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INCREASED ANTIMICROBIAL RESISTANCE DUE TO COVID-19 PANDEMIC, A REALITY OR MYTH; A COMPREHENSIVE REVIEW

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ABSTRACT

Covid-19 (Corona virus) pandemic was the most unanticipated challenge of this century, not only for healthcare but almost all countries. The sudden pandemic challenge leads to an increase in antimicrobial administration due to unavailability of definite treatment, additional infection control practices, excessive use of disinfectants, extra vigilant about personal hygiene to use sanitisers and surface cleaners. These practices were recommended and followed to control the covid-19 threat at that time. This was realised and proven, which led to another silent pandemic "Increased Antimicrobial Resistance (AMR)". Many factors are associated with an increased AMR trend, and all were increased in the last year. The AMR also has no boundaries, as it is a global threat, and all countries need a collaborative strategy to protect not only human health but the terrestrial health and environment also."The global collaborated efforts need to design and implement to deal with such life-threatening pandemics. Both developed and developing countries need to formulate one solution because bacteria and viruses have no boundaries.

Keywords: Antimicrobial, Antibiotics, Antimicrobial resistance, COVID-19,Pandemic, SARS-CoV-2.

INTRODUCTION

The year 2020 was a challenging year for the global healthcare community due to the Covid-19 pandemic. It reshaped the scenario of the whole world because of the unanticipated social, financial, and ecological calamities. Covid-19 begun with fear and hope, social isolation, economical fragility, and environmental destruction [ECDC, 2020; Cassini *et al.,* 2019;Monnet and Harbarth, 2020]. Due to the Covid-19 pandemic, almost 250,000 deaths were reported in the United Kingdom, European Union, and European Economic Area alone. During the Covid-19 pandemic, there was increased antibiotic resistance [ECDC, 2020;Cassini *et al.,* 2019]. The yearly conclusive antimicrobial resistance (AMR) report of 2020 revealed 30,000 Europeans due to bacterial infections and antibiotic resistance [Monnet and Harbarth, 2020]. Antimicrobial resistance (AMR) is independently a cross-sectional health challenge. The term "AMR" got recognition in 2015 by the World Health Organisation (WHO) report. Based on WHO findings, multidrug-resistant tuberculosis (MDR-TB) reported 182,000 deaths globally in 2019. These deaths were reported from one single organism only, Mycobacterium tuberculosis. Conclusively, AMR reportedly contributed as a third major reason for deaths as SARS-CoV-2 in 2020, i.e., 1.8 million globally [Knight *et al.,* 2021]. The scientific community is trying to identify the mechanism of Covid-19 transmission and its interaction with other infections. Antimicrobial resistance is not confined to one country, it is a worldwide danger and accountable for 700,000 deaths globally. AMR is a more potent threat than cancer in terms of mortality and a probability of millions of deaths globally per year by 2050. Developing countries are more vulnerable regions due to less health and diagnostic facilities and accessibility of more potent antimicrobial agents [Ukuhor, 2021;EU, 2017]. There are many bacterial diseases which already a cost burden for the global healthcare sector only because of antimicrobial resistance, such as tuberculosis, respiratory infections, bacillary dysentery, and sexually transmitted infections (STIs) [Ukuhor, 2021;CDC, 2019].

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Approaches to mitigating AMR

By the end of 2020, the policy decisions in response to Covid-19 and its direct and indirect links with AMR have been evident and implemented globally [Knight *et al.,* 2021]. The London School of Hygiene and Tropical Medicine critically analysed the rising trend of this interaction. They analyzed the AMR and its impacts on Covid-19 care. Moreover, the effects of SARS-CoV-2 on the AMR and its rising resistance trend, transmission mechanism, and health care burden. The analytical focus explored three aspects: antibiotic use, infection control measures, and healthcare protocol modification [Knight *et al.,* 2021]. Antibiotic stewardship is another approach that emerged in the last decade to prescribe a safe and an effective antibiotic in case of emergency demand to control antibiotic resistance. Due to the emergence of the Covid-19 pandemic, there was no data available to prescribe an appropriate antibiotic if a patient comes with respiratory symptoms in the Emergency Department. This is a severe ongoing challenge to all healthcare settings [Pulia *et al.,* 2020]. This review investigates the contributing factors that influence the risen AMR and the approaches that have been implemented to mitigate it.

The emergence of AMR, A real fact

The evaluation of the AMR resistance pattern is still limited due to the lack of accurate data. It will require the evaluation of AMR data globally, before the Covid-19 pandemic and at some point, after Covid-19 has reduced to a minimal level. Several small-scale studies conducted recently have reported on the increased antimicrobial resistance after Covid-19. Gasperini*et al.* reported the increased Multidrug resistance (MDR) bacterial infections and mortality rate specifically in the bloodstream in post-covid-19 duration [Gasperini *et al.,* 2021]. Studies from Bangladesh and Iran reported the contribution of non-prescribed administration of antibiotics and bacterial co-infections in Covid-19 patients [Parveen *et al.,* 2020,Mahmoudi,

2020]. A further retrospective cohort study of Covid-19 patients from Mexico reported a 11.3% frequency of nosocomial infection, and Ventilator-associated pneumonia (VAP) was the leading one, followed by bloodstream infections with quite a high mortality rate of 40.5% [Martinez-Guerra *et al.,* 2021].Recently Afshinnekoo *et al.* evaluated the antimicrobial resistance in Covid-19 and its administered antimicrobial choices such as Dexamethas one, Remdesivir, Azithromycin, Hydroxychloroquine, Ritonavir, and Lopinavir. This study reported the increased antimicrobial resistance due to the Covid-19 pandemic. The increased demand and excessive misuse was possibly the reason for the increase [Afshinnekoo *et al.,* 2021]. Another neglected aspect of antimicrobial administration in Covid-19 patients leads to alteration of gut microbial flora. This alteration creates a favorable environment for gut microbes to modify and participate in antimicrobial resistance and dissemination [Afshinnekoo *et al.,* 2021, Zuo *et al.,* 2020].

Antibiotic Administration in Covid-19 patients

The supporting treatment was the only choice available for Covid-19 patients when it emerged due to lack of definite therapeutic or vaccine availability Covid-19 infections were treated with the support of a variety of antimicrobials and oxygen therapy [Miranda *et al.,* 2020; Beović *et al.,* 2020]. The mild Covid-19 cases were treated only with antipyretics, and severe cases required hospital admission, antimicrobial and oxygen therapy support [Miranda *et al*., 2020].At the beginning of the Covid-19 pandemic, there was more aggressive use of antibiotics. A large multicenter study from China reported the use of intravenous antibiotics in 58% of admitted patients. Some small-scale studies from Wuhan and Jiangsu even reported using antibiotics in almost all admitted patients. These figures vary among different studies due to non-defined criteria. There were many outlined situations when the administration of antimicrobials was the only choice. Most individuals exposed to the Covid-19 virus developed a mild infection. However, in 14% of cases, hospital admission and oxygen support were required. Only 4% of hospitalized patients required Intensive care (ICU) support [Beović *et al.,* 2020-18]. The World Health Organization (WHO) published complete guidelines for the Management of Covid-19. In addition to oxygen therapy, to prevent infection complications, and secondary infection treatment was given [Miranda *et al.,* 2020, WHO, 2020]. Around 58% of admitted Covid patients received intravenous (IV) antimicrobial treatment; some studies even reported 71% antimicrobial administered cases [Beović *et al.,* 2020; Guan *et al.,* 2020; Kim *et al.,* 2020]. Moxifloxacin, Carbapenems, beta-lactams, macrolides, and fluoroquinolones were the most commonly administered antibiotics in Covid-19 patients, and these meant to cure bacterial infections [Beović *et al.,* 2020]. Piperacillin/tazobactam was the most prescribed one for ICU patients, a broad-spectrum antibiotic for both gram-positive and gram-negative bacteria [Beović *et al.,* 2020, Kim *et al.,* 2020]. Figure 1 describes the conditions of antimicrobials administration in Covid-19 patients and its possible impacts [Miranda *et al.,* 2020, WHO, 2020].

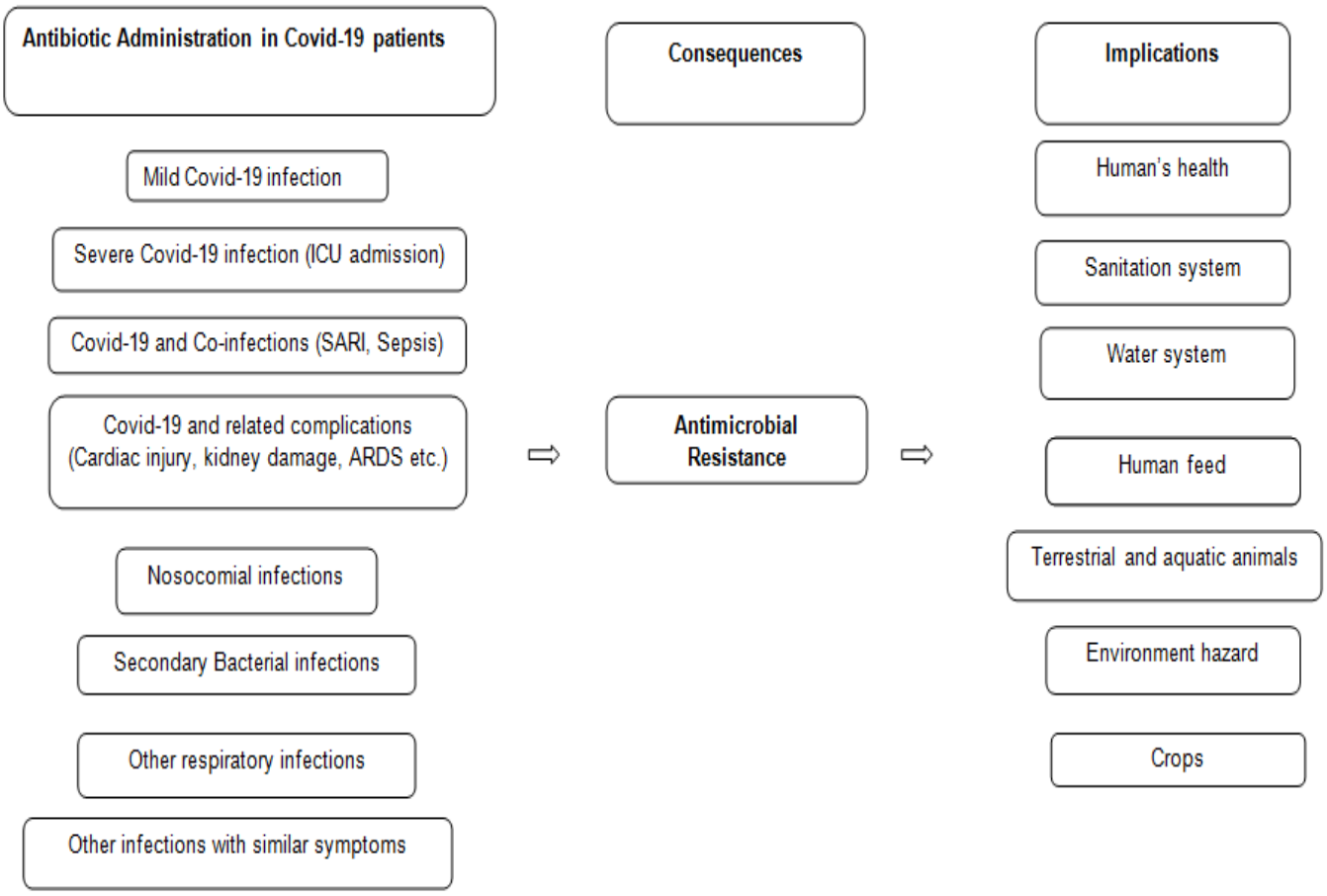

Table 1: Covid-19 and the potential reasons to increase Antimicrobial resistance

Potential reason and its impacts	Supportive intervention	Threat	Reference No.
The demand for Hand hygiene to reduce the spread of infection	Increased demand for hand sanitiser	Developing antimicrobial resistance and its spread	[21, 22]
Increased demand for a high dose of disinfectants	Increased use of a high dose of disinfectants		[23, 24]
Social distancing, and lack of antimicrobial prescription or self-medication	Strengthened people's engagement		[5, 21]
Inadequate process of antimicrobial regulation and poor pharmaceutical controlling system (especially in developing countries)	Strict antimicrobial policies	Developing antimicrobial resistance, spread, adverse effects, and even death	[5, 21, 25]
Inappropriate selection of antimicrobials and non-compliance to the antimicrobial treatment course	Patient's guidance and counseling		[5, 21, 25]
Lack of liability in Healthcare service providers	Strict policy to control the selling of antibiotics without a doctor's prescription and promote the culture of susceptibility testing in healthcare settings, especially in developing countries. If in case of emergency prescription, follow the process of antimicrobial stewardship to minimize the risk of resistance development		[5, 8, 21, 26]
Antimicrobial prescription by a pharmacist, Antimicrobial prescription by Clinician without Culture and sensitivity testing.			
Less antimicrobial sensitivity reporting due to pandemics like MDR TB, MRSA etc. and lack of rapid diagnostics availability especially for Microbiology laboratories. Culture and sensitivity reporting usually takes 36-48 hours.	Misuse of antibiotics and selection of an inappropriate one.		[5, 21, 26]
Non-availability of new antimicrobials or increased burden to available antimicrobials (Difficult to treat MDR and XDR bacteria, resistance to all broad-spectrum antibiotics have been reported)	Must need to design new antimicrobials		[5, 21, 26, 27]
Lack of vaccine availability	Development and administration of a safe vaccine	Use of antimicrobial as supportive treatment to developing antimicrobial resistance, and its spread	[5, 21, 27]
Increased demand for antimicrobials (Due to the supportive treatment of Covid-19 pandemic/non-availability of specific treatment)	Control prescription of antimicrobials as per need	Developing antimicrobial resistance, spread, adverse effects, and even death	[5, 28]
Cost of antimicrobials (In case of the high cost of antibiotics, the patient may choose low-cost antibiotics from a non-medical person or pharmacist advice)	Availability of affordable antimicrobials	Developing antimicrobial resistance, spread, and adverse effects	[5, 29, 30]
Commensals microbial environment (reporting of a resistance gene from the natural habitat of microorganisms)	Control policies, especially for soil microorganisms which leads to health hazards both for animals and humans	Developing antimicrobial resistance, and its spread	[5, 21, 23]
Cross-resistance of antimicrobials (antimicrobials usually broad-spectrum, can kill different groups of microorganisms, and one class of resistance can make the antibiotic-resistant to other class also)	Prescribe appropriate antibiotic based on culture and sensitivity testing		[5, 31]
Global Climate Change (Increased temperature is linked to increased antimicrobials resistance in some groups)	Need to rule out the solution		[5, 21]
International travelling International travelling is one of the main reason for antimicrobial resistance, and the Covid-19 pandemic is its recent example	Control policies of international travel and medical testing	Developing antimicrobial resistance, spread, adverse effects, and even death	[5, 32]

Covid-19 and the potential healthcare practices to increase Antimicrobial resistance

The true picture of increased resistance pattern is yet to reveal. However, recent small-scale studies are reporting an increased resistance patterns of antimicrobial resistance [10-14]. This is in agreement with the majorly of the healthcare and scientific community. This pandemic may lead to other therapeutic issues due to urgent treatment decisions based on limited clinical data that might be against the healthcare setups of the antimicrobial protocol. Some of the leading factors contributing to antimicrobial resistance are summarized in Table 1 [Miranda *et al.,* 2020, Rawson *et al.,* 2020].

Increased demand for Hand hygiene

Hand hygiene is always a crucial infection control practice for every healthcare setting. The increased demand for hand sanitisers with different potency ingredients may contribute to AMR. It is expected that the Infection control Surveillance monitoring will uncover the accurate picture [Rawson *et al.,* 2020].

Increased use of high dose disinfectants

The Covid-19 responsible raises several other healthcare and environmental concerns, and the overuse of disinfectant was one of those. Only China utilized 2000 tons of disinfectants and antiseptics alone in Wuhan city, and the worldwide utilisation is indeterminable. Due to pandemic fear, "high dose" was advised and dispensed globally. This increased utilization and high dose lead to increased tension on environmental, ecological, and human safety. Scientific studies reported that the research of high dose disinfectants resulting in both horizontal and vertical gene transfer and mutate the microbes into resistant ones. These microbes blend into our systems and consume through drinking water, food intake, and inhalation of air [Chen *et al.,*2021, Felis *et al.,* 2020].

Social Distancing, lack of antimicrobial prescription, self-medication, and inadequate regulatory system

Social distancing and restricted hospital visits lead to the non-regulation of antimicrobials. Developed countries usually have policies for prescription requirements on antimicrobial purchases and can monitor the system if ordered online. In most developing countries, due to poor regulations, antimicrobials are easily available without any prescription. This also linked to wrong antibiotic choice, poor storage conditions, and inappropriate dose and duration of antimicrobials treatment [Ukuhor, 2021, Rawson *et al.,* 2020, Nelson *et al.,* 2009].

Culture and Sensitivity Reporting

"Culture and Sensitivity" is the core testing methodology of microbiology and prescription of antimicrobials. The inefficient system of prescribing antibiotics without ordering Sensitivity testing is lethal to our antimicrobial management system. Although, in some cases, antibiotics advised before the culture report coming out due to the patient's illness. A quick diagnostic testing system is also crucial for microbiology laboratories to implement [Ukuhor, 2021, Rawson *et al.,* 2020, Maurer *et al.,* 2017].

Lack of vaccine availability and new antimicrobials

The pandemic was also an alarm to all healthcare, pharmaceutical, and research communities that we are yet not prepared to deal with new challenges. It may be is worth adding in some on the Asian Flu, which gives warning signs, including Ebola. Several papers warn of the pandemic problem well before Coivd-19. Healthcare, pharmaceutical, and research communities had warned, but the government did not talk notice of the science.

1957 Asian Flu Pandemic

In 1957, Asian flu was, on the whole, a much milder illness than that of 1918; the global death toll was estimated to be around 2 million. In 1957, the Asian flu pandemic resulted in about 70,000 deaths in the United States. An excess of 30,000 deaths occurred in England and Wales of which 6,716 were ascribed to influenza itself. Estimates in the United Kingdom (UK) ranged from 1.3 to 3.5 deaths/1,000 cases. An estimate from 29 British general practices was 2.3 deaths per 1,000 cases attended. In February 1957, the Asian influenza pandemic was first identified in the Far East. Immunity to this strain was rare in people less than 65 years of age and predicted a pandemic. In preparation, vaccine production began in late May 1957, and health officials increased surveillance for flu outbreaks. The 1957 pandemic is instructive in that the first US cases occurred in June, but no community outbreaks occurred until August, and the first wave of illness peaked in October. Although the AMR already was declared a global threat of the century by WHO in 2017 with an estimation of 10 million annual deaths by 2050 [Ukuhor, 2021, Maurer *et al.,* 2017]. This pandemic realized us that we do not have any preserved antimicrobial, resistance to all broad-spectrum antimicrobial have been reported and we yet not introduced any new broad-spectrum and safe therapeutic. Due to the sudden outbreak of Covid-19 all antimicrobials, controlling and managing the threat were used. Vaccine research, development, and the trial was a long process to introduce a safe vaccine option for the general population. Infection of new Covid-19 variants were also taking additional research and time for vaccine development. Forecasting vaccine demand was the neglected research domain, and pharmaceuticals did not produce the required vaccines at the optimal level [Rawson *et al.,* 2020, Kremer and Snyder, 2003].

Increased demand, quality, and cost of antimicrobials

There are many factors associated with the increased demand for antimicrobials in the Covid-19 pandemic. A US-based study reported that almost 71% of Covid-19 positive patients used antibiotics; however, only 4% reportedly had bacterial co-infection; developing countries have a more threatening situation [Arshad *et al.,* 2020]. The poor quality and cost of antimicrobial also associated with developing countries. The antimicrobials efficacy, potency, and expiry are the most minor concerns in developing countries, and reports of even expired antimicrobials consumption were recorded in low developing countries. It was estimated before the Covid-19 pandemic that the antimicrobial cost in the US will reach $100 trillion by 2050 [Lucien *et al.,* 2021, O'Neill, 2016].

Commensals and Natural microbial habitat

Extensive use of disinfectants, hand sanitisers, and livestock production of antimicrobials leads to unimaginable microbial resistance effects. The human microbial flora, environmental, sanitary, and water systems were exposed to these hazardous chemicals, which ultimately led to massive threats because we were not prepared with new and safe options. This not only affects human health but a great danger to the global environment also [Ukuhor, 2021, Rawson *et al.,* 2020, Chen *et al.,* 2021].

Cross-resistance of antimicrobials

Cross-resistance was the old discovered phenomenon of antimicrobial resistance. The simple phenomenon is one antimicrobial exposure, and resistance can lead to resistance of all antimicrobials

of the same class. The extensive antimicrobial exposure to the large population group due to covid-19 potentially leads to no susceptible antimicrobials available [Ukuhor, 2021, Eduardo-Correia *et al.,* 2020].

National and International travelling

Covid-19 is not the first bacteria or virus to spread through travelling. Travelling has a long history of spreading different bacterial and viral infections such as *Streptococcus pneumoniae* infection, *Escherichia coli*traveler's diarrheaetc. [Collignon and Beggs,2020].Covid-19 and its pandemic had a massive and profound effect on travel policies and procedures. When the pandemic was declared, most countries restricted international travel. Strict policies were implemented upon allowing international travel by all Airlines to minimize the spread possibly. Moreover, travelling screening, health insurance, and travelling standard operating system (SOPs) requirements were also modified. These practices were much helpful in the spread of intercontinental spread. National travels were also affected, and social distancing was the only recommended cure besides travel was only allowed with proper SOPs [Collignon and Beggs, 2020].

Conclusion

Antimicrobial resistance has been declared as a silent pandemic. The WHO already issued a warning in 2017 that AMR is the most crucial global healthcare issue of the century. We just need to prepare for new threats and vigilant against new pandemics and challenges like Covid-19. The adapted therapeutic and management process must not invite another health burden that is a danger to healthcare and human health as well as the environment, terrestrial, and commensals.

Future Perspective

Covid-19 and possible management to reduce the AMR risk

The covid-19 wave is still here/active and affecting thousands of human lives daily. There are some critical factors listed for better management and reduction of AMR risk.

- Increase competence and training of the healthcare team; Initial screening and diagnostic testing are crucial to choosing a proper antimicrobial.
- Ensure continual quality health services; choose affordable and effective therapeutics and vaccinate the non-exposed population, especially the high-risk group.
- Improved diagnostic facility; reduced turnaround time (TAT) of covid-19 reporting.
- Be extra cautious about using biocides, personal disinfectants, antiseptics, surface and environmental cleaning methodology and the use of chemicals
- Identify research gaps and suggest better strategies and prepare to respond to any future pandemic [Getahun *et al.,* 2020].

Unanticipated Outbreaks, epidemics, and pandemics

Covid-19 was the unpredicted warning to all healthcare, pharmaceutical, and environmental agencies that we yet not prepared to handle these crises. Availability of appropriate, safe, and timely accessible antimicrobials is a great need to deal with future pandemics. High-income or developed countries still have better therapeutic options, healthcare facilities, and advanced infrastructure. Whereas low-income countries are entirely unable to face any of these challenges due to inadequate facilities, healthcare practices, and regulations. Pandemics have no boundaries due to excessive travelling and migration. Every country has different resources, and a single government cannot solve the pandemic threat alone. A Global plan of the "One Health approach" must be designed and implemented throughout to prepare for new healthcare challenges [GARDP, 2020].

Conflict of interest

No conflict of interest is declared.

Disclosure of interest

We disclose that this review didn't get any financial, personal, and financial aid during this research writing. This is our solely intellectual interest to contribute our role in medical knowledge.

Ethical statement

This study fulfilled all ethical parameters; no human and animal's right violations were made.

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