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Review Article

Microbiology Section

Global Impact of COVID-19 Pandemic on Antimicrobial Resistance: An Overview

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ABSTRACT

Antimicrobial Resistance (AMR) is a condition which occurs, when pathogens evolve and no longer respond to antibiotics, making infections more difficult to treat and leads to death. Apart from the truth that antibiotics have increased the life expectancy of human, AMR is a serious threat. AMR is a major public health threat declared by World Health Organisation (WHO) since 2014. During the different waves of the pandemic, patients with Coronavirus Disease-2019 (COVID-19) infection caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) accounted for the majority of hospital admissions, frequently necessitating an antibiotic upon admission. Among hospitalised patients with COVID-19 infection, a major cause of mortality was mainly due to secondary infections, which was due to overuse of antibiotics and poor infection control procedures which may lead to rapid emergence of Multidrug Resistance (MDR). Before COVID-19 pandemic, AMR was estimated to kill around 700,000 people yearly that are predicted to increase upto 10 million by 2050. Before COVID-19 pandemic, there was lower incidence of hospital associated infections across world. AMR was surprisingly prevalent in patients with bacterial co-infections during the first 18 months of the COVID-19 pandemic. The latest update as per WHO guidance for antibiotic stewardship, which does not recommend antibiotic therapy or prophylaxis for patients with mild/moderate COVID-19 unless signs and symptoms of a bacterial infection. Now, the researchers must consider secondary bacterial infection rate, MDR isolation rate, and high mortality among COVID-19 with secondary infection. This shows the urgent need for surveillance, reinforcement of infection control practices and strict antimicrobial stewardship to combat increasing AMR.

Keywords: Antibiotic stewardship, Coronavirus disease-2019, Multidrug resistant, Nosocomial infection

INTRODUCTION

One of the major concerns to public health in 21st century is AMR, which happens when changes in microorganisms render the medications used to treat diseases less effective [1]. The emergence of SARS-CoV-2 and subsequent pandemic has placed an immense impact on healthcare systems globally [2]. This has required unprecedented responses to control the spread of infection and protect the most vulnerable. A peek under the hood of studies reporting on patients hospitalised with COVID-19 reveals widespread use of antimicrobial therapies as part of the package of clinical care in some countries [3]. The COVID-19 epidemic presents further difficulties for antibiotic stewardship tactics and consumption measurements. During the initial wave of the pandemic, COVID-19 patients accounted for the majority of hospital admissions, frequently necessitating an antibiotic prescription upon admission or treatment for superinfection [4].

In a recent research, Cox MJ et al., highlighted a need to prospectively monitor co-infections in patients with COVID-19 to understand whether co-infection affects disease progression and to enable antimicrobial stewardship [5]. It is of the utmost importance that the potential of the global pandemic to increase AMR is taken seriously. AMR is a growing problem that has implications for global health and the world economy [3]. During the 1918 and subsequent influenza pandemics, *Streptococcus pneumoniae* and other bacterial superinfection were common causes of mortality and morbidity [6]. Prior to emergence of COVID-19, an estimated 3 million Americans were infected each year with a high-priority antimicrobial resistant pathogen [7,8].

Several factors constrain the antimicrobial marketplace. Antimicrobials are generally administered for short treatment courses. Older agents remain active against a vast majority of infections. Responsible stewardship practices restrict use of newer agents to AMR infections in which older drugs are inactive. Overly restrictive stewardship may limit uptake of new antimicrobials in favour of cheaper, less effective alternatives [9].

The goal of this article was to identify variables that contribute to AMR, discuss the aspects that prescribers consider when writing an antibiotic prescription and investigation factors that affect the outcomes of improper antimicrobial usage.

AMR: GLOBALLY

The AMR is a reality that is “far from an apocalyptic fiction,” according to the WHO’s most recent global surveillance report [10]. It is occurring right now in every region of the world and has the potential to afflict anyone, of any age, in any country [11]. Over the past several decades, antimicrobials have facilitated improvements in medicine. Although, efforts to achieve universal health coverage and the health-related sustainable development target are slowed down by the ongoing emergence of antibiotic resistance, we are still able to treat diseases. A neglected worldwide catastrophe called AMR needs to be addressed immediately [12]. AMR caused an estimated 4.95 million (3.62-6.57) deaths in 2019, of which 1.27 million (95 percent UI 0.911-1.71) were directly linked to the disease. As per calculation of the regional all age mortality rate owing to resistance was 27.3 deaths per 100,000 people (20.9-35.3) in western sub-Saharan Africa and 6.55 deaths (4.3-9.4) per 100,000 people in Australasia [1]. An estimated 34.8 billion antibiotic doses consumed by humans each year, with worldwide consumption increasing 65% between 2000 and 2015. In UK, one out of five antibiotics are prescribed unnecessarily. In the US, this number upsurges to 1 in 3. Meanwhile, 17% of the substandard or falsified medicines reported to the WHO are antibiotics, which have further contributed to drug resistance. Maximum pharmaceutical companies are no longer making new antibiotics. In current time, half of all antibiotics that are being used were discovered during the 1950s.

Factors Influencing AMR

One of the main causes of the emergence of antibiotics resistance is the irrational use of antibiotics [13]. Other factors may include in-experienced medical professionals, inaccurate diagnoses and medical judgments influenced by patient caregivers. Monitoring AMR is essential for spotting new resistance trends, creating mitigation tactics and evaluating their efficacy [14]. A number of factors, including social factor, untrained medical practitioner, lack of proper guidelines/Standard Operating Procedures (SOP) for antimicrobial therapy, lack of antimicrobial surveillance and lack of new research of new antibiotics are discussed below:

(A) Social factor: Some of the main social reasons causing antibiotic resistance are insufficient access to effective therapies, self-medication and shortage of money to pay for suitable, high-quality medications. Some patients frequently self-medicate despite being aware that using antibiotics improperly might result in resistance [15]. Misuse of antibiotics is one of major social factor for increasing AMR.

(B) Untrained/unskilled medical practitioner: Doctor's disregard for recommended treatments, their ignorance of antibiotics, their lack of training in their use, their lack of access to diagnostic tools, their uncertainty about the diagnosis, pressure from the pharmaceutical industry, their fear of clinical failure, the financial rewards they receive from prescribing antibiotics, and their lack of time to educate their patients, can all have an impact on the course of treatment and contribute to AMR [16].

(C) Lack of antimicrobial surveillance system for AMR: There is a shortage of information on comprehensive population-based surveillance of antibiotic resistance in low and middle-income nations. Due to weak administration of the healthcare system, a lack of health information systems and lack of resources, the problems are significant. Increased antibiotic resistance rates can be brought on by inaccurate data, which also makes it difficult to monitor and map the development of resistance, identify early outbreaks, and establish public health policies to address resistance [17].

(D) Lack of proper guidelines: A local stewardship guideline, which is frequently based on local antibiotic susceptibility data, impacts a clinician's choice of antimicrobial for their patients. Empiric therapy aims to cover a wide variety of suspicious organisms. As a result, AMR will alter the antimicrobials administered to people with COVID-19. Clinicians are thus faced with competing priorities: prescribing a broad enough spectrum antimicrobial to ensure the organism's sensitivity while avoiding the unnecessary use of antimicrobials, when a more commonly used or narrower-spectrum antimicrobial would be enough [18].

(E) Lack of research of new antibiotics: According to WHO, efforts to tackle drug resistant diseases are being undermined by declining corporate investment and a lack of innovation in the discovery of new antibiotics [19]. AMR research is also expected to have slowed significantly during COVID-19. Staff, as well as diagnostic laboratory equipment and reagents, have been redeployed to COVID-19 research.

Despite the obvious need for additional antimicrobial medicines, no such medications have been developed. In COVID-19, one can observe many factors such as long-term hospital admission, over use of antibiotics, decline in diagnosis processes are also responsible for increase in rate of AMR cases [4]. According to a survey conducted in Global Antimicrobial resistance and use Surveillance System (GLASS) countries, showed that majority of the responding nations had declined in the demand for screening (65%; 44/68) and clinical (67%; 46/69) cultures. Many (48/69; 70%) of them described a decrease in their capacity to provide training for laboratory staff, while more than half (42/70; 60%) reported no influence on the processing time of antimicrobial susceptibility test results. A 46% (27/59) and 43% (29/68) also reported decrease in their capacity to conduct molecular screening and quality management activities, respectively [20].

Superinfection and AMR in pre COVID-19 and COVID-19

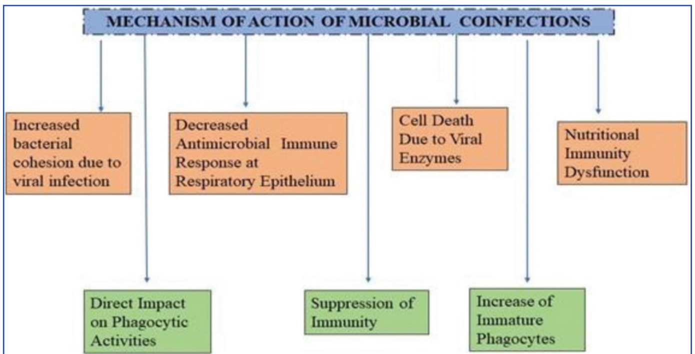
AMR was a high priority for global public health prior to COVID-19 pandemic. AMR, which is already a complicated subject, must now be tackled in the context of a changing healthcare sector. Many changes occur during COVID-19 in terms of antibiotic usage and superinfection which impact the onset, spread and burden of AMR.

Superinfection and Antimicrobial Usage Before COVID-19 Pandemic

Antibiotics have been enormously successful in improving health outcomes and have aided in the global reduction of under-5 mortality from 216 deaths per 1000 live births in 1950 to 39 deaths per 1000 live births in 2017, as well as an increase in men's life expectancy at birth from 49-82 years and women's life expectancy from 54-87 years over at same period [21]. Increase in resistance rate for the common antibiotics is very often encountered among common illnesses, such as Urinary Tract Infections (UTIs) or different types of diarrhoeas, showed that the world is running out of effective ways to combat these notorious bugs. According to WHO, 33 reporting nations the rate of resistance to ciprofloxacin, an antibacterial often used to treat UTIs, ranged from 8.4-92.9% [22]. AMR is on the rise globally, posing a danger to the beneficial effects of antibiotics on health and many low and middle-income nations (LMICs) lack of access to basic medicines [23].

Superinfection and Antimicrobial Usage in COVID-19 Pandemic

Patients who are critically ill and hospitalised are more likely to develop bacterial and fungal superinfection, when they are having risk factors like ageing population, underlying systemic diseases, immunocompromised individuals, long-term systemic corticosteroid use, mechanical ventilation, extended hospital, Intensive Care Unit (ICU) stays and can also complicate COVID-19 disease [24]. Numerous bacteria, including MDR bacteria were found to be associated with superinfection in COVID-19 patients [25]. Whereas *Aspergillus flavus, Aspergillus fumigatus, Candida albicans,* and *Candida glabrata* were some of the most frequent fungi that have been identified as superinfecting COVID-19 patients [24,26]. Secondary infections were reported in 5-27% of adults infected with SARS-CoV-2 in several hospitals in Wuhan, China, through mid February 2020, including 50-100% of those who died [27]. There are various mechanisms such as decrease in immune response against microbes, increased bacterial cohesion, cell death due to viral enzymes etc., by which various bacteria and fungi can cause secondary infections in COVID-19 patients [Table/Fig-1] [28,29]. Prior to the onset of COVID-19 pandemic, drugs that had already been authorised for treating other conditions were quickly repurposed as potential treatments for the COVID-19/SARS-CoV-2. Worldwide, medical professionals suggested using a wide range of drugs to treat these kinds of patients [25]. According to data from research on antibiotic use in the treatment of COVID-19 patients, an average of 70% of patients takes antibiotics [30].



[Table/Fig-1]: Mechanism of action microbial co-infection [28,29].

Disruption in Clinical Care System due to COVID-19 Pandemic

Global health system has been greatly impacted by COVID-19. Due to this strain, healthcare organisations and governments have been obliged to prioritise medical treatment and postpone everything but the most critical surgeries [31].

Delay in Diagnosis of AMR and its Sequealae

Due to COVID-19, there was a delay in testing for other diseases. A delay in diagnosis of secondary infection caused by Antibiotic Resistant Organisms (AROs) may remain contagious for long-term and hence transmit to others for longer with a delay in diagnosis and effective adequate treatment. For example, in the first quarter of 2020, Tuberculosis (TB) and Multidrug Resistance Tuberculosis (MDR-TB) tests significantly decreased in China [32]. COVID-19 also had an impact on vaccination. The number of measles vaccinations decreased by about 50% in the first quarter of 2020 compared to the same period in 2019, according to the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Data Link [33]. This decline has occurred throughout the world as nations impose various levels of lockdown. The majority of nations had suspended large polio vaccination programmes, while 25 countries had delayed mass measles vaccine campaigns [34]. Another survey on 73 countries by GLASS had showed that more than half of the reporting nations (35/56; 63%) reported increase in overall antibiotic prescription. In particular, 47% (23/49), 57% (27/47) and 40% (18/45) of countries reported increasing usage of WHO access, watch, and reserve antibiotics [20].

Diagnostic Uncertainties

COVID-19 symptoms might be like bacterial pneumonia. When urgent treatment is required, diagnostics used to identify viral from bacterial pneumonia may be inefficient or have turnaround times of hours or days. As a result, many patients admitted with COVID-19 were given antibiotics, often in the absence of microbiological confirmation of the diagnosis.

Lack of Improper Supply Chain of Antibiotic

The burden of ARO related diseases is determined by the quantity and character of infections, as well as the availability, efficacy, and safety of alternate therapies. COVID-19 has the ability to alter all three of these components, either directly or indirectly. As a result, the availability of antibiotics has been disrupted by the pandemic because government led initiatives have included local and international travel restrictions, which generate supply chain delays. Uneven supplies of different antimicrobials across all income settings raised concerns about AMR emergence due to suboptimal antibiotic usage [18].

Global Impact of AMR on Secondary Infection in COVID-19 Pandemic

Over the last two decades, common viral infections have contributed considerably to mortality including both developed and developing countries, and in most situations, deaths are caused by subsequent bacterial infections rather than direct viral harm [35]. Before COVID-19, increasing AMR or secondary infection around the world was a major issue to concern.

Many different researches have been done in recent years on AMR and other different secondary infections. A retrospective study in India by Saini V et al., observed bacterial co-infections of *Staphylococcus aureus* (12.80%), Coagulase negative *Staphylococcus* (29.40%), *Enterococcus* spp. (10.80%), *Klebsiella pneumoniae* (10.80%), *Acinetobacter baumannii* (10.50%), *Pseudomonas aeruginosa* (4.20 %), *Escherichia coli* (21.40%) in total 844 cases [36]. A study conducted in USA by Weiner-Lastinger LM et al., showed that 1689 cases of MRSA and 9,910 cases of *Clostridioides difficile* (CDI) are predominately reported from 3,106 and 3,190 hospitals respectively from January to March 2020 [37]. A study in Brazil by Bes TM et al., in 2017 found 2.3% prevalence of MRSA colonisation in individuals from the general community [38]. Another study by Karatas M et al., showed the prevalence of secondary infection of Extended-spectrum beta-lactamases (ESBLs) producing Enterobacterales and *Acinetobacter baumannii* among 3532 patients which is 20.76% and 3.49% respectively [39]. An observational study by Ntirenganya C et al., showed the prevalence of *Escherichia coli* and *Klebsiella* isolates and found that antimicrobial resistance rates were high [Table/Fig-2] [29,36-40,42-44].

The COVID-19 epidemic is having extensive consequences for many sectors of our healthcare systems. These have thrown multiple layers of AMR surveillance, prevention and control into disarray. Superinfection is significant risk factor for unfavourable outcomes and hospitalised patients with severe illness are more likely to be infected. Rawson TM et al., and Langford BJ et al., conducted meta-analyses and discovered that approximately 75% of hospitalised COVID-19 patients received antibiotics, despite the fact that 3.5% and 8.5% were estimated to have bacterial co-infections on presentation and bacterial/fungal co-infections during admission, respectively [2,41].

A study by Chowdhary A et al., have found MDR resistance *Candida auris* in patients infected with COVID-19 [42]. A comparative study by Weiner-Lastiger LM et al., showed increase in rate of AMR in comparison with pre COVID-19 [Table/Fig-2]. They studied on MRSA infections, CLABSI (central-line-associated bloodstream infection); CAUTI, (catheter-associated urinary tract infection), VAE (ventilator-associated event) and *Clostridioides difficile* infection (CDI) and found that except CDI all other infections are greater than cases in

Pre COVID era					Post COVID era				
Author	Year/ Country	Sample	Organism	Secondary infection/AMR	Author	Year/ Country	Sample	Organism	Secondary infection/ AMR
Saini V et al., [36]	2021/ India	Blood and urine	*Staphylococcus aureus*, CONS, *Enterococcus* spp. *Klebsiella pneumoniae* *Acinetobacter baumannii* *Pseudomonas aeruginosa* *Escherichia coli*	11.54%	Chowdhary A et al., [42]	2020/ India	Blood	*Candida auris*	2.5%
Weiner-Lastinger LM et al., [37]	2022/ USA	Blood, urine	*Clostridioides difficile* (CDI) and Methicillin-resistant *Staphylococcus aureus* (MRSA)	-7.2% (MRSA), -17.5% (CDI)	Weiner-Lastinger LM et al., [37]	2022/ USA	Blood, urine	*Clostridioides difficile* (CDI) and *MRSA*	33.8% (MRSA), -5.5% (CDI)
Bes TM et al., [38]	2018/ Brazil	Pus, blood and body fluids	Methicillin-resistant *Staphylococcus aureus* (MRSA)	7/300 (2.3%)	Mahmoudi H [29]	2020/ Iran	Blood culture	*Klebsiella* spp., MSSA, *Escherichia coli*, MRSA, *Enterobacter* species, *Streptococcus pneumoniae* and *P. aeruginosa*	12.46% (43/340)

Karataş M et al., [39]	2021/ Turkey	Blood, urine, respiratory samples, pus	ESBL- producing Enterobacterales, *Acinetobacter baumannii*	20.76% (ESBL), 3.49% (*A. baumannii*)	Li J et. al., [43]	2020/ China	Culture	*A. baumannii, K. pneumoniae* and *S. maltophilia*	6.8% (102/1495)
Ntirenganya C et al., [40]	2015/ Rawanda	Urine, blood, wound swab and sputum	*Escherichia coli* and *Klebsiella* isolates	31.4% (*E. coli*) and 58.7% (*Klesbsiella*)	Khurana S et al., [44]	2021/ India	Blood, urine, respiratory samples, pus	*K. pneumoniae* (33.3%) *A. baumannii* (27.1%).	13% and 84% AMR

[Table/Fig-2]: Prevalence of secondary infection /AMR in pre COVID-19 and post COVID-19 era [29,36-40,42-44].
CoNS: Coagulase-negative staphylococci; MSSA: Methicillin-sensitive *Staphylococcus aureus*

2019, which might be attributed to poor management methods [37]. Another research by Mahmoudi H, on different bacterial infections on 340 patients showed prevalence of 12.46% [29]. In another study by Li J et al., showed the prevalence of secondary infection of *A. baumannii, K. pneumoniae* and *S. maltophilia* was 6.8% among a total of 1495 COVID-19 cases [Table/Fig-2] [43]. Another study by Khurana S et al., showed secondary infections in 151 (13%) among a total of 1179 patients with overall resistance upto 84% in which majority of the organisms were MDR [44].

Consequences of Rising AMR during COVID-19

The COVID-19 and AMR have a number of negative effects on the health system, as well as on the economy, society and international politics. Due to limited resources and prolonged hospital stays, AMR and other secondary infections have increased. This leads to prolonged treatment delays, hospital epidemics and a shortage of beds, raising ethical concerns regarding the prioritisation of care.

(a) Economic consequences: In developing and underdeveloped countries, where resources are limited, above given problems arises more frequently. Antimicrobial medications are already insufficiently available in these nations, but the rate of AMR is expected to rise 4-7 times faster [45,46].

Additionally, it puts a financial strain on governments. Due to reduced production as a result of sick days and protracted recovery times, significant AMR related costs are anticipated. AMR's implications on the labour market are anticipated to have significant cumulative consequences on the world economy, particularly in service sectors that depend on human contact. Stronger labour rights and gender appropriate access to healthcare and alternate arrangements for child and senior care should all be part of a comprehensive AMR strategy that effectively tackles the unequal biological and social effects of AMR [47].

The breaking of international collaboration based on norms during COVID-19 has shown the vulnerability of that cooperation. In order to stop the virus from spreading inside their own borders during the pandemic, many nations disregarded the WHO advice and broke the legally binding International Health Regulations (2005) by prohibiting the export of medical supplies, enforcing severe travel restrictions and violating human rights obligations [48].

(b) Increase in mortality rate: According to a report by CDC, more than 29,400 persons died from antimicrobial resistant diseases frequently linked with healthcare during the first year of the epidemic. Nearly 40% of these COVID-19 infected persons were secondarily infected while in the hospital stay [49].

(c) Emergence of new pattern of resistance: The emergence and spread of drug resistant pathogens that have acquired new resistance mechanisms, leading to AMR, continues to threaten our ability to treat common infections. Especially alarming is the rapid global spread of multi and pan resistant bacteria (also known as "superbugs") that cause infections that are not treatable with existing antimicrobial medicines such as antibiotics [50].

The clinical pipeline of new antimicrobials is dry from last so many years, only modified salts or congener of old salts are now being tried and used for better efficacy. In 2019 WHO identified 32 antibiotics in clinical development that address the WHO list of priority pathogens, of which only six were classified as innovative. Furthermore, a lack of access to quality antimicrobials remains a major issue [50].

Prevention of AMR

The AMR is a slow-moving issue that affords a rare chance to proactively create treatments to lessen the effects of COVID-19. While COVID-19 response is presently receiving the world's attention, which is understandable, there is a moral need to reflect on lessons learned and potential for future global health emergencies. There are two options for dealing with the growing problem of antibiotic resistance: either develop new medicines, or utilise existing antibiotics more prudently. Both solutions will be required and useful [51].

(A) Optimising usage of antibiotics: Antibiotic stewardship programmes strive to optimise the use of antibiotics while lowering the risks associated with the development of antibiotic resistance, side-effects and pharmaceutical costs. Antibiotic stewardship tactics reduce the need for antibiotics, therefore national and international recommendations must encourage hospitals to follow local its guidelines to improve de-escalation and treatment strategies [52]. COVID-19 targeted antibiotic stewardship treatments have been few thus far, despite their enormous promise in pandemic management by optimising treatment regimens and antibiotic usage [53]. The performance of host response biomarkers and patterns of antibiotic prescription among patients with confirmed or suspected COVID-19 are both in urgent need of further study. It is important to publicly communicate antibiotic stewardship techniques and use them to guide future pandemic responses. These techniques have been demonstrated to successfully reduce the impact of COVID-19 in emergency rooms [54].

(B) Five D's by antibiotic stewardship program: Antibiotic stewardship is mainly framed by five D's ie., diagnosis, drug, dose, duration and de-escalation [55]. For approaching antibiotic stewardship for COVID-19, all above given factor must be in mind. Diagnosis should be appropriate and there is need of well computerised system with less turnaround time. Right empiric drug should be used with help of selective and cascade reporting of antibiotic susceptibility and provider education, to avoid AMR. Use of right dose based on infection and diagnosis report. Duration of antibiotic use must be taken into consideration; mentality of "longer is better" can be harmful for patient. De-escalation is also very important and must be done by help of post prescription review. Above to provide the greater opportunity for an efficient coordinated response to AMR across areas, world society should deliberately seek for an equally appealing rallying cry [47].

(C) Research and development of newer antibiotics/antimicrobial agents: The AMR sector should make investment in diagnostic infrastructure and adapt their usage for quick identification of both the infection's cause and any related treatment resistance. The diagnostic difficulties encountered by COVID-19 are typical worries for bloodstream infections, suspected pneumonia and other situations [18]. The development of a low-cost, trustworthy, and quick point-of-care test should continue at the current pace. Also there is need of new antibiotics which can effective on broad range of resistant bacteria.

CONCLUSION(S)

The global threat of AMR will persist even beyond the COVID-19 pandemic. The use of antibacterial agent was seen in alarming rise following the initial wave of the COVID-19 pandemic. Recent data on the prevalence of AMR infections before and after the pandemic should be gathered to determine the dissemination of AMR organisms particularly in developing countries. Antibiotic prescription practices might be improved to reduce the chances of resistance and as a result, improve the clinical outcomes. This is something to consider in the context of AMR, since MDR organisms are developing and pushing us closer to a day when infection caused by these organism will be no longer curable. The awareness and management of infectious agents, as well as the invention of newer, more useful antimicrobials is required on large scale. One of the significant approaches to control AMR is to make investments in improving healthcare systems along with good infection control practices and preparing for such pandemics associated with superinfection. The present epidemic has taught us a valuable lesson about the need of having appropriate, robust and effective reporting and surveillance mechanisms.

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