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Impact of Convergence of Antimicrobial Resistance (AMR) and COVID-19 on Population Health, Actions to Improve Health Outcomes

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ABSTRACT

Antimicrobial resistance (AMR) is a continuously growing and substantial threat of the twenty-first century to global health and development and its convergence with the current COVID-19 pandemic poses even a worse impact to population health. This viewpoint focuses on combined impact and determinants of AMR and Covid-19 on population health. Furthermore, it outlines potential procedures and interventions to moderate the burden of worldwide AMR in current and future pandemics.

Keywords: *Antimicrobial resistance; Covid-19; Health; Impact*

INTRODUCTION

Antimicrobial resistance (AMR) is emerging as a global public health risk. Bacterial AMR accounted for estimates of 1.27 million deaths in 2019. Reportedly AMR affects all the countries but the low- and middle-income countries are most affected. AMR jeopardizes several of the advances in contemporary medicine.[1] AMR not only causes death and disability but also has large economic repercussions.[2]

In the year 2019, the World Health Organization published a list of ten major threats to global health. The list included a range of diseases and conditions such as vaccine preventable diseases, increasing antimicrobial resistant (AMR) pathogens, increase in physical inactivity and obesity, impacts of change in climate and environmental pollution on health and several humanitarian crises. The report also predicted an influenza pandemic that will occur soon with serious threats to global health.[3] Three years later after the WHO report, The Lancet Commission on 21st-Century Global Health Threats reported that the three Cs: climate change, COVID-19 and Conflict along with increase in obesity, aging population, food insecurity and antimicrobial resistance (AMR) are currently threatening achievements of the past seventy years in global health.[4]

Antimicrobial resistance (AMR) and its health and economic impact

Antimicrobial resistance (AMR) is a phenomenon that arises when disease-causing bacteria, fungi, parasites and viruses change themselves over a period and no longer respond to the medicines. With the increase in AMR, existing antimicrobial drugs like antibiotics, antifungal and other drugs become ineffective to treat infections. This phenomenon leads to the creation and global spread of an antimicrobial resistant bacteria also called "superbugs".[5] These superbugs and their genes have capability to spread among people in hospitals, primary care centers, home for aged care and in the community rapidly and even unnoticed.[6] The impact of increasing AMR is reflected not only in increased duration of hospital stay, disability and deaths, but also in increase in treatment costs. A review "Tackling Drug-resistant Infections Globally" chaired by The Lord Jim O'Neil

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estimates that there will be 700,000 deaths annually due to pathogens resistant to antimicrobial drugs and the death toll may reach up to 10 million annually by year 2050 with visible disparity in distribution of death among high and low-middle income countries.[7] The inequalities are not limited to health outcomes among rich and poor countries, but it hits the economic growth of these countries in similar fashion. Underdeveloped and developing countries will face more economical challenges that will advance social inequality. Experts have predicted a loss of 1.1%- 3.8% of the global annual gross domestic product as a result of growing infection due to AMR pathogens by 2050 and forcing 24 million people from low-income countries into extreme poverty by 2030.[8] While the alarming health and economic impacts of AMR are clear, it is important to understand the determinants of this issue to describe the current context, their interrelation with other threats to global health, e.g. COVID-19 and gain novel insights for current and future mitigation processes for this progressive problem.

Determinants of AMR in COVID-19 pandemics

Antimicrobial resistance is a process that occurs naturally but the acceleration of this process by excessive and inappropriate use of antimicrobial agents has created a serious threat to the world. This part of the article focuses on how the major determinants of AMR and COVID-19 inter played directly or indirectly with each other. It also further explores their bidirectional effect to each other; most of the time, COVID-19 fuelling AMR and sometimes the devastating effect of already existing AMR on health outcome of those with COVID-19.

Inappropriate prescribing and use of antimicrobial

One of the greatest achievements of medical science in the 20th century was the introduction of antibiotics into clinical practice. Antibiotics have contributed to an increase in average life expectancy throughout the world, especially by helping children to survive into adulthood.[8] Whereas, in resource poor countries where sanitation is still an issue, antibiotics contribute to decrease the infection related morbidity and mortality.[9] While the global burden of diseases data suggests that the battle against the infectious diseases is still far away to win, the precious antimicrobial drugs started to develop resistance. According to an estimate, infections are still a cause of 17 million deaths per year.[10] Along with many other factors, the leading cause for antimicrobial resistance is inappropriate prescription and use of antimicrobial drugs across the globe. While in developing countries, AMR is causing deaths often due to unavailability of affordable and appropriate antimicrobial drugs, it is a bitter truth to note that at least 50% of the antimicrobial agents currently used worldwide are inappropriate and unnecessary.[11] While inappropriate use of antimicrobial agents has always been the key factor for development of AMR, the recent COVID-19 pandemic has further fuelled this practice. In the paragraph below, few facts that have accelerated AMR through irrational use of antimicrobial agents while managing COVID-19 cases have been examined.

There has been a tremendous affinity of health workers to treat COVID-19 cases with antibiotics despite a comparatively low proportion of proven secondary bacterial infections. One of the studies confirms that 72% of the COVID-19 cases were treated with antimicrobial agents when only 8% of them had proven bacterial or fungal infection and the rest of them were mild COVID-19 cases.[12] Data from a hospital-based study in Wuhan reveals that 95% out of 191 admitted patients received antibacterial treatment and only 21% of them received antiviral therapy.[13] The American CDC estimated an increase in antibiotic resistance (AMR) by 15% within a short period between 2019-2020 during COVID-19 pandemic. It resulted in 29,400 extra deaths due to so-called "superbugs" infection, 40% of which were acquired from the hospitals.[14] If this trend of inappropriate use of antibiotics continues, it will expedite the growth rate of AMR. It is obvious from the data of antibiotic uses during COVID-19 pandemic that this process has already been sped up.

Disruption of health services

Due to COVID-19 after the recommendation of WHO, countries worldwide executed different prevention and control measures to fight against the transmission of COVID-19 virus. These included quarantine, hand hygiene, social distancing, contact tracing, travel restriction, closure of schools and lockdown. However, these instruments were applied to prevent virus transmission, they have unintentionally affected several public health programs e.g. disease prevention and health promotion activities, outpatient clinical services, mass campaigns, and activities related to management of public health priority diseases and AMR related activities. Human resource and budget were diverted to COVID-19 related activities thus affecting the rest of the health system functioning.[15] During the COVID-19 pandemic, there has been disruption in health care service provision at each level. COVID-19 has imposed changes in the shape of the organizations that provide services and at the same time in consumer's service seeking behavior.

While AMR prevention, surveillance, and monitoring activities are mostly attached to healthcare services, disruption of these services will shape the future of AMR burden and impact.[16] This evidence shows that this change in service provision and service seeking behavior will further expose the population to antimicrobial

resistance and adversely affect their health outcomes. There has been evidence of disruption of few vital health care services that has further fuelled AMR.

Immunization program

Prevention of infectious diseases at the population level decreases the transmission of AMR genes, which can be achieved by routine and periodic immunization activities.[17] However, during the COVID-19 pandemic there was a discontinuation of the routine vaccination program worldwide. Among the population, there was a fear of contracting COVID-19 while attending immunization clinics and at the same time the supply side was unable to provide service adequately that resulted in global vaccine coverage reduction.[18] Global data suggests that the diphtheria, pertussis and tetanus (DPT) vaccine third dose administration to children decreased by 33% in the first half of 2020 compared to 2019.[19] Vaccines decrease the use of antibiotics by preventing infectious diseases. It is therefore an important instrument to decrease the burden of AMR.

The adverse impact of COVID-19 on immunization services will lead to more cases of diseases that are preventable by vaccination and complications associated with these diseases, which will further motivate the use of antibiotics and create a favorable environment for development of AMR.[20] The level of impact for this effect also varies among countries with higher, low, and middle-income. The decline in vaccine coverage is higher among countries with low-income and poor health systems that poses an increased chance of outbreak of diseases, hence increasing the use of antibiotics, AMR and inequality in health outcomes.[21] Similarly, studies have shown that people vaccinated with COVID-19 vaccines were at lower risk of developing secondary bacterial infection and less use of antimicrobial, contributing to lower the AMR risk.[22] However, when high-income countries were stockpiling vaccines for booster dose, low and middle-income countries were deprived of COVID-19 first dose, making them more vulnerable for developing secondary bacterial infections, use of excessive antimicrobial and contributing to the growth of AMR.

High income countries should treat COVID-19 vaccines as global public health good and donate them to the most resource-constrained countries to eliminate the inequity in vaccine access and make the world safer.[23]

COVID-19 pandemic, TB, HIV, and AMR

COVID-19 pandemic has added challenges in management of diseases of public health priority like tuberculosis (TB) and HIV. The difficulties in direct observed treatment strategy (DOTS) for tuberculosis caused by highly drug resistant pathogens has facilitated the spread of antimicrobial resistant (AMR) bacteria causing tuberculosis (TB) and there is a high possibility of missing many cases.[24] A modeling report by Stop TB Partnership, Geneva estimates 1.4 million additional deaths due to tuberculosis in a period between 2020 and 2025 as an effect of COVID-19 on TB management.[25] Similarly, patients living with HIV (PLWH) are at high risk of infection with antimicrobial resistance pathogens. Studies suggest that PLWH are more susceptible to resistant strains of bacteria as compared to those without HIV infection.[26] Uninterrupted healthcare services should be provided to people living with HIV to lower the transmission of HIV, stabilize the viral suppression status, improve clinical outcome by promptly treating any coinfection with AMR and expand lifespan.[27] Unfortunately, the prevalence of AMR due to interruption in services, largely due to COVID-19 pandemic, is higher in low-income countries. These countries have limited resource and treatment options to combat these resistant pathogens and play a vital role in further spread of AMR.

Disruption of lab activities and AMR surveillance during COVID-19

Along with other health care services, COVID-19 has also affected diagnostic laboratory services, routine surveillance, and screening activities for antimicrobial resistant pathogens. According to a survey conducted by the WHO Antimicrobial Resistance Surveillance and Quality Assessment Collaborating Centres Network, 67% of the participating countries admitted limited activities for AMR surveillance, prevention as well as control. One of the major causes for reduced activities related to AMR during COVID-19 pandemic in low and middle-income countries was decrease in financial resources.[28] This irregularity of AMR related activities during COVID-19 pandemic would result in excessive transmission of resistant pathogens within the healthcare system and beyond. This can be evidenced by the fact that about half of the deaths in COVID-19 patients were associated with bacteria and fungi among which there were AMR pathogens.[29] It is therefore important to continue routine surveillance and monitoring activities according to the antimicrobial stewardship (AMS) framework to be vigilant on occurrence of AMR and find the ways forward to prevent and spread of AMR pathogens.

Excessive use of antimicrobial and biocides in other one-health sectors

It will not be correct to blame only the human health sector for creating the AMR crisis, but other health stakeholders from "One Health" should equally take the responsibility of this burden. Other non-health sectors include veterinary, agriculture, and food production.

The contribution of these sectors may even contribute more than human health in creation of AMR. The interesting fact shows that almost 50% of the antibiotics produced in the United States of America is utilized in

the livestock sector.[30] Adding to this, out of the 700 tons of antimicrobial agents imported in Australia, 78% (550 tons) is consumed in the livestock sector to increase the rate of weight gain and treatment of infections.[31]

It should also be noted that in case of any outbreak in livestock, farmers tend to treat all animals rather than treating the infected ones. This further adds the risk of development of AMR pathogens in livestock sectors and unfortunately, some of these AMR pathogens have capability of transmission to humans making them ill.[32] Animal sector along with human hygiene and sanitation sector use biocides (antiseptics, disinfectants and sanitizers, etc.) which also contribute to development of AMR pathogens. The excessive use of hand sanitizer during COVID-19 pandemic for hand hygiene may help dangerous spore forming bacteria to survive and create even more resistant pathogens.[33] It is therefore important to work through the "One Health "initiatives for the prevention and control of AMR"" across all sectors.

Scarcity of new antimicrobial drugs

The AMR growth rate had a steady rise, and the current COVID-19 pandemic has fuelled the process by creating a good ground for misuse of antimicrobials and contributing to develop more antimicrobial resistant pathogens worldwide. Even though AMR is an increasing global threat, there has been a lack of interest among pharmaceutical companies to research and develop new antibiotics.[34] Drug manufacturing companies consider that the outcome of investment in research and development of new antibiotics is poor as they are used for a shorter time as compared to the drugs for treatment of non-communicable diseases.[35] If this scenario continues, we will soon be in the situation of the pre-antibiotic era, where no existing antimicrobial will be effective to treat infectious diseases. It is recommended that global leading health organizations, regulatory bodies, and bureaucratic channels should work together with pharmaceutical companies to facilitate the development of new stronger antibiotics that will help us to fight against the current and emerging superbugs.

Actions to improve health outcomes

The World Health Organization on May 5, 2023, declared COVID-19 as an ongoing health issue and it is no longer a public health emergency of international concern due to COVID-19 pandemic (PHEIC). While the world is preparing to overcome the several other devastating impacts of COVID-19 pandemic, it is even more important to be prepared for the ongoing and future impacts of this pandemic on antimicrobial resistance. It is now understood that inappropriate use of antimicrobial agents and biocides in human and other one-health sectors along with disruption of essential health services during the pandemic have a disastrous impact on AMR related activities.[36] The spectrum of the problem, which extends beyond the health sector, requires an approach that incorporates the one health concept. In this context, antimicrobial stewardship (AMS) can provide a long-term comprehensive solution to the AMR issue. Antimicrobial stewardship, as defined by Dyar et al., Is "A coherent set of actions which promote the responsible use of antimicrobials. This can also be applied to actions at the individual level as well as the national and global level, across human health, animal health, and the environment".[37] AMS is a multidisciplinary and collaborative approach, which involves healthcare leaders, physicians, nurses, infectionists, clinical pharmacist, veterinarians, farmers, and IT experts to minimize development of AMR and improve treatment outcome and patient safety.[38] The involvement of health and non-health stakeholders reflects the one health approach in AMS. They can communicate and work together to formulate and implement policies, programs, legislation, and research for better public health outcomes.

AMS aligns with the principle of universal health coverage (UHC) to provide equitable and quality health care through infection control and prevention, patient safety, AMR surveillance and adequate and affordable supply of quality medicines. AMS also includes the core elements of WHO global action plan on AMR and there has been a recent recommendation from WHO to include AMS interventions in the COVID-19 response programs. However, current evidence speaks that AMS has been successful particularly in developed countries, which demands an implementation of an effective AMS program at resource constrained settings.[39] There is also a need for expansion of AMS activities from hospital-based to community level as the antimicrobial misuses at the community may impact hospitals and vice versa. Health promotion activities (awareness programs and campaigns on use of antimicrobials) should be conducted in the community as well as incorporated in the school curriculum.

WAY FORWARD

WHO has defined AMR as one of the top 10 threats to global health in the 21st century. At the same time, the recent COVID-19 pandemic has fuelled the AMR growth rate, the true effect of which is yet to be seen soon. The AMR has escalated due to various reasons, such as inappropriate and excessive use of antimicrobial agents and biocides in human and other non-human sectors, disruption of the vital health services, envisioned to tackle AMR burden, inequity in access to COVID-19 vaccines in low and middle-income countries, and diversion of resources for AMS activity to prevention and control of COVID-19. While COVID-19 is not the last pandemic to hit humankind as well as AMR, it is therefore important

to establish better global coordination among leading health agencies and governments to develop relevant guidelines and protocols to combat future pandemics, facilitate to develop stronger antimicrobial against upcoming powerful superbug and make them available to all in affordable price , give access to global public health goods in equitable manner, share the technology beyond borders for the benefit of the humanity.

As the issue of AMR extends beyond the health sector, it is equally important to educate communities and coordinate with other stakeholders through the principles of one health within the country and across the globe also priority setting, antimicrobial stewardship and people centered approach may be the great milestone in tackling this silent pandemic. The AMR superbug does not recognize international borders. It is therefore important to help each other in the fight against AMR, as no one is safe until everyone is safe.

CONFLICT OF INTEREST:

None

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