

## COVID-19 Pandemic: Upswing in Antibiotic Misuse

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### Abstract

The ongoing COVID-19, caused by the new coronavirus, SARS-CoV-2, after originating from the Wuhan City of China, was declared a “pandemic” on 11 March 2020 by the World Health Organization (WHO). Availability of a number of vaccines against COVID-19 may prove a game-changer. However, in the absence of an acceptable specific antiviral agent, therapeutic approaches in an overwhelming majority of the cases are a cocktail of symptomatic/supportive measures, immunity boosters, immunomodulators, immunotherapy, steroids and antimicrobials. In life-threatening situations in hospitalized patients, critical care measures are adopted. In deference to the recommendations of the WHO, antibiotics such as azithromycin and doxycycline continue to be consumed irrationally in a large proportion of the patients even in absence of a bacterial coinfection, especially in the resource-limited countries. The widespread misuse of antibiotics is likely to have worsened the already existing problem of antimicrobial resistance (AMR). The endeavors aimed at controlling the COVID-19 pandemic (that has been causing huge morbidity and mortality worldwide and adversely impacting economy), need to be complemented with spirited and restrengthened campaign against irrational antibiotic use that is augmenting the AMR. Also, there is a need for promoting antibiotic prudence through alternative and complementary therapies. Most importantly, developing the new antibiotics from new classes should be a top priority.

**Keywords:** Antibiotic prudence; Antimicrobial resistance; Multidrug resistance; New antibiotics; Superbugs

### Introduction

All through the current pandemic of the novel Coronavirus disease (COVID-19), the recommended standard therapeutic measures have remained more or less symptomatic /supportive with life-support in serious cases. Notwithstanding the repeated assertions of the World Health Organization (WHO) to avoid antibiotic use except in patients developing documented or strongly suspected co-infection with bacterial pathogens, [1] antibiotics continue to be consumed irrationally in a large proportion of the patients worldwide, especially in the resource-limited countries.

This communication aims at highlighting the adverse consequences of the ongoing practice of irrational use of antibiotics in COVID-19 subjects with special reference to the likelihood of worsening of the perplexing antimicrobial resistance (AMR). A plea is advanced for developing new antibiotics from new classes on a priority basis.

### Covid-19 Pandemic in a Nutshell

With swings from time to time and region to region, COVID-19 pandemic continues to be very much around. The new coronavirus, *severe acute respiratory syndrome-CoV-2 (SARS-CoV-2)*, infection is believed to have originated as a viral pneumonia in November-De-

cember 2019 from the Wuhan City in mainland China. WHO declared it a “public health emergency” on 30 January 2020 and a “pandemic” on 11 March 2020 [1, 2]. By now, the pandemic has caused huge morbidity and mortality globally.

According to the global estimates, by now the pandemic has caused huge morbidity and mortality world over. According to the global estimates, until last week of October 2021, out of over 22.6 crore cases, more than 46 lakh have died [3]. Back home in India, out of over 3.3 crore COVID-19 cases, death toll exceeds 4.3 lakhs [4]. Additionally, as a result of COVID-19 related preventive and control measures such as lockdowns, curfews, shutdowns, travel restrictions, etc, a massive adverse impact on the health projects, economy and social milieu has been noticed globally.

The extraordinary capability of the etiologic virus to undergo mutations has led to emergence of several variants, including Delta-plus - a sub-lineage of the Delta variant [5]. The Delta variant was first detected in India and has now surfaced in 132 countries and territories. It has a quicker transmission, causes more severe disease and is emerging as a dominant variant in many regions [6, 7]. The Delta plus is supposed to be yet more transmissible and virulent [6].

Mercifully, thanks to the herculean efforts of the scientists, a number of vaccines against COVID-19 have become available in a record time [7]. Widespread vaccination against COVID-19 is anticipated to turn out as a “game-changer” - in a way, a “turning point” - in the fight against the novel corona virus. WHO is engaged in monitoring the fallout of these variants on the vaccine efficacy [8].

### Overview of Covid-19 Therapeutics

There is as yet no acceptable specific antiviral agent that has stood the test of time against the causative virus [1, 8].

In the absence of any specific antiviral agents, therapeutic approaches have been a cocktail of symptomatic/supportive measures, immunity boosters, immunomodulators, steroids, and antimicrobials (including antivirals). In severe cases with life-threatening complication such as acute respiratory distress syndrome (ARDS), such critical care measures as mechanical ventilation are employed.

### Standard Recommendation for Antibiotic Use in Covid-19

Antibiotics, as we all know, are effective only against bacterial infections. They are of no use against viruses. Undoubtedly, the COVID-19 is caused by a corona virus. Hence, as repeatedly emphasized by the WHO, antibiotics must not be routinely used for prevention or therapy of COVID-19 [1]. Nonetheless, there are three exceptions to this standard approach:

1. If a patient of COVID-19 is having a documented or strongly suspected coinfection/superinfection with bacterial pathogens e.g. *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* etc, appropriate antibiotics may be administered to treat the bacterial infection.
2. In COVID-19 patients with comorbidities like diabetes, cardiovascular disease and morbid obesity.
3. In covid-19 patients in Intensive Care Unit (ICU), especially when on ventilator. In this situation, chances of nosocomial/ opportunistic infections are very high.

### World Scenario on Antibiotic Use in Covid-19

Overall, since the novel corona virus pandemic got off the ground, available data from several countries indicate high rates of antibiotic use in COVID-19 patients [10-15]. Significantly, at the same time, low rates of bacterial co-infections have been observed. A study by Nori and coworkers [15] from the United States has revealed 71% of covid-19 patients as receiving antibiotics against just 4% having a bacterial coinfection in actuality. The researcher also observed 10% hike in the incidence of resistant bugs which they ascribed to the rise in the use of antibiotics.

Based on observations from 10 African countries, Adebisi et al's findings show that various antibiotics were used in the management of COVID-19 [10]. The researchers have expressed their concern in the overuse of antibiotics in COVID-19 though only a few COVID-19 patients were likely to suffer from a bacterial coinfection necessitating antibiotic therapy.

On the contrary, only occasional studies have shown that, during the COVID-19 pandemic, antibiotic consumption in certain hospitals/health facilities of the west had a decline [13]. This has been attributed to postponement of elective surgeries and other medical procedures and boost in infection control measures [9], including an access to clean water, sanitation and high-quality healthcare. Additionally, the availability of the antibiotic stewardship program, in operation for many years in the said centers, may have contributed to this observation. In a study from Norway, Blix and Howe [16] have reported fall in the antibiotic use during the COVID-19 pandemic. Mind you, Norway has been spearheading a spirited campaign for many years to reduce consumption of antibiotics successfully and has a robust antibiotic stewardship program.

The bottomline is that, by and large, the use of antibiotics has been out of proportion to the frequency of co-infections globally. Obviously, this raises concerns about the upsurge in unnecessary antibiotic use during the pandemic and the likelihood of its worsening impact on the already alarming problem of antimicrobial resistance (AMR). It is akin to adding fuel to fire.

## The Situation in India

### Genesis of Antibiotic Misuse

No doubt, the beginning of the antibiotic misuse in COVID-19 cases erupted from medical profession's prescriptions per se. Since, there was widespread ignorance about the therapeutics of this causative coronavirus, antibiotic inclusion in the hotchpotch therapeutic regimens/protocols was generally considered important. Precisely, the perceptible reasons for this inclusion included the following:

- During the early stage of the infection, lack of clarity whether it was a COVID or a bacterial infection.
- Delay in obtaining COVID testing report.
- Apprehension of a coinfection with multidrug resistant (MDR) bacterial in complicated cases, especially with a comorbidity. Microbial coinfection is likely to exacerbate the processes of the occurrence, development, treatment and outcome in patients suffering from COVID-19. Clinical diagnosis and treatment.
- Critical cases in ICU where risk of nosocomial and opportunistic infections is high.

Understandably, administration of antibiotics in serious hospitalized cases (not all) of COVID-19 was justified to a considerable extent.

So far, so good. Unfortunately, the use of antibiotics didn't remain limited to that far.

### The Ground Situation

In India, antibiotic misuse, nay abuse, has been rampant since long. During the COVID-19 pandemic, not before long, the quacks and self-styled practitioners entered the arena in a big way and a rapidly-growing manner. The inability of the hospitals/health facilities to deal with the heavy load of patients further contributed to this development. Even when hospital care was available, many preferred to approach the quacks.

*Result:* a large chunk of management of corona cases fell in the domain of the unregulated and fragmented private sector that accounts for 75-90% of antibiotic consumption in the low and middle income countries (LMICs). The therapeutic kits of these practitioners invariably included antibiotics on top of other agents. This raises colossal concerns about the potential effects of Covid-19 on antibiotic prescribing and dispensing practices and upswing in antibiotic misuse by the community.

In this behalf, it is pertinent to recall the study by Sullis et al. [15] recording a significant increase in antibiotic sales in India during the peak phase of the first COVID-19 wave. Indicating the need for urgent antibiotic stewardship measures. According to the researchers from the Washington University in the United States, Covid-19 contributed to 216.4 million excess doses of antibiotics, including 38 million more doses of azithromycin, in adults from 20 June 2020 through September 2020, a period of peak Covid-19 activity in India. It is most likely that similar trends of significant hike in antibiotic consumption occurred in the second wave in India as well as other LMICs countries that are known for irrational use of antibiotics.

Our own unpublished observations from North India show that, both in first and second waves of the current pandemic, antibiotics have been a routine component of the therapeutic kits of the confirmed COVID-19 patients and a frequent therapy in contacts of such patients even though the diagnosis of COVID-19 remained unconfirmed. Around 75% usage is on the advice of unqualified practitioners and by word of mouth. A common admission is: “We started them since our friends recovered with this treatment”.

The two antibiotics that have been most misused or sold over the counter (OTC) irrationally are azithromycin and doxycycline. Another antimicrobial, an anti-parasitic agent (ivermectin), too has had a field day.

### *Repercussions of Antibiotic Overuse/Abuse*

This irrationality is expected to add up to the already existing problem of AMR [17-21] that has emerged as one of the ten top public health problems of the world.

Just as in case of most global public health problems, the AMR awareness approaches [12-15] have suffered considerably because of the overwhelming attention taken away by the COVID-19 pandemic. Pelfrene et al. [22] have sarcastically dubbed the problem of antimicrobial multidrug resistance in the era of COVID-19 as “a forgotten plight”.

Undoubtedly, the further upswing in irrational use of antibiotics during the pandemic is very likely to have enhanced the existing problem of MDR infections. As far as the quantum of its magnitude is concerned, a high level focused surveillance is warranted.

As a consequence, the superbugs may well have a yet more spacious field day. Sooner than previous speculations, we may be left with no effective antibiotic against the serious infections in the near future. Still worse, emergence of new pathogenic bacteria and re-emergence of some infectious diseases that had been totally or largely wiped out may follow. Understandably, highly escalated morbidity and mortality in the foreseeable future shall be a huge threat to humans and livestock.

### *The Solution: Development of New Antibiotics*

What to do? While the fight against COVID-19 is in progress, we must simultaneously refocus attention to endeavors addressed at infection control strategies and rational use of antibiotics, thereby rejuvenating the prevention and control of AMR. Effective antibiotic stewardship interventions [23-25] are mandatory for optimizing practices related to antibiotic use and ensuring patient safety across the health care settings. Also, needed is high level research and promotion of “antibiotic prudence” through alternative and complementary therapeutics such as antibodies, immunotherapy, probiotics, bacteriophage, faecal microbiota transplant, antimicrobial peptides, Oligonucleotide therapy etc. [27]

As suggested by Arshad et al. [14] strategies must be developed to counter the detrimental effect of misinformation on the use of antimicrobials through online media campaign and prevent further deterioration in the global crisis in antimicrobial resistance.

Unfortunately, only this will not be enough in order to contain the worsening situation. We have got to go beyond this strategy.

According to the WHO [26], none of the antibiotics that are currently in the pipeline sufficiently address the menace of AMR. What is desperately needed is research and development of new antibiotics from classes other than those already in the grip of AMR. Admittedly, this is an exorbitantly expensive, cumbersome and time-consuming area. Hence, support from various governments, philanthropic bodies/organizations and multinational pharmaceutical industry to the scientists involved in developing effective new antibiotics is needed forthwith. The newly-developed antibiotics will also need hand-holding for manufacturing and distribution. The non-profit research and development organization, Global Antibiotic Research and Development Partnership (GARDP) [28] can play a “pivotal” role in this pursuit of accelerating the development of new antibiotics from new classes [27] to overcome the problematic superbugs. In this behalf, let’s not forget that we are already somewhat late. Further delay in the field may well be an invitation to doom. And, let no mistake be made, the worst sufferers shall be the newborns, infants, debilitated elderly subjects and those with life-style diseases (diabetes, cardiovascular illnesses and obesity), chronic lung disease and poor immune-competence.

All in all, it is strongly felt that developing new antibiotics from new classes may well be a gateway to fighting MDR infectious diseases and, thereby, contributing to attain a brighter and more prosperous future for humans, animals and environments. The so-called "One Health" approach should be the eventual aim. Though the road ahead is daunting, we must bat on the front foot for attaining our goal.

## Summary and Conclusion

The WHO has repeatedly asserted for restricting the use of antibiotics in the ongoing COVID-19 pandemic to cases with documented or strongly suspected bacterial coinfections. Yet, the ground reality is that antibiotics such as azithromycin and doxycycline continue to be consumed irrationally in a large proportion of the COVID-19 patients in resource-limited regions in the Indian subcontinent in particular. This practice is likely to have worsened the ongoing problem of AMR which has emerged as a huge challenge over the recent decades. Since we are heading for a sorry situation where the existing antibiotics may become useless in infections from superbugs, there is a desperate need for developing new antibiotics from classes other than the existing ones. Meanwhile, antibiotic prudence through alternative and complementary therapies too warrants high level research and promotion.

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