

Antimicrobial resistance and conflict in the Middle East: A systematic review

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Abstract

Background: In spite of the evident general negative effects of armed conflict on countries' health systems and populations' health outcomes, little is known about similar impacts of conflicts on the spread of antimicrobial resistances (AMR). This review was to address this evidence gap and describe:

1. Patterns of AMR in the Middle East (ME) and resistance profiles of pathogens included in the Global AMR Surveillance System (GLASS) supported by the World Health Organization;
2. Differences in proportions of AMR isolates between conflict and non-conflict countries.

Methods: A systematic literature review was conducted following PRISMA guidelines and searching five electronic databases. Subject heading and free text were searched for "antimicrobial resistances" and "Middle East", to identify observational studies on AMR published from January 2011 to June 2018. Data were extracted from included articles on a predefined set of variables. Percentages of AMR were analysed as median and interquartile ranges. Risk of bias was assessed using the Newcastle-Ottawa Scale.

Results: A total of 132 articles met the inclusion criteria. Included studies showed heterogeneity in study design, laboratory methods and standards for interpretation of results, and an overall high risk of bias. Main findings were the following:

1. High proportions of carbapenem resistance in *Acinetobacter spp.* (median 74.2%: range), and both carbapenem resistance (median 8.1% and 15.4% for *E. coli* and *K. pneumoniae* respectively) and ESBL-production (median 32.3% and 27.9% for *E. coli* and *K. pneumoniae* respectively) amongst *Enterobacteriaceae*. *S. aureus* isolates showed a median methicillin resistance percentage of 45.1%, while vancomycin resistance was almost absent. A median of 50% of the strains of *S. pneumoniae* showed non-susceptibility to penicillin.
2. Similar trends were observed in conflict and non-conflict affected countries.

Conclusions: There is a lack of standardization in the methodological approach to AMR research in the Middle East. The proportion of antibiotic resistances among specific GLASS pathogens is high, particularly among *Acinetobacter spp.*

Background

Antimicrobial resistance (AMR), and more specifically antibiotic resistance (ABR), have become in the past two decades a globally rising concern. Since 2001, the World Health Organization (WHO) called for joining efforts in addressing the growing threat of AMR (1), following the pioneer example of the Pan-American Health Organization (PAHO) in establishing a surveillance network at regional level (2). However, it was not until 2009–2010 that other regional action plans and surveillance systems were put in place. Such actions took place initially in high income countries: both the Centre for Disease Prevention

and Control (CDC) of Atlanta and the European Centre for Disease Control (ECDC) in Europe are in fact since then releasing yearly surveillance reports publicly available on their websites (3, 4).

In 2014, the World Health Assembly (WHA) issued resolution WHA67.25, calling for the development of a global action plan against AMR (5). WHO took the lead of such process, publishing in 2015 a Global Action Plan on AMR (6), in which it defined a set of strategic objectives to address the growing threat, and setting the ground for the development of country-specific action plans and surveillance systems harmonized at global level. As part of this effort, the Global AMR Surveillance System (GLASS) was established in order to ensure evidence base and integrated data collection and surveillance across countries (7). GLASS focuses on eight bacteria considered of public health importance: *Acinetobacter* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Salmonella* spp., *Shigella* spp., *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

The global call against AMR has found echo in many regions since then, with the progressive establishment of harmonized surveillance systems in Eastern Europe and Central Asia (8), and throughout situation analysis conducted in the South East Asia WHO Region (9).

Critically, many Low and Middle-Income Countries (LMIC), particularly in Africa and the Middle East, appear to be still struggling in establishing similar regional networks. Recently, systematic reviews on AMR have been conducted in the West Pacific Region (10) and, more extensively, in Africa, showing high prevalence of resistances to the most commonly used antibiotics, and highlighting the critical evidence gap from many countries of the African Region (11–13). No similar attempts to collate evidence available in the Middle East have been performed so far. Recent studies conducted in high income countries on AMR in refugees, including refugees from the Middle East, have led to hypothesize an association between refugee status and risk of AMR transmission. However, such studies have failed to provide any evidence on whether the AMR was acquired in the home country, during the journey or in the host countries (14, 15).

The lack of evidence on the magnitude of AMR in the Middle East is not surprising, considering the well-known health effects of the peculiar geopolitical dynamics of this area of the world: in fact the Middle East has witnessed over the past decades a sustained social and political turmoil, with more than half of the countries members of the Arab League being theatre of protracted armed conflict (16). Since 2011 the situation has further escalated, with the Arab Spring and the conflicts of Syria, Yemen and more recently Mosul in Iraq (17).

The impact of the Arab Spring and of the recent conflicts in the Middle East on health has been well described, both at the level of health systems and at the level of individual health outcomes. Middle Eastern health systems in countries witnessing protracted armed conflict or carrying the burden of populations fleeing from those, have been progressively weakened, have seen their basic services disrupted, their health infrastructures damaged or destroyed, and a substantial proportion of their workforce either fleeing or being killed (18, 19). Armed conflicts have been already shown to have, in virtue of the above mentioned effects on the health system, a tremendous impact on the health outcomes

of the populations affected, in terms of increased morbidity, mortality and disability notably on women and children's health, on increased transmission of infectious diseases (20, 21), and through potential deleterious effects of AMR on treatment outcomes for Non-Communicable Diseases (NCDs) (22), which have become over the past two decades the leading causes of death and disability in the Middle Eastern Region (23, 24).

Armed conflict and political instability in the Middle East constitute obstacles for the implementation of health policies and global action plans, including those related to proper AMR surveillance and stewardship. However, despite the fact that emergence of drug resistance has already been described as one of the potential effects of armed conflict since over more than one decade (25), no formal and systematized evidence has been gathered so far. Sporadic evidence has recently highlighted that victims of armed conflict might be at higher risk of harbouring and/or being infected by multidrug resistant (MDR) bacteria (26, 27), but overall AMR in the Middle East remains poorly documented, and no study conducted so far has ever attempted exploring the magnitude of the problem of AMR in conflict-affected settings in the region.

There are multiple pathways through which armed conflict can contribute to the creation and spread of AMR in the Middle East: disruption of healthcare systems; delayed access to healthcare; increased nosocomial transmission of resistant pathogens; increased community transmission of resistant pathogens in settings as refugee camps; poor antimicrobial stewardship in the countries affected and in humanitarian interventions; etc. (16, 20, 23, 28, 29). In the Middle East, conflicts have not only produced a high death toll as an immediate effect, but they have also contributed to reversing the previously attained improvements in both the public health and animal health outcomes (21, 24). However, it has been only recently that the academic and international community has called for more research to explore the potential role of armed conflicts in fostering the creation and spread of AMR (30).

This is the first review addressing explicitly the evidence gap on AMR in the Middle East, and the first one in attempting to explore specifically the hypothesized association between conflict and AMR.

The main objectives of this review are:

1. To describe the patterns of AMR in the Middle East and the specific resistance profiles of pathogens listed in the WHO-supported GLASS; and
2. To identify any differences in AMR profiles in populations in conflict affected settings as compared to populations in non-conflict affected settings.

Methods

Search strategy

A systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (31) and searching the following electronic databases:

PubMed, MEDLINE, Embase, Global Health, CINAHL Plus, IMEMR (Index Medicus for the Eastern Mediterranean Region), Médecins Sans Frontières (MSF) and the International Committee of the Red Cross (ICRC) websites and the reference lists of the selected articles.

The search strategy included subject heading searches and free text searches for the following keywords: “antimicrobial resistances”, “antibiotic resistances”, “antimicrobial susceptibility” and, the name of countries in the review, in addition to all relevant synonyms. The detailed search strategy is reported in Appendix 1.

A standard definition of “Middle East” is difficult to retrieve (32), and several sources include different countries under such title. Within the scope of this review, Middle East has been defined as the geopolitical area comprising all countries part of both the WHO Eastern Mediterranean Region (EMR) (33) and the World Bank Middle East and North Africa (MENA) Region (34), and members of the League of Arab States (35), in order to include settings sharing the same language and whose political and social dynamics are strictly intertwined. As a result, eighteen countries are included in this study (Fig. 1).

Search items were imported in the reference manager software EndNote version X8.2. After removal of duplicates, screening of titles and abstracts was performed, and articles selected for full text screening were obtained. Articles for which no access was granted through the different sources used including contacting the author(s) were excluded from the review.

Selection criteria

Observational studies included in this review were cohort and cross-sectional studies describing the proportion, prevalence or incidence of AMR in Arab Middle Eastern civilian populations of both sexes and all ages (neonates: aged less than 28 days; infants: aged 28 days to 1 year; children: more than 1 year to 17 years of age; adults: aged 18 years or more), living in the above-named countries. Any other study, regardless of study design, which clearly specified the total number of isolates as denominator and the resistance profiles of individual pathogens, was also included, as suggested by Omulo et al. in a recent review on AMR research (13).

Eligibility criteria

Peer reviewed papers published since 2011 (beginning of the Arab Spring and the Syrian crisis) until mid-2018 in Arabic, English, French, Italian, Portuguese and Spanish were sought, on bacterial resistances in civilian populations living in the Middle East, reporting on data collected after the beginning of 2011 on AMR in the eight GLASS pathogens.

Papers dealing with non-Arab migrants in the Middle East, or military personnel deployed from non-Middle Eastern countries for combat operations in the Middle East, were excluded, considering that AMR carriage and/or infection profiles of these populations could not be representative of the patterns of AMR in the area under study, as they could harbour AMR contracted in their home countries. Similarly, papers on AMR profiles in Arab Middle Eastern refugees in high income countries were excluded, as it would be

impossible to ascertain whether the AMR profile was acquired in the home countries, during the migration journey, or in the host countries.

Exclusion criteria adopted were applied hierarchically in the following order: peer reviewed papers describing studies conducted outside the above defined geographical area of interest; reporting AMR data collected before 2011 or on AMR in other pathogens not included in GLASS; articles describing veterinary or environmental studies; studies on AMR patterns in military personnel deployed from non-Middle Eastern countries in the Middle East, or collected from non-Middle Eastern populations residing in any of the included countries; articles characterizing exclusively clusters of AMR bacteria and without information on the total of isolated microorganisms regardless of resistance profiles; intervention and analytical studies recruiting participants or specimens on the basis of a specific ABR profile; articles not available in full text in any of the above mentioned languages; Correspondence, comments, case reports and case series.

Types of exposures

Countries were classified as “conflict-affected” if they were included in the World Bank list of “fragile and conflict-affected situations” (36). According to the list, the following eight countries included in the review were defined as conflict-affected: Djibouti, Iraq, Israel and the Occupied Palestinian Territories (West Bank and Gaza), Lebanon, Libya, Syrian Arab Republic, and Yemen (Fig. 1), and the rest of studied countries were non-conflict affected.

Types of outcome measures

Primary outcome measures extracted were; incidence risk, prevalence, and proportion of AMR isolates.

Data collection process

A data extraction form was designed including: 1) Article information: first author, year of publication, year(s) of data collection, country in which the study was conducted, classification of the country as conflict-affected or non-conflict-affected; 2) Study information: type of study, study setting (community, primary care or hospital), study population, classification of the study population as conflict-affected or non-conflict-affected, sample size, age group(s), number of samples (or non-duplicate isolates, if available) collected, clinical syndrome(s) under study, primary outcome measure(s); 3) Microbiological information: pathogen(s) isolated, laboratory methodology employed for identification and antibiotic susceptibility testing (AST), criteria used for interpretation of resistances, AMR profile(s).

The data extraction form was designed based on the recommendations formulated by Omulo in her 2015 work (13), in order to promote comparisons of results across different low and middle income settings, as these were also adopted in a recent systematic review on AMR in Africa (11). For the definition of the AMR profile, the total number of isolates included in the study was extracted, along with the number of non-susceptible isolates for all the antibiotics tested. The main AMR profiles were defined as those identified by WHO as “priority pathogens” for the public health significance they have; in the specific case

of GLASS pathogens, which include: carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant and Extended Spectrum Beta Lactamase (ESBL)-producing Enterobacteriaceae (*E. coli* and *K. pneumoniae*), third generation cephalosporin-resistant *N. gonorrhoeae*, methicillin-resistant and vancomycin-resistant *S. aureus* (MRSA and VRSA respectively), fluoroquinolone-resistant *Salmonella* spp. and *Shigella* spp., and penicillin non-susceptible *S. pneumoniae* (37).

For articles presenting data on multiple pathogens, data were collected exclusively on the resistance profiles of the GLASS pathogens. Where resistance profiles were indicated exclusively for MDR pathogens, data were extracted only on primary resistance profiles demonstrated in the initial total sample included in the study.

The data extraction form is detailed in Appendix 2. Data were successively extracted in Microsoft Excel 2016 for analysis. It was not possible to perform a meta-analysis, due to the heterogeneity of methodologies adopted. However, a quantitative analysis was performed on 116 articles reporting on the above mentioned specific antibiotic resistances of public health significance: such quantitative analysis consisted in the calculation of resistance median percentages and interquartile range (IQR).

Assessment of risk of bias

A screening tool for overall quality appraisal was used. The in-depth assessment of risk of bias was performed adopting a modified version of the Newcastle-Ottawa Scale for cohort studies (38), and an adapted version to cross-sectional studies (available in Appendix 2), as recommended by the Cochrane Collaboration for the assessment of risk of bias in non-randomized studies (39).

The following categories were assessed: selection of participants or specimens, comparability of study groups, and outcome or exposure assessment according to the study type. Within each category, a variable number between two and three items was assessed, and colour coded according to the extent to which the study demonstrated a good (green), moderate, incomplete or doubtful (yellow), or poor (red) adherence to the epidemiological standards and good practices for the study design chosen.

Articles were classified as at high, moderate or low risk of bias according to the following criteria: a) High risk: poor epidemiological design in the three categories; b) Moderate risk: good epidemiological design in two categories or acceptable design in the three categories; and c) Low risk: good epidemiological design across all categories.

Results

Study selection and characteristics

A total of 13'166 records were identified; 4'228 items in Embase, 2'223 in Medline, 3'541 in Global Health, 2'603 items in PubMed, and 571 in CINAHL Plus and additional 71 records were identified, 68 items in IMEMR and 3 items in the MSF Field Research Website (40). After removing duplicates, titles and

abstracts of 6'684 records were screened, of which only 431 were eligible for full text screening. Of the 431 articles read in full text, 132 met the inclusion criteria (Figure 2) and were included.

Table 1 describes the study characteristics. All the articles selected for inclusion in the study were in English except one study that was in French (100). More than half of included studies were conducted in only three countries: Egypt (26.5%), KSA (18.9%), and Iraq (18.2%). In all the other countries included in the review only between one and less than ten articles were included, and two countries, Djibouti and Qatar, had no included article.

A higher proportion (61.4%) of articles were from stable countries and 51 articles, described AMR in fragile and conflict-affected countries and almost half of these published in Iraq (Table 1).

Out of the 132 articles, 107 did not specify the nationality of the individuals from which the specimens were obtained. No assumption was made that a study conducted in one country would describe exclusively the population native of the same country, in virtue of the intense migration patterns from outside and within the Middle East (173, 174).

The vast majority of studies included were conducted in hospital and hospital's laboratory settings (50.0% and 41.7% respectively). Community and primary health care settings were largely underrepresented (5.3%). Inpatients constituted the source of half of the data (50.0%) compared to outpatients. The source of microbiological data was not specified in 21.2% of studies.

Similarly, almost half (48.5%) of the included articles did not specify the age groups and/or genders included in the study population. When specified, adults were the most commonly studied population (33.3% of the included papers), followed by children (25.0%). Only one paper reported results from a study population entirely represented by men (48).

Only five articles were investigating AMR in immunosuppressed populations, represented either by HIV-infected patients (59), subjects who underwent liver transplantation (47), or patients affected by different types of malignancies (91, 115, 172).

Appraisal of risk of bias

The detailed summary of the assessment of risk of bias performed is available in Appendix 2 and 3.

All studies included in this review were screened for the completeness of information provided including; the study design, research question and objectives, and description of the findings in terms of person, place and time, along with the justification of the sample size included and the provision of a measure of random variation of the presented results.

The study design was clearly stated in 29 out of the 132 articles included (Table 1). Although the study question was rarely focused in terms of population of interest, geographic area and time span of observation (18.9%, 25/132), the study objectives were detailed in the majority of papers (77.3%,

102/132). Time period of observation and geographical area of interest were clearly specified in 96.2% (127/132) of articles, while detailed demographic information on the study population, at least in terms of age groups and gender included, were available for 32.6% (43/132).

Only one study reported sample size calculation and employed representative population although not powered for the prevalence detected nor for the comparison between the sub-groups performed (95). Measures of sampling variation in the results were reported by only four studies (95, 161, 165, 168).

Statistical methods were in general poorly detailed, and mostly summarized in terms of descriptive statistics. Only three studies described the use of multivariate analysis – usually logistic regression – to control for confounding (45, 147, 168). None of the studies took missing data into account in the analysis nor in the discussion, and similarly limitations and potential sources of bias were never mentioned in the discussion, with the exception of one surveillance study performed in Lebanon (123).

A substantial number of articles mentioned exclusively clinical suspicion from the attending physician as diagnostic criteria and rarely a clear case definition was detailed for the clinical syndrome under study. No clear sources for patient's socio-demographic data were described.

In general, cross-sectional studies presented major flaws in terms of sample selection, statistical methods employed (not described in the majority of cases), and possibility of misclassification of both exposures and outcome under study.

The cohort studies included in the review (52, 131, 161) showed overall lower risk of bias compared to other study designs. Two out of the three studies (52, 131) lacked detailed description of the statistical methods employed, in particular if and how control for confounding was performed and how losses to follow up were dealt with. Remarkably, one of the cohort studies included was conducted in a non-conflict affected country, but describing findings on a conflict-affected population, as it investigated AMR in war wounded civilian Syrian patients admitted to a Jordanian hospital (161).

The two case-control studies included (57, 165) poorly described the inclusion criteria for the cases and did not clearly detail the recruitment of controls. Data extracted from these two studies were not included in the quantitative analysis.

Synthesis of results

Patterns of ABR in the Middle East and differences between conflict-affected and non-conflict-affected countries

The most commonly described pathogens were, in order of frequency, *E. coli* (40.9% of the included studies, 54/132), *S. aureus* (34.1%, 45/132), *Acinetobacter* spp. (29.5%, 39/132), and *K. pneumoniae* (25.8%, 34/132), both in conflict and non-conflict affected settings. Other bacteria were less represented in this review, and no study investigated AMR in *N. gonorrhoeae*.

Antibiotic susceptibility testing (AST) was performed for a total of 73 different antibiotics, with substantial inhomogeneity across studies for each pathogen. Such heterogeneity, together with that observed in terms of study settings, laboratory methodologies employed, and clinical conditions investigated, along with the high overall risk of selection bias, misclassification of the exposure categories, and lack of control for confounding, did not allow to perform a meta-analysis as quantitative synthesis of the results from the standpoint of AMR profile of the studied pathogens. However, in Table 2 median percentages and IQR of specific AMR profiles are reported for selected GLASS pathogens, focusing on the most frequently reported ones.

A third (32.3%) of *E. coli* isolates showed ESBL-producing profile, and 8.1% resistance to carbapenems (IQR 0.6-25.3). In both cases, the proportion of resistant isolates appeared to be higher in non-conflict affected countries compared to conflict-affected ones.

Regarding *S. aureus*, the overall median percentage of methicillin-resistance was 45.1% (IQR 26.0-61.6). Unfortunately, the number of articles was too small in conflict affected compared to non-conflict affected countries to make a reliable comparison, and again study populations were very heterogeneous (44, 95, 144). However, from the few studies included, no major difference was detected between the two contexts.

Proportion of carbapenem resistance among *Acinetobacter spp.* isolates was significant (74.2%) and appeared slightly higher in conflict-affected settings compared to stable countries (78.0% vs 72.7%, respectively).

Only a small proportion of samples of *K. pneumoniae* was tested for carbapenem resistance and ESBL-production (56.5% and 42.7% respectively) and 28.0% of samples appeared to be ESBL producers, with a substantial difference between conflict and non-conflict affected countries (75.5% vs 22.5%, respectively). The carbapenem resistance profile did not vary significantly between the two contexts, with an overall proportion of cases of 15.4%.

As for *S. pneumoniae*, half of all isolates were detected as non-susceptible to penicillin, with substantially higher proportion in stable contexts (55.0%) compared to conflict-affected settings (10.9%).

Salmonella spp. and *Shigella spp.* AMR were investigated in too few studies (five and three respectively) to allow a valid summary to be included.

Table 3 and 4 in the annex offer more details on the number of studies on each pathogen per country in conflict-affected vs non-conflict-affected countries, respectively. Table 5 and 6 provide details on the number of studies per site of infections in conflict-affected vs non-conflict-affected countries, respectively. From these tables we can observe that studies conducted in non-conflict affected countries appeared to be slightly more focused in terms of site of infection under investigation compared to studies conducted in conflict affected countries, where in a substantial proportion of cases the site of infection

was not specified, or the authors were analysing resistance profiles of bacteria isolated from a miscellanea of specimens.

Discussion

While it is undoubted that AMR constitutes one of the most dangerous threats to public health on a global scale, the scientific community has reached no consensus yet on how to estimate and quantify the burden of AMR (175, 176). This can be partly explained by the complex interactions between upstream and downstream determinants of AMR, which require a system level analysis through conceptual frameworks that need to be both context-specific and coherent at global level (177, 178).

In terms of upstream determinants, the Middle Eastern conflict-affected countries are low and middle income countries, while stable settings, particularly the Gulf Cooperation Council States, are high income economies (179). These differences will influence the affordability to enforce measures, laws, and regulations regarding AMR. Beside the differences in wealth macro-indicators, common traits among the different countries emerge from the literature when investigating more proximal determinants of AMR, such as antibiotic prescription and self-medication practices (180, 181).

The interplay between the different determinants can be more pronouncedly hard to understand in fragile settings, particularly in situations of armed conflict, where additional drivers of AMR can complicate the picture. This has been insightfully analysed by Abbara and colleagues in a recent series of papers, in which it is described how the Syrian conflict has exacerbated the risk of AMR emergence and spread among the affected populations at a local level, and on a more global scene when considering the number of countries in which those fleeing are seeking refuge (182, 183).

Summary of evidence

Only six out of the 18 countries included in this systematic review have adhered to the GLASS (Bahrain, Egypt, Lebanon, Oman, KSA, and UAE) and are at different stages of the development or implementation of their National Action Plan on AMR, and amongst these only one – Lebanon – is considered a fragile context (184). The substantial number of articles retrieved in this review denotes an active research on the topic in the region, both in conflict and non-conflict affected settings. However, the vast majority of evidence comes from only three countries: Egypt, KSA, and Iraq.

The findings of the 132 studies included in this review cannot be easily summarised, in virtue of the demonstrated heterogeneity and inconsistencies in terms of study designs, laboratory methodologies and standards adopted, and variety of clinical scenarios included. The lack of harmonization in the regional surveillance system is not a prerogative of the Middle East, as it has been highlighted also in reviews conducted in other geographical areas outside the Western countries (10, 11, 13).

The majority of the included articles were cross-sectional studies, focusing on proportion and prevalence as outcome measures, with only two studies reporting incidence measures (131, 161). Moreover, the

sources of data being limited to hospitals and hospital laboratories, do not allow to describe the burden of AMR at community and primary care level, where more than 80% of the total volume of antibiotics is used according to Western estimates (185), and where antibiotic prescription and consumption practices are less regulated than in hospital settings (186), particularly in the Middle East (187, 188).

The most frequently reported GLASS pathogens in the studies included in this review were those belonging to the Enterobacteriaceae family (*E. coli* and *K. pneumoniae*), *Acinetobacter* spp., and *S. aureus*, both in conflict and non-conflict affected countries (see Tables 3 and 4).

The proportion of ABR emerging from the studies included in this review is concerning. In fact, among the Enterobacteriaceae included, around one third of the isolates showed an ESBL-producing profile. *K. pneumoniae* in conflict-affected countries appeared to have higher degrees of resistance to third generation cephalosporin, however random variation cannot be ruled out considering the limited number of studies conducted in these settings. The highest proportion of studies on both *E. coli* and *K. pneumoniae* were related to urinary tract infections, both in conflict and non-conflict affected countries (Tables 5 and 6). The carbapenem-resistance proportion among GLASS Enterobacteriaceae included in this review appear to be much higher than what is described in European settings and in the Mediterranean region (189, 190), however it is important to reiterate that the vast majority of studies included were hospital based, and investigating AMR in patients with underlying medical conditions, who are notoriously at higher risk of harbouring MDR strains.

The methicillin-resistance patterns in *S. aureus* detected in this review are similar to those described in a specific review on MRSA prevalence in the Middle East and North Africa (191), and the proportion of MRSA over the total number of *S. aureus* isolates appears to be higher than what described in other geographical regions such as Africa (192) and Europe, although again close to the figures of the European Mediterranean countries (189). Among the articles reporting the AMR profile of *S. aureus*, nasal carriage was the most frequently studied condition (Tables 5 and 6).

The figures of carbapenem-resistance among *Acinetobacter* spp. are comparable with those of Southern Europe, particularly Spain, Italy and Greece, where the proportion vary between 69.9% and 94.9% (189). While three out of the 12 studies on *Acinetobacter* spp. in conflict affected countries were associated with skin and soft tissue infections, only two out of the 27 retrieved from non-conflict affected settings were investigating this specific site of infection (see Tables 5 and 6). MDR *Acinetobacter baumannii* in particular has been described in the Middle East as associated with war-related wounds (193) already since the USA military interventions in Afghanistan and Iraq (194). This has re-emerged recently in the literature related to wounded Syrian civilians since the onset of the Syrian crisis (195, 196), and confirmed also in the study by Rafei et al. included in this review (101), in which Syrian refugees admitted mostly for war-related wounds to a Lebanese hospital were significantly more likely ($p < 0.001$) to harbour carbapenem-resistant strains than Lebanese patients (74% versus 47%). This peculiar feature, particularly in conflict-affected settings, deserves undoubtedly further investigation.

S. pneumoniae was less represented than other pathogens in this review, however a sufficient number of studies allowed to attempt a quantitative summary of the proportion of penicillin resistance observed: the findings of this review are consistent with those of other studies conducted in the region, and confirm that penicillin non-susceptibility among *S. pneumoniae* in the Middle East is frequently reported around 50% (197).

It is worth to underline the lack of research about *N. gonorrhoeae* in this region: this might be due to cultural and social aspects surrounding sexual and reproductive health knowledge, attitude, practices and taboos related to healthcare seeking for sexually transmitted infections (STIs) in the Middle East. The knowledge gap on STIs in this region is still significant, despite the recently describe increase in focus (198), and more research is needed to understand the prevalence of STIs and AMR related to them.

It is remarkable that a substantial proportion of studies were not investigating specific clinical conditions but were rather reporting unspecified or miscellaneous sites of infection (Tables 5 and 6): this is probably linked to the convenience sampling almost exclusively used in the research design of the included articles, and therefore to the poor methodological rigour of the evidence available from this geographical context.

Specific considerations on conflict-affected settings

With the currently available evidence it is not possible to draw definitive conclusions on whether the burden of AMR is differential between conflict and non-conflict affected settings in the Middle East, as different pathogens show conflicting results. The inconclusive findings of this review mirror those of similar studies conducted on AMR in *M. tuberculosis* among conflict-affected populations, which similarly failed to detect a significant difference in the levels of resistances to antimicrobials when comparing displaced populations to populations in the home countries (199).

Several elements can potentially explain the lack of differences detected between stable countries and conflict-affected countries in this review. First of all, in conflict-affected settings the availability and accessibility of antibiotics could be severely compromised, thus minimizing the selective pressure on bacteria for the development of resistances. Secondly, publication bias might limit the availability of evidence from fragile contexts, due either to lack of access of researchers to the most at risk populations or to prioritization of research on most pressing public health needs and/or life-threatening conditions (such as war trauma or acute malnutrition). Lastly, there might be less awareness, both among health authorities and humanitarian health organizations delivering health services in conflict-affected countries, of the potential public health threat that an unregulated and uncontrolled distribution of antibiotics might represent for the population.

In summary, the pathways through which conflict and non-conflict-affected countries can develop antibiotic resistances might differ based on the social, economic and political context. This stresses the importance of strengthening national and regional surveillance systems and adopting harmonized approaches that tackle antibiotic resistances at all levels, from agriculture and food safety to veterinary

medicine, from legislative regulation to improved quality of scientific research, through a One Health approach as advocated by WHO.

Limitations

This systematic review presents some limitations that need to be taken into account when interpreting the results described.

The strict focus on GLASS bacteria might have led to overlook important pathogens, bacterial and non-bacterial, that might be relevant to the Middle Eastern context, such as *Pseudomonas aeruginosa* (200–202), *Neisseria meningitidis* (203), or viral infections – such as respiratory viruses – that are prevalent and of significant public health importance in this context (204).

From a standpoint of completeness and validity of the evidence retrieved, there are several elements that need to be mentioned as caveats before making any inference on the magnitude of the problem of AMR resistances in the Middle East. One element that needs to be mentioned is the fact that grey literature was not specifically searched for this review, and therefore some evidence might not be represented in the presented results. This was primarily due to the difficulties in retrieving unpublished reports particularly in conflict-affected settings. The main aspect to be cautiously appraised lies in the methodological weaknesses of the studies included in this review, including sampling. It is not possible in fact to rule out sampling variation as first possible explanation of the magnitude of proportions of AMR observed. The hospital-based cross-sectional study design dominating the published literature on the topic adds uncertainty to the validity and the generalizability of findings to the wider Middle Eastern population.

The limitations generated by these factors are further impaired by the high risk of selection bias, information bias, misclassification, and the limited control for the potential confounding effect of socio-demographic variables detected in a considerable proportion of studies (Appendix 3).

The strict inclusion and exclusion criteria applied, along with the descriptive analysis performed, that takes into account the variability observed and is methodologically aligned with that reported in similar studies in other contexts (11), are an attempt to both provide a reliable summary of the evidence available and make the findings interpretable and comparable from the perspective of scarce homogeneity and systematization of knowledge on the issue of AMR in resource limited settings.

The consistency of the findings described with those available in the literature on specific pathogens in the region leads to hypothesize that, despite the limitations above described, the concerning high proportion of AMR strains detected in this review has a certain degree of validity.

Conclusions

Based on the findings described in this systematic review, the first aspect that emerges is the clear lack of standardization in the methodological approach to AMR research in the Middle East, which hinders any possibility of drawing conclusions on the incidence or prevalence of specific resistance patterns at

population level in the Middle East. This is mainly due to the predominantly hospital-based, cross-sectional nature of the studies performed, and is further aggravated by some methodological aspects: first of all, the convenience sampling almost universally adopted to investigate AMR, and secondly the lack of stratification or other statistical approaches to control for the multiple potential confounding effects that can play a role in the emergence and spread of AMR.

From what emerges from the descriptive analysis offered as a summary in this review, the proportion of antibiotic resistances among specific GLASS pathogens is concerning, particularly in the case of *Acinetobacter* spp., which deserves further investigation, particularly considering its predominance in war-related wounds.

However, it is not possible to draw any conclusion on the hypothesized differences in the magnitude of the problem of AMR between conflict and non-conflict affected countries, due to the flaws above described.

It is recommended that Middle Eastern country who have not done so yet, join the second phase of implementation of GLASS: to facilitate this, an Arabic version of both the GLASS website and GLASS manual will be needed.

The Middle Eastern scientific community should also adhere to the standardized methods promoted and supported by GLASS for AMR research and reporting, in order to improve the accuracy, quality and comparability of data collected on AMR in this region. Such harmonization effort will allow a more in-depth understanding of the drivers and patterns of acquisition and transmission of antibiotic resistances in the Middle East.

A stronger focus on population-based and primary care-based research will be needed, in order to avoid capturing exclusively high-risk populations in hospital settings, which could distort the findings. Such knowledge is necessary for improving national and local treatment guidelines, tailoring them to the specificities of each context.

Governments, academics, as well as aid agencies in conflict-affected countries, should try in parallel to promote research on and implementation of appropriate antibiotic resistance surveillance system and antibiotic stewardship programs at all levels of care, in order to timely tackle the threat of AMR through optimization of antibiotic prescription and consumption practices based on the resistance profiles circulating in this region.

List Of Abbreviations

ABR Antibiotic resistance

AIDS Acquired Immune Deficiency Syndrome

AMR Antimicrobial resistance

API Analytical Profile Index

AST Antibiotic Susceptibility Testing

BSAC British Society for Antimicrobial Chemotherapy

CA-SFM Comité de l'Antibiogramme de la Société Française de Microbiologie

CDC Centre for Disease Prevention and Control

CLSI Clinical and Laboratory Standards Institute

ECDC European Centre for Disease Control

EMR Eastern Mediterranean Region

ESBL Extended Spectrum Beta Lactamase

EUCAST European Committee on Antimicrobial Susceptibility Testing

GLASS Global Antimicrobial Resistance Surveillance System

HIV Human Immunodeficiency Virus

ICRC International Committee of the Red Cross

IMEMR Index Medicus for the Eastern Mediterranean Region

IQR Interquartile Range

KSA Kingdom of Saudi Arabia

LMIC Low and Middle Income Countries

MDR Multidrug Resistant

MENA Middle East and North Africa

MIC Minimum Inhibitory Concentration

MRSA Methicillin-Resistant Staphylococcus aureus

MSF Médecins sans Frontières

NCDs Non-Communicable Diseases

PAHO Pan-American Health Organization

PCR Polymerase Chain Reaction

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis

STIs Sexually Transmitted Infections

UAE United Arab Emirates

VRSA Vancomycin-Resistant Staphylococcus aureus

WHA World Health Assembly

WHO World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable in virtue of the study design (systematic literature review).

Consent for publication

Not applicable in virtue of the study design (systematic literature review).

Availability of data and materials

The data that support the findings of this study are available upon request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CT formulated the research questions, contributed to the definition of the search strategy, performed the first screening of titles and full texts reviews, read full the full texts of the selected articles to assess

eligibility for inclusion, extracted the data from the articles, assessed the risk of bias for the included studies, analysed the results, and drafted all sections of the manuscript.

MNAS contributed to the formulation of the research questions, revised the search strategy, the screening of titles and full texts, the data extraction from the selected articles, the assessment of risk of bias for the included studies, the analysis of results, and commented and edited all sections of the manuscript.

Both Authors read and approved the final manuscript.

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Tables

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Figures

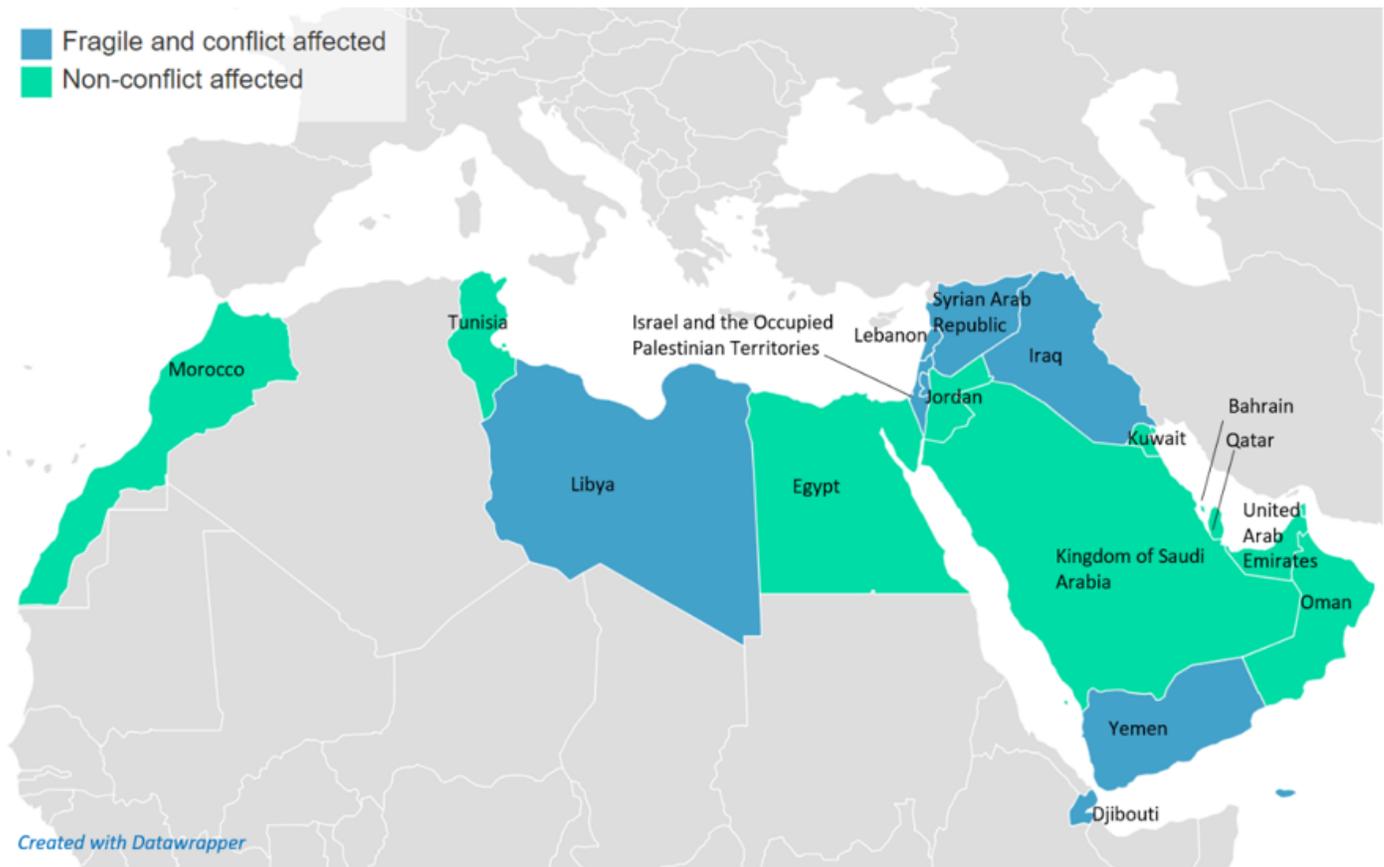


Figure 1

Map of countries included in this systematic review on AMR and conflict in the Middle East (the identification as fragile and conflict affected and non-conflict affected is based on the World Bank classification, 2011-2018)

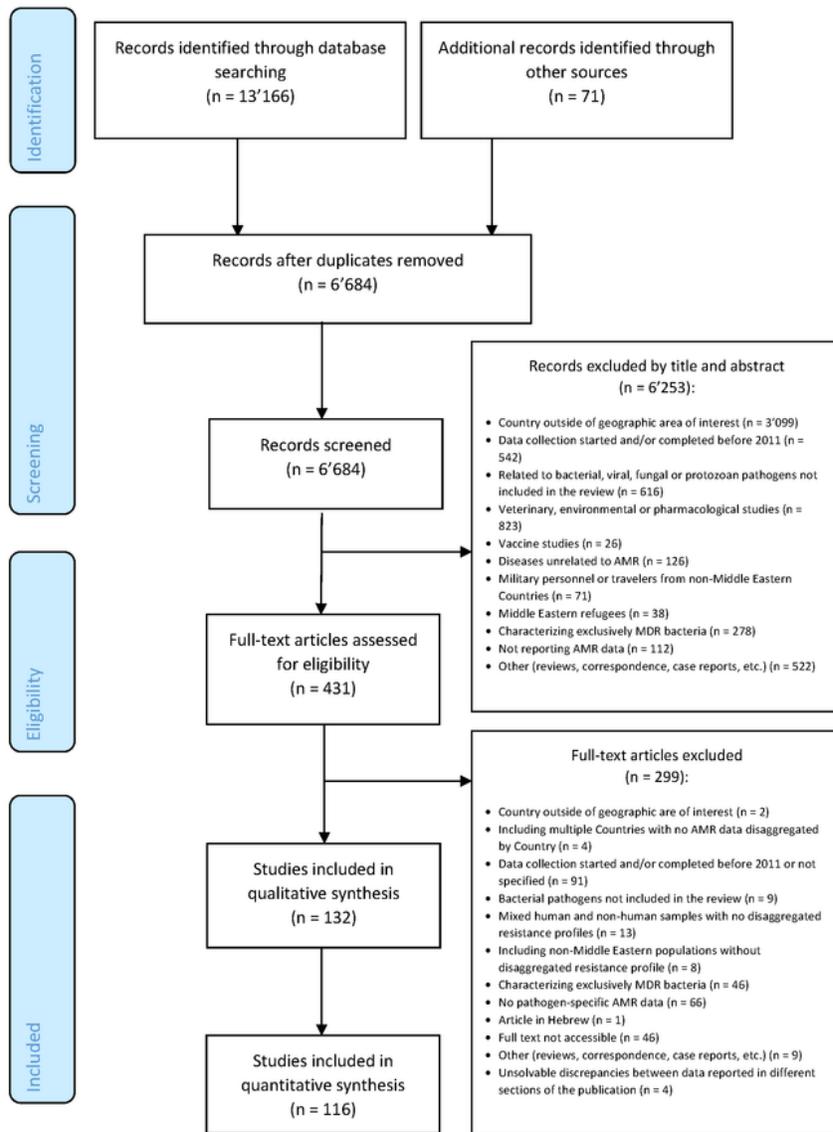


Figure 2

PRISMA flow diagram of the selection of articles for this review

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