TYPHOID FEVER OUTBREAK INVESTIGATION IN SEKHUKHUNE DISTRICT, LIMPOPO PROVINCE, SOUTH AFRICA, NOVEMBER 2017 TO JANUARY 2018

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Executive Summary

Typhoid fever remains an endemic disease in South Africa, and the risk of transmission is associated with poor sanitation, unsafe water, and unsafe food production and handling processes. In South Africa, laboratory-based surveillance for typhoid fever is co-ordinated by the National Institute for Communicable Diseases (NICD). Fewer than 130 cases were reported annually since 2012, indicating low endemicity. The findings of a typhoid outbreak investigation in Sekhukhune District, Limpopo Province, from November 2017 to January 2018 are reported here.

An investigation was conducted to quantify the outbreak, identify the source, and make recommendations to stop the outbreak and prevent future events. Epidemiologic, laboratory and environmental investigations were conducted. *Salmonella enterica* subspecies *enterica* serotype Typhi (*S*. Typhi) isolates were submitted to the Centre for Enteric Diseases (CED), NICD, and whole genome sequencing (WGS) was conducted by the Sequencing Core Facility, NICD. Polymerase chain reaction (PCR) testing for *Salmonella* species in water samples was conducted by the Council for Scientific and Industrial Research (CSIR). Location and distribution of cases and water sources were mapped using a geographic information system (GIS) mapping tool. Amongst 122 cases with a median age of 11 years (interquartile range, 2 to 83 years), 66/122 (54%) were female and 7/122 (6%) were laboratory confirmed. *Salmonella* species were detected in 10/27 (37%) water samples collected in the district. GIS mapping showed clustering of cases in Tswaing-Kgwaripe and Vlakplaas villages, with 58% laboratory-confirmed cases and 68% of probable cases from the former. WGS results indicated that isolates for cases from Tswaing-Kgwaripe and Strydkraal villages (5/6) were genetically highly related (<22 single nucleotide polymorphisms).

The molecular epidemiology of available isolates suggests a common source outbreak, supported by the detection of *Salmonella* spp. in samples from multiple water sources in the affected district. Access to safe and clean water, an inter-

sectoral health, water and sanitation committee, and continuous community health education were recommended.

Introduction

Typhoid fever is a systemic bacterial illness caused by *Salmonella enterica* subspecies *enterica* serotype Typhi (*S.* Typhi),[1] characterised by prolonged fever, nausea, headache, loss of appetite and gastrointestinal symptoms, including abdominal pain, constipation or diarrhoea.[2,3] Severe disease can lead to life-threatening complications including intestinal perforation, intestinal haemorrhage and encephalopathy with haemodynamic shock. The incubation period ranges from 3 to 60 days, but is usually 7 to 14 days.[2] *S*. Typhi is transmitted through ingestion of food or water contaminated by faeces or urine of symptomatic cases and asymptomatic carriers.[2,4]

Humans are the only reservoir and a carrier state may follow acute illness or subclinical infection.[2] Typhoid fever occurs mostly in areas with poor sanitation and lack of potable water. According to the most recent World Health Organization estimates (published in 2014), approximately 21 million cases and 222 000 typhoid-related deaths occur annually worldwide.[4] *Salmonella* Paratyphi A, B or C cause paratyphoid fever, which is clinically indistinguishable from typhoid fever. Typhoid fever and paratyphoid fever are collectively termed enteric fever.

As typhoid fever is clinically indistinguishable from a wide range of other common febrile illnesses, laboratory testing is recommended in all patients presenting with clinically-compatible disease. The diagnosis of typhoid fever requires the isolation of *S.* Typhi from blood, bone marrow, stool or other tissue specimens. Serological tests such as the Widal test are not recommended for screening or diagnosis of typhoid fever due to variable host antibody responses and cross-reactivity with other enteric bacteria.

Typhoid fever is endemic in South Africa. However, the number of cases has declined over the last 22 years from an estimated 6 000 in 1985 to 200 cases in 2002.[7] Large outbreaks of typhoid fever occurred in Delmas, Mpumalanga Province in 1993 and 2005, when over 600 cases were reported.[5-6] Low numbers of cases continued to be observed between 2013 and 2015 (Figure 1) through a national, active laboratory-based surveillance system at the National Institute for Communicable Diseases (NICD).[7]

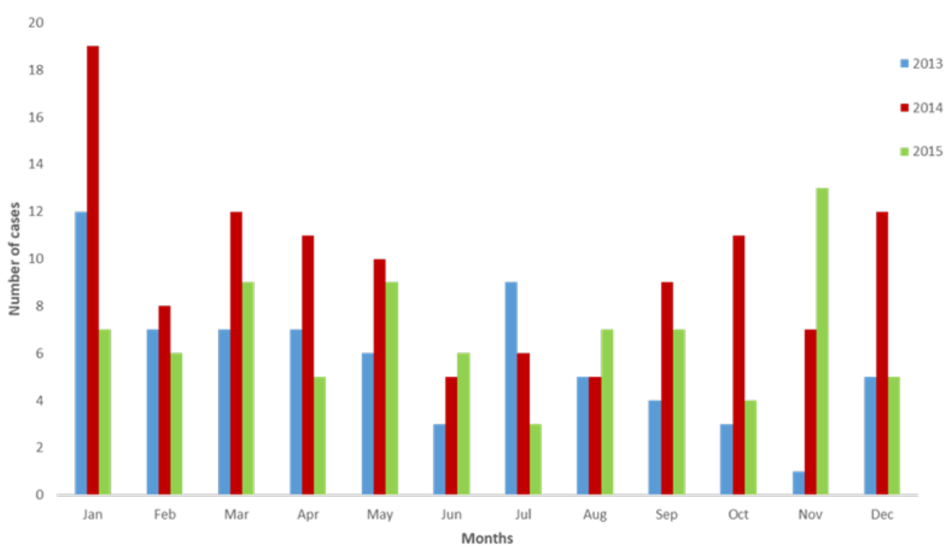

Figure 1. Numbers of laboratory-confirmed *Salmonella* Typhi cases by month in South Africa, 2013 – 2015.

In 2016, case numbers were comparable with previous non-outbreak years, with 123 cases recorded. Molecular epidemiological analysis of cases revealed both endemic strains and strains with identical patterns to those responsible for the typhoid outbreak in Zimbabwe during 2010.[8]

While 83% of South African households have water provided by municipal structures, 43% of households in Limpopo Province experienced water interruptions of any duration during 2016.[9] Sekhukhune District, approximately 150 km from Polokwane city in Limpopo Province, consists of four local sub-district municipalities (Figure 2). The district lies in the south-eastern part of the province and it is mostly rural, with almost 605 villages and an estimated 5% of the population living in urban areas. Potable water supply by the municipality is inconsistent. Residents in villages rely on private boreholes and untreated drinking water reservoirs including ground wells, rivers, irrigation furrows, boreholes, rainwater, and large plastic storage (Jojo) tanks.

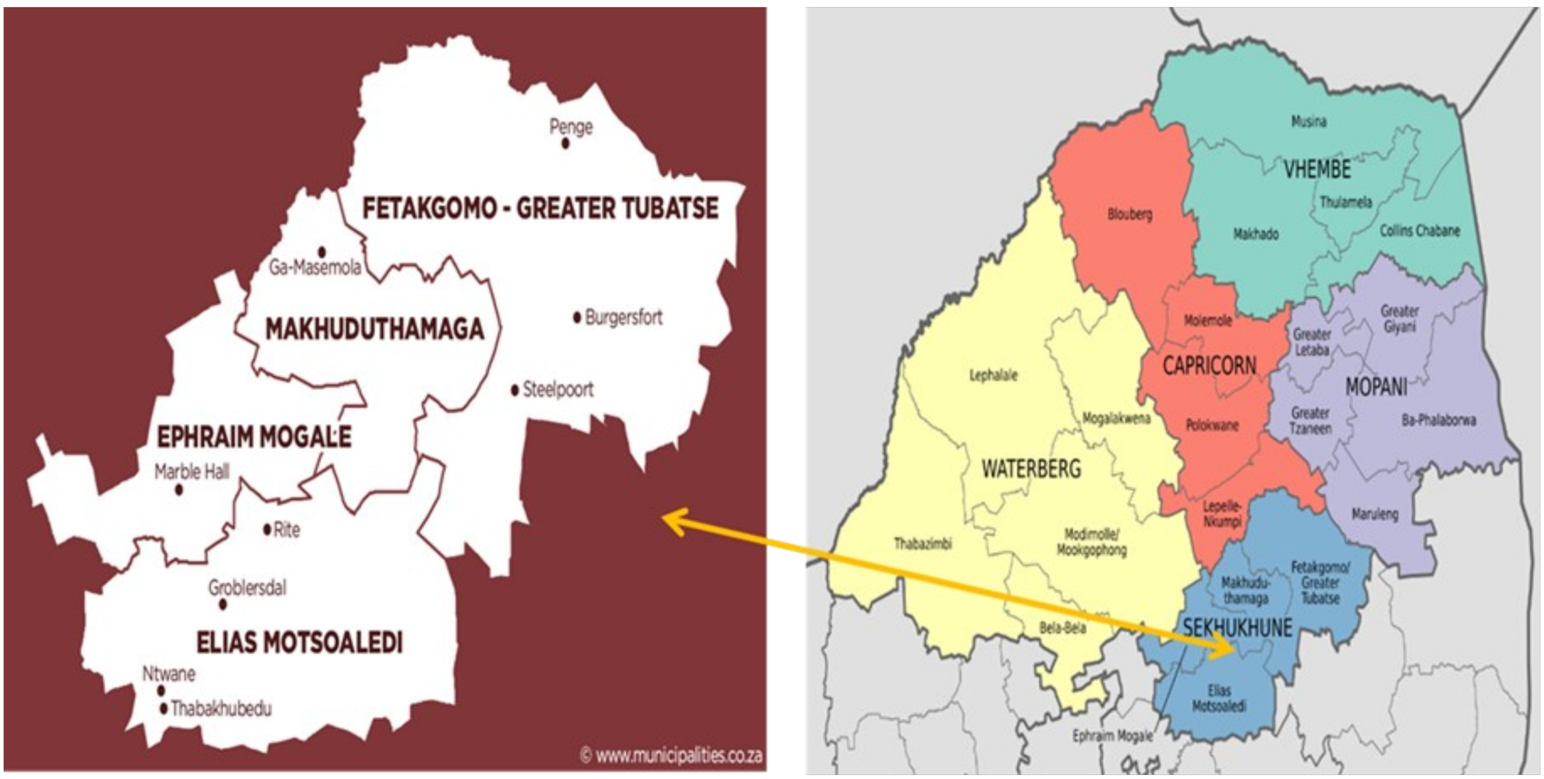

Figure 2. Right: Limpopo Province, South Africa, showing location of Sekhukhune District. Left: Sekhukhune District showing sub-districts.

On 15 November 2017, Sekhukhune District Department of Health (DoH) received a notification about a laboratory-confirmed case of typhoid fever initially admitted to Pietersburg Tertiary Hospital, then transferred back to the district hospital. The Outbreak Response Unit (ORU) at NICD was alerted of a suspected typhoid fever outbreak in Limpopo Province on 22 November 2017. Collaborative actions and investigations to support response interventions were commenced. The findings from an investigation of a typhoid outbreak in Sekhukhune District, Limpopo Province, from November 2017 to January 2018 are here described.

Methods

Investigating and response teams

Following the notification, the district epidemic preparedness and response (EPR) team was activated and met to co-ordinate response activities. The district EPR team consists of the Sekhukhune Provincial and District Communicable Disease Control team (Department of Health), Deputy Director Health Promotion, hospital environmental health practitioners (EHPs), Provincial Field Epidemiologist and sub-district mobile teams. On two occasions (25 January 2018, and 31 January - 2 February 2018), a team of medical epidemiologists, field epidemiology training programme resident, public health registrars, and a geographic information system GIS specialist from the Outbreak Response Unit, NICD conducted site visits to provide feedback on investigations, training of health practitioners, and to conduct further investigations.

Case definitions

The following case definitions were formulated from the national typhoid guidelines:[3]

- A confirmed typhoid case: any person from Sekhukhune District with isolation of *S.* Typhi, or *S.* Paratyphi A, B or C from a clinical specimen in the presence of symptoms compatible with enteric fever from 6 November 2017 to January 2018.
- A probable typhoid case: any person from Sekhukhune District with symptoms compatible with enteric fever who is epidemiologically linked to a confirmed case, from 6 November 2017 to January 2018, with negative malaria rapid test to exclude malaria.
- A typhoid carrier (convalescent or chronic carrier):
  - ◊ A convalescent carrier: any person in Sekhukhune District who is still excreting *S.* Typhi or *S.* Paratyphi A,B or C after receiving two courses of appropriate antibiotic therapy.
  - ◊ A chronic carrier: any person in Sekhukhune District who continues to excrete *S.* Typhi or *S.* Paratyphi 12 months after receiving appropriate antibiotic therapy.

Epidemiological and clinical investigations

A retrospective descriptive cross-sectional study was conducted using data collected from case-patient interviews.

Case finding and sources of data

Attending clinicians at district hospitals identified and investigated persons with suspected typhoid fever based on the case definitions above. The provincial epidemiologist together with the Communicable Disease Control team coordinated the investigation of cases and completion of case investigation forms (CIFs) by the three district hospitals in Sekhukhune District where case-patients were admitted. Limpopo Province is a malaria-endemic area, therefore the clinical investigation of typhoid cases presenting with fever included a malaria rapid diagnostic test to exclude malaria. The CIF used to interview case-patients and contacts focused on respondent demographics, clinical presentation, and potential exposure risk factors such as water sources and type of toilet use. A line list to record all cases was developed. Additional patient data were obtained through the National Health Laboratory Service (NHLS) TrakCare Web results viewer system. Health facilities and mobile teams were responsible for daily reporting to Sekhukhune DoH, public health unit.

Laboratory investigations

Attending clinicians at the three district hospitals where patients presented, submitted clinical specimens for laboratory investigations including full blood count, urea and creatinine, blood and stool or rectal swabs and blood for serology (Widal test) to the NHLS. The Widal test is not recommended for the diagnosis of typhoid fever; however, due to the unavailability of blood culture bottles in health facilities, serological testing was requested. In cases where *S*. Typhi was identified, the health authorities were notified by the NHLS. The NHLS submitted *S*. Typhi isolates to the Centre for Enteric Diseases (CED), NICD, for confirmatory testing and whole-genome sequencing (WGS). WGS is a widely-used technique for molecular subtyping of bacteria, providing data that enable high-resolution typing for surveillance, and additional data regarding further characterization of emerging clones based on genetic differences.[10]

Environmental investigations

Water samples were collected by the EHPs from several water sources identified through interviews with cases and at community meetings. Food samples were not available for collection. Water samples were sent to the Council for Scientific and Industrial Research (CSIR) laboratory, where a real-time PCR test was performed to detect the presence of *Salmonella* spp. The PCR-based test used by CSIR detects all *Salmonella enterica* subspecies, as well as *Salmonella bongori,* by targeting the *invA* gene that is located on the pathogenicity island 1 of *Salmonella* spp. The methodology is not able to distinguish between typhoidal and non-typhoidal *Salmonella* species.[11-13]

GIS mapping

During the NICD team visits, additional data were collected, including interviews of cases and contacts to complete CIFs, and GIS locations of case-patients' places of residence and open water sources. A GIS tool is a computer system with the capacity to capture, store, analyse and display geographically-referenced information.[14] GIS provides ways of visualizing and analysing epidemiologic data, and helps in identifying disease trends and multi-disease surveillance activities.[14-15] Health organisations can visualize, analyse and interpret geo-location data through the use of GIS tools or mapping applications. Specific diseases and other public health events can be mapped to monitor and manage of epidemics[15]. The GIS mapping was limited to villages with typhoid fever cases and water sources that were sampled for typhoid investigation purposes within Sekhukhune District.

The case-patients' home addresses were obtained from completed CIFs, Tswaing local clinic daily register for patients and the ward-based outreach team (WBOT), who work in collaboration with the clinic. The location of water sources sampled (which included taps, boreholes, furrows and wells) was obtained from the CSIR report. The trained NICD team together with the GIS specialist used mobile phones to determine spatial distribution of cases and water sources. The Collector for ArcGIS (South Africa, Midrand) mapping tool was used for field data collection. Information such as patient demographics and Global Positioning System (GPS) coordinates were collected. We used colour-coded points to indicate cases (confirmed and probable) and water sources tested for *Salmonella* spp.

Data processing and analysis

Data on CIFs were captured into Microsoft (MS) Excel 2016 (Microsoft Corporation, Redmond, Washington, USA). Cleaning of data was done using MS Excel by checking for duplicate records, missing data, etc. Data was analysed using STATA version 15 (StataCorp LP, College Station, Texas, USA) and descriptive statistics (mean, range and percentages) were used. Geographic maps were prepared using Collector for ArcGIS.

Results

Epidemiological and clinical findings

The first laboratory-confirmed case of typhoid fever was reported on 15 November 2017. The patient's initial consultation was the district hospital, and was later transferred to Pietersburg Tertiary Hospital. As of 31 January 2018, 122 confirmed and suspected cases were reported, of which 6% (7/122) were confirmed by blood culture (Tables 1 and 2, Figure 3). The median age of confirmed and suspected was 11 years (IQR, 2 - 83 years). Children of school-going age were mostly affected (64%, 78/122). The most common presenting symptoms were fever, diarrhoea and abdominal cramps/pain (Figure 4). Two local municipalities were affected (Makhudumathaga and Tubatse-Fetakgomo) with the majority of cases from Tswaing (67%, 82/122), Vlakplaas (10%, 12/122) and Strydkraal (9%, 11/122) (Table 2). Figure 5 shows clusters of laboratory-confirmed cases (58%, 4/7) in Tswaing, and clusters of probable cases in Vlakplaas and Strydkraal. Case-patients were treated with intravenous ceftriaxone and/or oral ciprofloxacin according to South African national guidelines.[3] Table 1 outlines the demographic and clinical characteristics of laboratory-confirmed cases and Figure 3 illustrates the number of cases by date of symptom onset.

Table 1. Demographic and clinical characteristics of confirmed typhoid cases, Sekhukhune District, Limpopo Province, South Africa, 6 November to 31 December 2017 (n=7).

Case no.	Age (yrs.)	Sex	Place of residence	Clinical presentation	Specimen types	Date of diagnosis	Type of water source
1	23	F	Strydkraal	Diarrhoea, malaise	Blood culture	15/11/2017	Stream
2	4	F	Tswaing	Fever, diarrhoea, painful legs	Blood culture	22/11/2017	Furrow
3	19	M	Apel Cross	Vomiting, diarrhoea, malaise	Stool, blood culture	23/11/2017	Communal tap
4	9	F	Tswaing	Fever, diarrhoea	Rectal swab, blood culture	23/11/2017	Stream
5	12	F	Tswaing	Fever, abdominal cramps, painful legs	Stool, rectal swab, blood culture	23/11/2017	Furrow
6	15	M	Tswaing	Diarrhoea, malaise, respiratory symptoms, abdominal cramps	Rectal swab, blood culture	23/11/2017	Furrow
7	71	F	Ga-Phaahla (Mamatsekele)	Not known	Stool, blood culture	24/11/2017	Well

Table 2. Typhoid cases characterised by age, gender, location and water sources, Sekhukhune District, Limpopo Province, South Africa, 6 November to 31 December 2017 (n=122).

Variable	Total cases (N=122) n/(%)	Suspected (N=115) n/(%)	Confirmed (N= 7) n/(%)
Age group in years			
≤4	14 (11)	13 (11)	1 (14)
5 - 14	78 (64)	76 (66)	2 (29)
15- 49	25 (21)	22 (19)	3 (43)
≥ 50	5 (4)	4 (4)	1 (14)
Sex			
Female	66 (54)	62 (54)	5 (71)
Male	56 (46)	53 (46)	2 (29)
Villages			
Apel cross	2 (2)	1 (1)	1 (14)
Ga-Masemola	6 (5)	6 (5)	0 (0)
Ga-Phaahla	1 (1)	0 (0)	1 (14)
Tswaing	82 (67)	78 (68)	4 (58)
Vlakplaas	12 (10)	12 (10)	0 (0)
Strydkraal	11 (9)	10 (9)	1 (14)
Other	8 (6)	8 (7)	0 (0)
Water Sources			
Stream	9 (7)	7 (6)	2 (29)
Furrow	70 (57)	67 (58)	3 (43)
Jojo tank	1 (1)	1 (1)	0 (0)
Borehole	2 (2)	2 (2)	0 (0)
Communal taps	2 (2)	1 (1)	1 (14)
Well	1 (1)	0 (0)	1 (14)
Unknown	37 (30)	37 (32)	0 (0)
Type of toilet			
Pit latrine	110 (90)	103 (90)	7 (100)
Unknown	22 (10)	22 (10)	0 (0)

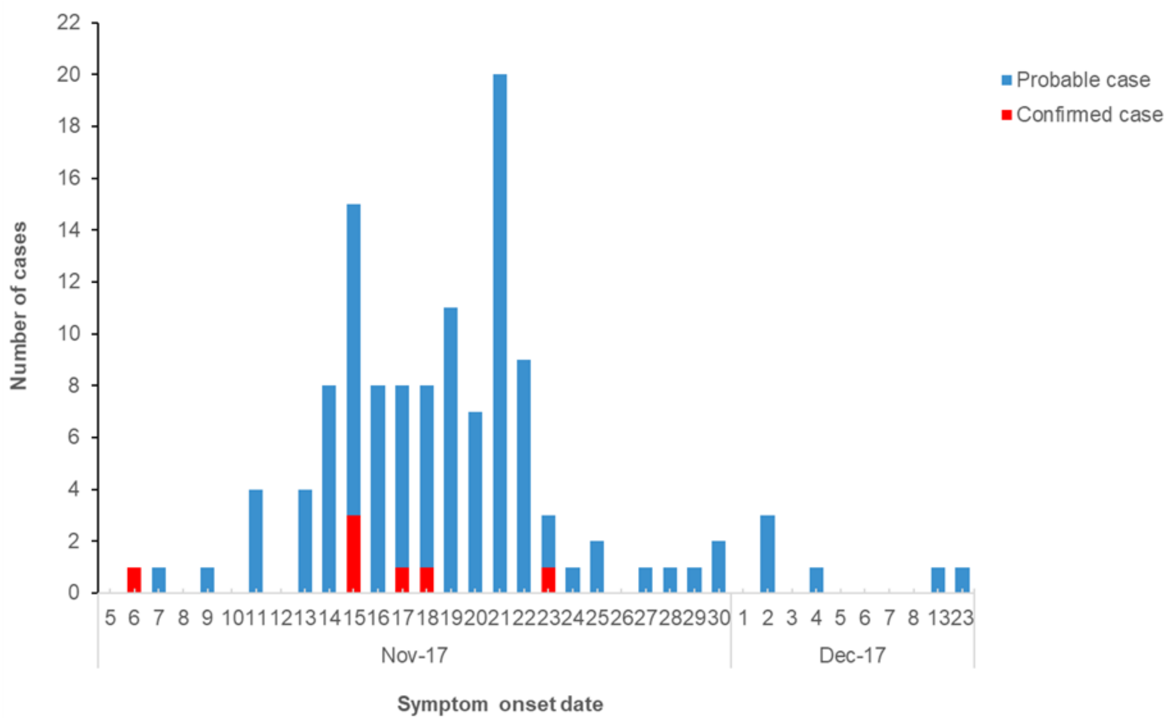

Figure 3. Epidemic curve showing distribution of typhoid cases by date of onset of symptoms, Sekhukhune District, Limpopo Province, South Africa, 6 November to 31 December 2017 (n=122).

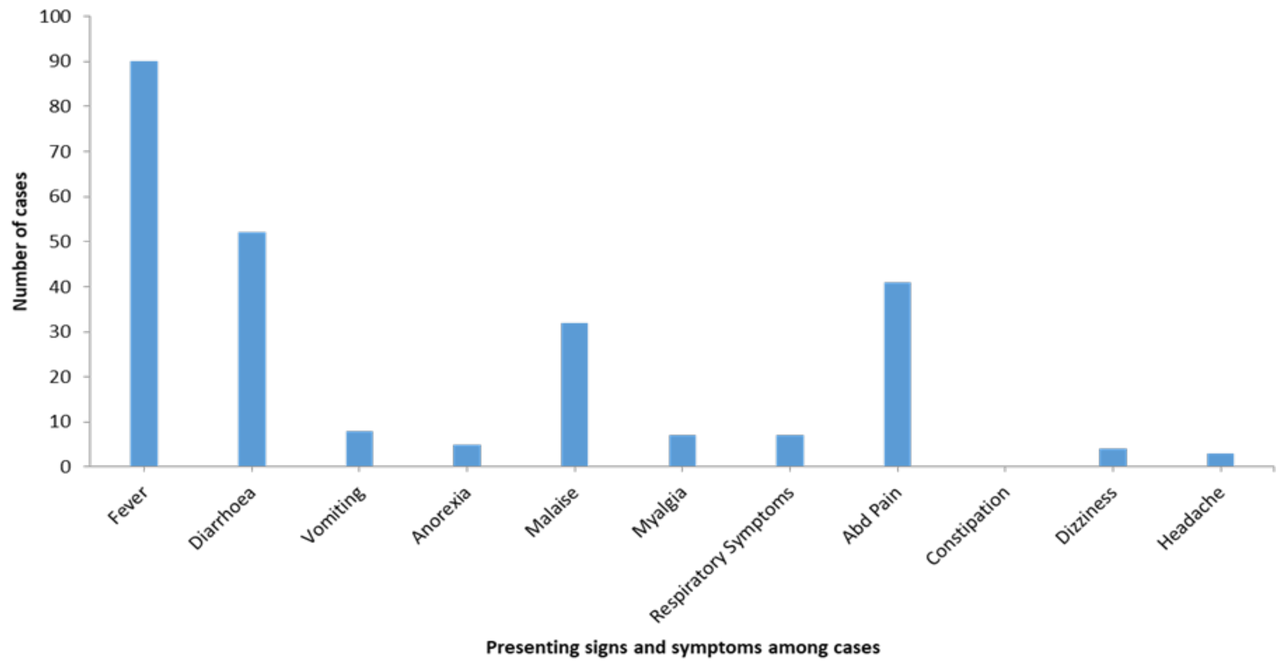

Figure 4. Presenting signs and symptoms among typhoid cases, Sekhukhune District, Limpopo Province, South Africa, 6 November to 31 December 2017.

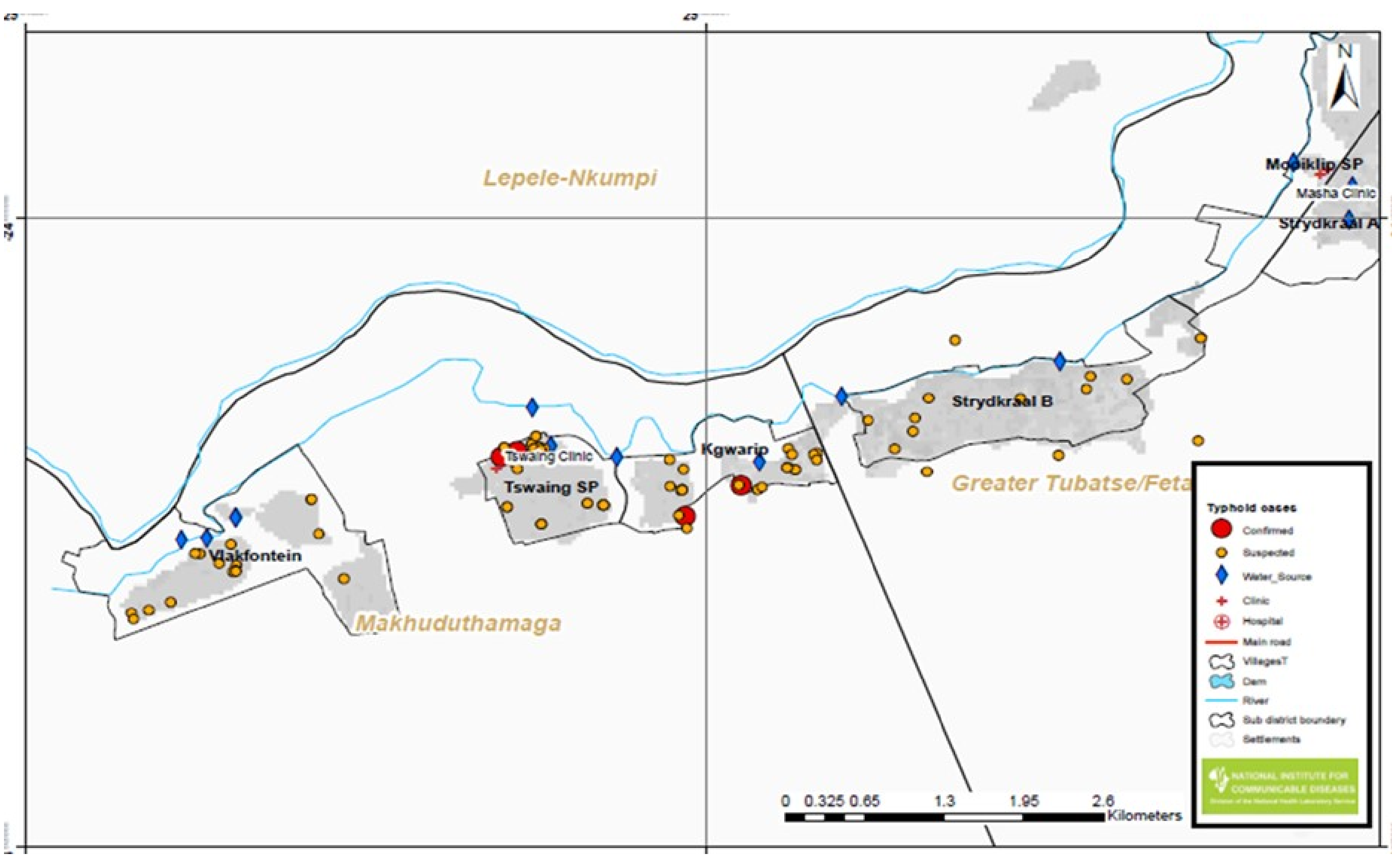

Figure 5. Geographic distribution of typhoid fever cases and water sources used, Sekhukhune District, Limpopo Province, South Africa, 6 November to 31 December 2017.

Laboratory findings

The NHLS received specimens from 106 suspected typhoid fever cases under investigation. This included blood cultures (65/106), stool cultures (6/106), rectal swabs for stool culture (3/106) and serology (Widal test, 32/106). Of the 122 cases reported, 16 (13%) had no record of specimens submitted for culture. For 16 probable cases, it could not be ascertained whether any specimens were collected. Amongst laboratory-confirmed cases, all were positive for *S*. Typhi on blood culture, while five also had stool or rectal swabs culture-positive for *S*. Typhi. WGS results indicated that five of six isolates obtained from cases resident in Tswaing and Strydkraal were genetically highly related (<22 single nucleotide polymorphism) (Figure 6). A single, un-clustered strain was closely related to the 2016 Zimbabwe typhoid outbreak isolates.

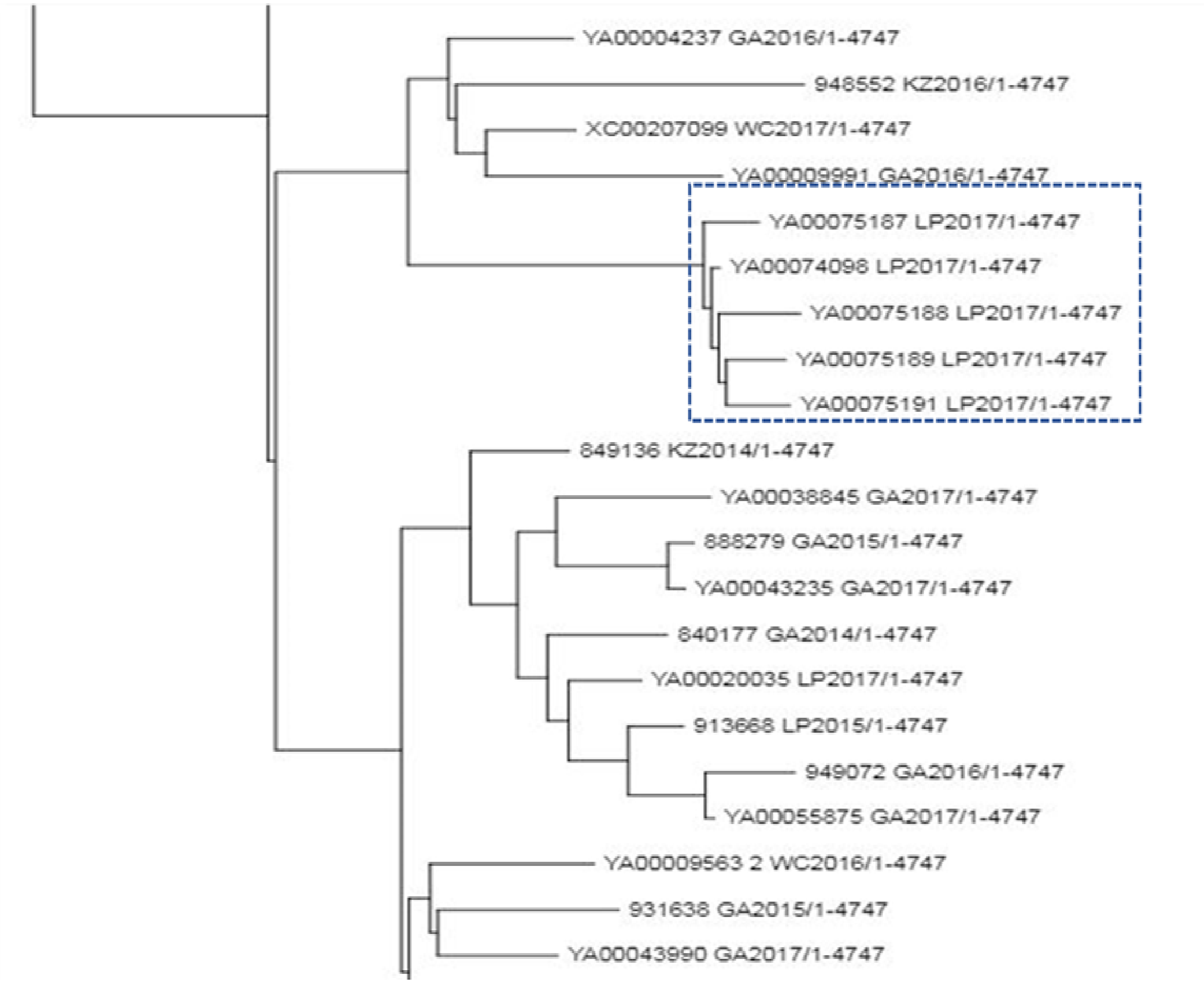

Figure 6. Molecular characterization of *Salmonella enterica* subspecies *enterica* serotype Typhi clinical isolates among confirmed cases, showing a cluster of related isolates, Sekhukhune District, Limpopo Province, South Africa, November to January 2018. The figure shows a snapshot from a maximum likelihood phylogenetic tree drawn using SNP alignments from WGS data of isolates.

Environmental findings

In Sekhukhune District, approximately 65% of cases reported the use of water from untreated open water sources such the furrows, streams and wells due to lack of access to clean water. The furrow that ran parallel to the river and adjacent to villages where cases were clustered was intended for crop irrigation and for the use of domestic animals. Amongst 27 water samples, 37% (10/27) were positive for *Salmonella* spp. on PCR. Of the 27 water sources tested for *Salmonella* spp., 44% (12/27) were linked with villages where case-patients resided. *Salmonella* spp. was identified in 83% (10/12) of the water sources linked with the outbreak villages (Table 3). Of the seven confirmed cases, 86% (6/7) reported obtaining water from the untreated open water sources. Although one confirmed case from Apel Cross (not shown in Figure 6) reported using water from the communal tap, he was a learner in one of the schools located in Tswaing.

Interventions implemented

The Sekhukhune District EPR team was activated on 20 November 2017, and an intervention plan was developed. The district municipality was informed of the detection of *Salmonella* spp. in water samples, and subsequently treated water was distributed by water tankers in the affected villages. In addition, a water treatment plant that was previously erected in Vlakplaas was repaired so that piped potable water provision could resume. The municipality district office procured bleach and distributed it in all affected areas. Environmental health practitioners (EHPs) conducted home visits to monitor sanitation, hygiene and food and water safety in the households.

Multiple community outreach activities, including door-to-door home visits, school visits and outreach through media platforms, were conducted by health officials and community health workers. These included education on water and foodborne illnesses. Community members with symptoms compatible with typhoid fever were encouraged to seek medical care at health facilities.

From 21 November to 31 December 2017, mobile clinic teams conducted contact tracing. All contacts with symptoms compatible with typhoid fever were referred to the nearest healthcare facility for investigation. Clinical samples were only collected from symptomatic contacts. Awareness campaigns about waterborne diseases, the prevention measures and when to seek medical attention was facilitated by ward councillors in the communities.

Training of health professionals and community health workers was conducted at the three district hospitals where patients presented for care. Regular EPR meetings were held for discussions and follow up of executed plans.

Discussion

Based on these clinical, epidemiological and molecular findings, we hypothesise that the typhoid outbreak in Sekhukhune District was caused by contaminated water. This outbreak illustrates the importance of thorough investigation of suspected waterborne illness and the need for uninterrupted supplies of clean, safe water.

Unregulated, untreated open water sources are major contributors to typhoid outbreaks. The association of typhoid outbreaks with contaminated water has been observed in other sub-Saharan African countries including Zambia, Malawi, Uganda and Zimbabwe.[16 - 19] In Zimbabwe, a large typhoid outbreak in Harare in 2011 with over 4 000 cases was associated with drinking water from a well (AOR=5.8; 95% CI 1.9-17.78) and a burst sewage pipe (AOR=1.2, 95% CI 1.10-2.19).[16] The outbreaks of typhoid fever in Delmas, Mpumalanga Province, were associated with unregulated contaminated water supplies.[5-6] A number of recent typhoid cases that occurred in South Africa were associated with imported S. *Typhi*,[7] including strains similar to those identified in the 2010 Harare outbreak. Our case-patients' isolates were not similar to these strains. Only a single strain, from GaPhaahla, was related to the 2016 Zimbabwe typhoid outbreak strains. However, this case-patient did not live in the villages of interest (Figure 6). Although this case-patient did not report a travel history, healthcare workers did not explore travel history of his/her contacts.

The Constitution of the Republic of South Africa, the National Development Plan (NDP) and the Sustainable Development Goals (SDGs) introduced in 2016 all emphasise that access to sufficient water and adequate sanitation is essential to preserve public health. In Limpopo Province, only 79% of persons have access to piped water, compared with the national average of 89%.[9] Further, 79% of Limpopo households that experienced water interruptions in the previous three months of a survey conducted in 2016 reported that these that lasted longer than two consecutive days.[9] This outbreak illustrates the health consequences of the interruption of safe water supplies, when residents are forced to use other available water sources, which may not be treated, or safe.

This outbreak highlighted challenges in the diagnosis of typhoid cases. The gold standard of typhoid fever diagnosis is culture of the organism from a clinical specimen, preferably blood or bone marrow.[3] A shortage of blood culture bottles at district hospitals within Sekhukhune District meant that initial cases were not identified until they were referred to a tertiary hospital where blood cultures were performed. As an interim measure, clinicians resorted to the Widal test, which is not recommended as a diagnostic test, due to variable host antibody responses and cross-reactivity with other enteric bacteria. When blood culture bottles were made available at the district hospitals, most suspected cases had already received antibiotic treatment. This may have accounted for the low rate of culture-based confirmation amongst case-patients.

Regarding case management, South African national typhoid fever guidelines advise that all typhoid fever cases should have three follow-up stool specimens to confirm clearance of the organism. The stool sample should be collected one week after completion of antibiotics, and two subsequent samples should be collected 48 hours apart. If all follow up stool samples are negative, the case can be released from surveillance.[3] Further, guidelines recommend that contacts of cases submit stool specimens for culture to exclude asymptomatic carriage. These recommendations were not adhered to in the Sekhukhune typhoid outbreak, so there remains a risk of transmission by typhoid carriers.

A number of recommendations were made to provincial and local authorities, including:

- The formation of an inter-sectoral health, water and sanitation committee to facilitate communication between departments and to ensure that challenges pertaining to access to clean water and sanitation are timeously addressed.
- Purification and chlorination of public water supplies should be monitored by the by inter-sectoral health, water and sanitation committee. Chlorination may minimise or limit contamination when possible backflow connections between potable water and open water sources occur.[2]
- Continuous community health education and awareness regarding the importance of handwashing, correct disposal of human faeces, and maintenance of fly-proof latrines should take place.
- Case management should include contact tracing with investigation for asymptomatic carriage, documentation of eradication of carriage, and restrictions on food handling practices amongst laboratory-confirmed cases until at least three consecutive negative stool cultures have been taken.[3]
- Health professionals to complete CIFs to ensure that quality data is collected.

Conclusion

This outbreak investigation suggests that contamination of open water sources and an interruption of municipal water supply led to an outbreak. The investigation highlights the importance of the provision of safe water and sanitation, and highlights the ability of district surveillance systems to identify and contain outbreaks.

Acknowledgements

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