

Assessment of Clinical Presentation, Performance of Diagnostic Methods and Antibiotic Susceptibility Testing for *Salmonella* among Patients Attending Kangema Sub-County Hospital, Kenya

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Abstract

Background: Typhoid disease remains a major public health problem globally, especially in developing countries in sub-Saharan Africa. Symptoms associated with typhoid disease mimic those of other febrile illnesses and are thus difficult to make an accurate diagnosis. A confirmed diagnosis requires the determination or isolation of the bacteria in well-equipped laboratories. Developing countries are faced with a huge limitation of the laboratory infrastructure to diagnose typhoid disease, which would otherwise guide in treating, managing, controlling, and halting the spread of drug resistant mutants. **Objective:** This study, therefore, was aimed at determining the clinical presentation, performance of diagnostic tests and antibiotic susceptibility testing of *Salmonella* among adults attending Kangema Sub-County Hospital. **Study Population:** The study population was residents of Kangema Sub-County in Murang'a County, Kenya while the target population was adults. **Methods:** The study adopted a cross-sectional study design that employed a systematic random sampling procedure. The study took place between April and June 2021. The sample size was 97 respondents who all consented and were enrolled in the study. Interviewing the respondents was carried out by administering structured questionnaires to collect quantitative data. Stool samples were obtained and cultured in Cary Blair transport media and then cultured in appropriate media at the Murang'a County Referral Hospital Laboratory. A rapid *Salmonella* Antigen (SAT) test was also performed on all the stool sam-

ples. **Data Analyses:** Word Statistics and Data (STATA) v 13 was used for statistical analysis. **Results:** The prevalence of Typhoid Fever was at 6.2% (95% CI) which included *S. Typhi* (n = 1; 16.7%) and *S. Paratyphi B* (n = 5; 83.3%). No isolate showed resistance to Ciprofloxacin. The sensitivity of SAT is 100% and a specificity of 98.9% with a kappa statistic of almost perfect agreement (0.9641) with culture. Patients who had fever $p = 0.001$, abdominal distention $p = 0.028$, diarrhoea $p = 0.038$, loose or watery stool $p = 0.021$ and mild general condition $p = 0.02$ remained independently associated with *Salmonella* infection. **Conclusion:** Typhoid Fever being endemic, laboratory diagnosis was a key for confirmation after clinical diagnosis. SAT can accurately be used to detect the disease where culture is unavailable. However, antibiotic sensitivity tests were crucial when determining the drug of choice as *Salmonella* isolates were multi-drug resistant. Establishment of prescribing antimicrobial policies and guidelines can periodically monitor the antibiogram patterns.

Keywords

Salmonella Infection, Culture, *Salmonella* Antigen Test, *Salmonella Typhi*, *Salmonella Paratyphi*, Enteric Fever, Antibiotic Susceptibility Testing, Sensitivity, Specificity

1. Introduction

Salmonella, a Gram-negative rod-shaped bacterium, of the family Enterobacteriaceae is attributed to cause Salmonellosis [1]. More than 2500 Serotypes of *Salmonella* have been identified but only less than 100 Serotypes are associated with to cause the disease in humans [2]. Typhoidal *Salmonella* (Typhi, Paratyphi A-C) are grouped as *Salmonella enterica* serovars that cause enteric fever in humans, whereas nontyphoidal *Salmonella* (NTS) colonize a range of vertebrates or non-human animal species mostly leading to gastroenteritis [3]. The most reported serovars in Africa are *S. Typhimurium* and *S. Enteritidis* [4].

The global burden of typhoidal *Salmonella* and NTS is not well defined. Yearly, an estimated 11 - 20 million people get sick from typhoid and between 128,000 and 161,000 people die from it worldwide [5]. In 2006, NTS was estimated to cause 155,000 deaths [6], while in 2010, 190,200 deaths were attributed to typhoid and Paratyphoid fever with as high as 12.2 million disability-adjusted life years which initiated the disease inclusion in the Global Burden of Disease project [7] [8]. A decade earlier, typhoid fever caused 21.7 million illnesses and 216,000 deaths while Paratyphoid fever was linked to causing 5.4 million illnesses [9].

Invasive NTS (iNTS) disease is elusive in sub-Saharan Africa and is attributed to cause high mortality and morbidity. The global estimates on iNTS disease, included in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, indicated that the highest incidences occurred in SSA [10]. NTS serovars and sequence types that are endemic in SSA include the highly invasive *S. Typhimurium* Type (ST) 313 associated with the cause of large outbreaks and

highly Multi-Drug Resistant (MDR) [11] [12]. *S. Typhimurium* ST313 and *S. enteritidis* ST11 are common isolates from studies that employed NTS genome-sequencing between 2007 and 2014 in Kenya [13]. Typhoid is now estimated to have an average annual incidence of 263 per 100,000 person-years of observation (95% CI: 199 - 347) in all age groups in Kenya and causes more illness among older children compared to NTS [14].

Salmonella is transmitted through the faecal-oral route through contaminated food, water, and poor sanitation. The acquisition of typhoidal *Salmonella* is higher in endemic regions of developing countries, especially where sanitation and hygiene are not well observed [5]. In high-income countries, enteric fever is often associated with travel to endemic areas [15] or acquired from food handlers who are chronic carriers of *S. Typhi* [16]. There is now a considerable body of research that asymptomatic patients may shed *Salmonella* through faecal matter [17]. Shedding of viable bacteria into the environment leads to its transmission and spread to new hosts.

Symptoms of *Salmonella* infection vary and are clinically difficult to distinguish from other febrile illnesses [4]. Often, during outpatient visits, symptoms are limiting but if not treated promptly complications such as intestinal perforation, typhoid encephalopathy, and intestinal bleeding severe anaemia may develop and must require hospital admission [4]. Symptomatic illness is associated with high fever in over 80% of cases, abdominal discomfort, headache, and malaise [18]. The laboratory infrastructure is limited in many rural and semi-urban settings to accurately and timely diagnose invasive and noninvasive typhoid disease. Preventive options have been explored and vaccines against typhoid disease have shown promising outcomes. Attenuated and inactivated vaccines against typhoid are available and have significantly reduced typhoid fever cases [19]. However, despite the availability of the typhoid vaccine, vaccination coverage is limited in most developing countries, lacks inclusion in the national immunization programs and is faced with weak surveillance and laboratory systems [20].

Antibiotic resistance-associated infections are currently a global catastrophe that is directly linked to poor clinical outcomes and high case fatality rates [21]. In the USA, *Salmonella* susceptibility was assessed across all states to provide surveillance data for the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) 2012. NARMS highlighted *Salmonella* strains resistant to Ampicillin, Chloramphenicol, Streptomycin, Sulfonamide (Sulfamethoxazole/Sulfisoxazole), and Tetracycline [22]. Drug resistance to the first-line treatment of *Salmonella enterica* infections has been reported and is widespread. *S. Typhimurium*'s resistance to an array of 15 antibiotics comprising 6 or 7 Clinical and Laboratory Standards Institute (CLSI) drug classes has been reported [23]. Extensively drug-resistant ST 313 sublineage associated with a combined MDR, extended-spectrum beta-lactamase (ESBL) production and resistance to Azithromycin was reported in the Democratic Republic of the Congo [24]. Ceftriaxone-resistant *S. Typhimurium* ST313 poses a major threat to the

management of iNTS in Kenya and SSA [25].

This study, therefore, aimed to determine the clinical presentation, performance of diagnostic tests and antibiotic susceptibility testing of *Salmonella* among adults attending Kangema Sub-County Hospital in Kenya.

2. Methods

2.1. Study Population

The study took place between April and June 2021. The study participants were recruited from a population of Kangema Sub-County residents in Murang'a County. Kangema Sub-County is one of the 8 sub-Counties in Murang'a County with a population density of 80,447 as of the 2019 Kenya Population & Housing Census while the County's overall population was 1,056,640 [26]. All the study participants presented with typhoid-like symptoms at Kangema Sub-County Hospital, which is the main Government healthcare facility in the area.

2.2. Study Design

This cross-sectional study was conducted among patients who presented with typhoid-like symptoms at Kangema Sub-County Hospital in Murang'a County. Upon obtaining informed written consent, 97 study participants were enrolled at the outpatient department (OPD).

2.3. Eligibility Criteria

Inclusion criteria used included patients presenting with typhoid-like symptoms at Kangema Sub-County Hospital OPD, ≥ 18 years, and those who were willing and able to give written informed consent. Patients unable to give a stool sample and those who were not referred to the laboratory by a clinician for typhoid diagnosis and confirmation were excluded from the study.

2.4. Sample Size Determination

The formula for estimating the population proportion with specified absolute precision by Daniel [27] was used to determine the number of patients recruited in this study. Setting α at 0.05 and typhoid prevalence of 6.3% [28], a total of 97 patients were recruited to achieve the 0.95 power.

2.5. Sampling Procedure

A systematic sampling procedure was employed by picking every k^{th} adult patient sent to the Laboratory for a typhoid test until the sample size was achieved. To obtain the k^{th} adult patient, the previous year's three months data (April, May, and June) for patients referred for typhoid tests were abstracted, and the total number of adult patients was divided by the sample size.

2.6. Data Collection

Patients were referred to the laboratory department by a clinician for test con-

firmation of *Salmonella* disease. All the study participants presented with typhoid-like symptoms that included headache, fever, myalgia, malaise, abdominal pain, abdominal distention, diarrhoea, nausea, and cough. The general physical condition was graded as either mild, moderate, or severe. Enrollment of the study participants was carried out at the laboratory department and patients who met the inclusion criteria were recruited upon giving informed consent. The study participants were interviewed with the help of a structured questionnaire and a stool sample was obtained in a sterile container. The questionnaire contained four sections that evaluated the socio-demographic, clinical, sanitation & hygienic characteristics and knowledge of typhoid fever among the study participants. The appearance of the stool sample was documented and immediately inoculated in Cary Blair transport media (Thermo Scientific, Loughborough, UK). The cultured sample was stored at 4°C - 8°C for 24 hours before transporting samples to Murang'a County Referral Hospital laboratory at the Department of Medical Microbiology following strictly the institutional collection, storage, and shipment of human Biological samples. Immediately, approximately 1 gram of stool sample was inoculated into 10 mL of Selenite F broth and incubated at 37°C for 18 - 48 hours. Culture, isolation, and identification of *Salmonella species* were performed following recommendations published in the Bacteriological Analytical Manual as provided by Feng [29]. Antibiotic susceptibility testing was performed following the CLSI 2020 guidelines [30]. Rapid Serology testing was conducted using the SAT kit. Positive results were interpreted qualitatively by a visual clear coloured red line, whereas a negative result had no visible line on the test area.

2.7. Study Validity & Reproducibility

A pre-test was conducted in February and March 2021, 2 months before the actual enrollment study process. The pre-test was meant to assess the feasibility of data collection tools and patients flow at the different OPD service points for corrective action. The final data capture tools were adjusted accordingly to enhance the study validity. All laboratory tests were conducted following approved protocol, Standard Operating Procedure guidelines and setting controls whenever necessary.

2.8. Data Analysis & Interpretation

Categorical variables were analyzed and interpreted using descriptive statistics. Frequency (%), mean, standard deviation, and median (interquartile ranges at 25% and 75%) were used to describe the qualitative and laboratory parameters. Chi-square tests were used to test for significance where applicable. In bivariate and multivariate analyses, odds ratios (OR) and 95% confidence intervals (CI) for the association between *Salmonella* infection among study patients and socio-demographic, clinical presentation variables were calculated using regression analyses, including factors that were associated with pathogenic bacterial isolates

at the significance level of $P < 0.05$.

The test sensitivity was calculated using the formula; Sensitivity = number of true positive (TP)/sum of the number of TP and number of false-negative (FN). Specificity was calculated as follows; Specificity = number of true negatives (TN)/sum of TN and the number of false positives (FP). The positive predictive value (PPV) which is the proportion of patients with positive test results who are correctly diagnosed was determined as follows; $PPV = TP / (TP + FP)$; while the negative predictive value (NPV) is defined as the proportion of patients with negative test results who are correctly diagnosed was determined as follows; $NPV = TN / (TN + FN)$. All statistical analyses were performed using STATA v 13 (StataCorp LP, College Station, TX, USA).

2.9. Ethical Consideration & Approval

This study was conducted as per the Declaration of Helsinki and the International Conference on Harmonization Guideline on Good Clinical Practice (ICH-GCP). The protocol and informed consent form were reviewed and approved by the Mount Kenya University Ethics Research Committee (MKU-ERC) before the commencement of the study (Ref no: MKU/ERC/0614). A research permit was obtained from the National Commission for Science, Technology, and Innovation (NACOSTI) (Ref no: NACOSTI/P/18/95130/20871). At the same time, authorization was granted from the Director of Health, Ministry of Education (Ref no: MGA/CTY/GEN/64/VOL: II/79) and County Commissioner (Ref no: PUB. 24/11/VOL.11/253), Murang'a County. Informed consent of the client was obtained by explaining the purpose of the study. Unique identification numbers were used to ensure the confidentiality of the study participants. The researcher treated all the information acquired with utmost privacy and confidentiality

3. Results

In this study, all the 97 patients enrolled provided the required samples and responded to the structured questionnaire. Out of the 11 patients who presented with fever, 5 (45.5%) of them had *Salmonella* infection. Out of the 6 patients who had headache 2 (25%) were infected with *Salmonella*. The distribution of *Salmonella* by other clinical presentations was as follows; 4 out 20 (20%), 5 out 82 (6.2%), 5 out 85 (5.9%), 4 out 9 (44.4%) and 5 out 34 (11.8%) of *Salmonella* infections were among patients with myalgia, malaise, abdominal pain, abdominal distention, and diarrhoea respectively. Further, 4 out 34 (11.8%), 4 out 11 (28.6%), 4 out 10 (40%) and 3 out 10 (30%) of *Salmonella* infections were among patients with nausea, cough, moderate general physical condition and had loose and water stool presentations respectively (Table 1).

In the bivariate analysis, patients who had fever (uOR 39.1, 95% CI 4.6 - 334; $p = 0.001$), had headache (uOR 5.6, 95% CI 1.1 - 3.4; $p = 0.048$), had myalgia (uOR 7.7, 95% CI 1.4 - 42; $p = 0.018$), had abdominal distention (uOR 19.1, 95% CI 3.6 - 106; $p = 0.028$), had diarrhoea (uOR 9.6, 95% CI 1.1 - 83; $p = 0.038$), had

Table 1. Association with clinical presentation and *Salmonella* infection.

Variables	All	<i>Salmonella</i> infection		Bivariate		Multivariate	
	Population	FQ	%	uOR (95% CI)	<i>P</i> -value	aOR (95% CI)	<i>P</i> -value
Had Fever							
Yes	11	5	45.5	39.1 (4.6 - 334)	0.001	12.1 (3.6 - 40.1)	0.0001
No	86	1	1.2	Reference	Reference	Reference	Reference
Headache							
Yes	6	2	25	5.6 (1.1 - 3.4)	0.048	0.6 (0.05 - 8.1)	0.736
No	91	4	4.5	Reference	Reference	Reference	Reference
Myalgia							
Yes	20	4	20	7.7 (1.4 - 42)	0.018	2.5 (0.7 - 16.9)	0.645
No	77	2	2.6	Reference	Reference	Reference	Reference
Malaise							
Yes	82	5	6.2	1.1 (0.1 - 8.7)	0.991	2.3 (0.2 - 26.3)	0.51
No	15	1	6.3	Reference	Reference	Reference	Reference
Abdominal pain							
Yes	85	5	5.9	0.8 (0.09 - 6.6)	0.815	0.9 (0.3 - 6.6)	0.995
No	12	1	7.7	Reference	Reference	Reference	Reference
Abdominal Distention							
Yes	9	4	44.4	19.1 (3.6 - 106.8)	0.001	4.3 (1.2 - 16.3)	0.028
No	88	2	2.3	Reference	Reference	Reference	Reference
Diarrhoea							
Yes	34	5	15.2	9.6 (1.1 - 83)	0.038	13.8 (1.5 - 126.5)	0.02
No	63	1	1.6	Reference	Reference	Reference	Reference
Nausea							
Yes	34	4	11.8	3.7 (0.7 - 20.1)	0.13	1.9 (0.4 - 10.4)	0.436
No	63	2	3.2	Reference	Reference	Reference	Reference
Cough							
Yes	14	4	28.6	11.9 (2.2 - 64.7)	0.004	1.9 (0.5 - 7.3)	0.319
No	83	2	2.4	Reference	Reference	Reference	Reference
General physical condition							
Mild	85	1	1.2	0.02 (0.01 - 0.4)	0.008	0.03 (0.001 - 0.7)	0.033
Moderate	10	4	40	0.8 (0.2 - 12.8)	0.842	0.2 (0.02 - 3.4)	0.291
Stable	2	1	50	Reference	Reference	Reference	Reference
Stool consistency							
Loose/Watery	10	3	30	14.4 (1.5 - 138)	0.021	16.7 (1.6 - 177.8)	0.02
Mucoid	9	1	11.1	5.3 (0.3 - 85.6)	0.237	9.8 (0.8 - 120.8)	0.075
Semi formed	31	1	3.3	1.6 (0.1 - 25.4)	0.74	1.8 (0.1 - 22.6)	0.635
Formed	47	1	2.1	Reference	Reference	Reference	Reference

OR—Odds ratio; CI—confidence interval; u—unadjusted and a—adjusted odds ratio; ND—Not done; *P*-value—significance level.

cough (uOR 11.9, 95% CI 2.2 - 64.7; $p = 0.004$) and those who had loose or watery stool (uOR 14.4, 95% CI 1.5 - 138; $p = 0.021$) were more likely to be infected with *Salmonella*. Patient who presented with mild general physical condition were less to be infected with *Salmonella* compared to those who were stable (uOR 0.02, 95% CI 0.01 - 0.4; $p = 0.008$) (Table 1).

In multivariate analyses, patients who had fever (aOR 12.1, 95% CI 3.6 - 40.1; $p = 0.0001$), abdominal distention (aOR 4.3, 95% CI 1.2 - 16.3; $p = 0.028$), had diarrhoea (aOR 13.8, 95% CI 1.5 - 126.5; $p = 0.04$), had loose or watery stool (aOR 16.7, 95% CI 1.6 - 177.8; $p = 0.02$) and those who presented with mild general physical condition (aOR 0.03, 95% CI 0.01 - 0.7; $p = 0.02$) remained independently associated with *Salmonella* infection among study patients (Table 1).

3.1. Prevalence of Typhoid Fever

3.1.1. Prevalence of *Salmonella* Infection by Test

Prevalence of *Salmonella* infection among the patients varied depending on the test used: Using SAT and culture to detect *Salmonella* infection the following prevalence were observed: 7/97 (7.2%) 95% CI by SAT and 6/97 (6.2%) 95% CI by culture as shown in (Figure 1).

3.1.2. Distribution of *Salmonella* Infection by Isolates

Out of these 6 *Salmonella* isolates, were *S. Typhi* ($n = 1$; 16.7%) while the rest were *S. Paratyphi B* ($n = 5$; 83.3%) (Figure 2).

3.2. Sensitivity and Specificity of SAT against Culture

Because SAT is routinely used to detect *Salmonella* infection in Kangema Sub County Hospital, Murang'a County, Kenya, the test performance was compared using culture as the gold standard. Data were used for performance analyses only if the results were definitive. Results concordant with those of culture score were obtained in 96/97 (98.9%; 95% CI 94.4% - 99.9%) of the patients by SAT. The kappa of tests which measures the level of agreement showed almost perfect agreement between SAT and culture to detect *Salmonella* infection in this study kappa (0.9641—almost perfect agreement).

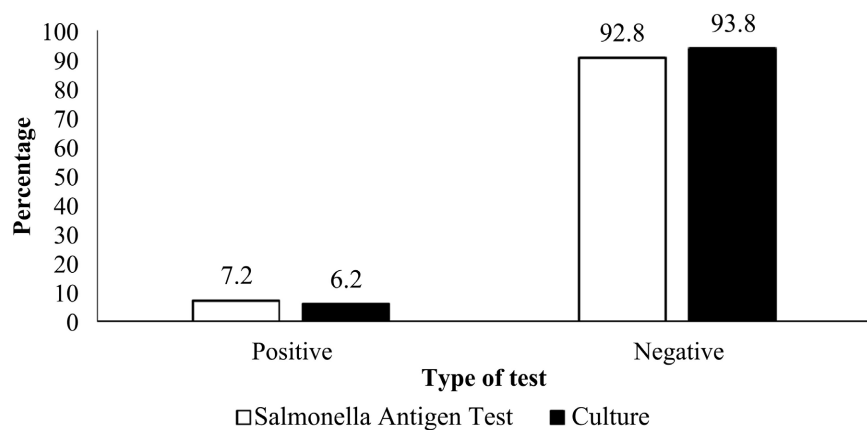


Figure 1. Prevalence of *Salmonella* infection by test.

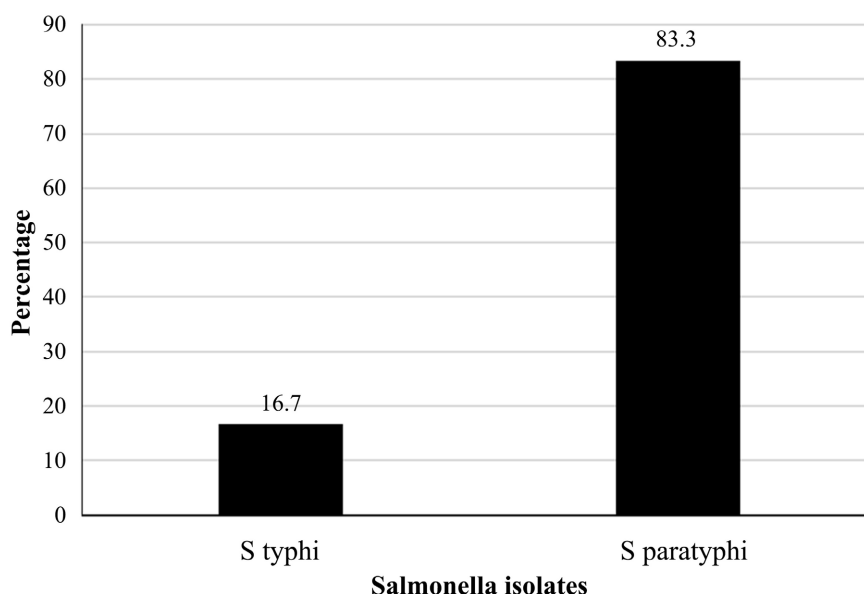


Figure 2. Prevalence of *Salmonella* infection by isolates.

Based on the culture results as the gold standard, the sensitivity of SAT was 6/6 (100%; 95% CI 54.1% - 100%) with a specificity of 91/92 (98.9%; 95% CI 94.1% - 99.9%). The positive predictive value (PPV) of SAT was 6/7 (85.7%; 95% CI 42.1% - 99.6%) with a negative predictive value (NPV) of 91/91 (100%; 95% CI 96% - 100%) (**Table 2**).

3.3. Antibiotic Susceptibility Profile of *Salmonella* Strains

Isolates were tested for their antimicrobial susceptibility by the Kirby-Bauer disk diffusion method according to CLSI guidelines (CLSI, 2016). The drugs tested included Ampicillin (AMP), Nalidixic acid (NA), Chloramphenicol (CRO), Gentamicin (GEN), Ciprofloxacin (CIP), Trimethoprim-sulfamethoxazole (SXT), Tetracycline (TET). The antimicrobial susceptibility was classified using the CLSI guidelines, as susceptible, intermediate, or resistant to each antibiotic. In addition, we also classified the isolates as either non-susceptible (including both intermediate and resistant isolates) or susceptible.

Resistance to AMP, TET, GEN, CRO, NA and SXT was 100%, 100%, 83.3%, 50%, 33.3% and 33.3% respectively. No isolate showed resistance to CIP. All the *S. Typhi* and *S. Paratyphi* B were Multidrug-resistant (**Table 3**).

4. Discussion

Salmonella enterica serovars Paratyphi B isolated in this study were responsible for typhoid fever and associated with symptoms of fever, headache, myalgia, diarrhoea, cough, and abdominal distension. Studies have shown that upon ingestion and incubation phase, some patients develop subclinical symptoms or may be asymptomatic during the primary phase, and faecal shedding of the bacteria can occur [18]. Fever dominates, whereby, the body temperature rises gradually

Table 2. Comparison of SAT against culture (N = 97 samples).

Test	Culture (Gold standard)					
	Concordant results (%) 95% CI	Sensitivity (%) 95% CI	Specificity (%) 95% C	NPV (%) 95% CI	PPV (%) 95% CI	K
Salmonella antigen	98 (94 - 99)	100 (54 - 100)	98 (94 - 99)	100 (96 - 100)	86 (42 - 100)	0.98

N—Number; %—Percentage; CI—Confidence Interval; NPV—Negative Predictive Value; PPV—Positive Predictive Value; K—Kappa.

Table 3. Antibiotic susceptibility of *Salmonella* isolates.

Isolate	Strain	Antibiotic susceptibility profiles						
		AMP	NA	CRO	GEN	CIP	SXT	TET
Isolate 1	<i>S. Paratyphi B</i>	R	S	S	R	S	S	R
Isolate 2	<i>S. Paratyphi B</i>	R	R	S	R	S	S	R
Isolate 3	<i>S. Paratyphi B</i>	R	S	R	R	S	R	R
Isolate 4	<i>S. Paratyphi B</i>	R	S	S	R	S	S	R
Isolate 5	<i>S. Paratyphi B</i>	R	R	R	I	S	S	R
Isolate 6	<i>S. enterica</i>	R	S	R	R	S	R	R

S—Susceptible; R—Resistant; I—Intermediate-resistant; AMP—Ampicillin; NA—Nalidixic acid; CRO—Chloramphenicol; GEN—Gentamycin; CIP—Ciprofloxacin; SXT—Trimethoprim-sulfamethoxazole; TET—Tetracycline.

during the first and second week followed by influenza-like symptoms, headache, malaise, dry cough, anorexia, and sometimes abdominal pains and diarrhoea [4]. From this study, the disease presentation among the study participants was a mild infection and was mainly managed within the outpatient department of the hospital. Most of the study participants presented with high fever and these findings are broadly similar to the findings from a multicounty study in Bangladesh, Nepal, and Pakistan that indicated fever was a prevalent symptom in patients whose samples tested positive for *S. Typhi* or *S. Paratyphi* [31]. Although the typhoid causative agents were isolated from stool samples in this study indicating typhoid fever, NTS should always be considered because much recent work within the region and elsewhere has indicated nontyphoidal outbreaks and MDR strains [14] [26].

In the current study, the test performance of immunochromatographic SAT was compared to culture as the “gold standard” from stool samples collected from patients reporting to Kangema Sub-County hospital with typhoid-like symptoms. The sensitivity of SAT (100%) and a specificity of 98.9% concurred with the findings from a study that evaluated the sensitivity performance of SD Bioline RDT (100%), near sensitivity rate using Creative Diagnostics (98.1%) [32] and 96.7% in Laos [33]. Although the researchers from the former study used spiked blood culture broth to evaluate the validity of *Salmonella* RDTs, the current study used fresh stool samples from symptomatic patients with typho-

id-like symptoms to compare test performance of the rapid test. Although microbiological examination and isolation of the bacteria from blood or bone marrow samples remains the standard reference laboratory test for the confirmation of salmonellosis, a rapid serologic test based on antibody detection may provide a convenient supplementation. The use of a rapid and sensitive test is vital to bacterial control and its spread [34]. However, some of the commonly used rapid tests are faced with limitations and are no longer in use in the national laboratory diagnostic programs in some countries. The diagnostic value of the Widal agglutination test that detects antibodies against O (surface) and H (flagellar) antigens is often questioned because of its false-negative and false-positive, poor test performance, cutoff titer levels, and poor agreement with culture tests. The more sensitive and specific assay, Enzyme-Linked Immunosorbent Assay (ELISA), that identifies antibodies to the capsular polysaccharide Vi antigen is superior to identifying carriers but limited to diagnosing acute enteric fever due to lack of specificity [35]. Polymerase chain reaction (PCR) and proteomic assays have a high degree of sensitivity and specificity to detect enteric fever but are cost-prohibitive especially in developing countries [36].

For these reasons, a sensitive, simple, and cost-effective SAT diagnostic method for the diagnosis of *Salmonella* infection may result not only in rapid salmonellosis control and surveillance measures but also in prompt diagnosis followed by appropriate treatment. In this study, the kappa statistic of almost perfect agreement (0.9641) with culture provides some significant evidence to suggest that the antigen test is applicable in the diagnosis of *S. Typhi* among the study population although the problem of antibiotic selection is limited without culture testing. Confirmation by culture (or validated molecular methods, as available) is essential as typhoid fever, Paratyphoid fever and another invasive salmonellosis can present as a non-specific febrile illness, and current serological tests lack diagnostic specificity. It can be argued that those patients who sought laboratory confirmation had clinical signs and symptoms of enteric fever. Confirmation is essential to assess the proportion of enteric fever caused by these different organisms, determine antimicrobial susceptibility, and perform molecular epidemiology studies [37].

Antibiotic susceptibility profiles of *Salmonella* strains in this study conformed with the findings from a previous study from stool samples of patients at the Aga Khan University Hospital in Kenya that highlighted high resistance of *Salmonella* against NAL, CRO, AMP, CHL, SXT [26]. We tested the susceptibility of the commonly used antibiotics prescribed to patients when they present with typhoid-like symptoms or during a confirmed case of typhoid disease within the study region. Strains of *S. Paratyphi* B and *S. enterica* isolated in this study were MDR to AMP, NA, CRO, GEN, SXT and TET which were also similar antibiotics highlighted in the NARMS that captured *Salmonella* surveillance data across all the USA states [22]. *Salmonella* strains exhibited high resistance rates when subjected to an array of these antibiotics. The current study illuminates a light on the current response of commonly prescribed antibiotics even as major con-

cerns have been expressed about AMR. For years, CRO demonstrated a good efficacy against *Salmonella* infection and was used as a first-line drug, but widespread resistance was reported shortly. Resistance in the self-transmittable plasmid H1 incompatibility group was reported [38], in addition to the ability of genes in the plasmids to confer resistance to other antibiotics [39]. For this reason, AMP, SXT and TET became common as first-line antibiotics to treat enteric fever but eventually gradually reduced efficacy against resistant *Salmonella* strains [22]. The bacterial resistance data generated from this study affirms the findings of most researchers that AMP, SXT and TET are of less use in the treatment of typhoid disease [40] with these drugs demonstrating 100% resistance rates in this study.

In the current study, Ciprofloxacin demonstrated the best MIC and achieved a 100% susceptibility rate against all *Salmonella* isolates. The use of Fluoroquinolones in the treatment of enteric fever is common, especially in regions reported to exhibit low resistance rates to this class of antibiotic. Earlier studies showed that Ciprofloxacin and Ofloxacin concentrations were above the MIC [41], achieved an optimal drug concentration at the site of infection [42] and employs a bactericidal mode of action both *in vivo* and *in vitro* [43]. Ciprofloxacin being the most ideal antibiotic of choice in this study chimes with recent findings on its use in the treatment of *S. Typhi* infection, whereby, it surpassed the MIC in a controlled human infection model. [44].

However, over time, *in vitro* MIC of Ciprofloxacin against strains has gradually reduced and some studies have recommended its withdrawal in the treatment of enteric fever [45]. In recent data from Pakistan published as part of the surveillance for enteric fever in Asia Project (SEAP), Fluoroquinolone resistance was noted in nearly 90% of *S. Typhi* and *S. Paratyphi* isolates [46]. The rapid resistance against Fluoroquinolones is linked to molecular evolutionary biology and direct response toward drug pressure (Redgrave *et al.*, 2014). Fluoroquinolones targets DNA gyrase and topoisomerase IV, thereby inhibiting bacterial DNA synthesis, but chromosomal mutations in the quinolone resistance-determining regions of *gyrA*, *gyrB*, *parC* and *parE* genes have been determined [47]. Plasmid-mediated resistance is also a mechanism acquired by the bacterium against the action of quinolones [48].

The findings of this study are restricted to the study population and researchers were primarily concerned with test performance of SAT usage in the diagnosis of typhoid disease and antibiotic susceptibility. There has been much interest lately to develop tools that are more sensitive and specific to rapidly diagnose typhoidal *Salmonella* and NTS such as genomic studies targeting nucleic acid, bacterial gene expression, proteomic and immunoscreening strategies, removal of human DNA contaminant in PCR [4].

5. Conclusion

In conclusion, our study findings offer suggestive evidence that it is important to

further investigate the typhoid-like symptoms by conducting SAT to confirm enteric fever accurately and rapidly. SAT performance is comparable to culture and might be used to accurately detect *Salmonella* infection where culture is typically not available. The antibiotic sensitivity tests offer the best guidance for the selection of antibiotics to guide treatment, especially with the MDR *Salmonella* strains.

Limitations of the Study

Although we reported high carriage of MDR *Salmonella*, we cannot conclusively predict the source of exposure to these multidrug-resistant isolates; whether it is due to the modern food-animal production characterized by densely concentrated animals and routine antibiotic use or is due to misuse of antibiotics in the human population, which is a common phenomenon in Kenya.

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Authors' Contributions

All authors listed have made a substantial, direct, and intellectual contribution to the article, and approved it for publication. Saweria W. Mbuthia was involved in conception and design, data collection, and data analysis and assisted in the drafting of the manuscript. Eliab S. Some and Mbaruk Suleiman were involved in the supervision of the project. Oliver W. Mbuthia assisted in the review of data analysis and manuscript writeup while Musa O. Ngayo assisted in the data analysis.

Conflicts of Interest

The authors have declared that no competing interests exist.

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Appendix I: Questionnaire

**Factors Associated with Typhoid Fever Amon Attending
Kangema Sub County Hospital, County, Kenya** **Ng Adults Murang'A**

Serial No:

Date:

Please *tick* where applicable

PART 1: DEMOGRAPHIC CHARACTERISTICS

1	What is your sex?			
	Male	<input type="checkbox"/>	Female	<input type="checkbox"/>
2	What is your age (<i>In years</i>)			
3	What is your religion?			
4	What is your ethnicity?			
5	What is your marital status?			
	Married	<input type="checkbox"/>	Single	<input type="checkbox"/>
	Divorced	<input type="checkbox"/>	Widowed	<input type="checkbox"/>
6	Which is your highest level of education attained?			
	University	<input type="checkbox"/>	O-level	<input type="checkbox"/>
	College	<input type="checkbox"/>	Primary	<input type="checkbox"/>
	None	<input type="checkbox"/>		
7	What is your occupation?			
	employed	<input type="checkbox"/>	Unemployed	<input type="checkbox"/>
	self-employed	<input type="checkbox"/>		
8	What is the reason for you seeking medical care in this facility?			
	Sick	<input type="checkbox"/>	go to question 9	
	Vaccination	<input type="checkbox"/>		
	Medical certificate	<input type="checkbox"/>		Go to part 2
	Other reasons (<i>Indicate</i>)	<input style="width: 100%;" type="text"/>		
9	How long have you been unwell?			
	0 - 2 days	<input type="checkbox"/>	9 - 11 days	<input type="checkbox"/>
	3 - 5 days	<input type="checkbox"/>	12 - 14 days	<input type="checkbox"/>
	6 - 8 days	<input type="checkbox"/>	>14 days	<input type="checkbox"/>
10	Were there any medical care sought?			
	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
				<i>If no go to part 2</i>
11	Where did you seek health care?			
	Public	<input type="checkbox"/>	Friends	<input type="checkbox"/>
	Private	<input type="checkbox"/>	Others	<input type="checkbox"/>
	Pharmacy	<input type="checkbox"/>		
	Traditional healers	<input type="checkbox"/>		

Continued

- 12** Were you done any laboratory test?
 Yes No
- 13** Were you given any medication?
 No
 Yes
 (If YES and aware indicate name)
- 14** How long have you taken the medicine?
 In days
 I don't know

PART 2: CLINICAL CHARACTERISTICS

- 15** Is the client having a fever?
Record °C
- 16** Does the client suffer from
- | | | | | |
|-----------------------|-----|----------------------|----|----------------------|
| Headache | Yes | <input type="text"/> | No | <input type="text"/> |
| Myalgia | Yes | <input type="text"/> | No | <input type="text"/> |
| Malaise | Yes | <input type="text"/> | No | <input type="text"/> |
| Abdominal pains | Yes | <input type="text"/> | No | <input type="text"/> |
| Abdominal. Distention | Yes | <input type="text"/> | No | <input type="text"/> |
| Diarrhoea | Yes | <input type="text"/> | No | <input type="text"/> |
| Nausea | Yes | <input type="text"/> | No | <input type="text"/> |
| Cough | Yes | <input type="text"/> | No | <input type="text"/> |
| Mental confusion | Yes | <input type="text"/> | No | <input type="text"/> |
| Stupor | Yes | <input type="text"/> | No | <input type="text"/> |
| Coma | Yes | <input type="text"/> | No | <input type="text"/> |
- 17** General condition? (*rate*)
- | | |
|----------|----------------------|
| Severe | <input type="text"/> |
| Moderate | <input type="text"/> |
| Mild | <input type="text"/> |
- 18** Stool consistency?
- | | | | |
|---------------|----------------------|-------------|----------------------|
| Loose/watery | <input type="text"/> | Formed | <input type="text"/> |
| Blood stained | <input type="text"/> | Semi-formed | <input type="text"/> |
| Mucoid | <input type="text"/> | | |
- 19** How often do you use the latrine/toilet?
- | | | | |
|--------|----------------------|-----------|----------------------|
| Always | <input type="text"/> | Sometimes | <input type="text"/> |
| Often | <input type="text"/> | Never | <input type="text"/> |
- 20** Does your latrine/toilet have a cover?
- | | | | |
|--------------|----------------------|----|----------------------|
| Yes | <input type="text"/> | No | <input type="text"/> |
| I don't know | <input type="text"/> | | |

Continued

21 Where do you dispose sludge water?

Sewage	<input type="text"/>	Environment	<input type="text"/>
Septic tank	<input type="text"/>	Others	<input type="text"/>

22 Who is providing water at the source?

Authority	<input type="text"/>	Private operator	<input type="text"/>
NGO	<input type="text"/>	Natural source	<input type="text"/>
I don't know	<input type="text"/>		

23 What is your main source of drinking water in your household?

Piped water	<input type="text"/>	Surface water	<input type="text"/>
Open well	<input type="text"/>	Rain water	<input type="text"/>
Borehole	<input type="text"/>	Water vendors	<input type="text"/>

24 Do you make water safe for drinking?

Yes	<input type="text"/>
No	<input type="text"/>

(If NO go to question No. 28)

Boiling	<input type="text"/>	Others	<input type="text"/>
Use of filters	<input type="text"/>		
Use of Chemicals	<input type="text"/>		
Solar disinfection	<input type="text"/>		
Let stand & settle	<input type="text"/>		

26 Do you store drinking water separate from water for other domestic purposes?

Yes	<input type="text"/>
No	<input type="text"/>

27 How often do you take your breakfast from hotel/restaurant?

Always	<input type="text"/>	Sometimes	<input type="text"/>
Often	<input type="text"/>	Never	<input type="text"/>

28 How often do you take your lunch from hotel/restaurant?

Always	<input type="text"/>	Sometimes	<input type="text"/>
Often	<input type="text"/>	Never	<input type="text"/>

29 How often do you eat raw vegetables or fruits?

Always	<input type="text"/>	Sometimes	<input type="text"/>
Often	<input type="text"/>	Never	<input type="text"/>

PART 3: HYGIENE & SANITATION CHARACTERISTICS

30 When do you wash your hands?

After toilet	<input type="text"/>	How often?	Always	<input type="text"/>
			Often	<input type="text"/>
			Sometimes	<input type="text"/>

Continued

Before meals	<input type="text"/>	How often?	Never	<input type="text"/>
			Always	<input type="text"/>
			Often	<input type="text"/>
			Sometimes	<input type="text"/>
Before food prep	<input type="text"/>	How often?	Never	<input type="text"/>
			Always	<input type="text"/>
			Often	<input type="text"/>
			Sometimes	<input type="text"/>
			Never	<input type="text"/>

31 How often do you use soap and/sanitizers?

Always	<input type="text"/>	Sometimes	<input type="text"/>
Often	<input type="text"/>	Never	<input type="text"/>

32 What would be the reason for not using soap/sanitizers always while washing hands?

Forget	<input type="text"/>	Others	<input type="text"/>
Soap unavailable	<input type="text"/>		
Habit	<input type="text"/>		

PART 4: KNOWLEDGE OF TYPHOID FEVER

33 Have you ever heard of typhoid fever?

Yes	<input type="text"/>
No	<input type="text"/>

End questions

I don't know	<input type="text"/>
--------------	----------------------

34 Why does someone get typhoid fever? (*to mention 5 reasons*)

- 1 _____
- 2 _____
- 3 _____
- 4 _____
- 5 _____

35 What helps prevent typhoid fever? (*to mention 5 ways*)

- 1 _____
- 2 _____
- 3 _____
- 4 _____
- 5 _____

THE END

Thank you and God Bless!