the burden of Typhoid fever (*Salmonella enterica* serovar Typhi (TF)) and invasive non-typhoidal *Salmonella* (iNTS). In this secondary analysis, incidences from in infants, stratified by age and region were calculated. A total of 30.1% (37/123) TF infections and 78.9% (71/90) iNTS infections were observed in children aged <5 years. No TF and 8.9% (8/90) iNTS infections were identified in infants <9 months of age. The annual TF incidence calculated for children aged <1 and 1 to <2 years was 5 and 39 per 100,000 person-years of observation (PYO), respectively, with the highest incidence of 304/100,000 PYO observed in children aged 4 to <5 years. The annual iNTS disease incidence for the same age groups were 81, 233, and 46.2 per 100,000 PYO. Geographically, higher incidences of both TF and iNTS disease infections were observed in West African TSAP sites. The cumulative incidence of typhoid in those aged <5 years was 279/100,000 in West Africa, compared to 154/100,000 in East Africa. The iNTS incidences in individuals aged <5 years were 828/100,000 and 48/100,000 in West and East Africa, respectively. A high TF burden in children <5 years of age supports the introduction of TCV in infants at nine months of age in Africa; for iNTS disease younger age-groups should be targeted. In the future, additional vaccines to comprehensively address the burden of invasive *Salmonella* infections observed in children will potentially be required.

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INCREASING ANTIBIOTIC RESISTANCE IN *SALMONELLA ENTERICA* AND *SHIGELLA* SPP. ISOLATES FROM CHILDREN UNDER-FIVE IN WESTERN KENYA, 1997-2010: INSIGHTS INTO SOURCES OF SELECTION PRESSURE FROM SURVEILLANCE IN A LOW-INCOME, RURAL SETTING

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While antibiotic resistance (AR) is a threat to public health throughout the world, longitudinal population-level AR surveillance is limited, especially in low-income settings with high burdens of enteric infections. Since 1997, the Centers for Disease Control and Prevention has collaborated with the Kenya Medical Research Institute to conduct antimicrobial susceptibility testing on 331 *Shigella* spp. and 369 non-typhoidal *Salmonella enterica* isolates from children &lt 5 years old presenting with diarrhea to sentinel clinics in rural, western Kenya. In this population from 1997-2010, we observed high *Shigella* spp. resistance to amoxicillin-clavulanic acid (AMC, 42% of isolates), ampicillin (AMP, 68%), chloramphenicol (CHL, 49%), streptomycin (STR, 91%), sulfisoxazole (SULF, 96%), sulfamethoxazole-trimethoprim (SXT, 97%), and tetracycline (TET, 88%). *S. flexneri*, was most commonly isolated (200/331), and had greater odds of AR than other *Shigella* species. For *Salmonella enterica*, resistance to AMC (32%), AMP (66%), CHL (53%), STR (67%), SULF (84%), and SXT (67%) was high. Serogroup B *Salmonella enterica* was most commonly isolated (236/369), followed by serogroup D (57/369). Both had comparatively higher odds of AR than other serogroups detected. Odds of SXT resistance in isolates of both pathogens increased with the child's age, and increased significantly over the 13-year period. *Salmonella enterica* resistance to CHL, STR, and SULF also increased significantly during this time. Despite prevalent *Salmonella enterica* and *Shigella* spp. infections resistant to AMP or SXT, patients with these infections were given AMP (or related drugs) 16% and SXT 17% of the time. Overall, despite high initial levels of resistance in 1997, population-level resistance to core drugs (such as SXT) increased over the 13-year period, especially among the most prevalent species/serogroups of *Shigella* and *Salmonella enterica* isolated from young children in a rural, low-income setting. These results highlight the potential for sustained increases in AR driven by antibiotic selection pressures in high-burden settings.

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SPATIAL AND GENOMIC DATA TO IDENTIFY TRANSMISSION ROUTES OF TYPHOID FEVER IN BLANTYRE, MALAWI

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Queen Elizabeth Hospital (QECH) in Blantyre, Malawi, experienced a sharp increase in cases of typhoid fever starting in 2011, the majority being multi-drug resistant. Despite ongoing transmission today, the dominant mechanisms of persistence remain unknown, posing a challenge for effective control interventions. Spatial patterns of genetic relatedness of clinically isolated *Salmonella* Typhi may offer insight into the mechanisms of transmission occurring, and we aimed to quantify and understand these trends in Blantyre. Beginning in 2015, *S.* Typhi isolated from cases presenting to QECH were whole-genome sequenced, and households were geo-located. Variable regions of the sequences (i.e. highly recombinant and prophage regions) were excluded, leaving 400 informative single nucleotide polymorphisms (SNPs) across isolates. Resulting pairwise SNP distances were converted into informative variables for statistical modeling using multidimensional scaling. Genetic patterns of *S.* Typhi isolates across Blantyre showed a heterogenous distribution of genotypes, with spatial correlation occurring among isolates of cases living up to 2 kilometers apart. Risk factor analyses have previously identified cooking and cleaning with river water as a potential exposure pathway for S. Typhi in Blantyre, so we then evaluated the ability of river catchment to explain the spatial patterns using a linear model with a spatial random effect, implemented in R statistical software. Results from the analysis indicate that the spatial genetic patterns seen across the city are influenced by three primary components: river catchment, close neighbors (living a maximum of 200 meters apart), and household units. Results from this study highlight the value of genomics in better understanding the complex transmission mechanisms of typhoid fever, and support control approaches targeting multiple scales of transmission, such as pairing vaccines with targeted water and sanitation interventions.

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COST-EFFECTIVENESS OF TYPHOID CONJUGATE VACCINE STRATEGIES IN 54 GAVI-ELIGIBLE COUNTRIES

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The World Health Organization recently recommended the programmatic use of typhoid conjugate vaccine (TCV) in endemic countries, and Gavi has pledged support for vaccine introduction. While TCV strategies are likely cost-effective in medium- to high-incidence settings, country-specific evaluations are warranted. We compared four strategies: no vaccination; routine immunisation at 9 months; or routine immunisation at 9 months with catch-up campaigns to either age 5 or 15 years. For each of 54 Gavi-eligible countries, output from an age-structured transmission dynamic model was combined with country-specific treatment and vaccine-related costs, treatment outcomes, and disability weights to estimate disability-adjusted life-years (DALYs) to identify: (1) the preferred strategy, based on the highest average net benefit for a range of willingness-to-pay

(WTP) values; (2) how certain we are about the preferred strategy; and (3) the minimum economic and epidemiological conditions under which vaccination is preferred. At a vaccine price of US$1.50 per dose and a WTP value of US$1,000 per DALY averted, routine vaccination including a catch-up campaign to 15 years of age is the preferred strategy in 46 countries. However, for half of these countries, the probability that this strategy results in the highest net benefit is <60%. Vaccination is increasingly likely to be preferred at higher rates of typhoid incidence and mortality, and at higher WTP values. While routine TCV immunisation with a catch-up campaign is preferred over no vaccination in most Gavi-eligible countries, investing in obtaining improved estimates of typhoid age-specific incidence and mortality may be valuable for many countries.

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ADVERSE EVENTS FOLLOWING IMMUNIZATION WITH TYPHOID CONJUGATE VACCINE: MASS IMMUNIZATION AGAINST CEFTRIAXONE RESISTANCE TYPHOID FEVER IN HYDERABAD, PAKISTAN

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Pakistan is facing the largest outbreak of extensive drug resistant typhoid. The outbreak started from Hyderabad and predominantly affected children less than 10 years of age. The Aga Khan University in collaboration with department of health, Government of Sindh, procured the WHO pre-qualified Typhoid conjugate vaccine (TCV), to initiate a mass immunization campaign in Hyderabad as a response to the outbreak. Door to door immunization of children 6months to 5 years of age was started in January 2018. In order to ascertain the adverse events following immunization (AEFI), a subset of children was actively followed on day 7 and 14 following the vaccination. Information about any illness, disability, hospitalization or death was collected by trained staff through a standard AEFI form translated in local language. In case of hospitalization or visit to a general physician, information on admissions, discharge, and prescriptions were obtained. Caretakers of all the vaccinees were also provided 24hrs emergency contact number to report any illness. A total of 4070 vaccinated children; 655 aged 6-12months, 851 aged 1-2 yrs, 911 aged 2-3, 836 aged 3-4 and 823 aged 4-5 yrs were actively followed and only 21, 13, 24, 16 and 22 children respectively in each of the age groups had some kind of AEFI. All of the AEFIs identified actively were mild in nature; 69/4076(1.7%) fever, 15(0.4%) diarrhea, 5(0.1%) vomiting, 3(0.07%) abdominal pain, 2(0.05%) chest infection, cough and swelling on injection site was 1(0.02%) each. Besides, out of total 32,215 doses administered there were 09(0.03%) of AEFI observed either immediately within 30 minutes of vaccination or passively reported through emergency contact number. 4/32215(0.01%) developed high grade fever, 2(0.006%) developed a rash on the whole body and severe vomiting, seizure, and swelling at the injection site were 1(0.003%) each. Typbar-TCV vaccine was found to be safe for administering in emergency situation during mass immunization campaign in Hyderabad city of Pakistan. Mild fever and diarrhea are the most frequent AEFIs. Seizure is extremely rare (1 in 32000 doses).

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ASSESSMENT OF IMMUNE AVIDITY TO DETERMINE THE COURSE OF DISEASE IN ACUTE AND CHRONIC STATE OF NATURAL *SALMONELLA TYPHI* INFECTION

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An assessment of the duration of immune response to natural typhoid (TF) infection was performed as a part of Severe Typhoid in Africa (SETA) study. Immune avidity assay was used for testing serum samples of acute cases and asymptomatic controls during one year follow-up. The avidity assay is based on Vi-ELISA assay, involving antigen-antibody binding in the presence of chaotropic agent (Gu HCl). Antigen-antibody complexes present in serum of chronic infection bind strongly to Vi antigen and dissociate weakly in presence of chaotropic agent, whereas in recent infection cases, antibodies dissociate easily. This assay will help identify carriers during follow-up visits and, thus, reduce risk of unrecognized TF transmission. The Vi-avidity assay was established and internally qualified. Using avidity assay we tested serum samples from febrile cases from Ghana sites of West Africa for Vi IgG and IgM ELISA & avidity. Addition to febrile cases we also tested neighborhood healthy controls, healthy household contacts. Initial data suggests all blood culture positive and several negative samples having high anti Vi-IgM titers and anti Vi-IgG titers of >100 ELISA units. High titers were also detected in healthy neighborhood controls and house hold contacts. Interestingly many of this subjects with high Vi- antibody titers also have high antibody avidity suggesting probability of repeat infection or persistent chronic state. Samples with high IgG avidity (80-100 avidity index) may be consider as repeat infection. Samples with high IgM avidity (80-100 avidity index) may be consider as recent infection with repeat exposure. Sample with both high IgG and IgM avidity may be consider as chronic state with persistence of *S typhi*. The avidity cut off estimates were done on basis of other reports on pneumococcal and cholera natural infection studies. Further additional analysis are needed to better understand the cutoffs. Bactericidal antibodies were also tested in blood culture positive patients. High bactericidal antibody titers were detected in this subjects, suggesting antibodies generated by natural infection have functional role in killing *S typhi*.

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UNPRECEDENTED PNEUMONIC PLAGUE EPIDEMIC IN MADAGASCAR, 2017: CAN WE MAKE PLAGUE HISTORY?

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Yersinia pestis continues to threaten the Malagasy population with around 300 reported cases/year during September - April. In 2017, Madagascar experienced a large epidemic of Pneumonic Plague (PP). We present the epidemiological analyses of plague cases based on the official national database from the Central Laboratory for Plague (CLP, a WHO Collaborating Center) at the Institut Pasteur de Madagascar (IPM), which combined case notification forms with results from biological analyses. Cases were classified as confirmed/probable based on positive culture and/or positive qPCR (*pla, caf* 1 and *inv* genes) and/or positive rapid diagnostic tests (RDT, locally-produced by IPM) performed by the CLP. On September 11, successive deaths of unknown cause triggered an alert in a plague-free area. Plague was diagnosed by RDT in one deceased case in Antananarivo (the capital city). Subsequent investigation led to identification of 5 unnoticed suspected plague deaths that occurred during the 2 weeks before the alert, including the index case. The risk of geographic extension of the PP epidemic triggered a national and international response. Between August 1 and November 26, 2,414 clinically-suspected plague cases were reported, of which 1,878 (78%) were PP cases and 395 (16%) were Bubonic Plague (BP). Confirmed/probable cases represented 22% (418/1,878) of PP and 35% (139/395) of BP cases. Confirmed/probable cases were reported from 41/114 (36%) administrative districts. PP hotspots were mainly identified in Antananarivo and Toamasina, the main seaport. The case fatality rate was 13% for confirmed/probable and 8% for suspected cases. Rapid confirmation of cases and identification of contacts was difficult due to the urban and highly populated setting