Armed conflicts and antimicrobial resistance: A deadly convergence

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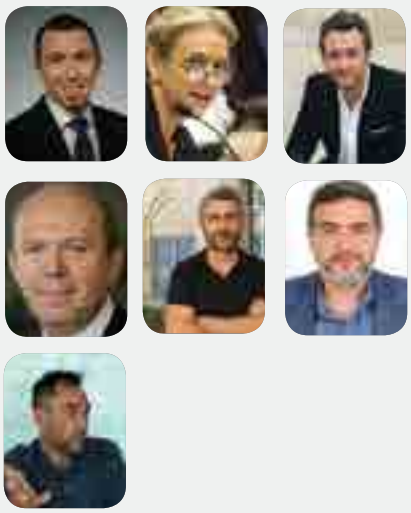

Armed conflicts occur primarily in low- and middle-income countries, which already face tremendous challenges with regards to antimicrobial resistance (AMR) surveillance and control, such as the lack of functioning microbiology laboratories, the dearth of antibiotic stewardship and infection prevention and control programmes, and unregulated biohazard control. In such settings, armed conflicts act as force multipliers of infection and AMR. These challenges are further compounded in those regions also affected by violations of international humanitarian law, the imposition of sanctions and the manipulation of aid. AMR is thus of particular concern in armed conflicts. Unlike in more "controlled" settings, it is harder to contain, it compromises rehabilitation, and antibiotic stewardship approaches are more difficult to implement. Furthermore, the insidious spread of AMR genes into the environment irreversibly resets the resistome to a "new normal", creating a more resistant reservoir of genes that lingers long after the cessation of hostilities with the potential to propagate globally.

The global challenge of antimicrobial resistance

Antimicrobial resistance (AMR) stands as one of the most pressing global public health problems, as highlighted by the United Nations (UN) General Assembly *(1)*, the World Health Organization, the World Bank, and by numerous governments. The predominant narratives put forward to tackle AMR have focused on antimicrobial stewardship programmes, as well as on global governance arrangements with regard to both human and animal health, food production and agriculture. While progress in these areas will assuredly contribute to the control of AMR in some regions with stable governance, they fail to take into account the challenges inherent to conflict and post-conflict zones.

The nature and global reach of infectious diseases (IDs) have been radically changed by protracted armed conflicts increasingly targeting civilians in dense urban settings, and resulting in extensive population displacements *(2)*. Although armed conflicts are usually associated with "fast" and dramatic epidemics, their role in driving "slow" and covert threats such as AMR is overlooked *(3)*. While the ongoing Ebola outbreak in the Democratic Republic of Congo (2018–2019) exemplifies the difficulties in managing serious IDs in conflict zones *(4)*, the focus on such high visibility and fast-moving biothreats may come at the expense of AMR, a global public health challenge with a far greater long-term impact.

A panel on the subject of AMR in armed conflicts was convened in November 2018 at the Graduate Institute of Geneva in collaboration with Université de Sherbrooke (Canada). Academics from different backgrounds (medicine, social sciences, law) along with representatives from non-governmental organizations, international health institutions, private research groups, the industry and diplomatic missions, met to consider the scope of the challenges relevant to AMR in armed conflicts and to propose approaches to address them. Discussions centred on how armed conflicts act as major incubators and propagators of AMR in the context of clinical,

epidemiological, economic, political and environmental conditions creating a perfect storm for its emergence and spread.

AMR in armed conflicts

Armed conflicts occur primarily in low- and middle-income countries (LMICs), which already face tremendous challenges with regards to AMR surveillance and control, such as the lack of functioning microbiology laboratories, the dearth of antibiotic stewardship and infection prevention and control (IPC) programmes, and unregulated biohazard control. In such settings, armed conflicts act as force multipliers of infection and AMR. These challenges are further compounded in those regions also affected by violations of international humanitarian law (IHL), the imposition of sanctions and the manipulation of aid.

In armed conflicts, health systems are degraded by direct attacks, while targeting of healthcare workers leads to attrition of trained staff *(5)*. Penetrating wounds caused by explosive weaponry are at high risk for contamination. Civilian surgeons untrained in war surgery and pressed for time often fail to properly debride the devitalized tissues that act as the perfect medium for bacteria. Medical personnel, overwhelmed by mass casualties, can barely stabilize patients before discharging them back into the community with open wounds, in order to make room for the next influx of injured *(6)*. The paucity of functioning microbiology laboratories and trained microbiologists are eroded by armed conflicts, further straining the ability to guide targeted antimicrobial therapy *(7)*. Antibiotic availability and quality are affected by inconsistent supply chains, sanctions during and after conflicts (e.g., Iraq in the 1990s), and targeting of pharmaceutical factories. This promotes the rise in falsified drugs, while dumping of soon-to-expire antibiotics from donors and lack of regulation of over-the-counter antibiotics leads to self-prescription and misuse. Thus, patients rarely receive the same drug along the treatment pathway, impeding any form of antibiotic stewardship. Coupled with malnutrition and chronic medical conditions, suboptimal care hinders healing, promotes infections with high rates of AMR (e.g., osteomyelitis) *(8)*, which in turn makes these infections more difficult to treat and contributes to mounting rates of disability. In conflict-affected regions, such as the Middle East, AMR is increasingly recognised as the main obstacle to rehabilitation, as well as leading to rising societal costs.

Insecurity, lack of access by relief organizations and manipulation of humanitarian aid often result in shortages of medical supplies. Sanctions may also reduce the availability of basic disinfectants, such as chlorine. The dearth of IPC and the lack of regulation of biohazard disposal lend themselves to nosocomial infections and turn hospitals into foci for the dispersal of AMR into communities marked by overcrowding due to forced population displacements and by the neglect or destruction of water, sanitation and hygiene infrastructures. Together with contamination by heavy metals from munitions and destruction of buildings and agro-industries, the increasingly toxic environment becomes a driver of AMR.

AMR is thus of particular concern in armed conflicts. Unlike in more "controlled" settings, it is harder to contain, it compromises rehabilitation, and antibiotic stewardship approaches are more difficult to implement. Furthermore, the insidious spread of AMR genes into the environment irreversibly resets the resistome to a "new normal" *(9)*, creating a more resistant reservoir of genes that lingers long after the cessation of hostilities, with the potential to propagate globally.

Acinetobacter baumannii

Acinetobacter baumannii stands out as one of the most common pathogens associated with military conflicts. Over the last 20 years, this bacterium has evolved from being an infrequent opportunistic pathogen to gaining worldwide attention as an important cause of infections in patients in intensive care units and with trauma-induced injuries *(10)*. Along with this increased incidence of infections has come a sharp rise in the proportion of strains that are multidrug resistant. Resistance to carbapenems has become the most pressing issue in *A. baumannii*. In February 2017, the World Health Organization (WHO) released a list of 12 antibiotic-resistant priority pathogens divided among critical, high and medium priorities. Carbapenem-resistant *A. baumannii* was ranked among the WHO's critical list, conferring it the highest priority level *(11)*.

Strong evidence for the link between armed conflict and *A. baumannii* infections emerged with the 2003 invasion of Iraq. Starting in 2004, reports of severe infections caused by *A. baumannii* among soldiers injured as part of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom were unexpected and caused great *(12)*. Further research indicated that one of the earliest reports linking military conflicts with *A. baumannii* infections and subsequent nosocomial spread described a link between the resurgence of hostilities during the Lebanese civil war in the early 1980s and an increase in *A. baumannii* infections observed *(13)*.

OIF was launched on 20 March 2003. The first *A. baumannii* positive culture of the Iraq conflict occurred three weeks later on 11 April, 2003, from the sputum of an Iraqi national at a US Army hospital. The first *A. baumannii* positive culture from a US service member occurred on April 20, 2003. Within one week, twelve additional cases were reported. Between 2003 and 2011, over 100 *A. baumannii* cultures were recorded on an annual basis by the US military, with peaks nearing 400.

The majority of infections with *A. baumannii* during OIF were recorded between 2003 and 2011; during this period the US military noted a correlation between "combat intensity" as gleaned from combat fatalities and clinical cases of *A. baumannii*. The emergence of multidrug-resistant strains of *A. baumannii* (MDRAb) during OIF led to greater reliance on carbapenem antibiotics; the resistance to imipenem – one of the carbapenem antibiotics – among strains with a link to OIF increased from 12% in 2003 to 97.4% in 2011 *(1)*.

High rates of MDRAb persist in many countries of the Middle East, whether in post-conflict Iraq or in the more recent combat zones of Syria and Yemen. Along with this association, a new appraisal of *A. baumannii* has emerged. Conventionally viewed as adept at acquiring mobile genetic elements conferring AMR, it is nowadays recognized as an important source of spread of new antibiotic-resistance genes, most notably blaNDM, the most prevalent carbapenemase worldwide. Indeed, extensive molecular sequencing data corroborates retrospective microbiological analyses linking the origin for blaNDM to *A. baumannii (14)*. In addition to the dissemination of other antibiotic resistance genes originating from *A. baumannii*, the triangulation of armed conflicts, MDRAb and AMR spread is one of the most striking examples of the deadly convergence of armed conflicts and AMR.

International humanitarian law, armed conflicts and AMR

The challenges outlined so far are exacerbated by the transgressions of the three cardinal principles enshrined within international humanitarian law. Necessity, proportionality and distinction underlie the functional concept of armed conflicts aiming at the defeat of the enemy, rather than at wanton destruction, and protection of civilians. Necessity implies a functional notion, that is the (regulated) use of armed violence for political and military reasons, a means to an end; proportionality refers to the balanced use of force in the context of the objectives of an armed conflict; finally, distinction entails the discrimination between targets, for instance between armed combatants and civilians, bunkers and hospitals. Together, these three principles define the development of the law regulating armed conflicts and the range of legitimate weapons since the end of the nineteenth century. This advancement had the clear aim of humanizing war, especially with technological progress making weaponry and military activities increasingly more destructive. Unfortunately, recent conflicts abound with violations of these principles, with catastrophic effects on the health of populations living in war zones, whether it be in the launch of chemical attacks or the use of outlawed weapons; the massive destruction and permanent alteration of the built environment in entire neighbourhoods and cities, violence disproportionate to the stated goals of the conflict and aiming at terrorizing the civilian population; and the weaponization of healthcare: the targeting of civilians, hospitals, paramedical services and healthcare workers and the selective withholding of humanitarian supplies in such a way as to compromise public health. The consequences of such abuses amplify the number of wounded individuals developing infectious complications, enhance the development of AMR through environmental pathways, force human migrations in the context of changing ecosystems, and fragilize the provision of healthcare to these vulnerable populations.

Working towards solutions

Greater attention must be paid to better understand how armed conflicts contribute to the global AMR crisis in order to implement mechanisms that address underlying governance issues and logistical challenges. The international community has expressed a firm willingness to tackle AMR from a global perspective and to strengthen local capacity to achieve results. We need to seize on this momentum to shed light on the complex interactions and causative pathways participating in the emergence and spread of AMR in armed conflicts in order to address them. Initial steps include bringing together stakeholders from the various fields whose expertise serves to delineate the most pressing concerns. Such steps will be facilitated by the World Health Organization's recognition, in its 2019–2023 General Programme of Work, of the threats posed by armed conflicts and by AMR *(15)*.

Enhancing medical curricula, as well as reinforcing diagnostic capacity and IPC would improve the care in conflict zones and further limit the risks of AMR emergence and spread. Supporting laboratories in LMICs and their sustainability during armed conflicts are essential through funding, collaborations, and the development of adapted equipment. The World Health Organization recently issued its first Essential diagnostic list, which includes culture and antimicrobial susceptibility, the basic tests to detect AMR. Both this document and its Essential medicines list, which includes antibiotics, should clearly state that testing and treatment of infectious diseases should be exempted of sanctions.

Healthcare workers (HCWs) in LMICs are poorly prepared to provide services in the context of armed conflicts. Medical curricula lack training in the management of war-related injuries, such that civilian HCWs who stand at the frontline all too often struggle when faced with the types of trauma encountered, and the ensuing wound care. For instance, blast injuries inoculate the body with dirt and biological material in addition to the metal shrapnel from the bomb. Civilian surgeons lacking proper training in war surgery and pressed for time are

not able to properly debride the devitalized tissues in these wounds that would act as the perfect medium for the growth of bacteria. Suboptimal debridement and surgical techniques and inadequate pain management from short supplies of analgesics – also often the target of sanctions – contribute to worse outcomes with greater risk of infectious complications and the development of biofilms which further contribute to AMR. Improving curricula, offering rotations in high-trauma settings, and collaborating with military institutions would work to alleviate some of these problems. Progressively, networks are forming around global health security with civilian and military members working together and combining their experience to tackle health threats like AMR.

The health effects of warfare are central to the implementation and enforcement of international legal instruments pertaining to armed conflicts. Revising the content and the capacity of international legal mechanisms to ensure compliance with these updated treaties and protocols would provide more muscle to existing instruments and deter their violations. The development of international criminal law since the 1990s and the establishment of the International Criminal Court in 1998 are cases in point. Bolstering the application of international humanitarian and criminal law would deter their violation. There also needs to be substantial change to military doctrines, such as Military Operations in Urban Terrain, with regards to the impact on urban environments and targeting of facilities that lead to environmental toxification, a potent driver of AMR.

Finally, discussion of AMR in armed conflicts carries the risk of being misappropriated by individuals and governments seeking to advance a populist agenda. Statements stigmatizing migrants and refugees fleeing conflict zones should not be tolerated. Civilians escaping war have already suffered greatly. Any measures that discriminate against them exacerbate the human rights violations they have already suffered, and carry the serious risk of pushing AMR, as well as other health threats, further underground. ■

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Professor Richard Sullivan, MD, PhD, is Professor of Cancer and Global Health at King's College London, and Director of the Institute of Cancer Policy (ICP) and co-Director of the Conflict and Health Research Group (CHRG). He was Clinical Director of Cancer Research UK between 1999 and 2008. Following a period at the London School of Economics working on complex healthcare systems, he moved to King's College London in 2011. Professor Sullivan qualified in medicine and trained in surgery (urology), gaining his PhD from UCL. In conflict systems, His research teams have major programmes in capacity-building in conflict medicine across the Middle East and North Africa (r4hc-mena.org), as well as a range of major programmes from global health security to VR-enhanced humanitarian surgical training.

Professor Gian Luca Burci, was named Adjunct Professor at the Graduate Institute of International and Development Studies in Geneva in 2012. He has served in the Legal Office of the World Health Organization since 1998 and was appointed Legal Counsel in 2005. Professor Burci previously served as Legal Officer at the International Atomic Energy Agency in Vienna and in the United Nations Secretariat in New York for nearly a decade. At the Institute he has taught in the joint LLM in Global Health Law and International Institutions Programme, in partnership with Georgetown University. He holds a post-graduate degree in law from the Università degli Studi di Genova, Italy. His areas of expertise are in international law and international organizations, as well as governance and law related to international health.

Dr Omar Dewachi is Associate Professor of medical anthropology at Rutgers University and is the co-founder and co-Director of the Conflict Medicine Program at the American University of Beirut's Global Health Institute. Trained as a physician in Iraq during the 1990s, he received his doctorate in social anthropology from Harvard University in 2008. Dewachi's work examines the social, medical and environmental impacts of decades of war and violence in Iraq and the broader Middle East. His book, Ungovernable Life: Mandatory Medicine and Statecraft in Iraq *(SUP 2017), is the first study documenting the untold story of the rise of state medicine in Iraq under colonial and post-colonial regimes of rule and the unmaking of state infrastructure under decades of US interventions*

in the country. He is currently working on an ethnographic project that examines the ecologies of wounds and wounding. The research chronicles the biosocial life of war wounds, the rise of multidrug-resistant bacteria, and the reconfigurations of healthcare and humanitarian mobilities across East of the Mediterranean states. He is the author of numerous publications that have appeared in a number of medical, anthropological, and global health journals, including the Lancet. *He is a long-term advisor to organizations, such as MSF and ICRC on the medical and humanitarian crisis in the region, and currently serves as a Commissioner on the Lancet Commission on Syria: Health in Conflict.*

Dr Ghassan S Abu-Sittah, MBchB, FRCS (Plast), is a British-Palestinian plastic and reconstructive surgeon. He has worked as a war surgeon in Iraq, South Lebanon and the Gaza Strip. He was recruited by the American University of Beirut Medical Center in 2011 and became Head of its Division of Plastic and Reconstructive Surgery in 2012. He co-founded and directs the Conflict Medicine Program at the AUB Global Health Institute. He completed his medical education at University of Glasgow in the UK, then his postgraduate residency training in London. He also did Fellowships in Paediatric Craniofacial Surgery and in Cleft Surgery at Great Ormond Street Hospital, and in Trauma Reconstruction at the Royal London Hospital. Dr Abu-Sittah serves as a reviewer at the National Institute of Health Research and is on the Board of Advisors at its Global Research Group on Burn Trauma. He has published extensively on war injuries, including a medical text book: Reconstructing the War Injured Patient.

Professor Vinh-Kim Nguyen, MD, PhD, is a medical anthropologist and physician who practices in acute care and humanitarian settings. His clinical practice has specialized in HIV and sexual health; his teaching links global health and social theory and his research examines efforts to eradicate epidemics, particularly HIV, Ebola, and drug-resistant bacteria, in Africa, Europe and the Middle East. He is Professor of Anthropology at the Graduate Institute in Geneva, Switzerland.

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