

## Viewpoint

# Microbiome research potential for developing holistic approaches to improve refugee health

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Morbidity from disease is increasingly being understood as dependent on wellbeing of the ecosystem, as opposed to an isolated element. However, the combined burden of disequilibrium of the gut microbiome ecosystem – which can facilitate proliferation of antimicrobial resistance (AMR) – is not well understood. The gap in knowledge grows when considering regions, such as the Gaza Strip, where the population continues to experience recurrent conflicts, movement restrictions, and high rates of poverty, food insecurity and unemployment.<sup>1</sup> The concurrent rise of gut microbiome disequilibrium, AMR proliferation, and displacement of populations globally – combined with lack of data – poses significant but unknown risk to public health, in displaced and host communities alike. Examining the current landscape of research, and existing gaps solidifies the need for interdisciplinary perspectives to address AMR through exploration of the gut microbiome. This holistic approach can help account for the political, socio-economic, and material factors, in the context of regions experiencing conflict/war. The growing role of microbiota in health may hold answers to questions surrounding understudied conditions such as AMR, and even non-communicable or chronic diseases.

Over the millennia, microbes have formed a conditionally mutualistic relationship with humans.<sup>2–4</sup> The indigenous human microbiome hosts several such microbial communities in biological fluids, and tissues. These microbial communities are most abundant in assortment in the gastrointestinal tract, achieving densities of up to  $10^{12}$  CFU/ml.<sup>5</sup> They engage in close and complex interactions with host and environment, making the gut microbiome an area of growing exploration and interest. We now know that it is involved in immune system function, salvaging nutrients/energy, exerting trophic effects, and protecting the host against pathogenic invasion.<sup>6</sup> Research has shown the importance of gut microbiota in health, and development of diseases. Gut microbiota dysbiosis can increase chances for occurrence of common chronic disease like inflammatory bowel disease (IBD),<sup>7</sup> colorectal cancer,<sup>8</sup> and cardiovascular issues.<sup>9</sup> Several factors can influence dysbiosis which occurs rapidly, and with lasting effects. These factors include immunodeficiency, alcohol consumption, inadequate nutrition<sup>10</sup>; and crucially, antibiotic use.

The wellbeing of gut microbiota and the use of antibiotics is a dual-edged sword for human health. The effective but indiscriminate approach of antibiotics causes loss of commensal gut bacteria, enabling their replacement by non-mutualist bacteria, including Multi Drug Resistant Organisms (MDROs).<sup>11</sup> This dual threat has the potential to exponentially worsen in the context of armed conflict, subsequent violent dispossession, and displacement of affected

populations. The circumstances of conflict entail severe disruption of access to adequate nutrition, clean water, sanitation, shelter, and medical care. Along with forced displacement within or across borders, affected persons stand to bear an unknown, potentially high, burden of synergetic gut dysbiosis, and MDRO colonization/infection, especially in highly stressful situations. Despite the interlinked nature of these three phenomena (gut dysbiosis, AMR proliferation, forced displacement crises), limited data exists on the interaction between them, and the extent of the problem. The prevailing pandemic has shown how significantly health is connected globally; that our healthiest communities are only as healthy as the most marginalized and under-cared for. Better care for these communities begins with dedicating interdisciplinary efforts to direct holistic interventions.

## MICROBIOME AND AMR: CIRCUMSTANTIAL SYNCHRONY

The advent of antibiotics nearly a century ago changed the landscape of bacterial infectious diseases and the mortality associated with them. Up until then casualties were so rampant, that from 1775-1918 more US armed personnel lost lives to infectious diseases than direct enemy actions.<sup>12</sup> The boom in antibiotic therapeutics that followed penicillin, made it seem like bacterial infections were a concern of the past. However, it remains important to consider the evolu-

tionary advantage of bacteria. Since before the advent of human beings, microorganisms have inevitably evolved defenses against antibiotic agents, resulting in the emergence of Multi-Drug Resistant Organisms (MDROs).<sup>13</sup> Their ability to thwart antibiotics through chromosomal mutation, or exchange of mobile genetic elements (MGEs) like plasmids enabled bacteria to become resistant to most, if not all, antibiotics administered, and that resistance can transfer through reproduction, as well as horizontal gene transfer (HGT).<sup>14</sup>

Worryingly, the microbiome also has an environment conducive to the transfer of Antibiotic Resistance Genes (ARGs) on MGEs and through HGT.<sup>14,15</sup> The gut antibiotic resistome consists of ARGs that are both evolutionarily distinct from known resistance genes in addition to ones identical to the pathogenic species. Both, commensal and opportunistic pathogens harbor these ARGs. Occurrence of Antimicrobial Resistance (AMR) and rising microbiota imbalances is prevalent globally, even in urban environments.<sup>16–19</sup> Atypical from other infectious diseases, AMR can nullify antibiotic therapeutics and at once jeopardize health outcomes of easily treatable infections,<sup>20</sup> as well as major procedures such as organ transplants, chemotherapy or surgeries.<sup>21</sup>

Several factors concurrently contribute to reduction of microbiota diversity and provide conditions that favor proliferation of MDROs. Foremost, antibiotic use impacts not just commensal gut microbiota but also leads to resistance in the population, through multiple pathways. In humans, ARGs can be acquired through meat of livestock that were given antibiotics.<sup>22</sup> Moreover, as much as 75% of consumed antibiotics are egested unchanged in animals and humans alike.<sup>23</sup> These excreted antibiotics – along with ARGs – then find their way into the environment through run off, or travel through sewage systems, and lead to development of AMR in both contexts.<sup>24</sup> Resistance to antibiotics can further occur in hospital-settings, spreading directly among patients or indirectly through care providers or the environment,<sup>25</sup> and within the community, through interaction, or co-habitation with MDRO colonized/infected persons.<sup>26</sup>

In combination with high use of antibiotics, urbanization and its impacts also aid the synergetic chaos of AMR and gut dysbiosis. Industrialized, urban cities and regions experience consistent exchange of migrants, as rural poverty drives them to seek better living conditions.<sup>27</sup> Without proper planning for such influxes, public health issues arise and negatively impact quality of life. Crowding, low levels of physical activity, and nutritional imbalances mean that urban poor populations bear risk of communicable diseases, in coexistence with non-communicable disease prevalent in wealthy communities.<sup>28,29</sup>

AMR continues to advance, even in the gut microbiome. Further, the gut often experiences dysbiosis in parallel. Our understanding of the dynamics of both remains limited. As the COVID-19 pandemic has shown, public health surveillance, infection control and elimination, quarantine abilities, and even communication of public health/epidemiological data is critically compromised.<sup>30–33</sup> Similar themes define the history of AMR as an infectious disease.<sup>34</sup> Much more concerning, however, are the potential future trajectories of AMR.

The proliferation of AMR is already causing disruption in health, nutrition, and therapeutics alike.<sup>35,36</sup> AMR disrupts access to and delivery of healthcare even in regions with generally high income, and developed economic/health status.<sup>37,38</sup> Meanwhile, forcibly displaced persons – and Palestinians, particularly – have limited or non-existent access to medical care.<sup>39,40</sup> The prevailing scarcity, enforced blockade, geographic isolation, and displacement also means an increased risk of exposure to substandard, expired or counterfeited medical supplies – including antibiotics.<sup>41–43</sup> Consequently, the situation in Gaza bears the hallmarks of having reached or even exceeded, the minimum threshold for prompt action. The prevailing COVID-19 pandemic has managed to strain the medical care systems of even well-resourced, and medically advanced nations. Considering the impact of repeated conflict, and displacement along with the added pressures of COVID-19 we believe there *must be* a formidable risk of burden from AMR and gut dysbiosis, which thrive in such unmonitored and under-resourced conditions. We say “must be” because part of the potential risk includes the near total void of research into the likelihood and severity of AMR and the impact of microbiome health on the same, within Palestinian and particularly, Gazan communities.

## FORCED DISPLACEMENT, AMR AND GUT DYSBIOSIS: CASE STUDY OF GAZA, OCCUPIED PALESTINE

Over the past 54 years, war and conflict in Gaza have grown to disproportionately impact Palestinian civilians. The complexity of the situation is compounded by the physical restraints of Gaza, which has an area of 365km<sup>2</sup> – just above twice that of Washington, DC.<sup>44</sup> A population of 2.1m means the Gaza Strip, however, is four times more densely populated than Bangladesh.<sup>45</sup> Isolation of the Gazan population enforced via militarized borders generates acute scarcity of healthcare facilities, jobs, education, and food. Despite nearly 70% of the population being refugees,<sup>46</sup> the enclave has been under land, air, and sea blockade since 2006. Consequently, the outcomes of repeat military action on Gaza – as recently as May/June 2021 – are devastating. Results from a rapid needs assessment (RNA) conducted following the recent round of assault on Gaza by CARE,<sup>47</sup> depicts extremely worrying trends ([Table 1](#)).

Beyond impacting people, conflict and forced displacement also devastate the environment, infrastructure, livelihoods, and social wellbeing. As such, the crisis in Gaza, necessitates exploring the potential for negative effects of AMR, gut dysbiosis, and forced displacement simultaneously. The Internal Displacement Monitoring Centre highlights 7 aspects of life affected by forced displacement: livelihoods, education, health, security, social life, environment and access to housing and infrastructure.<sup>48</sup> The effects on each aspect, in turn ripple through to others. In areas as densely populated as Gaza, it is important to recognize the inseparability of populated spaces from the “natural environment”.<sup>49</sup> Indeed, the health and well-being of the populace depends on the balance between both. Clean air, water, and land for instance, require upkeep of popu-

**Table 1. CARE West Bank/Gaza rapid needs assessment (RNA) summary – May/June 2021 (n=62 respondents)**

Survey category	Response
Health	24% w/o access to health services 39% have chronic illness
Livelihood	45% noted loss of income
Shelter/Non-food Items	40% without electricity 44% without water 44% reported damaged homes
Food	23% report skipping meals 48% reliant on humanitarian agencies

lated spaces via sanitation, sewage, electricity, and other vital infrastructure.

Examining the nature of armed conflict today, points to a key shift in strategy towards these critical facilities. Improvements in remote, unmanned, and long-range weaponry means warring powers increasingly opt for targeted strikes over mass deployment of troops. Despite the ability to effectively discriminate targets now, “duress bombing” – the targeting of civilian infrastructure – has been and is being deployed, particularly in the Middle East and North Africa.<sup>50–52</sup> Ordinances deployed by armed forces exact heavy fatalities on affected people, then unleash secondary strife through the damage to resources, and ability to access them. Civilianization of war via duress bombing has been a key compounding factor for the population of Gaza. Examples include the illegal targeting of a United Nations Relief and Works Agency (UNRWA) shelter, a sewage plant, critical freshwater wells, flour mills, and poultry farms.<sup>53</sup> These incidents are not isolated; in 2014 Gaza’s only power plant was reportedly struck by Israeli fire. In summer of 2021, airstrikes damaged “six hospitals, nine primary healthcare centers, and a desalination plant”.<sup>54</sup>

Critically, the deterioration of vital infrastructure and industries due to strikes, ripples in parallel into the natural environment. The maintenance of human populations in any region is dependent on access to natural resources, and ability to refine them into food, products, and supplies. This dependence intensifies due to the enforced isolation of Gaza’s populace. Historically, Gaza and the surrounding lands have been populated for millennia, supported by arable topography, and natural water supplies.<sup>55,56</sup> The situation today is drastically different. Access to clean water is of paramount importance for sanitation, hygiene, irrigation, and consumption. However, safe potable water is essentially non-existent in Gaza.<sup>57</sup> Destruction of wastewater treatment, and solid waste disposal systems, pollution, contamination, and the use of cesspits due to lack of centralized sewage all contribute to this scarcity.<sup>58–62</sup> As such, 60–80% of domestic wastewater is discharged into the environment without treatment.<sup>57</sup> When the Beit Lahia wastewater treatment plant flooded in March 2007, it killed 2 children, and 3 women, displaced others, damaged livestock, and farms, and forced the closure of surrounding groundwater wells due to contamination.<sup>63</sup>

Land in Gaza also suffers from conflict. The *camp-villes* (city camp) nature of Gaza’s refugee camps and settlements have evolved from isolated, temporary settlements to the

establishment, and subsequent destruction, of quasi-permanent cities. Expansion and rebuilding of residences alike causes resource deterioration, soil/ecosystem disruption, and pollution.<sup>58</sup> Due to the physical constraints of Gaza, arable land is limited, and that which is available is under threat from increased construction and conflict. Contractors increasingly want to use green spaces in Gaza for construction projects, furthering the depletion of resources. Israel also maintains a buffer zone around Gaza, with *ad hoc* limits of extent. This buffer zone covers significant tracts of arable land, made completely unavailable.<sup>64</sup> The land persistently suffers direct damage from airstrikes, shelling, or heavy-vehicle tracking – a United Nations Operational Satellite (UNOSAT) preliminary analysis found nearly 1,800 hectares of agricultural lands had been razed or heavily damaged, after the August 2014 assault on Gaza.<sup>65</sup>

Recurring conflicts – including the most recent episode of violence in the summer of 2021 – lead to loss of precious life and also contribute to the destruction of the environment that can lead to long-range impact on the gut microbiome and proliferation of drug resistant organisms.<sup>66</sup>

Any one of the compounding factors of forced displacement would be enough to create favorable conditions for the rise of diseases including drug resistant infections, and gut dysbiosis. Indeed, refugee camps and settlements have faced outbreaks of infectious diseases including malaria, tuberculosis and HIV/AIDS, described extensively in the literature.<sup>67,68</sup> Based on trends of preceding infectious disease outbreaks, *all* these conditions persisting simultaneously signifies an exceptionally high risk for synergetic AMR and gut dysbiosis.

#### CAUSE AND EFFECT: AMR AND MICROBIOME IMBALANCE AMONG FORCIBLY DISPLACED

The intersection of microbiome diversity, AMR, and the environment is of particular concern, where chronic exposure to conflict, the inevitable heavy metal pollution it brings, and infrastructural/environmental collapse perpetuate gut dysbiosis and AMR.<sup>69</sup> In Gaza and beyond, interventions to resolve inter-linked issues holistically must begin by addressing the most vulnerable populations, in this case displaced persons. More specifically, forced displacement disproportionately affects pregnant persons and young children, creating a ‘most vulnerable of the most vulnerable’ scenario. By 2015, up to 80% of displaced people world-

wide were women and children.<sup>70</sup> Mortality among displaced women and children rises in line with risk of infection, malnutrition, increased stress, and burden from having to be the caretaker, and lack of access to care.<sup>71,72</sup> The risk of complications during pregnancy and delivery, such as postpartum hemorrhage and pre-eclampsia, become exacerbated.<sup>73</sup> Concurrently, infants face challenges from two fronts, as both malnutrition during gestation and within the first 12 months of life introduce significant risks for neonatal mortality,<sup>74</sup> impairs physical and cognitive development,<sup>75,76</sup> and predisposes malnourished children to endocrine and metabolic dysfunction later in life.<sup>77</sup> The mother-to-infant transfer of microbiota in the formation of the neonate gut microbiome poses a unique threat, as reduced microfloral diversity and ARGs within the mother's microbiome during childbirth can be transmitted to the neonate.<sup>78</sup> Indeed, low birth weight, childhood stunting, anemia, and chronic malnutrition are all associated with reduced microbiome diversity and gut dysbiosis.<sup>79,80</sup> Reduced microfloral diversity and impaired nutrient absorption and gut metabolism due to MDRO overgrowth can exacerbate chronic malnutrition in children living in precarious, food-insecure contexts.<sup>81</sup> This MDRO overgrowth in turn compounds issues of diarrheal disease, poor nutrition, and impaired immunity that serve as significant sources of childhood morbidity within refugee settlements.<sup>82</sup> The close association between AMR and gut imbalance induced morbidity suggests addressing one might have positive feedback onto the other. However, the scale, persistence, and complexity of forced displacement and AMR in that context mean that despite the problem being potentially prevalent, it remains understudied, under surveilled and on the cusp of receiving a significant leg up through the global upheaval of the past year.

Conventionally, strategies to curb AMR have been ad hoc, and populations have relied often on over-the-counter use of antibiotics in case of infections. However, overuse of antibiotics is a well-established pathway for the selection of AMR.<sup>83</sup> The use of antibiotics and their consequences are influenced by several factors, especially in low- and middle-income countries, hosts to most of the global displaced population. Refugee populations are already at risk of acquiring resistant bacterial infections due to poor hygienic and sanitation conditions, and no access to care. Additionally, limited access to quality assured antibiotics<sup>84</sup>, unskilled/insufficient practitioners,<sup>85</sup> self-medication,<sup>86</sup> and a perceived need for antibiotics to cure or prevent diseases<sup>87</sup> all lead to an increased burden of AMR proliferation. Incomplete or inadequate filtration of waste also releases antibiotics into the natural environment, which finds its way into the food chain and compounds AMR further. The ripple effects of Explosive Remnants of War (ERWs) are evidenced in AMR proliferation as well. Due to their high stability, explosive compounds in ERWs bind readily with organic components of soil, remain deposited, and leech into the water, and biomass of the region.<sup>88,89</sup> Heavy metals allow for selective pressure for resistance over a long period of time. This phenomenon has cascading effects not only in the proliferation of MDROs in an environment conducive to HGT, but also in nutrient uptake and non-communicable diseases involving the endocrine and digestive systems,<sup>90,91</sup> partic-

ularly for vulnerable populations within Gaza that are susceptible to nutrient deficiencies and infectious disease.

## CONTEMPORARY RESEARCH AND REQUIEM FOR INTERDISCIPLINARY INTERVENTION

The Madrid Operational Framework of 2010, formulated at the first Global Consultation on Migrant Health,<sup>92</sup> called for a host of measures intended to harmonize migrant/host population health and the host country's response. This framework included ensuring migrant health data standardization, mapping good practices, promoting standards to protect migrant right to health globally, and policy coherence among different sectors. Perhaps most importantly, it called to 'establish and support migration/health dialogues and cooperation across sectors and countries of origin, transit and destination'. Adaption of this framework to respond concurrently to gut dysbiosis and AMR, has enormous potential to improve holistic health outcomes. Current research aimed at the gut dysbiosis-AMR junction is (1) nascent but growing and yet (2) not in line with the Operational Framework's recommended measures. Generating new and crucial insight into the microbiome and its role in AMR proliferation, by accounting for potential intensity of burden depending on length of forced displacement, or the burden of colonization among 'otherwise healthy' displaced persons are just some areas for potential improvement. Despite this it is important to recognize the complexity of forced displacement and subsequent complication of conduct of ethical, transparent, and multifactorial research.

Among the few studies reporting on gut microbiome and AMR overlap in refugees, Hasler et al.<sup>93</sup> report on newly admitted refugees in Germany, and diversity in both their microbiome and antibiotic resistome compared to resident Germans. The emergence of MDROs in people fleeing conflicts in Syria and Iraq has also been documented across medical centers in Turkey, Lebanon, and across Europe. Isolates of carbapenem-resistant *Acinetobacter baumannii* were identified in Syrian asylum seekers admitted to a medical facility in Adana, Italy,<sup>94</sup> and a *bla*NDM-1-positive carbapenem-resistant *A. baumannii* reservoir was discovered among war-injured Syrian civilians admitted to the Tripoli Government Hospital in Lebanon.<sup>95</sup> A review by Nellums et al.<sup>96</sup> found AMR carriage or infection in migrants to be at 25.4% in 2319 people across 23 studies. The review, however, did not find evidence of high rates of transmission from migrant to host populations.

Vonaesch et al.<sup>97</sup> describe how disturbance to equilibrium of the microbiome (during development, or post-antibiotic treatment) creates competition for space and nutrients through the priority effect. Following the disturbance, the first species to recolonize the gut creates scarcity of space and nutrients for other species. The paper emphasizes the competitive nature of the microbiome environment, which spells trouble considering the replacement of commensal bacteria by MDROs in the wake of antibiotic use. Vonaesch et al, voice support for an 'ecological Koch's postulates' framework, which states that morbidity is dependent on the equilibrium of the whole ecosystem, as opposed to a solitary element.

Historically, global response to emergent disease threats have largely been reactive, and not preventive. Going ahead, reactivity cannot be afforded, as the lessons of the COVID-19 pandemic have shown. Simultaneous gut microbiome and AMR exploration, would help develop a more nuanced approach, especially in the context of forced displacement. In Gaza for example, a preliminary or pilot study can (1) help gather foundational knowledge, (2) use newly gathered foundational knowledge to assess contextual efficacy of interventions like fecal/microbiome transplants vs. diet fortification, (3) help address larger concerns of microbiome health such as the exchange of commensal/pathogenic microbiome communities between host/refugee/migrant populations. Further, we need not be restricted to exploring multifactorial issues through the lens of a single discipline. Increasing numbers of scholars in global health emphasize the importance of collaboration between disciplines, both natural and social sciences, when working with issues that are multifaceted, like AMR<sup>98</sup> and gut dysbiosis. For interventions to be effective and sustainable, they need to be locally adapted to the specific social, cultural, political, and material conditions,<sup>99</sup> and these perspectives are best achieved through qualitative research.

Fulfilling this need for adapted interventions, in turn requires an understanding of the prevailing landscape. However, intrinsic, and external factors of forced displacement raise significant barriers to research in this context. Foremost, protracted states of forced displacement have forced most asylum-seekers and refugees globally, to move into urban areas within their host nations, in search of better opportunities for livelihood and settlement.<sup>100</sup> Here, they may face challenges with access to services, assimilation into local communities, health variability, and livelihood security<sup>101</sup>: all of which can affect MDRO proliferation.

Further, growing antagonization of migrants, and increased employment of deterrence policies towards migrants and asylum-seekers, means that forcibly uprooted persons are less likely to participate in research projects that extract sensitive information. Indeed, this hesitancy is not unfounded as examples of data collected on refugees have been repeatedly utilized against them in detention or deportation efforts.<sup>102</sup> With most refugees living in countries neighboring original conflicts, collection of identifiable data can further put refugees, and researchers, in the way of harm. Research in forced displacement also faces obstacles in the bureaucratic, technical, or linguistic contexts which are often politicized, and entail unequal power dynamics.

## CONCLUSIONS

Despite evidence of gut dysbiosis and MDRO proliferation in stable, urban environments and through voluntary travel/migration,<sup>103</sup> forcibly displaced persons stand to be worst hit by disease burden – whether communicable or not. Understanding and responding to these interlinked crises is complicated by ripple effects of displacement and conflict, especially in areas like Gaza. Decades of war, blockade, governance issues, and economic difficulties have rendered Gaza virtually unlivable as of this writing. We hope that this paper would foster discussion and initiative among researchers in a variety of disciplines to form research on the role of microbiome and AMR/disease burden in Gaza.

Interdisciplinary research, to explore sustainable interventions to limit further evolution and spread will need to break from traditional approaches to research in forced displacement. A starting point in this context, will be developing ethical, comprehensive, and participant-sensitive/inclusive methodology for research conducted. This robust methodology can then be deployed to assess key questions about the extent that gut dysbiosis, MDRO carriage/infection, and multifactorial deficiencies intersect long-term refugee settlements, and urban refugee populations alike.

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## COMPETING INTERESTS

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