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Review

A systemic review of literatures on human *Salmonella enterica* serovars in Nigeria (1999-2018)

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Abstract

Introduction: *Salmonella* infections are endemic in Nigeria. There is lack of reliable data on culture-positive *Salmonella* with national coverage. This systemic review of literatures was undertaken to aggregate data on culture proven cases of human *Salmonellae* and to determine the prevailing serotypes for disease burden estimations.

Methodology: This involved comprehensive search engines of Pubmed, Google Scholar, Google and Embase for the literatures on culture positive human *Salmonellae* from 1999-2018. This review documented the prevalence, common *Salmonella* serotypes. antibiotic resistance and risk factors associated with human *Salmonella* infections.

Results: This study revealed that 21out of 36 States in Nigeria reported *Salmonella*-associated diseases, spanning the six geopolitical zones. Our study revealed prevalence of 1.9% (2,732/143,756) *Salmonella*-bacteraemia and 16.3% (1,967/12,081) *Salmonella*-associated gastroenteritis. Fifty-three 53 *Salmonella* serotypes were identified. 39 serotypes were associated with *Salmonella*-bacteraemia and 31 serotypes with *Salmonella*-gastroenteritis. *Salmonella typhi* remains the commonest serotype accounting for 85.2% for *Salmonella*-bacteraemia and 73.1% *Salmonella*-gastroenteritis. *S. typhimurium* (3.8%) was mostly implicated invasive non-typhoidal serotype followed *S. enteritidis* (2.8%) among others. Human Immunodeficiency Virus-infected individuals, malnutrition was among factors predisposing *Salmonella* infections. Over 60% of the reported *Salmonella* isolates developed resistance to two or more of 23 antibiotics recorded, mostly ampicillin, cotrimoxazole, tetracycline and amoxicillin.

Conclusions: This study revealed 39 Invasive and 31 non-invasive *Salmonella* serotypes. Ampicillin, cotrimoxazole, amoxicillin-clavulanate and tetracycline are the most frequently reported antibiotics resisted by *Salmonella* isolates. This antimicrobial resistance exhibited poses a threat to public health. Data generated from this review would serve as a baseline information for future surveillance studies.

Key words: Culture; human; prevalence; *Salmonella;* serotypes; systemic review.

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Introduction

Salmonella infections are grouped into typhoidal salmonellosis (enteric fever) caused by *Salmonella enterica* serovars *typhi* (typhoid fever) and *S. paratyphi* A, B and C (paratyphoid fever) which are restricted to human host. The second is non-typhoidal *Salmonella*-associated infections caused by other *Salmonella enterica* serovars such as *S. typhimurium, S. enteritidis* and *S. choleraesuis* otherwise called non-typhoidal *Salmonellae* (NTS). *Salmonella* infections generally result in considerable morbidity and mortality with a significant socioeconomic impact worldwide [1]. The Global Burden of Disease (GBD) through the Institute for Health Metrics and Evaluation estimated enteric fever morbidity at approximately 15.5 million with 154,000 deaths in 2016 [2]. These estimates rely on a modeling approach and heterogeneity of diagnostic tools and resource limitations. Typhoid fever is an acute, life-threatening, febrile illness with an estimated global disease burden ranges between 11 and 21 million cases and approximately 145,000 to 161,000 deaths annually, majority of cases occur in South/South-East Asia, and sub-Saharan Africa [3,4]. Invasive non-typhoidal *Salmonella* (iNTS) disease continues to be a public health problem with a global estimate between 2.1 and 6.5 million cases annually. The sub-Saharan Africa and other underdeveloped countries, accounting for 25% of the mortality rate [5]. Invasive non-typhoidal *Salmonella* disease remains a major neglected tropical disease and problem in Africa. The possible reasons had been attributed to host immunity, pathogen virulence and routes of transmission. Invasive non-typhoidal *Salmonella* disease is caused mainly by *Salmonella enterica serovars S. typhimurium* and *S. enteritidis*, but other serovars have been implicated [6]. Non-typhoidal *Salmonella*-gastroenteritis is understood to acquire from animal reservoirs. The transmission to humans can occur via many routes such as animal wastes, contaminated water, animal food products, poultry, undercooked meat and environment among others [6-8] however, little is known about the reservoirs of infection and routes of transmission of iNTS [6]. Definitive diagnosis of *Salmonella* infections by automated blood culture apparatus such as BacTec or BacT/ALERT usually enhances the sensitivity of the culture that is mostly unaffordable by many developing countries. The conventional culture method adopted by developing nations often comes with low sensitivity [9,10], a similar situation observed over the years in Nigeria. The rate of prolonged illness in patients with S*almonella* blood stream infections in high-burden countries is a continuing public health challenge due to treatment failure. Antimicrobial resistance is a growing concern in typhoidal and non-typhoidal *Salmonellae* in Nigeria. Resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole also known as multidrug resistance (MDR) had since been documented [11]. More recently, fluoroquinolone resistance has been reported in parts of Nigeria [12]. The paucity of epidemiological data on number of culture positive *Salmonella* isolates and prevailing *Salmonella* serotypes across geographical zones in Nigeria over the years has made it difficult to estimate the true burden of human salmonellosis. In 2017, World Health Organization (WHO) called for country and continent-wide approach in generating more accurate disease data regarding *Salmonella* bacteraemia and non-invasive *Salmonella* disease in Asia and sub-Saharan Africa for effective vaccine administration [3]. Unfortunately, the last estimated data on global burden of *Salmonella* blood stream infections excluded Nigeria [1] due to absence of reliable data with national coverage. Cultured proven cases of *Salmonellae* remain pivotal determinants to estimate the real burdens of *Salmonella*-associated diseases. Although, there have been several published reports on *Salmonella* infections in Nigeria, most of these reports are either serologically dependent or sparse, and have not been aggregated [13,14]. The aim of the current study is to address the knowledge gap of reliable data with national coverage by conducting a systemic review of available reports on culture positive human *Salmonella* bacteremia and gastroenteritis, and to determine the prevailing *Salmonella* serotypes and their geographical spread in Nigeria. The information data will help in health decision-making process and program, and serve as a policy guide for prompt interventions.

Methodology

The systematic review protocols (PRISMA-P) 2015 [15] checklist was followed for the review of meta-analysis of original research studies that reported culture positive human *Salmonella* serotypes from blood and stool samples of patients across 36 states of six geopolitical zones of Nigeria including Federal Capital Territory (FCT) Abuja. The PubMed (Mediline) (http://www.ncbi.nlm.nih.gov/pubmed), the Google search and Google scholar (https://scholar.google.com/) electronic databases were searched. The following search strings were also used which are: “fever” OR “febrile” OR “bacteremia” OR “septicaemia” OR “septicaemias” OR “septicaemic” OR “*Salmonella”* OR “*Salmonellas”* OR “*Salmonellae”* OR “bloodstream infections” OR Gastroenteritis`’ OR “bloodstream pathogen” OR “febrile AND (infant)” OR “child” OR “adolescent” OR “adult” OR “patients” OR “human” OR “travel” OR :community” OR “village” OR” incidence” OR” prevalence” OR “hospital” OR “man”. The national list of the 36 states of Nigeria was used as the basis for searching. English key words (i.e. MESH terms in PubMed) and English full-length research articles were considered. The search results were limited to publications from 1st Jan 1999 up to 31st December, 2018, because initial searches failed to find any papers prior to 1999. To ensure a comprehensive search of the literature, an independent search on and Embase-Ovid (https://library.maastrichtuniversity.nl/collections/databases/embase/) database were considered using a similar search string and strategy. Additional publications (original full-length article) were obtained by the manual scanning of the reference list from the retrieved publications on *Salmonella* infections.

Selection criteria

The full text of the search results of online articles/abstracts were reviewed independently with the aim of including articles that performed culture on human clinical samples (blood and stool) to obtain *Salmonella* isolates in Nigeria. The full text version either obtained on line or ordered when only the abstract was available online. Relevant articles were retrieved and thoroughly reviewed using inclusion and exclusion criteria set for this study. The reference sections of retrieved publications were reviewed thoroughly in search of further potential articles for inclusion.

Inclusion criteria

Research articles on cross sectional and cohort studies were included if they reported *Salmonella* isolated from blood and stool culture of human samples, if samples were collected from a named hospital or within a named community, if the symptomatic study subjects were recruited and research was conducted in Nigeria.

Exclusion criteria

Studies were excluded if the *Salmonella* – associated diseases reported were not based on blood and stool culture reports, if *Salmonella* species were not from human samples, while reports based on serological surveys, clinical diagnosis (such as typhoid perforations without culture), ecological correlation, systematic reviews, books and book chapters were also excluded from the studies and research works that were not conducted within Nigeria. Duplicated reported works were verified and excluded using two de-duplication options which include Mendeley citation manager and Ovid multifile search.

Validity assessment

Study validity was established by accurately assessing all original research articles for inclusion and exclusion criteria described above, ensuring that only reliable data were used.

Review of the selected literatures

In data extraction and collection process, relevant descriptive and quantitative variables were extracted from each of the selected articles. A standardized template was used for the data extraction in form of a Microsoft Excel 2013 workbook with each column of the database corresponding to one of the fields in the template. Double data extraction and entry was performed to ensure accuracy. The following parameters were used to extract information from the articles used in this study which included name of journal, title of article, publication date, study location (including city and region in Nigeria), study setting, (hospital-based, community based, hospital and community-based), study period, patient age, patient gender and the inclusion criteria. Quantitative data collected included number of potential study participants, subjects enrolled, specimen type (blood and stool), source of sample (human), number positive culture *Salmonella* isolates, *Salmonella* at both genus and serotypes level (if stated), risk factors such as infection with malaria or human immunodeficiency virus (HIV) (if known), the antibiotics tested and phenotypic resistance recorded.

Data analysis

Data were cleaned and a descriptive analysis performed. All reported *Salmonella* isolates and serotypes were directly drawn from the literatures. Duplicate reports were sorted and removed from the final analysis. The sorting was done by grouping all reports according to state and then comparing variables, which included study dates, name and location of the study site, age group of subjects reported, number of blood cultures taken and number of *Salmonella* isolated across the studies from each state for potential overlaps. Prevalence was calculated in this study as percentage of positive samples for *Salmonella* in the total samples recorded. Proportion was determined as number of *Salmonella* bacteraemia or *Salmonella* gastroenteritis positive culture in each zone divided by total number of *Salmonella* bacteraemia or *Salmonella* gastroenteritis in six zones of Nigeria. Relevant studies included prospective hospital-based or community-based culture series for subjects presenting with fever or with no known focus of infection or groups of subjects not selected for possible associated risk factors as anaemia, HIV, malaria and malnutrition. Summary data were extracted from the articles where available for risk factors associated with *Salmonella* diseases. Resistance phenotype was defined when at least 50% of identified *Salmonella* isolates developed resistance to test antibiotics. Summary data for risk factors associated with culture-proven human *Salmonella* infections were extracted directly from the studies where available. Statistically significant measures of association, such as odds ratio (OR), risk ratio (RR) and prevalence were extracted from the studies. The meta-analysis MedCalc version 19.4.1 software was used to pool the individual studies of interest from each geopolitical zone. Heterogenicity was assessed visually using Forrest plot and quantitatively using I^2 statistic and associated p-value. Results were considered statistically significant (p-value <0.05) at 95% confidence intervals. The analysis was presented as odd ratio based on the likelihood of the null hypothesis of possible publication bias was ruled out.

Results

The online database search performed on Google search, Google Scholar and PubMed from January 1, 1999 to December 31, 2018, yielded 18,603 articles. These were reviewed manually for relevance, based on the inclusion criteria and 102 articles were found to be eligible. A similar search strategy was used on the Embase database with 40 eligible articles identified. Critical screening revealed 86 articles used for descriptive analysis in this study.

Table 1. Published reports on culture positive human *Salmonella*-associated diseases in Nigeria (1999-2018).

Author	Region	State	Type of sample	Number of sample	Total Salmonella	INVASIVE SALMONELLOSIS/ BLOOD								NONINVASIVE SALMONELLOSIS/ STOOL								US	AMR	Case of study	Time of study	Age/ year
					T.L	**ST**	**PA**	**PB**	**PC**	**SM**	**SE**	**OS**	**TT**	**ST**	**PA**	**PB**	**PC**	**SM**	**SE**	**OS**	**TT**	-				
[a](20)	NC	Abuja/FCT	Bl.	NA	26	-	-	-	-	11	0	15	**26**	-	-	-	-	-	-	-	**0**	-	S,A,T,CH	HB	2008–2015	<5
[b](16)	NC	Abuja/FCT	Bl.	22,862	240	230	10	0	0	0	0	0	**240**	-	-	-	-	-	-	-	**-**	-			2008-2018	
(54)	NC	Nasarawa	Sl.	125	94	-	-	-	-	-	-	-	**0**	94	-	-	-	-	-	-	**94**	-	NA	C.B	2017	16-35
(21)	NC	Nasarawa	Sl.	400	196	-	-	-	-	-	-	-	**0**	78	118	0	0	0	0	0	**196**	-	AX,AC,T	H B	2015	all
(22)	NC	Niger	Bl.	100	45	45	0	0	0	0	0	0	**45**	-	-	-	-	-	-	-	**0**	-	AC,AX,CP,CT,CE, A	H B	2012	all
(23)	NC	Plateau	Bl. Sl	3509 5428	89	4	0	4	1	7	1	28	**45**	3	1	2	0	4	1	27	**38**	4 2	AC,C,AX	H B	2006-2011	All
	TL		Bl. Sl.	**26,471** **5,953**	**690**	**279**	**10**	**4**	**1**	**18**	**1**	**43**	**356**	**175**	**119**	**2**	**0**	**4**	**1**	**27**	**328**	**4** **2**	NA	**NA**	NA	NA
(24)	NW	Kaduna	Sl.	220	63	-	-	-	-	-	-	-	**0**	16	0	0	0	0	0	0	**16**	47	AX,AC,CTX,C	H B	Sep., 2014- April, 2015	all
(25)	NW	Kaduna	Sl.	219	14	-	-	-	-	-	-	-	**0**	0	0	0	0	0	0	0	**0**	14	AX,T,C	H B	2016	All
(26)	NW	Kaduna	Sl.	420	27	-	-	-	-	-	-	-	**0**	7	4	1	0	5	7	3	**27**	-	NA	H B	Jan-Dec. 2015	All
(61)	NW	Kaduna	Bl.	713	102	71	15	16	0	0	0	0	**102**	-	-	-	-	-	-	-	**0**	-	AX,A,AC,T	H. C	Dec. 2007-June 2008	
(27)	NW	Kano	Sl.	500	134	-	-	-	-	-	-	-	**0**	34	15	12	17	31	25		**134**	-	A,C,CH,NA	H B	May, 2012- March, 2014	
(28)	NW	Kano	Bl.	225	39	27	1	0	0	0	0	0	**28**	-	-	-	-	-	-	-	**0**	11	A,C	H B	2017	0-6
[a](20)	NW	Kano	Bl.	NA	74		0	0	0	34	39	0	**73**	-	-	-	-	-	-	-	**0**	1	S,CH,C,A		Sep.2014- April, 2015	
[b](16)	NW	Kano	Bl.	86,342	924	920	4	0	0	0	0	0	**924**	-	-	-	-	-	-	-	**-**	-	NA	NA	NA	NA
(29)	NW	Kano	Sl.	300	41	-	-	-	-	-	-	-	**0**	12	6	0	0	23	0	0	**41**			H B	2009	0-2
(30)	NW	Kano	Bl.	90	10	0	0	0	0	0	10	-	**10**	-	-	-	-	-	-	-	**0**			H B	N S	0–59
(31)	NW	Kano	Bl.	500	104	39	5	11	14	35	0	0	**104**	-	-	-	-	-	-	-	**0**		A,CH,NA,C	H B	May,2012- March,2014	All
(32)	NW	Katsina	Bl. Sl	120 120	29	11	3	0	0	0	0	0	**14**	5	0	0	0	3	7	0	**15**	-	A,CH,C	H B	April-Dec.2011	All
(33)	NW	Katsina	Sl.	220	11	-	-	-	-	-	-	-	**0**	0	0	0	0	0	0	0	**0**	11	A,AX,AC,T,CTX	H B	2015	0-5
(34)	NW	Katsina	Bl.	300	14	9	5	0	0	0	0	0	**14**	-	-	-	-	-	-	-	**0**		A,P	H B	N S	All
	TL		Bl. Sl.	**88,29** **1,999**	**1,586**	**1077**	**33**	**27**	**14**	**69**	**49**	**0**	**1,269**	**74** **74**	**25**	**13**	**17**	**62**	**39**	**3**	**233**	**12** **72**				
(35)	NE	Bauchi	Bl. Sl	210 154	9	4	0	0	0	0	0	0	**4**	5	0	0	0	0	0	0	**5**	-	A,AX,AC,AK,CT,CA,CH,C,E IMP, NA	H B	N S	N A
(36)	NE	Bauchi	Bl. Sl	249 135	11	4	0	0	0	0	0	0	**4**	7	0	0	0	0	0	0	**7**	0	ND	H B	June-Nov.2016	1-70
	TL		Bl. Sl.	**459** **289**	**20**	**8**	**0**	**0**	**0**	**0**	**0**	**0**	**8**	**12**	**0**	**0**	**0**	**0**	**0**	**0**	**12**	**0** **0**	NA	NA	NA	NA
(37)	SW	Lagos	Sl.	105	2	-	-	-	-	-	-	-	**0**	0	0	0	0	0	2	0	**2**	--	ND	HB	Jan.-June, 2014	0-12
(55)	SW	Lagos	Sl.	37	21	-	-	-	-	-	-	-	**0**	0	0	0	0	12	9	0	**21**		A,CH,T, CL,C, G,AX	CB	97,99,2002,Dec 2004 -Jan 2005	N A
(38)	SW	Lagos	Bl. Sl.	10 20	13	0	0	0	0	0	0	2	**2**	3	0	0	0	1	2	5	**11**		T,A,CL,C	HB	Sept., 2013 Feb., 2014	N A
(64)	SW	Lagos	Bl. Sl.	235 206	77	19	7	0	0	0	9	7	**42**	2	4	0	0	0	18	11	**35**	-	A,C,CH,T	HC	Oct. 2004 - Sept. 2005	0-46
(58)	SW	Lagos	Bl. Sl.	27 206	35	-	-	-	-	-	-	-	**0**	14	3	0	0	0	11	7	**35**	-	A,CH,C	CB	June, 2006 and June, 2007	Ad
(57)	SW	Lagos	Sl.	53	7	-	-	-	-	-	-	-	**0**	3	0	0	0	0	3	1	**7**	-	A,CH,C	CB	June -July, 2006	Ad
(61)	SW	Lagos	Bl. Sl.	135 23	37	25	8	0	0	0	2	0	**35**	0	0	0	0	0	2	0	**2**	-	A,T,AC,CA,	HC	Oct. 2010 - July 2011	All
(19)	SW	Lagos	Bl.	635	101	68	17	0	0	0	0	16	**101**	-	-	-	-	-	-	-	**0**	-	CH,A,C	HB	May 1997 - July 1998	All
(17)	SW	Lagos	Bl.	103	41	41	0	0	0	0	0	0	**41**	-	-	-	-	-	-	-	**0**	-	A,C,CH,T	HB	N S	NA
[b](16)	SW	Lagos	Bl.	20059	440	440	0	0	0	0	0	0	**440**	-	-	-	-	-	-	-	**0**	-	A,CH,T	HB	1993-2015	All
(39)	SW	Ogun	Sl.	200	7	-	-	-	-	-	-	-	**0**	7	0	0	0	0	0	0	**7**	-	AZ,CA,AC,G	HB	N S	All
(40)	SW	Ogun	Sl.	57	20	-	-	-	-	-	-	-	**0**	14	0	0	0	0	0	6	**20**	-	ND	HB	2015	All
(41)	SW	Osun	Bl.,	107	1	0	0	0	0	0	0	0	**0**	-	-	-	-	-	-	-	**0**	1	ND	HB	Feb., 1994 - Jan., 1995	<4 months
(42)	SW	Osun	Bl.	96	10	5	5	0	0	0	0	0	**10**	-	-	-	-	-	-	-	**0**	-	ND	HB	Feb. - March, 2017	All
(18)	SW	Osun	Bl.	650	15	10	4	0	0	0	0	0	**14**	-	-	-	-	-	-	-	**0**	1	PF,A,CL,CA CF,T	HB	N S	All
(11)	SW	Osun	Bl. Sl.	52 204	19	0	0	0	0	2	0	0	**2**	0	0	0	0	17	0	0	**17**	0	AX, A, CH, C, T	HB	N S	All
(65)	SW	Oyo	Bl.	991	39	7	0	0	0	7	13	12	**39**	-	-	-	-	-	-	-	**0**	-	AC,A, ST,T	HC	2004 - 2005	All
(43)	SW	Oyo	Bl.	3184	146	146	0	0	0	0	0	0	**146**	-	-	-	-	-	-	-	**0**	-	C, CH,A	HB	March, 2008 - Jan., 2009	All
(66)	SW	Oyo	Bl.	223	16	0	0	0	0	7	0	0	**7**	-	-	-	-	-	-	-	**0**	9	A,CH,ST,C	HC	2004 - 2005	0-10 yrs
(44)	SW	Oyo	Bl.	442	25	19	6	0	0	0	0	0	**25**	-	-	-	-	-	-	-	**0**	-	C, AX	HB	May - Oct., 2002	0-11
(62)	SW	Ekiti	Sl.	750	603	-	-	-	-	-	-	-	**0**	603	0	0	0	0	0	0	**603**	-	ST,CH,CF,NA,T,C	HC	Feb., 2009 - Sept., 2011	All
(56)	SW	Ekiti	Sl.	510	195	-	-	-	-	-	-	-	**0**	195	0	0	0	0	0	0	**195**	-	CA, CF	CB	N S	16-35
(45)	SW	Ekiti	Bl.	99	2	0	0	0	0	0	0	0	**0**	-	-	-	-	-	-	-	**0**	2	CA, AC, A, CF	HB	Aug. - Nov. 2011	All
	TL		Bl. Sl.	**27,048** **2,371**	**1,872**	**780**	**47**	**0**	**0**	**16**	**24**	**37**	**904**	**841**	**7**	**0**	**0**	**30**	**47**	**30**	**955**	**13** **0**	NA	**NA**	NA	NA
(46)	SE	Anambra	Sl.	256	38	-	-	-	-	-	-	-	**0**	17	17	0	0	4	0	0	**38**	-	ND	HB	Jan. to Aug., 2008	!-35
(47)	SE	Ebonyi	Bl. Sl.	296 486	98	46	0	0	0	0	0	0	**46**	52	0	0	0	0	0	0	**52**	-	CA,CF,AC	HB	May, 2015 - June, 2016	>11
(48)	SE	Imo	Sl.	105	60	-	-	-	-	-	-	-	**0**	0	0	0	0	0	0	0	**0**	60	C,NA,CL,AC	HB	2017	Mrz 81
(49)	SE	Imo	Sl.	150	84	-	-	-	-	-	-	-	**0**	84	-	-	-	-	-	-	**84**	-	A,AX,T AC,C,G,	HB	NS	ND
(59)	SE	Imo	Bl.	185	25	25	0	0	0	0	0	0	**25**	-	-	-	-	-	-	-	**0**	-	ND	C.B	NS	0-61
(50)	SE	Ebonyi	Bl.	250	2	2	0	0	0	0	0	0	**2**	-	-	-	-	-	-	-	**0**	-	ND	HB	Feb.-Aug.,2007	0-70
	TL		Bl. Sl.	**997** **731**	**307**	**73**	**0**	**0**	**0**	**0**	**0**	**0**	**73**	**153**	**17**	**0**	**0**	**4**	**0**	**0**	**174**	**0** **60**	NA	**NA**	NA	NA
(60)	SS	Bayelsa	Sl.	380	117	-	-	-	-	-	-	0	**0**	57	13	11	12	0	0	0	**93**	24	CA,CT,AC, CF	CB	Oct., 2012 - July, 2013	!-65
(51)	SS	Cross-River	Bl.	250	2	0	0	0	0	0	2	0	**2**	-	-	-	-	-	-	-	**0**	-	ND	HB	Jan. - Dec., 2016	!-75
(52)	SS	Delta	Bl.	136	20	0	0	0	0	0	0	0	**0**	-	-	-	-	-	-	-	**0**	20	AC,C,T	HB	May - Dec., 2009	ND
(53)	SS	Edo	Bl.	271	60	60	0	0	0	0	0	0	**60**	-	-	-	-	-	-	-	**0**	-	ND	HB	NS	>18
(12)	SS	Akwa-Ibom	Bl. Sl.	100 92	25	9	2	0	0	0	0	0	**11**	10	4	0	0	0	0	0	**14**	-	CTX,C,P	HB	NS	0-60
	TL		Bl. Sl.	**757** **472**	**224**	**69**	**2**	**0**	**0**	**0**	**2**	**0**	**73**	**67**	**17**	**11**	**12**	**0**	**0**	**0**	**107**	**20** **24**	NA	NA	NA	NA
GRAND TOTAL			Bl. Sl.	**143,756** **12,081**	**4,699**	**2286**	**92**	**31**	**15**	**103**	**76**	**80**	**2683**	**1,322**	**185**	**26**	**29**	**100**	**87**	**60**	**1,809**	**49** **158**	NA	NA	NA	NA

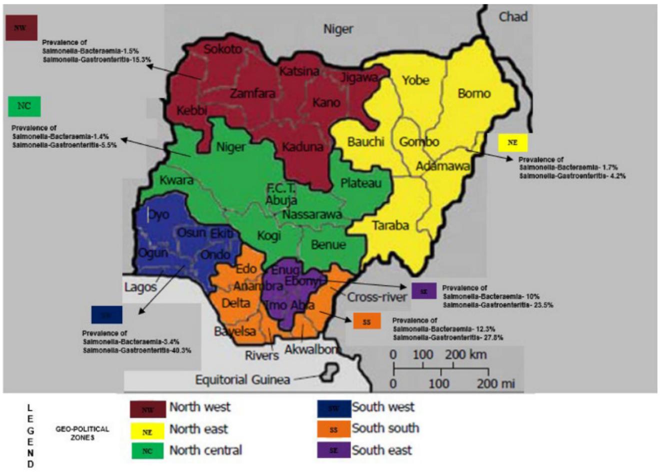
ST: *S. typhi*; PA: *S. paratyphi* A; PB: *S. paratyphi* B; PC: *S. paratyphi* C; SM: *S. typhimurium;* SE: *S. enteritidis*; US: Un-typed *Salmonella*; AMR: Antimicrobial resistance; A: Ampicillin; AC: Amoxicillin and Clavulanate. AX: Amoxicillin; T: Tetracycline; C: Cotrimoxazole; CH: Chloramphenicol; CL: Colistin; NA: Nalidixic acid; G: Gentamycin; ST: Streptomycin; CA: Ceftazidime; CTX: Cefotaxime; CF: Cefuroxime. P: Penicillin; CT: Ceftriaxone; CP: Ciprofloxacin; IMP: Imipenem; AZ: Azithromycin; CE: Cefipime; S: Sulfamethazine; PF: Pefloxacin; E: Erythromycin; AK: Amikacin; CB: Community based; HB: Hospital based; HC: Hospital and Community based; NS: Not specified; ND: Not determined; NA: Not applicable; [a]: contained report from one other zone; [b:] contained report from two other zones. SS: South-south; SE :South-east; SW: South-west; NC: North-central; NE: North-east; NW: North-west. TL: Total. Bl.: Blood. Sl.: stool.

The articles were further reviewed quantitatively with duplicate studies removed leaving only 56 articles. A total 53 articles were finally considered for this study, after exclusion of authors whose articles were reflected in multiple zones (Figure 1). Thirty seven out of the 53 published reports [11, 12, 13, 14, 16, 17-36, 39-45, 47-53] were hospital-based, nine [38, 46, 57-60] were community based and seven [37, 61-66] were both community and hospital-based studies.

Prevalence and Diversity of culture-proven Salmonella serotypes associated with blood stream infections and gastroenteritis in Nigeria

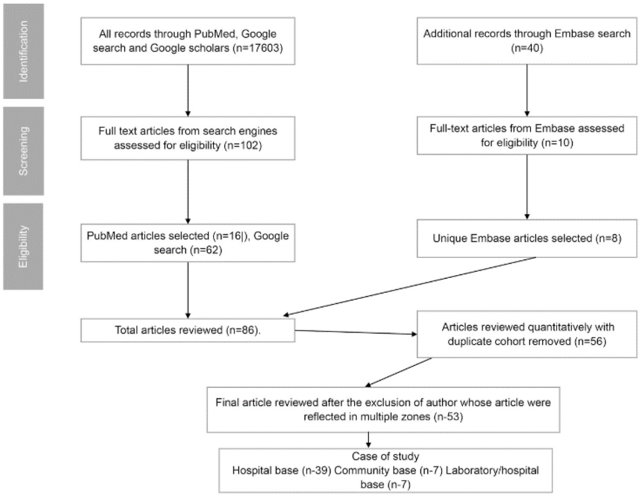
In this study, 4,699 (3.0%) *Salmonellae* were recovered from 155,837 clinical samples (blood and stool) of patients with *Salmonella* infections, extracted from 53 scientific publications that met the inclusion criteria. Of the 4,699 *Salmonellae*, 2,732 (58.1%) were from blood and 1,967 (41.9%) from stool (Table 1). Specifically, 2,732 out of the 143,756 blood samples were positive for *Salmonellae* giving prevalence of 1.9% culture-proven *Salmonella* blood-stream infections. Of 2,732 S*almonellae,* 2,286 (83.7%) were *S. typhi*, 138 (5.1%) *S. paratyphi* A, B and C, 259 (9.5%) iNTS and 49 (1.8%) un-typed *Salmonella* (US). The 259 iNTS comprised of 103 (39.8%) *S. typhimurium,* 76 (29.3%) *S. enteritidis* and 80 (30.9%) other iNTS serotypes (Table 1). Similarly, prevalence of 16.3% (1967/12081) *Salmonella*-associated gastroenteritis was recorded. Out of 1,967 *Salmonellae,* 1,322 (67.2%) were *S. typhi,* 240(12.2%) *S. paratyphi* A, B and C, 100 (5.1%) *S. typhimurium*, 87 (4.4%) *S. enteritidis* and 60 (3.1%) other NTS serotypes (Table 1). Overall, 53 serotypes were reported among 4,492 typed *Salmonella* isolates (2,683 blood isolates and 1,809 stool isolates) across the six geopolitical zones (Table 2). *S. typhi* is the most common *Salmonella*-bacteraemia (85.2%) and *Salmonella* gastroenteritis (73.1%) while *S. typhimurium* remains the most common serotype reported (3.8%) for iNTS disease (Table 2). Figure 2 shows the map of Nigeria indicating the six geopolitical zones and prevalence of *Salmonella* infections. The prevalence of *Salmonella*-bacteraemia was highest in South-South 12.3% followed by South-East 10%, South-West 3.4% and the least was recorded in North-Central 1.4%. South-West recorded 40.3% prevalence for *Salmonella*-associated gastroenteritis followed by South-South 27.8% while the least 4.2% was found in North-East (Figure 2).

Figure 2. Map of Nigeria showing States in six geo-political zones and prevalence of Salmonella infections.



The colour in the Map indicate the zones.

Figure 1. Strategy for selection of eligible articles.



Adapted from the PRISMA group.

States in six geopolitical zones reporting Salmonella-associated diseases in Nigeria

Salmonella-associated diseases were reported in 21 of the 36 states in Nigeria plus Federal Capital Territory (FCT) Abuja. The majority of the reports 23/53 (43.4%) were from South-west (SW) geopolitical zone (including 10 reports from Lagos, 3 from Ekiti, 2 from Ogun and 4 each from Osun and Oyo States). Specifically, 22.6% (12/53) from North-west (NW) (5 reports from Kano, 4 from Kaduna and 3 from Kastina State), 11.3% (6/53) from South-east (SE) (3 reports from Imo, 2 from Ebonyi State and one from Anambra State) and 9.4% (5/53) from North-central (NC) (2 reports from Nasarawa, one each from Niger, Plateau and FCT Abuja).

Table 2. Different *Salmonella enterica* serovars reported across the studies from geopolitical zones in Nigeria.

***Salmonella* Serotypes**	**No. of isolates from blood**	**Percentage (n= 2683)**	**No of isolates from stool**	**Percentage (n=1809)**	**No of articles reporting blood isolates (%)**	**No of articles reporting stool isolates (%)**	**Zone (no of blood isolates representing each serotype)**	**Zone (no of stool isolates representing each serotype)**
typhi	2,286	85.2	1,322	73.1	26	23	NC(279),NW(1,077), NE(8),SW(780), SE(73), SS(69)	NC(175),NW(74), NE(12), SW(841), SE(153), SS(67)
paratyphi a	92	3.4	185	10.2	14	10	NW(10), NW(33), SW(47), SS(2)	NC(119), NW(25), SW(7), SE(17), SS(17)
paratyphi b	31	1.2	26	1.4	3	4	NC(4), NW(27)	NC(2), NW(13), SS(11)
paratyphi c	15	0.6	29	1.6	2	2	NC(1), NW(14)	NW(17), SS(12)
typhimurium	103	3.8	100	5.5	7	9	NC(18), NW(69), SW(16),	NC(4), NW(62), SW(30), SE(4)
enteritidis	76	2.8	87	4.8	7	11	NC(1), NW(49), SW(24), SS(2)	NC(1), NW(39), SW(47)
arizona	23	0.9	13	0.7	2	3	SW(23)	SW(13)
choleraesuis	2	0.1	16	0.9	1	4	SW(2)	SW(16)
dublin	12	0.4	0	0	2	0	NC(5), SW(7)	-
infantis	1	0.04	3	0.2	1	1	SW(1)	NW(3)
virchow	1	0.04	1	0.06	1	1	NC(1)	-
apapa	1	0.04	0	0	1	0	SW(1)	-
jukenstown	1	0.04	0	0	1	0	SW(1)	-
oritamerin	1	0.04	0	0	1	0	SW(1)	-
monschaui	1	0.04	0	0	1	0	S-W(1)	-
durban	1	0.04	0	0	1	0	NC(1)	-
abony	1	0.04	1	0.06	1	1	NC(1)	NC(1)
bredeney	1	0.04	0	0	1	0	NC(1)	-
pasing	1	0.04	0	0	1	0	NC(1)	-
poona	3	0.1	0	0	1	0	NC(3)	-
colindale	1	0.04	0	0	1	0	NC(1)	-
galiema	1	0.04	0	0	1	0	NC(1)	-
rissen	0	0	2	0.1	0	1	-	NC(2)
korbol	1	0.04	1	0.06	1	1	NC(1)	NC(1)
lomita	2	0.1	0	0	1	0	NC(2)	
brazaville	1	0.04	1	0.06	1	1	NC(1)	NC(1)
lamberhaust	2	0.1	0	0	1	0	NC(2)	
koessen	1	0.04	0	0	1	0	NC(1)	
glassgow	0	0	1	0.06	0	1	-	NC(1)
kingston	0	0	1	0.06	0	1	-	NC(1)
chester	1	0.04	0	0	1	0	NC(1)	-
stanleyville	0	0	1	0.06	0	1	-	NC(1)
schwarzangra	0	0	1	0.06	0	1	-	NC(1)
lagos	1	0.04	0	0	1	0	NC(1)	-
mono	0	0	1	0.06	0	1	-	NC(1)
agona	1	0.04	0	0	1	0	NC(1)	-
eppendorf	1	0.04	0	0	1	0	NC(1)	-
newport	0	0	1	0.06	0	1	-	NC(1)
kentuckey	0	0	1	0.06	0	1	-	NC(1)
larochele	0	0	1	0.06	0	1	-	NC(1)
djeifa	1	0.04	0	0	1	0	NC(1)	-
aba	1	0.04	0	0	1	0	NC(1)	-
kastrup	0	0	1	0.06	0	1	-	NC(1)
kisii	0	0	1	0.06	0	1	-	NC(1)
othmarschen	1	0.04	0	0	1	0	NC(1)	-
margherafelt	0	0	1	0.06	0	1	-	NC(1)
israel	1	0.04	0	0	1	0	NC(1)	-
okerara	1	0.04	0	0	1	0	NC(1)	-
ngor	0	0	1	0.06	0	1	-	NC(1)
masembe	0	0	1	0.06	0	1	-	NC(1)
aminatu	0	0	1	0.06	0	1	-	NC(1)
anatum	1	0.04	0	0	1	0	NC(1)	-
bagney	5	0.2	6	0.3	1	1	NC(5)	NC(6)
saint paul	5	0.2	1	0.06	1	1	NC(5)	NC(1)
sub sp salome	1	0.04	1	0.06	1	1	NC(1)	NC(1)
Total	2,683	100	1809	100				

The South-south (SS) zone recorded 9.4% (5/53) (one report each from Akwa-Ibom, Bayelsa, Delta, Edo and Cross-river State) and 3.8% (2/53) from North-east (NE) (2 reports were from Bauchi State) (Table 1). The four most frequently reported human associated serotypes are *S. typhi*, *S. paratyphi*, *S typhimurium* and *S. enteritidis.* However, *S. typhi*-associated bacteraemia was mostly reported from NW (1,077) and SW (780). The highest number of serotypes, *typhi* was reported in SW (841) and NC (175) from cases of gastroenteritis. Serotype *arizona* was confined to SW and *dublin* to NC and SW zones. Other reported serotypes are listed in (Table 2).

Trends of reported culture positive human Salmonella infections in Nigeria (1999-2018)

The earliest report on salmonellosis for positive human cultured samples was 1999 in SW [46]. There was a general fluctuation in the trends of *Salmonella* infections in Nigeria over time. For *Salmonella* bacteraemia, increase in the occurrence of the disease between 1999 and 2001 through 2005 and 2007 with peak occurrence between 2008 and 2013 was observed (Table 3 and Figure 3). Interestingly, there was a decline in the trend of bacteraemia and gastroenteritis between 2014 and 2018 with corresponding increase in the number of researchers or published articles in most geographical zones (Table 3). There was general fluctuation in the trend of *Salmonella* gastroenteritis in each of the zones studied, with highest between 2008

Figure 3. Trends of culture positive human *Salmonella* infections in Nigeria (1999-2018).

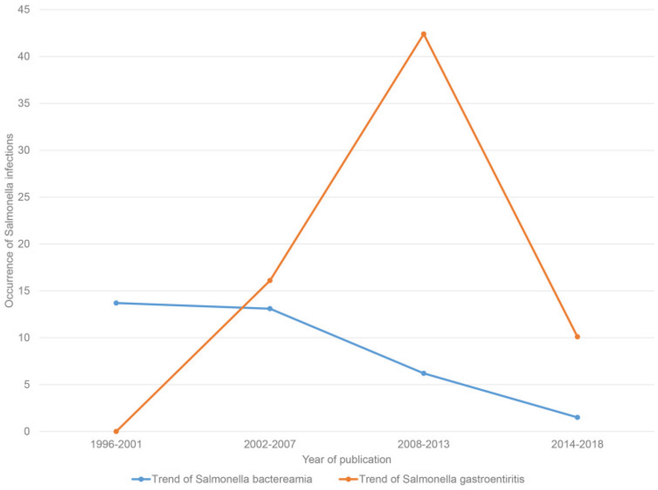


Table 3. Geographical distribution of culture positive human *Salmonella* infections Nigeria (1999-2018).

Region	Year of publication	Number of blood sample	Number of stool sample	*Salmonella* from blood	*Salmonella* from stool	Occurrence of *Salmonella* bacteraemia	Occurrence of *Salmonella* gastroenteritis	Number of Authors
N-C	1999-2001*	0	0	0	0	0	0	0
N-C	2002-2007	0	0	0	0	0	0	0
N-C	2008-2013	100	0	45	0	45	0	1
N-C	2014-2018	26,371	5,953	315	330	1.1	5.5	4
Total		26,471	5,953	360	330	1.4	5.5	5
N-W	1999-2001*	0	0	0	0	0	0	0
N-W	2002-2007	0	0	0	0	0	0	0
N-W	2008-2013	833	420	116	56	13.1	13.3	2
N-W	2014-2018	87,457	1,579	1,165	249	1.3	15.8	10
Total		88,290	1,999	1281	305	1.5	15.3	12
N-E	1999-2001*	0	0	0	0	0	0	0
N-E	2002-2007	0	0	0	0	0	0	0
N-E	2008-2013	0	0	0	0	0	0	0
N-E	2014-2018	459	289	8	12	1.7	4.2	2
Total		459	289	8	12	1.7	4.2	2
S-W	1999-2001*	742	0	102	0	13.7	0	2
S-W	2002-2007	832	447	110	73	13.2	16.3	5
S-W	2008-2013	5,075	1,009	216	645	4.3	63.9	7
S-W	2014-2018	20,399	915	489	237	2.4	25.9	9
6Total		27,048	2,371	917	955	3.4	40.3	23
S-E	1999-2001*	0	0	0	0	0	0	0
S-E	2002-2007	185	0	25	0	13.5	0	1
S-E	2008-2013	250	406	2	122	0.8	30	3
S-E	2014-2018	296	591	46	112	15.5	19	2
Total		731	997	73	234	10	23.5	6
S-S	1999-2001*	0	0	0	0	0	0	0
S-S	2002-2007	100	92	11	14	11	15.2	1
S-S	2008-2013	136	380	20	117	14.7	30.8	2
S-S	2014-2018	521	0	62	0	11.9	0	2
Total		757	472	93	131	12.3	27.8	5
Grand Total	1999-2018	143,756	12081	2732	1967	1.9	16.3	53

*represents range of 3 years.

and 2013 in SW (63.8%), SE (30%) and SS (37%), while NW recorded peak gastroenteritis between 2014 and 2018 (Table 3). The highest occurrence and proportion of *Salmonella* bacteraemia was recorded in SS 12.3% (93/757) and NW 46.9% (1,281/2,732) respectively. Similarly, *Salmonella* gastroenteritis recorded both highest occurrence 40.3% (955/2,371) and proportion 48% (955/1991) in SW zone. The NE and NC zones recorded least values in both cases (Table 3 and Figure 4).

Reported risks associated with Salmonella- diseases in Nigeria

In this study, 48 out of 53 reviewed articles with age-associated *Salmonella* infections reports were observed. Forty of these articles reported on all age groups and eight articles were mainly on young children of less than 12 years. Over 46% (1,264/2,732) *Salmonella* bloodstream infections were recorded in children <12 years as reported by five studies [20, 28, 41, 44, 64]. About 50% of *Salmonella* bacteraemia were observed from all age groups as reported by 20 authors [11-12, 16, 18, 19, 22, 31, 32, 34, 36, 40, 41, 43, 45, 50, 51, 61, 63, 65]. Only two authors [53, 58] reported mainly on adult population. Similar observations were noted in *Salmonella*-associated gastroenteritis (Table 1). One study [28] reported sickle cell anaemia as a risk factor in *Salmonella* bloodstream infection in children, although this risk factor is not statistically significant (*p* >0.05) (Tables 1 and 4). Two studies observed an association between HIV and *Salmonella*-associated diseases [21]. It was reported that HIV infected patients with bacteraemia had significantly lower CD4+ count, while fever complication arising from multiple drug resistant *Salmonella* infection among HIV patients with bacteraemia was more than those HIV patients without

Figure 4. Proportion of *Salmonella* isolates across the six geo-political zones with the number of publications.

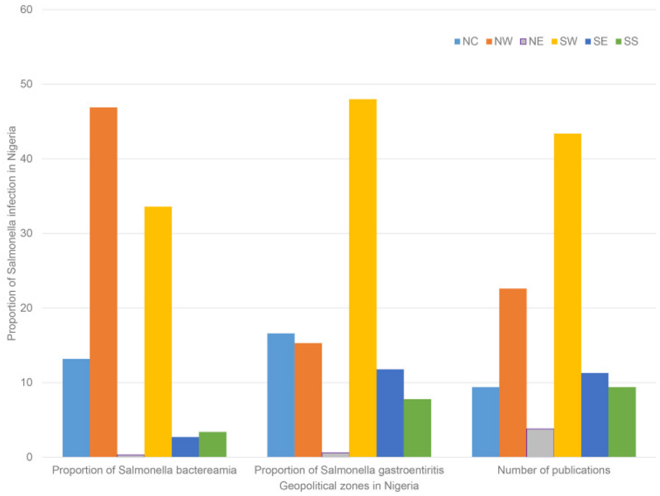


Table 4. Reported risk factors associated with *Salmonella* Infections in Nigeria.

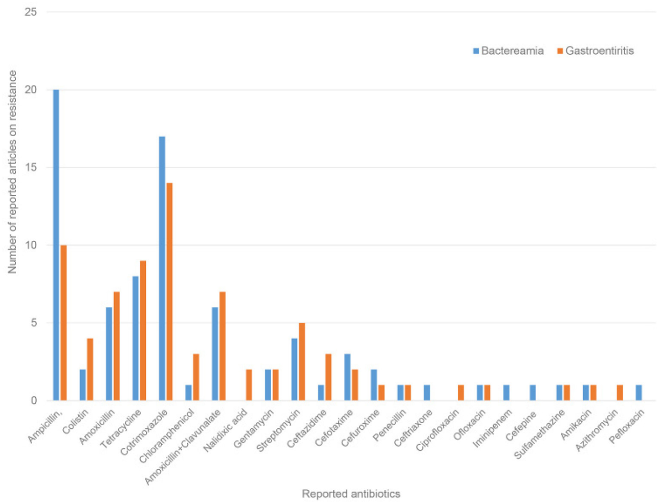
Risk factor	References	Measure of association reports (Confidence Interval = CI)	Comments
Malaria (*Plasmodium falciparum*)	(46, 64)	*p* > 0.05	Malaria was positively associated with typhoid fever mostly in complicated cases.
HIV	(17, 21)	2.3. p = 0.005 for mortality or 3.4, p = 0.000; or 2.4, p = 0.014	Non-typhoidal *Salmonellae* were more predominant in HIV patients than non-HIV and were more resistant to common antibiotics.
Malnutrition	(30)	Odds ratio = 2.56, CI = 1.45-5.22	Bacteremia was highly prevalent among malnourished children.
Sickle cell anaemia (SCD)	(28)	p > 0.05	Bacteremia in SCD confirmed children in three hospitals reportedly caused by a combination of 11 bacteria genera with lesser bacteremia found in non-SCD children, possessing increased resistant to most commonly used antibiotics.
Age	(25)	p > 0.05	Patients under age bracket of 0-9 years reportedly found to be more susceptible to typhoidal *Salmonella* bacteraemia with 6 (43%) positive cases.
	(24)	p > 0.05	Patients under 10yrs possessed the highest *Salmonella* species prevalence rate.
	(33)	x^2 =1.454, p ≤ 0.05, df = 4	A high frequency of isolation among children aged 13-24 and 25-36 months (36.4%) reportedly observed.
	(21)	x^2 = 5.6976, p < 0.05	*S.* Typhi infection was higher (23.1%) among ages 21-30 years. Patients of ages 21-30 also recorded higher prevalence in *S.* Paratyphi-associated infections.
	(54)	p > 0.05	Highest prevalence was observed among the age group of 21-25 years with 86.96% (60/69) students tested positive.
Gender	(21, 29, 31, 33, 34, 54)	p > 0.05	All the six authors reported high prevalence of *Salmonellae* in male patients than female patients with a statistical significant association.

bacteraemia (median 28 vs. 88 cells/ml, p=0.01) [21]. Malnutrition was identified as a risk factor by a study [30] in *Salmonella* bacteraemia and high proportion of this infection occurred more among malnourished children (Table 4). Furthermore, *Plasmodium falciparum* co-infection with *Salmonella* bacteraemia was reported by two studies [46, 64] with significant association put at $p > 0.05$.

Reports on Antimicrobial Resistance

More than 80% of the authors reported antimicrobial resistance on the *Salmonella* isolates. In all, *Salmonella* isolates were found to develop resistance to 23 different antibiotics (Table 1 and Figure 5). The periods of antibiotic resistance development as reported by different authors is shown in Table 1. For example, in 2012, one author [22] reported six antibiotics resistance (amoxicillin-clavulanate, amoxicillin, ciprofloxacin, ceftriaxone, cefipime and ampicillin) in *Salmonella*-bacteraemia (Table 1). Generally, at least 60% of the reported isolates developed resistance to one antibiotic or the other. Ampicillin, cotrimoxazole, amoxicillin-clavulanate and tetracycline are the most frequently reported antibiotics resisted by *Salmonella* isolates. Two authors reported fluoroquinolones antibiotic resistance (ciprofloxacin and perfloxacin) in *Salmonella* bacteraemia [18, 22]. An author reported each colistin resistant *Salmonella* gastroenteritis [65] and colistin resistant-*Salmonella* bacteraemia [37]. This study revealed that *Salmonella-associated* bacteraemia and S*almonella*-associated gastroenteritis mostly developed resistant to three cephalosporin antibiotics: ceftriaxone [22, 24, 35], cefotaxime [12, 33] and cefuroxime [18, 45, 47, 56, 60].

Figure 5. Antibiotic resistance reports on culture positive *Salmonella* infections.



Discussion

To the best of knowledge, this is the first systemic review of human *Salmonellae* and diversity of its serotypes in Nigeria. It was found that 47% of eligible published articles reported culture-proven *Salmonella*–associated infections in human from 21 of the 36 states (including FCT, Abuja). Lack of data from the remaining fifteen other states is an indication of gaps in the published articles partly due to a lack of culture-based studies, poor infrastructure to undertake blood culture for definitive diagnosis of *Salmonella*-associated diseases and lack of researcher interest to conduct research and publish reports on *Salmonellae*.

In this review, 53 human *Salmonella* serotypes were recorded. Four of these serotypes; *S. typhi, S. paratyphi*, *S typhimurium* and *S. enteritidis* were frequently reported. The prevalence of 1.9% and 16.3% culture-proven *Salmonella* blood-stream and *Salmonella*-associated gastroenteritis was recorded respectively. This result clearly showed that typhoidal and non-typhoidal salmonellosis is a public health issue. It is also interesting to note that prevalence of *S. typhi,* the most common serotype in blood stream infections is 1.6% (2,286/143,756). This serotype accounted for 83.7% S*almonellae* bacteraemia and over 70% *Salmonella* gastroenteritis in proportion. This high prevalence and proportion of *S. typhi* reported may be due to population explosion, poor health care facilities, poor portable water distribution network, inadequate sewage treatment/ disposal system and low per capital income as identified in previous study [16]. Study from the systemic reviews elsewhere indicated wide variation in *S. typhi* positivity rates between countries over time, from 0.05% among ambulatory patients in Thailand in 2007 to 24.1% in Cambodia in 2009 and to less than 4% in Kuwait [67] was reported. In this study, nearly half of the included literatures reported data on typhoid fever outcomes, with paratyphoid fever being relatively under-represented. Specifically, 0.06% prevalence and 5.1% proportion of *S. paratyphi* (A, B and C) in blood stream infections were obtained. However, the sub-national studies from Burkina Faso, Ghana, Guinea-Bissau, Kenya, Madagascar, Mozambique, Tanzania and Senegal, reported the prevalence of *S. paratyphi* A, B, and C to be less than 0.7%, whereas in Kuwait it was between 0.11% and 0.82% [67]. Specifically, 36 different iNTS serotypes were reported in nine published articles with *S. typhimurium* being the most common reported serotype (39.8%) associated with iNTS disease mainly from NC, NW and SW zones. Close to this, is *S. enteritidis* from NC, NW, SW and SS. This study revealed that

Salmonella serovars *enteritidis, S. choleraesuis, S. dublin, S. arizonae, S. bagney, S. saint paul and S, poona* are also associated with invasive diseases. NTS serotypes other than *S. typhimurium* such as *Salmonella* serovars *S. heidelberg, S. dublin, and S, choleraesuis* had been implicated in hospitalized invasive disease in patients more than *S. typhimurium* [68].

There is variability in occurrence of *Salmonella*-associated diseases and proportion of *Salmonella* pathogens across the states with published articles, based on the summation of reported published data in those states. For instance, SS recorded highest occurrence (12.3%) of *Salmonella* blood stream infection from four scientific publications [12, 51-53] and the SW geo-political zone with highest published articles [11, 16-18, 19, 38, 41, 42-44, 58, 63-66] recorded 3.4% prevalence of *Salmonella* bacteraemia. Interestingly, highest proportion of *Salmonella* bacteraemia 46.9% (1,281/2,732) was found in NW zone from eight studies (Table 1). Furthermore, *Salmonella* gastroenteritis has its peak proportion in SW (48%). There was statistically significant difference ($p < 0.05$) in the number of published articles and the number of *Salmonella* isolates recorded between zones. The high heterogeneity in the estimated *Salmonella* occurrence and proportion in each zone may be attributed to many factors but not limited to; number of published articles, detection method used, and amount of sample processed, available `facilities, accessibility to health facilities and conflict or stability of the zone. In NE for instance, a general death of published articles and very low proportion of *Salmonella* isolates were noticed. These are likely connected to the security issues and crisis confronting the zone in the last one decade with attendance humanitarian assistance from international communities.

There was general fluctuation in the trend of *Salmonella* infections over time. It was observed that zone with occurrence of typhoidal *Salmonellae* and NTS are historically with an increasing trend over time (Table 2 and Figure 4). These observations could in part, be attributed to decreased access to improved sanitation facilities and quality water, as well as malnutrition and poverty. Malnutrition was identified by a study [30] to have a significant association with increased *Salmonella* infection.

In this review, 75% of scientific articles evaluated, reported *Salmonella* infections, to cut across all age groups. However, a high proportion (46%) of *Salmonella* bacteraemia in children under 12 years of age was found. Statistical significance association of typhoidal salmonellosis with age had been documented and with children at the high risk of salmonellosis [21, 24, 25, 33, 54]. HIV infection, malaria parasitaemia co-infection with typhoid [17, 21] sickle cell anaemia [28] and gender among others are certain predisposing factors reported to influence occurrence of *Salmonella*-associated diseases in this study.

Antimicrobial resistance in *Salmonella* serotypes was reported by 80% of the published articles in this review. Of which more than 60% of *Salmonella i*solates developed resistant to one or more of 23 antibiotics reportedly tested and mostly to first line empirical antibiotics. In addition, fluoroquinolone antibiotic (ofloxacin and ciprofloxacin) resistance in *Salmonella* serotypes were recorded. It has been documented that infections caused by multiple drug resistant strains are more severe than those caused by susceptible strains [69]. In Nigeria, efficacies of the first line empirical antibiotics such as ampicillin, tetracycline, co-trimoxazole, chloramphenicol against *Salmonella* blood stream infections had been documented to be doubtful and are such no longer effective [16, 20]. The observed reported fluoroquinolone resistance is likely to be the consequence of widespread replacement of these traditional first-line antibiotics with fluoroquinolones, which has now become a threat to public health. Multiple drug resistant and/or reduced fluoroquinolone susceptibility had been an issue in Nigeria [16] and other West African countries such as Malawi and Tanzania [6]. *Salmonella* isolates were found to develop resistant to ceftazidime, cefotaxime, and cefuroxime in this review, an indication that alternative antibiotics to *Salmonella* infections is becoming doubtful. The complete suspension of ampicillin, tetracycline, chloramphenicol and cotrimoxazole in the treatment of *Salmonella*-blood stream infections is suggested for now in Nigeria and other developing countries where high burden of selective pressure on these antibiotics is rampant. It is obvious that findings from this systemic review would serve as baselines information on *Salmonella* blood stream infections. It would resolve the problem of paucity of aggregated national data on culture proven *Salmonella* cases and might help in the estimation of the true burden of *Salmonella* blood stream infections in Nigeria. For now, information data on culture proven salmonellosis is unavailable and/ or inaccessible at both State and Federal Ministries. In addition, data on culture positive salmonellosis in most of the referral hospitals are mirage, while data from private hospitals remain a conjecture. This observation is critical for policy makers and stakeholders in the health sector. The need to insist on culture-proven bloodstream infection diagnosis, even when symptomatology and serological diagnosis are inevitable during emergency, should form parts of Health Ministry policy directions. The action taken by some departments in the Ministry of Health in 2011 to establish Nigeria Centre for Disease Control (NCDC) recently became a reality, when the Federal Government of Nigeria signed a Bill for an Act to establish NCDC [70] in December 2018. The decision of the government is an intervention geared towards developing and sustaining a network of reference specialized laboratories, effective surveillance coordination systems and strategic management of diseases of public health importance.

Limitations: There are limitations and gaps in knowledge in this systemic review on the availability and quality of data in the published literatures. The possibility of estimating mortality rate and case fatality ratio due to the dearth of data on *Salmonella*-associated diseases was not determined. There was also a notable number of variations in testing methodologies in the included published literatures. Presently, blood and stool cultures are the gold standard for diagnosing typhoid and non-typhoidal diseases in most developing countries, thus, the standard of identification techniques and interpretation of results used for *Salmonella* isolates is another challenge. The source of isolation and variability of strains among the same serovars may influence antibiotic susceptibility test results as observed in this study. Proper coordinated hospital and laboratory-based studies would have added to the quality of the results. New prospective hospital-culture based studies in 36 States in Nigeria would have been more useful.

Conclusions

The study revealed between 1999 to 2018 prevalence of 1.9% and 16.3% culture-proven *Salmonella* blood-stream infections and gastroenteritis in Nigeria respectively. Typhoidal and non-typhoidal salmonellosis remain a public health challenge. *S. typhi* is the most common serotype associated with *Salmonella* infections out of 53 identified human *Salmonella* serotypes currently circulating in Nigeria, while *S. typhimurium* remains the most common serotype reported for iNTS disease. Over 46% *Salmonella* bloodstream infections were recorded in children <12 years. Human Immunodeficiency Virus (HIV)-infected individuals, sickle cell-anaemic individuals, children, malaria-coinfection and malnutrition are identified factors predisposing *Salmonella* infections. The study revealed that at least 60% of the reported isolates are multiple drug resistance. Fluoroquinolone and cephalosporin resistant isolates were recorded. A comprehensive epidemiological data to estimate the true burdens of *Salmonella* blood stream infections is paramount and achievable. Lack of researcher interest to conduct research and publish reports on *Salmonellae* among other gaps identified in this study, could be addressed by examining the health facilities, services, records and administration, in those states with little or no tools for definitive diagnosis of *Salmonella*-associated diseases. The National Surveillance program should be strengthened to ameliorate imperil caused by invasive non-typhoidal *Salmonella* disease. The data generated from this review would serve as a baseline information for future surveillance studies. A combined approach strategy that would include improvement in sanitation, water safety and use of vaccine is necessary.

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Authors’ contributions

KOA conceived the study and designed the study protocol; SOA and COF carried out literatures search for the review; KOA, SOA and COF organized, integrated all data and carried out the analysis and interpretation of data; KOA and SOA drafted the manuscript; KOA critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. KOA is a guarantor of the paper.

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