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Cost-effectiveness of using environmental surveillance to target the roll-out typhoid conjugate vaccine

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1. Introduction

Since the prequalification of the Typhoid conjugate vaccine (TCV) by the WHO and subsequent position paper published in 2018, strategies for roll-out of the vaccine have been under discussion [1]. The 2018 position paper recommends the introduction of TCV to be prioritized in countries with the highest burden of typhoid disease or a high burden of antimicrobial resistant S. Typhi [1]. The paper further suggests that "Decisions on the age of TCV administration, target population and delivery strategy for routine and catch-up vaccination should be based on the local epidemiology of typhoid fever…". However, local epidemiology of typhoid fever is often poorly documented, due to the paucity of diagnostic facilities in many high typhoid incidence settings. However, most low- and middle income- countries (LMIC) rely on ad hoc reporting of typhoid fever, and very few have data from more than one city in the country. There have been substantial efforts aimed at strengthening blood culture surveillance for typhoid fever in Africa [2], yet there are still only 13 sentinel sites in 10 countries; a similar initiative in Asia covers only four countries [3]. Data sets that are utilized to estimate global burden are therefore limited by the lack of surveillance [4–7]. Based on the prohibitive costs [2] and efforts required to strengthen blood culture surveillance in LMIC, expansion of these efforts to capture both national and sub-national trends of typhoid on a global scale are not likely on a time scale relevant to vaccine roll-out.

Incidence mapping using statistical models can aid in predicting incidence in areas without surveillance, using spatial covariates relevant to risk of disease, and has been used for diseases such as malaria [8]. This approach has been attempted for typhoid through global burden models [4], but out-of-sample validation, though accurate in some areas, was not reliable, indicating a lack of useful indicators that can be consistently used to predict typhoid incidence. Further, the current breadth of data is heavily biased by reporting from a handful of well-funded sites, so predicting sub-national incidence across large regions is a challenge. A country's ability to roll out TCV in accordance with the WHO's position paper is therefore hindered by a lack of knowledge of local epidemiology of the disease. Additionally, Gavi, The Vaccine Alliance, recommends that countries requesting TCV funding should submit epidemiological data from within-country whenever possible, though this is not strictly a requirement.

Alternative tools are needed for planning TCV strategies in the absence of blood culture surveillance. Of particular interest is environmental surveillance, where, instead of relying on clinical detection of the disease, catchments in the environment such as water or sewage systems are surveilled. This approach has been successfully used in the polio eradication campaign. [9] Though case-based surveillance for polio is widespread, the disease is known to undergo sub-clinical (silent) transmission. ES has enabled detection when there is not a known outbreak and has been demonstrated to be a useful tool in program decision making [10,11]. Since typhoid and polio share similarities with regards to transmission routes and sub-clinical disease, it is possible that the approach and the network of laboratories developed for polio could be adapted for typhoid.

There remain significant technical challenges to implementing typhoid environmental surveillance (ES); optimal sampling strategies and detection methods, and their reliability as an indicator of ongoing transmission, remain unclear. Historically, Moore swabs have been used to isolate *S.* Typhi from sewage [12,13], however present day ES initiatives have been more focused on molecular approaches, specifically polymerase chain reaction (PCR)-based detection of *S* Typhi [14–16].

Economic analyses have largely supported the cost-effectiveness of the roll out of TCV in high and medium- incidence areas, particularly when routine vaccination strategies are paired with catch-up campaigns [17,18], however, there is more uncertainty around

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cost-effectiveness in low-incidence areas [19]. In this study, we examine the use of a hypothetical environmental surveillance program as a method for quickly gathering evidence on which an introduction decision can be based. This is especially relevant in places where there are inadequate burden estimates or in which a national introduction may not be affordable due to funding constraints or competing priorities. Specifically, we evaluate the value of environmental sampling as a means of detecting circulating typhoid in order to guide local or national targeting of catch-up vaccination campaigns. We aim to determine the most cost-effective sampling and roll-out strategies, given the limited information and substantial uncertainty about the true underlying prevalence of typhoid.

2. Methods

This was a simulation study with an integrated epidemiological and economic model, which was used to evaluate the cost-effectiveness of surveillance and vaccination strategies.

2.1. Mathematical model structure

Disease transmission mechanisms and individual-level immunity were simulated using an individual-based mathematical model, EMOD [20], with detailed model structure and assumptions previously described [21], outlined in Fig. 1A, and included in the supplement. Briefly, the model assumes typhoid fever infections may be acute or subclinical after an incubation period, with a proportion of cases becoming chronic carriers, which is assumed to be a lifelong state. We simulate two distinct transmission routes, short- and long-cycle. Short-cycle transmission represents infections acquired from food or water contaminated by an individual in the immediate environment (i.e. household or school), while long-cycle transmission indicates infections acquired from exposure to S. Typhi in the environment, which could include drinking contaminated water or exposure to sewage. Infectious individuals shed into simulated composite of contaminated vehicles of transmission, or CCVT, for each transmission route. The probability of

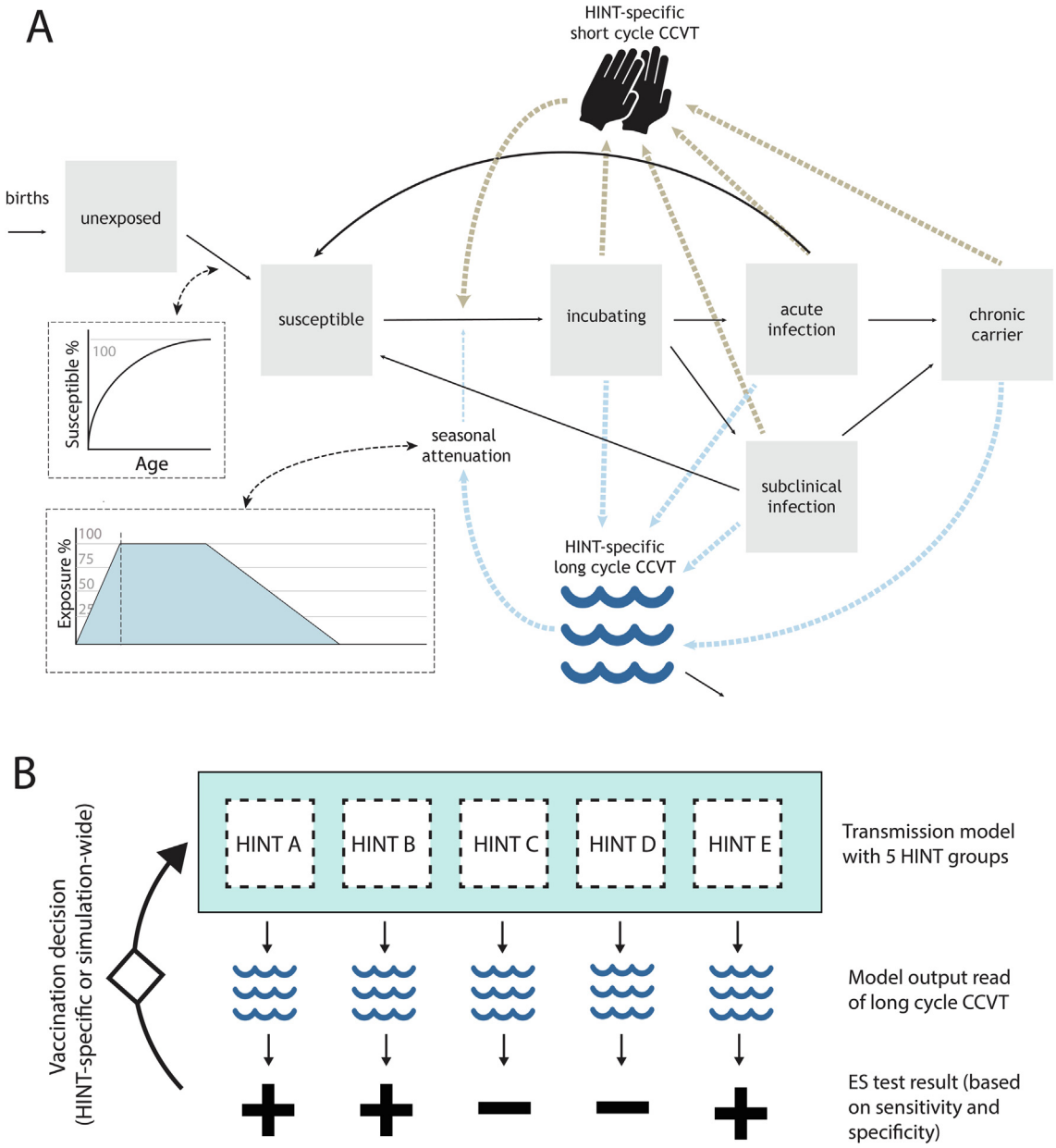

Fig. 1. A. Disease transmission model structure. B. HINT structure and environmental surveillance mechanism.

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infection is calculated by a dose-response function for long-cycle exposures using population-scaled CCVT as a simulated 'dose' [22], while for the short-cycle, the probability of infection is calculated as the population-scaled short-cycle CCVT divided by the total potential short-cycle CCVT. Long-cycle exposure is mediated by seasonal attenuation, and we reduce proportion of children born into the simulation who become susceptible- these parameters are estimated through model fitting

One primary modification was made to the model for this study. We adapted the model to allow us to divide the simulated population into pre-specified transmission groups, referred to as heterogeneous intra-node transmission (HINT) groups (Fig. 1B). Transmission rates within and between HINT groups can be modified, with within-HINT transmission altered as a multiplier on both the long- and short-cycle CCVT. We utilized this feature to simulate a heterogenous disease landscape within a single simulation model. When we attempt to represent typhoid transmission over a large geographic region, HINT groups represent epidemiologically-relevant areas within which transmission is assumed to be consistent. For example, a HINT group could represent a city or a state that contains one set of transmission dynamics but may have distinct characteristics compared to a neighboring population. We refer to these as transmission locales.

2.2. Disease transmission model fitting

We aimed to fit our model to represent transmission of typhoid fever in Malawi. A single reporting hospital in Blantyre, Malawi, maintains blood culture surveillance for typhoid fever [22], and we used data from both inpatients and outpatients in this surveillance system to fit our model. Typhoid incidence outside of Blantyre is not well characterized. Given the limited data, we divided the country into five transmission locales. Although there is likely a gradient of transmission that exists across Malawi, we represent transmission using two possible landscapes representing endemic and low transmission, based on economic analyses which have identified low incidence settings as a lower bound of cost-effectiveness of the vaccine [17]. We fit endemic locales to the annual unadjusted incidence rates, age distribution, and seasonality of reported typhoid fever in Blantyre from 2015 to 2016, while the low transmission locales were fit to the annual unadjusted incidence rates of typhoid in Blantyre between 1998 and 2010. Risk of exposure in the model does not include migration between transmission locales, which allows us to maintain heterogeneity of the incidence landscape over time. Further detail on the model structure and fitting are included in the supplement.

2.3. Environmental surveillance framework

We added an environmental surveillance (ES) diagnostic feature to the mathematical model for the purposes of this analysis. This was a hypothetical automated and responsive tool that tracks the simulated environmental CCVT for each transmission locale.

The development of an environmental sampling method is still ongoing. For these purposes, we work on the premise that a test that was accepted by the public health community for wide deployment would be reliable and would concentrate fecal matter from the environment into a manageable sample. We assume that sites selected for ES would be representative of the catchment area.

We selected a threshold of CCVT for a detection "positive" that reflected underlying endemicity in the simulation. We first applied a test sensitivity (85%) and specificity rate (80%) that create uncertainty of whether the diagnostic would signal correctly in the simulation. We additionally modified the portion of individuals in a given locale that are sampled by the environmental diagnostic (80%); in the real world, an ES system could never cover all possible transmission routes, and this allowed us to capture this effect. As a baseline, we assume that samples are taken weekly for a year, prior to any decision about vaccination being made. We assume that at least one third of the year's samples would need to be positive before a decision maker would be willing to conclude that typhoid is indeed endemic in their area. This is likely a high threshold for positive responses given real-world detection rates in known chronic carriers to be only 25%, as reported in Santiago, Chile using Moore swabs [23].

We tested the robustness of the results by varying the heterogeneity in the incidence landscape and surveillance coverage. We did so by sweeping the proportion of transmission locales that are endemic, between 1 and 5 of 5, with the remaining set to low transmission. We also varied the proportion of transmission locales sampled by the ES system, from 1 to 5 of 5.

2.4. Vaccination decisions

We assumed that routine immunization (RI) would be rolled out for all children at 9 months of age, consistent with the existing EPI schedule for measles-containing vaccine, as recommended by the WHO [19,20]. This was implemented simultaneously with the beginning of any ES-derived catch-up campaign, as is under consideration for funding by Gavi, the Vaccine Alliance in eligible countries [26]. We assumed that any catch-up campaign would reach 85% of the target population aged 9 months-15 years and vaccine efficacy was set at 87% based on the clinical protection estimated in challenge models [27].

We explored policy frameworks to decide whether and where to do a catch-up vaccination campaign in response to the ES results. Catch-up campaigns were responsive to the environmental surveillance system, and two primary strategies were explored. In some scenarios, a country may decide to implement a national catch-up vaccination campaign after detection in a major city or sentinel site. Others may decide to only implement localized catch-up vaccination in areas that are considered high risk due to likely endemic transmission (as detected by ES sampling). These are referred to as national and local (sub-national) catch-up campaign strategies.

2.5. Economic model

The economic model took two perspectives: programmatic and health system.

The programmatic perspective included the cost of vaccines and supplies purchased, vaccination delivery, and environmental sample collection and testing. We varied the unit cost for vaccination depending on the delivery method, since there are operational cost differences between vaccines delivered via a supplementary immunization activity (SIA) for a catch-up campaign versus routine immunization after the vaccine is added to the standard EPI schedule. Syringe and waste boxes are procured in large volumes by UNICEF to support multiple vaccines, so we did not simulate uncertainty in their pricing. Wastage and transportation rates are well established by Gavi, so we did not simulate uncertainty in their levels.

For the health system perspective, we also included the cost of treatment for both typical and multi-drug resistant typhoid cases, direct non-medical costs, and lost wages (indirect costs) for inpatient cases. Average treatment costs were calculated based on septicemia discharges reported at the Queen Elizabeth Central Hospital in Malawi, adjusted for inflation from 2014 to 2018 US dollars [28]. We used the average daily cost in US dollars for the portion that was due to the ward stay to estimate the daily ward cost and multiplied that with the typical length of stay for hospital-treated cases. We included the average investigation and

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procedure cost, the direct non-medical costs, and the lost wages (indirect) costs as well for inpatient cases. Finally, we calculated the expected drug cost for uncomplicated (outpatient) typhoid based on Medicines Sans Frontieres's treatment guidelines for low resource settings [29] and based on ceftriaxone plus seven days of ciprofloxacin at 750 mg dosage for inpatient treatment (as is currently done in Blantyre), using current UNICEF supply prices [30]. MDR case treatment costs are higher than non-MDR cases primarily due to more expensive drug costs.

We assessed the impact of stochastic variation in the model parameters by using a Monte Carlo simulation to simultaneously vary both the economic and epidemiological parameters. The simulation sampled values for the unit costs for vaccines, vaccination delivery, and environmental sampling. Ranges for each parameter were simulated as triangular distributions, with 95% CI values listed in Table 1. The model generated a stochastic economic model estimate for each EMOD simulation. These results were used to calculate the simulated 95th percentile simulated intervals for each scenario, which are the result of both epidemiological and cost uncertainty. In addition to the scenario comparison, which reflects the unknowns about the true epidemiology of Malawi, we also conducted a one-way sensitivity analysis on the cost model parameters in Table 1, varying each one independently from one half to twice the expected value (maxing out at 100% where applicable), to assess the effect of each parameter on total programmatic and societal cost.

Aggregated cost and disease impacts were summarized using an incremental cost-effectiveness ratio (ICER) by dividing the difference in total costs by the difference in the number of cases. Using this method, any scenario for which there is an alternative scenario that has fewer cases of typhoid and also lower costs is considered "dominated" and discarded as an alternative. The remaining options are on the efficient frontier (aka. the most impact for the dollar spent) and are compared. (Table 2).

We tested for statistically significant differences between strategies and between levels of ES, for both costs and incidence. These results by conducting a Welch 2-sample *t*-test for each pairing and confirmed it by considering the non-parametric Wilcox test as well, since the simulated results violate the equal variance condition for the Welch test when comparing the baseline to vaccination.

3. Results

3.1. Simulation models were reliably fit to historical incidence

Estimated model parameters fitted well to age distribution, seasonality, and incidence rate in endemic and low incidence trans-

Table 1
Economic Model Parameters. Outpatient treatment costs include drug costs only. Inpatient treatment costs include investigation and procedure costs, direct non-medical costs, and lost wages (indirect) costs.

Parameter	Value	Simulated Range	References
Vaccine cost	$1.50 per dose, 5-dose vial	Fixed, negotiated prices	[30]
Syringe cost	$0.04 per syringe, single use	Fixed, negotiated prices	[31]
Wastage box	$0.45 per box, 100 capacity	Fixed, negotiated prices	[31]
Supply wastage rate	10%	Fixed, planning standard	[32]
Transportation cost	3% of vaccine cost	Fixed, planning standard	[32]
Vaccination delivery, SIA	$0.74 per dose	±50%	[33]
Vaccination delivery, RI	$0.59 per dose	±50%	[34]
Uncomplicated outpatient treatment (typical/MDR)	$1.50 / $2.40	±50%	[27–29]
Inpatient treatment (all)	$238.34	±50%	[27–29]
Portion of all cases that are uncomplicated (vs. severe)	90%	75%–100%	[35]
Portion of all cases that are multi-drug resistant	95%	75%–100%	[21]
Environmental sampling (PCR)	$33.00 per sample	±50%	Personal correspondence; cost in the context of a mature laboratory
Discount rate (applied to both costs and cases)	3%	Standard economics assumption	[36]

Table 2
Incremental cost-effectiveness ratios (ICER). The ICER table is sorted by the simulated average number of cases and then the ICER is calculated as the incremental cost per incremental reduction in cases. Scenarios that are both more expensive and have higher number of cases than an alternative are considered dominated and the ICER is not calculated. All costs reported in 2018 US dollars. "L# dominated" indicates that this line is an inferior option compared to the referenced line and is thus considered dominated, i.e. it both costs more and has higher incidence than the reference line. NA = Not applicable, as these are the baseline from which ICER is calculated for the remaining lines in the table; the program and total costs are presented here for reader interest only.

Scenario	# ES Locales	Incidence per 100 k	Avg. Program Cost (1000s)	Avg. Total Cost (1000s)	Treatment % of Total Cost	ICER,Program Cost	ICER,Total Cost
Baseline	0	101.33	$0.00	$13.3	100%	NA	NA
RI Only	0	95.63	$52.3	$64.7	18%	NA	NA
Local	1	81.59	$57.3	$68.1	15%	$67.63	$46.52
Local	2	67.30	$62.2	$71.2	12%	$66.11	$41.78
Local	3	52.95	$67.4	$74.4	9%	$68.07	$41.58
National	1	39.69	$77.4	$82.8	7%	L7 dominated	L7 dominated
Local	4	38.65	$72.5	$77.6	6%	$68.19	$43.41
National	2	30.74	$84.1	$88.3	5%	L11 dominated	L11 dominated
National	3	36.49	$88.5	$92.1	4%	L11 dominated	L11 dominated
National	4	24.91	$91.1	$94.5	4%	L11 dominated	L11 dominated
Local	5	24.65	$77.5	$80.7	4%	$68.58	$41.99
National	5	23.95	$92.8	$96.1	3%	$4161.25	$4183.57

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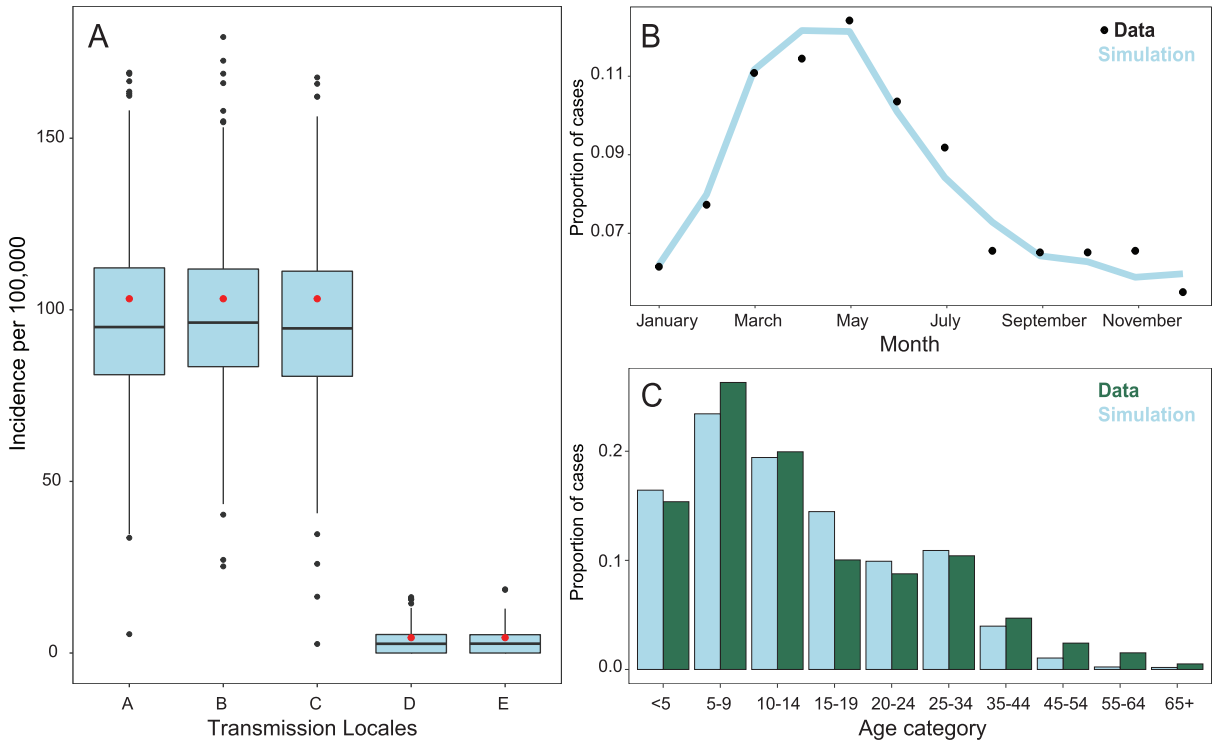

Fig. 2. Fitted parameters. A. Boxplots of incidence per 100,000 in the fitted model, with Blantyre data represented as a red point this example is for a scenario with 3 of 5 transmission locales set to endemic transmission. B. Fit of the endemic locales to observed seasonality. C. Fit of the endemic locales to observed age distribution of cases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

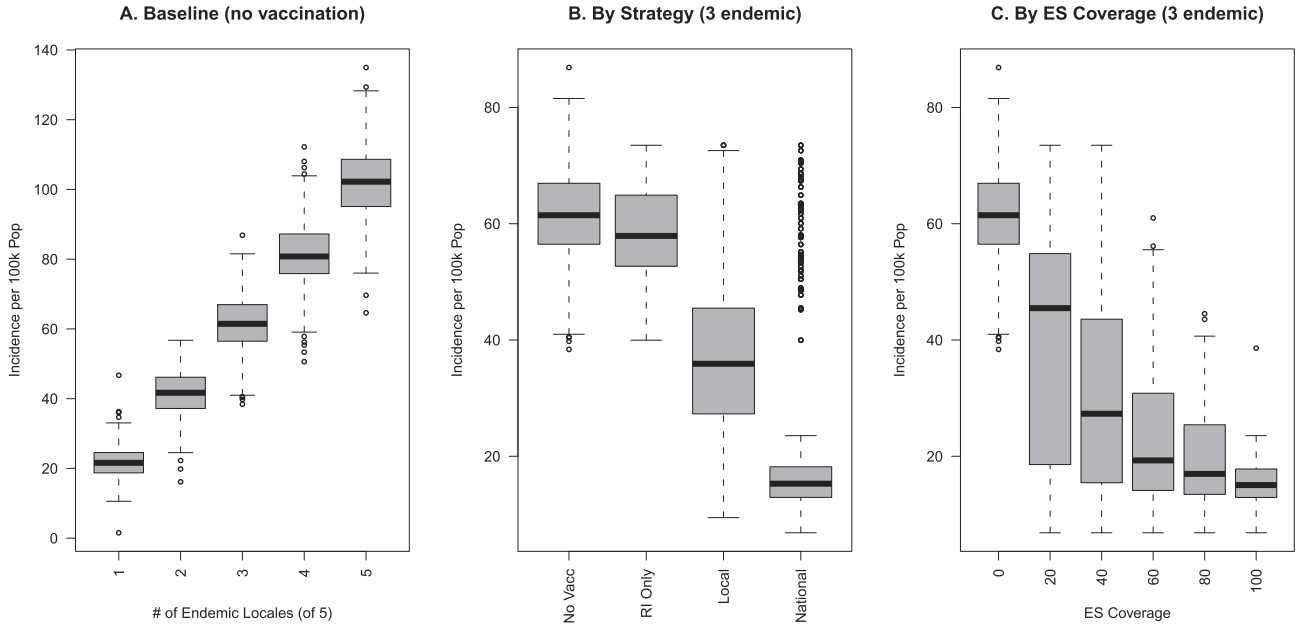

Fig. 3. Simulated disease incidence per 100,000 person-years. Each boxplot displays the typhoid case incidence per 100,000 person-years over ten simulated years. They display the median as a central line in the box, which extends to the 1st and 3rd quartiles; the lines extend to the max and min, excepting outliers which are displayed as points. Plot A displays the incidence level in baseline scenarios where there was no vaccination, broken out by the underlying disease incidence. Plots B and C summarize results for simulations where 3 out of 5 simulated locales were endemic (2/5 had low incidence). Plot B compares the baseline incidence with routine immunization only and ES-informed local (sub-national) and national catch-up campaigns. Plot C displays the results from catch-up campaigns that are informed by increasing levels of ES coverage (i.e. the more surveillance, the more likely the simulation is to detect typhoid and vaccinate appropriately).

mission time periods in Blantyre (Fig. 2). A summary of fitted parameters is in Supplementary table S3.

The simulation model results were aggregated by scenario and the resulting patterns in total incidence were as expected (Fig. 3). With higher endemicity (ranging from one to five endemic locales, out of five total), we see increasing incidence in the total population (Fig. 3A). The introduction of routine immunization only (without a catch-up campaign) has a limited impact on incidence

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(Fig. 3B), due to the slow pace of vaccine-derived immunity. Since routine immunization (RI) is only being provided to the birth cohort as it reaches the age of 9 months, so we do not detect a large impact in the total population's incidence over our 10-year model. The sub-national and national catch-up campaigns reduce incidence, with the national campaigns suppressing disease further, given that it is inherently a larger-scale vaccination program. Additionally, we found that with increasing environmental surveillance (ES) coverage, incidence was lower (Fig. 3C), reflecting our ability to appropriately detect and respond to ongoing transmission with better ES coverage.

3.2. Over- and under-vaccination were both risks

The most optimal use of vaccine would be to vaccinate all of (but only) the endemic locales. Since we hid the true endemicity from our simulated decision making and only provided ES-derived information, the campaign choices are frequently sub-optimal in the simulation.

We considered any instance where a low-transmission locale was vaccinated to be "non-endemic vaccination". We considered any instance where an endemic (high transmission) locale was never vaccinated to be a "missed opportunity", since there were many cases that could have been prevented but were not.

The national strategy, where all children are vaccinated based on endemicity anywhere, resulted in high rates of non-endemic vaccination. However, there are relatively few missed opportunities, especially when there are high levels of environmental surveillance. In contrast, the local strategy, where children are vaccinated if and only if they live in a locale with detected endemicity, resulted in high levels of missed opportunities, although these decline considerably as ES coverage increases. Simultaneously, there is low probability of non-endemic vaccination with a local strategy, since it is unlikely that the environmental surveillance diagnostic would generate enough false positives to trigger an unneeded campaign (Fig. 4). Though the precise ES methodology has yet to be recommended for typhoid, with PCR methods, the risk of false positives for Salmonella species exist [31]. Further simulation work would be useful to explore these results across a range of specificity values.

3.3. National catch-up campaigns reduced burden but cost more than local campaigns

Total program costs include the cost of environmental surveillance, routine vaccination, and catch-up campaigns. These are exactly zero in the baseline scenario, are an average per capita of $0.76 ($0.58, $1.00) for a local (sub-national) strategy and $1.00 ($0.58, $1.15) for a national campaign strategy.

Total societal costs include program costs, plus the direct medical treatment costs, direct non-medical costs, and the indirect lost productivity costs for acute cases (Fig. 5). These are an average per capita of $0.15 ($0.02, $1.41) in the baseline scenario, $0.85 ($0.63, $1.12) for local (sub-national) strategies, and $1.04 ($0.63, $1.21) for national strategies. Treatment is 100% of total societal costs for baseline, 5% (1%, 17%) for national strategies, and 10% (1%, 27%) for local strategies.

Both local and national strategy costs are significantly more than the baseline scenario and national strategies cost more than local (p-values <0.001). Total costs were significantly higher as a result of additional environmental surveillance for all comparisons within local and within national strategies (p-values <0.01).

Both local and national strategy costs achieved lower incidence than the baseline scenario (p-values <0.001) and national strategies achieved lower incidence than local in aggregate (p-value <0.001) (Fig. 4). Incidence rates were significantly lower as a result of additional environmental surveillance for all comparisons (p-values <0.01) except when comparing within national strategies with 3–5 locales with ES (Fig. 5), though these were distinct from strategies relying on either 1 or 2.

As endemicity increased, the national strategy converged to a consistent outcome, regardless of the level of ES coverage (Fig. 6). With high levels of transmission, the difference between the (any) national and high coverage-ES local strategies became relatively indistinguishable. ES provided the most benefit at low

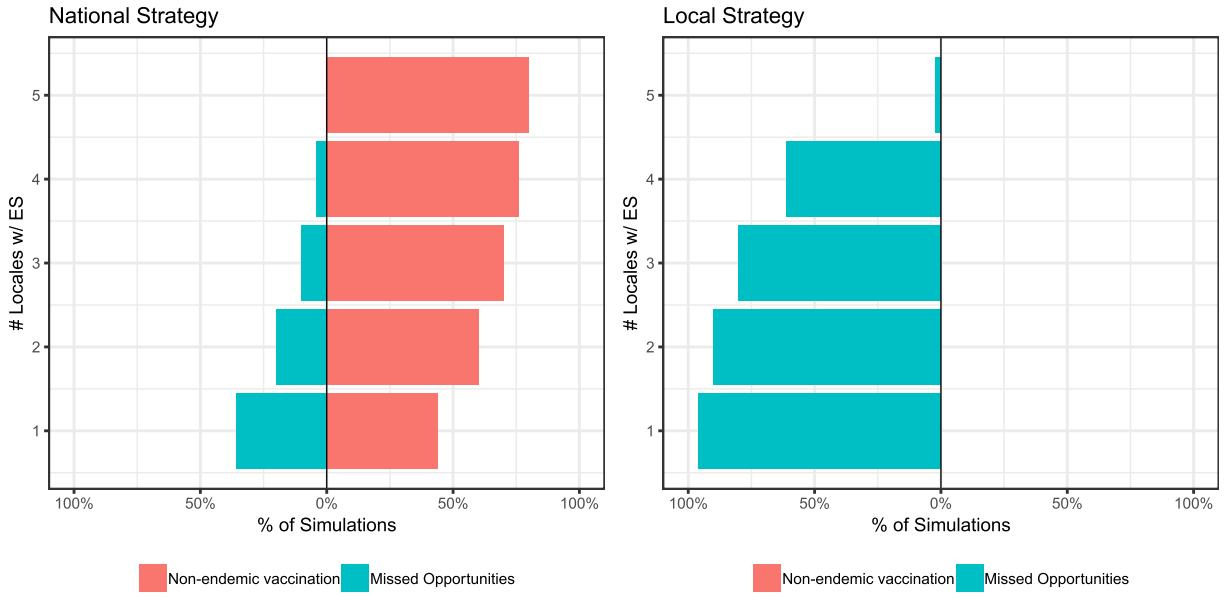

Fig. 4. Catch-up campaign precision. Impact of environmental surveillance levels on the successful targeting of national vs. local vaccination strategies. The bars indicate the percentage of simulation runs in which either non-endemic vaccination or missed opportunities occurred, for a given national/local strategy and level of ES coverage. Simulations with optimally-targeted campaigns (i.e. when all endemic locales – and only endemic locales – are vaccinated) are not shown; as a result, the bars do not sum to 100%.

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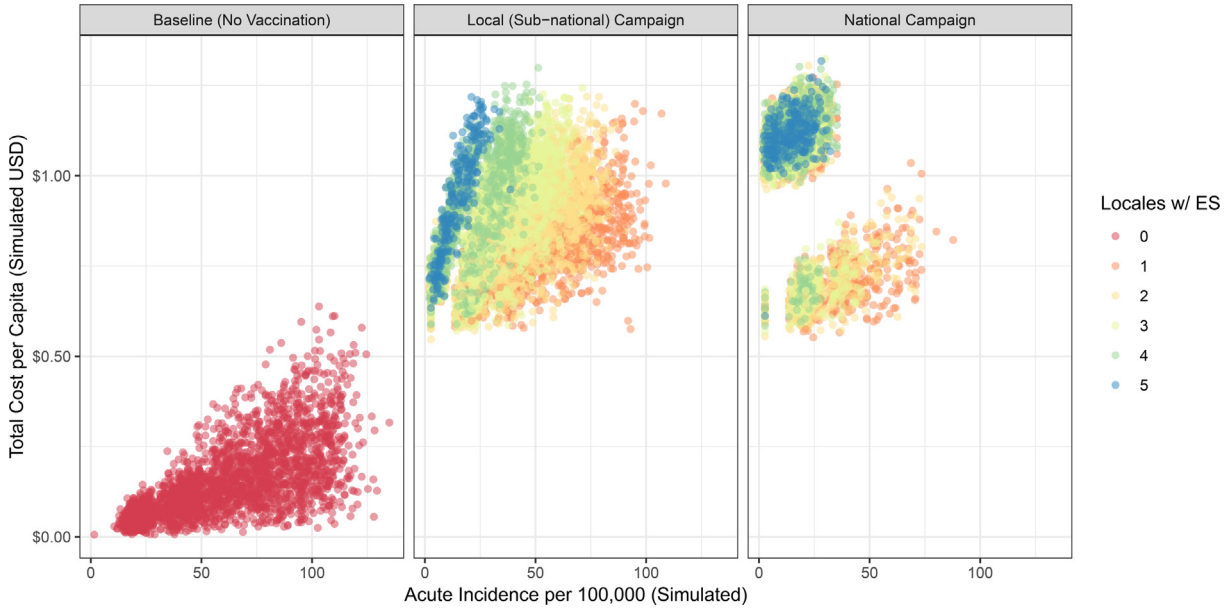

Fig. 5. Simulated incidence and total costs per capita. Each point represents the outcomes of a single simulation run. Simulations are color coded to differentiate by vaccination strategy and level of environmental surveillance that was deployed in the modeled scenario. The leftmost panel represents the baseline status quo, where no vaccination is performed. All values reported in 2018 US dollars.

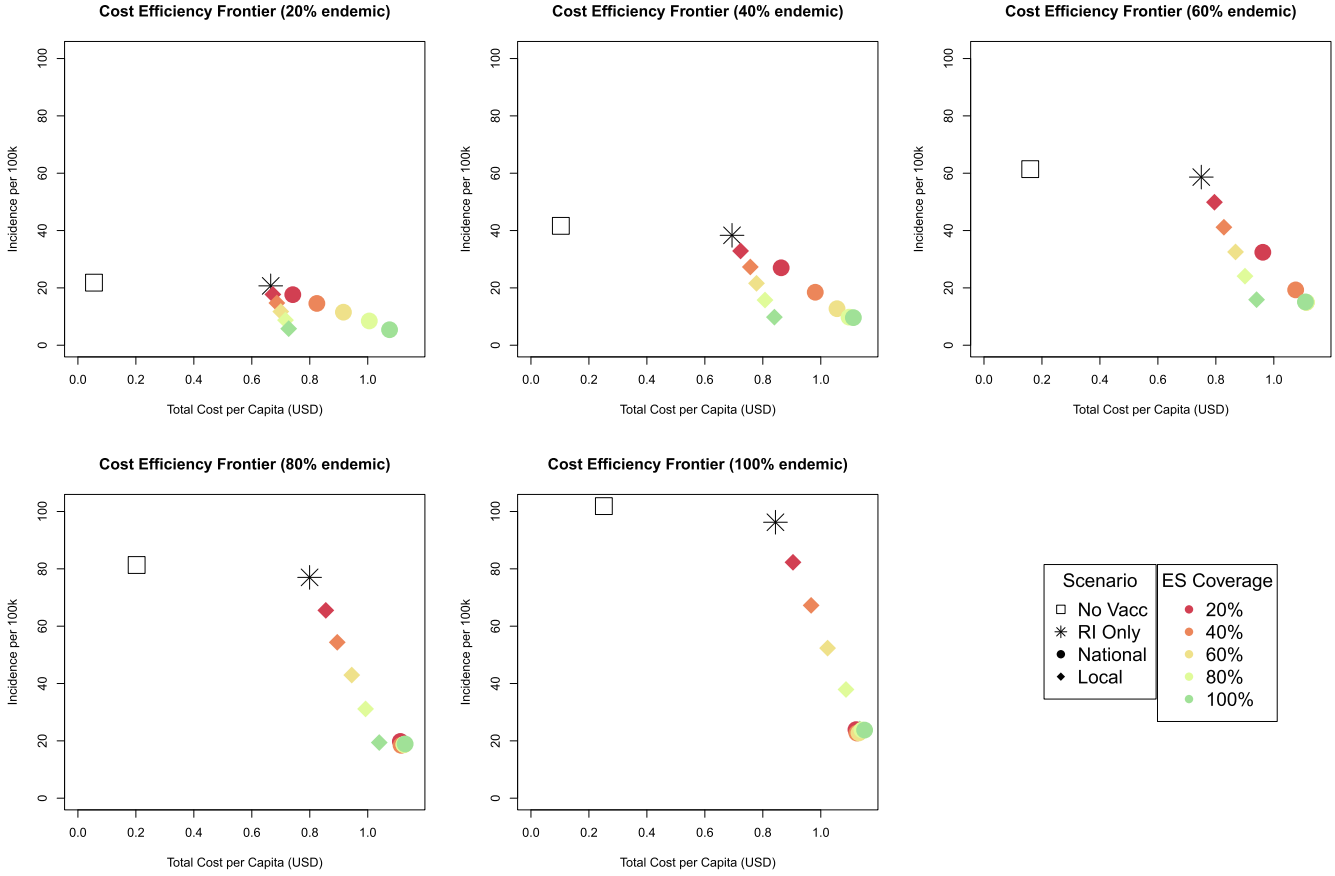

Fig. 6. Cost efficiency frontier. The simulated total cost per capita includes vaccination, environmental surveillance, and treatment costs for acute cases. The incidence rate is calculated over ten years. Both values are discounted at a rate of three percent per year.

incidence scenarios, because a local strategy was able to detect and target high risk locales with catch-up vaccination. (Fig. 6)

We calculated the incremental cost effectiveness ratio for each scenario, compared to the next-best option as measured by the simulated number of acute typhoid cases. Considering only programmatic costs, the ICER for adding environmental surveillance and the resulting catch-up campaign ranged from $66.11-$4161.25 per case avoided. The ICER was similar but lower for total

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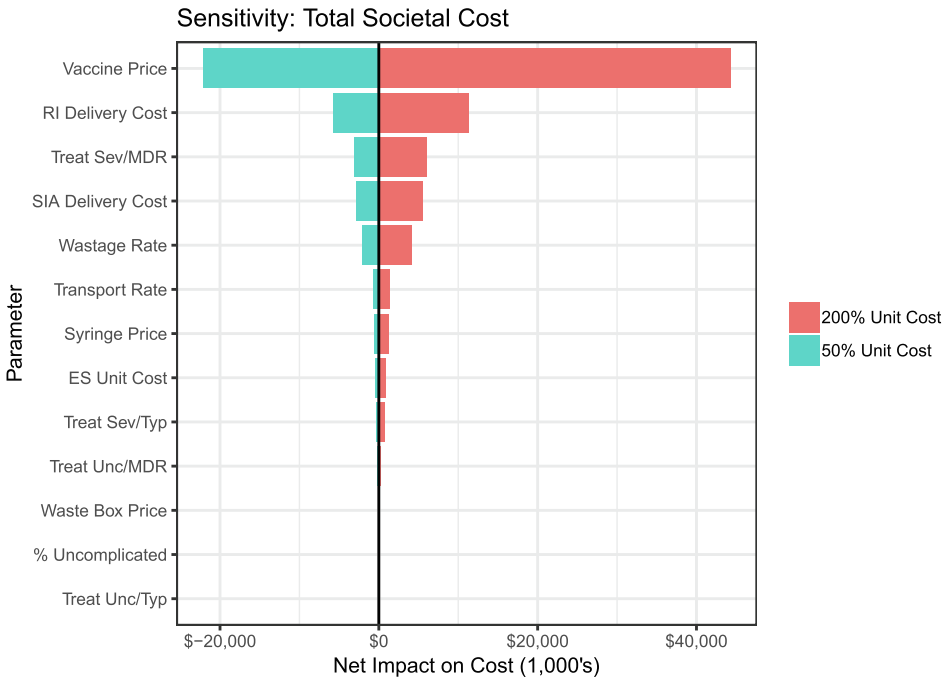

Fig. 7. Sensitivity analysis results. The modified total societal costs are calculated by multiplying the unit cost, price, or value of the cost model parameter by 50% and then by 200% in order to assess the impact of parameter uncertainty. The net impact is the modified cost, less the original estimate. All values reported in thousands of 2018 US dollars. Treat = treatment cost. Sev = severe. MDR = multi-drug resistant. SIA = supplementary immunization campaign. RI = routine immunization. Typ = typical (non-MDR). ES = environmental surveillance. Unc = uncomplicated.

costs (including the cost of treatment) and ranged from $41.58-$4183.57 per case avoided. (Table 2.) As the number of cases declined, so did the proportion of costs that are due to treatment of acute cases.

There is inherent uncertainty in relying on point estimates for any cost value in an economic analysis and this is particularly true for a new vaccine, aimed at a global market that only just now being introduced. We conducted a one-way sensitivity analysis to assess the impact of the individual parameters on the total cost estimate and find that the price of the vaccine itself, the cost of treatment for severe MDR cases, and the cost of vaccine delivery are the parameters with the most impact. (Fig. 7).

4. Discussion

In this simulation study, we found that typhoid ES-based catch-up TCV vaccination campaigns are beneficial for efficiently reducing the incidence of typhoid in a population as a supplement to introduction of routine immunization. When compared to only routine immunization, catch-up campaigns are a low-cost strategy for both national and local (sub-national) targeting decisions (ICER as low as $42.00).

A strategy that relies on a national campaign is highly responsive to surveillance and results in the decision to vaccinate the entire country in most simulation runs, especially where there is high surveillance coverage. In fact, ES adds a minimal value if the catch-up decision is going to be made at the national level, especially if there are high levels of underlying endemicity. However, in the absence of blood culture-based surveillance, it remains a critical trigger to access funds to deploy TCV at all. This leads us to conclude that while ES is helpful, if a country had evidence that there is endemicity in some part of the country (e.g. from a sentinel site), then ES may not be necessary – and in fact, basing a catch-up campaign on positive ES creates a risk for missed opportunities in cases where ES results in a false negative.

Since national campaigns maximize burden reduction, if local evidence of widespread disease transmission exists (whether from ES or other sources), a national catch-up campaign will minimize missed opportunities. However, with a national campaign strategy, there is a high probability of vaccination of low-risk populations. This increases the ICER, but not enough to discourage a national campaign in the absence of surveillance data.

A local strategy is more cost-effective per case avoided (see Table 2 for ICER values), compared to a national strategy. This is because there is a lower probability of unnecessarily vaccinating low-risk populations. However, there is a much higher risk of missed opportunities, since incomplete surveillance coverage results directly in cases that could have been avoided by vaccination. Thus, local vaccination strategies are preferable to national strategies from a cost-effectiveness perspective, if high quality and high coverage levels of typhoid ES can be achieved. In a situation with underlying endemicity in only a few places, only those high-risk individuals would be vaccinated, avoiding costs from a non-endemic campaign based on a relatively small investment in ES. In contrast, if there is high endemicity, very high coverage of ES is required to ensure that no local transmission is overlooked.

Regardless of the scale of response (national or local), ES roll-out would require careful planning in order to ensure adequate coverage of the transmission locales, reflected in our finding that the incremental portion of the population covered by ES was a significant driver of disease burden and cost for both national and local (sub-national) strategies. This finding is robust across scenarios, as long as the test itself is a reliable indicator of underlying transmission.

As we report in Fig. 5, 'non-endemic vaccination' resulted in a higher programmatic cost per case avoided because vaccine was given to those who were at a very low risk of infection. In contrast, scenarios with high levels of 'missed opportunities' result in lower cost-effectiveness, because there are many cases that could have been avoided for a low vaccination cost.

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It is important to note that while we have framed this analysis in the context of country-level decision making, the results are not dependent on the size of the population. Transmission locales could easily be defined on different scales: neighborhoods, cities, states, countries, or even regions, though assumptions around migration or incidence heterogeneity may alter the results somewhat.

There are several limitations to the conclusions from this study. The most important is that the method to detect typhoid via environmental surveillance is still in development, which creates substantial uncertainty around the true test sensitivity and cost once it has been finalized. There is a potential to infer prevalence from ES samples, and the methods have been developed for polio ES [10], particularly during the Israeli outbreak of 2013 [11], but the operational and scientific feasibility of this for typhoid has not been proven. Additionally, we assumed that ES could be placed efficiently to test a concentrated water or sewer source, but this may not always be possible, which would require duplicative sites. This is somewhat mitigated by the fact that ES would be a relatively small proportion of the total cost of typhoid control, but further refinement of the ICER estimates would be useful once testing and deployment methods have been further refined; once that has been done, the ICER should be compared to a willingness-to-pay threshold to determine whether it is a cost-effective intervention. We also assumed that a routine immunization program would be rolled out in all scenarios (except baseline) and calculated ICERs including those costs. While it is unusual to do a mass vaccination campaign in the absence of routine immunization, it is possible that a country would opt for this strategy. However, this would likely further reduce the ICER, so it is not a significant concern for our conclusions. Another limitation is that our model relies on data from a single sentinel site in Blantyre, which may or may not represent the force of infection or seasonality found in the rest of the country. Finally, this study makes assumptions of both geographic and temporal stability in incidence for the purposes of evaluating a one-time tool, despite the rapid increase of typhoid fever in Blantyre. Incorporating data that spans multiple locations and including variability over time to further evaluate ES in changing incidence landscapes would be beneficial. Including high migration rates between the transmission locales in the model would almost certainly favor a national vaccination strategy, regardless of ES detection. It should be noted that migration should be considered when evaluating strategies in settings with rapid emergence and spread of typhoid fever, like what has been observed with extensively drug-resistant (XDR) typhoid in Pakistan [32]. Nonetheless, even in these high migration settings, ES may be a useful tool for prioritizing locations when vaccine resources are limited, in the absence of clinical surveillance.

This study highlights the use-case of environmental surveillance in the context of vaccination decision-making for typhoid conjugate vaccines and offers a flexible framework for additional scenarios. For example, alternate and more complex decision-making strategies, such as such as altering the number and portion of positive samples required to make a decision, consideration of migration patterns and its effect on risk of introduction, and the use of quantitative PCR that could support more nuanced targeting. In the absence of blood culture surveillance in many locations, countries may be limited in their ability to utilize this vaccine without novel methods of rapid evaluation. Beyond ES as a one-time evaluative tool, there is additionally an opportunity to explore the costs of using ES for ongoing monitoring and outbreak detection due to reintroduction. These findings highlight a need for understanding the limitations of detection of typhoid ES, and the potential for other rapid diagnostics or evaluation strategies to aid in decision-making. Overall, we find that time-limited environmental surveillance can be a cost-effective tool to support decision making and improve targeting for catch-up vaccination campaigns.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.12.061.

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