Infection and Drug Resistance

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ORIGINAL RESEARCH

Landscape of Multidrug-Resistant Gram-Negative Infections in Egypt: Survey and Literature Review

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Purpose: This article is the first to review published reports on the prevalence of multidrug-resistant (MDR) gram-negative infections in Egypt and gain insights into antimicrobial resistance (AMR) surveillance and susceptibility testing capabilities of Egyptian medical centers.

Materials and Methods: A literature review and online survey were conducted.

Results: The online survey and literature review reported high prevalence of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (19–85.24% of *E. coli*, and 10–87% of *K. pneumoniae*), carbapenem-resistant Enterobacteriaceae (35–100% of *K. pneumoniae* and 13.8–100% of *E. coli*), carbapenem-resistant *Acinetobacter baumannii* (10–100%), and carbapenem-resistant *Pseudomonas aeruginosa* (15–70%) in Egypt. Risk factors for MDR Gram-negative infections were ventilated patients (67.4%), prolonged hospitalization (53.5%) and chronic disease (34.9%). Although antimicrobial surveillance capabilities were deemed at least moderate in most centers, lack of access to rapid AMR diagnostics, lack of use of local epidemiological data in treatment decision-making, lack of antimicrobial stewardship (AMS) programs, and lack of risk prediction tools were commonly reported by respondents.

Conclusion: This survey has highlighted the presence of knowledge gaps as well as limitations in the surveillance and monitoring capabilities of AMR in Egypt, with most laboratories lacking rapid diagnostics and molecular testing. Future efforts in Egypt should focus on tackling these issues via nationwide initiatives, including understanding the AMR trends in the country, capacity building of laboratories and their staff to correctly and timely identify AMR, and introducing newer antimicrobials for targeting emerging resistance mechanisms in Gram-negative species.

Keywords: Egypt, Gram-negative bacteria, hospital-acquired pneumonia, intra-abdominal infections, multidrug resistance, urinary tract infections

Introduction

Gram-negative species are ubiquitous in nature and associated with a plethora of infections in different body sites.[1] Gram-negative bacteria are intrinsically resistant to many antibiotics.[2] Antimicrobial resistance (AMR) in Gram-negative bacteria has become increasingly problematic for healthcare systems over the past 20 years, with escalating costs and mortality.[1] Gram-negative species are frequently associated with nosocomial infections, including bloodstream infections (BSI), hospital-acquired pneumonia (HAP), urinary tract infections (UTI), skin and soft-tissue infections (SSTI) and complicated intra-abdominal infections (cIAI).[3,4]

Resistance becomes particularly problematic when organisms become multi-drug-resistant (MDR) or extensively drug-resistant (XDR) as physicians are then

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Received: 17 January 2021
Accepted: 26 March 2021
Published: 24 May 2021

limited by the treatment options they can use.[5] In addition to the increasing resistance to available treatments, concerns regarding the limited number of new treatments under development have also been raised.[6] In response to these concerns, the World Health Organization (WHO) published the global priority list of antibiotic-resistant bacteria, identifying resistant species deemed to be the most significant globally, and for which there is an urgent requirement for new antimicrobials to be developed.[7] Three Gram-negative species were deemed "critical" under priority-one: carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant and third-generation cephalosporin-resistant Enterobacteriaceae.[7]

As new classes of antibiotics have been developed, Gram-negative bacteria have gained resistance through a variety of β-lactamase enzymes: initially through penicillinases, then cephalosporinases, extended-spectrum β-lactamases (ESBLs) and carbapenemases.[8] Carbapenem resistance can result from the production of carbapenemase enzymes, or the combined activity of ESBL and efflux pumps, or porin mutations.[1] Both intrinsic and acquired carbapenem resistance has been observed in Gram-negative bacteria, with acquired resistance in Enterobacteriaceae being mainly plasmid-mediated leading to horizontal gene transfer.[8] Carbapenems are highly effective broad-spectrum antibiotics; there is therefore an urgent need for carbapenem-sparing strategies to reduce the spread of multidrug resistance globally.[9]

Treatment of MDR Gram-negative infections requires high levels of clinical and microbiological expertise as well as knowledge of the local epidemiology and patient risk factors.[10] Commonly used antimicrobial agents to treat MDR Gram-negative infections include colistin, aminoglycosides, tigecycline, carbapenems and Fosfomycin.[10–15] Novel treatment options for MDR gram-negative infections include the β-lactam/β-lactamase inhibitor (BL–BLI) combinations (ceftazidime–avibactam, meropenem–vaborbactam, ceftolozane–tazobactam and imipenem cilastatin relebactam), eravacycline and cefiderocol.[10,16–19] Challenges in the treatment of MDR Gram-negative infections include the emergence of resistance to novel antimicrobials, such as ceftazidime–avibactam,[20] meropenem–vaborbactam,[21] ceftolozane–tazobactam,[22] and cefiderocol.[23] Implementing restrictions on the overuse of these antibiotics is therefore required whilst ensuring early and appropriate treatment for critically ill patients.[10] Further challenges include the ineffectiveness of newer agents against CRAB[24] and the need for carbapenemase identification prior to BL-BLI treatment.[10] There is growing complexity surrounding the treatment of MDR Gram-negative infections, with the necessity to understand both national and local epidemiology, how to provide adequate empiric coverage, and have sufficient surveillance to identify opportunities to treat bacteria with emerging resistance mechanisms with new agents.

Aims

This article aims to:

1. Review the prevalence of MDR Gram-negative infections in Egypt from published literature
2. Gain a better understanding of the epidemiology of MDR Gram-negative infections as well as AMR surveillance and susceptibility testing capabilities of medical centers in Egypt through an online survey

We focused on the WHO priority-one MDR Gram-negative pathogens. This is the first publication of its kind to summarize published data concerning the prevalence of MDR Gram-negative infections in Egypt and to obtain additional insights using a survey.

Materials and Methods

Literature Search

A literature search of publications reporting prevalence of MDR Gram-negative human infections in Egypt was performed. Publications were considered if they: included full-text articles with data concerning infections from medical or surgical units of hospitals in Egypt between 2004 and 2020, were written in English, included data concerning multidrug resistance, carbapenem resistance (or carbapenemase production) or third-generation cephalosporin-resistant (or extended-spectrum beta-lactamase production) in Enterobacteriaceae, *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii* or *Pseudomonas aeruginosa* and if they contained data concerning infections in humans. References within the publications were also screened for potential inclusion.

A MedLine database search was conducted through PubMed using the search string and filters: (Egypt[Text Word] OR Egyptian[Text Word]) AND (Gram-negative OR Gram negative OR Enterobacteriaceae OR

Escherichia coli OR Klebsiella pneumoniae OR Acinetobacter baumannii OR Pseudomonas aeruginosa) AND (infection OR bacteria OR organism OR pathogen) AND (multidrug resistant OR multidrug-resistant OR multi-drug resistant OR MDR OR carbapenem resistance OR carbapenem-resistant OR carbapenemase OR extended-spectrum beta-lactamase OR ESBL OR third-generation cephalosporin resistant OR MBL OR metallo-beta-lactamase); filters: Full text, English, from 2004/1/1–2020/11/28; sorted by: First Author. The last search was conducted on the 28 November 2020. Titles and abstracts were first screened for inclusion, followed by a full-text review. Data was then extracted and tabulated for included publications.

Online Survey

The online survey was created using SurveyMonkey®. Questions were generated to focus on the most common bacteria causing nosocomial infections, especially the WHO "critical" priority pathogens,[7] and on the capabilities of centers across Egypt and the barriers they face. Questions were all closed-ended questions with yes/no or multiple-choice answers only to ensure reliability of the survey. Survey results were collected anonymously, with only center names and specialty collected for the participating physicians to encourage honest reporting of information.

Validity of the survey was established using published methodologies:[25,26] firstly, the survey was reviewed on two levels, by a group of experts in antimicrobial resistance who evaluated if the survey questions sufficiently captured the topic of interest and by a medical communications agency with experience in questionnaire development who evaluated the survey for clarity, consistency and errors. Secondly, a pilot was conducted on 8 participants to determine the acceptability and clarity of the questions, and to confirm its face validity. The questionnaire was modified accordingly, and the responses obtained in the pilot study were excluded from the study analysis.

For centers to participate in the survey, they had to meet the following eligibility criteria: (1) tertiary care hospital, (2) more than 30 intensive care unit (ICU) beds, (3) functional laboratory with supplies and personnel able to perform culture and full bacterial identification and antimicrobial susceptibility testing, and (4) infectious

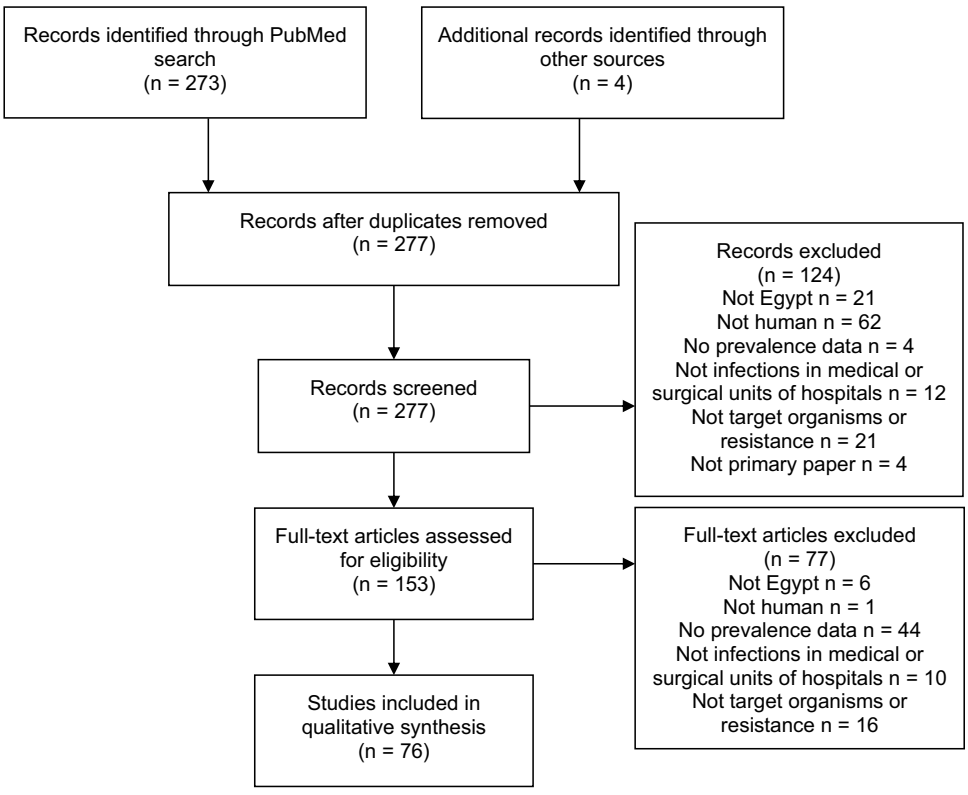


Figure 1 PRISMA flow diagram of literature search.
Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology.* 2009;62(10). Creative Commons.

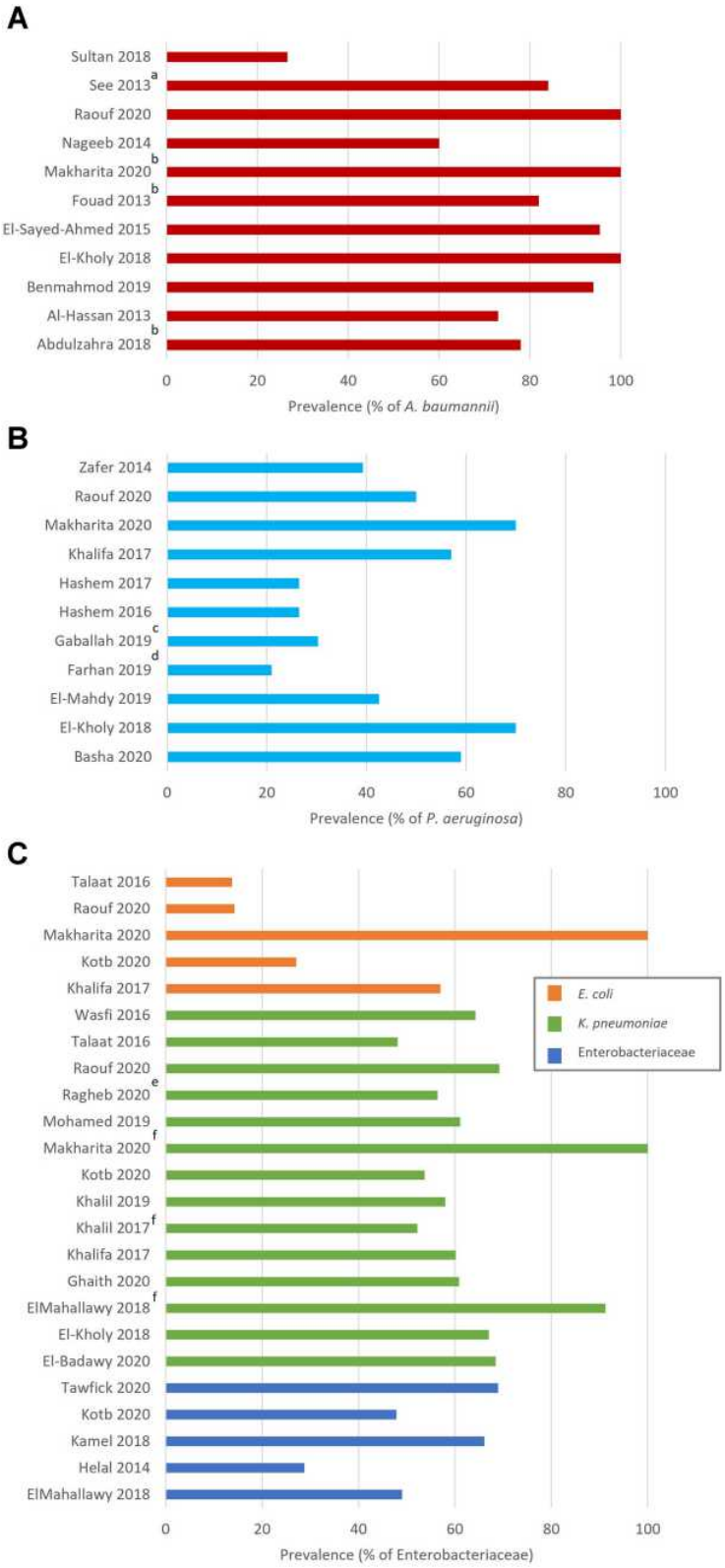


Figure 2 Summary of the prevalence (%) of reported carbapenem-resistant/carbapenemase-producing Gram-negative species: (**A**) *A. baumanii*; (**B**) *P. aeruginosa*; and (**C**) Enterobacteriaceae.

Notes: Data from references [27,32–63]. [a]*Acinetobacter spp.*; [b]% of CRAB; [c]% of *P. aeruginosa* isolates resistant to one or more β-lactams; [d]% of MDR *P. aeruginosa*; [e]% of carbapenem-non-susceptible *K. pneumoniae*; [f]% of CRKP

disease physicians or ICU physicians with expertise in infectious diseases and AMR, based on selection criteria for Egypt's national hospital-acquired infections (HAI) surveillance program.[27] The survey was circulated to physicians on September 21, 2020 with a follow-up sent on September 28, 2020. The survey was closed on October 20, 2020. Analysis included descriptive statistics of survey responses, median and interquartile range (IQR). Responses were summarized where a response was given, excluding missing values. All statistical analyses were performed using StataIC (StataCorp, Version 16).

The study protocol was approved by the Research Ethics Committee of Cairo University Medical School in accordance with the Declaration of Helsinki (Ethical approval number: N-13-2020). All physicians who responded to the survey consented to participation in the study and publication of the data.

Results

Literature Search

A total of 277 studies were screened. It was deemed that 201 publications were not eligible for inclusion. A total of 76 publications were included (Figure 1).

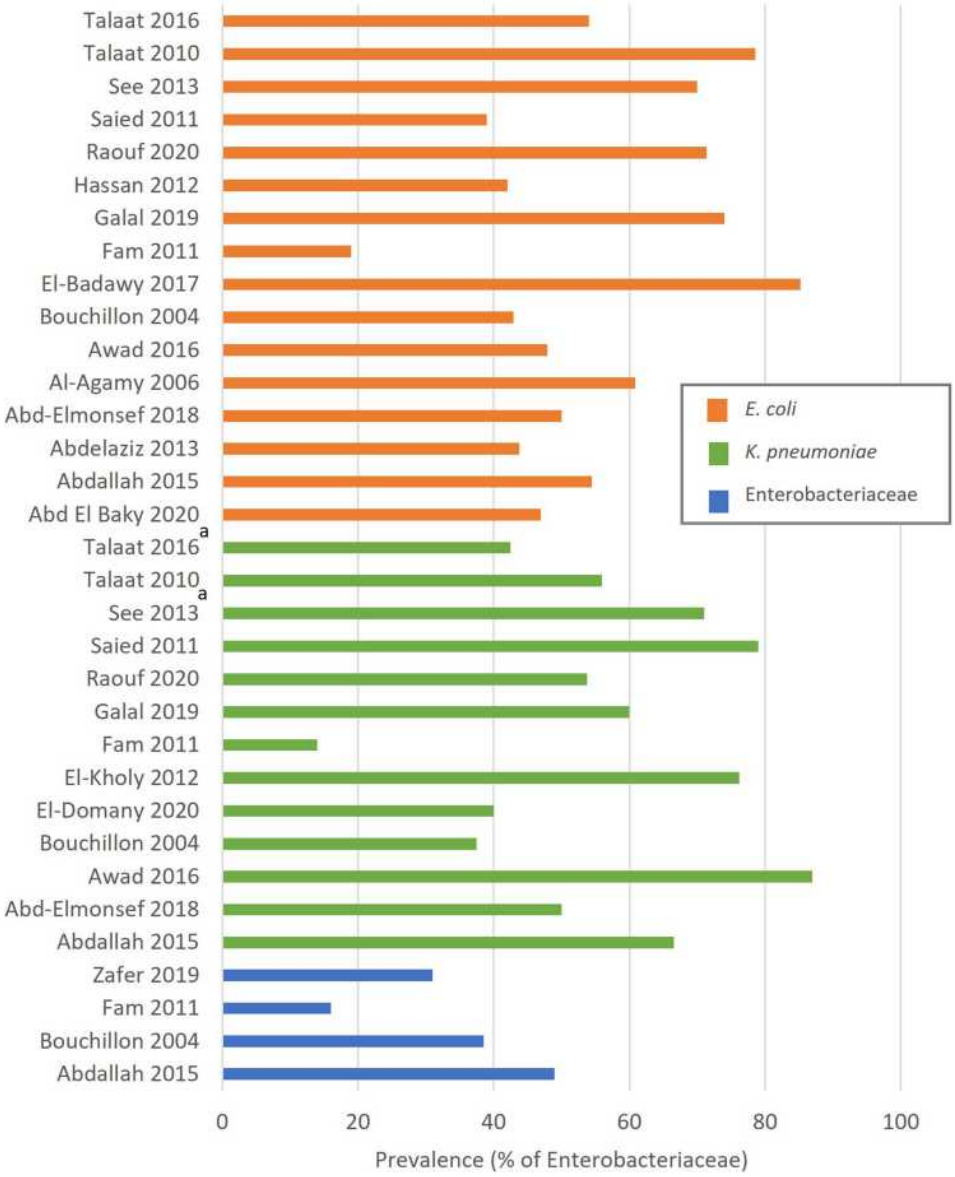
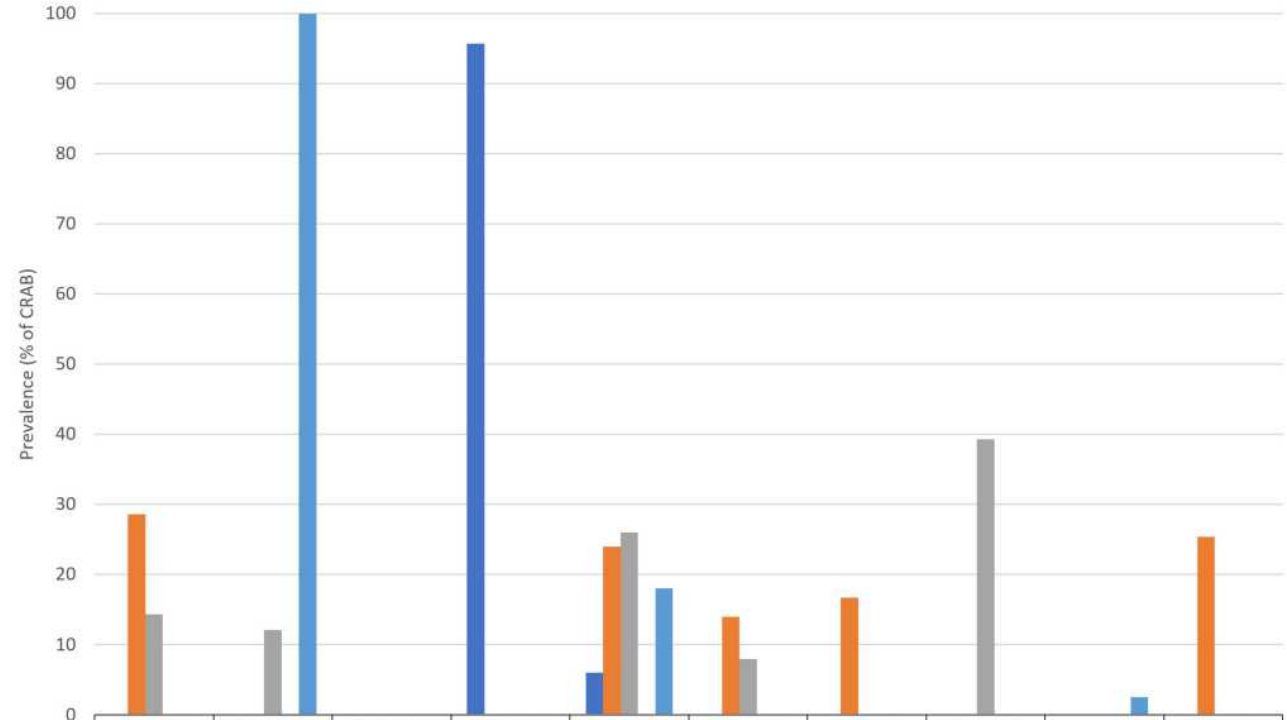


Figure 3 Summary of the prevalence (%) of ESBL-producing/third-generation cephalosporin-resistant Enterobacteriaceae (ESBL-E).
Notes: Data from references [27,33,42,64–79]. [a]*Klebsiella* spp.

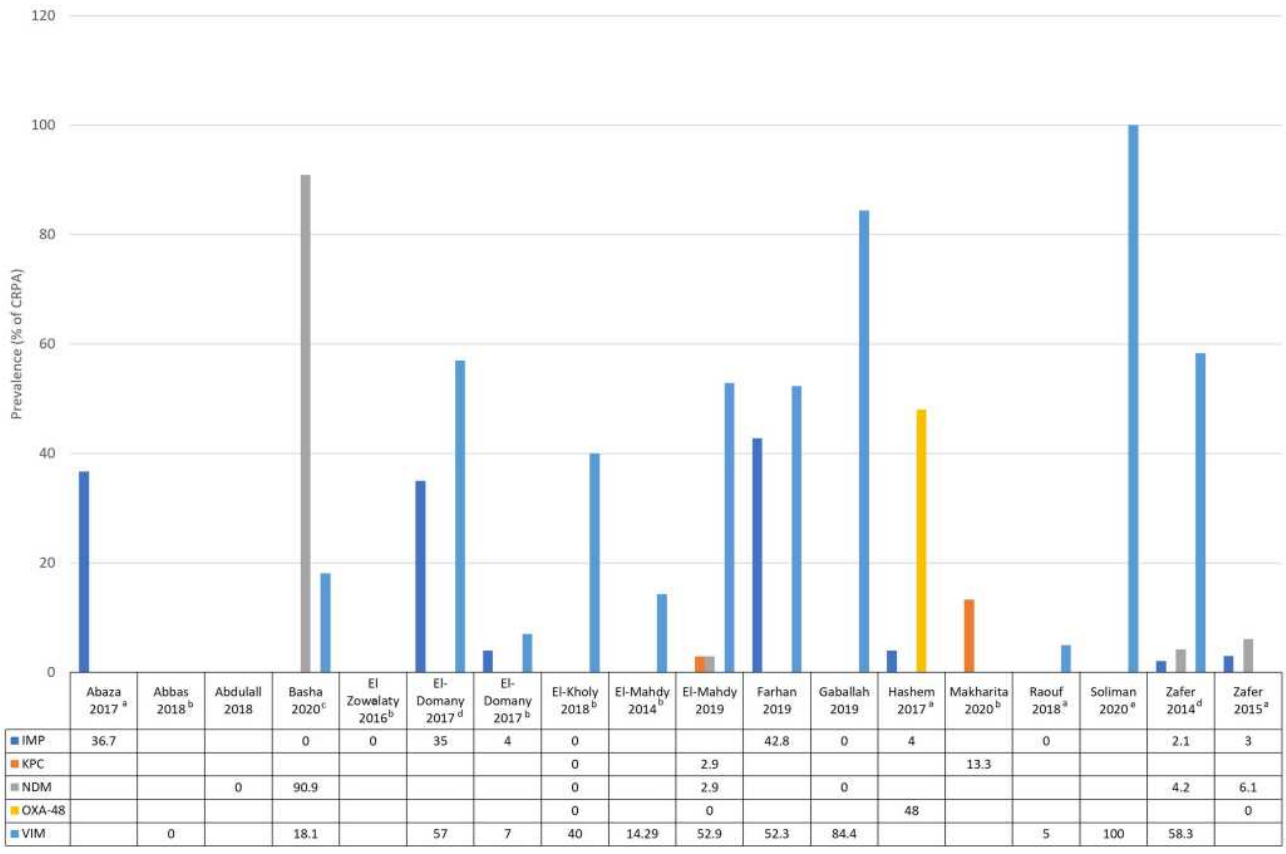
Prevalence of MDR Gram-negative infections in Egypt described in the literature is summarized in Figures 2–8, details of the studies are provided in Supplementary File 1 and additional data in Supplementary File 2. Reports of multidrug resistance in Gram-negative bacterial species are high in Egypt with 21–100% of *P. aeruginosa*, 30–100% of *A. baumannii*, 42.5–98.73% of *K. pneumoniae* and 22.8–96.07% of *Escherichia coli* defined as MDR.

Carbapenem resistance was reported in 26.6–100% of *A. baumannii*, 21–70% of *P. aeruginosa* and 28.8–69% of Enterobacteriaceae (*K. pneumoniae* 48.1–100% and *E. coli* 13.8–100%) in Egypt (Figure 2). ESBL production or third-generation cephalosporin resistance was reported in 16–48.93% of Enterobacteriaceae, 14–87% of *E. coli*, and 19–85.24% of *K. pneumoniae*, respectively (Figure 3). Carbapenemase genes New Delhi metallo-β-lactamase (NDM) and *K. pneumoniae* carbapenemase (KPC) were commonly reported in *A. baumannii* with a prevalence of 0–39.3% and 0–28.6%, respectively (Figure 4). Verona integron-encoded metallo-β-lactamase (VIM) and imipenemase metallo-β-lactamase (IMP) were commonly reported in *P. aeruginosa* with a prevalence of 0–100% and 0–42.8%, respectively (Figure 5). NDM and oxacillin carbapenemase 48 (OXA-48) genes were commonly reported in Enterobacteriaceae with a prevalence of 26.-04–68.88% and 30–58.62%, respectively (Figure 6). NDM genes were also commonly reported in *E.coli* with a prevalence of 13.7–80.39% (Figure 7). In *K. pneumoniae*, there was a high prevalence of KPC, NDM and OXA-48 genes at 0–95.8%, 20.9–100%, and 0–80.65%, respectively (Figure 8). ESBL genes cefotaximase-Munich (CTX-M), sulphydryl variable (SHV) and Temoniera (TEM) were highly prevalent in 20.2–89.13%, 10.1–50% and 31.5–56.52% of Enterobacteriaceae, respectively (Figure 6). In *E. coli*, CTX-M and TEM prevalence was 32.8–100% and 4.2–100%, respectively



	Abdulall 2018	Abouelfetouh 2019	Al-Agamy 2014[a]	Alkasaby 2017[b]	Benmahmod 2019[b]	El Bannah 2018	El-Kholy 2018[b]	El-Sayed-Ahmed 2015[b]	Fouad 2013	Makharita 2020
IMP		0		95.7	6	0	0			
KPC	28.6	0	0		24	14	16.7			25.4
NDM	14.3	12.1			26	8	0	39.3		
OXA-48	0						0			
VIM		100		0	18	0	0		2.5	

Figure 4 Summary of the prevalence (%) of carbapenemase genes in *A. baumannii*. **Notes:** Data from references[36–40,80–84]. [a]% of imipenem-insusceptible *A. baumannii*; [b]% of *A. baumannii*.



	Abaza 2017 [a]	Abbas 2018 [b]	Abdulall 2018	Basha 2020 [c]	El Zowalaty 2016 [b]	El-Domany 2017 [d]	El-Domany 2017 [b]	El-Kholy 2018 [b]	El-Mahdy 2014 [b]	El-Mahdy 2019	Farhan 2019	Gaballah 2019	Hashem 2017 [a]	Makharita 2020 [b]	Raouf 2018 [a]	Soliman 2020 [e]	Zafer 2014 [d]	Zafer 2015 [a]
IMP	36.7			0	0	35	4	0			42.8	0	4		0		2.1	3
KPC								0		2.9				13.3				
NDM			0	90.9				0		2.9		0					4.2	6.1
OXA-48								0		0			48					0
VIM		0		18.1		57	7	40	14.29	52.9	52.3	84.4			5	100	58.3	

Figure 5 Summary of the prevalence (%) of carbapenemase genes in *P. aeruginosa*.
Notes: Data from references [37,40,44–47,49,51,80,85–92]. [a]% of MBL-producing *P. aeruginosa*; [b]% of *P. aeruginosa* isolates resistant to one or more β-lactams; [c]% of XDR-CRPA; [d]% of imipenem-resistant *P. aeruginosa*; [e]% of carbapenemase genes

(Figure 7). In *K. pneumoniae*, CTX-M, SHV and TEM prevalence was 38.9–100%, 0–81% and 0.4–57.1%, respectively (Figure 8).

Survey Results

Survey results are discussed below and provided in full in Supplementary File 3.

Participating Physicians

Of the 99 physicians who were sent the survey, 46 (46.5%) responded. Where specialty was specified (n = 40), 53.49% (n = 23) of the physicians were intensivists, 39.53% (n = 17) microbiologists, 4.65% (n = 2) infectious disease specialists, and 2.33% (n = 1) internal medicine specialists. Responding physicians were from 14 centers across Egypt.

Risk Factors and Types of HAI

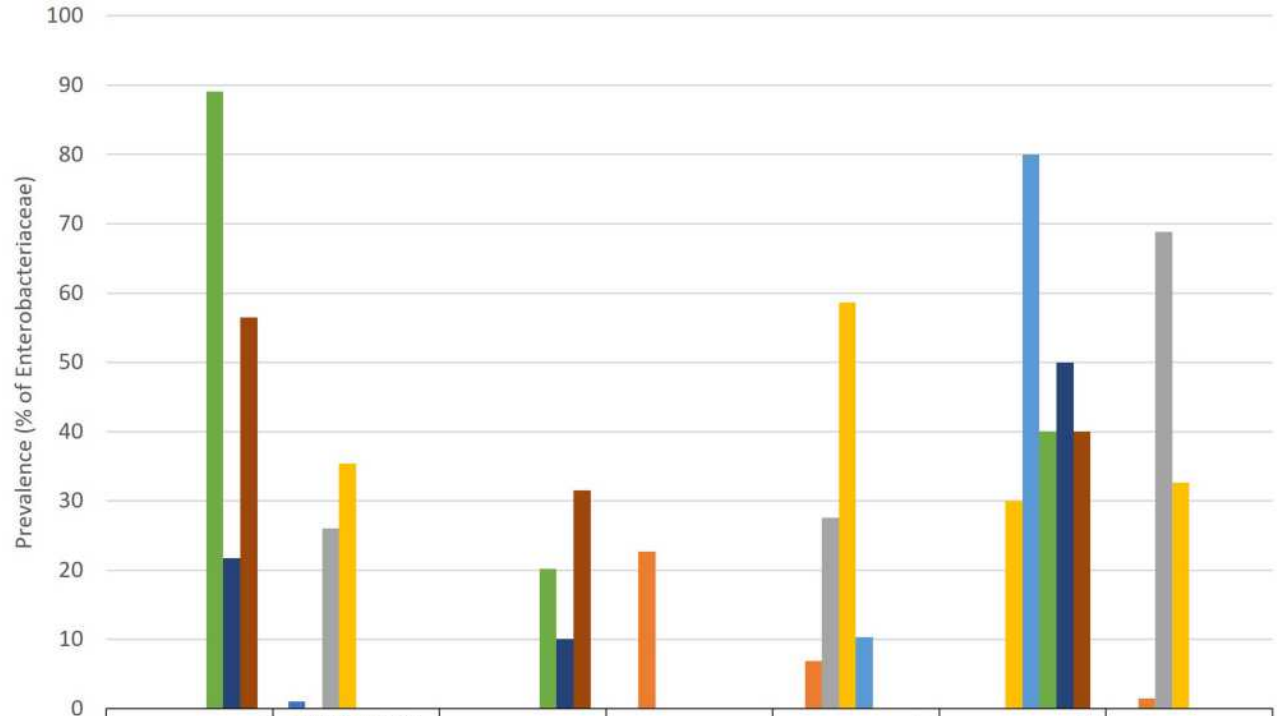
Respondents reported the most common risk factors for MDR Gram-negative infections were ventilated patients (67.4%) or those experiencing prolonged hospitalization (53.5%). Chronic disease (34.9%), prior antibiotic use (32.6%) and elderly (23.3%) were also relatively common (Figure 9). The most common type of HAI in their centers was HAP (65.9%), followed by UTI (12.2%), and BSI (9.8%) (Figure 10, Figure 11, Figure 12, Figure 13).

Prevalence of Gram-Negative MDR Species

Median (IQR) prevalence of Gram-negative species, Gram-negative MDR species and carbapenemases reported by responding centers are shown in Figures 11–13. Most respondents reported increased prevalence of MDR gram-negative infections over the past 5 years in their centers (95.83%), with most of these reporting an increase of 25–50% (60.87%). Many respondents predicted that prevalence of such infections is likely to increase over the next 10 years (58.33%).

Capabilities

Whilst 16.67% of respondents reported best-practice capabilities, the majority of respondents reported either good (37.50%) or moderate (29.17%) AMR surveillance



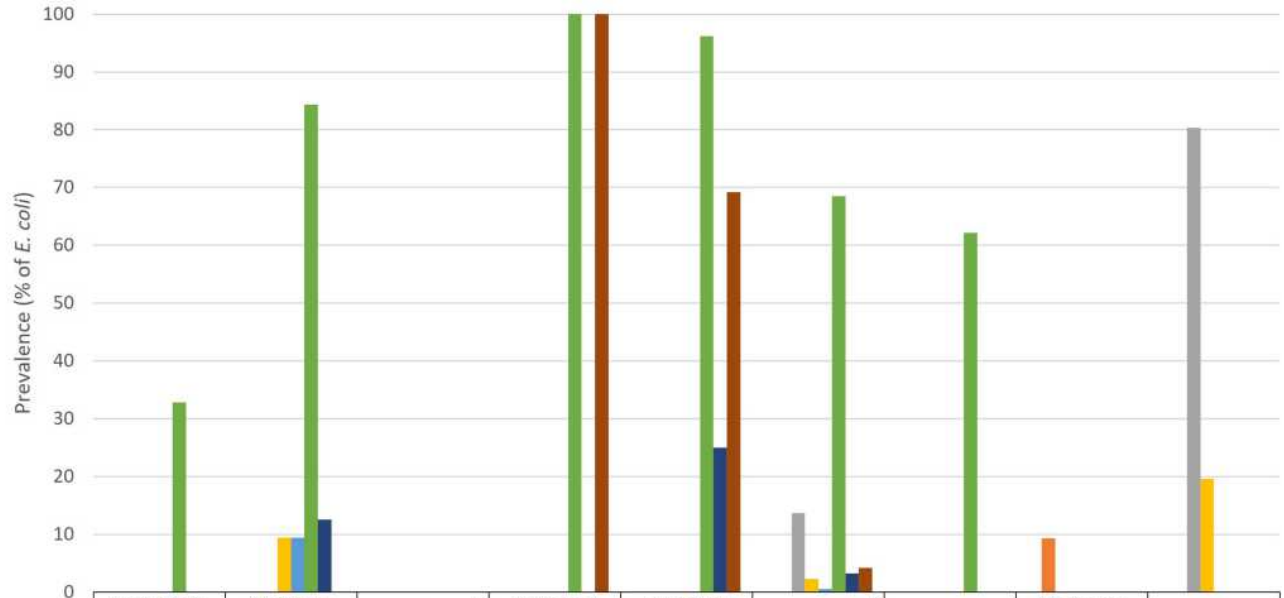
	Abdallah 2015[a]	ElMahallawy 2018	Galal 2019	Helal 2014	Kamel 2018[b]	Poirel 2013[c]	Tawfick 2020
IMP		1.04					0
KPC		0		22.7	6.89		1.48
NDM		26.04			27.58		68.88
OXA-48		35.42			58.62	30	32.59
VIM		0			10.3	80	0
CTX-M	89.13		20.2			40	
SHV	21.74		10.1			50	
TEM	56.52		31.5			40	

Figure 6 Summary of the prevalence (%) of carbapenemase and ESBL genes in Enterobacteriaceae.
Notes: Data from references [52–55,64,72,93]. [a]% of ESBL-E; [b]% of carbapenemase genes; [c]% of CRE

capabilities in their centers, with more than half (58.33%) of respondents reporting that surveillance cultures were being performed for colonization at their center. In terms of antimicrobial susceptibility testing (AST), a large proportion of respondents reported that their centers performed culture antimicrobial susceptibility testing for all ICU patients (86.36%). One respondent reported that only patients at high risk of MDR infection were tested. Vitek® 2 was the most common automated AST system available to the respondents (50%). Other available automated AST systems or devices included Beckman Coulter Microscan® (5%), BD Phoenix™ Emerge™ (5%), BioFire® FilmArray® (20%), and other (15%). Most respondents reported that their centers were changing AST technology to take advantage of susceptibility panels with a greater range of more recent antimicrobial agents (81.82%). Only seven (35%) respondents reported having access to rapid AMR detection diagnostics, with singleplex PCR (n = 3), multiplex PCR (n = 2), microarray nanoparticle identification (n = 2), and GeneXpert® (n = 1) being the available platforms specified.

Clinical Practice Procedures

The Infectious Diseases Society of America (IDSA) was the most used source of guideline recommendations in clinical practice (65%), with national guidelines (40%), hospital guidelines (30%), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (25%), WHO (20%), and The British Society for Antimicrobial Chemotherapy (5%) also reported. Half of physicians also



	Abd El Baky 2020	Abdelaziz 2013[a]	Abdulall 2018[b]	Al-Agamy 2006[a]	El-Badawy 2017[a]	El-Kholy 2020[c]	Helmy 2017[a]	Makharita 2020	Tawfick 2020
IMP							0		
KPC			0			0		9.3	
NDM						13.7			80.39
OXA-48		9.37	0			2.3			19.6
VIM		9.37				0.5	0		
CTX-M	32.8	84.37		100	96.15	68.5	62.16		
SHV		12.5		0	25	3.2	0		
TEM				100	69.23	4.2			

Figure 7 Summary of the prevalence (%) of carbapenemase and ESBL genes in *E. coli.*
Notes: Data from references [40,55,75–78,80,94,95]. [a]% of ESBL-producing/third-generation cephalosporin-resistant *E. coli*; [b]% of CREC; [c]% MDR *E. coli*

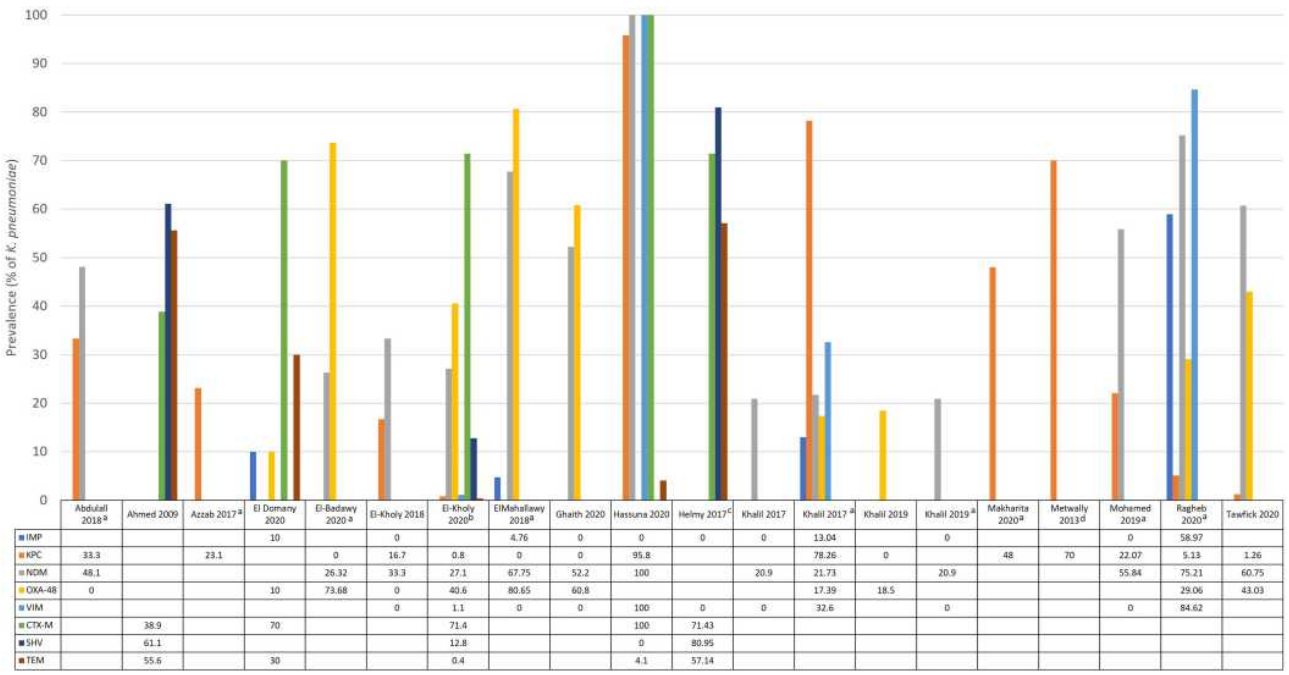
reported other guidelines that significantly impacted on their clinical practice in treating Gram-negative infections. Most respondents reported that the guidelines implemented were either partially adequate (45%) or not adequate (40%) for managing MDR gram-negative infections. Whilst 60% of respondents reported hospital-specific protocols or standard operating procedures for the treatment of Gram-negative infections, the majority (75%) reported that Gram-negative infection risk prediction protocols were not used. Twelve respondents (65%) reported that local epidemiology data was used in treatment decision-making and contributed to antimicrobial stewardship (AMS), five respondents (25%) reported that it was not used. Eleven respondents (55%) reported the presence of a specific AMS program in their center.

Barriers and Challenges

More than half of respondents reported a lack of collaboration and communication between the laboratory and clinical staff (54.55%) as one of the key issues relating to AMR surveillance; incomplete data (36.36%) and lack of regulation governing surveillance (31.82%) were also key issues. Cost of tests (62.50%), knowledge gaps in clinicians of relevance to antimicrobial surveillance (56.25%), speed of test result reporting (43.75%), and availability of tests in laboratory (37.50%) were barriers to ideal susceptibility testing. The cost of newer treatments (55%), lack of access to newer antibiotics (50%), lack of formal AMS programs (45%), and clinical teams' poor compliance with recommendations (30%) were considered barriers to successful management of MDR Gram-negative infections.

Discussion

The survey and the literature review both highlight the magnitude of the AMR problem across Egypt, with reports of very high rates of ESBL-E, CRE, CRAB, and CRPA. According to the survey, carbapenem resistance was



	Abdulall 2018[a]	Ahmed 2009	Azzab 2017[a]	El Domany 2020	El-Badawy 2020[a]	El-Kholy 2018	El-Kholy 2020[b]	ElMahallawy 2018[a]	Ghaith 2020	Hassuna 2020	Helmy 2017[c]	Khalil 2017	Khalil 2017[a]	Khalil 2019	Khalil 2019[a]	Makharita 2020[a]	Metwally 2013[d]	Mohamed 2019[a]	Ragheb 2020[a]	Tawfick 2020
IMP				10		0		4.76	0	0	0	0	13.04		0			0	58.97	
KPC	33.3		23.1		0	16.7	0.8	0	0	95.8			78.26	0		48	70	22.07	5.13	1.26
NDM	48.1				26.32	33.3	27.1	67.75	52.2	100		20.9	21.73		20.9			55.84	75.21	60.75
OXA-48	0			10	73.68	0	40.6	80.65	60.8				17.39	18.5					29.06	43.03
VIM						0	1.1	0	0	100	0	0	32.6		0			0	84.62	
CTX-M		38.9		70			71.4			100	71.43									
SHV		61.1					12.8			0	80.95									
TEM		55.6		30			0.4			4.1	57.14									

Figure 8 Summary of the prevalence (%) of carbapenemase and ESBL genes in *K. pneumoniae*.
Notes: Data from references [40,55–62,70,80,94–99]. [a]% of carbapenemase-resistant/-producing *K. pneumoniae*; [b]% of MDR *K. pneumoniae*; [c]% of ESBL-producing/third-generation cephalosporin-resistant *K. pneumoniae*; [d]% of ertapenem non-susceptible *K. pneumoniae*.

reported in 20% (10–45%) of *E. coli*, 35% (25–60%) of *K. pneumoniae*, 15% (3–40%) of *P. aeruginosa*, and 10% (5–30%) of *A. baumannii*. ESBL production was reported in 20% (10–60%) of *E. coli*, 10% (5–50%) of *K. pneumoniae*, and 17% (7–20%) of other Enterobacteriaceae. Key challenges faced by physicians within the country relate to a lack of access to the necessary tools, such as rapid diagnostics, molecular testing, local epidemiology data and newer antibiotics, as well as a lack of healthcare infrastructure, stewardship, regulation, and collaboration.

A recent review of the epidemiology of MDR infections across the Arab League has shown that Egypt reports high resistance levels compared to its neighbors.[28] ESBL-E prevalence was 4–25% in the Gulf Cooperation Council (GCC), 31–66% in the Levant, and 9–35% in the rest of the African countries versus 55% in Egypt.[28] CRE

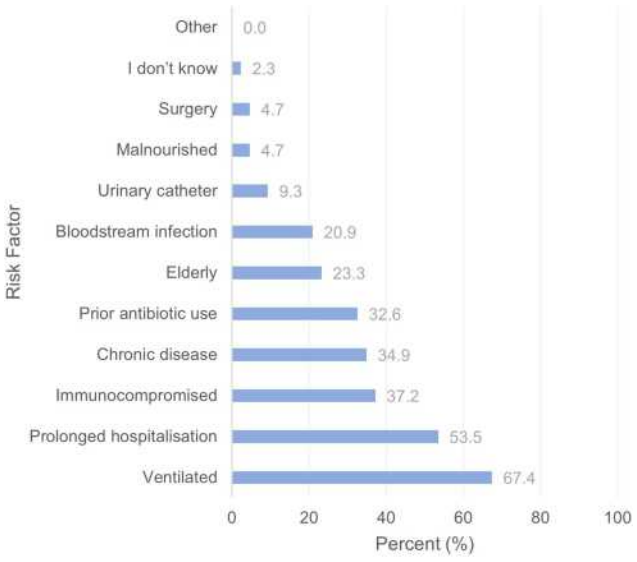


Figure 9 Risk factors for MDR Gram-negative infections.

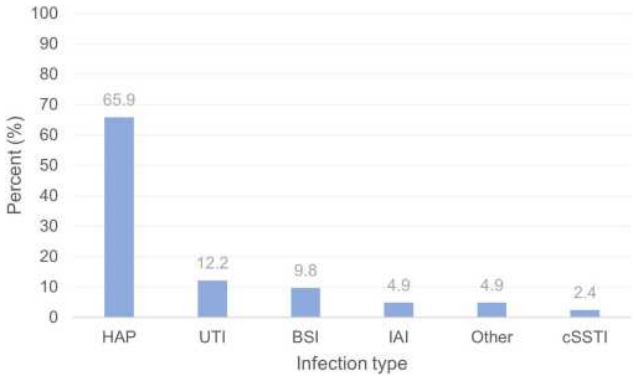


Figure 10 Types of HAI in Egyptian centers.
Abbreviations: cSSTI, complicated skin and soft-tissue infection; BSI, bloodstream infection; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; UTI, urinary tract infection.

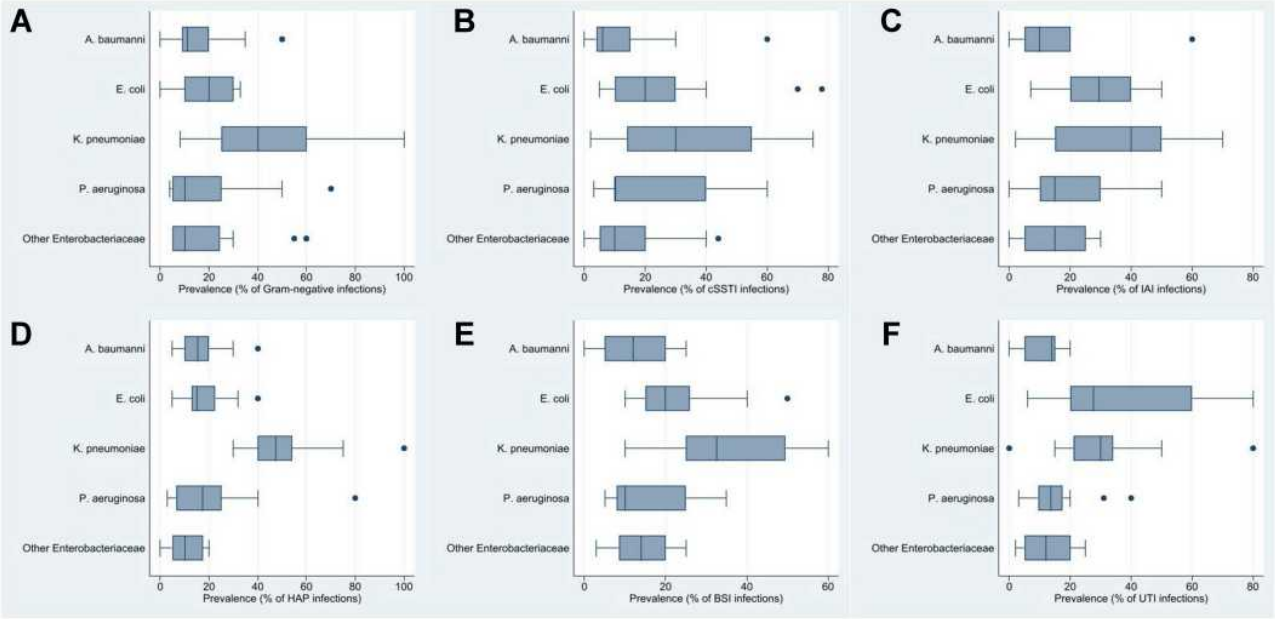


Figure 11 Gram-negative species prevalence across Egyptian centers: (**A**) all Gram-negative infections; (**B**) cSSTI; (c) IAI; (**D**) HAP; (**E**) BSI; (**F**) UTI.
Abbreviations: cSSTI, complicated skin and soft-tissue infection; BSI, bloodstream infection; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; UTI, urinary tract infection.

prevalence was 0–1% in the GCC, 1–22.5% in the Levant, and <2% in the rest of the African countries versus 28% in Egypt. CRPA prevalence was 3–21% in the GCC, 28–93% in the Levant, and 19–56% in the rest of the African countries versus 51% in Egypt. Finally, CRAB prevalence was 36–100% in the GCC, 64–89% in the Levant, and 75–88% in the rest of the African countries versus 93% in Egypt.[28] Such high levels of resistance in Egypt compared to neighboring countries are thought to be the result of challenges in infection prevention and control,[29] high levels of antibiotic consumption,[30] and use in non-human populations.[31] The levels of resistance reported in our online survey are lower than those reported within this review, potentially a result of differences in the populations or hospitals included in both studies.

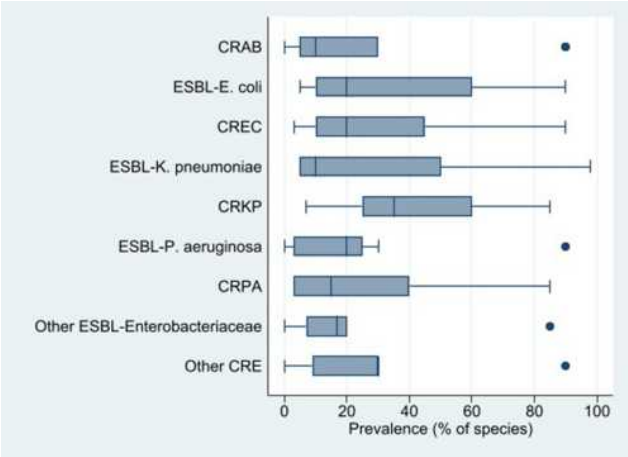


Figure 12 Prevalence of MDR Gram-negative species.
Abbreviations: CRAB, carbapenem-resistant *A. baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CREC, carbapenem-resistant *E. coli*; CRKP, carbapenem-resistant *K. pneumoniae*; ESBL, extended-spectrum β-lactamase.

The survey and the literature review also highlight the large variation in prevalence of MDR infections across hospitals or centers. Some of this variability might be a result of many studies reporting prevalence within a small number of centers or hospitals (typically between one and six hospitals) or with small number of samples or isolates. However, three published studies have described prevalence of MDR Gram-negative HAI via Egypt's national HAI surveillance program, reporting data from up to 310 ICUs from 72 hospitals.[27,32,33] Whilst historically Egypt has reported limitations in its surveillance and microbiology capabilities,[29] the national HAI surveillance program paves the way to obtaining epidemiological data which will help to inform infection control and prevention strategies.[27] A further potential reason for the variability in prevalence may be the nature of the Egyptian healthcare system: a complex and fragmented network of Ministry of Health and Population facilities, private hospitals, university hospitals, and military hospitals, as well as other ministry-associated hospitals with varied levels and availability of medical

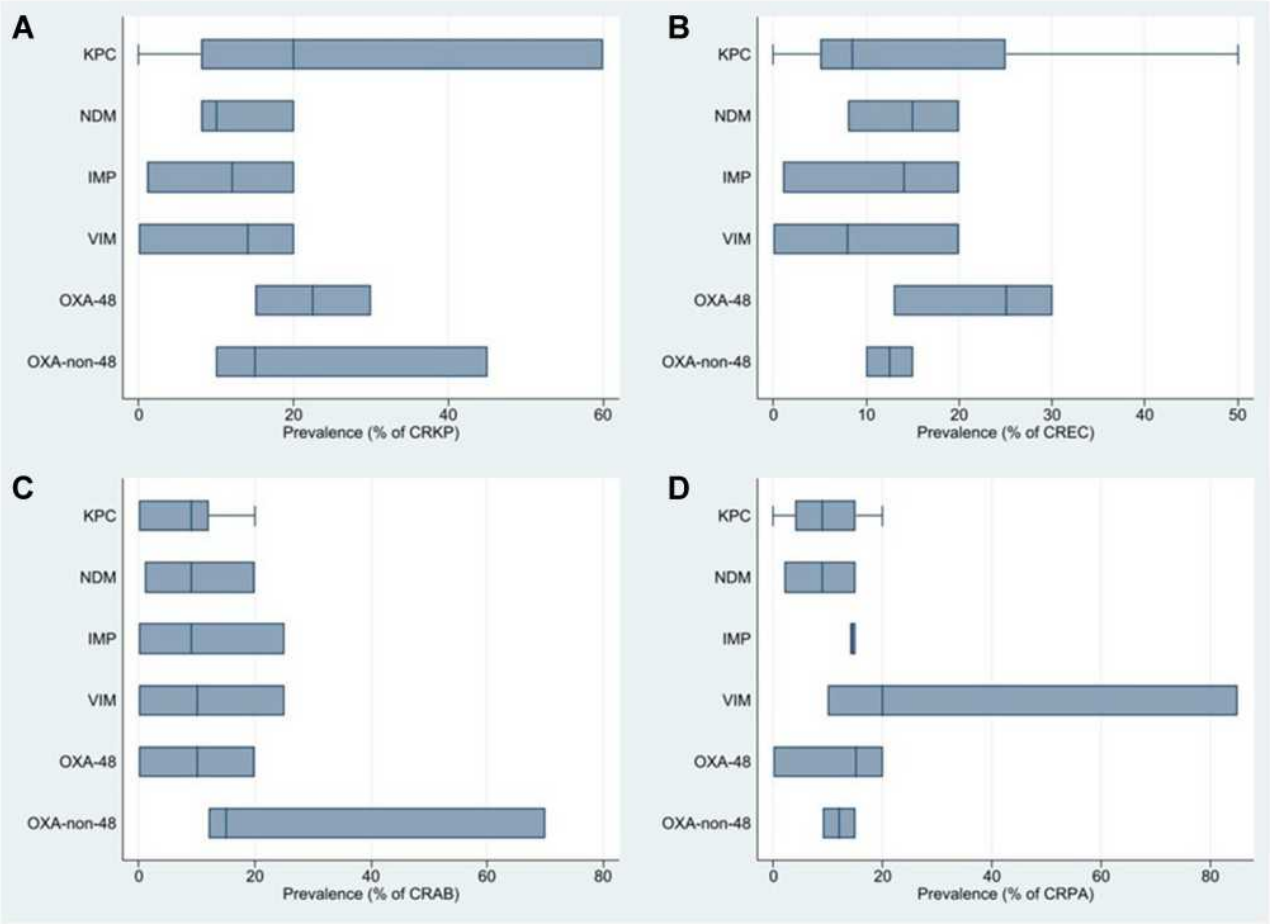


Figure 13 Prevalence of carbapenemases: (**A**) CRKP; (**B**) CREC; (**C**) CRAB; (**D**) CRPA.
Abbreviations: CRAB, carbapenem-resistant *A. baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CREC, carbapenem-resistant *E. coli*; CRKP, carbapenem-resistant *K. pneumoniae*; IMP, imipenemase metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillin carbapenemase 48; OXA-non-48, oxacillin carbapenemase (non-48); VIM, Verona integron-encoded metallo-β-lactamase.

services.[29] This poses significant challenges in terms of AMS and AMR control initiatives. Furthermore, in contrast to many countries, the infectious disease specialty is almost absent in Egypt, which impedes prudent use of antimicrobials, adequate cross-specialty communication, institution-wide infectious disease leadership, and the development and management of AMS systems. Finally, the process of data collection varies between different centers, with no single authority responsible for organizing data collection concerning AMR. A further gap in MDR Gram-negative infection reporting in Egypt includes the lack of data concerning community acquired MDR infections.

The survey has provided valuable information concerning MDR Gram-negative infections in Egypt and has collected a broad range of data concerning prevalence of such infections, capabilities of centers, and key barriers and issues faced in AMR surveillance, susceptibility testing, and management of MDR Gram-negative infections. The survey was anonymous to encourage honest reporting of data by physicians; nevertheless, the accuracy of the data reported cannot be verified. Furthermore, only tertiary care hospitals with capabilities to perform bacterial identification and AST were included in the survey; this has the potential to overestimate the prevalence of MDR Gram-negative species across the country. The number of responses to questions relating to carbapenemase prevalence within the survey was low, resulting from the lack of molecular testing capabilities within the country. Therefore, cautious interpretation of carbapenemase prevalence is required. Future efforts in Egypt should focus on collecting additional data concerning molecular characterization of resistance genes across a variety of healthcare centers in Egypt. Such molecular data will provide a true understanding of the resistance patterns in MDR Gram-negative infections in the country, facilitate future

use of novel antimicrobials such as BL-BLIs and, therefore, is required to combat recent trends of increasing antimicrobial resistance. Future steps in the fight against AMR in Egypt should include antimicrobial stewardship to optimize the use of antibiotics, improve laboratory capacities and national initiatives to control antimicrobial resistance.

Conclusion

The survey has provided valuable information concerning the epidemiology and resistance patterns of MDR Gram-negative infections in Egypt, whilst highlighting the challenges and barriers faced by physicians. Collective efforts to overcome these challenges and reduce the burden of MDR Gram-negative infections across the country are urgent and critical to preventing the spread of multidrug resistance. Nationwide initiatives are needed for understanding the AMR trends in the country, capacity building of laboratories and staff to correctly and timely identify AMR as well as introducing newer antimicrobials for treatment of MDR Gram-negative infections.

Acknowledgments

We thank all participating physicians who completed the survey. Medical writing support was provided by Dr. Abigail Holland of Connect Communications, Dubai.

Funding

This work, including medical writing support, was supported by Pfizer, Egypt.

Disclosure

Professor Noha Elsharnouby reports non-financial support from Pfizer, during the conduct of the study. Dr Mohamed Abdel Aziz, Ahmed Mohamed Helmy, and Ramy Kotb report being employees of Pfizer during the conduct of the study and outside the submitted work. The authors report no other potential conflicts of interest for this work.

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