Evidence-Based Interventions For Antimicrobial Resistance In Conflict-Afflicted Lmics

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EVIDENCE-BASED INTERVENTIONS FOR ANTIMICROBIAL RESISTANCE IN CONFLICT-AFFLICTED LMICS

Scoping Review and Structured Recommendations

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Thesis Submitted: April 2020

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Secondary Reader: Dr. Louise-Marie Dembry
ABSTRACT

Introduction: Although control strategies for antimicrobial resistance (AMR) have been described in high-income settings, interventions to curb the emergence and spread of AMR in conflict-afflicted low- and middle-income countries (LMICs) have not been systematically explored.

Objective: The objective of this review was to identify and assess the effectiveness of various control strategies in curbing the emergence and spread of AMR in conflict-afflicted LMICs.

Methods: A systematic scoping review of the literature was conducted using Embase, PubMed, and Scopus to identify primary literature reporting on AMR in Pakistan, Lebanon, Jordan, or Turkey published in the last decade (Jan. 2010 – Jan. 2020). Papers were eligible for inclusion if they discussed conflict or the effects thereof, AMR, and control strategies for AMR. Summary and reporting of the findings were informed by guidelines presented by Tricco et al. 2018 and the JBI Reviewer’s Manual for scoping reviews. Semi-structured interviews with experts were conducted to substantiate review findings. All interviews were audio-recorded and transcribed in full using the website OTranscribe and the software Descript V.3.3.2.

Results: Sixteen articles were deemed eligible for inclusion. Control strategies discussed in these articles fell into five categories: infection prevention and control (n=4); antibiotic stewardship programs (n=3); diagnostics and surveillance (n=7); education (n=2); and other (n=2).

Conclusion: The challenges associated with controlling the emergence and spread of AMR are exacerbated by violent conflict and displacement. Conflict-afflicted LMICs not only face resource limitations, but must also find ways to care for and treat injured individuals carrying increasingly-resistant pathogens. The literature and expert opinions suggest that improved lab diagnostics, implementation of surveillance programs, and infection prevention and control should be prioritized as AMR control strategies in conflict-afflicted LMICs. However, there is limited research on the
effectiveness of these interventions in such settings. Future research is needed before adequate interventions can be designed and implemented.
ACKNOWLEDGEMENTS

Thank you foremost to Dr. Kaveh Khoshnood for his guidance, advise, and expertise, without which this thesis would not have been possible. His mentorship has been integral to my MPH experience and I am very grateful for his guidance and ongoing support. Thank you also to Dr. Louise-Marie Dembry for serving as a reader and for helping me to formulate my thoughts at the inception of this project. Yale Librarian Kate Nyhan played a formative role in the structure and design of the search methodology used in this paper. Her availability as a resource to students is a privilege that I greatly benefited from. I am further grateful to each expert who agreed to be interviewed and provided insights that greatly shaped my thinking and writing on this topic. Thank you to Lizzie White at the Poorvu Center for Teaching and Learning Graduate Writing lab for her edits to this piece. Lastly, I am indebted to my friends – in particular, Arvind Venkataraman, Joseph Gaylin, and Isabella Berglund-Brown – for their willingness to hear me speak and stress about this project for months, without deviation in their patience or kindness.

To produce scholarship that might better the lives of those displaced and otherwise negatively affected by conflict and violence has long motivated my academic pursuits. This research is dedicated to those around the world who struggle each day to survive at the crossroads of political instability and humanitarian disaster. In the words of the Palestinian poet Mahmoud Darwish:

اﺮﻓﺎﺴﻣ ﺖﺴﻟ ﺎﻧأو ،ﺮﻔﺳ ﺔﺒﯿﻘﺣ ﺲﯿﻟ ﻲﻨطو نإ

“My homeland is not a suitcase, and I am no traveler.”

Until global injustice ceases to make transient those who would prefer to stay sedentary, our work as academics, students, and advocates must continue.
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COMMONLY USED ACRONYMS

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<tbody>
<tr>
<td>ABR</td>
<td>Antibiotic resistance/resistant</td>
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<tr>
<td>AMR</td>
<td>Antimicrobial resistance/resistant</td>
</tr>
<tr>
<td>ASP</td>
<td>Antibiotic stewardship program</td>
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<tr>
<td>DS</td>
<td>Diagnostics and surveillance</td>
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<tr>
<td>E</td>
<td>Education</td>
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<tr>
<td>FLAR</td>
<td>First-line antibiotic resistance</td>
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<td>HAI</td>
<td>Hospital-associated infection</td>
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<tr>
<td>INH</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>IPC</td>
<td>Infection prevention and control</td>
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<tr>
<td>JBI</td>
<td>Joanna Briggs Institute</td>
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<tr>
<td>LMIC</td>
<td>Low- to middle-income country</td>
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<tr>
<td>MENA</td>
<td>Middle East and North Africa</td>
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<tr>
<td>MDR</td>
<td>Multi-drug resistance/resistant</td>
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<tr>
<td>MSF</td>
<td>Médecins Sans Frontières /Doctors Without Borders</td>
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<tr>
<td>O</td>
<td>Other</td>
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<tr>
<td>PTO</td>
<td>Post-traumatic osteomyelitis</td>
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<td>RIF</td>
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INTRODUCTION

Background & Rationale

Rates of antimicrobial resistance (AMR) are on the rise globally.\textsuperscript{1} Resistance itself emerges when a subset of pathogens survives within an individual following treatment with an antimicrobial. These surviving pathogens are oftentimes fitter strains of the microbe which have developed mechanisms to evade both drug treatment and the immune system. The use of antimicrobials, such as antibiotics, kill off commensal and pathogenic bacteria in a host. In the absence of competition, resistant microbes multiply. Resistance is subsequently spread to other individuals and, in some cases, resistance may be passed directly from one microbe to another.\textsuperscript{2} While complications associated with the treatment of resistant infection and disease endanger the wellbeing of individuals around the world – claiming nearly 700,000 lives yearly – the burden of AMR is disproportionality felt by low- and middle-income countries (LMICs).\textsuperscript{1,4} This imbalance is due to challenges such as weak governance, economic factors, and technological limitations which oftentimes make it difficult for LMICs to appropriately manage the emergence and spread of AMR within their borders.\textsuperscript{4}

As the body of literature on AMR in LMICs continues to grow, the difficulties that these countries face in curbing the emergence and spread of AMR become increasingly apparent. Solutions such as increased screening for infectious disease,\textsuperscript{5,6} infection prevention and control,\textsuperscript{5-7} and improved policy implementation\textsuperscript{8} have all been suggested. However, the implementation of such interventions is difficult given resources limitations in many LMICs. The barriers to AMR control are even greater in LMICs affected by conflict,\textsuperscript{ii} as can be seen in several countries in the Middle East and North Africa (MENA) region. In Syria, for example, existing drivers of AMR –

\textsuperscript{1} A country is designated an LMIC based on gross national income per capita cut-offs defined by the World Health Organization.\textsuperscript{3}

\textsuperscript{ii} “Conflict,” as it will be used throughout this paper, is defined by Bowsheer et al. 2019 and Pettersson et al. 2015 as “violent armed struggle between hostile groups, resulting in over 25-battle related deaths per year.”\textsuperscript{3,9}
including the misuse of antibiotics and a lack of early diagnosis of communicable diseases – were exacerbated by the onset of the civil war in 2011, in part due to the breakdown of the healthcare system.\textsuperscript{5,10} Studies on Iraq, a country plagued with political instability and violence since the United States invaded in 2003, speculate that lack of adequate infection prevention programs in healthcare clinics, along with poor management of antibiotics, have led to the emergence and nosocomial transmission of multi-drug resistance (MDR).\textsuperscript{11,12} Other drivers of AMR worsened by conflict include delayed access to care, crowded and unsanitary healthcare facilities, shortages in vaccine supply, and disruption of vaccination schedules.\textsuperscript{10,13}

What’s more, refugees and civilians displaced from conflict-affected\textsuperscript{9} regions may themselves serve as carriers of MDR pathogens, exposing populations in neighboring countries to increasingly difficult-to-treat diseases.\textsuperscript{10,14,15} Factors such as poor hygiene, lack of adequate housing, and inaccess to healthcare services along migration routes all perpetuate this spread of AMR.\textsuperscript{6,16,17} AMR therefore poses threat not only to citizens of countries affected by active conflict, but also to surrounding LMICs that serve as host and caretaker of the massive number of displaced individuals.

According to a 2018 report released by the United Nations Refugee Agency (UNHCR), the LMICs with the highest number of refugees and displaced peoples relative to their national population include Lebanon (1 in 6 individuals currently living in Lebanon is a refugee), Jordan (1 in 14), and Turkey (1 in 22).\textsuperscript{18} This same report lists Pakistan as the country hosting the second largest total number of refugees, with Turkey hosting the most out of any country in the world.\textsuperscript{18} The political, social, and ecological realities in each of these four countries vary vastly. However, they are alike in that recent studies indicate that the emergence and spread of AMR in these countries is

\textsuperscript{iii} “Conflict-affected,” as it will be used throughout this paper, may refer to a region actively experiencing violent armed struggle or otherwise experiencing the social and political after-effects of conflict.\textsuperscript{3} These social and political effects may include internal displacement or a high volume of refugees entering the country.\textsuperscript{3}
partially attributable to the flow of migrants, refugees, and injured civilians through their borders. In Turkey, which contained nearly 2.7 million Syrian refugees in 2016, increased rates of MDR bacterial infections in war-wounded patients – along with the re-emergence of measles, poliomyelitis, leishmaniasis, and MDR-tuberculosis (TB) – have provoked concerns over biosecurity within the country. In Jordan, a systematic review found that measles, MDR-TB, and cutaneous leishmaniasis are also re-emerging there due to the rapid influx of Syrian refugees. In Lebanon, a review of data from 13 hospitals across the country found that there was an observed decrease of 5-10% in the susceptibility of bacteria to major classes of antibiotics in 2015-2016 compared to 2011-2013. In Pakistan, there is a growing epidemic of cutaneous leishmaniasis in towns neighboring Afghanistan and in cities with a high number of refugees; increased variability in the clinical presentation of this disease had complicated treatment and diagnosis.

The emergence and re-emergence of resistant infectious diseases in these countries demonstrates the need for increased research on how to control AMR in conflict-affected settings. To the author’s knowledge, this paper will be the first time that the literature has been systematically searched in order to compile research on control strategies and recommendations put forth by individuals working in places most affected by the conflict and displacement in the MENA region. The objective of this review is to compile evidence-based control strategies for AMR in conflict-affected LMICs and to identify existing research gaps. The goals of this thesis are threefold: (1) present what is currently being done to address AMR in conflict-affected LMICs; (2) compile recommendations for control put forth by scholars, scientists, and others in the MENA region; (3) conduct interviews with experts in order to substantiate findings and expand recommendations for AMR control in resource-variable settings. The qualitative component of this thesis was deemed exempt by the Institutional Review Board at Yale University.
It is the author’s hope that this project will help stakeholders to identify gaps in the literature and inform future research projects on the complex interactions between conflict, displacement, and AMR. Persistent instability in the MENA region threatens the health and well-being of millions of people. It is urgent that the global health community more seriously consider conflict as a public health threat and work toward effective and feasible interventions in the regions most affected.

METHODS

Search Strategy

A systematic scoping review of the literature was conducted using the Joanna Briggs Institute (JBI) Reviewer’s Manual guidelines on scoping review methodology and summary of evidence. The search was conducted using Embase, PubMed, and Scopus to identify peer-reviewed primary literature reporting on AMR in Pakistan, Lebanon, Jordan, or Turkey published in the last decade (Jan. 2010 – Jan. 2020). The structure of the search and summary of the findings was informed by guidelines presented by Tricco et al. 2018 and the JBI Reviewer’s Manual for scoping reviews.

The author used a Boolean search strategy to combine search terms related to three topic areas: (1) antimicrobial resistance AND (2) conflict or displacement AND (3) study based in one of the four specified countries of interest. An initial search was conducted in PubMed. The author reviewed topical articles, reports, and editorial pieces in order to generate a comprehensive list of relevant keywords. All identified keywords were carefully tracked in a Microsoft Excel V. 16.31 spreadsheet. A Medical Subject Headings (MeSH) search was conducted using an initial list of keywords and a review of MeSH tree structures helped to identify additional terms related to the topics of interest. A complete search of all relevant keywords and MeSH terms was then conducted in PubMed and 220 records were returned (Table 1).

The platform OVID was used to search articles in Embase. The list of terms identified in the PubMed search was expanded to include search terms specific to Embase. The author used the
“Tree Search Tool,” which compiles a list of related searches based on one keyword, to identify Embase-specific terminology relevant to each of the three topic areas of interest. A comprehensive search of all identified terms was conducted and 158 records were identified (Table 1). Finally, a search was conducted in Scopus using the previously identified terms related to the three topic areas of interest. This search returned 221 records (Table 1).

Table 1 in the Appendix includes a full list of the search terms used for each database. In total, searches across the three databases returned 599 records.

As per JBI guidance, the author also conducted a number of interviews in order to substantiate the findings of this scoping review. The goal of these interviews was to gain expert opinion on evidence-based control strategies for AMR in LMICs. Furthermore, these interviews provided the opportunity to much more explicitly explore the role of violent conflict in the emergence and spread of AMR, as each interlocutor had some amount of expertise working in regions or with patients affected by warfare. All interviews were audio-recorded and transcribed in full by the author using the website OTranscribe and the software Descript V.3.3.2. Major themes that emerged from these interviews are explored in the Discussion section of this paper.

**Inclusion Criteria**

All records identified in the search stage were imported to EndNote X9, a citation management software. One hundred fifty-two duplicate records were eliminated and 447 records were identified for title and abstract screening. Three hundred ninety-nine articles were subsequently excluded for the following reasons: published before January 2010 (n=156); not topically relevant (i.e., no explicit discussion of the three topic areas of interest) (n=237); full-text article was not in English (n=6). Forty-eight records were thus identified for full-text screening.

To be eligible for inclusion in the review, studies had to be primary research on a topic related to both antimicrobial resistance and conflict, and be based in Turkey, Pakistan, Jordan, or
Lebanon. Study types could include retrospective or prospective cohort studies, randomized control trials, database analyses, or qualitative research studies. Systematic reviews, opinion pieces, editorials, letters, conference abstracts, and pilot studies were excluded (n=23). To be eligible for inclusion, articles also had to discuss interventions or strategy recommendations for AMR control. Articles did not have to discuss the effectiveness of recommended control strategies to be included in this review. While some studies did provide supporting evidence for the effectiveness of their suggested control strategies, most mentioned control in their discussion section. Nine articles were excluded because they did not discuss control.

RESULTS

After screening, 16 articles met the eligibility criteria and were included in this scoping review (Fig. 1). Six studies were based in Jordan,12,24–28 two in Pakistan,29,30 six in Lebanon,31–36 and two in Turkey.37,38 Study populations included Iraqi, Yemeni, and Syrian civilians/patients,12,24,26,37,38 Palestinian refugees,27 Syrian refugees,31–33,36 Afghani refugees,29 Lebanese patients and/or individuals residing in Lebanon,32–35 physicians in Jordan,25,28 Turkish patients,38 and others30 (Table 2). These descriptions of study populations mimic the language used by study authors to describe them, as not all study authors provided sufficient information on the migration status of their study population. Ten studies were conducted in a hospital or healthcare clinic,12,24–28,31,32,37,38 two studies were community based,29,30 and four studies were laboratory based.33–36 Further details on each study can be found in Table 2 in the Appendix.
All 16 studies included in this scoping review contained interventions or strategy recommendations for the control of AMR in conflict-afflicted LMICs. Control strategies fell into five categories: infection prevention and control (IPC); antibiotics stewardship programs (ASP); diagnostics and surveillance (DS); education (E); and other (O).

A complete list of strategy recommendations can be found in Table 3 in the Appendix. Each strategy type will be explored in further detail below.

**Infection Prevention and Control (IPC)**

There is some literature to support the effectiveness of infection prevention and control (IPC) to reduce the emergence and transmission of MDR pathogens in high-income settings. IPC interventions include: patient screening, patient isolation, disease surveillance, improved environmental hygiene, education and training of healthcare personnel, and “judicious use of antimicrobial agents.” The goals of IPC are to either prevent infection altogether – thus preventing the emergence of resistant pathogens – or to control infections such that patients carrying resistant pathogens are unable to spread them, particularly nosocomially. Four studies included in this review suggest IPC as a control strategy for AMR in LMICs.

In Lebanon, Rafei and Dabbousi et al., 2013 tested patient samples obtained from war-wounded Syrian refugees treated for carbapenem-resistant *Acinetobacter baumannii* in 2012 at the Tripoli Government Hospital. *A. baumannii* is an opportunistic nosocomial pathogen that is associated with high morbidity and mortality and also has an ability to rapidly acquire resistance. It is a common cause of infection in war and combat wounds. The researchers tested four isolates from patients and found that each contained the resistance-causing gene $bla_{NDM}$ – “the first detection of carbapenem-resistant *A. baumannii* carrying the $bla_{NDM}$ gene in Lebanon.” They were unable to identify the source of *A. baumannii* infection, but concluded that Syria likely serves as a reservoir for NDM-producing bacteria. Based on these study findings, the authors recommend that Lebanese
hospitals treating Syrian refugees implement infection control measures to prevent the spread of MDR *A. baumannii* in healthcare institutions.\(^{31}\)

A subsequent study by Rafei (Rafei and Pailhories et al. 2015) tested 116 samples obtained from Syrian and Lebanese patients (78% male, mean age 40) treated at different hospitals in Tripoli, Lebanon between 2011 and 2013 for antibiotic susceptibility.\(^{32}\) They found that 60% of the isolates showed phenotypes consistent with carbapenem resistance: five isolates (four from Syrian patients and one from a Lebanese patient) exhibited the *bla*\(^{\text{NDM}}\) gene.\(^{32}\) The authors speculate that Syrian refugees likely acquired the infection during a hospital stay in Syria and carried the resistant-pathogen to Lebanon, but data to support this speculation was limited.\(^{32}\) In Europe, *A. baumannii* susceptibility to antibiotics has decreased from 52.9% in 2009 to 37.7% in 2011; the study authors share concerns that the emergence of NDM in Lebanon may result in comparable reductions in antibiotic susceptibility of this nosocomial pathogen.\(^{32}\) Based both on their findings and the fact that Tripoli is proximate to the Syrian border, the study authors conclude that effective measures to control the spread of infection in Lebanon are necessary.\(^{32}\) However, the authors do not offer examples of any specific measures.

In Turkey, Yuce et al. 2017 retrospectively analyzed data collected from Syrian patients treated for conflict-associated burns at the Dr. Lutfi Kirdar Kartal Educating and Training Hospital Burn Centre of Istanbul between 2011 and 2015.\(^{37}\) The purpose of this study was to describe the type of burn wounds that Syrian patients presented with and to provide details on wound-management at the burn center.\(^{37}\) According to the authors, analysis of tissue cultures from these burn victims revealed resistant microorganisms “specific to the battlefield.”\(^{37}\) The authors also reported nosocomial spread of these resistant-microorganisms in their treatment center, despite attempts to isolate Syrian patients presenting with war wounds.\(^{37}\) The authors conclude that rapid transfer of patients with war-associated burns to treatment centers equipped to treat such wounds is
crucial for infection prevention. Early debridement and sterilization of such wounds further helps to improve treatment outcomes.

Alga and Herzog et al. 2018a conducted a qualitative study with physicians employed in a hospital supported by Médecins Sans Frontières (MSF) in Jordan. The goal of their study was to understand how physicians working in an LMIC and treating war-wounded patients think about AMR and healthcare-associated infections (HAI). The authors interviewed 10 physicians (55% male, mean age 37). All interviews were transcribed and content analyzed by the study authors. When asked about HAI, physicians recognized a lack of staff adherence to hospital protocols as attributable to the spread of pathogens. However, physicians qualified this lack of adherence with a limitation of resources as a reason that adherence proved difficult. Specifically, physicians cited lack of bed sheets, shortage of appropriate antibiotics, and space limitations as barriers to infection prevention. On the topic of AMR, participants cited main challenges as being costs associated with antibiotic treatment and space limitations that precluded antibiotic-resistant patients from being isolated. Physicians also pointed out that antibiotics are commonly available over the counter in Syria and Lebanon, and therefore patient behavior might also be a contributing factor to AMR emergence. The findings from this study present just some of the challenges to IPC in a resource-limited setting. The authors believe that increased access to resources (e.g., bed sheets, antibiotics, etc.) is necessary for control AMR in this setting.

Antibiotic Stewardship Program (ASP)

Inappropriate antibiotic use and prescribing are not only burdensome and costly to healthcare systems, but also drive the emergence of multi-drug resistant pathogens and organisms. An ASP is a program in which antibiotic use within a healthcare institution is monitored or directed by a trained group of individuals such that antibiotic use is standardized and evidence based. Interventions used in ASPs include avoidance of use of broad-spectrum antimicrobials, optimization
of dose and route of administration per patient, and customization of duration of therapy such that antibiotic use is curative, rather than palliative, in nature. In high-income settings, ASPs have been shown to reduce the emergence of AMR, but evidence for their effectiveness in LMICs is limited. Three studies included in this review suggest implementation of ASPs as control strategies for AMR in LMICs.

Bhalla et al. 2016 assessed the effectiveness of an ASP implemented in the MSF Reconstructive Surgery Project in Amman, Jordan. The Reconstructive Surgery Project treats about 50 patients per month, predominantly from Iraq, Syria, and Yemen. At this center, patients with suspected osteomyelitis (a type of bone infection) undergo exploratory surgery, during which tissue samples are collected and tested for resistance. The authors found that of those carrying resistant pathogens, the most common were cephalosporin-resistant Enterobacteriaceae or methicillin-resistant Staphylococcus aureus. To help control spread of these resistant pathogens, an ASP team was assembled in October, 2013 and composed of a physician and a pharmacist. They were tasked with using patient-level microbiology results to inform decisions of antibiotic selection, dose of medication, duration of treatment, and route of administration. Within the first year of the program, the ASP team recommended a change in the antibiotic regimen of 45% of patients (106 of 233 patients); the rate of acceptance of these recommendations by the medical team was 88% (94 of 106 patients). The authors found that though patient load at this MSF center remained relatively the same, the ASP reduced antibiotic costs from $252,077 to <$159,948 in just one year. They credit the reduction in improper use of imipenem, shifts in prescribing practices (e.g., waiting to initiate treatment until after culture reporting), and increased responsibility for antibiotic management by surgeons as program changes that helped to reduce costs.

Fily et al. 2019 retrospectively analyzed laboratory data from the same MSF Reconstructive Surgery Project assessed by Bhalla et al. They analyzed 727 bone samples collected between October
2006 and December 2016 from war-wounded Iraqi, Yemeni, and Syrian patients. Their objective was to describe first-line antibiotic resistance (FLAR) among civilians at risk for post-traumatic osteomyelitis (PTO) and to identify patient risk factors for PTO. Commensal pathogens, environmental contamination, and nosocomial spread of MDR pathogens are all causes of PTO in LMICs and particularly in conflicted-afflicted LMICs. PTO treatment includes prolonged antibiotic use, aggressive debridement and, in some cases, reconstructive surgery may be required. Thus, the emergence or transmission of MDR pathogens poses significant threat to effective PTO treatment and may impact patient outcomes. The authors found that of the 727 patient isolates analyzed, roughly 50% were FLAR; of those resistant pathogen strains identified, 60.5% were S. aureus. These pathogens were found to be resistant to fluoroquinolones, rifampin, and oxacillin. A multivariable analysis conducted by the authors revealed that FLAR infections were associated with lower extremity infection, time since injury \( \leq 12 \) months (compared with >30 months), and with \( \geq 3 \) previous surgeries. Based on their findings, Fily et al. suggest the implementation of a strong ASP and use of second-line antibiotics when treating PTO in war-wounded patients. However, the authors make no references to the ASP implemented at this study site in 2016, as described by Bhalla et al., which is a limitation of their discussion.

Alga and Wong et al. 2016 conducted an open cohort study with longitudinal data collected from war-wounded Syrian civilians seeking care at an MSF-supported hospital in Jordan between 2014 and 2016. They collected data on 457 patients (86% male, mean age 27). The authors used logistic regression models to understand differences in outcome and resource use based on infection status. Infection status was determined by culture results and clinical presentation of the wound. Eleven percent of their cohort had an infected war wound and of these, 73% of the infections were MDR. They identified Klebsiella pneumoniae, Enterobacteria, and Escherichia coli as the pathogen strains resistant to the most antimicrobials. According to their statistical analysis, those with infected war
wounds required an average of 12 surgeries when compared to non-infected patients, who required an average of five surgeries \((p<0.00001)\). Further, infected patients were hospitalized for about 77 days, as compared to 35 days for non-infected patients \((p=0.000001)\). Patients with infected injuries were also subject to a higher number of amputations. The authors conclude that war-wound infections are associated with high resource consumption, worsened clinical outcomes for patients, and a higher occurrence of MDR pathogens. Based on these findings, they call for the development of “antibiotic protocols and adaptations of surgical management” to better the quality of care received by patients suffering from war-related injuries.

Diagnostics and Surveillance (DS)

The capacity for microbiological surveillance of disease emergence and spread is oftentimes limited in LMICs due to resource constraints. Challenges include financial barriers, absence of culture samples, and infrastructural constraints (e.g., water supply, electricity supply, waste management, etc.). Given these challenges, resistance is only sporadically tested for in many low-resource health clinics and hospitals. In extremely resource-limited regions, such as Gaza, AMR is only reported anecdotally with no capacity to gather data to support the extent of its prevalence. In order for ASPs to be effective, prescribers require specific and accurate information on the type of resistant pathogens that a patient carries in order to inform clinical decisions. Furthermore, ineffective or insufficient disease surveillance programs may be detrimental to infectious disease prevention and control efforts. One example is the spread of TB in LMICs. In 2016, nearly 40% of individuals worldwide – that is, nearly 4.1 million individuals – either failed to be diagnosed with TB or failed to have their disease status reported to a national TB surveillance program. Such gaps in surveillance efforts are significant given that TB ranked as the ninth leading cause of deaths globally that year and also that TB-causing pathogens rapidly acquire resistance to treatment. Specific and sensitive diagnostics and robust surveillance systems are therefore necessary for the control of infectious
diseases. By extension, these measures may also be necessary for adequate AMR control. Seven studies included in this review, a number of which focused on TB, discuss the importance of diagnostic tools and surveillance in AMR management.

In Lebanon, Hamze et al. 2015 evaluated the efficacy of pyrosequencing technology to detect mycobacterium tuberculous resistant to rifampicin (RIF) and isoniazid (INH) in isolates collected from Syrian refugees and Lebanese patients. RIF and INH were of interest to the researchers as MDR-TB is defined by a resistance to both these antibiotics. Before the Syrian civil war started, Lebanon had seen a decrease in incident TB cases. However, as of 2014, nearly 14% of all TB cases in Lebanon were among Syrian nationals, with some number of these cases being MDR-TB. Traditional culture-based tests for resistant TB may take up to 4 weeks to yield results; the researchers wanted to test pyrosequencing assays as an alternative diagnostic tool. They found that pyrosequencing, which sequences short DNA segments, applied to 66 clinical isolates was able to detect INH-resistant strains with 72.6% sensitivity. Thus, the authors recommend the use of pyrosequencing as a rapid and sensitive diagnostic tool that should be used to inform clinical decisions regarding TB treatment.

Araj et al. 2016 conducted a retrospective study to generate data on TB and MDR-TB in Lebanon, given the lack of robust surveillance programs in the country. Their data sources included the National Tuberculosis Program (NTP) and the Clinical Microbiology Lab (CML) at the American University of Beirut. The goal of this study was to assess trends in TB incidence and prevalence in Lebanon from 1999 to 2013. The researchers found that in 2001, the incidence of TB was 13/100,000 population; by 2006, the incidence had dropped to 9/100,000 population. However, by 2013 – two years after the onset of the civil war in Syria – the incidence of TB reached 20/100,000. They conclude that this rise in TB incidence is attributable to TB cases in non-Lebanese nationals and Syrian refugees. Among the identified MDR-TB cases, resistance was
highest to INH followed by resistance to RIF. The author’s cite limitations of their study as being incomplete and non-comprehensive data due to restricted reporting to TB surveillance programs. They conclude that “rapid and reliable” diagnostics are necessary such that TB may be diagnosed early and treated. In their own labs at the American University of Beirut Medical Center, the authors employ automated instruments and the TB Gene Xpert (Cepheid) as diagnostic tools.

In another study based in Lebanon, El Achkar et al. 2019 tested 720 samples collected by the Lebanese National TB program from patients suspected of having TB between June 1, 2016 through May 31, 2017. Samples were collected from individuals from Syria, Lebanon, Ethiopia, Palestine, Bangladesh, and elsewhere. Two-hundred eighty four cases of TB were confirmed based on culture results and Xpert MTB/RIF (Cepheid) molecular testing. Xpert testing was also used to determine resistance. The authors found that of a subset of 250 patients, 2.8% were resistant to RIF. The authors used multivariable regression to test if prior TB infection was associated with RIF resistance and found that resistance was 22.8% among patients previously treated with the drug. They conclude that while resistance to RIF in their study population was fairly low, the three MDR-TB and three XDR-TB strains discovered in their study had “strong epidemic potential and complex resistance patterns.” The authors thus recommend that TB-positive patients in Lebanon be tested for drug resistance in order to better inform treatment decisions and to ensure that appropriate antibiotics are used.

In Pakistan, Ghafoor et al. 2012 conducted a cross-sectional study on TB management involving 139 patients (51% male, mean age 31) who resided in the Khyber Pakhtunkhwa (KP) Province. The KP Province was selected for this study in part due to the large population of Afghan refugees who live there, and also because conflict and displacement in the KP Province have disrupted past TB control efforts. The goal of this study was to describe the prevalence of MDR-TB in this region by recruiting patients and sorting them into two groups: residents with TB who
never received treatment (CAT I) and residents with TB who received treatment but failed to respond or relapsed (CAT II). The authors found that nearly 58% of patients in their study had MDR-TB: of those individuals, MDR-TB was more prevalent in the CAT II patients who failed treatment (76% prevalence) than in CAT I patients (62% prevalence). The authors conclude that patients with a history of TB treatment failure are uniquely at risk for MDR-TB. They further state that improved disease and resistance surveillance are important aspects of TB management in this region.

In Turkey, Dogru et al. 2017 conducted a retrospective comparative analysis of incident TB cases and treatment success between Turkish and Syrian patients registered at the TB Outpatient Clinic in the Hatay Province between 2010 and 2013. This province was selected for the study as it is home to a high number of displaced Syrian refugees. The goal of the study was to record incident TB cases and compare treatment success between Turkish and Syrian patient populations. The authors enrolled 178 Turkish patients (67% male, mean age 45) and 33 Syrian patients (61% male, mean age 32) to the study (n=211). It was found that treatment success rates amongst Syrian patients were lower than Turkish patients (64% vs. 89%, p<0.001) and that Syrian patients failed to complete treatment at a higher rate than Turkish patients (30% vs. 4%, p<0.001). Resistant TB was documented in 3 Turkish patients and 1 Syrian patient in this study population. To account for the lower treatment success rate in Syrian refugee patients, the authors recommend the implementation of a national TB control program that emphasizes the surveillance and treatment of refugees with TB.

The authors of two studies discussed improved diagnostics and surveillance for diseases other than TB. The first study was by Salloum et al. 2018. As a part of their case report, these researchers conducted a comparative genome analysis of a MDR *Streptococcus pneumoniae* responsible for the death of a 10-month old Syrian infant in Lebanon. They compared this isolate with 24
other *S. pneumoniae* genome sequences which they obtained from a publicly available database. The researchers investigated virulence factors, resistance mechanisms, and other characteristics of the strains in their comparison. They found that the isolate from the Syrian infant exhibited resistance to a number of drugs and also that regions of the genome were highly diverse, which the authors state “could account for the pronounced invasiveness of this isolate.” Given the isolate’s potential for rapid spread, the authors suggest the implementation of surveillance for *S. pneumoniae* in Lebanon, and recommend the use of whole genome sequencing to support these efforts.

The second study was by Fily et al. 2019, who analyzed bone biopsy samples collected from Iraqi, Syrian, and Yemeni patients with infected war wounds presenting for care at an MSF-supported program in Jordan (full study described under ASP). These authors cite missing data (particularly on Iraqi patients), sample contamination, and the “laboratory origin of their database” as limitations of their analyses. To circumvent sample contamination concerns, the authors only tested bone biopsy cultures for antibiotic susceptibility, as tests using deep tissue samples lack sensitivity and specificity. Based on their experiences, the authors state that improved laboratory conditions and enhanced data collection and management are necessary to appropriately manage *S. aureus* and *Enterobacteriaceae* resistance in patients with PTO.

*Education (E)*

The use of any antimicrobial applies selective pressure on pathogenic organisms, facilitating the emergence of drug-resistant pathogen strains. The overuse and misuse of antibiotics exacerbates this process. For example, despite antibiotics being ineffective for the treatment of viral infections, they are oftentimes prescribed in high-income settings to treat coughs, colds, and viral sore throats. In countries such as Syria and Lebanon, antibiotics are readily available for purchase over the counter and without a prescription, which make the problem of overuse particularly challenging to address. Therefore, increased education on appropriate antibiotic usage on the population and
clinical level is often cited as necessary steps towards controlling these key drivers of AMR. Two studies included in this review address education as an AMR control strategy.

In Jordan, Al Baz et al. 2017 used a cross-sectional, interviewer administered survey to study the knowledge, attitudes, and behaviors of Palestinian refugees (18% male, median age 32) regarding their antibiotic use. The 250 refugees who participated in this study were recruited at one of four United Nations Relief and Works Agency (UNRWA) health centers. Antibiotic use amongst this population was high, with 47% reporting one or more uses of antibiotics in the three months prior to survey administration. Self-medication – defined by study authors as “using leftover antibiotics, sharing antibiotics at home and purchasing antibiotics over the counter without prescription” – was also high. Of the respondents, 63% reported that they shared their antibiotics with others, 38% had used leftover antibiotics, and 60% purchased their drugs over the counter. The authors used logistic regression to model inappropriate antibiotic use. After adjusting for potential confounders, they found that patients who perceived there to be long wait times at health clinic had two times the risk of self-medication compared to those who perceived short wait times. These individual also had 1.7 times the odds of purchasing drugs over the counter. Income, age, employment, and education level were not found to significantly affect self-medication in this study population. Given these findings, the authors recommend that interventions work on the community-level to promote education on appropriate antibiotic use. Also, given that 90% of respondents indicated that they trust their healthcare providers, the authors encourage increased counseling from the medical staff on appropriate antibiotic use.

Another study based in Jordan was by Alga and Herzog et al. 2018a, who conducted a qualitative study on physicians employed in an MSF-supported hospital to capture their perspective on AMR and hospital-based infections (full study described under IPC). Physicians in this study regarded patient behavior as a contributing factor to AMR: notably, they cited concerns over
patients’ ability to purchase drugs over the counter, as well as premature discontinuation of antibiotic use by patients.\textsuperscript{25} No physician in this study identified a direct link between the emergence of a HAI and the spread of AMR, despite these two factors being interrelated.\textsuperscript{25} Further, physicians had variable opinions on behaviors that may result in HAIIs – e.g., hand hygiene was mentioned by some physicians as a behavioral factor that does contribute to the emergence of HAIIs, while it was mentioned by others as a factor that does not contribute to HAIIs.\textsuperscript{25} Based on these findings, the authors recommend increased training of healthcare professionals on the importance of hand hygiene compliance.\textsuperscript{25} They also recommend increased resource allocation as an intervention to improve adherence to hygiene protocols.\textsuperscript{25}

\textit{Other (O)}

\textbf{Combination antibiotic therapies} are believed to be an effective treatment approach for patients carrying resistant pathogens.\textsuperscript{49} Many infectious agents mutate and acquire resistance faster than new medications can be developed to treat patients; careful combination of existing therapies is a means of killing these resistant agents and allows for increased therapy options in lieu of novel scientific advances.\textsuperscript{49} Combination therapies are currently in use to treat resistant TB, human immunodeficiency virus (HIV), and malaria.\textsuperscript{29,49} One study included in this review considered combination therapy use as an intervention on AMR.

In Pakistan, Kolaczinski et al. 2012 recruited 308 Afghan refugees (58% male) with falciparum malaria from five villages near the Peshawar Province for a randomized control trial.\textsuperscript{29} They randomized participants to one of six treatment arms in order to determine which treatment arm was most effective against malaria.\textsuperscript{29} The treatment arms were as follows: (1) chloroquine (CQ); (2) CQ + single dose of gametocytocidal primaquine (PQ); (3) CQ + three doses of artesunate (AS); (4) sulfadoxine-pyrimethamine (SP); (5) SP + single dose PQ; (6) SP + three doses AS.\textsuperscript{29} At the time that the study was initiated, CQ was the first-line treatment used for malaria, despite widespread
resistance to the drug. In their study, the authors found that patients treated with CQ had a treatment failure rate of 81% at 28 days follow-up. However, patients treated with SP + AS had a failure rate of 2.4% at follow-up. Based on these findings, CQ treatment was replaced with SP + AS combination therapy in the World Health Organization Eastern Mediterranean Region. The authors caution, however, that mono-therapeutic use of SP, which is still common in the region, may lead to future resistance to SP.

Protocols and guidelines used to treat civilians with war injuries were first developed by the International Committee of the Red Cross (ICRC) as early as 1988. Today, MSF-supported hospitals continue to adhere to ICRC guidelines for the treatment of civilians harmed during conflict. As discussed in the IPC section of this paper, appropriate management of war wounds is necessary to circumvent infection and the subsequent emergence and spread of AMR pathogens. However, healthcare workers in resource-limited settings are not always able to fully comply. One study included in this review considered the development of new guidelines and protocols for conflict-afflicted settings as a way to improve adherence and compliance.

Alga and Herzog et al. conducted two separate qualitative studies with physicians employed by an MSF-supported hospital in Jordan. The first study (Alga and Herzog 2018a) was described in the IPC and E sections of this review. Their second study (Alga and Herzog 2018b) sought to capture physician opinion regarding perceived challenges to war wound management in the hospital setting. In total, they conducted 10 semi-structured interviews with physicians (60% male, mean age 37), transcribed the interviews, and content analyzed them. They found that the largest barrier to appropriate wound management reported in this setting was poor protocol adherence. Some barriers to adherence identified by physicians included: “(i) lack of medication or equipment, (ii) lack of space, (iii) patient and caregiver behavior.” The authors point out that these barriers are not
insurmountable. To overcome them, they suggest that future studies be conducted in order to develop new guidelines and protocols for resource-constrained hospitals.\textsuperscript{28}

**DISCUSSION**

*Main Findings*

The interventions identified in this scoping review predominantly fall into five categories: infection prevention and control (discussed in four studies); antibiotic stewardship programs (discussed in three studies); diagnostics and surveillance (discussed in seven studies); education (discussed in two studies); and other (discussed in two studies).

While an initial goal of this analysis was to identify “best” control strategies for AMR in conflict-afflicted LMICs, a majority of the articles deemed eligible for inclusion did not offer a discussion of the effectiveness of their proposed interventions. Further, the complexity of the issue at hand makes it apparent that no one intervention is likely to be sufficient in managing the emergence and spread of AMR. Only three studies included in this review assessed the effectiveness of their proposed interventions. Bhalla et al. 2016 assessed the implementation of an ASP in a health clinic in Jordan and found that it did reduce antibiotic costs and improved antibiotic utilization practices.\textsuperscript{24} Hamze et al. 2015 explored lab diagnostics and found that use of pyrosequencing technology improved sensitivity testing for MDR-TB in Jordan and also allowed for more rapid testing for resistance.\textsuperscript{33} Kolaczkinski et al. 2012 showed that individuals treated with SP + AS had lower clinical failure rates during malaria treatment than those treated with CQ, a drug which malarial pathogens are highly resistant to.\textsuperscript{29} These studies provide support for ASPs, DS, and combination therapy, respectively.

Though based on primary research findings and the authors’ expertise, recommendations offered in the remaining papers were at best speculative given the limited research to support the effectiveness of the interventions in low-resource settings. Research on the feasibility and utility of
IPC, education, and implementation of new guidelines is especially needed given that no studies included in this review spoke to their effectiveness.

To further contextualize the findings of this scoping review, semi-structured qualitative interviews were conducted with experts to gain their opinions on the identified intervention categories. Interlocutors included: a physician at the Syrian America Medical Society (SAMS) (P1); an academic with expertise on AMR in conflict-afflicted countries (P2); a doctor and clinical leader on AMR at MSF (P3); and a microbiologist at MSF (P4). Two main takeaways emerged from these interviews: (1) heavy metals and environmental contaminants due to warfare are key drivers of AMR and (2) interventions must be tailored to the resource availability of a given region.

**Role of Heavy Metals**

*A. baumannii* is regarded as one of the most burdensome pathogens to emerge and cause infection in times of conflict. This bacterial pathogen readily acquires multi-drug resistance and spreads quickly both nosocomially and within the community. *A. baumannii* has a number of resistance mechanisms, but a primary mechanism is biofilm formation, which protects the pathogen from drugs and host immune response. *A. baumannii* was documented as being the most prevalent infection-causing pathogen in war-wounded individuals during wars in Iraq, Lebanon, and Afghanistan. In fact, this pathogen became so well known for its role in causing wound infections in U.S. soldiers returning from Iraq that it was nicknamed “Iraqibacter.”

Heavy metals play a role in selecting for resistance amongst pathogen species and are increasingly being identified as key drivers of resistant *A. baumannii* infection in war-wounded individuals. Heavy metals, defined as a “group of non-biodegradable metals and semi-metals (Metalloids),” are readily available in the environment and are often used in the development of

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iv This pathogen is also described by Rafei and Dabbousi et al. 2013 and Rafei and Pailhories et al. 2015 in the IPC section of this paper.
antimicrobials and chemotherapies. Heavy metals are also used in weapon production, and are present in large quantities in missiles, bullets, military vehicles, and explosives. Specific resistance mechanisms related to heavy metals are beyond the scope of this paper and are described elsewhere by Bazzi et al. 2020. However, their main importance to this discussion is their role in applying a selective pressure that allows for the persistence of resistant pathogens.

Widescale weapon use contaminates the environment with abnormal levels of heavy metals and, therefore, warfare has direct ecological impacts that drive AMR. While supplementary factors such as inappropriate antibiotic use and inadequate antibiotic stewardship likely play a role in the emergence and spread of AMR in conflict-affected regions, it is critical that the issue of AMR at large not be reduced to a behavioral one. This point is best explained by P2, an academic with expertise in the political and environmental ramifications of warfare on AMR. When asked what he believed the role of antibiotic stewardship to be in the global response to AMR, he said the following:

“Yes, I think that the risk of... of obscuring the conflict, in terms of what it's doing and in terms of the environmental damage and the physical injuries and the destruction of these healthcare, you end up really reducing this problem to really, a behavioral problem. And you are expecting people in a war zone or in a conflict setting, that they will have to kind of abide by WHO guidelines while they are being bombed left and right by whoever... I mean, it feels like sometimes people are living in La La Land when they talk like that, you know? But all we need to improve stewardship and improve antibiotic prescription. I mean, but when you go to Idlib or Mosul and you see the situation... this is the last of your concerns. Having said that, that's not necessarily a bad idea, to begin to raise awareness and explore these problems and the prevention. But again, the issue – the bigger issue – is the whole war and the war ecology...”

This excerpt makes clear the additional considerations that must be kept in mind when an LMIC is confronted not only with a limitation of resources, but also active violent conflict. While there are behavioral components of AMR that health systems might address with interventions identified in this paper – notably, education and the implementation of ASPs – it is crucial to recognize that some barriers to effective AMR control are simply beyond the capacity of already struggling health
systems and people. In idealistic terms, the best control for AMR in conflict-affected LMICs would be an immediate ceasefire of all violent conflict, especially in the MENA region. In the absence of such ceasefire, however, the global health community must think more strategically about AMR interventions that are tailored to local capabilities and capacities. MSF has been a leader in such thinking, and has presented a structure for deciding on effective AMR interventions in conflicted-affected LMICs. Their intervention recommendations are explored below.

**Tailoring Interventions**

In 2015, the WHO released a report titled the “Global Action Plan on Antimicrobial Resistance.” The five objectives identified in this plan include: (1) increased educational awareness of AMR and its drivers; (2) improved surveillance of and research on AMR; (3) infection prevention and control; (4) optimization of antibiotic use in humans and animals; and (5) sustained investment in the development of new drugs, therapies, and diagnostics. While this report acknowledges that AMR prevention and control necessarily looks different in LMICs, the guidance offered to these countries is minimal and ultimately lacks the specificity required for effective intervention. The authors of the report recognize this limitation and identify lack of research on treatment and IPC, as well as minimal data, as barriers to effective AMR control in LMICs.

In the same year, MSF released their “Roadmap on Antibacterial Resistance.” Given the presence of MSF predominately in LMICs, this document explicitly addresses control and its associated challenges in low-resource settings. Many of the objectives identified in the MSF plan are comparable to those in the WHO plan – e.g., stewardship, surveillance, improved lab diagnostics, infection prevention, etc. However, the plans differ in that MSF writes specifically on antibiotic resistance (ABR), rather than AMR more generally, and MSF also tailors their recommendations based on existent lab and diagnostic infrastructure in each of their operational sites. In a subsequent 2019-2020 strategic plan released by MSF, they propose two “packages” for ABR
control. The first package recommends that all MSF healthcare facilities – regardless of their capacity to conduct microbiology research – should, at the minimum, implement an ASP and an IPC plan. The second package, called a “full package,” recommends the implementation of an ASP, IPC, and “access to microbiology.” This access would ensure that appropriate diagnostic tools and lab infrastructure are in place such that identification of infection-causing agents, tailored antibiotic treatment with specificity to the infectious pathogen, and time-sensitive detection of resistance are possible. Given the importance of microbiology data in ABR control, MSF has helped to support microbiology labs at 14 of their project sites, including a lab in Jordan.

However, the establishment of a lab is not always feasible, and it is in the absence of microbiology that interventions must be creatively modified to fit local capacities and resources. According to an MSF researcher who works on ABR (P3), education- and behavior-based interventions become particularly important in regions that lack microbiology access. P3 identifies the following as supplemental actions that might be taken in regions where full-package ABR control is not possible:

“The only thing that we do in places that is where there is no access to antibiotic… we try to improve the clinical scheme of the people doing external consultation, or we call it OPD, is outpatient departments. This person is key as well in the most of the places that we work because this person will decide if one patient will get some antibiotics or not or if the patient needs to be hospitalized or not. We developed… a tool that is called e-Care and the e-Care is kind of like an app based with the tablet and the ideas to help the clinician to take the right decision.”

Here, P3 is describing an iteration of an ASP program which uses the outpatient setting as a backdrop for intervention. While an app-based system presumes access to technology and Internet service, this strategy provides an example of how interventions identified in this paper may be adapted to the context in which they are implemented. Investment in improved lab diagnostics is sorely needed in LMICs most affected by conflict; however, there are other opportunities to intervene in the absence of microbiology. When asked if they believed that improved lab diagnostics
was the predominant intervention needed to curb AMR, a microbiologist who has helped MSF to open a number of labs around the world (P4) disagreed and said the following:

“No, I would say infection prevention and control as... as it is really like the, the, the main pillar. It’s like, without that, you can rationalize the use of all the antibiotics, you can put diagnostic tests everywhere. You are just going to diagnose what you are creating in your own hospital, which is going to be a loss of time, loss of money, and loss of life.”

In other words, hospitals and healthcare facilities must take sufficient action to try and prevent the emergence of resistance-prone infections altogether. Otherwise, the implementation of ASPs and the use of lab diagnostics may just be reactionary measures that fail to adequately address the roots of the problem. However, P4 cautions that the implementation of IPC measures is no easy task. Challenges to IPC range from war-related factors (e.g., heavy metals in the environment) to resource constraints in the hospital setting. As thus, P4 believes that future research is needed in order to inform effective IPC program design and to improve adherence to IPC guidelines by medical staff.

In the interim, actions taken by MSF and other organizations with expertise in conflict-afflicted LMICs should be studied closely as examples of how interventions on AMR may be formulated and implemented. As P3 states in their interview, despite there being a number of different guidelines that have been proposed by public and global health bodies, the most successful control of AMR will only be possible if healthcare systems themselves are provided with the capacity to conduct research and understand the epidemiological spread of pathogens and resistance in their facilities. In the absence of such research and data, AMR interventions will continue to lack the epidemiologic grounding needed to be effective. Furthermore, as P2 and P4 discuss, interventions must equally target both the emergence and spread of AMR; while these phenomena are certainly related to one another, they are also distinct issues that require their own specific interventions.
LIMITATIONS

There are a number of limitations to this scoping review. Foremost, all searchers were conducted in English and only papers published in English were eligible for inclusion, despite the focus of this review on regions where English is not the predominant language. Additionally, this review was limited to primary research on only four conflicted-afflicted LMICs in the MENA region. It is possible that other intervention strategies might have been identified if the search were expanded to include grey literature or other conflict-afflicted countries around the world. A limitation of the qualitative component of this paper was that only four interviews were able to be completed, despite the extension of more than ten interview requests. However, the completed interviews did provide key insights – a greater number and diversity of interviews in future research of this nature would allow for more rigorous and theory-based thematic analyses of expert opinion.

CONCLUSION

The challenges associated with containing the emergence and spread of AMR are exacerbated by violence, conflict, and displacement. Conflict-afflicted LMICs not only face resource limitations, but must also find ways to care for and treat injured individuals who carry increasingly-resistant pathogens. This scoping review identified five key intervention categories for AMR control in conflict-afflicted LMICs: (1) infection prevention and control; (2) antibiotic stewardship programs; (3) diagnostics and surveillance; (4) education; and (5) other. Based on what is currently known in the literature and expert opinions, a major takeaway from this review is that improved lab diagnostics, implementation of surveillance programs, and infection prevention and control should all be prioritized in efforts to control AMR in conflicted-afflicted LMICs. However, there is limited primary research on the effectiveness of all identified intervention strategies in such settings. In
particular, a major gap in the literature identified by this review was the absence of primary studies on the effectiveness of education-based interventions and IPC in conflict-afflicted countries.

As violent conflict persists around the world, it is critical that the threat of antimicrobial resistance is responded to appropriately and immediately. In order to respond, however, increased data and primary research on AMR in conflict-afflicted regions is sorely needed. To be effective, interventions must be uniquely tailored to the political, social, and ecological realities of the countries that they are implemented in. Furthermore, the problems and challenges identified throughout this paper go far beyond countries actively experiencing violence or warfare: resistant pathogens oftentimes become unwanted cargo, carried unknowingly by those fleeing humanitarian disaster. The global health community should leverage this fact to increase research funding and attention to the unique dangers of AMR in conflict-afflicted regions – e.g., its exacerbated potential for spread in these settings. In engaging in such research, however, it is critically important that displaced individuals and refugees themselves are not pathologized and solely blamed for AMR. As P2 explained in his interview, the entire war system – including the targeted breakdown of healthcare infrastructure, sanctions that render it impossible to import needed medications and medical supplies, impact of weaponry on the environment and water sources, and so on – must all be considered as drivers of AMR. Ultimately, the struggle to provide care to those most in need will only increase as antibiotics continue to fail to cure illness and infection. Prompt action by the global health community is necessary; the findings of this analysis provide preliminary guidance on where to begin in the fight against AMR in conflict-afflicted LMICs.
REFERENCES


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## APPENDIX

Table 1. Full Search Strategy per Database

<table>
<thead>
<tr>
<th>Search Category</th>
<th>PubMed</th>
<th>Embase</th>
<th>Scopus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conflict</td>
<td>(1) conflict*[tw] OR warfare*[tw] OR war*[tw] OR displace*[tw] OR refugee*[tw] OR violence[mesh] OR violen*[tw] OR war-related injuries[mesh] OR warfare and armed conflicts[mesh] OR refugees[mesh] OR wound infection[mesh] OR &quot;asylum seeker&quot;<em>[tw] OR &quot;war wound</em>[tw]</td>
<td>(1) (((violence*[tw] OR armed conflict OR war-related injuries OR refugee*[tw] OR displace*[tw] OR wound infection OR asylum seeker OR war wound*[tw]).mp.) OR (*war/ OR *refugee/))</td>
<td>(1) TITLE-ABS-KEY (conflict* OR war* OR displace* OR refugee* OR &quot;armed conflict*&quot;) OR &quot;war-related injuries&quot; OR violence OR &quot;asylum seeker&quot; OR &quot;war wound&quot;)</td>
</tr>
<tr>
<td>Region</td>
<td>(3) Turkey*[tw] OR Turkish*[tw] OR Jordan*[tw] OR Jordanian*[tw] OR Lebanon*[tw] OR Lebanese*[tw] OR Pakistan*[tw] OR middle east*[tw] OR Middle East[mh:noexp] OR Turkey[mh] OR Jordan[mh] OR Pakistan[mh] OR Lebanon[mh]</td>
<td>(3) ((Middle East/).mp.) OR (Jordan OR Jordanian OR Lebanon OR Lebanese OR Turkey OR Turkish OR Pakistan OR Pakistani OR Middle East).mp.)</td>
<td>(3) TITLE-ABS-KEY (Turkey OR Turkish OR Jordan OR Jordanian OR Lebanon OR Lebanese OR Pakistan OR Pakistani OR “Middle East”)</td>
</tr>
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<td>Full Search</td>
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<td>1 AND 2 AND 3</td>
<td>1 AND 2 AND 3</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Site</td>
<td>Study Population</td>
<td>Study Details</td>
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<tr>
<td>Bhalla et al., 2016</td>
<td>Jordan</td>
<td>Iraqi, Syrian, and Yemeni patients with chronic multidrug-resistant infections</td>
<td>Patients treated at the MSF Reconstructive Surgery Project in Amman; ASP implemented by MSF at this site; program reduced antibiotic cost by \sim $92,129 over one-year period</td>
</tr>
<tr>
<td>Al Baz et al., 2017</td>
<td>Jordan</td>
<td>Palestinian refugees (18% male, median age 32)</td>
<td>Patients treated at one of four UNRWA health centers; interviewed regarding knowledge and use of antibiotics; 63% shared antibiotics, 38% used leftover antibiotics, 60% purchased drugs over-the-counter</td>
</tr>
<tr>
<td>Alga &amp; Herzog et al., 2018a</td>
<td>Jordan</td>
<td>Physicians (55% male, mean age 37)</td>
<td>Physicians employed by an MSF-supported hospital; interviewed regarding views and attitudes on AMR and HAI; most providers did not acknowledge a link between AMR and HAI</td>
</tr>
<tr>
<td>Alga &amp; Herzog et al., 2018b</td>
<td>Jordan</td>
<td>Physicians (60% male, mean age 37)</td>
<td>Physicians employed by an MSF-supported hospital; interviewed regarding perceived challenges to war wound management; identified lack of resources as barrier to protocol adherence</td>
</tr>
<tr>
<td>Alga &amp; Wong et al., 2018</td>
<td>Jordan</td>
<td>Syrian civilians (86% male, mean age 27)</td>
<td>Patients received surgical treatment for conflict-related injuries at an MSF-supported hospital; open cohort study with longitudinal data collection was conducted; 73% of patients had MDR infections; length of stay for patients with MDR infection was about 42 days longer than patients without infection</td>
</tr>
<tr>
<td>Fily et al., 2019</td>
<td>Jordan</td>
<td>Iraqi, Syrian, and Yemeni civilians with war-related injuries</td>
<td>Patients admitted to an MSF-supported program in Jordan for treatment; lab data from the MSF database was retrospectively analyzed; 77% of patients had \geq 1 sample positive for FLAR; FLAR was associated with lower limb injury, \geq 12 months since injury, and more than 3 previous surgeries</td>
</tr>
<tr>
<td>Ghafoor et al., 2012</td>
<td>Pakistan</td>
<td>Residents of Khyber Pakhtunkhwa province (51% male, mean age 31)</td>
<td>Cross-sectional study to determine prevalence of MDR-TB in this region was conducted; recruited patients who never received treatment for TB (CAT I) and patients who received treatment and failed or relapsed (CAT II); MDR-TB found to be more prevalent in CAT II patients who previously failed treatment than CAT I patients</td>
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<tr>
<td>Kolaczinski et al., 2012</td>
<td>Pakistan</td>
<td>Afghan refugees (58% male) with falciparum malaria</td>
<td>Refugees recruited from five different villages near the Peshawar Province; randomized to one of six treatment arms; chloroquine was deemed inappropriate for malaria treatment; sulfadoxine-pyrimethamine (SP) + artesunate (AS) were deemed most effective</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>Rafei &amp; Dabboussi et al., 2013</td>
<td>Lebanon</td>
<td>Syrian refugees with war-related wounds</td>
<td>Patients treated at the Tripoli Government Hospital; patient isolates were collected and tested for carbapenem-resistant <em>A. baumannii</em>; four isolates identified with high-level resistance</td>
</tr>
<tr>
<td>Rafei &amp; Pailhories et al., 2015</td>
<td>Lebanon</td>
<td>Syrian refugees and Lebanese patients (78% male, mean age 40)</td>
<td>Patients treated at different hospitals in Tripoli, Lebanon; isolates were collected and tested for resistance to antibiotics; 60% of isolates exhibited carbapenem resistance</td>
</tr>
<tr>
<td>Hamze et al., 2015</td>
<td>Lebanon</td>
<td>Syrian and Lebanese patients</td>
<td>Patient isolates collected by the National Commission for Biotechnology in Syria and the Azm Center for Research in Biotechnology in Beirut; utility of pyrosequencing technology for the detection of MDR-TB was evaluated; technology was found to be 72.6% sensitive to INH resistance</td>
</tr>
<tr>
<td>Araj et al., 2016</td>
<td>Lebanon</td>
<td>Individuals residing in Lebanon</td>
<td>Data collected by the National Tuberculosis Program (NTP) or the Clinical Microbiology Laboratory (CML) at the American University of Beirut Medical Center; data was retrospectively analyzed; &gt;7500 cases of TB reported since 2011; increase in TB cases likely attributable to influx of Syrian refugees</td>
</tr>
<tr>
<td>Salloum et al., 2018</td>
<td>Lebanon</td>
<td>Syrian infant</td>
<td>Case report on <em>S. pneumoniae</em> responsible for the death of 10-month old Syrian infant; comparative genome analysis of <em>S. pneumoniae</em> from infant and 24 other <em>S. pneumoniae</em> genomes from publicly available dataset was conducted; isolate collected from infant exhibited potential for “pronounced invasiveness” and resistance</td>
</tr>
<tr>
<td>El Achkar et al., 2019</td>
<td>Lebanon</td>
<td>Individuals with suspected cases of TB (51% male, mean age 34)</td>
<td>Data reported to a national TB program in Lebanon; data was retrospectively analyzed; 250 confirmed cases of TB; 3% of cases found to be resistant to RIF</td>
</tr>
<tr>
<td>Yuce et al., 2017</td>
<td>Turkey</td>
<td>Syrian patients (58% male, mean age 27)</td>
<td>Patients treated for burns at the Dr. Lutfi Kirdar Kartal Educating and Training Hospital Burn Centre of Istanbul; patient data retrospectively analyzed; high prevalence of infection with resistant pathogens observed in patients with conflict-related burns</td>
</tr>
<tr>
<td>Dogru et al., 2017</td>
<td>Turkey</td>
<td>Syrian patients (61% male, mean age 32) and Turkish patients (67% male, mean age 45)</td>
<td>Patients registered to the Hatay TB Outpatient Clinic; retrospective comparative analysis of incident TB cases and treatment success between Turkish and Syrian patients was conducted; treatment success rate amongst Syrian patients found to be lower than Turkish patients (64% vs. 89%, p&lt;0.001)</td>
</tr>
</tbody>
</table>
### Table 3. Recommended AMR Control Strategies

<table>
<thead>
<tr>
<th>Author</th>
<th>Recommendation Type(s)*</th>
<th>Recommendation Details</th>
<th>Duration of Study/Data Collection Period</th>
<th>Intervention Outcomes and Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhalla et al., 2016</td>
<td>ASP</td>
<td>Implementation of antibiotic stewardship program that adhere to guidelines set by the Centers for Disease Control (CDC)</td>
<td>2013-2014</td>
<td>When compared to the previous year, antibiotic costs following ASP implementation dropped from ~$252,077 to ~$159,948</td>
</tr>
<tr>
<td>Hamze et al., 2015</td>
<td>DS</td>
<td>Use of pyrosequencing for rapid and highly-sensitive detection of MDR-TB resistant to RIF and INH</td>
<td>-</td>
<td>Culture-based screening for MDR-TB can take up to 4-weeks; pyrosequencing technology more rapidly detects resistance to INH with 72.6% sensitivity</td>
</tr>
<tr>
<td>Kolacinski et al., 2012</td>
<td>O</td>
<td>Change in first-line malaria treatment from chloroquine to combination therapy (SP + AS)</td>
<td>2000-2003</td>
<td>Patients treated with chloroquine had a clinical failure rate of 81% at 28 days follow-up; patients treated with SP + AS had a treatment failure rate of 2.4% at follow-up</td>
</tr>
<tr>
<td>Ghafoor et al., 2012</td>
<td>DS</td>
<td>Implementation of MDR-TB surveillance program; monitor patients with past treatment failure</td>
<td>2009</td>
<td>-</td>
</tr>
<tr>
<td>Rafei &amp; Dabboussi et al., 2013</td>
<td>IPC</td>
<td>Utilization of IPC measures to prevent transmission of carbapenem-resistant A. baumannii</td>
<td>2012</td>
<td>-</td>
</tr>
<tr>
<td>Rafei &amp; Pailhories et al., 2015</td>
<td>IPC</td>
<td>Utilization of IPC measures to prevent spread of resistant A. baumannii</td>
<td>2011-2013</td>
<td>-</td>
</tr>
<tr>
<td>Araj et al., 2016</td>
<td>DS</td>
<td>Improved lab diagnostics for more rapid and accurate MDR-TB testing</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Al Baz et al., 2017</td>
<td>E</td>
<td>Increased education on proper antibiotic use amongst refugee groups</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dogru et al., 2017</td>
<td>DS</td>
<td>Implementation of national TB surveillance program</td>
<td>2010-2013</td>
<td>-</td>
</tr>
<tr>
<td>Salloum et al., 2017</td>
<td>DS</td>
<td>Use of whole genome sequencing for TB surveillance</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yuce et al., 2017</td>
<td>IPC</td>
<td>Accelerated transfer of burn victims to treatment centers</td>
<td>2011-2015</td>
<td>-</td>
</tr>
</tbody>
</table>

**Strategy Recommended but no Evidence for Effectiveness Provided in Article**

<table>
<thead>
<tr>
<th>Author</th>
<th>Recommendation Type(s)*</th>
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<tbody>
<tr>
<td>Rafei &amp; Pailhories et al., 2015</td>
<td>IPC</td>
<td>Utilization of IPC measures to prevent spread of resistant A. baumannii</td>
<td>2011-2013</td>
<td>-</td>
</tr>
<tr>
<td>Authors</td>
<td>Category</td>
<td>Description</td>
<td>Year(s)</td>
<td>Notes</td>
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<td>--------------------------</td>
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<tr>
<td>Alga &amp; Herzog et al., 2018a</td>
<td>E, IPC</td>
<td>Increased physician education on antibiotics and HAIs; improved IPC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alga &amp; Herzog et al., 2018b</td>
<td>O</td>
<td>Development of war wound management protocols/guidelines specific to conflict-affected settings</td>
<td>2015</td>
<td>-</td>
</tr>
<tr>
<td>Alga &amp; Wong et al., 2018</td>
<td>ASP</td>
<td>Implementation of more rigorous protocols for antibiotic use</td>
<td>2014-2016</td>
<td>-</td>
</tr>
<tr>
<td>Fily et al., 2019</td>
<td>ASP, DS</td>
<td>Implementation of high-skill laboratories; implementation of ASPs</td>
<td>2006-2016</td>
<td>-</td>
</tr>
<tr>
<td>El Achkar et al., 2019</td>
<td>DS</td>
<td>Increased testing of TB resistance prior to treatment decisions; improved lab diagnostics</td>
<td>2016-2017</td>
<td>-</td>
</tr>
</tbody>
</table>

* Abbreviations for control strategy categories: infection prevention and control (IPC); antibiotic stewardship program (ASP); diagnostics and surveillance (DS); education (E); other (O).
** Interventions in this category were suggested by the study authors, but no or limited supporting evidence for the strategy’s effectiveness was provided.
Fig. 1 Study Selection

599 records identified through database searching
- PubMed: n=220
- Embase: n=158
- Scopus: n=221

447 records identified for title and abstract screening

152 duplicate records removed

399 records excluded
- Published before Jan. 2010: n=156
- Not topically relevant: n=237
- Full-text not in English: n=6

48 records identified for full-text screening

32 records excluded
- Not primary research: n=23
- No discussion of control: n=9

16 studies included in review