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Review

Antimicrobial resistance in the context of the Syrian conflict: Drivers before and after the onset of conflict and key recommendations

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ABSTRACT

Current evidence describing antimicrobial resistance (AMR) in the context of the Syrian conflict is of poor quality and sparse in nature. This paper explores and reports the major drivers of AMR that were present in Syria pre-conflict and those that have emerged since its onset in March 2011. Drivers that existed before the conflict included a lack of enforcement of existing legislation to regulate over-the-counter antibiotics and notification of communicable diseases. This contributed to a number of drivers of AMR after the onset of conflict, and these were also compounded by the exodus of trained staff, the increase in overcrowding and unsanitary conditions, the increase in injuries, and economic sanctions limiting the availability of required laboratory medical materials and equipment. Addressing AMR in this context requires pragmatic, multifaceted action at the local, regional, and international levels to detect and manage potentially high rates of multidrug-resistant infections. Priorities are (1) the development of a competent surveillance system for hospital-acquired infections, (2) antimicrobial stewardship, and (3) the creation of cost-effective and implementable infection control policies. However, it is only by addressing the conflict and immediate cessation of the targeting of health facilities that the rehabilitation of the health system, which is key to addressing AMR in this context, can progress.

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Introduction

Multilateral action by international health bodies and governments is required to combat the global threat of antimicrobial resistance (AMR). Failing to address issues at the local level can have regional and global implications. The fallout of the Syrian conflict is not restricted to Syria and neighbouring countries: in 2015 alone, 378 000 Syrians entered Europe – roughly one-third of the 1.3 million refugees seeking asylum there (Connor, 2015). The European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) have stated that the risk of infections resulting from the living conditions that refugees encounter are greater than the risks of them importing infections (WHO, 2017; Brusin et al., 2015; European Centre for Disease Prevention and Control, 2016). Nevertheless, potentially high rates of AMR amongst Syrians require us to address the causes, risks, costs, and future considerations of this challenge both for Syrians living in conflict and for Syrian refugees.

The *Lancet* Series on the promotion of universal access and sustainable effectiveness of antimicrobials in the context of AMR includes policy recommendations for national and regional interventions to combat resistance (Dar et al., 2016). These include infection prevention and control (IPC), surveillance, monitoring, stewardship, and the strengthening of health systems. It highlights the importance of access to effective antimicrobials whilst also ensuring effective stewardship and vaccination as a means of addressing AMR globally. For Syria and other conflict-affected countries to participate in the WHO Global Action Plan (GAP) on AMR, a pragmatic focus on what can be achieved in these countries is required. This is particularly the case in Syria where a comprehensive national action plan to address AMR is currently unrealistic given the parallel health systems functioning inside its borders.

This article identifies the drivers of AMR that existed before the conflict and those that have occurred since the onset of conflict in March 2011. It also makes recommendations as to how these can be addressed.

Drivers of AMR in the Syrian context

This section examines the potential drivers of AMR in Syria before and after the onset of conflict, highlighting those most relevant to the Syrian context. Figure 1 summarizes the main drivers and their consequences.

Drivers of AMR in the Syrian context: pre-2011

Prior to the conflict, health indices for Syria, a middle-income country, showed many parallels with those of Western countries, such as completion of the epidemiological transition and a life-expectancy in excess of 70 years. In contrast to Western countries, neither microbiology nor infectious diseases were recognized as speciality areas of training, nor were they financially rewarding. Little training was provided beyond medical school; there were few opportunities for continuing medical education. The laboratories established in public hospitals under the Ministry of Health (MoH) and Ministry of Higher Education were variably equipped with manual (Kirby–Bauer) and automated (Phoenix and Vitek) AMR testing. IPC was inadequate, with poor implementation of the National Protocol for Infection Control, and protocols for universal precautions were absent. Efforts towards antimicrobial stewardship are seen in the legislation drawn up by the Syrian Syndicate

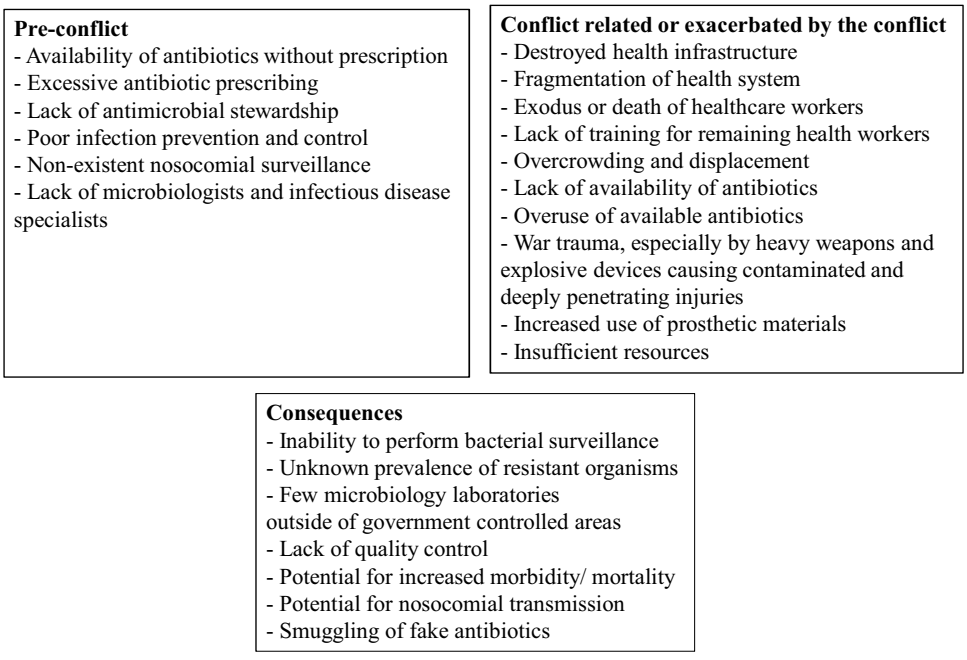

Figure 1. Drivers and consequences of antimicrobial resistance in the Syrian conflict and their consequences.

for Pharmacists concerning the over-the-counter (OTC) sale of antibiotics, passed in 1994 (Syrian Syndicate for Pharmacists, 1994). This effort to regulate OTC availability of antibiotics was not enforced by the government.

The notification of communicable disease was legislated by the Syrian Arab Republic in 2007 (Decree No. 7, 2007) (Anon, 2018) and surveillance guidelines were issued by the MoH in 2010 for both public and private sectors. However, as with the regulation of antibiotic sales, this legislation was not enforced. Reporting tended to be done on an ad hoc basis, usually without laboratory confirmation.

Nosocomial infections were poorly reported, but frequently described anecdotally. Well before the onset of the conflict, Acinetobacter was reported to be the most common cause of ventilator-acquired pneumonia across intensive care units in public hospitals of Damascus (personal communications with Syrian microbiologists, surgeons, and internal medicine specialists). Notably, nosocomial or community-acquired infections with Acinetobacter beyond the respiratory system were rarely or not described prior to 2012, which marked the first use of heavy and explosive weaponry.

Consistent with this context, there is evidence to support high population rates of antimicrobial usage, poor knowledge of drivers of AMR, little regulation in the distribution and OTC sale of antibiotics, and excessive self-medication. In 2007, Barah and Goncalves conducted a cross-sectional study exploring citizens' usage, knowledge, and attitudes towards antimicrobials in the Kalamoon region of Syria (Teicher et al., 2014). Four hundred and thirty households were sampled randomly and 366 (85%) responders reported using antimicrobials in the preceding 4 weeks, with only 43% of these courses being prescribed by a healthcare professional (Barah et al., 2009). This is mirrored by other studies that demonstrated high use and readily available OTC supplies of antibiotics; these potentially contributed to selective pressure leading to AMR (Al-Faham et al., 2011). Antibiotics purchased OTC included amoxicillin–clavulanate, amoxicillin, cefadroxil, clarithromycin, and azithromycin (Al-Faham et al., 2011).

In healthcare, antibiotic stewardship programmes were poor, with over-prescribing amongst doctors driven by patient expectations. Data on compliance with the prescribed antibiotic course or the quality of antibiotics produced are not available. The paucity of surveillance data inside Syria is consistent with the lack of a systematic process through which laboratories report results to track AMR. Challenges relating to this include a health system pre-conflict that was increasingly privatized, with a growing number of private laboratory facilities or public–private partnerships with little standardization (Teicher et al., 2014). Developing a robust surveillance system for AMR in line with the WHO Global AMR Surveillance System (GLASS) is important although challenging during conflict (Fleming Fund, 2016).

Neglect of water chlorination and sanitation services in certain areas is evidenced by cholera outbreaks that occurred in 2008 and 2009 in Deir Ezzor and Ar-Raqqa (Anon, 2015). Furthermore, there was dissonance in the rates of vaccination against routine childhood diseases reported by official agencies and the surveillance agencies used by the WHO and the United Nations Children's Emergency Fund (UNICEF): in 2008, the MoH reported national coverage rates of 98–99% (Qamishli and Bab, 2004), compared with 76.3–82% recorded by the Syrian Commission for Family Affairs in the 2008 population survey (Syrian Center for Policy Research SCPR, 2016).

Drivers of AMR in the Syrian context: after the onset of conflict

Multiple drivers of AMR since the onset and expansion of the conflict are identifiable: the crowded and unsanitary living conditions due to forced displacement, the neglect and destruction of public healthcare, and insecurity caused by war compromising access to healthcare. Concerning human resources, thousands of professional and allied healthcare workers, including laboratory technicians, have left the country, voluntarily or involuntarily, in both government and non-government areas. Reasons include physical and financial insecurity, the military draft, the incarceration and execution of medical personnel, and targeted assaults on clinics and hospitals. This has left a gap of trained staff competent in the diagnosis and management of infections, particularly those caused by resistant organisms (Fouad et al., 2017).

The collection and processing of samples is also affected by the gaps in training and education. Remaining residents and nursing staff are untrained in the collection of samples, which may lead to contamination at collection. Contamination of samples may also occur on receipt of the samples by untrained laboratory staff in public hospitals. Both manual tests (Kirby–Bauer) and automated tests are dependent on skilled processing of samples to produce reliable results. The shortage of laboratories and paucity of adequate quality control in the processing of samples impedes surveillance and appropriate diagnosis. Inadequate culture and sensitivity testing and the unreliability of results will lead to over-treatment compared to antibiotic therapy guided by laboratory reports. This practice is exacerbated both by the lack of skilled microbiologists to provide guidance to clinicians, as well as the lack of experienced clinicians to interpret laboratory results without guidance from microbiologists. No reliable quality control testing of locally made antibiotics is available; hence vancomycin is the only antibiotic that can be tested for active ingredients.

The degree to which AMR exists amongst patients is unknown. Monitoring of compliance is compromised by the difficulty posed to patients in presenting to hospitals and primary health centres, given the insecurity and violence. The absence of standardized syndromic guidelines may exacerbate the clinical tendency towards usage of available broad-spectrum antibiotics for prolonged periods of time, as indicated by the preferential purchase of carbapenems and fourth-generation cephalosporins (WHO EMRO, 2016).

Onward transmission of resistant organisms is exacerbated by the overcrowding resulting from forced displacement and the lack of adequate water supplies and sanitation. Safe water levels are less than half of pre-war levels (International Committee of the Red Cross, 2015). With the progression of the conflict, the capacity of health centres to sterilize medical instruments generally and surgical instruments specifically has become weaker due to a lack of disinfectants and required consumables. Chlorine, the primary agent for decontaminating water and widely used in sterilization and disinfection, has faced stricter regulation following its use as a chemical weapon. The overuse of metronidazole in response to an escalation of water-borne diseases causing gastroenteritis has led to widespread clinical concerns about resistance. As metronidazole no longer appears to be effective in triple therapy for *Helicobacter pylori*, it has necessitated substitution, in turn dependent on the availability of clarithromycin.

Economic sanctions have restricted the availability of medical materials and equipment. Spare parts for autoclaves and other disinfection equipment are not available. There is only one certified microbiologist in Syria (US board-certified), and only five physicians with experience in microbiology could be located across the country. There are very few laboratory engineers capable of maintaining existing equipment. New brands imported by UN agencies and international non-governmental organizations in Damascus may follow tendering protocols, but are rarely familiar to hospital engineers. Irregular electricity and internet supplies are a consistent concern across the country, compounding this issue of sterilization. Obtaining the necessary security approvals for transportation of medicines is time-consuming.

These challenges may be greater in besieged and hard-to-reach areas, one example being the systematic removal of antibiotics from convoys to besieged or recently besieged areas. In May 2017, paediatric antibiotics were removed from a WHO convoy to Madaya (Anon, 2016).

Economic sanctions also negatively affect the supply of reagents for AMR testing, from agar plates and discs for manual Kirby–Bauer tests, to software updates for the Phoenix automated machines to include newer antibiotics such as ticarcillin. This increases the challenges of accurate diagnosis and management of infections. The restrictions on importation of high quality foreign manufactured medicines have exacerbated this issue: in 2016, the Syrian MoH and the Ministry of Foreign Affairs banned the import of all medicines that could be purchased locally. As a result, the quality control previously ensured by international agencies such as the WHO, UNICEF, the United Nations High Commissioner for Refugees (UNHCR), and the International Committee for the Red Cross in procuring medications under strict quality assurance is now lost.

Obtaining the necessary security approvals for transportation is time-consuming, taking up to 4 to 6 months. This fuels the smuggling of imported and expensive medicines from Lebanon, pushes up the price of already scarce drugs on the market, and increases the dependency on smuggled drugs. In consequence, impoverished Syrians are dependent on locally manufactured medicines of poor quality.

In areas outside of government control such as Idlib – a governorate bordering Turkey, adjacent to Aleppo, and housing some 2.5 million Syrians, many internally displaced – there is widespread distrust of drugs sent from Damascus. However, the difficulty and delay in arranging legitimate cross-border convoys drives the smuggling of fake antibiotics. An example of this is the availability of fake spiramycin, an antiparasitic used to treat toxoplasmosis in pregnancy, which was supplied to Idlib in 2015. As a consequence, in 2016 the Directorate of Health in Idlib set up a quality control laboratory to ensure quality assurance of medicines, and in the near future, antimicrobial resistance.

Alongside challenges resulting from the damaged health system, the war trauma produced by the heavy weaponry used in this conflict has led to an exponential increase in the number of infection-prone high-risk injuries such as contaminated open wounds and fractures. After three decades of peace following the previous government's repression of the popular uprising in 1982, surgeons and other healthcare workers lacked the training and experience required to deal with war trauma. Early in the conflict, the inappropriate use of internal fixators in open or contaminated wounds and surgery by untrained staff may have contributed to an increased risk of deep bone infections and infected prostheses, further exacerbated by the lack of supportive diagnostic facilities to allow optimal diagnosis and management. In besieged areas like Eastern Ghouta, homemade external fixators have been used due to denial of surgical supplies.

The nature of weaponry contributes to the range of wounds and the degree of contamination. The conventional weapons in use can result in a range of injuries including open wounds, fractures, amputations, and brain or spinal cord injuries, which may be contaminated at the time of injury or subsequently in the course of treatment (Eardley et al., 2011). Barrel bombs containing shrapnel, nails, and explosives such as TNT are commonly used in Syria, causing catastrophic damage. Acute lung injury is common after the inhalation of dust, with subsequent requirement for intubation and the attendant risk of ventilator-associated pneumonia (Alsadat et al., 2010). The use of antibiotics in these instances, particularly for prolonged periods and without guiding microbiology, add to the selective pressures driving AMR. There have also been suggestions that the heavy metals present in weaponry contribute to AMR (Hobman and Crossman, 2015).

As the conflict has progressed, not only have there been fewer functioning health facilities, but patients have been unable to access medical care due to insecurity, poverty, or fear. This may have contributed to self-prescribing with inappropriate or incomplete courses of antibiotics, worsening what was already a social norm prior to the outbreak of the conflict (Hamzeh et al., 2012). In addition, the diminishing supply of clean water and antiseptics, and the lack of access to wound care and facilities in which debridement can occur, has contributed to infection and poor bone or soft tissue healing. The use of long-term catheters in patients with spinal cord injuries or impaired mobility will promote susceptibility to infections with the subsequent use or inappropriate use of antibiotics, further increasing the risk of AMR (Al-Assil et al., 2013).

Hospitals are a key place where AMR strains develop and flourish under normal conditions. In non-government controlled areas in Syria, these conditions are worsened: hospitals are being built in basements or even purpose-built several floors underground to avoid targeting, they are dark and often damp, there is an absence of natural sunlight and ventilation, and there is a lack of sterilization equipment and adequate disinfection materials.

In addition to these factors, the large-scale population movements resulting from the conflict may also have contributed to human-to-human transmission and the potential spread of resistant organisms through air travel (Holmes et al., 2015). Of considerable concern is Gaziantep, just 50 km from the Syrian border, home to half a million of Turkey's three million refugees, and a major site of international medical tourism. This has been seen at other sites of medical tourism such as New Delhi (Kaul and Chhina, 2010), but the potential for superbugs to be introduced and spread within these vulnerable populations of refugees and surgical frequent flyers is a unique and grave concern.

How can this be addressed?

Tackling AMR amongst Syrians inside Syria and those seeking refuge in neighbouring countries or Europe requires multifaceted action at the local, regional, and international levels. Addressing the conflict in Syria as a political facet is key. The immediate cessation of the targeting of healthcare facilities, cease-fires, and a solution to the civil war are urgently needed to reduce the burden of injured and allow the return of healthcare workers and the rehabilitation of the health system. In addition, we call on the WHO to adhere to their GAP on AMR, launched at the World Health Assembly in 2015, addressing antibiotic stewardship, infection prevention and control, and access to appropriate therapy (Anon, 2017). Others have advocated for a One Health approach to tackle AMR given the widespread use of antibiotics in agriculture, with the threat to global food security compounded by climate change.

Notwithstanding the importance of the WHO GAP and the imperative for a One Health approach, there is an obvious need for pragmatic, actionable recommendations in Syria and other settings of conflict and insecurity. Table 1 sets out the key recommendations and discusses the challenges faced in the Syrian context. These include measures to support the mapping of microbiology facilities inside Syria, participation in surveillance amongst healthcare facilities, capacity-building through the training of staff, and ensuring the availability of equipment and consumables. The regulation of OTC antibiotic availability, while critical to responsible antibiotic stewardship, is dependent on the government for enforcement of the existing legislation and is demonstrably unsuccessful in this context. Similarly, the control of diseases with epidemic and pan-epidemic potential depends on excellent surveillance, sample collection, quality assured laboratory testing, and reporting by the Member State in adherence to the International Health Guidelines. A programme of education for

Table 1
Recommendations for tackling antimicrobial resistance inside Syria and in facilities treating Syrian refugees.

Recommendation	Action needed to achieve core measure	Primary organizations responsible
Surveillance	On-call service at laboratories for weekends and holidays; improved monitoring services	WHO, local and international health organizations working in conflict
Improve quality control (QC)	Easing sanctions for drugs and equipment; the Ministry of Health must lift the ban on imported medicines	UN Security Council, UN General Assembly, and all UN Member States
Training and development of key staff	Improve access to training courses, updates, and modules; either remotely with telemedicine or as short courses in neighbouring countries Reduce the gap in trained medical laboratory specialists and technicians	WHO, international and regional medical, public health, and allied health academic institutions and organizations
Ensure learning	Utilize the One Health approach in future research; continue to build the evidence base for action on issues of AMR; additional retrospective studies should be conducted in Turkey	Academic and non-academic researchers
Make resources available in microbiology services	Mobilize and allocate resources to health workers in response plans, including for human resources planning	Donors
Research/surveillance/ antibiotic stewardship	Improve the collection and reporting of local data in hospitals that are unable to report on AMR broadly, and specifically in the ICU, surgical ward, or maternal ward, etc.; guide clinical practice of doing cultures for testing; widespread training of residents and nurses to avoid contamination in laboratory testing; leading to specific treatment and informing syndromic guidelines	

AMR, antimicrobial resistance; ICU, intensive care unit; UN, United Nations; WHO, World Health Organization.

healthcare workers and the general public to alter established practice and cultural expectations is unlikely to be successful under the current conditions. It is clear, however, that this problem must be addressed urgently; this urgency is underscored by the relatively new initiative – the Syrian Association for Infectious Diseases. Investing in basic, cost-effective microbiology services in hospitals and centralized regional microbiology references to act as referral centres should allow cost-effective processing of samples as well as potential for training of staff and improved quality control measures. There is also the opportunity for innovation including the use of rapid diagnostic tests to identify particular bacteria or for increased public–private partnerships as was often the case before the war.

Despite the paucity of robust evidence to support it, a concern that refugees may transmit infections including AMR organisms to local populations prevails (Angeletti et al., 2016). A full review of AMR amongst refugees and migrants in Europe has been addressed elsewhere (Heudorf et al., 2016). The ECDC has issued a rapid risk assessment on communicable diseases in general (Brusin et al., 2015) and on carbapenem-resistant *Enterobacteriaceae* (CRE) (European Centre for Disease Prevention and Control, 2016), with recommendations that focus on infection control and the adequate capacity of microbiology laboratories with prompt notification of clinical teams. A recommendation for screening and pre-emptive contact precautions and isolation of patients considered at high risk of CRE carriage is recommended (European Centre for Disease Prevention and Control, 2016). However, it remains vital for each country hosting refugees to assess the AMR access and stewardship needs of refugee communities within its borders through the International Health Regulations Joint External Evaluation Tool process (which can support their health security plans) and harmonize it with the roll-out of their AMR national action plans (World Health Organization, 2005).

Conclusions

The conditions created by the conflict in Syria both exacerbate existing drivers and create powerful new drivers of AMR. The unique challenges presented by the growing threat of AMR in conflict require a pragmatic, multi-faceted approach to detect and manage the potentially high rates of multidrug-resistant infections. Such an approach must be tailored to the current status of the health system(s) in Syria, with the priorities being (1) the development of a competent surveillance system for hospital-acquired infections, (2) antimicrobial stewardship, and (3) the creation of cost-effective and implementable infection control policies. Hospitals are a key place where AMR strains develop and flourish, particularly in Syria. Accordingly, effective infection prevention and control procedures could play a major role in decreasing the occurrence of outbreaks of infections and in limiting the opportunities for aggressive bacterial strains to acquire new resistance genes. Innovative approaches could include strategies to build patient resistance, such as targeted immunization with measles or BCG vaccine to boost immunity.

Building the capacity for clinical laboratory diagnosis and optimizing the management of patients with communicable diseases will increase the ability of local medical facilities in Syria to make fast and precise diagnosis of transmissible infections, provide targeted antibiotic treatment, minimize the spread of antibiotic-resistant strains, and limit the occurrence of large outbreaks of infections. This is vital given the internal population movements and the movements of refugees both in countries neighbouring Syria and internationally.

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Ethical approval

We have read the policy on ethical consent and ethical approval is not required for this work.

Conflict of interest

All authors confirm that they have no conflict of interest.

Aims

(1) Define the main factors driving antimicrobial resistance in settings of conflict, exemplified by the Syrian context. (2) Propose policy recommendations. (3) Identify key research areas.

Author contributions

AA conceived the idea and 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.

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