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Antibiotic Resistance: A Global Problem and the Need to Do More

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The discovery of penicillin in 1928 and its initial use in the 1940s to treat serious infections marked a turning point in modern medicine saving millions of lives [1]. However, antibiotic resistance (AR) has long threatened the advances of modern medicine. Widespread use of penicillin in clinical therapy started in 1943, and a decade later penicillin resistance had already become a major clinical problem [2]. This same phenomenon has been seen with each new antibiotic that has been approved for clinical use. A landmark study recently published showed that in 2019 AR killed more people than any other infectious diseases including human immunodeficiency virus (HIV) and malaria [3]. One in 8 deaths globally are linked to bacterial infections, the second leading cause of death after ischemic heart disease [4].

In the midst of the ongoing AR crisis in 2020, the global population was faced with another major public health crisis resulting from the emergence of a new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to 6.6 million deaths due to coronavirus disease 2019 (COVID-19) so far and one of the worst pandemics in history [5]. As a result of this pandemic, many reports have been published from high-income countries (HIC) on increased use of antibiotics and growing resistance [6, 7]. In the United States, the Centers for Disease Control and Prevention (CDC) reported increases in multidrug-resistant

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infections during the COVID-19 pandemic driven by hospital-onset infections, reverting the recent progress the country had made toward AR prevention of priority pathogens as previously reported [8]. The negative impact on AR during the COVID-19 pandemic was not restricted to HIC; this *Clinical Infectious Diseases* Supplement, titled "The Evolving Challenge of Antibiotic Resistance in Low- and Middle-Income Countries: Priorities and Solutions," now brings a series of articles from low- and middle-income countries (LMICs) showing substantial increases in broad-spectrum antibiotics and multidrug-resistant (MDR) infections during the COVID-19 pandemic with increases in antibiotic resistance genes previously uncommon in these countries.

Patel et al [9] reports 31.3%–82.5% increases in use of β-lactam antibiotics with activity against *Pseudomonas aeruginosa* across hospitals in South America during the first year of the pandemic. Outpatient prescribing data from Brazil demonstrates an increase of up to 360% in azithromycin and 90% in ceftriaxone prescriptions among adults [10]. Kiffer et al [11] using data from the Brazilian national AR surveillance system show an increase of 65.2%, 77.7%, and 61.3% in the total number of isolates of Enterobacterales, *Acinetobacter baumannii* complex, and *P. aeruginosa*, respectively, referred to the national laboratory after the pandemic onset. However, more concerning is the increase Kiffer et al [11] observed from 2015 to 2022 in prevalence of New Delhi metallo-β-lactamase (bla_{NDM}) among Enterobacterales and *P. aeruginosa* isolates from 4.1% to 39.4% and from 0.3% to 6.9%, respectively. A similar increase in bla_{NDM} was observed in Chile by Allel at al [12] among carbapenem-resistant *Klebsiella pneumoniae* isolates, with whole genome sequencing demonstrating appearance and rapid expansion of ST45 lineage in 2021. It will be important to understand if the emergence of bla_{NDM-7} ST45 in Chile is related to increases in bla_{NDM} among Enterobacterales and *P. aeruginosa* isolates in Brazil and in other countries in Latin America. In October 2021, the Pan American Health Organization issued an alert on the emergence and increase of new combinations of carbapenemases in Enterobacterales in the region making treatment of these infections even more challenging [13]. Genomic analysis of the Brazilian and other Latin American carbapenem-resistant Enterobacterales isolates is an important next step.

This supplement also contains manuscripts showing, even before the pandemic, the high burden of MDR-organism colonization in hospitals and communities among children and adults across 6 countries (Bangladesh [14], Botswana [15], Chile [16], Guatemala [17], India [18, 19], and Kenya [20]). Colonization with extended-spectrum cephalosporin-resistant Enterobacterales (EsCRE) and carbapenem-resistant Enterobacterales (CRE) in hospitalized patients was as high as 82% and 37%, respectively. In communities, EsCRE and CRE colonization was as high as 78% and 15%, respectively. Robinson et al [19] demonstrated that maternal colonization is not the main driver of drug resistant gram-negative bacteremia among neonates in a neonatal intensive care unit (NICU) in India, but rather healthcare transmission suggesting that infection prevention and control practices such as hand hygiene and environmental cleaning along with early identification and isolation of patients infected with drug-resistant organisms should be reinforced.

The data presented across these papers highlight several concerns, including: (1) high baseline rates of AR in both hospitals and communities with potential spill over from

the former to the latter [14–20]; (2) increases in inappropriate use of antibiotics during the pandemic [9, 10, 12]; (3) healthcare transmission of drug-resistant organisms among vulnerable populations even before the pandemic; and (4) rapid horizontal transmission of AR genes in hospitals during the pandemic, as demonstrated by the rapid dissemination of *bla*$_{\text{NDM-7}}$ ST45 in Chile [12]. The increases in AR infection reported by several countries during the pandemic [8, 12, 13] highlights the importance of surveillance among pediatric and adult populations and make us wonder whether the global burden of AR-attributable deaths in the pandemic years may have surpassed the latest estimates of 1.27 million based on 2019 data [3]. On a global scale the COVID-19 pandemic overwhelmed healthcare systems. The significant increase in antibiotic use and resistance was likely driven by increased volumes of patients with severe illness, supply challenges, healthcare personnel shortages, and longer hospital stays during the pandemic. These unprecedented challenges likely led to difficulty in following infection prevention and control guidance and contributed to suboptimal infection prevention and antibiotic stewardship practices, which are key to combating AR.

Despite the challenges of AR, two papers in this supplement present data on opportunities to control the spread of AR. Salomao et al [21] showed that an intervention in their overcrowded emergency department consisting of empiric contact precautions for patients staying >24 hours in the emergency department (ED), CRE colonization screening, and rapid communication of CRE screening results to the ED staff resulted in a 74% decrease in CRE acquisition rates. Fabre et al [22] identified barriers for implementation of antimicrobial stewardship programs (ASPs) in LMICs that have relatively easy solutions.

CDC recognizes the vital need to support efforts to combat the global spread of AR. To help fill critical detection and response gaps globally, CDC launched the Global Antimicrobial Resistance Laboratory and Response Network (Global AR Lab & Response Network) (US & Global Antimicrobial Resistance Lab Networks | CDC) in 2021, a comprehensive, One Health-focused network to improve the detection of AR threats and prevent their spread globally. This network spans nearly 50 countries and works with close to 20 organizations worldwide to build laboratory capacity to detect AR organisms, prevent infections in healthcare and the community through proven infection control practices, and apply new and innovative ways to respond to antimicrobial resistance threats. The Global AR Lab & Response Network also helps support the CDC collaborative work with the World Health Organization (WHO) in its role as an AR Network collaborating center, supporting countries in building capacity to track AR by strengthening international collaboration and improving coordination. Through these efforts, CDC also works to support country reporting into WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) [23].

Through the Global AR Lab & Response Network, CDC is also implementing the Global Action in Healthcare Network (GAIHN) (GAIHN | Global Safe Healthcare | Infection Control | CDC) with the objective to rapidly detect, prevent, and contain emerging infectious diseases threats, including AR, in healthcare settings. GAIHN has 2 modules, healthcare-associated infections and AR, and is working with 6 partners across more than 27 healthcare facilities (HCFs) in 13 countries around the world. Rapid detection and communication of AR threats is critical to trigger appropriate measures to stop the spread of the pathogen.

GAIHN-AR module seeks to enhance laboratory capacity in HCFs, national and regional reference laboratories for a set of common priority AR threats, to prevent transmission of AR threats in HCFs through implementation of evidence-based strategies and functional infection prevention and control programs, to improve rapid communication of these threats within and across HCFs, and finally to work collaboratively across institutions, countries, regions, and global partners to rapidly respond to emerging AR threats. GAIHN-AR includes detection, prevention, and response of AR threats in pediatric and adult populations.

Resource-limited HCFs may lack expertise, laboratory capacity, data systems, and educational tools to combat AR spread. Being part of these CDC networks can provide distinct advantages including access to laboratory, infection prevention and control and stewardship expertise, training resources, standardized laboratory, prevention and containment protocols, new laboratory technology, and shared data infrastructure that can further optimize network activities. The ongoing and evolving work within the CDC networks helps slow the spread of AR and ensure these threats are stopped when and where they emerge. *Going together* instead of *going alone* is critical in the fight against AR.

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