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Coalescence of co-infection and antimicrobial resistance with SARS-CoV-2 infection: The blues of post-COVID-19 world

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ABSTRACT

In viral respiratory infections, bacterial co-pathogens are widely known to co-infect, and they significantly increase the morbidity and mortality rate. During the influenza season, the advent of 2019-nCoV (novel coronavirus) has led to the widespread use of oral and intravenous antibiotics and inhibitors of neuraminidase enzyme. Owing to causes such as extended intubation, the ubiquitous use of intrusive catheters, and compromised host immunity, coronavirus disease (COVID-19) patients are at heightened risk of secondary bacterial and fungal infections, leading to the difficulty in their treatment. Apart from the pandemic, the primary risk is a likely surge in multidrug resistance. In this work, we evaluated the coalescence of present co-infection alongside the COVID-19 and post-pandemic antimicrobial resistance due to high ongoing drug use for the treatment of COVID-19. We found that while there is currently limited evidence of bacterial infections in COVID-19, available proof supports the restricted use of antibiotics from an antibiotic stewardship viewpoint, primarily upon entry. Paramount attempts should be made to collect sputum and blood culture samples as well as pneumococcal urinary antigen monitoring in order to endorse stringent antibiotic usage. For antimicrobial stewardship, inflammatory markers like procalcitonin have been added, but such biomarkers are typically upraised in COVID-19. Antimicrobials cannot be completely removed in wastewater treatment plants (WWTPs) and once they enter the water environment, possesses a great risk of inducing resistance to drugs in microbes. Hence, their prescription and administrations should be regulated and alternate solutions such as vaccines, preventive measures and personal hygiene should be given top priority. It is imperative to establish an antimicrobial strategy discrete to COVID-19, as this pandemic has caused an outbreak of numerous other associated diseases and has the potential to drive microbial resistance. Coordinated plans are essential for this at the citizen, health-care and policy levels.

1. Introduction

Antibiotics have had a decent mantle in the treatment of bacterial co-infections with respect to the treatment of COVID-19. Nevertheless, asseverations suggest that antimicrobials have been prescribed unfairly. In comparison, in a futile effort to shield themselves from the infection, many individuals self-medicate with antibiotics. In developing countries, this convention is particularly prevailing [1]. In viral respiratory tract infections like influenza, bacterial co-pathogens are widely recognized, requiring prompt diagnosis and antibacterial treatment [2–4]. The prevalence, occurrence and characteristics of bacterial infection in patients with severe acute coronavirus 2 respiratory syndrome (SARS-CoV-2) is off the beaten track and has been established as a major information deficit [5,6]. Several guidelines promote the use of first-hand antibiotics for acute COVID-19 patients, extrapolating questions about elevated impermanence in patients with bacterial superinfection throughout influenza pandemics [7,8]. This hypothesis, however, raises concerns about antibiotic usage and ensuing bacterial resistance-related damage. Basic conditions and risk factors for bacterial and fungal infections, such as chronic respiratory diseases, corticosteroid treatment, immunoinflammatory reaction (cytokine storm) and intubation/mechanical ventilation, are shared by COVID-19 hospitalized patients in intensive care units (ICUs). In 50% of COVID-19 deaths, secondary infections were detected. Bacterial and fungal secondary infections or co-infections are also a likely cause impacting the mortality of COVID-19 patients who are seriously ill [9].

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The new COVID-19 pandemic will definitely change the landscape of antimicrobial resistance (AMR), as many hospitalized COVID-19 patients are medicated with broad-spectrum antibiotics with uncertain effectiveness [10–18]. Redundant doses of antibiotics upon hospitalization can raise the individual risk of severe hospital-acquired pneumonia (HAP) and other adverse events, as COVID-19 patients also require respiratory assistance and extended hospitalization [19,20]. The prevalence of use of antibiotics (94–100%) was much greater in-hospital care than the recorded occurrence of secondary infection (10–15%) [21]. The average fraction of COVID-19 patients with bacterial co-infection was found to be 6.9% [22]. In general, antibiotic usage was widespread, with fluoroquinolones and cephalosporins comprising 74% of the prescribed antibiotics. Eleven percent of patients were estimated to have co-infections, mainly secondary infections in the largest SARS-CoV-1 series of patients, and a small role for bacterial infections in Middle East respiratory syndrome coronavirus (MERS-CoV) among studies reporting on other coronaviruses [23]. Among other coronavirus outbreak records, 11% of the COVID-19 patients were estimated to have bacterial co-infections, chiefly secondary infections in the prodigious SARS-CoV-1 patients, and minimal involvement of bacterial infections in MERS [24]. Respiratory infections of viral origin that were previously reported as epidemics and pandemics have documented bacterial co-infections that complicate the inceptive viral disease. The H1N1 flu pandemic (2009), encountered 30% bacterial infection in seriously ill patients [25,26] and 12% in non-ICU hospitalized patients [27]. The most frequently known bacterial co-pathogens were identified to be *Streptococcus pneumoniae* and *Staphylococcus aureus* [25,27].

The ubiquity of secondary infection in SARS-CoV-2 infected patients is not well known. Present wastewater treatment technology cannot provide complete removal of antibacterial biocides. These compounds will then aggregate in various environmental compartments, affecting the functioning of autochthonous microbes. Consequently, the occurrence of antimicrobials in the environment can promote the prevalence of AMR [28–30]. Considering the above said reasoning, we put an effort first to understand the possibilities of other microbial co-infections alongside of COVID-19; and then evaluate the rationale of multidrug prescriptions for the treatment of COVID-19 to finally assess the threat of antimicrobial resistance scenario in the post-COVID-19 era. We wish to contribute raising awareness so that the pre-problem measures can be subsequently taken via an antibiotic stewardship perspective.

2. Coalescence of COVID-19 and other microbial co-infection

The novel coronavirus infects its target cells with the help of the angiotensin-converting enzyme 2 (ACE2) receptors, which is eminently expressed in the epithelial cells of the alveoli, and also in the intestinal cells, kidney and heart [31,32]. While SARS-CoV-2 is recognized as an airborne respiratory virus, the identification of the virus in fecal matter and dark water is indicative of its enteric presence in prudent aquatic ecosystems [33]. Bronchial aspirate cultures from COVID-19 patients were analyzed for colonized bacterial and fungal species of which 57% turned positive for co-infection [34]. Pathogenic fungi species identified by Matrix-Assisted Laser Desorption Ionization- Time of Flight Mass Spectrometry (MALDI--TOF) were: 1 *Aspergillus fumigatus* (3%), 4 *Candida glabrata* (11.4%) and 14 *Candida albicans* (40%). In rest samples, *Pseudomonas aeruginosa* (n = 6, 17%), *Klebsiella pneumoniae* (n = 1, 3%), *Staphylococcus epidermidis* (n = 1, 3%), *Staphylococcus aureus* (n = 2, 5%), *Klebsiella oxytoca* (n = 1, 3%), *Escherichia coli* (n = 1, 3%), *Enterobacter cloacae* (n = 1, 3%) were identified. Out of other 8.6% (3) samples, both *P. aeruginosa* and *C. albicans* were obtained. Marcy l'Etoile and bioM_erieux Vitek cards (France) were used to determine antimicrobial susceptibility of the clinical isolates. Of the 35 patients with SARS-CoV-2 lung infection and accompanying positive co-infections, 80% (28) were either fungal or *P. aeruginosa* colonized. On the contrary, in 2019, ICU patients negative with COVID-19, *P. aeruginosa* or fungal (*A. fumigatus*, *C. parapsilosis* and *C. albicans*) colonization was barely seen in 20% per cent of the patients.

Table 1
Highlights of COVID-19 positive patients reported with secondary/co-infections.

Patients Age	Gender	Disease	Country	Infection type	Culture type/source	Drug(s) type/dose	Resistance	Reference
54	Male	COVID-19 (hospitalized)	Bronx, USA	*E. cloacae*, MRSA, *S. marcescens*, *K. pneumoniae*	Respiratory and blood	Tigecycline, Gentamicin, Aztreonam, Ceftazidime-Avibactam	*E. cloacae* resistant to Aztreonam, Ceftazidime-avibactam, Meropenem, Meropenemvaborbactam	[45]
63	Male	COVID-19 (hospitalized)	Brooklyn, USA	*S. capitis*, *E. cloacae*, *C. albicans*	Blood and respiratory	Tigecycline, Gentamicin	*E. cloacae* resistant to Aztreonam, Ceftazidime-avibactam, Meropenem, Meropenemvaborbactam	[45]
57	Male	COVID-19 (hospitalized)	Bronx, USA	*E. cloacae*, *E. aerogenes*	Urine – catheter, blood and respiratory	Tigecycline	*E. cloacae* resistant to Aztreonam, Ceftazidime-avibactam, Meropenem, Meropenemvaborbactam	[45]
68	Female	COVID-19 (hospitalized)	Bronx, USA	*C. albicans*, *E. faecalis*, *S. epi*, *E. cloacae*, *K. pneumoniae*	Peritoneal fluid and urine –catheter, blood and respiratory	Tigecycline, Ceftazidime-Avibactam, Aztreonam	*E. cloacae* resistant to Aztreonam, Ceftazidime-avibactam, Meropenem, Meropenemvaborbactam	[45]
63	Female	COVID-19 (hospitalized)	Bronx, USA	MRSA, *E. cloacae*, *S. marcescens*, *K. pneumoniae*	Respiratory and blood	Tigecycline, Gentamicin, Aztreonam, Ceftazidime-Avibactam	*E. cloacae* resistant to Aztreonam, Ceftazidime-avibactam, Meropenem, Meropenemvaborbactam	[45]
56 (mean)	Female (32.3%)	COVID-19 (hospitalized)	Wuhan, China	Bacterial co-infection	Respiratory	70.7%	Unspecified	[46]
71	Female	COVID-19 (hospitalized)	Spain	Influenza and *Enterococcus faecium*	Respiratory and blood	Oseltamivir	–	[86]
61	Female	COVID-19 (hospitalized)	Spain	Influenza	Respiratory	Oseltamivir	–	[86]
47	Male	COVID-19 (hospitalized)	Philippines	Influenza	Respiratory	Oseltamivir	–	[86]
62	Female	COVID-19 (hospitalized)	USA	Influenza	Respiratory	Levofloxacin, Vancomycin	–	[87]

In three distinct Dutch core studies, bacterial secondary infections were reported in 29, 100 and 107 SARS-CoV-2 positive patients [35–37]. The number of patients with possible bacterial respiratory co-infection upon diagnosis in these three cohorts was 8% or fewer and further down (<3%) in patients in ICU, relative to the two COVID-19 patient groups (7–8%). Two reports from Wuhan (China) communicated bacterial co-infections in COVID-19 positive patients admitted in hospitals [38, 39]. Recorded incidence of secondary infection was inconsistent amid COVID-19 patients in various trials. Nevertheless, it may be as high as 50% amidst the non-survivors [40]. Bacterial pathogens found comprised *Staphylococcus aureus*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Klebsiella pneumonia* and *Chlamydia pneumonia*; fungi: *Aspergillus flavus* and Candida species and viruses: coronavirus, metapneumovirus, influenza, enterovirus/rhinovirus, human immunodeficiency virus (HIV), parainfluenza and influenza B virus.

Respiratory viruses like SARS-CoV-1 and MERS-CoV that cause seasonal and/or pandemic influenza exhibit different degrees of fungal and bacterial infections. Independent corroborations suggest that secondary infections are rare in SARS-CoV-1 patients and there is no evidence of such infections in the case of MERS-CoV [41,42]. In addition, co-infection has been linked with more serious results in seasonal and pandemic [43]. Thirty trials were involved, with 3834 patients. Overall, bacterial co-infection resulted in 7% of hospitalized patients with SARS-CoV-2 infection (n = 2183, 95% CI 3–12%, I2 = 92·2%). In mixed ward and ICU conditions (4%, 95% CI 1–9%, I 2 = 91·7%), a smaller number of patients were co-infected as compared to patients in ICU (14%, 95% CI 5-26, I 2 = 74 ·7%). *Pseudomonas aeruginosa*, *Mycoplasma pneumonia* and *Haemophilus influenzae* were the typical causal bacteria for the co-infection. The combined proportion of co-infection with viruses, commonly influenza A and Respiratory Syncytial Virus, was only 3% (95 % CI 1-6, n = 1014, I 2 = 62 · 3%). There were also fungal co-infections identified in three trials [44]. Positive infections in case (2 out of 5) of nosocomial disease were reported to have bloodstream colonization with *Candida albicans*. Bloodstream infection/septicemia with metallo-β-lactamase (MBL) producing *E. cloacae* and *K. pneumonia* were identified [45]. One hundred seventy-four pathogens identified in COVID-19 positive patients with potential secondary infection were predominantly *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Exclusively 3 Gram-ve bacterial species had been identified in two patients. *Acinetobacter baumannii* and *Klebsiella pneumoniae* were isolated from the respiratory tract from one COVID-19 patient in China [46]. A few other studies include 1 positive report of PCR for *Mycoplasma pneumonia*, 0 positive for *Legionella* [47]. One from the two reports for secondary infection published on bacterial pathogens [48,49]. Again, in another study from China, among 3 g-negative species, 1 out of 29 (3%) *A. baumannii* and 2 out of 29 (7%) *Enterobacter cloacae* were reported [50]. Table 1 shows some of the features of COVID-19 positive hospitalized cases with secondary/co-infections. While all of the reported cases showed co-infections with other diseases such as influenza and pneumonia as the most common in them, some cases have also revealed the multi-drug resistance nature of these pathogens isolated from blood, urine and respiratory fluids.

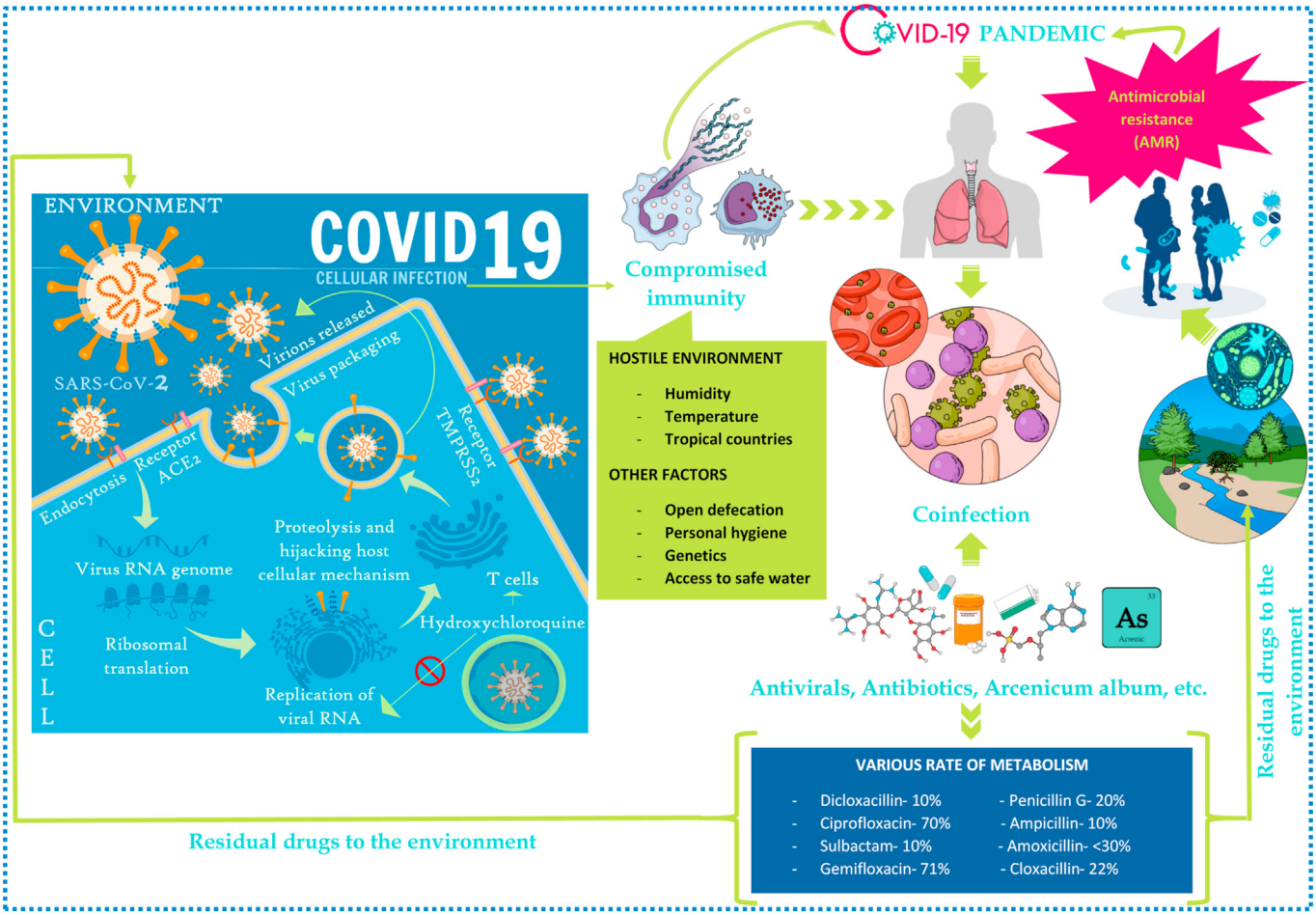

Fig. 1. Pernicious cycle of COVID-19, co-infection and AMR.

3. Antiviral and antimicrobial drug use scenario for COVID-19 treatment

Presently, no antiviral medication is available to cure SARS-Cov-2 infection; and it will also take a couple of years to produce one and achieve clearance for it [51]. The vaccine developed by Pfizer-BioNTech has passed safety and effectiveness checks, but as it is rolled out to millions of people, scientists and experts do have numerous concerns about how this and other vaccines will work [52]. On the other hand, countries India with their own developed vaccines will face technological difficulties in vaccinating its large population. A big challenge would be ensuring sufficiently suitably qualified individuals to deliver jabs [53]. At the moment, Remdesivir, Ribavirin (nucleoside analogues), Favipiravir, Griffithsin (inhibitor of SARS and MERS spike proteins) and Ritonavir/Lopinavir (protease enzyme inhibitors) [54], Abidol (Umifenovir) [55], Oseltamivir (neuraminidase inhibitors), EK1 peptide, and anti-inflammatory drugs are being employed to treat the patients. Capsules Lianhua qingwen and ShuFeng JieDu (conventional Chinese antibiotic drugs) [56,57], and 3 TC and TDF (RNA synthesis inhibitors) are used as available treatment alternatives for emerging respiratory infectious diseases caused by SARS-CoV-2 [58]. All of these medications have been utilized to cure past coronavirus outbreaks (SARS and MERS) or other viral infections such as Ebola, influenza and HIV [59].

Two of the highly proficient drugs viz., Chloroquine and Remdesivir were exclusively found efficient in aiding treatment of COVID-19 in vitro, as compared to the various other drugs mandated by the U.S. Food and Drug Administration's (FDA's) such as Penciclovir, Nafamostat, Ribavirin, Favipiravir, Nitazoxanide, etc. The therapeutic efficiency of Chloroquine is well known as the drug initially used for treating malaria and several autoimmune diseases, is now being produced and imported/exported worldwide to treat 2019-nCoV (2019 novel coronavirus) infection [60,61]. Remdesivir, possessing an analogous structure to inhibitors of HIV reverse transcriptase, is reportedly under clinical trials for curing 2019-nCoV ailment [62]. For the prevention of coronavirus diseases such as acute influenza, the use of Ribavirin and Fabiravir in combination with Oseltamivir shows a greater impact than that of Oseltamivir alone [63]. In peracute hypoxemia, symptoms can be successfully mitigated by combining antibiotics, lopinavir, alpha-interferon and providing mechanical ventilation [64]. While there is no contemporary treatment for 2019-nCoV infection, immunomodulatory agents like tocilizumab (a monoclonal antibody against interleukin-6/IL-6), corticosteroids, etc., have been investigated to regulate the cytokine storm that frequently emanates in the course of the COVID-19 infection [65]. In clinical trials, intervening drugs can be categorized on the basis of their essence and commendatory effects. In this respect, in addition to the combination of remedial treatments, nutritional products, immunomodulators, antivirals, immunosuppressants, some well-known drugs and antiparasitic drugs are contemplated in recent trials for disease prevention supportive care and/or therapy. Within and beyond each category of drugs, one can scarcely see the concordant mechanism of action, but several drugs are contrived for a discrete ailment and repurposed afterwards for another condition [66]. Nanotherapeutics has also been explored and in-depth observations briefed the suitability of such nanomedicines to control COVID-19 outbreaks [67].

4. Antimicrobial resistance erred with COVID-19

COVID-19 renders favorable conditions for secondary infections and aggravates AMR. Fig. 1 depicts the vicious cycle of COVID-19, co-infections, antibiotic and antiviral drugs in the environment. It explains in brief the cellular infection when SARS-CoV-2 enters the cells of the host and the effect of various environmental and other factors that aids in the occurrence of infection. The immuno-compromised patients are further vulnerable to various diseases/co-infections (bacterial and viral) and thus, are treated with antivirals and antimicrobials to treat the secondary infection. These drugs and their metabolites are released into the environment and are often only partially removed/degraded in WWTPs. When they are released into the environment and are exposed to natural microbiota in the environmental water, they can induce antimicrobial resistance and spread via horizontal gene transfer (HGT). 6·9% of the COVID-19 patients diagnosed from 5 different countries indicate the presence of bacterial infections of which 3·5% acquired concurrently with the disease and 14·3% post COVID-19), exacerbating in ICU patients [68]. *Aspergillus fumigatus* in seriously immunocompromised hosts behaves as an opportunistic pathogen causing invasive pulmonary aspergillosis (IPA). Prelusive studies indicated 19–33% SARS-CoV-2 related IPA occurred in patients hospitalized in ICU with serious COVID-19 [69,70]. Triazole-resistant *A. fumigatus* along with IPA was reported in a 56-year-old COVID-19 patient admitted in ICU [71]. The existence of *Aspergillus* is a prognostic sign of severity or is only related to degenerating patient's health is still, possibly leading to death remains uncertain. Carbapenemase-producing Enterobacterales (CPE)-*E. coli* has been observed in COVID-19 patients. Rectal swabs screenings patients were conducted and analyzed with the help of multiplex PCR as well as by culturing on selective chromogenic media [72]. At the peak of the COVID-19 outbreak 5 instances of New Delhi Metallo-betalactamase (NDM) causing Enterobacterales infections along with serious hypoxemic respiratory failure were reported at Bronx, NY medical centre which later was confirmed to be COVID-19 associated pneumonia [45]. The theoretical action against NDM-producing Enterobacteria is shown by the administration of a mixture of Ceftazidime-avibactam and Aztreonam [73]. Like other multidrug-resistant species such as Methicillin-resistant *Staphylococcus aureus* (MRSA), Carbapenem-resistant Enterobacteriaceae and *Candida auris* can be spread in healthcare environments [74]. Before the vaccines for COVID-19 were developed and reached phase 2 of the clinical trials, various antiviral drugs such as Lopinavir, Oseltamivir, Remdesivir, etc., were administered to the patients for reducing the symptoms and treatment. These drugs are partially metabolized in the human body and also are not completely degraded in WWTPs and/or altered into different forms. Wild animals such as, bats, pangolins, camels, boars, etc., which are natural reservoirs of viruses, when come in contact with antiviral drug or their metabolite-containing environmental water, triggers selective pressure leading to mutations that may contribute to resistance in these viruses to antiviral drugs [28].

As antibiotics are anticipated to have a marginal advantage as pragmatic therapy in COVID-19 treatment and results in auxiliary pernicious effects viz., toxicity, adverse events, antibiotic resistance, and *Clostridioides difficile* sepsis, it is advisable for clinicians to advocate them aptly [75–78]. Increasing the statistics of presumptuous stratagems linked with the prescription of antibiotics, immunomodulatory drugs such as steroidal anti-inflammatory drugs and overpopulated in clinics can contribute to an increase in nosocomial diseases. Simultaneously, there could be a chance of worsening of the Healthcare-Associated Diseases due to the sensitivity of the patient's microbiota to these stimuli, through the emergence and distribution of resistance aspects and further virulent strains. In manually ventilated COVID-19 patients undergoing immunomodulatory therapy, a tracheal aspirate test needs to be done at the earliest and antibiotic treatment can be postponed till the test results are accessed. Depending on the localized circumstances, the use of empiric, broad-spectrum antibiotics in a vast number of cases was found to be ineffective while, narrow-spectrum antibacterial drugs was favored [79]. Both the World Health Organization (WHO) and the UK National Institute for Health and Treatment Excellence's COVID-19 related recommendations prohibit antibiotic treatment or prevention in the case of suspicious and positive asymptomatic COVID-19 patients or patients with paltry ailment but recommend administering antibiotics for suspected bacterial co-infections [80,81]. The recommendation from the US National Institutes of Health [82] reports inadequate evidence for antibiotic treatment but concedes that all patients with mild to serious hypoxemia are regularly administered broad-spectrum antibiotics by certain clinicians. The current edition of the Chinese clinical guidance released in

March 2020, for the diagnosis and treatment of COVID-19 patients also indicates that the improper use of antibiotics, largely broad-spectrum drugs, without lucid details for factual antibacterial treatment or prophylaxis should be prevented [83].

5. Tackling measures

The prevalence of telemedicine to control antimicrobial stewardship has previously demonstrated an improved selection of antibiotics and decline in resistance [84]. It is important to collect microbiological data, primarily to classify formerly identified or evolving pathogens linked to secondary co-infections in patients with SARS [85]. Epidemiological investigations with AMR surveillance systems that endorse the generation of the standard datasets on the efficacy of antimicrobial intercession in COVID-19 patients, particularly in acute stage patients in ICUs, should be sustained [86]. Measures taken by people would also be quintessential in sustaining the pandemic and mitigating its effect on our routine lives. Appropriate use of personal hygiene devices like personal protection equipment (PPE) kits, masks, adequate handwashing and maintaining physical distancing should be continued to be safe from getting infected and prepared for future waves [87]. The continuation of antimicrobial treatment and duration of hospital stay of COVID-19 patients can be shortened substantially with stewardship measures. Antimicrobial governance initiatives should actively involve and train medical practitioners and pharmacists to reduce mishandling of antibiotics during the COVID-19 pandemic [88,89]. The recommendations made in this study and their efficient inclusions in the formation of applicable policies and the preparation of concrete instructions/guidelines will be crucial to ensure our battle against AMR continues and the quest to conquer it consummates.

6. Conclusion

We conclude that the overall proportion of secondary infection has been poor among patients with COVID-19, but the prescription of antimicrobials is soaring. There is inadequate proof to encourage the extensive usage of empirical antibiotics, particularly in those COVID-19 hospitalized cases without serious illness. The average percentage of COVID-19 patients with secondary co-infection is smaller than in prior influenza pandemics, with minimal documentation of *S. pneumonia*, S. Aureus and/or *S. pyogenes*, having a critical role to play. Predominantly, these reports favor the termination of empiric antibiotics and antimicrobials in the patients afflicted with COVID-19 infection. The disbursement of antibiotics to COVID-19 patients depends majorly on the expertise and judgement of frontline medical practitioners, especially at the initial phase of the outbreak of a pandemic. Antimicrobial stewardship projects have a vital role to play in reducing unnecessary antibiotic usage and delivering expertise on highly AMR infections. Additional guidelines on antibacterial therapy as in the case of patients with nosocomial and ventilator-associated pneumonia, needs to be followed for COVID-19 patients with secondary bacterial respiratory infection. More comprehensive research on the epidemiology of secondary co-infections in COVID-19 patients is exigently required to validate our conclusions. It is the need of the hour to establish an antimicrobial strategy unique to COVID-19 to tackle AMR. Investments in the development of wastewater facilities, policy upgradation and public awareness are pivotal. Furthermore, to recognize the environmental effects of COVID-19 pandemic, global surveillance systems and multidisciplinary research collaborations are required.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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