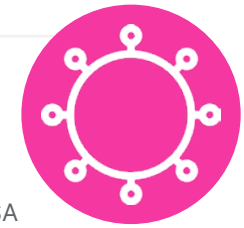
A Perfect Storm: COVID-19 and Antimicrobial Resistance



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INTRODUCTION

For decades, infectious disease and public health experts have recognised antimicrobial resistance (AMR) and resulting infections due to multidrug resistant organisms as a persistent and increasingly urgent threat to public health at the local, national, and global level. The years leading up to the COVID-19 pandemic were marked by important victories in the battle against AMR, including a surge in scientific inquiry on the topic, the development of multinational best practice consensus statements, the establishment of regional and global venues to share information, and a partially-funded commitment by world leaders to address the topic in a serious and sustained manner. In the USA and many other countries, there were some data to suggest these efforts may be generating positive results. The Center for Disease Dynamics, Economics & Policy (CDDEP), a USA-based not-for-profit that tracks antimicrobial resistance for the USA, Canada, and over 30 European countries, observed a recent plateau and even decrease in antimicrobial resistance across some nations for certain key organism-drug combinations like *Escherichia coli*-fluoroquinolones and *Streptococcus pneumoniae*-penicillins.[1] However, a more recent global analysis of bacterial

antimicrobial resistance-projected AMR will become the leading global cause of death by 2050 if existing trends continue.[2]

In late 2019 the world changed, as did the landscape for addressing the global threat of AMR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated clinical syndrome (COVID-19) continue to drive a global pandemic of viral respiratory illness that has subjected the world's population to unprecedented morbidity and mortality that is ongoing, and will not be fully understood for years to come. Although the latest COVID-19 wave related to the Omicron BA.5 subvariant is receding, the resolution of the pandemic is not yet in sight, and may never be. Nevertheless, it is a critical moment to consider potential collateral damage to the global fight against AMR resulting from the pandemic. Although data is sparse, the available reports from several countries indicate acceleration of AMR in the post-COVID era.[3-8] Here, the authors highlight key factors that contributed to the impact of the COVID-19 pandemic on AMR, with an eye towards lessons learned and next steps.

IMPACT OF HEALTHCARE SYSTEM STRAIN ON INFECTION CONTROL AND ANTIMICROBIAL STEWARDSHIP

As the operational capacity of healthcare systems across the globe was severely strained during the pandemic, disruptions to standard infection control (IC) and antimicrobial stewardship (AMS) were inevitable. These practices are key to keeping AMR in check by limiting the spread of multidrug resistant organisms (MDRO) within healthcare settings (e.g., long-term care facilities, inpatient wards), and decreasing selective pressure related to inappropriate or unnecessary antimicrobial therapy respectively. The Centers for Disease Control and Prevention (CDC) has tracked sporadic outbreaks of MDROs, including *Acinetobacter* and *Candida*, during the pandemic.[9] These outbreaks were linked to a breakdown of IC procedures (e.g., less personal protective equipment use and decreased screening) during COVID-19 surges.[10]

Disruptions to standard IC measures designed to mitigate AMS are compounded by the disproportionately long hospital and intensive care unit lengths of stay observed in patients with COVID-19 compared with patients infected with other viral pathogens. Critically ill patients usually require lines, tubes, and/or drains, which pose an increased risk of secondary bacterial infections the longer they are in place. These infections are notoriously difficult to treat due to the lack of blood flow combined with a plastic matrix that facilitates bacterial growth and creates conditions ripe for the development of AMR. This results in a negative feedback loop, with MDRO concern increasing broad spectrum antimicrobial use (e.g., carbapenems), which in turn drives resistance at the unit and hospital level.[11] While this synergistic challenge to IC and AMS is formidable, established programmes manage it as part of routine operations. However, the pandemic introduced system level disruptions to IC and AMS, including shortages in personal protective equipment, increased workload, staffing issues, and units operating beyond typical capacity limits. Two surveys of AMS pharmacists identified significant disruptions to routine AMS activities, such as auditing and quality improvement initiatives, during the pandemic.[12,13]

LACK OF AVAILABLE THERAPEUTIC OPTIONS EARLY IN THE PANDEMIC

Given the novel nature of SARS-CoV-2, researchers, public health officials, clinicians, and even patients have searched frantically for therapeutic interventions to mitigate the morbidity and mortality related to COVID-19. Among the potential candidates for therapeutic intervention, several antimicrobial agents were identified and investigated, some scientifically, and others in an *ad hoc* manner. For instance, a comparison of antibiotic use in 1,944 nursing homes and long-term care facilities in the USA between January 2019–October 2019 and January 2020–October 2020, respectively, observed a 563% increase in antiparasitic hydroxychloroquine use in April 2020.[14] Unsurprisingly, this spike corresponds with a U.S. Food and Drug Administration (FDA) emergency use authorisation for the use of hydroxychloroquine for treatment of COVID-19 on 28th March 2020. The subsequent drop

back to baseline of both hydroxychloroquine use in long-term care facilities in May 2020 likewise corresponds with a subsequent FDA release on 24th April 2020, warning of heart arrhythmias in patients with COVID-19 treated with the combination of hydroxychloroquine and azithromycin. These sudden and dramatic swings in prescribing habits during this period, and continued public debate over the efficacy of azithromycin and ivermectin despite the absence of supporting evidence, highlights the persistent, detrimental effects stemming from the dearth of therapeutic options early in the pandemic.

ANTIBIOTIC UTILISATION IN PATIENTS WITH SUSPECTED AND CONFIRMED COVID-19

Perhaps the most striking example of COVID-19-related collateral damage to the fight against AMR is the widespread utilisation of antibiotic therapy in patients with suspected and confirmed COVID-19.[15-17] Although reports related to the most recent waves are notably lacking, the available pooled data indicate that a significant percentage of patients admitted with COVID-19 receive antibiotic therapy.[16] For example, Rose et al.[15] compared antibiotic use in 716 hospitals in the USA between 2019–2020, and found that although total antibiotic use during 2020 was lower, nearly 80% of inpatients hospitalised with COVID-19 received empiric antibiotic. This was most prominent during the first pandemic wave, despite identification of bacterial co-infections in only 3.5% of patients at admission, and secondary bacterial infections developing in only 14.0% of patients during hospitalisation.[15] Given the already noted disruptions in AMS, overuse of empiric antibiotics appears to have gone relatively unchecked during at least the first year of the pandemic. Ceftriaxone and azithromycin, a combination frequently used to treat bacterial lower respiratory tract infection in patients who have been hospitalised, made up the vast majority of antibiotic use in this population.[15] Ongoing surveillance in the coming years will be critical to determining if this unnecessary prescribing accelerated resistance patterns in clinically important bacterial pathogens such as *S. pneumoniae*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. Understanding the primary drivers of the massive discordance between bacterial co-infection and antibiotic utilisation is key to preventing this behaviour going forward.

Diagnostic uncertainty related to the substantial overlap in clinical presentation between patients with COVID-19 and bacterial pneumonia was potentiated by limitations in the availability of rapid diagnostic tests.[18] Frontline clinicians were frequently forced to make a decision to initiate empiric antibiotic therapy without the benefit of knowing the result of the SARS-CoV-2 assay.[19] While rapid identification of a viral pathogen can assist frontline clinicians faced with choosing therapeutic options for a respiratory infection, these assays are most effective when paired with information about host response.[20] Although procalcitonin is a biomarker approved by the FDA to assist clinicians differentiate bacterial and viral pulmonary infections, reports related to the utility of procalcitonin to reduce unnecessary antibiotic prescribing in patients with COVID-19 have been mixed.[21-23]

Beyond the clinical conundrum, frontline providers in the USA are also subject to a regulatory mandate that creates significant time pressure to initiate antibiotic therapy. In 2015, Centers for Medicare & Medicaid Services (CMS) instituted an all-or-nothing Severe Sepsis and Septic Shock Management Bundle (SEP-1), with the goal of encouraging high-quality, cost-effective care, and ultimately improving sepsis mortality. Performance on the measure is considered a marker of hospital quality of care, and health systems receive financial incentives for high performance. The SEP-1 bundle calls for, among other interventions, early administration (<3 hours) of parenteral antibiotics, typically broad spectrum, for patients who meet sepsis criteria. This definition of sepsis is built upon the suspicion of an infection and presence of systemic inflammatory response syndrome criteria. Of course, due to the non-specific nature of systemic inflammatory response syndrome, many patients with COVID-19 presented to acute care settings meeting these criteria presumably received broad-spectrum antibiotics by providers looking to adhere to the SEP-1 measure. While CMS was relatively quick to exclude COVID-19 patients from the SEP-1 measure, it remains unclear how aware frontline providers are of this exception and to what extent delays in confirmatory SARS-CoV-2 testing render this guidance moot.

Finally, the recent Omicron wave revealed significant ongoing deficiencies in the availability of both rapid testing and genomic sequencing, which remain functionally unavailable for large portions of the population. Until significant improvements in the availability of rapid and accurate tests for identification of SARS-CoV-2 for both the public and healthcare providers, and incorporation of host response biomarkers into care pathways involving empiric antibiotics, are made, uncertainty of diagnosis will continue to be the primary driver of antibiotic overuse.

SILVER LININGS: POTENTIAL POSITIVE EFFECTS OF THE PANDEMIC ON ANTIMICROBIAL RESISTANCE

In all likelihood, not every consequence of the COVID-19 pandemic will be synergistic with AMR. There is a compelling argument that AMR could show a downtrend in well-resourced countries based on decreased frequency of human travel and general improvement in IC practices. It has been hypothesised that AMR is proportionally driven more by close human interaction and poor IC than by antimicrobial overuse. Given the societal level shifts in hand hygiene, mask wearing, and physical distancing, it begs to reason we may see a decline in AMR in some settings.

It is also important to note that the pandemic had some positive effects on AMS at a systems level. For instance, significant drops in antibiotic prescribing in ambulatory care settings were observed; there are accelerating efforts to develop rapid biomarkers that can help frontline providers differentiate viral from bacterial respiratory infections; and an increased recognition that systems engineering approaches are necessary to build resiliency into IC and AMS processes during times of operational upheaval.[9,12,24]

CONCLUSION

In summary, the COVID-19 pandemic has posed a significant threat to the longstanding fight against AMR. Whether or not future variant-driven waves disrupt society and healthcare operations, the fallout from what we have already experienced will continue to play out in the years to come. While the available reports examining AMR pre- and post-pandemic demonstrate an alarming trend, it is unlikely that a causal mechanism will ever be clear, given the snarling and pervasive nature of this global natural experiment. Moving forward, emphasis should be placed on bolstering IC and AMS infrastructure and programmes, as they represent the most potent interventions to mitigate AMR in healthcare settings. During the current relative lull in the pandemic, it is important to reflect on missteps and lessons learned so that we can be better prepared for future, inevitable AMR-related threats to patient safety and public health.

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