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Review

A summary and appraisal of existing evidence of antimicrobial resistance in the Syrian conflict

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ABSTRACT

Antimicrobial resistance (AMR) in populations experiencing war has yet to be addressed, despite the abundance of contemporary conflicts and the protracted nature of twenty-first century wars, in combination with growing global concern over conflict-associated bacterial pathogens. The example of the Syrian conflict is used to explore the feasibility of using existing global policies on AMR in conditions of extreme conflict. The available literature on AMR and prescribing behaviour in Syria before and since the onset of the conflict in March 2011 was identified. Overall, there is a paucity of rigorous data before and since the onset of conflict in Syria to contextualize the burden of AMR. However, post onset of the conflict, an increasing number of studies conducted in neighbouring countries and Europe have reported AMR in Syrian refugees. High rates of multidrug resistance, particularly Gram-negative organisms, have been noted amongst Syrian refugees when compared with local populations. Conflict impedes many of the safeguards against AMR, creates new drivers, and exacerbates existing ones. Given the apparently high rates of AMR in Syria, in neighbouring countries hosting refugees, and in European countries providing asylum, this requires the World Health Organization and other global health institutions to address the causes, costs, and future considerations of conflict-related AMR as an issue of global governance.

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Introduction

Despite the proliferation of contemporary conflicts, the emergence of antimicrobial resistance (AMR) in settings of war and distressed migration has been neglected. This has been of particular concern in Syria where the protracted and increasingly destructive conflict has also been a driver of large-scale population movements both regionally and in Europe. Since 2012, the conflict has become the leading cause of death and injury in Syria. In the absence of accurate recent figures, it is estimated, as of the end of 2015, that 470 000 have been killed and 1.9 million injured (Syrian Center for Policy Research, 2018). With high rates of injury, the potential for infection is exacerbated by the crowded and often unsanitary conditions in health facilities, combined with the nature of injuries produced by heavy weaponry.

The destruction of health facilities, the exodus or death of healthcare workers, and the increasing fragmentation of Syria's health system have all contributed to the myriad of challenges in addressing AMR (Fouad et al., 2017). By April 2017, only 56 out of 111 public hospitals were still offering services (WHO, 2018), while it has been estimated that over 70% of all health professionals have left the country since the conflict began. Of the 6.4 million internally displaced persons (IDPs) estimated by the United Nations Office for the Coordination of Humanitarian Affairs (OCHA), more than one million live in unhygienic conditions in overcrowded camps and collective shelters, at increased risk of typhoid, hepatitis, cholera, polio, and cutaneous leishmaniasis, among other infectious diseases (Ismail et al., 2016).

Under conditions of conflict, many of the safeguards against AMR are broken and drivers are accentuated; these include damaged health and sanitation infrastructure, disrupted medical supplies, the exodus of expert and trained health professionals, and increasing exposure in compromised healthcare settings. War further disrupts the political and regulatory bodies that often lead, monitor, and enforce policies that tackle the drivers of AMR. This first part of a two-part series presents a review and analysis of the literature on what is known about AMR in the Syrian conflict. The second part explores the pre-existing drivers of AMR in Syria and those that have occurred since the onset of conflict; recommendations on how these can be addressed are also made.

Evidence of AMR in the Syrian context

Rigorous studies addressing microbiology or AMR in Syria, either before or since the onset of the conflict in March 2011, are scarce. Published studies have often been from a single centre and have presented limited data of variable quality. Functioning laboratories are restricted to major cities such as Damascus, Aleppo, and Lattakia, mainly in government-controlled areas (GCAs). Whether private or hospital-based, all laboratories close between Thursday afternoon and Sunday morning. As there is no on-call service, laboratory services are unavailable for 2.5 days each week. These laboratories are inaccessible to health workers serving the outskirts of these cities and rural areas in GCAs, in addition to the estimated 10 million people living in non-government-controlled areas (NGCAs), served by six laboratories (verbal communication) (Plate 1).

There are two parallel systems of surveillance. From Damascus, the Syrian Arab Republic Ministry of Health with the support of the World Health Organization (WHO) collects reports of notifiable diseases through the Early Warning and Response System (EWARS), but without laboratory testing of samples or contact tracing. Operating from Gaziantep in southern Turkey, the Early Warning and Response Network (EWARN) system is hampered by the paucity of laboratory services and the absence of local referral laboratories for verification and typing. Data from these systems may not be reliable in this context, nor generalizable across the country (Ismail et al., 2016; Sparrow et al., 2016). Neither system requires reporting on AMR, nosocomial infections, or response to therapy. Both systems are hampered by limited surveillance in governorates under the control of ISIS (Raqqa and Deir Ezzor) and the lack of quality control services and access to accredited referral laboratories. In GCAs this requires shipping of samples to Egypt; in NGCAs this requires cross-border transport to Turkey or Jordan, subject to permission from the relevant ministry of health. Both circumstances are challenging given the insecurity, difficulty in transporting specimens under controlled temperature conditions, and restricted access across borders.

A review of the scientific literature describing AMR amongst Syrians who remain in Syria and those who are refugees either in the region (Jordan, Lebanon, Turkey) or in Europe was performed to accurately describe the current literature on AMR in the Syrian conflict. The search methods are given in the Appendix A. Table 1 summarizes studies addressing AMR before and after the onset of the conflict, including all published articles relating to refugees or Syrians inside Syria.

Evidence of AMR in the Syrian context: pre-conflict

Before the conflict, several reports suggested the widespread availability of antibiotics through pharmacies without safeguards and/or poor knowledge amongst recipients of the risks associated with injudicious antibiotic use (Barah and Gonçalves, 2010). Anecdotally, extensive antibiotic overuse and antimicrobial failure were common. Limited evidence documenting the existence and prevalence of AMR was found in the perusal of the scientific literature. Studies identified were notable for their small size, inconsistent reporting, and questionable methodology, compromising the potential to identify trends or draw conclusions concerning AMR. Most studies were reported from the cities of Damascus and Aleppo, limiting generalization across and to other governorates.

Seven studies describing antibiotic susceptibility amongst different isolates were found (Table 1). The majority focused on specific bacteria including *Acinetobacter baumannii*, *Streptococcus pneumoniae*, and *Brucella melitensis* (Hamzeh et al., 2012; Turkmani et al., 2006; Obeid and Obeid, 2005). Hamzeh and colleagues reported high levels of AMR in 260 unique patients with *A. baumannii* infections from Aleppo in 2008–2011 (Hamzeh et al., 2012). Resistance to imipenem and meropenem (carbapenems)

Plate 1. This is a map of Syria which shows the location of the major cities, Damascus, Lattakia and Aleppo where the main functioning laboratories remain.

was reported at 66%, to ciprofloxacin (fluoroquinolone) 81%, piperacillin–tazobactam (penicillin-beta-lactamase) 87%, amikacin (aminoglycoside) 78%, and to co-trimoxazole (sulfonamide) 74%. Resistance to third- and fourth-generation cephalosporins was also high, with ceftazidime resistance reported at 80.6% and cefepime at 84.7%. Colistin remained active with only 7% reported resistance. The main drawback of this study was the use of an automated system for species identification, bearing in mind that these systems are unable to precisely distinguish isolates from the *A. baumannii–Acinetobacter calcoaceticus* complex to the species level. Keddo et al. reported that 25% of *Klebsiella pneumoniae* isolates amongst children with recurrent tonsillitis were carbapenem-resistant (Keddo and Al-Omari, 2012). With regards to Gram-positive isolates, the most recent study found was conducted in 2005: Obeid and colleagues reported high rates of resistance to penicillin (64%) and trimethoprim–sulfamethoxazole (48%) in 25 isolates of *S. pneumoniae* from cerebrospinal fluid samples, but found no resistance to cephalosporins (including cefotaxime and ceftriaxone), often used as first-line therapy for bacterial meningitis (Obeid and Obeid, 2005).

Although these reports describe small numbers, they raise concern regarding the high rates of AMR reported. The high proportion of carbapenem-resistant Gram-negatives is alarming given that carbapenems are used as broad-spectrum or salvage therapy following failure of empiric therapy. The percentage of penicillin-resistant *S. pneumoniae* is troubling, as overuse of antibiotics in the treatment of viral illness is a driver of penicillin resistance in this isolate.

Evidence of AMR in the Syrian context: since the onset of the conflict in 2011

Since the first use of armed force and subsequent expansion of violence, data on the availability and efficacy of antimicrobial therapy within Syria have become increasingly limited. Six studies from inside Syria since late 2011 have reported concerns over the increasing burden of resistant Gram-negative infections and methicillin-resistant *Staphylococcus aureus* (MRSA), four of these being focused on Aleppo (Alheib et al., 2015; Mahfoud et al., 2015; Al-Assil et al., 2013; Tabana et al., 2015). It is notable that few datasets from within Syria have reported on war-related injuries and their infectious complications; this is likely driven by several factors including political sensitivities and the overwhelmed health systems.

Studies of resistance from inside Syria on specific isolates have reported high levels of AMR. Zain and colleagues examined 236 *Escherichia coli* isolates and found 26% of these to be extended-spectrum beta-lactamase (ESBL) producers (Baaity et al., 2017). Alheib and colleagues examined 123 ESBL-producing *E. coli* and *K. pneumoniae* specimens in 2015 and found 66% of these isolates to be phenotypically resistant to ciprofloxacin (Alheib et al., 2015). Mahfoud and colleagues tested 177 *Pseudomonas aeruginosa* urinary and lower respiratory isolates from patients in three intensive care units in Aleppo and showed significant resistance to common anti-pseudomonal agents (piperacillin–tazobactam: 46%; meropenem: 41%; ceftazidime 73%) with colistin as the most reliable antibiotic (11% resistance) (Mahfoud et al., 2015). Al-Assil reviewed 104 patients with positive urine samples to understand the risk factors for the development of ESBL infections and isolated ESBL *E. coli* in 52% of cases (Al-Assil et al., 2013). Co-resistance to other antibiotics was found in 82% of cases. Risk factors identified as increasing the risk of ESBL acquisition in that study included older age (>52 years), hospitalization, urinary catheterization, and previous exposure to third-generation cephalosporins or quinolone antibiotics (Al-Assil et al., 2013).

Of the few large regional studies, a recent retrospective study in Lebanon analysing 55 594 Gram-negative isolates between 2011 and 2013 reported ESBL rates amongst *E. coli* and *Klebsiella spp* of 32.3% and 29.2%, respectively (Chamoun et al., 2016). Lebanon and Jordan, countries neighbouring Syria and hosting an estimated total of 1.7 million refugees, both reported the emergence of multidrug-resistant (MDR) Gram-negative infections complicating war-related injuries (Teicher et al., 2014; Abbara et al., 2017; Rafei

Table 1
Characteristics of key studies: divided into pre and post onset of the conflict in Syria, regional studies including Syrian refugees, and other studies describing Syrian refugees.

Group (year of publication)	Year	Location	Study description	Sample	Key findings
Pre-conflict					
Al-Omar (2005)	2004	Misiaf, Syria	Prospective culture of urine samples from all patients in the community	127 positive urine samples	• 68.6% of isolates were *Enterobacteriaceae* • 30.6% were Gram-positive (22.8% *S. aureus*) • Overall resistance reported at: 69% ampicillin, 55% TMP–SMX, 37% amoxicillin–clavulanate, 35% ofloxacin
Obeid and Obeid (2005)	Sep 2003 to May 2004	Damascus, Syria	*S. pneumoniae* from CSF samples; susceptibility of strains using disc diffusion methods (NCCLS breakpoints)	25 isolates	• Reported resistance: 64% were resistant to penicillin, 48% to TMP–SMX, 16% to erythromycin, and 16% to tetracycline • None resistant to ceftriaxone, cefotaxime, amoxicillin–clavulanate
Al-Qwaret et al. (2010)	2010	Damascus, Syria	Prospective cohort study of aerobic organisms isolated from diabetic foot ulcers and their reported antibiotic sensitivities	100 specimens, 128 organisms	• 61% of *S. aureus* isolates were MRSA • N CPE/CRO identified
Al-Qwaret et al. (2010)	2012	Damascus, Syria	Review of all aerobic bacterial conjunctivitis with antibiotic susceptibilities	51 patients	• High levels of susceptibility to first- and second-line agents reported
Keddo and Al-Omari (2012)	2012	Damascus Syria	Paediatric recurrent tonsillitis cases that underwent tonsillectomy Review of aerobic isolates from tonsil core culture	80 patients	• 25% of the *K. pneumoniae* isolates were carbapenem-resistant • 15% of *E. coli* were also imipenem-resistant
Hamzeh et al. (2012)	2008–2011	Aleppo, Syria	Retrospective review of *A. baumannii* isolates	260 patients with 260 isolates tested	• Resistance to specific antibiotics: 65% imipenem, 87% piperacillin–tazobactam, 78% amikacin, 81% ciprofloxacin, 74% co-trimoxazole, 7% colistin
Turkmani et al. (2006)	1995–2005	Eastern Mediterranean	Isolates of *B. melitensis* from animals in Syria	5 isolates	• Highly susceptible to most tested antibiotics
Post commencement of the conflict – Syria					
Al-Kadrou et al. (2013)	2013	Damascus, Syria	Aerobic bacterial infections in burns patients managed within a Syrian government hospital	109 isolates from 53 samples	• No polymyxin resistance in Gram-negatives identified
Tabana et al. (2015)	2015	Aleppo, Syria	Laboratory evaluation of prevalence of PMQR genes at Aleppo University	123 ESBL-producing isolates of *E. coli* and *K. pneumoniae*	
Al-Assil et al. (2013)	2011	Aleppo, Syria	Three hospitals in Aleppo; 75 patients with UTIs	75 patients with UTIs caused by trimethoprim-resistant *E. coli*; 104 unique isolates	• 96% susceptible to nitrofurantoin • Reduced susceptibility to: amoxicillin–clavulanate 43%, 3/4 GNB to cephalosporins 50–60%, piperacillin–tazobactam 66%, tetracyclines 44%, TMP–SMX 20%
Alheib et al. (2015)	2015	Aleppo, Syria	PMQR genes among ESBL *E. coli* and *K. pneumoniae*	123 isolates	• 66% of ESBL-positive isolates were resistant to ciprofloxacin • 83% of *E. coli* compared to 87% of *K. pneumoniae* harboured PMQR genes, but this did not necessarily confer phenotypic resistance
Mahfoud et al. (2015)	2011–12	Aleppo, Syria	Three major hospitals in Aleppo Lower respiratory tract and urine samples with nosocomial infections from intensive care patients in whom *P. aeruginosa* was isolated	177 samples (tested against CLSI guidelines)	• 59 female/118 male • Samples: 138 lower respiratory tract and 39 urinary • Selected susceptibility: piperacillin–tazobactam 54.5%, amikacin 42.8%, ceftazidime 28.6%, meropenem 59.1%, imipenem 56.1%, colistin 89.1%
Nofal (2016)	2016	Damascus, Syria	Retrospective review of species and sensitivities of otitis media cases	87 patients, 49 isolates	• 52% male, 48% female • *K. pneumoniae* ($n = 3$): 100% sensitive to imipenem and levofloxacin • *S. aureus* ($n = 16$): 100% sensitive to imipenem
Al-Assil et al. (2013)	2011	Aleppo, Syria	Three hospitals in Aleppo Risk factors for ESBL infections	104 patients with positive urine samples	• MDR *E. coli* ~63% • ESBL *E. coli* ~52%

Table 1 (*Continued*)

Group (year of publication)	Year	Location	Study description	Sample	Key findings
			assessed by multivariate regression analysis		• Levels of co-resistance high in ESBLs (82%) • Age >52 years, hospitalization, urinary catheters, prior third-generation cephalosporin use, and previous quinolone therapy were all associated with ESBLs in this study
Baaity et al. (2017)		Latakia, Syria	Al-Assad Teaching Antibiotic susceptibility and ESBL production by disc diffusion using CLSI/EUCAST	236 *E. coli* isolates	• 32% of the *E. coli* isolates were MDR and 26% were ESBL-producers
Post commencement of the conflict – outside Syria					
Teicher et al. (2014)	2011–13	Amman Jordan	Médecins Sans Frontières surgical project managing MDR defined as: (1) ESBL-expressing *Enterobacteriaceae*; (2) *P. aeruginosa* and *A. baumannii* isolates resistant to at least one agent in three antimicrobial categories typically used for treatment; or (3) MRSA	61 Syrian orthopaedic patients with suspected infections undergoing surgical sampling intraoperatively	• Age 26 years (IQR 22–34 years); 98% male • Injury to admission approximately 5 months (IQR 1.2–8.1 months): gunshot wounds $n = 31$, explosion wounds $n = 20$ • 45 of these patients had at least one organism, with 69% (31/45) MDR organisms: *P. aeruginosa* (10/31), *E. coli* (5/8), carbapenem-resistant *A. baumannii* (4/5), MRSA (7/17)
Kassem et al. (2017)	2013–2016	Israel	Microbiological surveillance screening of severely ill or injured Syrian children Screened for: ESBL, CRE, MRSA, MDR *A. baumannii*, and VRE	128 children	• MDR carriage found in 83%, with NDM CRE most prevalent • 24/128 had MDR infections (90% were wounded): ESBL 66%, MDR *A. baumannii* 20%, CRE 15%
Angeletti et al. (2016)	2016	Italy	Microbiological surveillance using rectal, pharyngeal, and nasal swabs	48 refugees	• High rates of Gram-negative non-lactose-fermenting organisms such as *Pseudomonas* and *Aeromonas* species, with 5 carbapenem-resistant isolates • No CRE • 24% (6/25) of *S. aureus* isolates were methicillin-resistant
Bhalla et al. (2016)	2016	Amman, Jordan	Observational study at the Médecins sans Frontières surgical programme hospital managing chronic trauma-related infections colonized or infected with AMR organisms	NA	NA
Abbara et al. (2017)	2015	Amman, Jordan	Microbiological samples from infected injuries (bone and soft tissue) amongst injured Syrian refugees	75 patients	• 20% had osteomyelitis, 53% had prosthetic material • 30 bacterial isolates of which 97% were GNB • 66% were MDR and 37% were carbapenem-resistant
Ravensbergen et al. (2016)	2016	Groningen, Netherlands	Screening of asylum seekers for MDROs upon admission to hospital	130 asylum seekers; 36.5% Eritrean and 18.6% Syrian	• 31% colonized with an MDRO: 7.7% with MRSA; 20% ESBL (20 *E. coli*, 4 *K. pneumoniae*, 1 *M. morganii*, and 1 *E. cloacae*) • 10% resistant to fluoroquinolones • No carbapenemases
Reinheimer et al. (2016)	2015	Germany	Microbiological surveillance screening of patients admitted to Frankfurt hospital for MDROs, for GNB (ESBL and *A. baumannii*), and MRSA	143 refugees, including 47 (43%) from Syria, 29 from Afghanistan, 14 from Somalia	• 60.8% colonized with MDR GNB in Refugee population compared to 16.8% in the general population • ESBL *E. coli* and *K. pneumoniae* were significantly more common (23.8% vs. 4.9% and 4.2% vs. 0.8%) • 1 CRE and 2 carbapenem-resistant *A. baumannii* • MRSA 5.6% vs. 1.2% in the general population
Heudorf et al. (2016)	2015	Frankfurt, Main, Germany	Microbiological surveillance screening of unaccompanied minors (aged <18 years) screened for MDR *Enterobacteriaceae* in stool samples	119 individuals, 7 Syrians	• Total: 35% had ESBL *Enterobacteriaceae*, including 8% GNB resistant to three antibiotic groups • Syrians: 3 had ESBL *Enterobacteriaceae*; none had MDR

Tenenbaum et al. (2016)	2015–2016	Germany	Retrospective observational study of screening of paediatric refugee patients admitted to hospital	325 patients	• MDR detected in 33.8% • 110 of 113 samples GNB • 87 MDR GNB/ESBL • 22 MRSA • 1 VRE
Heydari et al. (2015)	2014	Turkey	Microbiological surveillance screening of all *A. baumannii* resistant to carbapenems collected over the year period and screening for NDM-1-producing organisms	2 Syrian refugees admitted to ICU	· 1 isolate of 2 from a Syrian refugee admitted to ICU with acute renal failure and gastritis
Peretz et al. (2014)	2014	Galilee Medical Centre, Israel	Microbiological surveillance screening of Syrians admitted to hospital Screened for: ESBL, CRE, MRSA, MDR *A. baumannii*, and VRE	27 children and 60 adults	• Children: 21 isolates of MDROs in 19/27 patients; 20/21 ESBL *Enterobacteriaceae*; MRSA = 1/21 • Adults: 28/60 carriers; 5 patients, CRE (2 × NDM); 11 patients, MRSA; 5 *A. baumannii*; 7 ESBL
Rafei et al. (2014)	2012	Lebanon	Syrians admitted to Lebanese hospitals Carbapenem-resistant *A. baumannii* isolates investigated using PCR to identify OXA and NDM producing organisms	4 patients with war wounds	• All 4 had carbapenem-resistant *A. baumannii* identified as carrying the *bla*-NDM-1 gene • These organisms all had phenotypic susceptibility to aminoglycosides, colistin, and tigecycline
Rafei et al. (2015)	2011–13	Lebanon	Review of isolates from Lebanese and Syrian wounded; respiratory, wound, urine, catheters, and blood isolates	116 isolates	• 90 male, 26 female • 70/116 (60%) had carbapenem-resistant phenotype (including NDM-1 and OXA-23) • Syrian refugees had a greater number of carbapenem-resistant *A. baumannii* (74% vs. 47%)

A. baumannii, *Acinetobacter baumannii*; AMR, antimicrobial-resistant; *B. melitensis*, *Brucella melitensis*; CLSI, Clinical and Laboratory Standards Institute; CPE, carbapenemase-producing *Enterobacteriaceae*; CRE, carbapenem-resistant *Enterobacteriaceae*; CRO, ; CSF, cerebrospinal fluid; *E. coli*, *Escherichia coli*; *E. cloacae*, *Enterobacter cloacae*; ESBL, extended-spectrum beta-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; GNB, Gram-negative bacilli; ICU, intensive care unit; IQR, interquartile range; *K. pneumoniae*, *Klebsiella pneumoniae*; MDR, multidrug-resistant; MDRO, multidrug-resistant organism; *M. morganii*, *Morganella morganii*; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, no; NCCLS, National Committee for Clinical Laboratory Standards; NDM, New Delhi metallo-beta-lactamase; OXA, ; *P. aeruginosa*, *Pseudomonas aeruginosa*; PMQR, plasmid-mediated quinolone resistance; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; TMP–SMX, trimethoprim–sulfamethoxazole; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci.

et al., 2015; Rafei et al., 2014). In 2014, Teicher and colleagues reported on the experience of a Médecins sans Frontières (MSF)-led surgical management project in Amman, Jordan (Teicher et al., 2014). A cohort of 61 young men (median age 26 years) presented to the hospital with clinically infected chronic war wounds (injury to presentation time median 5 months, interquartile range 1.2–8.1 months). Gunshot (31 patients) and explosion-related (20 patients) wounds were the most common injuries. Of the 61 patients, 45 had at least one positive culture, with 69% (31/45) of isolates being MDR. Although numbers were small, high rates of carbapenem-resistant *A. baumannii* (80%; 4/5), ESBL-producing *E. coli* (62%; 5/8), and MRSA (41%; 7/17) were isolated. Similar rates of MDR organisms have been reported related to war injuries (Teicher et al., 2014; Abbara et al., 2017), and refugees have been reported to have significantly higher rates of carbapenem-resistant *A. baumannii* (Rafei et al., 2014). No data are available from Turkey, which hosts nearly three million Syrian refugees.

A more robust evidence base of AMR and the Syrian refugee crisis has come from an increasing number of reports on MDR organism carriage in refugees admitted into European hospitals. Syrian refugee patients screened in Europe have shown higher rates of carbapenemase-producing *Enterobacteriaceae* (CPEs) compared with local populations (Kassem et al., 2017; Angeletti et al., 2016; Ravensbergen et al., 2016; Reinheimer et al., 2016; Heudorf et al., 2016; Tenenbaum et al., 2016; Heydari et al., 2015). Estimates of MDR carriage within paediatric and adult populations in these studies range from 33% to 83%, with high rates of New Delhi metallo-beta-lactamase (NDM)-producing carbapenem-resistant *Enterobacteriaceae* (CRE), *A. baumannii*, and ESBL-producing *Enterobacteriaceae* (Rafei et al., 2014; Kassem et al., 2017; Angeletti et al., 2016; Ravensbergen et al., 2016; Reinheimer et al., 2016; Heudorf et al., 2016; Tenenbaum et al., 2016). This is significantly greater than the background carriage rates of the local populations such as in Germany, where colonization with MDR Gram-negatives was identified in 60.8% of a refugee population (of whom 18.6% were Syrian) screened on admission to hospital versus 16.8% in the general population (Ravensbergen et al., 2016).

Comparative data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) showed rates of resistance for seven specific pathogens in 2015.[28] Penicillin non-susceptibility in *S. pneumoniae* ranged from 0.6% in Belgium to 39% in Romania. Carbapenem resistance was 0.1%, 8.1%, and 17.8% in *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, respectively, with the highest rate of 93.5% seen in *Acinetobacter sp* in Greece. Polymyxin resistance was 0.8%, 4%, and 8.8% in *P. aeruginosa*, *Acinetobacter sp*, and *K. pneumoniae*, respectively. Most *K. pneumoniae* isolates with combined polymyxin and carbapenem resistance were reported from Greece and Italy. MRSA rates ranged from 0% in Iceland to 57% in Romania.

Conclusions

This review of evidence of AMR inside Syria and in countries hosting Syrian refugees demonstrates a paucity of rigorous studies describing this increasingly important phenomenon. Before the conflict, published studies inside Syria were often from single centres and presented limited data of variable quality. Since the onset of the conflict, no studies have described the prevalence of AMR in those with injuries within Syria. However, evidence from neighbouring countries suggests that this is an increasing phenomenon. It is important to address this research and reporting gap, as defining the current extent of AMR among Syrians will help to inform interventions that address the drivers of AMR in this population. This is particularly relevant given the population movements that have resulted from the conflict and the likelihood of ongoing challenges in addressing this issue which is of global importance. However, there are barriers to filling this evidence gap due to a combination of factors relating to the complex humanitarian situation inside Syria and the overwhelmed health systems in neighbouring countries. Collaboration and innovations are required to address this issue, which is of global importance.

The second part of this two-part series addresses the drivers of AMR before and after the onset of conflict and makes recommendations as to how these can be addressed.

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Conflict of interest

No conflict of interest to declare.

Author contributions

AA conceived the idea, contributed to the literature review, the first draft and revisions of the manuscript. TMR, NK, WE-A, JH, contributed to the literature review, writing of the text and made significant contributions to revisions of the manuscript. BT, ODa, ODe, GAS, BEU made contributions to the text, literature review and revisions of the manuscript. AS contributed to the original text and subsequent revisions, the figures and tables and developed key concepts in the manuscript.

Aims

1. Compare what is known about antimicrobial resistance in Syria and neighbouring countries hosting Syrian refugees before and after the onset of the conflict.
2. Identify geographical and population areas where there are evidence gaps.

Compare what is known about antimicrobial resistance in Syria and neighbouring countries hosting Syrian refugees before and after the onset of the conflict.

Identify geographical and population areas where there are evidence gaps.

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Appendix A

Search methodology for the review of the literature on antimicrobial resistance in Syria pre and post the onset of conflict

Drug-resistant bacteria were defined according to the US Centers for Disease Control and Prevention (CDC) definition as "microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents"; multidrug-resistant (MDR) bacteria were defined as microorganisms that are resistant to one or more agents in at least three separate classes, methicillin-resistant *Staphylococcus aureus* (MRSA), or an extended-spectrum beta-lactamase (ESBL)-producing organism.

Information about antimicrobial resistance in Syria or amongst Syrian refugees was collected. A detailed scoping review was performed to summarize the available literature on AMR affecting Syrians pre and post conflict. This aimed to identify the key emerging themes and current concepts, and to highlight gaps in current evidence on AMR in Syria. MEDLINE, PubMed, Embase, and the World Health Organization (WHO) Global Health Library were searched using the terms 'Syria' and 'antibiotic resistance'. The grey literature was searched using other search engines with the following additional terms: 'Syria', 'refugee', 'antimicrobial resistance', 'screening', 'war-injury'. Only articles in English were included. The journal of the Syrian Clinical Laboratory Association was also searched. This was included to ensure that relevant literature was not missed; however the peer review process for this journal is unknown. Any identified references within the literature that were deemed relevant were also included in the final review.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.06.010.

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