



Broad spectrum β -lactamase producers Gram-negative bacilli (GNB) in the Gulf Cooperation Council (GCC) states. "The known and the known unknown".



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Abstract

Introduction: Various reports from the GCC countries have described the isolation of many extended-spectrum β -lactamase (ESBL), plasmid mediated AmpC and carbapenemase producing GNB. Although the states are closely located and demographically similar, different enzymes have been described from each country. Other widely spread enzymes elsewhere have not ever been or rarely described in the region. Here we list the reported broad spectrum β -lactamase enzymes produced by GNB in the GCC states and document our justified expectations for future reports.

Methods: We searched MEDLINE, ICAAC and ICPC 2011 abstract databases for the terms "antibiotics", "resistance", and, "Saudi Arabia", "UAE", "Kuwait", "Oman", "Bahrain" or "Qatar". The word "lactamase" was also combined with the countries' names individually to replace the "antibiotics" and "resistance" terms. The results were excluded to cover the literature published between 1980 and 2010. We used the reference lists from articles identified as further sources. Finally, we studied reports of widely spread β -lactamase enzymes reported elsewhere, to try and identify similar aspects to our regions. Our search was restricted to papers in English.

Results: The CTX-M, SHV and TEM enzymes have been found to be the most common ESBL in the GCC. Different variants have been characterized from isolates of Saudi Arabia, UAE, Oman, and Kuwait including the rare CTX-M-55, SHV-28, and the recently described SHV-112 and SHV-122. Other less frequently reported ESBL in the GCC states include OXA-1, OXA-9, VEB-1a, and VEB-1b. The novel ESBL PME-1 is also believed to be of Gulf origin. The only reported plasmid mediated AmpC from the region is the worldwide spread DHA-1, which was firstly characterized after the isolation of *Salmonella* spp from Al-Dhahran city. Class D carbapenemases are the most common enzyme reported from the GCC. *Acinetobacter baumannii* collected from the GCC states expressed a variety of OXA enzymes including the novel OXA-90, -130, -131, and -132, while other isolates expressed OXA-23, -25, -26, -58, -66, -72, -78, and -91. Recently, a novel OXA-181 enzyme has been reported from *Klebsiella pneumoniae* collected from Oman. The widely disseminated group A β -lactamase KPC enzyme has been only described from Saudi Arabia and Kuwait in two separate case reports. Although metallo- β -lactamase enzymes are reported worldwide, VIM-types have been characterized from limited isolates in Saudi Arabia and Kuwait, while the "panic causing" NDM-1 has only been reported twice from Oman and Kuwait. Due to the socio-economic structure of the GCC states, significant migration activity is prevalent. Saudi Arabia is also visited annually by more than 1.5 million pilgrims. Travel has been found to be a significant contributor in spreading antibiotic resistant bacteria, particularly if hospitalization occurs during travel.

Conclusion: Widely spread β -lactamase enzymes like KPC, VIM, NDM, and OXA-48 are increasingly noticed in the GCC countries. And since novel resistance mechanisms have emerged from this region, new enzymes should be expected. We suggest keeping track of emerging resistance mechanisms by adopting region-wide surveillance. Information provided will help to halt the problem by developing further interventional activities including strong infection control practices and antimicrobial stewardship programs.

Background

The emergence and increase in antibiotic resistant organisms is a serious concern for modern healthcare practice. In GNB an important cause of multi-drug resistance is the production of broad spectrum beta-lactamases. In the early 1980s, extended-spectrum β -lactamases (ESBLs) that hydrolyze penicillins and third-generation cephalosporins emerged¹. In more recent years, beta-lactamases that hydrolyze carbapenems have become prominent².

Different reports around the world have described the isolation of ESBL and carbapenemase producing bacteria. Here we reviews types of broad spectrum β -lactamase producing GNB in the Middle East, with a primary focus on states of the Gulf Cooperation Council (GCC). Based on the challenges and potential risk factors, we will predict future reports of beta-lactamase enzymes producing by GNB in the GCC states.

Methods

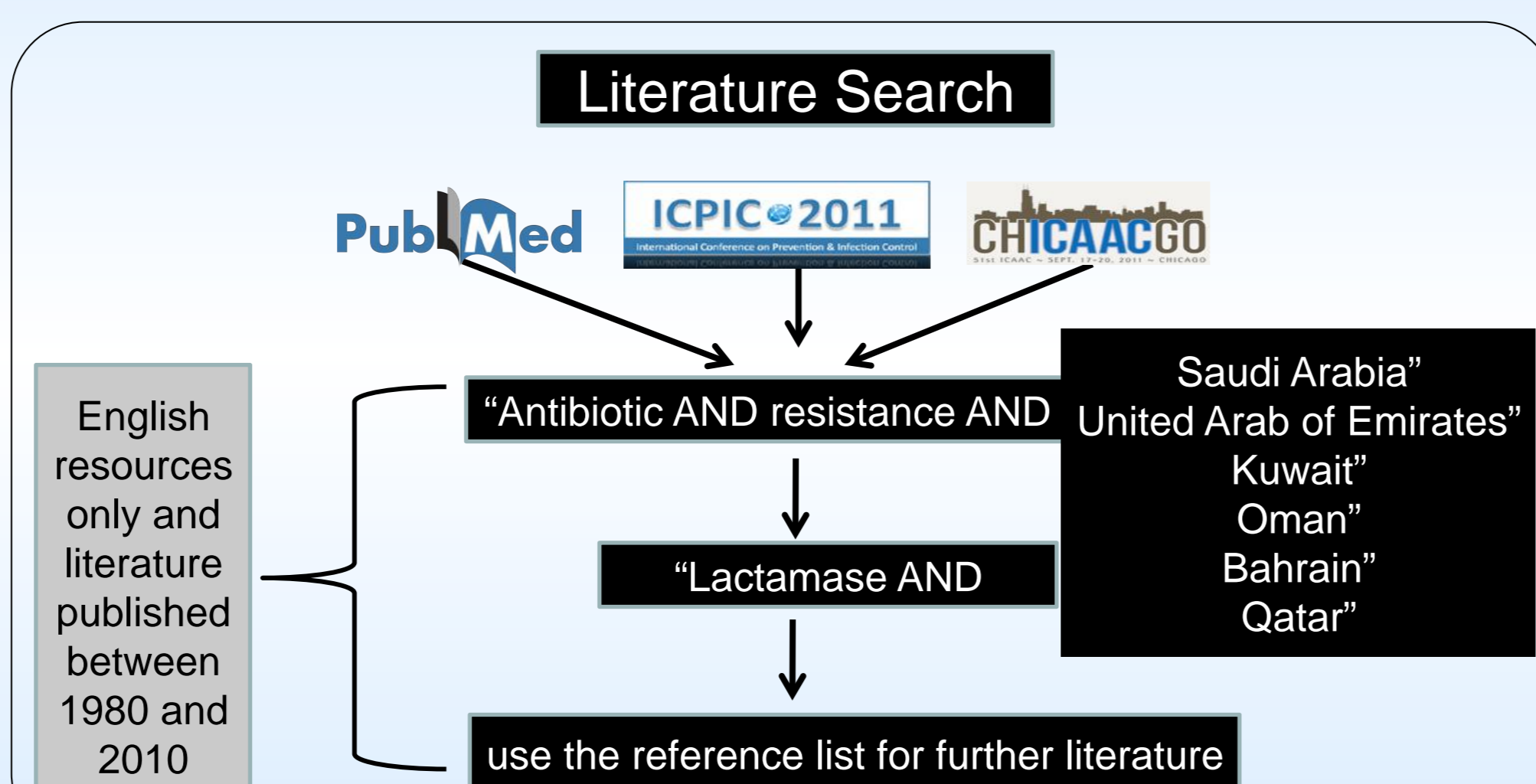


Figure 1. Summary of the methodology used to search for the literature.

Results

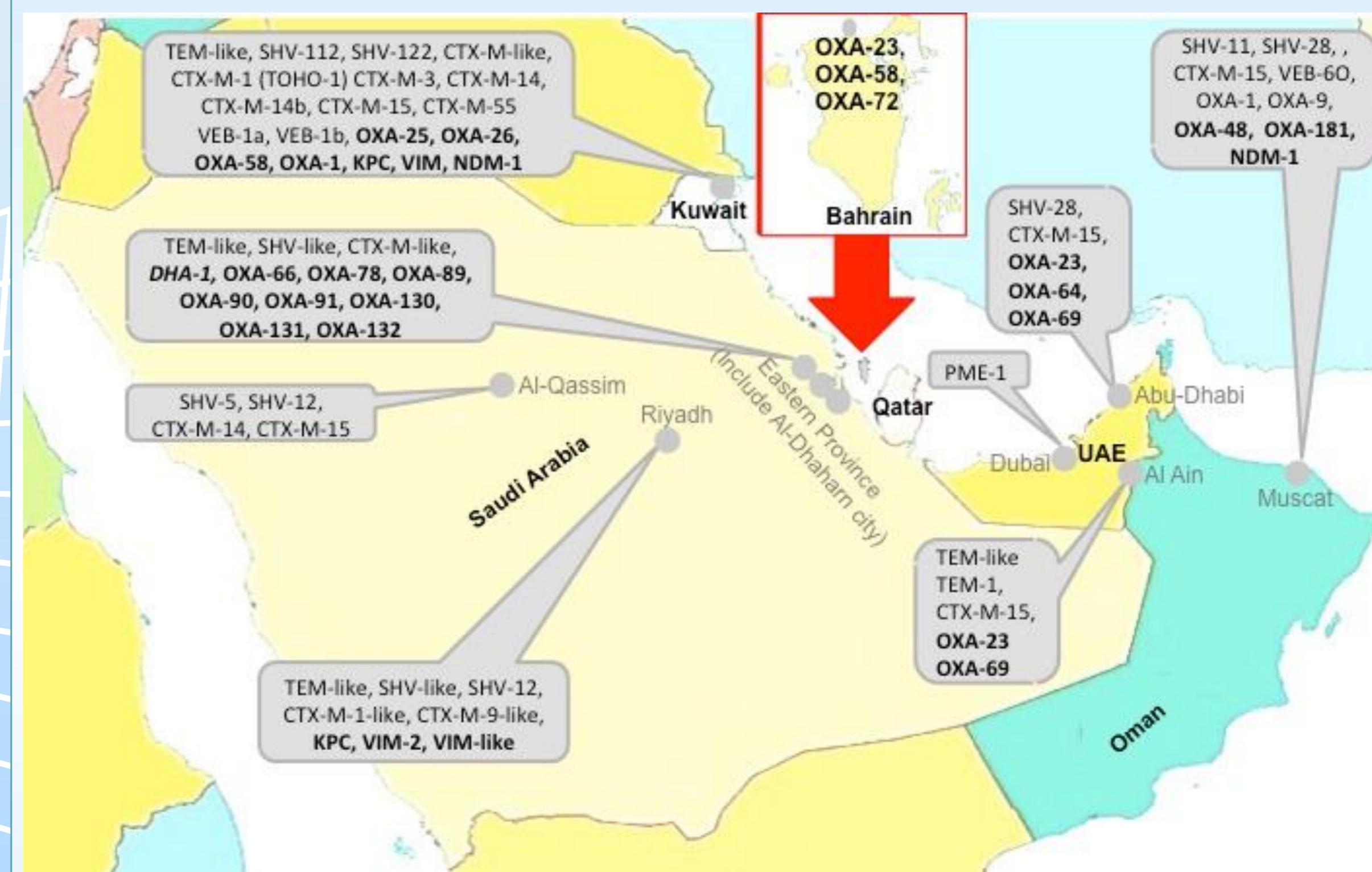


Figure 2. The geographical distribution of broad spectrum β -lactamases in the GCC states.

"The known known"

ESBLs

- SHV, TEM, and CTX-M are the most common ESBLs.
- CTX-M-15 is the predominant ESBL in different GCC states³⁻¹⁰.
- Less common CTX-M-ESBLs present in the region^{4, 11}.
- VEB-1a and VEB-1b emerged in Kuwait from *Pseudomonas aeruginosa* isolated from two different hospitals¹².
- *Proteus mirabilis* producing VEB-6 was isolated from Oman¹³.
- SHV-112 and SHV-122 emerged and identified in Kuwait^{5,6}.
- PME-1 was emerged in UAE. It was identified in Pittsburgh from a patient who had admission in Dubai¹⁴.

Carbapenemases

- The novel chromosomally encoded OXA-90, 130, 131, 132 in *A. baumannii* have emerged in Saudi Arabia¹⁵.
- Plasmid carried *bla*_{OXA-23} was found in *A. baumannii* isolates of UAE and Bahrain^{16, 17}.
- OXA-58 was found in *A. baumannii* isolated from Kuwait and Bahrain^{17, 18}.
- Different *K. pneumoniae* isolated from Oman carried plasmids encoding:
 - *bla*_{OXA-1}, *bla*_{OXA-9} and other ESBL genes with the *bla*_{NDM-1} gene⁸.
 - The recently emerged OXA-48-like enzyme OXA-181⁹.
- KPC was isolated in Saudi Arabia¹⁹ and *bla*_{KPC} gene was found in an *E. coli* isolated from Kuwait that also harboured *bla*_{VIM} and the emergent SHV-122⁶.
- Two reports documented the detection of NDM-1 producing *K. Pneumoniae* from Oman and Kuwait^{8, 20}.
- VIM enzymes produced by *Pseudomonas aeruginosa* in Saudi Arabia^{21, 22}.

Plasmid mediated AmpC

- DHA-1 emerged in Saudi Arabia and was named after Al-Dahran city²³.
- No further plasmid mediated AmpC have been ever reported from the region.

Mobile genetic elements

- Class 1 integron¹³
- insertion sequence^{7, 10}
- Conjugative plasmids^{4, 8, 9}
- Transposons⁹

"the known unknown" and why ?!

- PREDICTIONS -

ESBLs

- *E. coli* producing CTX-M-15-ESBL is likely to keep spreading.
- SHV-112 and SHV-122 will be seen more in *K. pneumoniae* and in other organisms in the GCC states and will extend gradually from there.
- Less common ESBLs (e.g. VEB) will be rarely detected.
- *P. aeruginosa* producing PME-1 will extend rapidly outside of UAE.
- Novel ESBL enzymes will keep emerging from this region.

Carbapenemases

- Outbreaks caused by KPC-producing Enterobacteriaceae²⁴ will be seen more.
- Most carbapenem resistant *P. aeruginosa* are likely to be due to VIM-production.
- OXA-48 will be increasingly reported from Enterobacteriaceae²⁵.
- GCC states will have a very high prevalence of NDM-1 producing bacteria.

Plasmid mediated AmpC

- DHA is disseminated in its origin.
- CMY will be detected in association with NDM-1 producing bacteria.

Why ?!

- The presence of successful clones in the region (e.g. ST131 *E. coli*^{6, 26}).
- The overuse and misuse of antibiotics.
- Suboptimal hand hygiene and environmental cleaning.
- Frequent travel and residence from where NDM-1 is in high prevalence (foreign workforce, pilgrims, and hospital transfer).

Conclusion

Many laboratories located in the GCC states as increasingly documenting phenotypic observation of broad spectrum β -lactamase resistance among GNB. Widely spread β -lactamase enzymes like KPC, VIM, NDM, and OXA-48 are increasingly noticed in the GCC countries, and with out active control will become more evident and might increase in prevalence. Since novel resistance mechanisms have emerged from this region, new enzymes should be expected. We suggest keeping track of emerging / introduced resistance mechanisms by adopting region-wide surveillance. Information provided will help to halt the problem by developing further interventional precautions including strong infection control practices and implementation of antimicrobial stewardship programs.

Acknowledgment

We would like to thank the GCC centre for Infection Control for supporting this study. We also thank King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia for academically sponsoring HMZ through King Abdullah Scholarship program.



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