Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Coalescence of co-infection and antimicrobial resistance with SARS-CoV-2 infection: The blues of post-COVID-19 world

Payal Mazumder a,*, Ajay Kalamdhad b, GG Tushara Chaminda c, Manish Kumar d

a Centre for the Environment, Indian Institute of Technology Guwahati, Assam, 781039, India
b Department of Civil Engineering, Indian Institute of Technology Guwahati, Assam, 781039, India
c Department of Civil and Environmental Engineering, University of Ruhuna, Galle, Sri Lanka
d Discipline of Earth Science, Indian Institute of Technology Gandhinagar, Gujarat, 382309, India

ARTICLE INFO
Keywords:
SARS-CoV-2
COVID-19
Antimicrobial resistance
Antibiotics
Co-infection

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, severations 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 permanence 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, immuno-inflammatory 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].

* Corresponding author.
E-mail addresses: payal.spinnersend@gmail.com, payal93@iitg.ac.in (P. Mazumder).

https://doi.org/10.1016/j.cscee.2021.100093
Received 16 December 2020; Received in revised form 16 February 2021; Accepted 18 February 2021
2666-0164/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 infection in MERS [24]. Respiratory infections of viral origin that were previously reported as epidemics and pandemics have documented bacterial co-infections that complicate the infective 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 to first 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. Merey’s Etoile and bioMérieux 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 | Gender | Disease | Country | Infection type | Culture type/source | Drug(s) | Resistance | Reference |
|----------|--------|---------|---------|---------------|---------------------|---------|------------|----------|
| 54       | Male   | COVID-19| Bronx, USA | Respiratory and blood | Tigecycline, Gentamicin | Aztreonam, Ceftazidime-Avibactam | - | [45] |
| 63       | Male   | COVID-19| Bronx, USA | Respiratory | Tigecycline, Gentamicin | - | [45] |
| 38       | Male   | COVID-19| Bronx, USA | Respiratory and blood | Tigecycline, Gentamicin | - | [45] |
| 68       | Female | COVID-19| Bronx, USA | Respiratory and blood | Tigecycline, Gentamicin | - | [45] |
| 62       | Female | COVID-19| Bronx, USA | Respiratory | Tigecycline, Gentamicin | - | [45] |

...
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% amongst 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; 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%). 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 pneumoniae 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 metal-lo-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]. 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.
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 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 ShuPeng JieDu (conventional Chinese anti-biotic drugs) [56,57], and 3 TC and TDF (RNA synthesis inhibitors) are used as available treatments, 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 ailemt [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 emerged 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 Enterobacteriaceae (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 Enterobacteriaceae infections along with serious hypoxic 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 *Clostridoides 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 Care Excellence (NICE) recommended treatment and 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 inclinations 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. pneumoniae, 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.

Acknowledgements

Support (lab space, equipment, etc.) from Indian Institute of Technology Guwahati and Indian Institute of Technology Gandhinagar is greatly acknowledged. Any opinions, findings and conclusions or recommendations expressed in this manuscript are those of the authors and do not necessarily reflect the views of IIT Guwahati, IIT Gandhinagar or University of Ruhuna.

References

[1] M. Usman, M. Farooq, K. Hanna, Environmental side effects of the injudicious use of antimicrobials in the era of COVID-19, Sci. Total Environ. 745 (2020) 140153.
[2] F.P. Esper, T. Spahlinger, L. Zhou, Rate and influence of respiratory virus coinfection on pandemic (H1N1) influenza disease, J. Infect. Dis. 113 (2001) 260–266.
[3] E.Y. Klein, B. Monteforte, A. Gupta, W. Jiang, L. May, Y.-H. Hsieh, et al., The frequency of influenza and bacterial coinfection: a systematic review and metaanalysis, Influenza Other Respir Viruses 10 (2016) 394–403.
[4] T.W. Rice, L. Rubinison, T.M. Uyeki, F.L. Vaughn, B.B. John, R.R. Miller, et al., Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States, Crit. Care Med. 40 (2012) 1487–1498.
[5] B. Huttner, G. Catko, J.R. Pano-Pardo, C. Pulcini, J. Schouten, COVID-19: don’t neglect antimicrobial stewardship principles!, Clin. Microbiol. Infect. 26 (2020) 808–810.
[6] M.J. Cox, N. Loman, D. Bogaert, J.O. Grady, Co-infections: potentially lethal and unexplored in COVID-19, Lancet Microbe 1 (1) (2020), https://doi.org/10.1016/S2666-5327(20)30059-4.
[7] World Health Organization, Clinical Management of COVID-19 Interim Guidance [Internet], WorldHealthOrganization, Geneva, Switzerland, 2020. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acuterespiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
[8] W. Alazzani, M.H. Møller, Y.M. Arabi, M. Loeb, M.N. Goe, F. Pan, et al., Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19), Crit. Care Med. 48 (2020) 440–469.
[9] F. Zhou, T. Yu, R. Du, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet (London, England) 395 (2020) 1054–1062.
[10] W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, et al., Clinical Characteristics of Coronavirus Disease 2019 in China, the New England Journal of Medicine, 2020.
[11] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet (London, England) 395 (10229) (2020) 1054–1062.
[12] G. Chen, D. Wu, W. Guo, Y. Cao, D. Huang, H. Wang, et al., Clinical and immunologic features in severe and moderate Coronavirus Disease 2019, The Journal of clinical investigation, 2020.
[13] Y. Du, L. Tu, F. Zhu, M. Mu, R. Wang, P. Yang, et al., Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. American Journal of Respiratory and Critical Care Medicine, 2020.
[14] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, et al., Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, Japan, 2020.
[15] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, et al., Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet. Respiratory Medicine, 2020.
[16] L. Zhang, F. Zhu, L. Xie, C. Wang, J. Wang, R. Chen, et al., Clinical characteristics 368 of COVID-19 infected cancer patients: a retrospective case study in three hospitals within Wuhan, China, Annals of oncology, official journal of the European Society for Medical Oncology, 2020.
[17] Z. Wang, B. Yang, Q. Li, L. Ren, R. Zhang, Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China, Clinical Infectious Diseases, an official publication of the Infectious Diseases Society of America, 2020.
[18] T.M. Rawson, L.S.P. Moore, N. Moore, N. Ranganathan, K. Skolimowska, M. Gilchrist, et al., Bacterial and Fungal Co-infection in Individuals with Coronavirus: A Rapid Review to Support COVID-19 Antimicrobial Prescribing, Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 2020.
[19] A.C. Kaul, M.L. Mestersky, M. Klopas, J. Muscadero, D.A. Sweeney, L.B. Palmer, et al., Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society 65 (5) (2016) e11-e111. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America.
[20] V. Stevens, G. Dumiaty, L.S. Fine, S.G. Fisher, E. van Wijegaard, Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection, Clin. Infect. Dis.: Off. Publ. Infect. Dis. Soc. Am. 53 (1) (2011) 42–48.
[21] X. Yang, Y. Yu, J. Xu, et al., Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir Med. 8 (2020) 475–481.
[22] B.J. Langford, M. So, S. Raybarthanan, V. Leung, D. Westwood, D.R. MacPadden, J.P.R. Souey, N. Daneman, Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clinical Microbiology and
L. Lansbury, B. Lim, V. Baskaran, W.S. Lim, Co-infections in people with COVID-19: clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

H. Ledford, d. Cyranoski, R. Van Noorden, The UK has approved a COVID-19 vaccine—here’s what scientists now want to know, Nature. Available from: https://www.nature.com/articles/d41586-020-00852-2.pdf.

Z. Wang, B. Yang, Q. Li, L. Wen, R. Zhang, Clinical features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China, Clinical Infectious Diseases, 2020 an official publication of the Infectious Diseases Society of America.

C. Huang, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

Available from: https://www.nice.org.uk/guidance/ng173/chapter/4-Assessing-critical-care-guidance-update-2020-07-06.pdf.

Oxford Analytica, India’s vaccine roll-out faces key obstacles, Expert Briefings (2021), https://doi.org/10.1108/OXAN-D2859713.

C. Chu, et al., Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical results, Lancet 359 (9259) (2002) 252–256.

X. Xie, et al., CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing, 2020, 200343, Radiology.

M. Corpuz, J. Torres-Isasiga, R. Bartash, U. Felsen, V. Chen, Y. Guo, Emerging Co-infections of COVID-19: A Systematic Review and Meta-Analysis, J. Infect. 81 (2020) 266–273, https://doi.org/10.1016/j.jinf.2020.05.026.

J. Murk, R. Van de Biggelaar, J. Stohr, J. Verweij, A. Buiting, S. Wittens, et al., The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza A(H1N1)pdm09, BMC Infect. Dis. 18 (2018) 637.

M. Kumar, K. Kuroda, K. Dhagar, P. Mazumder, C. Sonne, J. Rinklebe, M. Kimija, Potential emergence of antiviral-resistant pneumonia viruses via environmental drug exposure of animal reservoirs, Environ. Sci. Technol. (2020), https://doi.org/10.1021/acs.est.0c03105.

B. Bierboz da Cunha, L.P. Fonseca, C.R.C. Calado, Albumin antibody discovery: where have we come from, where do we go? Antibiotics (Basel) 8 (2019) 45.

T.B. Nielsen, E.P. Brans, D.N. Gilbert, et al., Sustainable discovery and development of antibacterials - is a nonprofit approach the future? N. Engl. J. Med. 381 (2019) 503–505.

K. Yuki, M. Fujiogi, S. Koutsogiannaki, COVID-19 pathophysiology: a review, Clin. Intra, J., C. Sarto, E. Beck, N. Tiberti, V. Leoni, P. Brambilla, M. Kumar, S. Mohapatra, P. Mazumder, A. Singh, R. Honda, C. Lin, R. Kumari, N. Van der Moeren, S. Talman, W. Van den Bijllaardt, M. Kant, P. Heukels, G. Zahariadis, T.A. Gooley, P. Ryall, C. Hutchinson, M.I. Latchford, M.A. Fearon, et al., Case Studies in Chemical and Environmental Engineering 3 (2021) 100093.

G. Satta, G. Cooke, A. Holmes, Bacterial and fungal co-infection in individuals with COVID-19: a descriptive study, Lancet (London, England) 395 (10229) (2020) 1054–1062.

E. Farfour, M. Lecuru, L. Dortet, M.L. Guen, C. Cerf, F. Karnycheff, R.A. Bonnin, et al., Aspergillus fumigatus in respiratory specimen of COVID-19 patient in ICU, Fungal Infections (2020), https://doi.org/10.1016/j. cmi.2020.07.016 published online July 22.

A. Alanio, S. Delliame, A. Sindi, S. Delliame, A. Sindi, F. Goyder, R. Tan, G. Viard, et al., Clinical characteristics of COVID-19 patients with community-acquired pneumonia treated with Ertapenem: A retrospective cohort study, J. Microbiol. Infect. (2020), https://doi.org/10.1016/j. cmi.2020.07.016 published online July 22.

A. Alanio, S. Delliame, A. Sindi, S. Delliame, A. Sindi, F. Goyder, R. Tan, G. Viard, et al., Clinical characteristics of COVID-19 patients with community-acquired pneumonia treated with Ertapenem: A retrospective cohort study, J. Microbiol. Infect. (2020), https://doi.org/10.1016/j. cmi.2020.07.016 published online July 22.

B. Liao, Y. Wu, X. Fang, L. Pan, et al., Clinical features and outcomes of patients with COVID-19 who were co-infected with SARS-CoV-2 and other respiratory pathogens, J. Microbiol. Infect. (2020), https://doi.org/10.1016/j. cmi.2020.07.016 published online July 22.

L. Lansbury, B. Lim, V. Baskaran, W.S. Lim, Co-infections in people with COVID-19: clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet (London, England) 395 (10223) (2020) 1054–1062.

C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet (London, England) 395 (10223) (2020) 497–506.

P. Mazumder et al. Case Studies in Chemical and Environmental Engineering 3 (2021) 100093
antibiotics do not impact mortality in critically ill patients with COVID-19, J. Infect. 81 (2) (2020) e148–e149, https://doi.org/10.1016/j.jinf.2020.06.004.

[76] S. Coppola, A. Ciabattoni, T. Pozzi, V. Castagna, G.L. Bassi, D. Chiumello, Hazardous mismatch between pulmonary pathogens and antibiotic treatments in COVID-19 patients, Br. J. Anaesth. (2020), https://doi.org/10.1016/j.bja.2020.07.001 e380 - COVID-19 Correspondence.

[79] Available at; COVID-19 Rapid Guideline: Managing Suspected or Confirmed Pneumonia in Adults in the Community, 2020. Accessed [June 24 2020], https://www.nice.org.uk/guidance/ng165.

[80] Available at; Clinical Management of COVID-19, 2020. Accessed [June 24 2020], https://www.who.int/publications/i/item/clinical-management-of-covid-19.

[81] COVID-19 Treatment Guidelines Panel, Coronavirus Disease 2020 (COVID-19) Treatment Guidelines, Available at; National Institutes of Health, 2020. Accessed [June 24 2020], https://www.covid19treatmentguidelines.nih.gov/.

[85] N. Chen, M. Zhou, X. Dong, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513.

[86] L. Rossato, F.J. Negri, S. Simionatto, Could the COVID-19 pandemic aggravate antimicrobial resistance? Am. J. Infect. Contr. 48 (9) (2020) 1129–1130.

[90] Available at; 4 4. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment, seventh ed. in Chinese), 2020 [June 24 2020], http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4ce80dc75f912eb1969.shtml.

[93] K.N. Ray, Z. Shi, C.A. Gidengil, S.J. Poon, L. Uscher-Pines, A. Mehrotra, Antibiotic prescribing during pediatric direct-to-consumer telemedicine visits, Pediatrics 143 (2019) 20182491.