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Antibiotic Susceptibility Profile and Prevalence of AmpC among Clinical Bacterial Isolates obtained From Northwestern Nigeria

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Abstract

Antibiotic Resistance is spreading all over the world conferring multiple resistant in the treatment and management of life threatening infections. Cephalosporins are antibiotics prescribed daily for a wide variety of infections in Nigerian hospitals. The production of bla-AmpC enzymes by many *Enterobacteriaceae* conferred resistance to such class of antibiotics. The aim of the study is to determine the antibiotic susceptibility and prevalence of AmpC among clinical bacterial isolates obtained from Northwestern Nigeria. A total of 1000 clinical bacterial isolates were collected from seven states of north western Nigeria and were screened Phenotypically for AmpC production using Disk Approximation test. Antibiotic sensitivity test was performed according to clinical and laboratory standard Institutes guidelines (CLSI). *Acinetobacter baumanii, Serratia liquefaciens* and *Providence sp* showed 100% resistance to third generation cephalosporin antibiotics as well as Levofloxacin, Impinem and Tigercycline, moderate susceptibility was observed with Colistin, followed by *Proteus Mirabilis* (85%) resistance to Ceftizoxime. Tigercycline and Colistin were the most active drugs against the Isolates. The prevalence of AmpC production among the isolates showed that *Acinetobacter baumanii, Aeromonas sp., Providence sp., Serratia liquefaciens* and *Citrobacter freundi* had the highest prevalence of 100% each. *Enterobacter clocae* had least value of 50%. Similarly, high Multi-Drug Resistance (MDR) 100% was shown by *A. baumannii*, *Aeromonas sp*, *Providence sp* and *S. liquefaciens* with least values from *Staphylococcus aureus* (33.1%). The occurrence of AmpC was higher among male patients with prevalence rate of 54.1%, p-value >0.001.The occurrence of these resistance conferring enzymes was chronologically sensitive as its prevalence is more pronounced among patients aged >60 years (64.5%) with least value among patients aged 21-30 years (23.1%), (p-value>0.001). The trend in the prevalence of AmpC production and MDR resistance among the states of Northwestern Nigeria is in the following order: Sokoto>Kaduna>Katsina>Kebbi>Kano>Jigawa>Zamfara. The results from this study implied that, AmpC production is on the increase in Northwestern Nigeria and that the spread of these resistance conferring enzymes among bacterial isolates is an issue of public health concerned. Therefore, proper monitoring and surveillance for proper prevention and infection control may limit the further spread of these isolates.

Keywords: Antibiotics, Bacteria, Isolates, AmpC, Northwest, Nigeria, MDR

Seven different antibiotic discs:

INTRODUCTION

There is an increasing concerned over the rising prevalence of multidrug-resistant bacteria among patients posing greatest challenges to quality healthcare delivery with a greater burden on developing nations, accounting for a large proportion of hospital-acquired infections (Conen *et al.*, 2015; Okoche *et al.*, 2015; Mofolorunsho *et al.*, 2021). Previous studies have highlighted the magnitude of infectious diseases in the human population (WHO, 2012; Andersson *et al.*, 2014). Most of infectious diseases were treated using antibiotics. However, these antibiotics have become less effective or even ineffective; resulting in an accelerating global health emergency that is rapidly outpacing available treatment options (WHO, 2014). This problem is escalating daily in Nigeria due to antibiotic self-prescription, poor sanitary conditions even at our hospitals setting as well as ignorance (Hadi *et al.*, 2006). The global spread of antibiotics resistance among bacterial pathogens is a serious threat to public health. It poses a threat to modern medicine with significant impact on health care cost (Pitout and Laupland, 2008). Resistant bacteria therefore lead to an increase in morbidity and mortality since it increases the risk of inappropriate therapy (Kapil, 2005; Levy *et al.*, 2009).

This resistance may delay and hinder treatment, resulting in complications or even death (FairandTor, 2014; Prestinaci *et al.*, 2015). A recent report estimated that 10 million deaths will be attributed to antimicrobial resistance by 2050 and 100 trillion USD of the world's economic outputs will be lost if substantive efforts are not made to contain this threat (O'Neill, 2016; WHO, 2017).

ß-lactam antibiotics are the most common treatment for bacterial infections. Production of ß-lactamases is the main mechanism of bacterial resistance to these classes of antibiotics (Kotra *et al.*, 2002). The ß-lactam antibiotics are widely used antibiotics in the treatment and management of infectious diseases in Nigerian hospitals (Yusuf and Arzai, 2011). The cephalosporins were among the antibiotics daily prescribed for a wide variety of infections. Their well-known quality is widely accepted, they have lesser allergenic reactions and toxicity. Also, they are group of antibiotic with broad spectrum of activity, most of the cephalosporins prescribed daily in Nigeria, are the third generation cephalosporins particularly in the surgical departments as preferred choice for prophylaxis (Yusuf and Arzai, 2011). The high levels of chromosomal enzymes as well as plasmid – mediated ß-lactamases produced by several bacterial species are the major cause of cephalosporin resistance (Dancer, 2001). AmpC ß-lactamases are class C cephalosporinases that mediate bacterial resistance to cephalosporins and cephamycins. They also exhibit low rates of monobactam, cefepime and carbapenem hydrolysis (Fouch, 2015) and usually resist the inhibition by clavulanic acid (Agouri, 2014). Normally, AmpC is a chromosomal encoded ß-lactamase that is regulated by ampR gene and expressed constantly (Abdelrahman *et al.*, 2020). Ironically, in the North-western Zone of Nigeria there is continuous and high usage of cephalosporin antibiotics with lack of proper attention to detect the enzymes which results in treatments failure. This study therefore aimed at studying the antibiotic susceptibility profiles and prevalence of AmpC among clinical bacterial isolates obtained from the Seven States of North – Western zone of Nigeria.

MATERIALS AND METHODS

Collection of Clinical Isolates

A total of one thousand (1000) clinical bacterial isolates were collected from Teaching Hospitals and Federal Medical Centers across Northwestern Nigeria. The samples were collected from sixteen different wards from 2018 to 2020. The taxonomic identities of isolates were confirmed by combinations of Gram- staining, microscopy and Biochemical tests. The colonial appearance of the bacterial isolates was also examined on CLED, McConkey and Chocolate Agar. The features observed include size, odor, and pigmentation in accordance with methods described by Cheesebrough (2010).

The isolates obtained were; *Acinetobacter baumannii, Aeromonas spp, Burkholderia cepacia, Citrobacter freundii, Enterococcus faecalis, Elizabethkingia meningoseptica, Enterobacter clocae ,Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Proteus vulgaris, Providence sp, Staphylococcus epidermidis, Salmonella spp, Serratia liquefaciens, Staphylococcus aureus* and *Vibrio cholerae*.

Antibiotics Susceptibility Testing

The antibiotic susceptibility tests carried out on all the clinical isolates collected according to (CLSI 2019) guidelines. The zone diameter of each antibiotics used were measured in millimeter and interpreted as resistance, intermediate and susceptible according to CLSI guidelines (2019). Seven different antibiotic discs: Ceftriaxone (30µg), Ceftazidime (30µg), Cefixime (30µg), Levofloxacin (30µg), Tigercycline (30µ), Impinem (10µg) and Colistin (10µg) (Oxoid, UK) were used for the antibiotic susceptibility tests with *Escherichia coli ATCC 25922* strain used as the control.

Screening of AmpC

Using sterile wire loop, 4 discrete colonies were picked and emulsified in a sterile normal saline in sterile test tube. The turbidity of normal saline was matched with the turbidity of 0.5 McFarland's standard solution. Using sterile cotton swab stick, the swab stick was dipped into the suspension of the test organism and the excess fluid was removed by pressing and rotating the swab against the side of the test-tube above the suspension level and it was then streaked on the surface of blood agar plate. The plate was inoculated with the suspension. Cefoxitin (30µg) discs placed at the center of the inoculated plate; the plates were inverted and incubate at 35˚C overnight. After overnight incubation the plate was interpreted as, zone of 18mm or less than 18mm around the 30µg cefoxitin disk showed positive result. Mcfarland suspension of ATCC *E. coli* 25922 was inoculated on to the surface of Mueller Hinton (Oxoid, UK) plate. Cefoxitin (30µg) disc (Oxoid, UK) was placed on the inoculated surface of the agar (Cheesbrough, 2010).

Confirmatory Test for AmpC production

Bacterial suspensions were prepared Using sterile wire loop were 4 discreet colonies were picked and emulsified in a sterile normal saline in sterile test tube. The turbidity of normal saline was matched with the turbidity of 0.5 McFarland's standard. Sterile swab stick was dipped into the suspension of the test organism and excess fluid was removed by pressing and rotating the swab against the side of the test tube above the suspension level, then streaked on the surface of Mueller Hinton agar plate inoculated with the bacterial suspension. Using Ceftazidime 30µg disc at the center of the plate, and cefoxitin 30µg, imipenem 10µg and amoxicillin-clavulanic disc 30µg at 20mm distance away from ceftazidime disc. The plates were inverted and incubated at 35˚C overnight and the plates were read for any blunting or flattening of zone of inhibition between the ceftazidime disc and any of antibiotic discs Appearance of blunting or flattening of the zone, indicates positive result for *Amp*C production (Gunjan *et al.,* 2016).

Data Analysis

Statistical analysis software (SAS, 2012) was used as the statistical package. Prevalence of Cephalosprins resistant isolates was analyzed in frequency and percentages while Chi-square was used to test for the level of association at 5% level.

RESULTS

The Antibiotic susceptibility among clinical isolates obtained in Northwestern Nigeria is presented in Table 1. The result showed that, the clinical bacterial isolates were resistant to the third generation cephalosporin antibiotics (ceftazidime, ceftriaxone, cefoxitin, and cefpodoxime) commonly prescribed in the Northwestern hospitals. However, majority of the isolates showed resistance to imipenem, levofloxacin, tygercyline and colistin. *Providence sp* and *Serratia liquefaciens* were totally resistant to majority of the antibiotics used but showed activity to tigercycline and colistin respectively.

However, the result for AmpC production among the clinical isolates (Table 2) revealed that 51.3% of the screened isolates produced AmpC enzymes and 49.7% were Multidrug Resistance (MDR). The highest prevalence of AmpC was found in *A. baumannii, Aeromonas spp, Providence sp* and *Serratia liquefaciens* (100%) followed by *Citrobacter freundii* and *E. faecalis* (66.7%). *Burkholderia capacia* and *Elizabethkingia meningoseptica* had the least AmpC prevalence (0.0%), with *p-value >0.005*

The highest prevalence of MDR among 1000 clinical bacterial isolates were found in *A. baumanii, Aeromonas spp, Providence spp* and *Serratia liquefaciens* (100%) followed by *Proteus mirabilis* (76.2%) and *Citrobacter freundii (*66.7%), with *p-value<0.005*

Furthermore, these resistant isolates (Table 3) were found to occur more frequently in males (54.1%) and higher among old aged greater than 60 years (64.5%) followed by 41-50 years (63.5%). The least number of occurrences was found among those aged 21-30 years. With *p-value >0.005.*The highest prevalence of cephalosporins resistant isolates was found among isolated derived from Sokoto state with 73.6% occurrence followed by Kaduna (60.1%). The least was found among isolates from Zamfara (34.2%), with *p-value >0.005,* therefore, significant.

Similarly, the result for the distribution of AmpC producing isolates is shown in Table 4. The result indicated highest prevalence among isolates obtained from Emergency pediatric unit (EPU) and Female Medical ward (FMW) with 75.9% relative occurrence. The least occurrence was found in isolates from Intensive Care Unit (ICU) (25.0%).

Table 1: Percentage of Antibiotic Resistant Isolates Collected from Northwest Nigeria

	Resistant (%)							
Isolates	CAZ	CRO	CFM	FOX	LEV	TGC	CT	IMP
Acinetobacter baumannii	0 (0.0)	1(100.0)	1(100.0)	1(100.0)	0 (0.0)	1(100.0)	0 (0.0)	1(100.0)
Aeromonas spp,	2(66.7)	3(100.0)	3(100.0)	2(66.7)	3(100.0)	1(33.3)	0 (0.0)	0 (0.0)
Burkholderia cepacia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Citrobacter freundii	4(44.4)	5(55.6)	6(66.7)	3(33.3)	5(55.6)	3(33.3)	1(11.1)	1(11.1)
Enterococcus faecalis	1(33.3)	1(33.3)	2(66.7)	2(66.7)	0 (0.0)	1(33.3)	1(33.3)	1(33.3)
Elizabethkingia meningoseptica	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Enterobacter clocae	5(50.0)	5(50.0)	6(60.0)	5(50.0)	4(40.0)	4(40.0)	2(20.0)	1(10.0)
Escherichia coli	181(46.1)	243(62.3)	292(74.9)	177(45.4)	232(59.5)	127(32.6)	65(16.7)	91(24.9)
Klebsiella oxytoca	27(67.5)	22(55.0)	27(67.5)	21(52.5)	17(42.5)	9(22.5)	4(10.0)	5(12.5)
Klebsiella pneumonia	91(55.2)	106(64.2)	113(68.5)	86(52.1)	78(47.3)	50(30.3)	24(14.6)	36(21.8)
Pseudomonas aeruginosa	20(41.7)	29(60.4)	38(79.2)	26(54.2)	21(43.8)	17(35.4)	7(14.6)	15(31.3)
Proteus mirabilis	10(47.6)	15(71.4)	18(85.7)	14(66.7)	11(52.4)	12(57.1)	3(14.3)	5(23.8)
Proteus vulgaris	19(42.2)	21(46.7)	36(80.0)	20(44.4)	17(37.8)	9(20.0)	11(24.4)	8(17.8)
Providence spp	1(100.0)	1(100.0)	1(100.0)	1(100.0)	1(100.0)	0 (0.0)	0 (0.0)	1(100.0)
Staphylococcus epidermidis	1(50.0)	1(50.0)	1(50.0)	1(50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(50.0)
Salmonella spp	7(35.0)	9(45.0)	8(40.0)	7(35.0)	5(25.0)	3(15.0)	3(15.0)	1(5.0)
Serratia liquefaciens	1(100.0)	1(100.0)	1(100.0)	1(100.0)	1(100.0)	1(100.0)	0 (0.0)	1(100.0)
Staphylococcus aureus	83(35.3)	89(37.9)	125(53.2)	104(44.3)	83(35.3)	60(25.5)	33(14.0)	33(14.0)
Vibrio cholera	1(33.3)	1(33.3)	3(100.0)	2(66.7)	0 (0.0)	0 (0.0)	1(33.3)	0 (0.0)

Key: CAZ-Ceftazidime, LEV-Levofloxacin, TGC-Tygercyline, CT-Colistin, IPM-Imipenem, CRO -Ceftrioxone CFM-Ceftizoxime, FOX-Cefoxitin.

Table 2: Prevalence of AmpC Production and MDR among Bacterial Isolates from Northwestern Nigeria

Isolates	***AmpC producers***		***MDR Bacteria***	
	No. Examined	***Positive (%)***	***No. Examined***	***Positive (%)***
Acinetobacter baumannii	*1*	*1(100)*	*1*	*1(100)*
Aeromonas spp,	*2*	*2(100)*	*2*	*2(100)*
Burkholderia cepacia	*1*	*0(0.0)*	*1*	*0(0.0)*
Citrobacter freundii	*9*	*6(66.7)*	*9*	*6(66.6)*
Enterococcus faecalis	*3*	*2(66.7)*	*3*	*1(33.3)*
Elizabethkingia meningoseptica	*1*	*0(0.0)*	*1*	*0(0.0)*
Enterobacter clocae	*10*	*5(50.0)*	*10*	*6(60.0)*
Escherichia coli	*390*	*248(63.6)*	*390*	*224(57.4)*
Klebsiella oxytoca	*38*	*27(71.1)*	*38*	*20(52.6)*
Klebsiella pneumonia	*167*	*111(66.5)*	*167*	*86(51.5)*
Pseudomonas aeruginosa	*47*	*29(61.7)*	*47*	*26(55.3)*
Proteus mirabilis	*21*	*17(80.9)*	*21*	*16(76.2)*
Proteus vulgaris	*44*	*26(59.1)*	*44*	*18(40.9)*
Providence spp	*1*	*1(100)*	*1*	*1(100)*
Staphylococcus epidermidis	*2*	*0(0.0)*	*2*	*1(50.0)*
Salmonella spp	*20*	*9(45.0)*	*20*	*8(40.0)*
Serratia liquefaciens	*1*	*1(100)*	*1*	*1(100)*
Staphylococcus aureus	*239*	*0(0.0)*	*239*	*79(33.1)*
Vibrio cholera	*3*	*2(66.7)*	*3*	*1(33.3)*
Total	***1000***	***513(51.3)***	***1000***	***497(49.7)***

Table 3: Distribution of AmpC Production and MDR Bacteria Based on Demographic Factor and Hospital in Northwest Nigeria

	AmpC producers		MDR Bacteria	
Gender	**No. Examined**	**Positive (%)**	**No. Examined**	**Positive (%)**
Female	481	255(53.0)	481	233(48.4)
Male	519	281(54.1)	519	264(50.9)
Total	1000	536.0(53.6)	1000	497(49.7)
Df		**1**		**1**
X^2		**0.128**		**0.588**
P. value		**0.721**		**0.443**
Age range				
<1	53	30(56.6)	53	28(52.8)
1-10	127	73(57.5)	127	73(63.1)
11-20	54	30(55.6)	54	51(57.4)
21-30	269	124(23.1)	269	112(41.6)
31-40	245	120(49.0)	245	127(51.8)
41-50	115	73(63.5)	115	60(52.2)
51-60	75	46(61.3)	75	30(40.0)
>60	62	40(64.5)	62	49(79.0)
Total	1000	536(53.6)	1000	497(49.7)
Df		**7**		**7**
X^2		**18.523**		**16.851**
P- value		**0.010**		**0.018**
Hospital				
AKTH	229	122(53.3)	229	113(49.3)
Jigawa	141	58(41.1)	141	43(30.5)
Kebbi	108	60(55.6)	108	61(56.5)
Katsina	142	80(56.3)	142	63(44.4)
Sokoto	121	89(73.6)	121	96(79.3)
Zamfara	111	38(34.2)	111	58(52.3)
	148	89(60.1)	148	63(42.6)
Zaria				
Total	1000	536(53.6)	1000	497 (49.7)
X^2		48.064		70.234
Df		6		6
P-value		0.000		0.000

Table 4: Distribution of AmpC Production and MDR Bacteria Collected from Different Hospital Wards in Northwestern Nigeria

	BlaAmpC producers		MDR Bacteria	
Ward	**No. Examined**	**Positive (%)**	**No. Examined**	**Positive (%)**
A&E	55	29(52.7)	55	26(47.3)
ANC	17	8(47.1)	17	6(35.3)
ENDO	2	1(50.0)	2	1(50.0)
ENT	7	5(71.4)	7	5(71.4)
EPU	53	33(75.9)	53	31(58.5)
FMW	58	44(75.9)	58	29(50.0)
FSW	30	13(43.3)	30	15(50.0)
GOPD	488	243(49.8)	488	230(47.1)
GYNAE	88	45(51.1)	88	1(25.0)
ICU	4	1(25.0)	4	1(15.0)
MMW	63	40(63.5)	63	31(49.2)
MSW	67	35(53.7)	67	37(55.2)
Orthopedic	3	1(33.3)	3	2(66.7)
PNW	33	20(60.6)	33	16(48.5)
SCBU	15	6(40.0)	15	8(53.3)
Urology	17	11(64.7)	17	13(76.5)
Total	1000	536(53.6)	1000	497(49.7)

DISCUSSION

The high prevalence of cephalosporins resistance among clinical bacterial isolates reported by the present study agrees with the findings of Mofolorunsho *et al*. (2021) who reported similar finding among clinical bacterial isolates obtained from selected hospitals of Anyigba, Nigeria. This high prevalence can be attributed to improper diagnosis and misuse of antibiotics in the study area. The prevalence is higher among the males than females. The findings in table 3 also corroborates with that of Gashe *et al*. (2021) who reported high prevalence of cephalosporins resistance among isolates obtained from males. The high frequency of AmpC production among the isolates is in line with the work of Abdelrahman *et al*. (2020) who reported high frequency of ESBLs genes encoding the production of AmpC production. However, this finding contradicts that reported in pune, India by Grovera *et al*. (2013) where Ampc frequency was very low (14.8%).

The increase rate of Antibiotic resistance among the *Enterobacteriacea* is a remarkable example of how bacteria can secure, sustain and evince new genetic information that can confer resistance from one antibiotic to several classes of antibiotics. AmpC ß-lactamases are clinically important cephalosporinases encoded on the chromosomes of many *Enterobacteriaceae,* and also in few other gram-negative bacteria.Amp C ß-lactamases can be chromosomally or plasmid mediated and they showed an enormous variation in geographic distribution worldwide. Prevalence of cephalosporinase production among *K.pneumonieae* in This finding is in conformity with the finding by Critchley *et al*. (2019) in spero therapeutic, Iowa USA who reported *E. coli* as the predominant organism and resistant to third generation cephalosporins with percentage prevalence of 54.9%. This is also similar to the recent finding of Sebastian *et al*. (2021) in Kerala, India were *E.coli* and *K. pnemoniae* were also found to be resistant to third generation cephalosporin indicating production of cephalosporinases. Similarly, Egbule and Odih (2020) reported AmpC among *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* among clinical isolates obtained from hospitalized children in Abraka and Eku communities, Delta State, Nigeria.

The overall percentage prevalence of cephalosporin resistance in seven state of Northwest Nigeria was 53.6%. This finding is in contrast to that of Saarwar *et al*. (2019) in Pakistan where the percentage prevalence of 16% was reported. This is probably due to the low economic income of the north western region and of high population thus higher outcome. However, this study is also in conformity with the findings by Abdallah *et al*. (2018) in Riyadh KSA where *Providence spp* were found to be resistant to tigercycline and colistin and other third generation cephalosporins. Furthermore the high incidence of MDR among *E. coli* (57.4%), *K. pneumonia* (51.6%) reported by the present study agrees with that of Atieh *et al*. (2015) who reported similar finding among isolates obtained from University Teaching Hospital,Kashan, Iran where prevalence of 50% and 46.6% were reported for *E. coli* and *K. pneumonia* respectively. Similar findings were reported in the University of Parma Italy by Andrea *et al*. (2019) where prevalence of 61.5% was reported in *P. aeruginosa*.

The prevalence of AmpC production and MDR in this finding among the male patients (54.1%) and age-range (53.6%) and (50.9%) in male patients (49.7%) respectively agrees with the finding of Duwadi *et al.*(2020) who reported high prevalence ofAmpC among males than females in Koirala Memorial Cancer Hospital, Chitwan, Nepal. This finding is also in conformity with that of Flor *et al*. (2018) in Aguascalients, Mexico where MDR bacteria associated more with male patients (70.8%) than female patients (66.7%). The high prevalence of AmpC producing bacteria isolated among bacteria the old-aged can probably be due to the rampant misuse of antibiotics by this group due to frequent complications. This may contributes to the resistance of third generation cephalosporin antibiotics. Resistance to third generation of cephalosporins in this finding were also observed among bacteria isolated from age group 41-50 (n=73, 63.5%); in this age group most patients are battling with family responsibilities, economic situations and other socioeconomic matters as well as health matters such as blood pressure , diabetes, hepatitis and other health matters. As a result of these the immunity is usually declining which gives rise to treatment failure and or longer hospital stay. This report is in agreement with that of Kiran *et al.*(2020) in Chitwan Nepal China were high percentage prevalence resistance to third generation cephalosporins were observed in patients aged >60(26.8%), In male patients (52.3%) and (53.8%) were MDR. It is also in conformity with the study of Ramirez *et al.*(2018) in non-cancer patients, from Aguascalientes, Mexico were MDR phenotypically were more associated to male

patients (83.33%)and MDR phenotype is also more prevalent among older patients >60 years.

CONCLUSION

The results from this study implied that AmpC production is on the increase in Northwestern Nigeria and that the spread of these resistance conferring enzymes among bacterial isolates is an issue of public health concerned. Therefore, proper monitoring and surveillance for proper prevention and infection control may limit the further spread of this Enzyme.

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