



Suboptimal antimicrobial stewardship in the COVID-19 era: is humanity staring at a postantibiotic future?

Oloche Owoicho^{1,2,3}, Kesego Tapela^{1,2,4}, Alexandra Lindsey Djomkam Zune^{1,2}, Nora Nganyewo Nghochuzie^{1,2,5}, Abiola Isawumi^{1,2}  & Lydia Mosi*^{1,2} 

¹West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), University of Ghana, Accra, Ghana

²Department of Biochemistry, Cell & Molecular Biology, College of Basic & Applied Sciences, University of Ghana, Accra, Ghana

³Department of Biological Sciences, Benue State University, Makurdi, Nigeria

⁴West African Network of Infectious Diseases ACEs (WANIDA), French National Research Institute for Sustainable Development, France

⁵Medical Research Council Unit, The Gambia at London School of Hygiene & Tropical Medicine, Banjul, The Gambia

*Author for correspondence: Imosi@ug.edu.gh

In the absence of potent antimicrobial agents, it is estimated that bacterial infections could cause millions of deaths. The emergence of COVID-19, its complex pathophysiology and the high propensity of patients to coinfections has resulted in therapeutic regimes that use a cocktail of antibiotics for disease management. Suboptimal antimicrobial stewardship in this era and the slow pace of drug discovery could result in large-scale drug resistance, narrowing future antimicrobial therapeutics. Thus, judicious use of current antimicrobials is imperative to keep up with existing and emerging infectious pathogens. Here, we provide insights into the potential implications of suboptimal antimicrobial stewardship, resulting from the emergence of COVID-19, on the spread of antimicrobial resistance.

First draft submitted: 15 January 2021; Accepted for publication: 15 June 2021; Published online: 28 July 2021

Keywords: antimicrobial resistance • coronavirus • COVID-19 • hand sanitization • hand washing • SARS-CoV-2

Antimicrobial resistance (AMR) refers to the adaptation of microbial pathogens (bacteria, viruses, fungi and parasites) to antimicrobial drugs thereby resulting in drug inefficiency, persistent infections and increased risk of severe disease and transmission. AMR is one of the three greatest threats to global health [1], and could hamper prevention and treatment of common infections [2]. The burden of resistant infections is comparable to that of influenza, tuberculosis and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) combined [3]. In the absence of potent antimicrobial drugs, it is estimated that bacterial infections alone could cause hundreds of millions of deaths [4]. Hence, antimicrobial stewardship, a systematic approach aimed at optimizing antimicrobial use, is paramount. The increasing demand for antibiotic use, inappropriate prescription of antibiotics in high-income countries and over-the-counter sales of antibiotics in developing countries are some of the factors driving AMR globally [5]. Antimicrobial stewardship, if correctly implemented, has the potential to curb the increasing challenge of AMR. Indeed, some successes have been achieved in curtailing inappropriate use of antibiotics through antimicrobial stewardship. However, owing to the emergence of COVID-19, a novel disease yet to be fully understood in terms of pathophysiology and treatment, antimicrobial stewardship appears neglected [6–8], which may put humanity at a risk of widespread AMR and dearth of potent antimicrobial drugs.

In December 2019, COVID-19, caused by SARS-CoV-2, was reported in Wuhan city, China and had been associated with several deaths globally [9]. SARS-CoV-2 is a new member of coronaviruses, which are a group of highly diverse enveloped, positive-sense, single-stranded RNA viruses [10]. The control measures adopted to curb the spread of the virus include mandatory wearing of face masks, personal distancing, hand washing and sanitization [11] and recently, vaccination. The complex pathophysiology of COVID-19 and possible bacterial and/or fungal coinfections and superinfections have prompted the use of various antimicrobial drugs for its management [12].

The degree of antibiotic-resistant infections is strongly related to the level of antibiotic consumption [13]. Therefore, the repurposing, overuse and misuse of antimicrobials for COVID-19, as has been observed [14,15], may negatively impact human health. The development of AMR may be attributed to many factors, fundamental among them is the overutilization of prescribed antimicrobials. Once a microbe develops resistance to a single or multiple classes of antibiotics [16], it may spread the AMR gene(s) within and across species or genera [17]. Additionally, the current antibiotic pipeline is fragile, having narrow-spectrum or pathogen-specific potential drugs [18]. Thus, nonjudicious use of antimicrobials in the COVID-19 era could result in large-scale drug resistance.

The potential impacts of suboptimal antimicrobial stewardship in the COVID-19 era should be considered in the management of the ongoing pandemic. Therefore, this article focuses on how the emergence of COVID-19 era has compounded suboptimal antimicrobial stewardship and the potential implications for AMR development and spread within and across microbial species and genera. In addition, the need to remain committed to antimicrobial stewardship is emphasized and strategies to maintaining antimicrobial stewardship in the context of the pandemic are highlighted.

Antimicrobial stewardship: is it a challenge in the context of COVID-19?

The COVID-19 has resulted in increased usage of antimicrobials [8,11,19]. This could be attributed to the limited knowledge about the virus, its complex pathophysiology, possible syndemic with bacterial, fungal or protozoal infections, and a remarkable clinical similarity with sepsis [20]. Even though ruling out SARS-CoV-2 coinfection with bacterial or fungal infection could improve antimicrobial stewardship, secondary infections in COVID-19 patients is faced with diagnostic challenges. Notably, the high infectivity of the virus limits the use of invasive diagnostic procedures, such as bronchoscopy and radiologic imaging, which could generate aerosols thereby exposing health workers to the virus. This is further compounded by the poor sensitivity of conventional diagnostic tests in identifying the etiologic organisms responsible for respiratory infections; hence the use of a broad array of antibiotics may be inevitable.

Heightened hand sanitization: implications for the spread of antibiotic resistance

Many public health agencies and governments around the world have been promoting hand hygiene, which includes hand washing and hand sanitization, to limit the spread of SARS-CoV-2 [11]. Indeed, the sale of hand sanitizers surged by 3–5-times in 2020 compared with same period in 2019 in some countries [21]. Some antibacterial soaps and other disinfectants used to prevent the spread of SARS-CoV-2 contain hydrogen peroxide, sodium hypochlorite, benzalkonium chloride or many other antimicrobial agents. Further, hand sanitizers containing suboptimal concentrations of alcohol are on the market. The widespread use of these hand sanitizers and other disinfectants during the COVID-19 era could potentiate the development and spread of AMR traits. There is a likelihood of the emergence of alcohol-tolerant bacteria, a phenomenon already reported across several bacterial genera [22]. Other antibacterial compounds in soap, particularly triclosan and triclocarban could enhance AMR development. Although banned by the US FDA in 2016 [23], the high demand for antibacterial hand washing products has prompted the use of triclosan and triclocarban [24] in some countries. Triclosan is broad-spectrum antibacterial compound, with some antifungal and antiviral activity [25]. Resistance to triclosan develops via multiple mechanisms, including efflux pumps, which confers resistance to multiple antibiotics [26]. Thus, the use of triclosan-containing hand washing soaps in the COVID-19 era could result in cross-resistance to several antibiotics. Disinfectants, such as hydrogen peroxide, which could alter bacterial DNA may as well cause resistance development in bacteria.

Overuse of antibacterial drugs among COVID-19 patients

Rational antibacterial use in clinically stable patients requires culture and sensitivity test result [27]. Where culture and sensitivity test could not be performed, therapy is empiric but guided by epidemiological evidence [27]. Are these rational considerations made in the management of bacterial infections in the COVID-19 context? Antibacterial use in COVID-19 management is hinged on a SARS-CoV-2-associated superinfection with endogenous or hospital-acquired bacteria [28]. However, the rate of antibacterial drug usage is disproportionately higher than the rate of bacterial coinfection in the patients [29]. Some antibacterial drugs commonly prescribed for COVID 19 patients include fluoroquinolones, cephalosporins, carbapenem and linezolid, which are all broad-spectrum antibiotics, and macrolides [30]. It has been suggested that amidst the pandemic, the continuing threat posed by AMR may no longer be at the forefront of many peoples' minds [31], and as mentioned earlier, the over prescription of these

drugs among others could result in a widespread antibiotic resistance. Therefore, to tackle this peril, an integrated prepared strategy is paramount [32].

Repurposing of antiparasitic drugs for the management of COVID-19

Repurposing of existing anti-parasitic drugs gained traction for the management of COVID-19, especially in the early phase of the pandemic [33]. For example, ivermectin, a broad-spectrum antiparasitic agent, has been suggested as an immunomodulator inhibiting the nuclear import of viral proteins [34]. Consequently, ivermectin has been tried both *in vitro* and *in vivo* for COVID-19 therapy [35,36]. Considering its broad anti-parasitic activity, a widespread use of ivermectin for COVID-19 treatment could lead to rapid development and spread of ivermectin resistance. Other antiparasitic drugs such as diethylcarbamazine, niclosamide and nitazoxanide, and hydroxychloroquine and chloroquine have been explored for COVID-19 treatment [37–39]. If successful, the widespread use of these drug to fight the pandemic may as well result in resistance.

Use of antiviral drugs against SARS-CoV-2 & other viral coinfections in COVID-19 patients

Severe COVID-19 is associated with immune dysregulation which may result in secondary viral infections [40]. Several antiviral drugs have been incorporated into the management of COVID-19, with some meant for diseases such as HIV and influenza are being diverted to COVID-19 treatment [41]. Administration of antivirals shortly after the onset of COVID-19 symptoms can reduce viral shedding. Furthermore, prophylactic treatment of contacts reduces their risk of being infected [42].

Remdesivir is one of the commonly used drugs in the COVID-19 context [43]. Remdesivir has a broad-spectrum antiviral activity incorporating both RNA and DNA viruses [44]. The drug inhibits viral RNA synthesis and viral mRNA capping in a wide range of viruses, including influenza virus and HIV [45]. A combination of HIV drugs, lopinavir/ritonavir, which are protease inhibitors, are being used to inhibit SARS-CoV-2 replication. Unfortunately, antiviral resistance against lopinavir/ritonavir has been reported previously [46]. Other antivirals such as umifenovir, a broad-spectrum drug that inhibits membrane fusion of the viral envelope by targeting the S protein–ACE2 interaction [41], and favipiravir, an RNA polymerase inhibitor initially used for Ebola and influenza [47], are also used. Notably, drug resistance has been reported for favipiravir [48].

The high demand of these antiviral drugs for treatment and prophylaxis of COVID-19 requires adequate stock of drugs. This may create two major problems. First, it may quicken the development of drug resistance. With already existing cases of antiviral resistance [49] for some of the drugs proposed for COVID-19 management, and the fact that most viruses develop mutations rapidly [50], overuse will escalate resistance to many viruses rendering the drugs ineffective. Second, the increased usage may lead to shortage of drugs not only for COVID-19 patients, but also HIV/AIDS patients. The influenza outbreaks in future might become pandemic if the influenza drugs are rendered ineffective due to resistance.

Treating fungal superinfections in COVID-19 patients with antifungal drugs

There are reports of deadly fungal superinfections caused by *Aspergillus* species and *Candida albicans* among severe COVID-19 patients across many regions [12,51]. This is worrying since there are few effective antifungal drugs; moreover, the few available antifungal drugs have serious side effects [52]. In an attempt to manage secondary fungal infections, antifungal drugs have been incorporated into the management of COVID-19 [53]. For instance, voriconazole and savuconazole, which both inhibit the cell membrane synthesis and caspofungin, which blocks cell wall synthesis [54] have been used to treat fungal superinfections associated with COVID-19 [51].

Cases of resistance against the above antifungal drugs have been reported [55,56]. Most of the antifungals drugs have broad-spectrum of activity as they target ergosterol, which is common in fungi [57], hence, development of resistance to one drug could affect many antifungals. With the slow discovery and development of antifungals, the widespread and indiscriminate use of the few available antifungals could render the antifungal armamentarium impotent and jeopardize the treatment of opportunistic fungal infections, especially among immune-compromised patients.

Strategies to maintain antimicrobial stewardship in the context of a pandemic: COVID-19

Antimicrobial stewardship is needed to curb the suboptimal use of antimicrobials in the ongoing and future pandemics. Strict policies should be set on the use of antimicrobials, with more sensitization to educate health workers and the public on AMR. The use of biocides for environmental and personal disinfection should be

done cautiously and biocidal agents without or with a low selection pressure for antibiotic resistance should be prioritized. Rigorous infection prevention and control measures should be implemented to prevent hospital-acquired infections among COVID-19 patients. Additionally, efforts should be made toward reducing the turnaround time of COVID-19 tests through improved testing methods and facilities, as this will decrease the urge to initiate antibiotics empirically. Furthermore, studies toward improving antimicrobial stewardship should be an integral part of the pandemic response and beyond. Lastly, rapid and inexpensive diagnostic tests to distinguish between bacterial and viral respiratory tract infections, where available, should be deployed for coinfection testing in COVID-19 patients. Nonetheless, antimicrobial stewardship strategies for COVID-19 have previously been reviewed [58].

Future perspective

As previously highlighted, lack of timely and accurate differential diagnostic method for bacterial– and fungal–viral coinfections is a major driver for antibiotics overuse in COVID-19 treatment. Hence, advances in point-of-care (POC) diagnostics designed for timely identification of pathogenic bacteria or fungi in various clinical samples will potentially shape antibiotics therapy in the clinics in the years to come. Notably, POC biosensors and isothermal-based nucleic acid amplification tools, especially if they are miniaturized and optimized for both pathogen and resistance gene(s) detection, will pave the way for timely diagnosis of coinfections and obviate empiric treatment. Investigation of host or pathogen-derived biomarkers of bacterial, fungal and viral coinfections, as well as the translation of the discovered biomarkers into diagnostic tools, therefore, remains an interesting area of research that should be well explored in the coming years.

Executive summary

Antimicrobial stewardship: is it a challenge in the context of COVID-19?

- The high infectivity of SARS-CoV-2 has led to increased use of disinfectants and hand sanitizers to curb its transmission.

Heightened hand sanitization: implications for the spread of antibiotic resistance

- The desperate desire to avert COVID-19-related mortalities has occasioned suboptimal antimicrobial stewardship which could enhance the emergence of resistance.

Maintaining antimicrobial stewardship in the context of a pandemic

- While pharmaceutical companies and researchers work harder to avail new antibiotics, proposed stewardship interventions for COVID-19 should be put in practice to prevent resistance.

Author contributions

O Owoicho, K Tapela, ALD Zune and NN Nghochuzie conceived and prepared the first draft of the manuscript. AI revised the draft for important intellectual content. LM made substantial contributions to the draft, critically reviewed the manuscript and approved the final version for publication. All the authors approved the final draft of the manuscript for submission.

Financial & competing interests disclosure

O Owoicho, K Tapela, NN Nghochuzie and ALD Zune are supported by a WACCBIP-World Bank ACE PhD fellowship (ACE02-WACCBIP: Awandare) and a DELTAS Africa grant (DEL-15-007: Awandare). The DELTAS Africa Initiative is an independent funding scheme of the African Academy of Sciences (AAS)'s Alliance for Accelerating Excellence in Science in Africa (AESA) and supported by the New Partnership for Africa's Development, Planning and Coordinating Agency (NEPAD Agency) with funding from the Wellcome Trust (107755/Z15/Z: Awandare). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

- Asokan GV, Kasimanickam RK. Emerging infectious diseases, antimicrobial resistance and millennium development goals: resolving the challenges through one health. *Cent. Asian J. Glob. Heal.* 2(2), 76 (2014).
- World Health Organization. *WHO | Antimicrobial Resistance: Global Report on Surveillance 2014*. WHO (2016).
- **This is a database is a global collection on the surveillance activities of different countries with respect to antimicrobial resistance.**
- Cassini A, Högberg LD, Plachouras D *et al.* Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect. Dis.* 19(1), 129–130 (2019).
- Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. *Virulence* 4(2), 185–191 (2013).
- Berndtson AE. Increasing globalization and the movement of antimicrobial resistance between countries. *Surg. Infect. (Larchmt)*. 21(7), 579–585 (2020).
- Karami Z, Knoop BT, Dofferhoff ASM *et al.* Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in The Netherlands. *Infect. Dis. (Lond)*. 53(2), 102–110 (2021).
- Nori P, Cowman K, Chen V *et al.* Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. *Infect. Control Hosp. Epidemiol.* 42(1), 84–88 (2021).
- Townsend L, Hughes G, Kerr C *et al.* Bacterial pneumonia coinfection and antimicrobial therapy duration in SARS-CoV-2 (COVID-19) infection. *JAC – Antimicrobial Resist.* 2(3), dlaa071 (2020).
- **Identifies a low co-infection rate of bacteria in COVID-19 albeit long antibiotic therapy administration. A recommendation from this article was that antimicrobial stewardship should be active in order to adhere to optimum prescription.**
- John Hopkins University of Medicine. ‘Coronavirus (COVID-19) Information and Updates’ (2020) www.hopkinsmedicine.org/coronavirus
- Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 367(6485), 1444–1448 (2020).
- Berardi A, Perinelli DR, Merchant HA *et al.* Hand sanitisers amid CoViD-19: A critical review of alcohol-based products on the market and formulation approaches to respond to increasing demand. *Int. J. Pharm.* 584, 119431 (2020).
- **Assesses the formulation and usage of various hand sanitizers currently being used in the COVID-19 era and its potential effect on the development of antimicrobial resistance.**
- Chen N, Zhou M, Dong X *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395(10223), 507–513 (2020).
- Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 365(9459), 579–587 (2005).
- Cox MJ, Loman N, Bogaert D, O’Grady J. Co-infections: potentially lethal and unexplored in COVID-19. *Lancet Microbe* 1(1), e11 (2020).
- **Stresses on the complexity of co-infections in COVID19-positive patients and the need to rapidly identify them for better treatment options to improve antimicrobial stewardship.**
- Hsu J. How covid-19 is accelerating the threat of antimicrobial resistance. *BMJ* 369, m1983 (2020).
- Bin Zaman S, Hussain MA, Nye R, Mehta V, Mamun KT, Hossain N. A review on antibiotic resistance: alarm bells are ringing. *Cureus* 9(6), e11403 (2017).
- Schwarz S, Loeffler A, Kadlec K. Bacterial resistance to antimicrobial agents and its impact on veterinary and human medicine. *Vet. Dermatol.* 28(1), 82–e19 (2017).
- Theuretzbacher U, Outterson K, Engel A, Karlén A. The global preclinical antibacterial pipeline. *Nat. Rev. Microbiol.* 18(5), 275–285 (2020).
- Lian J, Jin X, Hao S *et al.* Analysis of epidemiological and clinical features in older patients with coronavirus disease 2019 (COVID-19) outside Wuhan. *Clin. Infect. Dis.* 71(15), 740–747 (2020).
- Olwal CO, Nganyewo NN, Tapela K *et al.* Parallels in sepsis and COVID-19 conditions: implications for managing severe COVID-19. *Front. Immunol.* 12, 91 (2021).
- Huddleston T Jr. ‘The history of hand sanitizer – how the coronavirus staple went from mechanic shops to consumer shelves’ (2020). www.cnn.com/2020/03/27/coronavirus-the-history-of-hand-sanitizer-and-why-its-important.html
- Ingram LO. Ethanol tolerance in bacteria. *Crit. Rev. Biotechnol.* 9(4), 305–319 (1989).
- McNamara PJ, Levy SB. Triclosan: an instructive tale. *Antimicrob. Agents Chemother.* 60(12), 7015–7016 (2016).

24. Ishmail S. Covid-19: Hand sanitisers, disinfectants potentially harmful to environment (2020). <https://www.iol.co.za/news/south-africa/western-cape/covid-19-hand-sanitisers-disinfectants-potentially-harmful-to-environment-45259078>
25. Aiello AE, Larson EL, Levy SB. Consumer antibacterial soaps: effective or just risky? *Clin. Infect. Dis.* 45(Suppl. 2), S137–S147 (2007).
26. Carey DE, McNamara PJ. The impact of triclosan on the spread of antibiotic resistance in the environment. *Front. Microbiol.* 5, 780 (2014).
27. de With K, Allerberger F, Amann S *et al.* Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. *Infection* 44(3), 395–439 (2016).
28. Yang X, Yu Y, Xu J *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(5), 475–481 (2020).
29. Langford BJ, So M, Raybardhan S *et al.* Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin. Microbiol. Infect.* 26(12), 1622–1629 (2020).
30. Millán-Onte J, Millan W, Mendoza LA *et al.* Successful recovery of COVID-19 pneumonia in a patient from Colombia after receiving chloroquine and clarithromycin. *Ann. Clin. Microbiol. Antimicrob.* 19(1), 16 (2020).
31. Lynch C, Mahida N, Gray J. Antimicrobial stewardship: a COVID casualty? *J. Hosp. Infect.* 106(3), 401–403 (2020).
32. Pelfrene E, Botgros R, Cavaleri M. Antimicrobial multidrug resistance in the era of COVID-19: a forgotten plight? *Antimicrob. Resist. Infect. Control* 10(1), 21 (2021).
33. Amawi H, Abu Deiab GA, Aljabali AAA, Dua K, Tambuwala MM. COVID-19 pandemic: an overview of epidemiology, pathogenesis, diagnostics and potential vaccines and therapeutics. *Ther. Deliv.* 11(4), 245–268 (2020).
34. Şimşek Yavuz S, Ünal S. Antiviral treatment of covid-19. *Turk. J. Med. Sci.* 50(SI), 611–619 (2020).
35. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. *Antiviral Res.* 178(104787), 1–4 (2020).
36. Khan MSI, Khan MSI, Debnath CR *et al.* Ivermectin treatment may improve the prognosis of patients With COVID-19. *Arch. Bronconeumol (Engl Ed).* 56(12), 828–830 (2020).
37. Frie K, Gbinigie K. 'Chloroquine and hydroxychloroquine: current evidence for their effectiveness in treating COVID-19' (2020). <https://covid19-evidence.paho.org/handle/20.500.12663/862>
38. Abeygunasekera A, Jayasinghe S. Is the anti-filarial drug diethylcarbamazine useful to treat COVID-19? *Med. Hypotheses* 143, 109843 (2020).
39. Mostafa A, Kandeil A, Elshaier YAMM *et al.* FDA-approved drugs with potent *in vitro* antiviral activity against severe acute respiratory syndrome coronavirus 2. *Pharmaceuticals* 13(12), 443 1–24 (2020).
40. Chen G, Wu D, Guo W *et al.* Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Invest.* 130(5), 2620–2629 (2020).
41. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proc. Natl Acad. Sci. USA* 114(2), 206–214 (2017).
42. Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. *Lancet Glob. Health.* 8(5), e639–e640 (2020).
43. Bergman S. 'COVID-19 treatment: investigational drugs and other therapies' (2021). <https://emedicine.medscape.com/article/2500116-overview>
44. Snell NJC. Ribavirin - current status of a broad spectrum antiviral agent. *Expert Opin. Pharmacother.* 2(8), 1317–1324 (2001).
45. Patterson JL, Fernandez-Larsson R. Molecular mechanisms of action of ribavirin. *Rev. Infect. Dis.* 12(6), 1139–1146 (1990).
46. Champenois K, Baras A, Choisy P *et al.* Lopinavir/ritonavir resistance in patients infected with HIV-1: two divergent resistance pathways? *J. Med. Virol.* 83(10), 1677–1681 (2011).
47. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc. Japan Acad. Ser. B Phys. Biol. Sci.* 93(7), 449–463 (2017).
48. Goldhill DH, Te Velthuis AJW, Fletcher RA *et al.* The mechanism of resistance to favipiravir in influenza. *Proc. Natl Acad. Sci. USA* 115(45), 11613–11618 (2018).
49. Pennings PS. HIV drug resistance: problems and perspectives. *Infect. Dis. Rep.* 5(Suppl. 1), 21–25 (2013).
50. Duffy S. Why are RNA virus mutation rates so damn high? *PLoS Biol.* 16(8), e3000003 (2018).
51. Bouadma L, Wicky P-H, Le Hingrat Q *et al.* Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect. Dis.* 20(6), 697–706 (2020).
52. Girois SB, Chapuis F, Decullier E, Revol BGP. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. *Eur. J. Clin. Microbiol. Infect. Dis.* 24(2), 119–130 (2005).
53. Clancy (Neil) JC. 'COVID-19: Role of superinfections in novel coronavirus deaths highlights urgent need for sustainable development of new antibiotics' (2020). <https://sciencespeaksblog.org/2020/04/06/covid-19-role-of-superinfections-in-novel-coronavirus-deaths-highlights-urgent-need-for-sustainable-development-of-new-antibiotics/>

54. Zhang B, Liu S, Tan T *et al.* Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. *Chest* 158(1), e9–e13 (2020).
55. Paul RA, Rudramurthy SM, Dhaliwal M *et al.* Magnitude of voriconazole resistance in clinical and environmental isolates of *Aspergillus flavus* and investigation into the role of multidrug efflux pumps. *Antimicrob. Agents Chemother.* 62(11), e01022–18 (2018).
56. Yang F, Zhang L, Wakabayashi H *et al.* Correction: Tolerance to caspofungin in *Candida albicans* is associated with at least three distinctive mechanisms that govern expression of FKS genes and cell wall remodeling. *Antimicrob. Agents Chemother.* 61(5), e00071–17 (2017).
57. Mazu Tryphon K, Bricker BA, Flores-Rozas HY, Ablordeppey S. The mechanistic targets of antifungal agents: an overview. *Mini Rev. Med. Chem.* 16(7), 555–578 (2016).
58. Pulia MS, Wolf I, Schulz LT, Pop-Vicas A, Schwei RJ, Lindenauer PK. COVID-19: an emerging threat to antibiotic stewardship in the emergency department. *West. J. Emerg. Med.* 21(5), 1283–1286 (2020).