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Cost-Effectiveness Analyses of Typhoid Interventions in Epidemic and Endemic Settings

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Abstract

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Background: Typhoid fever is a major source of morbidity and mortality in developing countries, accounting for approximately 12-21 million infections, 119,000-269,000 deaths, and 2-23 million disability-adjusted life years (DALYs) annually. Typhoid fever is caused by infection with the bacteria *Salmonella enterica* serovar Typhi, which is mainly transmitted through fecal contamination of food or water. Due to these modes of transmission, most cases occur in low- and middle-income countries (LMICs) where sanitary conditions are poor and access to clean water and sanitation is not common. However, the scale of disease incidence is uncertain. Studies suggest that facility-based laboratory-confirmed estimates, the numbers used for reporting and decision-making, are considerably lower than the actual numbers. As a result, typhoid likely has an even higher global burden than is reported.

While typhoid remains a major cause of morbidity and mortality, it is preventable. Interventions against typhoid exist, with varying degrees of efficacy and costs. Investments in water and sewer systems in the early 20th century are thought to have been responsible for the decline of typhoid in many developed countries; however, no economic evaluations have quantified the costs and impact of improvements in sanitation. Additionally, a typhoid conjugate vaccine (TCV) has been approved, but research regarding its long-term efficacy and use in outbreak settings is limited. Cost-effectiveness evaluations of TCVs recommend their use in endemic settings, but modelling suggests that vaccination alone will not eliminate disease.

Methods & Results: Before we can evaluate the impact of interventions, we need accurate estimates of baseline disease incidence. Therefore, in Chapter 1, we developed a Bayesian framework to combine multiple data sources to estimate the population-based typhoid incidence based on passive surveillance data from Blantyre, Malawi; Kathmandu, Nepal; and Dhaka, Bangladesh. The ratio of observed to adjusted incidence rates was 7.7 (95% credible interval (CrI): 6.0-12.4) in Malawi, 14.4 (95% CrI: 9.3-24.9) in Nepal, and 7.0 (95% CrI: 5.6-9.2) in Bangladesh. Adjusted incidence rates were within or below the seroincidence rate limits of typhoid infection. Estimates of blood-culture-confirmed typhoid fever without these adjustments results in considerable underestimation of the true incidence of typhoid fever.

In Chapter 2, we evaluated the cost-effectiveness of typhoid conjugate vaccine use in response to outbreaks of typhoid fever. We fit a modified version of an existing dynamic compartmental model of typhoid fever to Malawi outbreak data and evaluated preventive and reactive vaccination strategies. We then conducted a cost-effectiveness analysis using the net-benefits framework to compare no vaccination to routine vaccination at 9 months of age with and without a catch-up campaign up to 15 years old. We examined variations in outbreak definitions, delays in implementation of reactive vaccination, and the timing of preventive vaccination relative to the outbreak. We estimated that vaccination would prevent 15-60% of disability-adjusted life-years (DALYs) in the outbreak scenarios. Some form of routine vaccination with a catch-up campaign was preferred over no vaccination for willingness-to-pay (WTP) values of at least $110 per DALY averted. Countries where outbreaks of typhoid fever due to introduction of antimicrobial resistant strains are likely to occur should consider TCV introduction. Reactive vaccination can be a cost-effective strategy, but only if delays in vaccine deployment are

minimal; otherwise, introduction of preventive routine immunization with a catch-up campaign should be considered.

Lastly, in Chapter 3, we quantified the relationship between investments in water and sanitation infrastructure and long-term typhoid transmission rates using historical data from 16 U.S. cities. We fit two models for each city: (1) we modified a Time-series Susceptible-Infectious-Recovered (TSIR) model and extracted long-term transmission rates, and (2) we measured the association between the transmission rates and financial variables using hierarchical regression models. Overall historical $1 per capita ($16.13 in 2017) investments in the water supply were associated with approximately 5% (95% confidence interval: 3-6%) decreases in typhoid transmission, while $1 increases in the overall sewer system investments were associated with estimated 6% (95% confidence interval: 4-9%) decreases.

Conclusions: A combination of statistical and mathematical modeling permits us to evaluate the cost-effectiveness of typhoid interventions across settings. We are able to estimate the true population-based incidence of typhoid fever in Africa and Asia, weigh the costs and effects of vaccination strategies in an outbreak setting, and estimate the impact of water and sanitation investments in an endemic setting. These findings can help to inform decision-making regarding typhoid control and prevention. The results can play an essential role in making the case for improvements in water and sanitation and/or vaccination to reduce the global burden of typhoid fever.

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Introduction

The importance of accurate estimates of population-level typhoid fever incidence

Typhoid fever is a major source of morbidity and mortality in developing countries. Approximately 12-21 million infections and 119,000-269,000 deaths are attributed to typhoid each year [1, 2], accounting for 2-23 million disability-adjusted life years (DALYs) [3]. Most cases occur in Asia and Africa, predominantly among children [4].

Humans are the only hosts for the bacteria *Salmonella enterica* serovar Typhi [5], which causes typhoid fever. Once ingested through feces-contaminated food or water, *S.* Typhi has an incubation period of 7-14 days. Bacteria enter the gut mucosa, replicate, and travel to the liver, spleen, and gallbladder before entering the bloodstream, marking the onset of clinical symptoms [5]. Symptomatic cases generally present with fever, abdominal pain, malaise, and headache [6]. Symptoms can last 4-6 weeks if untreated. Following recovery from symptomatic illness, an estimated 1-5% of hosts become long-term carriers [5].

Decisions for typhoid control are often based on crude estimates of incidence. These estimates depend on facility-based laboratory-confirmed cases, which are likely substantial underestimates of the actual incidence. Limits of using facility-based estimates alone—lack of specific clinical diagnostic criteria, poorly sensitive diagnostic tests, and scarcity of data—contribute to difficulties in calculating population-level incidence of typhoid.

Studies estimate that 60-90% of individuals with typhoid do not receive medical attention, likely because they either do not seek treatment, or they seek help through less traditional avenues[4, 7]. Even if a person seeks care, typhoid fever is often confused with other febrile illnesses [8]. Symptoms of typhoid, particularly fever onset, are also the main symptoms of other common diseases [8]. Furthermore, not all patients have a blood culture test performed,

usually because parents sometimes do not want their sick child to have blood drawn, or people are turned away due to lack of supplies or healthcare personnel [9]. Suboptimal diagnostic tests further contribute to underestimation of disease incidence. Blood culture is the mainstay of typhoid diagnosis and is highly specific, but its sensitivity ranges from 0.51-0.65 [10].

Modeling is needed to estimate the true incidence of typhoid fever in order to establish the baseline disease burden against which to evaluate the need for potential interventions. Models must take into account the cases lost at each step of the reporting process to be accurate.

Complications with treatment and antimicrobial resistance

Typhoid can be effectively treated with antibiotics, given correct diagnosis and strain susceptibility [6]. However, due to the widespread availability of antimicrobials without a prescription in many parts of the world, antimicrobial resistance has been increasing in recent years [11-14]. The first reports of emerged before 1970, leading to outbreaks and resulting in the need for alternative treatments [15-17]. Resistance to ampicillin and trimethoprim-sulfamethoxazole soon followed, such that multi-drug-resistant (MDR) strains (defined as resistance to all three antimicrobials) now pose a threat to typhoid control [18-20]. More recently, extensively drug-resistant (XDR) *S.* Typhi, which also exhibits non-susceptibility to fluoroquinolones and resistance to third-generation cephalosporins, were reported in 2017 in a large typhoid outbreak Pakistan [21-23]. Increasing rates of MDR and XDR have led to clinical treatment failures, the need for more expensive treatments, and a rise in complications and hospital admissions [11]. Alternative interventions are needed to reduce antibiotic use and limit the threat of MDR and XDR *S.* Typhi [11, 24, 25].

The existence of effective typhoid fever control interventions

In many developed countries, typhoid incidence declined drastically in the early 20th century such that occurrences of the disease are now rare. This decline has been attributed to investments in water and sanitation, though the relationship has not been fully characterized. Prior studies estimate that investments in clean water technologies reduced typhoid mortality by 25% and overall mortality by half in the early 20th century [26, 27]; however, these estimates do not take into account the disease transmission process.

In 2018, the World Health Organization (WHO) recommended programmatic use of typhoid conjugate vaccines (TCV) in addition to other interventions in settings with high rates of typhoid [6]. In endemic settings, studies suggest that the most cost-effective strategy is either no vaccination or routine vaccination plus catchup campaigns, depending on the typhoid incidence rate [28, 29].

The WHO also recommends the use of TCV in outbreak settings [6]. However, current data are limited on how and when it might be introduced, and vaccine stockpiles do not yet exist [11, 30]. While reactive vaccination can be effective, if implemented late or focused inappropriately, the number of cases averted will be small [31-33]. To ensure that the appropriate vaccine stockpiles, accurate estimates of disease incidence and knowledge of vaccine coverage requirements are also necessary.

Research comparing typhoid interventions in endemic and epidemic settings is limited. With recent WHO recommendations for TCV use and pilot studies assessing efficacy and impact underway [6, 34], governments are looking to prioritize the allocation of resources to prevent typhoid. With recent typhoid epidemics across Africa [35-39] and high burdens in endemic countries, studies are needed to compare prevention strategies across different settings, including

the use of TCV in response to outbreaks and in comparison to water and sanitation investments. Typhoid control can be expensive; cost-effectiveness analyses are needed to inform decisions for the optimal allocation of funding.

References

1. Antillon M, Warren J, Crawford F, Weinberger D, Kurum E, Pitzer V. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis. 2017;11(2). doi: 10.1371/journal.pntd.0005376.
2. Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. The Lancet. 2014;2(10):e570-80. doi: 10.1016/S2214-109X(14)70301-8.
3. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle2017. Available from: http://ghdx.healthdata.org/gbd-results-tool.
4. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid Fever. New England Journal of Medicine. 2002;347:1770-82. doi: 10.1056/NEJMra020201.
5. Bahn MB, R. Bhatnagar, S. Typhoid and paratyphoid fever. Lancet (London, England). 2005;366(9487):749-62. doi: 10.1016/S0140-6736(05)67181-4.
6. World Health Organization (WHO). Typhoid vaccines position paper. Weekly epidemiological record. 2018;13(93):153–72.
7. Panzner U, Pak GD, Aaby P, Adu-Sarkodie Y, Ali M, Aseffa A, et al. Utilization of Healthcare in the Typhoid Fever Surveillance in Africa Program. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;62:S56-68. doi: 10.1093/cid/civ891. PubMed PMID: 26933023.
8. Crump J, Youssef F, Luby S, Wasfy M, Rangel J, Taalat M. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. Emerging Infectious Diseases. 2003;9(5):539–44. doi: 10.3201/eid0905.020428.
9. Meiring J. Reasons for not having a blood culture taken. In: Phillips M, editor. 2018.
10. Antillon M, Saad NJ, Baker S, Pollard AJ, Pitzer VE. The Relationship Between Blood Sample Volume and Diagnostic Sensitivity of Blood Culture for Typhoid and Paratyphoid Fever: A Systematic Review and Meta-Analysis. The Journal of Infectious Diseases. 2018:jiy471. doi: 10.1093/infdis/jiy471.
11. World Health Organization. Typhoid vaccines: WHO position paper, March 2018 – Recommendations. Vaccine. 2019;37(2).
12. Shankar PR. Medicines use in primary care in developing and transitional countries: fact book summarizing results from studies reported between 1990 and 2006. Bulletin of the World Health Organization. 2009;87(10):804. doi: 10.2471/09-070417.doc. PubMed Central PMCID: PMC2755322.
13. Holloway KA, Kotwani A, Batmanabane G, Puri M, Tisocki K. Antibiotic use in South East Asia and policies to promote appropriate use: reports from country situational analyses. BMJ. 2017;358. doi: 10.1136/bmj.j2291. PubMed PMID: 28874360.
14. Nepal G, Bhatta S. Self-medication with Antibiotics in WHO Southeast Asian Region: A Systematic Review. Cureus. 10(4). doi: 10.7759/cureus.2428. PubMed PMID: 29876150; PubMed Central PMCID: PMC5988199.
15. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. Clin Microbiol Rev. 2015;28(4):901-37. doi: 10.1128/cmr.00002-15. PubMed PMID: 26180063.
16. Colquhoun J, Weetch R. Resistance to chloramphenicol developing during treatment of typhoid fever. The Lancet. 1950;256(6639):621-3. doi: 10.1016/S0140-6736(50)91585-6.
17. Murti BR, Rajyalakshmi K, Bhaskaran CS. Resistance of Salmonella typhi to chloramphenicol : Part I A preliminary report. J Clin Pathol. 1962;15(6):544-8. doi: 10.1136/jcp.15.6.544. PubMed PMID: 13936803; PubMed Central PMCID: PMC480455.
18. Zaki SA, Karande S. Multidrug-resistant typhoid fever: a review. Journal of infection in developing countries. 2011;5(5):324-37. Epub 2011/06/02. doi: 10.3855/jidc.1405. PubMed PMID: 21628808.
19. Rowe B, Ward L, Threlfall E. Treatment of multiresistant typhoid fever. The Lancet. 1991;337(8754):1422. doi: 10.1016/0140-6736(91)93116-Q. PubMed PMID: 1674805.
20. Mirza SH, Beechmg NJ, Hart CA. Multi-drug resistant typhoid: a global problem. 1996;44(5):317-9. doi: 10.1099/00222615-44-5-317.
21. Chatham-Stephens K, Medalla F, Hughes M, Appiah G, Aubert R, Caidi H, et al. Emergence of Extensively Drug-Resistant Salmonella Typhi Infections Among Travelers to or from Pakistan — United States, 2016–2018 | MMWR. Morbidity and Mortality Weekly Report. 2019;68(1):11-3.

22. Andrews JR, Qamar FN, Charles RC, Ryan ET. Extensively Drug-Resistant Typhoid — Are Conjugate Vaccines Arriving Just in Time? New England Journal of Medicine. 2018;379:1493-5. doi: 10.1056/NEJMp1803926.
23. Centers for Disease Control and Prevention. Drug-Resistant Salmonella Serotype Typhi Fact Sheet 2019. Available from: https://www.cdc.gov/drugresistance/pdf/threats-report/salmonella-typhi-508.pdf.
24. Andrews JR, Baker S, Marks F, Alsan M, Garrett D, Gellin BG, et al. Typhoid conjugate vaccines: a new tool in the fight against antimicrobial resistance. Lancet Infectious Diseases. 2019;19(1):e26-e30. doi: 10.1016/S1473-3099(18)30350-5.
25. Kaufhold S, Yaesoubi R, Pitzer VE. Predicting the Impact of Typhoid Conjugate Vaccines on Antimicrobial Resistance. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019;68(Suppl 2):S96-S104. doi: 10.1093/cid/ciy1108. PubMed PMID: 30845324.
26. Cutler D, Miller G. The role of public health improvements in health advances: The twentieth-century United States. Demography. 2005;42(1):1-22. doi: 10.1353/dem.2005.0002.
27. Esrey SA, Feachem RG, Hughes JM. Interventions for the control of diarrhoeal diseases among young children: improving water supplies and excreta disposal facilities. Bulletin of the World Health Organization. 1985;63(4):757-72. Epub 1985/01/01. PubMed PMID: 3878742; PubMed Central PMCID: PMCPMC2536385.
28. Antillon M, Bilcke J, Paltiel AD, Pitzer VE. Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low- and middle-income settings. Vaccine. 2017;35(27):3506-14. Epub 2017/05/22. doi: 10.1016/j.vaccine.2017.05.001. PubMed PMID: 28527687; PubMed Central PMCID: PMCPMC5462484.
29. Bilcke J, Antillon M, Pieters Z, Kuylen E, Abboud L, Neuzil KM, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study - The Lancet Infectious Diseases. Lancet Infectious Diseases. 2019;19(7):728-39. doi: doi:10.1016/S1473-3099(18)30804-1.
30. Watson CH, Edmunds WJ. A review of typhoid fever transmission dynamic models and economic evaluations of vaccination. Vaccine. 2015;33:C42-C54. doi: 10.1016/S0022-5193(03)00031-6.
31. Azman AS, Luquero FJ, Rodrigues A, Palma PP, Grais RF, Banga CN, et al. Urban Cholera Transmission Hotspots and Their Implications for Reactive Vaccination: Evidence from Bissau City, Guinea Bissau. PLoS Negl Trop Dis. 2012;6(11):e1901. doi: 10.1371/journal.pntd.0001901.
32. Azman AS, Lessler J. Reactive vaccination in the presence of disease hotspots. Proc Biol Sci. 2015;282(1798). doi: 10.1098/rspb.2014.1341. PubMed PMID: 25392464.
33. Grais RF, Conlan AJK, Ferrari MJ, Djibo A, Menach AL, Bjørnstad ON, et al. Time is of the essence: exploring a measles outbreak response vaccination in Niamey, Niger. Journal of the Royal Society Interface. 2008;5(8):67–74. doi: 10.1098/rsif.2007.1038.
34. Meiring J, Gibani M, The TyVAC Consortium Meeting Group. The Typhoid Vaccine Acceleration Consortium (TyVAC): Vaccine effectiveness study designs: Accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a meeting held on 26–27 October 2016, Oxford, UK. Vaccine. 2017;35(38). doi: https://doi.org/10.1016/j.vaccine.2017.08.001.
35. Pitzer VE, Feasey NA, Msefula C, Mallewa J, Kennedy N, Dube Q, et al. Mathematical Modeling to Assess the Drivers of the Recent Emergence of Typhoid Fever in Blantyre, Malawi. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61:S251-8. Epub 2015/10/10. doi: 10.1093/cid/civ710. PubMed PMID: 26449939; PubMed Central PMCID: PMCPMC4596932.
36. Nelson C. Controlling the Typhoid Epidemic Plaguing Sub-Saharan Africa. The Atlantic. 2012 2012-04-04.
37. Imanishi M, Kweza PF, Slayton RB, Urayai T, Ziro O, Mushayi W, et al. Household water treatment uptake during a public health response to a large typhoid fever outbreak in Harare, Zimbabwe. The American journal of tropical medicine and hygiene. 2014;90(5):945-54. Epub 2014/03/26. doi: 10.4269/ajtmh.13-0497. PubMed PMID: 24664784; PubMed Central PMCID: PMCPMC4015591.
38. Hendriksen RS, Leekitcharoenphon P, Lukjancenko O, Lukwesa-Musyani C, Tambatamba B, Mwaba J, et al. Genomic Signature of Multidrug-Resistant Salmonella enterica Serovar Typhi Isolates Related to a Massive Outbreak in Zambia between 2010 and 2012. J Clin Microbiol. 532015. p. 262-72.
39. Neil KP, Sodha SV, Lukwago L, S OT, Mikoleit M, Simington SD, et al. A large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese District, Uganda, 2008-2009. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(8):1091-9. Epub 2012/02/24. doi: 10.1093/cid/cis025. PubMed PMID: 22357703.

Chapter 1

A Bayesian approach for estimating typhoid fever incidence from large-scale facility-based passive surveillance data

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Abstract

Decisions about typhoid fever prevention and control are based on estimates of typhoid incidence and their uncertainty. Lack of specific clinical diagnostic criteria, poorly sensitive diagnostic tests, and scarcity of accurate and complete datasets contribute to difficulties in calculating age-specific population-level typhoid incidence. Using data from the Strategic Alliance across Africa & Asia (STRATAA) programme, we integrated demographic censuses, healthcare utilization surveys, facility-based surveillance, and serological surveillance from Malawi, Nepal, and Bangladesh to account for under-detection of cases. We developed a Bayesian approach that adjusts the count of reported blood-culture-positive cases for blood culture detection, blood culture collection, and healthcare seeking—and how these factors vary by age—while combining information from prior published studies. We validated the model using simulated data. The ratio of observed to adjusted incidence rates was 7.7 (95% credible interval (CrI): 6.0-12.4) in Malawi, 14.4 (95% CrI: 9.3-24.9) in Nepal, and 7.0 (95% CrI: 5.6-9.2) in Bangladesh. The probability of blood culture collection led to the largest adjustment in Malawi, while the probability of seeking healthcare contributed the most in Nepal and Bangladesh; adjustment factors varied by age. Adjusted incidence rates were within the seroincidence rate limits of typhoid infection. Estimates of blood-culture-confirmed typhoid fever without these adjustments results in considerable underestimation of the true incidence of typhoid fever. Our approach allows each phase of the reporting process to be synthesized to estimate the adjusted incidence of typhoid fever while correctly characterizing uncertainty, which can inform decision-making for typhoid prevention and control.

Background

Current estimates of typhoid fever incidence serve as a basis for decision-making around typhoid control. However, facility-based cases of blood-culture-confirmed typhoid fever are considerably lower than the true number of those with the disease [1] because the reported numbers do not account for individuals with typhoid fever who do not seek healthcare, fail to receive a diagnostic test, or falsely test negative for typhoid (Fig 1). Annually, typhoid fever is estimated to cause 11-18 million infections and 100,000-200,000 deaths [2, 3], but there is considerable uncertainty in these estimates.

Studies suggest that somewhere between 60-90% individuals with typhoid fever do not receive adequate medical attention, in part because they do not to seek formal treatment [4, 5]. Previous studies have found that healthcare utilization is correlated with the number of household members, distance to the healthcare facility, financial affordability, and trust in formal healthcare [6, 7]. Furthermore, typhoid fever is often misdiagnosed based on physical examinations alone [1]. Inconsistent clinical diagnoses arise because symptoms of typhoid, particularly prolonged fever, are also the main characteristics of other common infectious diseases in typhoid endemic settings [1, 8]. Even if a blood culture test is recommended and laboratory facilities are available, not all patients will consent. Diagnostic tests can be invasive, and parents or guardians of young children sometimes do not want their children to have large amounts of blood drawn when they are already ill. In resource-poor countries in particular, lack of supplies and personnel lead to long wait times for receiving healthcare, further adding to lower rates of confirmatory testing. Clinical opinion on the cause of fever can also affect the likelihood of blood being drawn for culture [9].

Suboptimal diagnostic tests further contribute to underestimation of cases. Blood culture collection is the mainstay diagnostic test for typhoid fever [10], but it fails to capture approximately half of the true cases. The test sensitivity depends on the volume of blood drawn and whether a patient has recently received antibiotics [11]. Thus, even if an individual with typhoid receives a blood culture test, he or she may falsely test negative and not be included in the reported number of confirmed cases.

The true incidence of typhoid fever cannot be directly assessed but can be estimated by accounting for steps in the reporting process. Methods to combine data from several sources to adjust for underestimation while accurately quantifying the uncertainty have been previously applied to estimate the incidence of HIV and influenza [12-16]. Bayesian methods are conducive to integrating multiple data sources in this way. In this work, we developed a Bayesian multiplier framework to estimate population-based incidence of typhoid fever based on data collected from study sites in Africa and Asia.

Methods

Study design & data.

We developed a framework within the Bayesian setting to integrate data from multiple sources to estimate the population-based incidence of typhoid fever based on passive surveillance in Malawi, Nepal, and Bangladesh, three typhoid-endemic countries with different demographics, healthcare systems, and access to diagnostics [17]. Using this model, we sought to estimate the adjustment factors needed to calculate the "true" incidence of typhoid fever occurring in the population under surveillance, and to examine how these values varied by age across the three study sites, by combining information collected from the study population with

estimates from prior published studies. We also compared our final estimates to serosurveillance data collected from the same population catchment areas.

Data came from the Strategic Typhoid Alliance across Africa & Asia (STRATAA) Programme, a prospective observational, population-based epidemiological study of typhoid incidence, transmission, and antibiotic resistance. From 2016-2018, the STRATAA investigators conducted demographic censuses, healthcare utilization surveys (HUS), passive surveillance, and serosurveys at each of three sites (Blantyre, Malawi; Kathmandu, Nepal; and Dhaka, Bangladesh). STRATAA's study design and methods have been detailed elsewhere [17], and are briefly described below.

Demographic census data.

The demographic census was used to estimate the overall person-time contribution for incidence rate calculations. The survey documented household locations and individual characteristics for each geographically demarcated study area. The census provided information on each individual's birthdate, sex, position in the household, marital status (if applicable), education level, and employment status (if applicable). Participants were surveyed and consented as households. Approximately 100,000 individuals were enrolled at each site, and census updates were carried out one to three times depending on the site. Over the two-year study period, this population amounted to 200,018 person-years of observation (pyo) in Malawi, 203,444 in Nepal, and 222,636 in Bangladesh.

Passive surveillance.

Clinical cases of culture-confirmed typhoid fever were identified through passive surveillance. Individuals living in the study areas who presented at partner facilities with a documented temperature of $\geq$ 38.0°C or a history of fever lasting at least two days upon

presentation were eligible for enrollment. Healthcare workers collected clinical and demographic information from enrolled febrile individuals, as well as microbiological samples (urine, feces, and blood).

Healthcare utilization survey.

To estimate the proportion of cases captured by study facilities, we collected data from the head of household regarding actual and hypothetical usage of healthcare facilities for febrile episodes among household members from each of three age groups (<5 years, 5-14 years, >14 years), if available. Approximately 735 households were randomly chosen at each site, with the requirement that all households have at least one child (14 years or younger). The HUS contained questions regarding household and individual health behavior; house and household characteristics; water, sanitation and hygiene practices; and healthcare utilization (actual and hypothetical).

Serosurveillance.

Serosurveys were conducted in the census population to assess the underlying rate of seroconversion to typhoid, and to identify potential chronic carriers, initially based on anti-Vi immunoglobulin G (IgG). Approximately 8,500 participants from each site were randomly selected in an age-stratified manner. Healthcare workers collected serum samples from each individual upon enrollment and again three months later. Seroconversion was defined as a $\geq$ 2-fold rise in anti-Vi IgG titre between the first and second sample drawn and an absolute titre $\geq$50 EU/ml at the second time point to account for small variations above the lower limit of detection for the assay. We estimated the seroincidence by dividing the number of seroconversions by the person-time contribution between serum samples in each age group; 95% binomial confidence intervals (CI) were estimated.

Approach and data analysis.

We adjusted the reported number of blood-culture-positive cases of typhoid fever for each of the three phases of the reporting process: blood culture detection, blood culture collection, and healthcare seeking. We used information on healthcare seeking for fever and the proportion of fever cases who were enrolled and had blood taken for culture and combined this information with published data on risk factors for typhoid fever to reach our final adjusted numbers. We then examined whether our adjusted estimates were within the maximum range expected based on seroincidence estimates, which capture all clinical and sub-clinical cases.

The estimation of typhoid fever incidence is complicated by the relationship between fever and typhoid fever. In each phase of the reporting process, we can observe whether a person has a fever, but not necessarily whether he/she has typhoid fever. Thus, the symptomatic typhoid fever pyramid is nested within a larger fever pyramid (Fig S1).

We assumed that the observed number of blood-culture-positive individuals ($n_{\text{observed},a,c}$) follows a Poisson distribution given as

$$n_{\text{observed},a,c} \sim \text{Poisson}\left(\frac{\lambda_{\text{observed},a,c}}{\text{person\_time}_{a,c}}\right) \quad (1)$$

where $\lambda_{\text{observed},a,c}$ is the observed incidence rate of typhoid fever, adjusted for pyo from the demographic census ($\text{person\_time}_{a,c}$) (Fig 1, Table 1). Subscript a represents age category, where

$$a = \begin{cases} 1 \text{ for children} < 5 \text{ years old} \\ 2 \text{ for children } 5-9 \text{ years old} \\ 3 \text{ for children } 10-14 \text{ years old} \\ 4 \text{ for individuals } 15-29 \text{ years old} \\ 5 \text{ for individuals } \geq 30 \text{ years old} \end{cases},$$

and subscript c represents the site, where

$$c = \begin{cases} 1 \text{ for Malawi} \\ 2 \text{ for Nepal} \\ 3 \text{ for Bangladesh} \end{cases}.$$

The incidence rate of reported cases can be rewritten as the product of the healthcare-seeking typhoid incidence rate and the probability of a case being captured at each of the three steps of the reporting process,

$$\lambda_{\text{observed},a,c} = \lambda_{adjusted,a,c} * \phi^{S}_{a,c} * \phi^{B}_{a,c} * \phi^{H}_{a,c}, \quad (2)$$

where $\lambda_{adjusted,a,c}$ is the final adjusted incidence of typhoid fever incidence, $\phi^{S}_{a,c}$ is blood culture sensitivity, $\phi^{B}_{a,c}$ is the probability of receiving a blood culture test, and $\phi^{H}_{a,c}$ is the probability of seeking healthcare for typhoid fever. Superscript *S* denotes that the parameter refers to the blood culture detection (i.e. sensitivity) phase of reporting, superscript *B* denotes that the parameter is referring to the blood culture collection (i.e. testing) phase of reporting, and superscript *H* denotes that the parameter is referring to the healthcare-seeking phase of reporting.

All model input parameters, with their prior distributions and corresponding data sources, are listed in Table 1. The three steps in the adjustment process (blood culture detection, blood culture collection, and healthcare seeking), are detailed below.

Adjustment for blood culture sensitivity ($\phi^{S}_{a,c}$)

For each individual who received a blood culture test, we inferred whether or not they were a "true" typhoid fever case by adjusting for the specificity and sensitivity of blood culture for typhoid diagnosis (Table S1). First, we assumed that the specificity of blood culture is 100%; thus, all individuals who tested positive for typhoid were assumed to be true cases of the disease. Second, we assumed that among those who tested negative, the probability of being an actual typhoid fever case depended on the volume of blood drawn and prior antimicrobial use, both of which were recorded in the passive surveillance data. Previous studies have shown that the sensitivity of blood culture for typhoid diagnosis is on average 59% (95% CI: 54-64%) but increases by 3% for each additional mL of blood drawn, and decreases by 34% with antibiotic

use in the past two weeks [11]. Thus, each individual who tested negative for typhoid had a probability 1-$w_{i,v(i),u(i)}$ of being a false negative and thus a true case of typhoid fever, where $w_{i,v(i),u(i)}$ is the blood culture sensitivity for individual i, $v(i)$ is the volume of blood collected from individual i, and $u(i)$=1 if individual i reported prior antibiotic use in the previous two weeks and $u(i)$=0 otherwise. Blood culture sensitivity is defined as

$$w_{i,v(i),u(i)} = (e^{-0.73+0.03v_{(i)}}) * (1 - 0.34u_{(i)}). \quad (3)$$

The use or non-use of antibiotics created a bimodal distribution for the sensitivity based on the observed individual-level data calculated using Equation 3 (Fig S2). Thus, we chose to model the distribution of sensitivity among the full population using a normal mixture model with a separate mean and standard deviation for the distribution of blood culture sensitivity with and without the use of antibiotics, varied over blood culture volume. This mixture model is denoted

$$\begin{aligned} \phi^S_{a,c} \,|U_{a,c} &\sim \mathrm{N}(m_{u,a,c}, d_{u,a,c}) \\ U_{a,c} &\sim \mathrm{Bernoulli}(r_{a,c}) \end{aligned} \quad (4)$$

where $\phi^S_{a,c}$ is the blood culture sensitivity adjustment from Equation 2, $r_{a,c}$ is the proportion of individuals who took antibiotics in the past two weeks, and $m_{u,a,c}$ and $d_{u,a,c}$ represent the mean and standard deviation of the distribution of blood culture sensitivity after adjusting for blood culture volume among those who did (U=1) and did not (U=0) take antibiotics (from the distribution created using Equation 3), again estimated separately for each age category and site.

Adjustment for the probability of receiving a blood culture test ($\phi^B_{a,c}$)

The probability of receiving a blood culture test was estimated differently for Malawi versus Nepal and Bangladesh due to data availability and differences in the primary reasons why individuals were not tested. In Malawi, the main reason why individuals meeting the fever criteria for enrollment did not receive a blood culture test was due to limited capacity and long

waiting times at the primary health facility. Individuals often arrived at the clinic early in the morning for clinical review. Once they had seen the government clinician, they were referred for study enrollment and blood-culture collection. If there was a delay in enrollment activities, individuals often left prior to blood cultures being collected. Thus, we assumed that data for those who did not receive a blood culture test were missing completely at random. We used the passive surveillance screening data to estimate the probability of receiving a blood culture test in Malawi, and assumed that the probability followed a beta distribution,

$$\phi^{B}_{a,1} \sim \text{Beta}(g^{B}_{a,1i}, j^{B}_{a,1}), \quad (5a)$$

where $g^{B}_{a,1}$ was the number of eligible patients enrolled and $j^{B}_{a,1}$ was the number of eligible patients who were not enrolled.

In Nepal and Bangladesh, the primary reason febrile individuals did not receive a blood culture test likely depended on factors associated with their probability of testing positive (e.g., age, number of days of fever, and clinical suspicion of the disease); furthermore, screening data for the passive surveillance were not available. Instead, we relied on published estimates of the relative risk of typhoid fever among those who did not have blood taken for culture and screening data from the Typhoid Vaccine Acceleration Consortium (TyVAC) [18]. As part of TyVAC, typhoid conjugate vaccine trials are being conducted in the same populations as STRATAA utilizing the same passive surveillance facilities. Baseline information on eligible patients presenting to fever surveillance facilities was recorded both for those who did and did not have blood drawn for culture. Based on the analysis of these data in the TyVAC population in Nepal, the relative risk of blood culture positivity (R_S) was 1.87 times higher (95% CI: 0.9-3.9) among those who received a blood culture test compared to those who did not [9]. Thus, the

overall probability of receiving a blood culture test, after taking into account variations in the risk of typhoid fever among those who are and are not tested, is

$$\phi^{B}_{a,c} = 1 - \frac{(1-k_{a,c})}{R_S} \quad \text{for } c = 2 \text{ or } 3, \tag{5b}$$

where $k_{a,c}$ is the probability of receiving a blood culture test prior to adjusting for the relative risk of blood culture positivity. Prior to adjusting for the relative risk, the probability of receiving a blood culture test was assumed to follow a beta distribution, $k_{a,c} \sim \text{Beta}(g^{B}_{a,c}, j^{B}_{a,c})$, where $g^{B}_{a,c}$ was the number of eligible patients in age category *a* in country *c* who were enrolled and $j^{B}_{a,c}$ was the number of eligible patients who were not enrolled during TyVAC (for $c = 2$ or 3). While the previous analysis focused only on Nepal, we used the same adjustment for the relative risk of blood culture positivity in Bangladesh, since the reasons for having or not having blood drawn were similar.

Adjustment for healthcare-seeking behavior ($\phi^{H}_{a,c}$)

Previous multiplier methods assume that reported healthcare-seeking for a fever is the same as that for typhoid fever; however, this is not necessarily the case. Individuals with typhoid fever may be more or less likely to seek healthcare. In preliminary analyses, we found no difference in reported healthcare seeking by severity of a person's reported fever, but other factors may explain differential healthcare seeking among those with typhoid fever versus fever due to other causes. To correct for this difference, we measured the probability of seeking care for a fever adjusted for a specified typhoid risk factor to estimate the probability of seeking care for typhoid fever (Fig S1), as described below.

For this phase of reporting, we assumed that everyone in the population either had or did not have a typhoid risk factor, identified from the literature. For each site, we used a different risk factor, based on studies carried out in that specific site and variables for which data was

collected as part of STRATAA. The risk factor identified in Malawi was soap available after defecation [19]; in Nepal, it was unshared toilets [20], and in Bangladesh it was boiled drinking water [21].

In Malawi, the odds ratio for having typhoid fever was 2.0 (95% CI: 1.3-2.5) comparing those who did not use soap after defecation to those who did [19]. In Nepal, the odds ratio for having typhoid fever was 5.7 (2.3-14.4) comparing those who used a household latrine to those who shared a community latrine [20]. In Bangladesh, the odds ratio for having typhoid was 7.6 (2.2-26.5) comparing those who did not boil drinking water to those who did [21]. Since the overall prevalence of typhoid in the population is low, we used these odds ratio estimates from the literature to approximate relative risks for typhoid. We used the same relative risk estimates for all age groups. All other values for the healthcare-seeking adjustment were estimated separately by age and site, as noted below.

We can calculate the marginal probability of seeking care for a fever among those with typhoid fever (alternatively, the incidence of typhoid after adjusting for blood culture sensitivity and the probability of receiving a blood culture test) as:

$$\lambda_{a,c}^{S,B} = \lambda_{0,a,c}\left(h_{1,a,c}R_{TF,c}p_{a,c} + h_{0,a,c}(1 - p_{a,c})\right) \quad (6)$$

where $p_{a,c}$ is the probability of having the risk factor for typhoid fever among individuals in age group a in site c, $\lambda_{0,a,c}$ is the incidence of typhoid fever among those without the risk factor, $R_{TF,c}$ is the relative risk for typhoid among those with the risk factor (and hence $R_{TF,c}\lambda_{0,a,c}$ is the incidence among those with the risk factor), and $h_{1,a,c}$ and $h_{0,a,c}$ are the probability of self-reported healthcare seeking for a fever among those with and without the risk factor, respectively.

We can also estimate the overall adjusted incidence of typhoid as the weighted average of the population-based typhoid fever incidence (after adjusting for blood culture sensitivity, the probability of receiving a blood culture test, and healthcare-seeking) among those with or without the typhoid fever risk factor:

$$\lambda_{\text{adjusted},a,c} = R_{TF,c}\lambda_{0,a,c}p_{a,c} + \lambda_{0,a,c,}\left(1 - p_{a,c}\right). \quad (7)$$

Combining Equations 6 and 7, we can estimate the standardized risk of seeking healthcare for typhoid fever ($\phi_{a,c}^{H}$) as:

$$\phi_{a,c}^{H} = \frac{\lambda_{a,c}^{S,B}}{\lambda_{\text{adjusted},a,c}} = \frac{h_{1,a,c}R_{TF,c}p_{a,c} + h_{0,a,c}\left(1-p_{a,c}\right)}{R_{TF,c}p_{a,c} + \left(1-p_{a,c}\right)}. \quad (8)$$

The numbers of individuals with the risk factor and who sought healthcare for a fever were observed directly in a sample of the population in the HUS. We assumed that the probabilities for the occurrence of these numbers (p, h_0, h_1) followed an underlying beta distribution based on the observed values (Table 1).

Model validation and sensitivity analyses

The final adjusted incidence of symptomatic typhoid fever should be less than or equal to the seroincidence of typhoid infections captured in the serosurveillance data. In this study, seroconversion to typhoid was defined as a ≥ 2-fold rise in anti-Vi IgG titre between the first and second sample drawn and an absolute titre ≥50 EU/ml at the second time point. The seroincidence was estimated as the quotient of the number of people who seroconverted between the first and second blood sample and person-time in years (the number of people sampled multiplied by the mean time between serological samples in age group *a* in country *c*). The final adjusted incidence should fall below the estimated seroincidence rates.

To ensure the model was correctly formulated, we simulated data with known probabilities and incidence rates and compared model estimates to the true values used to generate the data. We simulated high and low values for all of the parameters estimated in the model, starting with a "true" typhoid fever incidence of 1,000 infections per 100,000 pyo. We began by assuming there were 1,250 cases of typhoid fever among 25,000 individuals with a typhoid fever risk factor (X_i=1) and 750 cases among 75,000 individuals without the risk factor (X_i=0) over two years of surveillance, such that R_{TF}=5. We then sampled from independent Bernoulli random variables, $H_i \sim \text{Bernoulli}(h_{X_i})$, $B_i \sim \text{Bernoulli}(b_{TF_i})$, and $U_i \sim \text{Bernoulli}(u)$, for the probability of seeking healthcare (***H***), the probability of having blood drawn for culturing (***B***), and the probability of antibiotic usage (***U***). We considered high and low values for each probability, which also varied depending on the risk-factor and typhoid fever status of individual *i* for *h* and *b*, respectively:

$$h_{X_i=1} = \begin{cases} 0.1 \text{ for low scenario} \\ 0.5 \text{ for high scenario} \end{cases}, \quad h_{X_i=0} = \begin{cases} 0.2 \text{ for low scenario} \\ 0.7 \text{ for high scenario} \end{cases}$$

$$b_{TF_i=1} = \begin{cases} 0.68 \text{ for low scenario} \\ 0.95 \text{ for high scenario} \end{cases}, \quad b_{TF_i=0} = \begin{cases} 0.4 \text{ for low scenario} \\ 0.9 \text{ for high scenario} \end{cases}$$

$$u = \begin{cases} 0.2 \text{ for low scenario} \\ 0.8 \text{ for high scenario} \end{cases}.$$

Among individuals with TF_i=1 and antibiotic usage U_i, the probability of testing positive for typhoid fever (i.e., test sensitivity) was $S_i \sim \text{Bernoulli}(s_{U_i})$, where

$$s_{U_i=1} = \begin{cases} 0.4 \text{ for low scenario} \\ 0.5 \text{ for high scenario} \end{cases}, \quad s_{U_i=0} = \begin{cases} 0.6 \text{ for low scenario} \\ 0.75 \text{ for high scenario} \end{cases}.$$

Under both scenarios, the mean test sensitivity was ~55%. We assumed perfect test specificity, such that s_i=0 if TF_i=0. The incidence of fever due to other causes was assumed to be 5% per year; we did not allow for multiple episodes of fever over the two-year period, such that

$$F_{\text{other},i} \sim \text{Bernoulli}(0.10)$$

Moreover, we assumed that the incidence of fever due to any cause was

$$F_i = \max\left(TF_i, F_{\text{other},i}\right),$$

i.e. all individuals could have at most one episode of fever, either due to typhoid fever or another cause. We then generated vectors for whether or not individuals who sought healthcare (***HC***), had blood drawn for culturing (***BC***), and tested positive for typhoid fever (***Y***) as:

$$HC_i = F_i * H_i \,,$$

$$BC_i = \begin{cases} HC_i * B_i & \text{if } HC_i = 1 \\ NA & \text{otherwise} \end{cases},$$

$$Y_i = \begin{cases} BC_i * P_i & \text{if } BC_i = 1 \\ NA & \text{otherwise} \end{cases}.$$

We simulated four scenarios using these probabilities: 1) low probability of seeking care, high probability of being tested, and low prior antibiotic usage; 2) low probability of seeking care, high probability of being tested, and high antibiotic usage; 3) high probability of seeking care, low probability of being tested, and low prior antibiotic usage; and 4) high probability of seeking care, low probability of being tested, and high prior antibiotic usage.

To evaluate whether the final estimates were sensitive to the number of individuals sampled in the HUS, we compared estimates for models that sampled approximately the same number of individuals in each age category as the HUS (735) to models that sampled more individuals (1,000 and 2,000 individuals).

We additionally compared the adjusted incidence estimates from our model to those from a simpler approach that assumed there was no variation in blood culture sensitivity due to prior antibiotic use (i.e., we used a normal distribution for $\phi^S_{a,c}$ instead of a normal mixture model) and no variation in typhoid incidence among those who were or were not tested (i.e. using the

simpler approach to estimate $\phi^B_{a,c}$ given in Equation 5a) and those who did or did not seek care (i.e. assuming $\phi^H_{a,c}$ is equal to the probability of seeking care for fever). This simpler approach is more commonly used in multiplier methods for adjustments; however, this approach often faces criticism since it inherently assumes that data are missing completely at random and that reported healthcare-seeking behavior for a fever is the same as that for typhoid fever.

Model fitting

To estimate the posterior distributions of the adjusted incidence rates, we collected 100,000 posterior samples from the adjustment factors described above following a burn-in period of 10,000 iterations prior to convergence. Convergence was assessed using the Gelman-Rubin diagnostic [22] for individual parameters. To ensure the model validation was done without knowledge of the true values, one person simulated the data and another person fit the model to the simulated data. Code for generating simulated data was written in MATLAB version 9.3.0 [23]. All other analyses were performed using JAGS version 4.3.0 [24] in R version 3.4.0 [25]. Model code, including code for generating the simulated data, is provided at https://github.com/mailephillips/adjusted-typhoid-incidence [26].

Results

The magnitude of the adjustment factors used to estimate the incidence of typhoid fever varied among the three sites (Table 2). In Nepal and Bangladesh, the probability of seeking healthcare was low ($\phi^H_{c=2}$=0.15, 95% credible interval (CrI): 0.09-0.22; and $\phi^H_{c=3}$=0.27, 95% CrI: 0.22-0.33, for all ages) and thus contributed the most to the adjustments, while the probability of receiving a blood culture test when eligible was high ($\phi^B_{c=2}$=0.84, 95% CrI: 0.67-0.92; and $\phi^B_{c=3}$=0.96, 95% CrI: 0.92-0.98) and contributed the least to adjustments. However, in

Malawi, the probability of seeking healthcare was relatively high ($\phi^{H}_{c=1}$=0.71, 95% CrI: 0.64-0.77), while the probability of receiving a blood culture test was low ($\phi^{B}_{c=1}$=0.35, 95% CrI: 0.34-0.36). Blood culture sensitivity was fairly consistent across sites, with median estimates of ϕ^{S}_{c}=0.54-0.55.

The different adjustment factors also varied by age. Blood culture sensitivity was slightly higher in older age groups compared to younger age groups (median estimates of individuals >14 years, $\phi^{S}_{a\in(4,5)}$=0.56-0.58; compared to children ≤14 years, $\phi^{S}_{a\in(1,2,3)}$=0.53-0.54). While there was no consistent pattern in prior antibiotic use by age, the amount of blood drawn for a blood culture test generally increased with age. As a result, blood culture sensitivity slightly increased with age. Had we not adjusted for blood culture volume or prior antibiotic use, the estimate for blood culture sensitivity would have been higher for all ages and countries (Fig S5, in blue).

The probability of receiving a blood culture test had different patterns across age groups depending on the country. In Malawi, the probability of receiving a blood culture test decreased with age ($\phi^{B}_{1,1}$ =0.40, 95% CrI: 0.38-0.41 for children <5 years versus $\phi^{B}_{5,1}$=0.20, 95% CrI: 0.17-0.23 for adults 30+ years), while in Nepal and Bangladesh, the probability increased ($\phi^{B}_{1,2}$ =0.81, 95% CrI: 0.61-0.91 and $\phi^{B}_{1,3}$ =0.94, 95% CrI: 0.87-0.97 for children <5 years versus $\phi^{B}_{5,2}$=0.91, 95% CrI: 0.71-0.98 and $\phi^{B}_{5,3}$=0.98, 95% CrI: 0.96-0.99 for adults 30+ years). If we had used a simpler approach (not adjusting for the variation in the risk of typhoid fever among those who were and were not tested) to adjust for the probability of receiving a blood culture test in Nepal and Bangladesh, we would have underestimated the probabilities and thus overestimated the contribution of this adjustment (Fig S5). In Nepal in particular, the simpler approach would have substantially underestimated the probability of receiving a blood culture test among younger age

groups. In Bangladesh, the unadjusted proportion of individuals receiving a blood culture test was already close to one, so the adjusted value did not increase the estimate considerably.

The probability of seeking healthcare did not have a consistent pattern across age groups, likely due to the different components contributing to the final estimate. Malawi overall had the highest rates of healthcare seeking, with the lowest rates among children under 5 and the highest rates among children 5-14 (Table 2). Nepal had the lowest rates of healthcare seeking overall, with slightly higher rates among children under 5. Bangladesh also had low healthcare seeking rates, with the lowest rates among adults 15+ years of age (Table 2). In Malawi and Bangladesh, the proportion of those with the relevant typhoid risk factor did not differ by age group (Table S2). Healthcare seeking for a fever was higher among those with the typhoid risk factor in Malawi, but lower among those with the risk factor in Bangladesh and Nepal. When compared to the simpler approach to estimate the probability of healthcare seeking (using the unadjusted proportion of those who sought care for fever), the estimates were similar but slightly higher in most age groups in Malawi but slightly lower in Nepal and Bangladesh (Fig S5).

The magnitude of the overall adjustment to estimate typhoid fever incidence $\left(\lambda_{\text{adjusted},a,c}/\lambda_{\text{observed},a,c}= \left(\phi_{a,c}^{S}\phi_{a,c}^{B}\phi_{a,c}^{H}\right)^{-1}\right)$ varied between countries and age groups. Nepal had the highest adjustment factors in every age group, with an overall adjustment factor of 14.4 (95% CrI: 9.3-24.9). Malawi and Bangladesh were similar, with adjustment factors of 7.7 (95% CrI: 6.0-12.4) and 7.0 (95% CrI: 5.6-9.2), respectively (Table 3). The highest adjustment factor was for the 5-9-year age group in Nepal (19.7, 95% CrI: 9.0-54.9), while the lowest was for the 5-9- and 10-14-year age groups in Bangladesh (5.8, 95% CrI: 4.1-8.6; and 5.8, 95% CrI: 3.9-8.9, respectively).

Most of the final adjusted incidence estimates fell within or below the range of the estimated seroincidence of typhoid infection (Table 4). In Malawi, all of the upper bounds of the estimates were well below the seroincidence values. However, in Nepal and Bangladesh, the bounds of the adjusted incidence rates overlapped with the estimated seroincidence. In Nepal, the adjusted incidence among children 5-9 years of age was higher than the seroincidence; however, the confidence/credible intervals overlapped. Similarly, children 10-14 years of age in Bangladesh had higher adjusted incidence rates than seroincidence (which was the lowest across all age groups and sites), but again the confidence/credible intervals overlapped.

When we evaluated the model against simulated data, the full model was able to reliably estimate both the "true" incidence of typhoid fever and the probabilities used to generate the simulated data for a range of values, while the simpler approach over- or under-estimated the true incidence in some scenarios (Figs 2 and S3). Estimates of blood culture sensitivity were similar to the true value, but incorporated additional uncertainty compared to the simpler approach, consistent with the different sensitivity of blood culture in those who reported prior antibiotic use compared to those that did not (Fig S3). The probability of receiving a blood culture test contributed most to the difference in accuracy between the two approaches. In every scenario, the full model reliably estimated the true value, while the simpler approach underestimated the true value (Fig S3). The adjustment for healthcare seeking in the full model again consistently captured the true value across levels of the probability as compared to the simpler approach, which generally had a narrower 95% CrI that did not always contain the true value (Fig S3). As expected, in both models, the uncertainty in the probability of seeking healthcare decreased as the sampling fraction for the hypothetical HUS increased. As a result, the

95% CrIs in the overall incidence estimates also narrowed as the sampling fraction increased (Fig 2).

Discussion

In order to make informed decisions regarding typhoid control and prevention, it is important to have accurate estimates of population-based typhoid fever incidence. Unreliable reports, inconsistent healthcare utilization, inconsistent clinical diagnoses, suboptimal diagnostic tests, and scarcity of accurate or full data contribute to difficulties in calculating the population-based incidence of typhoid fever. We developed a new methodology within the Bayesian setting to estimate population-based incidence in a context where cases often go undetected and under-reported. Through this approach, we were able to calculate the adjustment factors that can be applied to estimate the "true" incidence of typhoid fever in the STRATAA surveillance sites. These estimates suggested that the adjusted incidence of typhoid fever in Malawi, Nepal, and Bangladesh is 7- to 14-fold higher than the reported blood-culture-confirmed numbers.

It is commonly accepted that cases of typhoid fever go unrecognized at each phase of the reporting process, but the degree to which each step contributes to the underestimation of and uncertainty in the population-based incidence is often not fully quantified. Each of the three intervening processes contributed differently to the underestimation in each country and age group. The probability of seeking healthcare was responsible for the largest portion of underestimation in Nepal and Bangladesh, while the probability of receiving a blood culture test was the biggest factor in Malawi. These results reflect differences in the healthcare systems and fever surveillance processes at the different sites. In Nepal and Bangladesh, antibiotics are widely available and individuals tend to seek care first at a pharmacy instead of a healthcare

facility [27]. In Nepal, a considerable proportion of people with fever neither seek healthcare nor visit a pharmacy possibly due to lack of funds. In Malawi, healthcare seeking is high, but the resources at healthcare facilities are limited. As a result, many people report to healthcare facilities with a fever, receive antibiotics, but do not remain in the facility long enough to receive an additional blood culture test due to prolonged wait times.

Other studies use different approaches to estimate the true incidence of typhoid fever. In many cases, studies simply double the reported cases to account for blood culture sensitivity [28]. Numerous studies make use of a simple multiplier method [29-32], which often do not accurately reflect the uncertainty associated with the reporting process. Previous studies have not attempted to integrate data sources to account for potential differences between the observed healthcare seeking and testing probabilities for fever versus the corresponding unobserved probabilities specific to typhoid fever, which our analysis suggests can impact the final adjustment factors. Our approach can be used to estimate typhoid fever incidence in other study populations. Moreover, some of the issues we encountered (e.g. under-detection due to poor test sensitivity that varies depending patient characteristics, preferential testing of individuals more likely to have the disease of interest, and potential differences in healthcare seeking for those who have the syndrome versus disease of interest) are common to other diseases as well.

By utilizing a Bayesian approach, we were able to measure the contribution to underestimation at each phase of the reporting process while also properly quantifying the uncertainty for each of our estimates. When comparing our model to simulated data, we showed that having more data available (due to higher probabilities of seeking care and receiving a blood culture test) reduced uncertainty in the estimates. Furthermore, we showed that if more people had been sampled in the HUS, uncertainty would also have been reduced.

Our analysis and approach had some limitations. We assumed that healthcare-seeking behavior for fever in households without children is the same as households with children, because the HUS only sampled households with children. Less than a third of households did not have children and were not included in this survey across sites. Studies suggest that households with children are more likely to seek healthcare [33], which means that if our estimates are biased, the adjusted incidence estimates are likely conservative. We also were not able to differentiate between febrile illnesses at different parts of the reporting process. We addressed this issue by adjusting for possible differences in healthcare seeking among those with typhoid fever compared to other febrile etiologies using weighted averages based on known risk factors for typhoid fever, but other factors may also lead to differences in healthcare seeking for fever versus for typhoid fever. By comparing our adjusted incidence estimates to estimates of seroincidence, we are able to provide some assurance that the adjusted incidence is within the range of plausible values. However, methods and immunological markers for estimating the seroincidence of typhoid fever are not well established, and the cut-off we used (a ≥2-fold and absolute value of ≥50 EU/mL in anti-Vi IgG) may not be a reliable indicator of acute typhoid infection across all individuals and immunological backgrounds. Another limitation of the approach is that it can very labor-intensive and time-consuming to collect the necessary data.

Calculation of incidence based on data from passive surveillance of blood-culture-confirmed typhoid fever results in considerable underestimation of the true incidence of typhoid fever in the population. Our model provides an approach for estimating typhoid fever incidence while accounting for different sources of information from the reporting process. Typhoid fever remains a major cause of morbidity and mortality in developing countries, so control and prevention are needed. To effectively prioritize, implement and evaluate interventions, estimates

of the number of cases should accurately reflect the uncertainty in the reporting process. This analysis provides a platform that can be updated with new or additional data as they become available and can be adapted to other contexts. This model framework could also be used to adjust for underreporting in other diseases.

Figures and tables.

Figure 1. Flowchart of typhoid disease and observation process, and adjustment method to estimate the true number of cases. The pyramid (left) illustrates the different steps in the observation process for reporting typhoid incidence, with details on how parameters are estimated at each step. The flowchart (right) illustrates the corresponding Bayesian framework for each step of the observation process and which datasets and variables are used for adjustment. Adjustments for blood culture sensitivity are shown in purple, the probability of receiving a blood culture test is shown in red, and the probability of seeking healthcare is shown in blue. Variable definitions: λ, typhoid incidence rate; ϕ, a probability estimated in the model; S, sensitivity of blood culture; B, blood culture collection; H, healthcare seeking; a, age category; c, site. Abbreviations: BC, blood culture.

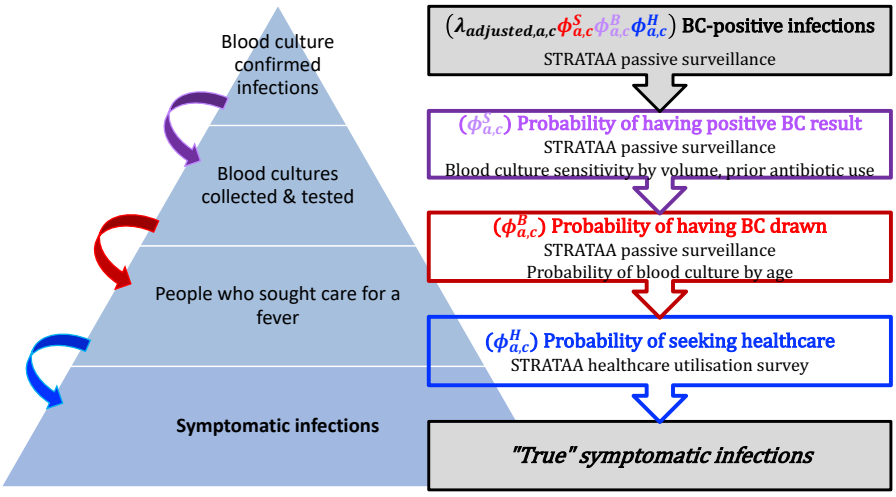

Figure 2. Estimated typhoid incidence based on simulated data: Full model vs. simplified approach. The typhoid incidence per 100,000 person-years of observation was estimated from simulated data based on a true incidence of 1,000 typhoid infections per 100,000 person-years (dashed horizontal black line). Data were simulated for low and high probabilities of seeking healthcare, receiving a blood culture diagnostic test, and antibiotic use. Scenarios were as follows: 1) low probability of seeking care, high probability of being tested, and low prior antibiotic usage; 2) low probability of seeking care, high probability of being tested, and high prior antibiotic usage; 3) high probability of seeking care, high probability of being tested, and low prior antibiotic usage; and 4) high probability of seeking care, high probability of being tested, and high prior antibiotic usage. Each simulation was performed sampling 735; 1,000; and 2,000 individuals from the population for the hypothetical healthcare utilization survey. Estimated "true" values are shown for models that did (red) and did not (blue) account for variation in blood culture sensitivity and variation in typhoid incidence among those who did or did not seek care and were or were not tested.

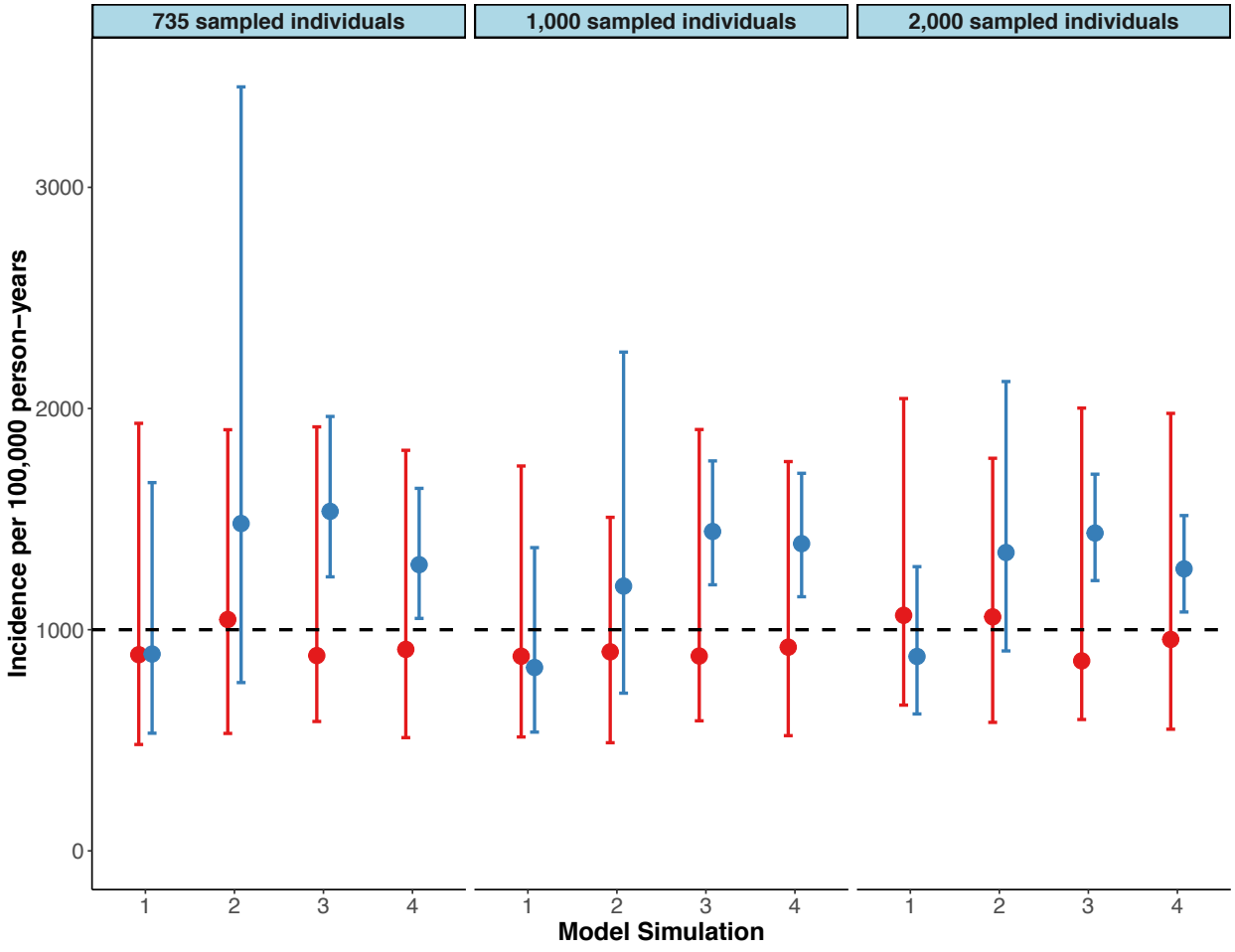

Table 1. Model input parameters. Parameters used in the incidence adjustment model are described below, with their corresponding uncertainty distributions and data sources. The symbols appear in the table in the order that they appear in the text, organized by the steps in the reporting process (Main model, Adjustment for blood culture sensitivity, Adjustment for the probability of receiving a blood culture test, and Adjustment for healthcare-seeking). All parameters are both age- and country-specific, except for p and R_{TF}, for which only a country-level estimate was available. Note that some of parameters in the adjustment for the probability of receiving a blood culture test are specific to only some countries (ϕ^B, g^B, j^B, k^B, and R_S).

Symbol	Description	Uncertainty distribution	Data Source
Main model (Equations 1-2)			
$\lambda_{\text{observed}}$	Observed incidence rate of typhoid fever among febrile individuals who sought care	$n_{observed} \sim \text{Poisson}\left(\frac{\lambda_{\text{observed}}}{\text{person\_time}}\right)$	See rest of table.
n_{observed}	Number of blood-culture-positive individuals	Observed directly	STRATAA PS
person_time	Person-years of observation over the two year study period	Observed directly	STRATAA Demographic Census
$\lambda_{\text{adjusted}}$	The incidence rate of typhoid fever after adjusting for all three phases of reporting (blood culture sensitivity, the probability of receiving a blood culture test, and the probability of seeking healthcare)	$\lambda_{\text{observed}} = \lambda_{adjusted} * \phi^S * \phi^B * \phi^H$	See rest of table.
Adjustment for blood culture sensitivity (Equations 3-4)			
ϕ^S	Blood culture sensitivity	$\phi^S \mid U \sim N(m_u, d_u)$	See rest of table.
U	An indicator variable for whether or not an individual took antibiotics in the past two weeks	$U \sim \text{Bernoulli}(r)$	See rest of table.
r	The proportion of individuals who took antibiotics in the past two weeks	Observed directly	STRATAA PS
m_u	The mean blood culture sensitivity for those who did and did not take antibiotics the past two weeks.	Calculated using observed data with adjustment from Antillon et al	STRATAA PS, Antillon et al [11]
d_u	The standard deviation of blood culture sensitivity for those who did and did not take antibiotics the past two weeks.	Calculated using observed data with adjustment from Antillon et al	STRATAA PS, Antillon et al [11]
Adjustment for the probability of receiving a blood culture test (Equations 5a-b)			
ϕ^B	***Malawi:*** Probability of receiving a blood culture test	$\phi^B \sim Beta(g^B, j^B)$	See rest of table.
	Nepal and Bangladesh: Probability of receiving a blood culture test after adjusting for variation in risk of typhoid fever among those who are and are not tested	$\phi^B = 1 + \frac{(1-k)}{R_S}$	See rest of table.
g^B	***Malawi:*** number of people who presented to a STRATAA facility with fever, were enrolled, and received a blood culture test	Observed directly	STRATAA PS
	Nepal and Bangladesh: number of people who presented to a TyVAC	Observed directly	TyVAC [18]

	facility with fever, were enrolled, and received a blood culture test		
j^B	***Malawi:*** number of people who presented to a STRATAA facility with fever but were not enrolled	Observed directly	STRATAA PS
	Nepal and Bangladesh: number of people who presented to a TyVAC facility with fever but were not enrolled	Observed directly	TyVAC [18]
k	***Nepal and Bangladesh:*** probability of receiving a blood culture test prior to adjusting for the relative risk of blood culture positivity	$k \sim Beta(g^B, j^B)$	See rest of table.
R_S	***Nepal and Bangladesh***: Relative risk of blood culture positivity among those who received a blood culture test compared to those who did not	$\log(R_S) \sim N(log(1.87), 0.37)$	[9]
Adjustment for the probability of healthcare seeking (Equations 6-9)			
ϕ^H	Probability of seeking healthcare	$\phi^H = \frac{\lambda^{S,B}}{\lambda_{adjusted}}$	See rest of table.
$\lambda^{S,B}$	The incidence rate of typhoid fever after adjusting for blood culture sensitivity and the probability of receiving a blood culture test	$\lambda^{S,B} = \frac{\lambda_{\text{observed}}}{\phi^S * \phi^B}$	See rest of table.
λ_0	Incidence of typhoid fever among those without the risk factor	$\lambda_0 = \frac{\lambda^{S,B}}{\left(h_1 R_{TF} p + h_0(1-p)\right)}$	See rest of table.
R_{TF}	Relative risk for typhoid fever among those with the risk factor compared to those without it	$\log(R_{TF}) \sim N(m_{TF}, d_{TF})$ *Malawi:* mean $m_{TF} = \log(0.5)$; standard deviation $d_{TF} = 0.34$ *Nepal:* $m_{TF} = \log(5.71)$; $d_{TF} = 0.47$ *Bangladesh:* $m_{TF} = \log(7.6)$; $d_{TF} = 0.64$	[19-21]
h_0	Probability of self-reported healthcare seeking for a fever among those without the risk factor	$h_0 \sim Beta(l_{h_0}, q_{h_0})$	See rest of table.
l_{h_0}	Number of individuals who sought care out of those without the risk factor	Observed directly	STRATAA HUS
q_{h_0}	Number of individuals who did not seek care out of those without the risk factor	Observed directly	STRATAA HUS
h_1	Probability of self-reported healthcare seeking for a fever among those with the risk factor	$S_1 \sim Beta(l^{S_1}, q^{S_1})$	See rest of table.
l_{h_1}	Number of individuals who sought care out of those with the risk factor	Observed directly	STRATAA HUS
q_{h_1}	Number of individuals who did not seek care out of those with the risk factor	Observed directly	STRATAA HUS
p	Probability of having the self-reported risk factor. In Malawi this was soap available after defecation, in Nepal this was unshared toilets, and in Bangladesh this was boiled drinking water.	$p \sim Beta(l_p, q_p)$	See rest of table.

l_p	Number of individuals with the identified typhoid fever risk factor	Observed directly	STRATAA HUS
q_p	Number of individuals without the identified typhoid fever risk factor	Observed directly	STRATAA HUS

PS = Passive Surveillance
HUS = Healthcare Utilisation Survey

Table 2. Posterior probability estimates for each adjustment factor by age and site. Each estimate (posterior mean) is shown with its 95% credible interval for the sensitivity of the blood culture (BC) given that healthcare (HC) was sought and a blood culture was taken ($\phi^S_{a,c}$), the probability of receiving a blood culture test given that healthcare was sought ($\phi^B_{a,c}$), and the probability of seeking healthcare ($\phi^H_{a,c}$). Estimated adjustment factors are shown by age category (a) and country (c).

Probability	Country (c)	Age category (a), in years					
		<5	**5-9**	**10-14**	**15-29**	**30+**	**all**
Sensitivity of BC, given HC sought, BC taken ($\phi^S_{a,c}$)	**Malawi**	0.53 (0.48-0.57)	0.53 (0.51-0.55)	0.53 (0.50-0.56)	0.58 (0.55-0.62)	0.58 (0.54-0.62)	**0.54 (0.35-0.60)**
	Nepal	0.54 (0.51-0.57)	0.54 (0.51-0.57)	0.54 (0.51-0.58)	0.56 (0.54-0.58)	0.56 (0.55-0.57)	**0.55 (0.51-0.58)**
	Bangladesh	0.53 (0.52-0.53)	0.53 (0.53-0.53)	0.53 (0.53-0.53)	0.56 (0.54-0.58)	0.56 (0.56-0.56)	**0.54 (0.51-0.57)**
Probability BC was drawn, given HC sought ($\phi^B_{a,c}$)	**Malawi**	0.40 (0.38-0.41)	0.38 (0.36-0.41)	0.33 (0.29-0.36)	0.21 (0.19-0.24)	0.20 (0.17-0.23)	**0.35 (0.34-0.36)**
	Nepal	0.81 (0.61-0.91)	0.87 (0.72-0.94)	0.87 (0.73-0.94)	0.91 (0.71-0.98)	0.91 (0.71-0.98)	**0.84 (0.67-0.92)**
	Bangladesh	0.94 (0.87-0.97)	0.97 (0.94-0.99)	0.97 (0.94-0.99)	0.98 (0.96-0.99)	0.98 (0.96-0.99)	**0.96 (0.92-0.98)**
Probability of seeking HC ($\phi^H_{a,c}$)	**Malawi**	0.62 (0.52-0.72)	0.83 (0.74-0.90)	0.83 (0.74-0.90)	0.71 (0.60-0.81)	0.71 (0.60-0.81)	**0.71 (0.64-0.77)**
	Nepal	0.21 (0.11-0.34)	0.11 (0.04-0.22)	0.11 (0.04-0.22)	0.13 (0.05-0.25)	0.13 (0.05-0.25)	**0.15 (0.09-0.22)**
	Bangladesh	0.32 (0.21-0.45)	0.34 (0.24-0.45)	0.33 (0.24-0.45)	0.19 (0.11-0.27)	0.19 (0.11-0.27)	**0.27 (0.22-0.33)**

Table 3. Estimated adjustment factors from final models. The ratio of the median estimate (95% credible interval) of adjusted-to-observed incidence rates is shown for each country and age category.

Age (years)	Malawi	Nepal	Bangladesh
0-4	7.6 (4.8-11.6)	10.7 (4.3-26.8)	6.3 (4.2-10.2)
5-9	5.9 (4.1-8.3)	19.7 (9.0-54.9)	5.8 (4.1-8.6)
10-14	6.9 (4.3-10.4)	19.6 (8.6-55.2)	5.8 (3.9-8.9)
15-29	11.4 (6.9-18.0)	15.8 (7.4-42.4)	9.8 (6.2-16.7)
30+	12.0 (6.0-21.7)	15.0 (4.6-48.8)	9.7 (5.5-17.9)
All ages	7.7 (6.0-12.4)	14.4 (9.3-24.9)	7.0 (5.6-9.2)

Table 4. Adjusted typhoid incidence estimates compared to seroincidence. The final adjusted typhoid incidence estimates from the models are shown with 95% credible intervals, as well as the seroincidence estimates with their 95% confidence intervals, by age and site.

Age	Malawi			Nepal			Bangladesh		
	Crude rates	Adjusted rates	Seroincidence	Crude rates	Adjusted rates	Seroincidence	Crude rates	Adjusted rates	Seroincidence
0-4 years	83 (53-124)	632 (398-965)	2,868 (1,153-5,911)	72 (33-136)	764 (307-1,921)	7,813 (2,537-18,232)	417 (337-511)	2,625 (1,764-4,244)	3,401 (1,904-5,610)
5-9 years	146 (103-201)	861 (599-1,203)	1,205 (146-4,352)	341 (250-455)	6,713 (3,085-18,730)	5,217 (1,915-11,356)	554 (456-666)	3,228 (2,276-4,757)	3,435 (1,571-6,521)
10-14 years	88 (56-132)	602 (377-915)	3,061 (631-8,946)	191 (128-275)	3,750 (1,653-10,559)	8,910 (4,075-16,916)	268 (203-348)	1,564 (1,050-2,384)	599 (15-3,336)
15-29 years	32 (20-48)	361 (219-567)	3,774 (1,384-8,213)	92 (71-119)	1,457 (684-3,918)	10,169 (5,255-17,764)	98 (76-124)	956 (603-1,635)	5,310 (2,744-9,275)
30+ years	21 (10-37)	248 (124-447)	2,076 (762-4,518)	6 (2-13)	92 (29,301)	7,322 (5,100-10,183)	29 (19-42)	279 (157-514)	2,988 (1,672-4,928)
All ages	58 (48-70)	444 (347-717)	2,505 (1,605-3,728)	74 (62-87)	1,062 (683-1,839)	7,631 (5,914-9,691)	161 (145-179)	1,135 (898-1,480)	3,256 (2,432-4,270)

References

1. Crump J, Youssef F, Luby S, Wasfy M, Rangel J, Taalat M. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. Emerging Infectious Diseases. 2003;9(5):539–44. doi: 10.3201/eid0905.020428.
2. Antillon M, Warren J, Crawford F, Weinberger D, Kurum E, Pitzer V. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis. 2017;11(2). doi: 10.1371/journal.pntd.0005376.
3. Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. The Lancet. 2014;2(10):e570-80. doi: 10.1016/S2214-109X(14)70301-8.
4. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid Fever. New England Journal of Medicine. 2002;347:1770-82. doi: 10.1056/NEJMra020201.
5. Panzner U, Pak GD, Aaby P, Adu-Sarkodie Y, Ali M, Aseffa A, et al. Utilization of Healthcare in the Typhoid Fever Surveillance in Africa Program. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;62:S56-68. doi: 10.1093/cid/civ891. PubMed PMID: 26933023.
6. Kassile T, Lokina R, Mujinja P, Mmbando BP. Determinants of delay in care seeking among children under five with fever in Dodoma region, central Tanzania: a cross-sectional study. Malaria journal. 2014;13(1):348. doi: doi:10.1186/1475-2875-13-348.
7. Dillip A, Hetzel MW, Gosoniu D, Kessy F, Lengeler C, Mayumana I, et al. Socio-cultural factors explaining timely and appropriate use of health facilities for degedege in south-eastern Tanzania. Malaria journal. 2009;8:144. Epub 2009/07/01. doi: 10.1186/1475-2875-8-144. PubMed PMID: 19563640; PubMed Central PMCID: PMCPMC2712476.
8. Elven J, Dahal P, Ashley EA, Thomas NV, Shrestha P, Stepniewska K, et al. Non-malarial febrile illness: a systematic review of published aetiological studies and case reports from Africa, 1980–2015. BMC Med. 2020;18(279). doi: 10.1186/s12916-020-01744-1.
9. Voysey M, Pant D, Shakya M, Liu X, Colin-Jones R, Theiss-Nyland K, et al. Under-detection of blood culture-positive enteric fever cases: The impact of missing data and methods for adjusting incidence estimates. 2020;14(1):e0007805. doi: 10.1371/journal.pntd.0007805.
10. World Health Organization (WHO). Typhoid vaccines position paper. Weekly epidemiological record. 2018;13(93):153–72.
11. Antillon M, Saad NJ, Baker S, Pollard AJ, Pitzer VE. The Relationship Between Blood Sample Volume and Diagnostic Sensitivity of Blood Culture for Typhoid and Paratyphoid Fever: A Systematic Review and Meta-Analysis. The Journal of Infectious Diseases. 2018:jiy471. doi: 10.1093/infdis/jiy471.
12. Reed C, Angulo FJ, Swerdlow DL, Lipsitch M, Meltzler MI, Jernigan DB, et al. Estimates of the Prevalence of Pandemic (H1N1) 2009, United States, April–July 2009. Emerging Infectious Diseases. 2009;15(13).
13. Presanis AM, De Angelis D, Hagy A, Reed C, Riley S, Cooper BS, et al. The Severity of Pandemic H1N1 Influenza in the United States, from April to July 2009: A Bayesian Analysis. PLoS Med. 2009;6(12). doi: 10.1371/journal.pmed.1000207. PubMed PMID: 19997612.
14. Health Protection Agency. HIV in the United Kingdom: 2008 Report. London, United Kingdom: 2008.
15. Goubar A, Ades AE, De Angelis D, McGarrigle CA, Mercer CH, Tookey PA, et al. Estimates of Human Immunodeficiency Virus Prevalence and Proportion Diagnosed Based on Bayesian Multiparameter Synthesis of Surveillance Data [with Discussion]. Journal of the Royal Statistical Society Series A (Statistics in Society). 2008;171(3):541-80.
16. Presanis AM, De Angelis D, Spiegelhalter DJ, Seaman S, Goubar A, Ades AE. Conflicting Evidence in a Bayesian Synthesis of Surveillance Data to Estimate Human Immunodeficiency Virus Prevalence. Journal of the Royal Statistical Society Series A (Statistics in Society). 2008;171(4):915-37.
17. Darton TC, Meiring JE, Tonks S, Khan MA, Khanam F, Shakya M, et al. The STRATAA study protocol: a programme to assess the burden of enteric fever in Bangladesh, Malawi and Nepal using prospective population census, passive surveillance, serological studies and healthcare utilisation surveys. 2017;7(6). doi: 10.1136/bmjopen-2017-016283.
18. Meiring J, Gibani M, The TyVAC Consortium Meeting Group. The Typhoid Vaccine Acceleration Consortium (TyVAC): Vaccine effectiveness study designs: Accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a meeting held on 26–27 October 2016, Oxford, UK. Vaccine. 2017;35(38). doi: https://doi.org/10.1016/j.vaccine.2017.08.001.

19. Gauld JS, Olgemoeller F, Nkhata R, Li C, Chirambo A, Morse T, et al. Domestic river water use and risk of typhoid fever: results from a case-control study in Blantyre, Malawi. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019. Epub 2019/05/31. doi: 10.1093/cid/ciz405. PubMed PMID: 31144715.
20. Karkey A, Thompson CN, Tran Vu Thieu N, Dongol S, Le Thi Phuong T, Voong Vinh P, et al. Differential epidemiology of Salmonella Typhi and Paratyphi A in Kathmandu, Nepal: a matched case control investigation in a highly endemic enteric fever setting. PLoS Negl Trop Dis. 2013;7(8):e2391. Epub 2013/08/31. doi: 10.1371/journal.pntd.0002391. PubMed PMID: 23991240; PubMed Central PMCID: PMCPMC3749961.
21. Ram PK, Naheed A, Brooks WA, Hossain MA, Mintz ED, Breiman RF, et al. Risk factors for typhoid fever in a slum in Dhaka, Bangladesh. Epidemiol Infect. 2007;135(3):458-65. Epub 2006/08/09. doi: 10.1017/s0950268806007114. PubMed PMID: 16893490; PubMed Central PMCID: PMCPMC2870597.
22. Gelman A, Rubin D. Inference from iterative simulation using multiple sequences. Statistical Science. 1992;7:457-72.
23. MATLAB. version 9.3.0 (R2017b) ed. Natick, MA: The MathWorks Inc; 2017.
24. Plummer M. rjags: Bayesian Graphical Models using MCMC. R package version 4-6 ed2016.
25. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
26. Phillips MT. Adjusted Typhoid Incidence 2020 [January 13, 2020]. Available from: https://github.com/mailephillips/adjusted-typhoid-incidence.
27. Ocan M, Obuku EA, Bwanga, Freddie, Akena D, Richard S, et al. Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. BMC Public Health. 2015;15(742). doi: 10.1186/s12889-015-2109-3.
28. Srikantiah P, Girgis F, Luby SP, Jennings G, Omar Wasfy M, Crump JA, et al. Population-based surveillance of typhoid fever in Europe. Am J Trop Med Hyg. 74(1):114-9.
29. Andrews JR, Barkume C, Yu AT, Saha SK, Qamar FN, Garrett D, et al. Integrating Facility-Based Surveillance With Healthcare Utilization Surveys to Estimate Enteric Fever Incidence: Methods and Challenges. J Infect Dis. 2018. Epub 2018/09/06. doi: 10.1093/infdis/jiy494. PubMed PMID: 30184162.
30. Carey ME, MacWright WR, Im J, Meiring JE, Gibani MM, Park SE, et al. The Surveillance for Enteric Fever in Asia Project (SEAP), Severe Typhoid Fever Surveillance in Africa (SETA), Surveillance of Enteric Fever in India (SEFI), and Strategic Typhoid Alliance Across Africa and Asia (STRATAA) Population-based Enteric Fever Studies: A Review of Methodological Similarities and Differences. CID. 2020;71. doi: doi.org/10.1093/cid/ciaa367.
31. Marks F, von Kalckreuth V, Aaby P, Adu-Sarkodie Y, El Tayeb MA, Ali M, et al. Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. Lancet Global Health. 2019;5(3). doi: 10.1016/S2214-109X(17)30022-0.
32. Breiman RF, Cosmas L, Njuguna H, Audi A, Olack B, Ochieng JB, et al. Population-Based Incidence of Typhoid Fever in an Urban Informal Settlement and a Rural Area in Kenya: Implications for Typhoid Vaccine Use in Africa. PLoS One. 2012;7(1):e29119. doi: 10.1371/journal.pone.0029119.
33. Soni A, Fahey N, Phatak AG, Desai RG, Roman J, Nimbalkar SM, et al. Differential in Healthcare-Seeking Behavior of Mothers for Themselves versus Their Children in Rural India: Results of a Cross Sectional Survey. International Public Health Journal. 2014;6(1):57.

Supplementary figures and tables.

Fig S1. Typhoid fever pyramid and febrile pyramid. The typhoid pyramid (green) is nested within the fever pyramid (grey). Some fraction of symptomatic typhoid fever cases and febrile cases seek care (shaded regions, *TF* and *F*, respectively). The average probability of seeking care for fever is measured (*h;* dashed purple line), but this may vary for individuals with typhoid fever versus fever due to other causes. Within the typhoid fever and fever pyramids, individuals may (X=1) or may not (*X*=0) have a risk factor for typhoid fever; the probability of seeking healthcare varies for those with or without the risk factor, and the risk factor is more prevalent among those with typhoid fever. One can observe whether a person has a fever, but not whether they have typhoid fever.

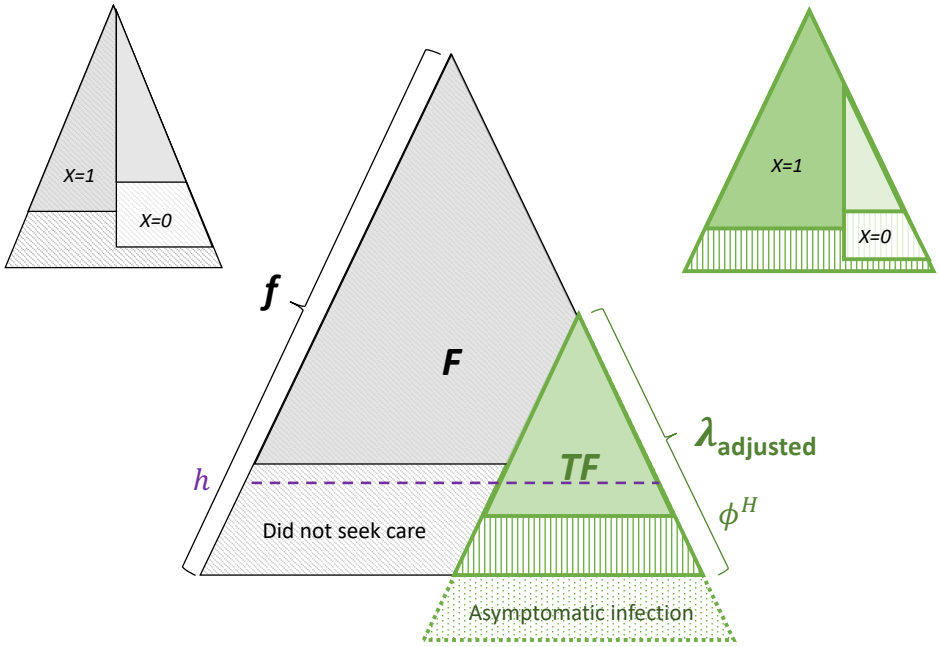

Fig S2. Plots of prior antibiotic use, blood culture volume, and blood culture sensitivity. The average proportion of those with antibiotic use in the past two weeks (A) and the average blood culture volume (B) by country and age group is shown in plots A and B, respectively. In plot C, the distribution of overall (across all age groups) blood culture sensitivity after adjusting for prior antibiotic use and blood culture volume drawn is shown.

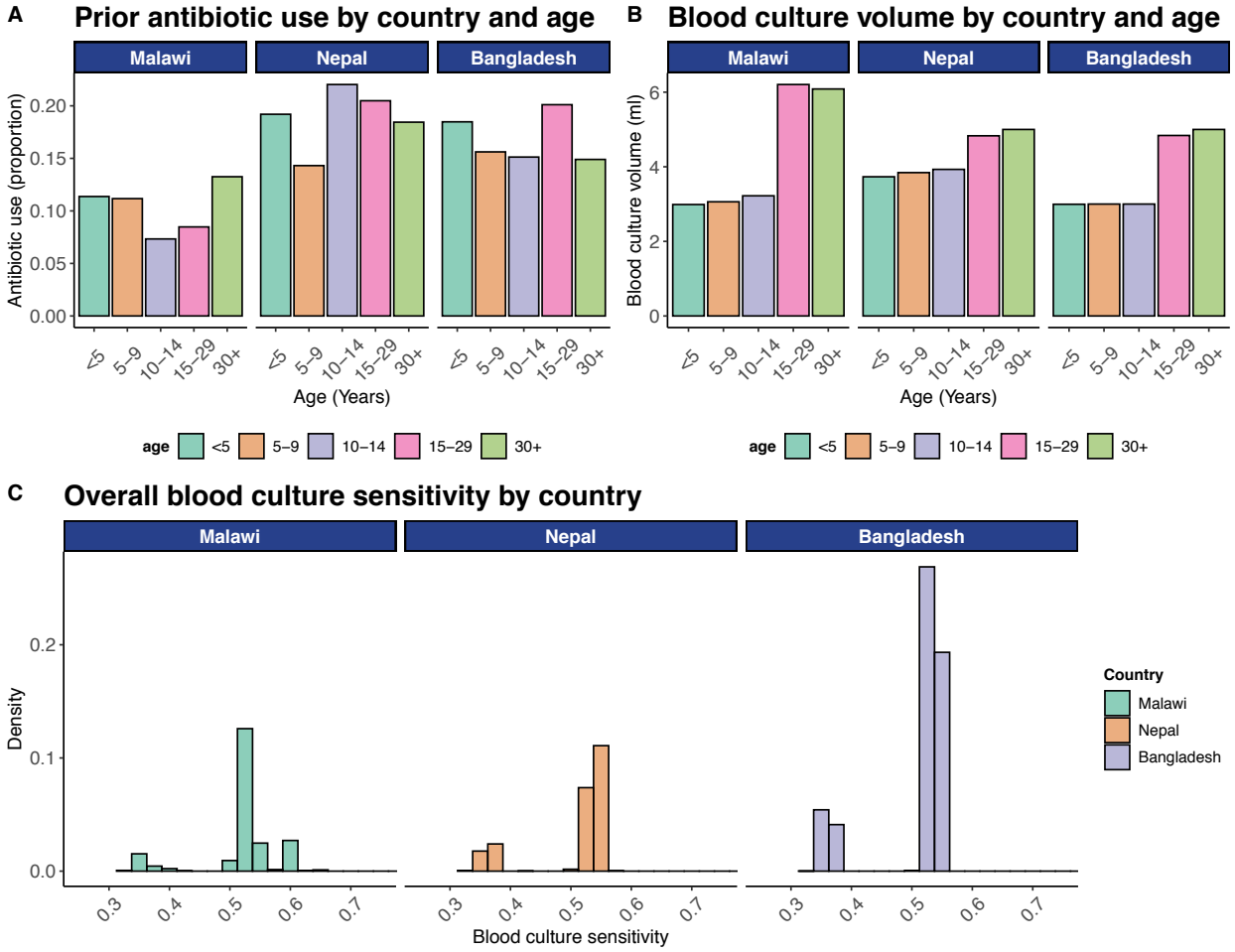

Fig S3. Estimated probabilities from simulated data. Data for the estimated typhoid incidence were simulated for low, medium and high probabilities of seeking healthcare (ϕ^H), receiving a blood culture diagnostic test (ϕ^B), and blood culture sensitivity (ϕ^S) (row panels); and each simulation was performed sampling 735; 1,000; and 2,000 individuals (column panels) from the population to be "observed" from the healthcare utilization portion. The true values used for simulation are shown in dashed horizontal black lines. The value for blood culture sensitivity without adjusting for prior antibiotic use is shown in dotted gray lines. Estimated values are shown for models that did (red) and did not (blue) account for variation in blood culture sensitivity and variation in typhoid incidence among those who did or did not seek care and were or were not tested.

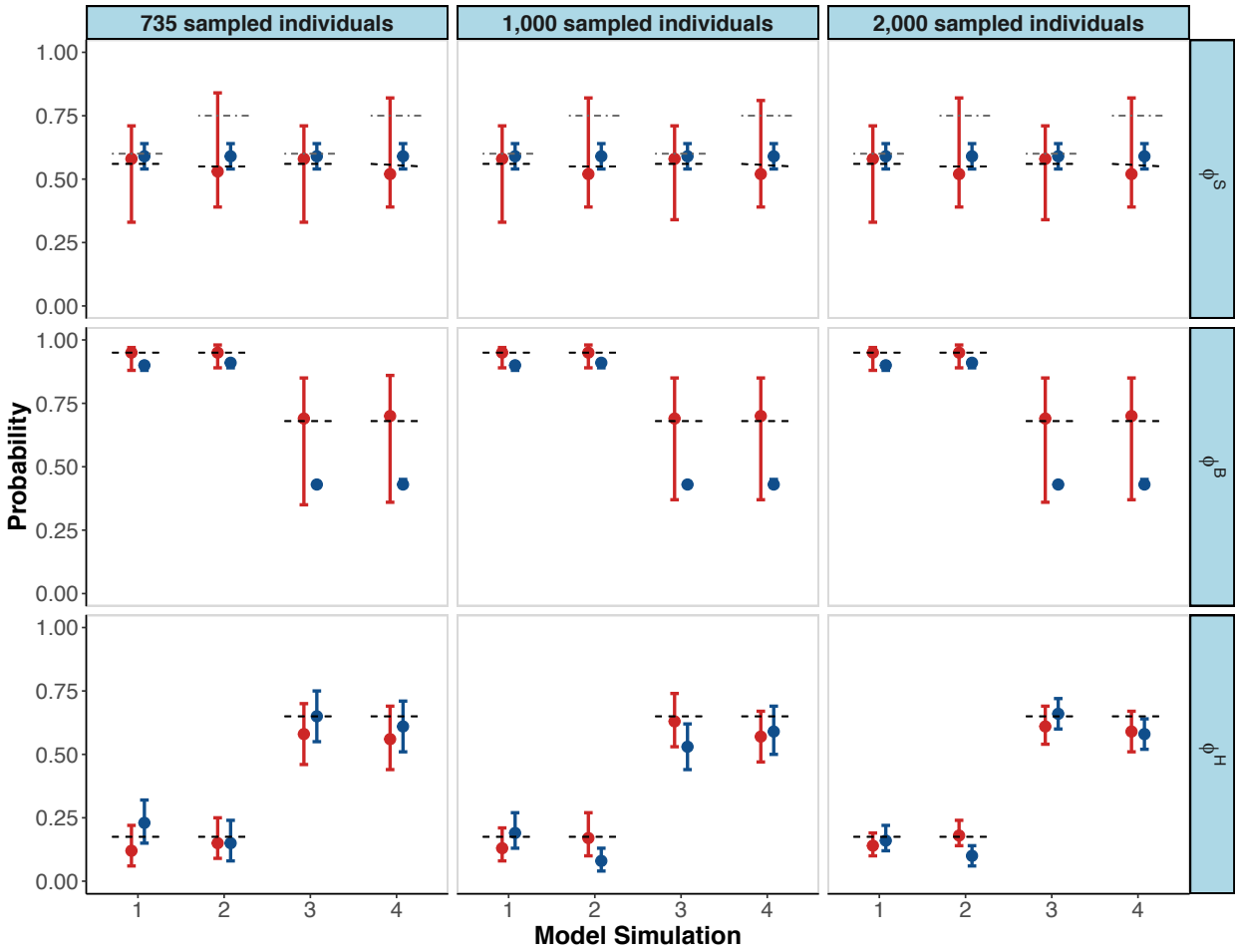

Fig S4. Estimated STRATAA typhoid incidence with full model versus a simplified approach. The estimated typhoid incidence per 100,000 person-years of observation is shown for models that did (red) and did not (blue) take into account variation in blood culture sensitivity and variation in typhoid incidence among those who did or did not seek care and were or were not tested for each age group and country. Note that the upper bounds on children 5-9 and 10-14 in Nepal are not shown.

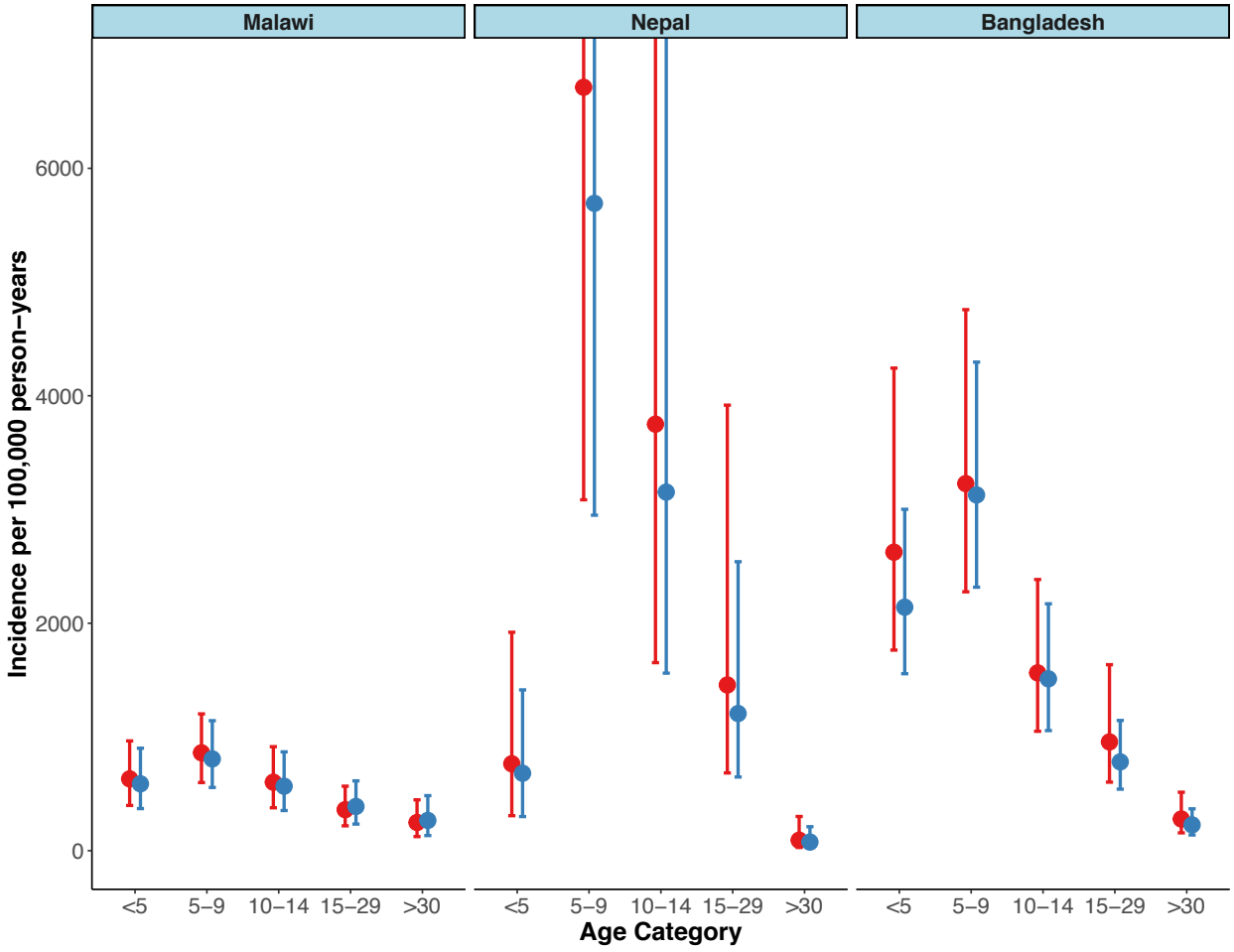

Fig S5. Estimated STRATAA probabilities from full model versus a simplified approach. The estimated probabilities of seeking healthcare (ϕ^H receiving a blood culture diagnostic test (ϕ^B), and blood culture sensitivity (ϕ^S) are shown for models that did (red) and did not (blue) take into account variation in blood culture sensitivity and variation in typhoid incidence among those who did or did not seek care and were or were not tested for each age group and country.

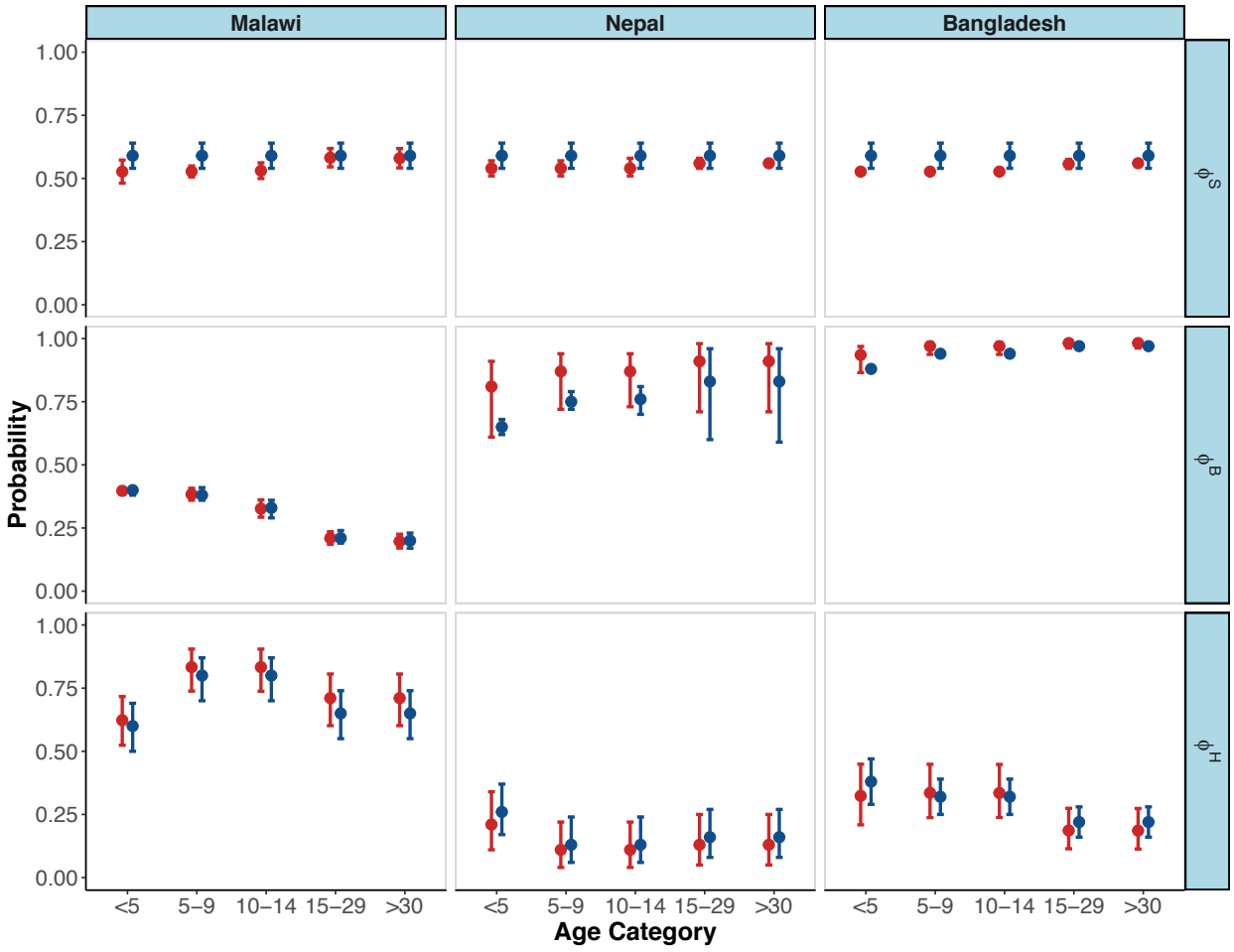

Table S1. Contingency table of an individual's sensitivity and specificity for blood culture diagnostic test. In this study, we assumed that all individuals who tested positive for typhoid fever were true cases of typhoid. Among those who tested negative, an individual *i*'s probability of being a true case of typhoid ($w_{i,v(i),u(i)}$) depended on the volume of blood drawn *v* and his or her reported prior antibiotic use *u*.

	Typhoid	**No typhoid**
BC+	$w_{i,v(i),u(i)}$	0
BC-	$1 - w_{i,v(i),u(i)}$	1

Table S2. Prevalence of typhoid fever risk factor, rates of reported febrile illness, and probability of healthcare seeking from the Healthcare Utilization Surveys. The prevalence (prev.) and numerator used to calculate the prevalence (*N*) of each factor used to estimate the probability of healthcare seeking by age and country are show in the table below. Values are shown for the probability of having the risk factor for typhoid fever (*p*), and the proportion of those who sought care at a STRATAA partner health facility among those with (h_1) and without (h_0) the risk factor are shown.

		p		***h*$_1$**		***h*$_0$**		***R*$_{TF}$**
	Age	***prev.***	***N***	***prev.***	***N***	***prev.***	***N***	***Mean (95% CI)***
Nepal	***all ages***	0.42	130	0.13	11	0.25	27	5.7 (2.3-14.4)
	u5	0.37	28	0.18	5	0.32	15	
	5-14	0.45	58	0.10	3	0.19	5	
	15+	0.42	44	0.12	3	0.20	7	
Bangladesh	***all ages***	0.30	863	0.26	35	0.31	95	7.6 (2.2-26.5)
	u5	0.29	146	0.29	10	0.41	31	
	5-14	0.30	306	0.35	16	0.31	34	
	15+	0.30	411	0.17	9	0.24	30	
Malawi	***all ages***	0.20	378	0.74	59	0.64	130	2.0 (1.3-2.5)
	u5	0.20	126	0.72	23	0.55	42	
	5-14	0.20	126	0.78	18	0.80	47	
	15+	0.20	126	0.72	18	0.62	41	

Data availability statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing Interest Statement
VEP is a member of the World Health Organization's (WHO) Immunization and Vaccine-related Implementation Research Advisory Committee. AJP chairs the UK Department of Health's (DoH) Joint Committee on Vaccination and Immunisation (JCVI) and the European Medicines Agency Scientific Advisory Group on Vaccines and is a member of the World Health Organization's (WHO) Strategic Advisory Group of Experts. The views expressed in this manuscript are those of the authors and do not necessarily reflect the views of the JCVI, the DoH, or the WHO.

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Chapter 2

Title: ***Cost-effectiveness analysis of typhoid conjugate vaccines in an outbreak setting***

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Abstract

Background. Several prolonged typhoid fever epidemics have been reported since 2010 throughout eastern and southern Africa, thought to be caused by the spread of multidrug resistant *Salmonella* Typhi. The World Health Organization recommends the use of typhoid conjugate vaccines (TCVs) in outbreak settings; however, current data are limited on how and when TCVs might be introduced in an outbreak setting. While vaccination can be an effective public health intervention, if resources are implemented late or focused inappropriately, fewer infections will be averted.

Methodology. We modified a dynamic transmission model of a typhoid fever outbreak in Malawi to evaluate preventative and reactive vaccination strategies. We then conducted a cost-effectiveness analysis using the net-benefits framework to compare no vaccination to routine vaccination at 9 months of age with and without a catch-up campaign up to 15 years old. We considered a 10-year time horizon and compared reactive vaccination strategies to preventative strategies with randomized outbreak timing over the 10-year period. We also compared this analysis to the cost-effectiveness of TCV introduction given the pre-outbreak typhoid incidence (with no outbreak on the horizon) and one with post-outbreak incidence (10 years after the outbreak). We examined variations in outbreak definitions, delays in implementation of reactive vaccination, and the timing of preventive vaccination relative to the outbreak.

Results. We estimated that vaccination would prevent 15-60% of disability-adjusted life-years (DALYs) in the outbreak scenarios. In the cost-effectiveness analyses, some form of routine vaccination with a catch-up campaign was preferred over no vaccination for WTP values of at least $110 per DALY averted. Reactive vaccination was the preferred strategy for WTP values of $110-430 per DALY averted, but became less optimal as delays in TCV deployment increased.

For WTP values >$430, introduction of preventative routine TCV immunization with a catch-up campaign was the preferred strategy assuming the outbreak occurred within 10 years. However, when no outbreak occurred and assuming the pre-outbreak incidence, no vaccination was the optimal strategy for WTP values <$980. For the current post-outbreak incidence, routine vaccination with a catch-up campaign is preferred for WTP values of $280 and above, consistent with previous analyses for Malawi.

Conclusions. Countries where outbreaks of typhoid fever due to introduction of antimicrobial resistant strains are likely to occur should consider TCV introduction. Reactive vaccination can be a cost-effective strategy, but only if delays in vaccine deployment are minimal; otherwise, introduction of preventive routine immunization with a catch-up campaign should be considered.
Keywords: typhoid fever; reactive vaccination; preventive vaccination; typhoid conjugate vaccines; economic evaluation

Introduction

Typhoid fever is a major source of morbidity and mortality in developing countries. Approximately 12-21 million infections and 119,000-269,000 deaths are attributed to typhoid fever each year [1-3], accounting for 2-23 million disability-adjusted life years (DALYs) [4]. Since 2010, there have been several prolonged typhoid outbreaks in eastern and southern Africa, which have imposed considerable costs to the populations impacted [5-8]. These outbreaks are thought to be caused by antimicrobial-resistant (AMR) strains and, as a result, more outbreaks are likely [5, 8, 9].

Typhoid conjugate vaccines (TCVs) are an effective means of typhoid prevention and control. They have been approved and recommended by the World Health Organization (WHO) and Gavi, the Vaccine Alliance, has pledged support for introduction of TCVs in typhoid-endemic countries. However, research regarding the vaccines' long-term efficacy and use in outbreak settings is lacking. Current data is limited on how and when TCVs should be introduced, and vaccine stockpiles do not yet exist [10, 11].

Reactive vaccination has become an important prevention measure for outbreaks of diseases such as cholera, influenza, and Ebola [12-19]. While reactive vaccination can be effective, if implemented late or focused inappropriately, the number of cases averted will be small [12, 16, 17]. While TCVs are recommended by the WHO for use in outbreak settings, there is no clear way of defining an outbreak of typhoid fever. Furthermore, policy makers are faced with inevitable delays in securing TCVs for outbreak response and applying for Gavi support to implement vaccination. Early introduction of TCVs may provide an effective means of preventing prolonged outbreaks of typhoid fever associated with introduction of AMR strains,

but the cost-effectiveness of preventative versus reactive vaccination strategies over different time horizons needs to be evaluated.

Here, we use a dynamic transmission model fitted to data from a typhoid fever outbreak in Blantyre, Malawi to investigate the health impact and costs associated with alternative vaccine delivery strategies to inform the use of TCVs in an outbreak setting. We explored a range of preventative and reactive vaccination scenarios to allow for uncertainty in outbreak timing, outbreak identification, and delays in vaccine introduction.

Methods

Transmission model and outbreak threshold

We developed an age-specific stochastic model to simulate typhoid fever transmission dynamics in Blantyre, Malawi from January 1995 to December 2031. Details of the model are provided in the Appendix. The model was parameterized based on the equivalent deterministic model fitted to routine blood-culture surveillance data from Queen Elizabeth Central Hospital (QECH) in Blantyre from January 1996 to February 2015 [9], which captures the multi-year outbreak of typhoid fever that occurred in Blantyre between 2011-2015. We assumed the outbreak was caused by an increase in the duration of infectiousness of *Salmonella* Typhi associated with the emergence of the multidrug-resistant H58 haplotype [9, 20]. We validated the model by comparing to blood-culture surveillance data from QECH for March 2015-December 2016. To scale the number of blood-culture-confirmed cases at QECH to the population-based incidence of typhoid fever in Blantyre, we used data from the recently completed Strategic Typhoid Alliance across Africa and Asia (STRATAA) cohort study (S1.1.4 Text) [21].

The stochastic model incorporated uncertainty in the transmission dynamics using a Poisson process for each transition between states and a binomial observation process for the (under)reporting of cases over the duration of an individual's infection. To simulate the impact of vaccination, we incorporated further uncertainty in vaccine efficacy at time 0, the waning of vaccine-induced immunity, and vaccine coverage during the catch-up campaign by sampling from the associated uncertainty distribution for each stochastic iteration (S1 Text). The dynamic model parameters, their estimates and uncertainty distributions, and sources are listed in Table 1. For each intervention strategy, we simulated the outbreak 1,000 times.

Table 1. Dynamic model input parameters

Characteristic	Value	Source
Demographic parameters		
Birth rate (B)	31.3-55.0 live births per 1,000 per year	[9]
Mortality rate (includes migration) (μ)	7.7-27.8 deaths per 1,000 per year	[9]
Disease parameters		
Duration of infectiousness ($1/\delta$)	4 weeks	[9, 22]
Seasonal offset parameter (timing of seasonal peak) (ϕ)	4.9 weeks	[9]
Fraction infected who become chronic carriers (θ)	0.003-0.101 depending on age	[23]
Disease-induced mortality (α)	0.001	[9, 24]
Duration of temporary full immunity to infection ($1/\omega$)	104 weeks	[9, 22]
Basic reproductive number (R_0)	3.29	Refit parameters from modified Pitzer et al model [9]
Amplitude of seasonal forcing (q)	0.35	Refit parameters from modified Pitzer et al model [9]
Relative infectiousness of chronic carriers (r)	0.09	Refit parameters from modified Pitzer et al model [9]
Outbreak parameters		
Beginning week of increase in duration of infectiousness (t_1)	April 10, 2011	Refit parameters from modified Pitzer et al model [9]
End week of increase in duration of infectiousness (t_2)	November 23, 2014	Refit parameters from modified Pitzer et al model [9]

Magnitude of increase in duration of infetiousness (m)	3.1954	Refit parameters from modified Pitzer et al model [9]
Reporting process		
Underreporting adjustment factor (a)	7.7 (95% CrI: 6.0-12.4)	[21]
Vaccine-related parameters		
Age groups vaccinated Routine Catch-up campaign	 9 months 9 months to <15 years	Based on WHO recommendation
Initial efficacy of TCV (v_0)	0.89 (95% CrI: 0.78-0.98)	Re-analysis based on Malawi TCV efficacy trial data from [25] and a previous estimate from [26]
Waning of vaccine-induced immunity ($1/\omega_v$) (years)	18.9 (95% CrI: 8.4-83.3)	Re-analysis based on Malawi TCV efficacy trial data from [25] and a previous estimate from [26]
Vaccine coverage Routine (κ_R) Catch-up campaign (κ_C)	 Increases from 0.85 to 0.95 over ten years Uniform(0.6,0.9)	Gavi demand forecasts under assumption of unconstrained supply, and commonly assumed coverage during a catch-up campaign during an outbreak

Since there is no globally-defined threshold for a typhoid fever outbreak, we explored different definitions of the epidemic threshold. For the purposes of our analysis and to facilitate outbreak identification from passive hospital-based surveillance data across different populations and contexts, we specified the epidemic threshold in terms of the number of standard deviations (SD) above the mean monthly reported typhoid fever cases for the baseline period of 2000-2010. We examined thresholds ranging from 6-16 SD above the mean, and defined the "true" start of the outbreak as April 10, 2011, identified previously during model-fitting. Setting a threshold too low would trigger too many false positive identifications of the outbreak, while setting the threshold too high could fail to identify a true outbreak in a timely manner. To address this issue, we compared the sensitivity and specificity of each definition of outbreak definition. We defined the sensitivity of each threshold as the percentage of simulations in which the outbreak was identified within 18 months of April 2011, while the specificity was defined as the percentage of simulations in which the outbreak threshold was not exceeded prior to April 2011. Once the

outbreak threshold was crossed, all subsequent months were considered to be part of the outbreak. For our primary analysis, we used the outbreak identification threshold that yielded the highest sum of sensitivity and specificity.

Vaccination scenarios

We compared scenarios in which TCV introduction occurs before the outbreak (preventive, assuming an outbreak is likely) versus after the outbreak starts (reactive). We modeled the impact of routine vaccination with TCV at 9 months old with or without a catch-up campaign up to 15 years of age. We assumed an initial vaccine efficacy of approximately 89% (95% credible interval (CrI): 78-98%) and an average duration of protection of 18.9 years (95% CrI: 8.40-83.3 years); we updated prior distributions for these parameters by fitting to data from a phase 3, double-blind, randomized active-controlled clinical trial of single-dose Typbar TCV in Blantyre, Malawi [25, 26] (S1.1.2.2 Text). Routine vaccination coverage was assumed to increase from 85% to 95% over the first ten years of vaccination and then remain at 95% [26]. For catch-up campaign coverage, we assumed that the proportion vaccinated varied uniformly from 0.6-0.9.

Since it is typically not known when an outbreak will occur, we randomized the timing of the start of the outbreak over a 10-year time horizon. The randomized timing followed a discrete uniform distribution over Years 0-10. We assumed only a single outbreak occurs. We simulated four alternative vaccination strategies: no vaccination, preventive routine TCV introduction at 9 months of age (in Year 0), preventive routine vaccination plus a one-time catch-up to age 15, and reactive routine vaccination plus a catch-up campaign once the outbreak was identified (Table 2[26]).

Table 2. Strategy comparisons for deploying typhoid conjugate vaccines to prevent or respond to an outbreak. Each of the scenarios examined compares four strategies: a base case (no vaccination), a preventive strategy with routine vaccination at 9 months of age ("routine"), a preventive strategy with routine vaccination and a catch-up campaign up to 15 years of age ("routine + catch-up"), and a reactive vaccination strategy with routine vaccination and a catch-up campaign.

Strategy type	Vaccination strategies
Base	no vaccination
Preventive	routine at 9 months
Preventive	routine + catch-up to age 15
Reactive	routine + catch-up to age 15

We compared our results to two scenarios in which an outbreak does not occur over the 10-year time horizon. These analyses are more comparable to previous cost-effectiveness analyses, and allow us to examine whether it would be beneficial to introduce TCV in an endemic setting when typhoid fever incidence is lower (pre-outbreak incidence) or higher (post-outbreak incidence). For the pre-outbreak scenario, we assume typhoid fever incidence is comparable to that estimated for Blantyre for 1995-2005, whereas for the post-outbreak scenario, we assume it is comparable to that estimated for Blantyre for 2021-2031.

Economic evaluation

We used the stochastic transmission model to simulate the number of typhoid fever cases and vaccine doses administered under each strategy, then used the model output to calculate the disability-adjusted life-years (DALYs) due to typhoid, costs of treatment, and costs of vaccine delivery. Costs of vaccination programs are generally incurred by the government and donors in Malawi; hence, we considered the healthcare-payer perspective and only accounted for direct treatment and vaccination costs accrued by the healthcare system. Costs were converted to 2020 USD, to convert to the most recent full year. We conducted the analysis in accordance with WHO guidelines and recommendations of the Bill and Melinda Gates Foundation's reference

case [27-30]. All costs and effects were discounted at a rate of 3% per year. We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [27] (S2.2.3).

Consistent with WHO guidelines and recommendations of the Bill and Melinda Gates Foundation's reference case [27-30], we evaluated the effectiveness of each strategy in terms of DALYs. DALYs represent the total years of life lost due to death (YLL) and lived with disability (YLD) due to the disease: $DALY = YLL + YLD$ [31]. To estimate the YLLs due to typhoid fever, we multiplied the number of cases of typhoid fever by the probability of hospitalization and the probability of death for inpatients (S1.2.4 Text) [32, 33]. We then divided by the proportion of deaths occurring in hospital, which we assumed was uniformly distributed between 0.25-1 [26], to obtain an estimate of the total number of deaths, and subtracted the average age of death from typhoid fever from Malawi's life expectancy [34]. The YLDs were calculated based on the number of cases, duration of illness, and disability weights (S1.2.2 Text).

To estimate the treatment costs for typhoid fever, we assumed 71% (95% CrI: 64-77%) of typhoid fever cases would seek medical care and 4% (95% CrI: 1-11%) would be hospitalized; we updated prior distributions for these parameters based on data from the STRATAA cohort study [21] (Table 3; S1.2.3-1.2.4 Texts). The number of outpatient cases was calculated by subtracting the number of hospitalized cases from the number of individuals seeking care. We assumed cases not seeking medical care would not incur treatment costs. As this cost-effectiveness analysis was carried out from the healthcare provider perspective, we included only direct medical costs. We estimated treatment costs for each individual with typhoid fever using WHO-CHOICE data [35].

Table 3. Input parameters for cost-effectiveness analysis.

Characteristic	Median value (95% CrI)	Source
Typhoid incidence and age distribution		
Annual number of symptomatic typhoid fever cases per 100,000 people (without vaccination)	26.1 (14.0-45.7) before outbreak; Up to 916 (823-1,543) during outbreak; 224 (169-368) after outbreak	Based on output from transmission dynamic model fit to incidence of typhoid
Average age of patients with typhoid infection (without vaccination) (years)	15.9 (13.8-19.3)	Based on output from transmission dynamic model fit to incidence of typhoid
Typhoid mortality		
Probability of death if patients are admitted to hospital for typhoid infection	0.09 (0.02-0.28)	[33, 36] [37]
Proportion of deaths from typhoid infection occurring in patients not hospitalized	0.38 (0.02-0.73)	Assuming that on average about one of three deaths occur outside the hospital setting from [26]
Average age at death from typhoid infection	15.9 (13.8-19.3)	Assuming age distribution of deaths is the same as the age distribution of patients with typhoid
Antimicrobial resistance		
Proportion of patients with typhoid infection with an AMR strain	0.001 (0.00-0.63) before outbreak; Up to 0.96 (0.86-1.00) during outbreak; 0.65 (0.31-0.98) after outbreak	[20, 37]
Burden of AMR cases relative to antimicrobial-sensitive cases	2 (1-3)	[26]
Healthcare use		
Probability of infected patients seeking healthcare	0.71 (0.64-0.77)	[21]
Probability that infected patients are admitted to hospital	0.04 (0.01-0.11)	[38] [37]
Length of stay in hospital (days)	6 (3-9)	[26]
Number of visits to medical doctors by inpatients and outpatients	1	[26]
Treatment costs		
Cost of inpatient treatment	$34.00 ($9.00-107.00)	[26]
Cost out outpatient treatment	$1.30 ($0.30-3.20)	[26]

Cost of treatment for a patient not seeking professional medical care	$0.81 (0.039-2.28)	[26]
Unit cost per bed-day for inpatients and unit cost per outpatient visit	$3.36 (0.81-9.02) $0.85 (0.14-2.66)	[26]
Relative adjustment factor for overestimation of unit cost per outpatient visit	0.63 (0.25-1.00)	[26]
Cost of drugs per inpatient	$8.30 (0.30-50.8)	[26]
Costs of laboratory tests per inpatient	$0.20 (0.00-60.00)	[26]
Cost of drugs per outpatient	$0.81 (0.039-2.28)	[26]
Costs of laboratory tests per outpatient	$0	[26]
Vaccine-related costs		
Vaccine procurement	See Bilcke et al for details	[26]
Injection and safety equipment	$0.23 (0.21-0.24)	[26]
Routine vaccine delivery cost per dose	$1.61 (0.36-4.23)	[26]
Number of years during which start-up costs of vaccine delivery program are incurred	2 (1-3)	[26]
Routine vaccine delivery costs (%)	64% (48-78)	[26]
Campaign vaccine delivery cost per dose	$0.040 (0.23-0.62)	[26]
Disability-adjusted life-years		
Disability-weights from 0 (perfect health) to 1 (death)	Severe illness, 0.21 (-.14-0.29); moderate illness, 0.052 (0.031-0.079); mild illness, 0.005 (0.002-0.011)	[39]
Relationship between disability weights for mild, moderate, and severe illness and outcomes on healthcare use	See description in supplement	[39]
Duration of illness in inpatients and outpatients (days)	16 (12-20)	[26]
Relative duration of illness for patients not seeking medical care (vs inpatients and outpatients)	0.5 (0.02-0.98)	[26]
Life expectancy	62.7	[34]

Antimicrobial resistance is likely to affect the burden and costs associated with typhoid fever. In the absence of sufficient data to parameterize the relative burden and costs of AMR typhoid fever, we assumed the case fatality risk, years of life lived with disability, and treatment costs were twice as high on average (uniformly 1-3 times higher) for AMR cases. Since recent outbreaks are thought to be caused by new AMR strains of typhoid, we allowed the proportion of AMR typhoid cases to vary with time based on data from a longitudinal study in Blantyre (S1.2.5 Text) [20].

For routine and campaign doses, we assumed a vaccine procurement cost of US$1.50 per dose and US$0.23 (95% confidence interval (CI): $0.21-0.24) per dose for injection and safety equipment, as in a previous study [26]. For routine doses, the delivery cost was assumed to be $1.76 (95% CI: 0.36-4.23) per dose based on the price of adding a new vaccine to routine vaccination across Gavi-eligible countries [26]; for campaign doses, we assumed the cost was $0.41 (95% CI: 0.23-0.62) based on a literature review that explored operational costs per vaccine doses for Supplementary Immunization Activities from 1992-2012 [40].

Sensitivity analyses

To assess the robustness of our economic evaluation to the underlying parameter uncertainty, we conducted two types of sensitivity analyses: 1) probabilistic sensitivity analyses, in which we examined cost-effectiveness acceptability frontiers to assess how parameter uncertainty contributes to uncertainty in the optimal strategy; 2) value of information analysis to identify the most influential parameters, by estimating the expected value of partially perfect information (EVPPI) for each parameter. We randomly drew 5,000 independent samples from the uncertainty distributions of each input parameter in the economic evaluation (Table S2). Each

sample was combined with one of the samples from the stochastic transmission model (1,000 simulations repeated five times to achieve a manageable computational burden) to estimate 5,000 net monetary benefit (NMB) values for each strategy and for a range of willingness-to-pay (WTP) values from $0-$1,000 in increments of $10. The NMB framework is represented as $NMB = \Delta E * WTP - \Delta C$, where ΔE is the averted DALYs through a strategy compared to the base case of no vaccination, ΔC is the incremental cost of the strategy compared to the base case, and *WTP* is the willingness-to-pay threshold. By calculating the proportion of samples for which a strategy yielded the highest NMB for each WTP, we quantified the uncertainty surrounding the optimal strategy. We also measured the contribution of parameter uncertainty to identifying the optimal vaccination strategy by calculating the EVPPI.

Scenario analyses

While countries have the option of introducing TCVs into the routine immunization program, to date no vaccine stockpile exists for TCV introduction in the event of an outbreak. To address this uncertainty, we account for varying delays in reactive vaccine deployment. For our primary analysis, we assumed an "idealized" scenario in which vaccination is introduced within 1 month of identifying the outbreak. In scenario analyses, we explored deployment delays of 6, 12, and 24 months after the epidemic threshold was exceeded.

Similarly, while decision-makers typically do not know when an outbreak may occur, the optimal strategy may depend on how far away the outbreak will start. We simulated TCV introduction occurring exactly 10 years to 1 year before the epidemic threshold was crossed. For these comparisons, we assessed the burden of typhoid fever and costs of treatment and vaccination for the preventative and reactive vaccination scenarios over a 20-year time horizon

spanning from 2000 to 2020. For all other analyses, we used the same 10-year time horizon to match previous cost-effective analyses.

The stochastic transmission model and economic model were implemented in R version 3.4.0 [41]. The transmission model code is available on GitHub at https://github.com/mailephillips/typhoid-outbreak.

Results

The model accurately reproduced the number and age distribution of observed blood-culture confirmed typhoid fever cases at QECH during both the fitting period (January 1996-February 2015) and the validation period (March 2015-December 2016) (Fig S5-S6). Over the 10-year simulation period with randomized outbreak timing in Blantyre, Malawi, we estimated a median of 7,019 (95% CrI: 742-12,380) cases and 63 (95% CrI: 3-517) deaths for a total of 1,389 (95% CrI: 76-11,394) DALYs and $32,672 (95% CrI: 2,099-133,417) in treatment costs for typhoid fever under the strategy of no vaccination (Table S3).

All vaccination strategies substantially reduced the expected number of typhoid fever cases, but did not completely prevent the outbreak from occurring. Preventive routine vaccination with a catch-up campaign delayed the start of the outbreak and reduced typhoid fever incidence substantially more than routine vaccination alone. When reactive vaccination was deployed within 1 to 6 months of the outbreak threshold being crossed, the epidemic was substantially smaller and delayed by 1-2 years (Fig S8). However, when reactive vaccination occurred 12 to 24 months after the outbreak was identified, it failed to prevent the peak in typhoid fever cases, although incidence was substantially reduced after vaccine deployment. The

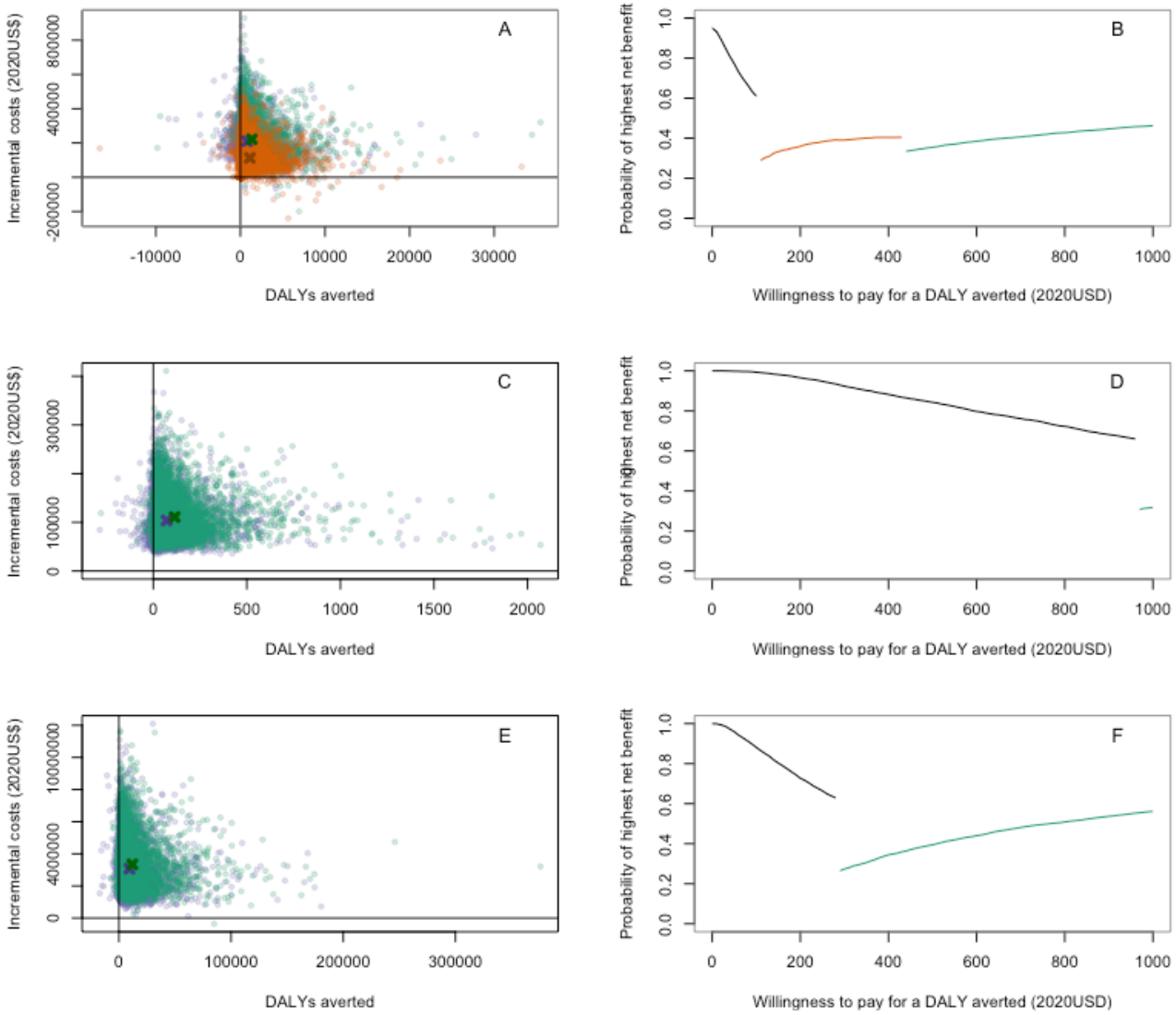
number of typhoid fever cases, deaths, and DALYs averted by each vaccination strategy compared to no vaccination, as well as the associated costs, are detailed in Table S4.

When we consider the cost-effectiveness of each strategy, our findings suggest that TCV introduction was optimal compared to no vaccination for WTP values greater than $100 (Table 4 and Fig 1B). Reactive vaccination (with a 1-month delay in implementation) was preferred for a WTP range of $110-$430, whereas preventive routine vaccination with a catchup campaign was optimal for WTP values above $430. Routine vaccination including a catch-up campaign to 15 years of age was always preferred over routine vaccination alone.

Table 4. Expected cost-effectiveness of vaccination strategies. Expected total costs, total disability-adjusted life-years (DALYs), incremental costs, DALYs averted, and incremental cost-effectiveness ratios (ICERs) are shown for each strategy in the scenarios in which (1) an outbreak is likely, (2) an outbreak is unlikely and the typhoid incidence is low (pre-oubreak incidence), and (3) an outbreak is unlikely and the typhoid incidence is high (post-outbreak incidence). Strategies are sorted from lowest to highest expected total costs.

Strategy	Expected Total Costs	Expected Total DALYs	Expected Incremental Costs	Expected DALYs Averted	ICER
When an outbreak is likely					
base case	40,840	2,533	--	--	16
reactRC	153,858	1,421	113,018	1,112	102
prevR	251,851	1,738	--	--	Dominated
prevRC	262,712	1,172	108,854	249	437
When an outbreak is unlikely (low incidence)					
base case	1,330	154	--	--	9
prevR	105,110	82	--	--	Dominated
prevRC	112,190	40	110,860	114	972
When an outbreak is unlikely (high incidence)					
base case	308,822	22,039	--	--	14
prevR	3,382,410	12,649	--	--	Dominated
prevRC	3,654,473	10,102	3,345,651	11,937	280

Fig 1. Cost-effectiveness planes and acceptability frontiers. The cost-effectiveness planes (left) and cost-effectiveness acceptability frontiers (CEAFs; right) are plotted for randomized outbreak timing (A-B), no outbreak assuming the pre-outbreak incidence (C-D), and no outbreak assuming the post-outbreak incidence (E-F). In the cost-effectiveness planes, each dot represents the additional cost (in 2020 USD) and DALYs averted for one simulation when compared with the strategy of no vaccination. The bold Xs denote the expected additional cost and DALYs averted for one strategy with respect to the strategy of no vaccination. Strategies are indicated by the color of the dot or X (purple: preventive routine vaccination; green: preventive routine vaccination plus a catchup campaign up to 15 years; or orange: reactive routine vaccination plus a catchup campaign). In the CEAFs, the preferred strategy (i.e. the strategy that yielded the highest *average* net benefit) for each willingness-to-pay threshold ($0-1,000; x-axis, 2020 USD) is again indicated by the color of the line (black: no vaccination; and same strategy colors as other panels), while the proportion of samples in which that strategy yielded the highest net benefit is indicated by the value on the y-axis (which can be interpreted as our certainty in the optimal strategy).



In the absence of an outbreak, and assuming the lower pre-outbreak incidence from 1995-2005, no vaccination is the preferred strategy for all WTP thresholds <$980 (Fig 1D). With the higher post-outbreak incidence, routine vaccination with a catch-up campaign is preferred for WTP values of $280 or higher (Fig. 1F). Again, routine vaccination alone is never the preferred strategy. The number of typhoid fever cases, deaths, and DALYs averted, as well as the costs for each scenario, are presented in Table S4.

The range of WTP values for which reactive vaccination strategy was the optimal strategy decreased as the delay in TCV deployment increased. For a 6-month delay, reactive vaccination was the preferred strategy for WTP threshold between $110-330, while for a 12-month delay, reactive vaccination was preferred at $130-200 (Fig 2). If the delay extended up to 24 months, reactive vaccination was never preferred; preventative vaccination with a catch-up campaign was the optimal strategy when the WTP threshold was at least $180.

The optimal vaccination strategy did not vary substantially depending on how long before the outbreak preventive vaccination was implemented. Whether the outbreak occurred within 10 years or 1 year of vaccine introduction for the preventive strategies, the preferred strategy remained essentially the same for the different WTP values. When the delay in reactive vaccination was 12 months or less, no vaccination was preferred for WTP thresholds up to $100. Reactive vaccination was the optimal strategy for WTP values of approximately $200-500 when the delay in reactive vaccination was 1 month, for WTP thresholds of approximately $200-400 for a 6-month delay, and for WTP thresholds of around $200-300 (10 years before) or $200 (1 year before) for a 12-month delay. Preventive routine vaccination with a catchup campaign was the preferred strategy for higher WTP thresholds, and for WTP thresholds >$200 when there was 24-month delay in reactive vaccination (Fig 3).

Fig 2. Cost-effectiveness acceptability frontiers for randomized outbreak timing with varying delays in reactive vaccination. The cost-effectiveness acceptability frontiers for randomized outbreak timing are shown for a range of willingness-to-pay thresholds ($0-1,000; x-axis, 2020 USD). The preferred strategy (i.e. the strategy that yielded the highest *average* net benefit) is indicated by the color of the line (black: no vaccination; purple: preventive routine vaccination; green: preventive routine vaccination plus a catchup campaign up to 15 years; or orange: reactive routine vaccination plus a catchup campaign), while the proportion of samples in which that strategy yielded the highest net benefit is indicated by the value on the y-axis (which can be interpreted as our certainty in the optimal strategy). Results are plotted for (A) a 6-month delay in reactive vaccination after the outbreak threshold is exceeded, B) a 12-month delay in reactive vaccination after the outbreak threshold is exceeded, and C) a 24-month delay in reactive vaccination after the outbreak threshold is exceeded.

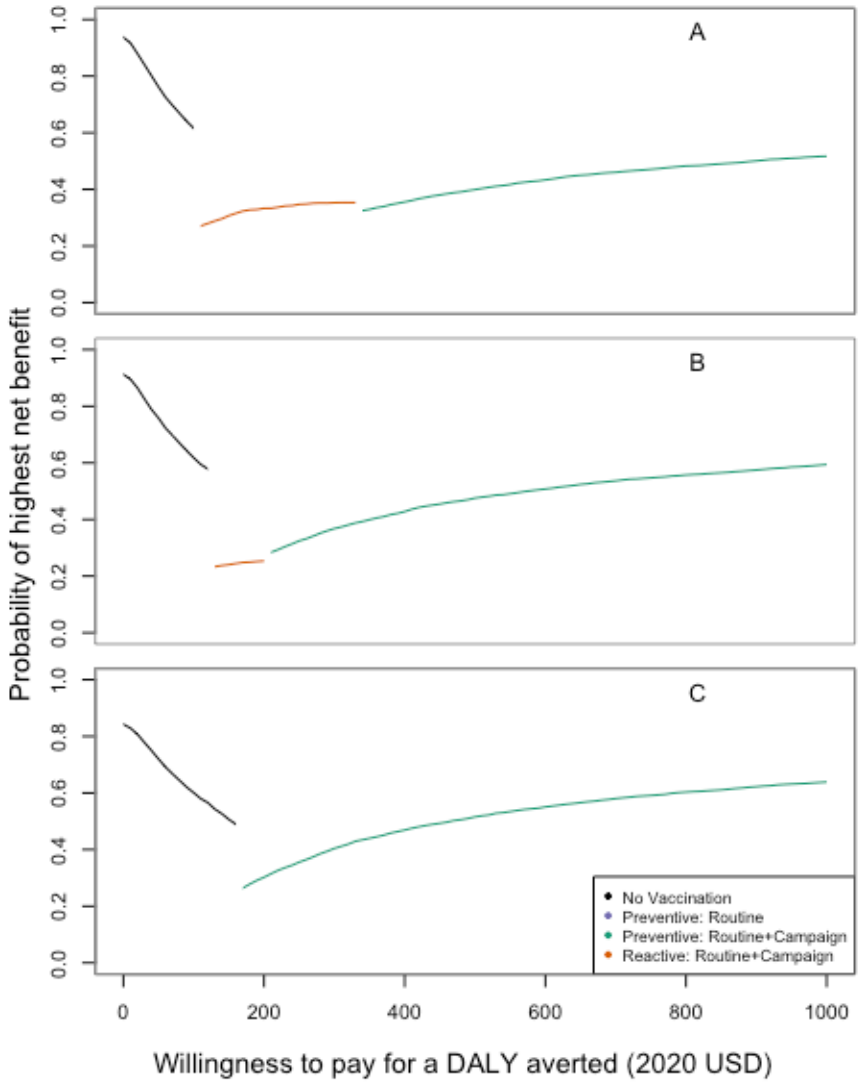
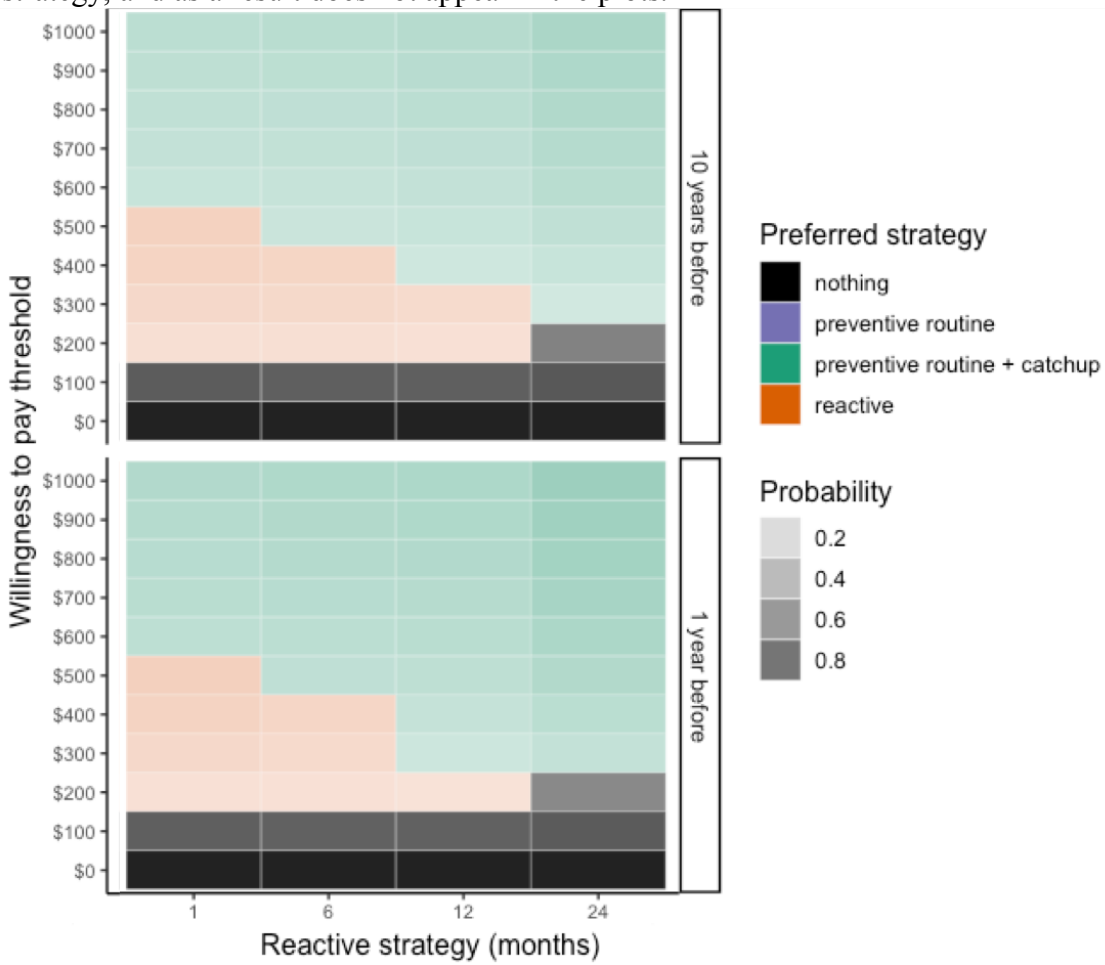


Fig 3. Heatmap of optimal intervention strategy and its estimated uncertainty across a range of willingness to pay values for each strategy comparison and a range of deployment delays, and years before the outbreak. Each column in a single panel shows the preferred strategy (i.e. the strategy that yields the highest average net benefit) for one cost-effectiveness analysis comparing no vaccination (grey), preventive routine vaccination (purple), preventive routine vaccination with a catch-up campaign (green), and reactive vaccination with a catch-up campaign (orange) for delays of 1, 6, 12, or 24 months after the outbreak has been identified (x-axis). The y-axis represents willingness-to-pay (WTP) values ranging from $0-$1000 (USD 2020). The shading represents the probability that the preferred strategy yields the highest net benefit (lighter: lower probability; darker: higher probability). Results are plotted for whether preventive vaccination is introduced 10 years (top panel) or 1 year (bottom panel) before the outbreak. Note that preventive routine vaccination without a catchup campaign is never a preferred strategy, and as a result does not appear in the plots.



The degree of uncertainty in the preferred strategy varied depending on the WTP threshold, the length of delay in the deployment of reactive vaccination, and (to a lesser extent) how many years before the outbreak preventive vaccination was introduced. The greatest

uncertainty in the preferred strategy occurred for WTP values of $100-$200. For WTP values of $0-$100, the probability that no vaccination would yield the highest net benefit was high (median probabilities of 0.60-0.95). The probability that reactive vaccination would yield the highest net benefit was generally lower, but was higher for shorter delays in deployment (median probabilities of 0.28-0.40 for a 1-month delay compared to 0.23-0.25 for a 12-month delay at WTP values between $100-500). The probability that preventive routine vaccination with a catch-up campaign would yield the highest net benefit increased as the delay in reactive vaccination deployment and WTP threshold increased (median probabilities of 0.27-0.64 for WTP values between $200-1,000).

For all of the economic evaluations, uncertainty around the probability of death among inpatients was estimated to contribute most to uncertainty in the preferred strategy, followed by the probability of hospitalization, percentage of deaths occurring among hospitalized patients, and routine vaccine delivery costs (Figs S9-S11).

Discussion

The analyses in this study depend on the information available to decision-makers at the time of decision-making. In a country where prevalence of AMR is low and a prolonged outbreak of typhoid fever has not yet occurred, but where surrounding regions are experiencing outbreaks of drug-resistant typhoid fever, it is likely that AMR will spread, triggering an outbreak in that country as well. Our findings indicate that if an outbreak of typhoid fever is likely, TCV routine vaccination with a catch-up campaign is preferred over no vaccination above a WTP threshold of $100. At WTP thresholds of $110 to $430, it is generally more cost-effective to wait to vaccinate until the outbreak has started, as long as the delay in deployment is short. As the WTP threshold increases, it is generally better (in terms of cost-effectiveness) to preventively

introduce routine vaccination with a catch-up campaign. These findings hold true regardless of when the outbreak occurs, provided it occurs within 10 years. However, if no outbreak occurs and incidence is low, TCV introduction is unlikely to be cost-effective for WTP thresholds <$980. At the higher post-vaccination incidence currently estimated for Blantyre, routine vaccination with a catch-up campaign is the preferred strategy for WTP thresholds of $280 and above. Routine vaccination alone is never a preferred strategy.

As TCV stockpiles do not yet exist, there is uncertainty in how long it will take to mobilize vaccine introduction once an outbreak is identified. The cost-effectiveness of reactive vaccination largely depends on the length of delay in vaccine deployment. We found that the range of WTP thresholds for which reactive vaccination is optimal decreases as the length of time for vaccine deployment increases. Decision-makers should try to determine how quickly they would be able to mobilize resources when considering reactive vaccination strategies and seek to minimize delays in vaccine deployment.

There is currently no threshold for defining and identifying outbreaks of typhoid fever across different settings. In our analysis, we found that an increase in the monthly number of blood-culture-confirmed typhoid fever cases of more than 15 standard deviations above the mean accurately identified the start of the outbreak in Blantyre, Malawi. It is not yet clear whether this threshold may be applicable to other settings. However, the results of our analysis are unlikely to depend on the outbreak identification threshold used. While lower thresholds may falsely identify an outbreak before it occurs, a false positive in this case may not be as problematic as it can be with other diseases. If the outbreak is falsely identified too early, “reactively” vaccinating in response to the false outbreak is comparable to a preventative vaccination strategy, which in our analysis was still cost-effective for WTP thresholds above $100 provided an outbreak is

likely to occur within the next 10 years. These findings are encouraging as typhoid resources and surveillances systems are not always optimal in areas where typhoid is endemic.

For scenarios in which an outbreak does not occur, our results are consistent with previous cost-effectiveness analyses. Before the outbreak in Blantyre, we estimate that typhoid fever incidence was approximately 26.1 cases (95% CrI: 14.0-45.7 cases) per 100,000 person-years; we found that no vaccination is the preferred strategy for WTP thresholds up to $970. In general, previous analyses have found that TCV introduction is unlikely to be cost-effective when incidence is less than 30-50 cases per 100,000 person-years [26, 42, 43]. Similarly, we estimate that the post-outbreak incidence in Blantyre was approximately 224 typhoid fever cases (95% CrI: 169-368 cases) per 100,000 person-years, and routine vaccination with a catch-up campaign was preferred at WTP thresholds of $300 and above, similar to results of a previous economic analysis for Malawi [26].

There is considerable uncertainty surrounding the incidence and burden of typhoid fever, which leads to uncertainty in the preferred vaccination strategy. Nevertheless, some of the uncertainty has been reduced in our analysis compared to previous cost-effectiveness analyses for Malawi. In Bilcke et al [26], lack of data surrounding the probability of hospitalization, the case fatality rate among inpatients, vaccine delivery costs, and typhoid incidence contributed substantially to uncertainty in the results. Since then, additional data have been collected in Malawi. While the parameters contributing most to uncertainty in our analysis included parameters that were and were not updated with new data, the overall expected value of information for the parameters contributing the most to uncertainty was substantially lower compared to the previous cost-effectiveness analyses.

There are several important limitations to our analysis. We assume TCV reduces the burden of typhoid fever by reducing the number of infections and lowering transmission. However, we lack direct data on vaccination impact in this population. We used results from the recent TyVAC trial in Malawi to update our estimates of vaccine efficacy and duration of protection, but observations of vaccine impact following widespread implementation are not yet available. This analysis also uses parameters and data based on an outbreak in one location. Since the timing of a typhoid fever outbreak is unknown, it is difficult to plan for control. The peak and length of outbreaks, as well as treatment costs and severity of disease, may differ in other contexts. It can also be difficult to collect site-specific data, as typhoid fever surveillance is limited in many countries. We made every effort to incorporate additional uncertainty in the model parameters (which were not only Malawi-specific) and the outbreak itself (using a stochastic model that varied the peak and length of the outbreak). The framework we present may be generalizable to other settings where the introduction of drug-resistant strains may lead to prolonged outbreaks of typhoid fever.

Research comparing typhoid vaccination strategies in epidemic settings is limited. With recent WHO recommendations for TCV use and pilot studies assessing efficacy and impact underway, governments are looking to prioritize the allocation of resources to prevent typhoid fever. With recent typhoid epidemics across Africa and high burdens in endemic countries, studies are needed to compare prevention strategies across different settings, including the use of TCV in response to outbreaks. Typhoid control can be expensive; cost-effectiveness analyses are needed to inform decisions for the optimal allocation of funding. Results from this research can inform policy- and decision-making regarding typhoid prevention and control strategies.

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month delay in reactive vaccination after the outbreak threshold is exceeded, B) a 12-month delay in reactive vaccination after the outbreak threshold is exceeded, and C) a 24-month delay in reactive vaccination after the outbreak threshold is exceeded.

Fig 3. Heatmap of optimal intervention strategy and its estimated uncertainty across a range of willingness to pay values for each strategy comparison and a range of deployment delays, and years before the outbreak. Each column in a single panel shows the preferred strategy (i.e. the strategy that yields the highest average net benefit) for one cost-effectiveness analysis comparing no vaccination (grey), preventive routine vaccination (purple), preventive routine vaccination with a catch-up campaign (green), and reactive vaccination with a catch-up campaign (orange) for delays of 1, 6, 12, or 24 months after the outbreak has been identified (x-axis). The y-axis represents willingness-to-pay (WTP) values ranging from $0-$1000 (USD 2020). The shading represents the probability that the preferred strategy yields the highest net benefit (lighter: lower probability; darker: higher probability). Results are plotted for whether preventive vaccination is introduced 10 years (top panel) or 1 year (bottom panel) before the outbreak. Note that preventive routine vaccination without a catchup campaign is never a preferred strategy, and as a result does not appear in the plots.

Table S1. Options for disability weights assigned to different healthcare use groups. Disability weights presented for the two options are for infectious disease, acute, and for the specified level of typhoid episode (mild, moderate, or severe).

Table S2. Input parameters for transmission model and cost-effectiveness analysis, with distributions.

Table S3. Predicted disease and economic burden in the absence of vaccination. The median (95% credible interval) estimates for predicted cases, deaths, DALYs, and treatment costs are shown for each non-vaccination strategy.

Table S4. Predicted vaccine impact with randomized outbreak timing, fixed outbreak timing, pre-outbreak incidence and post-outbreak incidence. The median (95% credible interval) estimates for averted cases, deaths, DALYs, treatment costs, costs of vaccinations and net costs are shown for each vaccination strategy compared to no vaccination for randomized outbreak timing (“randomized”), fixed outbreak timing (“fixed”), pre-outbreak incidence (“pre”), and post-outbreak incidence (“post”). Preventive routine vaccination strategies include routine vaccination at nine months of age in year 0 with or without a catchup campaign up to 15 years of age. Reactive routine vaccination strategies (with a catchup campaign) include delays of 1, 6, 12, and 24 months to deployment (“1m”, “6m”, “12m”, “24m”, respectively). In the fixed outbreak timing scenario, preventive strategy results are shown for 10, 5, 2, and 1 year(s) (“10y”, “5y”, “2y”, “1y”) before the outbreak starts. Results for the randomized and fixed outbreak timing strategies are shown using an outbreak identification definition of 15 standard deviations above the monthly mean number of typhoid cases. R=routine vaccination; RC=routine vaccination plus a catchup campaign.

Fig S1. Ordinary differential equations and corresponding dynamic compartmental model for typhoid disease dynamics. Black compartments and text indicate the scenario in which there

is no vaccination, and blue compartments and text indicate the added scenario in which there is vaccination. Note that this model is also age-structured, though not shown.

Fig S2. Sensitivity and specificity of outbreak identification threshold definitions. The sensitivity (purple) and specificity (green) are shown for each outbreak identification definition (x-axis; ranging from 6-16 standard deviations above the mean monthly reported typhoid fever cases).

Fig S3. Estimated specificity of outbreak identification thresholds 6 to 16 standard deviations above the monthly mean reported typhoid fever cases. The median outbreak identification date (dot) and 95% credible interval (line) is shown for outbreak identification thresholds of 6-16 standard deviations above the monthly mean number of typhoid cases for 1,000 simulations of the dynamic model. The black dashed line represents the "true" start date of the outbreak, and the shaded grey area represents 0-18 months after the outbreak started (sensitivity window).

Fig S4. Observed and fitted proportion of typhoid infections that are resistant to antimicrobial treatment in Blantyre, Malawi from 1995-2025. Observed data points of the yearly proportion of antimicrobial resistant typhoid fever infections over time are shown in black dots, while the fitted estimates from the beta regression model are shown in the dashed blue line and the prediction intervals are shown in the turquoise dotted lines.

Fig S5. Predicted and observed typhoid fever infections in the absence of vaccination. The 1,000 stochastic realizations of weekly typhoid infections individuals in the absence of vaccination from the dynamic transmission model are show in purple. The observed (reported) typhoid incidence used to fit the dynamic model is represented by the bold black line, while the observed incidence collected after model fitting is represented by the dashed red line.

Fig S6. Observed versus fitted age distribution of reported typhoid cases. The proportion of observed cases in each age group are denoted by light blue bars, while the fitted age distribution is shown in darker blue.

Fig S7. Predicted typhoid fever cases per 100,000 individuals in preventive vaccination scenarios. The 1,000 stochastic realizations of weekly typhoid cases per 100,000 people are shown in purple, with the median of all simulations shown in orange for each preventive vaccination strategy. Eight situations are shown, representing each preventive routine vaccination timing strategy (10, 5, 2, and 1 year(s) before; routine vaccination at 9 months of age) with and without a catchup campaign up to 15 years of age. The median number of typhoid infections per 100,000 individuals in the absence of vaccination from 1,000 realizations is shown in black, and the date of vaccination deployment for each situation is denoted by the vertical dashed green line.

Fig S8. Predicted typhoid infections per 100,000 individuals in reactive vaccination scenarios. The 1,000 simulated predictions for weekly typhoid infections per 100,000 people are shown in purple, with the median of all stochastic realizations shown in orange for each reactive vaccination strategy. Eight situations are shown, representing each of the outbreak identification

thresholds of 12 and15 standard deviations above the monthly mean (SD12 and SD15; columns) and the four different delays in timing to implement vaccination once the outbreak is identified (1, 6, 12, and 24 months; rows). The median typhoid infections per 100,000 individuals in the absence of vaccination from 1,000 realizations is shown in black, and the median date of vaccination deployment for each situation is denoted by the vertical dashed green line.

Fig S9. Expected value of partially perfect information for differing delays in vaccination deployment for reactive strategies with randomized outbreak timing. The expected value of partial perfect information (EVPPI) for each parameter is shown for a range of willingness-to-pay values. Results are shown for 5,000 parameter samples and 2020 $USD. Each panel shown represents the EVPPI for one cost-effectiveness analysis comparing 4 strategies: no vaccination (base case), preventive routine vaccination at 9 months, preventive routine vaccination with a catchup campaign up to 15 years, and reactive routine vaccination with a catchup campaign. Each panel shows the results for a cost-effectiveness analyses with the specified delay in months for the reactive strategy (1-, 6-, 12-, or 24-month delays).

Fig S10. Expected value of partially perfect information for pre-outbreak (non-outbreak) incidence. The expected value of partial perfect information (EVPPI) for each parameter is shown for a range of willingness-to-pay values. Results are shown for 5,000 parameter samples and 2020 $USD.

Fig S11. Expected value of partially perfect information for post-outbreak (non-outbreak) incidence. The expected value of partial perfect information (EVPPI) for each parameter is shown for a range of willingness-to-pay values. Results are shown for 5,000 parameter samples and 2020 $USD.

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Conflict of interests
VEP is a member of the World Health Organization's (WHO) Immunization and Vaccine-related Implementation Research Advisory Committee. The views expressed in this manuscript are those of the authors and do not necessarily reflect the views of the WHO. All other authors have no conflicts of interest to declare.

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References

1. Antillon M, Warren J, Crawford F, Weinberger D, Kurum E, Pitzer V. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis. 2017;11(2). doi: 10.1371/journal.pntd.0005376.
2. Buckle GC, Walker CLF, Black RE. Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. J Glob Health. 22012.
3. Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. The Lancet. 2014;2(10):e570-80. doi: 10.1016/S2214-109X(14)70301-8.
4. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle2017. Available from: http://ghdx.healthdata.org/gbd-results-tool.
5. Hendriksen RS, Leekitcharoenphon P, Lukjancenko O, Lukwesa-Musyani C, Tambatamba B, Mwaba J, et al. Genomic Signature of Multidrug-Resistant Salmonella enterica Serovar Typhi Isolates Related to a Massive Outbreak in Zambia between 2010 and 2012. J Clin Microbiol. 2015;53(1):262-72. doi: 10.1128/jcm.02026-14. PubMed PMID: 25392358.
6. Imanishi M, Kweza PF, Slayton RB, Urayai T, Ziro O, Mushayi W, et al. Household water treatment uptake during a public health response to a large typhoid fever outbreak in Harare, Zimbabwe. The American journal of tropical medicine and hygiene. 2014;90(5):945-54. Epub 2014/03/26. doi: 10.4269/ajtmh.13-0497. PubMed PMID: 24664784; PubMed Central PMCID: PMCPMC4015591.
7. Neil KP, Sodha SV, Lukwago L, S OT, Mikoleit M, Simington SD, et al. A large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese District, Uganda, 2008-2009. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(8):1091-9. Epub 2012/02/24. doi: 10.1093/cid/cis025. PubMed PMID: 22357703.
8. Gordon MA, Graham SM, Walsh AL, Wilson L, Phiri A, Molyneux E, et al. Epidemics of invasive Salmonella enterica serovar enteritidis and S. enterica Serovar typhimurium infection associated with multidrug resistance among adults and children in Malawi. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2008;46(7):963-9. Epub 2008/05/01. doi: 10.1086/529146. PubMed PMID: 18444810.
9. Pitzer VE, Feasey NA, Msefula C, Mallewa J, Kennedy N, Dube Q, et al. Mathematical Modeling to Assess the Drivers of the Recent Emergence of Typhoid Fever in Blantyre, Malawi. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61:S251-8. Epub 2015/10/10. doi: 10.1093/cid/civ710. PubMed PMID: 26449939; PubMed Central PMCID: PMCPMC4596932.
10. Watson CH, Edmunds WJ. A review of typhoid fever transmission dynamic models and economic evaluations of vaccination. Vaccine. 2015;33:C42-C54. doi: 10.1016/S0022-5193(03)00031-6.
11. World Health Organization. Typhoid vaccines: WHO position paper, March 2018 – Recommendations. Vaccine. 2019;37(2).
12. Azman AS, Lessler J. Reactive vaccination in the presence of disease hotspots. Proc Biol Sci. 2015;282(1798). doi: 10.1098/rspb.2014.1341. PubMed PMID: 25392464.
13. Alberti KP, King LA, Burny ME, Ilunga BK, Grais RF. Reactive vaccination as an effective tool for measles outbreak control in measles mortality reduction settings, Democratic Republic of Congo, 2005-2006. International health. 2010;2(1):65-8. Epub 2010/03/01. doi: 10.1016/j.inhe.2009.12.009. PubMed PMID: 24037053.
14. Tildesley MJ, Savill NJ, Shaw DJ, Deardon R, Brooks SP, Woolhouse MEJ, et al. Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK. Nature. 2006;440(7080):83. doi: doi:10.1038/nature04324.
15. Ciglenecki I, Sakoba K, Luquero FJ, Heile M, Itama C, Mengel M, et al. Feasibility of Mass Vaccination Campaign with Oral Cholera Vaccines in Response to an Outbreak in Guinea. PLoS Medicine. 2013;10(9):e1001512. doi: 10.1371/journal.pmed.1001512.
16. Azman AS, Luquero FJ, Rodrigues A, Palma PP, Grais RF, Banga CN, et al. Urban Cholera Transmission Hotspots and Their Implications for Reactive Vaccination: Evidence from Bissau City, Guinea Bissau. PLoS Negl Trop Dis. 2012;6(11):e1901. doi: 10.1371/journal.pntd.0001901.
17. Grais RF, Conlan AJK, Ferrari MJ, Djibo A, Menach AL, Bjørnstad ON, et al. Time is of the essence: exploring a measles outbreak response vaccination in Niamey, Niger. Journal of the Royal Society Interface. 2008;5(8):67–74. doi: 10.1098/rsif.2007.1038.
18. Rosado RM, Charles-Smith L, Daniel B. Control and Cost-benefit Analysis of Fast Spreading Diseases: The case of Ebola. Online J Public Health Inform. 2017;9(1). doi: 10.5210/ojphi.v9i1.7584.

19. Minetti A, Hurtado N, Grais RF, Ferrari M. Reaching Hard-to-Reach Individuals: Nonselective Versus Targeted Outbreak Response Vaccination for Measles. American Journal of Epidemiology. 2019;179(2):245-51. doi: 10.1093/aje/kwt236.
20. Feasey N, Gaskell K, Wong V, Msefula C, Selemani G, Kumwenda S, et al. Rapid Emergence of Multidrug Resistant, H58-Lineage Salmonella Typhi in Blantyre, Malawi. PLOS Neglected Tropical Diseases. 2015;9(4):e0003748. doi: 10.1371/journal.pntd.0003748.
21. Phillips MT, Meiring JE, Voysey M, Warren JL, Baker S, Basnyat B, et al. A Bayesian approach for estimating typhoid fever incidence from large-scale facility-based passive surveillance data. medRxiv. 2021. doi: 10.1101/2020.10.05.20206938.
22. Hornick RB, Greisman SE, Woodward TE, DuPont HL, Dawkins AT, Snyder MJ. Typhoid Fever: Pathogenesis and Immunologic Control (Part 1). New England Journal of Medicine. 1970;1970(283):686-91. doi: 10.1056/NEJM197009242831306.
23. Ames WR, Robins M. Age and Sex as Factors in the Development of the Typhoid Carrier State, and a Method for Estimating Carrier Prevalence *. Am J Public Health Nations Health. 1943;33(3):221-30. PubMed PMID: 18015749; PubMed Central PMCID: PMC1527221.
24. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bulletin of the World Health Organization. 2004;82(5):346-53. Epub 2004/08/10. PubMed PMID: 15298225; PubMed Central PMCID: PMCPMC2622843.
25. Patel PD, Patel P, Liang Y, Meiring J, Misiri T, Mwakiseghila F, et al. Safety and Efficacy of a Typhoid Conjugate Vaccine in Children in Blantyre, Malawi: A Randomized, Double-Blinded Active-Controlled Phase 3 Trial.
26. Bilcke J, Antillon M, Pieters Z, Kuylen E, Abboud L, Neuzil KM, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study - The Lancet Infectious Diseases. Lancet Infectious Diseases. 2019;19(7):728-39. doi: doi:10.1016/S1473-3099(18)30804-1.
27. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. 2013. doi: 10.1136/bmj.f1049.
28. World Health Organization. Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. WHO. 2003. doi: /entity/choice/book/en/index.html.
29. World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. Geneva : World Health Organization, 2008 2008. Report No.
30. NICE International. Bill and Melinda Gates Foundation Methods for Economic Evaluation Project (MEEP): Final Report. 2014.
31. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2197-223. Epub 2012/12/19. doi: 10.1016/s0140-6736(12)61689-4. PubMed PMID: 23245608.
32. Crump JA, Youssef FG, Luby SP, Wasfy MO, Rangel JM, Taalat M, et al. Estimating the Incidence of Typhoid Fever and Other Febrile Illnesses in Developing Countries. Emerg Infect Dis. 2003;9(5):539-44. doi: 10.3201/eid0905.020428. PubMed PMID: 12737736.
33. Pieters Z, Saad NJ, Antillón M, Pitzer VE, Bilcke J. Case Fatality Rate of Enteric Fever in Endemic Countries: A Systematic Review and Meta-analysis. Clinical Infectious Diseases. 2018;67(4):628-38. doi: 10.1093/cid/ciy190.
34. World Bank. Life expectancy at birth, total (years) 2021. 2019 Revision:[Available from: https://data.worldbank.org/indicator/SP.DYN.LE00.IN.
35. Stenberg K, Lauer JA, Gkountouras G, Fitzpatrick C, Stanciole A. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. Cost Effectiveness and Resource Allocation. 2018;16(1):1-15. doi: doi:10.1186/s12962-018-0095-x.
36. Marchello CS, Birkhold M, Crump JA. Complications and mortality of typhoid fever: A global systematic review and meta-analysis. Journal of Infection. 2020;81(6):902-10. doi: 10.1016/j.jinf.2020.10.030.
37. Darton TC, Meiring JE, Tonks S, Khan MA, Khanam F, Shakya M, et al. The STRATAA study protocol: a programme to assess the burden of enteric fever in Bangladesh, Malawi and Nepal using prospective population census, passive surveillance, serological studies and healthcare utilisation surveys. 2017;7(6). doi: 10.1136/bmjopen-2017-016283.
38. Abboud L. Global hospitalization rate of typhoid fever: a meta-regression. Antwerp: University of Antwerp; 2017.

39. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2129-43. Epub 2012/12/19. doi: 10.1016/s0140-6736(12)61680-8. PubMed PMID: 23245605.
40. Gandhi G, Lydon P. Updating the evidence base on the operational costs of supplementary immunization activities for current and future accelerated disease control, elimination and eradication efforts. BMC Public Health. 2014;14(1):1-16. doi: doi:10.1186/1471-2458-14-67.
41. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
42. Antillon M, Bilcke J, Paltiel AD, Pitzer VE. Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low- and middle-income settings. Vaccine. 2017;35(27):3506-14. Epub 2017/05/22. doi: 10.1016/j.vaccine.2017.05.001. PubMed PMID: 28527687; PubMed Central PMCID: PMCPMC5462484.
43. Lo N, Gupta R, Stanaway J, Garrett D, Bogoch I, Luby S, et al. Comparison of Strategies and Incidence Thresholds for Vi Conjugate Vaccines Against Typhoid Fever: A Cost-effectiveness Modeling Study. The Journal of infectious diseases. 2018;218(suppl_4). doi: 10.1093/infdis/jix598. PubMed PMID: 29444257.

Supplementary material: *Cost-effectiveness analysis of typhoid conjugate vaccines in an outbreak setting*

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Transmission-dynamic model

S1.1.1*. Description of the dynamic model.* We simulated the conditions under which an outbreak may occur using an existing dynamic transmission model. Briefly, in this model, individuals are born completely susceptible to typhoid, and they move through susceptible, infectious, chronic carrier, and immune compartments as specified through a system of differential equations (Fig S1). Individuals in the susceptible population (S_1) become infected at rate λ. Primary infections (I_s) may be symptomatic and remain infectious for length of time $\frac{1}{\delta}$, after which they experience one of three options: a proportion die from typhoid (α), a fraction θ_a become chronic carriers (C), and the remaining $1 - \theta_a - \alpha$ recover and are temporarily immune (R). Since age (a) is a factor in the development of the chronic carrier state[1], θ_a is age-dependent. Immune individuals lose immunity and become susceptible to reinfection (S_2) at rate ω. If an individual becomes re-infected, we assume the infection is subclinical (I_A). Subclinically infected people can become chronic carriers (at rate $\delta\theta_a$) or recover (at rate $\delta(1 - \theta_a)$). The same process of reinfection can occur. In all compartments, individuals die from non-typhoid causes at rate μ_a.

Symptomatic and subclinically infected individuals and chronic carriers all contribute to the force of infection, although chronic carriers contribute at a reduced rate (r). The force of infection λ_a is age-dependent (where a = 0 to <9 months; 9 months to <5 years; five-year-interval age groups from 5 to <80 years; and 80 years and older) and is the product of the age-dependent transmission rate (β_a) and the sum of all infectious states, divided by the total population N: $\lambda_a = \frac{\beta_a}{N_a} \sum_{\text{All ages}} (I_{S,a} + I_{A,a} + rC_a)$.

With and without vaccination

$$\frac{dS_1}{dt} = bN - \lambda S_1 - \mu S_1 - \kappa v S_1 + \omega_v V_1 s$$

$$\frac{dI_S}{dt} = \lambda S_1 - \delta I_S - \mu I_S$$

$$\frac{dR}{dt} = \delta(1-\theta-\alpha)I_S + \delta(1-\theta)I_A - (\omega+\mu)R - \kappa v R$$

$$\frac{dC}{dt} = \delta\theta I_S - \mu C$$

$$\frac{dS_2}{dt} = \omega R - \lambda S_2 - \mu S_2 - \kappa v S_2$$

$$\frac{dI_A}{dt} = \lambda S_2 - \delta I_A - \mu I_A$$

$$\frac{dV_1}{dt} = \kappa v S - \omega_V V_1$$

$$\frac{dV_2}{dt} = \kappa v (S_R + R) - \omega_V V_2$$

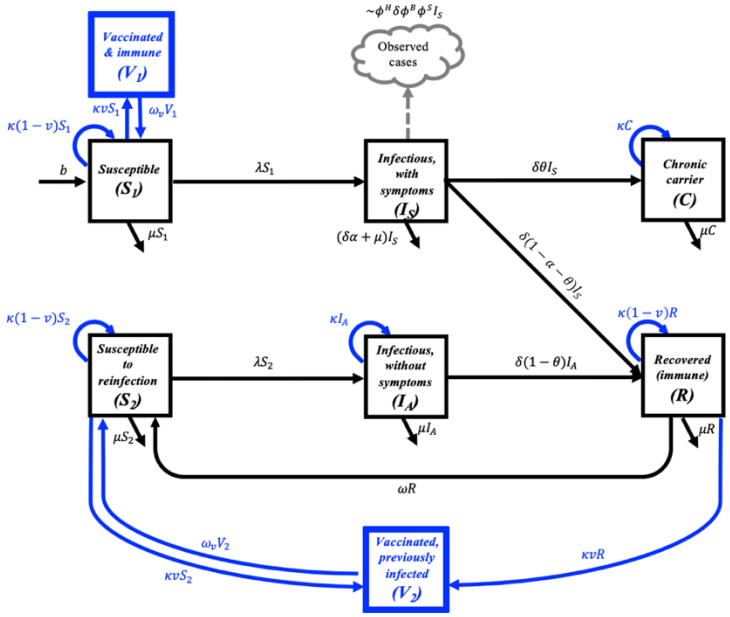


Fig S1. Ordinary differential equations and corresponding dynamic compartmental model for typhoid disease dynamics. Black compartments and text indicate the scenario in which there is no vaccination, and the blue compartments and text indicate the added scenarios in which vaccination is introduced. Note that this model is also age-structured, though not shown.

Observed symptomatic cases are a fraction $\phi^S\phi^B\phi^H$ of the true number of cases (S1.1.4 Text) [2]. The culture-confirmed cases are adjusted to account for the sensitivity of the blood culture test (ϕ^S), the probability of receiving a blood culture test (ϕ^B), and the probability of healthcare seeking (ϕ^H), which occurs sometime during the period $\frac{1}{\delta}$ of infection.

To adjust for the outbreak and vaccination scenarios, we simulated the weekly number of symptomatic cases for the 18 age groups. We modelled the outbreak by allowing for an increase in multidrug-resistant typhoid by increasing the duration of infectiousness. We estimated the date it increased (April 10, 2011) and the date it ended (November 23, 2014). The magnitude of the increase *m* was estimated to be 3.1954.

To stay consistent with recent estimates of the contribution of chronic carriers to transmission, we applied a prior distribution of $beta(6.34,19.4)$ on the range of values for *r* in the model-fitting process [3]. With these changes, we re-fit the dynamic model using the same

process to the same Malawi outbreak data to update the remaining parameters. This dynamic model and its model-fitting process are described in more detail elsewhere [4].

S1.1.2*. Modeling vaccination.*

S1.1.2.1. *Vaccination compartments.* To simulate vaccination and measure the overall impact of each strategy (with vaccine coverage κ), we added two vaccination compartments to the dynamic model (Fig S1, in blue). One compartment (V_1) represents individuals who have never been infected and hence may be protected from symptomatic disease if they successfully mount a protective immunological response to the vaccine. The second compartment (V_2) represents those who were previously infected and would only be protected against reinfection (and hence transmission), since they already have immunity to clinical disease. In both cases, vaccine-induced immunity eventually wanes at rate ω_v (S1.1.2.2).

S1.1.2.2. Vaccine efficacy and waning of vaccine-induced immunity

Typbar TCV (Bharat Biotech International) is the first WHO-pre-qualified typhoid conjugate vaccine (TCV). This TCV was licensed based on improved immunogenicity data (compared to previous typhoid fever vaccines) and efficacy data from a human challenge study [5-7]. For this analysis, we used results up to 24 months of follow-up from the phase 3, double-blind, randomized active-controlled clinical trial of single-dose TCV in Blantyre, Malawi [8, 9]. These are the first vaccine efficacy and safety results from Africa.

The TCV trial in Blantyre provided observed values for vaccine efficacy at 12 months, 18 months, and 24 months of follow-up. Due to the waning efficacy over time, we assumed that the mean vaccine efficacy μ at time t followed an exponential decay pattern

$$\mu(t) = \nu_0 * e^{-(\omega_v * t)}$$

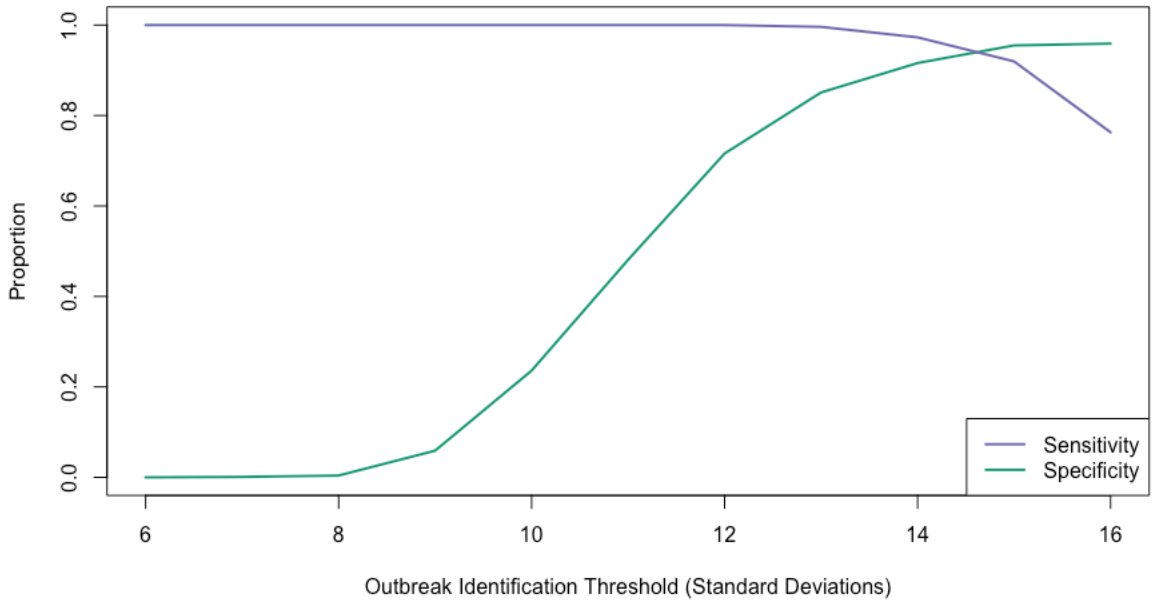
and that the observed response variable vaccine efficacy at time *t* ($v(t)$) was linked to μ with a normally distributed sampling error with standard deviation σ:

$$v(t) \sim N(\mu(t), \sigma).$$

We used an informative prior on duration of vaccine-induced immunity, based on data from 4 years of follow-up for the Vi-rEPA TCV: $\frac{1}{\omega_v} \sim Gamma(1.38, 0.048)$ [3]. We used a noninformative uniform prior on the standard deviation of the normally distributed sampling error of vaccine efficacy at time *t.* These distributions resulted in an estimated initial TCV efficacy of 0.89 (95% CrI: 0.78-0.98) and an estimated duration of vaccine-induced immunity of 18.87 (95% CrI: 8.40-83.33) years.

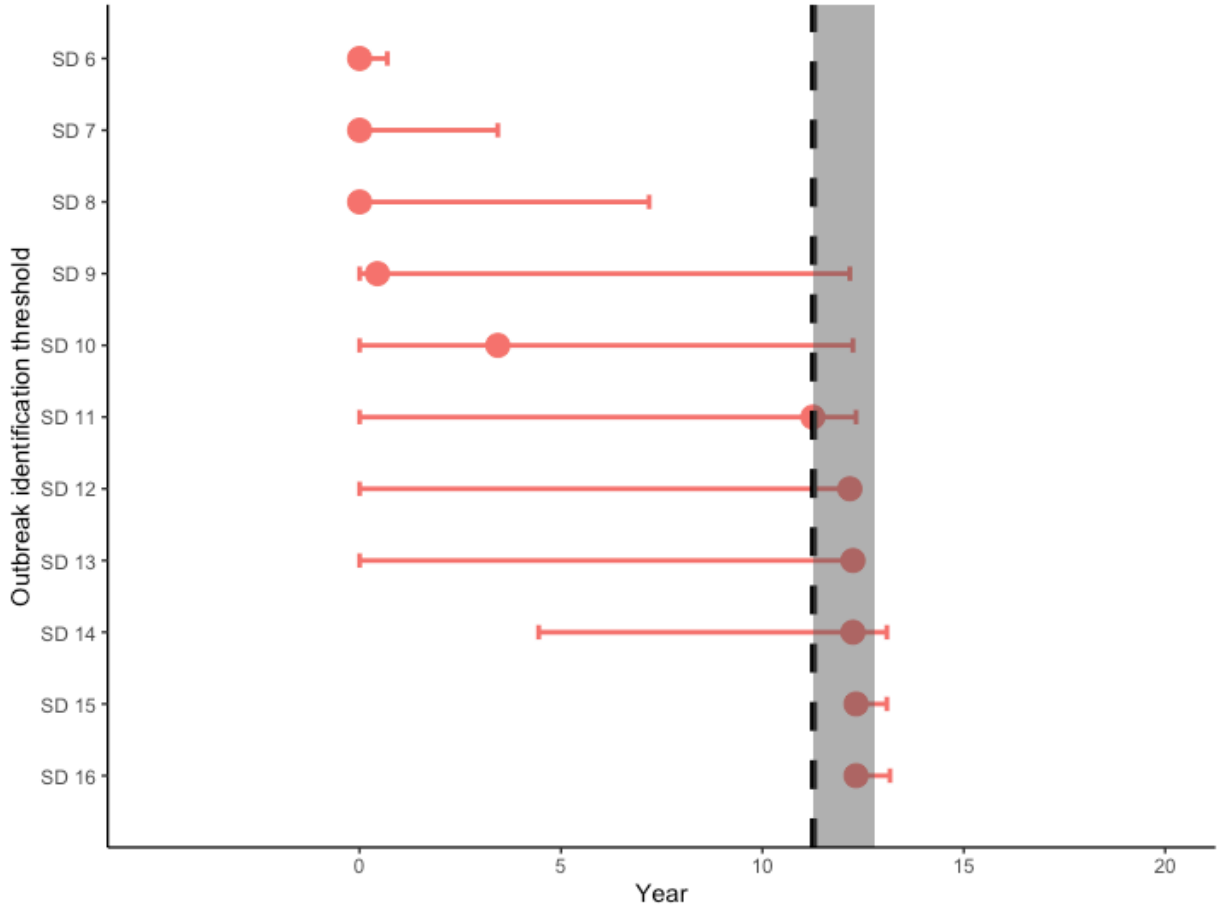
S1.1.3*. Outbreak threshold definitions.* We explored a range of thresholds to identify the start of the outbreak. For the main analysis, we varied the number of standard deviations (6-16) above the monthly mean reported typhoid fever cases in the previous 10 years to define the outbreak start. We defined the sensitivity of each threshold as the percentage of simulations in which the outbreak was identified within 18 months of April 2011, while the specificity was defined as the percentage of simulations in which the outbreak threshold was not exceeded prior to April 2011. As the standard deviation used to define the outbreak threshold increased, the specificity also increased (Fig S2).

Fig S2. Sensitivity and specificity of outbreak identification threshold definitions. The sensitivity (purple) and specificity (green) are shown for each outbreak identification definition (x-axis; ranging from 6-16 standard deviations above the mean monthly reported typhoid fever cases).



Across the different outbreak identification thresholds, the sensitivity remained high (76.3-100.0%) for the range of definitions we explored, while the specificity followed a sigmoid pattern (Fig S2). At a threshold of 16 standard deviations above the monthly mean number reported cases, the outbreak was identified within one and a half years of the pre-specified start date with a specificity of 96.5% and a sensitivity of 76.3% (out of 1,000 stochastic iterations); a threshold of 15 standard deviations identified the outbreak with a specificity 95.5% and sensitivity of 91.9%; while a threshold of 12 standard deviations identified it with a specificity of 71.6% and sensitivity of 100%. Lower thresholds exhibited poor specificity and incorrectly identified the outbreak as occurring before April 2011 more than 50% of the time (Fig S3).

Fig S3. Estimated specificity of outbreak identification thresholds 6 to 16 standard deviations above the monthly mean reported typhoid fever cases. The median outbreak identification date (dot) and 95% credible interval (line) is shown for outbreak identification thresholds of 6-16 standard deviations above the monthly mean number of typhoid cases for 1,000 simulations of the dynamic model. The black dashed line represents the "true" start date of the outbreak, and the shaded grey area represents 0-18 months after the outbreak started (sensitivity window).



Apart from the 6-16 standard deviations above the mean monthly typhoid infections reported in the main analysis, we also explored other outbreak thresholds. We defined outbreaks by raw counts and incidence rates, but these definitions, while reliable in identifying the outbreak, would be less applicable across countries because of the variation in incidence and population denominators for passive hospital-based surveillance across settings. We also tried to account for variation in typhoid fever incidence due to seasonality by allowing each month of the year to have a standard deviation threshold above the mean; however, while this method

accounted for seasonality, the data were sparse and oftentimes the outbreak was never identified. We did not want to include more data (farther back than 10 years) because many typhoid-endemic countries do not have long-established typhoid fever surveillance platforms.

S1.1.4. Underreporting adjustment. To adjust for underreporting of observed typhoid cases, we used estimates from an analysis that adjusted for underreporting in Malawi, Nepal, and Bangladesh based on data from the STRATAA study [2]. We based our estimate of the adjustment factor for Malawi on the posterior distribution obtained by adjusting for blood culture sensitivity, the probability of receiving a blood culture diagnostic test, and healthcare seeking. In Malawi, this adjustment factor was estimated to be 7.7 (95% CrI: 6.0-12.4), i.e. for every blood-culture confirmed case of typhoid fever presenting to healthcare facilities in Blantyre, there are an additional 6.7 undiagnosed cases of symptomatic typhoid fever occurring in the community. This underreporting adjustment was applied after model-fitting, which was fitted to the reported (unadjusted) number of cases.

S1.1.5. Chronic Carriers. We explored the contribution of chronic carriers to transmission during the model-fitting process. In previous model-fitting, the parameter for the relative infectiousness of chronic carriers was unidentifiable. There is a tradeoff between this parameter and the reproductive number R_0, which influences the prevalence of chronic carriers in the population. To explore this tradeoff, we fixed the relative infectiousness of chronic carriers r at different values (0.01, 0.10, 0.25, and 0.50) and refit the remaining parameters. We also tried a variation of model-fitting where we initialized the model with no chronic carriers.

The overall model fit (as measured by Akaike Information Criterion) tended to be poorer as *r* got farther away from the 0.1-0.5 range. This range is consistent with recent estimates of *r* (based on fitting to the observed overall and indirect effectiveness of vaccination with Vi-polysaccharide vaccine in a cluster-randomized trial in Kolkata [10, 11]) and what was used in the final model. To stay consistent with recent estimates of the contribution of chronic carriers to transmission, we applied a prior distribution of $Beta(6.34,19.4)$ on the range of values for *r* in the model-fitting process [3]. The mean of this prior distribution (0.25) is also within the range of our findings in the sensitivity analysis of the contribution of chronic carriers to transmission.

S1.2. **Input parameters for economic model**

S1.2.1. *Cost conversion and inflation*

All costs were converted to 2020 USD. First, they were converted from their original amount to USD in the same reported year using WHO exchange rates [12]. Second, they were inflated to the year 2020 using the consumer price index [13].

S1.2.2. *Disability weights*

We used mild, moderate, and severe disability weights for acute infectious diseases from the 2010 Global Burden of Disease study to reflect the severity of typhoid fever compared to other diseases [14, 15]. We chose to use the 2010 study instead of the newer estimates due to the fact that newer disability weights are based on updated data from upper-income countries that do not reflect the populations in which typhoid fever is endemic. Disability weights for mild episodes were characterized as having "low fever and mild discomfort, but no difficulty with daily activities," estimated to be 0.005 ± 0.002 [15]; for moderate episodes they were

characterized as having "a fever and aches and feels weak, which causes some difficulty with daily activities," estimated to be 0.053 ± 0.012 [15]; and for severe episodes they were characterized as having "a high fever and pain, and feels very weak, which causes great difficulty with daily activities," estimated to be 0.210 ± 0.040 [15]. These mild, moderate, and severe categorizations corresponded to inpatient, outpatient, and non-medical care episodes of typhoid fever in two different ways, resulting in different average disability weights, each with equal probability of occurring (Table S1).

We assumed the duration of illness increases with the need for medical care. In this case, we used the distribution of duration of illness for inpatients and outpatients from a previous random effects model by Bilcke et al. that integrated multiple estimates [3]. Similar to the previous study, we also assumed that individuals with typhoid who did not seek medical care recovered from illness twice as fast as those who did.

Table S1. Options for disability weights assigned to different healthcare use groups. Disability weights presented for the two options are for infectious disease, acute, and for the specified level of typhoid episode (mild, moderate, or severe).

	Option 1	**Option 2**
Inpatient	Severe	Severe
Outpatient	Moderate	Severe
Patient not seeking medical care	Mild	Moderate
Average disability weight	**0.04**	**0.15**

S1.2.3. *Probability of seeking professional medical care*

To calculate the probability of seeking medical care for typhoid fever, we again used estimates from the STRATAA study [2]. As part of STRATAA, healthcare utilization surveys were conducted in the Ndirande township of Blantyre to assess the probability of seeking care for fever [16]. Many methods assume that reported healthcare-seeking for a fever is the same as that for typhoid fever; however, this is not necessarily the case. Individuals with typhoid fever

may be more or less likely to seek healthcare. To correct for this difference, we measured the probability of seeking care for a fever adjusted for a specified typhoid risk factor to estimate the probability of seeking care for typhoid fever. In Malawi, this risk factor was soap available after defecation. After adjusting for this risk factor, the probability of seeking professional medical care in Malawi was approximately 0.71 (95% CrI: 0.64-0.77) [2].

S1.2.4. *Probability of hospitalization*

During the STRATAA study, we observed 8 hospitalizations among 105 blood-culture-confirmed typhoid infections. However, since the focus of this analysis is more broadly on Malawi as an example of a multi-year outbreak of typhoid fever associated with the emergence of AMR, we used the STRATAA data from Blantyre, Malawi to update a previous estimate of the probability of hospitalization among Gavi-eligible countries based on a meta-analysis by Abboud et al [3, 17].

We modeled probability of hospitalization using a binomial distribution for the likelihood contribution, where y_{hosp} was the observed number of "successes", p_{hosp} was the probability of hospitalization among culture-confirmed typhoid infections, and n_{hosp} was the number of "trials",

$$y_{hosp} \sim Binomial(p_{hosp}, n_{hosp}).$$

In the previous analysis, the denominator (blood-culture-confirmed infections) was adjusted for differences in surveillance method according to the probability of seeking professional medical care. Using the same model for adjustment as Section 1.2.5, our denominator for the total number of typhoid fever cases in the community could be as large as 429 (median estimate after adjusting for the probability of receiving a blood culture test and the probability of seeking healthcare). However, it is also possible that individuals who do not seek

care are less severe and unlikely to be hospitalized. Hence, we allowed the denominator n_{hosp} to vary between 105 and 429 by giving it a discrete uniform prior distribution:

$$n_{hosp} \sim Uniform(105,429).$$

The previous meta-analysis estimated the probability of hospitalization to be 0.04 (95% prediction interval (PI): 0.00-0.25). We incorporated this estimate as a prior distribution on the probability of hospitalization using an inverse logit of a normal distribution with mean equal to the common estimate from the Abboud et al meta-analysis ($\mu_{hosp} = -3.25$ on the logit scale), and standard error equal to the standard error based on the prediction interval around the common estimate ($\sigma_{hosp} = 1.20$ on the logit scale) [17]:

$$logit(p_{hosp}) \sim N(\mu_{hosp}, \sigma_{hosp}).$$

Combining the likelihood of the data with the probability of the prior distribution resulted in an estimated probability of hospitalization of 0.04 (95% PI: 0.01-0.11).

S1.2.5. *Probability of death if patients are admitted to hospital for typhoid infection*

In STRATAA, we observed 1 death among the 8 individuals hospitalized for typhoid fever in Malawi, and 1 death occurred in an individual who was not hospitalized. Similar to the probability of hospitalization, we combined the data with prior information from a previous meta-analysis to estimate the case fatality rate (CFR) among inpatients admitted for typhoid fever. We again modeled this estimate using a binomial distribution for the likelihood contribution, where $y_{IP.CFR}$=1 was the observed number of "successes", $p_{IP.CFR}$ was the probability of death among inpatients, and $n_{IP.CFR}$=8 was the number of "trials",

$$y_{IP.CFR} \sim Binomial(p_{IP.CFR}, n_{IP.CFR}).$$

In this case, we wanted to update our prior to include not only the meta-analysis by Pieters et al [18] used in the previous analysis by Bilcke et al [3], but to also include estimates from a more recent meta-analysis that had been carried out for inpatient CFR estimates by Crump et al [19]. The original inpatient CFR from Pieters et al was estimated to be 0.04 (95% PI: 0.01-0.20) based on 21 studies. Crump et al's new meta-analysis had a lower pooled inpatient CFR estimate of 0.02 (95% PI: 0.01-0.03) overall (109 studies), or 0.05 (95% PI: 0.03-0.09) for studies based in Africa[19]. To supplement the meta-analysis by Pieters et al, we added studies from Crump et al's meta-analysis that had the same inclusion criteria (no population subgroups, hospital-based studies only). This exclusion process identified 26 additional studies from Crump et al, 22 of which we were able to locate. Since multi-year typhoid outbreaks are primarily occurring in sub-Saharan Africa, we further limited the studies to only include those in sub-Saharan Africa. With this additional restriction, we included 12 additional studies and the estimated inpatient CFR was 0.07 (95% PI: 0.01-0.38).

We incorporated the updated estimate as a prior distribution using an inverse logit of a normal distribution with mean equal to the common estimate from the updated random-effects meta-analysis in sub-Saharan Africa ($\mu_{IP.CFR} = -2.52$), and standard error equal to the standard error based on the prediction interval around the common estimate ($\sigma_{IP.CFR} = 1.04$; both on the logit scale):

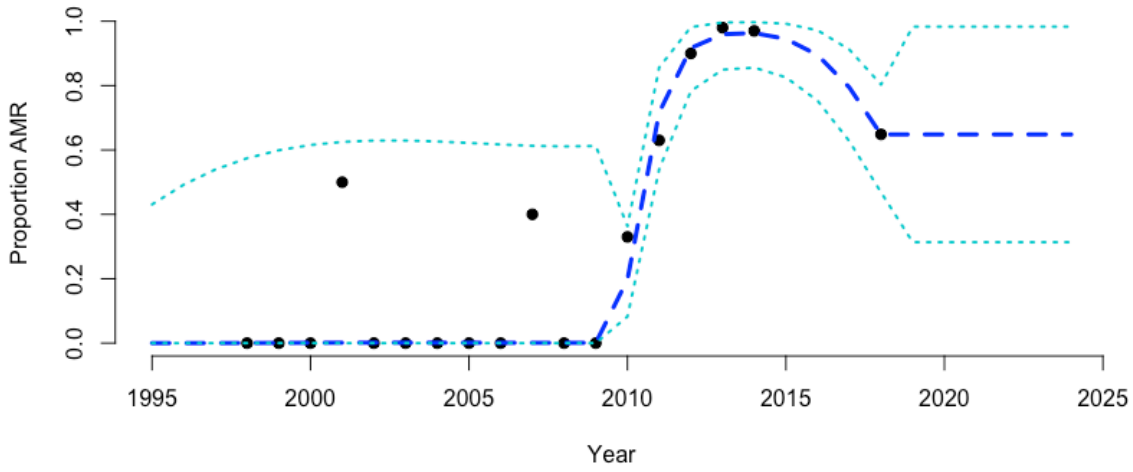
$$logit(p_{IP.CFR}) \sim N(\mu_{IP.CFR}, \sigma_{IP.CFR}).$$

Combining the likelihood of the data with the probability of the prior distribution resulted in a final estimated inpatient CFR of 0.09 (95% PI: 0.02-0.28).

S1.2.6. *Time-varying proportion of typhoid infections that are resistant to antimicrobial treatment*

Since the recent typhoid outbreaks are thought to be caused by antimicrobial resistant (AMR) strains, the proportion of typhoid infections resistant to antimicrobial treatment is assumed to be time-varying. A recent study from Feasey et al documented the annual proportion of AMR infections at Queen Elizabeth Central Hospital in Blantyre from 1998-2014 [20]. We supplemented these data points with estimates from Blantyre in the community-based STRATAA Programme in 2017-2018. With change point analysis, we identified that the AMR increase began in 2010, consistent with when we estimated the outbreak to begin using our transmission model. We fit a beta regression model with the logit-transformed proportion of AMR infections as the outcome and third-degree polynomial terms of time (year) as the independent variables. The beta regression model ensured that the proportions of AMR stayed in the interval (0,1). We compared commonly used links for the outcome variable (identity, log, log-log, and logit) and differing degrees of polynomial terms for time and chose the model with the lowest Akaike Information Criteria (AIC) value. This model provided time-varying estimates with prediction intervals for 1995-2018. We assumed that after 2018, the proportion AMR stayed the same; we doubled the standard deviations for the prediction intervals to allow for additional uncertainty in our future extrapolation (Fig S4).

Fig S4. Observed and fitted proportion of typhoid infections that are resistant to antimicrobial treatment in Blantyre, Malawi from 1995-2025. Observed data points of the yearly proportion of antimicrobial resistant typhoid fever infections over time are shown in black dots, while the fitted estimates from the beta regression model are shown in the dashed blue line and the prediction intervals are shown in the turquoise dotted lines.



S1.2.9. *All other parameters*

All other parameters not mentioned above that were used in the cost-effectiveness analysis (Table 3) have been described in detail elsewhere [3].

Table S2. Input parameters for transmission model and cost-effectiveness analysis, with distributions.

Characteristic	Uncertainty distribution	Page location
Typhoid incidence and age distribution		
Annual number of symptomatic typhoid fever cases per 100,000 people (without vaccination)	Estimated from dynamic transmission model	Based on output from transmission dynamic model fit to incidence of typhoid
Average age of patients with typhoid infection (without vaccination) (years)	Estimated from dynamic transmission model	Based on output from transmission dynamic model fit to incidence of typhoid
Typhoid mortality		
Probability of death if patients are admitted to hospital for typhoid infection	Binomial likelihood (1 success, 8 trials), inverse-logit-normal prior (mean=-2.52; standard deviation=1.04)	Page 11
Proportion of deaths from typhoid infection	Uniform from 0.25 to 1	[3]

occurring in patients not hospitalized		
Average age at death from typhoid infection	Estimated from dynamic transmission model	Assuming age distribution of deaths is the same as the age distribution of patients with typhoid
Antimicrobial resistance		
Proportion of patients with typhoid infection with an AMR strain	Change point analysis; beta regression	[16, 20]
Burden of AMR cases relative to antimicrobial-sensitive cases	Uniform from 1 to 3	[3]
Healthcare use		
Probability of infected patients seeking healthcare	Based on posterior distribution obtained by adjusting population-based incidence of typhoid	[2]; Page 9
Probability that infected patients are admitted to hospital	Binomial likelihood (8 successes, number of trials follow uniform distribution from 104 to 429), inverse-logit-normal prior (mean=-3.25; standard deviation=1.20)	Page 10
Length of stay in hospital (days)	Gamma distribution based on meta-analysis	[3]
Treatment, vaccine-related costs		
All treatment and vaccine-related costs	Varied	[3]
Disability-adjusted life-years		
Disability-weights from 0 (perfect health) to 1 (death)	Equal probability based on two scenarios	[15]; page 8
Relationship between disability weights for mild, moderate, and severe illness and outcomes on healthcare use	See description in supplement	[15]; page 8
Duration of illness in inpatients and outpatients (days)	Based on meta-analyses	[3]
Relative duration of illness for patients not seeking medical care (vs inpatients and outpatients)	Uniform from 0 to 1	[3]
Life expectancy	Fixed	[21]

S1.3. **Cost-effectiveness analysis.** *Determining the optimal strategy for each scenario.*

We calculated the associated costs and disability-adjusted life-years (DALYs) for each strategy (preventive routine vaccination, preventive routine vaccination with a catchup campaign, and reactive routine vaccination with a catchup campaign) and compared to no vaccination using the net monetary benefit (NMB) framework, where $NMB = \Delta E * WTP - \Delta C$ (where ΔE is the averted DALYs through a strategy compared to the base case of no vaccination, ΔC is the incremental cost of the strategy compared to the base case, and *WTP* is the willingness-to-pay threshold). Our measure of cost-effectiveness is the incremental net monetary benefit as opposed to the incremental cost-effectiveness ratio (ICER), because calculating the preferred strategy for more than two strategies is not always straightforward when using ICERs.

Since there is no standard WTP threshold to define whether an intervention is "cost-effective," we identified the optimal strategy (the highest average NMB) for a range of WTP values ranging from \$0-\$1,000 per DALY averted. For comparison, Malawi's 2019 gross domestic product (GDP) per capita was \$411.55 [22], within the range of these WTP values.

S1.3.1. *Uncertainty surrounding the optimal strategy in each analysis*

We randomly drew 5,000 independent samples from the uncertainty distributions of each input parameter in the economic evaluation and combined each sample with one of the samples from the stochastic transmission model to estimate 5,000 net monetary benefit values for each strategy and for a range of WTP values from \$0-\$1,000 in increments of \$10. The proportion of the 5,000 samples for which a strategy has the highest net monetary benefit among all strategies reflects our certainty regarding that strategy as the preferred one, presented as a cost-effectiveness acceptability frontier (CEAF). For example, in the non-outbreak scenario with low

incidence (pre-outbreak), the preferred strategy is no vaccination for all WTP values less than $980. However, the probability that no vaccination results in the highest net benefit decreases from 1.00 at $0 WTP to 0.66 at $970 WTP (Fig 1d). The optimal strategy is then routine vaccination with a catch-up campaign with increasing probability from 0.31 at $980 WTP to 0.32 at $1000 WTP. In the non-outbreak scenario with high incidence (post-outbreak), the probability that no vaccination is the optimal strategy decreases from 1.00 at $0 WTP to 0.63 at WTP $280. Then, our certainty that routine vaccination with a catchup campaign is preferred increases from 0.27 at a WTP of $290 to 0.56 at a WTP of $1000 (Fig 1f).

S1.4.1. *Identifying the main drivers of uncertainty.*

The expected value of partially perfect information (EVPPI) is the maximum willingness to pay for additional research regarding a specified parameter. Parameters with the highest EVPPI numbers contribute the most to uncertainty for a particular scenario and across a range of WTP values [23]. For each cost-effectiveness analysis and each uncertainty parameter, we estimated the EVPPI (Fig S9-S11).

Fig S5. Predicted and observed typhoid fever infections in the absence of vaccination. The 1,000 stochastic realizations of weekly typhoid infections individuals in the absence of vaccination from the dynamic transmission model are show in purple. The observed (reported) typhoid incidence used to fit the dynamic model is represented by the bold black line, while the observed incidence collected after model fitting is represented by the dashed red line.

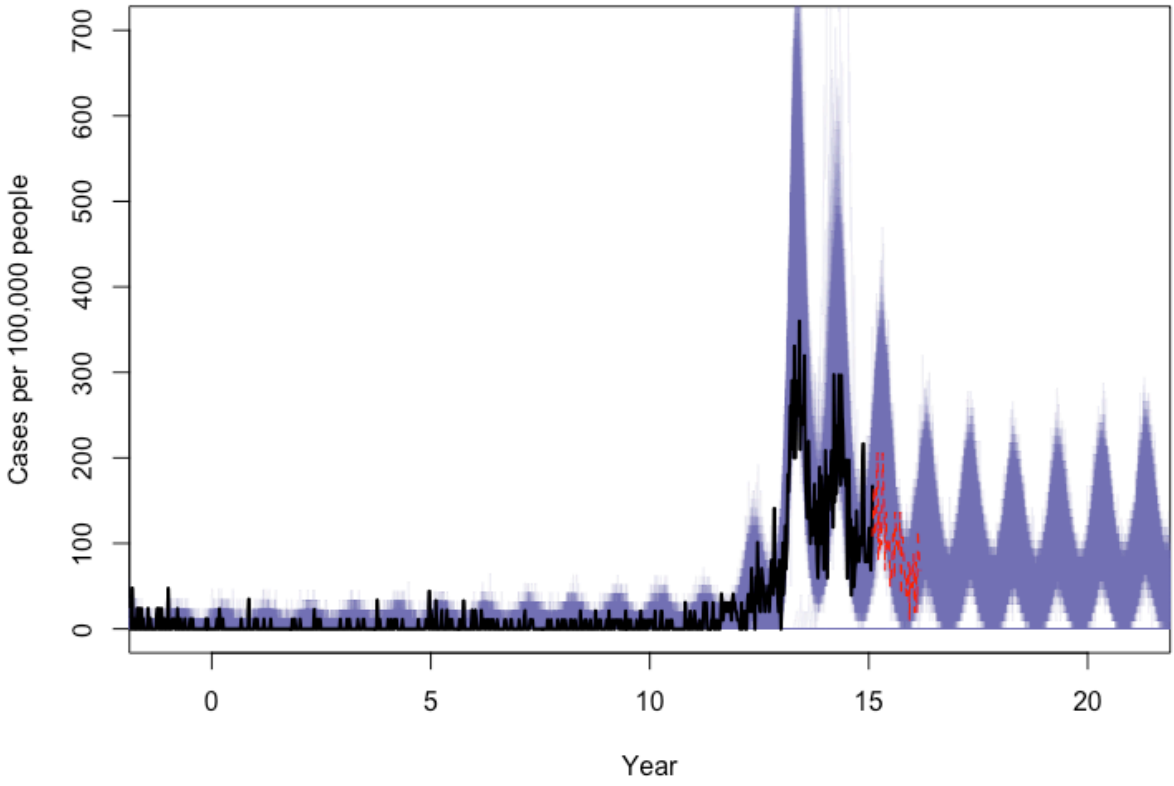


Fig S6. Observed versus fitted age distribution of reported typhoid cases. The proportion of observed cases in each age group are denoted by light blue bars, while the model-predicted age distribution is shown in darker blue.

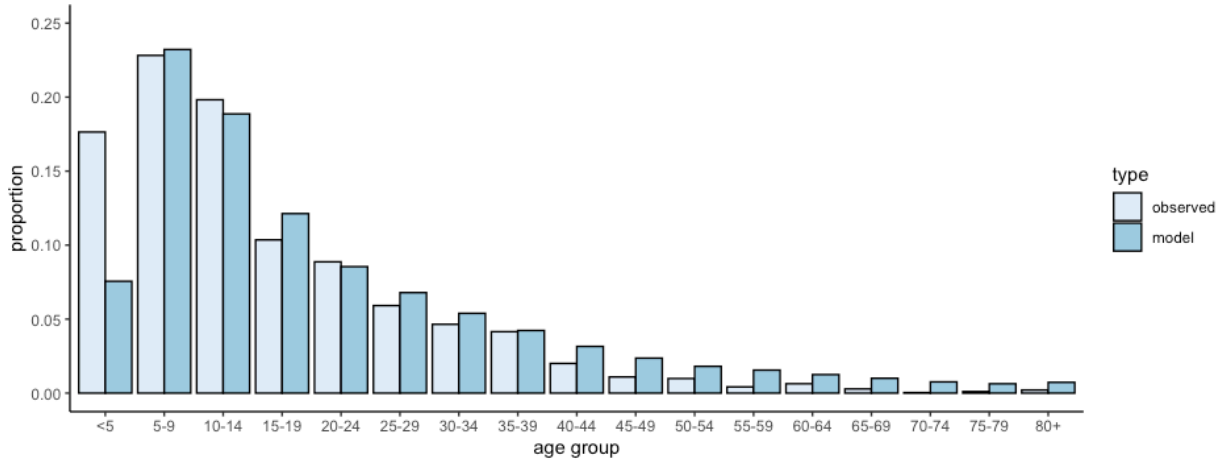


Fig S7. Predicted typhoid fever cases per 100,000 individuals in preventive vaccination scenarios. The 1,000 stochastic realizations of weekly typhoid cases per 100,000 people are shown in purple, with the median of all simulations shown in orange for each preventive vaccination strategy. Eight situations are shown, representing each preventive routine vaccination timing strategy (10, 5, 2, and 1 year(s) before; routine vaccination at 9 months of age) with and without a catchup campaign up to 15 years of age. The median number of typhoid infections per 100,000 individuals in the absence of vaccination from 1,000 realizations is shown in black, and the date of vaccination deployment for each situation is denoted by the vertical dashed green line.

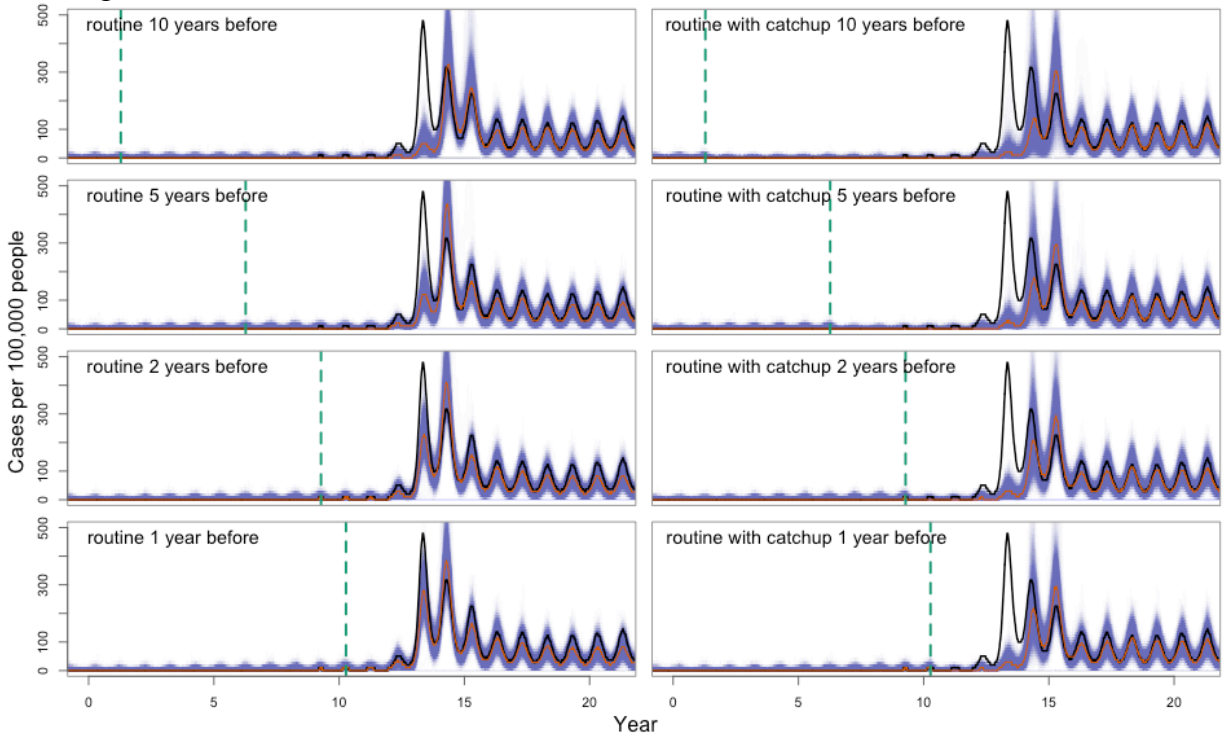


Fig S8. Predicted typhoid infections per 100,000 individuals in reactive vaccination scenarios. The 1,000 simulated predictions for weekly typhoid infections per 100,000 people are shown in purple, with the median of all stochastic realizations shown in orange for each reactive vaccination strategy. Four situations are shown, representing the four different delays in timing to implement vaccination once the outbreak is identified (1, 6, 12, and 24 months). The median typhoid infections per 100,000 individuals in the absence of vaccination from 1,000 realizations is shown in black, and the median date of vaccination deployment for each situation is denoted by the vertical dashed green line.

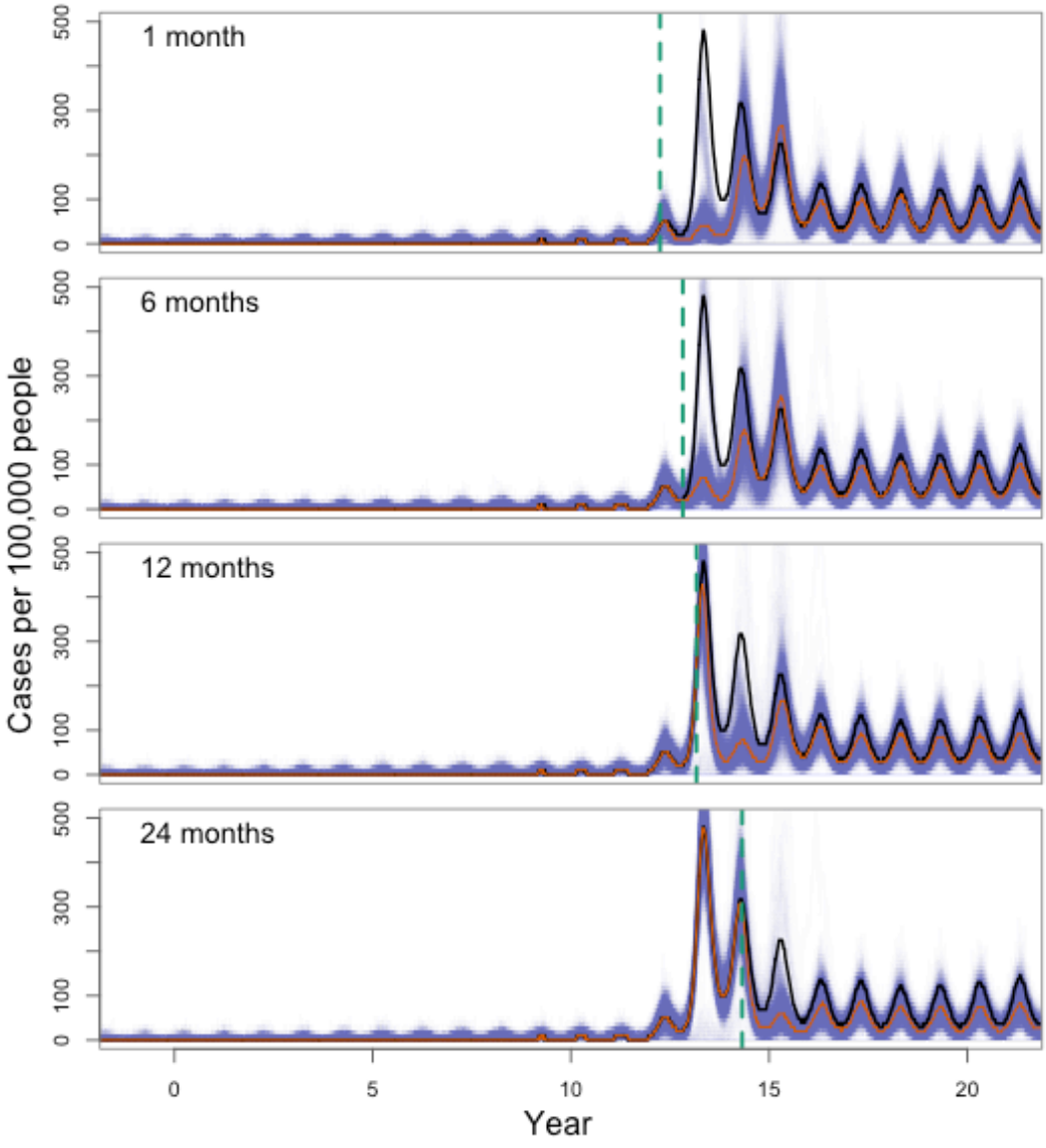


Table S3. Predicted disease and economic burden in the absence of vaccination. The median (95% credible interval) estimates for predicted cases, deaths, DALYs, and treatment costs are shown for each non-vaccination strategy.

Scenario	Cases	Deaths	DALYs	Treatment Costs
Randomized outbreak timing (starts year 0-10)	7,019 (742-12,380)	63 (3-517)	1,389 (76-11,394)	32,672 (2,099-133,417)
Fixed outbreak timing (starts year 10)	24,084 (18,201-39,943)	274 (33-1,832)	4,929 (742-31,596)	126,470 (35,688-446,186)
Non-outbreak: pre-outbreak incidence	528 (259-882)	4 (0-27)	92 (13-645)	1,014 (264-4177)
Non-outbreak: post-outbreak incidence	55,107 (41,594-87,417)	523 (65-3,405)	13,379 (1,996-83,772)	249,766 (70,140-882,877)

Table S4. Predicted vaccine impact with randomized outbreak timing, fixed outbreak timing, pre-outbreak incidence and post-outbreak incidence. The median (95% credible interval) estimates for averted cases, deaths, DALYs, treatment costs, costs of vaccinations and net costs are shown for each vaccination strategy compared to no vaccination for randomized outbreak timing (“ randomized”), fixed outbreak timing (“ fixed”), pre-outbreak incidence (“ pre”), and post-outbreak incidence (“ post”). Preventive routine vaccination strategies include routine vaccination at nine months of age in year 0 with or without a catchup campaign up to 15 years of age. Reactive routine vaccination strategies (with a catchup campaign) include delays of 1, 6, 12, and 24 months to deployment (“ 1m” , “ 6m” , “ 12m” , “ 24m” , respectively). In the fixed outbreak timing scenario, preventive strategy results are shown for 10, 5, 2, and 1 year(s) (“ 10y” , “ 5y” , “ 2y” , “ 1y”) before the outbreak starts. Results for the randomized and fixed outbreak timing strategies are shown using an outbreak identification definition of 15 standard deviations above the monthly mean number of typhoid cases. R=routine vaccination; RC=routine vaccination plus a catchup campaign.

	Strategy	Net Costs	Cost of Vaccination	Averted Treatment Costs	DALYs Averted	Deaths Averted	Cases Averted
randomized	**preventive R**	191,479 (72,058-456,733)	203,159 (90,632-468,040)	7,959 (-13,557-61,334)	376 (-569-4,223)	15 (-32-197)	1,713 (-1,974-6,939)
	preventive RC	202,723 (76,770-471,912)	223,297 (108245-489,334)	14,975 (-95-83,638)	704 (22-6,262)	29 (0-295)	3,142 (6-9,154)
	reactive 1m	99,007 (-787-312,044)	119,345 (0-322,656)	11,948 (-2,683-73,634)	563 (-109-5,330)	23 (-6-247)	2,547 (-589-7,921)
	reactive 6m	92,217 (-1,186-300,704)	112,177 (0-313,708)	10,707 (-5,741-69,999)	480 (-216-5,301)	20 (-12-246)	2,369 (-1,045-7,542)
	reactive 12m	86,580 (-2,648-286,133)	102,677 (0-296,295)	7,573 (-9,184-61,951)	320 (-496-4,440)	13 (-25-204)	1,664 (-1,808-7,232)
	reactive 24m	78,158 (-6,830-271,612)	86,562 (0-279,698)	3,219 (-22,319-52,342)	137 (-1,185-3,558)	6 (-59-162)	738 (-3,208-6,718)
fixed	**preventive R 10y**	765,534 (299,001-1,795,847)	810,759 (371,538-1,846,111)	34,199 (-26,488-208,519)	1,481 (-770-14,206)	68 (-68-748)	7,266 (-5,362-23,101)
	preventive RC	779,499 (306,879-1,820,621)	839,435 (395,514-1,872,884)	45,690 (-19,734-240,875)	1,959 (-249-17,441)	93 (-40-929)	9,685 (-3,366-25,521)
	preventive R 5y	657,558 (248,612-1,544,369)	693,563 (317,090-1,568,645)	27,476 (-36,801-189,218)	1,154 (-1,164-12,305)	53 (-94-681)	6,023 (-6,330-22,975)
	preventive RC	678,503 (270,336-1,549,494)	733,275 (355,445-1,609,560)	41,761 (-19,483-225,826)	1,778 (-286-15,408)	86 (-41-842)	8,908 (-3,515-25,455)
	preventive R 2y	560,966 (213,666-1,317,147)	590,663 (272,194-1,350,104)	22,518 (-51,963-166,904)	900 (-2,002-10,750)	42 (-142-589)	5,108 (-9,111-21,838)
	preventive RC	592,795 (238,565-1,348,901)	643,118 (319,071-1,391,903)	39,483 (-20,364-214,667)	1,646 (-349-14,970)	79 (-45-810)	8,180 (-4,230-24,351)
	preventive R 1y	526,046 (203,912-1,233,829)	549,938 (254,861-1,248,632)	19,911 (-57,442-157,859)	787 (-2,290-10,771)	37 (-159-580)	4,584 (-9,515-20,481)
	preventive RC	562,810 (223,034-1,260,712)	612,637 (311,868-1,300,391)	38,620 (-31,308-217,423)	1,630 (-719-15,271)	78 (-68-803)	8,257 (-6,029-24,581)
	reactive 1m	488,439 (188,101-1,116,378)	536,347 (277,278-1,172,571)	37,066 (-17,873-210,272)	1,532 (-394-14,463)	74 (-41-774)	7,695 (-3,836-23,693)
	reactive 6m	470,039 (184,171-1,071,152)	519,150 (269,346-1,106,166)	35,802 (-25,577-207,822)	1,458 (-684-14,299)	72 (-57-791)	7,281 (-5,357-24,274)
	reactive 12m	450,169 (171,307-1,012,565)	493,471 (259,415-1,047,490)	34,019 (-21,563-197,724)	1,375 (-682-13,068)	69 (-52-730)	7,056 (-5,045-23,137)
	reactive 24m	424,831 (172,084-960,493)	456,973 (245,547-984,038)	26,630 (-52,510-175,003)	997 (-2,130-11,389)	52 (-135-647)	5,770 (-8,344-21,143)
pre	**preventive R**	94,781 (47,775-210,401)	95,341 (48,304-211,430)	434 (-223-2,381)	37 (-22-353)	1 (-1-15)	236 (-110-646)
	preventive RC	102,145 (54,123-217,929)	103,143 (55,225-218,880)	728 (115-3,301)	66 (6-511)	3 (0-22)	389 (95-761)
post	**preventive R**	2,788,933 (1,131,853-6,659,140)	2,918,379 (1,289,445-6,793,822)	101,474 (3,853-448,009)	5,193 (170-40,515)	205 (6-1,658)	23,761 (1,817-55,030)
	preventive RC	3,059,779 (1,378,529-6,876,800)	3,222,488 (1,584,078-6,990,784)	125,363 (9,826-541,592)	6,740 (441-51,249)	260 (11-2,086)	29,398 (3,764-62,036)

Fig S9. Expected value of partially perfect information for differing delays in vaccination deployment for reactive strategies with randomized outbreak timing. The expected value of partial perfect information (EVPPI) for each parameter is shown for a range of willingness-to-pay values. Results are shown for 5,000 parameter samples and 2020 $USD. Each panel shown represents the EVPPI for one cost-effectiveness analysis comparing 4 strategies: no vaccination (base case), preventive routine vaccination at 9 months, preventive routine vaccination with a catchup campaign up to 15 years, and reactive routine vaccination with a catchup campaign. Each panel shows the results for a cost-effectiveness analyses with the specified delay in months for the reactive strategy (1-, 6-, 12-, or 24-month delays).

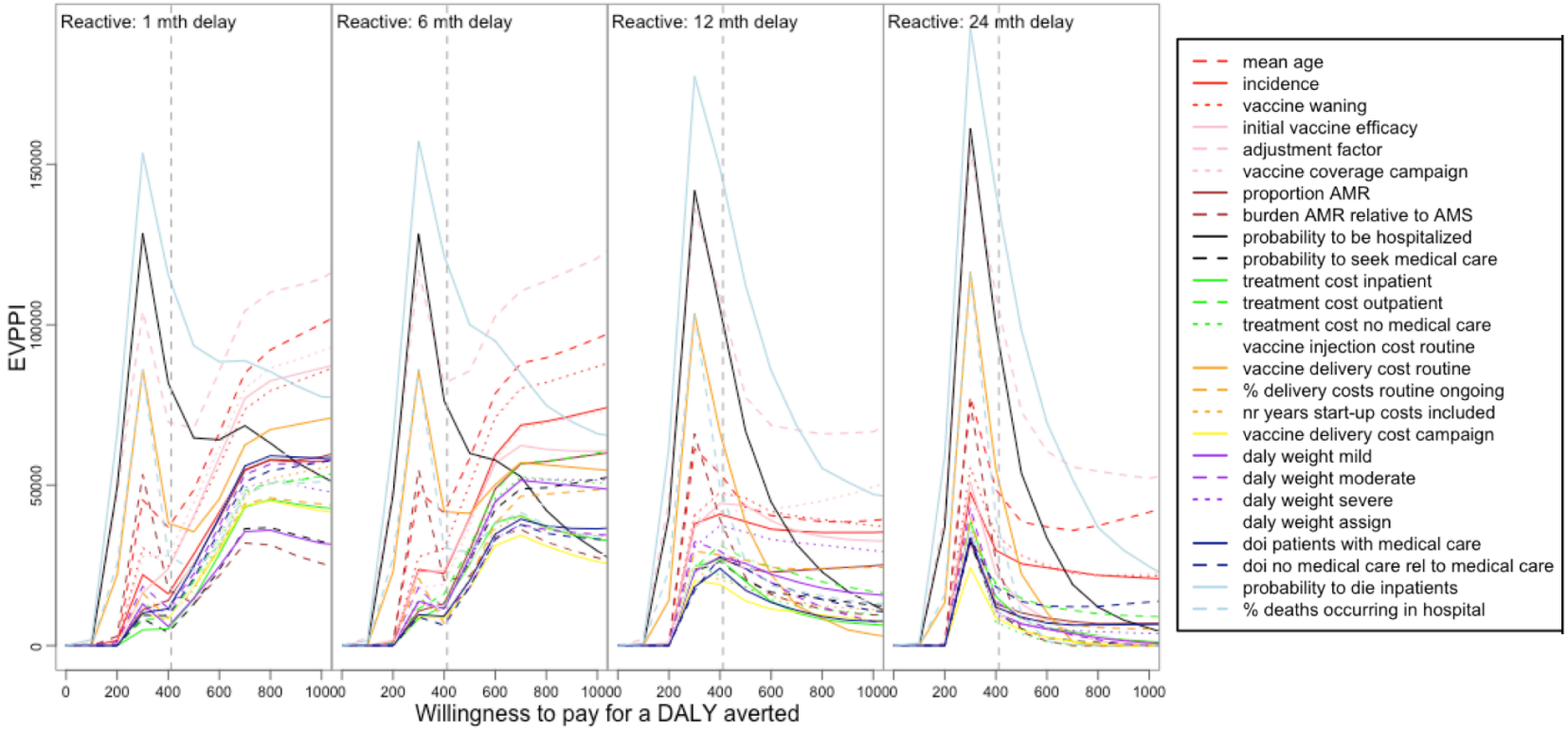


Fig S10. Expected value of partially perfect information for pre-outbreak (non-outbreak) incidence. The expected value of partial perfect information (EVPPI) for each parameter is shown for a range of willingness-to-pay values. Results are shown for 5,000 parameter samples and 2020 $USD.

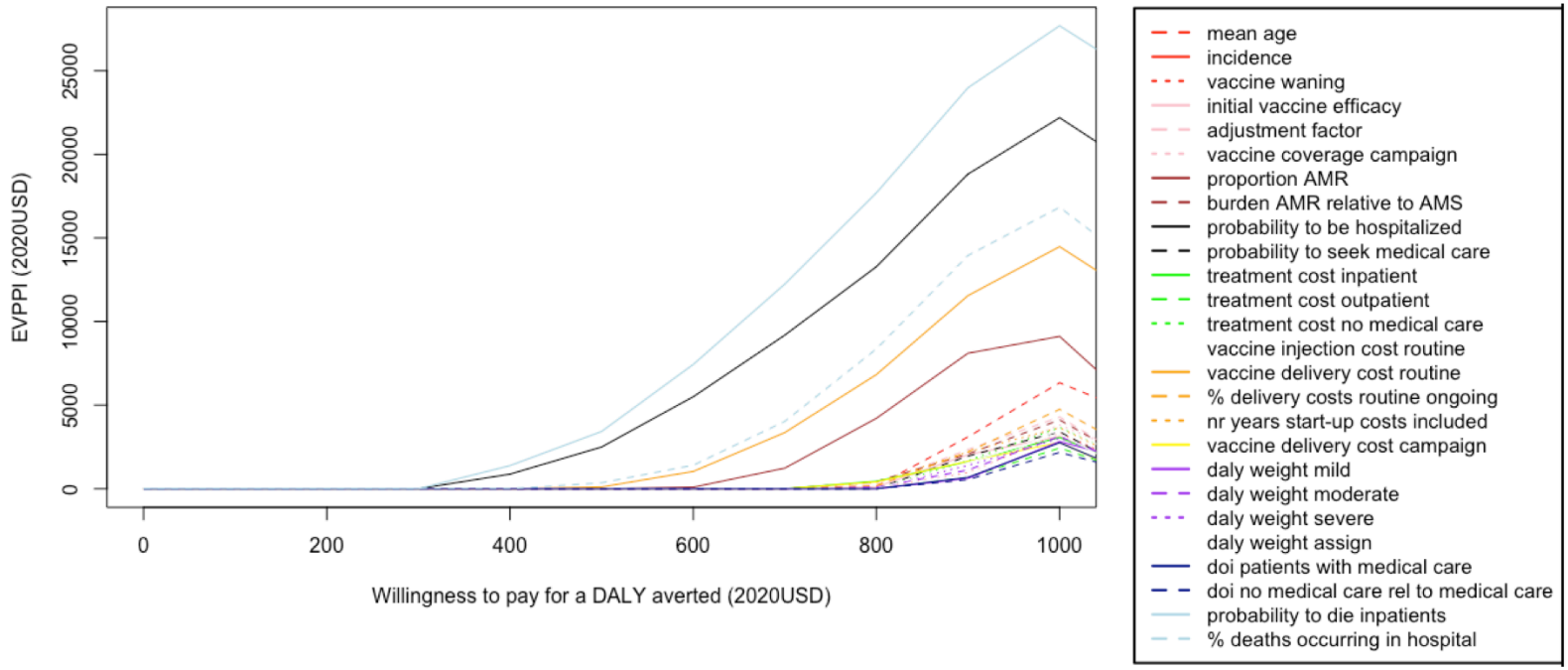
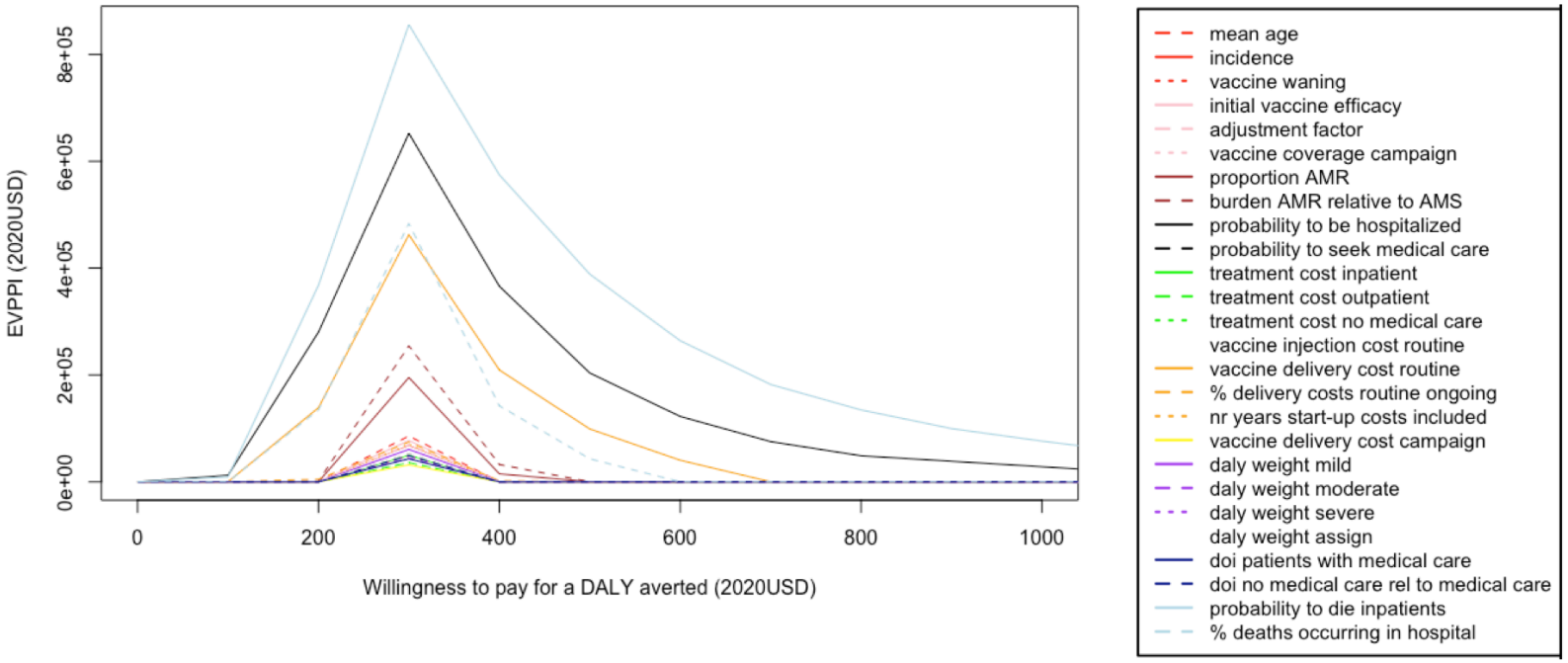


Fig S11. Expected value of partially perfect information for post-outbreak (non-outbreak) incidence. The expected value of partial perfect information (EVPPI) for each parameter is shown for a range of willingness-to-pay values. Results are shown for 5,000 parameter samples and 2020 $USD.



S2.2.3. Consolidated Health Economics Evaluation Reportings Standards (CHEERS) checklist

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page 4-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5; Supp page 2
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 5-6, 8
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 9
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 6-8
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 7-8
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 9
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 9
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	page 7

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 5; Supp page 2-5
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 9, Supp page 7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Supp page 2-3
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 9-10
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Supp page 2-7
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table S2-S4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	page 17-18; Figs S8-S10
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	page 18-21
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	page 24
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	page 24

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

References

1. Ames WR, Robins M. Age and Sex as Factors in the Development of the Typhoid Carrier State, and a Method for Estimating Carrier Prevalence *. Am J Public Health Nations Health. 1943;33(3):221-30. PubMed PMID: 18015749; PubMed Central PMCID: PMC1527221.
2. Phillips MT, Meiring JE, Voysey M, Warren JL, Baker S, Basnyat B, et al. A Bayesian approach for estimating typhoid fever incidence from large-scale facility-based passive surveillance data. medRxiv. 2021. doi: 10.1101/2020.10.05.20206938.
3. Bilcke J, Antillon M, Pieters Z, Kuylen E, Abboud L, Neuzil KM, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study - The Lancet Infectious Diseases. Lancet Infectious Diseases. 2019;19(7):728-39. doi: doi:10.1016/S1473-3099(18)30804-1.
4. Pitzer VE, Feasey NA, Msefula C, Mallewa J, Kennedy N, Dube Q, et al. Mathematical Modeling to Assess the Drivers of the Recent Emergence of Typhoid Fever in Blantyre, Malawi. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61:S251-8. Epub 2015/10/10. doi: 10.1093/cid/civ710. PubMed PMID: 26449939; PubMed Central PMCID: PMCPMC4596932.
5. Voysey M, Pollard A. Seroefficacy of Vi Polysaccharide-Tetanus Toxoid Typhoid Conjugate Vaccine (Typbar TCV). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018;67(1). doi: 10.1093/cid/cix1145. PubMed PMID: 29351594.
6. Jin C, Gibani M, Moore M, Juel H, Jones E, Meiring J, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. Lancet (London, England). 2017;390(10111). doi: 10.1016/S0140-6736(17)32149-9. PubMed PMID: 28965718.
7. Mohan V, Varanasi V, Singh A, Pasetti M, Levine M, Venkatesan R, et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(3). doi: 10.1093/cid/civ295. PubMed PMID: 25870324.
8. Meiring J, Laurens M, Patel P, al e. Typhoid vaccine acceleration consortium Malawi: A Phase III, randomized, double-blind, controlled trial of the clinical efficacy of typhoid conjugate vaccine among children in Blantyre, Malawi. Clinical Infectious Diseases. 2019;68:S50-8.
9. Meiring J, Sambakunsi R, Moyo E, al e. Community engagement before initiation of typhoid conjugate vaccine trial in schools in two urban townships in Blantyre, Malawi: Experience and lessons. Clinical Infectious Diseases. 2019;68:S146-53.
10. Sur D, Barkume C, Mukhopadhyay B, Date K, Ganguly NK, Garrett D. A Retrospective Review of Hospital-Based Data on Enteric Fever in India, 2014-2015. J Infect Dis. 2018. Epub 2018/10/12. doi: 10.1093/infdis/jiy502. PubMed PMID: 30307566.
11. Antillon M, Bilcke J, Paltiel AD, Pitzer VE. Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low- and middle-income settings. Vaccine. 2017;35(27):3506-14. Epub 2017/05/22. doi: 10.1016/j.vaccine.2017.05.001. PubMed PMID: 28527687; PubMed Central PMCID: PMCPMC5462484.
12. Stenberg K, Lauer JA, Gkountouras G, Fitzpatrick C, Stanciole A. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. Cost Effectiveness and Resource Allocation. 2018;16(1):1-15. doi: 10.1186/s12962-018-0095-x.
13. McMahon T. Historical Consumer Price Index (CPI): Capital Professional Services; 2021 [cited 2021 May 11]. Available from: https://inflationdata.com/Inflation/Consumer_Price_Index/HistoricalCPI.aspx?reloaded=true#Table?reloaded=true?reloaded=true.
14. Global Burden of Disease Study. Global Burden of Disease Study 2010 (GBD 2010) Results by Cause 1990-2010 Seattle, United States: Institute for Health Metrics and Evaluation (IHME); 2012. Available from: http://ghdx.healthdata.org/record/global-burden-disease-study-2010-gbd-2010-results-cause-1990-2010.
15. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2129-43. Epub 2012/12/19. doi: 10.1016/s0140-6736(12)61680-8. PubMed PMID: 23245605.

16. Darton TC, Meiring JE, Tonks S, Khan MA, Khanam F, Shakya M, et al. The STRATAA study protocol: a programme to assess the burden of enteric fever in Bangladesh, Malawi and Nepal using prospective population census, passive surveillance, serological studies and healthcare utilisation surveys. 2017;7(6). doi: 10.1136/bmjopen-2017-016283.
17. Abboud L. Global hospitalization rate of typhoid fever: a meta-regression. Antwerp: University of Antwerp; 2017.
18. Pieters Z, Saad NJ, Antillón M, Pitzer VE, Bilcke J. Case Fatality Rate of Enteric Fever in Endemic Countries: A Systematic Review and Meta-analysis. Clinical Infectious Diseases. 2018;67(4):628-38. doi: 10.1093/cid/ciy190.
19. Marchello CS, Birkhold M, Crump JA. Complications and mortality of typhoid fever: A global systematic review and meta-analysis. Journal of Infection. 2020;81(6):902-10. doi: 10.1016/j.jinf.2020.10.030.
20. Feasey N, Gaskell K, Wong V, Msefula C, Selemani G, Kumwenda S, et al. Rapid Emergence of Multidrug Resistant, H58-Lineage Salmonella Typhi in Blantyre, Malawi. PLOS Neglected Tropical Diseases. 2015;9(4):e0003748. doi: 10.1371/journal.pntd.0003748.
21. World Bank. Life expectancy at birth, total (years) 2021. 2019 Revision:[Available from: https://data.worldbank.org/indicator/SP.DYN.LE00.IN.
22. World Bank. GDP per capita (current US$) - Malawi: The World Bank Group; 2021 [cited 2021 May 11]. Available from: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=MW.
23. Strong M, Oakley JE. An Efficient Method for Computing Single-Parameter Partial Expected Value of Perfect Information:. Medical Decision Making. 2012;33(6):755-66. doi: 10.1177_0272989X12465123.

Chapter 3

Changes in historical typhoid transmission across 16 U.S. cities, 1889-1931: Quantifying the impact of investments in water and sewer infrastructures

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Abstract

Investments in water and sanitation systems are believed to have led to the decline in typhoid fever in developed countries, such that most cases now occur in regions lacking adequate clean water and sanitation. Exploring seasonal and long-term patterns in historical typhoid mortality in the United States can offer deeper understanding of disease drivers. We fit modified Time-series Susceptible-Infectious-Recovered models to city-level weekly mortality counts to estimate seasonal and long-term typhoid transmission. We examined seasonal transmission separately by city and aggregated by water source. Typhoid transmission peaked in late summer/early fall. Seasonality varied by water source, with the greatest variation occurring in cities with reservoirs. We then fit hierarchical regression models to measure associations between long-term transmission and annual financial investments in water and sewer systems. Overall historical $1 per capita ($16.13 in 2017) investments in the water supply were associated with approximately 5% (95% confidence interval: 3-6%) decreases in typhoid transmission, while $1 increases in the overall sewer system investments were associated with estimated 6% (95% confidence interval: 4-9%) decreases. Our findings aid in the understanding of typhoid transmission dynamics and potential impacts of water and sanitation improvements, and can inform cost-effectiveness analyses of interventions to reduce the typhoid burden.

Author summary

Typhoid fever remains a major source of morbidity and mortality in low- and middle-income countries. Historical investments in water and sanitation systems are thought to have led to the decline in typhoid fever in developed countries, such that most of the global burden of disease now occurs in regions with poor sanitary conditions and inadequate access to clean water and sanitation. However, there is limited empirical evidence to quantify the impact of investments in water and sanitation on typhoid fever incidence. We developed a mathematical model to examine trends in weekly typhoid mortality data from 1889-1931 in 16 U.S. cities. Through this analysis, we were able to examine how seasonal patterns of typhoid transmission varied geographically and historically depending on the water supply and treatment, and quantify the relationship between investments in water and sanitation infrastructures and long-term typhoid transmission rates. Our findings have important implications for the understanding of typhoid transmission dynamics and potential impact of improvements in water and sanitation infrastructure. Resource-poor countries must prioritize spending on public health issues, weighing the costs and benefits of interventions. Our results can help to inform comparative cost-effectiveness analyses of different interventions to reduce the global burden of typhoid fever.

Introduction

Typhoid fever is caused by infection with the bacteria *Salmonella enterica* serovar Typhi, which is mainly transmitted through fecal contamination of food or water [1]. In many developed countries, including the United States (U.S.), investments in water and sewer infrastructures led to the decline in typhoid incidence in the beginning of the 20th century, such that the majority of the global burden now occurs in countries where sanitary conditions are poor and access to clean water and sanitation is lacking [1-3].

Examining short- and long-term trends in typhoid incidence can provide insights into factors driving transmission [4]. In many countries, typhoid fever follows a seasonal pattern, with peak incidence occurring around the same time every year [5, 6]. Seasonality in typhoid exhibits distinct patterns by region and latitude, and can be influenced by rainfall, temperature, and other climatic factors [6]. However, drivers of seasonal patterns in typhoid are not yet fully understood.

Long-term patterns in typhoid cases have also been investigated, particularly in countries where cases have declined to almost zero [4]. In the U.S., the number of typhoid deaths decreased from a reported 35,000 in 1900 to three from 1999-2006 despite a 4.3-fold population increase [7-10]. While it is commonly accepted that investments in water and sanitation are responsible for the decline in typhoid fever, there is limited empirical evidence to support this claim. In one study, Cutler and Miller found that the introduction of clean water technologies was responsible for almost half of the mortality reduction in major cities at the beginning of the 20th century; however, they did not consider complexities of the disease transmission process [11].

In this study, we developed mathematical and statistical models to examine seasonal and long-term trends in typhoid transmission from 1889-1931 in 16 U.S. cities. Our objectives were two-fold: (1) to examine how seasonal patterns of typhoid transmission varied geographically and historically depending on the water supply and treatment; and (2) to quantify the relationship between investments in water and sanitation infrastructures and long-term typhoid transmission rates.

Methods

Study Design, Data, and Variables

We extracted reported weekly typhoid mortality from 1889 to 1931 at the city level from the Project Tycho database [12, 13]. Cities were chosen based on two criteria: (1) at least 1,000 typhoid deaths were reported during the study period, and (2) less than 25% of weekly data was missing. These exclusion criteria resulted in data for 16 U.S. cities (S1 Fig). While errors in disease diagnosis and missing data make underreporting likely, the consistency of reporting over time allows for our analysis [13, 14].

Yearly population estimates were obtained from the U.S. Census Bureau [15]. The population <1 year of age was used as a proxy for births, since birth rate data was not available and typhoid is rare in <1-year-olds [16]. New York City population estimates were adjusted for the consolidation of the five boroughs (including Brooklyn) in 1898 [17]. We also accounted for this change by multiplying the number of reported typhoid deaths in Brooklyn by a factor of 1.28 (i.e. the relative population size of the other boroughs, for which we did not have separate mortality data) and adding this to typhoid mortality data from New York City (previously only

Manhattan). For all cities, cubic splines were used to extrapolate weekly population estimates (S2 Fig).

Financial data on water supply and sewer systems for each city were extracted from U.S. Census Bureau yearly reports [15]. We obtained data on water and sewer systems across five categories: "receipts," "expenses," "outlays," "value," and "funded debt", and used the first three to estimate the "overall investment" (Table 1). The main financial variable of interest, "overall investment", represents the cumulative per capita investment in water supply and sewer systems. It was calculated as the sum of the annual acquisition/construction costs (cumulative outlays) and maintenance/operation costs (expenses) after subtracting yearly receipts (Table 1). All variables were adjusted yearly for inflation to 1931 dollars using the Bureau of Labor Statistics' Consumer Price Index [18], then divided by the yearly city population to generate per capita estimates. Data on specific water supply interventions for each city were extracted from a variety of sources (S1 Table) [19].

Table 1. Definitions of financial variables. Each of the six categories of financial variables used in this study are described, as defined by the U.S. Census Bureau in its annual "Financial Statistics" series (the source of these variables).

	Description
Maintenance and operation	
Receipts	Receipts for payments for governmental costs. These receipts usually take the form of money, bills receivable, land, and services. All city revenue receipts were recorded in the city books for municipally-operated water supply and sewer systems for the public or city (excluding interest from current deposits).
Expenses	City government costs, other than interest, of (1) services employed, property rented, and materials consumed in connection with maintenance and operation; (2) losses from deflation, bank failures, and related causes; and (3) depreciation of permanent properties and public improvements.
Acquisition and construction	

Outlays	Total annual amounts paid by the city for the acquisition or construction of permanent lands, properties and public improvements. These include payments for additions made to previously acquired or constructed properties.
Value and debt	
Value	Total estimated value of the public properties (including depreciation), including both the business value and the physical value of the building and equipment. This amount is estimated separately by city officials, and is acknowledged to not be estimated uniformly across cities.
Funded debt	Long-term debts or debt liabilities in the form of bonds or certificates of indebtedness that the city government is under obligation to pay.
Cumulative investment	
Overall investment	Overall investment in the water supply or sewer systems, defined as the cumulative sum of the amount spent each year on acquisition/construction (outlays) and maintenance/operation (expenses minus receipts) of water or sewer infrastructure.

All cities had missing data on weekly typhoid mortality, due to the nature of the historical data. In many cases, missing mortality counts were instances of zero cases, because cities frequently only reported during weeks when deaths occurred. To account for both true zero counts and missing data, mortality data were coded as zeroes if there were fewer than 13 consecutive weeks of missing death counts, and imputed as missing data if there were 13 or more consecutive weeks. We imputed missing data using the package "imputeTS" in R[20], performing Kalman smoothing (function *na_kalman*) to preserve the seasonality and overall trends of the time series (S3 Fig). This package and algorithm are commonly used for univariate time series imputation. We conducted a sensitivity analysis to assess how this arbitrary 13-week cut-off could impact our results (S2 Text).

After imputation, weekly typhoid mortality counts and population estimates were aggregated into four-week periods to approximate the generation interval of typhoid [21, 22]. The generation interval can be defined as the time between when an infector is infected and when an individual is infected by that the infector [22, 23]. In this study, the generation interval

was based on data from the natural history of typhoid infection, derived from human challenge studies. Other studies suggest that TSIR models are not overly sensitive to having a precise estimate for the generation interval [24]. Since the mortality data were later log-transformed, we added one to every four-week data point before adjusting for underreporting and before fitting the model; a sensitivity analysis was again performed to assess the impact of adding different values.

Statistical Methods

We conducted preliminary analyses to describe differences in typhoid mortality trends between cities and pre- to post-intervention. First, we fit generalized linear models (GLMs) with linear time trends and one-year and six-month harmonics to the pre- and post-intervention time series (defined as two years after the first water supply intervention) for each city. The "first" intervention is defined as the initial occurrence of a municipally-reported method or process that aimed to improve the water quality in a city's main water source, and was used only in the preliminary analyses to define the pre- and post- intervention period. The six- and 12-month harmonics allow for an overall annual variation plus additional fluctuations, if any; these were identified using Fourier and wavelet analyses. We compared intercepts, slopes, and six-month and one-year amplitudes for the pre- and post- periods in the GLMs, and plotted the overall six- and 12-month amplitudes on a map of the U.S. to examine spatial patterns.

We then fit Time-series Susceptible-Infectious-Recovered (TSIR) models [25] to each city's pre- and post-intervention time series to investigate seasonal and long-terms trends in typhoid transmission rates. TSIR models are a well-established approach to examine associations between external variables and infectious disease transmission rates by conditioning on the susceptible population and exposure to a pathogen to extract rates of infectiousness inferred from

the time series [26]. These models estimate the disease transmission rate by reconstructing the underlying susceptible and infectious populations. This method explicitly attributes autocorrelation in the data to the interaction between susceptible and infectious individuals.

In general, new infections at time t+1 (I_{t+1}) arise from transmission from infectious (I_t) to susceptible (S_t) individuals at time t:

$$I_{t+1} = \beta_t I_t^{\alpha} S_t \qquad (1)$$

where β_t is the disease transmission rate at time t. The exponent α allows for heterogeneous population mixing and corrects for discretization of the continuous-time infection process [27].

We modified Equation 1 to account for the unique features of typhoid epidemiology, including the contribution of chronic carriers (C) to the prevalence of infection. Furthermore, we separated the transmission parameter β_t into seasonal and long-term components (β_{seas} and β_{lt}, respectively). Thus, the TSIR model for typhoid is as follows:

$$I_{t+1} = \beta_{lt}\beta_{seas,j}(I_t + C)^{\alpha} S_t \qquad (2)$$

where $\beta_{seas,j}$ reflects the annual seasonally varying transmission parameter (j = 1,2,…13 for the number of distinct four-week generation intervals in one year), and β_{lt} (558 distinct values for the number of generation intervals over the 43-year period, minus 1 for the reconstruction of I_{t+1}) captures trends and any seasonal variation lasting longer than one year. We fixed $\beta_{seas,13} = 1$ and estimated the remaining j = 1,2,…,12 seasonal transmission parameter in comparison to the thirteenth month. We estimated β_{lt} using a semi-parametric method described below and in more detail in the S1 Text.

Equation 2 can then be log-transformed:

$$log(I_{t+1}) = log(\beta_{lt}) + log\left(\beta_{seas,j}\right) + \alpha\, log(I_t + C) + \log(S_t). \qquad (3)$$

The TSIR equation is now on the additive scale, and can be incorporated into regression frameworks (S1 Text). This method has been explained in detail elsewhere [25].

With the goal of extracting the seasonal and long-term transmission rates (β_{lt} and $\beta_{seas,j}$), we needed to first reconstruct the susceptible, infectious, and chronic carrier populations. We estimated some of these terms differently for our exploratory and main analyses, but both analyses utilized regression and maximum likelihood estimation to infer these terms from the disease and census data.

The susceptible population at time *t* is equal to the previous susceptible population plus new births minus new infections, summarized as follows:

$$S_t = \bar{S} + D_0 + \sum_{k=0}^{t-1} b_k - \sum_{k=0}^{t-1} I_k \qquad (4)$$

where $\bar{S}$ is the mean susceptible population over the study period, D_0 is the deviation of the susceptible population from the mean at time zero, $\sum_{k=0}^{t-1} b_k$ is the sum of births up to time *t*, $\sum_{k=0}^{t-1} I_k$ is the sum of "true" infections up to (but not including) time *t*, and *k* denotes the time point ranging from the beginning of the study up until just before time *t*. The number of "true" infections at time *t* (I_t) is estimated from the observed deaths at time *t* (Y_t) divided by the underreporting fraction (ρ), which in this case also accounts for the case fatality rate. Equation 4 can be rearranged as

$$\sum_{k=0}^{t} b_k = \left(\frac{1}{\rho}\right) \sum_{k=0}^{t} Y_k - D_0 + D_t \qquad (5)$$

to estimate the underreporting fraction (slope), deviation at time zero (intercept), and model residuals ($D_t = S_t - \bar{S}$) using linear regression. We used only the first ten years of typhoid mortality and census data (prior to the introduction of water and sanitation interventions) [24, 25] to estimate the rate of underreporting of infectious individuals, and assumed that ρ remained constant over the entire 43-year study period.

To estimate C and S_t $(= D_t + \bar{S})$ in the preliminary analysis, we maximized the likelihood of the fitted regression (Equation 5) over different values of C and $\bar{S}$, each ranging from 0 to the maximum population size over the time period. For the preliminary analysis, we then fit Equation 3 using ordinary least squares regression.

For our main analysis, we used the same estimates for the infectious population (adjusted for underreporting) and chronic carriers from the preliminary analysis, but modified the calculation for the susceptible population to include waning of immunity. Instead of using the residuals from Equation 5, we modelled the susceptible population at time t as a function of the total population at time t minus the previously infectious and recovered individuals:

$$S_t = N_t - \sum_{i=0}^{m} I_{t-i}\kappa_i \quad (6)$$

where κ_i is the degree of immunity i generation intervals after infection.

Once we had estimates for the susceptible, infectious, and chronic carrier components of Equation 3, we fit the model via weighted least squares regression using a range of values for smoothing and spline penalty parameters. For the final model, we chose the one with the smoothing and spline penalty parameters that resulted in the lowest sum of squared differences between each point and its out-of-sample prediction over all points.

The model-fitting process is described in detail in the S1 Text; additional details about TSIR models can be found elsewhere [25, 28, 29]. We performed sensitivity analyses on the various components of the model, as described in the S2 Text.

Examining predictors of seasonal and long-terms trends in transmission

Once we fit the optimal TSIR model for each city, we extracted the seasonal and long-term transmission rates. Seasonal transmission parameters were plotted separately for each city and aggregated by water source type. We calculated the mean estimate (among all cities and

across water source types) in each month. Months were considered to have significantly low or high seasonal transmission if their confidence intervals were entirely below or above one, respectively. The percentage of cities with seasonal transmission significantly below or above one in each month were calculated overall and by water source type.

To examine associations between long-term typhoid transmission and financial investments in water and sewer systems, we fit hierarchical regression models for each financial variable separately. We fit several variable transformations and model formulations and chose a linear model with a log-transformed outcome following exploratory analyses. The final approach has fixed and varying city-level intercepts and slopes:

$$\log(\beta_{lt,i,t}) = (d_0 + \delta_{0,i}) + (d_1 + \delta_{1,i})X_{i,t} \quad (7)$$

where fixed intercept d_0 is the average log-transmission rate of typhoid across cities with no investments in water and sanitation, random intercept $\delta_{0,i}$ represents the deviation from the fixed intercept for city i, fixed slope d_1 is the average change in log-transformed typhoid transmission across cities for a \$1 per capita increase in the financial variable, random slope δ_i is the deviation from the fixed slope for city i, and $X_{i,t}$ is the financial investment for city i in year t.

Missing financial variable data were assumed to be missing completely at random and were omitted from analyses. Due to multicollinearity between most of the financial variables, it was not possible to fit regression models with multiple predictors. However, the main variables of interest, overall investments in the water supply and sewer systems, provide a representation of cumulative financial investments as a whole over the time period.

Model Validation

To validate the TSIR models and assess their predictive ability, we went back and fit each TSIR model to the first 38 years of data (1889-1926). Using the fitted model parameters, we

projected forward for the last five years (1927-1931) and compared the observed and predicted typhoid mortality. To predict the long-term typhoid transmission rate, we used the relationship with overall investment in the water supply identified by the hierarchical regression analysis. This variable had the highest marginal and conditional R^2 among the financial variables.

All analyses were performed using R version 3.4.0 [30].

Results

Data description and preliminary analyses

From 1889-1931, there were 86,023 typhoid deaths across all cities (median: 3,382 deaths per city). S3 Fig shows the weekly time series of typhoid mortality in each city. Of the 16 cities, four used reservoirs or lakes as their water source, three drew water from the Great Lakes, and nine accessed water from rivers (Table 2; additional details in S2 Table). Most cities introduced water chlorination or filtration during the study period, but some cities implemented other interventions. Boston's Metropolitan Water District completed a new reservoir in 1908, while New York built several additional reservoirs between 1905-1915. The Sanitary District of Chicago changed the direction of flow of the Chicago River so sewage from the city would no longer be discharged into Lake Michigan, the city's water source. To address flooding problems from periodic hurricanes and its location below sea level, the New Orleans Drainage Commission began to periodically drain the water supply in 1900. San Francisco had no water supply interventions that we could identify; however, a major earthquake in 1906 resulted in severe infrastructure damage and changes to the water supply system, and was included as a proxy intervention in our analysis.

Table 2. Descriptive statistics of cities and their water supplies. "Total Deaths" are the number reported after imputation for missing data. Missing data numbers represent estimates after correcting for "true zeros" in the datasets, and before imputation.

City	State	Total Deaths 1889-1931	% (Number) Weekly Missing Mortality Data	Population in 1888	Water Source Type	Year of (1st) Intervention	Type of Water Supply Intervention(s) 1889-1931
Baltimore	*MD*	5,198	4.5% (100)	431,000	Reservoirs	1910	Chlorination; Filtration
Boston	*MA*	3,412	5.4% (117)	414,000	Lakes/ Reservoirs	1908	New reservoir
Chicago	*IL*	13,161	6.8% (150)	981,000	Great Lake	1900	Changed river flow; Chlorination
Cincinnati	*OH*	3,292	7.5% (167)	289,000	River	1908	Chlorination; Filtration
Cleveland	*OH*	3,622	5.1% (115)	241,000	Great Lake	1913	Chlorination; Filtration
Milwaukee	*WI*	1,912	16.0% (358)	187,000	Great Lake	1910	Chlorination
Nashville	*TN*	1,535	10.2% (227)	69,594	River	1908	Chlorination; Filtration
New Orleans	*LA*	3,352	2.0% (45)	237,000	River	1900	Drainage; Filtration
New York	*NY*	16,991	3.5% (79)	2,370,000	Reservoirs	1903	New Reservoirs; Chlorination; Filtration
Philadelphia	*PA*	13,927	16.3% (364)	1,010,000	River	1902	Chlorination; Filtration
Pittsburgh	*PA*	7,864	17.3% (386)	322,000	River	1908	Chlorination; Filtration
Providence	*RI*	1,106	13.1% (294)	127,000	River	1902	Filtration
Saint Louis	*MO*	3,271	21.9% (490)	432,000	River	1904	Chlorination; Filtration
San Francisco	*CA*	2,348	17.6% (393)	286,000	Lakes/ Reservoirs	1906	Earthquake*
Toledo	*OH*	1,381	22.8% (510)	75,167	River	1910	Chlorination; Filtration
Washington	*DC*	3,651	5.1% (113)	214,000	River	1903	Chlorination; Filtration

**No interventions were identified for San Francisco, but the 1906 earthquake was used as a proxy due to the necessary infrastructure improvements that followed.*

In the preliminary harmonic regression analysis, fluctuations in typhoid mortality generally became less extreme from pre- to post-intervention periods. The six-month amplitude in typhoid mortality decreased in all but two cities (Milwaukee and Nashville), while the one-year seasonal amplitude decreased in all cities but New Orleans post-intervention (S4-S5 Fig, S3 Table). In the two cities where the six-month amplitude increased, the amplitude was already

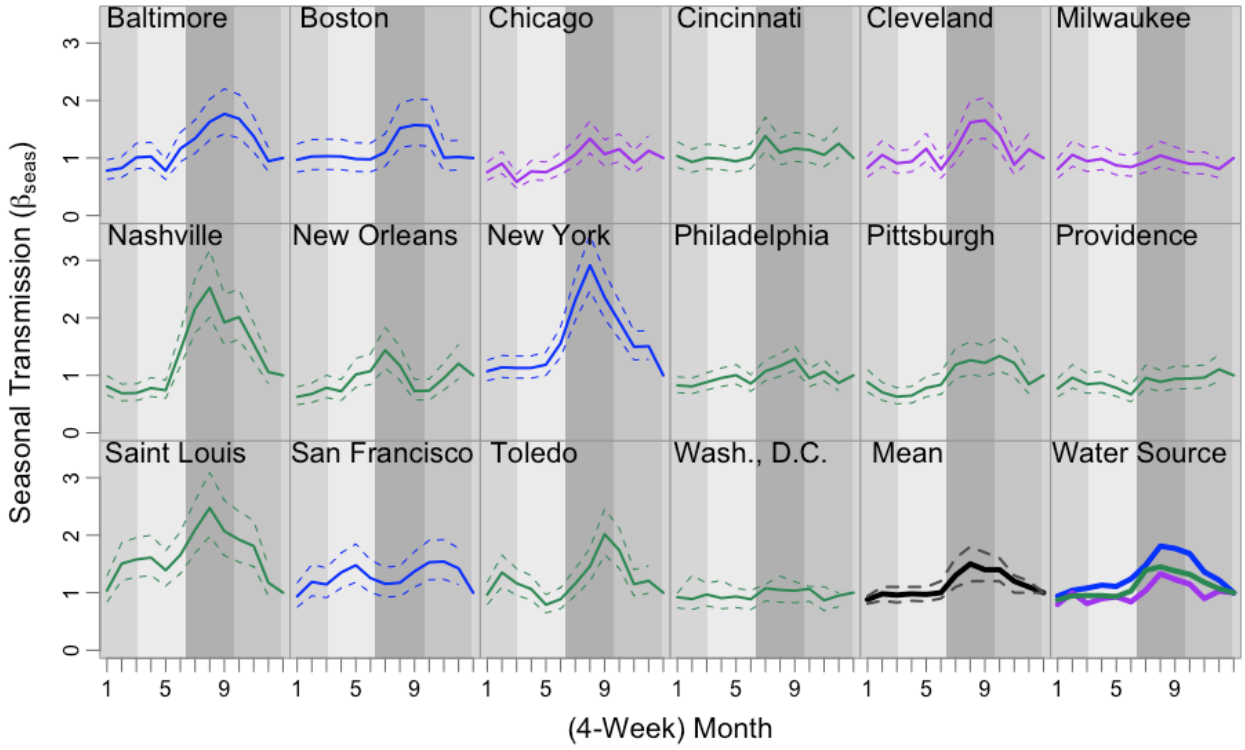
extremely low in the pre-intervention period and did not increase by much in the post-intervention period. In every city, typhoid mortality significantly decreased with time in the post-intervention period. The pre-intervention time trend was less consistent across cities.

While the harmonic regression analyses suggested changes in the seasonality of typhoid mortality following interventions, there was little to no difference in seasonality of typhoid transmission pre- versus post-intervention estimated using TSIR models upon visual inspection (S6 Fig). Thus, we estimated the seasonal transmission rate for the entire 43-year study period in subsequent analyses. The similarity between pre- and post-intervention seasonality in the TSIR models but not in the harmonic regression models in the preliminary analyses suggests the need for using models that incorporate disease dynamics as opposed to simpler analyses that do not take disease dynamics into account (S4, S6 Fig).

Variations in seasonal patterns

Based on the full TSIR model (including waning of immunity), seasonal typhoid transmission increased at the beginning of the year and peaked around late summer or early fall in most cities (months 8-10; Fig 1, S4 Table). This trend varied somewhat across cities. In New Orleans, peak transmission occurred earlier (months 7), while in San Francisco the peak occurred later (months 10-11). In several cities, there were additional peaks in the winter (months 1-3).

Fig 1. Annual seasonal typhoid transmission estimated from Time-Series Susceptible-Infectious-Recovered models. The estimated seasonal transmission rate in each 4-week period is plotted for each city (color-coded by water source type; solid lines are the mean estimates and dashed lines are the 95% confidence intervals). The second-to-last panel shows the mean seasonal transmission across all cities in bold black. The last panel shows the mean seasonal transmission rate for cities with a particular water source type, with reservoirs in blue, rivers in green, and Great Lakes in purple. Seasons are shown in the background in shades of grey (medium-light grey for winter, light grey for spring, dark grey for summer, and medium-dark grey for fall).



Seasonality in typhoid transmission also varied by water source type. While the seasonal trend was similar across different water source types, the magnitude of the peaks in transmission differed (bottom-right panel of Fig 1, S4 Table). Cities that relied on reservoirs had the highest amplitude of seasonal typhoid transmission, while cities that drew water from the Great Lakes had the least variability.

Long-term typhoid transmission and investments in water and sanitation

After the 1900s, long-term typhoid transmission began to decrease almost monotonically in every city (Fig 2). Conversely, overall investments in water and sewer systems increased over

time (Fig 2). Overall investments in both the water supply and sewer system were significantly associated with long-term typhoid transmission. Each $1 (in 1931) per capita increase in overall cumulative investment in water and sewer systems was associated with an estimated average 5% (95% confidence interval: 3-6%) and 6% (95% confidence interval: 4-9%) decrease in typhoid transmission, respectively (Table 3). Overall investments in both the water supply and sewer system were also significantly inversely associated (i.e. confidence interval entirely below one) with city-level transmission in 15 of the 16 cities (Table 3). The proportion of variability in long-term typhoid transmission explained by the both the fixed effects and random effects for overall investments was 98% for both variables, while average overall investments (i.e. fixed effects alone) explained 33% and 28% of the variability in typhoid transmission for the water supply and sewer system, respectively (S5 Table).

Fig 2. Long-term typhoid transmission rate by city estimated from Time-series Susceptible-Infectious-Recovered models. The estimated long-term transmission rate (β_{lt}, solid black line) is plotted for each city, by four-week generation interval. Overall per capita investments in the water supply (blue circles) and sewer system (green pluses) in 1931 US dollars are also shown for each city from 1902 – 1931.

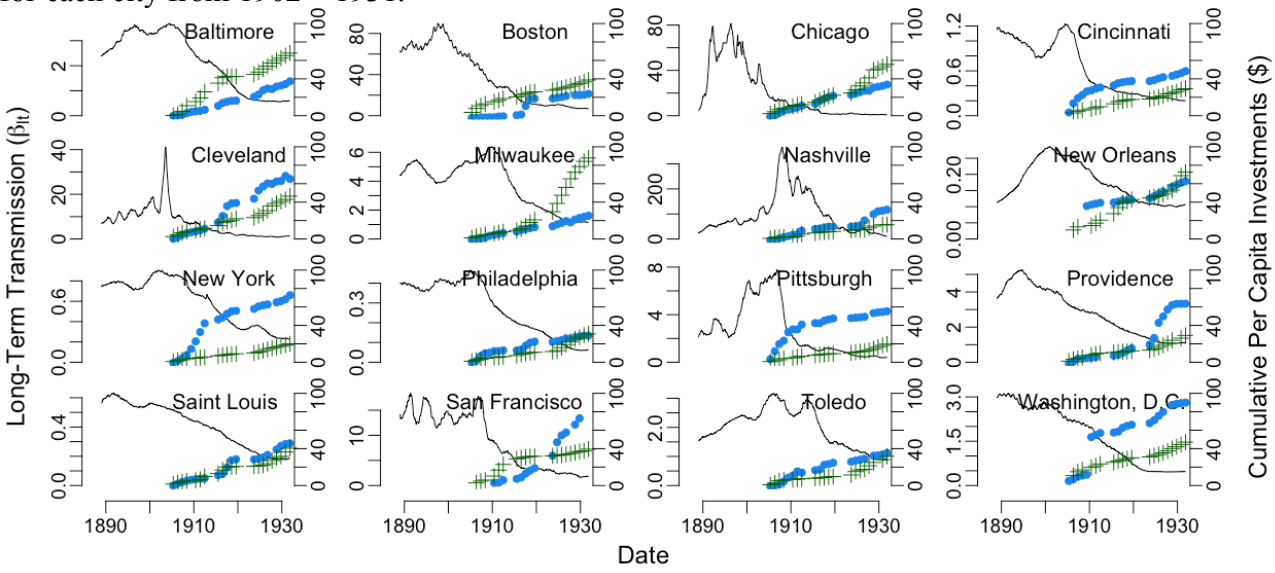


Table 3. Results of hierarchical regression analyses for overall investment variables: Random and fixed effects for yearly average long-term typhoid transmission vs. overall investments in water and sewer systems. Each estimate shows the associated multiplicative change in the estimated long-term typhoid transmission rate for each $1 per capita increase in overall investment for the water supply and sewer system (in 1931 US dollars). Both random and fixed effects are shown, with their 95% confidence intervals.

		Estimate	
		Water Supply	*Sewer System*
Random + Fixed	Baltimore	0.95 (0.93-0.96)	0.97 (0.95-0.99)
	Boston	0.94 (0.93-0.96)	0.93 (0.91-0.96)
	Chicago	0.91 (0.90-0.93)	0.95 (0.92-0.97)
	Cincinnati	0.95 (0.94-0.97)	0.95 (0.92-0.97)
	Cleveland	0.97 (0.95-0.98)	0.94 (0.92-0.97)
	Milwaukee	0.93 (0.91-0.94)	0.98 (0.96-1.00)
	Nashville	0.91 (0.90-0.93)	0.82 (0.79-0.85)
	New Orleans	0.97 (0.95-0.99)	0.98 (0.96-1.01)
	New York	0.98 (0.97-1.00)	0.93 (0.90-0.96)
	Philadelphia	0.93 (0.91-0.95)	0.93 (0.91-0.96)
	Pittsburgh	0.94 (0.92-0.95)	0.85 (0.82-0.88)
	Providence	0.98 (0.97-1.00)	0.95 (0.92-0.98)
	Saint Louis	0.99 (0.98-1.00)	0.94 (0.92-0.97)
	San Francisco	0.98 (0.96-0.99)	0.97 (0.94-0.99)
	Toledo	0.96 (0.95-0.98)	0.95 (0.93-0.98)
	Washington, D.C.	0.98 (0.97-0.99)	0.94 (0.92-0.97)
Fixed	-	0.95 (0.94-0.97)	0.94 (0.91-0.96)

When considering the other financial variables, the associations were not as consistent across cities. Annual investments in maintenance or operation (receipts or expenses) had more city-level associations as compared to acquisition or construction variables (outlays) (S6 Table). In some instances, the relationship between the individual investment variables and typhoid transmission was positive (S6 Table, S7-16 Figs).

TSIR model fit

In general, the TSIR models fit to the full 43-year time series provided an adequate fit to the data. The full TSIR models (including waning of immunity) explained approximately 66% (range: 45-90%) of the variability in typhoid mortality counts over the study period (S7 Table). When we validated the models by fitting to the data through 1926 then using the fitted models to

predict the last five years of typhoid mortality, in most cases the overall predicted trend and seasonal peaks in typhoid mortality were captured, but the model could not explain some of the mortality spikes (S17-S20 figs). Nevertheless, the models generally provided a good fit to the data, with small out-of-sample mean squared prediction errors (S5 Table).

Our results were not sensitive to methods of handling missing data and zeros or variations in model structure (S2 Text, S8-S10 Tables). Seasonal transmission patterns remained the same, and long-term trends retained their general shape (S2 Text, S21-36 Figs). Our results were also not sensitive to the threshold for the maximum duration of immunity (S8-S9 Tables). All cities had different patterns and functions of immunity decay, but the shapes of the seasonal and long-term transmission rates of typhoid were mostly preserved when the models were fit assuming the maximum duration of immunity (173 generation intervals, or approximately 13 years) or no waning of immunity.

Discussion

The decline in typhoid mortality in the early 20th century U.S. has been attributed to investments in water and sewer systems. Our analysis strengthens this hypothesis. Furthermore, we characterized seasonal and long-terms trends in typhoid transmission and quantified the relationship between overall infrastructure investments and declines in transmission rates.

Historically, typhoid fever cases peaked during late summer/early fall in the U.S. [5, 31]. Yearly peaks of typhoid transmission coincide with warmer temperatures, similar to global trends [6, 32-34]. This pattern may be related to the enhanced growth of the bacteria at warmer temperatures, seasonal changes in diet (i.e. increased consumption of uncooked fruit and vegetables in summer and fall), or the increased abundance of flies that may serve as mechanical

vectors of the bacteria [5, 6, 35, 36]. Additional fluctuations in typhoid transmission seen in some cities might be explained by seasonal variation in rainfall, which typically peaks in spring and summer in the eastern U.S. and winter on the west coast, and can impact the water supply to a city [33, 34, 37].

The overall amplitudes in typhoid seasonality did not appear to cluster geographically (S5 Fig), which led us to the hypothesis that the differences between cities may be due to differences in water source type. Variations due to water source type have a number of possible explanations. Cities relying on the Great Lakes for water had the least seasonal variability in transmission. Large bodies of water tend to be less impacted by seasonal changes in temperature and rainfall [38, 39]. The Great Lakes have a moderating effect on climate, absorbing heat and cooling the air in the summer, yet radiating heat and protecting from frost in the fall [40, 41]. Flowing water can slow down the movement of microbes [42], which may explain the lower seasonal variability in typhoid transmission among cities that draw water from rivers. Reservoirs and lakes are mostly smaller stagnant water sources, and may be more sensitive to seasonal changes in climate.

Differences in water source type may help to explain why some nearby cities exhibited different seasonal patterns. For example, New York and Philadelphia, though less than 100 miles apart, had different patterns of seasonal typhoid mortality and transmission (Fig 1, S3-S5 Figs). From 1890-1910, the typhoid mortality rate in New York was considerably lower than in Philadelphia (22.4 versus 43.1 deaths per 100,000 people per year, respectively). However, typhoid transmission was more seasonal in New York (which relied on rural reservoirs) compared to Philadelphia (which drew its water from rivers running through the city). While typhoid transmission consistently peaked in the late summer/early fall in New York, Philadelphia

had only small seasonal variations in the transmission rate. It is possible that these differences reflect differences in the predominant route of typhoid transmission (i.e. food- versus water-borne) in the two cities. Strong seasonality in typhoid incidence was also noted in Santiago, Chile in the 1970-80s, and was linked to seasonal irrigation of crops with contaminated wastewater; typhoid incidence declined sharply once this practice was ended [4, 43, 44]. A better understanding of the drivers underlying seasonal patterns of typhoid transmission, and the differences noted among the various water sources, can aid typhoid control efforts.

Overall investments in the water supply and sewer system were inversely associated with long-term typhoid transmission in every city. These two predictors explained most of the variability in long-term typhoid transmission when taking into account city-level random effects. These findings demonstrate the strong influence of investments in water and sanitation on typhoid transmission over time. However, other factors may also contribute. Associations also varied across cities, perhaps reflecting differences in water source types, public versus private ownership of water supplies, and rates of migration and poverty in the different cities.

A previous study by Cutler and Miller had similar findings [11]. They estimated that on average, filtration and chlorination reduced typhoid fever mortality by 25% from 1900 to 1936. They claimed that clean water technologies explained almost all of the decline in typhoid mortality, estimating that the cost of clean water technologies per person-year saved was $500 in 2003 ($666 in 2017), suggesting it was highly cost-effective. However, their analysis did not consider the complexities of typhoid transmission, such as chronic carriers, host immunity, and interactions between susceptible and infectious individuals, which makes it difficult to extrapolate their findings to better understand the impact of water and sanitation investments on typhoid transmission in modern contexts.

In the early 20th century, William Sedgwick studied what he referred to as the "Mills-Reincke Phenomenon", in which the introduction of sanitation and subsequent decrease in typhoid deaths was also associated with decreases in mortality from other diseases [45]. In the first half of the 20th century, all-cause mortality fell by 40% [11]. Typhoid fever and other waterborne diseases were not the only diseases to decline during this period; many non-enteric diseases were also reduced by 1931 [7].

It has thus far been difficult to evaluate the benefits of water and sanitation infrastructure investments compared to the deployment of new typhoid conjugate vaccines without data to quantify the costs and impact of the former [46]. With the recent World Health Organization recommendation for typhoid conjugate vaccine use and pilot studies underway [47, 48], governments are looking to prioritize the allocation of resources to yield the greatest decrease in typhoid burden. While long-term investments in water and sanitation systems are associated with decreased typhoid transmission, they also have benefits that extend beyond typhoid. Nevertheless, future studies should focus on comparing the cost-effectiveness and budget impact of the two interventions, bearing in mind the context and feasibility of deployment.

This study had some limitations. The weekly mortality counts likely suffer from lack of sensitivity and specificity in the diagnosis of typhoid fever. Additionally, we implicitly account for case fatality rates in our analysis. These issues are unlikely to bias our results provided the under- or over-reporting of typhoid mortality (and case fatality rate) was consistent over the study period. The cities chosen for our analysis were also limited by data availability. As a result, all of the cities were primarily in the northeastern U.S. All cities also had missing data, which had to be imputed. Furthermore, the roles of chronic carriers and immunity to typhoid are not fully understood. Our inclusion of carriers in the model matches the natural history of typhoid,

but we did not examine whether it was necessary to model carriers separately. Patterns in the decay of immunity to typhoid varied widely across cities. Nevertheless, transmission rate estimates were not sensitive to the way we modelled immunity to infection. Finally, due to high levels of correlation between the financial variables, we were not able to estimate the combined effect of water supply and sewer system variables. Some of the overall decline in transmission may have been attributable to other interventions such as economic and nutritional gains, and behavior-change campaigns targeting hand and food washing [11, 49-51].

Our results aid in the understanding of the dynamics of typhoid transmission and potential impact of improvements in water and sanitation infrastructure, which is still lacking in many parts of the world. Before improvements in water and sanitation systems in the U.S., typhoid fever and other water-borne diseases were common. In 1900, infectious diseases (and typhoid in particular) accounted for 44% (2.4%) of deaths in major cities in the U.S. [7], compared to 30-51% (0.3-0.7%) in current day low- and middle-income countries [52-54]. Worldwide, approximately 1.1 billion people lack access to clean water, and roughly 2.5 billion people lack adequate sanitation [55]. Water and sanitation technologies can have substantial health returns; however, the continued operation and maintenance of these systems can be costly. Resource-poor countries must prioritize spending on public health issues, bearing in mind the cost-effectiveness and affordability of implementing and maintaining interventions. Our results can help to inform comparative cost-effectiveness analyses of different interventions to reduce the global burden of typhoid fever.

References

1. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid Fever. New England Journal of Medicine. 2002;347:1770-82. doi: 10.1056/NEJMra020201.
2. Antillon M, Warren J, Crawford F, Weinberger D, Kurum E, Pitzer V. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis. 2017;11(2). doi: 10.1371/journal.pntd.0005376.
3. Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. The Lancet. 2014;2(10):e570-80. doi: 10.1016/S2214-109X(14)70301-8.
4. Gauld JS, Hu H, Klein DJ, Levine MM. Typhoid fever in Santiago, Chile: Insights from a mathematical model utilizing venerable archived data from a successful disease control program. PLoS Negl Trop Dis. 2018;(9):e0006759. doi: 10.1371/journal.pntd.0006759.
5. Johnson G. The Typhoid Toll. Journal (American Water Works Association). 1916;3(2):249-326.
6. Saad NJ, Lynch VD, Antillon M, Yang C, Crump JA, Pitzer VE. Seasonal dynamics of typhoid and paratyphoid fever. Scientific reports. 2018;8(1):6870. Epub 2018/05/04. doi: 10.1038/s41598-018-25234-w. PubMed PMID: 29720736.
7. U.S. Census Bureau. Section 12. Causes of Death. Census: Volume III Vital Statistics, Part 1. 1890, 1900, 1931;3:cxi-cclviii.
8. Centers for Disease Control and Prevention. Notifiable Diseases and Mortality Tables. Morbidity and Mortality Weekly Report. 2018;66(52).
9. Lynch MF, Blanton EM, Bulens S, Polyak C, Vojdani J, Stevenson J, et al. Typhoid Fever in the United States, 1999-2006:. JAMA. 2018;302(8):859-65. doi: 10.1001/jama.2009.1229.
10. U.S. Census Bureau. U.S. and World Population Clock 2018 [cited 2018]. Available from: https://www.census.gov/popclock/.
11. Cutler D, Miller G. The role of public health improvements in health advances: The twentieth-century United States. Demography. 2005;42(1):1-22. doi: 10.1353/dem.2005.0002.
12. Van Panhuis W, Cross A, Burke D. Counts of Typhoid fever reported in United States of America: 1888-1931. Project Tycho data release. 2018;version 2.0. Epub version 2.0. doi: 10.25337/T7/ptycho.v2.0/US.4834000.
13. Van Panhuis W, Grefenstette J, Jung SY, Chok NS, Cross A, Eng H, et al. Contagious Diseases in the United States from 1888 to the Present. N Engl J Med. 2013;369(22):2152-8. doi: 10.1056/NEJMms1215400. PubMed PMID: 24283231; PubMed Central PMCID: PMC4175560.
14. Cliff AD, Haggett P, Smallman-Raynor M, Stroup DF, Williamson GD. The importance of long-term records in public health surveillance: the US weekly sanitary reports, 1888-1912, revisited. Journal of public health medicine. 1997;19(1):76-84. Epub 1997/03/01. doi: 10.1093/oxfordjournals.pubmed.a024593. PubMed PMID: 9138222; PubMed Central PMCID: PMC9138222.
15. U.S. Census Bureau. Financial Statistics of Cities Having a Population of Over 100,000 1905-1938 [2018-May-1]. Available from: https://fraser.stlouisfed.org/title/164.
16. SAGE Working Group on Typhoid Vaccines, The WHO Secretariat. Background Paper to SAGE on typhoid vaccine policy recommendations 2017. Available from: http://www.who.int/immunization/sage/meetings/2017/october/1_Typhoid_SAGE_background_paper_Final_v3B.pdf.
17. Gibson C. Population of the 100 Largest Cities and Other Urban Places In The United States: 1790 to 1990. 1998. In: Population Division Working Paper [Internet]. Washington, DC: U.S Census Bureau. Available from: https://www.census.gov/population/www/documentation/twps0027/twps0027.html.
18. $1 in 1889 → 1931 | Inflation Calculator 2019 [August 26, 2019]. Available from: http://www.in2013dollars.com/1889-dollars-in-1931?amount=1.
19. U.S. Census Bureau. Description of General Tables 1902-1932 [cited 2018 May 1]. Available from: https://fraser.stlouisfed.org/scribd/?toc_id=130235&filepath=/files/docs/publications/finstat/1911_finstat.pdf&start_page=50.
20. Moritz S, Bartz-Beielstein T. imputeTS: Time Series Missing Value Imputation in R. *The R Journal*. 2017;9(1):207–18. Epub R package version 2.5. doi: 10.32614/RJ-2017-009.
21. Hornick RB, Greisman SE, Woodward TE, DuPont HL, Dawkins AT, Snyder MJ. Typhoid Fever: Pathogenesis and Immunologic Control (Part 1). New England Journal of Medicine. 1970;1970(283):686-91. doi: 10.1056/NEJM197009242831306.

22. Svensson Å. A note on generation times in epidemic models. Mathematical Biosciences. 2007;208(1):300-11. doi: https://doi.org/10.1016/j.mbs.2006.10.010.
23. Anderson RM, May RM. Infectious Diseases of Humans. New York: Oxford University Press; 1991.
24. Metcalf CJE, Bjørnstad ON, Grenfell BT, Andreasen V. Seasonality and comparative dynamics of six childhood infections in pre-vaccination Copenhagen. Proceedings of the Royal Society B. 2009;276(1676). doi: 10.1098/rspb.2009.1058.
25. Bjørnstad O, Finkenstädt B, Grenfell B. Dynamics of measles epidemics: Estimating scaling of transmission rates using a Time Series SIR model. Ecological Monographs. 2002;72(2). doi: 10.1890/0012-9615(2002)072[0169:DOMEES]2.0.CO;2.
26. Metcalf CJE, Walter KS, Wesolowski A, Buckee CO, Shevliakova E, Tatem AJ, et al. Identifying climate drivers of infectious disease dynamics: recent advances and challenges ahead. Proc Biol Sci. 2017;284(1860). Epub 2017/08/18. doi: 10.1098/rspb.2017.0901. PubMed PMID: 28814655; PubMed Central PMCID: PMCPMC5563806.
27. Glass K, Xia Y, Grenfell B. Interpreting time-series analyses for continuous-time biological models--measles as a case study. Journal of Theoretical Biology. 2003;223(1):19-25. doi: 10.1016/S0022-5193(03)00031-6.
28. Koelle K, Rodó X, Pascual M, Yunus M, Mostafa G. Refractory periods and climate forcing in cholera dynamics. Nature. 2005;436(7051):696. doi: 10.1038/nature03820.
29. Koelle K, Pascual M. Disentangling extrinsic from intrinsic factors in disease dynamics: a nonlinear time series approach with an application to cholera. The American naturalist. 2004;163(6):901-13. Epub 2004/07/22. doi: 10.1086/420798. PubMed PMID: 15266387.
30. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
31. Harmon GE, editor Seasonal Distribution of Typhoid Fever-- Southern and Northern States. 58th Annual Meeting of the American Public Health Association; 1929; Minneapolis, MN.
32. Siddiqui FJ, Rabbani F, Hasan R, Nizami SQ, Bhutta ZA. Typhoid fever in children: some epidemiological considerations from Karachi, Pakistan. International Journal of Infectious Diseases. 2006;10(3):215-22. doi: https://doi.org/10.1016/j.ijid.2005.03.010.
33. Dewan AM, Corner R, Hashizume M, Ongee ET. Typhoid Fever and Its Association with Environmental Factors in the Dhaka Metropolitan Area of Bangladesh: A Spatial and Time-Series Approach. PLoS Negl Trop Dis. 2013;7(1). doi: 10.1371/journal.pntd.0001998.
34. Wang LX, Li XJ, Fang LQ, Wang DC, Cao WC, Kan B. Association between the incidence of typhoid and paratyphoid fever and meteorological variables in Guizhou, China. Chinese medical journal. 2012;125(3):455-60. Epub 2012/04/12. doi: 10.3760/cma.j.issn.0366-6999.2012.03.010. PubMed PMID: 22490402; PubMed Central PMCID: PMC22490402.
35. Sant'Ana AS, Franco BD, Schaffner DW. Modeling the growth rate and lag time of different strains of Salmonella enterica and Listeria monocytogenes in ready-to-eat lettuce. Food microbiology. 2012;30(1):267-73. Epub 2012/01/24. doi: 10.1016/j.fm.2011.11.003. PubMed PMID: 22265311.
36. Kumar R, Datta TK, Lalitha KV. Salmonella grows vigorously on seafood and expresses its virulence and stress genes at different temperature exposure. BMC microbiology. 2015;15:254. Epub 2015/11/05. doi: 10.1186/s12866-015-0579-1. PubMed PMID: 26531707; PubMed Central PMCID: PMCPMC4632675.
37. The seasonal prevalence of typhoid fever and its relation to seasonal temperature. Journal of the American Medical Association. 1903;XL(21):1442-. doi: 10.1001/jama.1903.02490210034003.
38. Michigan State University. About the Great Lakes: Michigan Sea Grant; 2012 [updated 2012-05-25]. Available from: http://www.miseagrant.umich.edu/explore/about-the-great-lakes/.
39. Williamson J. The Inland Seas of North America; and the Natural and Industrial Productions of Canada, with the Real Foundations for its Future Prosperity. Kingston: John Duff; 1854.
40. Fink G, Schmid M, Wüest A. Large lakes as sources and sinks of anthropogenic heat: Capacities and limits - Fink - 2014 - Water Resources Research - Wiley Online Library. Water Resour Res. 2014;50:7285–301. doi: 10.1002/2014WR015509.
41. U.S. Environmental Protection Agency, Government of Canada. Natural Processes in the Great Lakes. The Great Lakes: And Environmental Atlas and Resource Book. Third ed. Toronto and Chicago1995.
42. Rusconi R, Guasto JS, Stocker R. Bacterial transport suppressed by fluid shear. Nature Physics. 2014;10(3):212. doi: 10.1038/nphys2883.
43. Sears SD, Ferreccio C, Levine MM, Cordano AM, Monreal J, Black RE, et al. The use of Moore swabs for isolation of Salmonella typhi from irrigation water in Santiago, Chile. J Infect Dis. 1984;149(4):640-2. Epub 1984/04/01. doi: 10.1093/infdis/149.4.640. PubMed PMID: 6373964.

44. Sears SD, Ferreccio C, Levine MM. Sensitivity of Moore sewer swabs for isolating Salmonella typhi. Applied and environmental microbiology. 1986;51(2):425-6. Epub 1986/02/01. PubMed PMID: 3513705; PubMed Central PMCID: PMCPMC238885.
45. Sedgwick W, Macnutt JS. On the Mills-Reincke Phenomenon and Hazen's Theorem concerning the Decrease in Mortality from Diseases Other than Typhoid Fever following the Purification of Public Water-Supplies : Macnutt, J. Scott : Free Download, Borrow, and Streaming : Internet Archive. The Journal of Infectious Diseases. 1910;7(4):489-564.
46. Antillon M, Bilcke J, Paltiel AD, Pitzer VE. Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low- and middle-income settings. Vaccine. 2017;35(27):3506-14. Epub 2017/05/22. doi: 10.1016/j.vaccine.2017.05.001. PubMed PMID: 28527687; PubMed Central PMCID: PMCPMC5462484.
47. Meiring J, Gibani M, The TyVAC Consortium Meeting Group. The Typhoid Vaccine Acceleration Consortium (TyVAC): Vaccine effectiveness study designs: Accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a meeting held on 26–27 October 2016, Oxford, UK. Vaccine. 2017;35(38). doi: https://doi.org/10.1016/j.vaccine.2017.08.001.
48. World Health Organization (WHO). Typhoid vaccines position paper. Weekly epidemiological record. 2018;13(93):153–72.
49. Fogel RW. Economic Growth, Population Theory, and Physiology: The Bearing of Long-Term Processes on the Making of Economic Policy. American Economic Review. 1994;84:369-95. doi: 10.3386/w4638.
50. McKeown T. The Modern Rise of Population. New York: Academic Press; 1976.
51. Ewbank D, Preston S. Personal Health Behaviour and the Decline in Infant and Child Mortality. What We Know About Health Transition: The Cultural, Social and Behavioural Determinants of Health. Canberra, Australia: Health Transition Centre, Australian National University; 1990. p. 116-49.
52. Stevens P. Diseases of poverty and the 10/90 Gap. 2004.
53. The World Bank. Cause of death, by communicable diseases and maternal, prenatal and nutrition conditions (% of total). 2019.
54. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle2017. Available from: http://ghdx.healthdata.org/gbd-results-tool.
55. Water and Sanitation Program. Scaling up rural sanitation: World Bank; 2018. Available from: https://www.wsp.org/global-initiatives/global-scaling-sanitation-project.

Supporting Information

S1 Text: Model-fitting process.

We fit Time-series Susceptible-Infectious-Recovered (TSIR) models to each city's time series to investigate seasonal and long-terms trends in typhoid transmission rates. In general, new infections at time t+1 (I_{t+1}) arise from transmission from infectious (I_t) to susceptible (S_t) individuals at time t:

$$I_{t+1} = \beta_t I_t^{\alpha} S_t \qquad (S1)$$

where β_t is the disease transmission rate at time t and α is a scaling factor that adjusts for heterogeneous mixing in the population (α=1 corresponds to homogeneous mixing, α=0 corresponds to no auto-correlation in the time series).

After modifying Equation S1 to account for the unique features of typhoid epidemiology (Equation 2 main text) and log-transforming the model, the equation is as follows:

$$\log(I_{t+1}) = \log(\beta_{lt}) + \log\left(\beta_{seas,j}\right) + \alpha \log(I_t + C) + \log(S_t). \qquad (S2)$$

We reconstructed the infectious and chronic carrier populations via maximum likelihood estimation using Equation 5 (main text) and adjusting for underreporting. We then we modelled the susceptible population at time t as a function of the total population at time t minus the previously infectious and recovered individuals:

$$S_t = N_t - \sum_{i=0}^{m} I_{t-i}\kappa_i \qquad (S3)$$

where κ_i is the degree of immunity i generation intervals after infection (determined by a decay of immunity function). We initially approximated S_t using a log-transformation and first-degree Taylor series expansion around the average susceptible population size:

$$\log(S_t) \approx \left[\log(S_{mean}) + \frac{N_t}{S_{mean}} - 1\right] - \sum_{i=0}^{m} \frac{I_{t-i}\kappa_i}{S_{mean}}. \qquad (S4)$$

Penalized cubic splines on κ were used to account for non-linearity in the duration and decay patterns in immunity. Equation S2 can then be rewritten as:

$$\log(I_{t+1}) = \log(\beta_{lt}) + \log(\beta_{seas,j}) + \alpha \log(I_t + C) - \sum_{i=0}^{m} \frac{I_{t-i}\kappa_i}{S_{mean}} + \left[\log(S_{mean}) + \frac{N_t}{S_{mean}} - 1\right] \quad (S5)$$

Note that the waning of immunity affects the number of susceptible individuals at time *t*, thereby indirectly affecting the number of new infections at time *t+1*. Since the duration of immunity to typhoid infection and disease is not well understood, we performed sensitivity analyses exploring different durations of immunity (S2 Text).

We used Equation S5 and the semi-parametric method described by Koelle and Pascual [1, 2] to estimate the variation in β_{lt} over the full 43-year study period from 1889-1931. One value of β_{lt} was estimated for each four-week period from 1889-1931 (except for the first, to be able to calculate I_{t+1}), resulting in 558 estimations. We also estimated 13 values of $\beta_{seas,j}$ corresponding to transmission during the same four-week period each year. This parameter was estimated as a categorical variable with 13 values, where the first 12 four-week months were estimated in comparison to the last month ($\beta_{seas,13} = 1$).

To fit the model, we used a back-fitting algorithm comprised of repeated penalized cubic splines on κ, recursive first-order Taylor series expansion approximations on the $\log(S_t)$ term, and weighted least squares regressions on iterations of Equation S5. The iterative process was necessary to allow for the more accurate approximation of the Taylor series expansion and the cubic splines to converge. For the weighted least squares regressions, the weights were calculated as **I-W**, where **I** was the identity matrix of the same dimension, and **W** was the truncated Gaussian kernel weight matrix calculated from the spline penalty weights.

After the above algorithm converged, we used the same truncated Gaussian kernel weight matrix **W** to smooth the residuals of the model fit with all other parameters estimated. The smoothed residuals were then used to estimate the nonparametric variation in the long-term transmission rate (β_{lt}). The final long-term transmission rate was multiplied by the population at each time point to calculate per capita estimates.

The smoothing parameter and spline penalty weights were selected using cross-validation and testing across a range of values. Each city was fit using all possible values of the smoothing parameter from 1 to 35 in one-unit increments and spline penalty values from -2 to 30 in one-unit increments. If the parameters chosen were at the ends of the respective ranges, the intervals were extended until the optimal values fell within the values tested. To identify the optimal model, we used leave-one-out validation, in which we dropped one data point at a time (for all data points), fit the model to the remaining data, and then used the fitted model to predict the out-of-sample data point. We calculated the sum of squared differences between each point and its out-of-sample prediction over all points, and stored this as the cross-validated (CV) value for each model fit. The optimal model for each city was the one with the smallest CV value.

S2 Text. Sensitivity analyses.

Description of different components of the model that were tested

We performed several sensitivity analyses to test the robustness of our model assumptions. We examined different components of the model, including our method of imputing missing data, the addition of small values to the reported death counts prior to log-transformation (to avoid taking the log of zero), the duration (or inclusion) of waning immunity, and the inclusion of chronic carriers in our TSIR models. We determined the impact of these assumptions on the seasonal and long-term transmission parameters, the relationship with the overall investment variables identified by the hierarchical regression models, and estimates of

the heterogeneous mixing parameter (α). The results of these sensitivity analyses can be found in S21-36 Figs and S8-10 tables.

Missing data

To address the issue of missing data, we had to make some decisions about what the meaning of the missing values might be. In many instances, cities only reported typhoid deaths if there were any; however, we had to differentiate between these zero counts and truly missing data points. For the primary analysis, we used a cut-off of 13 consecutive weeks to differentiate between when missing values represented zeros versus missing data. If there were fewer than 13 weeks of missing death counts, the data points were coded as zeroes, and if there were more, we used Kalman smoothing to impute the missing values based on the previous observation and the "filter," updated at each time point [3, 4]. Since this 13-week cut-off was arbitrarily chosen, we also fit the TSIR models using an 8-week and 26-week cut-off and compared the results.

Log-transformation

Some of the death counts were zero, which posed a problem for the logarithmic transformation in our main TSIR model equation. In our main analysis, we added one to every data point to preserve the shape of the distribution. As a sensitivity analysis, we re-ran all of the models instead adding 0.5 to every data point to compare the impact of this assumption.

Duration of immunity

Waning of immunity against typhoid infection is poorly understood. While epidemiological studies and human challenge studies indicate that individuals can be re-infected with typhoid after approximately one year, mathematical models of typhoid infection consistently estimate that immunity to typhoid disease is long-lived in order to explain why the incidence tends to decline with age, particularly in high incidence settings. We assessed the

assumption of waning immunity in our model, fitting additional models assuming only one year of immunity following infection and models with no waning of immunity (i.e. lifelong immunity following infection).

Chronic carriers

In fitting the TSIR models, we noted that the heterogeneous mixing parameter (α) was lower than estimated for other pathogens (e.g. measles) using TSIR models [5]. We hypothesized that this was likely due to the contribution of long-cycle transmission in the epidemiology of typhoid, i.e. transmission from chronic carriers and the environmental reservoir. To test this, we compared the α values estimated for TSIR models without waning immunity, without chronic carriers, or without either, and in the simple TSIR model (Equation S1).

Results of sensitivity analyses

The results of the analyses in this study were generally robust to the changes in the assumptions examined. The seasonal transmission rates remained almost unchanged, regardless of variations in missing data imputation, addition of small amounts to the reported death counts, and duration or exclusion of waning immunity (S21-36 Figs, top half of panels).

The long-term transmission rates mostly retained their overall shape, but the scale of the transmission rate changed in some instances (S21-36 Figs, bottom half of the panels). However, the results of the hierarchical regression models with the overall financial variables were all quite similar, and results were mostly within 2% of the original estimates (S8-9 Tables).

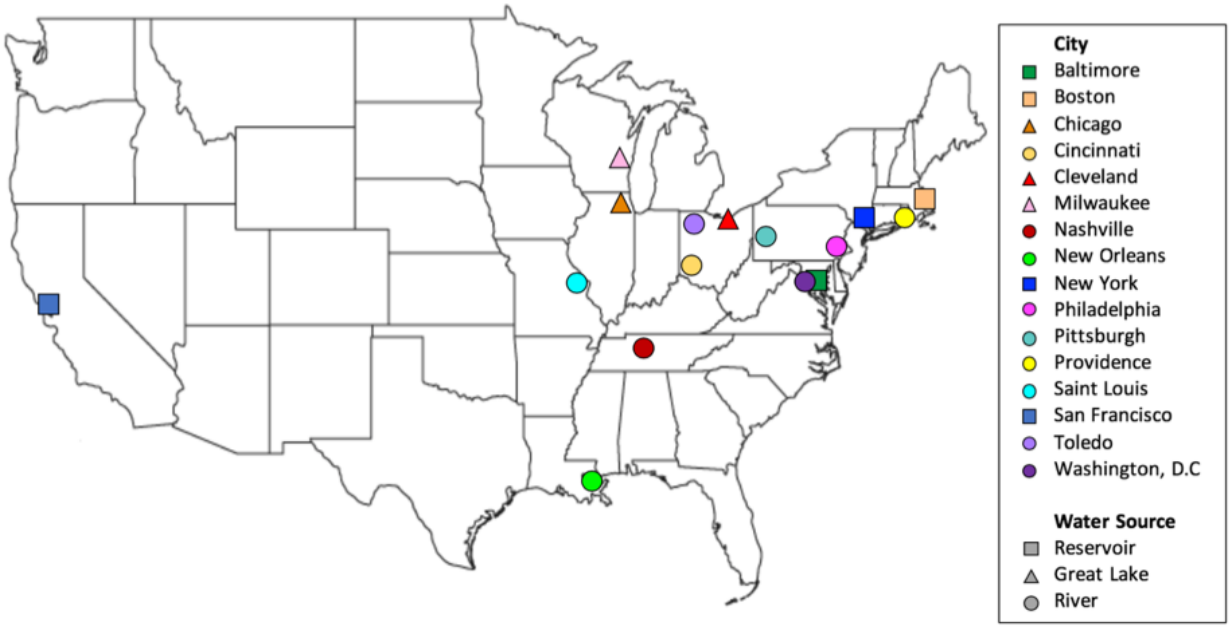
The heterogeneous mixing parameter varied slightly between the different models, but mostly kept their order between cities (S10 Table). New Orleans, New York, Philadelphia, and Pittsburgh typically had the highest estimated α values regardless of the model formulation. The highest α values were estimated for the model with no immunity, suggesting that there may be

some identifiability issues between the duration of immunity and the heterogeneous mixing parameter. Nevertheless, our results were robust to different durations of immunity, as noted above. Removing chronic carriers from the model generally led to estimated α values closer to zero, as expected, suggesting typhoid incidence is less dependent on acute cases in the previous generation. This suggests that long-cycle transmission of typhoid, which does not occur in direct proportion to cases in the previous generation, can help to explain some of the lack of autocorrelation in the data. Long-cycle transmission may be related to cases occurring two to three generations prior (since evidence suggests typhoid bacteria is not long-lived in the environment [6]) and/or cases residing in surrounding populations that could contaminate water catchment areas, which would not be captured by our model.

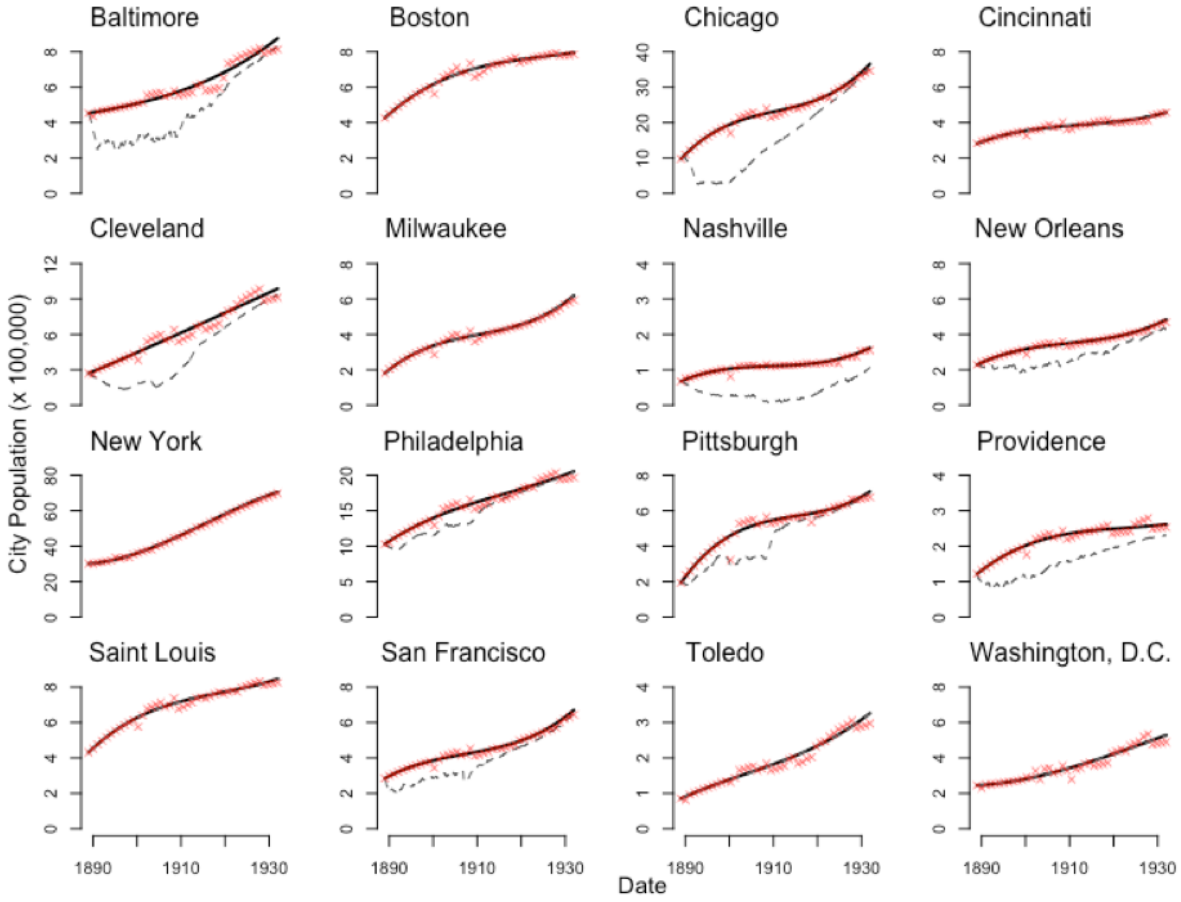
References

1. Koelle K, Pascual M. Disentangling extrinsic from intrinsic factors in disease dynamics: a nonlinear time series approach with an application to cholera. The American naturalist. 2004;163(6):901-13. Epub 2004/07/22. doi: 10.1086/420798. PubMed PMID: 15266387.
2. Koelle K, Rodó X, Pascual M, Yunus M, Mostafa G. Refractory periods and climate forcing in cholera dynamics. Nature. 2005;436(7051):696. doi: 10.1038/nature03820.
3. Chui CK, Chen G. Kalman Filtering with Real-Time Applications. 3 ed. Huang TS, Kohonen T, Schroeder MR, editors. Berlin: Springer-Verlag; 1999.
4. Harvey AC. Forecasting, structural times series models and the Kalman filter. Cambridge, UK: Press Syndicate of the University of Cambridge; 1989.
5. Bjørnstad O, Finkenstädt B, Grenfell B. Dynamics of measles epidemics: Estimating scaling of transmission rates using a Time Series SIR model. Ecological Monographs. 2002;72(2). doi: 10.1890/0012-9615(2002)072[0169:DOMEES]2.0.CO;2.
6. Cho J-C, Kim S-J. Viable, but non-culturable, state of a green fluorescence protein-tagged environmental isolate of Salmonella typhi in groundwater and pond water. FEMS Microbiology Letters. 1999;170(1):257-64. doi: 10.1111/j.1574-6968.1999.tb13382.x.

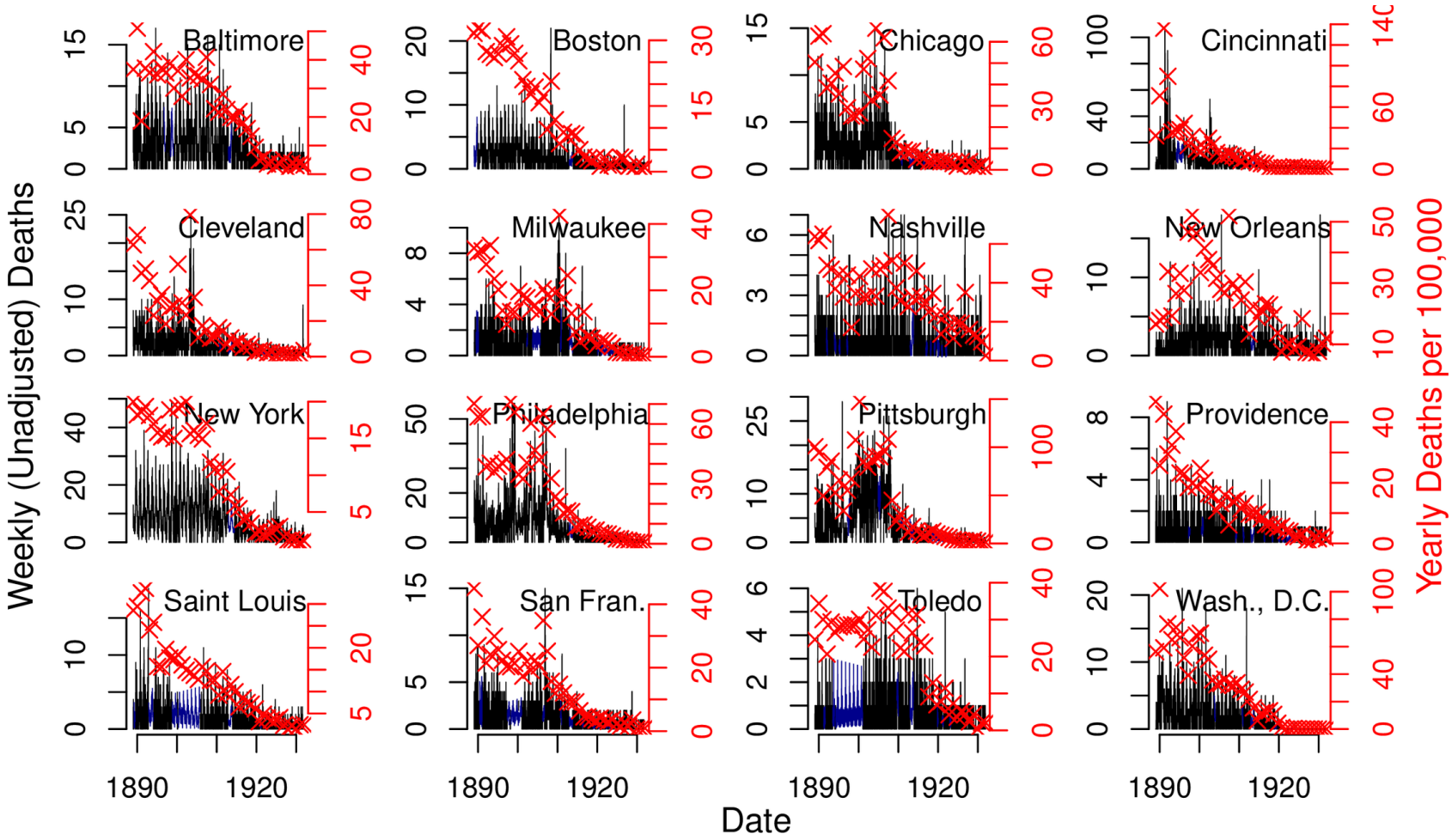
S1 Fig. Map of 16 cities with water supply types. Each city included in the analysis is denoted by a different color in its geographical location in the United States. Squares denote cities with reservoirs, triangles denote those using the Great Lakes, and circles denote those with rivers as their main water source. The underlying map is adapted from the United States Geological Survey LandsatLook < https://landlook.usgs.gov/viewer.html#>.



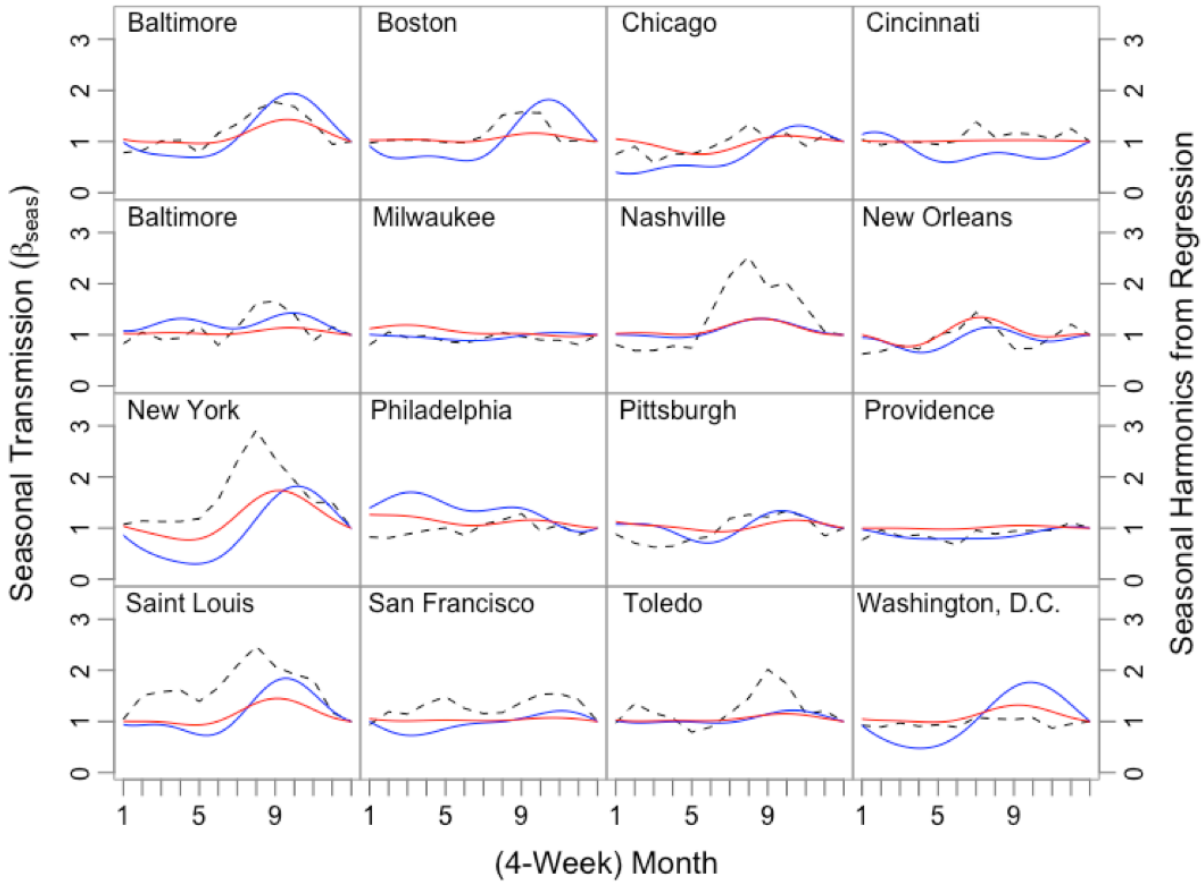
S2 Fig. Yearly reported population, extrapolated monthly population, and estimated susceptible population over study period. The yearly U.S. Census Bureau reported population (red Xs), monthly population extrapolated using cubic splines (solid black line), and susceptible population (dashed black line) estimated from the main TSIR models are shown for each city over the study period. Note that in some cities, the susceptible and total population are very close and cannot be differentiated in the plots.



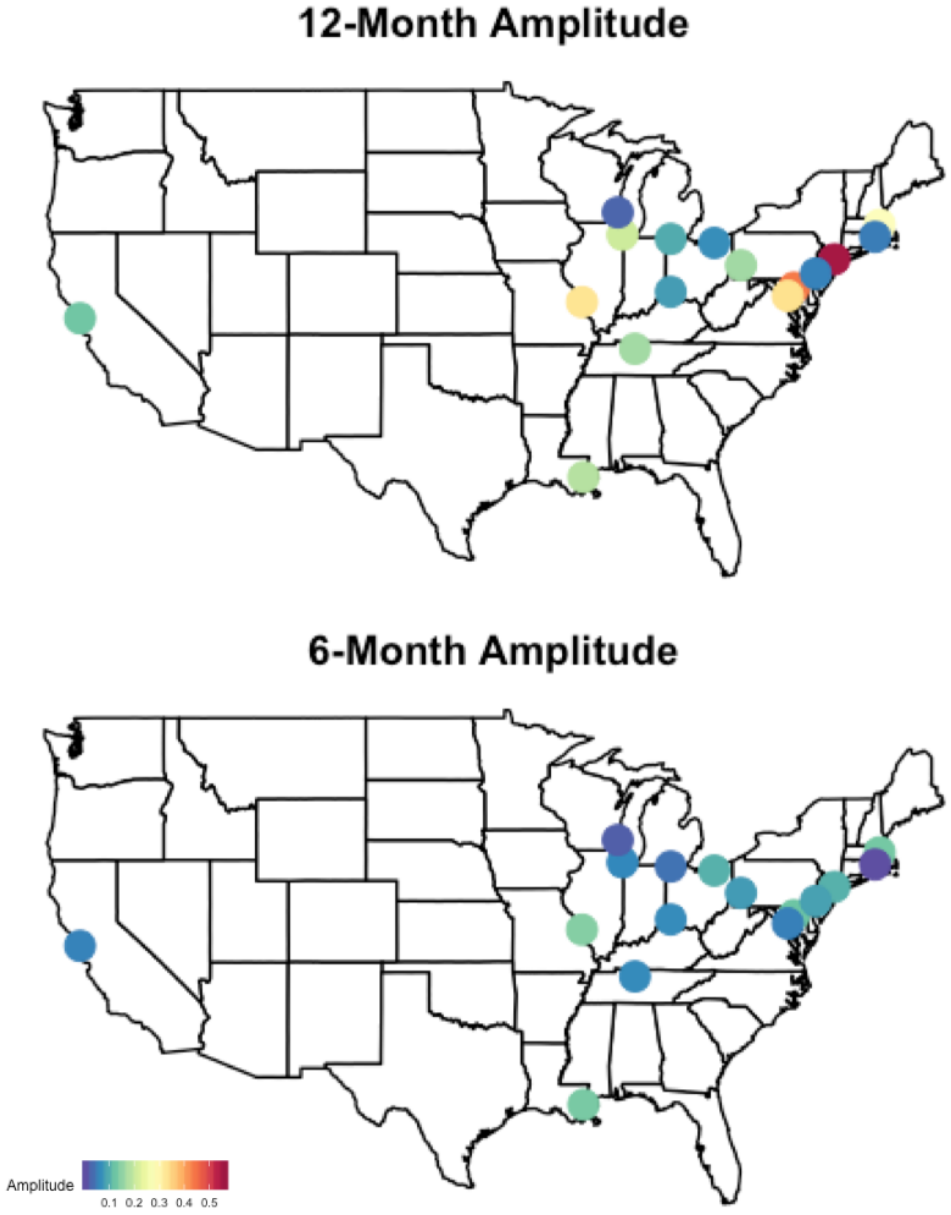
S3 Fig. Weekly time-series of reported typhoid mortality in each city. The observed (including imputation, in blue) time series of weekly deaths reportedly due to typhoid (black lines) and the yearly typhoid deaths per 100,000 people (red Xs) is shown for each city from 1889-1931.



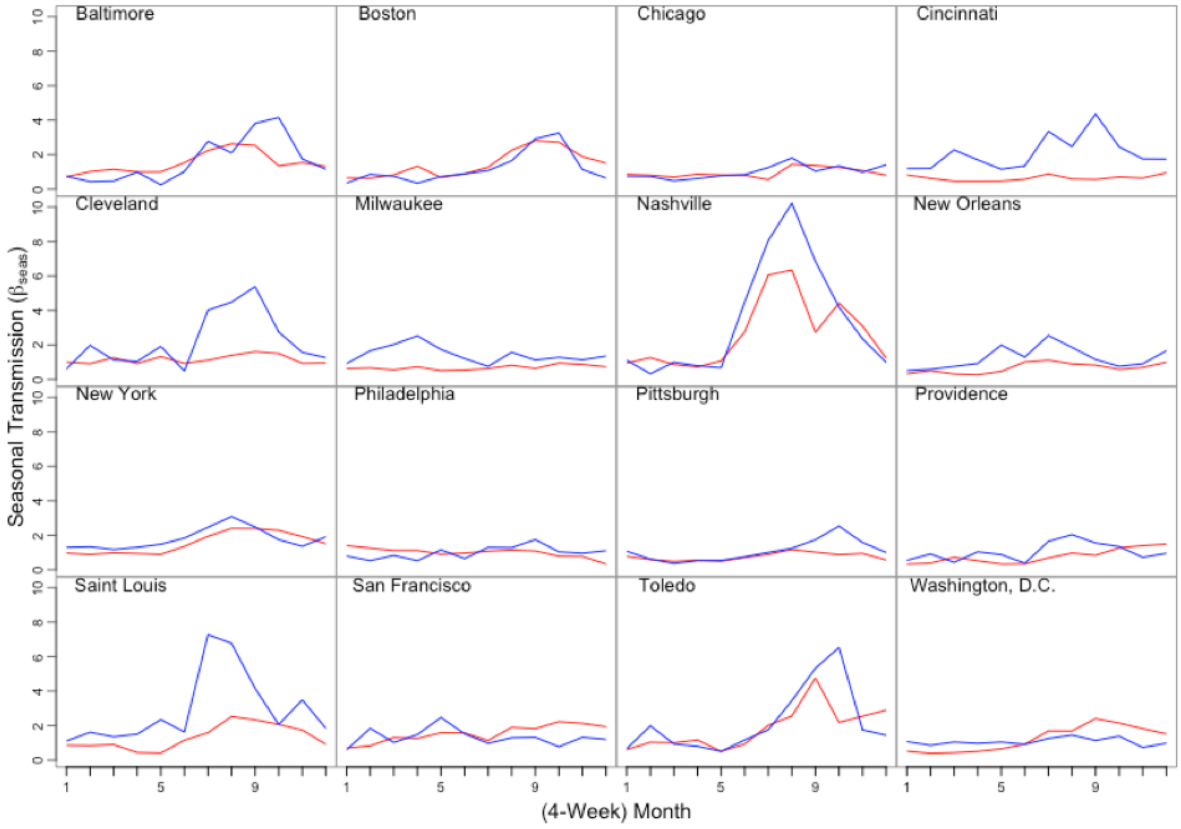
S4 Fig. Pre- -and post-intervention sinusoid curves from preliminary harmonic regression analyses. The pre- (blue) and post-intervention (red) six- and 12-month sinusoid curves fitted to the typhoid mortality data are shown for each city, along with the seasonal transmission rate estimated by the main TSIR model (dashed black line).



S5 Fig. Map of 12- and 6-month amplitudes of typhoid mortality counts, from preliminary harmonic regression analyses. The average 12- and 6-month amplitudes of seasonal variation in reported typhoid mortality estimated from the harmonic regression analyses are shown separately according to the color scale and plotted by geographic location.

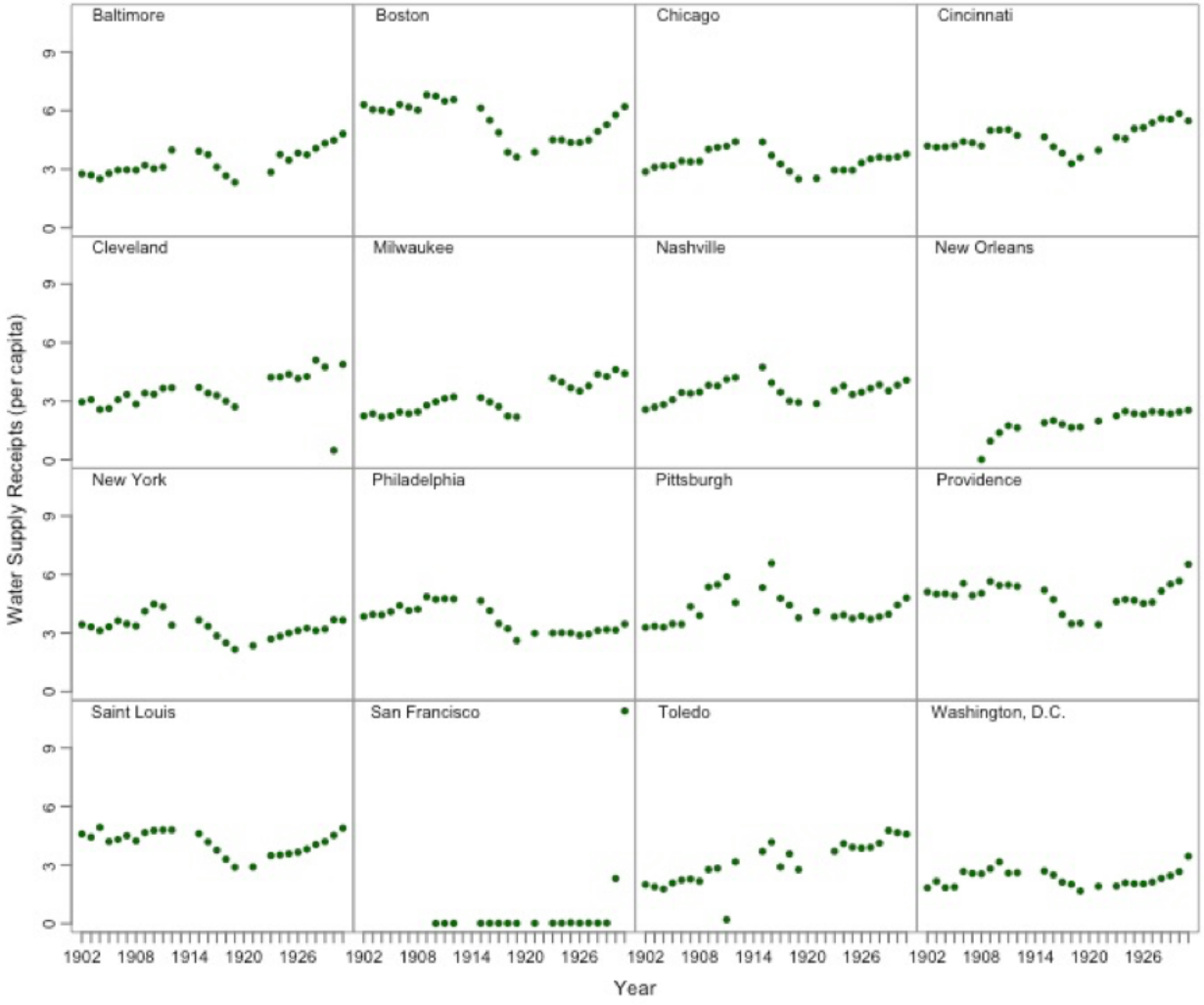


S6 Fig. Seasonal transmission rate for pre- and post- water supply intervention periods. The estimated four-week seasonal transmission rates extracted from each city's simple TSIR model (not including waning of immunity) are shown for each pre- (blue) and post- (red) water supply intervention period.

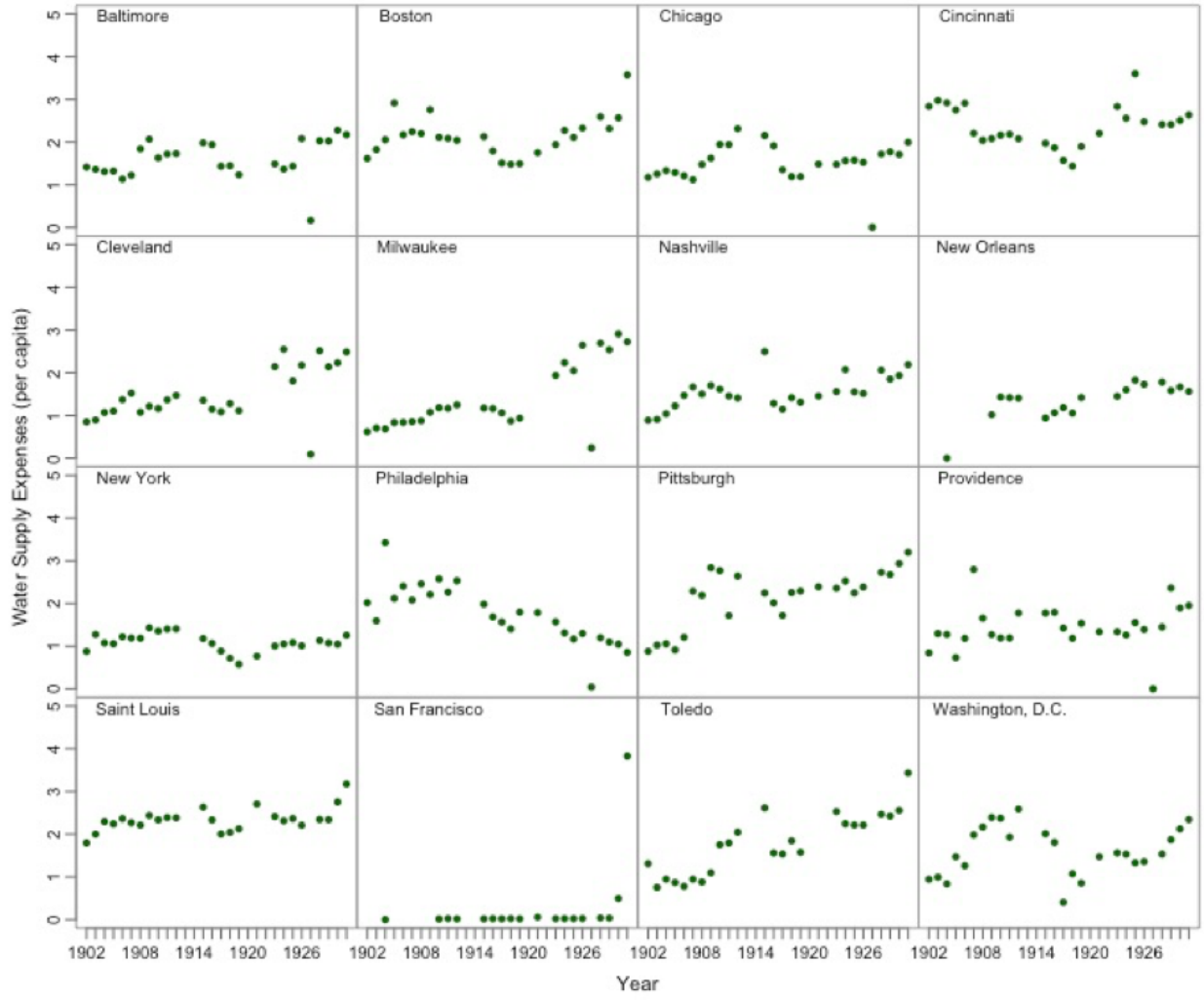


S7-16 Figs. Financial variable time series. The yearly time series of each of the ten financial water supply or sewer system variables is plotted over the study period in per capita increments. Dollar amounts are adjusted for inflation to 1931 US$.

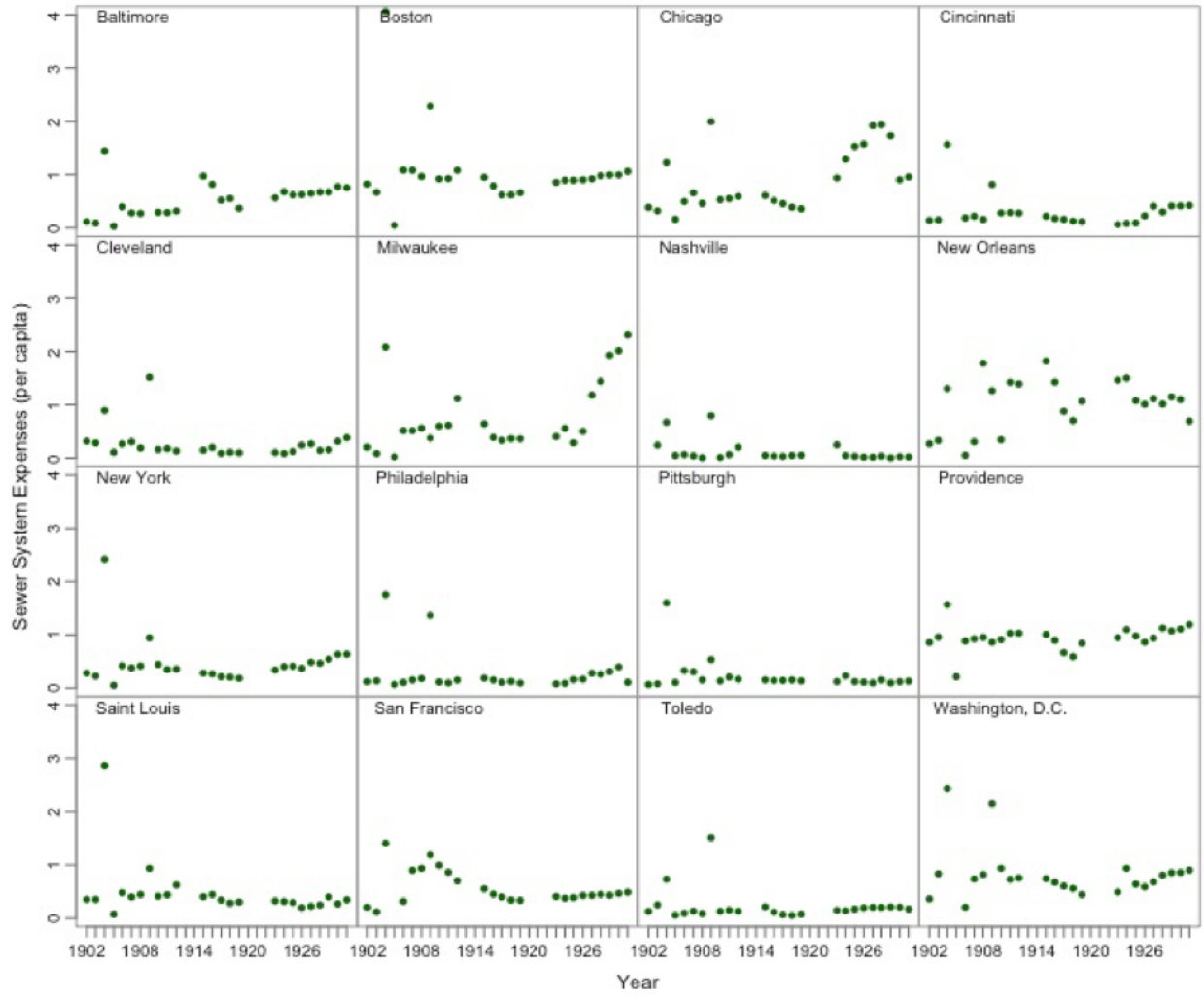
S7 Fig. Annual per capita water supply receipts. Annual water supply receipts from 1902-1931 are shown for each city in per capita increments (US$ per person).



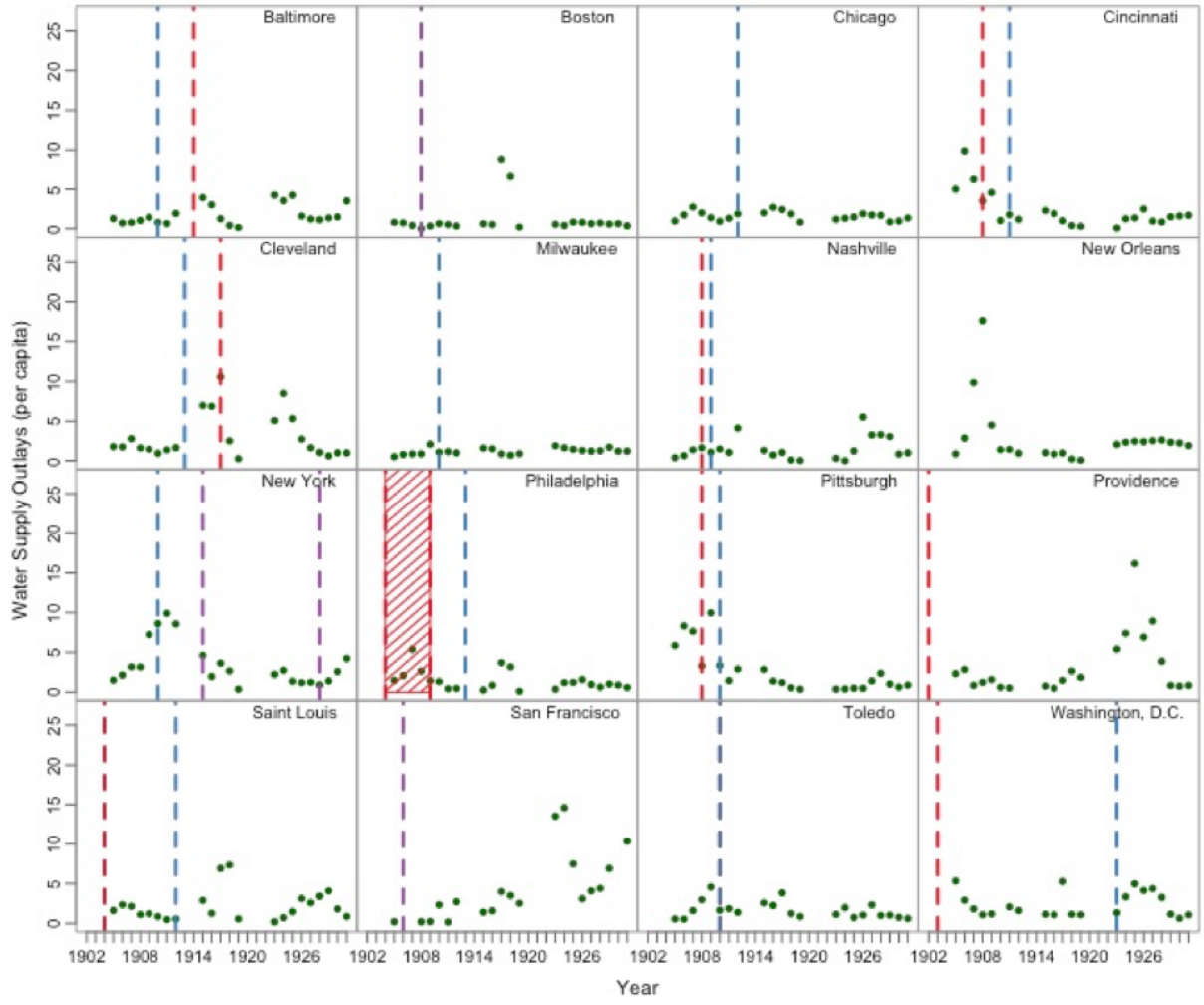
S8 Fig. Annual per capita water supply expenses. Annual spending on water supply expenses from 1902-1931 is shown for each city in per capita increments (US$ per person).



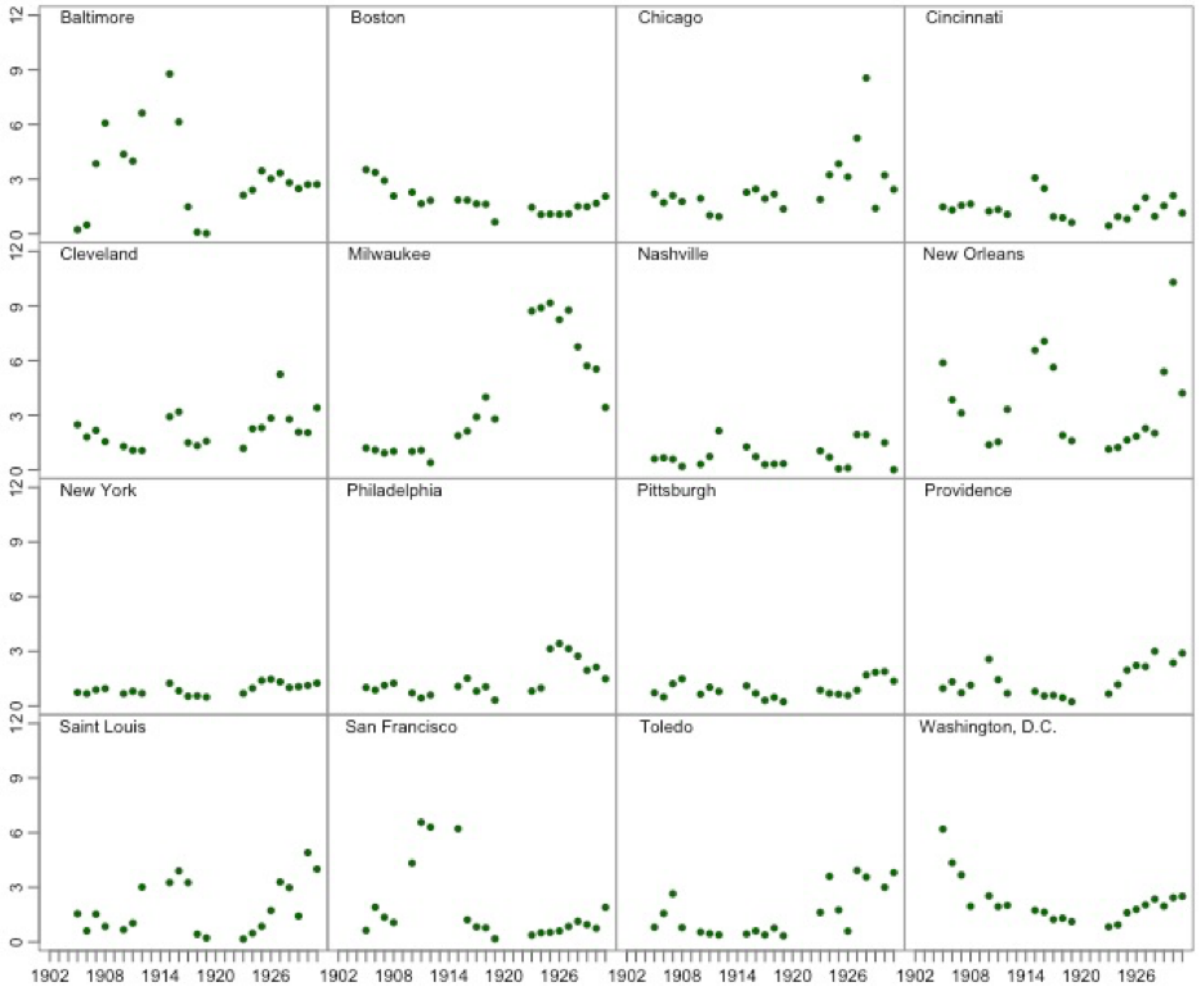
S9 Fig. Annual per capita sewer system expenses. Annual spending on sewer system expenses from 1902-1931 is shown for each city in per capita increments (US$ per person).



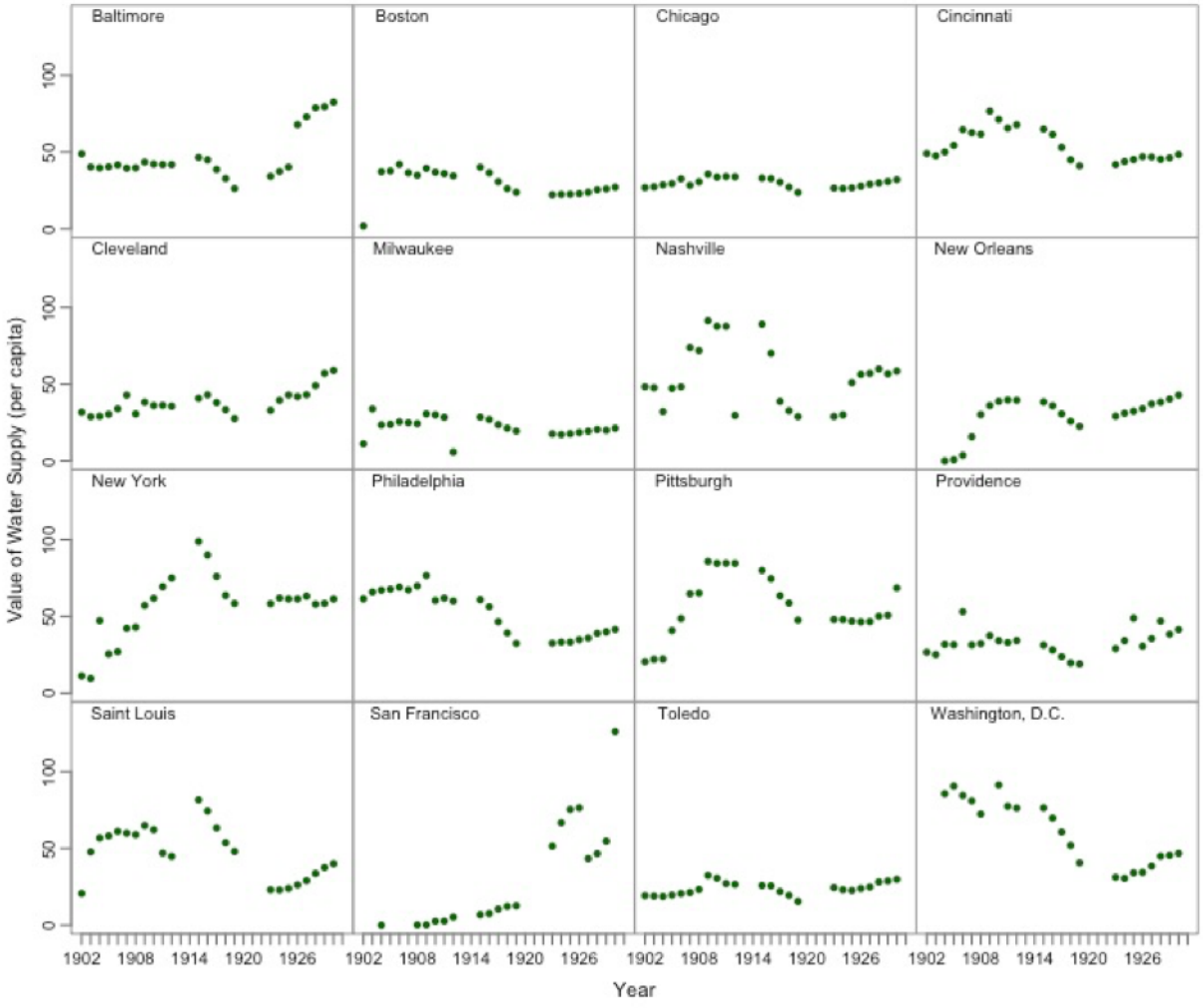
S10 Fig. Annual per capita water supply outlays. Annual spending on water supply outlays from 1902-1931 is shown for each city (green dots) in per capita increments (US$ per person). The year in which interventions were introduced are represented by the dashed lines for filtration (red), chlorination (blue), or other interventions (purple). The inclusion of intervention dates is for illustrative purposes. Outliers not seen: In 1930, water supply outlays from San Francisco totalled $70.97 per capita; this was the year in which the city purchased the water supply previously owned and operated by the Spring Valley Water Company. Chicago and New Orleans introduced water supply interventions in 1900, prior to the time period shown.



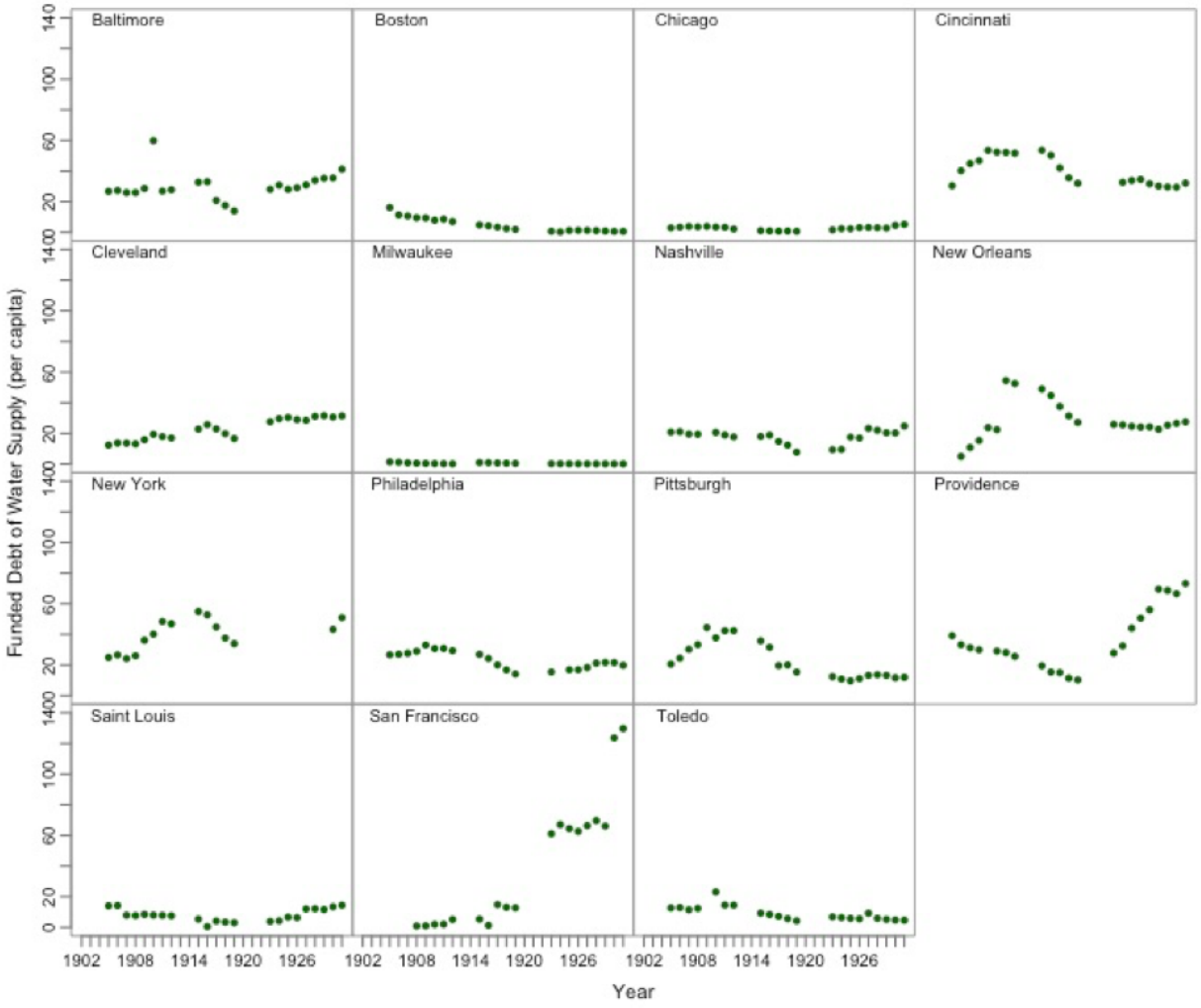
S11 Fig. Annual per capita sewer system outlays. Annual spending on sewer system outlays from 1902-1931 is shown for each city in per capita increments (US$ per person).



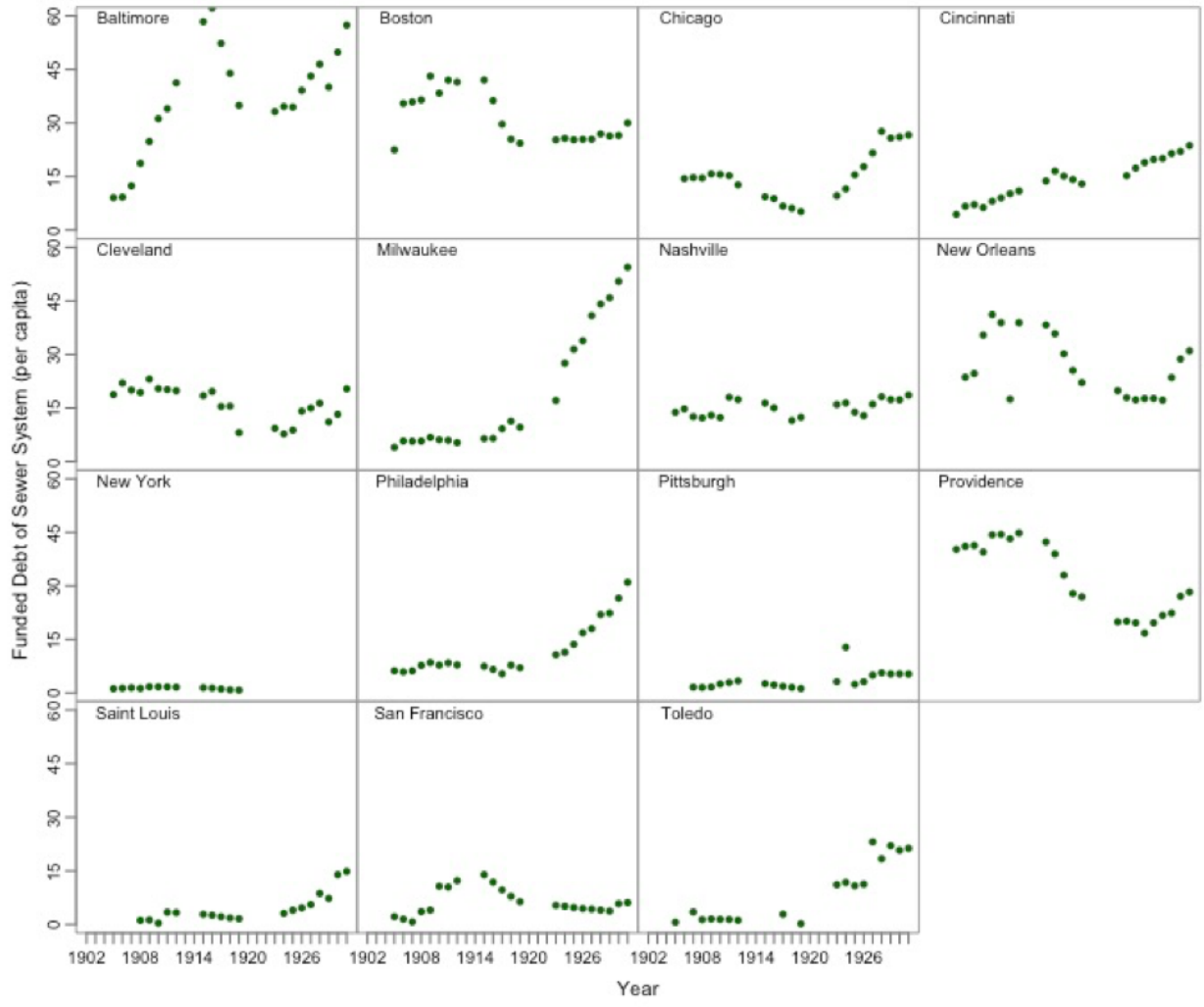
S12 Fig. Annual per capita value of the water supply system. The overall annual value of the water supply system from 1902-1931 is shown for each city in per capita increments (US$ per person). Outliers not seen: In 1897, the value of the water supply system totalled $508.55 per capita in Washington, D.C.



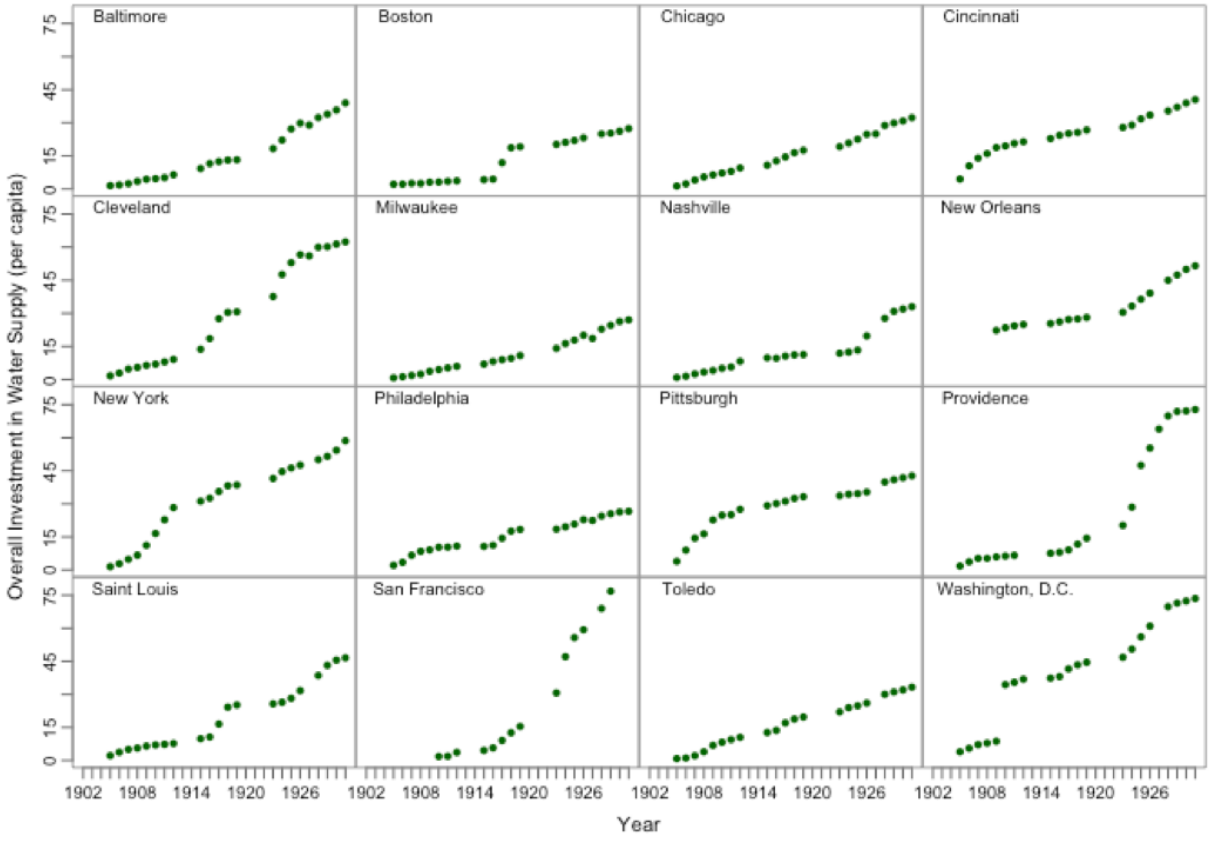
S13 Fig. Annual per capita funded debt of the water supply system. The overall annual accrued debt and/or funded loans for the water supply system from 1902-1931 is shown for each city in per capita increments (US$ per person). Note: Data were not available for this variable in Washington, D.C.



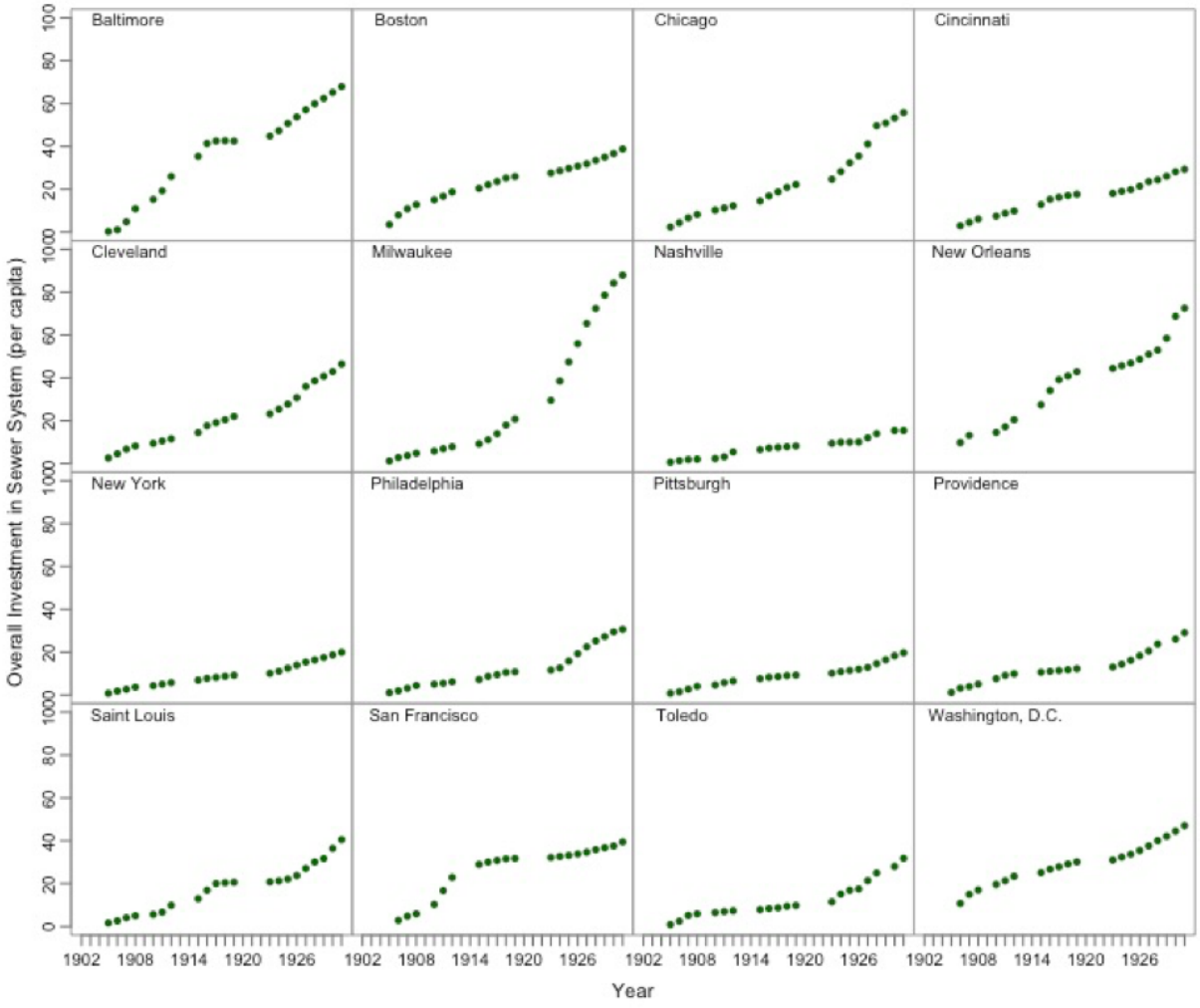
S14 Fig. Annual per capita funded debt of the sewer system. The overall annual accrued debt and/or funded loans for the sewer system from 1902-1931 are shown for each city in per capita increments (US$ per person). Note: Data were not available for this variable in Washington, D.C.



S15 Fig. Overall investment in the water supply system. The overall cumulative investments in the water supply system from 1902-1931 are shown for each city in per capita increments (US$ per person). This was calculated as the cumulative sum of annual expenses and annual outlays minus annual receipts for the water supply system.

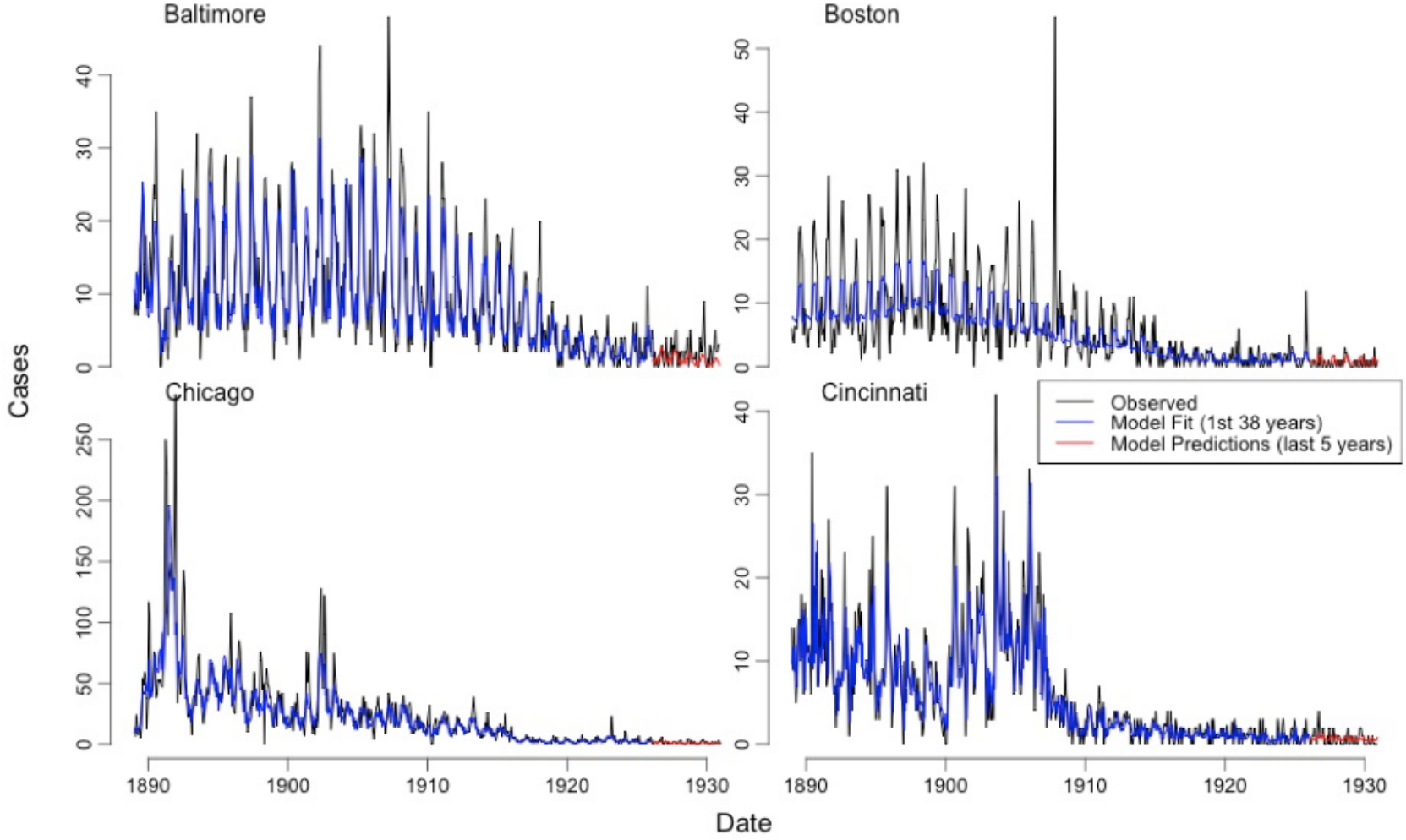


S16 Fig. Overall investment in the sewer system. The overall cumulative investments in the sewer system from 1902-1931 are shown for each city in per capita increments (US$ per person). This was calculated as the cumulative sum of annual expenses and annual outlays for the sewer system.

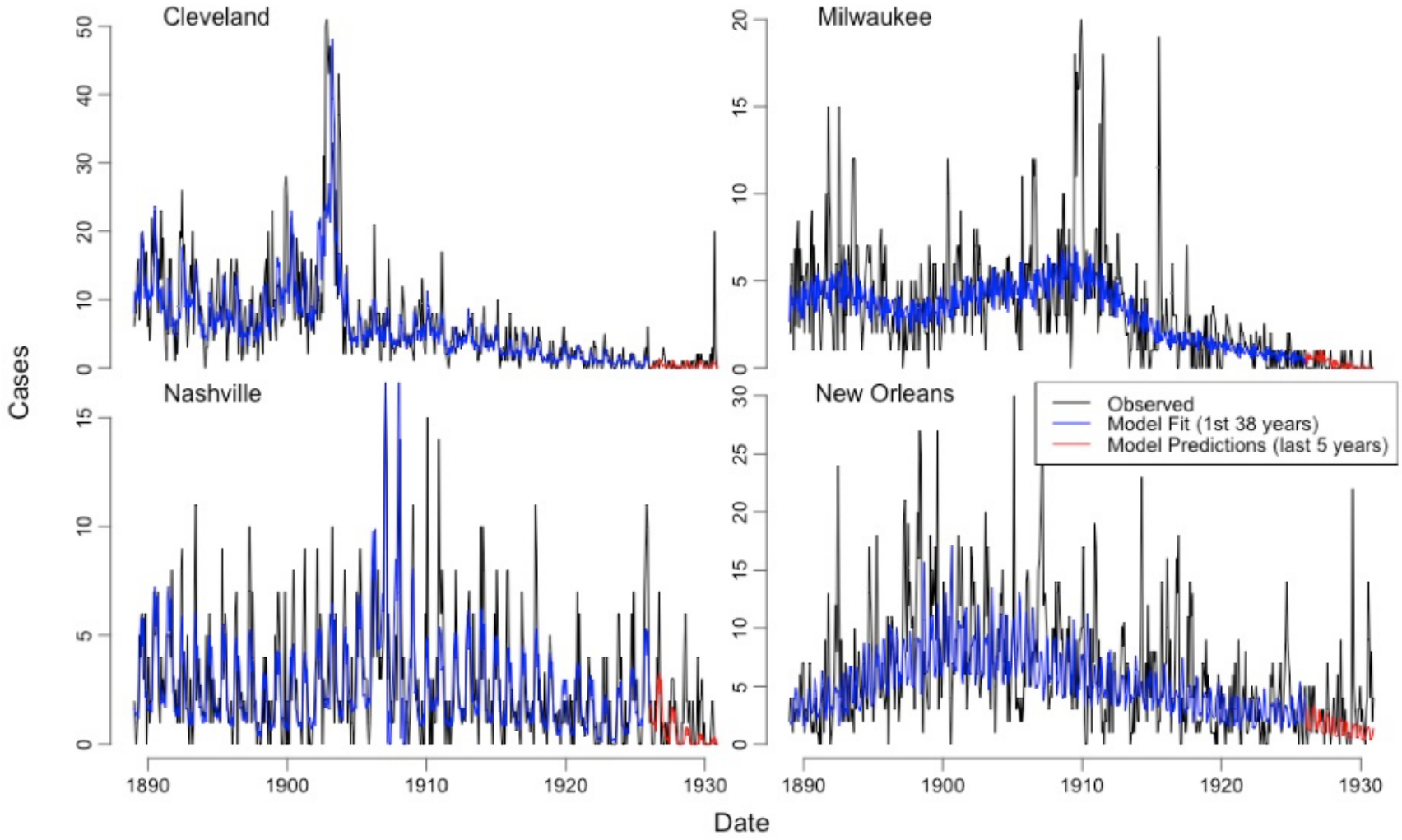


S17-S20 Figs. TSIR model predictions. For each city, the TSIR model is fit using the first 38 years of data, then used to predict the last 5 years of data. In each plot, the observed data is shown in black, the model fit to the first 38 years is shown in blue, and the predicted last 5 years is shown in red.

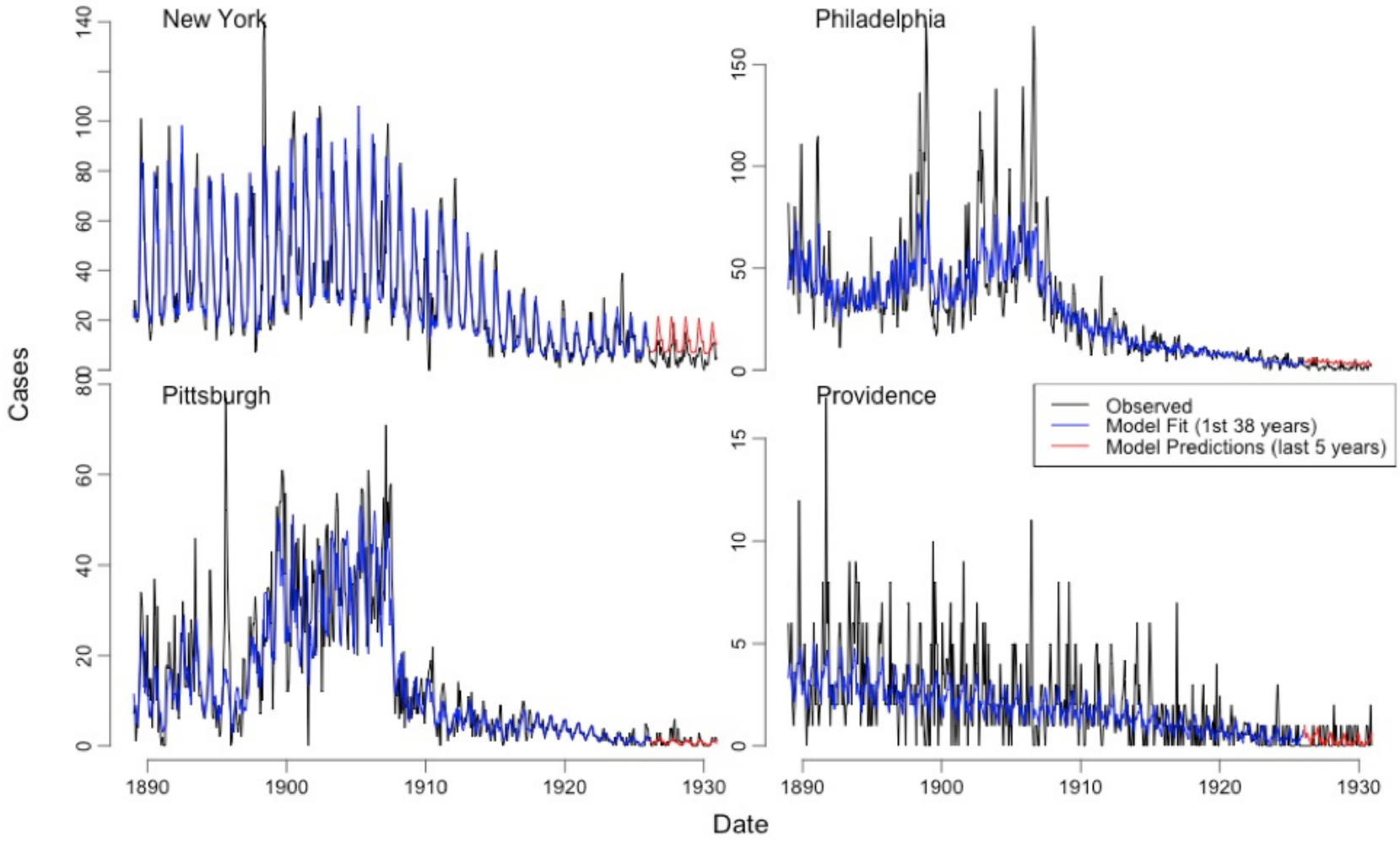
S17 Fig. TSIR model predictions for Baltimore, Boston, Chicago, and Cincinnati.



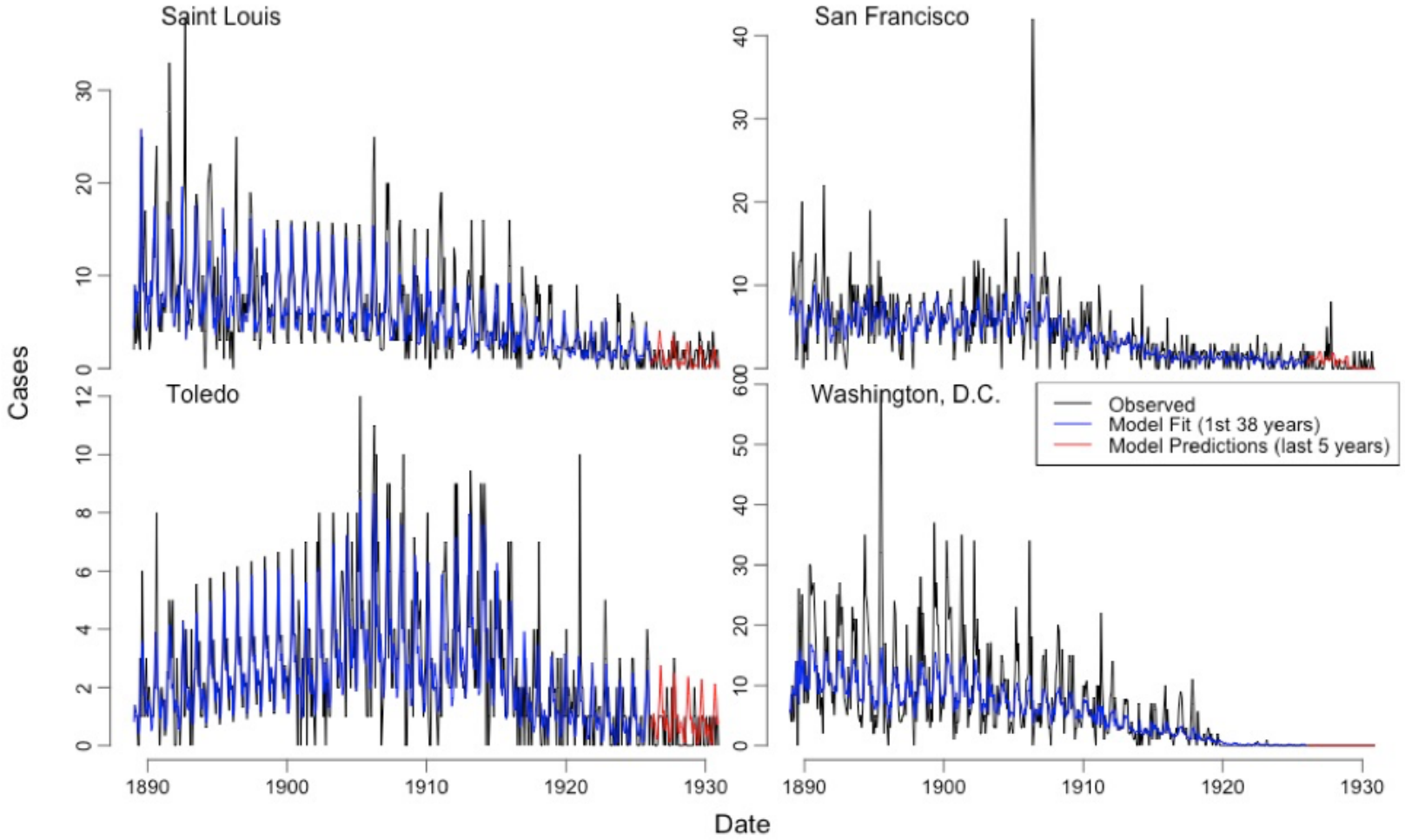
S18 Fig. TSIR model predictions for Cleveland, Milwaukee, Nashville, and New Orleans.



S19 Fig. TSIR model predictions for New York, Philadelphia, Pittsburgh, and Providence.



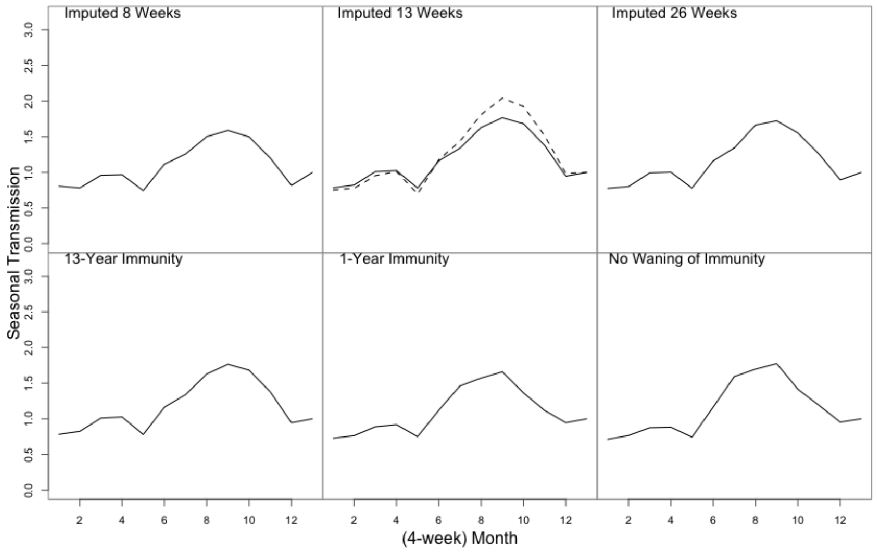
S20 Fig. TSIR model predictions for St. Louis, San Francisco, Toledo, and Washington, D.C.



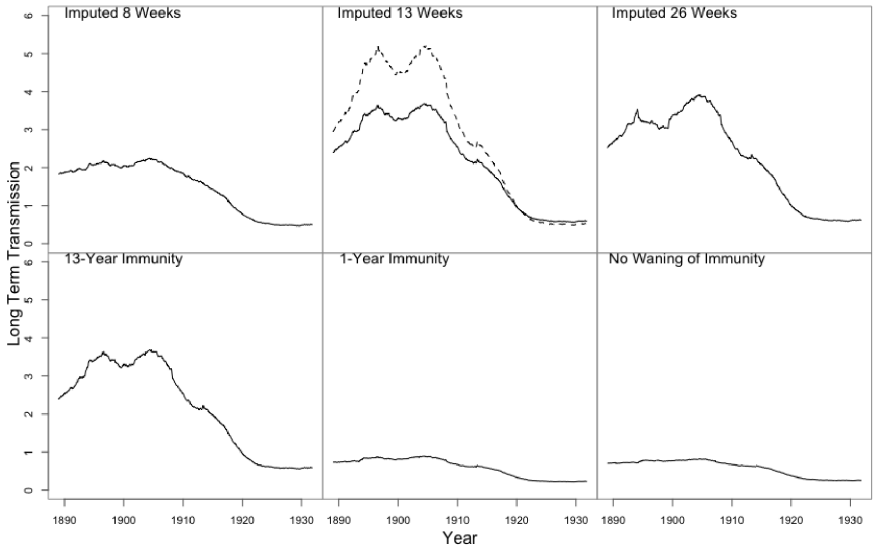
S21-S36 Figs. Plots of seasonal and long-term transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity. The plot of seasonal and long-term transmission is shown for each city separately. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity). Instances of outliers are noted, and are sometimes not entirely shown in the plot.

S21 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Baltimore. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Baltimore data.

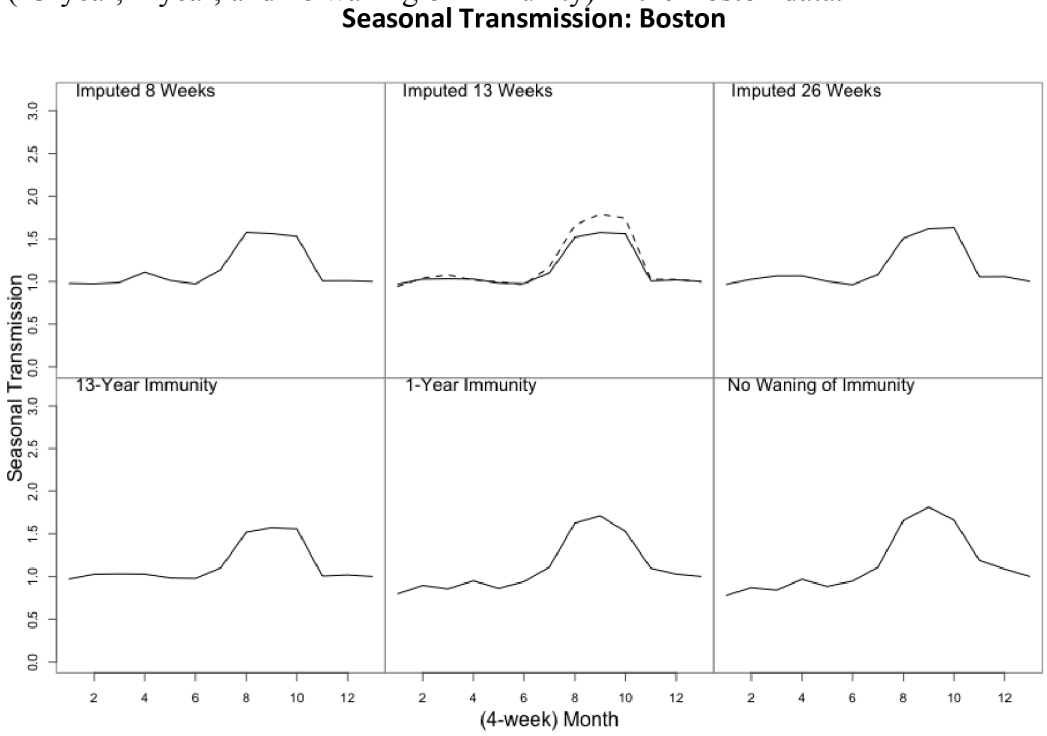
Seasonal Transmission: Baltimore

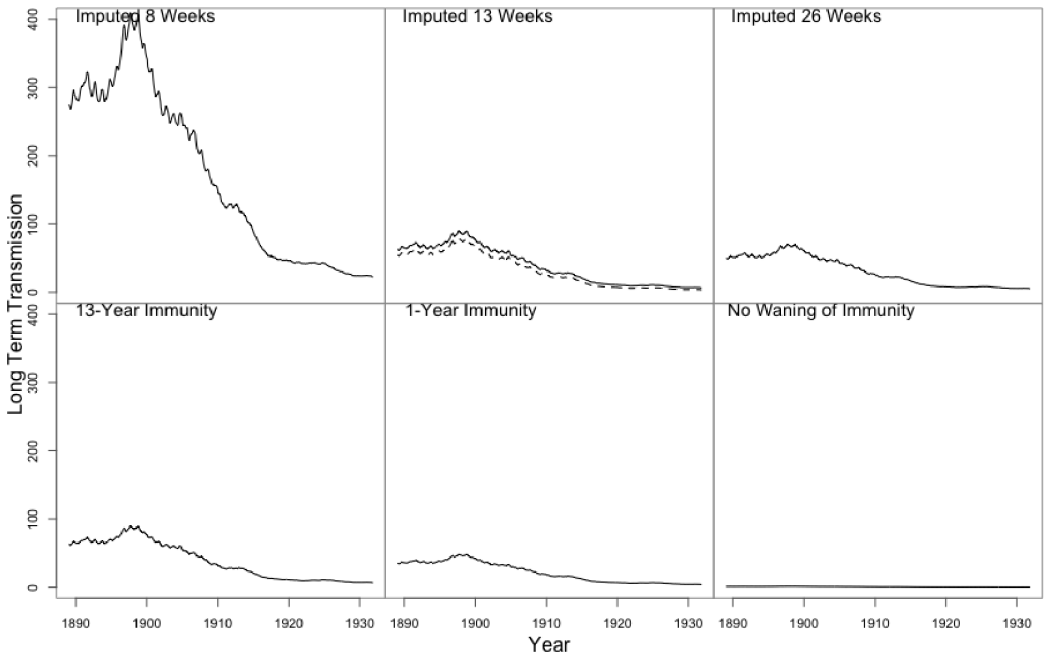


Long-term Transmission: Baltimore

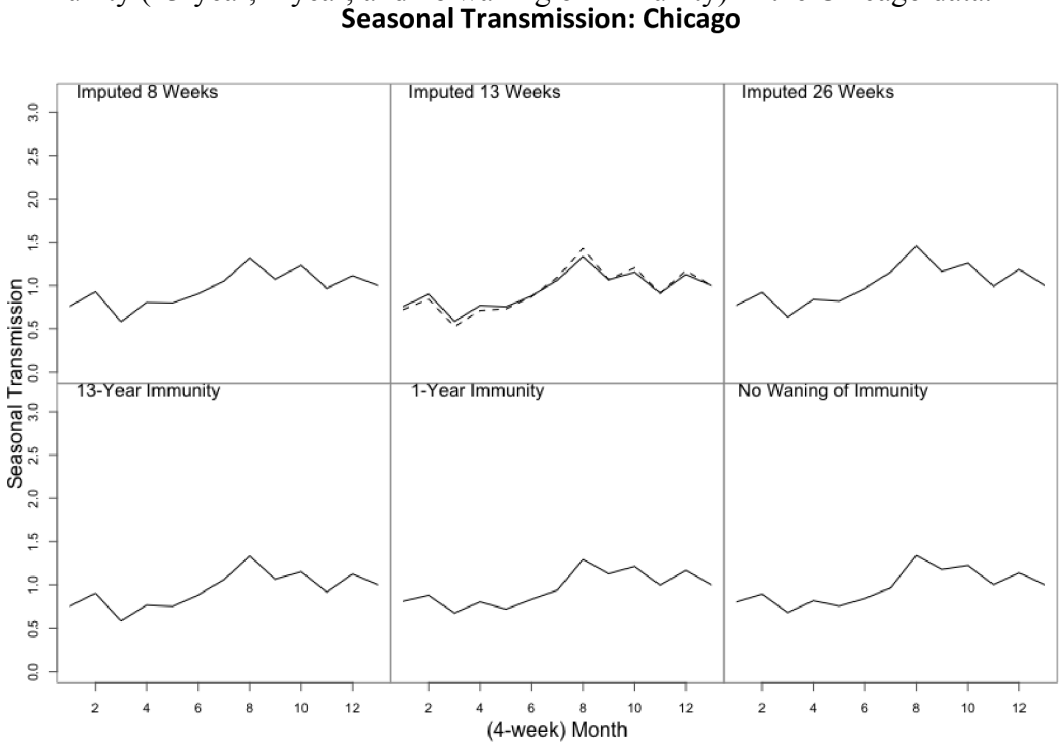


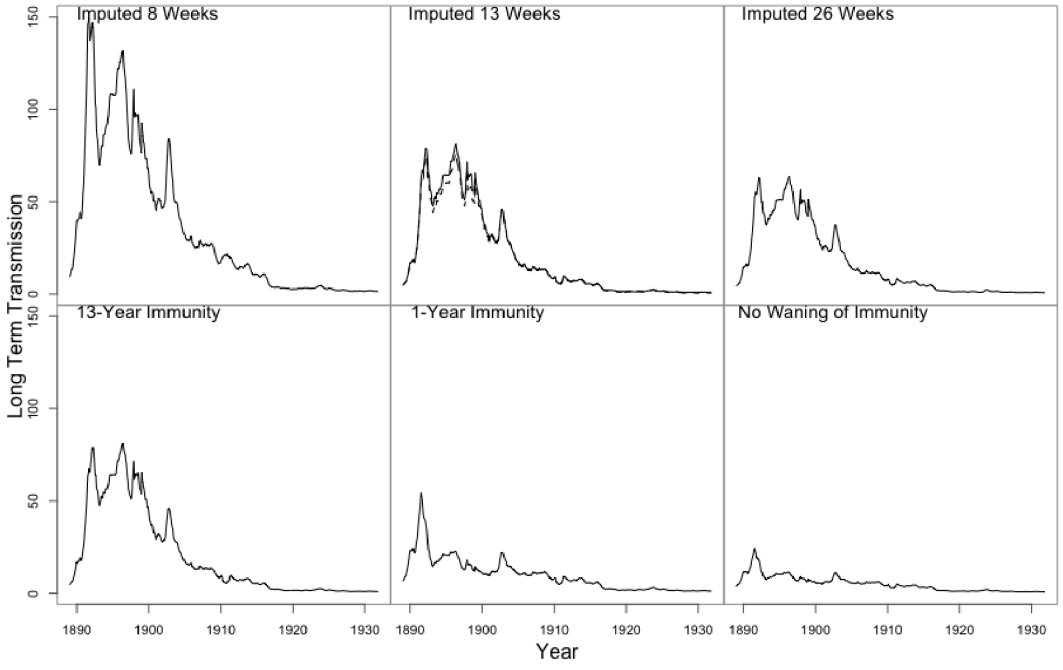
S22 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Boston. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Boston data.



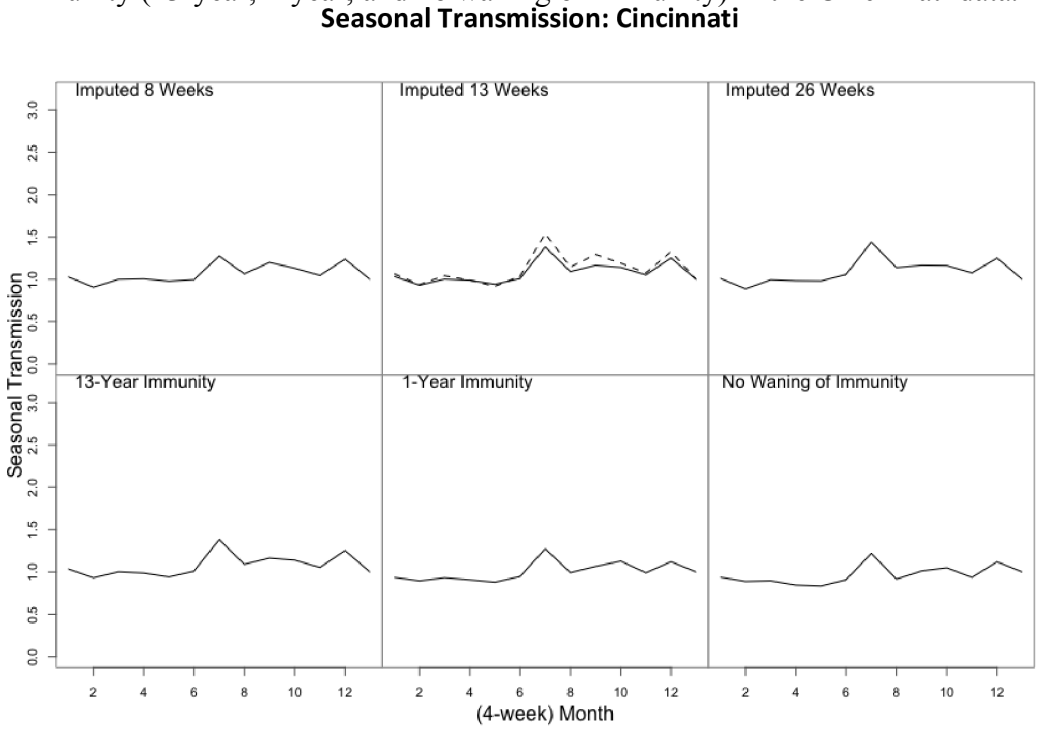


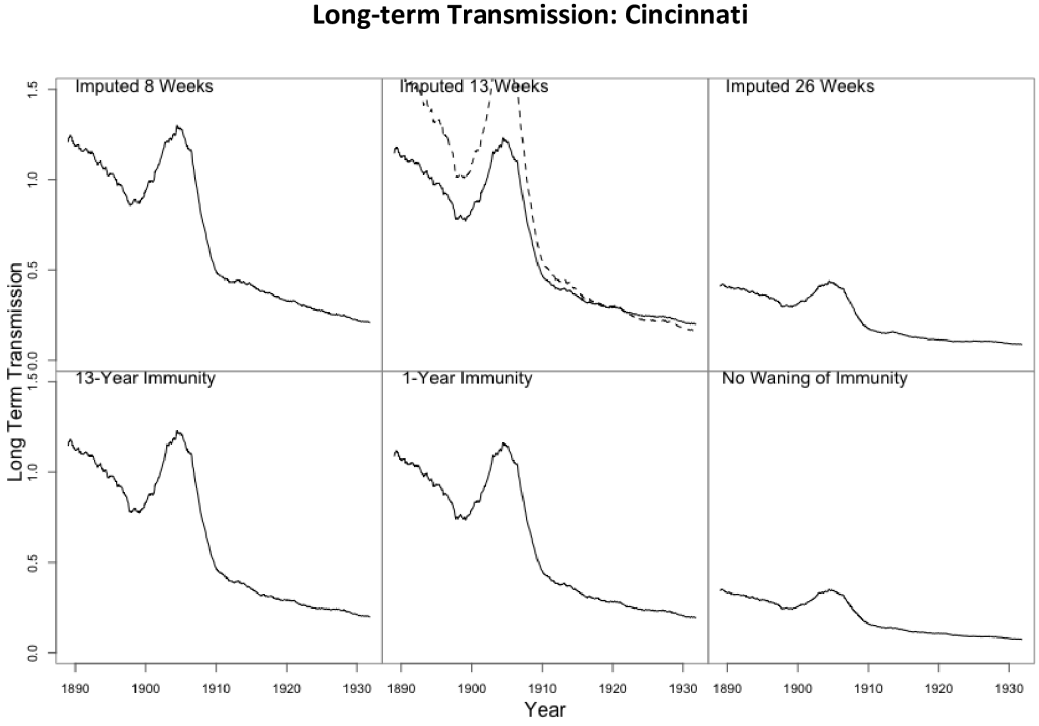
S23 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Chicago. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Chicago data.



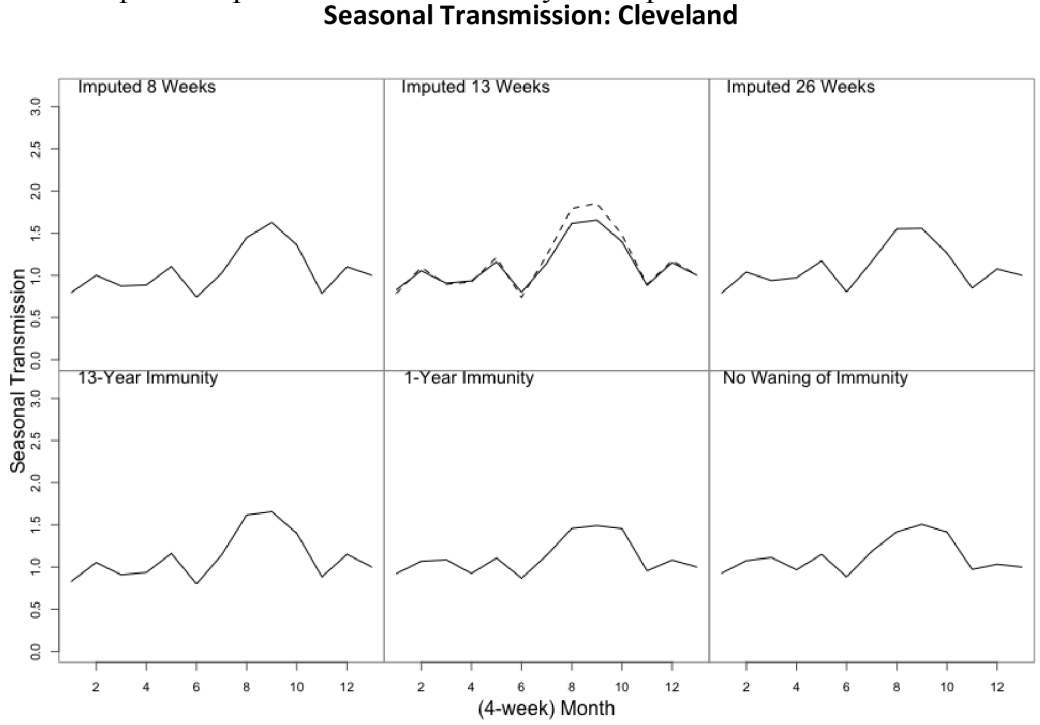


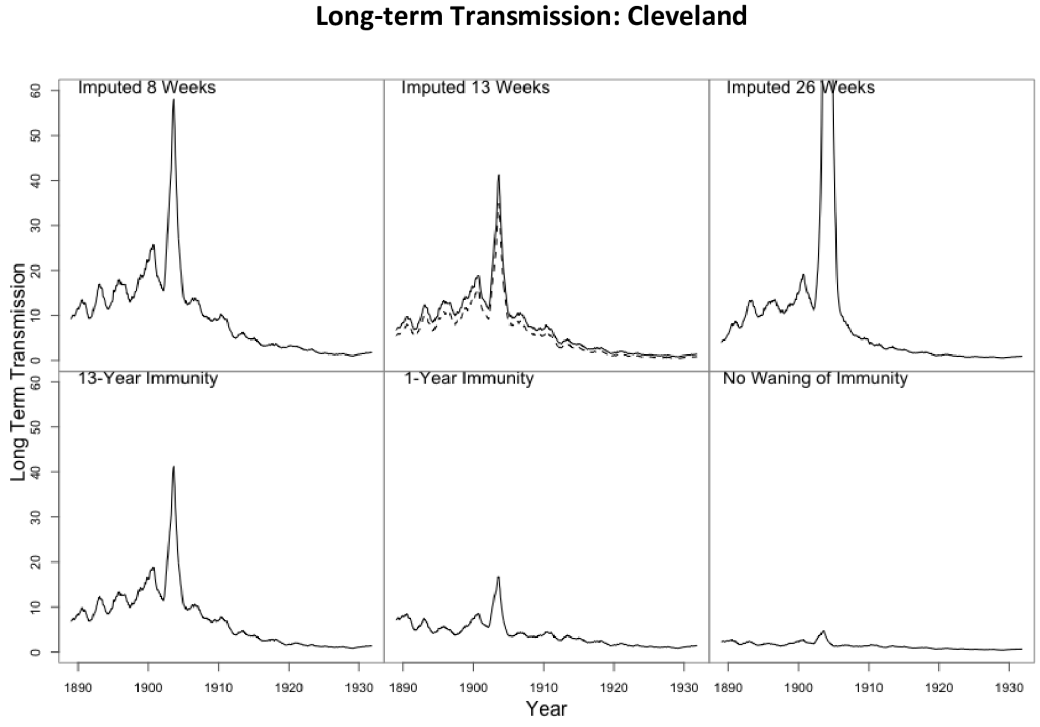
S24 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Cincinnati. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Cincinnati data.



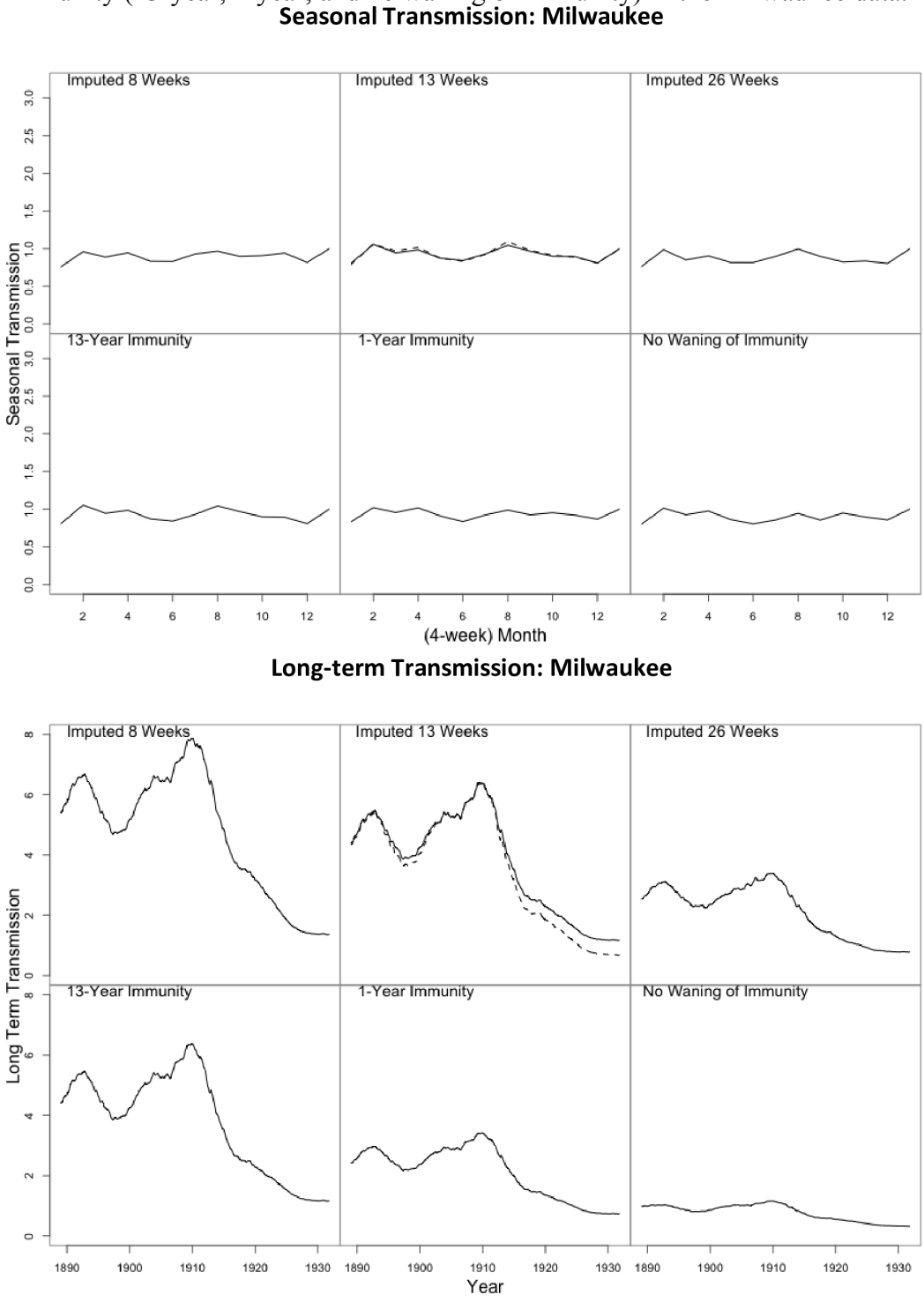


S25 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Cleveland. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Cleveland data. Note that the 26-week imputation plot is not shown entirely in the plot due to its outlier.

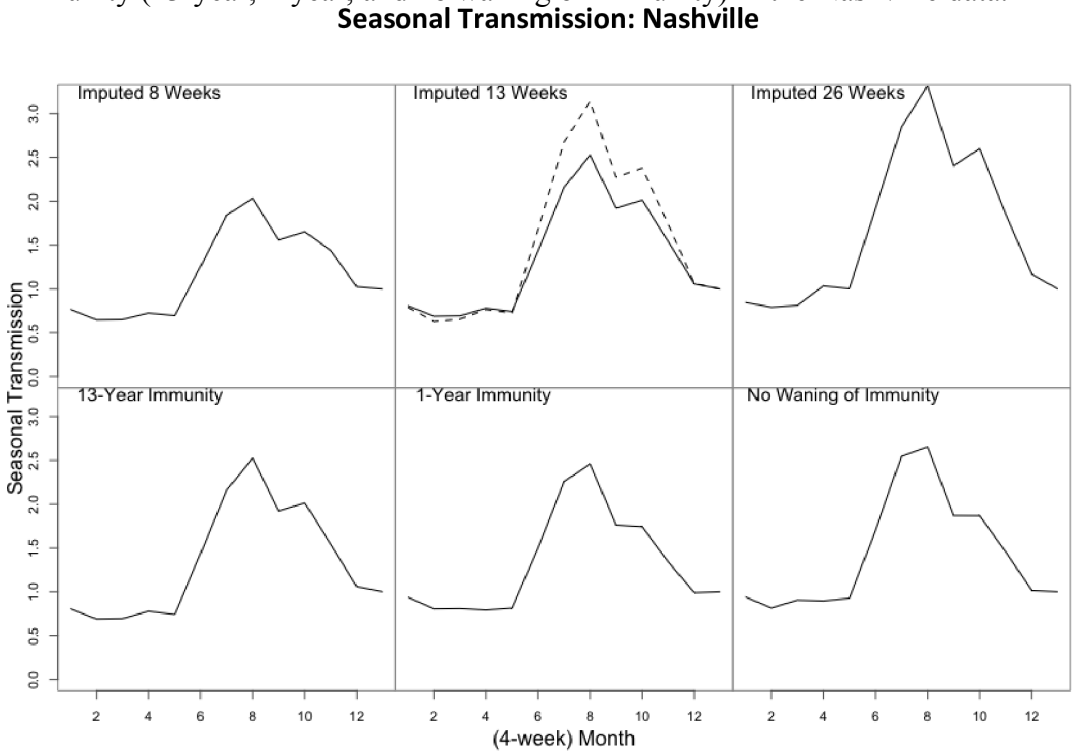


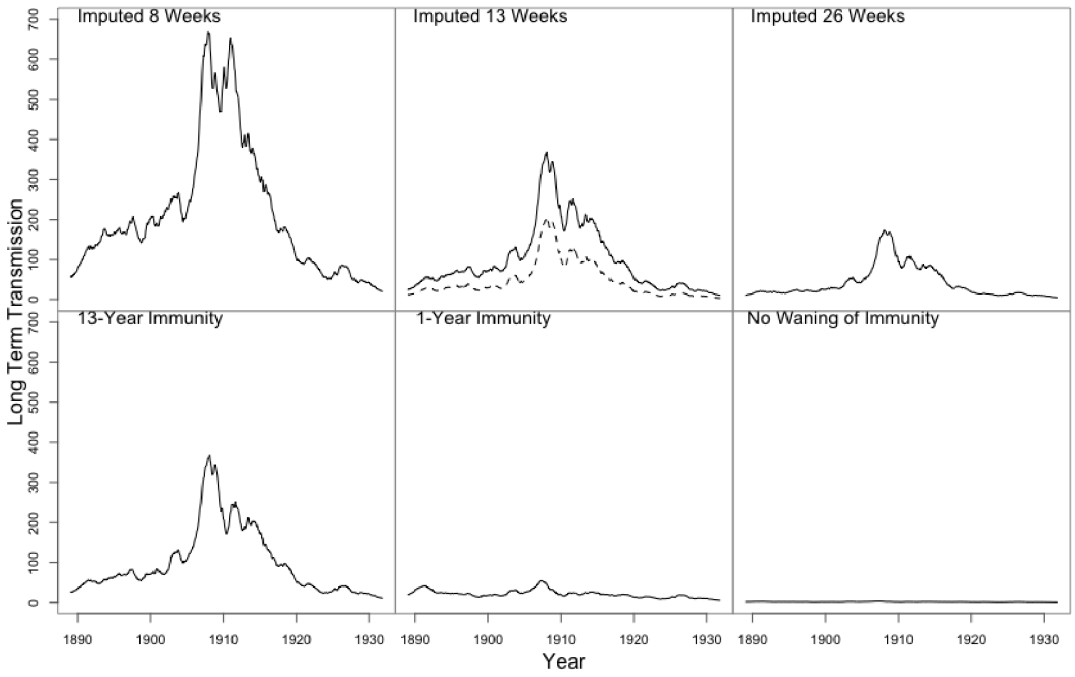


S26 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Milwaukee. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Milwaukee data.

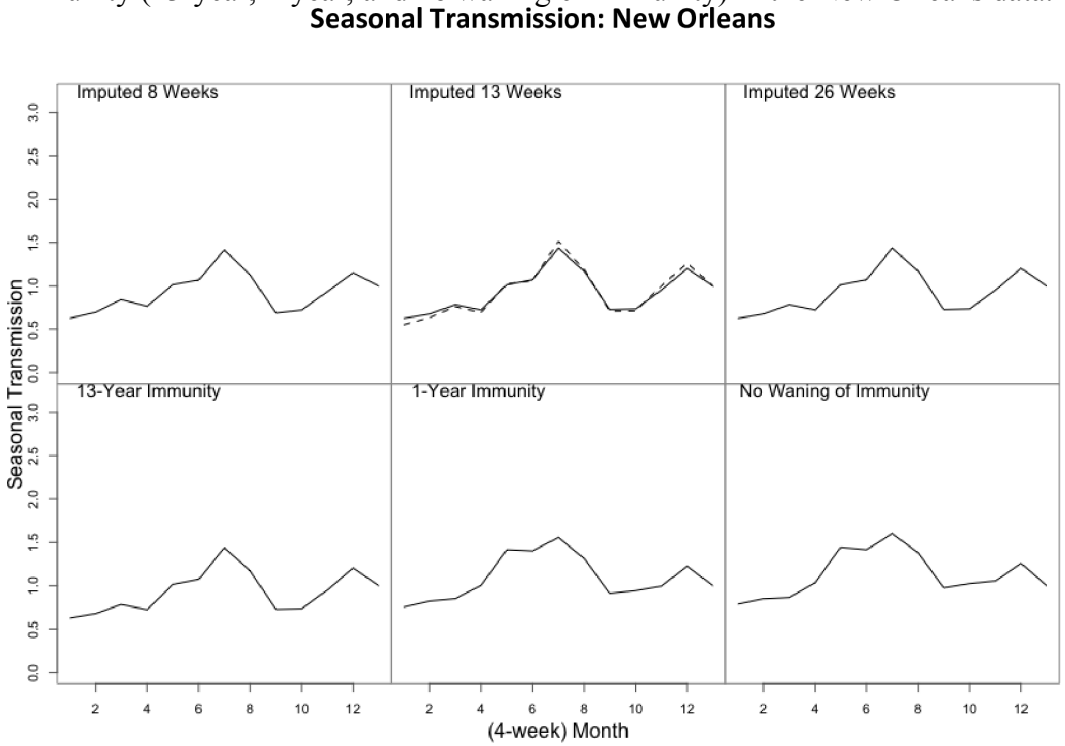


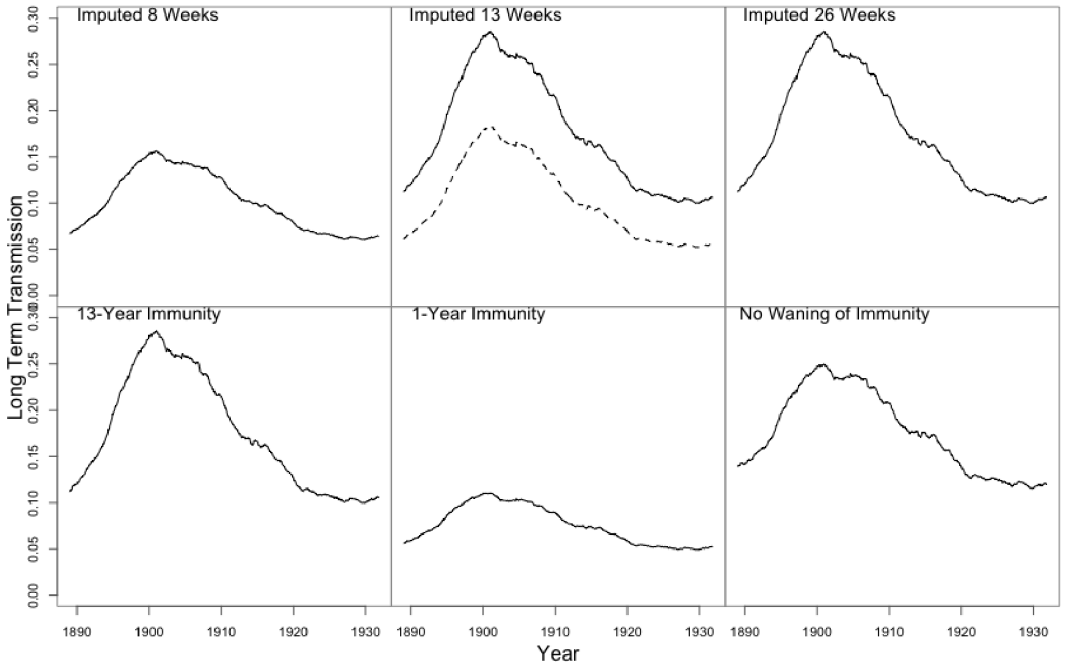
S27 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Nashville. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Nashville data.



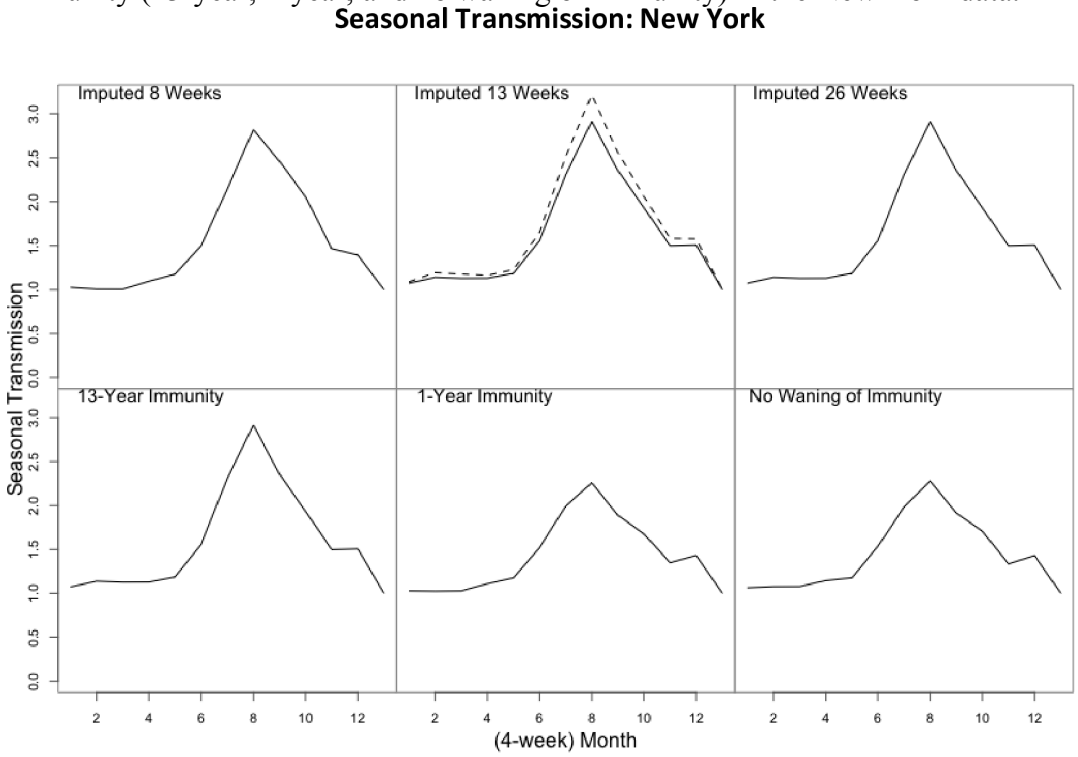


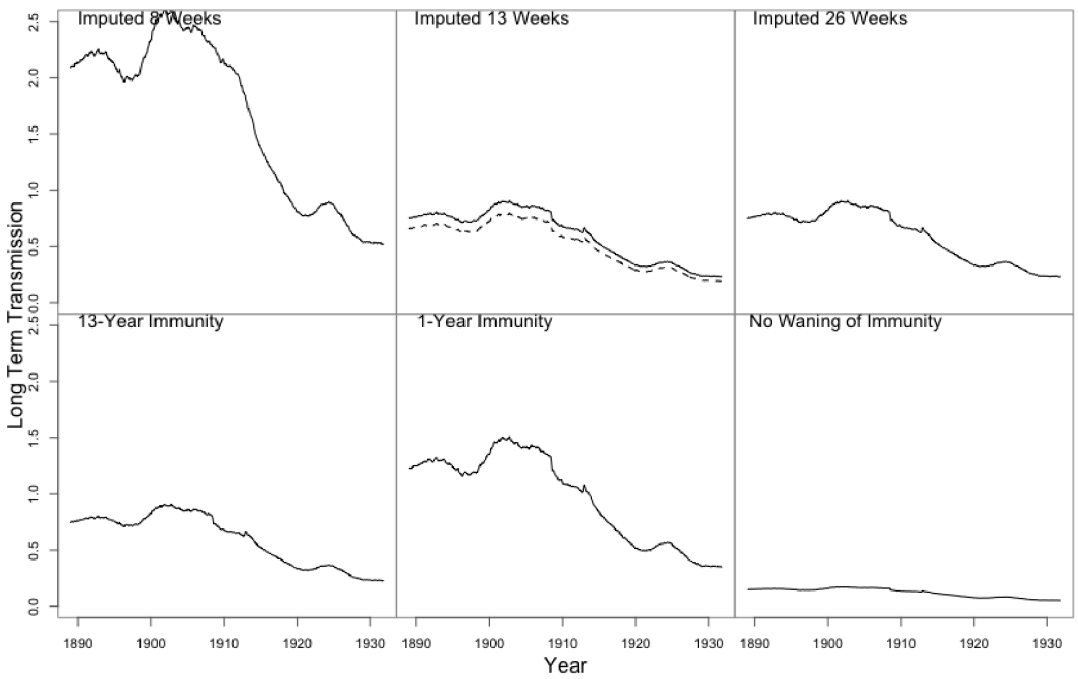
S28 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: New Orleans. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the New Orleans data.



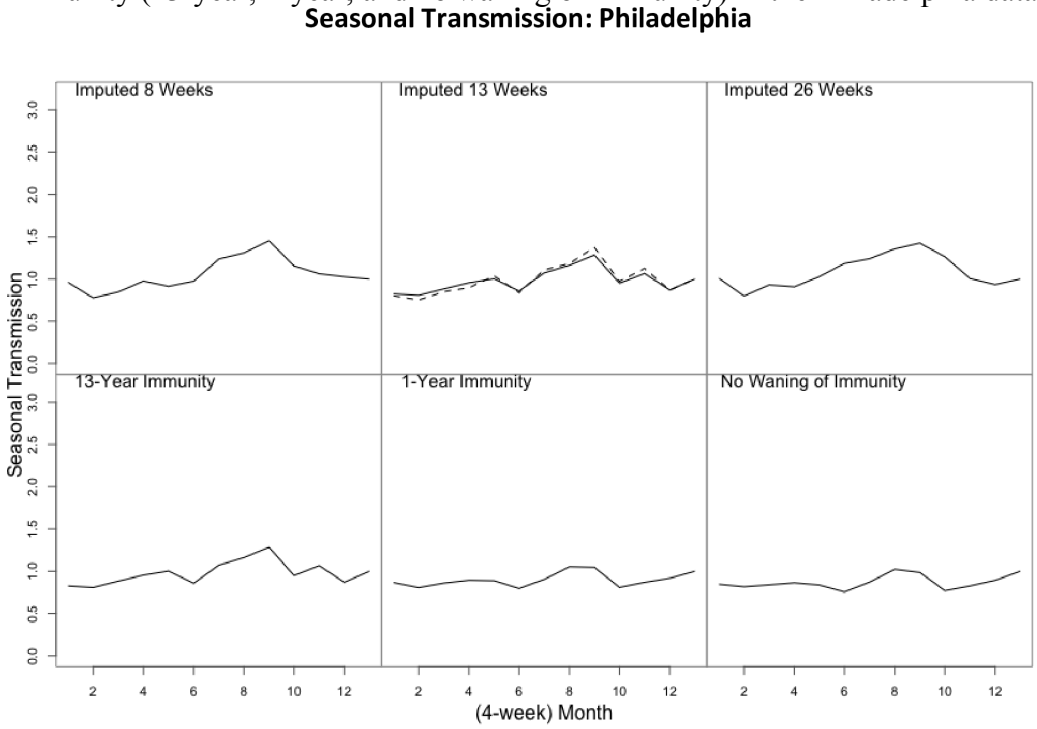


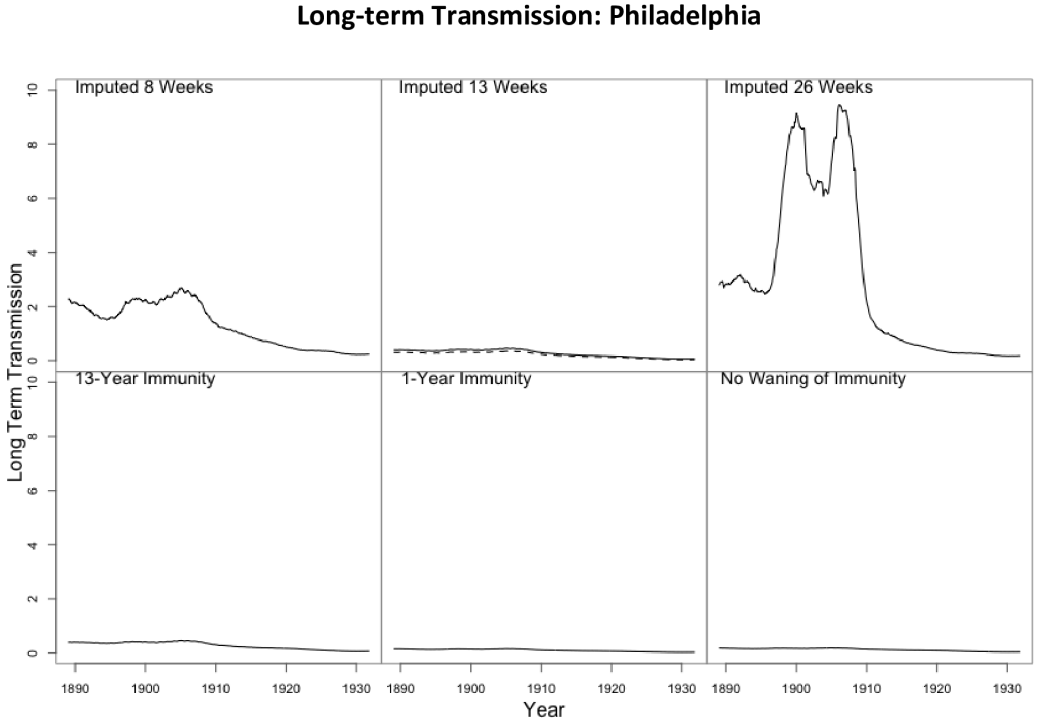
S29 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: New York. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the New York data.



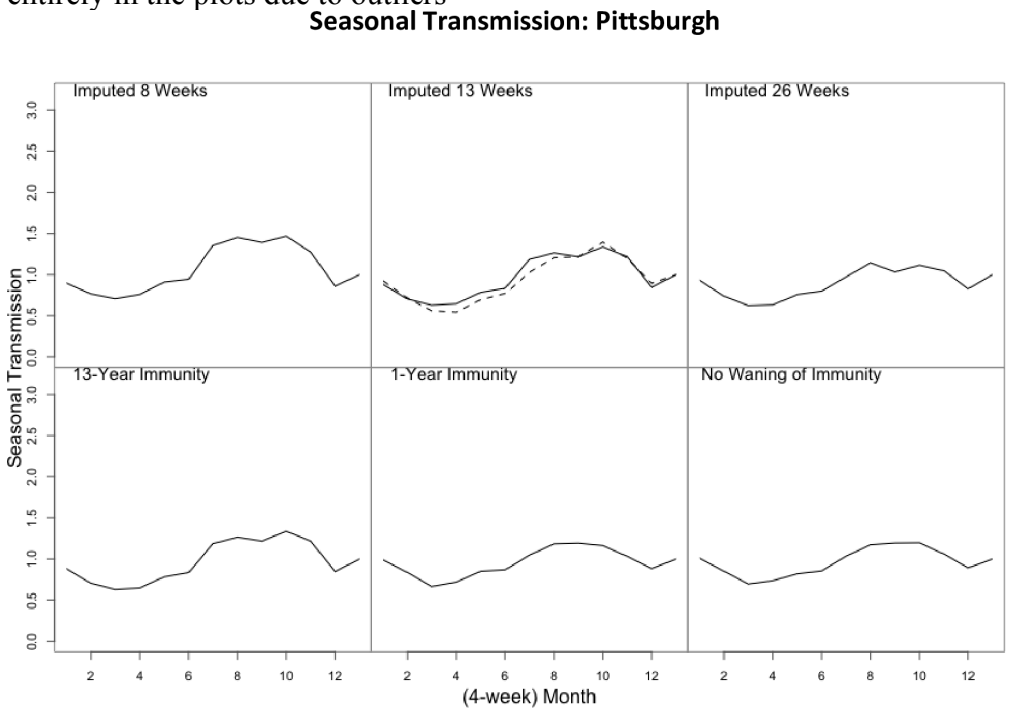


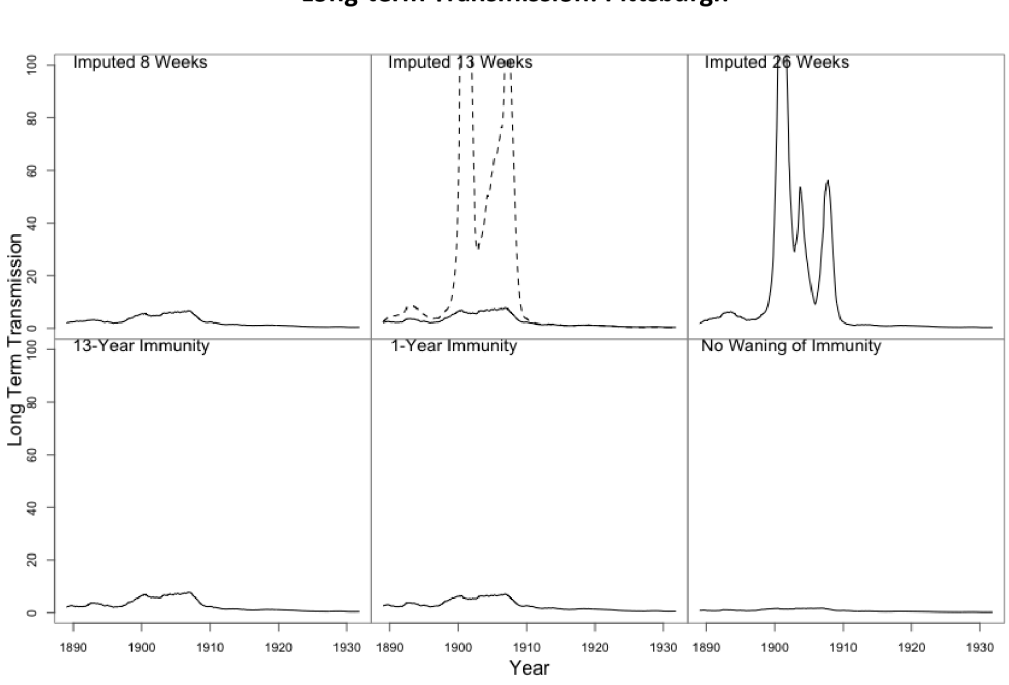
S30 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Philadelphia. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Philadelphia data.



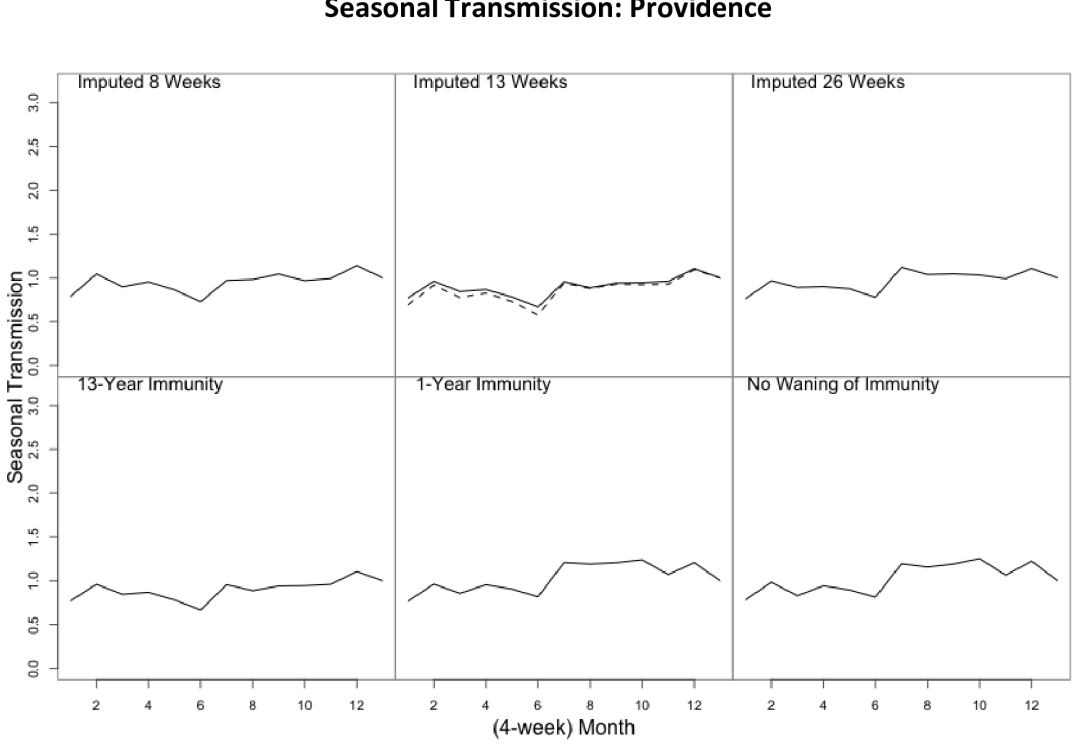


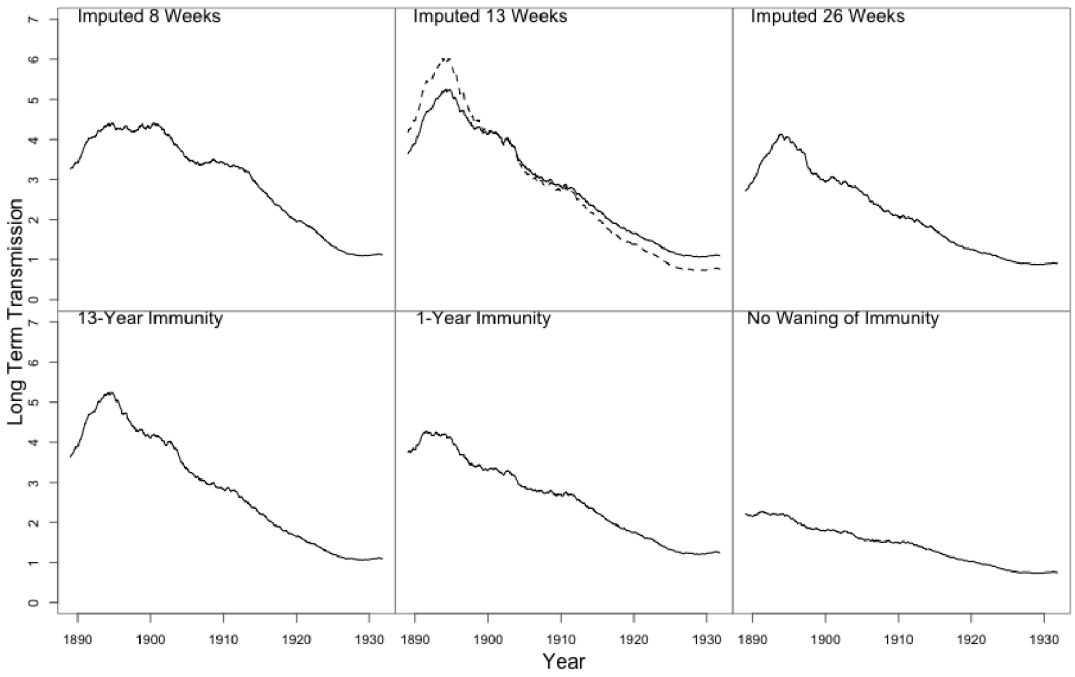
S31 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Pittsburgh. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Pittsburgh data. Note that the imputed 13-week algorithm (+0.5) and the imputed 26-week algorithm (+1) are not shown entirely in the plots due to outliers



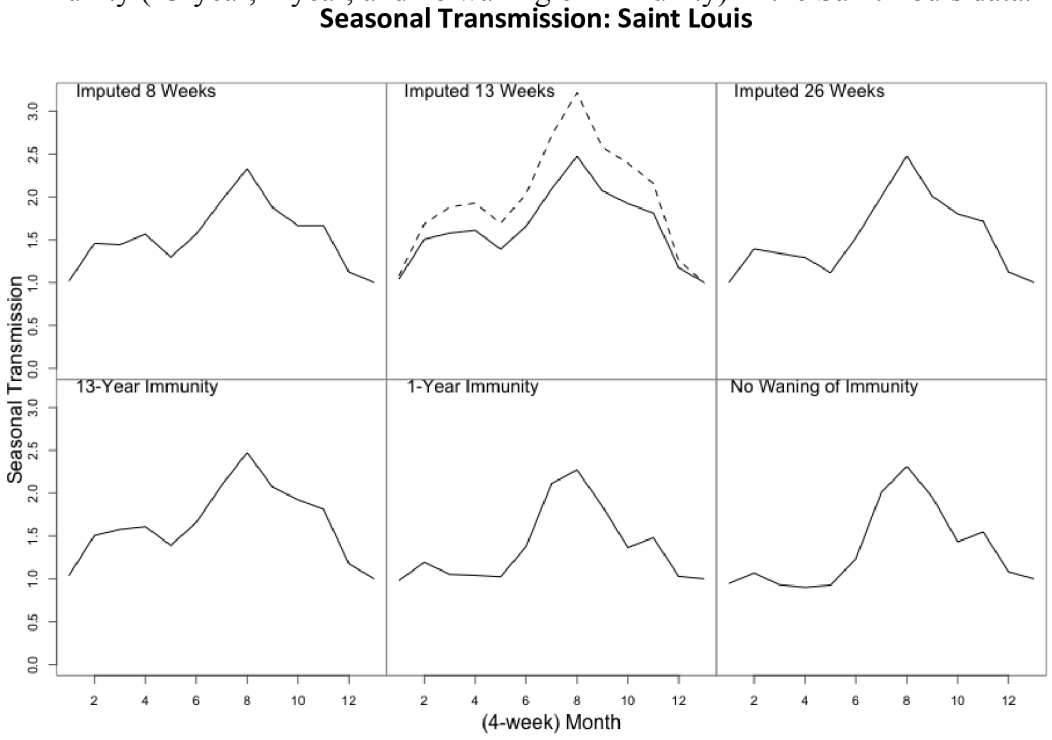


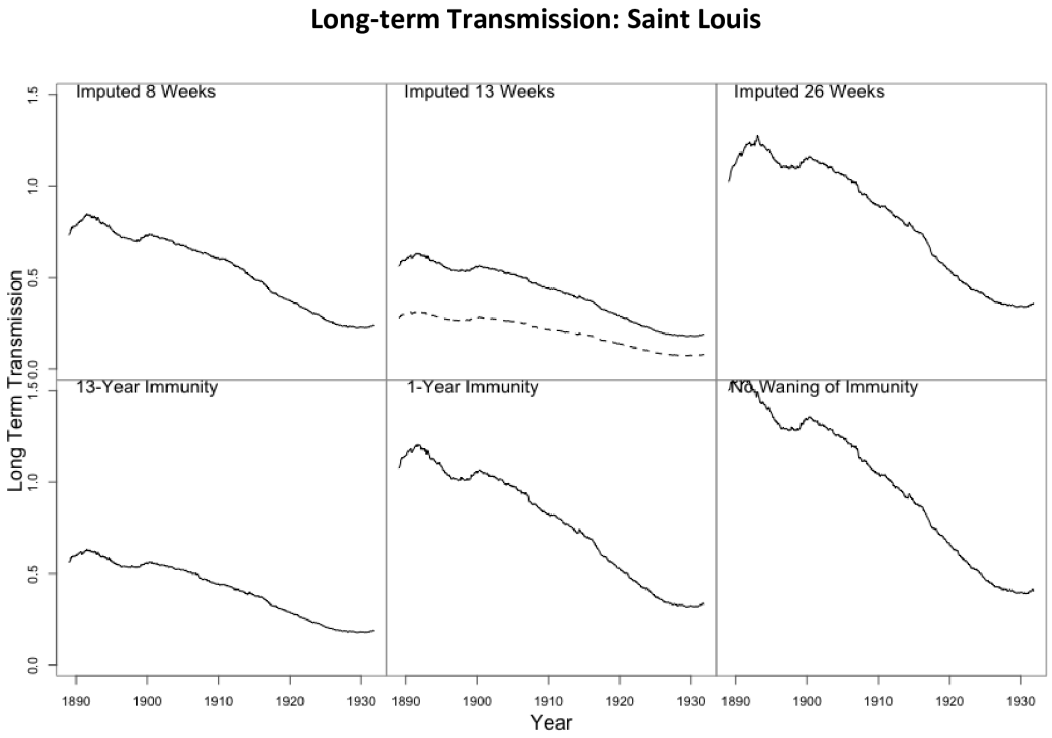
S32 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Providence. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Providence data.



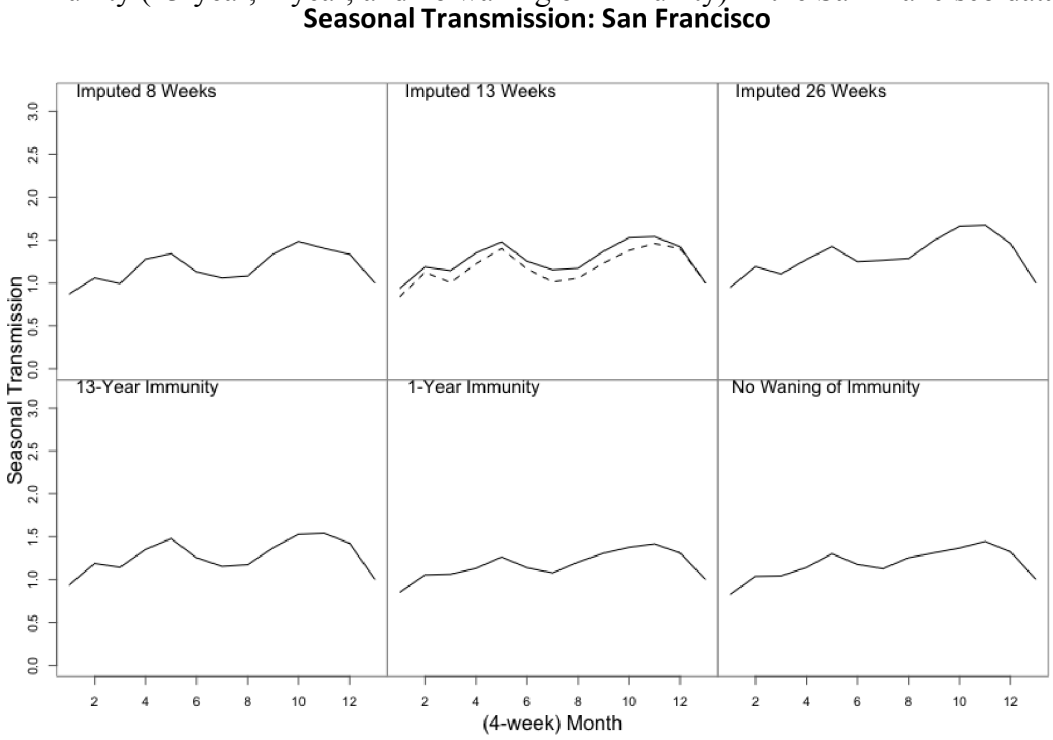


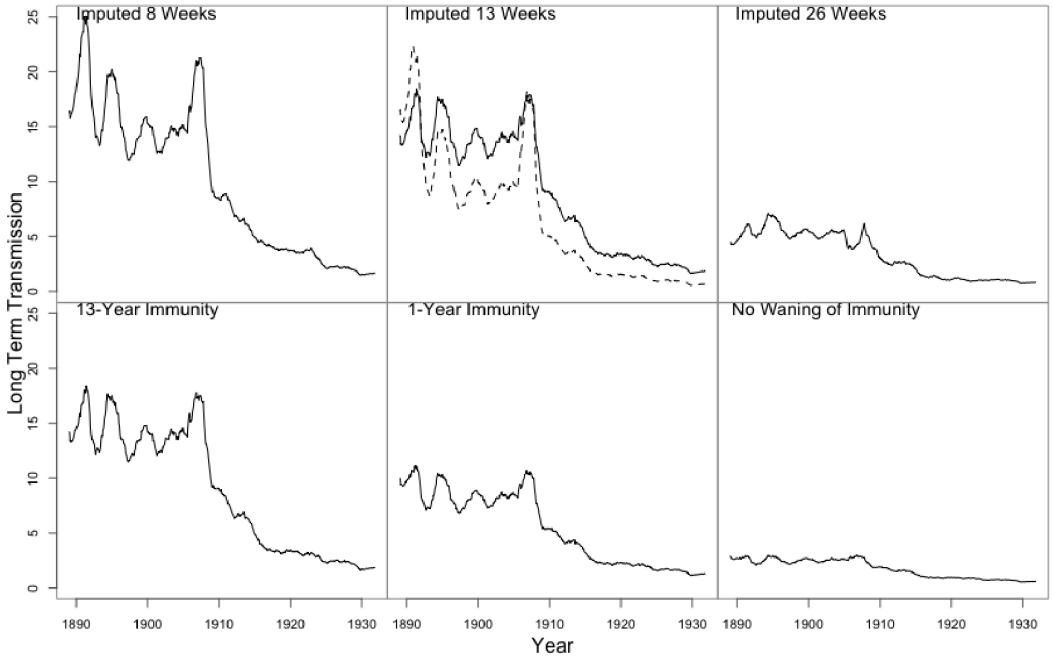
S33 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Saint Louis. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Saint Louis data.



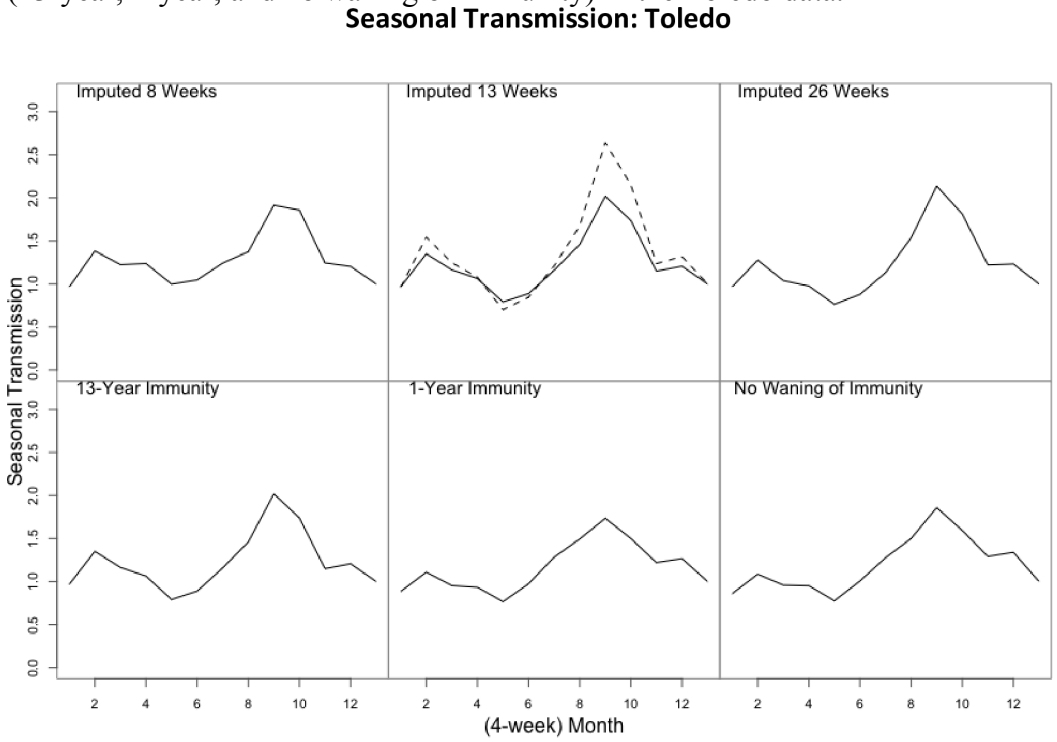


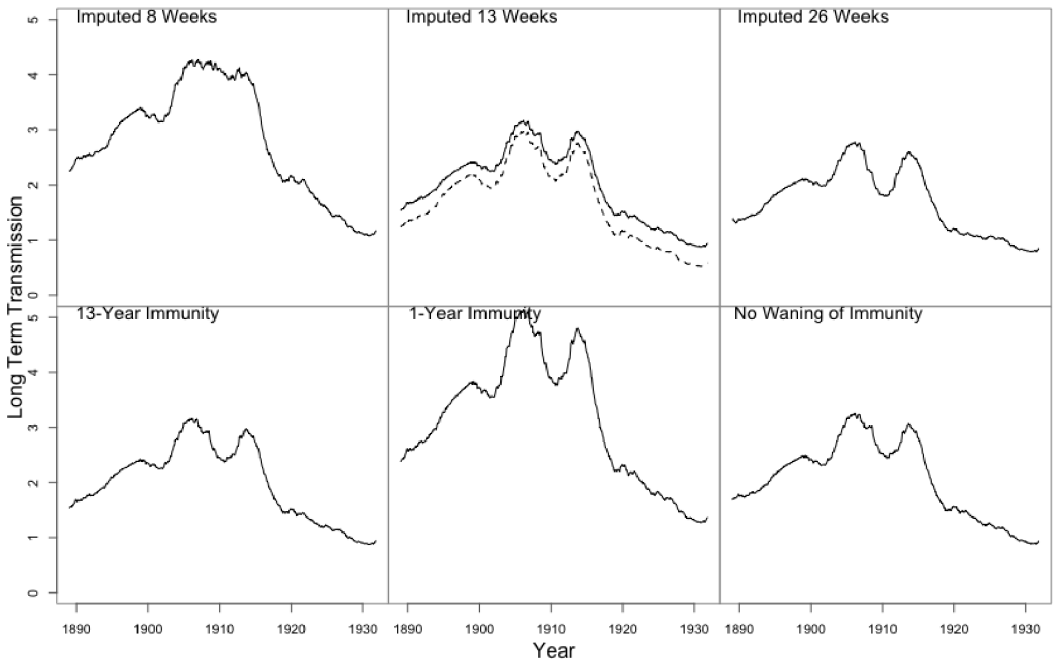
S34 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: San Francisco. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the San Francisco data.





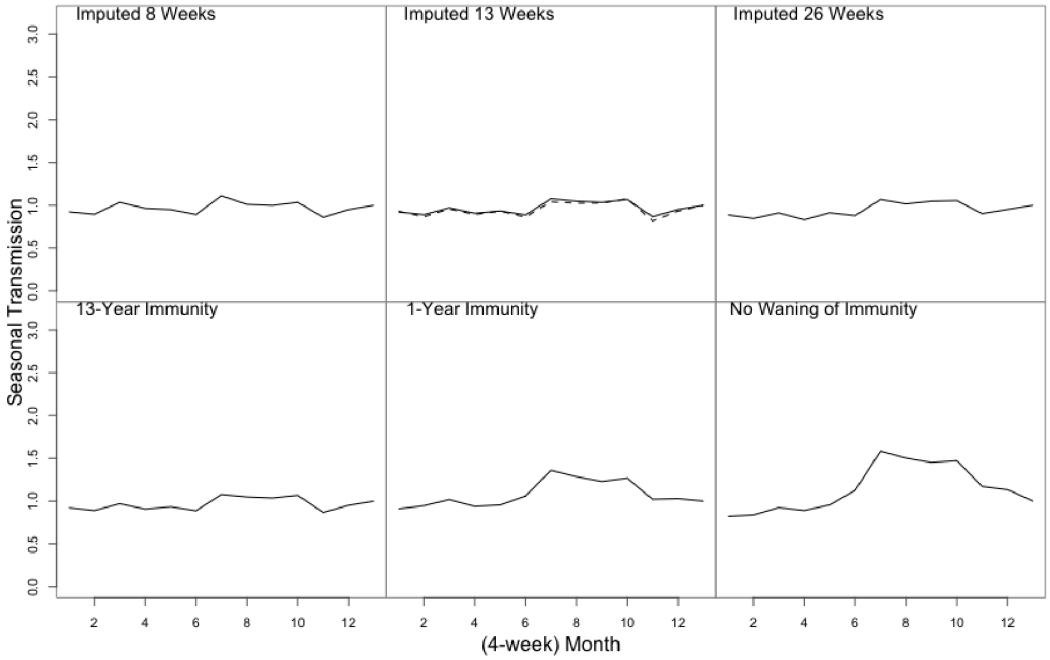
S35 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Toledo. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Toledo data.



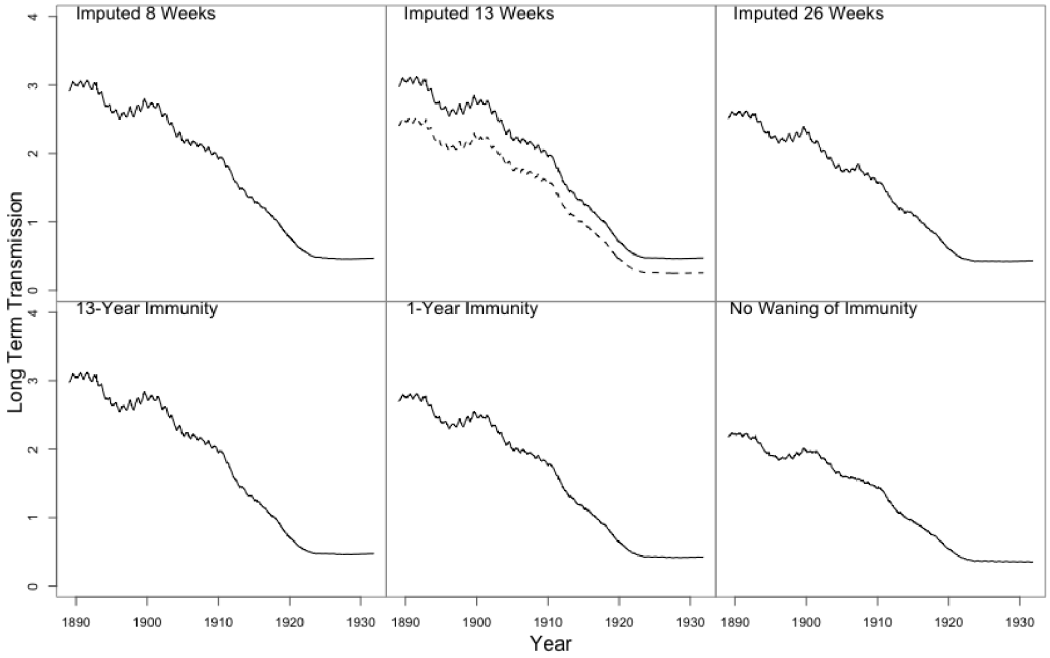


S36 Fig. Plots of seasonal transmission from sensitivity analyses for imputation, log-transformation, and duration of immunity: Washington, D.C.. Plots are shown for imputation of missing data (8-, 13-, and 26-week algorithm); addition to all weekly death counts (+1 shown in the solid line in every panel; +0.5 shown in the dashed line in the second panel); and duration of immunity (13-year, 1-year, and no waning of immunity) in the Washington, D.C. data.

Seasonal Transmission: Washington, D.C.



Long-term Transmission: Washington, D.C.



S1 Table. References for water supply source, interventions and dates. Information on water supply interventions and water sources were extracted from a variety of references, noted below. Most cities had data available from the U.S. Census Bureau in addition to individual municipal sources, noted in the table as "U.S. Census Bureau (Yes/No)".

City	State	Water Source	U.S. Census Bureau (Yes/No)	Additional Sources
Baltimore	MD	Jones Falls reservoir, Lake Roland/Lake Hampden/Mount Royal reservoirs (1862), Druid Hill reservoir (1873), Loch Raven reservoir and Lake Montebello (1881); chlorination 1910, filtration 1915	Yes (Filtration, Chlorination)	http://cityservices.baltimorecity.gov/dpw/waterwastewater02/waterquality3.html http://www.baltimorecity.gov/Government/AgenciesDepartments/PublicWorks/BureauofWaterWastewater/FactSheet.aspx
Boston	MA	Long Pond (Lake Cochituate) via Cochituate aqueduct and Brookline Reservoir; several reservoirs, aqueducts built between 1864 and 1900; Wachusett Reservoir/Dam/aqueduct completed in 1908	Yes (Filtration)	http://www.bwsc.org/ABOUT_BWSC/systems/water/Water_history.asp
Chicago	IL	Lake Michigan; flow direction of Chicago River reversed in 1900 to prevent waste water from entering lake	Yes (Filtration, Chlorination)	http://encyclopedia.chicagohistory.org/pages/1325.html
Cincinnati	OH	Ohio River (with subsiding, storage, & filtering reservoirs, e.g. Eden Park)	Yes (Filtration, Chlorination)	http://books.google.com/books?id=6vzVAAAAMAAJ&pg=PA42&lpg=PA42&dq=cincinnati+water+works+history&source=bl&ots=Qe82LaTBvG&sig=zGhGv6VH7yZ2LwXvdLySJ7B8OnI&hl=en&sa=X&ei=um7rTuCUPIT30gGDgpXQCQ&ved=0CGIQ6AEwBw#v=onepage&q=cincinnati%20water%20works%20history&f=false
Cleveland	OH	Lake Erie west of the Cuyahoga River; off-shore intake (Kinsman Reservoir) began operation in 1885; further off-shore intakes created 1890-1916; chlorination began in 1911, daily testing 1913, filtration 1917	Yes (Filtration, Chlorination)	http://www.clevelandwater.com/about_us/history.aspx

Milwaukee	WI	Lake Michigan via Kilbourne Reservoir; second pumping station at Milwaukee River in 1924	Yes (Chlorination)	http://city.milwaukee.gov/water/customer/FAQs/additionalinfo#4
Nashville	TN	Cumberland River via reservoirs used for settling and storage; pumping station relocated upstream of Brown's Creek in 1889; treatment with hypochlorite in 1908, liquid chlorine in 1920, filtration in 1928	Yes (Filtration, Chlorination)	http://www.nashville.gov/water/docs/other/water_history_additional_information.pdf
New Orleans	LA	Rainwater cisterns, Mississippi River, artesian wells; city subject to regular flooding at late as mid-1880s; drainage plan initiated in 1896; water treatment authorized/built in 1899	Yes (Filtration)	http://www.swbno.org/history_history.asp
New York	NY	Old Croton Reservoir (via Old Croton aqueduct, since 1842); distribution reservoirs at 42nd St, Central Park, Boyds Corner, Middle Branch; additional reservoirs in Catskills in 1905-1915	Yes (Filtration, Chlorination)	http://www.nyc.gov/html/dep/html/drinking_water/history.shtml
Philadelphia	PA	Schuylkill River, Delaware River, Leigh River, various creeks	Yes (Filtration, Chlorination)	http://www.phillyh2o.org/ http://www.phila.gov/water/PWD_Historical.html
Pittsburgh	PA	Allegheny River (with holding reservoirs); filtration began in 1909 (Southside) and 1914 (Northside); chlorination began in 1911; City of Pittsburgh merged with City of Allegheny (Northside) in 1907	Yes (Filtration, Chlorination)	http://www.pgh2o.com/history02.htm
Providence	RI	Pawtuxet River (at Cranston); filtration began 1906; filtered water stored in 3 open reservoirs; shortages during dry weather; Scituate Reservoir and treatment plant constructed in 1926 (by damming river)	Yes (Filtration)	http://www.provwater.com/history.htm
Saint Louis	MO	Mississippi River (via High Service pumping station at Bissels Point since 1871, also via Low Service Chain of Rocks plant since 1894); filtration plant dedicated in 1915	Yes (Filtration, Chlorination)	http://www.stlwater.com/history2.php

San Francisco	CA	Arroyo de la Laguna, Alameda Creek, artesian wells in Pleasanton (Hetch Hetchy reservoir in Yosemite since 1923); owned/operated by private company -- Spring Valley Water Co	No	http://www.sfmuseum.org/hist3/perry.html
Toledo	OH	Maumee River; filtration plant upstream of Broadway Pumping Station began operation in 1910; source changed to Lake Erie in 1940s	Yes (Filtration, Chlorination)	http://www.ci.toledo.oh.us/Departments/PublicUtilities/DivisionofWaterTreatment/HistoryofWaterTreatmentinToledo/tabid/375/Default.aspx
Washington, D.C.	-	Potomac River via Washington Aqueduct; McMillan Reservoir and Bryant Street high-lift pump after 1905	Yes (Filtration, Chlorination)	https://www.dcwater.com/history-water-system

S2 Table. Initial and estimated values for main TSIR models. Initial parameters (median susceptible population, median overall population, infectious, susceptible, and newborn populations) and values estimated from the TSIR models (chronic carriers, underreporting factors, and heterogeneous mixing parameters) are shown for each city.

	Median values		**Initial Values (at time 0)**			**Estimated from model**		
	Median susceptible population over time period	*Median population over time period*	*Infectious Population (after adjusting for underreporting)*	*Susceptible population*	*Births*	*Number of chronic carriers*	*Underreporting factor (ρ)*	*Heterogeneous mixing parameter (α)*
Baltimore	84000	672000	908	443653	670	87.4	0.017	0.25
Boston	70125	561000	597	425614	725	173.9	0.014	-0.27
Chicago	273750	2190000	214	973056	2147	19.9	0.023	0.18
Cincinnati	45500	364000	412	281345	517	112.8	0.022	0.11
Cleveland	70563	564500	747	266174	476	5.1	0.017	0.07
Milwaukee	46875	375000	419	180566	432	3.8	0.01	0.04
Nashville	13750	110000	158	66245	112	78.1	0.025	-0.4
New Orleans	42500	340000	140	227335	393	204	0.014	0.59
New York	597500	4780000	7335	3006890	8059	43.5	0.005	0.39
Philadelphia	193750	1550000	1803	1024268	1738	170.5	0.021	0.41
Pittsburgh	66875	535000	602	190287	658	58.9	0.022	0.31
Providence	28125	225000	249	118344	190	0	0.016	0.09
Saint Louis	86000	688000	684	431141	802	213.3	0.012	0.29
San Francisco	52250	418000	469	277260	368	46	0.017	-0.1
Toledo	21250	170000	76	85298	144	0	0.013	0.04
Washington, D.C.	41625	333000	157	244920	340	0	0.038	0.25

S3 Table. Harmonic regression analyses of typhoid mortality data pre- and post- water supply intervention. Time trends and seasonal amplitudes were estimated for each city pre- and post- intervention in preliminary analyses with harmonic regression. Values shown in grey were not statistically significant at the 0.05-level, while values in black had p-values<0.05. In the last column, the ratio (post-/pre- water supply intervention) was calculated from the six-month and one-year amplitudes estimated from the regression models.

	Pre-Intervention				**Post-Intervention**				*Ratio (Post/Pre)*	
	Time trend		*Seasonal Amplitude*		*Time trend*		*Seasonal Amplitude*		*of Seasonal Amplitude*	
	intercept	*slope*	*6-mo.*	*1-yr.*	*intercept*	*slope*	*6-mo.*	*1-yr* .	*6-mo.*	*1-yr.*
Baltimore	-3.35	0	0.15	0.62	76.94	-0.04	0.08	0.24	0.49	0.39
Boston	27.1	-0.01	0.22	0.55	25.75	-0.01	0.04	0.07	0.19	0.13
Chicago	27.78	-0.01	0.14	0.26	141.03	-0.07	0.04	0.18	0.32	0.68
Cincinnati	-18.04	0.01	0.15	0.18	4.85	0	0	0.02	0.03	0.1
Cleveland	41.5	-0.02	0.15	0.08	17.29	-0.01	0.04	0.06	0.25	0.67
Milwaukee	2.28	0	0.02	0.07	27.95	-0.01	0.04	0.06	1.91	0.81
Nashville	-11.36	0.01	0.06	0.17	12.44	-0.01	0.07	0.14	1.16	0.83
New Orleans	-151.79	0.08	0.14	0.13	43.97	-0.02	0.14	0.2	0.97	1.51
New York	-23.7	0.01	0.12	0.74	162.4	-0.08	0.11	0.47	0.88	0.64
Philadelphia	27.96	-0.01	0.17	0.16	199.33	-0.1	0.05	0.04	0.32	0.24
Pittsburgh	-154.97	0.08	0.14	0.23	64.03	-0.03	0.04	0.11	0.31	0.49
Providence	12.81	-0.01	0.03	0.12	7.48	0	0.01	0.03	0.43	0.26
Saint Louis	31.39	-0.02	0.21	0.47	43.31	-0.02	0.09	0.24	0.43	0.51
San Francisco	16.32	-0.01	0.08	0.21	20.84	-0.01	0.02	0.04	0.26	0.18
Toledo	-25.43	0.01	0.06	0.12	26.07	-0.01	0.03	0.08	0.5	0.66
Washington, D.C.	15.94	-0.01	0.07	0.64	53.81	-0.03	0.05	0.17	0.77	0.26

S4 Table. Estimates of seasonal transmission from TSIR models, with confidence intervals. Results of the seasonal transmission parameters estimated from the TSIR models are shown. In the top half of the table, the estimated values for each four-week month's typhoid transmission compared to the 13th month are shown with their 95% confidence intervals, by city. Estimates with confidence intervals that are entirely below one are shown in red, and those with confidence intervals entirely above one are shown in blue. In the bottom half of the table, the percentage of each water type with confidence intervals entirely below or above one are shown for each month, highlighted from lighter to darker red or blue indicating the magnitude of the percentage.

City	Month / Water Type	1	2	3	4	5	6	7	8	9	10	11	12
Baltimore	*Reservoir*	0.78 (0.63-0.97)	0.82 (0.66-1.02)	1.01 (0.81-1.26)	1.03 (0.83-1.27)	0.78 (0.63-0.97)	1.16 (0.94-1.44)	1.34 (1.08-1.66)	1.63 (1.31-2.02)	1.77 (1.42-2.20)	1.68 (1.35-2.10)	1.38 (1.11-1.72)	0.95 (0.76-1.17)
Boston	*Reservoir*	0.97 (0.76-1.24)	1.03 (0.80-1.32)	1.03 (0.80-1.33)	1.03 (0.80-1.32)	0.98 (0.76-1.26)	0.98 (0.76-1.26)	1.1 (0.86-1.42)	1.52 (1.18-1.95)	1.57 (1.22-2.03)	1.56 (1.21-2.02)	1.01 (0.78-1.30)	1.02 (0.79-1.31)
Chicago	*Great Lake*	0.75 (0.61-0.93)	0.9 (0.73-1.12)	0.58 (0.47-0.72)	0.77 (0.62-0.95)	0.75 (0.61-0.93)	0.88 (0.71-1.09)	1.06 (0.86-1.31)	1.34 (1.08-1.65)	1.07 (0.87-1.32)	1.15 (0.94-1.42)	0.92 (0.74-1.13)	1.13 (0.92-1.39)
Cincinnati	*River*	1.04 (0.84-1.28)	0.93 (0.75-1.15)	1 (0.81-1.24)	0.99 (0.80-1.22)	0.94 (0.76-1.17)	1.01 (0.82-1.25)	1.38 (1.12-1.71)	1.09 (0.88-1.35)	1.17 (0.94-1.44)	1.14 (0.92-1.41)	1.05 (0.85-1.30)	1.25 (1.01-1.55)
Cleveland	*Great Lake*	0.83 (0.67-1.02)	1.05 (0.85-1.30)	0.91 (0.73-1.12)	0.94 (0.76-1.15)	1.16 (0.94-1.43)	0.8 (0.65-0.99)	1.14 (0.93-1.41)	1.62 (1.31-1.99)	1.66 (1.34-2.04)	1.4 (1.13-1.74)	0.88 (0.71-1.10)	1.15 (0.93-1.42)
Milwaukee	*Great Lake*	0.81 (0.65-0.99)	1.05 (0.86-1.30)	0.94 (0.77-1.16)	0.98 (0.80-1.21)	0.87 (0.71-1.08)	0.84 (0.68-1.04)	0.93 (0.75-1.15)	1.04 (0.85-1.29)	0.97 (0.78-1.19)	0.9 (0.73-1.11)	0.89 (0.73-1.10)	0.81 (0.66-1.00)
Nashville	*River*	0.81 (0.65-0.99)	0.69 (0.56-0.85)	0.69 (0.56-0.85)	0.78 (0.63-0.96)	0.74 (0.60-0.91)	1.43 (1.16-1.77)	2.16 (1.74-2.68)	2.53 (2.01-3.17)	1.92 (1.53-2.41)	2.01 (1.63-2.49)	1.54 (1.24-1.91)	1.06 (0.86-1.31)
New Orleans	*River*	0.63 (0.49-0.80)	0.68 (0.53-0.87)	0.78 (0.61-1.00)	0.72 (0.56-0.92)	1.01 (0.79-1.30)	1.07 (0.84-1.37)	1.44 (1.12-1.84)	1.17 (0.92-1.50)	0.73 (0.57-0.93)	0.73 (0.57-0.94)	0.95 (0.75-1.22)	1.2 (0.94-1.54)
New York	*Reservoir*	1.07 (0.91-1.27)	1.14 (0.96-1.35)	1.13 (0.95-1.34)	1.13 (0.95-1.34)	1.19 (1.00-1.40)	1.56 (1.32-1.84)	2.31 (1.96-2.72)	2.91 (2.47-3.44)	2.36 (1.99-2.79)	1.93 (1.63-2.29)	1.5 (1.27-1.77)	1.51 (1.28-1.77)
Philadelphia	*River*	0.83 (0.70-0.98)	0.81 (0.68-0.95)	0.88 (0.75-1.04)	0.95 (0.81-1.13)	1 (0.85-1.19)	0.86 (0.72-1.01)	1.07 (0.91-1.27)	1.16 (0.98-1.37)	1.28 (1.09-1.52)	0.95 (0.80-1.12)	1.07 (0.90-1.26)	0.87 (0.74-1.03)
Pittsburgh	*River*	0.88	0.7	0.63	0.65	0.78	0.84	1.19	1.26	1.22	1.34	1.22	0.85

		(0.71-1.10)	(0.57-0.88)	(0.50-0.78)	(0.52-0.81)	(0.63-0.98)	(0.67-1.04)	(0.95-1.48)	(1.01-1.58)	(0.98-1.52)	(1.07-1.67)	(0.97-1.52)	(0.68-1.05)
Providence	*River*	0.77	0.96	0.85	0.87	0.78	0.67	0.96	0.89	0.94	0.94	0.96	1.1
		(0.63-0.95)	(0.78-1.18)	(0.69-1.04)	(0.70-1.07)	(0.64-0.96)	(0.54-0.82)	(0.77-1.18)	(0.72-1.09)	(0.76-1.16)	(0.77-1.16)	(0.78-1.18)	(0.90-1.36)
Saint Louis	*River*	1.04	1.51	1.58	1.61	1.39	1.66	2.09	2.47	2.07	1.92	1.81	1.17
		(0.84-1.29)	(1.21-1.87)	(1.27-1.96)	(1.30-2.00)	(1.12-1.73)	(1.33-2.06)	(1.69-2.60)	(1.98-3.09)	(1.65-2.61)	(1.53-2.41)	(1.46-2.25)	(0.94-1.46)
San Francisco	*Reservoir*	0.94	1.19	1.14	1.35	1.48	1.25	1.15	1.17	1.37	1.53	1.54	1.42
		(0.75-1.17)	(0.95-1.49)	(0.91-1.43)	(1.08-1.69)	(1.18-1.85)	(1.00-1.57)	(0.92-1.44)	(0.94-1.47)	(1.10-1.71)	(1.22-1.91)	(1.23-1.92)	(1.14-1.77)
Toledo	*River*	0.97	1.35	1.16	1.06	0.79	0.89	1.16	1.46	2.02	1.74	1.15	1.21
		(0.79-1.18)	(1.10-1.65)	(0.95-1.42)	(0.87-1.30)	(0.65-0.97)	(0.72-1.09)	(0.95-1.41)	(1.20-1.78)	(1.66-2.46)	(1.43-2.12)	(0.94-1.40)	(0.99-1.47)
Washington, D.C.	*River*	0.92	0.89	0.97	0.91	0.93	0.89	1.08	1.05	1.04	1.07	0.87	0.95
		(0.73-1.16)	(0.71-1.12)	(0.77-1.22)	(0.72-1.14)	(0.74-1.17)	(0.71-1.11)	(0.86-1.35)	(0.83-1.32)	(0.82-1.30)	(0.85-1.34)	(0.69-1.09)	(0.76-1.19)
% of confidence intervals below 1	*% of (4) Reservoirs*	25%	0%	0%	0%	25%	0%	0%	0%	0%	0%	0%	0%
	% of (3) Great Lakes	67%	0%	33%	33%	33%	33%	0%	0%	0%	0%	0%	0%
	% of (9) Rivers	44%	44%	33%	33%	44%	11%	0%	0%	11%	11%	0%	0%
	% of (16) All	44%	25%	25%	25%	38%	13%	0%	0%	6%	6%	0%	0%
% of confidence intervals above 1	*% of (4)Reservoirs*	0%	0%	0%	25%	50%	50%	25%	75%	100%	100%	75%	75%
	% of (3) Great Lakes	0%	0%	0%	0%	0%	0%	0%	67%	33%	33%	0%	0%
	% of (9) Rivers	0%	22%	11%	11%	11%	22%	44%	44%	44%	44%	22%	11%
	% of (16) All	0%	13%	6%	13%	19%	25%	31%	56%	56%	56%	31%	19%

S5 Table. Variability in long-term typhoid transmission explained by financial water supply and sewer system variables. Values shown are the conditional and marginal R^2 from the hierarchical linear regression analyses for each financial variable.

	Marginal R^2	Conditional R^2
Receipts: Water supply	0.00	0.85
Expenses: Water supply	0.01	0.86
Expenses: Sewer system	0.01	0.84
Outlays: Water supply	0.01	0.87
Outlays: Sewer system	0.01	0.88
Value: Water supply	0.00	0.91
Funded debt: Water supply	0.01	0.93
Funded debt: Sewer system	0.04	0.93
Overall investment: Water supply	0.33	0.98
Overall investment: Sewer system	0.28	0.98

S6 Table. Random and fixed effects for associations between yearly average long-term typhoid transmission and investments in water and sewer systems for individual financial variables. Each estimate shows the associated change (and 95% confidence interval) in typhoid transmission for each $1 (1931 US$) per capita increase in the financial variable for the water supply (WS) and sewer system (SS) for fixed and random effects. No data were available for Washington, D.C. for the variables Funded Debt of the Water Supply System or Funded Debt of the Sewer System.

	Receipts: Water supply	*Expenses: Water supply*	*Expenses: Sewer system*	*Outlays: Water supply*	*Outlays: Sewer system*	*Value: Water supply*	*Funded debt: Water supply*	*Funded debt: Sewer system*	*Overall investment: Water supply*	*Overall investment: Sewer system*
Baltimore	0.57 (0.38-0.86)	0.76 (0.45-1.33)	1.05 (0.72-1.55)	0.94 (0.81-1.08)	1.05 (0.87-1.26)	0.98 (0.96-1.00)	0.99 (0.95-1.04)	0.98 (0.93-1.02)	0.95 (0.93-0.96)	0.97 (0.95-0.99)
Boston	1.59 (1.15-2.22)	0.70 (0.40-1.22)	1.35 (0.82-2.18)	0.95 (0.84-1.07)	1.53 (1.10-2.12)	1.02 (0.99-1.05)	1.12 (1.06-1.19)	1.06 (1.01-1.12)	0.94 (0.92-0.96)	0.93 (0.91-0.96)
Chicago	1.15 (0.71-1.84)	0.79 (0.46-1.35)	0.46 (0.27-0.80)	1.05 (0.88-1.24)	0.77 (0.62-0.96)	1.02 (0.97-1.07)	1.03 (0.93-1.13)	0.95 (0.90-1.00)	0.91 (0.90-0.93)	0.95 (0.92-0.97)
Cincinnati	0.71 (0.47-1.09)	1.21 (0.70-2.10)	1.44 (0.69-2.99)	1.16 (1.03-1.30)	0.98 (0.69-1.41)	1.02 (0.99-1.04)	1.02 (0.98-1.06)	0.92 (0.87-0.98)	0.96 (0.94-0.97)	0.95 (0.92-0.97)
Cleveland	0.66 (0.47-0.93)	0.43 (0.27-0.69)	1.99 (0.93-4.25)	0.97 (0.88-1.08)	0.77 (0.59-1.02)	0.94 (0.91-0.97)	0.91 (0.87-0.95)	1.12 (1.05-1.20)	0.97 (0.95-0.98)	0.94 (0.92-0.97)
Milwaukee	0.58 (0.40-0.84)	0.57 (0.37-0.87)	0.73 (0.44-1.20)	0.98 (0.83-1.16)	0.85 (0.72-1.00)	1.02 (0.98-1.06)	1.03 (0.93-1.15)	0.97 (0.93-1.01)	0.93 (0.92-0.95)	0.98 (0.96-1.00)
Nashville	0.93 (0.58-1.52)	0.38 (0.21-0.67)	1.73 (0.72-4.12)	0.91 (0.79-1.05)	0.89 (0.63-1.26)	1.02 (1.00-1.04)	1.01 (0.95-1.07)	0.84 (0.77-0.93)	0.92 (0.90-0.93)	0.82 (0.79-0.85)
New Orleans	0.82 (0.52-1.28)	0.84 (0.46-1.52)	0.85 (0.46-1.52)	1.04 (0.95-1.14)	0.99 (0.83-1.19)	0.99 (0.96-1.01)	1.00 (0.96-1.03)	1.02 (0.97-1.07)	0.97 (0.96-0.99)	0.98 (0.96-1.01)
New York	1.25 (0.78-1.97)	1.19 (0.60-2.33)	1.14 (0.63-2.12)	1.08 (0.97-1.20)	0.79 (0.51-1.23)	0.99 (0.97-1.01)	0.98 (0.94-1.02)	1.00 (0.88-1.14)	0.98 (0.97-1.00)	0.93 (0.90-0.96)
Philadelphia	1.73 (1.16-2.55)	2.02 (1.28-3.17)	1.34 (0.69-2.58)	1.16 (1.00-1.33)	0.68 (0.51-0.91)	1.04 (1.01-1.06)	1.07 (1.02-1.13)	0.93 (0.88-0.98)	0.92 (0.91-0.94)	0.93 (0.91-0.96)
Pittsburgh	0.78 (0.54-1.12)	0.37 (0.23-0.58)	2.14 (1.02-4.54)	1.23 (1.11-1.37)	0.79 (0.54-1.18)	0.99 (0.97-1.01)	1.05 (1.01-1.09)	0.89 (0.82-0.98)	0.94 (0.93-0.95)	0.85 (0.82-0.88)
Providence	1.05 (0.72-1.56)	0.85 (0.51-1.41)	0.99 (0.45-2.21)	0.96 (0.88-1.05)	0.83 (0.61-1.12)	0.99 (0.96-1.02)	0.99 (0.96-1.02)	1.04 (0.99-1.09)	0.98 (0.97-1.00)	0.95 (0.92-0.98)
Saint Louis	0.93 (0.73-1.19)	0.78 (0.51-1.20)	1.95 (0.94-4.06)	0.98 (0.92-1.05)	1.11 (0.91-1.34)	0.99 (0.97-1.00)	0.99 (0.96-1.02)	0.96 (0.90-1.04)	0.99 (0.98-1.01)	0.94 (0.92-0.97)
San Francisco	1.22 (0.78-1.88)	0.72 (0.35-1.45)	1.28 (0.72-2.28)	1.02 (0.90-1.15)	0.91 (0.73-1.15)	1.01 (0.99-1.03)	1.00 (0.94-1.06)	0.95 (0.88-1.02)	0.97 (0.96-0.99)	0.97 (0.94-0.99)
Toledo	0.74 (0.54-1.02)	0.63 (0.40-0.98)	1.25 (0.59-2.68)	1.06 (0.91-1.23)	0.83 (0.65-1.06)	0.99 (0.95-1.03)	1.06 (1.00-1.13)	0.95 (0.91-1.00)	0.97 (0.95-0.98)	0.95 (0.93-0.98)
Washington, D.C.	1.09 (0.64-1.79)	0.94 (0.57-1.54)	1.33 (0.73-2.42)	1.02 (0.95-1.09)	1.22 (0.95-1.56)	1.00 (0.99-1.02)	--	--	0.98 (0.97-0.99)	0.94 (0.92-0.97)
Average (Fixed) Effects	0.94 (0.76-1.17)	0.75 (0.56-1.00)	1.23 (0.90-1.72)	1.03 (0.97-1.10)	0.92 (0.79-1.06)	1.00 (0.98-1.01)	1.01 (0.98-1.05)	0.97 (0.93-1.01)	0.96 (0.94-0.97)	0.94 (0.91-0.96)

S7 Table. Fit of the TSIR models to within- and out-of-sample data for each city. Variability in typhoid deaths explained (R^2) by TSIR models fit to data for the full study period (1889-1931) is shown, along with the within-sample mean squared errors (MSE) for 1922-1926 (i.e. the last five years of within-sample data used to generate the prediction model), the out-of-sample mean squared prediction errors (MSPE) for 1927-1931 (i.e. the out-of-sample data), and their ratio (MSPE/MSE) for comparison.

City	R^2 (full model fit)	MSE (within-sample)	MSPE (out-of-sample)	Ratio (MSPE/ MSE)
Baltimore	0.64	3.53	3.84	1.09
Boston	0.64	2.56	0.71	0.28
Chicago	0.86	8.1	1.85	0.23
Cincinnati	0.71	0.98	0.65	0.66
Cleveland	0.73	1.28	6.55	5.13
Milwaukee	0.56	0.54	0.21	0.39
Nashville	0.48	2.82	2.14	0.76
New Orleans	0.5	7.52	14.7	1.96
New York	0.86	39.59	38.17	0.96
Philadelphia	0.9	4.57	6.56	1.44
Pittsburgh	0.82	1.01	1.32	1.3
Providence	0.45	0.3	0.39	1.31
Saint Louis	0.6	2.43	1.8	0.74
San Francisco	0.61	0.88	1.9	2.16
Toledo	0.52	0.83	0.73	0.88
Washington, D.C.	0.74	0.04	0	0

S8 Table. Sensitivity analyses for hierarchical regression: Random and fixed effects for yearly average long-term typhoid transmission vs. overall investments in the water supply system. Each estimate shows the associated multiplicative change in the estimated long-term typhoid transmission rate for each $1 per capita increase in overall investment for the water supply system (in 1931 US dollars) for each model fit. Both random and fixed effects are shown, with their 95% confidence intervals.

Effect	City	Main Model (imputation 13 weeks, +1 to deaths)	Imputation 8 weeks	Imputation 26 weeks	+0.5 to deaths	1-year immunity	No waning of immunity
Random + Fixed	**Baltimore**	0.95 (0.93-0.96)	0.95 (0.94-0.97)	0.95 (0.93-0.97)	0.93 (0.91-0.95)	0.96 (0.95-0.97)	0.96 (0.95-0.98)
	Boston	0.94 (0.93-0.96)	0.93 (0.92-0.95)	0.94 (0.92-0.96)	0.93 (0.91-0.95)	0.95 (0.93-0.96)	0.96 (0.95-0.97)
	Chicago	0.91 (0.90-0.93)	0.91 (0.89-0.92)	0.91 (0.89-0.93)	0.90 (0.88-0.92)	0.93 (0.92-0.94)	0.93 (0.92-0.94)
	Cincinnati	0.95 (0.94-0.97)	0.96 (0.94-0.97)	0.96 (0.94-0.98)	0.94 (0.92-0.96)	0.96 (0.94-0.97)	0.96 (0.95-0.97)
	Cleveland	0.97 (0.95-0.98)	0.97 (0.95-0.98)	0.96 (0.94-0.98)	0.96 (0.94-0.98)	0.98 (0.97-0.99)	0.98 (0.97-0.99)
	Milwaukee	0.93 (0.91-0.94)	0.93 (0.91-0.94)	0.94 (0.91-0.96)	0.91 (0.88-0.93)	0.93 (0.92-0.95)	0.95 (0.93-0.96)
	Nashville	0.91 (0.90-0.93)	0.91 (0.90-0.93)	0.91 (0.89-0.93)	0.90 (0.88-0.92)	0.96 (0.94-0.97)	0.97 (0.96-0.98)
	New Orleans	0.97 (0.95-0.99)	0.97 (0.95-0.99)	0.97 (0.95-1.00)	0.97 (0.94-0.99)	0.98 (0.96-0.99)	0.98 (0.97-0.99)
	New York	0.98 (0.97-1.00)	0.98 (0.96-0.99)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.97-0.99)	0.98 (0.98-0.99)
	Philadelphia	0.93 (0.91-0.95)	0.92 (0.90-0.93)	0.87 (0.85-0.89)	0.92 (0.90-0.94)	0.94 (0.93-0.95)	0.94 (0.93-0.95)
	Pittsburgh	0.94 (0.92-0.95)	0.94 (0.93-0.96)	0.91 (0.89-0.93)	0.88 (0.86-0.90)	0.95 (0.93-0.96)	0.96 (0.95-0.97)
	Providence	0.98 (0.97-1.00)	0.98 (0.97-1.00)	0.99 (0.97-1.01)	0.98 (0.96-1.00)	0.99 (0.98-1.00)	0.99 (0.98-1.00)
	Saint Louis	0.99 (0.98-1.00)	0.99 (0.97-1.00)	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.99 (0.98-1.00)	0.99 (0.98-1.00)
	San Francisco	0.98 (0.96-0.99)	0.97 (0.96-0.99)	0.97 (0.95-0.99)	0.97 (0.95-0.99)	0.97 (0.96-0.99)	0.97 (0.96-0.98)
	Toledo	0.96 (0.95-0.98)	0.96 (0.94-0.98)	0.97 (0.94-0.99)	0.95 (0.93-0.97)	0.96 (0.95-0.97)	0.96 (0.95-0.97)
	Washington, D.C.	0.98 (0.97-0.99)	0.98 (0.97-1.00)	0.98 (0.96-1.00)	0.98 (0.96-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)
Fixed	-	0.95 (0.94-0.97)	0.95 (0.94-0.97)	0.95 (0.93-0.97)	0.94 (0.93-0.96)	0.96 (0.95-0.97)	0.97 (0.96-0.98)

S9 Table. Sensitivity analyses for hierarchical regression: Random and fixed effects for yearly average long-term typhoid transmission vs. overall investments in the sewer system. Each estimate shows the associated multiplicative change in the estimated long-term typhoid transmission rate for each $1 per capita increase in overall investment for the sewer system (in 1931 US dollars) for each model fit. Both random and fixed effects are shown, with their 95% confidence intervals.

Effect	City	Main Model (imputation 13 weeks, +1 to deaths)	Imputation 8 weeks	Imputation 26 weeks	+0.5 to deaths	1-year immunity	No waning of immunity
Random	**Baltimore**	0.97 (0.95-0.99)	0.97 (0.95-1.00)	0.97 (0.94-1.00)	0.96 (0.93-1.00)	0.98 (0.96-0.99)	0.98 (0.97-0.99)
	Boston	0.93 (0.91-0.96)	0.92 (0.90-0.95)	0.93 (0.90-0.97)	0.92 (0.88-0.96)	0.94 (0.92-0.95)	0.95 (0.94-0.97)
	Chicago	0.95 (0.92-0.97)	0.94 (0.92-0.97)	0.95 (0.92-0.98)	0.94 (0.91-0.98)	0.96 (0.94-0.97)	0.96 (0.95-0.97)
	Cincinnati	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.99)	0.93 (0.89-0.97)	0.95 (0.93-0.97)	0.95 (0.94-0.97)
	Cleveland	0.94 (0.92-0.97)	0.94 (0.92-0.97)	0.94 (0.91-0.97)	0.93 (0.90-0.97)	0.96 (0.95-0.98)	0.97 (0.96-0.98)
	Milwaukee	0.98 (0.96-1.00)	0.98 (0.95-1.00)	0.98 (0.95-1.01)	0.97 (0.94-1.01)	0.98 (0.97-1.00)	0.99 (0.97-1.00)
	Nashville	0.82 (0.79-0.85)	0.82 (0.79-0.85)	0.82 (0.78-0.86)	0.80 (0.76-0.84)	0.90 (0.88-0.93)	0.94 (0.92-0.96)
	New Orleans	0.98 (0.96-1.01)	0.98 (0.96-1.01)	0.98 (0.95-1.02)	0.98 (0.94-1.02)	0.99 (0.97-1.01)	0.99 (0.97-1.00)
	New York	0.93 (0.90-0.96)	0.91 (0.88-0.94)	0.93 (0.89-0.97)	0.92 (0.88-0.97)	0.92 (0.90-0.94)	0.93 (0.92-0.95)
	Philadelphia	0.93 (0.91-0.96)	0.92 (0.90-0.95)	0.89 (0.85-0.92)	0.92 (0.89-0.96)	0.94 (0.92-0.96)	0.94 (0.93-0.96)
	Pittsburgh	0.85 (0.82-0.88)	0.85 (0.83-0.88)	0.79 (0.76-0.83)	0.73 (0.70-0.77)	0.87 (0.84-0.89)	0.89 (0.87-0.91)
	Providence	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.99)	0.93 (0.90-0.98)	0.96 (0.94-0.98)	0.96 (0.95-0.98)
	Saint Louis	0.94 (0.92-0.97)	0.94 (0.91-0.96)	0.95 (0.92-0.98)	0.92 (0.88-0.96)	0.95 (0.93-0.96)	0.96 (0.94-0.97)
	San Francisco	0.97 (0.94-0.99)	0.97 (0.94-0.99)	0.96 (0.93-1.00)	0.96 (0.92-1.00)	0.97 (0.95-0.98)	0.97 (0.95-0.98)
	Toledo	0.95 (0.93-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.99)	0.94 (0.90-0.98)	0.95 (0.93-0.97)	0.95 (0.94-0.97)
	Washington, D.C.	0.94 (0.92-0.97)	0.94 (0.92-0.97)	0.95 (0.91-0.98)	0.93 (0.89-0.97)	0.94 (0.93-0.96)	0.95 (0.93-0.96)
Fixed	-	0.94 (0.91-0.96)	0.93 (0.91-0.96)	0.93 (0.90-0.96)	0.92 (0.88-0.95)	0.95 (0.93-0.96)	0.95 (0.94-0.97)

S10 Table. Heterogeneous mixing from sensitivity analyses for assumptions of waning immunity, chronic carriers, or using a simple TSIR model. Values are shown for each city and assumption. The second column shows the heterogeneous mixing parameter value in the final models fit, the "No K" column shows the value for models fit without including waning immunity, the "No C" column shows the value for models excluding chronic carriers as part of the transmission process, the "No K, No C" column shows the values for models excluding both waning immunity and chronic carrier populations, and the last column ("Simple TSIR Model") shows the value for models fit using ordinary least squares regression and does not use splines or smoothing weights.

	Final Model Used	No K	No C	No K, No C	Simple TSIR Model
Baltimore	0.25	0.42	0.17	0.29	0.17
Boston	-0.27	0.29	-0.08	0.14	0.2
Chicago	0.18	0.21	0.15	0.18	0.28
Cincinnati	0.11	0.56	0.08	0.31	0.4
Cleveland	0.07	0.24	0.08	0.23	0.22
Milwaukee	0.04	0.29	0.01	0.28	0.13
Nashville	-0.4	0.05	-0.05	0.05	0.07
New Orleans	0.59	0.53	0.25	0.28	0.28
New York	0.39	0.61	0.37	0.41	0.35
Philadelphia	0.41	0.74	0.27	0.5	0.51
Pittsburgh	0.31	0.43	0.2	0.33	0.34
Providence	0.09	0.12	0.09	0.12	0.01
Saint Louis	0.29	0.23	0.07	0.12	0.14
San Francisco	-0.1	0.14	-0.06	0.09	0.07
Toledo	0.04	0.05	0.05	0.05	-0.03
Washington, D.C.	0.25	0.28	0.25	0.28	0.18

Conclusion

This dissertation was innovative in both its methods and conclusions. The approaches we have taken allowed us to gain insights that otherwise would have been difficult to obtain. A variety of statistical and mathematical modelling made it possible to evaluate the cost-effectiveness of typhoid interventions in different settings. In this dissertation, we have estimated the true population-based incidence of typhoid fever in Africa and Asia; weighed the costs and effects of vaccination strategies in an outbreak setting; and estimated the impact of water and sanitation investments in a historical endemic setting. Governments are always looking to prioritize their allocation of resources for typhoid control. These findings fill in some gaps in knowledge and can help to inform decision-making for typhoid control and prevention.