The Burden of Invasive Non-Typhoidal Salmonella Disease in Six Sites in Africa : Results from the Severe Typhoid Surveillance in Africa Program

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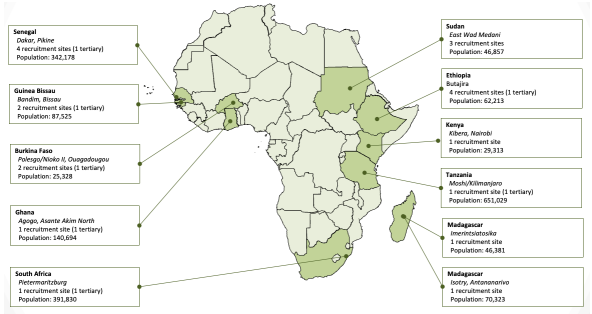
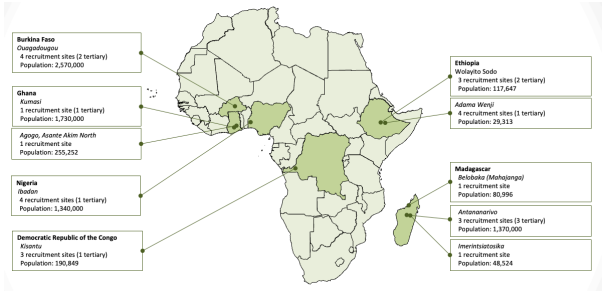
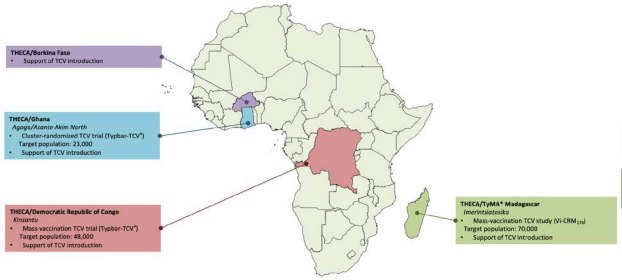
Background







TSAP (2010-2014)

Invasive Salmonella burden evidence from 10 African countries

Data supported SAGE, Gavi, WHO to introduce TCV into the Gavi portfolio

SETA (2015-2019)

Filling the gaps on severity, mortality and cost of invasive Salmonella in Africa

Data will support decision-makers and partners on TCV introduction

THECA (2019-2023)

Filling the gaps for TCV introduction in Africa

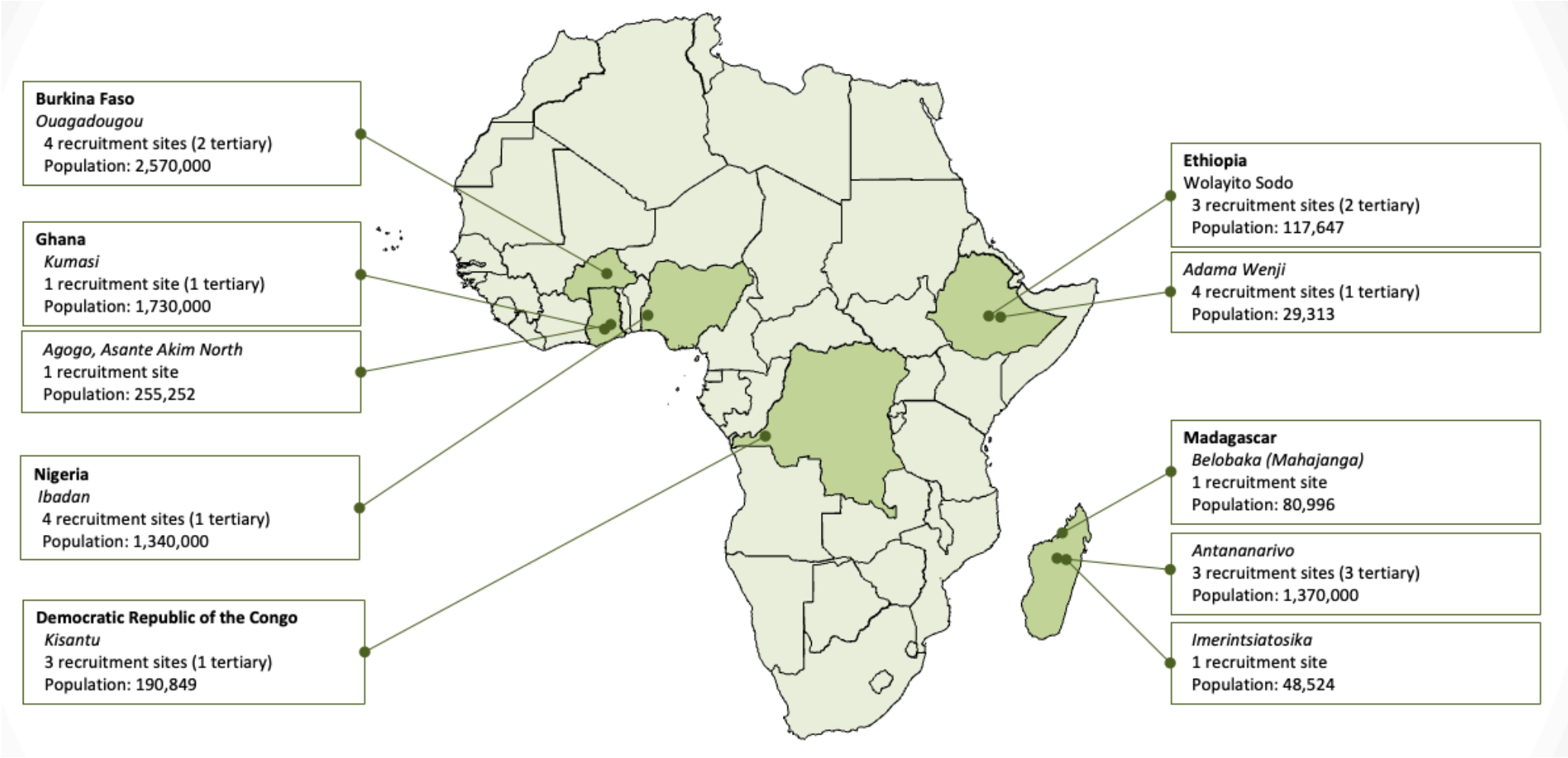
Data will provide evidence of TCV clinical efficacy, safety, immunogenicity and costs

SETA+/STIA (2020-2025)

Continuation of typhoid surveillance in Nigeria and SETA sites not covered through the THECA work ; Continuation of incidence data generation

Data will provide evidence of TCV protection at the population level

Severe Typhoid Surveillance in Africa Program (SETA)



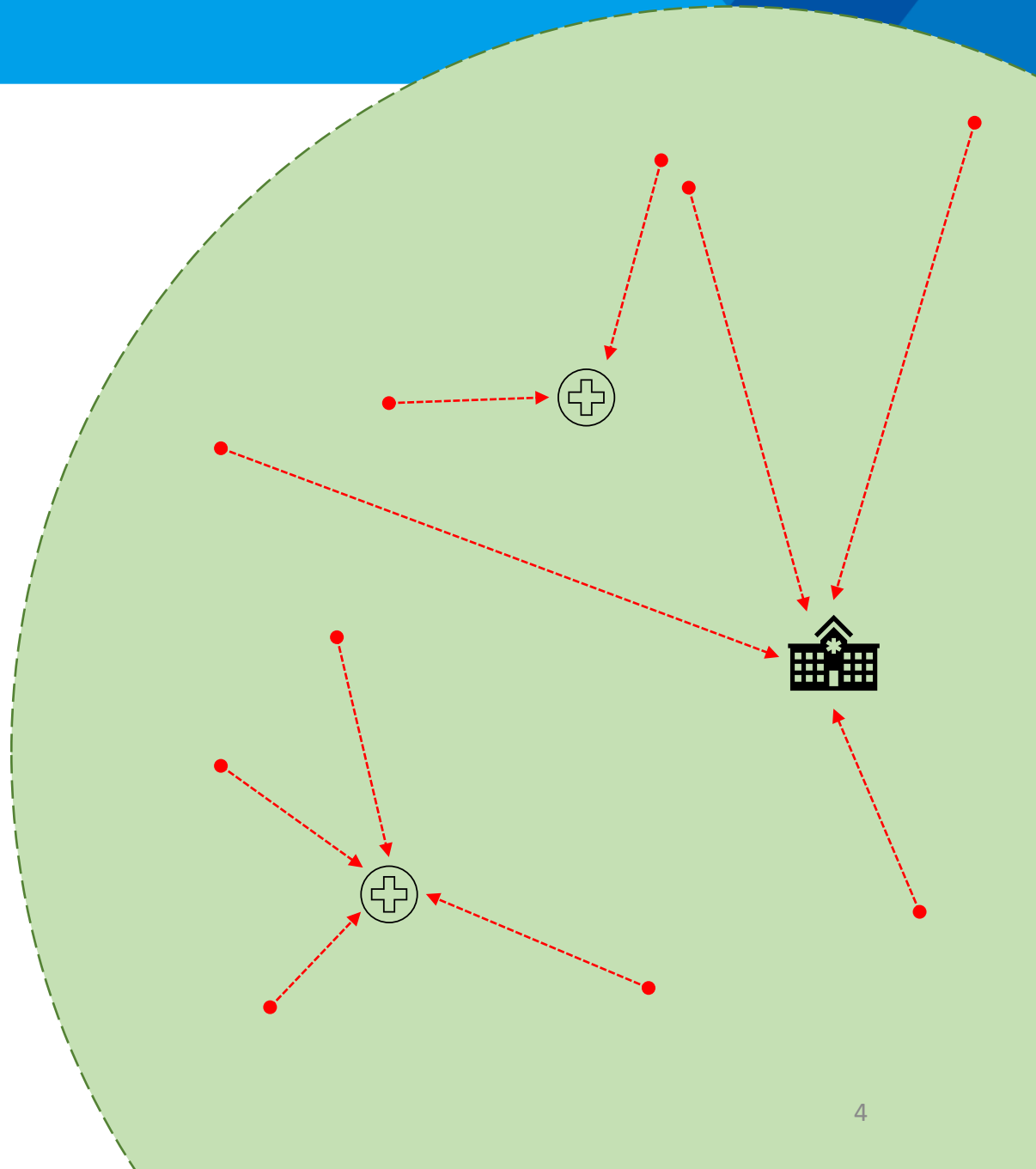
Surveillance sites and study population in the Severe Typhoid Surveillance in Africa Program (SETA/SETAplus) from 2014-2022

NB) Ethiopia was excluded from the SETAplus program from 2020.

Source: figure modified from "the Severe Typhoid in Africa Program: Incidences of Typhoid Fever in Burkina Faso, Democratic Republic of the Congo, Ethiopia, Ghana, Madagascar, And Nigeria"

SETA Surveillance strategy

- Fever
- Prospective population surveillance
- Recruitment centers included study hospitals and health-care facilities
- Passive inclusion
- Voluntary participation
- Children and adults of all ages were eligible for enrollment
- Healthcare Utilization Survey (HCUS)
- Primary/secondary centers captured mild disease (serving “nested” population)
- Tertiary centers captured severe disease



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Definition of clinical endpoints

Typhoid fever/ iNTS disease	Fever cases where *S.* Typhi or iNTS bacteria was recovered from venous blood using conventional microbiological culture from a blood sample taken at enrollment
Mild Typhoid fever/ iNTS disease	Blood culture confirmed typhoid fever or iNTS disease without observed systemic complications*
Severe Typhoid fever/ iNTS disease	Blood culture confirmed typhoid fever or iNTS disease accompanied by at least one observed systemic complication*
Contaminant organisms	Coagulase-negative *Staphylococcus*, *Corynebacterium* spp., and *Bacillus* spp.

*Complications: gastrointestinal bleeding, gastrointestinal perforation, encephalopathy, meningitis, hemodynamic shock, myocarditis, hepatitis, cholecystitis, pneumonia, pleural effusion, anemia, focal infection, or renal impairment

Confirmation of typhoid/iNTS infection[#]	
Repeat microbiological culture [DRC only]	On site
Quantitative polymerase chain reaction (qPCR)	On site
Whole genome sequencing (WGS)	Eurofins Genomics (Germany)

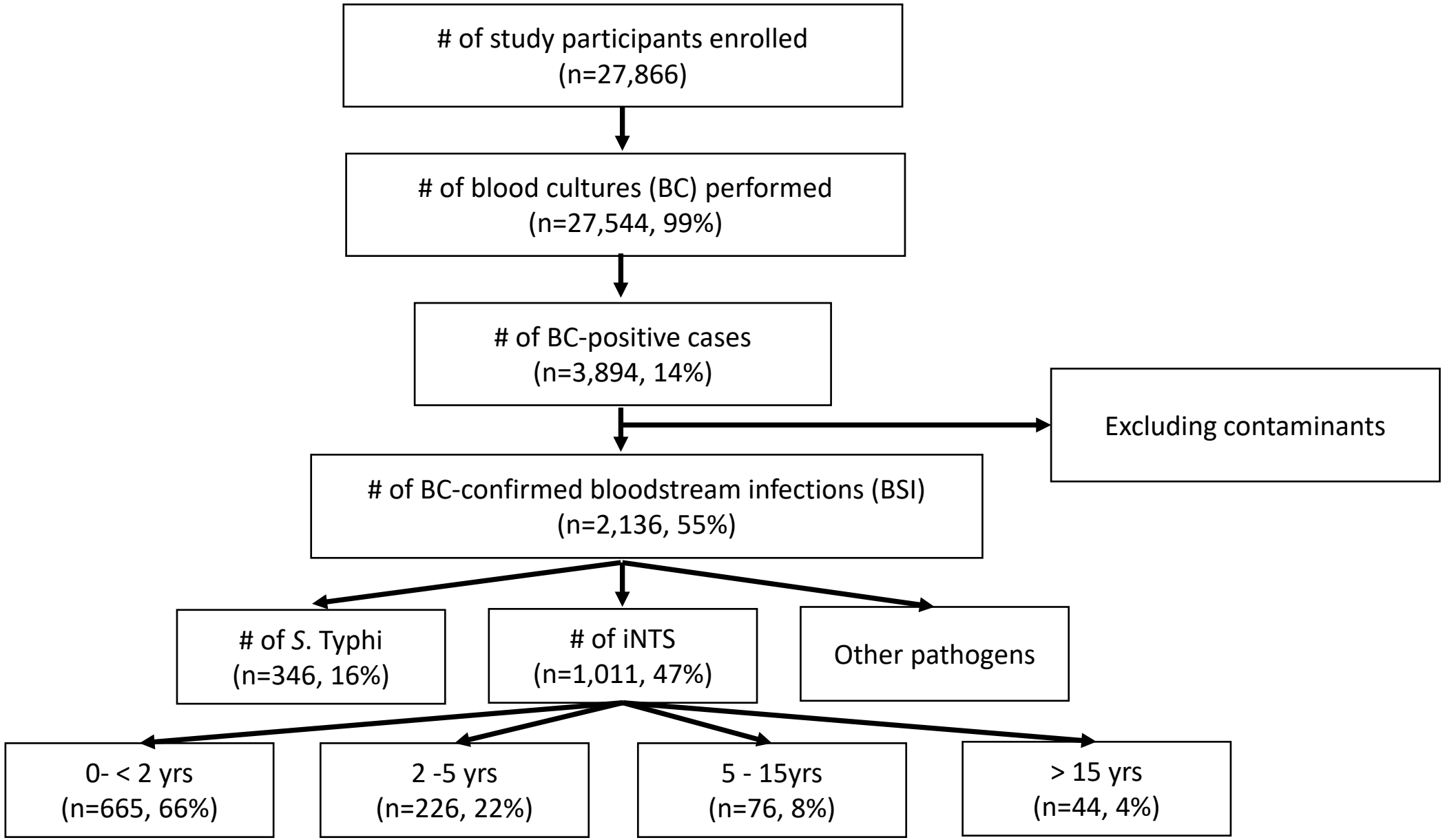
[#]For reporting, confirmation is prioritized in the following order: WGS > qPCR > culture; confirmatory testing was performed on available samples – the proportion of samples that were verified by each method differed by site

Source: modified from figure credited to Justin Im, 2022 Africa Regional Meeting on Typhoid and TCV, 8 December 2022

Results

- **Country-specific data: age-stratified incidence of iNTS disease**
- **Severity of iNTS disease**
- **Antimicrobial resistance profile of iNTS isolates**

SETA Flowchart



Country-specific Number of iNTS Cases by Serovar

Country	*S.* Typhimurium	*S.* Enteritidis	Other, non-typhoidal *Salmonella* spp.
Burkina Faso	2/16 (13%)	1/16 (6%)	13/16 (81%)
DRC	646/947 (68%)	150/947 (16%)	151/947 (16%)
Ethiopia	-	-	1/1 (100%)
Ghana	11/19 (58%)	5/19 (26%)	3/19 (16%)
Madagascar	-	-	-
Nigeria	3/28 (11%)	8/28 (29%)	17/28 (61%)
Total	662/1,011 (65%)	164/1,011 (16%)	185/1,011 (18%)

Incidence Calculation

- Incidence rate was calculated only in nested areas.
- Denominator: Number of person years of risk experienced by those living within each SETA surveillance area
  - ➢ population data from annual census and population growth projection from the world bank
- Numerator: The number of symptomatic iNTS infections that occurred among these individuals
  - ➢ crude number of cases adjusted for several factors*
- Bayesian mixture model was used, and the adjusted rates represents the mean of the sampled iterations followed by 95% credible intervals.

* probability of individuals seeking healthcare at the SETA healthcare facility for febrile illness , proportion of patients meeting the SETA inclusion criteria approached for recruitment, proportion of patients approached for recruitment consenting to participate, proportion of patients consenting to participate with a blood culture performed, sensitivity of blood culture

Site-specific, Age-stratified Incidence of iNTS Disease from SETA**(unpublished)*

Age group, years	Burkina Faso, Nioko and Polesgo	DRC, Kavuaya and Nkandu 1	Ethiopia, Adama	Ghana, Agogo	Nigeria, Ibadan
<2	339 (245; 498)	6,348 (4,918; 8,182)	-	82 (61; 110)	180 (54; 502)
2 to 4	606 (486; 773)	2,208 (1,782; 2,776)	-	167 (124; 219)	72 (48; 107)
5 to 14	-	418 (331; 526)	-	8 (6; 11)	24 (19; 31)
>/=15	23 (18; 30)	119 (96; 149)	14 (10; 18)	10 (8; 14)	3 (2; 4)
All	118 (95; 149)	840 (675; 1,054)	7 (5; 9)	25 (19; 33)	21 (14; 37)

*Country, site, and age-group specific incidence rate (95% credible interval) of blood culture-confirmed iNTS fever cases per 100,000 person-years of observation estimated from SETA, HPAfrica, and World Bank data

Frequency of iNTS Infections by Age from TSAP+SETA Combined Data

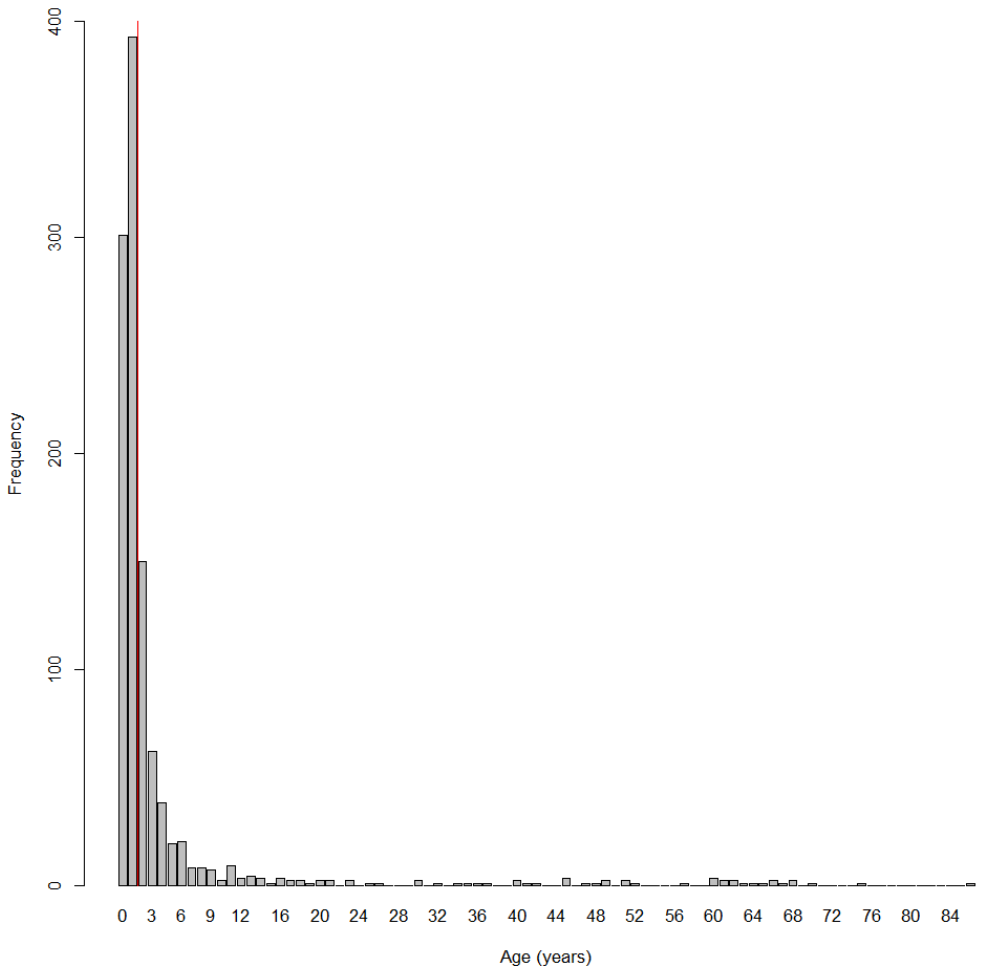


Figure 1. Frequency of iNTS infections by age among those enrolled in the TSAP and SETA programs

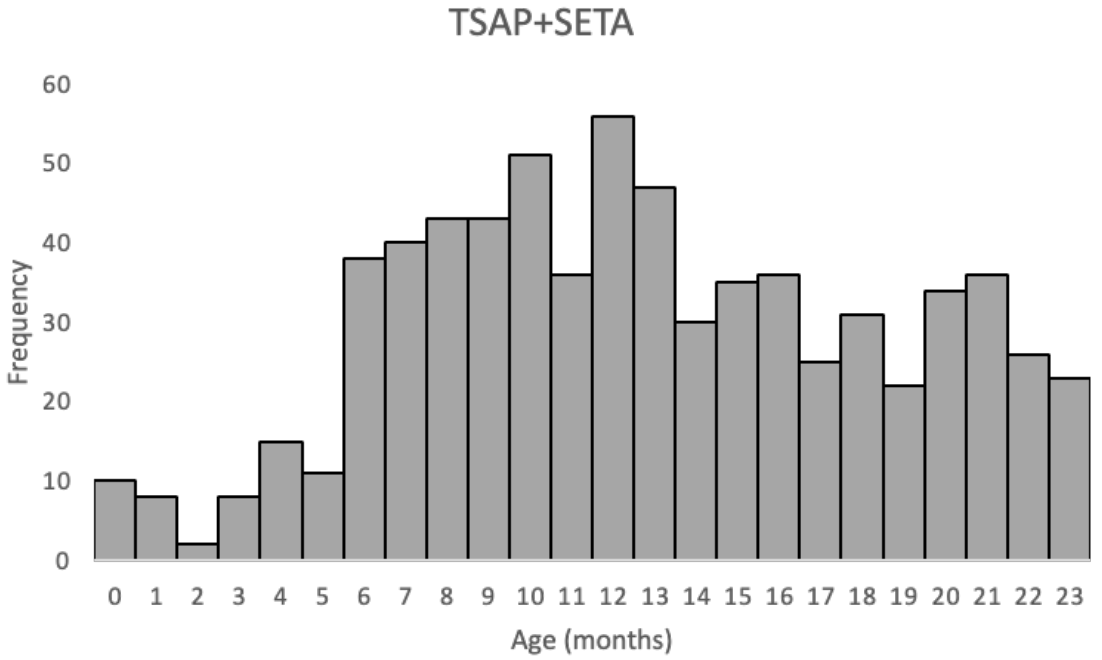


Figure 2. Frequency of iNTS infections in children under <24 months of age enrolled in the TSAP and SETA programs

Severity of iNTS disease *(unpublished)*

Country	Burkina Faso	DRC	Ethiopia	Ghana	Madagascar	Nigeria	Total
Hospitalizations, N	1523	1190	508	941	440	1027	5629
Female, n (%)	599 (39%)	557 (47%)	246 (48%)	435 (46%)	195 (44%)	437 (43%)	2469 (44%)
Age, median (25%-75%)	1(0-5)	1(1-7)	22(3-35)	4(1-9)	2(0-7·25)	5(1-10)	3(1-10)
Hospitalizations with culture confirmed iNTS, N	7/1523 (0.5%)†	799/1190 (67%)†	0‡	12/941 (1%)†	0†	16/1,027 (2%)‡	834/5629 (15%)‡
Salmonella Typhimurium, n (%)	2/7 (29%)	554/799 (69%)	0	0	0	2/16 (13%)	558/834 (67%)
Salmonella Enteritidis, n (%)	1/7 (14%)	129/799 (16%)	0	0	0	4/16 (25%)	134/834 (16%)
Other non-typhoidal Salmonella, n (%)	4/7 (57%)	116/799 (15%)	0	12/12 (100%)	0	10/16 (63%)	142/834 (17%)
MDR iNTS isolates, n (%)	0/7 (0)	617/799 (77%)	0	4/12 (33%)	0	6/16 (38%)	627/834 (75%)
Overall death, n (%)	0/7 (0)	62/799 (8%)		0/12 (0)		2/16 (12%)	64/834 (8%)
Salmonella Typhimurium, n (%)	0	51/62 (82%)	0	0	0	1/2 (50%)	52/64 (81%)
Salmonella Enteritidis, n (%)	0	4/62 (6%)	0	0	0	0	4/64 (6%)
Other non-typhoidal Salmonella, n (%)	0	7 (11%)	0	0	0	1/2 (50%)	8/64 (13%)
MDR iNTS isolates among death, n (%)	0	47/62 (76%)	0	0	0	1/2 (50%)	48/64 (75%)
Severe iNTS cases*, n (%)	0/7 (0)	96/799 (12%)	0	2/12 (17%)	0	6/16 (38%)	104/834 (12%)
MDR, n (%)	0	71/96 (74%)	0	2/2 (100%)	0	2/6 (33%)	75/104 (72%)
Death among severe iNTS cases, n (%)	0	21/96 (22%)	0	0/2 (0)	0	2/6 (33%)	23/104 (22%)

*Defined as a confirmed iNTS case accompanied by the presence of at least one of gastrointestinal bleeding, gastrointestinal perforation, encephalopathy, meningitis, hemodynamic shock, myocarditis, hepatitis, cholecystitis, pneumonia, pleural effusion, anemia, focal infection, or renal impairment. ; †confirmed by blood culture only.; ‡confirmed by blood, stool, peritoneal fluid, or tissue culture.

Antimicrobial Resistance Profile of iNTS Isolates *(unpublished)*

	Burkina Faso	Ghana	Madagascar	Ethiopia	DRC	Nigeria	All
iNTS isolates (N)	16	19	0	1	947	28	1,011
Resistant organisms*, n (% of tested)							
Ampicillin†	5/6 (83%)	13/19 (68%)	..	..	845/887 (95%)	18/22 (82%)	881/934 (94%)
Cotrimoxazole†	9/14 (64%)	10/19 (53%)	..	..	759/811 (94%)	16/23 (70%)	794/867 (92%)
Chloramphenicol†	6/10 (60%)	10/18 (56%)	..	0/1 (0)	818/887 (92%)	12/23 (52%)	846/939 (90%)
Ciprofloxacin	0/1 (0)	6/19 (32%)	..	0/1 (0)	97/437 (22%)	0/24 (0)	103/482 (21%)
Ceftriaxone/Cefotaxime	0/12 (0)	0/19 (0)	..	0/1 (0)	420/876 (48%)	0/25 (0)	420/933 (45%)
Amoxicillin-Clavulanic acid	6/15 (40%)	2/16 (12%)	..	0/1 (0)	3/3 (100%)	5/23 (22%)	16/58 (28%)
MDR‡	3/4 (75%)	9/18 (50%)	..	..	737/804 (92%)	7/17 (41%)	756/843 (90%)
Salmonella Typhimurium	0/3 (0)	0/9 (0)	..	..	507/737 (69%)	2/7 (29%)	509/756 (67%)
Salmonella Enteritidis	0/3 (0)	0/9 (0)	..	..	109/737 (15%)	1/7 (14%)	110/756 (15%)
Other non-typhoidal *Salmonella*	3/3 (100%)	9/9 (100%)	..	..	121/737 (16%)	4/7 (57%)	137/756 (18%)
MDR‡ & ciprofloxacin resistance	..	2/18 (11%)	..	..	79/416 (19%)	0/16 (0)	81/450 (18%)
MDR‡ & ceftriaxone/cefotaxime or ceftazidime resistance	0/2 (0)	0/17 (0)	..	..	11/11(100%)	0/15 (0)	11/45(24%)

* As determined by CLSI breakpoints where both intermediate and resistant classifications are considered as resistant.; † First line antibiotics against iNTS infection.; ‡ MDR: Multi-drug resistance – resistant to ampicillin, cotrimoxazole, and chloramphenicol '..' Indicates that no iNTS isolate was tested for AMR.

Summary

- iNTS disease remains an important cause of febrile illnesses in Africa with young children at risk.
  - ✓ Overall incidence rate was very high in DRC (>500/100,000 PYO), and high in Burkina Faso (>100/100,000 PYO).
  - ✓ Adjusted incidence of iNTS disease was higher in children under two years old compared to the other age groups.
  - ✓ Heterogeneity existed in disease burden data by age and by site.

- In most settings, iNTS isolates were identified as resistant to first-line antibiotics; in some settings multi-drug-resistant *Salmonella* isolates were common.

- High MDR among severe iNTS cases were observed.

Limitations of the study

- SETA sites were selected based on the known presence of typhoid disease and therefore iNTS disease incidence in the region could be underestimated as a result.
- Adjustments for blood culture sensitivity did not control for variation in blood volumes, pre-treatment with antibiotics, storage and transportation protocols, rates of contamination.
- The analytic approach may not have been sensitive enough to capture the impact of local events and site-specific protocol implementation challenges in incidence estimates.
- Access to healthcare services varied across sites. Unmeasured biases that were not captured by healthcare utilization questionnaires may exist.
- Study populations are relatively small and may not be representative of larger regions.

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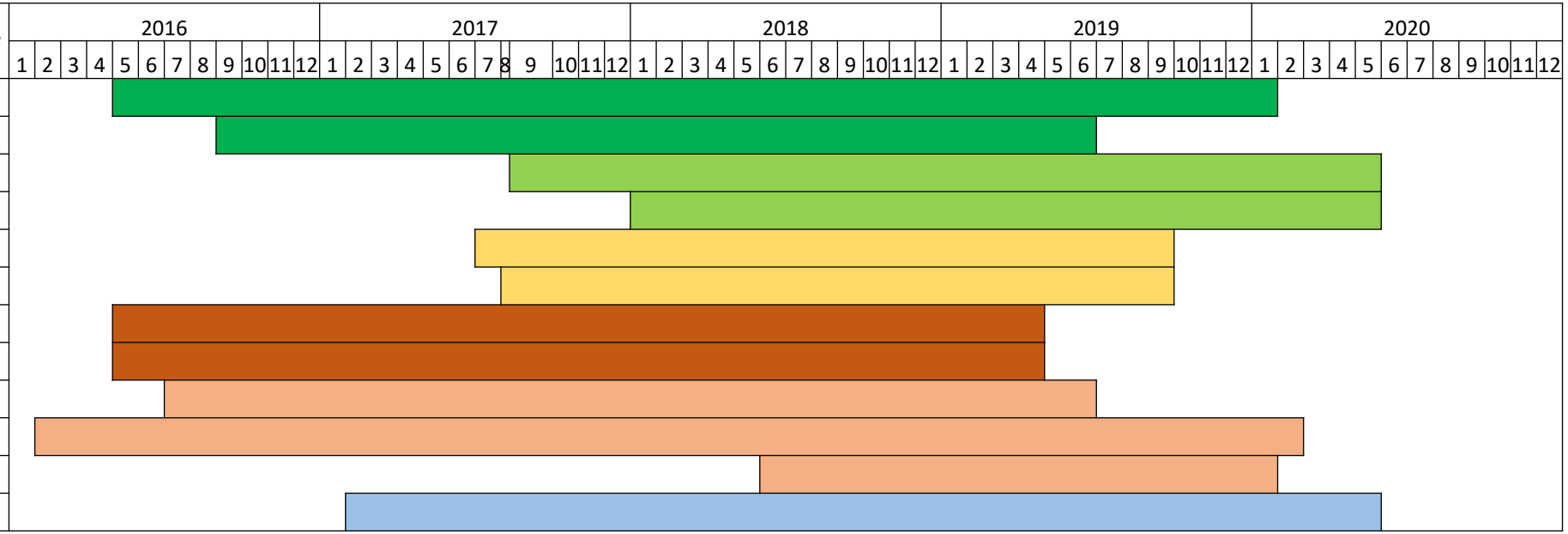
Thank you

Backup slides

SETA surveillance duration

Country	Site	Surveillance (months)
Burkina Faso	Nioko/ Polesgo	43
	Ouagadougou	33
DRC	Kisantu	33
	Kavuaya/Nkandu	29
Ethiopia	Sodo	27
	Adama	26
Ghana	Agogo	35
	Kumasi	35
Madagascar	Antananarivo	36
	Imerinsiatosika	49
	Mahajanga	20
Nigeria	Ibadan	38



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Site-specific, Age-stratified Incidence of Typhoid fever from SETA*

Age group, years	Burkina Faso, Nioko and Polesgo	DRC, Kavuaya and Nkandu 1	Ethiopia, Sodo	Ghana, Agogo	Madagascar, Imerintsiatosika	Nigeria, Ibadan
<2	..	322 (246; 418)	..	44 (32; 60)	..	77 (16; 238)
2 to 4	234 (182; 309)	379 (304; 476)	..	309 (230; 403)	24 (18; 32)	73 (50; 106)
5 to 14	206 (166; 258)	544 (432; 683)	36 (28; 47)	314 (238; 411)	285 (214; 380)	106 (83; 137)
>/=15	111 (90; 140)	179 (143; 224)	9 (7; 11)	21 (16; 28)	171 (133; 225)	4 (3; 5)
All	133 (110; 160)	315 (254; 390)	16 (13; 21)	114 (87; 148)	162 (126; 210)	36 (28; 49)

P. falciparum Malaria and iNTS Disease

Country	Site	Participants enrolled	# BC performed, n (of Patients enrolled)	Malaria tests performed , n (of enrolled)	Positive malaria, n (of malaria tests)	Malaria-iNTS coinfection, n (of positive iNTS disease cases)
Burkina Faso	Nioko/ Polesgo	4,472	4,399 (98%)	4,367 (98%)	1,786 (41%)	2/9 (22%)
	Ouagadougou	1,727	1,680 (97%)	1,284 (74%)	171 (13%)	1/7 (14%)
DRC	Kisantu	1,043	1,039 (100%)	1,038 (100%)	685 (66%)	637/803 (79%)
	Kavuaya/Nkandu	5,247	5,226 (100%)	5,244 (100%)	3,585 (68%)	104/144 (72%)
Ethiopia	Sodo	2,864	2,863 (100%)	2,550 (89%)	231 (9%)	-
	Adama	2,502	2,499 (100%)	1,725 (69%)	169 (10%)	0/1 (0%)
Ghana	Agogo	1,555	1,550 (100%)	1,486 (96%)	677 (46%)	8/13 (62%)
	Kumasi	627	614 (98%)	586 (93%)	134 (32%)	0/6 (0%)
Madagascar	Antananarivo	447	443 (99%)	439 (98%)	4 (1%)	-
	Imerinsiatosika	2,705	2,676 (99%)	2705 (100%)	40 (1%)	-
	Mahajanga	321	316 (98%)	321 (100%)	51 (16%)	-
Nigeria	Ibadan	4,356	4,239 (97%)	4,065 (94%)	904 (22%)	5/28 (18%)
TOTAL		27,866	27,544 (99%)	25,810 (93%)	8,437 (33%)	757/1011 (75%)

SETA site characteristics: Setting and population

Country	Site	Setting	Population size
Burkina Faso	Nioko/ Polesgo	Rural	27,148
	Ouagadougou	Urban	2.57M
DRC	Kisantu	Rural, Urban	190,849
	Kavuaya/Nkandu	Rural, Urban	50,161
Ethiopia	Sodo	Semi-urban	117,647
	Adama	Semi-urban	52,770
Ghana	Agogo	Rural, Urban	220,999
	Kumasi	Urban	1.73M
Madagascar	Antananarivo	Urban	1.37M
	Imerinsiatosika	Rural	48,524
	Mahajanga	Rural	80,996
Nigeria	Ibadan	Urban	1.34M