



WHO Global Priority Pathogens List: A Bibliometric Analysis of Medline-PubMed for Knowledge Mobilization to Infection Prevention and Control Practices in Bahrain

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ABSTRACT

Objectives: In 2017, the World Health Organization (WHO) published a list of global priority pathogens (GPP) – 12 species of bacteria with critical, high, and medium antibiotic resistance (AR). In this review, our goal was to quantify published reports of AR in this group of pathogens using the Medline-PubMed databases. We also sought to quantify, compare and rank the top five reported AR pathogens globally, regionally and for Bahrain, and describe the evidence from Bahrain for the purpose of infection prevention and control, and to help research and development. **Methods:** We conducted a bibliometric, retrospective, descriptive review to search the Medline-PubMed database for reports specific to the WHO GPP list published up to 19 April 2017. **Results:** Our search revealed 42 136 documents with an increase in the last five years. Globally, there were more high tier pathogen documents (33 640) than critical (6405) and medium (2091). Methicillin-resistant *Staphylococcus aureus* (MRSA) was the highest reported, followed by extended-spectrum beta-lactamases (ESBL) resistant *Enterobacteriaceae* and vancomycin-resistant *Enterococcus faecium*. Nine out of the 12 pathogens were gram-negative. MRSA was the topmost documented pathogen globally and in the Gulf Cooperation Council (GCC) region zone of classification, whereas ESBL resistant *Enterobacteriaceae* ranked the top in Bahrain. There were two critical tier pathogens in the global, GCC region, and Bahrain. We found 14 articles from Bahrain, four articles on ESBL resistant *Enterobacteriaceae*, three on MRSA, two on carbapenem-resistant *Acinetobacter baumannii*, and five on different pathogens. **Conclusions:** Our findings suggest the need for a comprehensive, multipronged policy response particularly at the time when the antibiotic pipeline is nearly empty. We recommend thoughtful, integrated infection prevention and control strategies to address the immediate and long-term threats of AR in Bahrain and the GCC.

Antibiotics have greatly reduced morbidity and mortality from classical and opportunistic infections in the last few decades.¹ Contrasting the gains made, the accelerated global consumption of antibiotics and lapses in the infection prevention and control practices, have hastened the frequency and severity of antibiotic resistance (AR). On average, 2 million people become infected with antibiotic-resistant bacteria and 23 000 people die each year in the US. In the European Union, AR

causes 25 000 deaths and 2.5 million extra hospital days per year.² Mediterranean countries record the highest prevalence of AR. Relatively, southern, Mediterranean, and eastern countries tend to have higher overall use of antibiotics (daily doses/1000 people) than the northern European countries.^{3,4} Among the Gulf Cooperation Council (GCC) countries, with probable unregulated prescribing practice and an unaudited use of antibiotics, the prevalence of AR has been reported to be rising.⁵

Antibiotic-resistant bacteria were defined as bacterial isolates that became resistant to the administered drug with a change from 'susceptible' to 'intermediate' or 'resistant,' or from 'intermediate' to 'resistant' in the susceptibility pattern.⁶ The main drivers of AR are misuse and overuse of antibiotics due to presumptive treatment and inappropriate use of broad-spectrum antibiotics with erratic dosing.⁷ Other factors include transmission of resistant bacteria between patients, from healthcare workers to patients and vice versa, prophylactic use in animal husbandry and lack of guidelines and policies for the use of antibiotics. A report from the World Bank forewarned that antimicrobial resistance that includes AR could cause as much damage to the global economy as the 2008 financial crisis.⁸

Antibiotic development

Obtaining regulatory approval takes approximately 7.2 years, and this excludes phases of research discovery and preclinical and animal testing. Clinical approval success is only 16%.^{9,10} A report from the European Medicines Agency and the European Centre for Disease Prevention and Control cautioned of an almost barren pipeline with only two new drugs with a mechanism of action. There have been no novel target agents for gram-negative organisms (the cause of two-thirds of multidrug-resistant deaths) for decades.¹¹ Research has revealed that the probability of reversing AR once it established in healthcare settings, the community, and the environment is low. Further, there is a broken market model for making new antibiotics; they do not appear profitable compared to drugs used for chronic diseases. An estimate suggests a risk-adjusted net present value of 100 for antibiotics, compared to 300 for an anticancer drug, 720 for a neuropsychiatric medication, and 1150 for musculoskeletal drugs.^{12,13}

WHO global priority list of antibiotic-resistant bacteria

The World Health Organization's (WHO) first multicountry public awareness survey on AR revealed a serious worldwide threat to public health compromising the treatment of infectious diseases making tackling AR a high priority.¹⁴ On 27 February 2017, the WHO published the list of global priority pathogens (GPP) – a catalog of 12 species of bacteria grouped under three priority tiers according to

their AR: critical (three species), high (six species), and medium (three species). The major objective was to encourage the prioritization of funding and incentives, align research and development priorities of public health relevance, and garner global coordination in the fight against AR bacteria.¹⁵

The GCC consists of six Arab states: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the UAE. Bahrain, in the Arabian Gulf, has a population of around 1.4 million, which includes Bahrainis and multiethnic expatriates. The Ministry of Health provides health care services through three hospitals, 24 health centers, and three clinics. The Salmaniya Medical Complex (SMC) is the oldest and largest multispecialty health care facility. Private health care of varying capacities complements the public services.

The AR of the GPP coupled with the grim projections of antibiotic development call for immediate attention to recognize and review the existing research documents on AR of pathogens on this list. Translational research, such as knowledge mobilization refers to moving available knowledge, often from formal research. More than just 'bridging the gap,' knowledge mobilization seeks to make connections between research/expertise and policy/practice to improve outcomes in healthcare.^{16,17} Knowledge mobilization is expected to inhibit AR particularly in times of the loss of antibiotics from our armamentarium (i.e., moving available knowledge of Bedside to Bench for research and development priorities, risk communication, and infection prevention and control practices into active use).

We hypothesized that infection prevention and control is the major option at hand to reduce the burden of AR due to GPP through knowledge mobilization. Therefore, our goals were to search and quantify the documented evidence of AR in this group of pathogens using the Medline-PubMed databases.¹⁸ We also sought to quantify, compare, and rank the top five reported evidence of AR globally, regionally and locally, and describe the reported evidence from Bahrain as a source of knowledge mobilization for infection prevention and control, and use the Bedside to Bench evidence to help align research and development priorities.

METHODS

Uninterrupted, accessible, and indispensable information from a reliable source is central to

knowledge mobilization to achieve the WHO goals for combating AR of GPP. The most popular, peer-reviewed, reliable, and accessible biomedical literature is the Medline-PubMed literature database of the National Library of Medicine. Medline-PubMed has free access and easy-to-use databases with a focus on medicine and biomedical sciences, whereas Scopus and Web of Science cover most scientific fields. The keyword search with Medline-PubMed offers optimal update frequency and includes online early articles. Scopus automatically index all Medline-indexed journals. Scopus is currently limited to recent articles (published after 1995). Scopus and Web of Science do not include online early versions.¹⁹ Thus, healthcare professionals and researchers often rely on Medline-PubMed for scientific information as it is considered the most exhaustive database in the biomedical field. Infrequently, this unique criterion may exclude articles published in other biomedical literature databases.

Bibliometric studies systematically evaluate and analyze the research output on a specific topic through an understanding of the growth, impact, trends, and flow of knowledge within a chosen field of scientific research and contribute to the advancement of public health. The documents indexed in the Medline-PubMed literature database are considered for producing evidence in knowledge mobilization to inform infection prevention and control practices and help align research and development priorities of GPP.

We conducted a bibliometric, retrospective, descriptive review to search the Medline-PubMed database for reports specific to the WHO GPP list published globally, regionally, and locally up to 19 April 2017. We used the advanced search option to search for each GPP with their correlated resistant antibiotic. We used the common term quinolone for the AR of fluoroquinolones, and for third generation cephalosporin-resistant, extended-spectrum beta-lactamases (ESBL) was used. We followed a similar search algorithm for the GCC and Bahrain. For the GCC, we conducted a country-specific search of the number of documents reported on each GPP with their correlated resistant antibiotic, and the results were pooled to sum up the regional list. Likewise, we carried out a similar search algorithm for Bahrain, and the documents were reviewed and illustrated cumulatively as a case study. Two independent researchers extracted the data and abstracted the

literature from the returned searches. When there were disagreements between them, the results were discussed with the other co-authors to resolve. No ethical approval was needed for this study due to the use of bibliometric data abstraction and review of publicly available data, which does not involve human subjects directly.

RESULTS

We identified 42 136 documents (including original research, reviews, editorials, letters to the editor) indexed by Medline-PubMed up to 19 April 2017. There has been an increase in the number of publications in the last five years (one-third of the documents). Globally, there were more 'high' tier pathogen documents (33 640) than 'critical' (6405) and 'medium' (2091) tier pathogen documents [Table 1]. Among the WHO GPP list, methicillin-resistant *Staphylococcus aureus* (MRSA) was the highest reported (28 023 documents with 25 986 original research articles), followed by ESBL resistant *Enterobacteriaceae* (4001 documents, all were original research articles), and vancomycin-resistant *Enterococcus faecium* (2622 documents with 2484 original research articles); penicillin-non-susceptible *Streptococcus pneumoniae* was the least reported with 164 documents [Table 1]. Nine out of the 12 pathogens were gram-negative.

MRSA was the topmost documented pathogen globally and in the GCC, whereas ESBL resistant *Enterobacteriaceae* ranked top in Bahrain. Likewise, there were two critical tier pathogens globally, and in the GCC region and Bahrain. Articles from Saudi Arabia led the list among the GCC countries.

Of the 14 articles documented from Bahrain [Table 2], we found four articles on ESBL resistant *Enterobacteriaceae* (critical tier), three articles on MRSA (high tier), two on carbapenem-resistant *Acinetobacter baumannii* (CRAB; critical tier), and five articles on five different pathogens. An article that reported the occurrence of MRSA/vancomycin-resistant *enterococci* (VRE) co-colonization was accounted for both MRSA and CRAB. We found one article each from the Bahrain Specialist Hospital and Bahrain Defence Forces Hospital, and the remaining 12 from SMC. The articles reported from Bahrain were reviewed, synthesized, and presented in Table 2 according to their tiers listed in the WHO GPP list.

Table 1: Number of publications globally, and from the GCC and Bahrain indexed in PubMed for 2017 WHO global priority pathogens list.

Priority category	Pathogens	Antibiotic resistance	Grams stain	Global	GCC	Bahrain
Critical	<i>Acinetobacter baumannii</i>	Carbapenem-resistant	Gram-negative	768	30	2
	<i>Pseudomonas aeruginosa</i>	Carbapenem-resistant	Gram-negative	467	9	NR
	<i>Enterobacteriaceae</i> [†]	Carbapenem-resistant	Gram-negative	1169	16	NR
	<i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , <i>Enterobacter spp.</i> , <i>Serratia spp.</i> , <i>Proteus spp.</i> , <i>Providencia spp.</i> , <i>Morganella spp.</i>	Third generation cephalosporin-resistant		4001**	33	4
High	<i>Enterococcus faecium</i>	Vancomycin-resistant	Gram-positive	2622***	12	1
	<i>Staphylococcus aureus</i>	Methicillin-resistant Vancomycin intermediate and resistant	Gram-positive	28 023* 775	278 3	3 NR
	<i>Helicobacter pylori</i>	Clarithromycin-resistant	Gram-negative	271	3	1
	<i>Campylobacter</i>	Fluoroquinolone-resistant	Gram-negative	404	4	1
	<i>Salmonella spp.</i>	Fluoroquinolone-resistant	Gram-negative	886	19	NR
	<i>Neisseria gonorrhoeae</i>	Third generation cephalosporin-resistant Fluoroquinolone-resistant	Gram-negative	219 440	1 NR	1 NR
Medium	<i>Streptococcus pneumoniae</i>	Penicillin-non-susceptible	Gram-positive	164 [§]	5	NR
	<i>Haemophilus influenzae</i>	Ampicillin-resistant	Gram-negative	1693	21	1
	<i>Shigella spp.</i>	Fluoroquinolone-resistant	Gram-negative	234	11	NR

[†] Group of bacteria under large single family; *Ranked 1; **Ranked 2; ***Ranked 3; [§]Least reported.
NR: not reported. GCC: Gulf Cooperation Council.

DISCUSSION

Knowledge mobilization through bibliometric studies on the AR of GPP has provided useful and objective data for infection prevention and control, and to minimize morbidity and mortality due to these pathogens. Nine (75%) of the 12 GPPs were gram-negative. ESBL producing bacteria have increased worldwide; *Escherichia coli* and *Klebsiella pneumoniae* were commonly reported. The reports on ESBL, the third generation cephalosporin-resistant *Enterobacteriaceae*, a critical tier GPP from Bahrain, were the highest yielding four publications, whereas these ranked second globally and in the GCC in terms of original research publications. The majority of ESBL isolates were *E. coli* and *K. pneumoniae*. The bla (CTX-M) gene was found predominantly indicating bacterial evolution due to over prescription or weak enforcement of existing antibiotics policies.²⁶ The use of extended-spectrum cephalosporins and others are compromised leaving carbapenems as the therapeutic option.²⁵

S. aureus is one of the most frequent causes of bacterial infections. MRSA is the most reported

AR GPP globally and regionally; it was ranked second among the publications from Bahrain and the GCC publications account for 1%. A multiresistant SCCmec type III and coagulase type 36 genotype, and a non-multiresistant SCCmec type IV with different genetic backgrounds of MRSA were identified in Bahrain.²⁸ Overuse or misuse of methicillin and flouting simple hand washing has contributed to the development of MRSA.²² The burden of MRSA infections escalated the use of vancomycin leading to the vancomycin-intermediate and resistant *S. aureus* strains to which we found 775 global and three GCC documentations. MRSA/VRE co-colonization with MRSA trafficking between the hospital and community environment was reported from Bahrain.²⁷

Carbapenems are used as 'last resort' antibiotics. We found that CRAB – a critical GPP has been reported globally, regionally, and in Bahrain, and has dramatically increased over the last decade.³⁴ The heterogeneity of carbapenem-hydrolyzing class D B-Lactamases (CHDL)-encoding genes as the source of CRAB isolates was identified among eight

Table 2: Number of publications indexed in PubMed for WHO global priority pathogens list 2017 categorized by the publication year and location for Bahrain.

Priority category	Pathogens	Antibiotic resistance	Reports, n	Year of publication	Location	Remarks
1. Critical	<i>Acinetobacter baumannii</i>	Carbapenem-resistant	2 ²⁰	2009 ²⁰	Salmanya	Among the 454 <i>A. baumannii</i> isolates recovered from deep tracheal aspirates, 58% were resistant or intermediately susceptible to imipenem. The heterogeneity of CHDL-encoding genes as the source of CRAB isolates was identified.
				2015 ²¹	Salmanya – part of a first snapshot GCC study	CRAB isolates were isolated from swab specimens, sputum, and blood samples; 24% of the isolates represented healthcare-associated infections, while 53% were associated with nosocomial infections, 7% were colonizing hospital patients, and 8% were community-acquired. OXA-23-type was the major carbapenemase mechanism responsible for the resistance phenotype.
	<i>Enterobacteriaceae</i> *	Third generation cephalosporin-resistant	4 ²³	2009 ²³	Salmanya-retrospective analysis of records	Of the 11 886 <i>Enterobacteriaceae</i> isolated, 22.6% were ESBL producers. The majority of ESBL isolates were from inpatients (87.7%). <i>E. coli</i> (52.2%) and <i>K. pneumoniae</i> (24.3%) were predominant while <i>Proteus spp.</i> was (17.6%). Urine was the primary source (52.2%). Resistance to three classes of antibiotics was exhibited by > 25% of ESBL strains. Nitrofurantoin resistance was identified in 38.2% of urinary isolates.
				2009 ²⁴	Salmanya	The rate of ESBL-positive <i>E. coli</i> isolated from a NICU, SMC between 2002 and 2004 was 28.7% and increased to 42% between 2005 and 2007. ESBL-positive <i>Klebsiella spp.</i> isolates increased from 22% to 27% for both periods.
				2011 ²⁵	Salmanya	Of the 230 isolates (<i>E. coli</i> , n = 180; <i>K. pneumoniae</i> , n = 50) studied, 98% were CTX-M type. For <i>E. coli</i> isolates, 36.1% harbored CTX-M+TEM combination, and 37.8% had CTX-M alone. Whereas, only 10% of <i>K. pneumoniae</i> isolates harbored the CTX-M combination, and none had CTX-M only. The bla (CTX-M) gene was found predominantly in urine isolates (63.0%) and was associated with the resistance to fluoroquinolones, trimethoprim-sulfamethoxazole, and aminoglycosides. The use of extended-spectrum cephalosporins, quinolones, and aminoglycosides is compromised.
				2014 ²⁶	Salmanya	A subset of 80 cephalosporin-resistant <i>Enterobacteriaceae</i> was characterized for the presence of specific genogroups of CTX-M β-lactamases by multiplex- and monoplex- PCRs; 93.8% isolates showed the amplicons corresponding to any of the genogroups (1, 2, 8, 9, 25) and the remaining 6.2% isolates were negative. Further confirmation with respective monoplex PCR on the isolates demonstrated that 93.3% harbored CTX-M genogroup-1, and 6.7% harbored genogroup-9. Sequencing results of genogroup-1 isolates demonstrated the presence of CTX-M-15-like ESBL; however, discrepant results were noticed in genogroup-9 isolates, sequencing showed them as blaCTX-M-55-like ESBL.

Table 2: Number of publications indexed in PubMed for WHO global priority pathogens list 2017 categorized by the publication year and location for Bahrain.

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Priority category	Pathogens	Antibiotic resistance	Reports, n	Year of publication	Location	Remarks
2. High	<i>Enterococcus faecium</i>	Vancomycin-resistant	1	2011 ²⁷	Salmanya	MRSA and methicillin-resistant coagulase-negative <i>Staphylococcus</i> (MRCoNS)-positive patients were assessed for VRE co-colonization and characterization of vancomycin resistance genotype by PCR. Of the 112 patients (62 MRSA; 50 MRCoNS) stool, 11.6% was VRE-positive, predominantly <i>Enterococcus gallinarum</i> with vanC1 genotype and one was <i>Enterococcus faecium</i> (vanB genotype). Two <i>E. gallinarum</i> isolates harbored an additional vanB gene. The majority (77%) of VRE isolates were from patients in medical and surgical units. Male gender, prolonged hospitalization, and presence of comorbidities were significantly associated with MRSA/VRE co-colonization.
	<i>Staphylococcus aureus</i>	Methicillin-resistant	3*	2008 ²⁸	Salmanya	A total of 53 consecutive MRSA isolates were studied using AR patterns, coagulase gene polymorphism, staphylococcal cassette chromosome <i>mec</i> (SCC <i>mec</i>) typing and pulsed-field gel electrophoresis (PFGE). PFGE identified five pulsotypes (types A-E) with PFGE type A and its subtypes comprising 83% of the isolates that were multiresistant and had the SCC <i>mec</i> type III and coagulase type 36 genotype. The SCC <i>mec</i> type IV isolates were non-multiresistant with a different genetic background.
				2011 ²⁷	Salmanya	MRSA and MRCoNS positive patients and VRE co-colonization.
				2013 ²⁹	Bahrain Specialist Hospital	The impact of the infection control protocol on the prevalence of hemodialysis-related bacteremia and vascular access infection was evaluated. Of the 6161 hemodialysis sessions, 15 episodes of dialysis-related bacteremia were noted in nine patients. Three required hospitalizations. Blood cultures in 93% of the infection episodes grew <i>Sphingomonas paucimobilis</i> ; one patient had MRSA. The infection control protocol used seems to have been successful in reducing hemodialysis-related bacteremia and eliminating vascular access infection.
	<i>Helicobacter pylori</i>	Clarithromycin-resistant	1	2001 ³⁰	Salmanya	The prevalence of resistance among 83 <i>Helicobacter pylori</i> isolates cultured from biopsies taken during routine endoscopies was evaluated. Minimum inhibitory concentration of amoxicillin, tetracycline, clarithromycin, and metronidazole were determined by Epsilometer test; 33% were resistant to clarithromycin, and 20 of the 27 strains resistant to clarithromycin were also resistant to metronidazole.

Table 2: Number of publications indexed in PubMed for WHO global priority pathogens list 2017 categorized by the publication year and location for Bahrain.

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Priority category	Pathogens	Antibiotic resistance	Reports, n	Year of publication	Location	Remarks
	<i>Campylobacter jejuni</i>	Fluoroquinolone-resistant	1	2007 ³¹	Salmanya Bahrain Defence Forces Hospital	The sensitivity of human (n = 117 from the stool samples of the patients) and chicken (n = 33 from the liver and stool samples of chicken obtained from the slaughterhouses) from the <i>Campylobacter jejuni</i> isolates to erythromycin, ciprofloxacin, tetracycline, and trimethoprim-sulfamethoxazole were determined by agar dilution, disc diffusion and the E test. Over 80% of human and chicken isolates were resistant to ciprofloxacin.
	<i>Neisseria gonorrhoeae</i>	Third generation cephalosporin-resistant	1	1991 ³²	Salmanya	Ninety-one isolates of non-penicillinase-producing <i>Neisseria gonorrhoeae</i> from patients were tested for serotype, auxotype, and antibiotic susceptibility. Ten serovars and three auxotypes were found. Seventy of the 91 isolates were tested against ciprofloxacin and ceftriaxone, and 57% and 37% had MICs greater than or equal to 0.03 mg/L, respectively. DNA from two penicillin-resistant isolates was capable of transforming recipient strain FA19 to donor level of penicillin and cephalosporin resistance in four steps. The first three steps were indicative of the acquisition of known resistance mutations. The existence of the fourth level transformants, with the ability of donor DNA to transform strain FA140 to higher levels of resistance, suggests the presence of another resistance mutation.
3. Medium	<i>Haemophilus influenzae</i>	Ampicillin-resistant	1	2016 ³³	Salmanya - part of a multi-centric study	Seven hundred and twenty-six respiratory isolates comprising 265 isolates of <i>Streptococcus pneumoniae</i> , 125 isolates of <i>Streptococcus pyogenes</i> , and 336 isolates of <i>Haemophilus influenzae</i> were collected from Bahrain, Lebanon, Oman, and the UAE. Susceptibility to most antibiotics was high, except for ampicillin (70.2%) and amoxicillin (95.4%). There was considerable variability in susceptibility among the countries in the same region.

*Ranked 1; **Ranked 2; ***Ranked 3.

CHDL: carbapenem-hydrolyzing class D β -lactamases; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CTX-M: *cefotaximases*; ESBL: extended-spectrum beta-lactamases; MRCoNS: methicillin-resistant coagulase-negative *Staphylococcus*; MRS-A: methicillin-resistant *Staphylococcus aureus*; NIC: neonatal intensive care unit; OXA: Oxacillimases; PFGE: pulsed-field gel electrophoresis; SCmec: *Staphylococcal cassette chromosome mec*; SMC: *Salmonella* Medical Complex; TEM: *Temoneta*; VRE: vancomycin-resistant enterococcus.

patients in different units of SMC, leading to the death of four patients.²⁰ Also, the first GCC regional study of the molecular epidemiology of CRAB found that the OXA-23-type was the major carbapenemase mechanism for the resistance phenotype; one-fourth represented healthcare-associated infections, while half associated with nosocomial infections indicating the need for optimizing infection control practices and antibiotic stewardship.²¹

Besides ESBL, MRSA, and CRAB, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter jejuni*, third generation cephalosporin-resistant *Neisseria gonorrhoeae*, and ampicillin-resistant *Haemophilus influenzae* were other documented AR GPP found in the GCC region and Bahrain. The isolates of *H. influenzae* from Bahrain and its neighbors found that the resistance to ampicillin was 70% with considerable variability in susceptibility.³³

The GCC is one of the wealthiest regions.³⁵ However, among the top five GPP, two reports from the GCC and Bahrain were similar.³⁶ Moreover, the GCC has a dependent international workforce, tourists traveling to GCC states have grown, and Hajj attracts many visitors to Saudi Arabia.³⁷ Pilgrims transit through Bahrain to Saudi Arabia, which is deemed to be a risk factor for the acquisition and transmission of AR bacteria in Bahrain and the GCC.³⁸ The issue of AR is further compounded by the free/subsidized healthcare services in the region (overuse/misuse of antibiotics). Although non-prescription sales of antibiotics are illegal in the GCC, a study reported that 68% of pharmacies in Abu Dhabi and many pharmacies in Saudi Arabia had sold antibiotics without a prescription. Besides, 75% of patients who received antibiotics in the intensive care unit of a hospital in Qatar did not have a microbiologically-proven infection.³⁹ Thus, it is not surprising that high numbers of critical tier GPP are found in Bahrain and the GCC compared to the global trend.⁵ Our analysis has concluded that overuse or misuse of antibiotics has contributed to the development of AR requiring clear guidelines, policies, and audits for the judicious use of antibiotics.

Human adaptation to the new niche has been relatively short; virulent pathogens confront and target the immune system.⁴⁰ Microbes select for more than just antibiotic resistance with enhanced gene transfer abilities and many non-antibiotic agents or settings select for or maintain AR traits.⁴¹

Therefore, antibiotic stewardship forms a crucial intervention, supporting access to and appropriate use of antibiotics. Antibiotic stewardship programs that included heterogeneous interventions (auditing, restriction, treatment duration, cycling, or combination of antibiotics) have significantly reduced hospital costs and antibiotics use.⁴²

Recently, the WHO revised the antibiotics section (essential medicines list) by grouping into categories of access, watch, and reserve to combat AR by ensuring the best use of antibiotics, prescribing the right antibiotics, and preserving the 'last resort' antibiotics,⁴³ suggesting optimization of antibiotic stewardship as the priority for Bahrain and the GCC.

The evidence on AR characterizing the genogroups and molecular types are fragmentary from the GCC and Bahrain. Identification of the multiresistant and non-multiresistant SCCmec types of MRSA, heterogeneity of CHDL-encoding genes of CRAB, OXA-23-type as the major carbapenemase mechanism, and the presence of CTX-M-55 of CTX-M β -lactamases would aid in research and development priorities globally. More studies addressing community-acquired AR infections and a focus on pediatric or geriatric populations should be prioritized. However, more regional and country-specific studies are needed, especially from the Bedside to Bench of AR at a molecular level. Understanding the role of resistance determinants (e.g., carbapenemases and efflux pumps) is crucial.

We recommend integrated infection prevention and control strategies to address the immediate and long-term threats of AR in Bahrain and the GCC. To corroborate, the infection control protocol introduced in the Bahrain Specialist Hospital has been successful in reducing hemodialysis-related bacteremia and eliminating vascular access infection.²⁹ Similarly, an active surveillance program after an outbreak of VRE at the University of Virginia Hospital drastically reduced the primary VRE bacteremia.⁴⁴ Likewise, a program of intensive surveillance and infection control reduced the risk of hospital-acquired ventilator-associated pneumonia at the University of Massachusetts Medical Center.⁴⁵ Further, a recent systematic review revealed that antibiotic stewardship programs with infection control measures were more effective (31% reduction), and programs emphasizing hand hygiene reduced the incidence of AR by 66%.⁴⁶ Hand hygiene

had the greatest impact when co-implemented with antibiotic cycling (51% reduction).⁴⁶

Our review is not bereft of limitations. First, articles were taken from the Medline-PubMed literature database only, which may have excluded articles published in journals indexed in other databases. Nonetheless, the Medline-PubMed literature database is the most exhaustive database in the biomedical field. Second, the global distribution of AR of GPP was not carried out owing to the enormity of the documents. Moreover, our aim was restricted to rank only the top five reported evidence on AR globally, regionally, and locally. Third, this study was restricted to the selection of English-only articles as Medline-PubMed consists largely of English-language journals. Fourth, we did not assess the bias and validity of studies as this was a bibliometric review.

CONCLUSION

We were able to substantially describe the major AR pathogens on the WHO's GPP list found in Bahrain and, to a lesser extent, in the GCC as well as a glimpse at the global scenario. Our findings suggest the need for a comprehensive, multipronged policy response since the antibiotic pipeline is barren. In Bahrain, there is a need for antibiotic stewardship and enforcement of stringent infection prevention and control practices in hospitals and community healthcare settings. Additionally, active surveillance of antibiotic resistance and research on AR of GPP will continue to grow to shape policy solutions to prolong antibiotic effectiveness and research and development to add new antibiotics. To our knowledge, this is the first study to examine and compare the frequency of GPP and characterize the studies published.

Disclosure

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