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Review Article

A Systematic review on the status of diarrheagenic *Escherichia coli* (DEC) pathotypes in Nigeria; the year 2000 – 2022

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ABSTRACT

This systematic review appraised the current status of DEC in Nigeria from the year 2000 to August 2022 with regards to their prevalence, pathotypes distribution, and dominance within the 6 geopolitical zones. Three research databases (AJOL, PubMed, and Google Scholar) were explored for articles of interest. From the outcome of the search, 19 full-length research articles from January 2000 to August 2022 that described the prevalence of DEC by molecular technique were recruited into the study. The results show that the studies of DEC were higher in the southern (52.63%) than in the northern (47.37%) region. Based on specimen types, 47.37% (9/19) and 52.63% (10/19) articles documented DEC from non-clinical and clinical sources, respectively. From the clinical sources, 70% of the studies targeted children of less than five years of age for the detection of DEC. The mean prevalence of DEC in Nigeria stands at 18.8%. The regional prevalence varies with the highest in the SW (32.57%) and the lowest in the NC (10.07%). The relationship between the prevalence of DEC to age group, gender, sample sources (clinical or non-clinical), study design (experimental and control groups), and regional differences were examined using odd ratios and chi-square statistics. Significance differences (P=0.0001) were obtained for all the parameters except gender which shows a lack of significant difference (P=0.1129). The most prevalent DEC pathotype was EAEC pathovar (44.62%) and the least was DAEC (2.23%). The regional distribution of the DEC pathotypes varies with the type of sample (clinical and non-clinical). Hybrid pathotypes were detected and constitute 4.89 % of the total DEC detected. The most prominent hybrid detected was EAEC/ETEC (39.13%). In that order, the DEC pathotypes were mostly resistant to ampicillin, penicillin, cotrimoxazole, and tetracycline, but were mostly susceptible to imipenem, gentamycin, and ofloxacin. We, therefore, advocate regular or periodic surveillance of DEC, and their drug resistance pattern, which will be useful to clinical personnel in their choice of a treatment regimen.

1. Introduction

Diarrhoea occur when an individual passes watery or loose stool 3 or more times a day accompanied in most cases by the intensified

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incidence of gut movement. The surge of diarrhoea may be in different forms; acute watery or bloody, persistent, and chronic diarrhea [1]. The intensity varies with the causative organisms and the predisposing factors or status of the host. A higher incidence of diarrhoea in sub-Saharan African countries is usually observed among children, particularly those that are less than 5 years of age. Studies have shown that diarrhoea accounts for about 1.3 billion cases with 4 million casualties yearly in children [2]. Commentaries from Nigeria indicate that a child that is less than 5 years of age may encounter yearly an average of 3-5 outbreaks of diarrhoea with nearly 150,000 deaths every year [1, 3].

In developing countries such as Nigeria, mortality associated with diarrhoea in this age group may be due to unswerving consequences or complications resulting from diarrhoea [1, 2]. Mortalities due to diarrhoea among children in developing countries are far beyond mortalities due to malaria, HIV/AIDS, and measles when put together [4]. As such, diarrheal diseases in this age group constitute a setback to the well-being of the populace.

Diarrhoea is caused by a wide array of microorganisms involving different species of bacteria, viruses, and parasites. The influence of these organisms in causing children's diarrhoea varies significantly from one locality to the other, which is subject to many factors such as socioeconomic and environmental requirements [1, 3]. Among the bacterial species, *Escherichia col*i is the most prominent species responsible for diarrhoea among children less than 5 years of age in sub-Saharan African countries [4, 5]. The *E. coli* strain responsible for diarrhoea is known as diarrheagenic *E. coli* (DEC). There are six (6) well-known DEC pathotypes namely; enterohemorrhagic *E. coli* (EHEC), also known as Shiga-toxin producing *E. coli* (STEC), enteropathogenic *E. coli* (ETEC), enterotoxigenic *E. coli* (ETEC), Enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), and diffusely adherent *E. coli* (DAEC). These pathotypes are differentiated by the expression of their unique cluster of virulence or genetic markers [6-8], the sites they establish themselves, the manner they establish infections, and the manifestations of the disease they cause [9].

Probable risk factors universally related to the transmission of DEC may include but are not limited to the followings; demographic, seasonal, indigent sanitation, and socioeconomic factors. Others may include the consumption of contaminated food and water and factors related to poor personal hygiene [9]. Because these factors are prominent in developing countries, DEC, therefore, is a disease that is common in developing countries.

Remarkably, because pathotypes of DEC are continually emerging and changing through the acquisition of transferrable hereditary traits, their occurrence, antibiotic susceptibility pattern, and epidemiologic characteristics and potentials differ from one territory to the other, even within the same geographical area. This, therefore, call for consistent surveillance [9, 10].

This systematic review, therefore, illustrates the distributions and prevalence of DEC pathotypes in Nigerian six geopolitical regions, their susceptibility to the commonly used antibiotics, and other characteristics of epidemiologic significance. This is useful in formulating and executing policies meant to regulate and lessen the burden of childhood diarrhoea in the country.

2. Materials and methods

2.1. Literature and sources of data

Google Scholar, PubMed, and African Journals online databases were used for the literature search. The criteria used for the search were based on "prevalence of diarrheagenic *E. coli* (DEC) in Nigeria", "genetic determinants of diarrheagenic *E. coli* pathotypes in Nigeria", and "Molecular detection of diarrheagenic *E. coli* pathotypes in Nigeria". The search phrase and keywords used include, but are not limited to, "diarrheagenic *E. coli* pathotypes and clinical samples in Nigeria", and "diarrheagenic *E. coli* pathotypes and non-clinical samples in Nigeria". "Diarrheagenic *E. coli* pathotypes and north-east (NE), northwest (NW), northcentral (NC), southeast (SE), southwest

(SW) and south-south (SS) Nigeria were also searched". "The outcomes of each search were evaluated by the authors.

2.2. Study selection criteria

Only cross-sectional full-text research articles reporting the prevalence of DEC pathotypes in any region of Nigeria by molecular technique from clinical and non-clinical sources were included in this systematic review. Articles that reported the detection of DEC by phenotypic methods or without a clear prevalence rate were excluded from the study. Similarly, all review articles were also not included in this study (Figure 1).

2.3. Data extraction

An archive was established to include study location, sample sources, year of publication, design types (experimental and control), targeted population, sample size, number of DEC detected, distribution and prevalence of DEC pathotypes, the most prevalent, among others as shown in Table 1 &2, and Figure 2

2.4. Statistical analysis

The data obtained were evaluated and organized in percentages. The relationship between DEC prevalence and gender, age group, study design type, types of sample sources, and regional differences were analyzed by odds ratio using SPSS version 17.0. A significant level of <0.05 was considered a significant statistical difference for the parameters tested.

3. Results

3.1. Article distributions of DEC detected by molecular methods in Nigeria

Searches from the electronic databases generated a total of 141 articles. After the application of the inclusion and exclusion criteria, a total of 19 studies were employed for this systematic review as shown in figure 1.

The southern region had 52.63% (10/19) articles while the northern region had 47.37% (9/19) articles. These articles were derived from 12 States of the Federation including the Federal Capital Territory (FCT), Abuja. Based on regional distribution, 5 studies from NW documented the detection of DEC by molecular techniques, while NC, SE, and SW States documented 4 studies each. Whereas 2 articles were documented in the SS region, none were suitable for inclusion in the NE region.

In the NW region, DEC studies were documented in 3 (Kano, Kaduna, and Sokoto) of the 7 States of the region. In the NC region, DEC studies were recorded in Nasarawa State and the FCT, Abuja, with the majority in Abuja. In the SE geopolitical zone, DEC studies included in this study were derived from 3 States Ebonyi, Enugu, and Anambra. In the same vein, 2 States each from the SS (Edo and Bayelsa) and SW (Osun and Ondo) that documented the detection of DEC pathotypes using molecular techniques were equally included in this study.

3.2. Distribution of sample sources and types

Based on specimen types, 47.37% (9/19) and 52.63% (10/19) articles documented DEC from non-clinical and clinical sources respectively. Of the non-clinical sources, 44.44% (4/9), and 22.22 (2/9) were from NW and SS regions respectively, while 11.11% (1/9) each came from NC, SE, and SW regions. From the clinical sources, NC, SE, and SW regions documented 30.0% (3/10) articles each, while only 10.0% (1/10) were recorded from the NW region. The NE and SS geopolitical zones recorded no single article derived from clinical sources that met the criteria for inclusion in this study.

From the non-clinical sources, 2 articles (Osun and Kaduna) documented DEC pathotypes in water sources, while 3 studies (Sokoto, Bayelsa, and Edo) documented the detection of DEC pathotypes from ready-to-eat (RTE) foods. Other non-clinical samples in which DEC pathotypes were detected include vegetables, abattoir effluent, treated wastewater, and meats.

From the clinical sources, 80% (8/10) and 20% (2/10) of the articles documented the detection of DEC pathotypes from direct stool and rectal swabs respectively.

3.3. Study population

From the clinical sources' samples, 70% (7/10) of the studies targeted DEC detection in children especially those less than 5 years of age, while a study each from Nasarawa, Osun, and Enugu/Anambra States research on stool samples from patients of all age groups (Table 2).

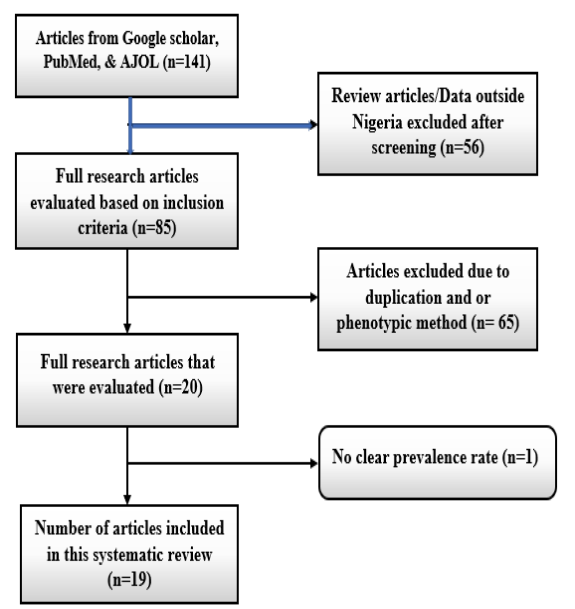

Fig. 1. Flow diagram summering the process of literature search and selection

3.4. Prevalence of Diarrheagenic *Escherichia coli* (DEC)

The reported prevalence of DEC in Nigeria from the articles used in this study range from 1.09 – 67.5%. From the accrued data of this study, however, the average mean sample size from both clinical (3654) and non-clinical (1351) sources was 5,005. Diarrheagenic *Escherichia coli* (DEC) detected from clinical (762) and non-clinical (179) sources were 941. Overall, the mean prevalence of DEC in Nigeria stands at 18.80% (Table 3). Of these, the mean prevalence from clinical and non-clinical sources was 20.85% and 13.25% respectively (Table 1 and 2). The result of the odds ratio and chi-square (OR=1.7252, CI=1.4462-2.0579, P=0.0001) showed that DEC is 1.7252 times significantly more likely to be detected in clinical than non-clinical sources (Table 4).

Only 30% (3/10) of the studied articles from clinical sources (1 each from NC, NW, & SE) relate explicitly the detection of DEC to the gender of the study populations. Two of the articles documented in males 27(57.45%) and 85(57.53%) detection of DEC when compared to 20(42.55%) and 63(42.57%) DEC in females respectively. Another study shows the detection of DEC in 59(57.84%) females than the male with 43(42.16%). In all instances, statistical tools were not used to demonstrate the level of significance. However, using the accrued data from these studies, the result of the odds ratio and the chi-square (OR=1.2624, CI=0.9464 – 1.6838) showed that DEC is 1.2624 times more likely to be detected in males than females, but with no statistical difference (P=0.1129) as shown in Table 4.

The prevalence of DEC based on regional differences or geopolitical zones documented 568(34.0%) and 373(15.59%) DEC in the southern and northern regions respectively. From there, the results of the odds ratio and chi-square (OR=2.1807, CI=1.8868 – 2.5205, P=0.0001) disclosed that DEC is significantly more detected in the Southern than in the Northern region (Table 4). Of these, SW States documented DEC with a 32.59% prevalence rate, whereas DEC with 22.21%, 18.77%, 15.62%, and 10.07% prevalence rates respectively was recorded in SE, NW, SS, and NC geopolitical zones (Table 3).

The prevalence rate in terms of age group revealed that DEC was detected in 526(22.93%) out of the 2294 children's stool and 236(17.36%) out of 1360 other age groups screened. Using the accumulated data from these studies, the result of the odds ratio and the chi-square (OR=1.4170, CI=1.1945 – 1.6809, P=0.0001) indicated that DEC is significantly more likely to be detected in children than in other age groups (Table 4).

3.5. Experimental Design

The experimental design from the literature used in this study was categorized into experimental and control groups. In studies involving clinical samples, 60% (6/10)

of the articles (3 from SW, and 1 each from NW, NC, and SE) designed their studies to include both experimental and control groups, while 40% (4/10) of the articles (2 each from NC and SE) design their studies without a control group (Table 1). A Control group was not used in the studies involving non-clinical samples (Table 2). Out of the total 2418 experimental tests or diarrheagenic stool samples screened in these studies, DEC was detected in 653 (27.01%) of the samples, while 109(8.74%) DEC was detected out of the 1236 control group samples. Furthermore, the result of the odds ratio and the chi-square (OR=3.8253, CI=3.0818 – 4.7482, P=0.0001) demonstrated that DEC is significantly more detected in experimental than control groups (Table 4). The pathotype EAEC was detected in 4(66.7%) out of the 6(60.0%) studies that included control groups in their studies, while the pathotype DAEC and EHEC/STEC was documented in a study each (Table 1). In the experimental group, however, EHEC/STEC was documented in 7(77.78%) out of the 9 studies that reported DEC from non-clinical sources, while EAEC was documented in 4(40.0%) out of the 10 articles that reported the detection of DEC from clinical samples.

Aside from this, some of the studies were designed to screen specifically a particular DEC pathotype; this was documented in 7 articles. Of these, 2(28.57%) and 5(71.43%) were from clinical and non-clinical sources respectively. Of those from non-clinical sources, 80% (4/5) of the articles concentrated their studies on the EHEC/STEC pathotype alone, particularly *E. coli* of the serotype 0157:H7, mostly in the NW region. whereas others were designed to screen for at least 5 or 6 of the known pathotypes; this was documented in 12 articles. Of these, 8(66.67%) and 4(33.33%) were from clinical and non-clinical sources respectively.

3.6. Prevalence and distribution of DEC pathotypes

Of the 762 DEC identified from clinical studies, 6 well-known DEC pathotypes were identified; 340(44.62%), 145(19.03%), and 83(10.89%) were categorized as EAEC, ETEC, and EPEC pathotypes respectively. Whereas 71(9.32%) each were identified as EIEC and EHEC/STEC, DAEC constitutes 17(2.23%) of the DEC from clinical sources. The hybrid pathotypes constitute 35(4.59%) of the total DEC detected from clinical samples (Table 1).

Furthermore, of the 179 DEC recovered from non-clinical sources, only 5 well-known DEC pathotypes were detected; they include 79(44.13%), 53(29.61%), and 20(11.17%) were identified as EHEC, ETEC, and EPEC respectively. Whereas 8(4.49%) each were identified as EAEC and EIEC, 11(6.15%) were acknowledged as hybrid pathotypes (Table 2).

Overall, of the 941 DEC encountered in this study, 348(36.98%), 198(21.04%), 150(15.94%), and 103(10.95%) were EAEC, ETEC, EHEC, and EPEC pathotypes respectively. Others include 79(8.39%) EIEC, and 17(1.81%) DAEC. The hybrid pathotype constitute 46(4.89%) of the total DEC (Table 1 and 2)

While EHEC/STEC, EIEC, and EPEC were documented in 14, 12, and 9 studies, EAEC and ETEC were each reported in 12 studies. Only a study from the SS region documented the detection of DAEC in a clinical sample. Hybrid pathotypes were registered in 3 studies, one each from Kaduna, Kano, and the Osun States. Two studies registered hybrid pathotypes from non-clinical sources, whereas a study reported the detection of hybrid pathotypes from clinical sources (Tables 1 and 2).

On the regional distribution of DEC pathotypes, the preponderance of EAEC pathovar from clinical sources was documented in NW, NC, and SW with a mean prevalence of 20.0% (90/450), 25.89% (29/112), and 68.02% (151/222) respectively, while EIEC pathovar was documented as the most prevalent DEC pathotype with 27.23% (55/202). From the non-clinical sources, the preponderance of STEC/EHEC pathovar was documented in NW, SW, and SS with a mean prevalence of 85.71% (18/21), 55.07% (38/69), and 42.31 (22/52), while ETEC pathovar was dominant in NC and SE regions respectively with 78.57% (11/14)

and 100% (23/23) mean prevalence rates (Tables 1 and 2).

Of the 9 articles that detected EPEC in their studies, only 5 studies from clinical studies (with a total of 50 EPEC) differentiated their isolated EPEC into typical and atypical EPEC. These include a study from NW(Kano), 2 from NC(Abuja), and 2 from SE(Ebonyi). While typical EPEC constitutes 76.0 % (38/50), atypical EPEC constitutes 24% (12/50) as shown in Table 1.

Also, 6 out of the 9 studies that detected DEC from non-clinical samples reported EHEC/STEC as the most predominant detected DEC pathotype; 4 of the articles were from the NW region (Table 2). Of these, *E. coli* of the serotype 0157:H7 was documented in 4 of the 6 articles.

3.7. Hybrid pathotype

A total of 46 hybrid strains were documented, which constitute a prevalence of 4.89 % of the total DEC detected. Of these, 6.15% (11/179), and 4.59% (35/762) were detected from non-clinical and clinical sources respectively. From the clinical sources, the hybrid DEC pathotypes were classified thus, 51.43% (18/35) EAEC/ETEC, 37.14% (13/35) EAEC/EPEC, and 11.43% (4/35) ETEC/EPEC, all derived from Kano State, Northcentral Nigeria. From the non-clinical sources, the hybrid pathotypes were categorized thus; 18.18% (2/11) STEC/EPEC, 45.46% (5/11) STEC/EHEC, 9.09% (1/11) EAEC/EPEC, 9.09% (1/11) EPEC/ETEC/STEC, documented from Osun State Southwestern Nigeria, while 18.18% (2/11) SubABEC (subtilase-producing *E. coli*; STEC that lost its Shiga toxin genes due to prolong storage) was documented from Kaduna State, Northwestern Nigeria (Figure 2).

3.8. Antibiotic susceptibility pattern of DEC pathotypes

Of the 19 articles in this study, 9(47.37%) documented the susceptibility of DEC to various antibiotics. Of these, 55.56% (5/9) and 44.44% (4/9) were articles whose samples were of clinical and non-clinical origin respectively. The number of antibiotics used on the DEC pathotypes ranges from 7-24 antibiotics. Some of these commonly used antibiotics include, but are not limited to amoxicillin, cotrimoxazole, gentamycin, ampicillin, tetracycline, streptomycin, imipenem, cefoxitin, cefotaxime, and ceftriaxone (Table 5).

From these, 4 (44.44%) studies documented that DEC pathotypes were mostly resistant to ampicillin followed by penicillin, and reduced susceptibility to cotrimoxazole and tetracycline was documented by two studies each. However, complete or high susceptibility of DEC to imipenem, gentamycin, and ofloxacin was registered by 4, 3, and 2 articles respectively. Aside from these, 3 (33.33%) studies each documented that EAEC and EHEC were the most resistant DEC pathotypes. The dominance of EPEC as the most resistant DEC pathotype was documented in 2 (22.22%) studies, while ETEC and or EIEC were reported as the most documented DEC pathotype a study each (Table 5).

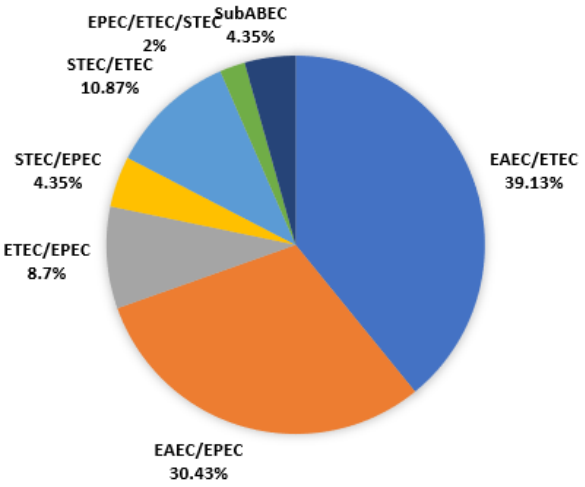

Fig. 2. Frequencies of hybrid DEC pathotype detected from both clinical and non-clinical sources

Table 1. Distribution of DEC pathotype from clinical sources

Region	State	Targeted population	Sample type	Design type	Total DEC	DEC pathotypes							Prevalent DEC	References
						EHEC	EPEC	ETEC	EAEC	EIEC	DAEC	Hybrid		
NW	Kano	Children (< 5yrs)	Rectal swab	Expt=400	165	0	13	39	79	0	0	34	EAEC	[11]
				Cont=50	18	0	2	4	11	0	0	1	EAEC	
				Total=450	183	0	15[a]	43	90	0	0	35	EAEC	
NC	Abuja	Children (< 5yrs)	Rectal swab	Expt=201	51	19	8[b]	7	16	1	0	0	EHEC	[12]
				Cont=529	10	0	1	4	5	0	0	0	EAEC	
				Total=730	61	19	9	11	21	1		0	EAEC	
	NSR	Gen patients	Stool	Expt=414	43	6	0	12	21	4	0	0	EAEC	[13]
	Abuja	Children (< 5yrs)	Stool	Expt=400	51	6	18[c]	16	8	3	0	0	EPEC	[14]
SE	Ebonyi	Children (< 5yrs)	Stool	Expt=80	54	0	5[d]	16	1	22	0	0	EIEC	[15]
	Ebonyi	Children	Stool	Expt=60	40	0	4[e]	12	8	16	0	0	EIEC	[16]
	Enugu/ Anambra	All age group	Stool	Expt=520	102	7	30	22	28	15	0	0	EPEC	[17]
				Cont=250	6	0	1	1	2	2	0	0	EAEC	
				Total=770	108	7	31	23	30	17	0	0	EPEC	
SW	Osun	Children (< 5yrs)	Stool	Expt=187	73	0	0	0	73	0	0	0	EAEC	[18]
				Cont=144	58	0	0	0	58	0	0	0	EAEC	
				Total=331	131				131	0	0	0	EAEC	
	Osun	Adults	Stool	Expt=113	70	23	0	10	18	7	12	0	EHEC	[19]
				Cont=63	15	4	1	2	2	1	5	0	DAEC	
				Total=176	85	27	1	12	20	8	17	0	EHEC	
	Ondo	Children	Stool	Expt=43	4	4	0	0	0	0	0	0	STEC	[20]
				Cont=200	2	2	0	0	0	0	0	0	STEC	
				Total=243	6	6	0	0	0	0	0	0	STEC	
				Expt=2418	653	65	78	134	262	68	12	34	EAEC	
				Cont=1236	109	6	5	11	78	3	5	1	EAEC	
				Total=3654	762	71	83	145	340	71	17	35	EAEC	

Legend: popn= population, prev=prevalent, Expt= experimental group, Cont= control group, Enu/Anam= Enugu/Anambra states, NSR=Nasarawa. **a**(tEPEC=8, aEPEC=7), **b**(tEPEC=14, aEPEC=4), **c**(tEPEC=8), **d**(tEPEC=5), **e**(tEPEC=4)

Table 2. Distribution of DEC from non-clinical sources

Region	State	Sample type	Sample size	No (%) DEC	DEC type	Prominent DEC type	References
Northwest	Kaduna	Water	80	3(3.75)	EHEC	EHEC	[21]
	Sokoto	Food product	175	10(5.71)	EHEC	0157:H7	[22]
	Kaduna	Meat	182	2(1.09)	EHEC	0157:H7	[23]
	Kaduna	Abattoir effluent/animal faeces	200	6(3.0)	STEC=3 EAEC=1 Hybrid=2	STEC	[24]
	TOTAL		637	21(3.29)	EHEC	EHEC	
Northcentral	Nasarawa	Irrigated vegetables	135	14(10.37)	ETEC=11 EHEC=1 EIEC=2	ETEC	[25]
	TOTAL		135	14(10.37)	ETEC	ETEC	
Southeast	Enugu	Treated wastewater	103	23(22.3)	ETEC	ETEC	[26]
	TOTAL			23(22.3)	ETEC	ETEC	
Southsouth	Bayelsa	RTE	300	33(11.0)	EPEC=13 ETEC=9 EAEC=6 EIEC=2 EHEC=3	EPEC	[27]
	Edo	Nono	33	19(57.58)	EHEC	0157:H7	[28]
	TOTAL		333	52(15.62)			
Southwest	Osun	Water	143	69(48.25)	STEC=35 EHEC=3 EAEC=1 EIEC=4 ETEC=10 EPEC=7 Hybrid=9	STEC	[29]
	TOTAL		143	69(48.25)		STEC	
	GRAND TOTAL		1351	179(13.25)			

Table 3. Regional prevalence of DEC in Nigeria

SN	Region	State	Sample type	Sample size	No (%) DEC	Regional Prevalence
1	Northwest	Kano	Clinical	450	183(40.67)	
2		Kaduna	Non-clinical	80	3(3.75)	
3		Sokoto	Non-clinical	175	10(5.71)	
4		Kaduna	Non-clinical	182	2(1.09)	
5		Kaduna	Non-clinical	200	6(3.0)	
		Total		1087	204	18.77
6	Northcentral	Abuja	Clinical	730	61(8.36)	
		Nasarawa	Clinical	414	43(10.39)	
		Abuja	Clinical	400	51(12.75)	
		Nasarawa	Clinical	135	14(10.37)	
		Total		1679	169	10.07
	Southeast	Ebonyi	Clinical	80	54(67.5)	
		Ebonyi	Clinical	60	40(66.67)	
		Enugu/Anambra	Clinical	770	108(14.03)	
		Enugu	Non-clinical	103	23(22.33)	
		Total		1013	225	22.21
	South-south	Bayelsa	Non-clinical	300	33(11.0)	
		Edo	Non-clinical	33	19(57.58)	
		Total		333	52	15.62
	Southwest	Osun	Clinical	331	131(39.58)	
		Osun	Clinical	176	85(48.29)	
		Ondo	Clinical	243	6(2.47)	
		Osun	Non-clinical	143	69(48.25)	
		Total		893	291	32.59
		Grand Total		5005	941	18.8

Table 4. Statistical values of some parameters

DEC variables	Parameters	DEC Positive	DEC negative	Odd ratio	95% CI	P-value
Sample Source	Clinical	762	2892	1.7252	1.4462-2.0579	0.0001
	Non-clinical	179	1172			
	Total	941	4064			
Gender	Male	155	230	1.2624	0.9464-1.6838	0.1129
	Female	142	266			
	Total	297	496			
Study design	Experimental group	653	1765	3.8253	3.0818-4.7482	0.0001
	Control group	109	1127			
	Total	762	2892			
Regional difference	Southern	568	1671	2.1807	1.8868-2.5205	0.0001
	Northern	373	2393			
	Total	941	4064			
Age group	Children	526	1768	1.4170	1.1945-1.6809	0.0001
	Others	236	1124			
	Total	762	2892			

Legend: CI= confidence interval, DEC=Diarrheagenic *E. coli*, DEC positive= number of samples that yielded DEC, DEC negative= number of samples that did not yield DEC.

Table 5. Antibiotic susceptibility of DEC in Nigeria

Region	State	Specimen	Antibiotics commonly used	Most resistant	Least resistant	References
NC	Nasarawa	Vegetable	amx, amc, ctx, cip, sxt, cn, fox, imp	sxt/EHEC	imp, cn/ ETEC	[25]
	Nasarawa	Stool	ESBL producers	EAEC & ETEC	EPEC	[13]
NW	Kaduna	Meat	amx, amc, pn, tet, s, sxt, cn, e, nit, kan	amp, pn/ EHEC	kan, cn	[23]
	Kano	Stool	cxm, cxt, caz, amc, cip, cn, sxt	sxt/EAEC	cn, cip	[11]
SE	Ebonyi	Stool	amp, amc, fox, imp, cip, lev	amp/EIEC	imp/ETEC	[15]
	Ebonyi	Stool	amp, amc, fox, imp, cip, lev, tet	tet/EPEC	imp/ETEC	[16]
SS	Bayelsa	RTE	amp, amc, s, imp, ctx, caz, cip, sxt, tet	amp/ETEC	Imp	[30]
	Edo	Nono	amp, pn, amc, cn, s, tet, imp, ctx, cip, sxt	amp/EHEC	cn, ofx	[28]
SW	Osun	Stool	sxt, amp, tet, s, cn, kan, cip, ofx, na	tet/EAEC	cip, ofx	[18]

Legend: ctx=cefotaxime, caz=ceftazidime, kan=kanamycin, e=erythromycin, nit=nitrofurantoin, pn=penicillin, lev=levofloxacin, amp=ampicillin, sxt=cotrimoxazole, imp=imipenem, fox=cefoxitin, cn=gentamycin, s=streptomycin, tet=tetracycline, cip=ciprofloxacin, amx=amoxacillin, amc=amoxacillin-clavulanic acid, cxm=cefuroxime, na=nalidixic acid

4. Discussion

The survey of works of literature in this study suggests that DEC, the causative pathovars of diarrhoea are mostly acquired from ready-to-eat foods and other food products, water, poor sanitary environment, and indigent hygiene. This implies that diarrhoea infections can be checked when adequate sanitation and potable water are provided, including improved personal and community hygiene.

The results of the DEC prevalence rate irrespective of the geographic regions and sampling sources in this study stand at an average of 18.8%. This can be comparable to the DEC prevalence rate of 20.0% documented in Burkina Faso [31]. A higher DEC prevalence of 45.0% was documented also in Burkina Faso [32]. However, prevalence rates of DEC lower than the one documented in this study were reported in various African and Asian countries. These include 14.7% [33], 13.8% [34], 10.5% [35], 7.8% [36], and 6.8% [37] documented in Burkina Faso, Mozambique, Tanzania, Côte d'Ivoire, and China respectively. The difference in the DEC prevalence between the present study and the comparatives could be due to variations in the geographical area, methods used, sanitation, and hygienic status of the different study locations.

The 18.8% mean prevalence rate documented in this study suggests the need for awareness in the local communities and hospitals on good personal and community hygiene practices, including the provision of potable water and enhanced sanitation to further mitigate the spread of childhood diarrhoea in Nigeria. Results from the systematic review showed that DEC is detected more in clinical than non-clinical sources. This could be because there were more clinical-based research studies in the articles considered for this study. It could also be because the clinical sample (stool) used in the isolation of *E. coli* serves as a better environment for the proliferation of DEC than samples from non-clinical sources. This also suggests that research in Nigeria is mostly concentrated on DEC isolated from clinical than non-clinical sources.

The findings of this systematic review revealed that most of the targeted population were children. The results further show the preponderance of DEC among age groups less than 5 years of age than other age groups. This corroborates reports from previous findings in Côte d'Ivoire [36], Mozambique [38], and Burkina Faso [33] which revealed that children that fall within this age group represent the most endangered population that are susceptible to diarrhoea caused by DEC [36]. This could be attributed to the underdevelopment of their innate and acquired immune system, and indigent hygiene status. Contrary to the finding of this study and many other studies in Africa, a study from China documented the preponderance of DEC in adult populations more than in children [39].

The higher detection of DEC in males than females in this study suggests that male children are more predisposed to sources of infection with DEC. However, the lack of statistical difference connotes that both genders are equally liable to sources of infection with DEC. This implies that childhood gender may not be a risk factor for infection with DEC.

The finding of this study also revealed that DEC prevalence is higher in the southern than northern regions of Nigeria. This may not be due to a lack of awareness or consciousness of the DEC mode of transmission in the region but could be attributed to the higher number of research on DEC in that region.

The results of the DEC pathotypes in this study show the preponderance of EAEC pathovar over other pathotypes, especially from clinical sources. This suggests that the EAEC pathovar is the most common pathovar associated with diarrhoea in Nigeria. This insinuation not only corroborates previous reports from Côte d'Ivoire [36], Kenya [40],

Tanzania [41], Peru [42], and Burkina Faso [31, 40] but also demonstrates that this pathovar is becoming more prominent and relevant as the etiologic agent of diarrhoea in developing countries like Nigeria [11].

Other countries of the world that documented the preponderance of EAEC pathovar over other DEC pathotypes in causing diarrhoea include China [39], Iran [43], Mozambique [34], and Mexico [44].

Interestingly and also a matter of concern was the fact that the prominent DEC pathotype (EAEC) in the experimental subjects was also the predominant pathovar in the control group. This phenomenon is consistent with reports of various investigations in other countries of the world and has been attributed mostly to developing countries of the world due to their impoverished socioeconomic and hygiene status [45]. However, this phenomenon is disturbing and confusing and constitutes a subject of discussion from different quarters on the aptitude of EAEC to induce diarrhoea. Of late, however, EAEC was not only restricted to travelers' diarrhoea but has also been documented as the causative agent of severe and persistent diarrhoea among individuals whose immune system is not well developed or compromised [32, 36]. More to this, numerous occurrences of diarrhoea in children involving EAEC pathovar were previously reported in various countries of the world, particularly Japan, and Europe, among others [46]. This, therefore, confirmed the pathogenicity of EAEC pathovar and also revealed that the ability of EAEC pathovar to induce diarrhoea varies with different geographical locations. Because the EAEC pathovar is mostly detected in human clinical stool than in non-clinical sources, it, therefore, suggests that this pathovar has an edge in our hospitals and human populations. This observation was supported by previous studies which reported that EAEC pathovar is well adapted to humans than other animal species or inanimate specimens [24].

In contrast to the observations of this review, other studies reported the preponderance of ETEC pathovar in causing childhood diarrhoea than other pathotypes. These include a study from Ghana[9], Gabon [47], and Bulgaria [48]. Another study from South Africa reported the detection of DAEC as the most prominent DEC in their study area [49].

The preponderance of typical EPEC from this study corroborates reports of previous studies from Tanzania [41] but contradicts reports of some other studies from Côte d'Ivoire [36], Vietnam [50], and Brazil [51]. This suggests that EPEC pathovar associated with diarrhoea in Nigeria is caused by the typical EPEC. Enteropathogenic *E. coli* (EPEC) are diarrheagenic *E. coli* that harboured the chromosomal encoded locus for enterocyte effacement (LEE) but lack the phage-borne Shiga toxins of EHEC. The presence of the virulence markers intimin (*eae*) and bundle-forming pili (*bfp*) on typical EPEC differentiate them from atypical EPEC that only have intimin (*eae*) coding genes [9].

The regional distribution of DEC pathotypes demonstrates the preponderance of 4 DEC pathotypes, namely EAEC, STEC/EHEC, ETEC, and EIEC. These differences portrayed the dominance of those pathotypes in each of the regions. It also suggests differences in risk factors and hygiene status.

The dominance of STEC/EHEC in the northern region could be due to its rich agricultural activities, especially its dominance in livestock farming over other regions. Studies have shown that a variety of animal species such as cattle, and sheep, asymptomatically harbour STEC/EHEC in their gastrointestinal tract [52]. Remarkably, even some of the serotypes of STEC such as 0157:H7 associated with infections in humans have also been isolated from animal species such as cattle and sheep [52, 53]. Possibly, this may be the reason that sparks so much interest or research on STEC/EHEC in the northern region. Moreso, the high detection of STEC/EHEC from environmental samples such as water, vegetables, and food products mostly in Northern Nigeria constitutes a public health concern. This is because this pathovar can live longer in various environmental samples, which then serves as

significant means through which they are spread to human populations [46, 54].

Diffusely adherent *E. coli* (DAEC) was the least occurring DEC pathotype in this study, and surprisingly only 1 out of the 19 studies included in this review attempted detecting the pathovar from a stool sample. This could be because many authors do not acknowledge or recognized this pathovar as one of the DEC pathotypes. More so, studies have shown that investigations into the epidemiologic characteristics of this pathovar are often impeded due to the challenges involved in its detection and classification [46, 55].

One of the remarkable observations of this review study was the detection of hybrid pathotypes. Hybrid pathotypes are pathotypes that are not easily or distinctly classified into a particular pathovar due to the possession of coding or virulent genes that expressed the characteristics of more than one pathotype. Studies have shown that the evolutionary phenomenon that leads to the development of hybrid DEC strain could be due to the acquisition of coding genes of one DEC pathotype by a different DEC pathotype through the horizontal movement of genetic materials [47, 56]. We, therefore, hypothesize that continual hybridization and exchange of genetic elements between DEC pathotypes may in the future lead to the evolution and emergence of novel DEC pathotypes with potentials and characteristics that may surpass those of the current pathotypes.

The most common hybrid detected in this study is the EAEC/ETEC combination. This was consistent with studies in Burkina Faso [33], Kenya [57], and India [58]. In Mozambique however, the EAEC/EPEC hybrid was documented as the common hybrid responsible for diarrhoea among children [34]]. Studies have shown that hybridization between EAEC and ETEC is on the rise [56, 59]. The reason for the rise was said to be because EAEC pathovar easily incorporates or assimilates other virulence determinants to engender epidemic strains [47, 60]. This phenomenon is particularly significant as the pathogenic potentials of the hybrid and the host range may be enlarged. This, therefore, call for regular surveillance to avoid a possible outbreak of diarrhoea.

The rate at which DEC pathotypes are increasingly exhibiting resistance to antimicrobial agents is quite pathetic, especially in socioeconomic impoverished countries like Nigeria. This is brought about by the lack of effective antibiotic stewardship which as a result enhances the easy accessibility of drugs and drug outlets even without the recommendations of qualified and authorized medical personnel. This subsequently leads to the haphazard use of antimicrobials [49, 61].

The high resistance of DEC to ampicillin, penicillin, cotrimoxazole and tetracycline as shown by the results of this study was consistent with the findings of various studies across the globe [42, 49, 50]]. High resistance to these antibiotics could be due to self-medication and unrestricted use of these antimicrobials.

In this study also, the susceptibility of DEC to imipenem, gentamycin, and ofloxacin was in some instances complete or high. This can be compared with some studies from South Africa [49] and Iran [62] that reported high susceptibility of DEC pathotypes to these antibiotics. The low resistance of DEC pathotypes to these antimicrobials could be because they are not easily accessible due to their relatively high cost.

5. Conclusion

The dominance of EAEC in the country, and the regional superiority of other pathovars highlight the fact that these pathotypes may be responsible for childhood diarrhoea and other forms of gastrointestinal disorders in Nigeria. Moreso, the mean prevalence rate and the regional distribution of the DEC pathotypes, including their high resistance to antibiotics often used in the treatment of diarrhoea calls for concern, and highlight the need for surveillance, improved sanitation, personal and community hygiene, and provision of potable water to mitigate the occurrence of childhood diarrhoea and other disorders caused by DEC.

Abbreviation

DAEC : Diffusely Adherent *E. coli*
DEC : Diarrh-Eagenic *E. coli*
EAEC: Entero-aggregative *E. coli*
EHEC : Entero-Hemorrhagic *E. coli*
EIEC : Entero-Invasive *E. coli*
ETEC : Entero-Pathogenic *E. coli*
ETEC : Entero-Toxigenic *E. coli*
NC: North-Central
NE: North-East
NW: North-West
SE: South-East
SS: South-South
STEC : Shiga-toxin producing *E. coli*
SW: South-West

Conflict of Interest

The authors hereby declare that they have no conflict of interest.

Authors' Contribution

The study was designed by author M.Y.T. who wrote the first draft of the manuscript. Author, J.F. and M.S.P. supervised and corrected the draft. All authors read and approved the final draft

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

Ethics approval and consent to participate

The authors did not use human or animals in the research

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