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Letter to the Editor

Emerging carbapenem resistance in ESKAPE pathogens in sub-Saharan Africa and the way forward

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Abstract

Enterococcus faecium, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (ESKAPE) and their role in the development and spread of multidrug resistance (MDR) is not well characterized in sub-Saharan Africa (SSA). Carbapenems possess a broad spectrum of activity and are often reserved for the treatment of MDR infections in developed countries. However, the emergence of carbapenem resistance (CR) is increasingly being reported and therefore presents a significant public health threat. Although carbapenems are generally unavailable in African hospitals due to high cost, a small number of studies have reported the occurrence of carbapenem-resistant bacteria (CRB) in SSA. This, therefore, shows that CRB is emerging in Africa. Thus, there is a critical need for deploying robust national and regional multidisciplinary, collaborative, and regulatory approaches aiming at elucidating the epidemiology of CRB, its burden on the health care system, and strategies for compacting the development and spread of CR. This report hopes to highlight the epidemiology of CRB and the main drivers of antibiotic resistance in SSA and proposes future strategies that can be used to combat the emergence of CRB in the region.

Keywords: Carbapenem resistance, Multidrug resistance, β-lactamases, Antibiotics

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Epidemiology of Carbapenem Resistance

The epidemiology of common opportunistic bacterial pathogens that often cause community/hospital-acquired infections and their role in developing and spreading multi-drug resistance (MDR) has been reported in many developing countries (Holmes et al., 2016). It is estimated that about 700,000 individuals worldwide die because of infections caused by resistant pathogens. It is expected that this number will rise to ten million by 2050 if this problem is not addressed soon. β-lactam antibiotics are the most critical group of bactericidal antibiotics containing a β-lactam ring in their molecular structure. Penicillins, cephalosporins, monobactams, and carbapenems are members of this group.

Carbapenems are broad-spectrum antibiotics with activity against a variety of both Gram-negative and positive bacteria. They are more stable against inactivation by many β-lactamases, are relatively well tolerated with comparatively fewer adverse effects, and are widely used in the developed world against MDR infections. Alternatives to treatment with carbapenems for MDR infections are often less effective and/or more toxic (Kapoor et al., 2017). Carbapenemase enzymes modulate resistance towards all β-lactam antibiotics, including carbapenems. These enzymes act by hydrolyzing the β-lactam ring of the drugs, thus making them ineffective against the bacteria. Carbapenemases have been identified in many MDR Gram-negative bacteria and are the main mode of resistance.

All β-lactamases are categorized into four major molecular classes, according to the Ambler classification. These include the *Klebsiella pneumoniae* carbapenemase (KPC). The KPCs comprises ten variants (KPC-2 to KPC-11) that differ from one to another by one to three amino acid substitutions. Although *K. pneumoniae* remains the most prevalent bacterial species carrying KPCs, the enzyme has been identified in several other Gram-negative bacilli including *Citrobacter freundii, Pseudomonas aeruginosa, Escherichia coli, Pseudomonas putida, Enterobacter aerogenes, Acinetobacter spp, Enterobacter cloacae,*

Enterobacter gergoviae, Klebsiella oxytoca, Proteus mirabilis, and *Salmonella enterica* (Arnold et al., 2011).

The best therapeutic approach to KPC-producing organisms is yet to be defined and standardized. However, common treatments based on *in-vitro* susceptibility testing are polymyxins, tigecycline, and less frequently aminoglycoside antibiotics. The second class includes Imipenem-hydrolyzing β-lactamases (IMI); class A. These form two subgroups: imipenemase metallocarbapenemase-A (IMI) and non-metallocarbapenemase-A (NMC-A), respectively. The NMC-A enzyme deviates by eight amino acid substitutions from the two IMI variants, which differ by two substitutions from each other. The enzymes have been found sporadically, both in clinical isolates and environmental isolates (Meletis, 2016). Thirdly, the New Delhi metallo-β lactamases (NDM); class B. Drug-resistant Gram-negative bacteria that produce NDM were first linked to India. They have increasingly been isolated in more than 15 countries in community and health care settings in a wide range of Gram-negative genera containing diverse *blaNDM*-harboring plasmids (Rasheed et al., 2013). Fourthly, class D: Oxallocillinases (OXA-48). The OXA-48 producing bacteria have been extensively reported from Turkey as a source of nosocomial outbreaks. Their worldwide distribution now includes countries in Europe, in the southern and eastern part of the Mediterranean sea, and Africa (Nordmann et al., 2011).

These enzymes are found globally in isolates associated with community and hospital-acquired infections (Shah et al., 2018). Other modes of resistance to carbapenems include decreased permeability of the outer membrane due to changes in porin proteins, which control the entry of compounds into the cells or active removal of drugs from the bacterial cytoplasm through the activation of the efflux pump. The WHO has listed pathogens with CR as most critical, requiring urgent research and development of new antibiotics (Sastry et al., 2017).

The *Enterobacteriaceae* family consists of several genera. Among them, *E. coli* and *K. pneumoniae* are the most frequently isolated species from clinical specimens of infected humans and animals. These are often associated with community and hospital-acquired infections and frequently exhibit MDR traits, making treatment options a significant challenge for infected patients (Pitout et al., 2008). These bacteria are part of the normal flora and can acquire resistance and virulence genes from other bacteria during interaction in the host or the environment. Recent data indicate that there are wide gaps in understanding the epidemiology of carbapenem-resistant *E. coli* and *K. pneumoniae* in Sub-Saharan Africa (SSA). The available data document moderate prevalence (ca 5%) of carbapenem-resistant *E. coli* and *K. pneumoniae* in SSA, with 22 and 9 countries reporting evidence of CR and no resistance, respectively (Mitgang et al., 2018).

Acinetobacter baumannii is an opportunistic pathogen implicated in a broad range of nosocomial infections such as pneumonia, septicemia, urinary tract infections (UTI), and wound infections, particularly in critically ill patients in ICU. Several MDR and carbapenem-resistant *A. baumannii* isolates have been reported in several African countries, including Kenya, indicating an emerging problem (Al-Agamy et al., 2014; Mushi et al., 2014; Lowings et al., 2015). *Pseudomonas aeruginosa* is also an opportunistic pathogen, notably in cystic fibrosis patients' capable of causing bloodstream, UTI, wound, and soft tissue infections. In Kenya, *P. aeruginosa* caused 5% and 4% of community and hospital-onset infections in a private teaching hospital in Nairobi (Maina et al., 2016). Despite gaps in surveillance in SSA, carbapenem-resistant *P. aeruginosa* has been reported in countries such as Kenya (Pitout et al., 2008; Maina et al., 2016), Tanzania (Mushi et al., 2014), and Egypt (El-Domany et al., 2017). Although various studies worldwide have characterized the different variants of each genetic determinant of CRB, these variants and their epidemiology are yet to be comprehensively elucidated in SSA.

The Way Forward

The main factors driving antibiotic access and misuse and/or overuse are complex and interlinked structural and social in nature including; empirical use of antibiotic use without proper diagnosis of infection, inappropriate prescription practices by health and non-health personnel, unregulated supply chains, and sale of drugs resulting to access and sale of antibiotics without medical prescription, self medication by patients, use of substandard or counterfeit antibiotics and sale of drugs with questionable pharmacological quality. Other notable practices include sharing of antibiotics among family members, dispensing of incomplete dosage based upon the patient's ability to pay, and storing the antibiotics for use during future infections when signs and symptoms begin to subside after an initial favorable therapeutic response. These factors lead the patients taking sub-optimal dosages of the drug thus exerting selective pressure on microor-

ganisms which in turn develops antibiotic resistance to the drug used (Figure 1).

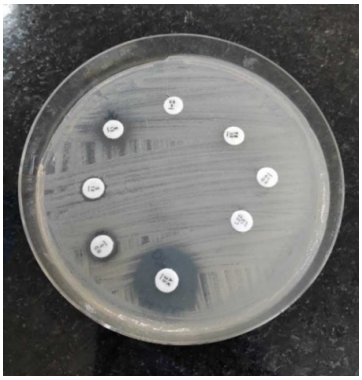

Figure 1: *Salmonella typhi* clinical strain that was resistant to seven out of eight antibiotics tested.

Although extensive usage of carbapenem antibiotics has not been reported in the previous studies in SSA, CR has been reported in ESKAPE pathogens in health facilities where the antibiotic is not routinely used. This shows that CRB is emerging in SSA despite its restricted access due to high cost. A way forward for the region is therefore to design collaborative efforts geared towards elucidating the epidemiology of CRB and its burden on health care systems, the underlying genetic mechanisms associated with phenotypic resistance to carbapenems and evaluate the effect of MDR on the biological fitness of the CRB.

Such efforts would ultimately enable understanding the existing and emerging CR hotspots, possible reservoirs, and possible practices, culture, and attitudes (KAPPs) that may predispose different communities to CRB infections. Such knowledge would be critical in formulating targeted policies on the rational use of carbapenems and strategies to control the emergence and spread of antimicrobial resistance, more generally. This will be important because carbapenems are expected to become cheaper and readily available after their respective patents expire.

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