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Original Research Article

Cost effectiveness analysis of typhoid fever vaccination in an endemic district of Kabale, Uganda

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ABSTRACT

Background: Typhoid fever is a preventable disease that affects the livelihood security of households and communities, accounting for a significant portion of the disease burden in Kabale district. Various preventive programs to control this burden such as curative services and vaccination are being implemented without empirical evidence of the effectiveness of either program in terms of costs and outcomes.
Methodology: The study design is a mixed methods design in which for specific research objectives a cross-sectional survey was carried out in addition to a retrospective costing analysis. The outcome being a cost effectiveness evaluation of vaccination against typhoid with the comparator being no vaccination, expressed as the incremental cost effectiveness ratio.
Results: Incidence rate of 39.8 per 1000, a case fatality rate of 0.061, and cost of illness of $75.62 for inpatient care and $33.85 for an outpatient case, with an average cost of illness of typhoid fever in Kabale district to be $54.74. In addition, typhoid fever costs Kabale district $217,158.8, of which $119,814.92 could be saved if a typhoid fever vaccination program is carried out, that will avert 2,189 cases of typhoid every year for three years. Vaccination results in 28,428.32 DALYs avoided. The resulting ICER of -6.348 reveals that the vaccination program against typhoid fever is both extremely cheaper and very effective in averting both typhoid cases and costs.
Conclusions: a one-time fixed-post typhoid vaccination campaign in Kabale District, Uganda, was estimated to be a very highly cost-effective intervention from the public sector health care delivery perspective.

Keywords: Typhoid fever, Endemic, Vaccination

INTRODUCTION

Typhoid vaccination is recommended for prevention of typhoid fever, a major cause of enteric disease in populations of low- and middle-income countries to reduce the relatively high disease burden they carry, but is glaringly absent from their routine immunization programs. Typhoid fever is a preventable disease that affects the livelihood security of households and communities, accounting for a significant portion of the disease burden in Kabale district. Various preventive programs to control this burden such as curative services and vaccination are being implemented without empirical evidence of the effectiveness of either program in terms of costs and outcomes. To generate this evidence, a cost-effectiveness study is necessary to reveal this evidence on which of the two programs is more cost effective.

Typhoid fever is an exclusively human, faecal-oral transmitted systemic disease caused by infection with the bacterium Salmonella enterica serovar Typhi. It is characterised by an acute illness that presents with a fever caused by infection with the bacterium Salmonella typhi. Typhoid fever has an insidious onset, with fever,

headache, constipation, malaise, chills, and muscle pain. Diarrhoea is rare, and vomiting is present but not usually severe. Confusion, delirium, intestinal perforation, and death may occur in severe cases (MedicineNet).[1] Persons living in areas without access to improved sanitation facilities in which exposure to fecally contaminated water and food, is common, carry the greatest risk for infections.[2] Timely access to effective antimicrobial therapy is central to preventing complications such as intestinal perforation and death. These cases largely occur in South and South-East Asia and sub-Saharan Africa. Without treatment, the case fatality rate of typhoid fever is 10-30%, dropping to 1-4% with appropriate therapy.[3] In a more recent study, the estimated adjusted typhoid fever associated morbidity and mortality in sub-Saharan Africa was found to be 725 cases and 7 deaths per 100,000 person-years.[4] In a published study of an outbreak of typhoid fever in Kasese District, 8092 persons fell ill of typhoid, from 27 December 2007 to 30 July 2009, resulting in at least 249 intestinal perforations and 47 deaths.[5] In another investigative study, done in Kampala, it revealed a large outbreak of typhoid fever that affected thousands of people in Kampala, Uganda, which appeared to have been caused by consuming contaminated water and local drinks made from it, and many other unpublished sustained outbreaks such as is occurring in Kabale district as observed in my clinical practice in Rugarama Hospital, demonstrating its epidemic potential and endemicity throughout Uganda.[6]

The world health organization (WHO) recommends typhoid fever vaccination for controlling endemic and epidemic typhoid fever, for infants and children over six months of age in typhoid-endemic countries (WHO Position paper, 2018).[7] The Vi capsular polysaccharide (ViCPS) vaccine is a single dose injectable subunit vaccine that showed high efficacy and effectiveness, with protection lasting at least three years in large scale trials.[8] Reported efficacy and field effectiveness in this trial ranged from 55% to 72%. Sanofi Pasteur produces the ViCPS vaccine that is licensed in many countries for persons 2 years of age and older and is WHO pre-qualified. The ViCPS vaccine has been widely adopted for programmatic use, to control outbreaks in a school in China and in a pre-emptive mass vaccination campaign in Fiji following a tropical cyclone.[9,10] More recent school based typhoid immunization campaigns were carried out in Pakistan.[11] Deferring vaccination against typhoid fever leaves large populations at risk of typhoid fever for several years and possibly much longer. There were nearly 211,000 Typhoid fever cases reported in Uganda between 2013 and 2016, which gives an incident rate of approximately 160 cases per 100,000 people per year, majority of which came from peri-urban central Uganda, followed by western Uganda.[12] This high incidence rate and disease burden translates into high costs of illness (COI). In Tanzania, the COI in a study done on Pemba Island was calculated at US$ 154.47 per episode, which compares agreeably well in similarity with a study done in Kasese, Uganda during an epidemic outbreak of typhoid, whose costs per case without consideration of other expenses such as travel, meals, and productivity lost was found to be, US$ 4.3 for each patient receiving outpatient care only, while the case costs for hospitalized patients was US$ 58.1 for individuals without Intestinal perforation (IP), and US$ 155.6 for individuals with IP.[13,14] Kabale, being one of the endemic districts in Uganda for typhoid fever, carries a considerable burden in terms of morbidity and mortality. There currently exists an information gap on the typhoid disease burden in Kabale district. Any alternative intervention programs to address the disease burden lacks evidential backing. There is therefore need for information to provide empirical evidence on the cost effectiveness of a vaccination program to address the high typhoid disease burden in Kabale district.

Aim and objectives

This study therefore set out to determine the incidence, case fatality rate of typhoid fever and its burden from a societal perspective in Kabale district. In addition, the cost of a one-time vaccination against typhoid from a provider's perspective in Kabale district was determined as the comparator to perform a cost effectiveness evaluation of a typhoid fever vaccination intervention in Kabale district. These objectives were determined in the above respective order.

METHODS

The research methodology consists of both descriptive epidemiological and analytic economic evaluation methods, and stated models as per the research objectives have been used and was conducted from the 1st of October 2021 to the 9 December 2021, in Kabale district, Uganda.

Study design

The study design is a mixed methods design in which a cross-sectional survey was carried out and a retrospective costing analysis was done ending with a cost effectiveness evaluation of vaccination against typhoid with the comparator being no vaccination. This design is presented in three parts;

Epidemiological parameters

The epidemiological parameters comprise the human study population for which a sample size was calculated and a surveillance tool (the community assessment survey) with a typhoid case definition were used to estimate the burden of disease in the general population, and other surveillance tools within the study hospitals were used to identify eligible candidates for the cost of illness component of the study, presenting this study as of mixed methods design. To calculate number of deaths due to typhoid fever, typical values used for the case fatality rate for typhoid patients was calculated from hospital data

collected and compared to a similar study done in Kasese (0.6-2.1%) across all age-group.[14] Average vaccine effectiveness over the duration of immunity of the vaccine (3 years) was considered to vary between 30% and 70%.

Model

This study sought to answer the question "should the under-utilized or new typhoid polysaccharide vaccine be introduced for mass vaccination campaigns?" Here the comparator is "no vaccination", in which current screening and treatment programs are run, against the proposed alternative of "vaccination" against typhoid fever. A comparison of the costs and benefits of a one-time fixed-post typhoid vaccination campaign using the single dose ViCPS vaccine with the baseline alternative of "no vaccine", over the period when the vaccine confers protection, which is three years. Benefits (in disability adjusted life years DALYs, and averted medical costs) were measured and discounted over 3 years, the time the vaccine is assumed to confer protection against typhoid was done. Costs were due to the vaccination campaign and occurred only at the beginning of the evaluation period. Applying standard cost effectiveness methodologies to evaluate the cost-effectiveness of immunization programs, including a standard discount rate (3%) and uniform age weights, then follows; by first measuring burden of disease in DALYs, with and without the vaccination campaign.[15] Disability adjusted life years incorporates both reductions in typhoid morbidity (years of life lost to disability, YLD) and typhoid mortality (years of life lost, YLL). The DALYs then were calculated using standardized vaccination impact formula provided by the WHO.[15]

$$DALYs\ averted\ per\ year = YLD\ averted\ per\ year\ per\ age\ group + YLL\ averted\ per\ year$$

$$YLD\ averted\ per\ year = (1 - CFR) * Eff * VC * N * I * length * DALY\ Weight$$

$$YLL\ averted\ per\ year = CFR * Eff * VC * N * I * (1 - exp - 0.03LE)/0.03$$

Where, CFR stands for case fatality rate, Eff for vaccine effectiveness for vaccine coverage, N for number of individuals targeted for the vaccination campaign, I for incidence of the disease, length for duration of illness (in years), and LE for life expectancy. Then finally modelled the averted burden due to a one-time vaccination campaign in year one, throughout the duration (Dur) of the vaccine as the discounted sum of the averted DALYs per year across all age-groups:

$$Total\ DALYs\ avoided = \sum DALYs\ avoided\ per\ year / (1 + 0.03)^t$$

The benefits from the vaccination campaign, or DALYs averted, consist of the differences between the burden of disease with, and without the vaccination campaign. Although the vaccine may confer herd immunity and therefore positive externalities, there is little data on the magnitude of such effects, and so I used a static model to generate a conservative estimate. The incremental cost effectiveness ratio was measured by dividing the program's costs by the program's benefit in averted DALYs, according to a public sector health care delivery perspective. This perspective was used since there is little information on patient time lost. The denominator of the incremental cost-effectiveness ratio thus consisted of the number of averted DALYs over the three years of immunity conferred by the vaccine, while the numerator of the incremental cost effectiveness ratio is the difference between the one-time costs of the vaccination program and the averted medical costs borne by the public sector over the three years the vaccine confers immunity. The averted medical costs borne by the public sector consist of the averted costs of typhoid related outpatient visits and hospitalizations. To estimate averted medical costs, I calculated the epidemiological burden of disease (expected typhoid cases), the burden expected to be averted by the vaccination campaign, and then multiply the latter by the expected case cost. It was assumed that cases resulting in death did not have additional medical costs.

$$ICER = Costs\ of\ no\ vaccination - costs\ of\ vaccination / DALYs\ with\ no\ vaccination - DALYs\ with\ vaccination$$

= Costs averted/ DALY averted

Cost effectiveness threshold; the threshold for this cost effectiveness study was determined using the GDP per Capita method. In 2020, Uganda's GDP per capita was 817 US dollars ($) and results of this study will be deemed cost effective if the CER is 1 to 3 times the GDP per capita.[15]

Costs

Cost of illness; the "costs of illness" comprised the second study population. To determine the cost of illness, we performed an incidence based "bottom-up" micro-costing approach from a societal perspective.[16] The incidence-based approach measures the economic burden on patients over the entire period of illnesses. It considers only new cases occurring within a study period and monitors them throughout the entire period of illnesses. Societal cost of illness is defined as a combination of direct medical costs, direct non-medical costs, and indirect costs. Direct medical costs are healthcare-related costs directly spent at the hospitals and other health facilities. Direct non-medical costs included travel, meal

and accommodation costs. Indirect costs included the opportunity cost of time spent by patients and caregivers for informal care. The costing method consisted of three steps: identifying, measuring, and valuing resources use. Costs of vaccination; total direct costs of a one-time fixed-post community vaccination campaign targeting all persons ≥2 years old was estimated from a public sector health care delivery perspective (providers perspective). The direct costs are the sum of the costs of campaign preparation (community organization and sensitization, cold chain maintenance, training, labor, and transportation of campaign workers and vaccine) and vaccine administration. Injection materials and labor costs will be assumed to be directly proportional to the costs of a 2018 measles vaccination campaign in Kabale. The vaccine was assumed to be a donation, therefore cost of vaccine itself is zero.

Study population

This study presents two study populations; the first study population are all persons at risk of typhoid fever living in Kabale, and the second are the costs of illness and vaccination of and against typhoid respectively. The target populations were persons at risk of typhoid, and the costs incurred in treatment or vaccination for typhoid fever. The study units were the human being and the individual cost of typhoid treatment or vaccination. The study site was Kabale District cold chain stores (four in total, each at the health sub-district) for vaccination costs, and both Rugarama hospital and Rubaya health centre IV for the hospital-based cost of illness costs. Kabale district in located in south-western Uganda about 421 km from the capital city Kampala and covers a total surface area of 1,827 square kilometers, 93% of which is arable land. Its capital town Kabale lies near 1o 15" south latitude and 300 East longitude towards the southern boundary of Uganda with Rwanda. The districts terrain is characterized by high hills dissected by steep sided valleys. The valleys at altitudes as low as 1,200m and the high ground rises to over 2,400m at several places. According to the 2014 national population census, Kabale has a population of 248,700 (as of 2020) persons of which 50.7% are below 17years, 21.9% 18-30years, 21.3% 31-59 years and the remaining falling in the 6.1% bracket. Of all the households counted, outside the municipality 20.4% lived more than 5km from a health facility and 13.8% lived less than 5km from a health facility. Within the municipality, only 8.2% of the nearly 50,000 persons lived less than 5km from a public health facility. Kabale district hosts a regional referral hospital, two PNFP hospitals and three Health Centre IVs all of which provide curative services for typhoid. The study was specifically carried out at Rugarama hospital and Rubaya health center IV for costs of illness, Kyanamira, Kekuubo and Kamuganguzi Subcounties for the community survey and cold chain stores in the health sub-districts to obtain some parameters for the cost-effectiveness analysis.

Sample size

In determining the sample size for the epidemiological parameter of typhoid incidence in Kabale district (human study population) where a community assessment survey was carried out, a confidence level of 95%, margin of error of 10% and standard deviation of .5 was used to obtain a sample size of 97 respondents. Secondly, in determining the sample size for the second study population which is the costs of illness and vaccination, a standard sample size of 30 respondents for the cost of illness and by default, only four cost centers exist for vaccination costs, which are; the district where the vaccines are received, then distributed to three health sub-districts at the cold chain stores, from where the personnel pick for onward administration into vaccine candidates. It therefore follows that a sample size calculation for vaccine costs is not applicable.

Sampling procedures

Procedure of sampling; cluster sampling technique for the epidemiological parameters were used since Kabale is comprised of several parishes and has different types of hospital settings (public, private and private not for profit). Each Subcounty was allocated a sample size from the total sample proportionate to the population that resides there. Within the Subcounty, parishes were picked randomly and households within the parish also picked randomly to administer the interview.

At household level, a random member of the household was selected for the interview by simple random sampling. For the hospital interviews, any patient who fitted the inclusion criteria was randomly sampled for administration of the costing interview. For the vaccination costing interview, the cost centers were fixed and therefore non-probabilistic approach was used.

Table 1: Incidence rate of typhoid fever in Kabale district.

Proportions	Binomial lower CI	Binomial upper CI	Poisson lower CI	Poisson upper CI
0.398	0.310	0.492	0.288	0.536

Confidence intervals were calculated using alpha=0.05.

Table 2: Distribution of admissions to hospital among the respondents.

Parameters	N	%
Yes	19	57.6
No	14	42.4
Total	33	100

RESULTS

Epidemiological parameters

From the community survey where 108 randomly selected households with a median number of six household members, the estimated incidence was 3980 per 100,000 persons (CI of 3100-4920).

A typhoid case was defined as "illness with onset between 1 September 2021 and 30 October 2021 in a person with fever, abdominal pain, and ≥1 of the following symptoms: gastrointestinal complaints (i.e., nausea, loss of appetite, vomiting, diarrhea constipation), general body weakness, joint pain, headache, altered mental state, hypotension and dry cough. There were 43 persons that met the case definition of typhoid out of the 108 household heads interviewed. To characterize health care seeking behavior, the community assessment survey revealed that 39% (42) sought treatment in a health facility for their signs and symptoms and of these, 19% (21) were hospitalized or admitted. None of the 108 respondents had ever been vaccinated for typhoid. 88 (81%) of the respondents would accept to receive the vaccine for typhoid fever if it were offered. The respondents were predominantly farmers and met all the eligibility criteria to participate in this study. From the hospital-based interviews in which 33 respondents who were diagnosed with typhoid, the case fatality rate was 0.061 (CI of 0.013-0.181). Of the 33 samples collected from these patients for culture and sensitivity, all turned positive on rapid diagnostic immunological test (IgG and IgM) and only 18 turned culture positive for salmonella typhi isolates, 4 complicated with intestinal perforation, and 2 died as a result of typhoid complications. Of the 33 interviewed in hospitals, 14 were treated as outpatients and 19 were admitted to hospital where they spent an average of 5 days undergoing treatment.

Table 3: Case fatality rate.

CFR	Binomial lower CI	Binamial upper CI	Poisson Lower CI	Poisson upper CI
0.061	0.013	0.181	0.007	0.217

Confidence intervals were calculated using alpha=0.05

Table 4: Aggregated case costs of typhoid in Uganda shillings.

Parameters	N	Minimum statistic	Maximum statistic	Mean statistic	Std. error
OPD costs	33	74,000	276,000	120,506.0606	8,178.25315
In-patient costs	33	84,000	1,188,000	269,211.1515	44,784.29044

Table 5: Case costs in US dollars.

Item	Cost (UGX)	Cost (US $)
Hospitalisation for typhoid	269,211.1515	75.62
Out-patient visit for typhoid	120,506.0606	33.85
Average cost	54.74	

Table 6: Point estimates of a vaccination program against typhoid fever in Kabale district.

Item	Point estimate	Distribution/range	Source
Vaccine effectiveness/base case	0.55	Uniform (0.3-0.7)	Anwar et al
Vaccine duration	3years		
DALY weights	0.27	Uniform (0.075-0.471)	Joseph cook et al
Kabale population estimates	248,700		UBOS 2020
Campaign type	Fixed post		-
Operational costs per dose (labor, transport, injection, freezer, building/storage etc)	133,930,000 UGX (36,693.15 USD)		Vaccination cost data, kabale district biostatistician and assistant DHO
Vaccine coverage	0.70	Uniform (0.60-0.70)	Biostatistician of kabale district

Case cost

The healthcare direct costs were estimated using two scenarios; outpatient treatment and inpatient treatment. The costs of medicines, supplies, and medical fees for each scenario were determined through a two-step process. First, the medical superintendent of Rugarama Hospital, a private-not-for-profit hospital in Kabale where surgical procedures to repair IP were performed during the study period, created a list of medications (including dosage and duration of treatment) and medical supplies used for a typical patient in each treatment situation. Itemized costs were then determined based on the Uganda National Medical Stores catalogue (2021). Total costs

were estimated in the local currency (Ugandan shillings), and then converted to 2021 US$, using the exchange rate published by the Bank of Uganda. The cost of care for patients that did not visit a provider and were cared for at home was considered to be zero, from a public sector health care delivery perspective. The cost of an outpatient visit included the cost of antimicrobials, and antipyretics (i.e., paracetamol), a consultation fee that takes into account medical labor, and a laboratory fee. The cost of a 7-day inpatient hospital stays for typhoid patients without IP included medications, intravenous fluids, medical supplies, a consultation fee covering medical labor, a laboratory fee, and daily bed costs. For IP associated hospitalizations, the cost of associated surgery was also included. The indirect costs included the tangible and non-tangible economic losses incurred due to the illness. These include transport to the hospital, missed wages, meals and hotel services and lost time spent seeking treatment or on admission. The costs were incurred at a time of COVID-19 standard operating procedures implementation. All these costs were then aggregated and presented here in summarized tables.

Table 7: Burden of typhoid disease and estimated impact in Kabale district with a vaccination program in place.

Item	Value
Burden (no vaccination) per year, total cases	3980
Averted burden per year, total cases	2,189 (55% of burden)
DALYs averted over duration	28,428.32
Costs of vaccination	$36,693.15
Medical care costs	$217,158.8
Averted case costs	$119,814.92
Program costs of vaccination	$36,693.15
Net cost per DALY averted	$4.22
Net cost per case averted	$54.74
GDP per capita	$817
Threshold to be considered cost effective	<$2,451

Vaccination program costs

Total direct costs of a one-time fixed-post community vaccination campaign targeting all persons ≥2 years old were estimated from a public sector health care delivery perspective. The direct costs are the sum of the costs of campaign preparation (start-up capitalization, community organization and sensitization, cold chain maintenance, training, labor, and transportation of campaign workers and vaccine) and vaccine administration. Injection materials and labor costs were assumed to be directly proportional to the costs of a 2018 measles vaccination campaign in Kabale.

Burden of disease and estimated impact of disease

ICER: using the formula mentioned in method section ICER was calculated to be -6.348. This gives a negative ICER, meaning that the intervention (vaccination) is less expensive and more effective as compared to the option of no vaccination/treatment of cases.

Key assumptions

In performing the data analysis, the following major assumptions were made for this study; that the incidence of typhoid is uniformly distributed across the study population, that the actual vaccine will be donated and therefore no costs of vaccine purchase were included. Only operational costs for vaccine administration have been covered and the life expectancy was considered to be 75 years.

DISCUSSION

In this study, our results reveal an incidence rate of 3980 per 100,000, a case fatality rate of 0.61, and cost of illness of $75.62 for inpatient care and $33.85 for an outpatient case, with an average cost of illness of typhoid fever in Kabale district to be $54.74. In addition, typhoid fever costs Kabale district $217,158.8, of which $119,814.92 could be saved if a typhoid fever vaccination program is carried out, that will avert 2,189 cases of typhoid every year for three years. The vaccination program would result in 28,428.32 DALYs avoided, demonstrating the remarkable public health impact this would have. The vaccination acceptance rate was very high at 88% of all respondents stating that they would take the vaccine if made available. The resulting ICER of -6.348 reveals that the vaccination program against typhoid fever is both extremely cheaper and very effective in averting both typhoid cases, burden and economic costs associated with the illness.

These results of incidence, 39.8 cases per 1000 are below the national average of 57.7.[17] In neighboring DRC, 1430 cases per 100,000 persons was reported in the midst of a typhoid epidemic in the same study. This reveals an endemic picture of typhoid fever in Kabale district but with potential to turn into an epidemic. The global case fatality rate is 0.95% which is higher than the finding in this study, which is arising from the scope of this study and some inherent limitations pointed out later in this section. Costs of both outpatient and inpatient typhoid illness, $75.62 and $33.85 respectively differ greatly with

those from a study done in Kasese in which inpatient cost and outpatient costs were found to be $4.3 and $53.8, because in the latter study, all indirect economic costs, such as lost productivity, transport and meals, were not considered in determining cost per episode. In contrast, costs of typhoid illness were found to be considerably higher in Tanzania where each episode cost $155.6 on average.[17] Unlike the context and setting of our study, in comparison to the Tanzania study, it was conducted in an urban center, with more economic activity which greatly impacted the costs especially from loss to productivity. In the characterization of the population's health seeking behavior to predict vaccination impact, the vaccine acceptance rate of 88% is well above the usual target of 70% that would make the intended impact realistic in all measures. Only 39% sought treatment for their typhoid symptoms in a health facility which reveals the prohibitive costs involved, and level of poverty in the district. It is also a wide spread practice to self-medicate since access to medicines in Uganda is largely unregulated and a major source of antibiotic resistance further complicating typhoid fever treatment and driving costs upwards. The ICER findings in this study of -6.348 is interpreted as being much less expensive and very effective. Using the quoted GDP per capita threshold to measure cost-effectiveness, the ICER value is much less than $817, making a vaccination intervention extremely cost effective, with net cost savings amounting to $119,814.92, over the three-year period when the vaccine offers protection. These results are similar and closely comparable to most of the existing literature. The government or public health system perspective was the most common perspective adopted among the published literature. The majority of existing evidence is from India and South Asia. The most common outcome measure (incremental cost-effectiveness ratio) evaluated was cost per disability-adjusted life-years (DALYs) averted and cost per case averted. Cook J et al study found ViPSs would produce net benefits if user fees or the social value of life were included in the analysis. The same study found their results to be very CE from a societal perspective, using 1 times the GDP per capita per DALY averted as a threshold. The parameters that most influenced CE include disease incidence, vaccine costs, and the economic benefits of disease risk reduction.[18] Across delivery platforms (campaign delivery in Uganda and a school-based delivery program in India, Indonesia, Pakistan, and Vietnam), these programs were very CE (using a threshold of 1 times the GDP per capita, per DALY averted) in all countries except Vietnam, which had a low typhoid incidence in the population studied. The higher the incidence, the more cost-effective vaccination will be, and the reverse is true.

Implications for policy

Cost-effectiveness analysis is a formal method of comparing alternative medical interventions with regard to their resource utilization (costs) and outcomes (effectiveness). The incremental cost-effectiveness ratio, the output of this study, is an informative measure generated from this analysis and represents the ratio of the difference in cost between two medical interventions, vaccination-against and treatment-for typhoid to the difference in outcomes between the two interventions. Thus, the incremental cost-effectiveness ratio summarizes the additional cost per unit of health benefit gained in switching from one medical intervention to another. The ICER of this study is negative, meaning that instead of incurring additional costs per benefit gained, cost savings are made with an even greater benefit. To determine the best allocation of public funds, policy makers need information about relative costs to determine what combination of interventions can yield the greatest improvements in health. From this study, the cost to the Kabale economy is $217,158.8 with no vaccination and a whopping $119,814.92 are saved from a single fixed post vaccination program. These benefits are not being realized because no resources are allocated to vaccination against typhoid. The status quo of "doing-nothing" is an expensive and with meagre benefits that perpetuates the typhoid disease burden in the population. Allocative efficiency in the context of public health can be achieved by moving resources from expensive and less effective interventions to more cost-effective interventions like typhoid fever vaccination once every three years. This has indeed been implemented in Africa, in Zimbabwe, where an eight-day campaign took place in nine high density suburbs from 25th February to 4th march 2019, and achieved 73% vaccine coverage by the 6th day.[19] Several other countries have developed typhoid fever vaccination programs such as Pakistan, India, Thailand where the vulnerable school going age children are routinely vaccinated, but why hasn't Uganda adopted a similar program? There has been a lack of information on the missed economic benefit of such an intervention, a gap that this study has to the best of my knowledge addressed, at least for Kabale district.[20,21]

Limitations

This study had three major limitations. First, the sample size was quite small, and the setting was in a peri-urban location, that would produce relatively conservative estimates of all costs, though the results can be generalized to localities or districts with the same characteristics of disease burden, economic level and geography/population features. Secondly, the incremental economic threshold used here, the GDP per capita method, in itself has its inherent limitations. It doesn't account for trade-offs that are real and consequential, even if selected programs all are below the GDP per capita thresholds. For example, a maternal and child health program may have a higher ICER than this Typhoid vaccination program, but opting for vaccination instead of maternal and child health will have real health consequences. Lastly, theoretically, some of the impact of vaccination may be off-set by acquired immunity in the absence of vaccination, a factor we did not account for in this analysis. In addition, our static model did not take

into account that after the three years of immunity conferred by the vaccine, incidence of typhoid may rebound. This occurs as the number of non-naturally immunized individuals builds up during the years the vaccine provides immunity. As a result, these estimates should be interpreted as particular to the three years following the onetime vaccination campaign, and the relatively short duration of protection given by vaccination underscores the need to consider long-term interventions, such as improved water sources and sanitation systems. These limitations though present have no substantial effect on the results or conclusions of this research but constitute research gaps that need further exploration in future cost effectiveness studies.

CONCLUSION

Information generated from this study clearly indicates the missed benefit of typhoid vaccination as the disease continues to remain endemic in the district. So, we derive two recommendations from this study: first of which is that a national strategy for the introduction of typhoid vaccine for public health use as a routine immunization program fitted within the expanded immunization programs for childhood diseases and secondly this information and cost-effectiveness evaluation studies should be used as tool for planning, implementation and delivery of health care services. It should also be used for resource mobilization for healthcare and prioritization of public health programs in resource limited settings. In conclusion, a one-time fixed-post typhoid vaccination campaign in Kabale District, Uganda, was estimated to be a very highly cost-effective intervention from the public sector health care delivery perspective. In India, similar outcomes were realized with the conjugate typhoid vaccine introduction, in which the campaign vaccination strategies were favored as compared to routine vaccination, though both were more cost effective than no vaccination and averted medical costs. Although not included in this analysis, if recent increases in the prevalence of drug-resistant typhoid strains continue, treatment would become less effective, increasing the costs and mortality from typhoid and thus increasing the benefits and cost savings from vaccination. This body of work therefore demonstrates the application of cost-effectiveness evaluation to a unique endemic setting and to the best of the researcher knowledge is the first of its kind in sub-Saharan Africa.

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