Issue 16, Volume 2 April 2024

The Impact of COVID-19 on Antimicrobial Resistance

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ACKNOWLEDGEMENTS

This paper was written for WRI 100: Advanced Writing with Heather Lanser.

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December 19th, 2023

Abstract

Studies have shown that the COVID-19 pandemic led to global panic and ultimately, an increase in antimicrobial resistance (AMR). Research has reported on the misuse of antimicrobials during the COVID-19 outbreak, which led to global complications. The misuse of antimicrobials discussed in the literature includes the empirical use of antibiotics, the knowledge gaps, and the excessive use of disinfectant products. There has been a greater impact of the misuse of antimicrobials on developing countries due to their lack of resources which will result in improper sanitation, inadequate infrastructure, and limited preparedness for future pandemics. To combat the increase in AMR, it is necessary to explore a variety of resolutions. These resolutions may include antimicrobial stewardship programs, rapid diagnostic methods, and funding for communicative research. Collaborative efforts between clinicians and researchers can lead to future advancements in AMR. To inhibit the progression of AMR, it is important to further research and further exploration.

Keywords: Antibiotic resistance, antimicrobial resistance, drug resistance AND problems, issues, challenges, difficulties, complications, AND COVID-19, coronavirus, 2019-nCoV, SARS-CoV-2

The Impact of COVID-19 on Antimicrobial Resistance

Studies have shown an increase in antimicrobial resistance (AMR) due to the misuse and overuse of antimicrobials during the COVID-19 (coronavirus-19 disease) pandemic (Lobie et al., 2021). This literature review addresses the question, *how did the COVID-19 pandemic impact antimicrobial resistance?* The emergence of the COVID-19 pandemic led to a global panic which resulted in an increased use of antibiotics (Khaznadar et al., 2023). Before the COVID-19 pandemic, antimicrobial resistance was gradually increasing, but post-pandemic, antimicrobial resistance is now at an all-time high. Unfortunately, knowledge gaps and prescription variation occurred during the pandemic which enforced the rise of AMR (Mahalmani et al., 2021). Due to the impact of AMR after the COVID-19 pandemic, further development of stewardship programs, diagnostic tools, and the funding of research is currently being implemented (Rodriguez-Alvarez et al., 2021). This literature review will report on the use of antimicrobials during the COVID-19 pandemic and the upsurge of AMR. There has also been a greater impact on third-world countries due to their lack of resources and advancements. Due to the rapid rise in AMR that is linked with the COVID-19 pandemic, there has been an increase in health implications. These health implications resulted from the overuse and misuse of antimicrobials that can be resolved with antimicrobial stewardship programs (AMSP), diagnostic testing, and future research funding. As a result, more research and resolutions will be needed to suppress the rise in AMR.

During this literature review's initiation, the UC Merced Library website was used to locate various databases. These databases included EBSCO, Science Direct, Web of Science, and PubMed. The sources that were used during the development of this literature review were dated from 2020 to 2023.

Overview of the COVID-19 Pandemic and Antibiotic Use

COVID-19 is depicted as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which resulted in global implications during and after the pandemic (Khaznadar et al., 2023). These global implications led to disaster planning and empirical use of a wide variety of antibiotics (Lobie et al., 2021). The spread of COVID-19 led to various public health implications which affected the daily lives of people all over the world (Mahalmani et al., 2021). According to the World Health Organization (WHO), there are over 173 million confirmed COVID-19 cases and over three million deaths due to COVID-19 as of June 8th, 2021 (Vidyarthi et al., 2021).

The increase in AMR during the COVID-19 pandemic led to various health issues that health authorities are currently dealing with. Health authorities implemented various prevention measures which included social distancing, hand hygiene, vaccinations, consistent testing, and antibiotic use (Khaznadar et al., 2023). These measures helped decrease the spread of COVID-19 and other infectious diseases, but AMR and multi-drug resistant (MDR) pathogens began to increase (Lobie et al., 2021; Khaznadar et al., 2023). As AMR and MDR pathogens increase, treating various infections in our body becomes more difficult. Bacteria and fungi learn to fight off the antibiotic or the drug used to kill them. The increase in AMR is due to the overuse of antibiotics during the COVID-19 pandemic (Lobie et al., 2021; Khaznadar et al., 2023; Mahalmani et al., 2021; Miranda et al., 2020). Lai et al. (2020) conducted a study at the National Taiwan University Hospital (NUTH) which portrayed increased rates of antibiotic consumption by COVID-19 patients. Lai et al. (2020) compared antibiotic consumption rates from January to June of 2019 against January to June of 2020. As a result, the antibiotics with higher consumption rates included beta-lactamase inhibitor combinations, quinolones, carbapenems, colistin, tigecycline, and Fosfomycin (Lai et al., 2020). These various antibiotics with higher consumption rates need to be analyzed further to indicate their level of effectiveness, especially during the COVID-19 pandemic. As shown in the works done by Khaznadar et al. (2023) and Vidyarthi et al. (2021), the Center for Disease Control and Prevention (CDC) reported that there are various pathogens that are highly resistant due to the inappropriate use of antimicrobials during the pandemic. The inappropriate use of antimicrobials that led to highly resistant pathogens includes the empirical use of antibiotics, excessive use of disinfectants, and knowledge gaps. These pathogens include Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, Enterococcus faecium, and Candida auris (Khaznadar et al., 2023; Vidyarthi et al., 2021; Rehman, 2023). These pathogens are important to keep records of to observe whether the pathogen's resistance decreases or increases over time as infection control practices are implemented.

Research has shown that AMR can be a possible pandemic of its own (Khaznadar et al., 2023). A recent report from the United Nations states that this AMR crisis can lead to 10 million deaths per year by 2050 if health authorities do not take accountability (Khaznadar et al., 2023; Dracea, 2021; Mahalmani et al., 2021; Vidyarthi et al., 2021; Miranda et al., 2020; Rehman,2023). As of right now, it might seem as if antimicrobials are used to treat millions of COVID-19 patients (Miranda et al., 2020). Due to the overuse of antimicrobials, the rise in AMR may be responsible for many deaths in the future (Miranda et al., 2020). All the research mentioned agrees that the increase in AMR is due to the abuse of antimicrobials during the COVID-19 pandemic and there is no disagreement.

Increase in Antimicrobial Resistance Due to the COVID-19 Pandemic

Various indications have led to the overuse and misuse of antimicrobials, especially during the COVID-19 pandemic. One of these indications is the empirical use of antibiotics in COVID-19 patients with co-infections (Lai et al., 2020; Zyoud et al., 2023; Mahalmani et al., 2021; Vidyarthi et al., 2021; Lobie et al., 2021; Miranda et al., 2020). The empirical use of antibiotics is solely based on observations of the patient's symptoms rather than conducting in-depth diagnostic testing strategies. This can lead to inaccurate prescription rates, especially if the patient has co-infections. Co-infections are present when a host cell is infected by several pathogens. The use of empirical treatments has increased due to limited medical and laboratory examinations of COVID-19 patients (Lobie et al., 2021). Antibiotics are currently being used for uncomplicated and acute diarrhea without detailed examination of the patient's symptoms (Rodriguez-Alvarez et al., 2021). The empirical overuse of these antibiotics will then be added to the total global usage but should be disregarded for unnecessary and excessive use (Rodriguez-Alvarez et al., 2021). The CDC indicated that in early 2020, 72% of patients worldwide were prescribed antibiotics to treat suspected co-infections, but only 8% of patients had bacterial co-infections (Johnson, 2021). An additional study discusses the relationship between symptoms in COVID-19 patients and pneumonia patients which led to clinicians empirically treating these patients despite the indication of a viral origin (Lai et al., 2021). It is important to bring up the misuse of antimicrobials due to empirical treatments because if it is not considered, empirical treatments can lead to an increased risk of spreading pathogens quickly.

Another indication that led to the inappropriate use of antimicrobials is the uncertainty and knowledge gap that was accompanied by the COVID-19 pandemic and antibiotic use (Mahalmani et al., 2021; Lai et al., 2020; Khaznadar et al., 2023). The global panic regarding the COVID-19 outbreak and the absence of treatment plans are contributors to the widespread of antibiotic prescriptions (Lai et al., 2020). The sudden upsurge in COVID-19 cases led to rapid progression in research for SARS-CoV-2 (Rodriguez-Bano et al., 2021). Since the development of COVID-19 research was being prioritized, the exploration of AMR was being delayed (Rodriguez-Bano et al., 2021). The scientific community had to focus its full attention on the COVID-19 outbreak which limited their abilities to fight AMR soon after (Lobie et al., 2021). Due to this knowledge gap, there have been widespread misconceptions seen among antibiotic use (Rehman, 2023). Closing the knowledge gap between AMR and COVID-19 will lead to further advancements in research that will decrease the spread of AMR.

A common misconception that is illustrated in the literature is that antibiotics like azithromycin, amoxicillin, and amoxiclav are effective in treating COVID-19 patients (Rehman, 2023). Azithromycin has doubled in consumption globally due to this misconception about antibiotic use during the COVID-19 outbreak (Khaznadar et al., 2023). Before the pandemic, azithromycin already had at least 30% bacterial species resistant to this antibiotic (Khaznadar et al., 2023). The increased usage during the pandemic has now spiked this percentage greatly (Khaznadar et al., 2023). In an additional study, there was an alternative scenario that led to the misinterpretation of the use of chloroquine and azithromycin as effective antibiotics during the COVID-19 outbreak (Rodriguez-Alvarez et al., 2021).

As described in a more detailed analysis, over five months during the pandemic, the number of prescriptions prescribed for azithromycin and chloroquine increased greatly (Rodriguez-Alvarez et al., 2021). Initially, 32,000 prescriptions were filled, and this rate eventually jumped to 93,000 prescriptions (Rodriguez-Alvarez et al., 2021). The combination of false media and panic-driven treatments led to an upsurge in ineffective antibiotic use (Rodriguez-Alvarez et al., 2021). This widespread use of antibiotics has resulted in a wide variety of antibiotic treatment plans being used in combination with each other (Miranda et al., 2020). Chen et al. (2020) reported that 15% of COVID-19 patients received anti-fungal treatment, 25% of patients received single antibiotics, 45% of patients received combination therapy, and 71% of patients received antibiotic treatment. This large range of treatment plans can lead to inaccurate data documentation or even undocumented data in general (Miranda et al., 2020). Misinterpretation of the function of antimicrobials during the COVID-19 pandemic increases the misuse and overuse of antimicrobials which can lead to a rise in AMR.

Additionally, bacterial pathogens have also become tolerant to the excessive use of disinfectants during the COVID-19 pandemic, which is another indication of the inappropriate use of antimicrobials (Lobie et al., 2021; Rodriguez-Bano et al., 2021; Vidyarthi et al., 2021; Rehman, 2023). Bacterial pathogens are known to become tolerant to alcohol-based disinfectants through molecular mechanisms

(Lobie et al., 2021). Various types of disinfectants and sanitizing products have chemicals (phenols and hydrogen peroxides) that create damaged DNA in bacterial pathogens (Lobie et al., 2021). Due to a mechanism called Translesion Synthesis (TLS) polymerase, the damaged DNA is bypassed by the bacteria (Lobie et al., 2021). After being bypassed, TLS will allow direct replication of the damaged DNA (Lobie et al., 2021). Direct replication of the damaged DNA will eventually lead to mutations in the genome of the bacteria, and the bacteria will evolve to become resistant to sanitation products (Lobie et al., 202). It is important to consider the excessive use of antimicrobials during the COVID-19 pandemic because this can lead to a rise in AMR.

An additional study discusses the increase in disinfectant products that contain biocides (Rehman, 2023). Biocides are products used to kill or control the spread of bacterial pathogens. Biocides can increase AMR because biocides can eventually be found in wastewater which can lead to resistant strains of bacteria (Rehman, 2023). Chemicals like biocides are also found in household cleaning products (Johnson, 2021). These chemicals can contribute to the rise in AMR by creating cross-resistance. Cross-resistance is when resistance occurs to all antibiotics in the same class because of a single mechanism (Johnson, 2021). To decrease the spread of AMR through biocides, Johnson (2022) recommended to use of biocides strictly in the hospital settings when necessary. The concentration of biocides has escalated because disinfectants have rapidly increased during the pandemic (Rehman, 2023). The main indications that led to the abuse of antimicrobials include empirical antibiotic treatments, widespread use of antimicrobial prescription due to knowledge gaps, and the extensive use of disinfectants/sanitizers. According to the literature, there is complete agreement that empirical treatments, knowledge gaps, and the overuse of disinfectants led to the misuse of antimicrobials during the COVID-19 pandemic.

The Greater Impact on Developing Countries

Studies found that underdeveloped countries have been greatly affected by AMR due to their lack of resources (Mahalmani et al., 2021; Vidyarthi et al., 2021). Not only did third-world countries get exposed to sudden fear, but third-world countries also have limited access to healthcare facilities and antibiotic control mechanisms (Mahalmani et al., 2021). Low- or middle-class countries (LMIC) have improper sanitation, poor infrastructure, and restricted preparedness for outbreaks which leaves these countries as the epicenter for AMR (Vidyarthi et al., 2021).

Since COVID-19 symptoms vary, it is more difficult to distinguish bacterial infections in developing countries which makes antibiotic use the most rational choice (Khaznadar et al., 2023). A current example of this could be Zimbabwe since infections like tuberculosis and malaria are very prominent in that country (Khaznadar et al., 2023). Developing countries contribute greatly to the spread of AMR because of poor health service management systems (Lobie et al., 2021). Therefore, third-world countries are more likely to become unaffected carriers of MDR pathogens, and relocating them from one region to another creates a new gene pool (Khaznadar et al., 2023).

For LMICs, physical distancing was not a practical way of living due to isolation from work and everyday living (Khaznadar et al., 2023). Physical distancing had very low effectiveness because in-person work was necessary for LMICs (Khaznadar et al., 2023). The literature states that to create effective measures for LMICs, it is important to begin with community-based strategies to lower AMR (Rodriguez Bano et al., 2021). Beginning with pharmacology-based strategies will not be an effective plan of action for third-world countries due to their limited resources (Rodriguez-Bano et al., 2021).

Johnson (2021) analyzed the drug resistance index (DRI). The DRI is a measure of the likelihood of bacterial pathogens becoming resistant to specified antibiotics over time. The results of the DRI proposed that both LMICs and high-income countries (HIC) do not take the effects of AMR into account because both country types all have high antimicrobial prescription rates (Johnson, 2021). Johnson (2021) concluded that the negative impact of AMR falls equally on LMICs and HICs. Most studies agree that third-world countries had a greater sudden impact due to post-pandemic AMR, but one of the studies disagrees with this proposal. As described, the disagreeing study incorporated the DRI, concluding that LMICs and HICs were impacted equally by AMR post-pandemic.

Resolutions and Future Development

Many strategic plans have been proposed to resolve the upsurge in AMR after the pandemic including the following: antimicrobial stewardship programs, diagnostic tools, and future funding of research through collaborative efforts (Dracea, 2021; Khaznadar et al., 2023; Lai et al., 2021; Mahalmani et al., 2021; Miranda et al., 2020; Rehman, 2023; Rodriguez-Alvarez et al., 2021; Rodriguez-Bano et al., 2021; Vidyarthi et al., 2021; Zyoud, 2023). Antimicrobial stewardship programs (AMSP) are portrayed by strategies meant to improve prescription rates of antibiotics by clinicians and healthcare workers (Dracea, 2021). There are many core elements required to coordinate an efficient AMSP. These elements include leadership, accountability, drug expertise, action, tracking, reporting, and education (Dracea, 2021). Before the COVID-19 pandemic, a survey was conducted on the effectiveness of stewardship programs (Khaznadar et al., 2023). The results portrayed 85% effectiveness out of 244 active members (Khaznadar et al., 2023). The results also reported that there was a 20% decrease in drug-resistant antimicrobials (Khaznadar et al., 2023). There is evidence that supports the implementation of stewardship programs before the COVID-19 pandemic. Due to this, utilizing AMSPs can help suppress AMR as society becomes more aware of AMR's significance through these programs.

Due to the wide variation in the empirical use of antibiotics, AMSPs have been looking into restrictive measures when administering empirical treatments (Vidyarthi et al., 2021). These restrictive measures include a set algorithm used for decision-making when administering antibiotic treatment to patients (Mahalmani et al., 2021). The algorithmic steps include a criterion for patient admission, testing blood, respiratory, and urine cultures, consideration of empirical antibiotics, and reassessment of patients in 48 to 72 hours (Mahalmani et al., 2021). A set algorithm will help improve prescribing patterns by monitoring and guiding the rational use of antimicrobials through dosing intervals, route of administration, and duration of treatment (Mahalmani et al., 2021). AMSPs could also help reduce the use of biocides in household sanitation/disinfectant products by restricting them only to hospital and institutional care settings (John, 2021).

There have also been advancements in various diagnostic testing strategies (Dracea, 2021; Khaznadar et al., 2023; Lai et al., 2021; Mahalmani et al., 2021; Zyoud, 2023). The National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) 2020-2025 reported the significance of developing innovative rapid diagnostic tests to indicate resistant bacteria in patients (Khaznadar et al., 2023). Diagnostic rapid testing can also lead to early detection of COVID-19 in patients. This early detection can prevent the progression of the disease and the rate of secondary infection will decrease (Mahalmani et al., 2021). This development will help identify resistant bacterial pathogens quickly and efficiently (Khaznadar et al., 2023). Diagnostic testing will lead to accurate antibiotic use resulting in a decrease in AMR (Khaznadar et al., 2023).

Currently, the clinical symptoms for many forms of viral respiratory infections are similar to those of bacterial respiratory infections (Zyoud, 2023). These similarities in infections lead to the overuse of broad-spectrum drugs, therefore, diagnostic testing will help differentiate between these various infections (Zyoud, 2023). The development of tools for rapid diagnosis of infectious bacterial pathogens in patients will lead to prompt and adequate treatment plans (Rodriguez-Alvarez et al., 2021).

Artificial intelligence (AI) could play a role in increasing the effectiveness of diagnostic testing

(Dracea, 2021). AI can be used to assist human thinking by predicting and evaluating infectious diseases and possibly making appropriate antibiotic prescriptions (Dracea, 2021). The aid of AI in combating AMR can be summarized in four groups which include diagnosis, mortality risk assessment, pandemic prediction and monitoring, and stewardship planning (Dracea, 2021).

Additionally, research has also analyzed biomarkers such as Procalcitonin (PCT) to differentiate between COVID-19 and other secondary infections in a patient (Mahalmani et al., 2021; Lai et al., 2021). Biomarkers can lead to early detection and confirmation of pathogens in the body that can be harmful to the patient. Lai et al. (2021) conducted a meta-analysis of 32 randomized controlled trials. The meta-analysis concluded that the use of PCT can initiate and indicate the duration of antibiotic treatment in patients with acute respiratory tract infections which will result in a decrease in antibiotic utilization and adverse events (Lai et al., 2021). However, another study concluded PCT is not a useful biomarker when specifically differentiating between COVID-19 and other bacterial coinfections (Mahalmani et al., 2021). PCT was unable to differentiate and indicate between COVID-19 and other coinfections in a patient which led to it being argued as a useless biomarker (Mahalmani et al., 2021). The literature then goes on to discuss that there is a lack of appropriate biomarkers available, and research needs to be done on other types of biomarkers instead of PCT (Mahalmani et al., 2021). Further research is needed on different types of biomarkers to confirm which biomarkers are useful in differentiating between COVID-19 and other bacterial coinfections in a patient.

The idea of international and local funding has been examined to promote collaboration between various industries to combat AMR (Rodriguez-Bano et al., 2021; Rodriguez-Alvarez et al., 2021; Miranda et al., 2020; Dracea,2021; Rehman, 2023; Vidyarthi et al., 2021). Collaborative efforts with the pharmacy industry can lead to the discovery of new molecules, drug diagnosis, and cost reduction (Dracea, 2021).

The fight against AMR can be approached more efficiently if government investment can be put into the pharmacy industry (Dracea, 2021). These investments will result in research for new molecules, international collaborative relationships through medical and scientific methods, and clear judgment in antibiotic decision-making (Dracea, 2021). The literature discusses that clinicians and researchers need to work together to study the whole genome sequence of clinical bacterial pathogens where the genome sequencing of bacterial pathogens will help with the interpretation of transitional changes in AMR mechanisms (Rehman, 2023). Clinicians need to be made aware of the advancements in microbiology (Vidyarthi et al., 2021). This advancement will result in clinicians being familiar with the newest version of antibiotics that will be consumed by their patients (Vidyarthi et al., 2021). Therefore, AMR research communities are in an ideal position to raise AMR awareness and build community engagement at the local level (Rodriguez-Bano et al., 2021).

To ensure AMR research and collaboration continue, AMR research funds at the national and international levels should be prioritized (Rodriguez-Bano et al., 2021). Overall, to resolve the issue of AMR, it is important to have various plans intact. All the studies agree that AMSPs, diagnostic tools, and funding are important elements to decrease the spread of AMR. However, one of the studies disagrees with the advancement of PCT as a potential biomarker for COVID-19 and secondary infections due to a lack of research (Mahalmani et al., 2021).

Conclusion

The COVID-19 outbreak led to global panic and increased use of antimicrobials. Due to unpreparedness, the use of antimicrobials has become inconsistent in healthcare facilities worldwide. The variation of drug-resistant bacterial pathogens increased due to the misuse and overuse of antimicrobials. Since the COVID-19 pandemic was an unexpected event, scientists halted their research on AMR and focused their time on the analysis of SARS-CoV-2. This led to knowledge gaps and inconsistencies when the upsurge in AMR began.

According to the drug resistance index, LMICs and HICs have been affected by AMR equally because neither LMICs nor HICs took the effects of AMR into account. However, underdeveloped countries do not have the required necessities to consider AMR as a factor due to limited access to health treatment plans. Underdeveloped countries should be funded and clinically engaged more than first-world countries. This is because, due to a lack of resources, third-world communities need more assistance and aid to enhance sanitary infrastructure and adequate treatment plans.

Due to the impact AMR had on society, there have been various plans considered in order to decrease the spread. These plans included stewardship programs, diagnostic tools, global funding, and collaborative research efforts. There is consistent agreement with the implementation of AMSPs to reach a level of stability between clinicians and patients.

Due to the rise in AMR after the COVID-19 pandemic, diagnostic tools and biomarkers like PCT can be used as effective resolutions to decrease the spread of AMR. Diagnostic tools are used to detect COVID-19 early on before co-infections arise in the patient. Effective types of diagnostic tools include biomarkers, which serve as an objective measure to indicate what is happening inside the cells of a patient. More research should be done on PCT, which can possibly be treated as an effective type of biomarker when differentiating between COVID-19 and secondary infections in patients. Due to disagreement with this type of biomarker, there should be more research implemented to find a consensus on PCT.

The sudden rise in AMR due to the COVID-19 pandemic has led to various health implications. Being able to identify several indications that directly led to the increase in AMR is a step in the right direction. As discussed previously, these indications can include the empirical use of antibiotics, the overuse of disinfectants, and knowledge gaps. These various implications also greatly affected developing countries due to their lack of resources and advancements. To implement plans to combat AMR, there needs to be constant communication between clinicians and researchers. Both health authorities need to be in continuous agreement to implement the most efficient treatment plans for patients. To advance in future research, health authorities agree that funding is needed at national and local levels. Continuous research requires government funding to maintain control of AMR. As time has passed, AMR has gradually become a global problem after the COVID-19 outbreak. This global problem can be resolved with community and international engagement in ASMPS, appropriate sanitation regulations, and quality funding.

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