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Critical threat associated with carbapenem-resistant gram-negative bacteria: prioritizing water matrices in addressing total antibiotic resistance

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Abstract

Purpose: The World Health Organization (WHO) in 2017 classified some carbapenem-resistant Gram-negative bacteria into a critical criterial group for research and development. This study reviews the need to prioritize the water matrices as hotspot in the development and transfer of antibiotic resistance determinants, where future total resistant superbug may emerge.

Methods: Published articles on Google Scholars, PubMed/Medline Search and other search tools were selected, with special interest in articles published in indexed journals. Search criteria were based on antibiotic resistance, antibiotic resistance determinants and emerging trend in the reported trend of antibiotic resistance among bacteria from water matrices.

Results: Research reports around the globe have identified carbapenem-resistant Gram-negative bacteria (CRGNB) in water matrices. These CRGNB have also been found to be resistant to other antibiotics in the last line of defence. Molecular typing of some carbapenem-resistant Enterobacteriaceae (CRE) in the environment through pulsed-field electrophoresis showed them to be the same as those in the hospital settings. CRGNB from various water matrices have been reported to harbour carbapenem resistance genes with phenotypic expression of carbapenemases' production. Water habitat provides a conducive environment for the development and spread of carbapenem resistance. Factors like residual antibiotics (RAbs), metals, biocide and water-borne mutagens aid the emergence of the resistance in water matrices. Irrespective of where it was contacted, carbapenem-resistant bacteria have poor prognosis. This is exemplified by resistance to 26 different antibiotics recently in the USA. The human health risk associated with the use of water harbouring these pathogens for irrigating fruits and vegetables may be alarming.

Conclusion: The reports of the rising trend of antibiotic resistance also necessitate prioritizing water matrices when addressing the problems from the reservoir. Surveillance and strict isolation, education and enlightenment, strict compliance with multiple barrier approach of the WHO and more search for more potent antibiotics remain some of the antidotes against the development and spread of resistance through the water matrices as discussed in this article.

Keywords: Water matrices, Carbapenem, Carbapenemases, Metals, Total resistance

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Introduction

The dangerous trend in the evolution of difficult-to-control bacteria, which sometimes originate from the hospitals and are released to the water matrices through the wastewater, is alarming. Health-related news around the globe are agoggled with the worsened prognosis of bacterial infection, which has been leading to the death of the patients. This is because the bacteria are becoming resistant to the existing antibiotics in the last line of defence. Statnews.com reported in January 2017 about the death of a Nevada woman who died of a superbug resistant to every available antibiotic in the USA. Worthy of note in this report was that the woman was infected with potential water contaminant bacteria, Enterobacteriaceae, which in this case was carbapenem-resistant Enterobacteriaceae, CRE. The death of the woman due to failure of 26 different antibiotics made the doctor in charge termed CRE a "nightmare bacteria" (Branswell, 2017). Earlier, another report from the "Science for the Curious Discover, 2015" elaborated on the discovery of a strain of *Escherichia coli*, which has shown resistance to all existing antibiotics. The said *E. coli* was resistant to all the antibiotics in the last line of defence, including colistin, known earlier for consistent effectiveness against the bacterium and other Gram-negative bacteria (GNB) (Zavascki et al. 2007). There is a high level of concern among the health care practitioners and global regulatory bodies due to the rising antibiotic resistance rates. The World Health Organization (WHO) (2017) published the list of bacteria requiring more input in research and development. They include major Gram-negative bacteria, which are known as nosocomial pathogens as well as water-related pathogens (Ramirez-Castillo et al. 2015; Stenström et al. 2016). These pathogens, which include carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant, ESBL-producing Enterobacteriaceae with critical priority (Ramirez-Castillo et al. 2015), are known water-borne pathogens (Ramirez-Castillo et al. 2015; Stenström et al. 2016). Water-borne *P. aeruginosa*'s relatives, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, have been classified for posing a great threat as having intrinsic extreme drug-resistant statuses (McGowan, 2006; Adegoke and Okoh, 2015). Water matrices therefore remain the phases for consideration in the emergence and spread of antibiotic resistance among Gram-negative pathogens (Adegoke et al. 2017). These groups of Gram-negative bacteria are of threat in water-borne infection as well as serious nosocomial infections due to their production of extended-spectrum β-lactamases (ESBLs). The enzyme (ESBLs) makes the bacteria resistant to the third-generation cephalosporins and results in prolonged hospital stays, higher health care costs and increased mortality. Resistance to antibiotics in the last line of defence by either the environmental strains or the clinical strains of bacterial pathogens leads to total drug resistance. Based on the clinical outcomes in the reports above, carbapenem-resistant Gram-negative bacteria are of greater threat in the emergence of total antibiotic resistance.

Water matrices are major breeding ground in the emergence of this magnitude of resistance, and they are continually impacted with multidrug-resistant (MDR) bacterial isolates from the hospital through poorly treated hospital sewage (Picão et al. 2013; Blaak et al. 2015). When these MDR bacteria include species in the genera *Acinetobacter*, *Pseudomonas*, *Aeromonas*, *Stenotrophomonas* among others, their chances of survival in these matrices are high. They get exposed to the residual antibiotics in this environment and may develop a high level of resistance (Adegoke et al. 2017). Carbapenem-resistant bacteria are, in principle, heading towards total antibiotic resistance, especially when they show resistance to colistin and fluoroquinolone (Endimiani et al. 2009; Kontopoulou et al. 2010; Zarkotou et al. 2010). This is usually peculiar for carbapenem and fluoroquinolone resistance with their determinants residing in the plasmid (Endimiani et al. 2009). Exposure to antibiotic residues in the environment (especially in the water matrices) or by self-medication where further development of resistance can be developed makes these bacteria be of greater threat with potentials to resist more antibiotics (Adegoke et al. 2017). This article examines the carbapenem-resistant Gram-negative bacteria as reported in water matrices, their reported carbapenemase production and the presence of other resistance determinants, the fate of these resistant bugs in the water environment, their critical impending threat and ways to mitigate the risks.

Methods

Search criteria

Published articles on Google Scholars, PubMed/Medline Search and other search tools were selected, with special interest in articles published in indexed journals. Search criteria were based on "antibiotic resistance", "antibiotic resistance determinants" and "emerging trend in the reported trend of antibiotic resistance among bacteria from water matrices". The keywords and search terms employed include, but not limited to, "carbapenem resistance AND water matrices, public health threat" AND "carbapenem resistance AND water matrices", "carbapenem; carbapenemases AND water matrices"; "metals; carbapenem resistance AND total resistance AND threat". "antibiotic resistant genes OR antibiotic resistant bacteria". For each case, the search outcomes were reviewed by the authors.

Inclusion and exclusion criteria

Articles published in the English language were selected for this study with less emphasis on the study location or year of publication. Articles which reported antibiotic resistance in surface water, tap water, wastewater, recreation water, etc. with emphasis on carbapenem antibiotics were considered. Other studies in clinical settings that also reported the threats associated with the resistance or mechanisms of resistance reported already in water matrices were sometimes used for comparative illustrations. Articles written in other languages were excluded.

Extraction of data

Information on the reported carbapenem resistance factors favouring the emergence of antibiotic resistance in water environment was extracted, and the distribution of associated threat of carbapenemases and reported mortality to carbapenem resistance towards total antibiotic resistance pattern etc. were extracted. Relevant tables and illustrative figures containing important summaries of resistance threat, associated factor and interpretive standards were developed.

Results

Out of about 536 articles searched, only 127 publications matched the described inclusion criteria and were eventually used for this study.

β-Lactamases produced by gram-negative bacteria

Gram-negative bacteria produce various β-lactam antibiotic degrading enzymes which destroy the penicillins, some inhibitor-based β-lactam antibiotics, cephalosporins, carbapenem etc. depending on the spectrum of the enzymes' activity. So, the beta-lactamases are categorized as depicted in Fig. 1.

The beta-lactamases contributing to the threat of antibiotic resistance include the following:

a. *Penicillases* which are those that are effective against the β-lactam ring of the penicillin antibiotics, but not effective against extended-spectrum antibiotics like cephalosporins
b. *Extended-spectrum beta-lactamases* (ESBLs): ESBLs hydrolyze extended-spectrum cephalosporins with an oxyimino side chain including cefotaxime, ceftriaxone and ceftazidime, as well as the oxyimino-monobactam aztreonam. They sometimes originate from genes coding for phenotypic production of beta-lactamases like TEM-1, TEM-2 or SHV-1 by mutations in which the amino acid configuration in the active site of these β-lactamases has been changed. There are reports on the rising detection of some specific ESBLs (Rodríguez-Baño and Pascual 2008) which are coded for by the plasmid and make the Cephem drugs ineffective. The ESBLs limit the treatment option for a broad range of infection from Gram-negative bacteria. A case of water-borne infection caused by ESBL producers in children or neonates would be difficult to treat, especially if the aetiology is carbapenem resistant, since fluoroquinolones are least indicated (unsafe) for these categories of patients (Goldman and Kearns 2010; Adefurin et al. 2011; Choi et al. 2013). ESBLs on its own do not inactivate carbapenems, but can confer resistance to carbapenem due to subsequent chromosomal porin mutations limiting the penetration of β-lactam agents in the bacteria (Lutgring and Limbago 2016).

Types of ESBLs

TEM (Temoneira) beta-lactamases (class a)

TEM-1 is the most prevalent beta-lactamase in Gram-negative bacteria. It is produced by majority of ampicillin resistance in *E. coli* (Ghafourian et al. 2015) "ampicillin and penicillin-resistance in" *Haemophilus influenzae* and *Neisseria gonorrhoeae*. The shield provided around the amino acid substitutions necessitated clustering around by ESBLs before access to the oxyimino-beta-lactam

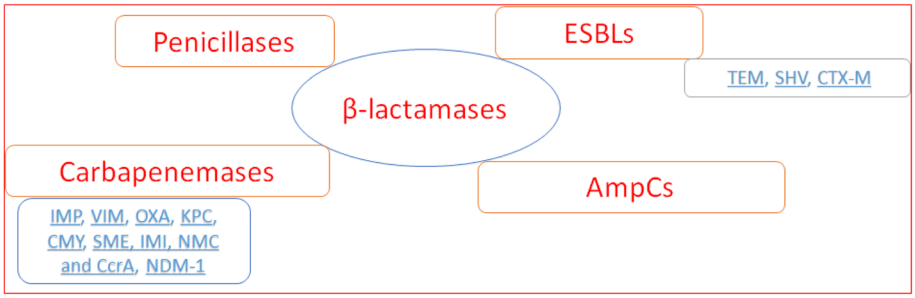

Fig. 1 β-Lactamases produced by Gram-negative bacteria. Key: IMP-type carbapenemases (metallo-β-lactamases) (class B), VIM (verona integron-encoded metallo-β-lactamase) (class B), OXA (oxacillinase) group of β-lactamases (class D), KPC (*K. pneumoniae* carbapenemase) (class A), CMY (class C), SME, IMI, NMC (metallo-β-lactamases) and CcrA, and NDM-1 (New Delhi metallo-β-lactamase) (class B)

substrates. Protease inhibitor, e.g. clavulanic acid, possesses activity against the ESBLs because of prior exposure of active site as induced by the presence of beta-lactam substrates. Out of about 140 different TEM beta-lactamase possible owing to changes via combinations, only TEM-10, TEM-12 and TEM-26 are prevalent in the USA (Bradford 2001; Paterson et al. 2003; Bush 2008). In surface water, Guyomard-Rabenirina et al. (2017) reported the detection of multidrug-resistant *E. coli* strain with TEM-1 beta-lactamase genes, showing the importance of water matrices in cycling of resistance genes in nature.

SHV beta-lactamases (class a)

Both TEM-1 and SHV-1 possess structural similarities with 68% similar amino acids.

The SHV-1 beta-lactamase stands as the most prevalent in *K. pneumoniae*. It undergoes conformational amino acid changes around the active sites to bring about 60 varieties of its enzyme, out of which SHV-5 and SHV-12 are the most prevalent (Paterson et al. 2003). The genes for the SHV-ESBLs reside on self-transmissible plasmids. The plasmids usually bear resistance genes to other antibiotics. The ESBL which is ubiquitous and rampant among Enterobacteriaceae globally has been described by Liakopoulos et al. (2016) as neglected yet ubiquitous. It is vital for resistance (Liu et al. 2016). Liu et al. (2016) showed that the location and transmission efficiency of SHV-12 ESBL are directly linked with the antibiotic resistance of *Enterobacter cloacae*. Conjugation assays conducted by Liu et al. (2016) which were transconjugated into *E. coli* C600 showed 84% partial expression and 10% complete expression of resistance from *E. cloacae* by plasmid-borne SHV-12 ESBL genes.

In South Western Nigeria, Adesoji and Ogunjobi (2016) observed the combinations of bla_{SHV} + bla_{TEM} in 11 *Klebsiella* species in water distribution channels buttressing the importance of water matrices in the distribution of the resistance determinants.

CTX-M beta-lactamases (class a)

These were name in more relativity to cefotaxime than other oxyimino-beta-lactam substrates like ceftazidime, ceftriaxone or cefepime. They have been widely reported in water-borne Gram-negative isolates around the globe (Adegoke and Okoh 2011; Stenström et al. 2016; Adegoke et al. 2017). Plasmids carrying $bla_{CTX\text{-}M}$ genes usually carry other antibiotic resistance determinants such as plasmid-mediated quinolone resistance (Canton et al. 2002). CTX-M enzymes, which contain over 80 CTX-M enzymes, have just about 40% identity with SHV and TEM. In South America, these enzymes are prevalently detected in *E. coli* and other species of Enterobacteriaceae (Delgado et al. 2016). Delgado et al. (2016) detected variants of CTX-M, with CTX-M-15 being the highest as well as 2 rare variants of CTX-M (CTX-M-15) which has also been reported in *K. pneumoniae* ATCC BAA-2146 in Asia (South Korea) (Cho et al. 2015). Environmental detection of these enzymes and its determinants, as well as other antibiotic resistance determinants previously believed to be in the exclusive preserve of the clinical isolates, calls for caution in handling environmental samples like the clinical samples (Adegoke and Okoh 2015). It also points to the importance of the environment, especially the water matrices, in the emergence and/or distribution of resistance. Isolates with these determinants in the environment have greater tendencies for further exposures to several mutagens in the environment (e.g. wastewater) than in hospital, increasing their resistant threat (Lutgring and Limbago 2016). This might also increase.

Other plasmid-mediated ESBLs

Rarely detected plasmid-mediated ESBLs which include "PER, VEB, GES and IBC" beta-lactamases are predominant among *P. aeruginosa*. Though rare as earlier noted, they have been isolated in various countries at different times. In South Africa, Adegoke and Okoh (2014) reported the maiden detection of GES-5 in South Africa which was the second in clinically isolated *P. aeruginosa*. On the environment, Al Yousef et al. (2016) discovered 83.3% VEB in *E. coli* from some Saudi Arabian household water samples in which the isolates showed 100% resistance to ampicillin, cefazolin and piperacillin. Korea, Belgium, Romania, France, the USA and Turkey have also prevalently reported PER-1 in *Acinetobacter* species (Peleg et al. 2008). Some of these rare enzymes (e.g. IBC-1, BES-1, IBC-1 etc.) contribute substantially to the emergence of resistance to antibiotics in the last line of defence among Enterobacteriaceae through mutation. This has been reported to be of concern in the usually prioritized hospital settings and mostly overlooked environment (D'Costa et al. 2006).

Factors for the emergence of antibiotic resistance in water environment

The emergence as well as progression to higher trend of antibiotic resistance in the water matrices is possible due to a number of factors or water components, which include residual antibiotics (RAbs) in water, metals, biocides and mutagenic contaminants (Zuccato et al. 2005). Table 1 shows the mechanisms by which the components may induce resistance or its progression as well as specific examples of reported or relevant cases. Exposure to the listed components (Table 1) may lead to progression of resistance in the following order: single antibiotic resistance (AR), multidrug resistance (MDR), extensive drug resistance (EDR), pandrug resistance (PDR), extreme

Table 1 Factors favouring the emergence of antibiotic resistance in the water environment

Water components/contaminants	Mechanism of resistance	Specific applicable example	References
Residual antibiotics (RAbs)	Bacterial exposure to sublethal concentration of RAbs leads to the emergence of resistance, post exposure resistance via selection for specific antibiotic-resistant genes (ARGs) or resistance determinants, bacterial mutation as a form of adaptation to the antibiotics in water habitat	β-Lactams by mutations in PBP5 and PBP2 among aquatic *Enterococcus faecium* and *Proteus mirabilis*	Adegoke et al. (2017); Li et al. (2009); Sosa et al. (2006)
Metals	Co-selection of resistance genes against antibiotics in which exposure/selection for metal resistance leads to antibiotic resistance	merA and KPC beta-lactamase. This may affect a wide range of β-lactam antibiotics including the carbapenems	Romero et al. (2017); Pal et al. (2015); Baker-Austin et al. (2006); Fang et al. (2016)
		Copper and silver may develop co-occurrence of resistance to beta-lactam and fluoroquinolone	Fang et al. (2016)
		Copper, mercury and silver Colistin may develop co-occurrence of resistance to ampicillin, sulfonamide, tetracycline, streptomycin and chloramphenicol	Li et al. (2016); Campos et al. (2016)
Biocide	Co-selection of resistance genes against antibiotics in which exposure/selection for biocide resistance leads to antibiotic resistance	Acriflavine, chlorhexidine and ethidium bromide may develop co-occurrence of resistance to gentamicin and amikacin	Wales and Davies (2015)
Water-borne mutagens	Alteration of drug target by mutagenesis	Bromoacetamide (BAcAm), trichloroacetonitrile (TCAN) or tribromonitromethane (TBNM) increased the resistance of *Pseudomonas aeruginosa* PAO1 to both individual and multiple antibiotics (ciprofloxacin, gentamicin, polymyxin B, rifampin, tetracycline, ciprofloxacin + gentamicin and ciprofloxacin + tetracycline)	Lv et al. (2014); Lv et al. (2015); Watanabe et al. (2006)

drug resistance (XDR) and total drug resistance (TDR) as elaborated by Adegoke et al. (2017).

Carbapenem resistance is an obvious XDR. A progression via exposure to mutagens (mutation), RAbs, metals, biocides etc. in water environment can easily lead to their progression to TDR. Water matrices therefore remain an aspect of the environment that requires important action in tracking and mitigating the risk associated with antibiotic resistance.

Distribution and associated threat of carbapenemases

As earlier noted in the various clinical reports of the gradual emergence of total drug resistance, carbapenem-resistant bacteria, also known to be carbapenemases' producers, resist all existing antibiotics. This has made carbapenemases to be recognized for posing a new threat, inactivating the last lines in antibiotic defence. Following the detection of the classic carbapenemases (metallo-β-lactamases, Ambler class B) in the 1990s, the distribution of different metallo-β-lactamase genes globally has been reported (Picao et al. 2013; Berrazeg et al. 2014; 59. Adam and Elhag 2018). In 2003, *Klebsiella pneumonieae* carbapenemases (KPC, Ambler class A serin β-lactamase) which are predominantly found in *Klebsiella* species (also in Enterobacteriaceae as well as other Gram-negative bacteria) were reported in North Carolina and it has spread across the globe (Yigit et al. 2001; Arnold et al. 2011). For Enterobacteriaceae, they singlehandedly house OXA-48 and its derivatives (Canton 2002; Nordmann and Poirel 2002; Nordmann et al. 2012). Meanwhile, metallo-beta-lactamases that used to be less rampant in the USA are now

becoming the most prevalent for carbapenem resistance (Canton et al. 2012), leading way to the "emergence of total drug resistance (TDR)". The gene bla_{KPC}, which codes for the KPC, is widely disseminated among species and geographical location. It is located within a Tn3-type transposon, Tn4401, with potential for insertion into various plasmids of GNB. Plasmids carrying *blaKPC* are usually linked with resistance determinants for antibiotics (Asit et al. 2016). Carbapenemase production is highly significant in the emergence of resistance, especially among carbapenem-resistant Enterobacteriaceae (CRE).

The presence of carbapenemase-producing Enterobacteriaceae (CPE) in a sample may connote the expression serin β-lactamases. Carbapenemase production is commonly detected among *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Bialvaei et al. 2015). There is also an increase in the likelihood of detecting carbapenemases in Central Europe. KPC is endemic in some countries like Italy or Greece (Nordmann et al. 2011; Hoenigl et al. 2012). Poirel et al. (2012) also reported the detection of KPC-producing Enterobacteriaceae from wastewater and river-water samples in Portugal, just as bacterial isolates from human in Austria were reported to harbour NDM-1, KPC, VIM, IMP and OXA-48. There is therefore an upward surge in the detection of KPC-producing Enterobacteriaceae (Nordmann et al. 2011; Zarfel et al. 2011; Heller et al. 2012).

Studies have shown that OXA-48 is rampant in Austria (Nordmann et al. 2011; Zarfel et al. 2011; Heller et al. 2012). However, the detection of "metallo-β-lactamase" has not been frequently reported. That was the first report of "OXA-48-producing Enterobacteriaceae in Taiwan and the second report to identify blaOXA-48 on an IncA/C plasmid in *K. pneumoniae*". Potron et al. (2011) gave a report on the intercontinental spread of OXA-48 beta-lactamase producing Enterobacteriaceae over 11 years. The report showed the emergence of an endemic situation occasioned by repeated importation of OXA-48 beta-lactamase producers in Europe and particularly in France. As far back as 2005, Austria had records of metallo-β-lactamase carbapenemase (Zarfel et al. 2011). Metallo-β-lactamases are recognized for environmental spread (Isozumi et al. 2012) but may obviously be following KPC and OXA-48 in the human and clinical settings. Both KPC-2 and OXA-48 carbapenemase-harbouring Enterobacteriaceae have been reported in an Austrian wastewater (Galler et al. 2014). This might be a true reflection of the statuses of the Enterobacteriaceae in the Austrian human environment as wastewater is an early warning system of the situation in the human population before outbreaks (Hellmér et al. 2014). This also brings to bare the need for the wastewater treatment plant to scale up the process to raise treatment efficiency. Hrenovic et al. (2017) reported the 54% reduction of the carbapenem-resistant bacterial population in the secondary wastewater treatment plants (WWTPs). The report shows that it is possible to stop the spread of carbapenem-resistant bacteria and its associated risk in the wastewater reuse by upscaling the WWTPs.

The spread to the environment through the wastewater is very frequent which in turn impacts the food cycles, human and animal health as well as contaminated inanimate objects. Environmental disseminations of KPC- and OXA-48-producing Enterobacteriaceae in Austria have been reported (Kittinger et al. 2016). It was found to be more prominent in the rivers and animals (Galler et al. 2014; Kittinger et al. 2016), which may mean that more animals are exposed and shed the organisms to the environment. These deposits in the environment are washed by runoffs into the rivers where they are recirculated to more animals by exposure. Meanwhile, attentions that are more specific have been drawn to the presence of NDM-1 in *E. coli* ST-type 131 in community-based infection as the bacteria are known for CTX-M ESBL production (Adegoke et al. 2017; Potron et al. 2011; Diancourt et al. 2005).

It is important to note that one CRE and CPE are released to the environment as well as to the food chain through wastewater from the infected residence or hospital. Several studies (Stenström et al. 2016; Xu et al. (2011), Liu et al. (2010) and Reinthaler et al. (2013) reported the presence of multidrug-resistant bacteria in the aquatic environment imparted by wastewater. Some of these studies implied that the production of carbapenemases produced by aquatic bacteria follows the same pattern as those by clinical strains. This is exemplified by the reports of water-borne carbapenemase-producing Enterobacteriaceae (Zurfluh et al. 2013).

Mortality related to CRB

Carbapenem-resistant bacteria (CRB) have been reported with poor prognosis, irrespective of the source of infection: either community-acquired or nosocomial (Bennett et al. 2009; Zhang et al. 2016). There have been controversies around recovery from the carbapenem resistance as cases of co-resistance to other drugs leading to death have been reported (Branswell 2017; Bennett et al. 2009; Zhang et al. 2016). Zhang et al. (2016) observed that though carbapenem resistance had a damaging impact on the mortality of *P. aeruginosa* bacteremia, its association with mortality is still controversial. Bennett et al. (2009) deduced that 26–44% of deaths were observed in 7 studies due to carbapenem resistance and the course may be a bit different when bacteraemia is involved. Zhang et al. (2016) reported that four studies reported

8–18.4% mortality due to carbapenem resistance within 30-day mortality. Buehrle et al. (2017) predicted certain factors that aid the course of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) bacteraemia towards mortality, in which early active therapy would have been redemptive. This shows that various factors facilitate the course of recovery or death in carbapenem-resistant bacterial infection, making it difficult to treat. The death of the US woman, earlier mentioned in this article due to carbapenem-resistant Enterobacteriaceae and subsequent failure of 26 different antibiotics (Branswell 2017), continues to position the carbapenem-resistant Gram-negative bacteria as a threat in both clinical settings and the environment. Liu et al. (2016) drew a conclusion that "CRPA had significantly higher mortality than those infected with carbapenem-susceptible *Pseudomonas aeruginosa* (CSPA)". These reports informed the classification of these CRB in the critical priority list, for which new R and D antibiotics are required (WHO 2017).

Mitigating the public health risks associated with CRB

Some schools of thought believe that the CRB from the hospital settings are responsible for the contamination of the environments (Liu et al. 2015). Others believe that the emergence of antibiotic resistance including CRB occurs in the environment due to exposure to antibiotic residues (Khan et al. 2013). The latter believe that water matrices create a very conducive environment for the development of antibiotic resistance (Li et al. 2009; Khan et al. 2013) even when there is no hospital in the vicinity. These researchers submitted that antibiotic resistance genes (Li et al. 2009; Davies and Davies 2010; Zhang et al. 2011) and other resistance determinants (Li et al. 2009; Manhal and Hashim 2016) in environments are exchanged in the environment. Adegoke et al. (2017) elaborated on the role of biofilms formed in wastewater and the surface water environments in providing a conducive avenue for the water-borne bacteria to exchange resistance determinants. Reports acknowledge that both the hospital settings and the community are important in the emergence and dissemination of antibiotic resistance (Zhang et al. 2011; Adegoke et al. 2010). Water matrices become very important because there have been reports of antibiotic resistance, including carbapenem resistance in various types of water, including drinking water (Table 2).

Environment, especially the water matrices, is important to prioritize in finding solutions to the threat associated with CRE, CRB and resistance to other antibiotics in the future. Certain steps to take are itemized as follows.

Surveillance and strict isolation

Following typing by pulsed-field gel electrophoresis, it has been reported that both clinical and environmental isolates of CRB were related (Kotsana et al. 2014). Surveillance in the environment should be intensified as much as the hospital settings to check the spread of the CRE and CRB (Calfee and Jenkins 2008; Kochar 2009; Ben-David et al. 2010; Centers for Disease Control and Prevention 2012). Patients recognized to have been colonized with CRE should be isolated to prevent being the reservoir for the spread (Munoz-Price et al. 2010a; Munoz-Price 2010b; Castilho et al. 2017). Isolation of patients with CRB is also very important. This is peculiar to those in the intensive care units (ICU). Castilho et al. (2017) reported a high incidence of carbapenem resistance (MDR) *A. baumannii* with the expression of OXA-23 genes. Even the wastewater from the isolation ward should be specially treated onsite to prevent the accidental leakage into the surface water while being transported through the municipal wastewater treatment plants. There have been reports showing that the drains, sinks, and faucets in hospitals are usually colonized by carbapenemase-producing *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Gordon et al. 2017). These Gram-negative bacteria, known for potentials to survive in the environment and water matrices, may pose a threat if released with wastewater, especially when there are accidental leakages. This shows the need to ensure the treatment of wastewater from hospital settings onsite and to put in place an automated recall system that returns the undone wastewater effluent for retreatment chambers. The existing WWTPs receiving wastewater from hospitals should be upgraded with modern facilities to ensure the eradication of CRB. It is worthwhile to ensure that hospital wastewater for reuse must be free of CRB to avoid the threat associated with such reuse. Due to the fund required, this preventive measure would need support in every country adopting locally, regionally and nationally.

While suggesting the way to alleviate the spread of carbapenem resistance, Palmore and Henderson (2013) recommended detailed environmental decontamination after aggressive microbial surveillance. Kochar et al. (2009) had reported that improved decontamination of hands and environmental surfaces as well as rectal surveillance reduced the incidence of carbapenem-resistant *K. pneumoniae.* Surveillance in both environment and hospital settings, especially in intensive care units, would reduce the spread as well as the need to administer colistin (An et al. 2017). Environmental cleaning and disinfection done thrice a day as well as other interventions lead to 88.3% decrease in the number of cases per thousand (odds ratio, 0.12; 95% confidence interval, 0.03 to 0.4; $p < 0.001$). This also translated to a reduction in the need for the administration of carbapenems (Cheon et al. 2016) following antibiotic susceptibility testing (AST) using approved interpretive standards e.g. (Table 3).

Table 2 Reported antibiotic profile of aquatic Gram-negative bacteria to carbapenem antibiotics in water matrices

Carbapenem antibiotics	Sample source	Reported % resistance	Other resistance status reported	References
Imipenem (+ cilastatin)	Swimming pool	26	30% Cefpodoxime-resistant *Pseudomonas aeruginosa*	Stenström et al. (2016); Picão et al. (2013); Magalhães et al. (2016); Freitas et al. (2019); Tacao et al. (2015); Akiba et al. (2016); Skariyachan et al. (2015)
	Surface freshwater	20	CTX-M-ESBLs producing *Acinetobacter* spp.	
	Wastewater effluent	17	CRE ESBLs and carbapenemase producing *E. coli*	
	Hospital effluent	20.5	KPC-producing *Aeromonas* spp. and Enterobacteriaceae	
	Sewage and receiving water[a]	18	bla_{NDM}-positive plasmids	
	River (drinking water source)	100	Carbapenem-resistant *Citrobacter*	
Ertapenem	Wastewater influent	61.5	ESBLS producing Gram-negative bacteria	Amine et al. (2013)
	Wastewater effluent	66.6	ESBLS producing Gram-negative bacteria	
	River (drinking water source)	100	"Carbapenem-resistant" *Citrobacter*	Skariyachan et al. (2015)
		100	"Carbapenem-resistant" *Proteus*	
		43	"Carbapenem-resistant" *Klebsiella*	
Meropenem	Surface freshwater	10	CTX-M-ESBLs producing *Acinetobacter* spp.	Stenström et al. (2016); Akiba et al. (2016); Skariyachan et al. (2015); Amine et al. (2013); Figueira et al. (2011)
	Surface water	3.9	Carbapenem-resistant *Aeromonas* species	
	Post-ozonated surface water	3.4	Clonal selection occasioned by ozones/mutation cum fluoroquinolone resistance	
	Hospital effluent	16.2	KPC-producing *Aeromonas* spp. and Enterobacteriaceae	
	Wastewater influent	10.2	ESBLS producing Gram-negative bacteria	
	Wastewater effluent	8.3	ESBLS producing Gram-negative bacteria	
	River (drinking water source)	42	Carbapenem-resistant *Citrobacter*	
Doripenem	River (drinking water source)	43	Carbapenem-resistant *Salmonella*	Skariyachan et al. (2015)
		100	Carbapenem-resistant *Citrobacter*	
		0	Carbapenem-resistant *Proteus*	
		33	Carbapenem-resistant *Klebsiella*	
Faropenem	River (drinking water source)	100	Carbapenem-resistant *Salmonella*	Skariyachan et al. (2015)
		100	Carbapenem-resistant *Citrobacter*	
		22	Carbapenem-resistant *Proteus*	
		100	Carbapenem-resistant *Klebsiella*	

[a]Isolates were pulled together from both interlinked matrices

Table 3 CLSI interpretive standards for carbapenems (CLSI M100-2017)

Carbapenems	Disc content, μg	Resistance		Intermediate		Susceptible		Remarks
		DD	MIC	DD	MIC	DD	MIC	DD = disc diffusion MIC = minimum inhibitory concentration
Imipenem	10	≥ 23	≤ 1	20–22	2	≤ 19	≥ 4	Enterobacteriaceae
Meropenem	10	≥ 23	≤ 1	20–22	2	≤ 19	≥ 4	
Ertapenem	10	≥ 22	≤ 0.5	19–21	1	≤ 18	≥ 2	
Doripenem	10	≥ 23	≤ 1	20–22	2	≤ 19	≥ 4	

Education and proper labelling of wastewater irrigated crops and vegetables

It would be beneficial for consumers of fruits and vegetables irrigated with wastewater effluents to be educated on the associated risks (Marti et al. 2013; Thanner et al. 2016). This will be a way of guiding them on the appropriate hygienic steps to prevent being infected by the pathogens from the irrigated water (Adegoke et al. 2016). Appropriate labelling of organically grown crops should be encouraged in all countries to prepare the consumers. The action, if properly implemented, would help to achieve the focus of multifaceted, elaborate and integrated measures in line with one health approach to stop infective diseases by curbing antibiotic resistance (Founou et al. 2016). The spread of pathogens bearing resistant determinants through food chain contributes essentially to the development of antibiotic resistance (Economou and Gousia 2015) right from the first antibiotics to the latest. Figure 2 illustrates the potentials for uptake and internalization of human pathogens into crops irrigated with wastewater. These human pathogens, which might be antibiotic resistant, may persist in edible fruit which may affect immunocompromised individuals who consume them (Bouakline et al. 2000; Brenier-Pinchart et al. 2006; Golberg et al. 2011; Iwu and Okoh 2019). Some projections have shown that 85% of gastroenteritis and mortalities are from such contaminated food in which *Salmonella* is implicated (Deng et al. 2012; Majowicz et al. 2010).

Consumption of internalized pathogen originating from organic fertilizers or wastewater used for irrigation in uncooked food, e.g. fruits and vegetables in salad, may lead to difficult-to-treat food infection or food intoxication (Adegoke et al. 2016). This was also illustrated in Fig. 2. It is imperative to properly label crops grown using organic fertilizers appropriately for the consumers to decide based on their immune statuses.

Hand hygiene and multiple barrier approach

Hand hygiene is an all-important process to reduce the adherence of the CRE and, generally, the CRB from contacted surfaces and to avoid the spread same to other animate or inanimate surfaces (Sickbert-Bennett et al. 2004; Goroncy-Bermes et al. 2010; Macinga et al. 2011). The use of bactericidal hand gel has been advised to reduce CRE population on the hands. This is also in line

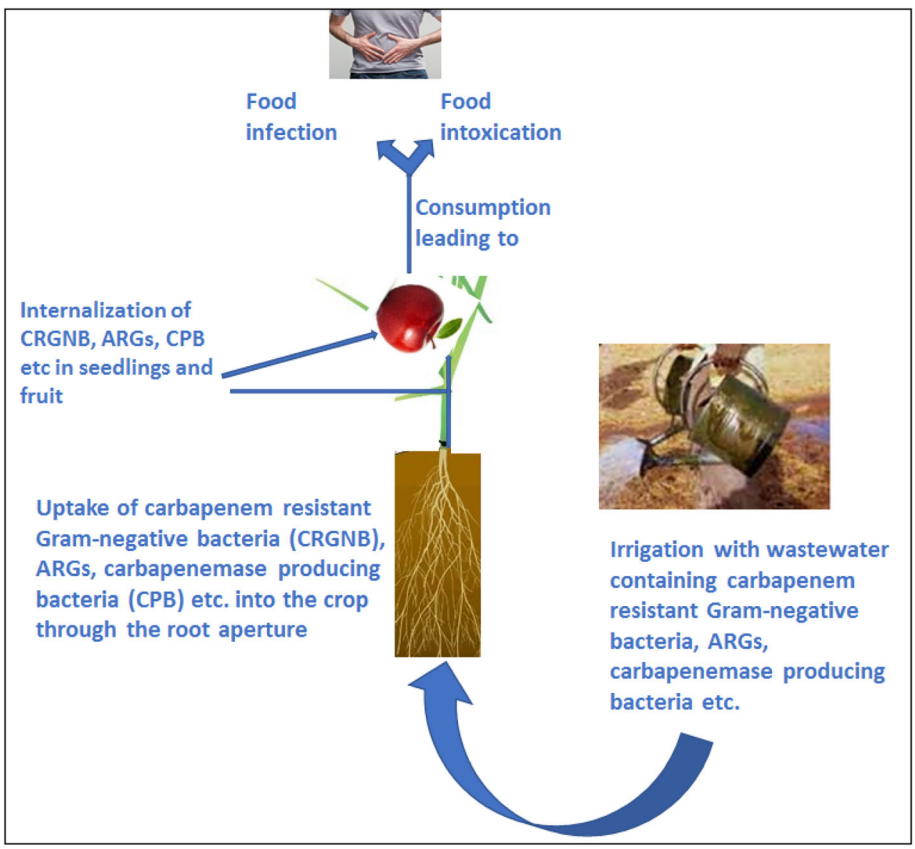

Fig. 2 Uptake and internalization of carbapenem-resistant Gram-negative bacteria (CRGNB), ARGs, carbapenemase-producing bacteria (CPB) etc. into edible fruits

with recommendations. Hand hygiene needs to be accompanied with general hygiene as well as steps to prevent contamination of food or water source. Hands should be washed anytime one gets in contact with wastewater, treated wastewater's recipient water bodies, untreated recreation waters etc. likely contaminated with antibiotic-resistant bacteria. This will decrease the transmission of antimicrobial resistance from water matrix.

This relates with the multiple barrier approach (WHO, 2006). The multiple barrier approach prevents or reduces the contamination of drinking water by high-risk pathogens, which include CRE. Combined utilization of advanced oxidative processes coupled to UV-irradiation with chemical disinfectants possesses potentials to eliminate ARB and ARGs (Sanganyado and Gwenzi 2019), though some disinfectants may form toxic complexes with residual antibiotics in water and lyse microbial cells to release their genome enhancing gene transfer to pathogens worsening their prognosis of the infection they cause (Faleye et al. 2019).

Conclusion

In conclusion, water matrices occupy 71% of the total space in the earth and the events within these matrices affect terrestrial life. This article reviewed the antibiotic-resistant Gram-negative bacteria, especially the carbapenem-resistant bacteria (classified with critical criteria for research by WHO) in water. It also considered the factors predicating the reported level of resistance as well as the potentials for total antibiotic resistance due to repertoires of these factors, while not leaving behind the related human health risk. Gene transfer, mutation and genetic recombination take place more effectively in water matrices, as organisms form more protective or effective biofilms and quorum sensing. ARGs are exchanged, and the new strains return easily to human and animal lives through the food chains or contact with the environment. These scenarios have contributed to the development of multidrug resistance, pan drug resistance, extreme drug resistance and, now, total drug resistance. Water from various sources should be subjected to multibarrier screening to prevent transmission of difficult-to-treat antibiotic-resistant bacteria from water to food cycle.

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Research involving human participants and/or animals

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