Development of antimicrobial resistance due to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Desenvolvimento de resistência antimicrobiana devido ao Coronavírus da Síndrome Respiratória Aguda Grave 2 (SARS-CoV-2)

Desenvolvimiento de resistencia a los antimicrobianos debido al Síndrome Respiratorio Agudo Grave Coronavirus 2 (SARS-CoV-2)

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Abstract
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a new coronavirus identified in 2019. This disease, which may cause a serious respiratory infection, has been designated an international public health emergency and is being treated with several types of antivirals, antibiotics, and antifungals. While society works hard to combat the coronavirus disease 2019 (COVID-19) pandemic, it is equally vital to be prepared for the outbreak's notorious effects on the development of antimicrobial resistance (AMR). Antibiotic misuse and overuse are predicted to have serious ramifications for antibiotic stewardship programs and AMR management worldwide. Importantly, the global influence on the creation of novel antimicrobial resistance is uncertain due to a paucity of data on antimicrobial usage during the COVID-19 pandemic. The current pandemic might be a useful tool for depicting the spread of antimicrobial resistance and underlining the difficulties in managing the issue once it has emerged. This review aims to assess available data on bacterial infections in coronavirus-infected patients and to offer insight into the development of AMR in the face of the current public health issue.
Keywords: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19; Pandemic; Public health; Antibiotics; Bacteria; Antimicrobial resistance; Bacterial infections.

Resumo
Coronavírus da Síndrome Respiratória Aguda Grave 2 (SARS-CoV-2) é um novo coronavírus identificado em 2019. Esta doença, que pode causar uma infecção respiratória grave, foi designada uma emergência internacional de saúde pública e está sendo tratada com vários tipos de antivirais, antibióticos e antifúngicos. Embora o mundo trabalhe para combater e controlar a pandemia da doença do coronavírus 2019 (COVID-19), é igualmente importante estarmos preparados para os efeitos devastadores desse surto no desenvolvimento da resistência antimicrobiana (AMR). Durante a atual pandemia, espera-se que o uso incorreto e excessivo de antibióticos tenha consequências graves nos programas de administração de antibióticos e gerenciamento de AMR em todo o mundo. É importante ressaltar que a influência global na criação de uma nova resistência antimicrobiana é incerta devido à escassez de dados sobre o uso de antimicrobianos durante a pandemia causada pelo SARS-CoV-2. No futuro, a atual pandemia pode ser uma ferramenta útil para descrever a propagação da resistência antimicrobiana e destacar as dificuldades em gerenciar o problema, uma vez que o mesmo tenha surgido. Esta revisão tem como objetivo avaliar os dados disponíveis sobre infecções bacterianas em pacientes infectados pelo novo coronavírus e oferecer uma visão sobre o que esperar da resistência antimicrobiana e do desenvolvimento de antimicrobianos em face do atual problema de saúde pública.
Palavras-chave: Coronavírus da Síndrome Respiratória Aguda Grave 2; COVID-19; Pandemia, Saúde pública; Antibióticos; Bactéria; Resistência antimicrobiana; Infecções bacterianas.

Resumen
Síndrome Respiratorio Agudo Grave Coronavirus 2 (SARS-CoV-2) es un nuevo coronavirus identificado en 2019. Esta enfermedad, que puede causar una infección respiratoria grave, ha sido designada como emergencia de salud pública internacional y está siendo tratada con varios tipos de antivirales, antibióticos y antifúngicos. Si bien el mundo trabaja arduamente para combatir y controlar la pandemia de la enfermedad del coronavirus 2019 (COVID-19), es igualmente fundamental estar preparado para los efectos devastadores de este brote en el desenvolvimiento de la resistencia a los antimicrobianos (AMR). Durante esta pandemia, se espera que el uso incorrecto y excesivo de antibióticos tenga graves consecuencias para los programas de administración de antibióticos y la gestión de la AMR en todo el mundo. Es

importante destacar que la influencia global en la creación de una nueva resistencia a los antimicrobianos es incierta debido a la escasez de datos sobre el uso de antimicrobianos durante la pandemia de COVID-19. En el futuro, la pandemia actual podría ser una herramienta útil para describir la propagación de la resistencia a los antimicrobianos y subrayar las dificultades para manejar el problema una vez que ha surgido. Esta revisión tiene como objetivo evaluar los datos disponibles sobre infecciones bacterianas en pacientes infectados por coronavirus y ofrecer información sobre qué esperar con la AMR y el desenvolvimiento antimicrobiano frente al problema de salud pública actual.
Palabras clave: Síndrome Respiratorio Agudo Grave Coronavirus 2; COVID-19; Pandemia; Salud publica; Antibióticos; Bactéria; Resistencia a los antimicrobianos; Infecciones bacterianas.

1. Introduction

Antimicrobial resistance (AMR) is currently responsible for roughly 700,000 fatalities per year throughout the world (IAGG, 2019). In 2014, it was anticipated that if the current pattern of growing resistance continues, AMR might cause approximately 10 million deaths globally by 2050, with a total loss of at least $60 trillion (O'Neil, 2016). Bacterial resistance can develop spontaneously as a result of the microorganism's genetic adaptation to environmental changes. Resistance can also occur due to the indiscriminate and often unnecessary employment of antimicrobial drugs in animals and humans. Antibiotic overuse in patients infected with coronavirus can increase AMR imposed by selection pressure. Due to the current state of the pandemic, AMR is expected to cause 130,000 more fatalities by the end of 2021 (Murray, 2020).

The primary cause of COVID-19 was identified as severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a new betacoronavirus, a few days after the outbreak was disclosed in China around the end of December 2019 (Gorbalenya et al., 2020). COVID-19 affects individuals of all ages, with most cases resulting in mild to moderate symptoms (WHO, 2021). More than 261 million coronavirus cases had been reported worldwide as of November 28, 2021, with 5,215,332 deaths (WHO, 2021). Some concerns might impair antimicrobial stewardship actions and drive antibiotic resistance during the current coronavirus pandemic. Preliminary research suggests that antibiotics are routinely recommended to COVID-19 patients, owing to potential bacterial co-infections (Langford et al., 2020; Rawson et al., 2020). Although antimicrobial drugs have been frequently used to treat individuals with COVID-19, the incidence of bacterial co-infection in the majority of cases is quite low, at 3.5% (Langford et al., 2020). A review of investigations found that while 72% (1450/2010) of hospitalized patients received antimicrobial therapy during COVID-19 treatment, only 8% (62/806) developed bacterial or fungal co-infections (Rawson et al., 2020). Moreover, antibiotic treatments are routinely recommended to non-hospitalized individuals with COVID-19 in various countries (Manohar et al., 2020).

Many nations had begun antibiotic stewardship initiatives prior to SARS-CoV-2, under the banner of the One Health idea, with humans, animals, and the environment all interrelated. For instance, if antibiotics are used in farm animals, resistance genes can be transmitted to human microbes. Antibiotic stewardship is intended to avoid the transmission of AMR genes by reducing antibiotic overuse and only using antibiotics when extremely necessary. Antibiotic stewardship programs focused on enhancing antibiotic usage appropriateness have been linked to lower antibiotic use and a lower incidence of drug-resistant bacteria (Baur et al., 2017). However, due to the pressure doctors are under during the coronavirus outbreak, these well-regarded initiatives may be hatred. Even though antibiotics are ineffective in treating COVID-19, they are recommended in patients with suspected or verified COVID-19 for several reasons. For example, the challenge of excluding bacterial co-infection during the initial stages of the illness and the risk of secondary bacterial infection later in the disease may lead doctors to prescribe antibiotics to treat COVID-19 (Langford et al., 2020). Understanding antibiotic prescribing trends in COVID-19 can help researchers identify intervention opportunities and focus on antibiotic stewardship measures to enhance the quality and safety of antibiotic therapies. Figure 1 shows the potential effects of antimicrobial-resistant pathogens caused by the indiscriminate use of antibiotics during the current pandemic on One Health's sectors, including food and feed, animals, environment (e.g., sanitation, water,

plants, and crops), and humans. This article aims to evaluate existing data on bacterial infections in coronavirus-infected individuals and to provide insight into the expectations regarding AMR amid the present public health crisis.

Figure 1. The use of antibiotics during the COVID-19 pandemic and One Health sectors.
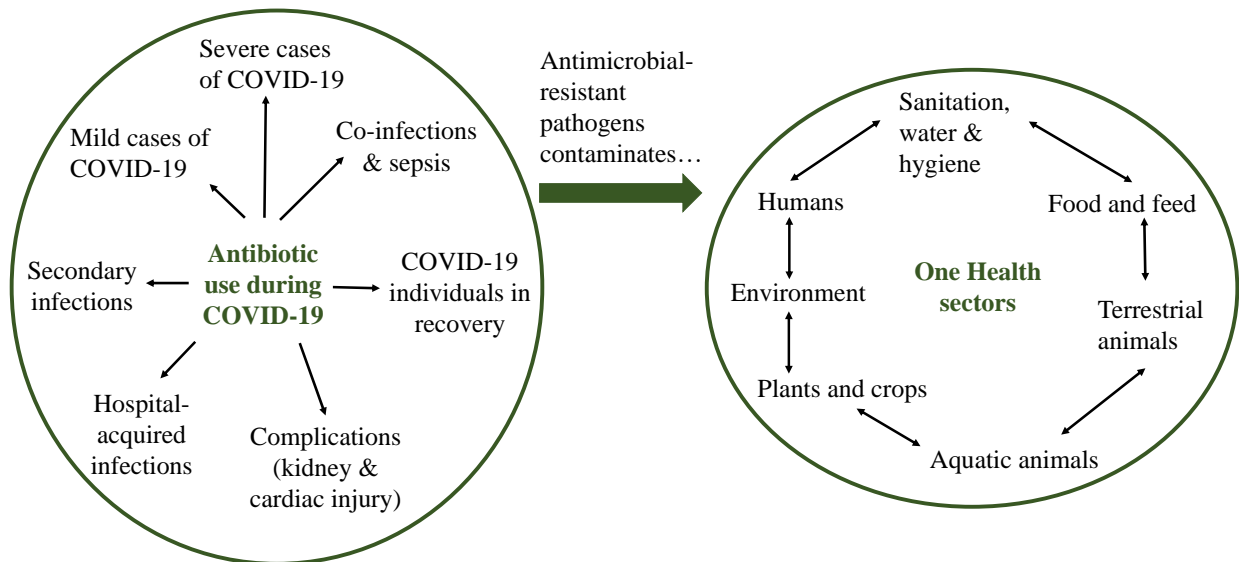
Source: Goulart, D. B. (current manuscript)

Figure 1 shows the various hospital scenarios in which antimicrobials can be administered during the current pandemic and the effects of the development of antimicrobial-resistant pathogens on One Heath sectors.

2. Methodology

The present work is an integrated literature review that synthesizes relevant and current information on the development of antimicrobial resistance due to SARS-CoV-2 and incorporates important research' findings in practice. Original research articles and literature reviews included in reliable scientific databases such as Scopus, Web of Science, PubMed, Science Direct, Directory of Open Access Journals (DOAJ), JSTOR, Wiley Online Library, and Scielo were used. To search for scientific articles, the author used terms such as "Severe Acute Respiratory Syndrome Coronavirus 2," "COVID-19," "antimicrobial resistance," "pandemic," "bacteria," "One Health," "antibiotics," "bacterial infections," "public health," "Wuhan," and "resistant genes." Criteria such as articles in English and preferably published between the years 2019 to 2021 were adopted to select the most relevant publications on the development of antimicrobial resistance following the current COVID-19 pandemic. However, it is important to note that although a few articles used in this review were published before 2019, they were still included in the present study due to their scientific importance. The author gave preference to include original research work with high scientifical impact; most of the cited investigations in the current review have more than five hundred citations.

3. Results and Discussion

3.1 General treatment of COVID-19

The World Health Organization (WHO) has released specific guidelines for the clinical treatment of COVID-19 (WHO, 2020a). Individuals with a mild condition, on the whole, do not need hospitalization, and therapy is primarily supportive and based on the symptoms. Antipyretics for fever can be given to individuals with mild COVID-19 symptoms. In severe COVID-

19 instances, oxygen therapy and monitoring are required, as well as proactive prevention of complications and subsequent infections, treatment of underlying disorders, and organ function support (Chen et al., 2020). Co-infections are treated with empirical antibiotics, which treat the majority of bacteria that might cause severe acute respiratory infection and septicemia. For individuals with confirmed COVID-19, there is currently no evidence to support any specific therapy. While antiviral peptides such as favipiravir and corticosteroids have been used to treat COVID-19, their role and mechanism of action are unknown (Bhatt et al., 2021). The corticosteroid dexamethasone has been proven to low mortality by roughly one-fifth to one-third in individuals who needed oxygen or a ventilator, respectively (WHO, 2020a). Remdesivir, an antiviral drug that suppresses the viral RNA-dependent RNA polymerase function, is the most promising therapy for COVID-19 (WHO, 2020a).

3.2 Secondary bacterial infections and superinfections in patients with COVID-19

Currently, there is a scarcity of data on COVID-19 patients acquiring secondary bacterial infections. It is challenging to predict the patterns of secondary bacterial diseases following the COVID-19 pandemic based on current statistics. Through mid-February 2020, secondary infections were documented in 5% to 27% of individuals infected with SARS-CoV-2 in various hospitals in Wuhan, China, including 50% to 100% of those who died (Cao et al., 2019; Chen et al., 2020; Dong et al., 2020; Huang et al., 2020; Zhou, 2020). COVID-19 was shown to cause secondary infections in 13.5% to 44% of intensive care unit (ICU) patients (Chen et al., 2020; Dong et al., 2020; Yang et al., 2020). Bacterial or fungal pneumonia was the most frequent illness among ICU patients; however, bloodstream and urinary tract infections were also found. Pathogens included pandrug-resistant *Candida albicans*, *Candida glabrata, Enterobacter cloacae*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Serratia marcescens*, *Acinetobacter baumannii*, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*, extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae*, and ESBL-producing *Pseudomonas* (Chen et al., 2020; Wang et al., 2020; Yang et al., 2020). Following the first COVID-19 symptoms, patients at two hospitals experienced median delays of 10 to 12 days to ICU admission and 17 days to the start of secondary infection, respectively (Huang et al., 2020; Zhou, 2020). Superinfections were generally fatal, with a median time to death of 19 days.

COVID-19 may be related to superinfections in two distinct ways. Firstly, hospitalized individuals, specifically those using mechanical ventilation or who are severely ill, are more likely to develop a serious infection (Clancy & Nguyen, 2020). Countries like China, Italy, and the Unites States, reported a range of 21% to 88% of COVID-19 patients in critical care units using mechanical ventilation (Du et al., 2020; Goyal et al., 2020; Grasselli et al., 2020; Wang et al., 2020; Yang et al., 2020). Secondly, serious COVID-19 is linked to immunological dysregulation, which may produce an environment conducive to bacterial or fungal growth, contributing to lung pathology (Huang et al., 2020). For example, patients severely affected by COVID-19 demonstrated higher levels of proinflammatory (e.g., interleukin [IL] 2, IL-6, and tumor necrosis factor alpha) and anti-inflammatory (e.g., IL-4 and IL-10) cytokines, lower levels of cluster of differentiation [CD]-4 and CD8 cells, and lower expression of interferon-gama by CD4 cells than those individuals with moderate conditions (Chen et al., 2020; Pedersen & Ho, 2020). The most prevalent superinfections will likely be pneumonia caused by bacteria, particularly ventilator-associated pneumonia; sick individuals may also be susceptible to infections.

3.3 Antimicrobial therapy in COVID-19 patients

Despite the low prevalence of secondary bacterial infections, there has been a rise in the volume of data stating the use of antibiotics when treating COVID-19 patients (Lai et al., 2020), with 45% of individuals receiving antimicrobial drugs (Xu et al., 2020). For example, after establishing effectiveness against coronaviruses, antibiotics like tecioplanin (a glycopeptide antibiotic) have been recommended as a potent antiviral (Baron et al., 2020). However, since antibiotic misuse or abuse is

recognized as a major contributor to the establishment of AMR, extreme caution should be exercised. The scarcity of information on antimicrobial therapy given to SARS-CoV-2 patients with secondary infections or superinfections might be attributed to various circumstances. For example, rather than gathering, assessing, and sharing clinical data, hospitals have prioritized providing immediate medical care, keeping severely sick patients alive. Moreover, microbiological testing in hospitalized patients has been reduced due to high workloads and to avoid virus exposure. In order to identify the most appropriate antimicrobials to limit the spread of AMR, microbiological investigation and antibiotic susceptibility testing (AST) of patients presenting with secondary infections should be employed. Furthermore, the use of efficient narrow-spectrum antibiotics in individuals infected with SARS-CoV-2 should be recommended whenever possible.

Although the antibiotics utilized in the treatment of COVID-19 have been documented in some investigations, their importance has not been well considered (Yang et al., 2020). To illustrate it, a study conducted in Wuhan, China, revealed that 71% of COVID-19 patients received antibiotic treatment, with 25% receiving only one antibiotic and 45% receiving a combination of antibiotics (Chen et al., 2020). The antimicrobials of choice included cephalosporins, quinolones, carbapenems, tigecycline, and linezolid. According to a research conducted in 552 clinics in 30 provinces in China, antibiotics were used to treat 58% of COVID-19 patients (Zhou, 2020). Antibiotics and antifungals were given to a range of 80% to 100% and 7.5% to 15% of severely sick COVID-19 individuals in Chinese ICUs, respectively (Cao et al., 2019; Dong et al., 2020; Du et al., 2020; Guan et al., 2020; Huang et al., 2020; Wang et al., 2020). Fluoroquinolones, cephalosporins, carbapenems, azithromycin, vancomycin, and linezolid were the most used empiric antibiotics in different Wuhan hospitals but there were no specifics on dose or treatment regimens (Cao et al., 2019; Chen et al., 2020; Du et al., 2020; Wang et al., 2020). Since 25% to 70% of individuals with COVID-19 showed sepsis symptoms, it was challenging to rule out bacterial superinfections based on symptoms, abnormalities in radiographic (especially the lungs), and laboratory exams; consequently, the use of empiric antimicrobials was most likely prevalent (Chen et al., 2020; Huang et al., 2020; Zhou, 2020). Another study conducted in Wuhan reported that individuals infected with SARS-CoV-2 were administered with antibiotics, including but not limited to azithromycin (18%), ceftriaxone (25%), and moxifloxacin (64%) (Wang et al., 2020). Other studies did not specify the antimicrobial utilized, stating that antibiotics and antifungal medications were given to 57% and 3% of individuals with SARS-CoV-2, respectively (Guan et al., 2020). Despite the previously noted findings, trials of COVID-19 conducted in January and February 2020 in 788 hospitalized individuals in Zhejiang, a province in China, and 24 patients in Seattle ICUs found no superinfections in the patients (Bhatraju et al., 2020; Lian et al., 2020). However, it was unclear if superinfections were not diagnosed, whether data was insufficient, missing, or not analyzed, or whether information was just not supplied. Cong and colleagues (2021) reported that among 78 investigations in which antibiotics were used to treat COVID-19, the majority of antimicrobials were broad-spectrum antibiotics. Figure 2 depicts the most common antibiotics used in the treatment of COVID-19 among 78 studies (Cong et al., 2021).

Figure 2. Frequently prescribed antibiotics used in the treatment of COVID-19 (results from 78 studies).
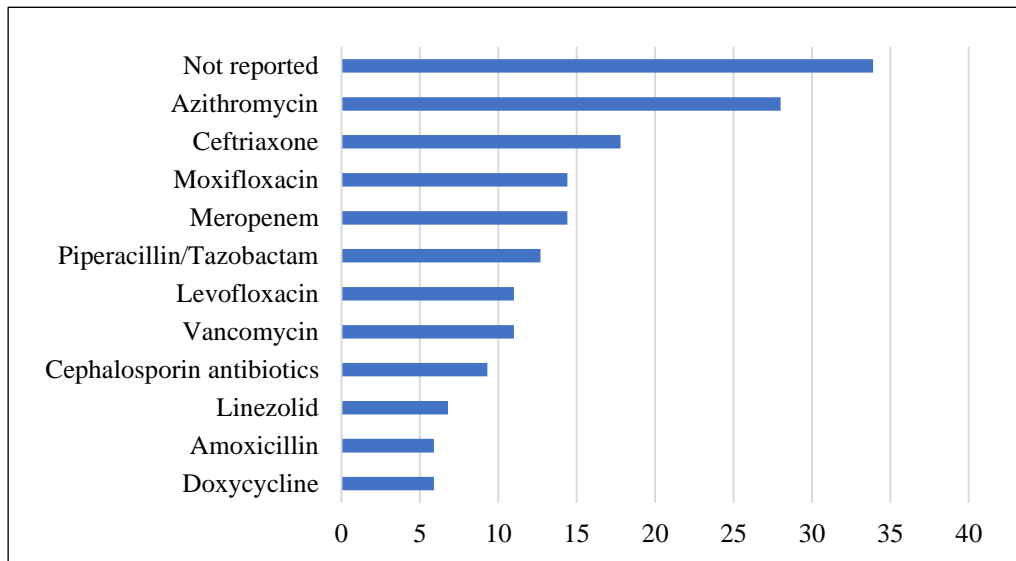
Source: Authors.

Figure 2 shows that azithromycin was the most commonly prescribed antibiotics (28.0%), followed by ceftriaxone (17.8%), moxifloxacin (14.4%), meropenem (14.4%), and piperacillin/tazobactam (12.7%).

3.4 Antimicrobial resistance and COVID-19 are parallel

Antibiotic overuse has resulted in the emergence of antibiotic-resistant bacteria and a decrease in the efficacy of important drugs, posing a threat to severe hospital infections, as well as reducing the physiological benefits of surgeries and cancer therapy (Borek et al., 2019; Laxminarayan et al., 2016). Furthermore, antimicrobial-resistant gene reservoirs have also been detected in domestic and wild animals. Notably, the use of antimicrobial drugs in livestock production to preserve health and productivity strongly adds to the transfer of resistance genes to humans via food animals and the environment (Kahn, 2017). It is critical to warn society about the undocumented volumes of antibiotics and antifungals that have been used worldwide during the pandemic. Antibiotics commonly used to treat individuals with COVID-19 infections are now saving millions of lives, but the present spike in their use may be responsible for a substantial number of fatalities in the coming decades. It is crucial to collect information on the incidence of infections caused by resistant bacteria before and after the pandemic to assess if the used antimicrobial agents will increase the incidence of superbugs. For example, one method that might reveal variations in AMR carriage circulating in clinical settings is comparing whole genome sequences of pathogens throughout the pandemic. Additionally, databases like BacWGSTdb might be used to track major AMR pathogen outbreaks down to the species and clonal complex (Ruan & Feng, 2016).

Healthcare systems throughout the world are under growing pressure to combat infections. This has resulted in many changes in the clinic that may influence AMR or be relevant to it. Interestingly, an investigation explored several variables and possible repercussions of AMR during the COVID-19 pandemic (Rawson et al., 2020). The investigation concluded that increased societal awareness of emerging infectious diseases and important sanitary practices during the pandemic could increase engagement in the fight against AMR. The United Kingdom government, for example, has issued various publications on COVID-19 management in therapeutic settings. Hospital rooms that have been used for a patient suspected of having COVID-19 should be closed and ventilation shut off until thorough sterilization has occurred, according to the primary care guidelines (*Guidance on COVID-19: Interim guidance for primary care*, 2020). Additional steps are advised for infection prevention,

including precautions with the contact of possibly contaminated surfaces, droplets, and aerosols. Extra hygiene awareness and additional sterilizing processes, in particular, may help to minimize the spread of AMR bacteria. The use of antimicrobial soaps in hospitals has significantly risen in recent months. Because of control policies or individual habits, higher consumption of disinfectant cleansers will probably continue after the pandemic. After the COVID-19 pandemic, these measures may help minimize the worldwide spread of AMR infections.

The spread of AMR will also be influenced by travel limitations imposed by the current epidemic (Murray, 2020). Notoriously, important AMR genes are spread among several countries. To illustrate it, one of the most prevalent genes causing resistance to carbapenem antibiotics (NDM-1) was found in India (Liang et al., 2011) and has since spread around the world (Nordmann et al., 2011). Moreover, the *mcr1* gene, responsible for colistin resistance, a last-resort antibiotic, was first discovered in China (Liu et al., 2016) but has now been identified all over the world (Castanheira et al., 2016). Two years ago, the *tet* (X4) gene for transferable tigecycline resistance was firstly discovered in China (Bai et al., 2019). The *ctx-m* genes originated in bacteria found in the environment, but they have subsequently been dubbed a "pandemic" (Cantón & Coque, 2006). Travelers can be contaminated by novel AMR genes or bacteria after visiting areas with a high prevalence of AMR. For example, contamination of Swedish tourists infected with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* rose from 2.4% to 68% after traveling to China, India, or northern Africa (ÖstholmBalkhed et al., 2018). It is possible that travel restrictions due to COVID-19 should have hindered the spread of AMR.

3.5 Antimicrobial stewardship challenges

Hospitals with a high incidence of AMR should expect possible increases in the number of illnesses caused by bacteria and fungi. According to early indications, *Aspergillus* species may play a significant role at some sites. Broad-spectrum antibiotic treatment, both empiric and pathogen-directed, is expected to be common in critically sick individuals. The concern of employing broad-spectrum antimicrobials is because they also negatively impact a large range of the normal microbiota, perhaps raising the chance of a superinfection or a secondary infection in an individual who already has a preexisting infection. When the antibacterial used to treat the previous infection kills the protective microbiota, another pathogen resistant to the antibiotic might thrive, leading to secondary infection. This process is showed by Figure 3.

Figure 3. The use of broad-spectrum antibiotics may result in the emergence of a superinfection.
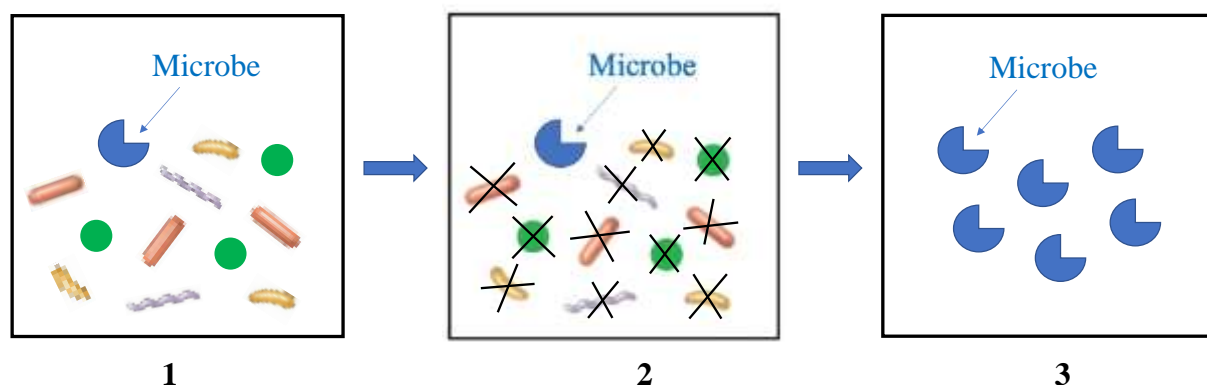
Source: Goulart, D. B. (current manuscript).

Figure 3 schematically shows the development of a superinfection caused by the use of a broad-spectrum antibiotic:

(1) Opportunistic pathogens (microbe) are kept in control by a healthy microbiome;

(2) Antibiotics with a broad spectrum of action kills susceptible bacteria constituted of the healthy microbiome; and

(3) Superinfection proceeds as a result of the development of antimicrobial-resistant bacteria.

It will be a stewardship challenge to manage antibiotic use. For example, the collection of samples for monitoring antimicrobial agents can be limited, influencing the usage of drugs like vancomycin (Clancy & Nguyen, 2020). Importantly, patients using antibiotics should be monitored for infections caused by *Clostridioides difficile* and candidiasis. Hospitals, laboratories, and public health entities should keep a close eye on the impact of increased antibiotic use in individual patients and the emergence of AMR. Interruptions in worldwide manufacturing, particularly at significant hubs for pharmaceutical components in China and India, might limit the supply of some antimicrobials as the COVID-19 pandemic develops (Barker, 2020). Understanding the consequences of COVID-19 on the development of AMR and what to expect if the trends stay the same or worsen will guide public health plans on the next steps in addressing AMR. Researchers should start gathering data to analyze how COVID-19 treatment affects AMR. The World Health Organization claims that antimicrobial stewardship actions should be incorporated into the pandemic response across the health system through five strategies, including:

(1) Improve clinical competence among health personnel who treat patients with Covid-19;

(2) Ensure that basic health services are available, as well as a steady supply of high-quality antimicrobials, including antiretroviral and tuberculosis drugs;

(3) Reduce the time to complete COVID-19 testing by improving testing procedures and expanding testing facilities, especially for suspected cases, to reduce the need for antibiotics;

(4) Employ extreme caution to select biocidal agents with a low selection pressure to develop AMR; and

(5) Fill research gaps to guarantee that antimicrobial stewardship practices are incorporated into the pandemic response.

These efforts would prevent the spread of untreatable drug-resistant illnesses and diseases, which might result in a new public health crisis. International initiatives like the annual World Antibiotic Awareness Week assist society understand the problem of AMR (WHO, 2020b). More regular handwashing (e.g., through Hand Hygiene Day) appears to be very effective when hygiene practices are prioritized. With the current pandemic bringing increased focus to proper handwashing procedures, it is anticipated that these practices will translate into long-term behavioral change.

3.6 One health

Antibiotic usage in food-producing animals should be reduced in order to protect the benefits of antimicrobial drugs for humans. In this context, the European Union (EU) prohibited the use of antimicrobial drugs in animal feed as a growth promoter in 2006 (*Ban on antibiotics as growth promoters in animal feed enters into effect*, 2005). Sales of antimicrobial drugs for use in food animals in the European Economic Area declined by more than 34% between 2011 and 2018, according to the European Surveillance of Veterinary Antimicrobial Consumption research issued in October 2020. Because carbapenem-resistant *Enterobacteriaceae* are resistant to almost all antibiotics, the attention in human infection has switched to last-resort antibiotics, including polymyxins, particularly colistin. The *mcr-1* gene was found in human and animal *Enterobacteriaceae* isolates, and it is the first known plasmid-mediated polymyxin resistance gene (Liu et al., 2016). As a result, the fast development of colistin resistance among different species would be a relevant evolution. Because of this danger, the use of colistin in animal feed has been severely limited or eliminated (Walsh & Wu, 2016). With the potential of resistance genes acquisition from food animals identified as a reservoir, it is more important than ever to consider the integrated One Health strategy, which impacts humans, livestock, wildlife, and the environment (*Ban on antibiotics as growth promoters in animal feed enters into effect*, 2005). Pollution from human and animal waste, pharmaceutical manufacturing, and the use of antimicrobial crops, among other

challenges, will necessitate more thought and coordination on a worldwide scale (White & Hughes, 2019). Raising awareness of the threats posed by AMR and legislative incentives and effective regulation all contribute to the fight against superbugs. The development of effective diagnostics, vaccines, and antimicrobial drugs, including alternative therapies such as bacteriophages and monoclonal antibodies, must be prioritized.

4. Final Considerations

Medical staff is under tremendous pressure due to the current worldwide public health concern caused by the novel coronavirus. It is urgent to saving the lives of individuals with COVID-19, even if that means using antimicrobials to treat or prevent secondary infections. On the other hand, several of these antibiotics are utilized in humans and animals and are classed as critically vital, with some being used as a last option. There has probably been a higher-than-normal level of antibiotic administration. Given the lack of data thus far, the number, type, and dosages of antibiotics administered are likely to be unreported and underestimated. It is anticipated that existing errors or excesses may hasten the onset of the next global public health catastrophe, which will be brought on by the resistance of a wide range of microbes to a wide range of treatments. Since the current AMR crisis affects humans, animals, and the environment, a sustained One Health strategy is required to engage and unify all stakeholders behind a shared vision and common goals. The management of antibiotic resistance issues requires actions from various sectors because human medicine, the food, and agriculture industries utilize antibiotics regularly. The COVID-19 pandemic might be a valuable reference in the future for illustrating the spread of AMR and emphasizing the difficulty of combating the development of superbugs once it has appeared.

AMR was one of the top concerns for public health before the current pandemic began. AMR, which is already a challenging problem, must now be handled in the context of a changing healthcare sector. For future work, it would be interesting to understand how changes in antibiotic use, prevention of infections, and health systems resulting from COVID-19 impact AMR's onset, transmission, and consequences. For example, increased personal hygiene, decreased national and international travel, and fewer elective hospital services like surgeries may impact the selection and transmission of AMR microbes in both the short and long terms. AMR is an inevitable side effect of the COVID-19 pandemic. The etiology is multifaceted, with a high incidence of antimicrobial agent usage in COVID-19 individuals with low rates of bacterial infections being a major contributor.

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