

Epidemiology and disease burden of typhoid fever and iNTS disease in sub-Saharan Africa

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*Coalition against Typhoid meeting
Kampala, Uganda
4 April 2017*

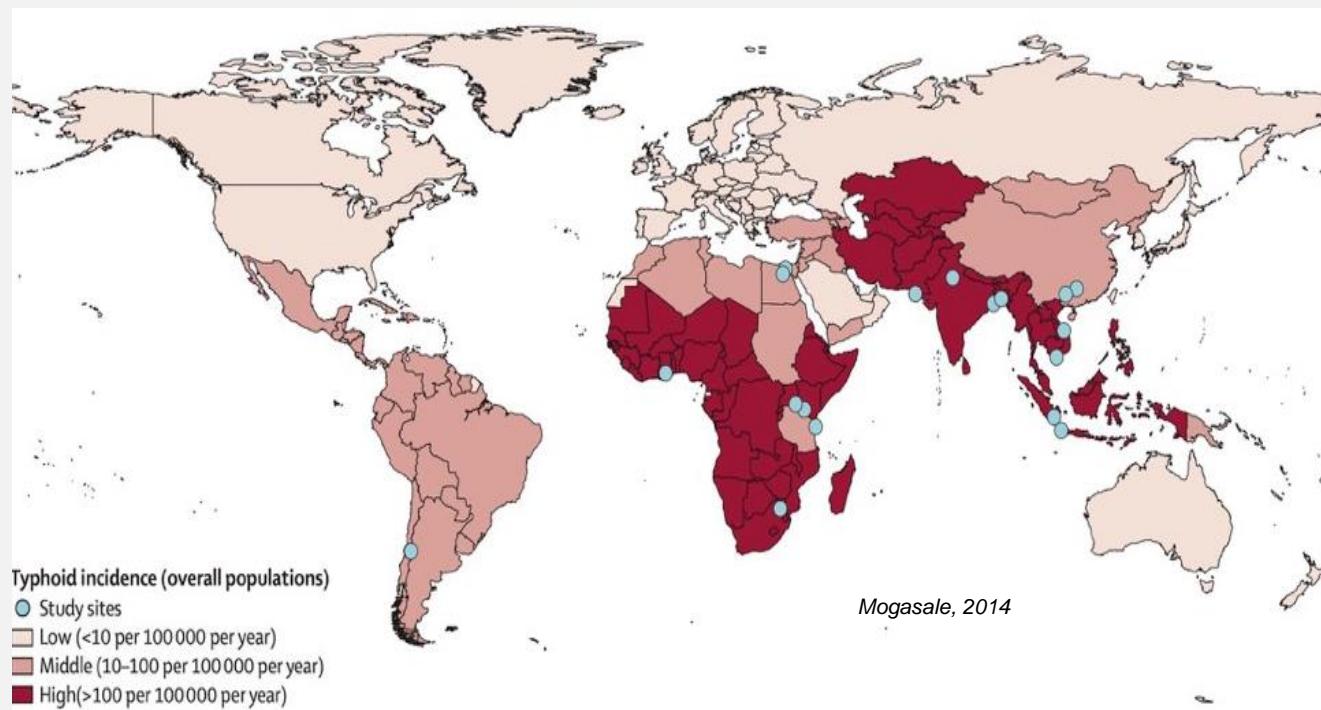
***Salmonella* infections – major cause of global morbidity and mortality**

Ivanoff (1994)
17 million cases and
600,000 deaths

Crump (2004)
21.7 million cases and
216,000 deaths

Buckle (2012)
26.9 million cases

Mogasale (2014)
20.6 million cases and
222,000 deaths



2008 - Need for epidemiological information
on invasive *Salmonella* disease in sub-Saharan Africa
(sSA) expressed by WHO

2009 - Consortium established to investigate
invasive *Salmonella* disease burden sSA

2010 – Surveillance implemented in sSA: The
Typhoid Surveillance in Africa Program (TSAP)

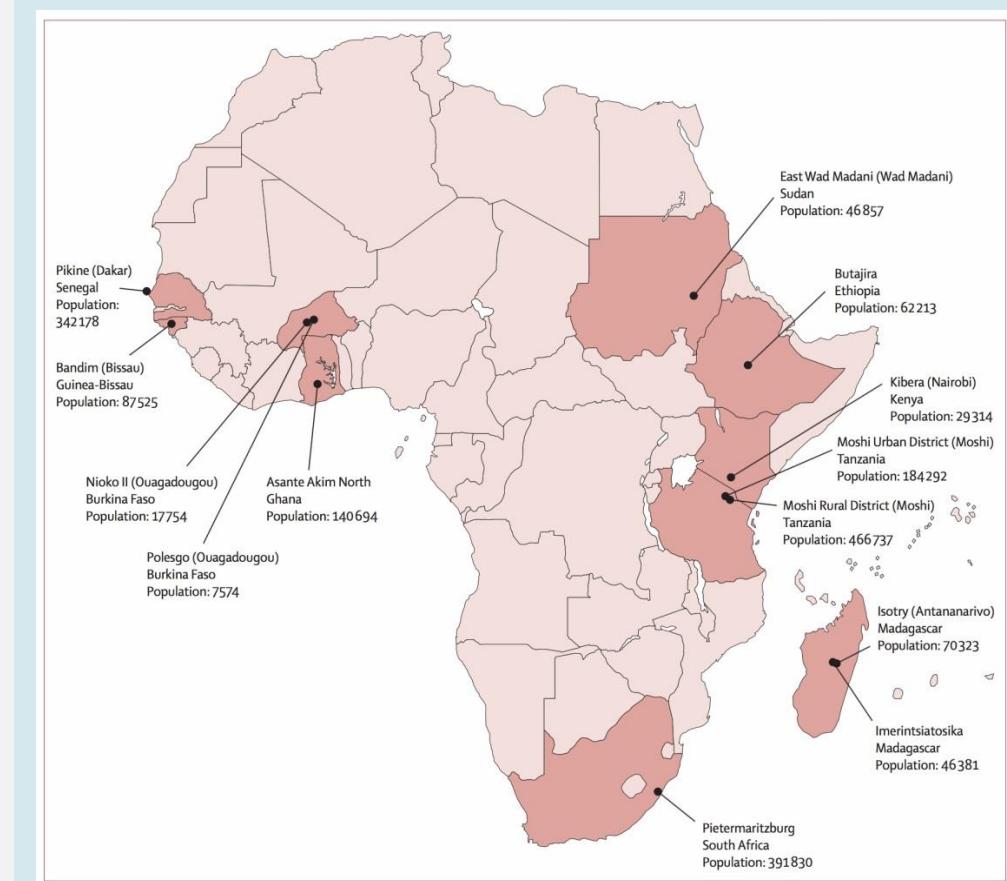


Typhoid Fever Surveillance in Africa Program (TSAP) - methods

TSAP methods

- ✓ Mar 2010 to Jan 2014
- ✓ 13 African sites
- ✓ 13,431 febrile patients sampled
- ✓ Standardized procedures
 - inclusion criteria
 - laboratory
 - case definition
 - healthcare utilization
 - database

**S. Typhi and iNTS positivity
Blood culture**



Typhoid Fever Surveillance in Africa Program (TSAP) – major findings¹

Typhoid fever disease

- ✓ Overall adjusted incidences – two to three times higher compared to previous estimates (10-100 cases/100,000 people²).
- ✓ In some settings – adjusted rates comparable to data from Asia. (Ghana, Burkina Faso, and Kenya).
- ✓ Greatest burden – in children aged 2-14 years.

Age group, years	Burkina Faso, Nioko II	Burkina Faso, Polesgo	Guinea Bissau, Bandim	Ghana, AAN	Tanzania, Moshi rural	Tanzania, Moshi urban	Kenya, Kibera	Madagascar, Imerintsiasika	Madagascar, Isotry
0 to 1	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	120 (49 - 290)	0 (0 - 0)	0 (0 - 0)	148 (48 - 458)	0 (0 - 0)	0 (0 - 0)
2 to 4	251 (107 - 590)	1,890 (1,202 – 2,972)	53 (13 - 208)	1,079 (762 – 1,528)	0 (0 - 0)	1,028 (472 – 2,237)	490 (264 - 912)	0 (0 - 0)	0 (0 - 0)
5 to 14	315 (191 - 519)	485 (263 - 896)	18 (5 - 72)	314 (230 - 430)	18 (8 - 44)	103 (54 – 199)	489 (338 - 709)	171 (81 - 360)	62 (11 - 359)
< 15	227 (148 - 350)	719 (500 – 1,035)	20 (8 - 53)	389 (310 - 486)	18 (7 - 42)	155 (94 – 256)	419 (308 - 569)	95 (45 - 201)	42 (7 - 247)
≥15	0 (0 - 0)	107 (46 - 252)	4 (1 - 20)	n.a.	28 (8 - 95)	201 (99 - 408)	141 (82 - 243)	20 (4 - 103)	42 (12 - 151)
All	104 (68 - 161)	383 (274 - 535)	10 (4 - 22)	n.a.	20 (10 - 41)	168 (111 – 253)	284 (217 - 371)	58 (29 - 114)	42 (15 - 119)

¹Incidence of invasive *Salmonella* disease in sub-Saharan Africa: a multicenter population-based surveillance study. *LANCET Global Health* 2017; 5: e310-23.

²Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ*. 2004;82:346–53.



Typhoid Fever Surveillance in Africa Program (TSAP) – major findings¹

iNTS disease

- ✓ Overall adjusted incidences – comparable to previous reports.
- ✓ Greatest burden – in children aged 0-5 years.
- ✓ Most common serovars
 1. *S. Typhimurium* (40%, 38/94)
 2. *S. Enteriditis* (12%, 11/94)
 3. *S. Dublin* (11%, 10/94)

Age group, years	Burkina Faso, Nioko II	Burkina Faso, Polesgo	Guinea Bissau, Bandim	Ghana, AAN	Tanzania, Moshi rural	Tanzania, Moshi urban	Kenya, Kibera	Madagascar, Imerintsatosika	Madagascar, Isotry
0 to 1	753 (460 – 1,233)	431 (162 - 1147)	291 (176 - 482)	1,733 (1,373 – 2,188)	0 (0 - 0)	427 (125 – 1,461)	49 (7 - 350)	100 (18 – 562)	0 (0 - 0)
2 to 4	753 (460 – 1,233)	630 (288 – 1,380)	53 (13 - 208)	1,908 (1,469 – 2,479)	0 (0 - 0)	0 (0 - 0)	49 (7 - 348)	0 (0 - 0)	0 (0 - 0)
5 to 14	236 (133 - 420)	0 (0 - 0)	53 (14 - 97)	147 (93 - 232)	0 (0 - 0)	0 (0 - 0)	17 (2 - 124)	0 (0 - 0)	0 (0 - 0)
< 15	475 (352 - 640)	255 (138 - 470)	116 (69 - 161)	742 (631 - 873)	0 (0 - 0)	26 (8 - 88)	31 (10 - 95)	18 (3 - 99)	0 (0 - 0)
≥15	35 (13 - 96)	54 (16 - 179)	0 (0 - 0)	n.a.	28 (8 - 95)	0 (0 - 0)	33 (10 - 101)	0 (0 - 0)	0 (0 - 0)
All	237 (178 – 316)	144 (83 - 249)	37 (24 - 57)	n.a.	7 (2 - 23)	19 (5 - 64)	32 (14 - 70)	9 (2 – 50)	0 (0 - 0)

¹Incidence of invasive *Salmonella* disease in sub-Saharan Africa: a multicenter population-based surveillance study. *LANCET Global Health* 2017; 5: e310-23.



Typhoid Fever Surveillance in Africa Program (TSAP) – major findings¹

Antimicrobial resistance patterns

- ✓ High number of MDR *S. Typhi* isolates – 47% (64/135)
- ✓ High number of MDR iNTS isolates – 48% (45/94)

	Burkina Faso	Guinea-Bissau	Senegal*	Ghana	Ethiopia	Madagascar	South Africa	Tanzania	Kenya	All
Total <i>S Typhi</i> isolates, N	18	3	7	30	3	9	2	9	54	135
Isolate with antimicrobial resistance, n (%)†										
Ampicillin	0	NR	NR	20 (67%)	2 (67%)	NR	0	8 (89%)	41 (76%)	71 (53%)
Amoxicillin-clavulanic acid	0	NR	NR	3 (10%)	0	NR	0	4 (44%)	24 (44%)	31 (23%)
Chloramphenicol	2 (11%)	NR	NR	23 (77%)	0	NR	0	5 (56%)	43 (80%)	73 (54%)
Co-trimoxazole	2 (11%)	NR	NR	24 (80%)	0	NR	0	8 (89%)	43 (80%)	77 (57%)
Ceftriaxone	0	NR	NR	0	0	NR	0	0	0	0
Ciprofloxacin	0	NR	NR	0	0	NR	1 (50%)	0	11 (20%)	12 (9%)
Multidrug resistance‡	0	NR	NR	19 (63%)	0	NR	0	5 (56%)	40 (74%)	64 (47%)
Total iNTS isolates, N	14	8	4	59	0	1	0	2	6	94
Isolate with antimicrobial resistance, n (%)†										
Ampicillin	10 (71%)	1 (13%)	NR	38 (64%)	NR	NR	NR	0	2 (33%)	51 (54%)
Amoxicillin-clavulanic acid	3 (21%)	0	NR	9 (15%)	NR	NR	NR	0	2 (33%)	14 (15%)
Chloramphenicol	12 (86%)	1 (13%)	NR	34 (58%)	NR	NR	NR	0	1 (17%)	48 (51%)
Co-trimoxazole	13 (93%)	1 (13%)	NR	34 (58%)	NR	NR	NR	0	2 (33%)	50 (53%)
Ceftriaxone	0	0	NR	0	NR	NR	NR	0	1 (17%)	1 (1%)
Ciprofloxacin	1 (7%)	0	NR	2 (3%)	NR	NR	NR	0	0	3 (3%)
Multidrug resistance‡	10 (71%)	1 (13%)	NR	33 (56%)	NR	NR	NR	0	1 (17%)	45 (48%)
Resistant isolates are reported per country, rather than per site. No <i>Salmonella enterica</i> serotype <i>Typhi</i> (<i>S Typhi</i>) or iNTS isolates were cultured in Sudan. iNTS=invasive non-typhoidal salmonella. NR=no resistant isolates identified. *Seven <i>S Typhi</i> , four iNTS, and three <i>S enterica</i> serotype <i>Paratyphi</i> (<i>S Paratyphi</i>) isolates. One of the <i>S Paratyphi</i> isolates was resistant to ciprofloxacin. †Includes isolates fully and intermediately resistant against the respective drug, as defined by the Clinical Laboratory and Standards Institute guidelines 2013. ¹⁵ ‡Defined as resistance against ampicillin or amoxicillin AND chloramphenicol AND co-trimoxazole.										

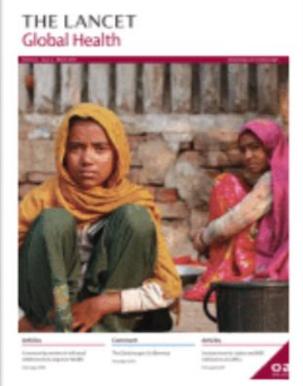
Table 3: Antimicrobial resistance patterns of *Salmonella enterica* serotype *Typhi* and iNTS isolates across sites

¹Incidence of invasive *Salmonella* disease in sub-Saharan Africa: a multicenter population-based surveillance study. *LANCET Global Health* 2017; 5: e310-23.



Manuscripts published

25 manuscripts published and several planned for 2017



Mar 2017

Articles

Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study

Florian Meiss, Ven van Kerkhout, Peter Aaby, You da Sordic, Munir Ahmed El Tayeb, Mohammad Al, Abraham Assefaw, Stephen Baker, Holly M. Biggs, Morten Børgenæs Andersen, Robert J. Björnsson, Jonas J. Campbell, Leonard Cosca, John Cump, Lige-Maria Cruz Espinoza, Jessica Fung, Debrah Myra Dabek, Barry J. Fields, Nelly Gessner, Julian T. Hertz, Nguyen Van-Hanh, Justinian Anne Jagger, Hyon Jo-Jean, Leon Peflitz Kabare, Karen H. Klitz, Frank Konings, Rolf Kornbrands, Benedict Ley, Souad Valéry, Leffing, Jérôme May, Christian G. Meyer, Eric D. Mintz, José M. Montoya, Alister J. Akerele Nzing, Chedza Nichols, Benedict Ofori, Gérard Park, Ursula Prentor, Jin Kyung Park, Se-en Park, Norinie Soe Rohanayana, Raphael Rakotondrazaina, Timo Mirroni Rimonius, Trinckenn, Jon Laro Rizziñdröq, Emmanuel Sampa, Heidi Schott-Gerwitt, Amy Gassama Sow, Nirmala Suryap, Hyun-Il Seo, Arvinda Sockch, Abduhamid Benslim Souri, Adnan Tali, Makonnen Teferi, Kamala Thirumur, Michelle E. Warren, Brink Yeshiha, John D. Clemens, Thomas P. Wierzba

Summary

Background Available incidence data for invasive salmonella disease in sub-Saharan Africa are scarce. Standardised, multi-country data are required to better understand the nature and burden of disease in Africa. We aimed to measure the adjusted incidence estimates of typhoid fever and invasive non-typhoidal salmonella (INTS) disease in sub-Saharan Africa, and the antimicrobial susceptibility profiles of the causative agents.

Methods We established a systematic, standardised surveillance of blood culture-based febrile illness in 13 African sentinel sites with previous reports of typhoid fever: Burkina Faso (two sites), Ethiopia, Ghana, Guinea-Bissau, Kenya, Madagascar (two sites), Senegal, South Africa, Sudan, and Tanzania (two sites). We used census data and health-care records to define study catchment areas and populations. Eligible patients were either inpatients or outpatients who resided within the catchment area and presented with typhoid ($\geq 38.0^\circ\text{C}$) or axillary temperature ($\geq 37.5^\circ\text{C}$). Inpatients with a reported history of fever for 72 h or longer were excluded. We also implemented a health-care utilisation survey in a sample of households randomly selected from each study area to investigate health-seeking behaviour in cases of self-reported fever lasting less than 3 days. Typhoid fever and INTS disease incidences were corrected for health-care seeking behaviour and recruitment.

Findings Between March 1, 2010, and Jan 31, 2014, 135 *Salmonella enterica* serotype Typhi (S Typhi) and 94 INTS isolates were cultured from the blood of 13 431 febrile patients. *Salmonella* spp accounted for 33% or more of all bacterial pathogens at nine sites. The adjusted incidence rate (AIR) of S Typhi in 100 000 person-years of observation ranged from 0·05% CI 0–0·1 in Sudan to 3·8 (2·4–5·3) in one site in Burkina Faso; the AIR of INTS ranged from 0 in Sudan, Ethiopia, Madagascar (INTS site), and South Africa to 2·7 (1·8–3·6) in the second site in Burkina Faso. The AIR of INTS and typhoid fever in individuals younger than 15 years old was typically higher than in those aged 15 years or older. Multidrug-resistant S Typhi was isolated in Ghana, Kenya, and Tanzania (both sites combined), and multidrug-resistant INTS was isolated in Burkina Faso (both combined), Ghana, Kenya, and Guinea-Bissau.

Interpretation Typhoid fever and INTS disease are major causes of invasive bacterial febrile illness in the sampled locations, most commonly affecting children in both low and high population density settings. The development of INTS vaccines and the introduction of S Typhi conjugate vaccines should be considered for high-incidence settings, such as those identified in this study.

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Introduction

Salmonella infections contribute substantially to global morbidity and mortality.^{1,2} The best described invasive salmonella serovars are *Salmonella enterica* serotype Typhi (S Typhi), causing typhoid fever, and *S enterica* serotype Paratyphi A, B, and C (S paratyphi A, B, and C), which cause paratyphoid fever. Other non-typhoidal salmonella (NTS) serovars that typically cause self-limiting diarrhoea can also cause systemic infections, referred to as invasive NTS disease.³ Globally, typhoid fever is estimated to cause 21·7 million illnesses and 217 000 fatalities annually, and INTS disease is estimated to cause 3·4 million illnesses and 681 000 fatalities annually.^{1,2}

Substantial knowledge gaps exist regarding the distribution of typhoid fever and INTS disease in Africa. The few existing studies,^{4–8} reported over differing time periods and using various protocols, have been extrapolated and contribute to existing typhoid fever estimates, which limits international generalisability. The scarcity of data in sub-Saharan Africa prompted

Clinical Infectious Diseases

Typhoid Fever Surveillance in Africa Program (TSAP)

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International Active Institute, GHANA, Burkina Faso, South Africa, and Tanzania

Lige-Maria Cruz Espinoza, Lorraine M. Gessner, Julian T. Hertz, Benedict Ley, Souad Valéry, Leffing, Jérôme May, Christian G. Meyer, Eric D. Mintz, José M. Montoya, Alister J. Akerele Nzing, Chedza Nichols, Benedict Ofori, Gérard Park, Ursula Prentor, Jin Kyung Park, Se-en Park, Norinie Soe Rohanayana, Raphael Rakotondrazaina, Timo Mirroni Rimonius, Trinckenn, Jon Laro Rizziñdröq, Emmanuel Sampa, Heidi Schott-Gerwitt, Amy Gassama Sow, Nirmala Suryap, Hyun-Il Seo, Arvinda Sockch, Abduhamid Benslim Souri, Adnan Tali, Makonnen Teferi, Kamala Thirumur, Michelle E. Warren, Brink Yeshiha, John D. Clemens, Thomas P. Wierzba

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Clinical Infectious Diseases

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TYPHOID FEVER SURVEILLANCE IN AFRICA PROGRAM (TSAP)

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Updated disease burden estimates

submitted

Table 1: Typhoid fever burden per 100,000 individuals in Africa

Region	2014 estimate ²	Updated estimates		
	Base estimates*	Base estimates*		Alternate estimates [†]
	Risk-factor adjusted [‡] (95% CI)	Risk-factor adjusted [‡] (95% CI)	Risk-factor un-adjusted (95% CI)	Risk-factor un-adjusted (95% CI)
North Africa	33,807 (25,809 – 44,185)	33,807 (26,213-44,165)	61,971 (50,089-75,713)	76,207 (60,448-94,790)
East Africa	1,749,861 (1,386,537-2,203,996)	1,270,040 (992,192-1,509,643)	1,715,321 (1,353,111-2,013,337)	2,109,357 (1,625,493-2,514,001)
West Africa	489,669 (309,531 – 729,282)	1,259,073 (998,327-1,536,530)	1,672,045 (1,325,851-2,011,005)	2,056,140 (1,582,635-2,530,004)
Middle Africa	713,517 (568,060-887,805)	713,517 (569,039-889,638)	881,368 (704,662-1,091,018)	1,083,833 (846,026-1,371,996)
Southern Africa	103,542 (76,359-140,868)	103,542 (75,835-140,861)	188,529 (143,043-244,423)	231,837 (170,995-304,842)
Africa total	3,090,395 (2,504,427-3,829,277)	3,379,978 (2,796,753-3,949,796)	4,519,234 (3,761,267-5,181,078)	5,557,373 (4,483,729-6,553,323)
Global	11,883,047 (9,925,551-14,751,214)	12,172,630 (9,999,237-14,845,639)	20,940,154 (17,730,988-24,426,186)	25,750,435 (21,203,991-30,637,959)

* Base estimates assume 61% blood culture sensitivity². †Alternate estimates assume 50% blood culture sensitivity. ‡Risk-factor adjustment extrapolates incidence from longitudinal studies directly to rural population lacking access to improved water and urban population living in slums; and extrapolates corrected incidence to rural population having access to improved water and an urban population not living in slums based on water-related risk correction factor of 2.4 (95% CI 1·7-3·6). Detailed methodology is available elsewhere². CI= confidence interval

Updated estimates mean annual typhoid fever incidence (/100,000)

- decreased from 526 to 376 in East Africa
- increased from 160 to 411 in West Africa

→ average annual incidence of 328/100,000 people in Africa
(an increase of 28/100,000 from the previous estimate)



Typhoid and iNTS disease burden in children and infants

Invasive *Salmonella* infections in young children across TSAP¹ sites

Age Group in years	# of enrolled patients	PYO ² by age group	S. Typhi			iNTS		
			Crude Cases	Cases adjusted for recruitment ³	Adjusted incidence per 100,000 PYO (95% CI)	Crude Cases	Cases adjusted for recruitment ³	Adjusted incidence per 100,000 PYO (95% CI)
0 to 1	1,217	8,658	1	1	4.1 (0.38-43.4)	14 (15)*	33	81.6 (25.5-261.0)
1 to 2	1,057	9,102	4	7	31.4 (7.6-130.5)	27	77	238.3 (77.4-733.8)
2 to 3	818	6,407	7	19	122.9 (34.0-445.0)	13	35	143.0 (45.1-453.4)
3 to 4	685	5,507	13	27	195.3 (55.3-689.6)	15	38	208.9 (66.4-656.7)
4 to 5	575	4,800	12 (16)*	28	245.2 (69.9-860.1)	2	8	47.1 (12.4-179.1)
Total	4,352	34,474	37 (41)*	82		71 (72)*	191	

¹Ethiopia, South Africa and Senegal are excluded in the analysis because no person time information is available in these sites.

²Study population was adjusted for health-seeking behavior.

³Crude cases were adjusted for recruitment proportion (number of patients analyzed divided by number of patients with febrile illness from study area who visited a recruitment health facility, multiplied by 100.)

*Crude cases have been adjusted for recruitment pattern unique to the site in Tanzania: before Nov. 11, 2011 every 5th eligible patient was recruited; from Nov. 11, 2011 every 2nd eligible patient was recruited. Adjusted cases (presented inside parenthesis) were used to calculate crude rates.

→ Poster

Higher risk for typhoid fever disease with increasing age

Invasive *Salmonella* infections in young children by TSAP region

Age Group in years	TSAP study sites in West Africa ¹				TSAP study sites in East Africa ²			
	# of adjusted cases	S. Typhi Adjusted incidence per 100,000 PYO (95% CI)	iNTS # of adjusted cases Adjusted incidence per 100,000 PYO (95% CI)	S. Typhi Adjusted incidence per 100,000 PYO (95% CI)	iNTS # of adjusted cases Adjusted incidence per 100,000 PYO (95% CI)			
0 to 1	0	0	29 (314.9-685.3)	464.5	1 (5.5-312.9)	4 (59.9-457.6)		
1 to 2	5 (33.4-203.7)	82.5	76 (948.1-1658.0)	1,254 (15.7-274.8)	2 (65.8)	1 (32.9)		
2 to 3	18 (265.7-687.8)	427.5	35 (578.9-1194.0)	831.2 (6.0-344.0)	1 (45.5)	0 (0)		
3 to 4	22 (437.6-1068.0)	683.7	37 (845.2-1717.0)	1,205 (82.9-508.5)	5 (205.3)	1 (41.1)		
4 to 5	18 (428.2-1109.0)	689	8 (130.1-551.9)	267.9 (457.1)	10 (241.3-865.8)	0 (0)		
Total	63		185		19	6		

NOTE.

¹TSAP West Region includes Burkina Faso, Ghana and Guinea Bissau.

²TSAP East Region includes Kenya, Madagascar, Sudan and Tanzania

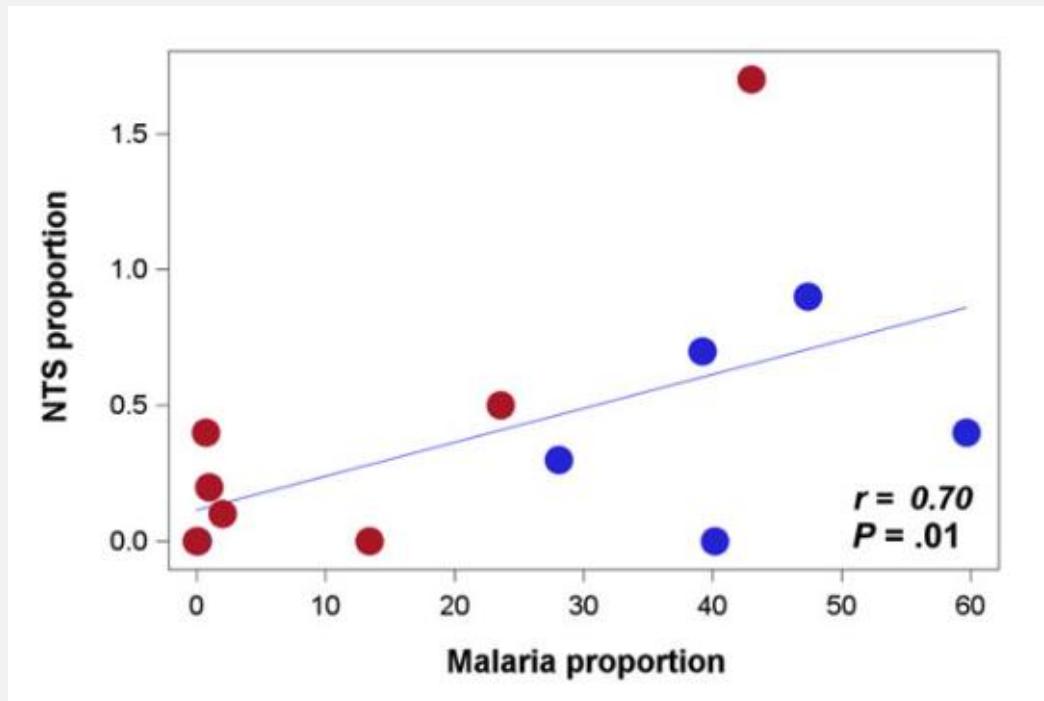
Higher risk of iNTS disease in infants and very young children

Higher risk of both diseases at sites located in West Africa



iNTS disease and malaria

- ✓ Positive correlation between frequency proportions of malaria and iNTS disease – observed at the TSAP sites endemic for malaria¹



¹ Park SE, Pak GD, Aaby P, et al. *Salmonella* disease, other bloodstream infections, and malaria in sub-Saharan Africa. *Clin Infect Dis.* 2016; 62: S23

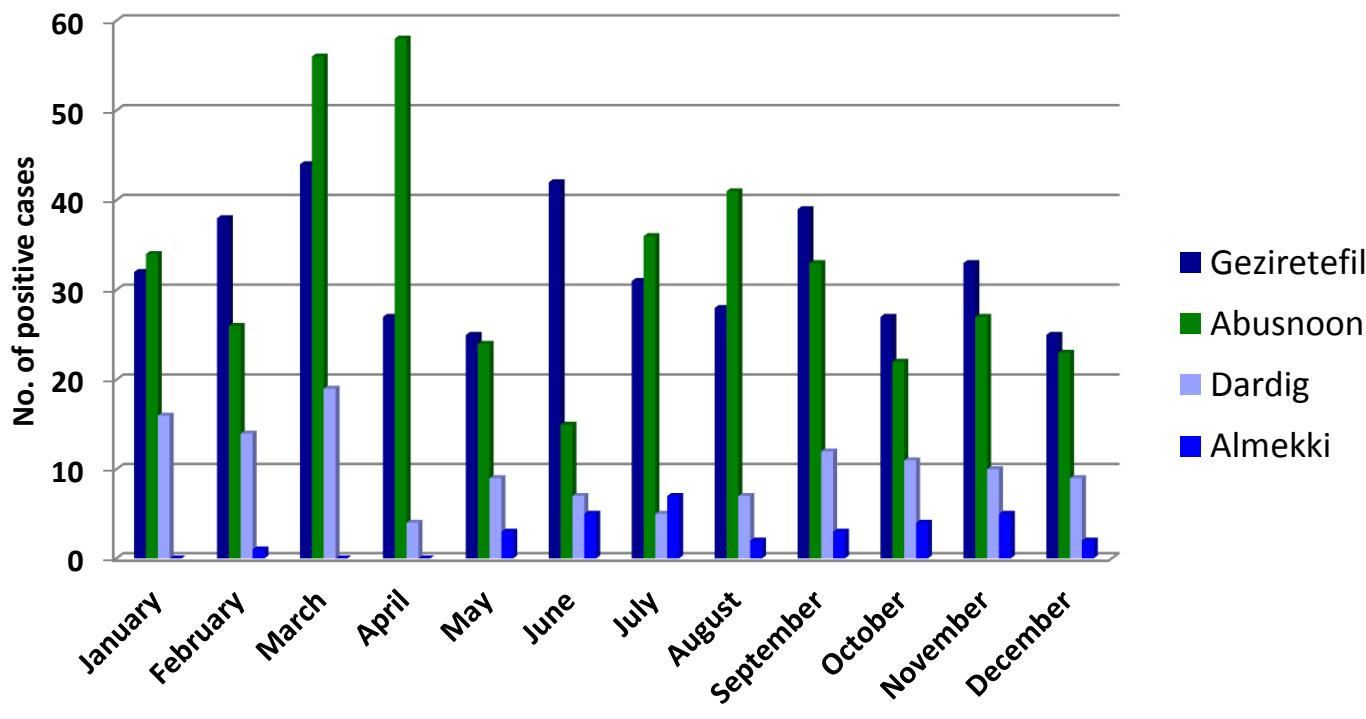


Widal test – Commonly used in many countries

- ✓ Measures agglutinating antibodies specific to *S. Typhi*
- ✓ Difficult to know if the patient is in the acute phase
- ✓ Patients rarely demonstrate a 4-fold increase
- ✓ Not rapid (takes 14 days)
- ✓ Not standardized
- ✓ Negative in 30% of culture-confirmed cases
- ✓ Often done in a single tube
- ✓ Lacks sensitivity and specificity



Number of TF cases in the study area 2010



Annual reports Ministry of Health Gezira State, 2010



Sudan, 2010

Nioko II, Burkina Faso	Polesgo, Burkina Faso	Bandim, Guinea- Bissau	Pikine, Senegal	Asante Akim North, Ghana	East Wad Medani, Sudan	Butajira, Ethiopia	Imerintsia- sika, Madagascar	Isotry, Madagascar	Pietermaritz- burg, South Africa	Moshi Urban District, Tanzania	Moshi Rural District, Tanzania	Kibera, Kenya*	
(Continued from previous page)													
Laboratory results													
Total blood culture, N	918	756	1021	1058	2651	644	847	976	1501	1128	406	274	1251
Total contaminated blood cultures, n (% of N)	220 (24%)	145 (19)	125 (12%)	96 (9%)	182 (7%)	54 (8%)	90 (11%)	6 (1%)	49 (3%)	192 (17%)	8 (2%)	13 (5%)	16 (1%)
Total positive blood cultures, n (% of N)	29 (3%)	31 (4)	30 (3%)	31 (3%)	175 (7%)	16 (2%)	26 (3%)	11 (1%)	30 (2%)	51 (5%)	17 (4%)	11 (4%)	110 (9%)
Positive for malaria, n (% of all patients tested)***	430/908 (47%)	444/744 (60%)	206/525 (39%)	297/1058 (28%)	1139/2651 (43%)	254/632 (40%)	110/822 (13%)	19/955 (2%)	2/274 (1%)	0	4/406 (1%)	2/274 (1%)	226/956 (24%)

UoO=University of Ouagadougou, Ouagadougou. BHP=Bandim Health Project, Bissau. IPD=Institute Pasteur de Dakar, Dakar. KCCR/BNITM=Kumasi Centre for Collaborative Research in Tropical Medicine, Kumasi/Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany. UoG=University of Gezira, Wad Medani. AHRI=Armauer Hansen Research Institute, Addis Ababa. UoA=University of Antananarivo, Antananarivo. NICD=National Institute for Communicable Diseases, Johannesburg. KCMC/Duke=Kilimanjaro Christian Medical Center, Moshi/Duke University Medical Center, Durham, NC, USA. KEMRI/US-CDC=Kenya Medical Research Institute/US Centers for Disease Control and Prevention, Nairobi. IPD=inpatient department. OPD=outpatient department. HDSS=Health and Demographic Surveillance System. KEMRI=Kenya Medical Research Institute. NA=not available. *In Kibera, active population mobilisation was done in addition to passive surveillance. †Setting reflects the classification commonly used at each site and does not refer to a standard definition. ‡Surveillance activities were scheduled for 12 months in Burkina Faso, Guinea-Bissau, Senegal, Sudan, Ethiopia, and Madagascar and for 24 months in Ghana, Kenya, South Africa, and Tanzania. If funds allowed, the scheduled period was extended. §Population data were provided from the HDSS country office. ¶Population data for Senegal and Madagascar were provided by Ministry of Health. Population data correspond to the 2012 population census and 2010 estimated population for the area, respectively. ||Population data for Ghana were obtained from the Ghana Statistical Service, 2010 population, and housing census. It includes 53 towns distributed in what is now Asante Akim North and Central. **Population data for Sudan were provided by the Statistics Department, Population Center, University of Gezira, Sudan, and correspond to year 2008. ††Population data for South Africa were provided by the Statistics Department in South Africa and corresponds to the 2011 census. §§Population data for Tanzania were provided by the National Bureau of Statistics and correspond to the 2012 population and housing census. §§Patients who met inclusion criteria, consented to take part in the study, and had a blood culture taken and a documented blood culture result. ¶¶Recruitment health-care facility providing outpatient services only. ||||Positive for non-contaminant isolates. ***Denominator differs from all blood cultures analysed because of missing values. Malaria results are based on blood smears, except for the site in Butajira (52% of patients positive for malaria were diagnosed with malaria rapid tests).

Table 1: Demographics and laboratory results of the sites in the Typhoid Fever Surveillance in Africa Program

¹Incidence of invasive *Salmonella* disease in sub-Saharan Africa: a multicenter population-based surveillance study. *Lancet Global Health* 2017; 5: e310-23.



Proportion of individuals from study population visiting recruitment facility in case of fever (95% CI)	PYO estimation			Recruitment proportion	iNTS								
	Study population	Study population adjusted by health-seeking behaviour	PYO		Crude cases	Crude incidence per 100 000 PYO	Cases adjusted for recruitment	Adjusted incidence per 100 000 PYO (95% CI)	Crude cases	Crude incidence per 100 000 PYO	Cases adjusted for recruitment	Adjusted incidence per 100 000 PYO (95% CI)	
(Continued from previous page)													
Asante Akim North, Ghana													
0-1 years	16% (14-18)	11 222	1 760	4 080	41%*	2	49	4·9	120 (49-290)	29	711	70·7	1733 (1373-2188)
2-4 years	16% (13-18)	8 086	1 268	2 940	41%*	13	442	31·7	1079 (762-1528)	23	782	56·1	1908 (1469-2479)
5-14 years	16% (15-17)	34 439	5 415	12 554	623/1657 (38%)	15	119	39·5	314 (230-430)	7	56	18·4	147 (93-232)
<15 years	NA	53 747	8 443	19 574	NA	30	153	76·1	389 (310-486)	59	301	145·3	742 (631-873)
≥15 years	NA	NA†	NA	NA	NA†	NA	NA	NA	NA	NA†	NA	NA	NA
All	NA	NA†	NA	NA	NA†	NA	NA	NA	NA	NA†	NA	NA	NA
Pikine, Senegal‡§													
0-1 years	39% (32-46)	20 120	7 837	11 194	NA	0	0	NA	NA	0	0	NA	NA
2-4 years	37% (33-41)	30 180	11 097	15 851	NA	0	0	NA	NA	0	0	..	NA
5-14 years	31% (28-34)	96 152	29 807	42 577	NA	3	7	NA	NA	1	5	..	NA
<15 years	NA	146 452	48 741	69 623	NA	3	4	NA	NA	0	0	..	NA
≥15 years	30% (28-31)	195 726	58 718	83 874	NA	4	5	NA	NA	3	6	..	NA
All	NA	342 178	107 459	153 496	NA	7	5	NA	NA	4	5	..	NA
East Wad Medani, Sudan§													
0-1 years	23% (14-32)	2 377	537	589	2/85 (2%)	0	0	0·0	0 (0-0)	0	0	0·0	0 (0-0)
2-4 years	22% (15-29)	3 566	781	857	29/108 (27%)	0	0	0·0	0 (0-0)	0	0	0·0	0 (0-0)
5-14 years	25% (21-28)	11 071	2 735	2 999	160/234 (68%)	0	0	0·0	0 (0-0)	0	0	0·0	0 (0-0)
<15 years	NA	17 014	4 053	4 445	NA	0	0	0·0	0 (0-0)	0	0	0·0	0 (0-0)
≥15 years	29% (27-31)	29 843	8 684	9 525	131/147 (89%)	0	0	0·0	0 (0-0)	0	0	0·0	0 (0-0)
All	NA	46 857	12 737	13 970	NA	0	0	0·0	0 (0-0)	0	0	0·0	0 (0-0)

¹Incidence of invasive *Salmonella* disease in sub-Saharan Africa: a multicenter population-based surveillance study. *LANCET Global Health* 2017; 5: e310-23.

Widal test does not reflect bloodculture-based results



Lessons learnt in conducting typhoid surveillance



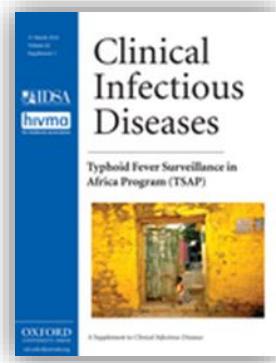
- Selection bias
- Representativeness
- Determining a denominator, catchment area
- Local capacity

- Protocol adherence
- Difficult to screen all febrile patients
- Period of surveillance: Variable disease burden in adjacent sites/between years
- Severe cases in tertiary care facilities

- Limited resources for blood culture
- Large volume of blood required
- Contamination
- Antibiotic pre-treatment
- Logistics of sample transport



Typhoid Fever Surveillance in Africa Program (TSAP) – Value and implications



THE LANCET Global Health



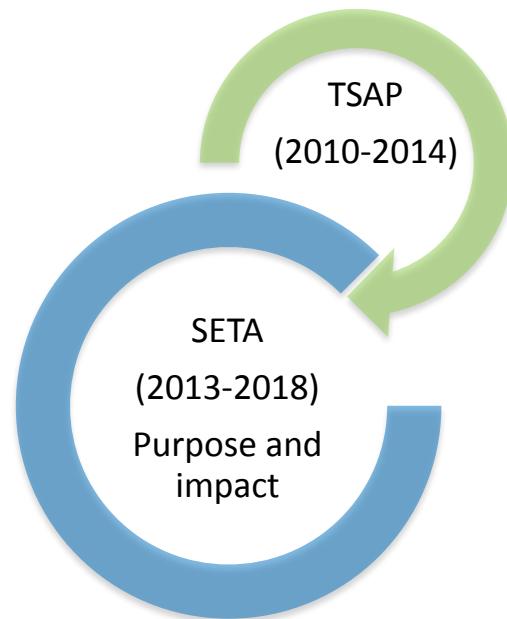
Added value

- ✓ Most comprehensive standardized analysis of the incidence and antimicrobial resistance patterns of invasive *Salmonella* infections in sub-Saharan Africa
- ✓ Results used by key stakeholders to decide on potential subsidies for typhoid fever vaccines

Implications of the evidence

- ✓ Results underscore the need for preventive measures, including vaccines
- ✓ Emphasize the potential increase of drug-resistance *Salmonella* strains in the region
- ✓ Need to further assess the severity and mortality of the disease





Filling the gaps on severity and mortality

- ✓ Network of surveillance sites across 6 countries in sSA
- ✓ To estimate the severity, immune response, long-term sequelae and the associated costs of invasive *Salmonella* infections in sub-Saharan Africa
- ✓ Further assessment of the incidence in infants
- ✓ Essential evidence for key stakeholders (WHO, GAVI) to develop prevention strategies including a strategy for advent typhoid vaccines.



Invasive *Salmonella* infections in sub-Saharan Africa

- ✓ TSAP results - invasive *Salmonella* infections are a major cause of invasive bacterial febrile illness in the sampled locations, specially in children, with incidence rates higher than previously estimated.
- ✓ This evidence will be used by key stakeholders to make decisions on introduction of available and advent vaccines against typhoid fever disease.
- ✓ Knowledge gaps on disease severity, mortality and associated costs are being assessed by SETA.



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