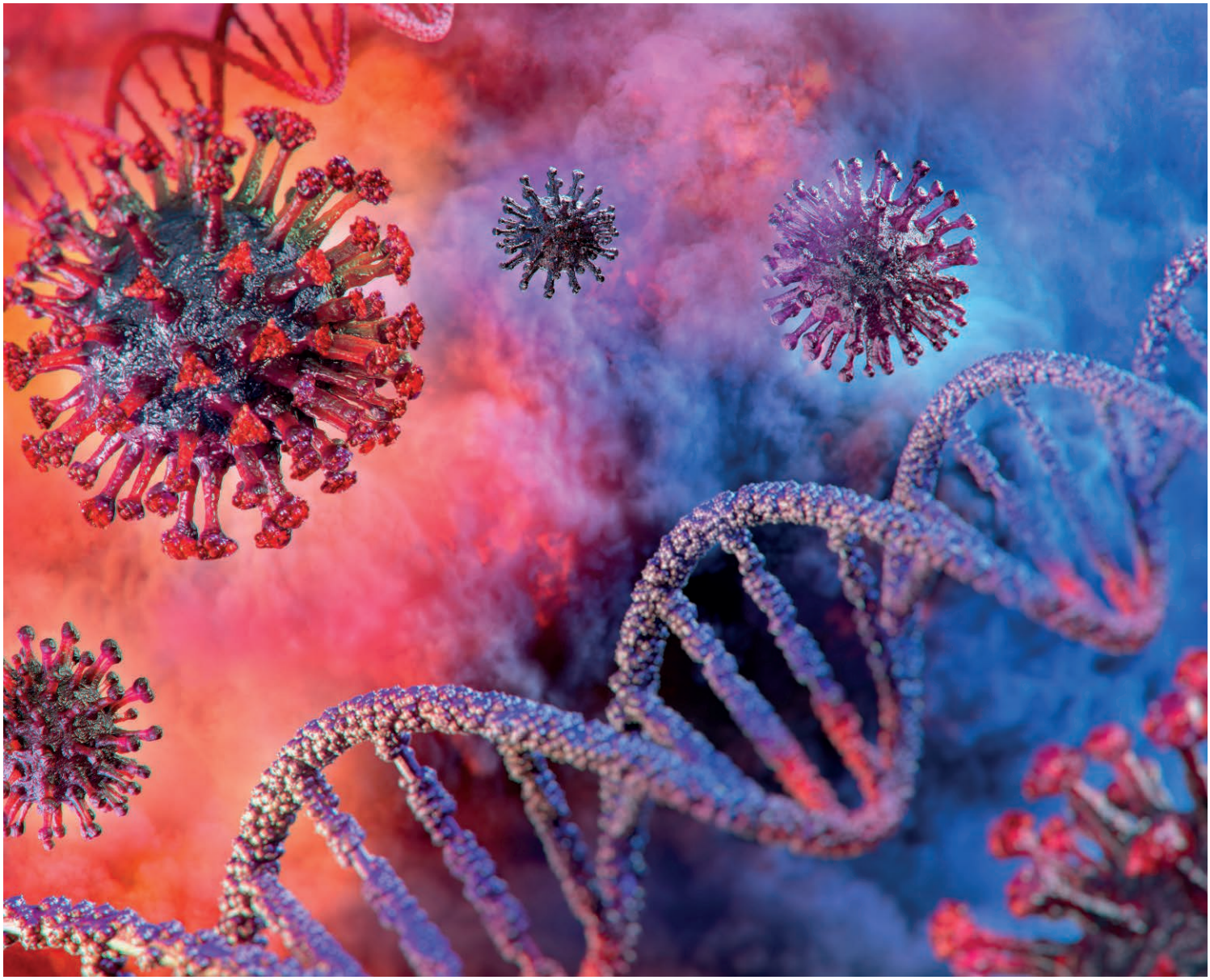


Diagnostics and Data Can Fill Gaps in Antimicrobial Stewardship Left by COVID-19

By Brian R. Raux, PharmD, BCPS, BCIDP, bioMérieux

Introduction: Antimicrobial Resistance (AMR) and Antimicrobial Stewardship (AMS)

Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms (https://apic.org/). In addition to the ongoing burden of COVID-19 to patient health, there is evidence COVID-19 accelerated the rise of AMR and caused a dual threat to public health.

AMR surveillance data collected by the CDC shows an increase of multi-drug resistant organisms (MDROs) in US hospitals during the start of the COVID-19 pandemic.[1] Healthcare-acquired infections (HAIs) and deaths from MDROs rose by 15% from 2019 to 2020. A meta-analysis study of bacterial infection in patients with COVID-19 determined that in 58% of studies, over half of COVID-19 patients received antibiotic agents in 2020. This is despite only an estimated 14% or less of patients having evidence of documented bacterial co-infections.[2]

As the CDC Report[1] points out emphatically, "Historic gains made on antibiotic stewardship were reversed as antibiotics were often the first option given to treat those who presented with a febrile pulmonary process even though this presentation often represented the viral illness of COVID-19, where antibiotics are not effective." In fact, using antimicrobials inappropriately leads to higher rates of bacterial resistance for patients – not just today, but in future infection outbreaks as well.

Diagnostics: Tools in the AMS Quiver Against AMR

To fight AMR, healthcare providers, laboratory professionals, and public authorities must work together at a global level to promote antimicrobial stewardship (AMS) practices. Rapid diagnostics have the potential to facilitate the diagnosis (or exclusion) of bacterial co-infections in viral illness to encourage the discontinuation or optimization of antimicrobials. Resistant infections cause significant morbidity and mortality, put pressure on health systems, and incur rising direct and indirect costs. COVID-19 showed the world the value of collaboration, data sharing, and rapid diagnostics, all of which will be critical to mitigate the rise of AMR. Above all, the critical use of diagnostics to determine the types and degree of infections could lead to better management of healthcare facilities (beds, isolation wards), practices (masking, hygiene), and more appropriate use of antibiotics, antimicrobials, and vaccines, thereby averting the increasing threats of MDROs.

> *"Implementing rapid, innovate diagnostic tests can enable healthcare providers to select the most effective treatments to improve patient health while contributing less to the growing issue of AMR"*

COVID's Impact on Antibiotic Use

Overall, US hospitals experienced an additional 24% of hospital-onset MRDOs than expected between March and September 2020.3 We repeat for emphasis the point in the Introduction that the mortality rate and number of HAIs attributable to MDROs increased by 15% from 2019 to 2020 according to the CDC (see graphic in **Figure 1**).[1] Notably, rates of HAIs and deaths from MDROs had been declining from 2017 to 2019. Some MDROs gained even higher levels of increased resistance. For example, cases of antifungal-resistant *Candida auris* increased by 60%, and cases of Carbapenem-resistant Acinetobacter increased by an estimated 78%.

Evidence supports that inappropriate antibiotic use during the early stages of the pandemic and high hospital bed occupancy contributed to accelerated rates of MDROS in hospitals, stalling infection prevention measures. Data from the Infectious Disease Society of America (IDSA) show clusters of HAIs correlated to COVID-19 surges, suggesting that higher occupancy rates, driven by record numbers of COVID-19 patients, accelerated transmission of HAIs (see **Figure 2**).[3] Severe COVID-19 cases required longer use of catheters and ventilators,[2] which can lead to ventilator-associated pneumonia (VAP) and catheter-associated urinary tract infections (CAUTIs) that may require antibiotic therapy to treat, thereby exacerbating the circumstances.

The burden of COVID-19 on healthcare systems coupled with a lack of data about the novel coronavirus itself were two contributory factors that drove inappropriate antibiotic use and drew attention away from AMS efforts. Although highly variable, bacterial co-infection in patients with severe influenza has been reported to be as high as 20 to 30%. Bacterial co-infection rates for COVID-19, however, are likely lower. A study in *Clinical Microbiology and Infection* reports up to 72% of COVID-19 patients received antimicrobials in the first months of the pandemic in the US.[2] Only 3.5% had a documented bacterial co-infection upon admission, and only 14.3% developed a secondary bacterial infection after initial presentation. This number is much lower than the percentage of patients given antibiotics, suggesting that their use was often unnecessary (see **Figure 3**).

COVID-19's Impact on Resource Availability to Fight AMR

Early confusion during testing

The burden of COVID-19 on individuals and national healthcare systems diverted resources and attention away from addressing the issue of AMR, adding to the impact COVID-19 already had on antibiotic prescribing practices. Although secondary and tertiary healthcare experienced an overall increase in inappropriate antibiotic use, outpatient prescribing actually decreased in 2020.[1] This lower level of use may be in part to the effectiveness of COVID-19 infection prevention measures and public health practices that lessened the spread of other respiratory illnesses (e.g., masking, ventilation improvement, crowd control measures, hand washing, etc.).

Another explanation is simply that some with bacterial infections did not seek medical care as a result of closed clinics, fear of exposure in waiting and examination rooms, and limited appointment availability.[1] Furthermore, the CDC's Antimicrobial Resistance Laboratory Network (AR Lab Network) reports that they received 23% fewer specimens in 2020 than in 2019 and were unable to create accurate nationwide resistance profiles as a result.[1] All these contributors conspired to complicate the execution and tracking of AMR programs early in the pandemic. As time passed, testing volumes increased and individuals across the US and

Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

- **Carbapenem-resistant *Acinetobacter* (↑78%)**
- **Antifungal-resistant *Candida auris* (↑60%)**
- **Carbapenem-resisatant Enterobacterales (↑35%)**
- **Antifungal-resistant *Candida* (↑26%)**
- **ESBL-producing Enterobacterales (↑32%)**
- **Vancomycin-resistant Entrococcus (↑14%)**
- **Multidrug-resistant *P. aeruginosa* (↑32%)**
- **Methicillin-resistant *Staphylococcus aureus* (↑13%)**

**Candida auris* was not included in the hospital-onset rate calculation of 15%. See Data Table and Methods for more information on this pathogen.

Figure 1: CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/covid19.html

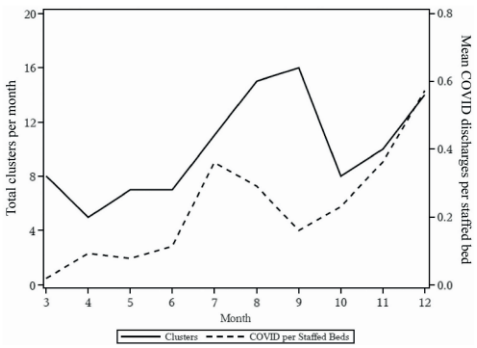


Figure 2: Monthly comparison of COVID discharges to clusters. COVID-19 discharges and the number of clusters of hospital-onset pathogens are correlated throughout the pandemic. The Impact of Coronavirus Disease 2019 (COVID-19) on Healthcare-Associated Infections, Clinical Infectious Diseases, Volume 74, Issue 10, 15 May 2022, Pages 1748–1754, https://doi.org/10.1093/cid/ciab688

other countries came to support testing to control COVID and its complications.

More planning needed

At a global level, a survey by the WHO showed that 90% of responding countries reported that COVID-19 had a negative impact on their national plans to tackle AMR.[4] This included the focus on development and implementations of National Action Plans[5] in support of the Global Action Plan on AMR. While developing or implementing National Action Plans is critical, only 33% of countries responding to the WHO survey have guidelines in place to optimize nationwide antimicrobial use.[4] Delays in the development and implementation of national actions plans may have already led propagation of AMR and could lead to AMR propagation in the future, particularly given the disruption to healthcare caused by COVID-19.

Impact of increased testing on clinical laboratory professionals

As is the case across all healthcare fields, the sheer number of COVID-19 patients and suspected COVID-19 cases drained clinical laboratory resources and added pressure on hospital healthcare providers. Pre-pandemic data from the US Bureau of Labor Statistics predicted a nationwide need for an 11% increase in clinical laboratory technologists by 2030, which is higher than the average 8% increase needed in personnel across all industries.[6]

Laboratory professionals, like so many other healthcare workers, have been at the center during the COVID-19 response and provided needed services as part of patient care. They have processed over 800 million COVID-19 tests in the US as of January 2022,[7] a number that has likely topped a billion since. In a 2020 survey of laboratory professionals, 85% reported burnout, nearly 60% reported inadequate compensation and more than a third complained of inadequate staffing.[8] According to the US Department of Health and Human Services, sixteen states are experiencing critical staffing shortages in at least 25% of their hospitals.[9] Staffing shortages and widespread occupational burnout translates to a lack of bandwidth to invest in maintaining and growing antimicrobial stewardship initiatives.

> *"The recent pandemic exemplifies the need for a global approach to 1) monitor the presence and spread of infectious agents and 2) be prepared to fight complex public health threats with optimized stewardship initiatives driven by diagnostics."*

The Role of Diagnostics in Improving Antimicrobial Stewardship (AMS)

The impact of COVID-19 on AMR means that now more than ever, strengthening AMS is critical to patient health today and sustaining appropriate antibiotic use in the future. Fast and actionable molecular diagnostics have the potential to enhance AMS and improve infectious disease management through informed antibiotic prescribing. As witnessed during the pandemic, pairing diagnostics with advanced data analytics demonstrated a near-real ability to transform stewardship of public health at a population level as well as inform public health policy.

IDSA, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), and other organizations agree that diagnostics are a key tool to ensure appropriate antimicrobial usage.[10] Implementing rapid, innovate diagnostic tests can enable healthcare providers to select the most effective treatments to improve patient health while contributing less to the growing issue of AMR.

Precision diagnostics in a stewardship strategy

Precision diagnosis impact on diagnosing infectious agents

Molecular diagnostics, like multiplex PCR syndromic testing can help providers identify and treat bacterial pneumonia in critically ill patients with COVID-19 and rule out cases where antibiotics are not needed. A performance study published with the American Society of Microbiology (ASM) demonstrated that a PCR-based, culture-independent laboratory assay allowed accurate diagnosis and streamlined antibiotic therapy for bacterial pneumonia in ICU patients with COVID-19.[11] Using this process, antibiotics were discontinued in a third of patients and were either escalated or deescalated in 88% of patients with positive results from the multiplex PCR.

Precision diagnosis impact on AMS strategy

Optimizing and tailoring antimicrobial use for individuals using diagnostic data is core part of a successful AMS strategy. Syndromic testing using molecular diagnostics can help support

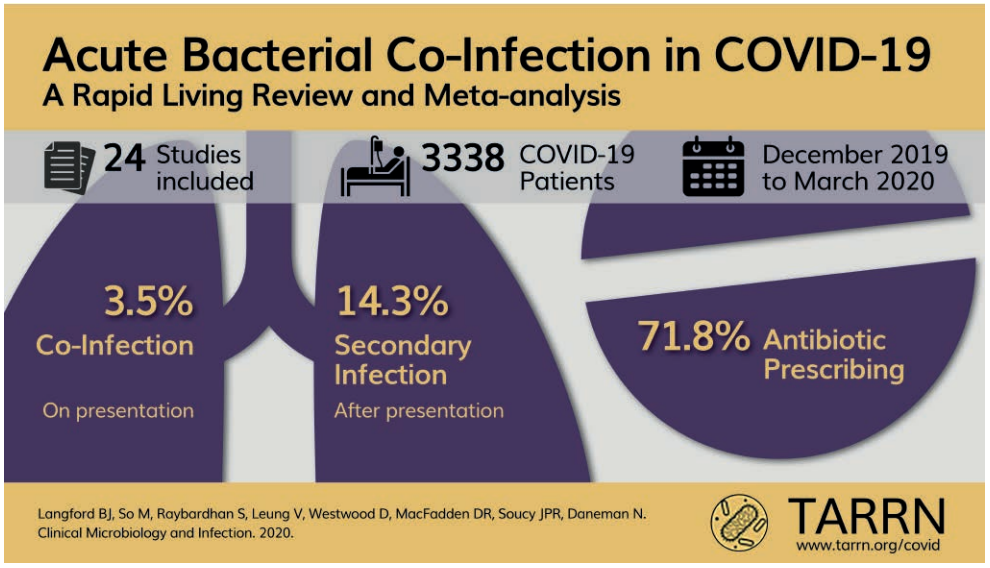
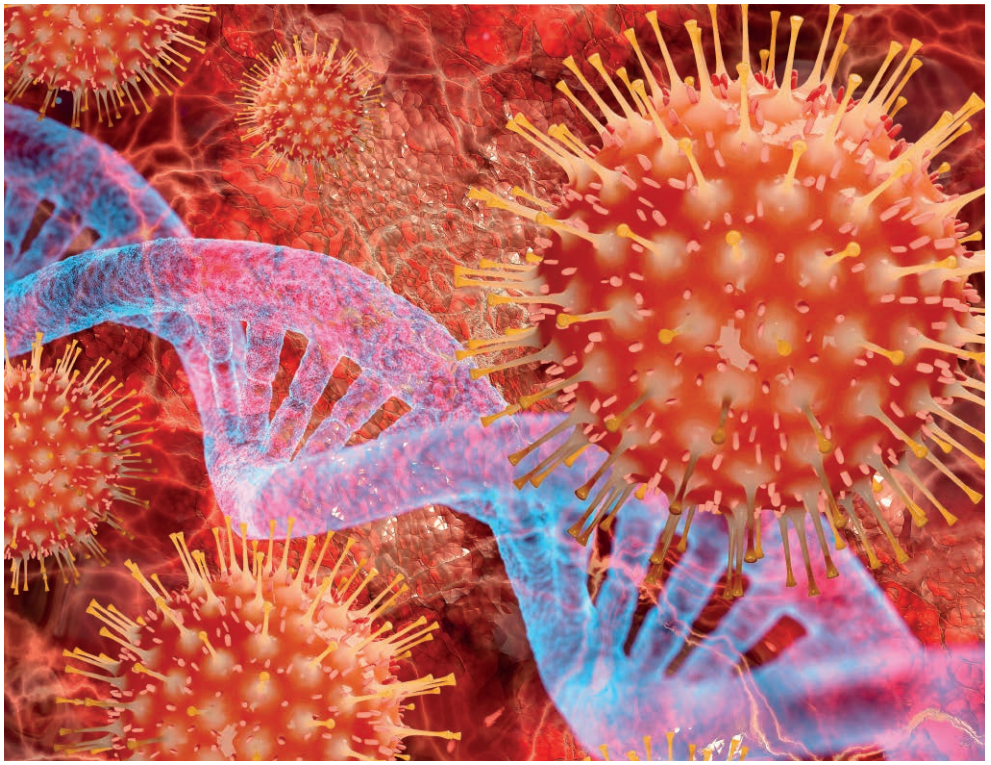


Figure 3: Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26(12):1622-1629. doi:10.1016/j.cmi.2020.07.016



diagnosis of bacterial infection and significantly reduce the turn-around time to results, particularly for organism identification and the detection of common AMR resistance genes. This can help ensure that appropriate antimicrobial therapy is delivered in a timely fashion and can also help support early de-escalation of therapy, supporting stewardship practices.

Handling antimicrobial-resistant organisms (AMROs) in the pandemic

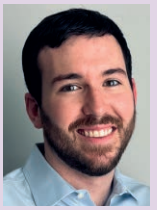
The Posteraro et al. study also found that 60% of bacterial pneumonia cases observed in COVID-19 patients were caused by antimicrobial-resistant organisms (AMROs).11 With the rise in infections caused by highly resistant organisms for COVID and non-COVID patients alike, performing antimicrobial susceptibility testing (AST) acts as another key component of a holistic stewardship strategy. Phenotypic AST provides individual, in-vitro results that tell the likelihood of success or failure of individual antimicrobials in the treatment of the specific infection. AST can aid in the delivery of optimal treatment and provide confidence in delivering narrow, targeted therapy.[12] With the rise in AMR, AST will become more and more important, with a focus on automation and reduced time to results.

Data from AST and other monitoring efforts form the foundation for national and international AMR surveillance networks, such as the WHO's GLASS system[13] and the CDC's AR Lab Network.[1] Knowing when and where changes in AMR profiles are occurring can inform public policy and infection control measures.

Summary: Challenges and Solutions for Antimicrobial Stewardship

Despite resource challenges facing many hospitals today, technological advances provide more opportunities for healthcare facilities to bolster their AMS programs. Advances in tools such as cloud-based software services are equipped to make data sharing and analysis more accessible, affordable, and equitable to institutions of all locations and sizes. By tracking information and trends for MDROs across multiple hospitals, healthcare providers can set thresholds, analyze, and compare MDRO incidence rates while monitoring the impact of antimicrobial stewardship efforts.

Diagnostic data and analytics are tools at the core of stewardship efforts in communities at large but especially in hospital settings. These tools have become invaluable for addressing AMR at both the patient and population level. COVID-19 presented the worldwide community with an immediate public health challenge that required the collaboration of public and private sectors to collect data to survey the infectious disease landscape. The recent pandemic exemplifies the need for a global approach to 1) monitor the presence and spread of infectious agents and 2) be prepared to fight complex public health threats with optimized stewardship initiatives driven by diagnostics. JPM



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