2021 Writing Contest Undergraduate Winner

A Systematic Review of Antimicrobial Resistance During the COVID-19 Pandemic

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Abstract

Antimicrobial-resistant pathogens, or "superbugs," cause more than 35 000 deaths and more than 2.8 million antibiotic-resistant infections in the US each year. Worldwide, antimicrobial resistance (AMR) has claimed at least 700 000 lives per year, including 230 000 from multi-drug resistant (MDR) tuberculosis. AMR-related deaths are projected to increase to 10 million by the year 2050. The use of biocides, improper prescribing of antibiotics for viral infections, prolonged hospital stays, and other issues contribute to AMR. The purpose of this study was to determine whether the COVID-19 pandemic has had an impact on the rates of AMR globally. While it is still early for the results of research studies, 4 articles indicated an increase, 2 found a decrease, and 2 had mixed results. It is possible that this pandemic may be contributing to an increase of medication-resistant infections.

Keywords

antimicrobial resistance, antibiotic resistance, multi-drug resistant, COVID-19

Abbreviations

AMR = antimicrobial resistance
CDC = Centers for Disease Control and Prevention
DFI = diabetic foot infections
DFU = diabetic foot ulcers
DM = diabetes mellitus
DOT = directly observed therapy
ICU = intensive care unit
MDR = multi-drug resistant
MDRGN = multi-drug-resistant-gram-negative
MRSA = methicillin-resistant Staphylococcus aureus
SBI = secondary bacterial infection
SES = socioeconomic status
STI = sexually transmitted infection

The term "superbugs" refers to pathogens that are medication-resistant. They are also known as antibiotic-resistant, multi-drug resistant (MDR), or antimicrobial-resistant (AMR) pathogens. These infections are caused by pathogenic microorganisms such as bacteria or fungi that have evolved to possess medication-resistant genes, therefore rendering treatment ineffective. According to the Centers for Disease Control and Prevention's (CDC's) *Antibiotic Resistance Threats in the United States, 2019* (2019 AR Threats Report), more than 2.8 million antibiotic-resistant infections occur in the US every year, causing more than 35 000 deaths and costing $20 billion in health care expenditures.[1] Globally, AMR causes approximately 700 000 deaths per year and these are projected to increase to 10 million deaths by the year 2050.[2]

COVID-19 has emerged during a time of great concern surrounding antimicrobial resistance. A common method of bacterial control and growth inhibition is the utilization of biocides, such as hand sanitizers, which have increased in use during this pandemic. However, the misuse or ineffective concentrations of alcohol in, for example, homemade hand sanitizers may increase the risk for developing medication-resistant infection.[3] Other risk factors for bacterial co-infection include prolonged hospital stays for COVID-19 positive patients, invasive therapeutic devices such as ventilators, and the misuse and/or improper prescribing of antimicrobials.[4,5] In a study of postmortem examinations of individuals from the 1918 Spanish Flu pandemic, results showed severe changes indicative of bacterial pneumonia. Bacteriologic and histopathologic results consistently implicated secondary bacterial pneumonia caused by common upper-respiratory-tract bacteria in most influenza fatalities.[6]

As such, bacterial co-infections with COVID-19 should be studied in order to devise and implement preventative strategies, which in turn, may address the projected increased rates of AMR.

Prevalence of Co-Infection and AMR

There are many challenges to estimating the burden of AMR. Information is not only limited but often unreliable due to the complex nature and factors of this issue.[7] For example, selection bias can be inherent in determining who is tested for AMR infections, but there is also inconsistency with information, specifically, whether it is even entered into laboratory data systems. Furthermore, it is not uncommon for data sources from both private and public sectors to not collate these data,[8] and this creates an even larger challenge at both national and international levels. Standardized protocols for diagnostic methods, data collection, and data entry are needed. These challenges are further exacerbated in low- and middle-income countries where there is little surveillance, minimal laboratory capacity, and limited access to essential antimicrobials.[8] In an early pilot study, researchers found *Acinetobacter* was present in 83.3% of COVID-positive patients, and 50% of the *Acinetobacter* isolates were multi-drug resistant and most commonly distributed in the COVID-positive group.[9] In another study, 14% (95% CI 5-26%) of critically-ill COVID-19 patients in the intensive care unit (ICU) between March 4, 2020 and June 2, 2020 had bacterial coinfections. Nine multi-drug resistant (MDR) strains represented 6% of the isolates; these included extended-spectrum beta-lactamase *E. coli* (4 strains), MDR *P. aeruginosa* (2 strains), and methicillin-resistant *Staphylococcus aureus* (MRSA) (3 strains).[10] In a recent study of patients admitted to a tertiary-care hospital in India, 13% of admitted patients (151/1179) had a secondary infection; most were infected within 14 days of admission. In this study, patients ages 50 years and older were more likely to develop severe symptoms and/or fatal outcomes; in-hospital mortality rates from *K. pneumoniae* were at 33%, and from *A. baumannii* were 27%. Drug-resistant pathogens were isolated from clinical samples of COVD-19 patients, and overall medication resistance by organism ranged from 9% to as high as 84%.[11]

Risk Factors and Drivers of AMR

While everyone is at risk for the 22 microorganisms listed in the 2019 AR Threats Report, children and older adults are at a higher risk, and immune-compromised individuals are at the highest risk.[12,13] Individuals with sexually transmitted infections (STIs) may also be also at increased risk for co-infection of COVID-19 and AMR, as antibiotic resistance is increasing rapidly in bacteria responsible for specific STIs.[14,15]

Clostridioides difficile, formerly *Clostridium difficile* or more commonly known as "C. diff," is classified as an urgent threat in the CDC's 2019 report. Although commonly viewed as a hospital-acquired infection, recent studies show that approximately 41% of *C. difficile* infections are community-acquired.[16] COVID-19 may be further complicating this picture. There is a relationship between overuse of antiseptics and disinfectants and AMR.[17] Research also suggests that a substantial proportion of COVID-19 patients are receiving antimicrobial therapy, despite relatively few reports of bacterial coinfection.[18]

While socioeconomic status (SES) and race/ethnicity are key factors in the social determinants of health,[19] there is little research defining the relationship between SES, race/ethnicity, and AMR. However, there may be a relationship between low health literacy and antibiotic misuse (1 of the main contributors to AMR). In a recent study on antibiotic misuse, 53.7% of participants admitted having "leftover" antibiotics; among these individuals, 77.0% reported "saving" antibiotics, and 4.6% gave their antibiotics to others.[20] Some patients on limited incomes may stop taking their medication once symptoms ease, in order to save pills in case of another infection, while others may assume that a specific antibiotic can treat health concerns other than the concern for which it was prescribed.[20,21]

Poverty and low health literacy can also support the circulation of practices and beliefs that foster inappropriate antibiotic use. These factors may encourage people to self-medicate against common infections, purchase medications from poorly-regulated drug dispensaries, or consult traditional practitioners for health concerns that require biomedical care.[20] Medicines obtained from traditional practitioners often contain unknown chemical agents mixed with antimicrobials in substandard doses, which foster AMR.[22] Improving access to biomedical health care, as well as more robust capacity within the health care system, such as more diagnostic laboratories, especially in low- to middle-income countries, may help to lower rates of AMR.[22]

The agricultural industry introduces another risk factor. The use of antibiotics in livestock contributes to rising rates of multidrug resistance.[23] In recent years, many countries, including the US, Canada, Japan, and China, have limited or restricted the use of antibiotics in food animals. In some cases, such restrictions have been associated with reductions in AMR in humans, suggesting a causal relationship between antimicrobial usage in animals and AMR in humans.[23]

In a recent epidemiological study examining the patterns of AMR in *Escherichia coli* isolates circulating in humans and livestock, *E. coli* isolates were tested for susceptibility to 13 antimicrobial drugs representing 9 antibiotic classes. High rates of AMR were detected, with 47.6% and 21.1% of isolates displaying resistance to 3 or more and 5 or more antibiotic classes, respectively.[24]

Climate change is another risk factor. Heat has been linked to antibiotic-resistant genes in many gram-negative bacteria. It is also a key factor for horizontal gene transfer, the main mechanism in which bacteria acquire resistance.[25] AMR is not limited to bacterial species.

Finally, natural disasters and/or extreme weather events also lead to infections. For example, flooding can cause water-borne diseases, infections due to overcrowding among people seeking shelter in large public spaces, contaminated water due to sewage spillover, and eutrophication.[25]

Methods

This systematic literature review was conducted to explore whether the COVID-19 pandemic has affected the number of cases of AMR globally.

Criteria for Considering Studies in this Review

Although AMR can occur in viruses, bacteria, and fungi, cases of bacteria and fungi that have become drug and MDR are increasing. In the CDC's 2019 AR Threats Report, only bacterial and fungal pathogens and their threat levels are categorized as urgent, serious, or concerning.[26] As such, for the purpose of this project, viral infections were excluded.

Search Strategy

This review was conducted utilizing PRISMA guidelines (**Figure 1**). A search was conducted via PubMed on the terms "COVID-19" and "Drug Resistance" (including Microbial, Bacterial, Fungal and Multiple). This search yielded 155 results.

References from PubMed were collected and recorded into Zotero. One duplicate was removed, along with 33 articles that did not meet PICOS (a framework used in evidence-based practice that stands for and involves the following criteria: Patient/Population, Intervention, Control/Comparison, Outcome) standards, and the remaining 121 article titles were then screened. Those that did not include reference to AMR or COVID-19 were removed (n=34). Accepted articles were further narrowed down by screening their abstracts (13 removed), and then the full articles looking for quantitative or qualitative studies in humans only (79 removed).

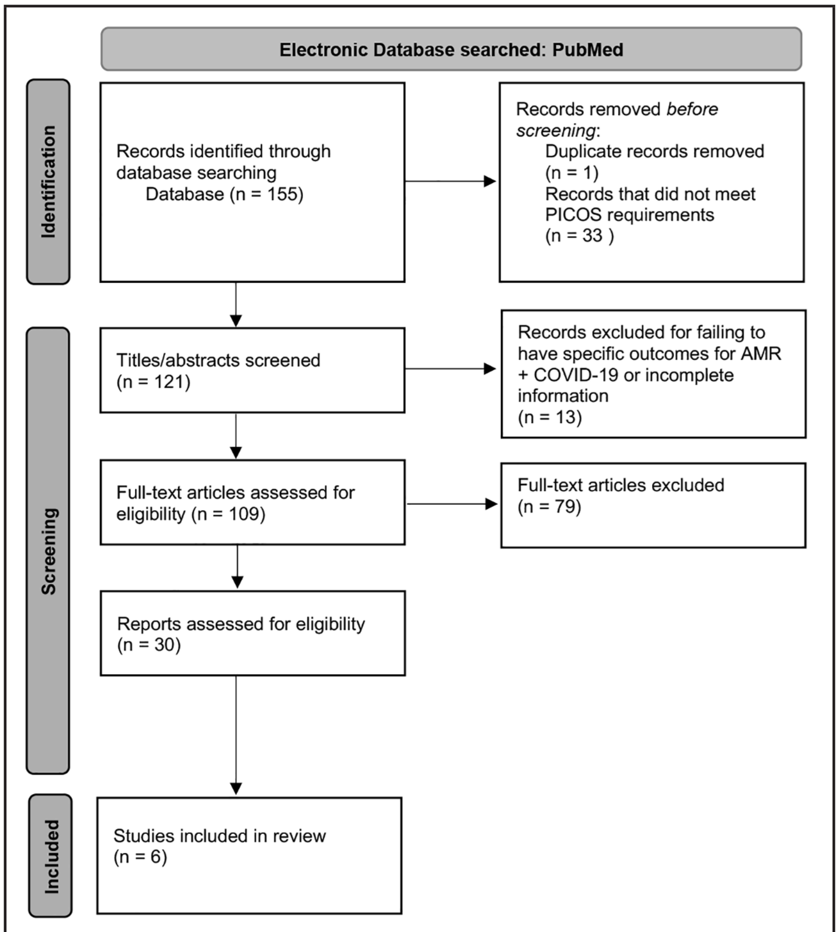

Figure 1. PRISMA Article Selection Flowchart[a]

[a] Figure reflects the flow of information via the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), an evidence-based, minimum set of recommendations designed primarily to encourage transparent and complete reporting of Systematic Reviews.[27]

Results

Out of the 30 articles that met the inclusion criteria, 6 measured the increase or decrease of antimicrobial-resistant infections (**Table 1**). In Gaspar et al, an observational and retrospective study, pre-and post-COVID-19 susceptibility to health care-associated infections in the ICU of a tertiary care hospital in Sao Paulo, Brazil was evaluated. The study population included adults admitted into the ICU and then later transferred to the COVID-19 ICU. Data were retrieved via electronic medical records and microbiological laboratory reports with clinical samples isolated from blood, surgical wounds, catheter tips, urine, tracheal secretions, and rectal swabs. Resistance rates during January 2018 and July 2020 were determined for *S. aureus* resistance to oxacillin (35 resistant cases of 47 total cases), *A. baumannii* resistance to carbapenem (136/173), *K. pneumoniae* resistance to carbapenem (153/246), and *K. pneumoniae* resistance to polymyxin B (153/246). Results revealed an increase of resistance rates during the pandemic for *A. baumannii,* and an even higher rate for *K. pneumoniae* from 5% to 50% for Polymyxin B, an antibiotic used to treat these infections. *K. pneumoniae* was also up 33.3% and the most common pathogen, followed by *A. baumannii* at 27.1%.[28]

In another retrospective study, Caruso et al examined cases of individuals with diabetes mellitus (DM) and diabetic foot ulcers (DFU), at a tertiary care center in Italy, and investigated the rate of antibiotic resistance and its main risk factors for patients with diabetic foot infection (DFI) during the COVID-19 pandemic. From a total of 225 patients with DFI, over the period of January 1, 2019 to December 31, 2020, comparisons were made via microbiological examinations of soft tissues or bone biopsy and were divided as 105 individuals with DM and DFU in 2019, and 120 in 2020. Among the population, 19 patients of the 2019 group, and 63 patients of the 2020 group were admitted with recent or current antibiotic therapy (P<.001). The 2020 group had a higher rate of antibiotic administration (53% vs 79%, P=.044). Of note, compared with 2019, a higher rate of antibiotic self-administration (5% vs 30%, P=.032) and an association with a significant reduction of prescriptions by specialists (79% vs 35%, P=.002) were found in 2020. Results indicated that patients with DFI had a higher incidence of antibiotic resistance in 2020 compared to 2019 from 36% to 63% (P <.001), and previous hospitalization, self-administration of antibiotics, as well as prescription by general practitioners were related to a higher risk of antibiotic-resistant infections.[29]

Another study utilized interrupted time series segmented regression to search for trends in antibiotic use and multi-drug-resistant-gram-negative (MDRGN) acquisition and relationship with COVID-19 in an academic hospital in Maryland. Over a 24-week period from January 5, 2020 to June 7, 2020, researchers looked for COVID-19 related trends, using the same period in 2019 as the control. Data were collected via the hospital's antimicrobial stewardship database that included records of daily dispensed antimicrobials, associated indications, and hospital census divided into 3 categories: total antibiotics, pneumonia antibiotics, and early pneumonia antibiotics (fewer than 7 days from admission). Early pneumonia data captured suspected community-onset bacterial coinfections. To account for the decrease in patient days in 2020 driving changes in antibiotic directly observed therapy (DOT) per 1000 patient days, a separate analysis was conducted of the proportions of DOTs for pneumonia and early pneumonia DOTs in the 2019 and 2020 post-pandemic-onset periods, as well as the monthly proportions of COVID-19 patients who received antibiotics for pneumonia in 2020. MDRGN incidence was measured via the number of clinical cultures per 10 000 patient days, for *Enterobacterales, Pseudomonas aeruginosa,* or *Acinetobacter baumannii* that were non-susceptible to more than 2 of the following antimicrobial agents: piperacillin/tazobactam, cefepime, or carbapenem. Hospital-wide MDRGN incidence and MDRGN

Table 1. Brief Summary of Antimicrobial Resistance During COVID-19 Studies

Lead Author / Year	Location	Summary of Study Findings	Impact on AMR
Gaspar et al, 2023	Sao Paulo, Brazil	*S. aureus* resistance to oxacillin 35/47 (74.4%), *A. baumannii* resistance to carbapenem 136/173 (78.6%), *K. pneumoniae* resistance to carbapenem 155/246 (62.1%), *K. pneumoniae* resistance to polimyxin B 37/246 (15.0%).[28]	Increase
Caruso et al, 2021	Naples, Italy	The incidence of antibiotic resistance among patients with diabetic foot infections was higher in 2020 compared to 2019 (36% vs 63%, P <.001).[29]	Increase
Bork et al, 2020	Maryland, USA	Total antibiotic use and antibiotic use for pneumonia specifically were higher after the onset of COVID-19, with a 3% increase of multi-drug gram-negative acquisition in positive COVID-19 tests per week.[30]	Increase
Cole et al, 2020	Los Angeles, California, USA	Multi-drug resistant organisms decreased from 0.3% per 1000 patient days to 0.2% per 1000 patient-days (P = .03).[31]	Decrease
Bentivegna et al, 2021	Rome, Italy	Higher incidence of 4 MDRO (MRSA, ESBL K. pneumoniae, HA-CD, *A. baumannii*) found in COVID floor patients compared to other departments, but lower in non-COVID floors.[32]	Mixed
Karatas et al, 2021	Bornova, Turkey	Multi-drug resistant *A. baumannii* was higher among COVID-19 patients (9.8%%) than pre-pandemic (3.5%, P < .002), and pandemic era control group (3.1%, P < .001). However, there was a decrease in ESBL-producing *Enterobacterales* (8.9%) compared to pre-pandemic samples (20.8%, P < .001) and pandemic era (20.7%, P < .002).[33]	Mixed

incidence among COVID-19-specific patients were calculated and results indicated that total antibiotic use in general, and specifically for pneumonia were higher after the onset of the pandemic, with a 3% increase of multi-drug gram-negative infection in positive COVID-19 tests per week.[30]

A retrospective cross-sectional study at 4 community hospitals in Los Angeles County, California, reviewed the prevalence of health care onset infections with multi-drug resistant organisms that included MRSA, extended spectrum beta-lactamase (ESBL), and Vancomycin-resistant *Enterococcus* pre-and-post-COVID-19 pandemic to determine the efficacy of an increase in health care workers' compliance with infection prevention. Specimens were collected from urine, wound, blood, or sputum cultures, with only patients who did not have a positive culture for the specific organism until on or after the 4th day of hospital admission. Infection prevention initiatives among health care workers have increased awareness of effective hand washing, cleaning equipment after use, and appropriate personal protective equipment (PPE) use, and the incidence of MDR infection decreased from 0.3% per 1000 patient days to 0.2% per 1000 patient days (P=.03).[31]

In a hospital in Rome, Italy, researchers conducted a case-control study to measure if the incident of MDR bacteria would be lower with preventive measures introduced in 2020. They compared the rates of MDR infections over a 4-month period between March 1 to June 30, in 2017, 2018, and 2019, to the same 4-month period in 2020, when the preventive measures were introduced. Incidence for the 4 most common bacteria (MRSA, ESBL *K. pneumoniae,* HAI (hospital-acquired-infection) *Clostridium difficile,* and *A. baumannii)* on the COVID floor was compared to other departments. During 2020, of the 1617 discharges, both the COVID-19 floor and non-COVID-19 floors showed lower incidences of total MDR infections (MDRI) compared to previous years (45.2% during 2017, 44.2% during 2018, and 41.4% during 2019)(P < .05). However, although lower than pre-pandemic years, the COVID-19 floor did present a higher incidence of all 4 MDRIs than the non-COVID-19 floor (29.2% compared to 19.2%, P <.05).[32]

Lastly, Karatas and colleagues conducted a case-control study at the Ege University Hospital in Izmir, Turkey. With a total of 3534 patients and 4859 positive cultures, they sought to evaluate the epidemiology and AMR patterns of bacterial co-infections and secondary bacterial infections (SBI) in COVID-19 patients and compared the results with 2 control groups of patients with SBIs and bacterial co-infections; from the pre-pandemic era with 2143 patients, and 3034 samples (December 15, 2019 – March 15, 2020) and during the pandemic from 1304 patients, 1702 samples, that did not have a COVID-19 diagnosis (March 16, 2020 – June 15, 2020).[33] Microbiological database records were evaluated retrospectively, and patients with acquired SBIs and bacterial co-infections were analyzed, along with etiology and AMR data of bacterial infections. Data from the 1447 COVID-19 diagnosed patients' were evaluated separately and comprised of 85 patients with 123 bacterial infections. Results were compared from the pre-pandemic control group and the pandemic era control group respectively. Detection of multi-drug resistant *A. baumannii* was significantly higher in patients with COVID-19 compared to the pre-pandemic control group, and the pandemic era control group (9.8%, 3.5% and 3.1%, respectively P <.001). However, there was a significant decrease of ESBL-producing Enterobacterales (8.9%) compared to pre-pandemic control group (20.8% P <.001) and pandemic era control group (20.7%, P < .002).[33]

Discussion

While there were only 6 articles found that indicated the impact of COVID-19 on AMR, it is still relatively early at the time of this paper, and additional studies are warranted for a more comprehensive picture. Regardless, it appears that cases of AMR infections during the COVID-19 pandemic are increasing. While scientists are looking for new antibiotics, and other forms of novel treatments such as nanoparticles and phage therapy, this increase indicates that antibiotic stewardship programs are more important than ever in this global "arms race." This importance has been reiterated throughout the years, including by the World Health Organization (WHO) in April 2014, when it stated that bacterial antibiotic resistance is a current and "major threat," that could affect "anyone, of any age, in any country." Later, in May 2019, at the World Health Assembly, Dr. Tedros Adhanom Ghebreyesus, the WHO Director-General stated that the fight against AMR is one of the most urgent health threats of our time. Nationally, these warnings are also echoed by the CDC in its 2013 and 2019 AR Threats Reports.

Strengths and Limitations

This systematic review relied upon and was limited to only PubMed for the identification of eligible studies. In addition, at the time it was conducted, the pandemic continued to peak all over the world, providing potentially more data on COVID-19 and AMR cases.

Conclusion

The COVID-19 pandemic has highlighted multiple challenges and issues globally with regards to public health and AMR. Earlier in the pandemic, some areas lacked testing and laboratory resources, which resulted in unnecessary antibiotic prescriptions – a known driver of AMR.[8] While aseptic measures were perhaps more vigilantly adhered to and rates of AMR decreased in hospitals, drug-resistant bacterial co-infection rates have increased in COVID-19 units.[32] While this paper was written during the pandemic, infections continue to increase. More recent data would provide a more accurate picture regarding the impact of the COVID-19 pandemic on AMR.

Conflict of Interest

None of the authors identify a conflict of interest.

Acknowledgements

The authors would like to thank Dr. Teena Michael for continuous mentorship and vast knowledge of microbiology, the staff and faculty of the undergraduate degree program at the Office of Public Health Studies, University of Hawai'i at Mānoa.

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