Antimicrobial resistance and the Iraq wars: armed conflict as an underinvestigated pathway with growing significance

Antoine Abou Fayad, Anthony Rizk, Samya El Sayed, Malak Kaddoura, Nadine K Jawad, Adel Al-Attar, Omar Dewachi, Vinh Kim Nguyen, Zahy Abdul Sater

INTRODUCTION
Antimicrobial resistance (AMR) is rising globally at an alarming rate and, if left unaddressed, expected to cause 10 million deaths per year by 2050.1 This growing threat has widely been attributed to the overuse and misuse of antibiotics and/or the use of substandard antibiotics in humans, livestock and as a byproduct of environmental contamination. While antibiotic use has often been the focus of AMR science and policy, only recently has clinical research in microbiology turned to evaluating other biocides, such as heavy metals and quaternary ammonium compound disinfectants (QACs), as potential drivers that co-select for resistant pathogens.2 In the Middle East, spiking rates of antibiotic resistance, especially in Gram-negative pathogens such as Acinetobacter baumannii, Pseudomonas aeruginosa and Klebsiella pneumoniae, have also implicated another underinvestigated pathway for AMR: the direct and indirect roles of wars and conflicts, and their associated implications to healthcare (these can include, but are not limited to, the breakdown of healthcare systems, the loss of skills and experience, deterioration in infection and sanitation controls in healthcare settings, and difficulty of access to effective therapy, therapeutics and diagnostics), in driving the emergence of resistant pathogens.

Investigating the relationship between wars, conflicts and transformations in antimicrobial susceptibility and resistance patterns is not unprecedented. War has been implicated in the emergence of AMR as far back at the 1940s, when widespread industrial-scale mass production and application of arsenicals, sulfonamides and disinfectant QACs, as well
as the mass introduction of penicillin as a prophylactic and in the treatment of soldiers' injuries during World War II, set the stage for the selection for drug resistance.3 These conditions and consequences have persisted and may have even intensified, with subsequent conflicts. Contemporary conflicts, waged in urban and industrialised landscapes, pressure microbes with selective environments that contain unique combinations and concentrations of toxic heavy metals and antibiotics, while simultaneously providing niches and dissemination routes for microbial pathogens. These can include the high number of wounded, the nature of wounds, refugee displacement, collapse of sanitation controls, loss of diagnostics and skilled healthcare personnel, the dismantlement of healthcare infrastructures and the placement of often under-resourced and improvised field hospitals where both injured combatants and civilians are exposed to harmful pathogens with limited care and resources to properly recover.4–6

Despite increased attention to AMR, however, the specific role of current armed conflicts and the resistance-inducing properties of non-antibiotic antimicrobials, such as heavy metals and QACs, in the development and proliferation of this phenomenon continue to be poorly understood. Iraq experienced a sequence of conflicts over the last four decades, prominently including the Iran-Iraq war (1980–1988), First Gulf War in 1991, the United Nations economic sanctions on Iraq following the Iraqi invasion of Kuwait (1990 until 2003), the US invasion and occupation of Iraq (2003–2011), including a period of militarised violence (2005-2007), and the conflicts with the ISIS (2014–2017). Although data on antimicrobial susceptibility in Iraq from the 1980s are scarce, literature from Iran during the same period indicate an emergence of resistant Gram-negative pathogens among Iranian soldiers throughout the Iran-Iraq war, with declining susceptibility to antibiotics commonly used at the time.7 8 Scientific literature on conflict-related antimicrobial resistance emergence in more prominence during and after the US invasion and occupation of Iraq since 2003, with both US military medicine research, situated in combat support hospitals and war theatres in Iraq, along with research conducted by humanitarian organisations such as Medecins Sans Frontieres (MSF), document an emergence and spread of antimicrobial resistance in tandem with the conflict in Iraq.6 As bombings, unsafe living conditions and destruction of public infrastructure became commonplace in Iraq, these factors overlapped with a catastrophic worsening of AMR, potentially the result of a broader ecology of war that has been decades in the making.9

**AMR IN THE HISTORY OF CONFLICT IN IRAQ**

Iraq witnessed devastating conflicts over the last four decades, prominently including the Iran-Iraq war (1980–1988), First Gulf War in 1991, the United Nations economic sanctions on Iraq following the Iraqi invasion of Kuwait (1990 until 2003), the US invasion and occupation of Iraq (2003–2011), including a period of militarised violence (2005-2007), and the conflicts with the ISIS (2014–2017). Although data on antimicrobial susceptibility in Iraq from the 1980s are scarce, literature from Iran during the same period indicate an emergence of resistant Gram-negative pathogens among Iranian soldiers throughout the Iran-Iraq war, with declining susceptibility to antibiotics commonly used at the time.7 8 Scientific literature on conflict-related antimicrobial resistance emergence in more prominence during and after the US invasion and occupation of Iraq since 2003, with both US military medicine research, situated in combat support hospitals and war theatres in Iraq, along with research conducted by humanitarian organisations such as Medecins Sans Frontieres (MSF), document an emergence and spread of antimicrobial resistance in tandem with the conflict in Iraq.6 As bombings, unsafe living conditions and destruction of public infrastructure became commonplace in Iraq, these factors overlapped with a catastrophic worsening of AMR, potentially the result of a broader ecology of war that has been decades in the making.9


During the US occupation, both the WHO and MSF reported growing concerns over severe shortages of both medicine and medical staff, a situation that dates back to UN economic sanctions on Iraq imposed after Iraq’s
invasion of Kuwait in 1990. By 2006, however, two-thirds of doctors reported unavailability of essential drugs and equipment more than half of the time and more than 90% reported lacking skilled health workers in their facilities and reduced quality of care.10 Many healthcare workers fled from Iraq since 2003, with many reporting violent attacks on health facilities or personnel as a primary driver.10 With a lack of a well-established antimicrobial stewardship system, especially compromised by the conditions of war faced by the country’s healthcare system, the administration of broad-spectrum antibiotics as empirical therapy for war wounds was widespread, leading to selection for highly resistant organisms.11 Moreover, the administration of even broader-spectrum drugs for the treatment of multidrug-resistant (MDR) infections further contributed to AMR by increasing the potential for nosocomial transmission. In one example of the extent of the problem of AMR during the US invasion, Murphy et al found that 55% of patients with suspected osteomyelitis had an MDR organism at their time of admission to the hospital and that there was a significant association between patient history of more than two surgical procedures performed in Iraq and having a positive MDR isolate.12

P. aeruginosa, Staphylococcus aureus, K. pneumoniae and A. baumannii were identified as major contributors to multidrug resistance in Iraq and were problematic for both military and civilian doctors.11 Drug resistance in these four microbes was exacerbated in such contexts as burn and field hospitals,13 with indications of regional and international transmission and spread.14 Currently available articles indicate that, although there are no mentions of A. baumannii in Iraq in the 1980s, resistant A. baumannii was detected by Iranian researchers among Iranian soldiers returning from the Iraqi warfront to a hospital in Shiraz.14 Sadeghi explained the emergence of resistant Acinetobacter as part of a general trend towards growing nosocomial spread of Gram-negative pathogens with reduced susceptibility to antibiotics in Iraqi hospitals throughout the period of the Iran-Iraq war.8 Resistant A. baumannii is now of growing global concern, having gained the moniker ‘Iraqibacter’ following its spectacular rise as a resistant and nosocomial pathogen in Iraq and spread, via injured soldiers, to hospitals in the USA and the UK, constituting a global ‘pathology of intervention’.15 In-depth historical and phylogenetic analysis is still needed to ascertain whether resistance mechanisms in these pathogens first emerged as early as the Iran-Iraq war in the 1980s and gained traction thereafter, or first appeared during the US invasion and occupation of Iraq.

ISIS CONFLICT (2014–2017)
In 2014, ISIS’s armed conflict against the Iraqi state led to the wounding and killing of hundreds of civilians and the displacement of thousands throughout the course of the Syrian conflict16 and further contributed to the dismantlement of what remained of the state’s economic, social and healthcare infrastructures once more.

Continued research is needed to understand the full effect of the ISIS conflict on AMR and in what ways it may have coincided or differed from previous conflicts. Reporting during the ISIS conflict was predominantly undertaken by humanitarian organisations active in Iraq at the time. In a report issued by MSF in 2019, for example, a hospital in East Mosul, a city heavily affected by the ISIS crisis, reported that 90% of patients with a microbiologically confirmed infection had been infected with an MDR microorganism.17 The same four bacteria (P. aeruginosa, S. aureus, K. pneumoniae and A. baumannii) that emerged during the US invasion were also prevalent during the conflict with ISIS. However, resistance to other classes of antimicrobial agents had since been further noted. For example, a study conducted by Lafi et al in a hospital in Ramadi revealed that while S. aureus and P. aeruginosa were still one of the most common isolates in wounds, S. aureus had developed growing resistance to vancomycin and P. aeruginosa to imipenem.18 Similarly, in 2016, Ghairma et al studied the antimicrobial susceptibility of A. baumannii from burns and wounds in patients in Baghdad hospitals and found that resistance had increased, especially to colistin.19

It is likely that drug resistance had been further aggravated during the ISIS conflict by long-standing shortages of healthcare workers, precarity of medical institutions and the nature of wounds among civilians and combatants alike. It is worth mentioning that tactics used during the ISIS conflict further blurred the lines between civilians and combatants and led to thousands being wounded and seeking treatment in the context of limited resources. The protracted conflict against ISIS has led to displacements of large groups of people, many of whom travelled widely within the country and abroad in the pursuit of healthcare. This, along with the movement of refugees, may continue to contribute to the spread of resistance genes and resistant infectious agents for years to come. In-depth ethnographic and epidemiological research, especially ones that stretch across regional and international borders, are still needed to ascertain the roles that the nature of wounds, environmental contamination, and the precarity of access to healthcare played in the development of chronic infections with MDR organisms during this phase of conflict in Iraq.

AMR IN CONFLICT SETTINGS: A PRESSING CONCERN
Protracted conflict in Iraq has had adverse implications to population health. And yet, it is worth noting that Iraqi institutions have rarely been the source of information on AMR in Iraq across these conflict periods. Rather, what we know about AMR in Iraq is largely sourced from US military medicine during the period of the US invasion and occupation and from humanitarian organisations operating in Iraq throughout these conflict period. One of the legacies of British rule in Iraq was the establishment
of an expansive healthcare system that attracted patients region-wide for medical treatment in Iraq. Armed conflicts since the 1990s have accompanied a progressive deterioration of Iraq’s national healthcare system, leading to lack or limitation in trained staff, infection prevention and control, access to many classes of antibiotics and proper clinical microbiology for guiding clinicians. Iraq’s biosurveillance and laboratory capacities have also been impacted, leading to gaps in core capacities and national disease surveillance. Wounds from explosives or burns may be highly contaminated with bacteria. Additionally, lack of training in proper wound debridement and lack of patient follow-up can lead to higher rates of health complications. Surgeons and healthcare personnel are often tasked with stabilisation as opposed to long-term care for wounds and infections. In such time-sensitive and under-resourced settings, all of the above, along with inappropriate diagnoses and drug regimens administered with expired or outdated drugs, may all be contributing to the rising rates of AMR in Iraq.

Conflict settings exacerbate bacterial spread due to insufficient sanitary resources to meet basic hygiene needs. In conflict settings, civilians and combatants suffer from the lack of access to proper water, sanitation and hygiene (WASH), thus increasing their exposure to pathogenic microbes. Furthermore, growing attention is being paid to the role that heavy metal contamination might play in triggering drug resistance. Heavy metals used in weapons persist in the environment, with explosives, for example, harbouring huge amounts of lead and mercury. In addition, metals such as chromium, copper, lead nickle and zinc are used to coat bullets, missiles, gun barrels and military vehicles, while antimony, barium and boron are weapon-priming compounds. In general, the use of heavy metals in weapons has increased since the end of World War II and many bacterial species have been shown to have evolved resistance mechanisms to combat heavy metals’ toxicity. These mechanisms are encoded by resistant genes to heavy metals and antimicrobial agents that are physically linked on mobile genetic elements. More importantly, heavy metals can induce selective pressure on microbial populations leading to AMR through a mechanism called ‘co-selection’ which occurs via three major ways: co-resistance, cross-resistance and co-regulatory resistance.

Taken together, a destroyed healthcare infrastructure, inappropriate microbial therapies, limited resources, high metal contamination in humans and the environment, and lack of WASH, combined, likely play instrumental roles in the catastrophic rise of AMR in Iraq and, by extension, regionally and globally. This remains, however, direly understudied. Clinical, microbiological, ethnographic and environmental research is needed to conclusively establish the multiple and compounding roles that wars and conflicts play in the rise of multi-drug resistant organisms. It is imperative for future research to address gaps in understanding how AMR came to be historically constituted across time, in interaction with social, political and economic processes and events. Understanding these linkages between AMR and conflict, especially across time, is essential for a global response to AMR, especially as there is little indication that conflict, worldwide, will abate in years to come.

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REFERENCES


### Supplementary Table 1: Timeline of antimicrobial resistance in Iraq (1980-2017)

<table>
<thead>
<tr>
<th>Year</th>
<th>Key findings on antimicrobial resistance in Iraq</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>90% of strains of <em>E. coli</em>, Pseudomonas spp. and Staphylococcus spp. samples from the river Tigris in Mosul are found to be resistant to one or more antibiotics [a]</td>
</tr>
<tr>
<td>1984</td>
<td>Basrah University Teaching Hospital reports high rates of bacteremia caused by <em>E. coli, K. pneumoniae, Staphylococcus spp. and salmonella spp.</em>, with 31.3% of isolates resistant to all but three antibiotics. There has been no detection of Acinetobacter species. [b]</td>
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<tr>
<td>1985</td>
<td>Methicillin resistant strain of Staphylococcus aureus from a blast-injured patient from Baghdad causes nosocomial outbreaks in Dublin hospitals. [c]</td>
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<tr>
<td>1987</td>
<td>Aarabi (1987) finds that Staphylococcus, Streptococcus and Acinetobacter species were the most prominent pathogens cultured from missile head wounds among Iraqi patients injured in the Iran-Iraq war. [d]</td>
</tr>
<tr>
<td>1990</td>
<td>Sadeghi (1990) detect a marked increase in Pseudomonas, Klebsiella, Enterobacter and Acinetobacter infections in Namazee Hospital, Shiraz, Iran, with “antibiotic sensitivity [that] has diminished dramatically during the 1980s”. Sadeghi attributes this, primarily, to the repercussions of the Iran-Iraq war. [e]</td>
</tr>
<tr>
<td>1999</td>
<td>General Basrah Hospital reports nosocomial outbreaks of resistant <em>Pseudomonas aeruginosa</em>. [f]</td>
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<tr>
<td>2002</td>
<td>High neonatal septicemia in Al-Anbar province attributed to <em>S. aureus, K. pneumoniae, and E. coli</em>, with many strains resistant to commonly-used antibiotics such as ampicillin and cloxacillin. [g]</td>
</tr>
<tr>
<td>2005</td>
<td>Davis et al. (2005) first describe the wide prevalence of resistant Acinetobacter infections among U.S. soldiers injured during military operations in Iraq. [h]</td>
</tr>
<tr>
<td>2006</td>
<td>Genotypically indistinguishable MDR and XDR <em>Acinetobacter baumannii</em> outbreaks begin to be reported in U.S. and U.K. facilities treating casualties of war from Iraq. [i]</td>
</tr>
<tr>
<td>2008</td>
<td>First reported indication of colistin resistance in <em>Enterobacter cloaeceae</em> and <em>Klebsiella pneumoniae</em> isolates from Iraq. [k]</td>
</tr>
<tr>
<td>2011</td>
<td>Carbapenem resistance detected in MDR <em>Acinetobacter baumannii</em> isolates collected in Iraq. [l]</td>
</tr>
<tr>
<td>2016</td>
<td>Microbiologists in Baghdad isolate XDR and PDR <em>Acinetobacter baumannii</em> among hospitalized patients. [m]</td>
</tr>
<tr>
<td>2017</td>
<td>Emergence of carbapenem resistance in Enterobacteriaceae cultured from wounded military personnel. [n]</td>
</tr>
<tr>
<td>2018</td>
<td>First reported indication of emergence of NDM-1 and NDM-2 <em>Pseudomonas aeruginosa</em> in Iraqi hospitals. [o]</td>
</tr>
<tr>
<td>2021</td>
<td>Researchers in Erbil detect XDR and PDR <em>Pseudomonas aeruginosa</em>. [p]</td>
</tr>
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REFERENCES


Decades of conflict in Iraq have fuelled “catastrophic” rise in antibiotic resistance

Serious implications for the entire region and the world, warn experts

Destroyed healthcare infrastructure, medicine shortages, limited resources, heavy metal contamination, poor sanitation likely to blame

Decades of wars and conflict in Iraq have led to a “catastrophic” rise in antibiotic resistance in the country, with serious implications for the entire region and the world, warn international experts in the open access journal *BMJ Global Health.*

The combination of destroyed healthcare infrastructure, medicine shortages, limited resources, high levels of heavy metal contamination, and poor sanitation is likely to blame, they argue.

Antibiotic resistance, or AMR for short, is rising globally at an alarming rate and is expected to cause 10 million deaths a year by 2050, if nothing is done about it, point out the authors.

Largely attributed to the overuse and misuse of antibiotics, attention is now turning to other factors, such as heavy metals and disinfectants containing quaternary ammonium compounds (QACs), which are widely used in the healthcare and hospitality sectors. War has been implicated in the emergence of AMR as far back as the 1940s, but has received little attention, say the authors.

Iraq is a stellar example of this neglect, as the country has experienced a sequence of conflicts since the 1980s that have coincided with the emergence and spread of pathogens with specific patterns of antibiotic resistance, they highlight.

These conflicts include the Iran-Iraq war (1980–88); the First Gulf War in 1991; United Nations economic sanctions following the Iraqi invasion of Kuwait (1990- 2003); the US invasion and occupation (2003–11), including a period of militarised violence (2005–07); and Iraqi state conflicts with ISIS (Islamic State of Iraq and Syria) in 2014–17.

“Contemporary conflicts, waged in urban and industrialised landscapes, pressure microbes with selective environments that contain unique combinations and concentrations of toxic heavy metals and antibiotics, while simultaneously providing niches and dissemination routes for microbial pathogens,” the authors write.

“These can include the high number of wounded, the nature of wounds, refugee displacement, collapse of sanitation controls, loss of diagnostics and skilled healthcare personnel, the dismantlement of healthcare infrastructures and the placement of often under-resourced and improvised field hospitals where both injured combatants and civilians are exposed to harmful pathogens with limited care and resources to properly recover.”

Such outcomes have occurred in Iraq, say the authors.

Heavy metals used in weapons persist in the environment, with explosives harbouring huge amounts of lead and mercury. Chromium, copper, lead nickel and zinc are used to coat bullets, missiles, gun barrels and military vehicles, while antimony, barium, and boron are weapon-priming compounds. And many bacterial species have been shown to have evolved resistance to combat heavy metals’ toxicity.

“Taken together, a destroyed healthcare infrastructure, inappropriate microbial therapies, limited resources, high heavy metal contamination in humans and the environment, and lack of [proper water, sanitation and hygiene], combined, likely play instrumental roles in the catastrophic rise of AMR in Iraq and, by extension, regionally and globally,” the authors write.
Research is urgently needed to understand the direct and indirect roles of armed conflict on the rise of AMR if it is to be stopped and millions of needless deaths prevented, they insist. “Understanding these linkages between AMR and conflict, especially across time, is essential for a global response to AMR, especially as there is little indication that conflict, worldwide, will abate in years to come.”