

Implications of antibiotics use during the COVID-19 pandemic: present and future

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COVID-19 is caused by the SARS-CoV-2 virus, which has infected more than 4 million people with 278 892 deaths worldwide as of 11 May 2020. This disease, which can manifest as a severe respiratory infection, has been declared as a public health emergency of international concern and is being treated with a variety of antivirals, antibiotics and antifungals. This article highlights the administration of antimicrobials in COVID-19 patients worldwide, during the 2019–20 pandemic. It is imperative to be aware of the unreported amounts of antibiotics that have been administered worldwide in just a few months and a marked increase in antimicrobial resistance should therefore be expected. Due to the lack of data about antimicrobial use during this pandemic, the global impact on the emergence of new antimicrobial resistance is as yet unknown. This issue must be at the forefront of public health policymaking and planning in order that we are prepared for the potentially severe consequences for human and animal health and the environment.

Introduction

At the end of December 2019, an outbreak of a respiratory disease affecting humans in China was reported.^{1,2} A few days after the outbreak was announced, the causal agent of coronavirus disease 2019 (COVID-19) was identified as severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), a novel betacoronavirus.³ COVID-19 affects people of all ages, most of whom will develop mild to moderate symptoms.⁴ The disease is rapidly progressing worldwide and the number of deaths is high. On 30 January 2020, the WHO declared a Public Health Emergency of International Concern.⁴ As of 11 May 2020, there had been more than 4 million confirmed cases and 278 892 deaths in 213 countries, areas or territories. These numbers possibly underestimate the total number of those infected and dead, as many people are likely to be asymptomatic, and testing is limited and surveillance is variable. Owing to the lack of effective therapeutics or vaccines to date, SARS-CoV-2 infections are being treated with a variety of antimicrobials in severe cases and the best measure to control the spread of the infection remains a strong public health surveillance system.⁵

COVID-19 treatment

Most people with COVID-19 (84%) develop a mild or uncomplicated illness. However, some develop severe disease requiring hospitalization and oxygen support (14%) with 5% requiring admission to an ICU.⁶ For COVID-19 patients admitted to ICU, the disease can be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, and multi-organ failure.⁷

The WHO has published detailed guidelines for clinical management of patients with COVID-19.⁸ In general, patients with mild disease do not require hospital interventions. Treatment is essentially supportive and symptomatic. For mild COVID-19 cases, patients can be provided with antipyretics for fever. The management of severe COVID-19 cases includes immediate oxygen therapy and monitoring, it may be necessary to proactively prevent complications and secondary infections, treat underlying diseases and provide organ function support.^{8,9} Treatment of co-infections relies on empirical antimicrobial therapy to treat all likely pathogens causing severe acute respiratory infection (SARI) and sepsis (Figure 1). Patients suspected to have COVID-19 should be administered

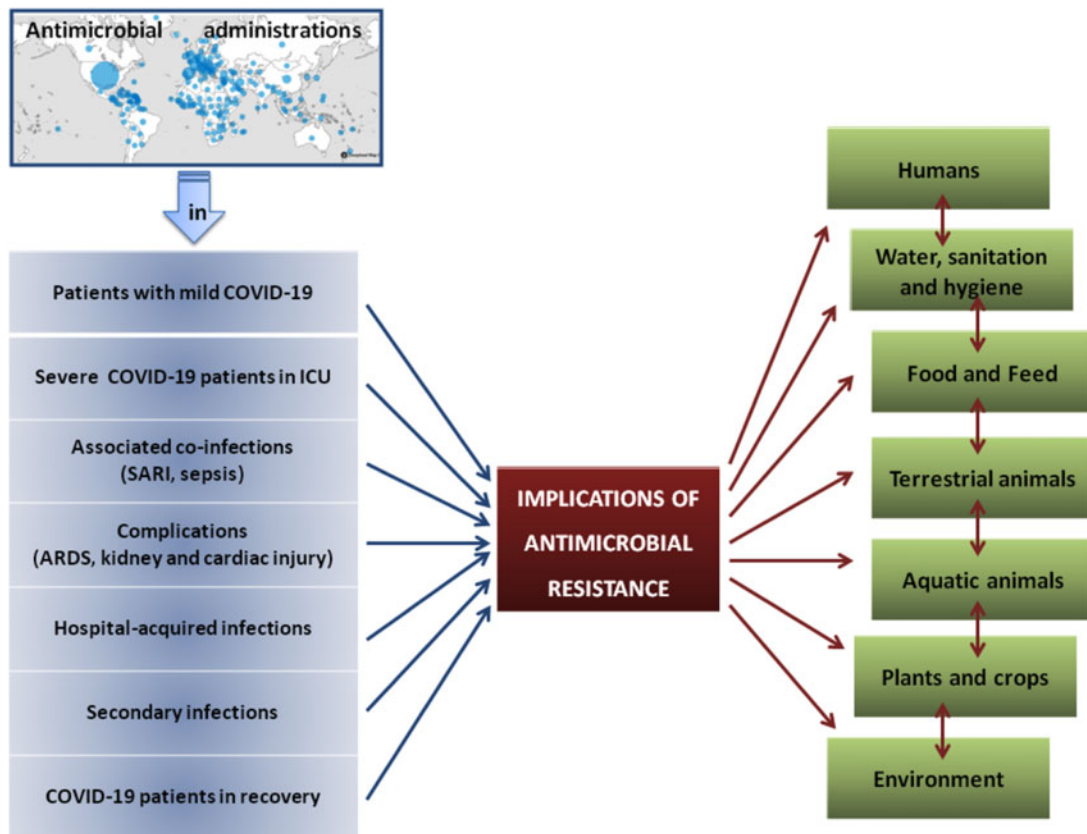


Figure 1. Administration of antimicrobials in different hospital situations during the COVID-19 pandemic and the implications for AMR in One Health sectors. Map source: WHO (reference 4). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

appropriate empirical antimicrobials within 1 h of identification of sepsis.⁸

There is no current evidence to recommend any specific treatment for patients with confirmed COVID-19. While a variety of antiviral agents, including antiviral peptides (e.g. favipiravir) and corticosteroids have been used in COVID-19 patients, their role and mode of action has yet to be established.^{8,10} Dexamethasone, a corticosteroid, has shown benefits in critically ill patients with COVID-19, reducing the mortality by about one-fifth or one-third in patients requiring oxygen or ventilator support, respectively.⁸ In one SARS-CoV-2 study, 76% of patients received antiviral treatments, such as oseltamivir, ganciclovir, lopinavir and ritonavir.¹¹ In another study, SARS-CoV-2 patients treated with lopinavir/ritonavir with ribavirin had better outcomes compared with those given ribavirin alone.^{10,11} The antiviral agent remdesivir is the most promising treatment for COVID-19, as it inhibits the activity of the viral RNA-dependent RNA polymerase.^{8,10}

Information on antimicrobial treatments given to patients with SARS-CoV-2 infection is scarce. Although the antimicrobials used have been reported in some studies, there is insufficient consideration of their importance or of the possibility that they are being used indiscriminately or inappropriately, especially when broad-spectrum antibiotics are used in combination.^{7,11} For example,

Chen *et al.*⁹ reported that 15% of COVID-19 patients received anti-fungal treatment and 71% received antibiotic treatment, 25% of whom were treated with a single antibiotic and 45% with combination therapy. The antibiotics used were cephalosporins, quinolones, carbapenems, tigecycline (against MRSA) and linezolid. Wang *et al.*¹² explained that many sick patients received anti-bacterial therapy, such as moxifloxacin (64%), ceftriaxone (25%) and azithromycin (18%). The administration of antibiotics was also reported in a case of a neonate with non-specific symptoms of COVID-19 infection; this neonate received fluid therapy, oxygen therapy and antibiotic therapy with vancomycin and amikacin.¹³ Other studies did not describe the antimicrobial types used, reporting only the administration of IV antibiotic and antifungal medications in 57% and 3% of COVID-19 patients, respectively,¹⁴ or that all of 41 patients (100%) received antibiotics and 93% received antiviral treatments.¹⁵

Other antibiotic therapeutics proposed for the treatment of COVID-19 disease are azithromycin, quercetin, rapamycin and doxycycline.¹⁶ However, the combination of hydroxychloroquine (an analogue of chloroquine considered an old antimalarial drug) and azithromycin appeared to be even more effective in COVID-19 treatment.¹⁷ Azithromycin also inhibits the replication of other viruses, such as Zika and Ebola.^{18,19} Azithromycin, doxycycline and rapamycin are antibiotic drugs that inhibit protein synthesis and

functionally reduce inflammation and viral replication. So, inhibiting virus production should help to clinically reduce virus transmission to other patients.¹⁶

One Health view of the COVID-19 pandemic consequences for antimicrobial resistance (AMR)

The COVID-19 pandemic has the potential to become a sustained major public health emergency. Containment of the outbreak requires the best of public health actions and skills. It is important for all who are providing health and medical services during this event to recognize the broader impact of such a disease outbreak and that the long-term global threat of AMR should not be overlooked.^{20,21}

The prolonged use of antimicrobials, their overuse and inappropriate use contribute to the development of AMR. In the COVID-19 pandemic, it is important to warn of the unreported amounts of antibiotics and antifungals that have been administered worldwide in just a few months. It should be noted that azithromycin (in the macrolide and ketolide class), as well as vancomycin, carbapenems, tigecycline, azithromycin, ceftriaxone and linezolid, were all classified as critically important antimicrobials (CIA) for human medicine by WHO.²² The antimicrobials used to treat patients with SARS-CoV-2 infections contribute to saving millions of lives now, but in decades to come the current upsurge in their use may be responsible for a large number of deaths.

Persistent use of antibiotics has provoked the emergence of MDR strains and a decline in the effectiveness of these compounds,²³ which poses a threat to survival rates from serious infections, neonatal sepsis and hospital infections, thus limiting the potential health benefits of surgery, transplants and cancer treatment.^{24,25} Moreover, pets and wild animals are reported to be reservoirs of AMR,^{26,27} and the use of antimicrobials in livestock production to maintain health and productivity still contributes to the spread of infectious diseases and transmission of resistance genes via food and the environment.^{25,28} In addition, the emergence of AMR bacteria from anthropogenic activities in natural environments are major concerns for human and animal health.²⁷ Rawson *et al.*²¹ highlighted several factors and potential impacts during the COVID-19 pandemic, as well as potential interventions in the AMR area. On the other hand, these authors also noted that with increased societal sensitization towards emerging threats from infectious diseases and good sanitary practices during this pandemic, this may subsequently drive greater engagement with combating AMR and mitigating the potential impact of the pandemic on rates and transmission of AMR through contingency interventions.

Currently, AMR leads to an estimated 700 000 deaths annually worldwide, including 230 000 from MDR tuberculosis. Every country is potentially affected. Regardless of the COVID-19 pandemic, AMR could force up to 24 million people into extreme poverty by 2030 and drug-resistant diseases could cause 10 million deaths each year by 2050, as described in a United Nations report for urgent action to avert the AMR crisis.^{29,30} A sustained One Health approach is essential to engage and unite all stakeholders around

a shared vision and common goals, since this global crisis includes humans, animals, plants, food and the environment and knows no borders (Figure 1). Multisectoral and multifaceted actions on AMR are crucial because human medicine, and the food and agricultural sectors use antibiotics daily.^{30,31}

Conclusions and future perspective

During the current global public health emergency caused by COVID-19, hospitals and medical workers are facing enormous pressure, including a high risk of infection. In this pandemic, it is paramount to save the lives of COVID-19 patients, even if this means recourse to using antimicrobials for treatment or prevention of complications and secondary infections. However, several of these antibiotics are used in human and animal medicine and are classified as being critically important, some as the only resort. It is expected that there has been a higher than normal level of administration of antibiotics, and considering the scarcity of data so far, it is likely that the number, type and amounts of antibiotics used are currently undocumented and thus underestimated. It is feared that current errors or excesses could accelerate the advent of the next global public health crisis caused by resistance of a large variety of microorganisms to a spectrum of drugs.

AMR is already globally recognized as a growing political concern with serious social, economic, human health and animal health repercussions. Only a One Health approach that implements programmes, policies, legislation and research will enable the multiple sectors and stakeholders engaged in human, terrestrial and aquatic animal and plant health, food and feed production and the environment, to communicate and work together to achieve better public health outcomes.

Furthermore, as we have witnessed with COVID-19, all are responsible for implementing and developing actions to control or stop the disease, and it is equally in our power to change dangerous practices, through appropriate and consensual use of antimicrobials. Only time will tell how this virus will affect worldwide public health, but this perspective is an urgent warning that with the massive amounts of antibiotics that have been administered worldwide in a few months, a marked increase of AMR should be expected with unimaginable implications for human and animal health and the environment.

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Transparency declarations

None to declare.

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