Mini-Review

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Antimicrobial resistance and COVID-19 syndemic: Impact on public health

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SUMMARY The COVID -19 pandemic has had a catastrophic impact on the global economy and the healthcare industry. Unfortunately, the scientific community still hasn't discovered a definite cure for this virus. Also, owing to the unscrupulous use of antibiotics in wake of the current situation, another ongoing pandemic of antimicrobial resistance (AMR) has been entirely eclipsed. However, increased compliance to infection control measures like hand hygiene (both at hospital and community level), and restricted travel might be favorable. It is evident that the AMR strategies will be impacted disproportionately varying with the respective policies followed by the countries and hospitals to deal with the pandemic. The vaccination drive initiated globally has provided a glimmer of hope. In this article, the possible reciprocity between the two contemporaneous pandemics has been addressed. The world needs to be vigilant to punctuate the symphony between these lethal threats to global health. The restraint to combat against AMR will be boosted as our discernment of the problem also changes with the epidemiological interplay becoming more apparent in near future.

Keywords COVID-19, antimicrobial resistance (AMR), MDR, pandemic

1. Introduction

It has been more than a year since the COVID-19 pandemic has had a catastrophic impact on the global economy and the healthcare industry. The world going into a complete lockdown was beyond imagination. According to the World Health Organization (WHO), even 173,331,478 confirmed cases and 3,735,571 deaths later (as on 8th June 2021 as per WHO COVID-19 dashboard) (*1*), and despite scientists and doctors working tirelessly, the world still hasn't managed to discover a definite cure for this virus. However, in our desperation to deal with the current situation, another ongoing pandemic of antimicrobial resistance (AMR) has been overshadowed. With an increased compliance to infection control measures like hand hygiene (both at hospital and community level), but also a documented rise in antimicrobial use, a debate is pertinent as to whether the COVID-19 pandemic has been a boon or bane for the menace of AMR (*2-4*). The recent vaccination drive across the world might bring an end to the pandemic, but the repercussions on the AMR program will subsequently be observed over a long period. The authors would discuss the same through this review.

2. How big is the problem?

AMR was certainly one of the biggest concerns of microbiologists and clinicians throughout the world in the pre-COVID era. High resistance rates have been reported for organisms like *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecium*, *Pseudomonas spp*., *Acinetobacter baumanii*, *etc*., causing common bacterial infections like urinary tract infections, respiratory tract infections, skin and soft tissue infections subsequently leading to life-threatening events. These organisms have developed resistance to even the last-resort antibiotics including carbapenems, polymyxins, and glycopeptides. Approximately, 700,000 deaths/year are attributed to AMR worldwide. At this rate, the number is expected to rise to an estimated ten million deaths by 2050 (*5,6*). India has been hit even worse with the challenge of AMR. Increasing rates of multidrug resistant pathogens have been reported across national surveys. As per available data, while in 2008, about 29% of *Staphylococcus aureus* isolates were methicillin resistant, by 2014, the percentage had risen to 47%. A multi-centric study carried across seven cities in India reported Extended Spectrum β-Lactamase (ESBL)

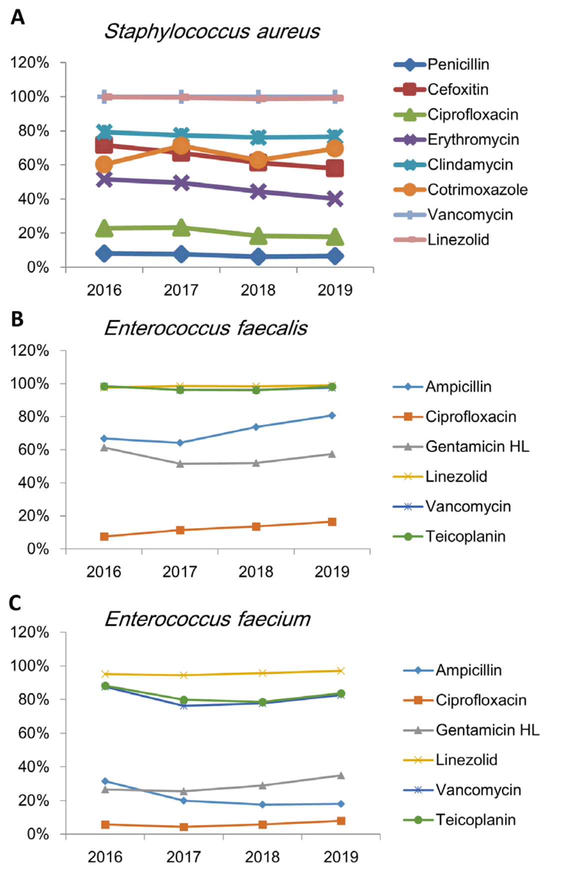

Figure 1. Susceptibility trends of commonly isolated Gram positive organisms. (A) *Staphylococcus aureus*, **(B)** *Enterococcus faecalis*, **(C)** *Enterococcus faecium*. The figure is prepared by the authors based on the published susceptibility data of commonly isolated Gram positive organisms in the Annual reports (2016-2019) of Antimicrobial Resistance Surveillance and Research Network, an initiative of Indian Council of Medical Research (ICMR).

production in 61% *E. coli* and carbapenem resistance in 31-51% *Klebsiella spp*. Amongst *Pseudomonas spp*., 65% were found to be resistant to ceftazidime and 42% to imipenem (*7*). The current susceptibility trends of commonly isolated Gram-positive (GP) and Gram-negative (GN) bacteria have been depicted in Figures 1 and 2 respectively (*8*). Along with being a public health problem, AMR is also a contributor to the economic loss for the country due to increased hospital stays and a requirement of repeat surgical interventions on account of complications as a result of infections.

3. What steps were being taken?

Fortunately, the governments across the world realized this issue in time and had started working on the menace of AMR far before the COVID pandemic doomed us. A multi-faceted approach needs to be followed to control the resistance development and transmission. Various stakeholders need to collaborate and work on altering human behavior, animal rearing practices, agricultural practices and the environment as a whole such that it results in good health for all. Excess use of antimicrobials ultimately leading to AMR might be dealt with surveillance of all these aspects under the One health approach (*9,10*). Interventions to emphasize rational use of antibiotics must address important issues like restricting antimicrobial use without impacting their availability for patients especially in low and middle-income countries (LMIC). The said response may be achieved by a two-tier approach, one targeting the AMR specifically and antimicrobial

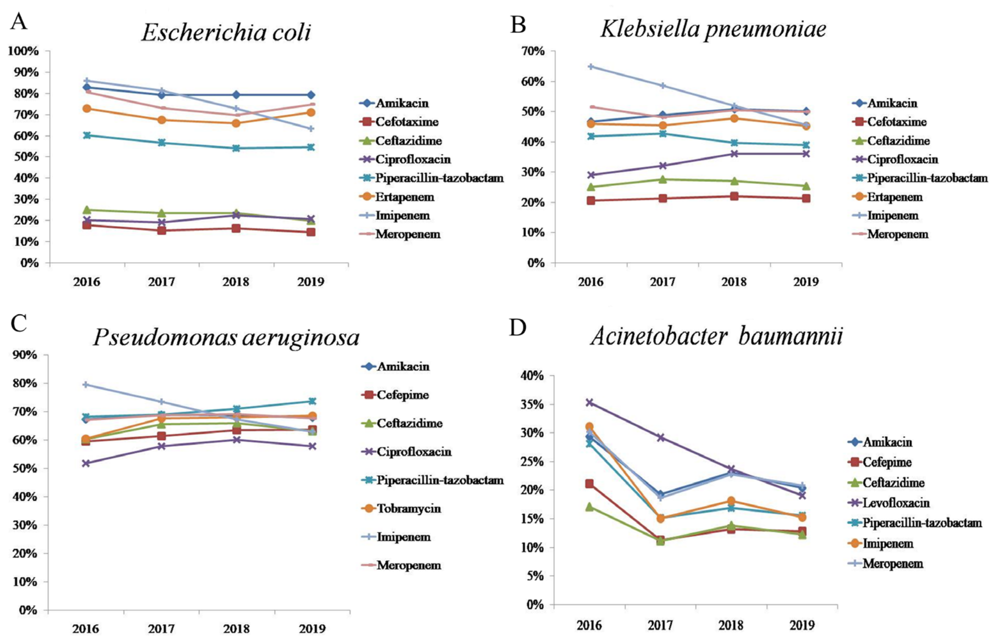

Figure 2. Susceptibility trends of commonly isolated Gram negative organisms. (A) *Escherichia coli*, **(B)** *Klebsiella pneumoniae*, **(C)** *Pseudomonas aeruginosa*, **(D)** *Acinetobacter baumannii*. The figure is prepared by the authors based on the published susceptibility data of commonly isolated Gram negative organisms in the Annual reports (2016-2019) of Antimicrobial Resistance Surveillance and Research Network, an initiative of Indian Council of Medical Research (ICMR).

usage and the other dealing with the aspects like improved infection control practices, sanitation, and hygiene in general. Globally, the United Nations (UN), Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the World Health Organization (WHO), formalized in 2010 as the Tripartite, have been the guiding forces to tackle AMR by coordinating and sharing relevant information amongst the stakeholders (*11*).

The 68th World Health Assembly (WHA), in May 2015, endorsed the Global Action Plan on Antimicrobial Resistance (GAP-AMR). Antibiotic resistance was included as being one of the most urgent drug trends. All member states were urged to align their National Action Plan on AMR with GAP-AMR by May 2017. The Government of India in collaboration with the World Health Organization (WHO) organized an international conference in February 2016 pertaining to "Combating Antimicrobial Resistance: A Public Health Challenge and Priority", which was attended by more than 350 participants. The UN General Assembly adopted the Political Declaration on Antimicrobial Resistance in September 2016. This marked the formalization of a major step towards strengthening the AMR response by collaborative efforts of various nations (*7*). The National Health Policy in India released in 2017 identified AMR as a menace and called for effective action to address it. India got enrolled in the Global Antimicrobial Resistance Surveillance System (GLASS) network in 2017. Globally, various hospitals and institutions have been sharing their data with the WHO to enumerate the exact situation of AMR for years so that an effective strategy might be worked out. To fortify and re-enforce AMR surveillance in India, the Indian Association of Medical Microbiologists (IAMM) is collaborating with the WHO to establish a supplementary AMR surveillance network called the WHO-IAMM Network for Surveillance of Antimicrobial Resistance (WINSAR). It shall serve as a common dynamic platform to share and assess dependable AMR data from hospitals/laboratories (both government and private) across India.

Hence, immense work was being done across the world on the line of AMR. However, it got entirely eclipsed in the COVID era.

4. Is COVID a blessing in disguise: A boon from AMR's perspective?

AMR is associated with numerous factors like an indiscriminate antibiotic use, suboptimal dosing, antagonistic combination prescription, *etc*. However, the global resistance rates are influenced by the spread of the organism as much as they depend on the irrational antimicrobial usage (*4*). Since time immemorial, microbiologists have been advocating the importance of hand hygiene on multiple platforms. But it took a massive pandemic for the public to understand the same. The COVID-19 pandemic has fortunately paved the way for improved infection control practices, both at the level of healthcare facilities as well as the community per se. Most resistant organisms like methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and carbapenem-resistant *Enterobacterales* (CRE) have been reported to get transmitted through person to person contact. People have now been washing hands more frequently, thus possibly limiting the spread of resistant micro-organisms (*4,12*). Another argument in favor of this pandemic is the immense reductions it brought in travel which may negatively impact the spread of AMR. There has been indisputable evidence for the transmission of AMR through the key genes (*13*). These genes are harbored and transferred by the organisms present not only in the contaminated food and vegetables but also those colonizing the animals and humans (*12,14*). For instance, as published by Shwartz *et al*., more than 60% of travelers to India were later found to be colonized with an ESBL organism while approximately 0.4% with CRE (*15*). The detection and global dissemination of carbapenem resistance through the *NDM-1* gene and colistin resistance through the *mcr-1* gene has been widely reported (*16,17*). And hence, the COVID pandemic might have proven to be a blessing in disguise from the AMR perspective.

5. Will it curtail our progress and worsen the challenge of AMR: A bane?

While we may acknowledge that the COVID-19 pandemic might have been a boon from the AMR perspective, there are various arguments against this belief. Firstly, although it is understandable that owing to the lockdown and a general fear of visiting hospitals, the patient attendance in outpatient departments of hospitals might have decreased. However, the probability of patients being administered empirical broad-spectrum antibiotics is quite high. Additionally, the risk factors predisposing for AMR infections like diabetes, chronic systemic illnesses, old age, malignancies, *etc*. are also the co-morbidities associated with worse outcomes in COVID-19. The prolonged stays in intensive care units, with increased morbidity and mortality amongst patients, along with clinicians' concern and probable inability to diagnose secondary bacterial infections due to lack of infrastructure, has not only augmented the prescribing of antimicrobials but also has indirectly contributed to the rise of AMR. A study done by Chen *et al*. reported that 15% and 71% of COVID-19 patients were administered anti-fungal and antibiotic treatments, respectively. Out of these 25% received a single antibiotic while 45% received combination therapy. The spectrum of antimicrobials used included cephalosporins, fluoroquinolones, carbapenems, tigecycline, and linezolid (*18*).

Randomized trials from China evaluating remdesivir and lopinavir/ritonavir reported that antimicrobials were prescribed in approximately 90% of patients (*2,19,20*). An eye-opener meta-analysis published recently by Langford *et al*. on the bacterial co-infections and secondary infections in COVID-19 patients, distinctly mentioned that although the bacterial infection was found to be ranging from 5.9-8.1%, the patients receiving antibiotics were almost 70% including mainly fluoroquinolones and third-generation cephalosporins (*21*). Another review from Asia with similar results reported the prescription of antimicrobials in around 70% of patients in spite of the bacterial or fungal co-infection rates reported to be less than 10% (*22*). Such non-judicious use of antimicrobials will negatively impact the antimicrobial stewardship program. Also, crowded living spaces like prisons, psychiatric hospitals, and nursing homes, *etc*. have been associated with a majority of their inhabitants getting infected and admitted with COVID-19 (*23*). Patients from these facilities especially nursing homes and hospitals may harbor highly resistant microbes including carbapenemase-producing organisms (CPO), MRSA, VRE, and fungi like *Candida* (*3*). Understanding transmission in such settlements would be challenging. Another worrisome consequence of this pandemic was the inadvertent use of broad-spectrum antimicrobials like azithromycin with/without hydroxychloroquine and doxycycline due to random reports claiming a possible therapy option (*24,25*) with inadequate evidence (*26*). While data is still scarce, the widespread prescription of these drugs has negatively impacted the AMR measures. Secondly, some of the countries worst hit by the pandemic including China, India, Italy, Spain, USA have already been AMR hotspots dealing with various multidrug-resistant (MDR) and pan drug resistant (PDR) bugs (*3,27,28*). Further, the LMICs, with improper sanitation, poor infrastructure, and quality of healthcare as well as restricted preparedness for outbreaks are prospective epicenters for AMR spread. Thirdly, the use of sanitizers, antimicrobial soaps, and disinfectant cleaners has exponentially increased, both in the hospitals as a part of the infection control protocols as well as in the community due to the sensitization of public in general. It can now be recognized as an individual habit that might prove instrumental in reducing the spread of AMR. However, the possibility of these products containing biocides, *i.e*, antimicrobials in disinfectants and cleaners cannot be ruled out (*29-33*). Their increased usage during the COVID-19 pandemic and beyond will lead to increased levels of biocides in wastewater treatment plants and the environment in general which will not only be a health hazard for the exposed individuals but also a public health concern due to its anticipated contribution towards AMR (*12*). Fourthly, the pandemic has not only caused an overloading of the healthcare capacities and laboratory systems but also contributed towards disruptions in working of various industries including research and development (pharmaceuticals), vaccine production, and agricultural industry. The environmental surveillance activities and screening cultures of patients for resistant organisms in hospitals have been affected as most of the workforce has been assigned towards COVID-19. The entire research industry has been redirected and obsessed with the development of new diagnostic tests, medicines, and vaccines for COVID-19. All work for other diseases like influenza, HIV, dengue, malaria, TB, *etc*. has suffered. Moreover, due to the lockdown, vaccine production and delivery systems have been affected. The catastrophic consequences due to shortages in vaccines for influenza, TB, measles, pneumococcal pneumonia, and other infectious diseases can be anticipated (*34*). The agricultural industry has also been hit thus endangering the food supply chains. Elevated usage of antibiotics for food production is associated with the risk of AMR by the development of resistance within the microbiome of exposed animals as well as by environmental leakage in excreta and wastewaters (*34*). Subsequently, the risk of circulation and dissemination of novel resistance genes will also rise once the travel resumes.

6. What might be done?

6.1. At the level of the laboratory

The clinical microbiologists, today have the cardinal responsibility of conquering antimicrobial resistance. Their work should not just be limited to reporting results in the laboratory but to discuss those reports with the respective clinicians. The clinicians need to be made aware of the advancements in the field of microbiology, the upcoming antibiotics, and the spectrum and uses of the existing ones. Regular training sessions should be held across specialties to discuss their concerns regarding the same. The antibiotic policies may be made not only considering the antibiogram of the hospital or ward but also the specialty involved. The microbiologists may be made a part of the clinical rounds so that they can participate and suggest with due consideration to infection control practices as well the antibiotic use. Escalation or de-escalation of the antibiotics may be suggested on the rounds as per the culture grown in the lab. Also, a very important step towards rationalizing the use of antibiotics is the strict compliance to graded reporting of antimicrobials as suggested by the Clinical and Laboratory Standards Institute (CLSI), *i.e*., the sensitivity pattern for higher second-line drugs might be held and not reported in case the first line is sensitive. In case the pattern for the second-line drug is specifically required, the clinician might discuss and inform.

6.2. At the level of the clinicians

The prime task of rational antimicrobial prescription lies at the hands of the clinicians. The right antimicrobial therapy depends on a lot of factors. The first and foremost is diagnosing the right site of infection with detailed history taking and adequate investigations, and prescribing targeted therapy for the same. This should be followed by the choice of the right antibiotic, right dose, and the right route. They need to take into account the pharmacokinetics-phamacodynamics (PK/PD) of the drug that they prescribe. Due consideration should be given to drug interactions. Also, renal or hepatic drug dose modifications need to be considered. The timing for sending culture samples has to be strictly monitored. The hospital should have an Antimicrobial Stewardship Program (AMSP) which should be instrumental in devising the antibiogram and antibiotic policy, guiding the empirical antimicrobial therapy, and monitor the compliance to policy, usage of restricted antimicrobials as well as escalation/de-escalation based on culture results and clinical scenario. The clinicians should actively participate in the policy-making of Hospital Infection Control (HIC) protocols and abide by the same.

6.3. At the level of Government

The government may help by incorporating AMR policies in the national programs. Data capturing might be made mandatory at a national level. Personnel may be held responsible at national and state levels to coordinate the data delivery and submission. All such data should be shared and analyzed at an international level by a single agency. Another step that might be significant is stopping the Over-The-Counter (OTC) sale of antimicrobials. They should be sold only on prescription by registered medical professionals so that indiscriminate use may be put to an end.

7. Conclusion

As is evident from the above review, the probability of the COVID-19 pandemic negatively impacting our fight against AMR far outweighs that of it having a positive outcome. However, reports are still scarce and the likelihood of the data being potentially underestimated and undocumented cannot be excluded. It can be well anticipated that the impact of the current pandemic, from AMR perspective might be disproportionate, varying with geographical regions and even different hospitals/areas within the same region. It will depend on the respective strategies followed by the countries and hospitals to deal with the pandemic. It still needs to be seen whether the vaccination drive started globally will be able to vanquish the pandemic or the world is still about to witness another wave of new mutated COVID strains. Nevertheless, with the current usage of antimicrobials, several of which have been classified as restricted and the last resort drugs, the implications of AMR on the human and animal health and per se environment will be unimaginable and should be dealt with caution.

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