multidrug-resistant isolates with decreased ciprofloxacin susceptibility. **SUMMARY:** Patterns of resistance in *Salmonella* are constantly changing. Continual surveillance of resistance levels is critical for clinicians to keep abreast of treatment options, but it is often lacking in resource-poor regions of the world with the highest disease burden.



Enteric fever burden in North Jakarta, Indonesia: a prospective, community-based study.

Author	Punjabi NH, Agtini MD, Ochiai RL, Simanjuntak CH, Lesmana M, Subekti D, Oyofa BA, von Seidlein L, Deen J, Shin S, Acosta C, Wangsasaputra F, Pulungsih SP, Saroso S, Suyeti S, R S, Sudarmono P, Syarurachman A, Suwandono A, Arjoso S, Beecham HJ 3rd, Corwin AL, Clemens JD.
Publication	J Infect Dev Ctries. 2013 Nov 15;7(11):781-7.
URL	http://www.jidc.org/index.php/journal/article/view/24240034/936
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

INTRODUCTION: We undertook a prospective community-based study in North Jakarta, Indonesia, to determine the incidence, clinical characteristics, seasonality, etiologic agent, and antimicrobial susceptibility pattern of enteric fever. **METHODOLOGY:** Following a census, treatment centre-based surveillance for febrile illness was conducted for two-years. Clinical data and a blood culture were obtained from each patient. **RESULTS:** In a population of 160,261, we detected 296 laboratory-confirmed enteric fever cases during the surveillance period, of which 221 (75%) were typhoid fever and 75 (25%) were paratyphoid fever. The overall incidence of typhoid and paratyphoid cases was 1.4, and 0.5 per thousand populations per year, respectively. Although the incidence of febrile episodes evaluated was highest among children under 5 years of age at 92.6 per thousand persons per year, we found that the burden of typhoid fever was greatest among children between 5 and 20 years of age. Paratyphoid fever occurred most commonly in children and was infrequent in adults. **CONCLUSION:** Enteric fever is a public health problem in North Jakarta with a substantial proportion due to paratyphoid fever. The results highlight the need for control strategies against enteric fever.

Drug resistance in *Salmonella enterica* serotype Typhi isolated from chronic typhoid carriers.

Author	Pratap CB, Patel SK, Shukla VK, Tripathi SK, Singh TB, Nath G.
Publication	Int J Antimicrob Agents. 2012 Sep;40(3):279-80.
URL	Not publically available

[START Summary]

This letter to the editor describes a study that examined the current levels of drug resistance to commonly used antibiotics, including ceftriaxone (CRO), in *Salmonella* Typhi isolated from chronic typhoid carriers in the eastern part of north India. The study showed that the mean minimum inhibitory concentration (MIC) and range were significantly higher ($P < 0.001$) for CRO (7.36 mg/L) along with quite a wide range (0.03125 – 64 mg/L) against *S. Typhi* isolated from chronic typhoid carriers during the period 2009-2011 compared with an earlier report from their center (range 0.0625 – 1 mg/L, mean 0.3652 mg/L). The gene responsible for resistance to CRO and ciprofloxacin (CIP) and was located on the chromosome, and resistance might be occurring as a result of adaptive mutations due to antibiotic pressured created on *S. Typhi* present in carriers.



Trends in antimicrobial susceptibility of Salmonella Typhi from North India (2001-2012).

Author	Singhal L, Gupta PK, Kale P, Gautam V, Ray P.
Publication	Indian J Med Microbiol. 2014 Apr-Jun;32(2):149-52.
URL	http://www.ijmm.org/article.asp?issn=0255-0857;year=2014;volume=32;issue=2;spage=149;epage=152;aualast=Singhal
Additional Categories	Disease and environmental surveillance

PURPOSE: Enteric fever is endemic in India with Salmonella Typhi being the major causative agent. Antibiotic therapy constitutes the mainstay of management. The present study was undertaken to find the susceptibility profile of Salmonella enterica var Typhi (S. Typhi) blood isolates in a tertiary care hospital between January 2001 and December 2012. **MATERIALS AND METHODS:** A retrospective analysis of laboratory records was carried out. Conventional blood culture method was used until 2009; from January 2010 onwards BACTEC 9240 system has been in use. Salmonella were confirmed by serotyping using group and type specific antisera. Antibiotic susceptibility was performed using the disk diffusion method. In addition, 116 isolates were subjected to minimum inhibitory concentration testing for chloramphenicol, ciprofloxacin, amoxicillin and nalidixic acid (NA) using agar dilution and for ceftriaxone and azithromycin using E-strips (Biomérieux). **RESULT:** A total of 1016 typhoidal salmonellae were obtained. The predominant serotype obtained was S. Typhi (852, 83.8%) followed by Salmonella enterica var Paratyphi A (164, 16.2%). We observed a re-emergence of susceptibility to first line antibiotics and a notable decline in multidrug resistant (MDR) strains. We also found all recent isolates resistant to NA and susceptible to third generation cephalosporins and 84.5% of isolates having decreasing ciprofloxacin susceptibility using revised criteria as per Clinical and Laboratory Standards Institute 2012 guidelines. **CONCLUSION:** There has been re-emergence of susceptibility to first line antibiotics and a notable decline in MDR strains of S. Typhi. We have a very high resistance to NA and decreasing susceptibility to ciprofloxacin. Third generation cephalosporins and azithromycin seem to be effective therapeutic options. Judicious use of these antibiotics is mandatory to prevent emergence of resistant strains.

A three-year review of antimicrobial resistance of Salmonella enterica serovars Typhi and Paratyphi A in Pakistan.

Author	Qamar FN, Azmatullah A, Kazi AM, Khan E, Zaidi AK.
Publication	J Infect Dev Ctries. 2014 Aug 13;8(8):981-6.
URL	http://www.jidc.org/index.php/journal/article/view/25116662

INTRODUCTION: Enteric fever is among the most common bacteraemic illnesses in South Asia. Multidrug resistance as well as fluoroquinolone resistance has severely limited therapeutic options in high disease burden countries such as Pakistan. This review was conducted to determine the frequency of drug-resistant Salmonella enterica serovar Typhi (S. Typhi) and Salmonella enterica serovar Paratyphi A (S. Paratyphi A) between 2009 and 2011. **METHODOLOGY:** This study was a review of laboratory data. The antibiotic susceptibility of typhoidal Salmonellae isolated from blood cultures submitted to the Aga Khan University Hospital's laboratory from all over Pakistan between January 2009 and December 2011 were reviewed. **RESULTS:** The sensitivity data of 4,323 positive isolates of S. Typhi and S. Paratyphi A isolated during the three-year period were reviewed. The majority of isolates were S. Typhi (59.6%). Over three years, the incidence of multidrug-resistant (MDR) S. Typhi remained high, ranging from 64.8%-66.0%,



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while MDR *S. Paratyphi A* decreased from 4.2% to 0.6%. Fluoroquinolone resistance increased for *S. Typhi* from 84.7% to 91.7%. Cefixime- and ceftriaxone-resistant *S. Typhi* were isolated in two children. CONCLUSIONS: Our results show high rates of multidrug and fluoroquinolone resistance among *S. Typhi* and *S. Paratyphi*. The occurrence of two cases of ceftriaxone resistance is alarming.

Antimicrobial susceptibility patterns of *Salmonella typhi* and *Salmonella paratyphi A* in a tertiary care hospital.

Author	Raza S, Tamrakar R, Bhatt CP, Joshi SK.
Publication	J Nepal Health Res Counc. 2012 Sep;10(22):214-7.
URL	Not publically available

BACKGROUND: Enteric fever is still an important public health problem in developing countries including Nepal. A changing antibiotic susceptibility pattern of *Salmonella typhi* and *Salmonella paratyphi A* and emergence of multi drug resistance has increased to a great concern. Aim of the study was to investigate the antibiotic susceptibility pattern of *Salmonella typhi* and *Salmonella paratyphi A*. METHODS: Study was carried out at the department of microbiology in Kathmandu Medical College. Blood culture samples were collected from suspected enteric fever patient and tested microbiologically by standard procedure. Antibiotic susceptibility test was performed by Kirby-Bauer disc diffusion method and results were interpreted by National Committee for Clinical Laboratory (NCCLS) guideline. RESULTS: Of total 78 (2.0%) *Salmonella* serotype isolated from 3,980 blood culture samples, in which 47 (60.3%) were *S. typhi* and 31 (39.7%) were *S. paratyphi A*. Isolates were from all age group median age being the 25 years. Among the tested antibiotics *S. typhi* was susceptible towards Ciprofloxacin (100%) followed by Gentamicin (97.9%), Ofloxacin (95.7%), Ceftriaxone (95.7%) and Chloramphenicol (93.6%). In case of *S. paratyphi A* most of the tested antibiotics showed high percentage of susceptibility and least susceptible antibiotic for *S. paratyphi A* was Ampicillin (25.8%). Three isolates of *S. typhi* showed multidrug resistance. CONCLUSIONS: A considerable variation was observed in the antimicrobial susceptibility pattern of *S. typhi* and *S. paratyphi A*. Hence antibiotic susceptibility test must be sought before instituting appropriate therapy to prevent from further emergence of drug resistance.

Emergence of multidrug-resistant *Salmonella* spp. and isolates with reduced susceptibility to ciprofloxacin in Kuwait and the United Arab Emirates.

Author	Rotimi VO, Jamal W, Pal T, Sonnevend A, Dimitrov TS, Albert MJ.
Publication	Diagn Microbiol Infect Dis. 2008 Jan;60(1):71-7.
URL	Not publically available

Kuwait and United Arab Emirates (UAE) are 2 countries with worldwide significance in the context of global epidemiology of antimicrobial resistance. The extent of drug resistance in *Salmonella* spp. isolated from these countries was investigated by determining their susceptibility to 9 antibiotics using the E-test method. Amikacin, cefotaxime, ceftriaxone, ciprofloxacin, and gentamicin had excellent activities against all Kuwait and UAE isolates with MIC (90)s ranging between 0.056 and 4.5 microg/mL. The resistance rates in Kuwait and UAE to ampicillin were 26.5% and 17.1%, cefotaxime/ceftriaxone 1.6% and 1.6%, ciprofloxacin 1.2% and 0.8%, chloramphenicol 5.6% and 5.7%, and trimethoprim-sulfamethoxazole 26.1% and 8.9%, respectively. A total of 9.8% of the Kuwait isolates were multidrug resistant versus 4.1% of UAE isolates. Reduced susceptibility to ciprofloxacin was observed in 14.2% and 7.4% of the nontyphoidal *Salmonella*, respectively, as were in 44% of *Salmonella enterica* serovar *typhi* and 66.7% *Salmonella paratyphi*. *Salmonella* spp. with reduced quinolones susceptibility have emerged



in the Gulf region, and this is of concern as it may compromise the treatment of infections caused by invasive strains.

Epidemiology and risk factors for endemic typhoid fever in Uzbekistan.

Author	Srikantiah P, Vafokulov S, Luby SP, Ishmail T, Earhart K, Khodjaev N, Jennings G, Crump JA, Mahoney FJ.
Publication	Trop Med Int Health. 2007 Jul;12(7):838-47.
URL	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2007.01853.x/epdf
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

BACKGROUND: To investigate the risk factors for infection with endemic typhoid fever in the Samarkand region of Uzbekistan. **METHODS:** Case-control study of culture-confirmed bloodstream infection with *Salmonella* Typhi. Patients were compared to age-matched community controls. *Salmonella* Typhi isolates were tested for antimicrobial susceptibility. **RESULTS:** We enrolled 97 patients and 192 controls. The median age of patients was 19 years. In a conditional regression model, consumption of unboiled surface water outside the home [adjusted odds ratio (aOR)=3.0, 95% confidence interval (CI)=1.1-8.2], use of antimicrobials in the 2 weeks preceding onset of symptoms (aOR=12.2, 95% CI 4.0-37.0), and being a student (aOR=4.0, 95% CI 1.4-11.3) were independently associated with typhoid fever. Routinely washing vegetables (aOR 0.06, 95% CI 0.02-0.2) and dining at a tea-house (aOR 0.4, 95% CI 0.2-1.0) were associated with protection against illness. *Salmonella* Typhi resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole was identified in 6 (15%) of 41 isolates tested. **CONCLUSIONS:** Endemic typhoid fever in Uzbekistan is transmitted by contaminated water. Recent use of antimicrobials also increased risk of infection. Targeted efforts at improving drinking water quality, especially for students and young adults, are likely to decrease transmission of typhoid fever. Measures to decrease the unnecessary use of antimicrobials would be expected to reduce the risk of typhoid fever and decrease the spread of multiple drug-resistant *Salmonella* Typhi.

Azithromycin and ciprofloxacin resistance in *Salmonella* bloodstream infections in Cambodian adults.

Author	Vlieghe ER, Phe T, De Smet B, Veng CH, Kham C, Bertrand S, Vanhoof R, Lynen L, Peetermans WE, Jacobs JA.
Publication	PLoS Negl Trop Dis. 2012;6(12):e1933.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3521708/pdf/pntd.0001933.pdf
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

BACKGROUND: *Salmonella enterica* is a frequent cause of bloodstream infection (BSI) in Asia but few data are available from Cambodia. We describe *Salmonella* BSI isolates recovered from patients presenting at Sihanouk Hospital Centre of Hope, Phnom Penh, Cambodia (July 2007-December 2010). **METHODOLOGY:** Blood was cultured as part of a microbiological prospective surveillance study. Identification of *Salmonella* isolates was performed by conventional methods and serotyping. Antibiotic susceptibilities were assessed using disk diffusion, MicroScan and E-test macromethod. Clonal relationships were assessed by Pulsed Field Gel Electrophoresis; PCR and sequencing for detection of mutations in Gyrase and Topoisomerase IV and presence of *qnr* genes. **PRINCIPAL FINDINGS:** Seventy-two *Salmonella* isolates grew from 58 patients (mean age 34.2 years, range 8-71). Twenty isolates were



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identified as *Salmonella* Typhi, 2 as *Salmonella* Paratyphi A, 37 as *Salmonella* Choleraesuis and 13 as other non-typhoid *Salmonella* spp. Infection with human immunodeficiency virus (HIV) was present in 21 of 24 (87.5%) patients with *S. Choleraesuis* BSI. Five patients (8.7%) had at least one recurrent infection, all with *S. Choleraesuis*; five patients died. Overall, multi drug resistance (i.e., co-resistance to ampicillin, sulphamethoxazole-trimethoprim and chloramphenicol) was high (42/59 isolates, 71.2%). *S. Typhi* displayed high rates of decreased ciprofloxacin susceptibility (18/20 isolates, 90.0%), while azithromycin resistance was very common in *S. Choleraesuis* (17/24 isolates, 70.8%). Two *S. Choleraesuis* isolates were extended spectrum beta-lactamase producer. **CONCLUSIONS AND SIGNIFICANCE:** Resistance rates in *Salmonella* spp. in Cambodia are alarming, in particular for azithromycin and ciprofloxacin. This warrants nationwide surveillance and revision of treatment guidelines.

Emerging *Salmonella* Paratyphi A enteric fever and changing trends in antimicrobial resistance pattern of salmonella in Shimla.

Author	Verma S, Thakur S, Kanga A, Singh G, Gupta P.
Publication	Indian J Med Microbiol. 2010 Jan-Mar;28(1):51-3.
URL	Not publically available

This retrospective study incorporates a six years, six months (January 2000-June 2006) laboratory data comprising 258 isolates of *Salmonella*. Cultures were identified by standard methods. *Salmonella* enterica serotype Typhi (*S. Typhi*) was the more frequent serotype isolated i.e., 61.62% with the remaining 38.37% being *Salmonella* enterica serotype Paratyphi A (*S. Paratyphi* A). There was emergence of *S. Paratyphi* A as the predominant serotype in 2003-2004 with resurgence of serotype Typhi thereon. A total of 66.27% isolates were resistant to one or more antibiotics. MDR *S. Typhi* was 10.69% and while 13.13% were MDR *S. Paratyphi* A. There was decrease in resistance to ampicillin, cotrimoxazole in 2004 and nalidixic acid beyond 2005 and increase in resistance to cefuroxime. We also documented a decrease in resistance to ciprofloxacin after 2005.

Typhoid fever.

Author	Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL.
Publication	Lancet. 2015 Mar 21;385(9973):1136-45.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance Challenge models and vaccine trials

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.

Typhoid and paratyphoid fever in Yunnan province: distributional patterns and the related meteorological factors.

Author	Wang LX, Yan MY, Fang LQ, Fu XQ, Wang DC, Sun JL, Cao WC, Zhang J, Kan B.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2011 May;32(5):485-9.
URL	http://zhlxboxzz.yiigle.com/CN112338201105/593807.htm?locale=zh_CN
Additional Categories	Epidemiological patterns and global burden of typhoid fever

[Article in Chinese]

OBJECTIVE: To characterize the spatial distribution of typhoid and paratyphoid fever (TPF) in Yunnan province, China and to determine the effectiveness of meteorological factors on the epidemics of TPF. **METHODS:** Data of reported TPF cases in Yunnan province (2001 - 2007) from the China Information System for Diseases Control and Prevention was applied to GIS-based spatial analyses to detect their spatial distribution and clustering of TPF incidence at the county level. Panel data analysis was used to identify the relationships between the TPF incidence and meteorological factors including monthly average temperature, monthly cumulative precipitation and monthly average relative humidity. **RESULTS:** During the study period, the average incidence of TPF in Yunnan province was 23.11/100 000, with majority of the TPF cases emerged in summer and autumn. Although widely distributed, two TPF clusters were detected in Yunnan province based on the spatial analysis: one area around Yuxi city with the average annual incidence as 207.45/100 000 and another at the junctions of Yunnan province with Burma and Laos. Based on results from panel data analysis, the incidence of TPF was shown to be associated with meteorological factors such as temperature, precipitation, relative humidity and one month lag of temperature increase [10°C increase in the monthly average temperature: IRR = 1.30 (95%CI: 1.24 - 1.36); 10% increase in monthly average relative humidity: IRR = 1.07 (95%CI: 1.05 - 1.09); 100 mm rise in monthly cumulative precipitation: IRR = 1.02 (95%CI: 1.00 - 1.03); and 10°C average temperature increase, the last month: IRR = 1.73 (95%CI: 1.64 - 1.82)]. **CONCLUSION:** Areas with high TPF incidence were detected in this study, which indicated the key areas for TPF control in Yunnan province. Meteorological factors such as temperature, precipitation and humidity played a role in the incidence of TPF.

Shifts in geographic distribution and antimicrobial resistance during a prolonged typhoid fever outbreak--Bundibugyo and Kasese Districts, Uganda, 2009-2011.

Author	Walters MS, Routh J, Mikoleit M, Kadivane S, Ouma C, Mubiru D, Mbusa B, Murangi A, Ejoku E, Rwantangle A, Kule U, Lule J, Garrett N, Halpin J, Maxwell N, Kagirita A, Mulabya F, Makumbi I, Freeman M, Joyce K, Hill V, Downing R, Mintz E.
Publication	PLoS Negl Trop Dis. 2014 Mar 6;8(3):e2726.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945727/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance Challenge models and vaccine trials

BACKGROUND: *Salmonella enterica* serovar Typhi is transmitted by fecally contaminated food and water and causes approximately 22 million typhoid fever infections worldwide each year. Most cases occur in



developing countries, where approximately 4% of patients develop intestinal perforation (IP). In Kasese District, Uganda, a typhoid fever outbreak notable for a high IP rate began in 2008. We report that this outbreak continued through 2011, when it spread to the neighboring district of Bundibugyo. **METHODOLOGY/PRINCIPAL FINDINGS:** A suspected typhoid fever case was defined as IP or symptoms of fever, abdominal pain, and ≥ 1 of the following: gastrointestinal disruptions, body weakness, joint pain, headache, clinically suspected IP, or non-responsiveness to antimalarial medications. Cases were identified retrospectively via medical record reviews and prospectively through laboratory-enhanced case finding. Among Kasese residents, 709 cases were identified from August 1, 2009–December 31, 2011; of these, 149 were identified during the prospective period beginning November 1, 2011. Among Bundibugyo residents, 333 cases were identified from January 1–December 31, 2011, including 128 cases identified during the prospective period beginning October 28, 2011. IP was reported for 507 (82%) and 59 (20%) of Kasese and Bundibugyo cases, respectively. Blood and stool cultures performed for 154 patients during the prospective period yielded isolates from 24 (16%) patients. Three pulsed-field gel electrophoresis pattern combinations, including one observed in a Kasese isolate in 2009, were shared among Kasese and Bundibugyo isolates. Antimicrobial susceptibility was assessed for 18 isolates; among these 15 (83%) were multidrug-resistant (MDR), compared to 5% of 2009 isolates. **CONCLUSIONS/SIGNIFICANCE:** Molecular and epidemiological evidence suggest that during a prolonged outbreak, typhoid spread from Kasese to Bundibugyo. MDR strains became prevalent. Lasting interventions, such as typhoid vaccination and improvements in drinking water infrastructure, should be considered to minimize the risk of prolonged outbreaks in the future.

Typhoid fever: facing the challenge of resistant strains.

Author	Weill FX.
Publication	Med Sci (Paris). 2010 Nov;26(11):969-75.
URL	http://www.medicinesciences.org/en/articles/medsci/abs/2010/10/medsci20102611p969/medsci20102611p969.html

[Article in French]

The introduction of chloramphenicol in 1948 revolutionised the outcome of typhoid fever but chloramphenicol-resistant strains of *Salmonella enterica* serotype Typhi were reported just two years later. Resistance followed also the introduction of ampicillin and co-trimoxazole. During the second half of the 1980s, strains resistant to the three first-line antimicrobial agents, chloramphenicol, ampicillin and co-trimoxazole emerged and spread rapidly throughout the Indian subcontinent and South East Asia. During the 1990s when fluoroquinolones had become a first-line treatment for typhoid fever, these multi drug resistant (MDR) strains acquired an additional resistance to nalidixic acid with decreased susceptibilities to ciprofloxacin (CIPDS) (MIC range, 0.125-1 mg/l). Considerable data have now accumulated to suggest that infections due to CIPDS strains may not respond satisfactorily to therapy with ciprofloxacin or ofloxacin. Furthermore, identification of such CIPDS strains in clinical laboratories is not easy without determination of MIC of ciprofloxacin. Recently, several isolates highly resistant to ciprofloxacin or to extended-spectrum cephalosporins of Asian origin have been reported.



Epidemiological characteristics of typhoid fever and antibiotic susceptibility testing of *Salmonella* Typhi isolates in Guangxi, 1994-2013.

Author	Wang M, Kan B, Yang J, Lin M, Yan M, Zeng J, Quan Y, Liao H, Zhou L, Jiang Z, Huang D.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2014 Aug;35(8):930-4.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance

[Article in Chinese]

OBJECTIVE: Through analyzing the typhoid epidemics and to determine and monitor regional resistance characteristics of the shift of drug resistant profile on *Salmonella* (S.) Typhi, to understand the related epidemiological characteristics of typhoid fever and to provide evidence for the development of strategies, in Guangxi. **METHODS:** Data of typhoid fever from surveillance and reporting system between 1994 to 2013 was collected and statistically analyzed epidemiologically. The susceptibility of 475 S. Typhi isolates from patients on ten antibiotics was tested by broth micro-dilution method and minimum inhibition concentration was obtained and interpreted based on the CLSI standard. **RESULTS:** From 1994 to 2013, a total of 57 928 cases of typhoid fever were reported in Guangxi province with an annual incidence of 6.29/100 000 and mortality as 0.03%. The higher incidence was observed in the population under 20 years of age. There was no significant difference on incidence between male and female, but farmers and students were among the hardest hit groups. More cases were seen from the northern part of the province. Cases appeared all year round with the peak from May to October. A total of 13 major outbreaks during 2001 to 2013 were reported and the main transmission route was water-borne. All the strains were sensitive to third generation cephalosporins cefotaxime and fluoroquinolones norfloxacin. The susceptibility rates to tetracycline, chloramphenicol, ampicillin and gentamicin was around 98% but relative lower susceptible rate to ciprofloxacin was seen as 89.89%. The lowest susceptibility was found for streptomycin and sulfamethoxazole agents, with the rates as 67.73% and 65.89% , respectively. One strain was found to have been resistant to ciprofloxacin and another 47 isolates with reduced susceptibility to ciprofloxacin. Twenty eight isolates were found to be resistant to multiple antibiotics and one displayed ampicillin, chloramphenicol, streptomycin, sulfamethoxazole tetracycline and nalidixic acid (ACSSxT-NAL) resistance profile. This was the first report in China. Multi-drug resistant strains were frequently isolated from small scale outbreaks of typhoid fever. **CONCLUSION:** The incidence of typhoid fever in Guangxi was still high and some strains showed multi-drug resistance and reduced susceptibility to ciprofloxacin, indicating that the surveillance and monitor programs on drug resistance of S. Typhi should be strengthened, to prevent large scale outbreaks of typhoid fever in this province.

Epidemiological and etiological characteristics of typhoid and paratyphoid fever in Ningbo during 1988 - 2007.

Author	Xu GZ, Xu JY, Zhou AM, Jin CG, Mao GH, Shi YZ, Dong HJ, Yang YB.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2009 Mar;30(3):252-6.
URL	Not publically available

[Article in Chinese]

OBJECTIVE: To study the epidemiological and etiological characteristics of typhoid and paratyphoid fever in high epidemic areas. **METHODS:** Reported data on typhoid and paratyphoid fever during 1988-2007 in Ningbo were analyzed epidemiologically. Shellfish from the market was collected for laboratory testing



and *Salmonella typhi* strains collected from the patients were also studied. RESULTS: Number of reported cases on both typhoid and paratyphoid fever was 19 404 with 7 deaths, from 1988 to 2007. The annual mean incidence was 17.68 per one hundred thousand with the fatality rate as 0.36 per thousand. Most cases were among adults aged 20-50 years and an obvious regional distribution was observed with high incidence seen in winter and spring. Since 1990s, the advantage strain had changed from *Salmonella typhi* to *Salmonella paratyphi* A. Etiologic studies showed that raw *Anadara subcrenata* and oyster were the main risk factors. One *Salmonella paratyphi* A strain was detected in both *Anadara subcrenata* and oysters collected from the market, which contained TEM-1 drug resistance gene. PFGE genotyping showed that PFGE-X2 was the strain which causing pandemic in Ningbo. CONCLUSION: Eating contaminated raw shellfish like oysters and hairy clams was the primary risk factor, responsible for the outbreaks. *Salmonella paratyphi* A was the advantages pandemic strain in Ningbo. Strategies as supervision on personal hygiene and health education should be strengthened.

Antimicrobial resistance surveillance of *Salmonella* isolates from the First People's Hospital of Yunnan Province, China.

Author	Yaxian J, Hui Z, Hua N, Xiaoqin M, Fengliang L, Ning X, Jiajia L, Jie J, Rui Z.
Publication	J Infect Dev Ctries. 2015 Apr 15;9(4):333-7.
URL	http://www.jidc.org/index.php/journal/article/view/25881520/1277
Additional Categories	Disease and environmental surveillance

INTRODUCTION: Typhoid fever is a common disease in Yunnan province; however, the resistant phenotype and epidemic characteristics of *Salmonella* in this area are still unclear. In this study, a 15-year surveillance of antimicrobial susceptibility of *Salmonella* is reported. METHODOLOGY: From January 1999 to December 2013, *Salmonella* isolates were recovered from patients in the First People's Hospital of Yunnan Province. Antimicrobial susceptibility was detected and data were analyzed using WHONET5.6. RESULTS: A total of 845 *Salmonella* isolates were recovered between 1999 and 2013. The most frequently isolated *Salmonella* serovar was *S. Paratyphi* A (93%), and 75.1% (635/845) of the isolates were from the young and middle-aged population. The resistance rates of *Salmonella* spp. to ciprofloxacin, ampicillin, and ceftriaxone increased dramatically during the 15 years. Carbapenems retained the highest and most stable activity against isolates. The resistance rates of all *Salmonella* isolates to chloramphenicol and sulfamethoxazole were 0.4% (3/845) and 1.8% (15/845), respectively. CONCLUSIONS: As *Salmonella* isolates have been observed to be resistant to first-line antibiotics, antimicrobial agents should be used rationally and prescriptions should be based on case-by-case susceptibility testing.

Characteristics of drug resistance and molecular type of *Salmonella typhi* and *Salmonella paratyphi* isolated in Henan province, 2009-2011.

Author	Zhao J, Xie Z, Mu Y, Su J, Xia S, Huang X, Xu B.
Publication	Zhonghua Liu Xing Bing Xue Za Zhi. 2016 Jan;37(1):111-4.
URL	Not publically available

[Article in Chinese]

OBJECTIVE: To investigate the antibiotic resistance and pulsed field gel electrophoresis (PFGE) patterns of clinical isolates of *Salmonella* (*S.*) *typhi* and *S. paratyphi* in Henan province during 2009-2011. METHODS: According to molecular typing and *Salmonella* K-B drug susceptibility test method published



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by international PulseNet bacterial infectious disease monitoring network and USA Clinical and Laboratory Standards Institute (CLSI), the drug susceptibility and PFGE molecule characteristics of 78 *S. typhi* and *S. paratyphi* strains isolated from sentinel hospitals in Henan were analyzed. RESULTS: The 78 strains of *S. typhi* and *S. paratyphi* were resistant to 13 kinds of antibiotics, in which 62 were multidrug resistant (79.5%), 4 were resistant to 2-3 kinds of antibiotics (5.1%), 41 were resistant to 5-8 kinds of antibiotics (52.6%), 14 were resistant to 9-10 kinds of antibiotics (17.9%), 3 were resistant to 11-12 kinds of antibiotics (3.8%). The resistant rate to cephalosporins, quinolones and other 3 kinds of antibiotic showed an increase trends. Seventy two strains of *S. typhi* and *S. paratyphi* could be divided 14 molecular patterns by digestion with Xba I and PFGE, each pattern contains 1-47 strains which shared the similarity of 66.03%-100.00%. CONCLUSIONS: The drug resistance of clinical isolates of *S. typhi* and *S. paratyphi* was serious in Henan. The PFGE patterns showed diversity, but the predominant patterns could be still found. The PFGE patterns of some strains were associated with their drug resistance.



CHALLENGE MODELS AND VACCINE TRIALS

Vaccines for preventing typhoid fever.

Author	Anwar E, Goldberg E, Fraser A, Acosta CJ, Paul M, Leibovici L.
Publication	Cochrane Database Syst Rev. 2014 Jan 2;(1):CD001261.
URL	http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001261.pub3/epdf

BACKGROUND: Typhoid fever and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and southeast Asia. Two typhoid vaccines are commercially available, Ty21a (oral) and Vi polysaccharide (parenteral), but neither is used routinely. Other vaccines, such as a new, modified, conjugated Vi vaccine called Vi-rEPA, are in development. **OBJECTIVES:** To evaluate the efficacy and adverse effects of vaccines used to prevent typhoid fever. **SEARCH METHODS:** In June 2013, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS, and mRCT. We also searched relevant conference proceedings up to 2013 and scanned the reference lists of all included trials. **SELECTION CRITERIA:** Randomized and quasi-randomized controlled trials (RCTs) comparing typhoid fever vaccines with other typhoid fever vaccines or with an inactive agent (placebo or vaccine for a different disease). **DATA COLLECTION AND ANALYSIS:** Two review authors independently applied inclusion criteria and extracted data. We computed vaccine efficacy per year of follow-up and cumulative three-year efficacy, stratifying for vaccine type and dose. The outcome addressed was typhoid fever, defined as isolation of *Salmonella typhi* in blood. We calculated risk ratios (RRs) and efficacy (1-RR as a percentage) with 95% confidence intervals (CIs). **MAIN RESULTS:** In total, 18 RCTs were included in this review; 12 evaluated efficacy (Ty21a: five trials; Vi polysaccharide: six trials; Vi-rEPA: one trial), and 11 reported on adverse events. Ty21a vaccine (oral vaccine, three doses) A three-dose schedule of Ty21a vaccine prevents around one-third to one-half of typhoid cases in the first two years after vaccination (Year 1: 35%, 95% CI 8% to 54%; Year 2: 58%, 95% CI 40% to 71%; one trial, 20,543 participants; moderate quality evidence; data taken from a single trial conducted in Indonesia in the 1980s). No benefit was detected in the third year after vaccination. Four additional cluster-RCTs have been conducted, but the study authors did not adjust for clustering. Compared with placebo, this vaccine was not associated with more participants with vomiting, diarrhoea, nausea or abdominal pain (four trials, 2066 participants; moderate quality evidence) headache, or rash (two trials, 1190 participants; moderate quality evidence); however, fever (four trials, 2066 participants; moderate quality evidence) was more common in the vaccine group. Vi polysaccharide vaccine (injection, one dose) A single dose of Vi polysaccharide vaccine prevents around two-thirds of typhoid cases in the first year after vaccination (Year 1: 69%, 95% CI 63% to 74%; three trials, 99,979 participants; high quality evidence). In Year 2, the trial results were more variable, with the vaccine preventing between 45% and 69% of typhoid cases (Year 2: 59%, 95% CI 45% to 69%; four trials, 194,969 participants; moderate quality evidence). The three-year cumulative efficacy of the vaccine is around 55% (95% CI 30% to 70%; 11,384 participants, one trial; moderate quality evidence). These data are taken from a single trial in South Africa in the 1980s. Compared with placebo, this vaccine was not associated with more participants with fever (four trials, 133,038 participants; moderate quality evidence) or erythema (three trials, 132,261 participants; low quality evidence); however, swelling (three trials, 1767 participants; moderate quality evidence) and pain at the injection site (one trial, 667 participants; moderate quality evidence) were more common in the vaccine group. Vi-rEPA vaccine (two doses) Administration of two doses of the Vi-rEPA vaccine prevents between 50% and 96% of typhoid

cases during the first two years after vaccination (Year 1: 94%, 95% CI 75% to 99%; Year 2: 87%, 95% CI 56% to 96%; one trial, 12,008 participants; moderate quality evidence). These data are taken from a single trial with children 2 to 5 years of age conducted in Vietnam. Compared with placebo, the first and second doses of this vaccine were not associated with increased risk of adverse events. The first dose of this vaccine was not associated with fever (2 studies, 12,209 participants; low quality evidence), erythema (two trials, 12,209 participants; moderate quality evidence) or swelling at the injection site (two trials, 12,209 participants; moderate quality evidence). The second dose of this vaccine was not associated with fever (two trials, 11,286 participants; low quality evidence), erythema (two trials, 11,286 participants; moderate quality evidence) and swelling at the injection site (two trials, 11,286 participants; moderate quality evidence). **AUTHORS' CONCLUSIONS:** The licensed Ty21a and Vi polysaccharide vaccines are efficacious. The new and unlicensed Vi-rEPA vaccine is as efficacious and may confer longer immunity.

Evaluation of immune responses to an oral typhoid vaccine, Ty21a, in children from 2 to 5 years of age in Bangladesh.

Author	Bhuiyan TR, Choudhury FK, Khanam F, Saha A, Sayeed MA, Salma U, Lundgren A, Sack DA, Svennerholm AM, Qadri F.
Publication	Vaccine. 2014 Feb 19;32(9):1055-60. Comment in Vaccine. 2014 Jul 7;32(32):4014. Vaccine. 2014 Jul 7;32(32):4013.
URL	http://www.sciencedirect.com/science/article/pii/S0264410X14000024

Young children are very susceptible to typhoid fever, emphasizing the need for vaccination in under five age groups. The parenteral Vi polysaccharide vaccine is not immunogenic in children under 2 years and the oral Ty21a vaccine (Vivotif) available in capsular formulation is only recommended for those over 5 years. We studied immune responses to a liquid formulation of Ty21a in children 2-5 years of age. Since children in developing countries are in general hypo responsive to oral vaccines, the study was designed to determine if anti-helminthic treatment prior to vaccination, improves responses. In a pilot study in 20 children aged 4-5 years, the immune responses in plasma and in antibody in lymphocyte secretions (ALS) to the enteric coated capsule formulation of Ty21a was found to be comparable to a liquid formulation ($P>0.05$). Based on this, children ($n=252$) aged ≥ 2 - <3 years and ≥ 3 - <5 years were randomized to receive a liquid formulation of Ty21a with and without previous anti-helminthic treatment. The vaccine was well tolerated with only a few mild adverse events recorded in $<1\%$ of the children. De-worming did not improve immune responses and both age groups developed 32-71% IgA, IgG, and IgM responses in plasma and 63-86% IgA responses in ALS and stool specimens to a membrane preparation (MP) of Ty21a. An early MP specific proliferative T cell response was also seen. We recommend that safety and efficacy studies with a liquid formulation of the vaccine are carried out in children under five, including those less than two years of age to determine if Ty21a is protective in these age groups and applicable as a public health tool for controlling typhoid fever in high prevalence areas of typhoid fever including Bangladesh.



Immunogenicity and safety of the Vi-CRM197 conjugate vaccine against typhoid fever in adults, children, and infants in south and southeast Asia: results from two randomised, observer-blind, age de-escalation, phase 2 trials.

Author	Bhutta ZA, Capeding MR, Bavdekar A, Marchetti E, Ariff S, Soofi SB, Anemona A, Habib MA, Alberto E, Juvekar S, Khan RM, Marhaba R, Ali N, Malubay N, Kawade A, Saul A, Martin LB, Podda A.
Publication	Lancet Infect Dis. 2014 Feb;14(2):119-29. Comment in Lancet Infect Dis. 2014 Feb;14(2):90-1.
URL	http://ac.els-cdn.com/S147330991370241X/1-s2.0-S147330991370241X-main.pdf?_tid=5419ea2e-6973-11e6-8cbb-00000aab0f02&acdnat=1471985653_b250513dbad30ecd4f6cd980b9adce52

BACKGROUND: Typhoid vaccination is a public health priority in developing countries where young children are greatly affected by typhoid fever. Because present vaccines are not recommended for children younger than 2 years, the Novartis Vaccines Institute for Global Health developed a conjugate vaccine (Vi-CRM197) for infant immunisation. We aimed to assess the immunogenicity and safety of Vi-CRM197 in participants of various ages in endemic countries in south and southeast Asia. **METHODS:** We did two randomised, observer-blind, age de-escalation, phase 2 trials at two sites in Pakistan and India (study A), and at one site in the Philippines (study B), between March 2, 2011, and Aug 9, 2012. Adults aged 18-45 years, children aged 24-59 months, older infants aged 9-12 months, and infants aged 6-8 weeks were randomly assigned (1:1) with a computer-generated randomisation list (block size of four) to receive either 5 µg Vi-CRM197 or 25 µg Vi-polysaccharide vaccine (or 13-valent pneumococcal conjugate vaccine in children younger than 2 years). Both infant populations received Vi-CRM197 concomitantly with vaccines of the Expanded Programme on Immunization (EPI), according to WHO schedule. With the exception of designated study site personnel responsible for vaccine preparation, study investigators, those assessing outcomes, and data analysts were masked to treatment allocation. We specified no a-priori null hypothesis for the immunogenicity or safety objectives and all analyses were descriptive. Analyses were by modified intention-to-treat. These studies are registered with ClinicalTrials.gov, numbers NCT01229176 and NCT01437267. **FINDINGS:** 320 participants were enrolled and vaccinated in the two trials: 200 in study A (all age groups) and 120 in study B (children and infants only), of whom 317 (99%) were included in the modified intention-to-treat analysis. One dose of Vi-CRM197 significantly increased concentrations of anti-Vi antibody in adults (from 113 U/mL [95% CI 67-190] to 208 U/mL [117-369]), children (201 U/mL [138-294] to 368 U/mL [234-580]), and older infants (179 U/mL [129-250] to 249 U/mL [130-477]). However, in children and older infants, a second dose of conjugate vaccine had no incremental effect on antibody titres and, at all ages, concentrations of antibodies increased substantially 6 months after vaccination (from 55 U/mL [33-94] to 63 U/mL [35-114] in adults, from 23 U/mL [15-34] to 51 U/mL [34-76] in children, and from 21 U/mL [14-31] to 22 U/mL [14-33] in older infants). Immune response in infants aged 6-8 weeks was lower than that in older participants and, 6 months after third vaccination, antibody concentrations were significantly higher than pre-vaccination concentrations in Filipino (21 U/mL [16-28] vs 2.88 U/mL [1.95-4.25]), but not Pakistani (3.76 U/mL [2.77-5.08] vs 2.77 U/mL [2.1-3.66]), infants. Vi-CRM197 was safe and well tolerated and did not induce any significant interference with EPI vaccines. No deaths or vaccine-related serious adverse events were reported throughout the studies. **INTERPRETATION:** Vi-CRM197 is safe and immunogenic in endemic populations of all ages. Given at 9 months of age, concomitantly with measles



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vaccine, Vi-CRM197 shows a promise for potential inclusion in EPI schedules of countries endemic for typhoid. An apparent absence of booster response and a reduction in antibody titres 6 months after immunisation should be further investigated, but data show that an immunogenic typhoid vaccine can be safely delivered to infants during EPI visits recommended by WHO. FUNDING: Sclavo Vaccines Association and Regione Toscana.

Global trends in typhoid and paratyphoid fever.

Author	Crump JA, Mintz ED.
Publication	Clin Infect Dis. 2010 Jan 15;50(2):241-6.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2798017/
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance Trends in antibiotic resistance of <i>S. typhoid</i>

Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and Southeast Asia, where enteric fever is associated with poor sanitation and unsafe food and water. High-quality incidence data from Asia are underpinning efforts to expand access to typhoid vaccines. Efforts are underway to develop vaccines that are immunogenic in infants after a single dose and that can be produced locally in countries of endemicity. The growing importance of *Salmonella enterica* serotype Paratyphi A in Asia is concerning. Antimicrobial resistance has sequentially emerged to traditional first-line drugs, fluoroquinolones, and third-generation cephalosporins, posing patient treatment challenges. Azithromycin has proven to be an effective alternative for treatment of uncomplicated typhoid fever. The availability of full genome sequences for *S. enterica* serotype Typhi and *S. enterica* serotype Paratyphi A confirms their place as monomorphic, human-adapted pathogens vulnerable to control measures if international efforts can be redoubled.

Typhoid epidemiology, diagnostics and the human challenge model.

Author	Darton TC, Blohmke CJ, Pollard AJ.
Publication	Curr Opin Gastroenterol. 2014 Jan;30(1):7-17.
URL	Not publically available

PURPOSE OF REVIEW: Infection caused by ingestion of human-restricted *Salmonella enterica* serovars Typhi and Paratyphi predominantly affects the most impoverished sections of society. In this review, we describe recent advances made in estimating the burden of illness and the important role improved diagnostic tests may have in controlling infection and report the development of a new human challenge model of typhoid infection. RECENT FINDINGS: Typhoid continues to be a major cause of morbidity, particularly in children and young adults in southeast Asia, although accurate assessments are still hindered by the lack of reliable surveillance data. Recent reports of high rates of infection in Africa and the dominance of paratyphoid in several geographic areas are of particular concern. Diagnosis of enteric fever remains frustrated by the nonspecific clinical presentation of cases and the lack of test sensitivity. Methods to improve diagnostic accuracy are hindered by the incomplete understanding of immunobiological mechanisms of infection and lack of a suitable animal infection model. SUMMARY: Enteric fever is a major global problem, the burden of which has only partially been recognized. Control strategies utilizing cheap accurate diagnostics and effective vaccines are urgently required, and their development should be accelerated by the use of a human challenge model.



Typhoid fever surveillance and vaccine use - South-East Asia and Western Pacific regions, 2009-2013.

Author	Date KA, Bentsi-Enchill AD, Fox KK, Abeyasinghe N, Mintz ED, Khan MI, Sahastrabuddhe S, Hyde TB; Centers for Disease Control and Prevention (CDC).
Publication	MMWR Morb Mortal Wkly Rep. 2014 Oct 3;63(39):855-60.
URL	http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6339a2.htm
Additional Categories	Challenge models and vaccine trials

Typhoid fever is a serious, systemic infection resulting in nearly 22 million cases and 216,500 deaths annually, primarily in Asia. Safe water, adequate sanitation, appropriate personal and food hygiene, and vaccination are the most effective strategies for prevention and control. In 2008, the World Health Organization (WHO) recommended use of available typhoid vaccines to control endemic disease and outbreaks and strengthening of typhoid surveillance to improve disease estimates and identify high-risk populations (e.g., persons without access to potable water and adequate sanitation). This report summarizes the status of typhoid surveillance and vaccination programs in the WHO South-East Asia (SEAR) and Western Pacific regions (WPR) during 2009-2013, after the revised WHO recommendations. Data were obtained from the WHO/United Nations Children's Fund (UNICEF) Joint Reporting Form on Immunization, a supplemental survey of surveillance and immunization program managers, and published literature. During 2009-2013, 23 (48%) of 48 countries and areas of SEAR (11) and WPR (37) collected surveillance or notifiable disease data on typhoid cases, with most surveillance activities established before 2008. Nine (19%) countries reported implementation of typhoid vaccination programs or recommended vaccine use during 2009-2013. Despite the high incidence, typhoid surveillance is weak in these two regions, and vaccination efforts have been limited. Further progress toward typhoid fever prevention and control in SEAR and WPR will require country commitment and international support for enhanced surveillance, targeted use of existing vaccines and availability of newer vaccines integrated within routine immunization programs, and integration of vaccination with safe water, sanitation, and hygiene measures.

Typhoid fever vaccination strategies.

Author	Date KA, Bentsi-Enchill A, Marks F, Fox K.
Publication	Vaccine. 2015 Jun 19;33 Suppl 3:C55-61.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever

Typhoid vaccination is an important component of typhoid fever prevention and control, and is recommended for public health programmatic use in both endemic and outbreak settings. We reviewed experiences with various vaccination strategies using the currently available typhoid vaccines (injectable Vi polysaccharide vaccine [ViPS], oral Ty21a vaccine, and injectable typhoid conjugate vaccine [TCV]). We assessed the rationale, acceptability, effectiveness, impact and implementation lessons of these strategies to inform effective typhoid vaccination strategies for the future. Vaccination strategies were categorized by vaccine disease control strategy (preemptive use for endemic disease or to prevent an outbreak, and reactive use for outbreak control) and vaccine delivery strategy (community-based routine, community-based campaign and school-based). Almost all public health typhoid vaccination programs used ViPS vaccine and have been in countries of Asia, with one example in the Pacific and one



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experience using the Ty21a vaccine in South America. All vaccination strategies were found to be acceptable, feasible and effective in the settings evaluated; evidence of impact, where available, was strongest in endemic settings and in the short- to medium-term. Vaccination was cost-effective in high-incidence but not low-incidence settings. Experience in disaster and outbreak settings remains limited. TCVs have recently become available and none are WHO-prequalified yet; no program experience with TCVs was found in published literature. Despite the demonstrated success of several typhoid vaccination strategies, typhoid vaccines remain underused. Implementation lessons should be applied to design optimal vaccination strategies using TCVs which have several anticipated advantages, such as potential for use in infant immunization programs and longer duration of protection, over the ViPS and Ty21a vaccines for typhoid prevention and control.

Typhoid vaccination: the Asian experience.

Author	DeRoeck D, Ochiai RL, Yang J, Anh DD, Alag V, Clemens JD.
Publication	Expert Rev Vaccines. 2008 Jul;7(5):547-60.
URL	Not publically available

The WHO has recently issued updated recommendations for the programmatic use of new-generation typhoid vaccines in high-risk areas of countries where typhoid fever is still endemic. Countries have subsequently been instructed to discuss how these recommendations can be implemented and to develop plans for targeted typhoid vaccination. These plans can be informed by the experiences with typhoid vaccination that several Asian countries have had. This article reviews past and current typhoid vaccination programs that have taken place in Thailand (using the old whole-cell vaccine) and in China, Vietnam and India (using the new-generation injectable Vi polysaccharide vaccine). This review also describes recent typhoid Vi vaccine demonstration projects that were conducted in five Asian countries.

Putting typhoid vaccination on the global health agenda.

Author	DeRoeck D, Jodar L, Clemens J.
Publication	N Engl J Med. 2007 Sep 13;357(11):1069-71.
URL	http://www.nejm.org/doi/full/10.1056/NEJMp078144

[START Summary]

This perspective paper calls for putting typhoid vaccination on the global health agenda. The paper begins with epidemiological data on the global typhoid fever burden (16 to 33 million cases and 500,000 to 600,000 deaths annually). It then discusses the reasons for why vaccination for typhoid fever does not receive the same attention as that for HPV and meningococcus (complacency due to initial success of antibiotics in treating typhoid fever, burden of typhoid fever not easily ascertained/estimated, and the endemic nature of typhoid). Using the success of mass vaccination against *S. Typhi* in Thailand and the increasing resistance of *S. Typhi* to first-line antibiotics, the authors then call for expansion of vaccination programs in endemic areas especially for school-aged children who are disproportionately affected by typhoid fever.



Typhoid fever vaccines: systematic review and meta-analysis of randomized controlled trials.

Author	Fraser A, Paul M, Goldberg E, Acosta CJ, Leibovici L.
Publication	Vaccine. 2007 Nov 7;25(45):7848-57. Comment in Vaccine. 2008 Jan 17;26(3):291.
URL	Not publically available

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

Vaccines for preventing typhoid fever.

Author	Fraser A, Goldberg E, Acosta CJ, Paul M, Leibovici L.
Publication	Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001261. Update in Cochrane Database Syst Rev. 2014;1:CD001261. Update of Cochrane Database Syst Rev. 2000;(2):CD001261.
URL	http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001261.pub2/full

BACKGROUND: Two typhoid vaccines are commercially available, Ty21a (oral) and Vi polysaccharide (parenteral), but neither is used routinely. Other vaccines, such as a new modified, conjugated Vi vaccine called Vi-rEPA, are in development. **OBJECTIVES:** To evaluate vaccines for preventing typhoid fever. **SEARCH STRATEGY:** In December 2006, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2006, Issue 3), MEDLINE, EMBASE, LILACS, and mRCT. We also searched relevant conference proceedings up to 2004 and scanned the reference lists of all included trials. **SELECTION CRITERIA:** Randomized and quasi-randomized controlled trials (RCTs) comparing typhoid fever vaccines with other typhoid fever vaccines or an inactive agent (placebo or vaccine for a different disease). **DATA COLLECTION AND ANALYSIS:** Two authors independently applied inclusion criteria and extracted data. We computed vaccine efficacy per year of follow up and cumulative three-year efficacy, stratifying for vaccine type and dose. We calculated relative risks (RR) and efficacy (1-RR as a percentage) with 95% confidence intervals (CI). **MAIN RESULTS:** Of the 17 included RCTs, 10 evaluated efficacy (Ty21a: 5 trials; Vi polysaccharide: 4 trials, Vi-rEPA: 1 trial), and 11 reported on adverse events. Ty21a vaccine (3 doses). According to one trial (20,543 participants), this vaccine provided statistically significant protection in each of the first three years (one: 35%, 95% CI 8% to 54%; two: 58%, 95% CI 40% to 71%; three: 46%, 95% CI -6% to 72%), and the cumulative efficacy for 2.5 to 3 years was 48% (95% CI 34% to 58%). Four cluster-RCTs that did not adjust for clustering were



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not included in the meta-analyses. Compared with placebo, this vaccine was not associated with an increased rate of fever, vomiting, diarrhoea, nausea or abdominal pain, headache, or rash. Vi polysaccharide vaccine (1 dose). This vaccine provided protection in year one (68%, 95% CI 50% to 80%; 99,979 participants, 3 trials) and year two (60%, 95% CI 31% to 76%; 142,555 participants, 2 trials), but not in year three (11,384 participants, 1 trial). The three-year cumulative efficacy was 55% (95% CI 30% to 70%; 11,384 participants, 1 trial). Compared with placebo, there was no statistically significant difference in the incidence of fever or erythema, but local swelling was more common with the vaccine. Vi-rEPA vaccine (2 doses). In one trial of 12,008 participants, this vaccine provided protection in year one (94%, 95% CI 75% to 99%) and year two (87%, 95% CI 56% to 96%). Cumulative efficacy at 46 months (3.8 years) was 89% (95% CI 76% to 97%). No swelling or erythema occurred in the vaccine or placebo group; fever was more frequent in the vaccine group. **AUTHORS' CONCLUSIONS:** The licensed Ty21a and Vi polysaccharide vaccines are efficacious. The new and unlicensed Vi-rEPA vaccine is as efficacious and may confer longer immunity.

Updated recommendations for the use of typhoid vaccine--Advisory Committee on Immunization Practices, United States, 2015.

Author	Jackson BR, Iqbal S, Mahon B; Centers for Disease Control and Prevention (CDC).
Publication	MMWR Morb Mortal Wkly Rep. 2015 Mar 27;64(11):305-8.
URL	http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a4.htm

These revised recommendations of the Advisory Committee on Immunization Practices update recommendations published in MMWR in 1994 and include updated information on the two currently available vaccines and on vaccine safety. They also include an update on the epidemiology of enteric fever in the United States, focusing on increasing drug resistance in *Salmonella enterica* serotype Typhi, the cause of typhoid fever, as well as the emergence of *Salmonella* serotype Paratyphi A, a cause of paratyphoid fever, against which typhoid vaccines offer little or no protection.

M-01ZH09, an oral live attenuated *Salmonella enterica* serovar Typhi vaccine for the prevention of typhoid fever.

Author	Jain SK.
Publication	Curr Opin Mol Ther. 2009 Oct;11(5):565-71.
URL	Not publically available

Typhoid fever remains a major health problem globally, particularly in the developing world. The increased emergence of several multidrug-resistant strains of *Salmonella enterica* serovar Typhi has made the management of the disease increasingly difficult. Although vaccines against typhoid fever are available, improvements are desired in dosage, immunogenicity and tolerability. Emergent BioSolutions Inc is developing M-01ZH09, a single-dose oral vaccine against typhoid fever based on an attenuated strain of *S enterica* serovar Typhi. Several clinical trials have been completed for the vaccine, including large phase II trials in the US and Vietnam. Additionally, a phase IIc clinical trial was ongoing in India at the time of publication. The available data suggest that M-01ZH09 is well tolerated in clinical trials, and is highly immunogenic, provoking broad immune responses. Because M-01ZH09 involves administration as a single oral dose, the vaccine has the potential to be used in a mass immunization program.



Head-to-head comparison of humoral immune responses to Vi capsular polysaccharide and Salmonella Typhi Ty21a typhoid vaccines--a randomized trial.

Author	Kantele A, Pakkanen SH, Karttunen R, Kantele JM.
Publication	PLoS One. 2013 Apr 8;8(4):e60583.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3620468/pdf/pone.0060583.pdf

BACKGROUND: The two typhoid vaccines, the parenteral Vi capsular polysaccharide and the oral live whole-cell Salmonella Typhi Ty21a vaccine, provide similar levels of protection in field trials. Sharing no antigens, they are thought to confer protection by different mechanisms. This is the first head-to-head study to compare the humoral immune responses to these two vaccines. **METHODS:** 50 age- and gender-matched volunteers were immunized, 25 with the Vi and 25 with the Ty21a vaccine. Circulating plasmablasts reactive with whole-cell Salmonella Typhi or one of the typhoidal antigenic structures, Vi, O-9,12, and H-d antigens, were identified as antibody-secreting cells (ASC) with ELISPOT. Homing receptor (HR) expressions were determined. These results were compared with ASC in four patients with typhoid fever. Antibodies to S. Typhi lipopolysaccharides were assessed in cultures of ALS (antibodies in lymphocyte supernatants) and in serum with ELISA. **RESULTS:** In 49 out of 50 vaccinees, no typhoid-specific plasmablasts were seen before vaccination. On day 7, response to Vi antigen was mounted in 24/25 volunteers in the Vi, and none in the Ty21a group; response to S. Typhi and O-9,12 was mounted in 49/50 vaccinees; and to H-d in 3/50. The numbers of typhoid-specific plasmablasts (total of ASC to Vi, O-9,12 and H-d antigens) proved equal in the vaccination groups. The HR expressions indicated a mainly systemic homing in the Vi and intestinal in the Ty21a group, the latter resembling that in natural infection. Plasmablasts proved more sensitive than serum and ALS in assessing the immune response. **CONCLUSIONS:** The typhoid-specific humoral responses to Vi and Ty21a vaccines are similar in magnitude, but differ in expected localization and antigen-specificity. The unforeseen O antigen-specific response in the Vi group is probably due to lipopolysaccharide contaminating the vaccine preparation. Only the response to Ty21a vaccine was found to imitate that in natural infection.

Epidemiology of typhoid and paratyphoid fever in India.

Author	Kanungo S, Dutta S, Sur D.
Publication	J Infect Dev Ctries. 2008 Dec 1;2(6):454-60.
URL	http://www.jidc.org/index.php/journal/article/view/19745523/79
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance Trends in antibiotic resistance of Salmonella typhi

Enteric fever (typhoid and paratyphoid fever) is a major human bacterial infection. Although the disease is not common in industrialised countries, it remains an important and persistent health problem in developing nations. Hospital-based studies and outbreak reports from India indicate that enteric fever is a major public health problem in this country, with Salmonella enterica serovar Typhi (S. Typhi) the most common aetiological agent but with an apparently increasing number of cases due to S. Paratyphi A (SPA). Because risk factors such as poor sanitation, lack of a safe drinking water supply and low socio economic conditions in resource-poor countries are amplified by the evolution of multidrug resistant salmonellae with reduced susceptibility to fluoroquinolone, treatment failure cases have been reported in India, which is associated with increased mortality and morbidity. Vaccination, which requires strict planning and proper targeting of the vulnerable age groups, is considered to be an effective tool in controlling



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this disease in endemic areas, given there is development of a conjugate vaccine against both serovars (S. Typhi and S. Para A).

Effectiveness of Vi capsular polysaccharide typhoid vaccine among children: a cluster randomized trial in Karachi, Pakistan.

Author	Khan MI, Soofi SB, Ochiai RL, Habib MA, Sahito SM, Nizami SQ, Acosta CJ, Clemens JD, Bhutta ZA; DOMI Typhoid Karachi Vi Effectiveness Study Group.
Publication	Vaccine. 2012 Aug 3;30(36):5389-95.
URL	http://ac.els-cdn.com/S0264410X12008560/1-s2.0-S0264410X12008560-main.pdf?_tid=d1159f4c-6a80-11e6-b6e8-00000aabb0f27&acdnat=1472101397_1692a4f5be584856022c73e1bbc81054

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.

Population impact of Vi capsular polysaccharide vaccine.

Author	Khan MI, Ochiai RL, Clemens JD.
Publication	Expert Rev Vaccines. 2010 May;9(5):485-96.
URL	Not publically available

Development of a safe and efficacious vaccine against typhoid fever has been the mainstay of enteric vaccinology since production of the first parenteral whole-cell typhoid vaccine in 1896. The new-generation Vi polysaccharide single-dose injectable typhoid vaccine developed in the 1980s is widely used in countries where it is locally produced, such as China, and in travelers from industrialized countries to typhoid-endemic settings. However, Vi vaccine use is limited to private practice at a small scale by residents of high-burden countries such as India, Pakistan and Bangladesh. Recognition of the public health importance of typhoid fever prevention has significantly increased due to the emergence of antimicrobial-resistant strains of *Salmonella enterica* serovar Typhi in recent years. Recent evidence of herd protection conferred by the Vi vaccine has highlighted the significance of the vaccine's effects beyond the vaccinated population. The large-scale use of this vaccine can yield protective benefits to a



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larger population and can reduce the epidemiologic and economic burden of typhoid fever in endemic countries.

Immunogenicity and safety of Vi capsular polysaccharide typhoid vaccine in healthy persons in Korea.

Author	Lim SM, Jung HS, Kim MJ, Park DW, Kim WJ, Cheong HJ, Park SC, Lee KC, Shin YK, Tan HK, Kim SL, Sohn JW.
Publication	J Microbiol Biotechnol. 2007 Apr;17(4):611-5.
URL	http://www.jmb.or.kr/journal/viewJournal.html?year=2007&vol=17&num=4&page=611

The purpose of this study was to evaluate the immunogenicity and safety of Salmonella Typhi Vi capsular polysaccharide vaccine (Vi vaccine) in Korea. The immunogenicity of a single dose of Vi vaccine was evaluated in 157 subjects (75 children and 82 adults) before and at 1, 6, and 12 months after vaccination. Immunogenicity was measured with a passive hemagglutination assay (PHA), quantified as geometric mean titers (GMTs) and seroconversion rates. The safety of the vaccine was investigated by determining adverse reactions occurring within 4 h, 3 days, and 1 month after injection. The seroconversion rate for children and adults 1 month after vaccination was 96.92% and 89.02%, respectively. In the case of children, the GMTs of Vi antibodies before vaccination were 5.87 ± 1.34 and 142.59 ± 2.39 at one month after vaccination. For adults, the GMTs before and one month after vaccination were 5.58 ± 1.28 and 58.56 ± 3.67 , respectively. Vi antibodies persisted for as long as 6 and 12 months after vaccination. All adverse reactions in adults and children were minor and did not require treatment. The Vi CPS vaccine was safe and immunogenic in adults and children older than 5 years.

Vaccines against invasive Salmonella disease: current status and future directions.

Author	MacLennan CA, Martin LB, Micoli F.
Publication	Hum Vaccin Immunother. 2014;10(6):1478-93.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4185946/

Though primarily enteric pathogens, Salmonellae are responsible for a considerable yet under-appreciated global burden of invasive disease. In South and South-East Asia, this manifests as enteric fever caused by serovars Typhi and Paratyphi A. In sub-Saharan Africa, a similar disease burden results from invasive nontyphoidal Salmonellae, principally serovars Typhimurium and Enteritidis. The existing Ty21a live-attenuated and Vi capsular polysaccharide vaccines target S. Typhi and are not effective in young children where the burden of invasive Salmonella disease is highest. After years of lack of investment in new Salmonella vaccines, recent times have seen increased interest in the area led by emerging-market manufacturers, global health vaccine institutes and academic partners. New glycoconjugate vaccines against S. Typhi are becoming available with similar vaccines against other invasive serovars in development. With other new vaccines under investigation, including live-attenuated, protein-based and GMMA vaccines, now is an exciting time for the Salmonella vaccine field.

Typhoid fever & vaccine development: a partially answered question.

Author	Marathe SA, Lahiri A, Negi VD, Chakravortty D.
Publication	Indian J Med Res. 2012;135:161-9.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3336846/

Typhoid fever is a systemic disease caused by the human specific Gram-negative pathogen Salmonella enterica serovar Typhi (S. Typhi). The extra-intestinal infections caused by Salmonella are very fatal. The



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incidence of typhoid fever remains very high in impoverished areas and the emergence of multidrug resistance has made the situation worse. To combat and to reduce the morbidity and mortality caused by typhoid fever, many preventive measures and strategies have been employed, the most important being vaccination. In recent years, many *Salmonella* vaccines have been developed including live attenuated as well as DNA vaccines and their clinical trials have shown encouraging results. But with the increasing antibiotic resistance, the development of potent vaccine candidate for typhoid fever is a need of the hour. This review discusses the latest trends in the typhoid vaccine development and the clinical trials which are underway.

Vaccines for typhoid fever and other salmonellosis.

Author	Martin LB.
Publication	Curr Opin Infect Dis. 2012 Oct;25(5):489-99.
URL	Not publically available

PURPOSE OF REVIEW: This review summarizes the recent advances in vaccination against *Salmonella* enterica serovar Typhi and highlights the data supporting the development of next generation vaccines to address paratyphoid fever and invasive nontyphoidal *Salmonella* (iNTS) disease. **RECENT FINDINGS:** There has been increasing awareness of the disease burden caused by *S. Typhi* particularly in Africa and greater recognition of *S. Paratyphi A*'s contribution to enteric fever episodes throughout Asia. Groups have been working to improve the existing typhoid vaccines and provide comprehensive data on the feasibility of their implementation in endemic settings. These data have resulted in modifications to the recommendations for typhoid vaccination in traveller markets and endemic settings, and has also led to the development of *S. Paratyphi A* vaccine components that can be combined with existing typhoid vaccines to generate bivalent formulations against enteric fever. The epidemiology of Ints serovars as cause of appreciable morbidity and mortality in Africa, and the need for vaccines, has also become more widely appreciated. **SUMMARY:** Current typhoid vaccines, although moderately effective for short periods of time, cannot be used in all age groups and only target one of the clinically relevant *Salmonella* serovars. Greater effort must be placed on the development and implementation of improved vaccines for the disease burden resulting from Typhi, Paratyphi A or iNTS infections.

Prospects for prevention of *Salmonella* infection in children through vaccination.

Author	McGregor AC, Waddington CS, Pollard AJ.
Publication	Curr Opin Infect Dis. 2013 Jun;26(3):254-62.
URL	Not publically available

PURPOSE OF REVIEW: Strains of *Salmonella* enterica subsp. enterica are amongst the most commonly identified invasive bacterial pathogens in resource-poor settings, and cause significant mortality, particularly in children. In this study we review recent progress in the development of vaccines against *S. Typhi*, *S. Paratyphi* and nontyphoidal *Salmonella* for children. **RECENT FINDINGS:** Typhoid remains common and *S. Paratyphi A* is increasingly recognized as a cause of enteric fever in Asia. In rural Africa, nontyphoidal salmonellae are among the most common invasive bacterial infections, although *S. Typhi* predominates in some urban centres. Licensed vaccines against typhoid have moderate but useful efficacy but neither of the two available vaccines can be used in infants. Although Ty21a may afford some cross-protection against *S. Paratyphi B*, there are no vaccines that specifically target paratyphoid or any nontyphoidal *Salmonella*. Several live attenuated vaccines are under development and may offer some advantages over Ty21a. Vi-conjugate vaccines should offer children excellent protection from



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typhoid once licensed. SUMMARY: There are few effective vaccines against *Salmonella* sp. and those that do exist target only one serovar, *S. Typhi*. Research is urgently needed to combat emerging agents of enteric fever such as *S. Paratyphi* A as well as nontyphoidal serovars, which commonly cause invasive disease in Africa.

Specific and cross-reactive immune response to oral *Salmonella* Typhi Ty21a and parenteral Vi capsular polysaccharide typhoid vaccines administered concomitantly.

Author Pakkanen SH, Kantele JM, Savolainen LE, Rombo L, Kantele A.

Publication Vaccine. 2015 Jan 9;33(3):451-8.

URL <http://www.sciencedirect.com/science/article/pii/S0264410X14015692>

BACKGROUND: Since protective efficacy of the current typhoid vaccines-oral whole-cell *Salmonella* Typhi Ty21a and parenteral Vi-capsular polysaccharide preparation-is not optimal, and no vaccines are available against paratyphoid or non-typhoidal *Salmonella* (NTS) serotypes, new approaches deserve to be explored. The immunological mechanisms elicited by the two typhoid vaccines are mainly targeted against different structures. We studied whether these vaccines would enhance *S. Typhi*-specific immune response and cross-reactivity against other *Salmonellae*, if administered concomitantly. **MATERIALS AND METHODS:** Volunteers were immunized simultaneously with Ty21a and Vi vaccines (Ty21a+Vi group) or with either of the two singly (Ty21a and Vi groups). All volunteers were investigated for circulating specific and cross-reactive plasmablasts, identified by ELISPOT as IgA, IgG or IgM antibody-secreting cells (ASC) reactive with *S. Typhi*, *S. Paratyphi* A/B/C, or selected NTS serotypes (*S. Enteritidis*, *S. Typhimurium*). **RESULTS:** In the Ty21a+Vi group, no specific or cross-reactive plasmablasts were detected before vaccination. After vaccination, the number of *S. Typhi*-specific plasmablasts (878 ASC/10(6) PBMC, 95%CI 554-1201) proved higher than in the Ty21a (339 ASC/10(6) PBMC; $p<0.001$) and Vi (149 ASC/10(6) PBMC; $p<0.001$) groups. Likewise, cross-reactive responses in the Ty21a+Vi group were higher than in the Ty21a and Vi groups (Ty21a+Vi vs Ty21a: ASC against *S. Paratyphi* A/B, *S. Enteritidis* and *S. Typhimurium* $p<0.05$, against *S. Paratyphi* C $p<0.01$; Ty21a+Vi vs Vi: against *S. Paratyphi* C not significant, others $p<0.0001$). A gut-directed homing profile was seen among O antigen-specific and a systemic one among Vi antigen-specific plasmablasts. **CONCLUSIONS:** Concomitant administration of Ty21a and Vi vaccines is well tolerated and induces an additive immune response to the two vaccines. Thus it enhances the magnitude of both typhoid-specific plasmablast responses and those cross-reacting with paratyphoid and most important NTS serotypes. The data encourage concomitant use of Ty21 and Vi vaccines for those at risk.

Recent advances in the field of *Salmonella* Typhi vaccines.

Author Paterson GK, Maskell DJ.

Publication Hum Vaccin. 2010 May;6(5):379-84.

URL Not publically available

Typhoid fever, caused by the bacterium *Salmonella enterica* serovar Typhi, remains a significant cause of human death and disease throughout large areas of the world. Although there are currently three vaccines available against *S. Typhi* they have a number of significant drawbacks which drive the development of much-needed new and improved versions. Here recent advances towards such vaccines, from basic research to human trials, are discussed.



Predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia: a mathematical modeling study.

Author Pitzer VE, Bowles CC, Baker S, Kang G, Balaji V, Farrar JJ, Grenfell BT.

Publication PLoS Negl Trop Dis. 2014 Jan 9;8(1):e2642.

URL <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3886927/>

BACKGROUND: Modeling of the transmission dynamics of typhoid allows for an evaluation of the potential direct and indirect effects of vaccination; however, relevant typhoid models rooted in data have rarely been deployed. **METHODOLOGY/PRINCIPAL FINDINGS:** We developed a parsimonious age-structured model describing the natural history and immunity to typhoid infection. The model was fit to data on culture-confirmed cases of typhoid fever presenting to Christian Medical College hospital in Vellore, India from 2000-2012. The model was then used to evaluate the potential impact of school-based vaccination strategies using live oral, Vi-polysaccharide, and Vi-conjugate vaccines. The model was able to reproduce the incidence and age distribution of typhoid cases in Vellore. The basic reproductive number (R_0) of typhoid was estimated to be 2.8 in this setting. Vaccination was predicted to confer substantial indirect protection leading to a decrease in the incidence of typhoid in the short term, but (intuitively) typhoid incidence was predicted to rebound 5-15 years following a one-time campaign. **CONCLUSIONS/SIGNIFICANCE:** We found that model predictions for the overall and indirect effects of vaccination depend strongly on the role of chronic carriers in transmission. Carrier transmissibility was tentatively estimated to be low, consistent with recent studies, but was identified as a pivotal area for future research. It is unlikely that typhoid can be eliminated from endemic settings through vaccination alone.

Conjugate vaccines for enteric fever: proceedings of a meeting organized in New Delhi, India in 2009.

Author Podda A, Saul AJ, Arora R, Bhutta Z, Sinha A, Gaiind R, Singhal T, Saha S, Brooks A, Martin LB, Amdekar Y, Chitkara AJ, Shieh M, Kapur AN, Chugh TD.

Publication J Infect Dev Ctries. 2010 Jun 30;4(6):404-11.

URL <http://www.jidc.org/index.php/journal/article/view/20601795>

Enteric fever is responsible for significant morbidity in South Asia and high prevalence of severe disease is seen in children under two years of age. Effective typhoid vaccines are available, but they cannot be used for children under two years of age and also have some limitations in older age groups. Participants supported development of a *Salmonella* Typhi conjugate vaccine able to induce effective, long-lasting immunity in young children. The role of *Salmonella* Paratyphi A as a cause of enteric fever was discussed and consensus reached that a bivalent *S. Typhi*-*S. Paratyphi* A conjugate vaccine is highly desirable; however, considering disease epidemiology and the advanced status of vaccine development, rapid introduction of monovalent *S. Typhi* conjugate vaccine into vaccination programs of South Asia was recommended. Prevention should be emphasized, available vaccines used, and efforts toward improving sanitation continued. Success of the new vaccine will depend on several factors, including delivery costs and governmental ability to adopt and implement suitable immunization programs. To ensure good immunization coverage, the conjugate vaccine could be administered either to young infants, concomitantly with infant EPI vaccines, or to older infants, concomitantly with measles vaccine, currently given at 9 to 12 months. The need for new combination vaccines, containing both EPI and typhoid antigens, was discussed as a tool to increase coverage and reduce the number of injections and priority conflicts in a crowded infant vaccination schedule. However, stand-alone enteric fever conjugate



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vaccines would allow more flexibility to immunize different age groups and therefore should be rapidly developed.

Vaccination for typhoid fever in sub-Saharan Africa.

Author	Slayton RB, Date KA, Mintz ED.
Publication	Hum Vaccin Immunother. 2013 Apr;9(4):903-6. Comment in Hum Vaccin Immunother. 2013 Nov;9(11):2316.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3903911/pdf/hvi-9-903.pdf

Emerging data on the epidemiologic, clinical and microbiologic aspects of typhoid fever in sub-Saharan Africa call for new strategies and new resources to bring the regional epidemic under control. Areas with endemic disease at rates approaching those in south Asia have been identified; large, prolonged and severe outbreaks are occurring more frequently; and resistance to antimicrobial agents, including fluoroquinolones is increasing. Surveillance for typhoid fever is hampered by the lack of laboratory resources for rapid diagnosis, culture confirmation and antimicrobial susceptibility testing. Nonetheless, in 2010, typhoid fever was estimated to cause 725 incident cases and 7 deaths per 100,000 person years in sub-Saharan Africa. Efforts for prevention and outbreak control are challenged by limited access to safe drinking water and sanitation and by a lack of resources to initiate typhoid immunization. A comprehensive approach to typhoid fever prevention including laboratory and epidemiologic capacity building, investments in water, sanitation and hygiene and reconsideration of the role of currently available vaccines could significantly reduce the disease burden. Targeted vaccination using currently available typhoid vaccines should be considered as a short- to intermediate-term risk reduction strategy for high-risk groups across sub-Saharan Africa.

A cluster-randomized effectiveness trial of Vi typhoid vaccine in India.

Author	Sur D, Ochiai RL, Bhattacharya SK, Ganguly NK, Ali M, Manna B, Dutta S, Donner A, Kanungo S, Park JK, Puri MK, Kim DR, Dutta D, Bhaduri B, Acosta CJ, Clemens JD.
Publication	N Engl J Med. 2009 Jul 23;361(4):335-44. Comment in N Engl J Med. 2009 Nov 26;361(22):2191; author reply 2192-3. N Engl J Med. 2009 Jul 23;361(4):403-5. Natl Med J India. 2010 Mar-Apr;23(2):90-1. N Engl J Med. 2009 Nov 26;361(22):2191-2; author reply 2192-3.
URL	http://www.nejm.org/doi/full/10.1056/NEJMoa0807521

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



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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.

Live attenuated vaccines for invasive Salmonella infections.

Author	Tennant SM, Levine MM.
Publication	Vaccine. 2015 Jun 19;33 Suppl 3:C36-41.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4469493/pdf/nihms682459.pdf

Salmonella enterica serovar Typhi produces significant morbidity and mortality worldwide despite the fact that there are licensed *Salmonella* Typhi vaccines available. This is primarily due to the fact that these vaccines are not used in the countries that most need them. There is growing recognition that an effective invasive *Salmonella* vaccine formulation must also prevent infection due to other *Salmonella* serovars. We anticipate that a multivalent vaccine that targets the following serovars will be needed to control invasive *Salmonella* infections worldwide: *Salmonella* Typhi, *Salmonella* Paratyphi A, *Salmonella* Paratyphi B (currently uncommon but may become dominant again), *Salmonella* Typhimurium, *Salmonella* Enteritidis and *Salmonella* Choleraesuis (as well as other Group C *Salmonella*). Live attenuated vaccines are an attractive vaccine formulation for use in developing as well as developed countries. Here, we describe the methods of attenuation that have been used to date to create live attenuated *Salmonella* vaccines and provide an update on the progress that has been made on these vaccines.

Oral Wild-Type Salmonella Typhi Challenge Induces Activation of Circulating Monocytes and Dendritic Cells in Individuals Who Develop Typhoid Disease.

Author	Toapanta FR, Bernal PJ, Fresnay S, Darton TC, Jones C, Waddington CS, Blohmke CJ, Dougan G, Angus B, Levine MM, Pollard AJ, Szein MB.
Publication	PLoS Negl Trop Dis. 2015 Jun 11;9(6):e0003837.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4465829/

A new human oral challenge model with wild-type *Salmonella* Typhi (*S. Typhi*) was recently developed. In this model, ingestion of 104 CFU of *Salmonella* resulted in 65% of subjects developing typhoid fever (referred here as typhoid diagnosis -TD-) 5-10 days post-challenge. TD criteria included meeting clinical (oral temperature $\geq 38^{\circ}\text{C}$ for ≥ 12 h) and/or microbiological (*S. Typhi* bacteremia) endpoints. One of the first lines of defense against pathogens are the cells of the innate immune system (e.g., monocytes, dendritic cells -DCs-). Various changes in circulating monocytes and DCs have been described in the murine *S. Typhimurium* model; however, whether similar changes are present in humans remains to be explored. To address these questions, a subset of volunteers (5 TD and 3 who did not develop typhoid despite oral challenge -NoTD-) were evaluated for changes in circulating monocytes and DCs. Expression of CD38 and CD40 were upregulated in monocytes and DCs in TD volunteers during the disease days (TD-0h to TD-96h). Moreover, integrin $\alpha 4\beta 7$, a gut homing molecule, was upregulated on monocytes but



not DCs. CD21 upregulation was only identified in DCs. These changes were not observed among NoTD volunteers despite the same oral challenge. Moreover, monocytes and DCs from NoTD volunteers showed increased binding to *S. Typhi* one day after challenge. These monocytes showed phosphorylation of p38MAPK, NFkB and Erk1/2 upon stimulation with *S. Typhi*-LPS-QDot micelles. In contrast, monocytes from TD volunteers showed only a moderate increase in *S. Typhi* binding 48 h and 96 h post-TD, and only Erk1/2 phosphorylation. This is the first study to describe different activation and migration profiles, as well as differential signaling patterns, in monocytes and DCs which relate directly to the clinical outcome following oral challenge with wild type *S. Typhi*.

A randomised trial evaluating the safety and immunogenicity of the novel single oral dose typhoid vaccine M01ZH09 in healthy Vietnamese children.

Author	Tran TH, Nguyen TD, Nguyen TT, Ninh TT, Tran NB, Nguyen VM, Tran TT, Cao TT, Pham VM, Nguyen TC, Tran TD, Pham VT, To SD, Campbell JI, Stockwell E, Schultz C, Simmons CP, Glover C, Lam W, Marques F, May JP, Upton A, Budhram R, Dougan G, Farrar J, Nguyen VV, Dolecek C.
Publication	PLoS One. 2010 Jul 26;5(7):e11778.
URL	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC20668668/

BACKGROUND: The emergence of drug resistant typhoid fever is a major public health problem, especially in Asia. An oral single dose typhoid vaccine would have major advantages. M01ZH09 is a live oral single dose candidate typhoid vaccine containing *Salmonella enterica* serovar Typhi (Ty2 aroC(-)ssaV(-)) ZH9 with two independently attenuating deletions. Studies in healthy adults demonstrated immunogenicity and an acceptable safety profile. **OBJECTIVES:** We conducted a randomised placebo controlled, single-blind trial to evaluate the safety and immunogenicity of M01ZH09 in healthy Vietnamese children aged 5 to 14 years. **METHODS:** Subjects were randomly assigned to receive either a nominal dose of 5×10^9 CFU of M01ZH09 or placebo and were followed up for 28 days. The primary safety outcome was the proportion of subjects with any adverse event attributed to M01ZH09. The primary immunogenicity endpoint was the proportion of subjects who showed a positive immune response to M01ZH09 in the *Salmonella* Typhi lipopolysaccharide (LPS) specific serum IgA and IgG ELISA. **PRINCIPAL FINDINGS:** One hundred and fifty-one children were enrolled, 101 subjects received M01ZH09 and 50 subjects received placebo. An intention to treat analysis was conducted. There were no serious adverse events and no bacteraemias. In the M01ZH09 group, 26 (26%; 95% CI, 18-5%) of 101 subjects experienced adverse events compared to 11 (22%; 95% CI, 12-36%) of 50 subjects in the placebo group (odds ratio (OR) [95%CI] = 1.23 [0.550-2.747]; $p = 0.691$). Faecal shedding of *S. Typhi* (Ty2 aroC(-)ssaV(-)) ZH9 was detected in 51 (51%; 95% CI, 41-61%) of 100 M01ZH09 subjects. No shedding was detected beyond day 3. A positive immune response, defined as 70% increase (1.7 fold change) in LPS specific serum IgG (day 14 or 28) and/or 50% increase (1.5 fold change) in LPS specific serum IgA (day 7 or 14) from baseline was detected in 98 (97%; 95% CI, 92-99%) of 101 M01ZH09 recipients and 8 (16%; 95% CI, 7-29%) of 50 placebo recipients. Twenty-eight (100%; 95% CI, 88-100%) of 28 vaccine recipients who were evaluated in the LPS specific IgA ELISPOT assay showed a positive response compared to none of the 14 placebo recipients tested. **CONCLUSIONS:** This was the first phase II trial of a novel oral candidate typhoid vaccine in children in an endemic country. M01ZH09 had an appropriate safety profile and was immunogenic in children.



Safety, immunogenicity and dose ranging of a new Vi-CRM₁₉₇ conjugate vaccine against typhoid fever: randomized clinical testing in healthy adults.

Author	van Damme P(1), Kafeja F, Anemona A, Basile V, Hilbert AK, De Coster I, Rondini S, Micoli F, Qasim Khan RM, Marchetti E, Di Cioccio V, Saul A, Martin LB, Podda A.
Publication	PLoS One. 2011;6(9):e25398.
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3184126/

BACKGROUND: Typhoid fever causes more than 21 million cases of disease and 200,000 deaths yearly worldwide, with more than 90% of the disease burden being reported from Asia. Epidemiological data show high disease incidence in young children and suggest that immunization programs should target children below two years of age: this is not possible with available vaccines. The Novartis Vaccines Institute for Global Health developed a conjugate vaccine (Vi-CRM₁₉₇) for infant vaccination concomitantly with EPI vaccines, either starting at 6 weeks with DTP or at 9 months with measles vaccine. We report the results from a Phase 1 and a Phase 2 dose ranging trial with Vi-CRM₁₉₇ in European adults. **METHODOLOGY:** Following randomized blinded comparison of single vaccination with either Vi-CRM₁₉₇ or licensed polysaccharide vaccines (both containing 25.0 µg of Vi antigen), a randomised observer blinded dose ranging trial was performed in the same center to compare three concentrations of Vi-CRM₁₉₇ (1.25 µg, 5.0 µg and 12.5 µg of Vi antigen) with the polysaccharide vaccine. **PRINCIPAL FINDINGS:** All vaccines were well tolerated. Compared to the polysaccharide vaccine, Vi-CRM₁₉₇ induced a higher incidence of mild to moderate short lasting local pain. All Vi-CRM₁₉₇ formulations induced higher Vi antibody levels compared to licensed control, with clear dose response relationship. **CONCLUSIONS:** Vi-CRM₁₉₇ did not elicit safety concerns, was highly immunogenic and is therefore suitable for further clinical testing in endemic populations of South Asia.

Typhoid fever.

Author	Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL.
Publication	Lancet. 2015 Mar 21;385(9973):1136-45.
URL	Not publically available
Additional Categories	Epidemiological patterns and global burden of typhoid fever Disease and environmental surveillance Trends in antibiotic resistance of Salmonella Typhi

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.



Revaccination with locally-produced vi typhoid polysaccharide vaccine among chinese school-aged children: safety and immunogenicity findings.

Author	Zhou WZ, Koo HW, Wang XY, Zhang J, Park JK, Zhu F, Deen J, Acosta CJ, Chen Y, Wang H, Galindo CM, Ochiai L, Park T, von Seidlein L, Xu ZY, Clemens JD.
Publication	Pediatr Infect Dis J. 2007 Nov;26(11):1001-5.
URL	Not publically available

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 mg 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.

