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Examining antimicrobial resistance in the light of the COVID-19 pandemic

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The AMR crisis

As the world struggles to control and slow down the COVID-19 pandemic caused by a novel coronavirus, SARS-CoV-2, it is clear that it is probably one of the most severe global health pandemics in our recent history. Infectious diseases have become a lot less common thanks in part to the improvements of sanitation, availability of immunizations and the introduction of antibiotics. These interventions have reduced the morbidity and mortality of many infectious diseases and have contributed to social and economic progress.[1] However, the COVID-19 pandemic has shown how vulnerable our health systems are even in the most well-resourced countries of the world. This vulnerability comes in part because there are no effective therapies that can treat, prevent or cure COVID-19. Therefore, countries have had to implement public health measures based on what is known from previous epidemics, such as strategies for infection prevention and control, physical distancing, using masks and hand washing as the main tools to help prevent further spread. Furthermore, this has also meant that clinicians have been using existing antimicrobials and antivirals as part of clinical trials, as prophylaxis and as supportive therapy in the hope that they may help patients recover.

The situation that the pandemic has brought about is, unfortunately, similar to what is happening at a slower pace due to antimicrobial resistance (AMR). Today, there are more and more cases of infections

Abstract

The COVID-19 pandemic provides an opportunity to strengthen the capacity of health systems not only to be better prepared for the next pandemic but also to address ongoing crises such as antimicrobial resistance. The unfolding crisis due to antimicrobial resistance is, unfortunately, similar to the current health crisis due to the COVID-19 pandemic, albeit at a slower pace. As countries address the pandemic, there is a need to identify interlinkages between the pandemic and antimicrobial resistance and to continue strengthening the actions needed to slow down the emergence of antimicrobial resistance.

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La pandémie de COVID-19 fournit une occasion pour renforcer la capacité des systèmes de santé non seulement à être mieux préparés pour la prochaine pandémie mais aussi à faire face à d'autres crises en cours, telle que la résistance aux antimicrobiens. La crise liée à la résistance aux antimicrobiens est malheureusement similaire à la présente crise sanitaire due à la pandémie de COVID-19, bien qu'à un rythme plus lent. Alors que les pays s'attaquent à la pandémie, il est nécessaire d'identifier les liens entre la pandémie et la résistance aux antimicrobiens et de continuer à renforcer les actions nécessaires pour freiner la résistance aux antimicrobiens.

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La pandemia de COVID-19 ofrece la oportunidad de fortalecer la capacidad de los sistemas de salud no sólo para estar mejor preparados para la próxima pandemia, sino también para hacer frente a las crisis actuales, como la resistencia a los antimicrobianos. La crisis que se está desarrollando debido a la resistencia a los antimicrobianos es, lamentablemente, similar a la actual crisis sanitaria debida a la pandemia COVID-19, aunque a un ritmo más lento. A medida que los países abordan la pandemia, es necesario identificar las interrelaciones entre la pandemia y la resistencia a los antimicrobianos y seguir reforzando las medidas necesarias para frenar la aparición de la resistencia a los antimicrobianos.

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that are no longer responding to the treatments available because pathogens are becoming resistant to the existing antimicrobials and creating what sometimes is referred to as "superbugs". This slow pandemic is gradually undermining the capacity of health systems to respond to infections[2] because antimicrobials are an essential tool to cure such as a simple throat infection, to enable more complex medical procedures such as surgeries and also such as to be able to provide cancer chemotherapy.[3] The United Nations (UN) Interagency Coordination Group (IACG) on antimicrobial resistance in its final report delivered to the UN Secretary-General in 2019 warned that: "Drug-resistant diseases already cause at least 700,000 deaths globally a year, including 230,000 deaths from multidrug-resistant tuberculosis, a figure that could increase to 10 million deaths globally per year by 2050 under the most alarming scenario if no action is taken."[4] As countries address the COVID-19 pandemic, they must continue to implement many of the measures in place to slow down the emergence of antimicrobial resistance.

There are multiple reasons for the increase of antimicrobial resistance, including the overuse and misuse of antimicrobials in health care settings but also their use in food production and aquaculture. The figure below provides information about some of the drivers of antimicrobials resistance including how the misuse and overuse in humans, animals, food production and the environment have an impact on morbidity and mortality but also on food production and in the economy.

Antibiotic use in the treatment of COVID-19 and secondary infections

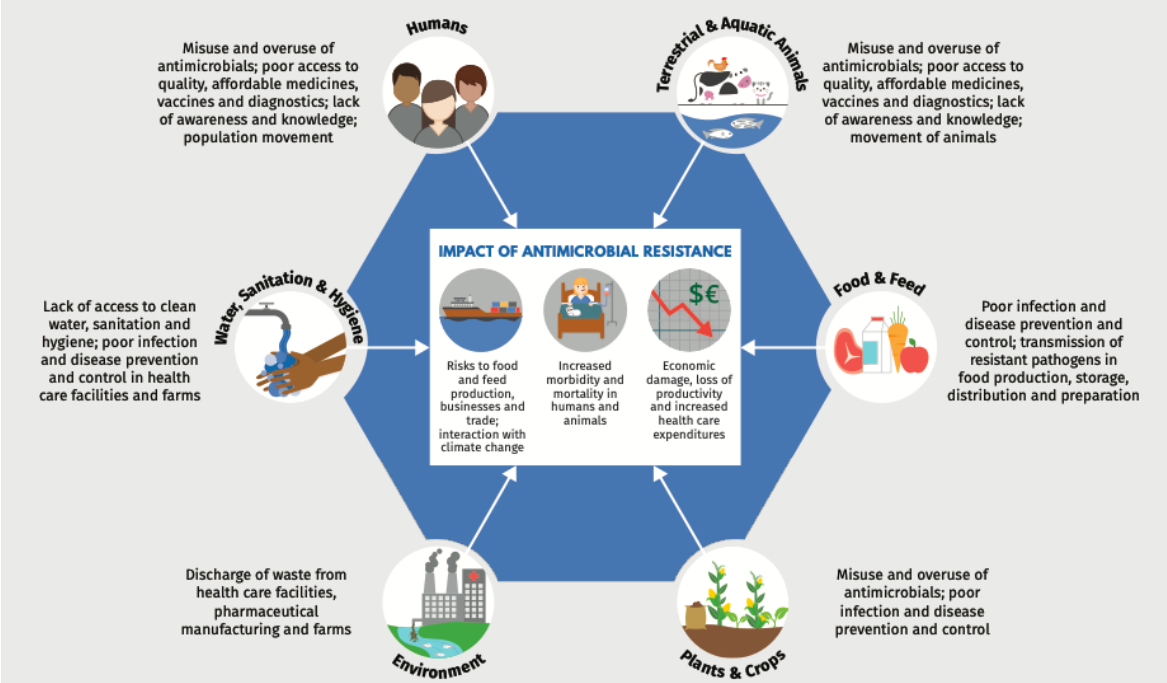
COVID-19 is caused by the SARS-CoV-2 virus for which antibiotics (antibacterials and antifungals) are not known to be effective for. Multiple studies are underway in over 50 countries to try to determine effective treatments for COVID-19, and there is a desperate need to find an effective therapy and vaccine.

In the initial phases of the pandemic, little was known about the virus and its symptoms, and bacteria were thought to play a role in the illness. However, even after weeks into the pandemic and the publication of several reports describing the disease, clinicians have continued prescribing antibiotics as part of their routine care in the severely ill and in some patients with mild and moderate symptoms.

The majority of hospitalized patients continue to receive broad-spectrum antibiotics, where a very small minority (less than 10%) have a bacterial co-infection or secondary bacterial infection where antibiotics are effective and an optimal therapeutic intervention.[6] It is very well established that indiscriminate antibiotic use leads to a rise in resistance.[7] Therefore, this practice threatens to roll back years of effort to establish stewardship programs to improve antibiotic use and manage antimicrobial resistance rates.[8]

It is crucial that the available evidence is considered in the development of national guidance and education for COVID-19 and that the prescriptions of antibiotics for COVID-19 are discouraged unless there is suspected bacterial infection. The latest World Health Organization (WHO) Clinical Management for COVID-19 interim guidance published in May 2020 advises against the use of

Figure 1: Drivers of antimicrobial resistance



Source: *No Time to Wait: Securing the future from drug-resistant infections*[5]

antibiotic therapy for suspected or confirmed mild COVID-19, and in the case of suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection.[9] The pandemic has evolved very rapidly, while data and research into effective treatments take time. This has led some experts to suggest a variety of repurposed drugs they consider to be effective for COVID-19 such as the antibiotic azithromycin in combination with the antimalarials hydroxychloroquine or chloroquine. Such claims were based on previous knowledge from the initial SARS epidemic, and a very heavily publicized small study and which led the public and medical professionals to use it indiscriminately.[10] The combination has led to significant adverse events in multiple patients globally. At this point, the long-term effect of the overuse of these two drugs on antimicrobial resistance remains to be determined but is likely to be detrimental.

Shortages of health technologies including antibiotics

The COVID-19 pandemic magnitude has shed light on significant global shortages of health technologies, including diagnostics, personal protective equipment, to be used by health workers to protect themselves from infection while caring for patients, as well as various drugs including antibiotics.

While discussing COVID-19 diagnostic testing shortages specifically, it is worth noting that the Polymerase Chain Reaction (PCR) test, which is the most widely used and recognized for diagnosis, relies on laboratory equipment but also on collection kits and reagents. Those have been in limited supply in various countries, including some high-income countries, significantly limiting the ability to test widely. The implications of the unavailability of testing for COVID-19 and the uncertainty in diagnosis have resulted in an increase in antibiotic use in patients with undifferentiated respiratory illnesses and pneumonia.

Supply chain disruptions in the hardest-hit countries became apparent and had a downstream effect globally. This was due to closure of manufacturing facilities during lockdowns, quarantined and ill workers, as well as disruptions in the transportation routes. Additionally, some countries have restricted the export of medical products, drugs, laboratory supplies and other health technologies.

The pandemic has shown that the antibiotic supply chain globally is weak and heavily relies on Active Pharmaceutical Ingredients (APIs), which are the prerequisites for manufacturing final pharmaceutical products such as antibiotics. A very large proportion of APIs is manufactured in China, which was hard hit by COVID-19 early on, in addition to manufacturing in India, who is currently in the containment phase of the virus. While India had instituted restrictions on exports of drugs initially[11], it has lifted restrictions on twenty-four drugs, including antibiotics, in April to allow such exports "in appropriate quantities" to neighboring countries and those severely hit by COVID-19.[12] Antibiotic shortages from all the WHO categories "Access, Watch and Reserve"[13] have been observed in many countries.[14] Issues around the supply of the 'access' category antibiotics have already been observed before the pandemic and could be exacerbated under the current conditions[15]. Unavailability of quality assured antibiotics can lead to patients receiving suboptimal treatment and broader antibiotics than necessary, fueling an increase in antimicrobial resistance and adverse effects.

The strengthening of national supply chains and global coordination to ensure access to quality-assured antibiotics, diagnostic tests and personal protective equipment for health workers is a must during the COVID-19 pandemic and beyond.

Surveillance

Surveillance is critical in responding to epidemics and pandemics in a timely manner because it can provide crucial data that helps public health authorities in taking timely decisions and designing policies. Surveillance helps with understanding the disease we are dealing with, causative organisms, factors that encourage the spread, severity, estimation of disease burden, monitoring the spread, disease changes and intensity[16]. Through surveillance, we are also able to monitor existential threats of antimicrobial resistance that lurks behind the pandemic. Antibiotic use tends to go up due to secondary infections, as we are currently seeing with COVID-19. Some studies are reporting an increase of up to 75% in antibiotic prescribing; therefore, data on the use of antibiotics would be needed to better assess the situation. For countries and the global community to respond effectively and timely, surveillance that produces reliable and accurate data is key to feed into the public health infrastructure.

Countries need robust surveillance systems that would systematically collect large volumes of data, and analyze it to inform rapid decision making. During pandemics, more people get sick and die, and more resources are needed. It is thus important to collect data timely to allow for evidence-based decision making. Critical decisions to be made include human resources required and allocation, material needs, beds in intensive care units (ICU), medical supplies, treatments, whether lockdown is necessary or not, in-service training of clinical staff, among others. Some of these decisions impact on socio-economic, cultural and environmental constructs of society.

Pandemics provide many challenges, which include dealing with the current problem while at the same time preparing for the next one and this requires more resources. This requires investing in robust and resilient surveillance systems that require trained human resources, quality labs to identify causative organisms we are dealing with, rapid diagnostic tests, quality-assured medicines and secure integrated information systems. Both routine surveillance as well as disease-specific sur-

veillance are critical during a pandemic.

However, most developing countries are challenged with low-resourced health systems that are not equipped to deal with pandemics while continuing to provide routine care. Laboratory infrastructure is often a challenge and so is their capacity to carry out diagnostic tests. Consumables such as reagents are often not available and for most developing countries, this is due to lack of financial resources and dependency on importation as most of these commodities are not produced locally. Sometimes even where labs are available and can conduct lab tests, clinicians often doubt the validity of the tests. This could be because of questioning the capacity of the staff, the test itself, fear of cross-contamination, including the clinical picture.

Countries thus need to continue providing training, have standards and competencies in place, do forecasting and strengthen their supply chain systems. Undergraduate curriculums may need to be strengthened to include training on pandemics and response. The current situation wherein most airports are closed, and imports cannot come into a country could cause more morbidities and mortality.

Investment into E-Systems that are integrated is also very important as many pieces of data collected need to be collected timely and aggregated to allow for analysis. Currently, most surveillance systems are paper-based, and data is collected from individual health facilities about suspected and confirmed notifiable diseases and associated mortalities. This data is then sent to the district or provincial level before being reported to the national surveillance system.[17] Delays in this process can be counterproductive in a pandemic response.

The current confirmed cases of COVID-19 in most developing countries, such as the case in the African region, have been far less than what has been seen in Europe and North America. One of the reasons is that few tests have been done, so the true extent of cases in Africa will never be known. This calls for further investments into research and development to support surveillance systems that are adequate for low resource settings.

Pandemics require the sharing of surveillance data not just within the country but between countries and with intergovernmental organizations such as the World Health Organization. This requires that standards are created for the collection of data to assure quality, help with analysis, and feed into decision making.[18] Regional and global data would be useful for coordinated response and resource mobilization.

Infection Prevention and Control

Infection prevention and control (IPC) is critical in both preventing and reducing the spread of COVID-19 and many other infectious diseases. Unfortunately, IPC practices are weak in several developing countries and under-resourced in the health sector. WHO and the United Nations Children's Fund (UNICEF)'s report for 2017 noted that 2 billion people had no access to basic sanitation facilities, with 1.2 billion people estimated to be drinking water with contaminants such as feces[19]. They also reported that 1 out of 4 healthcare facilities lacks running water, a recipe for the spread of hospital-acquired infections. Basic universal health precautions would go a long way in preventing the spread of COVID-19. Washing stations are often away from patient care areas. Hand sanitizers are often not found in many health facilities.

To expect health care facilities with no running water to contain COVID-19 and other hospital-acquired infections is hoping for what cannot be achieved. Water provision is a major challenge, for example, in Africa where 42% of all health facilities lack improved water sources at the facility[20].

Proper handwashing and wearing adequate protection equipment can reduce the spread of COVID-19 significantly. The United States Centers for Disease Control and Prevention (CDC) recommends interventions for reducing facility risks, isolation of symptomatic patients and protecting health care workers such as by providing handwashing facilities and personal protective equipment (PPE - facemasks, gowns and gloves)[21]. Surveillance includes monitoring the spread of the disease and its intensity, which helps to understand better how severe the disease is, risk factors, transmission and in burden estimation.[22] COVID-19 has exposed improper practices regarding the washing of hands or the use of face masks and other personal protective equipment. Therefore, there needs to be more investment in the training of communities and health care workers on their proper use. This would also have an effect on preventing other infections and in reducing the risk of antimicrobial resistance. Efforts around the provision of safe, clean water should continue to be one of the major priorities for developing countries.[23]

Preventing hospital-acquired infections (HAIs) in health care settings should be a major priority for all countries and in strengthening biosecurity efforts. HAIs are one of the most significant problems in developing countries, causing more morbidities and mortality from hospital infections. They also contribute to increased health care costs. COVID-19 could spread very quickly in health care settings with poor infection prevention practices as hospitals have sicker patients with compromised immunities, making them easier targets for COVID-19.

Hospitals and other health care settings would need to have IPC resources available that include capacities to do antimicrobial susceptibility testing, PPEs, in-service training, standards, standard operating procedures (SOPs) and staff dedicated to IPC. This means that there is a need to invest in IPC, procurement and making these essential equipment available. There is also the need to increase training in IPC personnel for healthcare. There are few IPC nurses for most African countries, for example, who can manage IPC programs in hospitals and other healthcare settings. One recommendation that came from the expert panel in China was for increased provision of

IPC education and training[24]. To better respond to this pandemic but also to the increase in antimicrobial resistance, IPC needs to be strengthened as well as capacities to carry surveillance.

Access to new health technologies

The lack of effective treatments and vaccines has made the management of the COVID-19 pandemic especially challenging. Once the virus was identified, a race ensued to find appropriate therapies. The WHO has documented over 70 therapeutic candidates in different stages of clinical trials at the moment[25] and the WHO has documented over 100 preclinical candidate vaccines[26]. Within the therapeutic candidates, some front-running candidate medicines had been previously used for other purposes[27] but may potentially be effective in the treatment of COVID-19. However, when effective treatments or vaccines are found, the challenge will be how to assure their availability and affordability to everyone who needs it.

During the recent discussions at the World Health Assembly in May, Member States of the WHO expressed the need for collective action for the timely, equitable and affordable access to health technologies related to COVID-19, including future vaccines, medicines and diagnostics.[28] However, concerns of how this would be operationalized and the need for appropriate global governance structures have been expressed by many governments, experts and civil society organizations. Experts have also warned of preventing a similar situation of what happened during the HIV-AIDS pandemic. Once effective medicines were developed for HIV-AIDS, their high prices and their intellectual property (IP) monopolies made it almost impossible for patients in developing countries, even in the places with the highest burden of the disease, to access them.[29] The concern with ensuring access to health technologies has been expressed in many calls proposing that these are treated as global public goods.[30]

Other challenges will also need to be overcome for the products to be accessible. These include issues of production and supply capacity. MSF Access Campaign in their recent policy brief on COVID-19 therapies explained that some of those challenges include "the use of intellectual property (IP) and other exclusivities to restrict manufacturing and supply options, delaying competition that would lower drug prices and increase patient access. Market dominance, including monopolies held by pharmaceutical corporations through patents and other types of IP and regulatory exclusivities may prevent other manufacturers from increasing global manufacturing capacity. These exclusivities may also enable companies to charge high prices and profiteer from the pandemic or prioritise wealthier countries over ones with less financial capacity."[31] Because of how these challenges could hinder access, experts have called on governments to take policy and legislative measures that can ensure that patents and other intellectual property do not become barriers to access as well as to enact measures to facilitate local manufacturing of medical technologies.[32] These are not only measures that would need to be taken but are a way in which governments can start to address some of the challenges that would need to be considered as the world gets closer to developing effective treatments and vaccines for COVID-19.

Moreover, since governments and charities have been investing substantive funds in carrying out clinical trials and in the research process, the funding that has been made available this way should come with conditions attached that would ensure that the products of research and development do reach everyone and that pricing would not be a barrier for access.[33] Governments should also incentivize more openness, collaboration, and sharing of data during the research process. This would also require more significant global cooperation and support, especially to developing countries so they would be able to increase their production capacity so that the products are made available everywhere.[34]

Addressing the gaps in research and development (R&D) in the case of antimicrobial resistance also presents similar concerns as the ones exposed by COVID-19, especially on how health technologies will be made available and accessible to everyone who needs them. However, one of the differences is that the landscape for treatments and vaccines for antimicrobials does not look promising for what is required to treat multidrug-resistant infections. The report of the UN High-level Panel on Access to Medicines already pointed out that there is "inadequate investment in R&D for diseases for which the market does not provide sufficient financial return, as is the case for antimicrobial resistance."[35] In the case of antimicrobial resistance, the challenge is two-fold. First, how do we encourage research and development for novel products based on the areas of most significant health need, and second, once these products are available, how do we ensure they will be accessible to everyone who needs them. The global nature of antimicrobial resistance will require a global response to address these challenges.

In 2016, the United Nations adopted a political declaration on antimicrobial resistance which emphasized "that all research and development efforts should be needs-driven, evidence-based and guided by the principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility."[36] The declaration also acknowledged that one of the ways in which R&D could be incentivized as to implement the agreed principles is through "delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development".[37] The resolution advocates for thinking of models of R&D that would ensure that the products developed are available to whoever needs them. The emphasis on a model that delinks the cost from the price and volume is one of the only ways in which there could be an assurance that prices of new

medicines would be affordable and that high prices would not keep them out of reach of patients and health systems. These agreed principles should also ideally be part of the conditions for funding that governments and charities are providing to support COVID-19 innovation which is not the case at the moment.

The UN Interagency Coordination Group (IACG) on antimicrobial resistance in its report points out that "existing and future global access initiatives should promote and support equitable and affordable access to existing and new, quality-assured antimicrobials, diagnostics, vaccines, waste management tools and safe and effective alternatives to antibiotics for human, terrestrial and aquatic animal and plant health."[38] Furthermore, the report also emphasizes that "the benefits of scientific innovation in the response to antimicrobial resistance will be lost if new health products are not made available to everyone who needs them, and they are not used in a responsible and sustainable manner."[39] The report notes that equitable access needs to be a requisite in the search for new treatments and in the pursuit of stewardship.

The implementation of the principles of equitable and affordable access to health technologies as well as the designation of these as global public goods together with appropriate global governance structures that would be needed to operationalize them continue to be an open question in the case of COVID-19 but also in how to do this for antimicrobial resistance.

Conclusions and Policy Recommendations

The COVID-19 pandemic provides an opportunity to strengthen the capacity of health systems not only to be better prepared for the next pandemic but also to address ongoing crises such as antimicrobial resistance. Even though resources are being prioritized in addressing the ongoing pandemic, efforts to prevent the development of further resistance need to continue as well as preventive measures such as immunizations to prevent outbreaks of other infectious diseases.

In the developing of national guidance for the management of COVID-19, it is essential that countries analyze current evidence and continue monitoring patterns of antimicrobial use and resistance in the context of COVID-19 and discourage the preventive or therapeutic prescription of antibiotics unless there is evidence of a bacterial co-infection.

Given the current challenges related to supply chains, it will be important that these are strengthened and to ensure access to quality-assured antibiotics, diagnostic tests and personal protective equipment for health workers in the context of the COVID-19 pandemic and beyond.

There is a clear need to invest in health infrastructure in developing countries and to increase capacity, including in infection prevention and control, as well as in carrying out surveillance. Efforts around the provision of safe, clean water need to be one of the significant priorities for developing countries, and support for this investment should be made available.

There is a need for appropriate access to diagnostics, treatment and vaccines and ensuring that once these products are available, they will be made accessible to everyone who will need them. The recognition by governments on the need to provide equitable access to the products for COVID-19 should serve as the benchmark for other global health crises such as AMR and should be accompanied by commitments through global collaboration that would operationalize the implementation of those principles.

Antimicrobial resistance is a silent pandemic; therefore, efforts to prevent further development of multidrug-resistant infections need to continue to be implemented. Furthermore, urgent global actions are needed to find new health technology tools that would secure the ability of health systems to treat infections and to provide critical medical procedures.

Endnotes:

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[36] See the UN political declaration on antimicrobial resistance at https://digitallibrary.un.org/record/842813?ln=en.

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