Turkish Online Journal of Qualitative Inquiry (TOJQI)
Volume 12, Issue 5, July, 2021: 4192-4200

Research Article

A qualitative global analysis of changing patterns in antimicrobial resistance and the insidious nature of the emerging sinister threats of resistance in HIV, Malaria, and Typhoid

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Abstract:
The first antibiotic was used 80 years ago. Research on antibiotics is an ongoing process with continuous learning of their effectiveness and efficiency in human and animal healthcare systems. A silent and insidious phenomenon that has escaped popular consciousness and discussions on which are limited to academia and the rarefied realms of professional bodies is Antimicrobial Resistance (AMR). This development has significant catastrophic potential and is not being given the political attention that it deserves, despite already having reached epidemic proportions. To the lay person, it is largely invisible. There have been 2 significant initiatives from global leaders to address the issue. The World Health Organization (WHO), Food and Agriculture Organization, and Organization for Animal Health tabled

a Global Action Plan which outlined the grave situation. The call from the United Nations general assembly in 2016 gave further clarity to the urgency of the matter. There was a recognition of the need for proactiveness and ownership from all governments. Some governments have drawn up action plans for AMR with fiscal allocations. These efforts are outnumbered by governments that have not done enough for in the initiative against AMR. The principal difficulty to be surmounted in AMR is the multisectorial nature of the phenomenon. AMR exists at the intersection of human health, animal health and environmental health. The One Health approach has not seen adequate uptake, rendering it limited to the category of a concept and not a practice with significant impact in managing epidemiological risk. The requirement for antibiotics in both humans and animals can be curtailed through the effective implementation of a three pronged approach that includes clean potable water and sanitation, reduction in incidence and prevalence of infections and enhanced vaccination coverage. Of critical importance will be to challenge and change the twin narratives of antibiotics being a cheap tool to combat illness and there being no unpleasant impact on populations. This will require strong ownership from government and regulatory bodies. Without laws to tackle this growing problem, AMR control will remain a pipe dream.

Keywords: antimicrobial resistance, AMR, HIV, Malaria, and Typhoid

Methodology: Comprehensive literature review with relevant search terms in Scopus, Web of Science, Pubmed and Google scholar databases

Introduction:

The first antibiotic was used 80 years ago. Research on antibiotics is an ongoing process with continuous learning of their effectiveness and efficiency in human and animal healthcare systems. A silent and insidious phenomenon that has escaped popular consciousness and discussions on which are limited to academia and the rarefied realms of professional bodies is Antimicrobial Resistance (AMR).[1] This development has significant catastrophic potential and is not being given the political attention that it deserves, despite already having reached epidemic proportions. To the lay person, it is largely invisible. There have been 2 significant initiatives from global leaders to address the issue. The World Health Organization (WHO), Food and Agriculture Organization, and Organization for Animal Health tabled a Global Action Plan which outlined the grave situation. The call from the United Nations general assembly in 2016 gave further clarity to the urgency of the matter.[2] There was a recognition of the need for proactiveness and ownership from all governments. Some governments have drawn up action plans for AMR with fiscal allocations. These efforts are outnumbered by governments that have not done enough for in the initiative against AMR. The principal difficulty to be surmounted in AMR is the multisectorial nature of the phenomenon. AMR exists at the intersection of human health, animal health and environmental health.[3]

The high prevalence of antibiotic usage in agriculture and aquaculture has been proven to be an important factor in the growth of AMR.[4] With growing global prosperity, especially in India and China, the demand for animal protein has grown at a rapid pace. This has resulted in a concomitant increase in the utilisation of antimicrobials for 2 purposes: Prevention and treatment of infections; and the promotion of rapid growth of livestock. In the light of these developments, it is becomingly increasingly clear that governments will need to intervene proactively to formulate evidence based policies and laws with the aim of reducing antibiotic use in livestock farming and aquaculture.[5]

Availability of and accessibility to life saving antibiotics in LMICs is a serious concern. In the LMIC context, the burden of mortality caused by a lack of access to antimicrobials is much higher than the burden of mortality from AMR. A critical component of the global strategy for AMR would be to

enhance access to antibiotics that are affordable and clinically appropriate. Another serious concern is antibiotic research and development not being able to keep pace with clinical requirements.[6] Current levels of antibiotic development are inadequate to effectively address the increase in resistance to antimicrobials in current clinical practice. At these levels, it becomes untenable to offer an adequate range of effective antibiotics. AMR strategies can currently make use of 2 tools: The Drug Resistance Index (DRI) and the Country Dashboards. DRI assesses the average effectiveness of an antibiotic in the treatment of a particular bacterial infection.[7] DRI can assess trends in AMR burdens nationally and subnationally. DRI can detect areas of AMR. Country dashboards reflect AMR status and antibiotic use in human and livestock in 40 countries. Every country is assessed on AMR across four categories of indicators: 1. Public health 2. Policy 3. AMR 4. Antimicrobial use.[8,9] Each of these categories is composed of multiple indictors. The Drug Resistance Index (DRI) and the Country Dashboards extend evidence based support to policy makers, government administrative officers and other stakeholders to assess AMR, compare and contrast the situation with other countries and take suitable action.

AMR: Fluid patterns

Resistance and genetics:

AMR is a survival mechanism for microbes. AMR is directly proportional to antibiotic usage levels. Bacterial mutations that increase chances of survival spread faster. This phenomenon decreases the lead time that bacteria need to develop AMR to newer antibiotics. This development along with the slow pace of research and development of novel antibiotics has contributed to increases in AMR.[10] The situation is particularly alarming in the case of selected priority pathogens which have very limited treatment options. Bacteria have evolved defence mechanisms: Blocking antimicrobial entry; secretion of enzymes that change or cause destruction of the antibiotic; bringing about changes in the antibiotic target cells. AMR causing bacterial enzymes are Narrow-spectrum beta-lactamases, Extended-spectrum beta-lactamases (ESBL) and Carbapenemases. Narrow-spectrum beta-lactamases are cephalosporinases, TEM-1 and 2, OXA type enzymes and SHV 1. These are active against penicillins and 1st generation cephalosporins. ESBLs are TEM-10, TEM-12, TEM-26, CTX-M, SHV-2, SHV-5, SHV-7, SHV-12, OXA-type ESBLs. These are active against penicillins and all four generations of cephalosporins. Carbapenemases are OXA type carbapenemases, KPC, VIM and IMP carbapenemases and NDM-1. These are active against carbapenems, penicillins and all four generations of cephalosporins.[11,12]

Research shows variations in AMR across pathogens. AMR in Acinetobacter baumannii was higher than in other bacteria. Enterococcus faecium showed highest AMR for broad spectrum penicillins. High AMR was seen in Klebsiella pneumoniae which is included in WHO's list of priority pathogens.1[3] An area of increasing concern is the rise in the prevalence of Carbapenem resistant gram negative pathogens. Several genes encode these pathogens: KPC, NDM-1, IMP, OXA-48, VIM. The first case of Klebsiella pneumoniae was reported less than 10 years ago. Since then, the spread of AMR across the globe has been rapid. The spread has happened across a range of species of bacteria, making the task of containment an onerous one. In the same time frame, there have also been significant strides made in man's ability to track the international spread of AMR. Another area of significant concern is the discovery of plasmid mediated genes: icr-Mo, mcr-1, mcr-2, mcr-3, mcr-4 and mcr-5,7. These genes facilitate the encoding of AMR to Colistin. Colistin is a last resort antibiotic.1[4] Mcr-1 was first discovered in China in 2016. It was isolated from Escherichia coli cultures that were sourced from a pig. However, since then, mcr-1 has been isolated across the world and in multiple species of bacteria. These include Enterobacter species and Klebsiella pneumonia.[15] There has also been a global spread of several gene variants that encode Extended Spectrum Beta Lactamases (ESBLs): these initiate AMR to monobactam, penicillin and cephalosporins. A high prevalence of these in Klebsiella pneumonia and

Escherichia coli has been reported from important surveillance systems like the European EARS-Net. Meat products and livestock have been found to harbour gram negative bacteria that are ESBL positive.[16] Australia and the United Kingdom have reported AMR to first line therapy with Ceftriaxone and Azithromycin for Neisseria gonorrhoeae. The United Kingdom isolate in particular has demonstrated AMR to the entire range of antimicrobial agents prescribed for Neisseria gonorrhoeae.[17] In the cases of Enterococcus faecium and Staphylococcus aureus, there have been no reports of any significant shifts in resistance. This is in connection with the international genetic molecular epidemiology for the encoding of vancomycin resistance (vanA and van B) or methicillin resistance (mecA). The time frame under consideration is the last decade. As an exception, there have been reports of the appearance and spread of methicillin resistance (mecC).[18]

Trends and rates of resistance:

AMR is an international concern. The prevalence of AMR across geographies varies with four variables: levels of consumption of antibiotics, proportion of population with access to potable water and acceptable levels of sanitation, proportion of population with access to good quality healthcare, and proportion of population with vaccine coverage.[19] WHO AMR data from 66 countries shows an alarming increase in AMR globally in antibiotics that are used in the treatment of commonly prevalent infections. Ciprofloxacin is an antibiotic used in the treatment of infections of the urinary tract. AMR rates to this antibiotic varied hugely from 8.4 percent to 92.9 percent for Escherichia coli and from 4.1 percent to 79.4 percent for Klebsiella pneumonia.[20] These results were extracted from AMR data sets from 33 and 34 countries respectively. Estimates put the number of annual AMR infections in the United States at 2.8 million with 35,000 deaths. An estimated 12,800 deaths resulted from 223,900 cases of AMR Clostridioides difficile in 2017.[21] Since 2000, the United States has seen a 124 percent increase in the prevalence of AMR gonorrhoea and a 50 percent increase in the prevalence of extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae. There are positives too. Since 2013, AMR related mortality has decreased by 18 percent. In the same time frame, cases of carbapenem-resistant Acinetobacter have decreased by 33 percent and cases of vancomycin-resistant Enterococcus have decreased by 41 percent. The AMR landscape is in flux.[22] It needs high quality surveillance and highly responsive policymaking to rein in the spread of AMR. Canadian data puts AMR to first line antibiotics at 26 percent. In 2018, mortality directly attributable to AMR was 5,400. Highest AMR rates were noted for urinary tract infections, intra-abdominal infections, skin and soft tissue infections, musculoskeletal infections and pneumonia.[23]

Analysis of reports and data from 30 countries in the European Union/European Economic Area (EU/EEA) shows significant levels of variation in AMR prevalence. Southern European and Eastern European countries had the highest AMR prevalence.[24] The European Antimicrobial Resistance Surveillance Network (EARSNet) report of 2019 says that more than fifty percent of the Escherichia coli isolates and more than thirty three percent of the Klebsiella pneumonia isolates had developed AMR to atleast one group of antibiotics. Carbapenem AMR greater than ten percent in Klebsiella pneumoniae has been reported in several countries. Methicillin Resistant Staphylococcus Aureus (MRSA) remains a serious concern in the EU/EEA. This is inspite of a decrease in the percentage of isolates of MRSA. The differences in AMR prevalence across EU/EEA countries merits a focussed strategy and high quality intergovernmental cooperation.[25]

A major lacuna is the presence of substantial gaps in knowledge of AMR prevalence in LMICs that have suboptimal levels of surveillance capacity, clinical wherewithal and laboratory capacity.[26] AMR data was unavailable for 40 percent of countries in Africa when a systematic review of 144 studies conducted across Africa was done. AMR to penicillin was seen in Streptococcus pneumonia (26.7%). AMR to amoxicillin was seen in Haemophilus influenzae (34.0%). AMR to gentamicin, trimethoprim

and amoxicillin (29.8%, 80.7% and 88.1%) was seen in Escherichia Coli. Evidence points to South East Asia having the highest risk of AMR spread and impact in the Asia Pacific region: an example is the New Delhi metallo-β-lactamase-1 (NDM-1) that has been seen to have exceptionally high transferability. More than 33 percent of Multi Drug-resistant Tuberculosis (MDR TB) incidence came from India and China. Lacunae in assessment of AMR prevalence in LMICs were attempted to be addressed in one study: AMR prevalence for select pathogenic microbes was estimated by studying the relationship between socioeconomic indicators and AMR prevalence.[27] Surveillance deficient areas were identified by assessing available prevalence data and World Bank indicators. Strengthening of surveillance was recommended for these areas. AMR for Carbapenem in Acinetobacter baumannii and for third generation cephalosporins in E.Coli are seen in sub Saharan Africa, Pacific islands and the Middle East.

Drug Resistance Index (DRI):

There is significant variation in the efficacy of drugs against pathogenic microbes. The matter of assessing this efficacy has several layers of complexity. This complexity makes the task of accurately quantifying and substantiating trends in national AMR burden very difficult. This is where the DRI plays a critical role: it fuses data on AMR and antibiotic usage to create one indicator that attempts to quantify the efficacy of antibiotics across geographies.[28] Data for AMR and antibiotic usage are collated for a multiplicity of antibiotic-pathogenic microbe combinations to deliver one indicator that is representative of the sum of drug resistance. This aggregate measure communicates the overall efficacy of a selection of antibiotics used in the treatment of a particular pathogenic microbial infection. As an illustration, a geography with a combination of high antimicrobial consumption per capita and low rates of AMR to the most commonly prescribed antimicrobials would not have a high DRI. The converse would also hold true: a geography with a combination of low antimicrobial consumption per capita and high rates of AMR to the most commonly prescribed antimicrobials would have a high DRI.[29] Suboptimal levels of antibiotic effectiveness in LMICs indicated by higher DRI numbers may be symptomatic of a deeper systemic and structural problem: reduced access to newer antibiotics. Unsurprisingly, richer countries (eg: Denmark, Sweden, Finland, Norway, Canada) had the lowest DRI numbers. LMICs had the highest DRI numbers, which means that antimicrobial therapy efficacy is the lowest in the geographies with the highest need.[30]

Upcoming areas of concern: AMR in HIV, Malaria and Typhoid

A significant portion of AMR comes from three communicable diseases that are prevalent in a large part of the population worldwide: HIV, malaria and typhoid.

HIV

In 2019, the number of people living with HIV (PLHIV) was 38 million. Data for June 2020 shows that 26 million PLHIV were able to access antiretroviral (ARV) drugs. ARVs have been a huge success story, having saved millions of lives over the past decade. The massive scale up in the access to ARVs has also resulted in the predictable phenomenon of increased resistance to ARV medications. The WHO has categorised HIV drug resistance into three categories: Acquired HIV drug resistance, transmitted HIV drug resistance and pretreatment HIV drug resistance.[31] Acquired HIV drug resistance develops in the course of ARV treatment. Transmitted HIV drug resistance occurs with infection with drug resistance mutation containing strains. Pretreatment HIV drug resistance develops in ARV naive patients being started on ARV treatment or in patients with previous ARV drug exposure being started or restarted on first line ARV treatment. The WHO HIV drug resistance report of 2019 states that twelve out of the eighteen countries (Zimbabwe, Argentina, Eswatini, Uganda, Cuba, South Africa, Guatemala,

Papua new guinea, Honduras, Nicaragua, Namibia and Nepal) had prevalence of AMR greater than 10 percent for non-nucleoside reverse-transcriptase inhibitors (NNRTIs). Two commonly used NNRTIs are Nevirapine and Efavirenz. Significantly, AMR to NNRTIs in females was double that in males. Also, AMR to NNRTIs was three times higher among patients who had received ARV treatment previously.[32] Taking cognisance of these developments, the ARV guidelines issued by the WHO in 2018 called for a quick change to Dolutegravir (DTG) based regimens as the first line treatment across all age groups. This update was made in the national level guidelines and program documents of all countries where the prevalence of AMR was greater than 10 percent for non-nucleoside reverse-transcriptase inhibitors (NNRTIs). There is no data available on the extent to which the updated guidelines have been implemented. Previous experiences suggest that the probability of the operational transitioning to updated guidelines and new recommendations being incomplete is very significant. A pertinent example is the 2013 recommendation for the switch to DTG based regimens for infants and children: As late as 2017, the switch had not happened for 77 percent of infants and children across the world; they were still being administered Nevirapine as first line treatment. This was because the child friendly alternative was in short supply. It is evident that public healthcare administrations will need to focus on surveillance for HIV AMR which will be the basis for the evidence based updation of policies and guidelines. A significant portion of the success will also depend on ensuring access to the latest recommended treatment options.[33]

Malaria

The evidence is very clear that international action on Malaria in the last two decades has been a great success. However, there has been a plateauing since 2015. The WHO's Global Malaria strategy had set targets for 2020 for reduction in Malaria prevalence and mortality: the data suggests that these targets were missed by 37 percent and 22 percent respectively.[34] The march towards elimination of malaria is incumbent on the functioning of a high quality Malaria AMR surveillance system that would pick up AMR to common antimalarial drugs. Artemisinin resistance surveillance on a large scale has been enabled by the discovery of a molecular marker - kelch1325 domain gene (K13), for Plasmodium falciparum that is artemisinin-resistant. This is a vast improvement on the earlier technology of parasite clearance studies. The first documented cases of partial resistance to artemisinin combination therapy (ACT) were in 2008 in Asia in Cambodia and Thailand. A decade down the line, South East Asia remains the hotbed of artemisinin partial resistance.[35] It is interesting to note that despite the high prevalence of artemisinin partial resistance in this region, the Global Malaria Strategy has managed to bring about a dramatic reduction in the number of cases reported between 2000 and 2019: 97 percent reduction in cases of P. falciparum malaria and 90 percent reduction in all malaria cases. AMR to ACT is not a concern yet in Africa. If AMR to ACT does appear in Africa, the probability of it having a disastrous impact is very high. Therefore there is a need for heightened surveillance. The African data shows failure rates for first line treatment for the most prevalent type of malaria (Plasmodium falciparum) at less than 10 percent.[36]

Typhoid fever

The annual incidence of Typhoid fever is estimated at between 11 million and 20 million cases. The annual mortality from Typhoid fever is estimated at between 128,000 to 161,000 deaths. Populations that lack dependable potable water supply and that do not have minimum acceptable levels of sanitation face high levels of risk for morbidity and mortality from Typhoid fever.[37] The risk is magnified even more in children. Typhoid fever treatment has become more complex because of the increase in prevalence of AMR to Salmonella typhi. This has been further compounded by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. These developments have necessitated the prescriptive use of the newer generations of antibiotics in regions with high burden of

Typhoid fever.[38] Among the newer antibiotics prescribed are azithromycin and cephalosporins. If AMR is treated suboptimally, transmission of typhoid fever can increase by prolonged shedding of bacteria, increasing prevalence of complications and incidence of mortality. From 2016 to 2018, Pakistan witnessed the outbreak of an XDR strain of Salmonella Typhi which was resistant to all lines of treatment. There was international concern over its potential to spread globally. The source of the outbreak was drinking water that had been contaminated. This outbreak brought to the fore the potentially catastrophic consequences of vaccine hesitancy. A conjugated vaccine for Typhoid was approved by the WHO in 2017 for children aged more than 6 months. This vaccine has 3 objectives: Reducing disease burden of typhoid fever, reducing antibiotic use and reducing AMR in Typhoid treatment.[39]

Conclusion

There was a worldwide effort to control AMR in the decade of 2010-2020. The pandemic has served as a harsh reminder of the potential of infectious disease for economic and social damage. Progress on AMR has also been adversely affected by the pandemic. The problematic area of antibiotic use for viral infections continues to exist. AMR rates for drugs usually prescribed for common infections remains significantly high. Of particular significance is emerging resistance to first line antibiotics in the bacteria responsible for Malaria, Typhoid and AIDS. This development threatens global advancement on key health indicators. This is especially pertinent for the emerging economies of the Low and Middle Income Countries (LMICs). A hugely influential variable in this development of AMR is the unscientific excessive prescription and wrong prescription of antibiotics in clinical settings. This harmful behaviour is more prevalent in the unregulated, underserved environments of the LMICs. International antibiotic consumption is accelerating on the back of increased availability and falling prices. In the 15 year period from 2000 to 2015, consumption of antibiotics classified as critical for human health by the WHO saw an increase of 91 percent globally and 165 percent in LMICs. Despite the availability of vaccines against several infectious agents, substantial parts of the population, especially in LMICs, remain prone to illness, thereby furthering their dependence on antibiotics. This is perpetuated by the twin factors of low vaccine coverage and poor quality water supply and sanitation. To overcome these barriers, governments will need to scale up investments in vaccine coverage and water and sanitation. An initiative that could prove to be a game changer in the battle against AMR is the implementation of the philosophy of antimicrobial stewardship.

The requirement for antibiotics in both humans and animals can be curtailed through the effective implementation of a three pronged approach that includes clean potable water and sanitation, reduction in incidence and prevalence of infections and enhanced vaccination coverage. Of critical importance will be to challenge and change the twin narratives of antibiotics being a cheap tool to combat illness and there being no unpleasant impact on populations. This will require strong ownership from government and regulatory bodies. Without laws to tackle this growing problem, AMR control will remain a pipe dream.

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