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The Syndemic Threat: A Review of the Health Security Implications of Concurrent and Interacting Outbreaks

Joori Ahmad Ibrahim Alessa [(1)] , Abdullah Abdulkarim Ibrahim Altuwayjiri [(1)] , Ahmed Abdullah Mohammed Almousa [(1)] , Sultan Abdulrazaq Saad Alanazi [(1)] , Atheer Mohammad Olayan Almutairi [(1)] , Reem Falah Ali Almutairi [(1)]

(1) Wathelan General Hospital, Ministry of Health, Saudi Arabia

Abstract

Background: The concept of syndemic has been particularly important in the modern idea of describing co-occurring health crises that interact synergistically. The COVID-19 pandemic and the continuing pandemic of AMR represent a prime example of such synergistic threats.

Aim: This review reflects on the health security implications of the COVID-19-AMR syndemic, with a specific focus on how these intertwined crises together overwhelmed the health systems and amplified vulnerabilities.

Methods: Literature synthesis from 2014 to 2024 was conducted to understand the mechanisms and implications of this syndemic interaction.

Results: The review found that COVID-19 exacerbated AMR through rampant antibiotic misuse, disrupted stewardship programs, and breakdowns in infection control. On the other hand, AMR complicates COVID-19 management through increased secondary infections and mortality. The syndemic also exposed broader system fragilities, including resource diversion, healthcare worker burnout, and collateral damage to essential services like immunization programs.

Conclusion: The COVID-19-AMR syndemic demonstrates that single-disease preparedness is inadequate. What is urgently needed to build back better is a reinforced health security framework based on integrated surveillance, "One Health" principles, resilient health systems, and proactive communication in response to future complex threats.

Keywords: syndemic, health security, COVID-19, antimicrobial resistance (AMR), health systems, One Health.

1. Introduction

Global health security for decades has been primarily approached through a single-disease and threat-specific standpoint, with a focus on preparedness against pandemics of influenza or other known pathogens (Haileamlak, 2022). But COVID-19 revealed how naively narrow that kind of thinking was. It soon became crystal clear that this virus, SARS-CoV-2, was not acting in a vacuum; its course and consequences clearly reflected a dynamic interplay with pre-existing and parallel public health crises. This fact is captured most succinctly by the term "syndemic," a portmanteau of "synergy" and "epidemic" first developed in its rigorous use in medical anthropology by Sangaramoorthy (2018) and later applied to explain the clustering and interaction of diseases within a population, which is conditioned by social, economic, and environmental factors (Singer et al., 2016). A syndemic perspective transcends a simple measure of the co-occurrence of diseases, analyzing instead their biological and social interactions in exacerbating each other and leading to greater disease burden than the sum of their parts (Mendenhall & Singer, 2020).

The most powerful and best-documented syndemic of the recent period is the interrelation between COVID-19 and antimicrobial resistance. Before the COVID-19 pandemic, AMR was already considered a "silent pandemic." It caused an estimated 1.27 million deaths around the world in 2019 and is predicted to kill 10 million annually by 2050 if left unchecked (Murray et al., 2022). The appearance of SARS-CoV-2 did not supplant this threat, but rather merged with it to produce a dangerous feedback loop. The WHO and other bodies have since warned that the COVID-19 pandemic has gravely undermined the global fight against AMR by turning what had been a simmering crisis into a raging one (WHO, 2022; Pelfrene et al., 2021).

This review provides a comprehensive analysis of the health security implications of this syndemic, focusing on the period of 2014-2024 to capture both the pre-COVID groundwork on AMR and the transformative impact of the pandemic. We will dissect the multifaceted pathways through which COVID-19 has exacerbated AMR, including the surge in empirical antibiotic prescribing, disruption of antimicrobial stewardship programs, and breakdown of infection prevention and control measures in

*Corresponding author e-mail: Joryalessa98@gmail.com (Joori Ahmad Ibrahim Alessa).

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overstretched health systems. At the same time, we will analyze how the background rates of AMR complicate COVID-19 patient management, leading to worse clinical outcomes and increased mortality from secondary bacterial and fungal infections. The scope of this review extends beyond the hospital walls into the examination of the syndemic's impact on broader health systems, including the diversion of resources, the collapse of essential health services, and the amplification of social inequities that underpin vulnerability. By synthesizing evidence from diverse fields—clinical medicine, public health, microbiology, and health policy—this review argues that a fundamental recalibration of health security frameworks is needed. We need to shift from a paradigm of single-pathogen preparedness toward one of systemic resilience able to absorb the synergistic shocks of concurrent and interacting outbreaks.

The COVID-19 Pandemic as an Amplifier of Antimicrobial Resistance

The first chaotic phase of the COVID-19 pandemic created a perfect storm for the acceleration of AMR. Faced with a novel, severe respiratory virus and limited treatment options, healthcare systems worldwide witnessed a dramatic and often inappropriate use of antimicrobials, setting back years of progress in antimicrobial stewardship.

Escalation of Empirical Antibiotic Use

A major driver of AMR during the pandemic was the wild empirical prescription of antibiotics for COVID-19 patients. Early in the pandemic, due to clinical similarities between COVID-19 pneumonia and bacterial co-infections, and in the context of diagnostic uncertainty and overwhelming patient loads, antibiotics were prescribed at an alarming rate. Systematic reviews have estimated that, despite a relatively low confirmed rate of bacterial co-infection at presentation (approximately 3.5%-8%), antibiotics were administered to 58-74% of hospitalized COVID-19 patients globally (Langford et al., 2021; Rawson et al., 2020). This represents a profound mismatch between treatment and etiology. In intensive care units, this figure was even higher, often exceeding 90%, as clinicians, fearing secondary bacterial pneumonia in ventilated patients, erred on the side of caution (Kariyawasam et al., 2022). This widespread "just in case" prescribing was a direct consequence of the pandemic's strain on diagnostic capacity; when rapid, reliable tests for SARS-CoV-2 were scarce, and traditional bacterial culture methods were slow, antibiotics became a default safety net (Hsu, 2020).

Worrisome, too, was the type of antibiotics utilized. Broad-spectrum agents, including third-generation cephalosporins, carbapenems, and glycopeptides, were commonly employed as first-line therapy (Perez et al., 2022). These are drugs of last resort for resistant infections. The increased use of these medications exerts strong selective pressure that promotes the emergence and survival of MDR organisms such as carbapenem-resistant Enterobacteriaceae (CRE) and methicillin-resistant Staphylococcus aureus (MRSA) (Knight et al., 2021). One study from the United States reported a significant increase in carbapenem consumption in 2020 compared with pre-pandemic levels, directly correlating with COVID-19 hospitalization waves (King et al., 2020). Such a surge in broad-spectrum use inflames future AMR, besides increasing the risk of adverse drug events, such as *Clostridioides difficile* infection, which further complicates care (Granata et al., 2022).

Disruption of Antimicrobial Stewardship and Surveillance Programs

The chaos caused by the pandemic dismantled systematically the very programs that should fight AMR. Antimicrobial Stewardship Programs-which are organized ways to ensure appropriate use of antimicrobials deprioritized and often dismantled when health personnel and resources were shifted to the response against COVID-19 (Buehrle et al., 2021). The stewardship pharmacists and infectious disease physicians were reassigned to COVID-19 wards, public health laboratories pivoted entirely toward SARS-CoV-2 testing, and hospital committees dealing with AMR were suspended (Subramanya et al., 2021). This was a critical lapse in oversight and accountability for antibiotic prescribing, enabling inappropriate use to thrive unchecked.

Concurrently, however, global AMR surveillance systems experienced severe disruptions. For example, the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) recorded significant data gaps from many member states during 2020-2021 (WHO, 2022). National and regional surveillance networks, dependent on routine clinical microbiology testing, also had their streams of data dry up as non-COVID testing was scaled back (Perez et al., 2022). This created an unsafe blind spot; thus, the real extent of AMR emergence and spread during the pandemic was understated. Without robust, real-time surveillance, public health authorities cannot track resistance trends, detect outbreaks of MDR pathogens, or inform empirical treatment the biggest setback that would make it impossible to fight against AMR (Collignon & Beggs, 2019).

Breakdowns in Infection Prevention and Control

Overwhelmed by shortages of PPE and trained staff, many hospitals suffered significant breakdowns in foundational IPC practices. High patient-to-staff ratios, fatigue, and the repurposing of non-clinical spaces into patient wards made strict adherence to contact precautions and hand hygiene protocols exceedingly difficult (Abubakar et al., 2023). These lapses provided fertile ground for the transmission of healthcare-associated, drug-resistant pathogens.

Various studies from different parts of the world reported the increased infections caused by MDR bacteria in COVID-19 ICUs. Outbreaks of CRAB, carbapenemase-producing *Klebsiella*

pneumoniae, and ESBL-producing *Enterobacteriaceae* were commonly seen in these settings. Razazi et al. (2020) and Contou et al. (2021) showed that the common implementation of corticosteroids and immunomodulatory therapies such as tocilizumab in severe COVID-19 managed to prevent a hyperinflammatory response from the host and subsequently exposed patients to secondary fungal infections caused by *Aspergillus* and *Candida auris*. *C. auris* is a multidrug-resistant yeast famous for its resilience in the healthcare environment. It has caused outbreaks in COVID-19 units from India to Brazil to the United States (Prestel et al., 2021). Taken together, a susceptible patient population, heavy antibiotic pressure, and poor IPC created a perfect incubator for these highly resistant organisms (Table 1 & Figure 1).

Table 1: Mechanisms of COVID-19-driven antimicrobial resistance amplification

Mechanism	Key Evidence	Impact on AMR
Empirical Antibiotic Use	- 58-74% of hospitalized COVID-19 patients received antibiotics, despite low bacterial co-infection rates (Langford et al., 2021). - Significant increase in consumption of broad-spectrum agents like carbapenems (King et al., 2020).	Increased selective pressure is driving the emergence of Multi-Drug Resistant (MDR) bacteria.
Disruption of Stewardship	- Reassignment of stewardship personnel to COVID-19 duties (Buehrle et al., 2021). - Suspension of stewardship activities and oversight committees (Subramanya et al., 2021).	Lapse in accountability and promotion of inappropriate prescribing practices.
Disruption of Surveillance	- Gaps in data reporting to global (e.g., GLASS) and national surveillance systems (WHO, 2022). - Scaling back of routine microbiological testing (Perez et al., 2022).	Blind spots in tracking resistance trends and detecting outbreaks of MDR pathogens.
Breakdown in IPC	- Shortages of PPE and staff leading to lapses in hand hygiene and contact precautions (Abubakar et al., 2023). - Outbreaks of CRAB, KPC, and *C. auris* in COVID-19 ICUs (Razazi et al., 2020; Prestel et al., 2021).	Increased transmission of healthcare-associated, drug-resistant infections.
Environmental Contamination	- Increased use of biocides and antibiotics leading to concerns about co-selection for resistance (McCarlie et al., 2020). - Potential for wastewater discharge to spread resistance genes (Singer et al., 2016).	Creates environmental reservoirs of AMR, posing a long-term community risk.

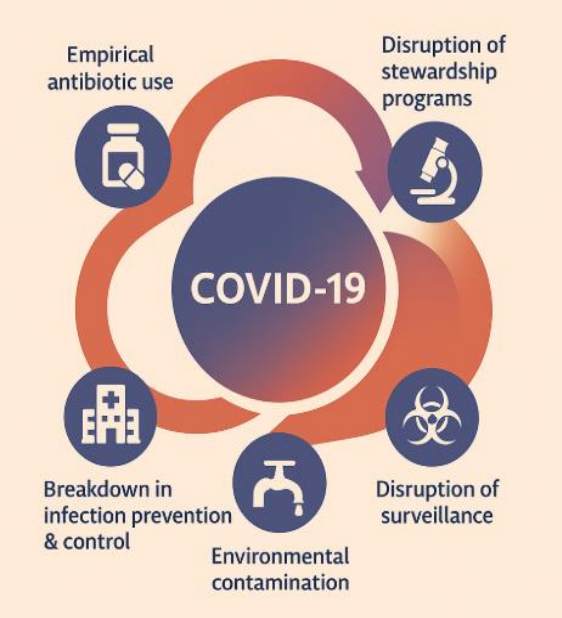

Figure 1: Mechanisms of COVID-19-Driven AMR Amplification

Antimicrobial Resistance as a Complicating Factor in COVID-19 Management

The syndemic relationship does not go one way. While COVID-19 acted as a powerful amplifier of AMR, the pre-existing and burgeoning crisis of AMR in turn profoundly complicated the clinical management and worsened the outcomes of COVID-19 patients. The "silent pandemic" silently exacerbated the acute one.

Bacterial and Fungal Co-infections and Superinfections

Although bacterial co-infection at the time of COVID-19 diagnosis was relatively uncommon, secondary bacterial and fungal infections that developed over the course of hospitalization emerged as a major cause of morbidity and mortality. Severe COVID-19 patients, especially those requiring mechanical ventilation and immunosuppressive therapy, are particularly susceptible to such superinfections. When these superinfections are caused by MDR pathogens, options for their treatment become extremely limited, resulting in treatment

failure and increased mortality. In a large multicenter study in Europe, almost 50% of COVID-19 patients who developed a secondary bacterial pneumonia during their ICU stay were infected with an MDR organism; this was independently associated with a higher risk of death.

The challenge is compounded by diagnostic difficulties. The clinical and radiological signs of superinfection often overlap with the progression of severe COVID-19 pneumonitis, making it difficult to distinguish between a viral and bacterial etiology. This diagnostic ambiguity, coupled with the high stakes, often leads to a cycle of prolonged or repeated courses of broad-spectrum antibiotics, further fueling the AMR cycle. The problem extends to fungal infections. COVID-19-associated pulmonary aspergillosis and *C. auris* bloodstream infections have been associated with mortality rates exceeding 50% in some cohorts, and their diagnosis requires a high index of suspicion and specialized testing that was often unavailable in overwhelmed settings.

Compromised Treatment Options and Clinical Outcomes

The presence of AMR directly undermines the therapeutic armamentarium available to the clinician. For the COVID-19 patient struggling for survival, the development of a ventilator-associated pneumonia due, for example, to carbapenem-resistant Pseudomonas aeruginosa or MRSA represents a catastrophic event. A few remaining effective antibiotics against such pathogens, such as colistin, are usually less effective and more toxic than standard therapies (Kadri et al., 2021). This entails delayed appropriate therapy, prolonged organ dysfunction, and longer lengths of stay on mechanical ventilation and in the ICU.

This translates clinically: a systematic review and meta-analysis showed that COVID-19 patients with bacterial co-/secondary infection had a 2.5- to 3-fold increased odds of mortality compared to those without the bacterial infections (Lansbury et al., 2020). This risk increases when the causative agent is drug-resistant. For example, studies have found that COVID-19 patients suffering from MDR bacteria-induced bloodstream infection experience significantly longer hospitalizations and increased in-hospital mortality in comparison to those suffering from susceptible isolates (de Kraker, 2023). This synergy between the viral infection and resistant bacterial complications creates a clinical scenario where the whole is decidedly worse than the sum of its parts, epitomizing the syndemic model.

The Broader Health System Impact: Overwhelmed and Fragmented Responses

The COVID-19-AMR syndemic did not occur in a vacuum but interacted and exposed profound weaknesses in the architecture of health systems globally. The concurrent pressures overwhelmed capacities and fragmented services, with impacts not only on the direct management of the syndemic but on the entirety of healthcare (Table 2).

Resource Diversion and Health System Strain

The singular focus on COVID-19 response led to a massive diversion of financial, human, and material resources away from other critical health programs, including those dedicated to AMR containment. National budgets were reallocated to procure ventilators, PPE, and vaccines, while funding for ASPs, microbiology laboratory strengthening, and AMR research was often cut or frozen (Högberg et al., 2010). This is a short-term prioritization that presents a severe long-term threat because the gains made against AMR are hard-won and easily lost.

The human resource strain was equally critical. Health workers, the backbone of any health system, were stretched to their limits. Burnout, trauma, and infection among doctors, nurses, and other personnel led to severe shortages (De Kock et al., 2021). This not only compromised the quality of COVID-19 care and IPC but also meant fewer skilled professionals available to manage complex AMR cases or to run stewardship initiatives. The mental health crisis among health workers is in itself a component of this syndemic, reducing system resilience and capacity to respond to future shocks (Greenberg et al., 2020).

Collateral Damage to Essential Health Services

Perhaps the most far-reaching impact of the syndemic was the collateral damage inflicted on other essential health services. Lockdowns, fear of infection, and the repurposing of health facilities led to dramatic reductions in the utilization of routine services. Childhood immunization programs were disrupted, with the WHO estimating that 25 million children missed out on routine vaccines in 2021 alone (WHO, 2023). This creates a high risk for outbreaks of vaccine-preventable diseases like measles and diphtheria, adding yet another layer of potential health crises to the syndemic mix.

Similarly, diagnosis and management of NCDs, such as cancer, diabetes, and hypertension, were severely interrupted (Søreide et al., 2020). In the context of a syndemic, this is particularly pernicious, since NCDs are established risk factors for severe COVID-19 outcomes (Formenti et al., 2022). Besides, disruptions in HIV and TB services are specifically worrisome because of the intrinsic linkage these conditions have with AMR. Particular concern was given to DR-TB management, which involves long, complex regimens requiring careful monitoring, thus risking increased transmission and development of even more resistant strains (Shariq et al., 2022). Diversion of GeneXpert machines used throughout the diagnosis of TB for COVID-19 testing is a poignant example of how one crisis can directly undermine the response to another (Cilloni et al., 2020).

Table 2: Broader Health Security Impacts of the COVID-19-AMR Syndemic

Impact Area	Manifestations	Consequences for Health Security
Health System Capacity	- Diversion of financial and human resources from AMR to COVID-19 (Högberg et al., 2010). - Healthcare worker burnout and attrition (De Kock et al., 2021).	Erosion of core health system resilience, reduced capacity to manage any health threat.
Essential Service Disruption	- Disruption to routine immunization programs (WHO, 2023). - Interruption in screening and care for NCDs, HIV, and TB (Søreide et al., 2020; Shariq et al., 2022).	Increased vulnerability to other diseases creates a cascade of secondary health crises.
Social & Economic Determinants	- Deepening of health inequities; marginalized populations disproportionately affected (Bambra et al., 2020). - Economic downturns reducing health spending and increasing poverty-related disease (McKee & Stuckler, 2020).	Widens the base of population vulnerability, making societies more susceptible to all health threats.
Public Trust & Communication	- Infodemic of misinformation undermining public compliance with measures (Zarocostas, 2020). - Erosion of trust in health authorities and institutions.	Hinders effective public health response and community engagement for both COVID-19 and AMR.
Global Health Architecture	- Exposed weaknesses in international health regulations and equity (Gostin et al., 2020). - "Vaccine nationalism" and hoarding of resources (Usher, 2021).	Undermines global solidarity and coordinated action needed to address transnational syndemic threats.

Towards a Syndemic-Ready Health Security Framework

The lessons from the COVID-19-AMR syndemic are unequivocal: our current health security paradigm is unequipped to deal with the challenge of complex, interacting crises. This requires going forward with a fundamental shift — from a pathogen-centric model to a systems-based approach that builds resilience against syndemic threats.

Integrated surveillance and "One Health" approaches

At the heart of this new architecture needs to be integrated, multi-pathogen surveillance. Instead of separate systems for influenza, AMR, and emerging pathogens, we need platforms that can monitor a wide range of human, animal, and environmental health threats simultaneously (Zinsstag et al., 2020). The "One Health" approach is not something niche; rather, it is a reality that recognizes the health of humans, animals, and ecosystems as actually interlinked in light of syndemic preparedness (Destoumieux-Garzón et al., 2018). Wastewater-based epidemiology, which proved so critical for tracking SARS-CoV-2, similarly provides a useful vehicle to monitor community circulation of MDR bacteria and resistance genes (Singer et al., 2016). Similarly, investment in next-generation sequencing and data analytics enables real-time identification of emerging threats and resistance patterns, thereby affording a much more proactive rather than reactive response (Trotter et al., 2019).

Building Resilient and Adaptable Health Systems

The pandemic showed that the health systems that would come out strongest are not necessarily those with the highest number of ICU beds, but rather those that are most adaptable and have a strong primary care backbone. Resilience will need to be inculcated at the heart of health systems: redundant supply chains for essential medicines and PPE; a surge-capable health workforce with cross-training; and robust primary healthcare that maintains essential services during a crisis (Kruk et al., 2018). Antimicrobial stewardship needs to be recognized as an essential service that should be integrated into countries' emergency response plans to ensure it is not abandoned in the next pandemic (Buehrle et al., 2021). This includes the development and dissemination of rapid diagnostic tests able to differentiate between viral and bacterial infections at the point of care technology, which, if it had existed, would have been invaluable during COVID-19 (Hsu, 2020).

Proactive Communication and Community Engagement

Accompanying COVID-19 was an "infodemic" of rapid misinformation and disinformation (Zarocostas, 2020). A syndemic-ready framework must also provide for a pre-emptive, proactive approach to risk communication and community engagement. In this, trust among communities should be developed in advance of any crisis; information should be shared transparently; and misinformation on infectious diseases and

antimicrobial use should be positively countered (Amara et al., 2022). Public messaging, on the risks of AMR and how to use antibiotics only when prescribed by a qualified professional, has to be clear, framing it as a common good and a security issue (Figure 2).

Figure 2: Towards a Syndemic-Ready Health Security Framework

Conclusion

The COVID-19 pandemic and the ongoing pandemic of antimicrobial resistance represent a quintessential syndemic of the modern era. This review has outlined the various ways in which these two crises have complexly and synergistically interacted to develop a vicious cycle that has overwhelmed health systems, complicated clinical management, and increased social vulnerabilities. COVID-19 acted as a potent accelerant for AMR through inappropriate antibiotic use, disrupted stewardship, and broken infection control. In turn, the background scourge of AMR worsened COVID-19 outcomes through difficult-to-treat bacterial and fungal superinfections.

Beyond this direct interaction, the syndemic has exposed and heightened deep-seated fragilities within global health security, from resource diversion and collapsed essential services to erosion of public trust. The core lesson is clear: our historical approach to health security is no longer fit for purpose. We cannot afford to prepare for threats in isolation. More syndemics are coming, whether in the form of climate-sensitive diseases interacting, conflict-induced malnutrition and infection, or the next novel pathogen emerging against a rising tide of NCDs. The COVID-19-AMR syndemic is a harbinger of this complex reality. The way ahead requires a paradigm shift: integrated surveillance, "One Health" in action, resilient and equitable health systems, and steadfast political and financial commitment. Setting defenses against the syndemic threat is the health security defining challenge of the 21st century, and it demands an unprecedented level of collaboration, innovation, and foresight commensurate with the complexity of the threats we face.

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