Typhoid burden and risk review in Rwanda, 2022: A pilot of the Burden and Risk Assessment of Typhoid (BRAT) framework and tool

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Executive summary

Typhoid fever, an acute generalized infection caused by *Salmonella* Typhi (*S.* Typhi), is an important public health problem in many low- and middle-income countries (LMICs).[1] An estimated 11 to 21 million cases and 128,000 to 161,000 deaths due to typhoid fever occur worldwide annually, predominantly in South and Southeast Asia and sub-Saharan Africa.[2] However, the emergence of multi-drug resistant (MDR) strains of *S.* Typhi and strains with resistance to azithromycin or extended spectrum cephalosporins has led to an increase in the proportion of patients experiencing clinical treatment failure and complications, such as intestinal perforations, and needing hospitalization.[1] Vaccination can help prevent typhoid fever. Since 2017, the World Health Organization (WHO) has recommended the programmatic use of typhoid conjugate vaccine (TCV) in children from six months of age in countries with endemic typhoid fever, with introduction prioritized in countries with a high burden of typhoid fever or a high burden of antimicrobial resistant *S*. Typhi.1 In Rwanda, the burden of typhoid fever is not well known, although the disease has been endemic for years, with outbreaks occurring occasionally.

The BRAT framework and tool, developed by US CDC and WHO with a group of international typhoid experts, provides a standardized methodology to collect, review, and interpret available typhoid fever burden and risk data. The framework includes six areas of assessment: incidence; prevalence of *S.* Typhi among other bloodstream infections (generally referred to as "prevalence" throughout the document); prevalence of antimicrobial resistance (AMR); outbreaks; intestinal perforations; and risk factors, including water, sanitation, and hygiene (WASH) indicators. Additionally, data on suspected typhoid cases and modelling data are collected and assessed but not scored. The Ministry of Health of Rwanda, through the Rwanda Biomedical Center (RBC), established a multi-sectoral technical working group, including laboratory, medical, surveillance, and WASH experts, to design, plan, and oversee the implementation of the pilot of the BRAT framework and tool in collaboration with US CDC and WHO (the BRAT core team). Data were searched through a literature review (incidence, AMR, outbreaks, WASH), from interviews with national and regional health officers (outbreak), review of five-year IDSR-HMIS data (suspected case data) and collected from health facilities (prevalence, AMR, intestinal perforations) and public laboratories (prevalence, AMR). The technical working group selected 13 health facilities or laboratories from all provinces (Kigali, Northern, Southern, Eastern, and Western Provinces) in 12 of 30 districts of Rwanda based on their capacity to perform blood culture or intestinal perforation surgery and to be generally representative of Rwanda. The National Reference Laboratory (NRL) was included a priori. Other facilities included and visited were Kigali Teaching University Hospital (CHUK), Butare Teaching University Hospital (CHUB), Rwanda Military Hospital (RMH), King Faysal Hospital (KFH), Ruhengeri Referral Hospital, Butaro District Hospital, Nemba District Hospital, Byumba District Hospital, Nyagatare District Hospital, Kibungo Referral Hospital, Gihundwe and Gisenyi District Hospital.

[1] World Health Organization. Typhoid vaccines: WHO position paper - March 2018. Weekly Epidemiological Record 2018; 13(93): 153-72.

[2] Typhoid GBD, Paratyphoid C. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 2019; 19(4): 369-81.

The findings are summarized by area of assessment:

- No studies on typhoid **incidence** were found in the literature. Therefore, this area of assessment was not scored.
- For **prevalence** of *S.* Typhi among bloodstream infections, we collected data on blood culture and the number of *S.* Typhi isolates identified during January 01, 2018– December 16, 2022. Of the 13 facilities visited, blood culture data were available from 8 facilities in 7 of the 12 districts visited. A total of 26,564 blood cultures were performed, with teaching hospitals performing the most blood cultures (92%). Five facilities performed blood culture for at least four years, while the remaining three (all district hospitals) performed blood culture for two or fewer years. Facilities reported a median of 9 different pathogens identified per year (IQR: 1.5–15.1). Six of the eight health facilities with available blood culture data reported at least one case of *S*. Typhi. Overall, 290 *S.* Typhi isolates were identified, representing 1% (n=290/26,564) of all blood cultures reported, with 56% (n=162) from the NRL. The median number of *S*. Typhi cases identified per health facility per year was 6 (IQR: 1–12). Detailed analysis of the NRL data showed that they received 1,930 blood samples for culture from all 30 districts, of which 162 were *S*. Typhi (8%). Four districts accounted for the majority of *S.* Typhi isolates (80%, n=130), suggesting differential geographic burden. There was an increasing trend of reported *S.* Typhi during 2018–2022, with the highest number reported in 2022 (49%, n=80/162). Most of those cases (74%, n=59/80) were reported from Gatsibo and Karongi districts, suggestive of potential outbreaks. In general, blood culture was not routinely ordered. It was occasionally conducted in district hospitals and based on clinician judgment in tertiary hospitals. Stockouts of reagents and supplies were frequent throughout the year in several facilities. Contaminants were detected in >10% of blood culture tests in several health facilities, indicating potential quality issues with blood collection and the need for further training of blood collection staff. The prevalence data suggest that *S*. Typhi is present in multiple geographic locations in Rwanda. Based on the BRAT framework, the median ranking of *S.* Typhi among bloodstream infections in health facilities with available blood culture data was sixth and *S.* Typhi ranked fourth or higher in 43% of the years with blood culture data based on cumulative years across 6 facilities, indicating medium burden with moderate to good confidence in the data. Due to the low sensitivity of typhoid surveillance associated with health-seeking behaviors, blood culture collection practices, test sensitivity, reagent availability, and concerns about blood culture quality, it is important to note that reported confirmed cases of *S.* Typhi represent only a small percentage of the true burden, and that the absence of data does not imply the absence of the disease.
- *S*. Typhi **AMR** data for 2018–2022 were available from 6 of 13 facilities visited (in 5 out of the 12 districts) included in the assessment. A total of 270 *S.* Typhi isolates were tested against at least one antimicrobial. Resistance to first line antimicrobials (ampicillin, chloramphenicol, cotrimoxazole) was high, ranging from 40% to 65%. Resistance to second line antimicrobials (fluoroquinolones and third generation cephalosporins) was less frequently reported (<40%), although still concerning.

Fluoroquinolones, the antimicrobials of choice for typhoid fever in Rwanda, showed an increasing resistance trend from 38% in 2018 to 70% in 2022. Resistance to third generation cephalosporins was 30%, with most resistant isolates (89%; n=67/75) reported by the NRL. Sixty-eight isolates underwent antimicrobial susceptibility testing (AST) for the three first-line antimicrobials. Of these isolates, 16 (24%) were classified as MDR. The inconsistent AST for first-line antimicrobials impeded the assessment of MDR prevalence as only 25% (n=68/270) of isolates were tested against all 3 first line antimicrobials. Thus, the MDR prevalence presented here may be an underestimate. Resistance to azithromycin was rarely reported (4 isolates). Although the reports of *S.* Typhi resistant to third generation cephalosporins and azithromycin are of concern, resistance to these antibiotics remains largely uncommon in Africa and thus these reports require further evaluation. Stockouts of AST discs and other reagents were frequently reported, with half of the sites reporting stockouts of >4 months in at least one year over the five-year period. The AMR data suggest that *S*. Typhi isolates with antimicrobial resistance, including MDR, fluoroquinolones, third generation cephalosporins, and potentially azithromycin resistance, are present in Rwanda posing a concerning threat.

The BRAT framework considered the AMR burden high based on reports of resistance to third generation cephalosporins and azithromycin with moderate to good confidence in the data.

- No **outbreaks** were reported in the last five years (2018–2022). However, high case reports of *S*. Typhi cases in several districts such as Gatsibo and Karongi in 2022 may indicate potential outbreaks and warrant further investigation.
- **Intestinal perforation** data were available from 10 of the 12 hospitals included in the assessment. Gross appearance at laparotomy (based on anatomic location or surgeon's judgment) was used as the minimum level of evidence required for an intestinal perforation to be considered as caused by *S.* Typhi. During 2018–2022, the 12 visited hospitals performed a total of 5,085 laparotomies. Five health facilities, including CHUK, RMH, Ruhengeri Hospital, CHUB, and Kibungo Hospital, each performed >300 laparotomies, accounting for 73% of all laparotomies performed. A total of 360 cases of intestinal perforation were reported that resided in 26 districts, of which 94 (26%) were diagnosed as typhoid-associated, although the information on the cause of intestinal perforations was often missing from surgical registers. These cases were reported from 5 health facilities, mostly CHUK (46%), Ruhengeri (28%), and CHUB (19%) and resided in 23 districts. We did not identify any apparent seasonal trends in intestinal perforation cases, which is consistent with previous research showing less seasonal variability for enteric and typhoid fever in areas closer to the equator.[3] Patient outcome data was rarely recorded in surgical registers, except at CHUB, so we were unable to report on mortality among typhoid associated intestinal perforation cases.

  These findings suggest severe typhoid cases (typhoid fever with intestinal perforation complications) are present in multiple geographic locations in Rwanda. However, the number of cases reported is

[3] Saad, N. J., Lynch, V. D., Antillón, M., Yang, C., Crump, J. A., & Pitzer, V. E. (2018). Seasonal dynamics of typhoid and paratyphoid fever. *Scientific reports*, *8*(1), 6870. https://doi.org/10.1038/s41598-018-25234-w

likely an underestimate of the true burden due to lack of information on the cause of intestinal perforations in most surgical registers. Based on the BRAT framework scoring criteria, the burden of severe typhoid fever was considered medium with moderate to high confidence in the data.

- The 2019–2020 Rwanda Demographic Health Survey (DHS) was used to collect information on **WASH and other risk factors**, 56% of households had access to basic water, 57% had access to basic sanitation, and 25% had access to handwashing facility at the national level. Access varies between urban and rural areas, with fewer rural households having access to basic water (49% vs 87%) and basic hygiene services (23% vs 37%). In terms of socioeconomic risk factors associated with typhoid fever, the DHS found that 32% of the population lived on <$2 per day (≥20% is considered high risk of typhoid fever) and that the prevalence of stunting was 33% (≥20% is considered high risk). At the provincial level, access to basic water ranged from 43–57% in 4 of the 5 provinces but was much improved in Kigali City (82%), access to basic sanitation ranged from 51–67%, and access to handwashing facilities was generally low, ranging from 13–36% with a high data quality score. Based on WASH and other risk factors, the risk for typhoid, based on WASH and other risk factors, was considered high at the national and provincial level with high confidence in the data.
- **Suspected typhoid cases** were reported to the Health Management Information System (HMIS). A total of 4,642 people were suspected of having typhoid fever. Reported suspected cases varied by district, the median suspected cases reported per district was 21.5 over the five years. Five districts reported >300 suspected cases during the assessment period, including Gasabo (n=2,068), Kicukiro (n=470), Nyarugenge (n=439), Kirehe (n=373), and Kayonza (n=355), accounting for 80% (n=3705/4642) of all reported cases. Eleven districts reported <10 suspected cases in the five-year period. Since the clinical presentation of typhoid fever is often indistinguishable from other acute febrile illnesses (e.g., malaria), typhoid fever diagnosed solely on clinical presentation is generally not considered reliable.[4] The BRAT framework does not score the suspected typhoid fever case data as part of the assessment as the quality and reliability of the evidence is not deemed to be sufficient. However, these data can be used to support the contextual picture of typhoid fever in Rwanda.
- **Modeling data** estimate a high burden of typhoid fever in Rwanda, with an incidence of 96 cases/100,000 population.[5]

The BRAT framework provides considerations for interpreting findings across all areas of the assessment to determine whether the epidemiological evidence gathered is sufficient to support a recommendation for TCV introduction. It is intended to gather available evidence from all data sources, including literature reviews. The findings from the Rwanda BRAT suggest typhoid fever is endemic in Rwanda with increasing antibiotic resistance and meet the BRAT criteria for moderate evidence to support TCV introduction.

[4] World Health Organization. Typhoid: Vaccine Preventable Diseases Surveillance Standards. 2018. https://www.who.int/publications/m/item/vaccine-preventable-diseases-surveillance-standards-typhoid.

[5] Institute for Health Metrics and Evaluation. Global Burden of Disease results tool. 2019. https://ghdx.healthdata.org/gbd-results-tool (accessed 04/17/2022.

Introducing TCV in Rwanda could help reduce typhoid fever and prevent the spread of antimicrobial resistant *S*. Typhi. The framework acknowledges that TCV introduction decision-making should be based on a number of additional factors outside of the scope of the BRAT assessment (e.g., cost-effectiveness, affordability, and programmatic feasibility of TCV use often in the context of other competing new vaccine introduction decisions) and is the ultimate responsibility of the national government with advice of the NITAG and other bodies as applicable. As such the primary BRAT outcome is not a decision on TCV introduction or not, but rather focuses on providing information regarding the disease burden and risk to inform the decision. As part of the process to gather evidence on typhoid fever burden in Rwanda, the BRAT identified several areas related to typhoid fever surveillance, diagnosis, outbreak detection and response, and prevention that could be strengthened, including optimizing blood culture capacity by using automated systems, standardizing guidance on appropriate use of bloodculture for febrile patients, implementing appropriate quality assurance and control procedures for AST, and improving access to good quality WASH infrastructure.

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Abbreviations

AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
BRAT	Burden and risk assessment of typhoid (BRAT)
BSI	Bloodstream infections
CDC	United States Centers for Disease Control and Prevention
CFR	Case fatality rate
DHS	Demographic and Health Surveys
EPA	Environmental Protection Agency
EPI	Expanded Programme on Immunization
FDA	Food and Drug Authority
HMIS	Health Management Information System
IDSR	Integrated Disease Surveillance and Response
JMP	Joint Monitoring Program
MDR	Multidrug resistant or multidrug resistance
MOH	Ministry of Health
NITAG	National Immunization Technical Advisory Group
NGO	Non-governmental organization
ODK	Open Data Kit
PCR	Polymerase chain reaction
PII	Personal Identifiable Information
RBC	Rwanda Biomedical Centre
RNEC	Rwanda National Ethics Committee
SAGE	WHO Strategic Advisory Group of Experts on Immunization
SETA	Severe Typhoid Fever Surveillance in Africa
TSAP	Typhoid Fever Surveillance in Africa Program
TCV	Typhoid conjugate vaccine
TWG	Technical working group
WASH	Water, sanitation, and hygiene
WHO	World Health Organization
XDR	Extensively drug resistant or extensive drug resistance

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1. Introduction

1.1. Typhoid Fever

Typhoid fever is an acute generalized infection caused by a highly virulent and invasive enteric bacterium, *Salmonella enterica* serovar Typhi, generally termed *Salmonella* Typhi (*S*. Typhi).[1] Typhoid fever can be a life-threatening febrile illness with a wide range of symptoms.[1] The most common include sustained fever, chills, and abdominal pain.[2,3] It is an important public health problem in many low- and middle-income countries (LMICs). An estimated 11 to 21 million cases and 128,000 to 161,000 deaths due to typhoid fever occur worldwide annually, predominantly in South and South-East Asia and sub-Saharan Africa.[4]

Humans are the only known reservoir of *S.* Typhi.[1] Transmission of infection is by the fecal-oral route from contact with contaminated food or water in the immediate environment or the broader environment.[1] Immediate environment contamination is due to temporary or chronic carriers shedding *S*. Typhi and inadequate hygiene and sanitation measures to prevent infection. Contamination of the broader environment is linked to sewage contaminated water supplies, inadequate treatment of piped water, or the use of untreated sewage as crop fertilizer. The risk of transmission is higher where the access to safe water and adequate sanitation is limited, and in the context of poor hygiene among food handlers.[1]

The non-specific presentation of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide range of other common febrile illnesses in regions where typhoid fever is endemic.[1] This is compounded by the limited availability of blood culture or other reliable laboratory methods. The World Health Organization (WHO) advises against using clinical diagnosis alone for typhoid fever surveillance as it can lead to inaccurate surveillance data and considerable misrepresentation of the incidence of typhoid fever and can also result in inappropriate treatment.[5] Typically, confirmation of the diagnosis relies on isolation of *S*. Typhi by blood culture, which has a sensitivity of 40%-60%.[1] In many LMICs, blood culture is not routinely performed.[1] Serological tests are available (e.g., WIDAL, TyphiDot), but lack diagnostic specificity and sensitivity in acute illness and thus are not considered reliable.[6] Molecular testing methods (e.g., PCR) are not commonly used for routine typhoid fever surveillance.

S. Typhi can be effectively treated with antimicrobials.[1] However, the emergence of multi-drug resistant (MDR) strains of *S*. Typhi (resistant to first-line antimicrobials ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole), strains with resistance to fluoroquinolones (which are now increasingly common in South Asia), and strains with resistance to azithromycin or extended spectrum cephalosporins (currently sporadically reported) has led to an increase in the proportion of patients experiencing clinical treatment failure and complications, needing hospitalization and longer hospital stays, and requiring more expensive treatment options.[7]

Complications of typhoid fever are estimated to occur in 10% to 15% of hospitalized patients and are more common in untreated or inadequately treated patients, whose illness has persisted for two weeks or more.[8] The most important life-threatening complications are intestinal hemorrhage, intestinal perforation, and encephalopathy with hemodynamic shock.[8] With adequate antimicrobial therapy, case-fatality rates in

typhoid fever range from 1% to 4%, rising to 10%–20% in untreated cases or cases treated with inappropriate antimicrobials.[9]

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination are all effective strategies for prevention and control of typhoid fever.[1] Improvements to water supplies, including filtration and chlorination, can reduce the burden of typhoid fever and have led to its elimination in many high-income countries.[1] Currently WHO recommends typhoid conjugate vaccine (TCV) as the preferred typhoid vaccine at all ages in view of its improved immunological properties, suitability for use in younger children, and expected longer duration of protection compared to the unconjugated Vi polysaccharide vaccine and live attenuated Ty21a vaccine.[1] In 2017, WHO recommended programmatic use of TCV in children from six months of age for countries with endemic typhoid fever, alongside health education, water, sanitation and hygiene improvements, and training of health professionals in diagnosis and treatment, with introduction to be prioritized in countries with the highest burden of typhoid disease or a high burden of antimicrobial-resistant *S*. Typhi.[1]

1.2. The BRAT Framework

In late 2017, WHO prequalified the first TCV and Gavi, the Vaccine Alliance approved the opening of a funding window for Gavi-eligible countries to apply for TCV introduction support. In line with the WHO recommendations, TCV introduction decisions should be based on an analysis of local data on the typhoid disease burden and risk factors for transmission. Furthermore, in the context of the potential need to prioritize among multiple vaccine introductions, countries may need to assess their typhoid fever burden and risk to justify the use of limited resources. However, a common barrier in many typhoid endemic countries has been the lack of or limited surveillance data to reliably estimate the disease burden.

The Burden and Risk Assessment for Typhoid (BRAT) framework, developed by US CDC and WHO with a group of international typhoid experts, outlines a systematic approach for collating and reviewing existing data sources on typhoid burden and risk at a national level to inform prevention and control decisions, including TCV introduction. It incorporates criteria for judging the quality of the data and focuses on six main areas of assessment:

1. Incidence of *S.* Typhi
2. Prevalence of *S*. Typhi among other bacterial bloodstream infections
3. Prevalence of antimicrobial resistance (AMR) among *S*. Typhi isolates
4. Typhoid fever outbreaks
5. Intestinal perforations
6. Risk factors for the transmission of typhoid (Water, Sanitation, & Hygiene [WASH] and others)

In addition, the framework allows for review and summary of related data from existing grey or published literature as well as primary data that do not fit into the six main areas of assessment, such as suspected case data and modelling data. It is important to note that while the term ‘burden’ is used in the BRAT framework, only components of burden are captured; the framework does not adhere to the strict definition of burden (e.g., a composite measure combining incidence, disability, duration, and death) but instead utilizes indirect

lines of evidence for some of these measures (e.g., incidence, prevalence, and clinical complications data). The BRAT Framework does not cover paratyphoid fever and invasive non-typhoidal salmonellosis.

2. Objectives

The primary objective was to review available data to assess the burden and risk of typhoid fever in Rwanda using the BRAT framework and tool to inform standardized data collection, quality review, summation, and interpretation.

The secondary objective was to evaluate the BRAT tool, including:

- To assess the feasibility and usability of the tool
- To review the validity of scoring of evidence and interpretation of the evidence
- To review the validity of scoring of data quality and interpretation of the data quality
- Identify challenges and areas for improvement of typhoid fever surveillance

The evaluation of the BRAT tool is reported in the addendum.

The specific data requirements for each area of assessment within the BRAT framework are described in detail in the Methods.

3. Methods

In collaboration with WHO and the US CDC (the BRAT core team), the Rwanda Ministry of Health, through the Rwanda BioMedical Center (RBC) planned and implemented the collection and review of available typhoid burden and risk data, informed by the BRAT framework and data collection tool.

A multi-sectoral technical working group was established by the RBC, including laboratory, medical, surveillance, immunization and WASH experts to design, plan, and oversee the assessment. A list of the technical working group members is provided in Appendix 1.

Based on the data needs for each of the areas of assessment as identified by the BRAT framework (Table 1), data were identified through a literature review (incidence, AMR, outbreaks, WASH), from interviews with national and regional health officers (outbreak), review of five-years of data of integrated disease surveillance and response (IDSR) data and collected from health facilities (prevalence, AMR, intestinal perforations), and public laboratories (prevalence, AMR). The technical working group selected health facilities or laboratories from all five provinces (Kigali, Northern, Southern, Eastern, and Western Provinces) based on their capacity to perform blood culture or intestinal perforation surgery and to be generally representative of Rwanda. The national reference laboratory (NRL) was included a priori. A list of the health facilities and laboratories included in the assessment is provided in Table 2 and Figure 1. Official letters were sent to each director of hospital and laboratory to facilitate access to data. Five years of data (2018–2022) were collected for blood culture and antimicrobial testing, as well as intestinal perforation data. Data collectors, with predominantly laboratory or data management backgrounds, were identified from the selected health facilities and trained on key data needs according to the BRAT framework and tool, potential data sources, data entry requirements for the BRAT tool, and the data quality review process. Data collection teams entered data into the Open Data

Kit (ODK)-based BRAT tool in the field. The data included in each area were assessed for quality against a pre-set list of quality indicators (Table 1).

National-level supervisors from RBC and WHO supervised the data collection teams in the field and helped facilitate data access and address data quality issues. The BRAT core team coordinated data collection with RBC, providing daily feedback on data and guidance to data collectors and supervisors. A consultant, supported by the BRAT core team, primarily collected WASH data, suspected case data, and outbreak data. Follow-up exchanges with data collection teams and supervisors were conducted to clarify any issues with the entered data. The preliminary findings were reviewed by a group of international typhoid experts.

The data sources recommended for each area of assessment by the BRAT framework are described, along with the scoring and quality assessment indicators (Table 1). Additional information on the potential recommended data sources is provided in more detail below for each area of assessment.

3.1. Adjusted incidence of *S*. Typhi

The crude incidence of typhoid is determined by the number of blood culture-confirmed cases divided by the total population in a catchment area. However, as blood culture testing is often limited, this measure may underestimate the true incidence of typhoid. To accurately measure population-based incidence, fully ascertained numerators and denominators are required and correction factors may need to be applied to generate more robust estimates. Thus, for the incidence area of assessment the BRAT framework recommends using the adjusted incidence, which accounts for test sensitivity, health-seeking behavior, and other factors. Adjusted incidence estimates should be based on blood culture or PCR confirmed *S*. Typhi cases. To estimate the adjusted incidence, we searched for prospective, active, population-based surveillance, or hybrid/multiplier studies that combined prospective, passive sentinel site surveillance with healthcare utilization surveys to adjust for under-ascertainment from the sentinel sites, typically, published and unpublished studies.[10]

3.2. Prevalence of *S.* Typhi among other bacterial bloodstream infections

Since fully ascertained incidence data are often unavailable, especially in LMICs, data on the prevalence of *S*. Typhi (proportion of population with *S*. Typhi in a given period) can be useful to draw conclusions on typhoid occurrence. Prevalence data from surveillance or studies of community-onset bloodstream infections can be used to indicate that typhoid is absent or present at a low or high level using the rank order of laboratory-confirmed *S*. Typhi compared to other pathogens.[11] Appropriate data sources include laboratory reports of bacterial pathogens isolated by blood culture, laboratory surveillance data, or published and unpublished studies. To determine the rank order of *S*. Typhi among other bacterial bloodstream pathogens, we collected information on the six most isolated pathogens, including *S*. Typhi, from the visited health facilities for each year of the last 5 years (2018–2022).

3.3. Antimicrobial resistance

The prevalence of antimicrobial resistant *S.* Typhi among culture-confirmed typhoid is an important measure of disease burden. With the emergence of *S*. Typhi strains with resistance to single or multiple antimicrobials,

treatment options are becoming increasingly limited in certain areas of the world. WHO recommends TCV introduction if there is evidence of high or increasing levels of antimicrobial resistant typhoid; therefore, monitoring AMR is critical.[1] Appropriate data sources would include laboratory reports of AMR testing of *S*. Typhi isolates, laboratory surveillance data, or (un)published studies that documented antimicrobial testing among *S*. Typhi isolates in the last 5 years. Antimicrobials of interest include ampicillin, chloramphenicol, cotrimoxazole (trimethoprim-sulfamethoxazole), fluoroquinolones (ciprofloxacin, levofloxacin, etc.), third generation cephalosporins, azithromycin, and carbapenems. *S*. Typhi isolates are classified as MDR if they are resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, and extensively drug resistant (XDR) if they are resistant to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins. To estimate the prevalence of AMR, we collected laboratory data of AMR testing of *S*. Typhi isolates from the visited sites that documented antimicrobial testing among *S*. Typhi isolates during 2018–2022.

3.4. Outbreaks of typhoid fever

The WHO surveillance standards for typhoid defines an outbreak as an increase in the absolute number of cases occurring in a population over a defined time period, above what would normally be expected for the particular community, geographical area or season.[5] A confirmed typhoid fever outbreak requires confirmation of S.Typhi in at least two reported cases by blood culture or PCR. Typhoid disease burden estimations focus on endemic disease and often exclude data from outbreaks, though outbreaks are important contributions to the burden of typhoid in a country or area. Collecting data on the size (number of cases), duration, frequency, case fatality ratio, and antimicrobial resistance patterns of outbreaks is a valuable measure of typhoid burden.[12] Appropriate data sources include outbreak reports, (un)published studies, and potentially surveillance data that have documented typhoid fever outbreaks in the last 5 years.

3.5. Intestinal perforations

Intestinal perforation, defined as a loss of continuity of the bowel wall, is a potentially devastating complication that can result from a variety of disease processes.[13] Intestinal perforation is the hallmark complication of typhoid fever and can be associated with high mortality rates.[1,14,15] Unless the incidence and proportion of perforations caused by typhoid is known, it is not possible to estimate burden based on perforations alone. While terminal ileal perforation is widely considered as pathognomonic of typhoid fever, other infectious diseases like tuberculosis may have a causative role especially in medium and low typhoid incidence settings. As the incidence of typhoid decreases, the likelihood of typhoid as the cause of perforations will also decrease. However, collecting data on the burden of intestinal perforations and analyzing trends over time may provide information on typhoid presence in a country and disease severity. If apparent seasonal increases in intestinal perforation are identified, this may indicate the presence of typhoid, as it is unlikely that other causes of intestinal perforation would result in seasonal increases. Methods of confirmation for intestinal perforations likely vary by hospital and by country. Per the BRAT guidelines, gross appearance at laparotomy based on anatomic location or surgeon's judgment is used as the minimum level of

evidence required for an intestinal perforation to be considered due to typhoid. This will identify as many typhoid-related intestinal perforation cases as possible but could include non-typhoid perforation cases too. Appropriate data sources include health facility registers for the last 5 years (2018–2022) to determine the annual number of suspected and confirmed typhoid associated intestinal perforation cases, likely from inpatient and surgical wards, as well as the District Health Management Information System (DHMIS), and (un)published studies.

3.6. Water, sanitation, and hygiene (WASH) and other risk factors for typhoid fever

Several studies have detailed the potential risk factors for typhoid, such as the use of unimproved or unsafe water, unimproved or damaged sanitation facilities, interrupted municipal water supply, eating food prepared at community markets, the proportion of the population living in extreme poverty, and prevalence of stunting, among others.[16,17] Based on the BRAT framework, both national and sub-national indicators for potential typhoid fever risk factors should be reviewed. The latest available national data on the proportion of the population living with less than $2 per day and the prevalence of stunting can be sourced from the Global Data Lab (globaldatalab.org). The latest national and sub-national (where available) coverage of basic water, sanitation, and handwashing can be sourced from the WHO/UNICEF Joint Monitoring Programme (washdata.org).

The definitions used are indicated below:

- **Basic Water**: Drinking water from an improved source (piped water, public tap, borehole, protected dug well, protected springs, rainwater), provided collection time is not more than 30 minutes for a roundtrip including queuing.
- **Basic Sanitation**: Use of improved sanitation facilities (flush toilet, pit latrine with slab, ventilated improved pit latrine, composting toilet) which are not shared with other households.
- **Basic Handwashing**: Availability of a handwashing facility on premises with soap and water.

The 2019–2020 Rwanda DHS was used to collect information on WASH and other risk factors.

3.7. Clinically suspected case data

The clinical presentation of typhoid is non-specific and can vary substantially. In areas with limited blood culture capacity, clinicians may diagnose typhoid based on clinical presentation alone or with the Widal test (a serological test). The Widal test has low specificity and cannot distinguish acute versus past infection.[18] Since the clinical presentation of typhoid fever is often indistinguishable from other acute febrile illnesses e.g., malaria, typhoid fever diagnosed solely on clinical presentation is not considered reliable.[5] However, suspected case data may suggest the presence of typhoid in the area, and seasonal trends in the data, particularly when consistent with known seasonal trends for typhoid, may further strengthen this evidence. Appropriate data sources include surveillance or health facility reporting data which can include clinically suspected typhoid fever cases for the last 5 years, with or without additional testing.

We collected suspected case data for 2018–2022 from the Rwanda HMIS data system at the national level.

3.8. Additional potential data sources (not directly collected through the BRAT tool)

A comprehensive grey and published literature review is recommended as part of the BRAT framework to support data collection for the specified areas of the tool, but also to capture essential information for assessing typhoid burden and risk that would not explicitly be documented in the six areas of assessment in the BRAT framework. Modeling data is a key example of this and can inform the risk of typhoid using data from past studies in that country, from neighboring or similar countries, or from regional data. Data from systematic reviews, vital registries, and other forms of high completeness data are used in the models and are often compelling justification of burden in a country of interest. Findings based on modeled typhoid burden, WASH assessments, or other risk factors for typhoid from the Institute for Health Metrics and Evaluation (IHME), Yale University, PATH, and other disease modelers should be compiled, and reviewed by the national immunization technical advisory group (NITAG) as supporting evidence alongside the data collected using the BRAT framework.

Table 1. The areas of assessment within the Burden and Risk Assessment of Typhoid (BRAT) framework, including the scoring and quality indicators, and potential data sources

Area of assessment	Scoring indicator(s)	Quality indicators	Potential data Sources
Incidence	Adjusted incidence	• Study period • Representativeness • Case definition • Adjustment factors • Duration of incidence study • Population estimates • Contamination rates and documentation • Testing delays due to stockouts • Protocols for bacterial isolation and identification available and reviewed • Quality control records	• Prospective, active population-based surveillance • Hybrid/multiplier studies that combine sentinel site surveillance with healthcare utilization surveys
Prevalence of *S*. Typhi	Rank order of *S.* Typhi in comparison to other bacterial blood infections Proportion of years where *S.* Typhi ranked 4th or higher	• Sample size • Case confirmation methods • Systematic blood collection for diagnosis • Laboratory contamination rates documented • Delays in testing due to stockouts • Protocols for bacterial isolation and identification available and reviewed • Quality control records	• Health facilities/laboratories • Community-acquired infection studies • National/sub-national surveillance data • Published and unpublished studies

Area of assessment		Scoring indicator(s)	Quality indicators	Potential data Sources
Antimicrobial Resistance		Antimicrobial resistance patterns	• AST frequency • Quality assurance testing • Participation and performance in External quality assurance programs for AST • Delays in testing due to stockouts • Availability of protocols for AST • Quality control records	• Health facilities/laboratories • National/sub-national surveillance data • Published and unpublished studies
Outbreaks		• Frequency, Duration, Size • Case fatality proportion • Antimicrobial resistance pattern of causative strain	• Surveillance data availability • Outbreak confirmation • Mortality data availability and line list completed for outbreak	• Outbreak reports • National/sub-national surveillance data • Published and unpublished studies
Intestinal perforations		• Mean proportion of typhoid-associated intestinal perforation cases among all non-traumatic intestinal perforations • Mean proportion of non-traumatic intestinal perforation cases among all laparotomies • Appearance of seasonal trends	• Information on causes of intestinal perforation • Confirmation methods of typhoid intestinal perforation	• Published and unpublished studies • Health facilities with surgical departments that perform intestinal perforation surgery • Health information systems
Typhoid risk factors	**Water, sanitation, and hygiene**	• Access to basic water, sanitation, handwashing	• Not applicable	• National o WHO/UNICEF Joint Monitoring Program o Global Data Lab o National surveys (MICS, DHS)
	Socioeconomic Status	• Proportion of population living on <$2/day • Prevalence of stunting		
Clinically suspected case data		Not applicable	Not applicable	• Surveillance systems • Health facilities

4. Findings

During December 5–16, 2022, 6 data collection teams visited 13 health facilities in 12 of the 30 districts of Rwanda to collect data on laboratory-confirmed cases of typhoid fever and cases of intestinal perforation. The health facilities visited, their capacity to perform blood culture, *Salmonella* serovar differentiation, and antimicrobial susceptibility data, and the teams' ability to access laboratory quality control records were documented. A review of literature was conducted for studies on incidence, prevalence, AMR, and intestinal perforation. RBC surveillance focal persons were contacted to collect information on outbreak reports and DHMIS staff to collect suspected typhoid fever cases. The findings are presented by area of assessment with an overall interpretation of the findings described in section 5.

Table 2. Health facilities and laboratories visited by province and district, Rwanda BRAT

Province	District	Name of the facility
City of Kigali	Nyarugenge	Kigali Teaching Hospital (CHUK)*$
	Nyarugenge	National Reference Laboratory (NRL)* $
	Gasabo	King Faisal Hospital (KFH)* $ &
	Kicukiro	Rwanda Military Hospital (RMH)* $
Northern	Musanze	Ruhengeri Hospital
	Gakenke	Nemba Hospital*$
	Gicumbi	Byumba Hospital
	Burera	Butaro Hospital*
Eastern	Ngoma	Kibungo Hospital*
	Nyagatare	Nyagatare Hospital
Western	Rubavu	Gisenyi Hospital
	Rusizi	Gihundwe Hospital
Southern	Huye	Butare Teaching Hospital (CHUB)* $

*Facilities that performed blood culture; $Facilities that reported laboratory-confirmed *S.* Typhi; &Public-private health facility

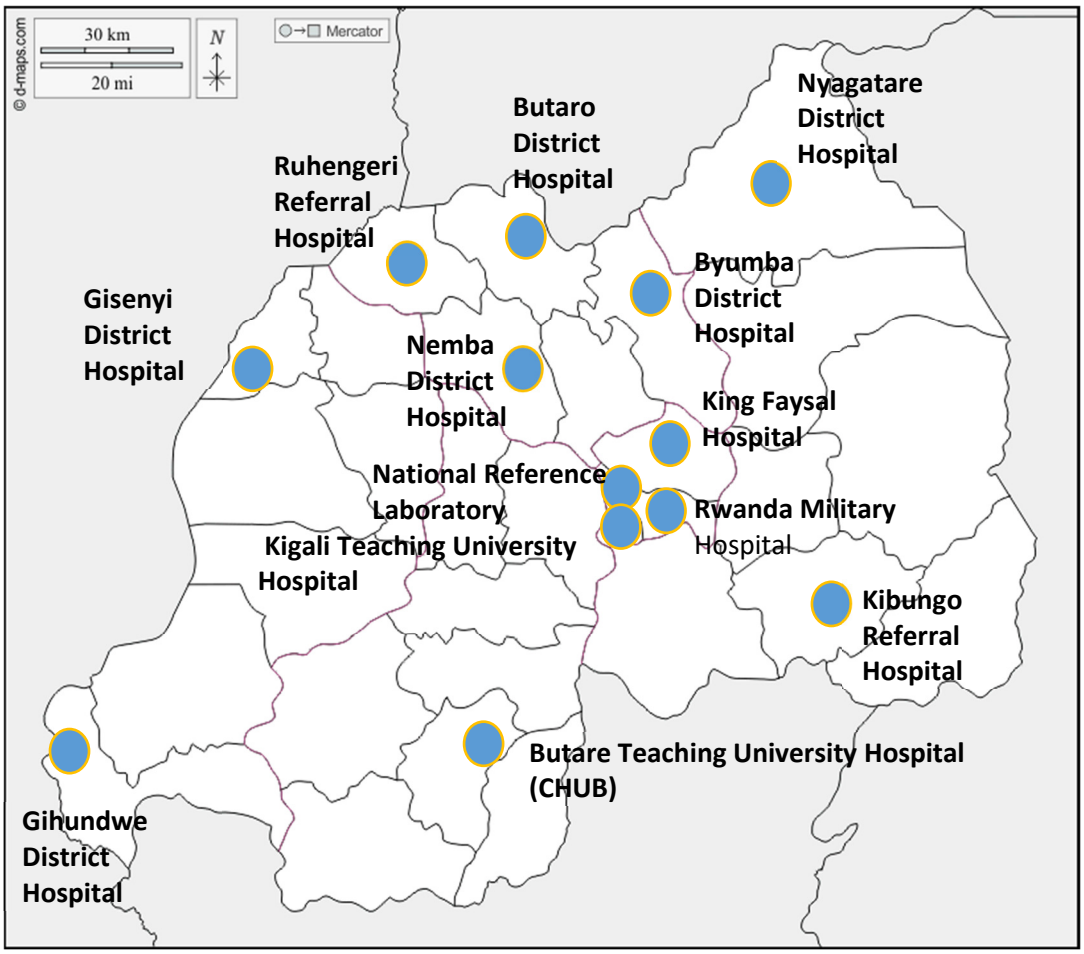

Figure 1. Geographic distribution of health Facilities and laboratory included in Rwanda BRAT

4.1. Incidence

No studies on the adjusted incidence of typhoid fever in Rwanda were found in the published and grey literature. Therefore, this area could not be assessed.

4.2. Prevalence

Findings

A total of 13 facilities in 12 districts were visited. Eight facilities had blood culture data available for January 01, 2018–December 16, 2022, with 26,564 blood cultures performed during the time period (Figure 2). These facilities included the four teaching hospitals, the National Reference Laboratory (NRL), and three district hospitals (Nemba, Kibungo, and Butaro). The teaching hospitals performed the most blood cultures (92%). Five facilities performed routine blood cultures for at least four years, while the remaining three (all district hospitals) performed any blood cultures for two or fewer years. Among the eight sites which conducted blood cultures, the median number of blood cultures performed per health facility per year was 524 (interquartile range [IQR]: 74–1,133; range: 14–2,645). Facilities reported a median of 9 different pathogens identified per year (IQR: 1.5–15.1), with 3 facilities, including 2 teaching hospitals and the NRL, reporting an average of ≥ 10

different pathogens per year. Teaching hospitals reported more blood cultures per year than the NRL, except for the Rwanda Military Hospital (RMH). Six of the eight health facilities with available blood culture data reported at least one case of *S*. Typhi. These facilities were in five of the 12 districts visited. During 2018–2022, 290 *S.* Typhi isolates were identified in these facilities, representing 1% (n=290/26,564) of all blood cultures reported (Figure 3). Of the 290 *S*. Typhi isolates, 56% (n=162) were from the NRL. A median of 6 *S*. Typhi cases (IQR: 1–12) were identified per health facility per year

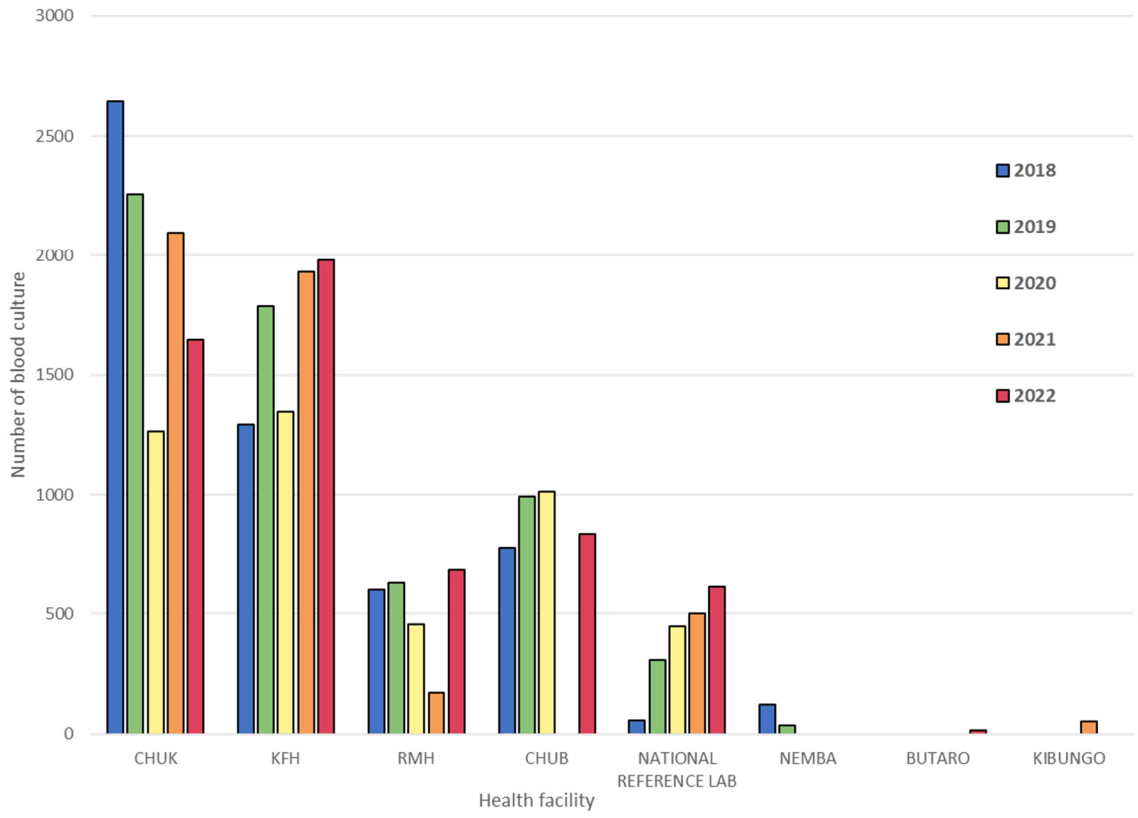

Figure 2. Blood cultures performed by health facility and year, Rwanda 2018–2022

The NRL plays a crucial role in the surveillance of typhoid fever, routinely assisting health facilities without blood culture capabilities by providing media bottles for specimen collection, overseeing specimen transport, and conducting testing. However, the NRL tested fewer specimens than the teaching hospitals, which is unexpected since it receives specimens from across the country. This was likely due to several challenges, including limited resources and inadequate supply monitoring, which have limited its performance.

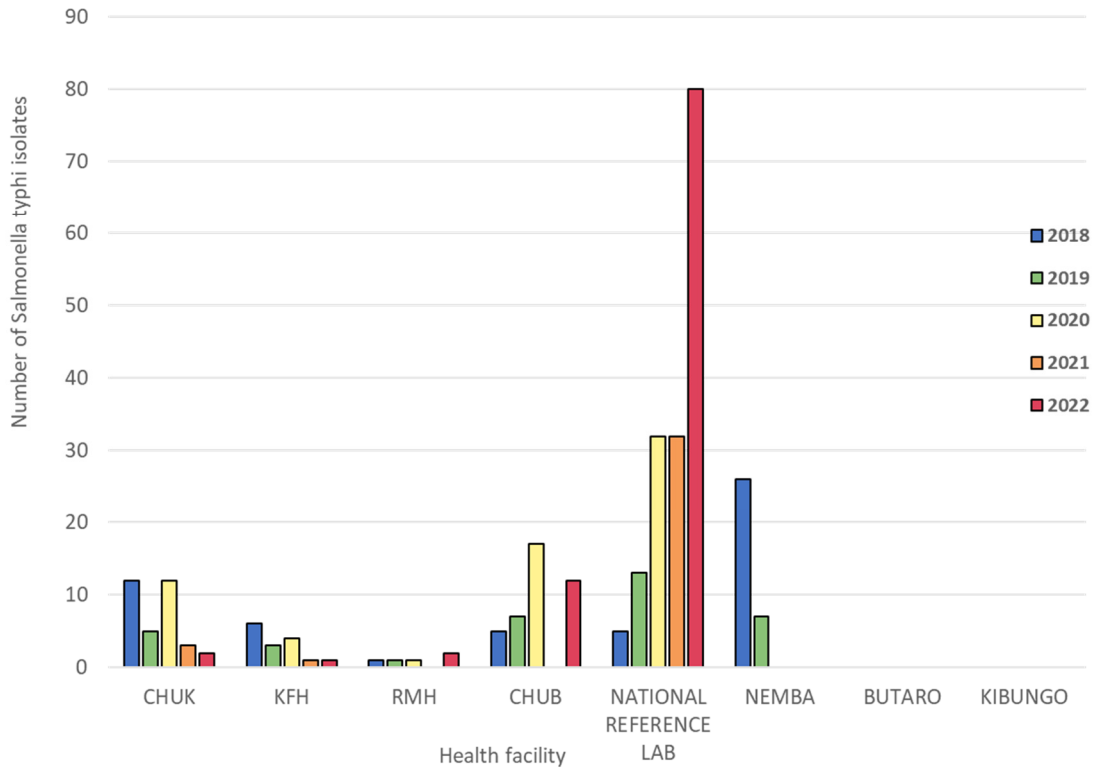

Figure 3. *S.* Typhi cases by health facility and year, Rwanda 2018–2022

During 2018–2022, the NRL received 1,930 blood samples for culture from all 30 districts. Among these blood samples, *S*. Typhi was isolated from 162 (8%), representing 18 districts (Figure 4). *S.* Typhi positivity varied by district, ranging from 1–23%. Four districts, including Gatsibo (29%, n=47/162), Karongi (18%, n=29), Nyaruguru (18%, n=29), and Rutsiro (15%, n=25), accounted for the majority of *S.* Typhi isolates (80%, n=130) and had the highest positivity proportion (12–23%), suggesting differential geographic burden. *S.* Typhi isolates from the NRL showed an increasing trend during 2018–2022, with the highest number reported in 2022 (49%, n=80/162); most (74%, n=59/80) were from Gatsibo and Karongi districts, suggestive of potential outbreaks. Compared to other bloodstream pathogens, *S*. Typhi was generally identified as the first or second most prevalent pathogen in each of the 5 years of data collected from the NRL.

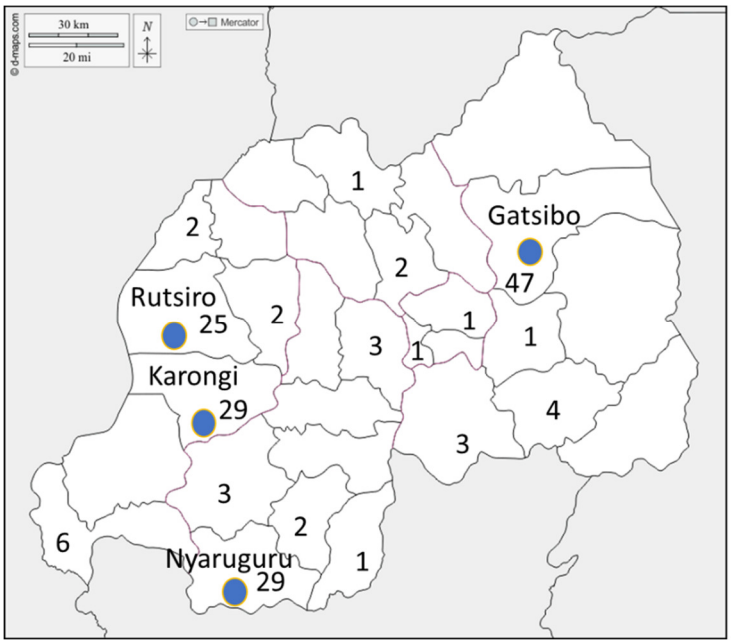

Figure 4. *S.* Typhi isolates by location of health facility at the National Reference Laboratory, Rwanda 2018-2022

In general, blood culture was not routinely performed outside of tertiary hospitals, and where blood culture capacity exists, blood culture was not routinely ordered by clinicians for febrile patients. It was done occasionally in district hospitals and generally based on clinician judgment in tertiary hospitals. Blood culture was reported to be the only typhoid fever diagnostic test used in the health facilities visited (all public health facilities). Stockouts of reagents and supplies were frequent in several facilities throughout the year (>4 months per year in three health facilities; one teaching hospital reported a stockout of >9 months). At the laboratory level, six health facilities performed quality control on media and reagents regularly. Teams reported several contaminants among the pathogens isolated (>10% in three health facilities), indicating potential quality issues with blood collection and the need for further training of blood collection staff.

Interpretation

The prevalence data suggest that *S*. Typhi is present in multiple geographic locations in Rwanda. Based on the BRAT framework, the median ranking of *S.* Typhi among bloodstream infections in health facilities with available blood culture data was sixth, as shown in Figure 5, and *S.* Typhi ranked fourth or higher in 43% of the years with blood culture data based on cumulative years across 6 facilities (Table 3), indicating medium burden with moderate to good confidence in the data. Due to the low sensitivity of typhoid surveillance associated with health-seeking behaviors, blood culture collection practices, test sensitivity, reagent availability, and concerns about blood culture quality, it is important to note that reported confirmed cases of *S.* Typhi represent only a small percentage of the true burden, and that the absence of data does not imply the absence of the disease.

Table 3. Number of years with blood culture data where Salmonella Typhi was ranked 4th or higher

Rank order	Years at rank (n=28)	% years at rank
1	5	18
2	3	11
3	3	11
4	1	4
5	1	4
6	15	54

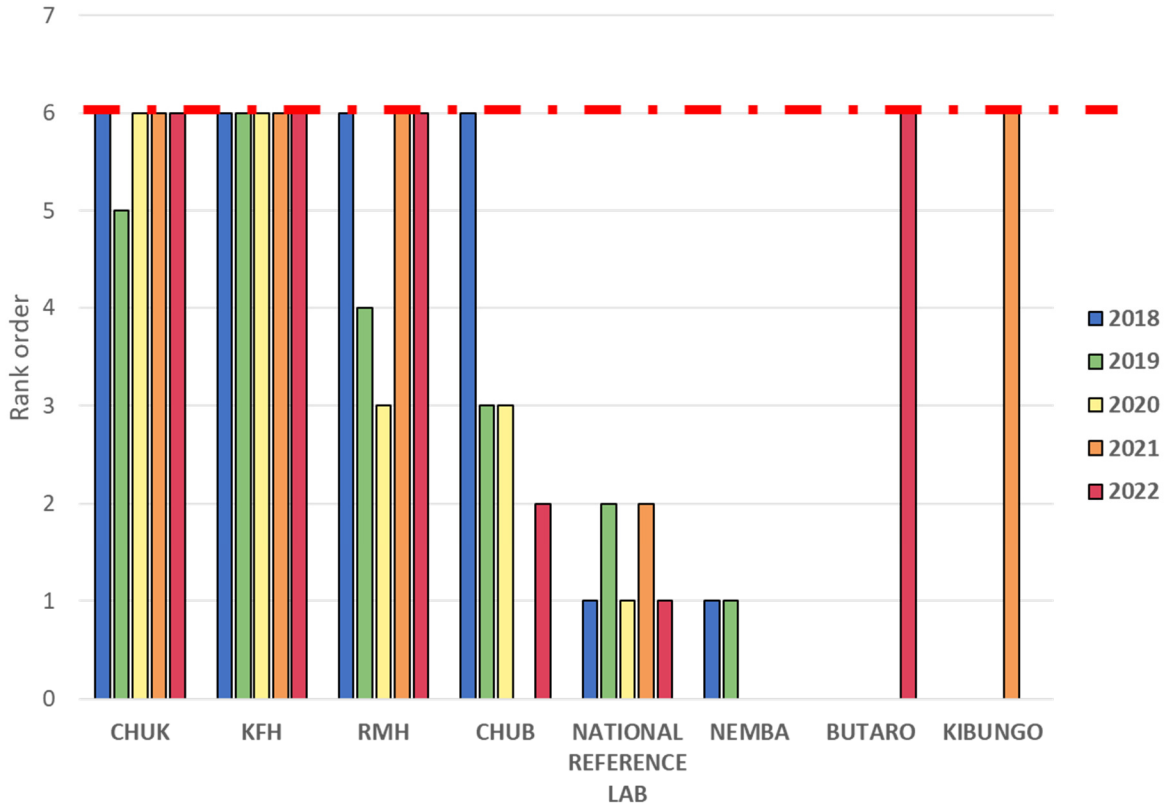

Figure 5. Rank order of S. Typhi among bloodstream infections

4.3. Antimicrobial resistance

Findings

Antimicrobial susceptibility testing (AST) was performed in all six facilities where *S.* Typhi was identified. A total of 270 *S*. Typhi isolates, including 269 isolates from blood samples and 1 isolate from a stool sample, underwent AST during 2018–2022. Six classes of antimicrobials were commonly tested, as shown in Table 4.

Resistance to at least one antimicrobial was reported across all five years under review and from patients residing in 21 districts. Resistance to first line antimicrobials (ampicillin, chloramphenicol, cotrimoxazole) was high, ranging from 40% to 65%, although, AST was not routinely performed for all three, with a noticeable reduction in testing for chloramphenicol (69 isolates resistant to both ampicillin and cotrimoxazole were not tested for susceptibility to chloramphenicol). Resistance to second line antimicrobials (fluoroquinolones and third generation cephalosporins) was less frequently reported (<40%), although still concerning. Fluoroquinolones, the antimicrobial of choice for typhoid fever in Rwanda, showed an increasing resistance trend from 38% in 2018 to 70 % in 2022. Overall resistance to third generation cephalosporins was 30%, with most resistant isolates (89%; n=67/75) reported by the NRL. Sixty-eight isolates underwent AST for the three first-line antimicrobials. Of these isolates, 16 (24%) were classified as MDR. The inconsistent AST for first-line antimicrobials impeded the assessment of MDR prevalence as only 25% (n=68/270) of isolates were tested against all 3 first line antimicrobials. Thus, the MDR prevalence presented here is likely an underestimate. Resistance to azithromycin was rarely reported (4 isolates). Although the reports of *S.* Typhi resistant to third generation cephalosporins and azithromycin are of concern, resistance to these antibiotics remains largely uncommon in Africa and thus these reports require further evaluation.[19]

Table 4. Antimicrobial sensitivity testing results for *S*. Typhi isolates identified at 13 health facilities visited, Rwanda BRAT, 2018–2022

Antimicrobial	Number of tested isolates (n=270)	Number of resistant (reduced susceptibility) isolates	Percent resistant (reduced susceptibility)
Ampicillin	213	137	64
Chloramphenicol	93	37	40
Cotrimoxazole (trimethoprim-sulfamethoxazole)	189	123	65
Fluoroquinolones	253	96 (43)	38 (17)
Third generation cephalosporins	247	75	30
Azithromycin	51	4	8
Multidrug resistant (MDR)*	68	16	24
Extensively drug resistant (XDR)	55	0	0

*MDR – resistant to ampicillin, chloramphenicol, and cotrimoxazole (trimethoprim-sulfamethoxazole), which are considered first-line antibiotics. $ XDR – resistant to ampicillin, chloramphenicol, cotrimoxazole (trimethoprim-sulfamethoxazole), fluoroquinolones, and third generation cephalosporins.

Information on quality indicators was available for the six health facilities visited. Stockouts of AST discs and other reagents were frequently reported, with half of the facilities reporting stockouts of >4 months in at least one year over the five-year period. All six health facilities had AST protocols that were readily available, and 2 of the 6 health facilities had reviewed them in the year prior to the assessment. Five of the six health facilities had quality control records available for media and reagents documenting that they had passed quality

control prior to use and had participated in an external quality assurance program for AST, with 2 health facilities scoring ≥95%.

Interpretation

The AMR data suggest that *S*. Typhi isolates with antimicrobial resistance, including MDR, fluoroquinolones, third generation cephalosporins, and potentially azithromycin resistance, are present in Rwanda posing a concerning threat. Based on the BRAT framework, the AMR burden was scored as high due to the presence of resistance to third generation cephalosporins and azithromycin with moderate to good confidence in the data.

4.4. Outbreak

The national surveillance division at RBC reported that no national and/or sub-national typhoid fever outbreaks were reported during 2018–2022. No reports of outbreaks were identified through the grey and published literature review. However, higher *S*. Typhi case reports (identified through the NRL database) from some districts in 2021 (Nyaruguru) and 2022 (Gatsibo and Karongi) may indicate potential outbreaks that would have warranted further investigation. These were not officially investigated or reported as outbreaks and may warrant a review of the procedures for triggering a typhoid fever outbreak investigation.

In conclusion, this area of assessment was not scored because there were no officially declared outbreaks during 2018–2022.

4.5. Intestinal perforations

Findings

Between 2018 and 2022, all 12 hospitals visited performed a total of 5,085 laparotomies. Five health facilities, including CHUK, RMH, Ruhengeri Hospital, CHUB, and Kibungo Hospital, performed >300 laparotomies each during 2018–2022, accounting for 73% (n=3,730/5,085) of all laparotomies performed (Table 5). Overall, 360 cases of intestinal perforation were reported that resided in 26 districts. Most (63%; n=225/360) were reported from CHUK and CHUB. Seven of the 12 hospitals, including six district hospitals and KFH, reported <5 intestinal perforation cases each over the five-year period. In total, 94 (26%) intestinal perforation cases were considered associated with typhoid fever. These cases were reported from 5 health facilities, mostly CHUK (46%, n=43/94), Ruhengeri (28%; n=26), and CHUB (19%; n=18)) and resided in 23 districts (Figure 6). Nearly all suspected typhoid associated intestinal perforation cases were confirmed by gross appearance at laparotomy (92%; n=94/102) (Figure 7). Seasonal trends among intestinal perforation cases could provide contributing evidence of typhoid fever. For Rwanda, we did not identify any apparent seasonal trends in intestinal perforation cases, which is consistent with previous research showing less seasonal variability for enteric and typhoid fever in areas closer to the equator).[20] Patient outcome data was rarely recorded in surgical registers, except at CHUB, so we were unable to report on mortality among typhoid associated intestinal perforation cases.

The information on quality indicators was available from all 11 health facilities conducting laparotomies. Information on the cause of intestinal perforations was often missing from surgical registers. Of the 10 health

facilities that reported cases with intestinal perforation, only 3 had more than 50% of cases with information on the cause of intestinal perforation. All 5 health facilities that reported typhoid-associated intestinal perforation confirmed the cases by gross appearance at laparotomy.

Interpretation

The intestinal perforation data suggest that severe typhoid cases, evidenced by typhoid associated intestinal perforations, are present in multiple geographic locations in Rwanda. However, the number of cases reported is likely an underestimate of the true burden due to lack of information on the cause of intestinal perforations in most surgical registers. Based on the BRAT framework, the intestinal perforation data was scored as medium burden with moderate to good confidence in the data.

Table 5. Laparotomies, intestinal perforation cases, and typhoid-associated intestinal perforation cases by facility visited, Rwanda BRAT, 2018–2022

Health Facility	Number of laparotomies	Number of intestinal perforation cases (% among all laparotomies)	Typhoid-associated intestinal perforations[1]	Typhoid-associated intestinal perforation cases[2] (% among all intestinal perforations)	Typhoid-associated intestinal perforation cases[2] (% among suspect/typhoid associated intestinal perforations)
CHUK	1,828	124 (7)	44	43 (35)	43 (98)
RMH	760	39 (5)	7	7 (18)	7 (100)
Ruhengeri	663	70 (11)	28	26 (37)	26 (93)
CHUB	485	101 (21)	20	18 (18)	18 (90)
Kibungo	381	16 (4)	1	0 (0)	0 (0)
Nyagatare	273	0 (0)	0	0	0
KFH	241	2 (0)	0	0	0
Gihundwe	186	1 (0)	0	0	0
Gisenyi	94	4 (4)	2	0 (0)	0 (0)
Butaro	88	2 (2)	0	0	0
Nemba	60	0 (0)	0	0	0
Byumba	26	1 (0)	0	0	0
Total	**5,085**	**360 (7%)**	**102**	**94 (26)**	**94 (92)**

[1]Suspected or confirmed typhoid associated intestinal perforation cases; [2]Confirmed by gross appearance at laparotomy.

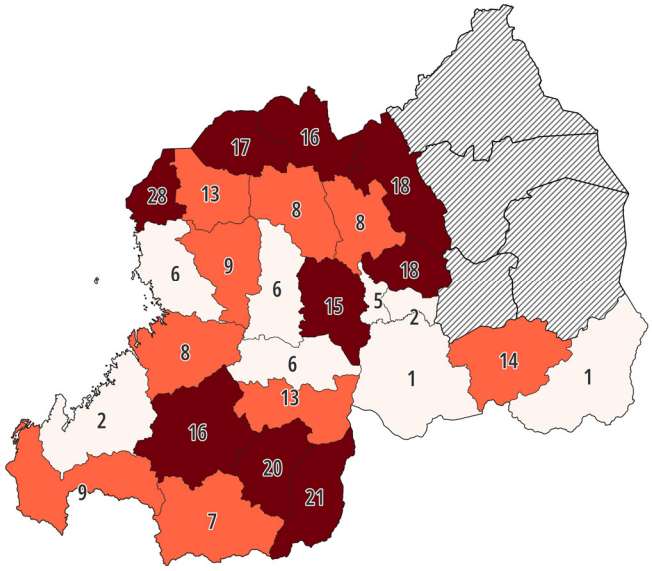

Figure 6. Distribution of intestinal perforation (any cause) cases by district of residence, 2018–2022

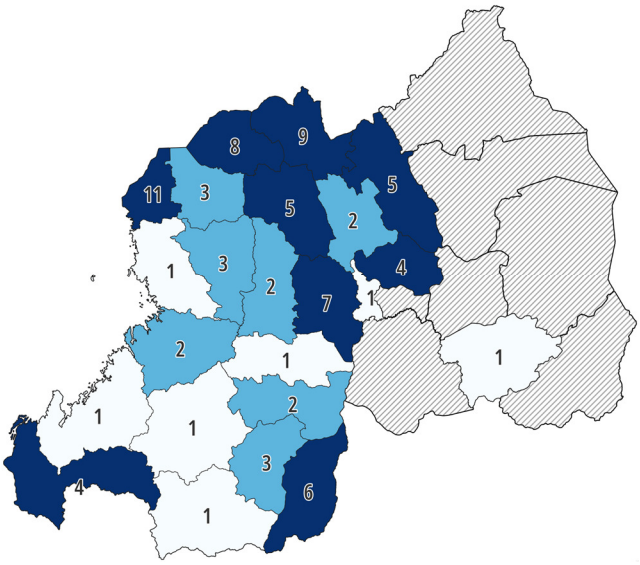

Figure 7. Distribution of typhoid-associated intestinal perforation cases by district of residence, 2018–2022

4.6. WASH and other risk factors

At the national level, the DHS data reported that 56% of households had access to a basic water source, 57% had access to basic sanitation, and 25% had access to handwashing facilities.[21]Access to a basic water source improved in urban areas (87%) compared to rural areas (49%); 41% of rural households reported having to walk >30 mins to access safe water compared to 11% in urban households. In contrast, access to basic sanitation was higher in rural areas (60%) compared to urban areas (44%). Access to basic handwashing remained low in both urban and rural areas but was slightly improved among urban areas (37% vs 23%). At the provincial level (DHS did not report district-level data), access to a basic water source was similar for four of the five provinces (43–57%), but much improved in Kigali City (82%; Table 6). Access to basic sanitation was similar in all five provinces (51–67%), with higher coverage (≥65%) in the East and West provinces. Access to basic handwashing was generally low across all provinces, ranging from 13–36%. Four provinces (South, West, North and East) were considered high risk for typhoid fever based on their reported household access to basic water and three (South, West, North) were considered high risk based on their reported household access to basic handwashing.

In terms of socio-economic risk factors associated with typhoid fever, the DHS found 32% of the population lived on <$2 per day (≥20% is considered high risk) and that the prevalence of stunting was 33% (≥20% is considered high risk).

Interpretation

Overall, both the national WASH and socio-economic status risk factor data and the provincial level data suggest Rwanda has a high risk of typhoid fever, with moderate to good confidence in the data.

Table 6. WASH indicators by province, DHS 2019–2020

Province	% households with access to basic water	% households with access to basic sanitation	% households with access to basic handwashing
City of Kigali	82	51	36
South	51	58	21
West	55	65	13
North	57	55	25
East	43	67	34

Areas are shaded to reflect their risk for typhoid: high (red), medium (yellow), low (green).

4.7. Suspected cases

Suspected typhoid fever case data for the past five years (2018–2022) were collected from HMIS district data. A total of 4,642 people were suspected of having typhoid fever. No patterns were observed between suspected cases and the number of blood cultures performed or *S*. Typhi isolates identified by district. This may reflect blood collection and case management practices for febrile patients, but also underscores the unreliability of the suspected case data. In summary, the suspected case data (2018–2022) reported to HMIS suggest that clinicians, in some districts, are more likely to suspect typhoid fever than in other districts.

4.8. Additional evidence on typhoid fever in Rwanda identified through the literature review

The Global Burden of Disease Study, 2019, estimated the adjusted incidence of *S*. Typhi in Rwanda to be 95.5 per 100,000 [95% CI: 59.2, 139.9], placing Rwanda in the high burden category for *S.* Typhi incidence according to the BRAT framework.[22] Between March 1, 2010 and January 31, 2014, the Typhoid Fever Surveillance in Africa Program (TSAP), a population-based and prospective study was conducted in 13 sentinel sites in 10 countries, including Burkina Faso, Kenya, Tanzania, Madagascar, Guinea-Bissau, Sudan, Ethiopia, Ghana, Senegal, and South Africa.[23] The program identified 135 *S.* Typhi isolates from 13,431 febrile patients and showed that adjusted typhoid fever incidence varied across these sub-Saharan African countries, ranging from 0/100,000 person-years under observation (PYO) in East Wad Medani, Sudan to 383/100,000 PYO in Polessgo, Burkina Faso. The participating East African countries near Rwanda showed high adjusted incidence per sentinel site, ranging from 168/100,000 PYO in urban Moshi, Tanzania to 284/100,000 PYO in Kibera, Kenya. Another study - the Severe Typhoid in Africa (SETA) program - conducted during 2016 and 2020 in sentinel sites in Burkina Faso, Ethiopia, Ghana, Madagascar, Democratic Republic of Congo, and Nigeria identified 346 *S.* Typhi isolates from 27,540 febrile patients. The SETA data also showed varied adjusted typhoid fever incidence between countries, ranging from 23/100,000 PYO in Sodo, Ethiopia to 1189/100,000 PYO in Polessgo, Burkina Faso.[24]

Antimicrobial resistance among *S.* Typhi isolates has been reported in Rwanda since the early 2000s.[25] Reports from King Faysal Hospital showed a significant increase in resistance to first-line drugs from 2007 to 2008.[25] Resistance to ampicillin increased from 18–53%, resistance to chloramphenicol increased from 18–25%, and resistance to cotrimoxazole increased from 18–50%; MDR isolates increased from 9–25%. The increase in resistance to nalidixic acid from 3% to 39% was a significant indicator of future resistance to fluoroquinolones. However, all isolates remained fully susceptible to levofloxacin and ciprofloxacin (fluoroquinolones) and to ceftriaxone (third generation cephalosporin). In a thesis reviewing NRL data from 2015–2019, high resistance among *S*. Typhi isolates to first-line antibiotics was reported.[26] Overall, 86% of isolates were resistant to cotrimoxazole, 86% to ampicillin, and 81% to chloramphenicol, resulting in 71% (n=108/152) MDR prevalence. Resistance to quinolones (nalidixic acid [60%] and ciprofloxacin [20%]) and third generation cephalosporins (ceftazidime [32.9%] and cefotaxime [7.2%]) was also documented. The data included in that review overlapped with two years of data included in the BRAT and described similar trends in antimicrobial resistance. Whole genome sequencing of historical *S*. Typhi isolates (1984–1985) and recent isolates (2010–2018) revealed that the H58 haplotype, which is associated with high levels of antimicrobial resistance, has largely spread in Rwanda, with the majority of recent isolates carrying markers for decreased susceptibility to ciprofloxacin (n=22/26; 84.6%; a fluoroquinolone), of which all but one carried MDR markers (n=21/26; 80.8%).[27]

From other studies across Africa, the TSAP found that 52% of the Salmonella strains circulating in the 10 participating African countries were MDR, with MDR identified in 56% of isolates from Tanzania, 74% from Kenya, and 63% from Ghana.[23] Reduced susceptibility to ciprofloxacin was also reported from the site in Kibera, Kenya. The SETA program found 16% (n=46/280) of isolates were not susceptible to ciprofloxacin.[24] A systematic review of 62 publications reporting AMR among *S.* Typhi isolates identified during 1973–2018 from across Africa and Asia found 13,833 isolates of which 15% were from Africa, predominantly the East and South-West regions.[28] Among African isolates, MDR typhoid was common, with over 90% resistance in some regions, while fluoroquinolone (although trending upwards) and third-generation cephalosporin resistance was low (< 1%). Despite this, resistance to third generation cephalosporins has been reported among 144 isolates detected during 2004-2007 from Kenya, 6% to ceftriaxone and 17% to cefotaxime.[29] A review from KEMRI, Kenya, found that 56% of 225 *S.* Typhi isolates from 2009–2014 were MDR and 18% were resistant to fluoroquinolones.[30]

In summary, data from the Global Burden of Disease study suggest Rwanda has a high typhoid fever incidence (96 per 100,000), published studies from Rwanda describe increasing resistance among *S.* Typhi isolates to first- and second-line antibiotics, and population-based studies in other African countries (TSAP and SETA) showed that adjusted typhoid incidence varies between and within the countries studied, and that MDR isolates represented a large proportion of the isolates tested. Together, these additional findings present a broader concern of expanding AMR among S. Typhi isolates in Africa, including Rwanda, with suggestive evidence of high public health burden of typhoid fever.

5. Overall interpretation of the findings

The pilot of the BRAT framework and tool was successfully implemented in Rwanda to collate and review data in multiple areas of assessment in a standardized manner to provide a picture of typhoid fever burden in the country. Through the BRAT assessment, several areas were identified, particularly relating to surveillance, laboratory testing, and WASH that the MoH Rwanda could consider for strengthening. The pilot also identified some limitations of the tool related to the scoring of prevalence and intestinal perforation, which led to an update of the scoring indicators in consultation with experts (see the addendum report).
A summary of the findings by area of assessment is provided in Table 7 and Appendix 3. Below are the main results and interpretation by area of assessment.

- Incidence
  Since no studies with adjusted incidence for typhoid fever were found for the five-year period, the incidence of typhoid fever could not be assessed.
- Prevalence of S. Typhi among other bloodstream infections
  The BRAT framework ranked the prevalence as medium with moderate to high confidence in the data, with *S.* Typhi ranked 4th or higher in 43% of the years for which data were available. Prevalence data suggest that typhoid fever is present in multiple geographical areas of the country, mainly in Western, Eastern and Southern provinces.
- Prevalence of AMR
  The BRAT identified MDR and other resistance patterns of concern in the health facilities visited, namely resistance to third-generation cephalosporins, fluoroquinolones and azithromycin, with resistance to ciprofloxacin, the antibiotic of choice in Rwanda, showing an increasing trend over the five-year period. The BRAT framework considered the AMR burden to be high based on reports of resistance to cephalosporins and azithromycin with moderate to good confidence in the data.
- Outbreak
  We found no officially reported outbreaks of typhoid fever between 2018–2022 and were therefore unable to score outbreak burden for Rwanda.
- Intestinal perforations
  Severe typhoid fever cases (typhoid fever with intestinal perforation complications) were present in multiple geographic locations in Rwanda and, based on the scoring criteria, indicated a medium burden of severe typhoid fever with moderate to good confidence in the data.
- The risk for typhoid, based on WASH and other risk factors, at the national and provincial level was considered high based on poor access to both basic water supply and basic hygiene facilities, with high confidence in the data.

The BRAT framework provides considerations for how to interpret the combined findings from all areas of assessment, focusing on the strength (or lack) of the evidence gathered to support a conclusion of high, medium, or low typhoid burden and risk, as shown in Appendix 2. The findings from the Rwanda BRAT suggest

typhoid fever is endemic in Rwanda with increasing antibiotic resistance and meet the criteria for moderate evidence to support TCV introduction (see Appendix 2 for full criteria). Introducing TCV in Rwanda could help reduce typhoid fever among the vaccinated cohorts and help to prevent the spread of antimicrobial resistant *S.* Typhi.

The framework acknowledges that decision-making on TCV introduction is the ultimate responsibility of the national government with the advice of the NITAG and other bodies as applicable, and recommends that decision-makers consider additional factors in their introduction decision-making process, such as vaccine performance (recommendations for use per the WHO Position Paper on typhoid vaccines[1] as well as additional data that are available e.g., data on TCV efficacy or effectiveness, data on co-administration of TCV with other routine vaccines, TCV use in special groups such as malnourished children, latest safety reviews, etc.), programmatic feasibility, cost-effectiveness and affordability, and prioritization among other new vaccines.

As part of the process to gather evidence on typhoid fever burden in Rwanda, the BRAT identified several areas related to typhoid fever surveillance, diagnosis, outbreak detection and response, and prevention that could be considered for strengthening. We outline these areas below for further consideration by the respective national authorities and for follow up action as appropriate:

- Surveillance of typhoid fever is critically dependent upon laboratory testing, more specifically blood culture, as typhoid fever presents as a non-specific febrile illness and current serological tests are limited by poor sensitivity and lack diagnostic specificity. Although some facilities in Rwanda had the capacity to conduct blood culture, blood culture for typhoid confirmation was performed irregularly due to stockouts or inappropriate blood collection practices. WHO recommends countries implement laboratory-based, facility-based passive surveillance reporting positive laboratory results as a minimum in endemic settings, with one or more sentinel site at each geographical area of interest. In facilities where blood cultures are performed, Rwanda may consider optimizing blood culture using automated systems, standardizing blood collection and culture for febrile patients, and sustaining the implementation of appropriate quality assurance and control procedures for AST. Standardization of blood collection practices for febrile patients, increased resources, and improved stock management could strengthen the system established by the NRL to support health facilities that lack blood culture capacity.
- Furthermore, WHO recommends the use of “manual” blood culture methods as a minimum standard for blood culture confirmation, which can be followed by biochemical testing algorithms for bacterial identification to differentiate between Salmonella serovars Typhi, Paratyphi A, and other invasive *Salmonella* species. The emergence of MDR *S.* Typhi will most likely challenge clinicians on which antibiotics to prescribe. To address this, Rwanda my consider continuous site-specific AST surveillance according to the Clinical & Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), review local typhoid fever treatment guidelines, and

collect antimicrobial use data to better inform patient management practices and understand the burden of AMR and be able to monitor changes in the AMR profile in Rwanda.[31,32]

- Participation in the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) could improve the country's ability to monitor antimicrobial stewardship and AMR surveillance in the regional and global context.
- Unusual resistance to third-generation cephalosporins and azithromycin requires further investigation of the diagnostic microbiology techniques used and can be complemented by participation in external quality assurance programs for typhoid fever.
- Through BRAT, we found a relatively high number of laboratory-confirmed cases and suspected cases reported in some regions; however, no outbreaks were reported during the study period (2018–2022). Establishing baseline thresholds for typhoid fever and improving typhoid fever laboratory diagnosis and surveillance could also strengthen typhoid fever outbreak detection and response.
- In general, improving WASH infrastructure in Rwanda should be prioritized and access to WASH services monitored. As the overall risk of typhoid fever varies by region, further studies may be needed to identify areas with high disease burden to better understand the dominant transmission pathways and to implement targeted WASH improvements for typhoid mitigation.

Table 7. Summary scores by area of assessment, Rwanda BRAT, 2022

Area of assessment	Criteria	Findings	Categorization of burden/risk[1]	Categorization of data quality[2]
Incidence	Mean adjusted incidence (per 100,000 person years under observation)	**No data**	-	-
Prevalence	Median rank order of *S*. Typhi among other bloodstream bacterial infections	6th	**Medium**	**Moderate to good**
	Proportion of years where *S*. Typhi ranked 4th or higher	>40%		
AMR	AMR patterns	Resistance to either cephalosporins or azithromycin alone or in combination with other antibiotics.	**High**	**Moderate to good**
Outbreaks	Frequency of outbreaks in last 5 years	No data	-	-
	Median duration of outbreaks	-		
	Median size of outbreaks	-		
	Highest case fatality ratio	-		
	AMR identified from any outbreak	-		
Intestinal perforation	Mean proportion of typhoid IP cases among all IPs	26%	**Medium**	**Moderate to good**
	Mean proportion of IP cases among all laparotomies	7%		
	Seasonality of all IP cases	No seasonal trends apparent		
WASH/ Risk factors **National**	Access to basic water source	56%	**High**	**High[3]**
	Access to basic sanitation	57%		
	Access to handwashing facility	25%		
	% population living with <$2/day	32%		

	Prevalence of stunting	33%		
Sub-national	Access to basic water source	53%	**High**	**High[3]**
	Access to basic sanitation	57%		
	Access to handwashing facility	23%		

1– Low, medium, high; 2– very low, low, moderate to good; 3 – national and subnational WASH data is considered to be of high quality. AMR – antimicrobial resistance, WASH – Water, Sanitation and Hygiene, IP – intestinal perforations.

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Appendices

Appendix 1: List of Technical Working Group members

Institution	Contact person	Email address	Role and responsibility
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Appendix 2: Guide for interpretation of overall risk and burden estimates derived from BRAT tool

Strong evidence	Moderate evidence	Weak evidence	No evidence
Very high or high adjusted typhoid incidence and high or medium level of evidence for 3 out of 4 areas of assessment, regardless of quality of WASH data	Medium adjusted typhoid incidence and a minimum of low levels of evidence for all other areas of assessment	No adjusted typhoid incidence data and low levels of evidence or insufficient evidence for all other areas of assessment	Low adjusted typhoid incidence and low levels of evidence for all other areas of assessment
Medium adjusted incidence and high levels of evidence for all other areas of assessment, not including WASH data	Low adjusted typhoid incidence and medium or high levels of evidence for at least one other area of assessment		
No adjusted incidence data and high adjusted incidence in 3 out of 4 areas of assessment plus medium or high level of evidence for WASH data	No adjusted incidence data and medium levels of evidence in 3 out of 4 areas of assessment and medium or high level of evidence for WASH data		
Medium adjusted incidence and medium levels of evidence in all areas of assessment and high or medium level of evidence for WASH data			

Appendix 3: Summary of evidence for categorization of each area, Rwanda BRAT, 2022

Area of assessment		Burden/risk categorization	Description	Categorization of data quality
Incidence		-	No data	-
Prevalence		Medium	Based on median ranking of *S.* Typhi among bloodstream infections in health facilities with available blood culture data of 6th and *S.* Typhi ranked 4th or higher in 43% of the years with blood culture data based on cumulative years across 6 facilities	Moderate to good
AMR		High	Based on reports of resistance to third-generation cephalosporins and azithromycin	Moderate to good
Outbreaks		-	No reported outbreaks	-
Intestinal perforation (IP)		Medium	Based on a mean proportion of typhoid IP cases among all IPs of 26%, a mean proportion of IP cases among all laparotomies of 7%, and no apparent seasonal trends.	Moderate to good
WASH/ Risk factors	National level	High	Overall high risk for typhoid fever, with moderate access to basic sanitation and low access to basic water supply and basic hygiene services	High
	Subnational (province)	High	Overall high-level risk for typhoid fever, with moderate access to basic sanitation and low access to basic water supply and basic hygiene services	