*JAC Antimicrob Resist*
doi:10.1093/jacamr/dlab038

JAC-Antimicrobial Resistance

# The potential impact of the COVID-19 pandemic on global antimicrobial and biocide resistance: an AMR Insights global perspective

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The COVID-19 pandemic presents a serious public health challenge in all countries. However, repercussions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections on future global health are still being investigated, including the pandemic's potential effect on the emergence and spread of global antimicrobial resistance (AMR). Critically ill COVID-19 patients may develop severe complications, which may predispose patients to infection with nosocomial bacterial and/or fungal pathogens, requiring the extensive use of antibiotics. However, antibiotics may also be inappropriately used in milder cases of COVID-19 infection. Further, concerns such as increased biocide use, antimicrobial stewardship/infection control, AMR awareness, the need for diagnostics (including rapid and point-of-care diagnostics) and the usefulness of vaccination could all be components shaping the influence of the COVID-19 pandemic. In this publication, the authors present a brief overview of the COVID-19 pandemic and associated issues that could influence the pandemic's effect on global AMR.

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## Introduction and overview of the global COVID-19 pandemic

In December 2019, several cases of atypical pneumonia were reported in Wuhan, China, and later confirmed as severe acute respiratory syndrome (SARS) coronavirus, which was named SARS-Cov-2 because of its genetic relatedness to the 2003 SARS outbreak.[1] Subsequent investigations of the novel virus showed a similarity of 79% to SARS-CoV and a 50% similarity to Middle East respiratory syndrome coronavirus (MERS-CoV).[2] Initially, on 12 January 2020, WHO named this new virus the 2019-novel coronavirus (2019-nCoV). Later, the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) proposed the name as SARS-CoV-2.[3] On 11 February 2020, WHO officially named the disease caused by this novel coronavirus as COVID-19.

The coronaviruses are enveloped viruses from the Coronaviridae family and possess positive-sense single stranded RNA as genetic material.[4] The Coronaviridae family is divided into four genera: α-, β-, γ- and δ-coronaviruses. α- and β-coronaviruses are able to infect mammals, whereas γ- and δ-coronaviruses mainly infect birds, or sometimes mammals.[5] In the past 20 years, three outbreaks—including SARS-CoV in 2003, MERS-CoV in 2012 and the much feared COVID-19/SARS-CoV-2 in 2020—have been recorded.[3,6–8] Additionally, several other coronaviruses (CoVs) belonging to both α- and β-coronaviruses circulate in humans causing mild respiratory diseases[9] and it is estimated that 15%–30% of common colds are caused by CoVs.[10] Among the seven human-associated strains (Figure 1), infection with two α-CoVs (HCoV-229E and HCoV-NL63) and two β-CoVs (HCoV-OC43 and HCoV-HKU1) lead to mild respiratory tract infections similar to the common cold, while infection with the three highly pathogenic β-CoVs (SARS-CoV, MERS-CoV and COVID-19/SARS-CoV-2) may result in severe disease.[5] At this point, it should be noted that some coronavirus outbreaks trace their origin to animal reservoirs of CoVs, such as the SARS-CoV outbreak in China in 2003,[11] and the MERS-CoV causing outbreaks in the Middle East in 2012.[12]

With specific respect to SARS-CoV-2 and COVID-19, fever and cough have been recorded as the predominant clinical symptoms, with more serious effects among elderly patients and those with underlying comorbidities such as hypertension, COPD, obesity, diabetes and other immunosuppressive conditions.[13,14] These patients may develop symptoms such as acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction and in some cases lead to death.[15] A study conducted by Guan *et al.*[16] recruiting 1099 laboratory confirmed cases found clinical manifestations such as fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), and pneumonia (91.1%) in affected patients. The SARS-CoV-2 virus has also been isolated from rectal swabs of patients with severe pneumonia and gastrointestinal tract symptoms such as diarrhoea, nausea and vomiting. However, only a low proportion of virus-positive rectal swabs have actually been reported (below 10% of patients), suggesting that virus transmissibility through the faecal-oral route is limited.[15,17–19] SARS-CoV-2 RNA is detectable 2–3 days prior to the onset of symptoms, but peaks with the start of symptoms (usually in the first week). During the period of overt symptoms, an individual is known to be infectious, with viable virus decreasing in quantity over the following days to weeks. However, although cultivable viable virus may be detected for up to 9 days, viral PCR remains positive for up to 3 months after infection.[20] According to the information received on 8 October 2020 [based on the number of total confirmed cases (36 002 827) and total deaths (1 049 810) caused by SARS-CoV-2], the mortality rate has been estimated to be 2.9%,[21] which is lower than that found with SARS-CoV (10%)[22] and MERS-CoV (37.1%).[23] However, the transmissibility of SARS-CoV-2 is much higher when compared with other CoVs.[24] Further, there is evidence to suggest that some racial and ethnic populations may be more affected than others.[25] Although case fatality rates are difficult to calculate during a pandemic—largely due to the heterogeneity of methodologies used in data collection—it is not unthinkable that a progressive decrease in the COVID-19 mortality rate will be observed as SARS-CoV-2 seroconverts and immunity spreads among the population.

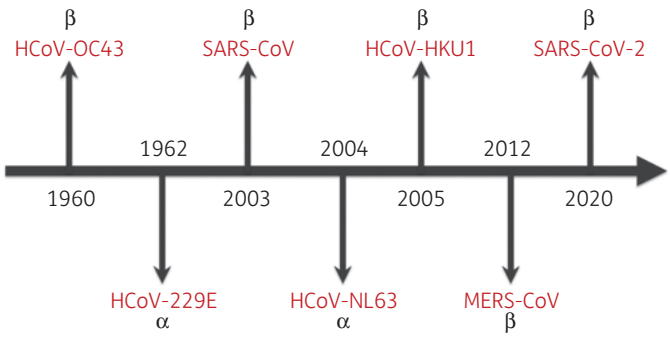


**Figure 1.** Timeline of severe human coronavirus strains.

## Literature search

To compile the information in preparing this manuscript, a PubMed and Google literature search was conducted by using the key terms 'COVID-19', 'COVID-19 pandemic', 'SARS-CoV-2', 'SARS-CoV-2019', 'coronavirus-2019', 'global burden of antimicrobial resistance', 'COVID-19 and secondary infections', 'COVID-19 and secondary bacterial infections', 'COVID-19 and secondary fungal infections', 'antimicrobial treatment of COVID-19 patients', 'COVID-19 and biocides', 'COVID-19 pandemic and biocides', 'COVID-19 and healthcare services', 'COVID-19 and compromised healthcare services', 'COVID-19 and antimicrobial stewardship', 'vaccines and antimicrobial resistance', and 'COVID-19 vaccines'. The authors included full text articles published in the English language only.

## The global burden of antimicrobial resistance (AMR)—an introduction

Similar to COVID-19, AMR presents a serious challenge to global public health in all countries across the world. In September 2016 (years prior to the emergence of the COVID-19 pandemic), the WHO committed itself to fighting AMR, which had become a problem of global public health importance.[26] For example, global infections due to antimicrobial resistant pathogens result in approximately 700 000 deaths annually, which has been estimated to increase to 10 million deaths by the year 2050.[27] The Global

Antimicrobial Surveillance System (GLASS) of WHO continues to report increasing levels of AMR in a range of pathogens that cause serious or common infections in many regions of the world.[28] Recently, an estimated 3 million annual infections in America were reported to be caused by high priority antimicrobial-resistant pathogens.[29,30] Moreover, the US CDC previously estimated that approximately 23 000 deaths will occur every year due to infections caused by antimicrobial resistant pathogens in the USA.[31] In 2019, ECDC reported the deaths of 25 000 patients in high-income countries of Europe.[32] Similarly, in low- and middle-income countries (LMICs) such as India and Thailand, infections caused by antimicrobial-resistant pathogens were responsible for the annual deaths of approximately 58 000 children and 38 000 adults, respectively.[33] In the current century, AMR is a substantial and continually growing problem, being considered one of the greatest threats to global health[34] with significant global economic burden.[35] For example, antimicrobial-resistant infections have been estimated to result in an extra economic burden of $20 billion in the USA alone.[31] In the EU and European Economic Area (EEA), AMR results in an extra healthcare cost of €1.1–1.5 billion.[32,36] By 2050, there is predicted to be a global loss of 1.1%–3.8% of the global annual gross domestic product due to antimicrobial-resistant infections. It is predicted that, in low-income countries, around 24 million people will be forced into extreme poverty by 2030, and one in six will die due to AMR-related infections.[35]

The increased incidence of infections by microorganisms resistant to the most recently developed antibiotics, e.g. the carbapenems, or to 'last resort' antimicrobial agents, such as colistin, is worrisome. While the emergence of AMR continues to increase, there has been a decline in the availability of newly developed antimicrobial agents on the market. If this continues, most of the currently prescribed antibiotics applied for human and animal infections will be ineffective within a decade, leading to conditions similar to that of the pre-antibiotic era. In this respect, it should be noted that programmes such as the US '10 × '20 initiative' have been implemented.[37] Although the AMR crisis has tended to be more serious in Gram-negative compared with Gram-positive bacterial infections, in recent years, an increased incidence of antibiotic resistant Gram-positive organisms has been reported.[38,39] The most serious group of MDR bacteria associated with AMR are those that pose a particular threat to hospitals and nursing homes; referred to by IDSA as 'ESKAPE' pathogens, which include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.[40] In 2017, WHO published its first 'Priority Pathogens List (PPL)' in order to help direct efforts into the research and development of new antibiotics. The PPL comprised a catalogue of 12 families of bacteria that pose the greatest threat to mankind, including both Gram-negative and Gram-positive bacteria. The PPL divides pathogens into three categories, namely 'critical', 'high' and 'medium' priority dependent on the urgency of the global need for new antibiotics.[41,42] Critical priority species include the carbapenem-resistant *A. baumannii, P. aeruginosa*, carbapenem-resistant and ESBL-producing Enterobacteriaceae such as *Klebsiella* spp., *Escherichia coli, Serratia* spp. and *Proteus* spp. These are associated with severe infections of the bloodstream and the lower respiratory tract. Bacterial species in the high priority category include vancomycin-resistant *E. faecium*, MRSA and vancomycin-intermediate/resistant *S. aureus*, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter* spp., *Salmonella* spp. and cephalosporin- and fluoroquinolone-resistant *Neisseria gonorrhoeae*. These are commonly associated with the general infections, gastroenteritis and gonorrhoea. Species in the medium priority category include penicillin-resistant *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae* and fluoroquinolone-resistant *Shigella* spp.[42]

## The COVID-19 pandemic and its potential relationship with the emergence of AMR

AMR naturally occurs as a mechanism by which microorganisms adapt to survive in hostile environments, such as those containing antibiotics. The high growth rate of most bacteria combined with microbial genomic mutation and the phenomenon of natural (Darwinian) selection results on the emergence of microorganisms adapted to withstand the presence of these antibiotics. Although this process occurs naturally, the inappropriate (over/misuse) use of antibiotics (and disinfectants/biocides) in many 'One Health' areas such as human health and hygiene, agriculture, animal husbandry and food production industries are major contributing factors in the emergence of AMR (or disinfectant/biocide resistance) in the last century.[43,44] The various prevention and treatment protocols being used for the management of the COVID-19 pandemic has heightened concern over the development and spread of existing and novel resistance mechanisms associated with pathogenic bacteria. One of the major concerns is the extensive and inappropriate use of antimicrobials in the treatment of critically ill COVID-19 patients.[45] However, this is not the only factor potentially linking COVID-19 infections to increasing AMR (and biocides). Details of these factors are provided below (Figure 2).

### *1. Bacterial and fungal infections in COVID-19 patients*

Critically ill COVID-19 patients admitted to the hospital, especially the ICU, suffer more frequent bacterial or fungal nosocomial infections. Patients with underlying risk factors such as advanced age, previous systemic diseases, mechanical ventilation, and prolonged hospital stay are more prone to these complications.[15,46] Furthermore, secondary bacterial infections may occur as a consequence of viral respiratory infections, being associated with high morbidity and mortality rates in affected patients.[47–49] Although the precise mechanisms facilitating secondary bacterial infections during viral respiratory infection have not been fully elucidated, dysregulation of the immune system,[15,50,51] virus-mediated immunosuppression,[52] immune response alterations generated towards one pathogen,[53] and increased susceptibility of mammalian cells to bacterial attachment when infected by viruses[54,55] are some of the published consequences of viral infections that contribute to the development of secondary bacterial infections in affected individuals. However, coinfections with bacterial or fungal pathogens are considered unlikely to be common in patients with mild COVID-19 when compared with those with more severe disease upon hospital admission.[56]

Mechanical ventilation and prolonged hospitalization or ICU stay has been found to be the most common risk factor for bacterial or fungal superinfections, irrespective of COVID-19 disease.[57–59] This fact becomes important as studies from many countries have

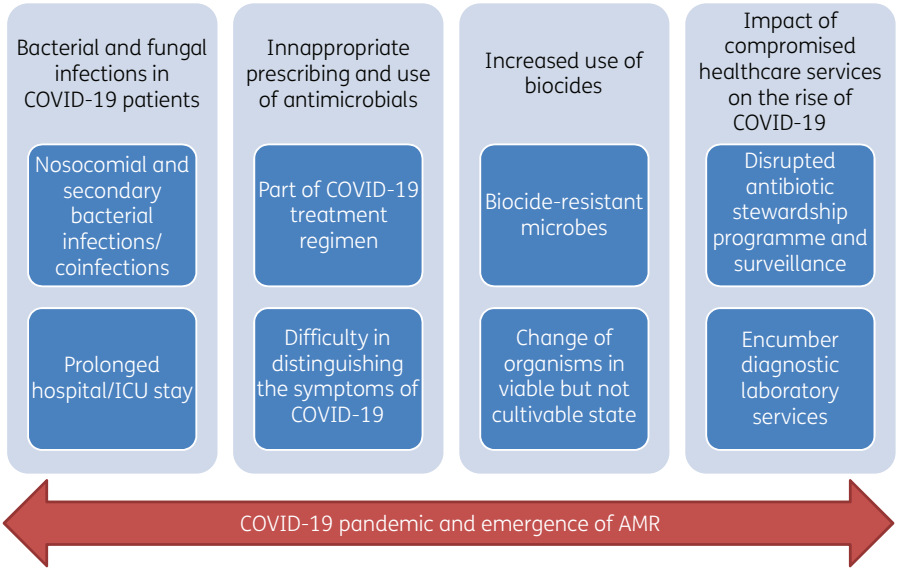


**Figure 2.** The most relevant predictors playing a role in the global development of AMR in the face of the worldwide COVID-19 pandemic.

shown the need for mechanical ventilation in 21%–88% of COVID-19 patients admitted to the ICU.[46,60–64] The development of secondary respiratory infection such as ventilator-associated pneumonia is also not surprising, as patients with severe COVID-19 have been reported to show the following: higher pro-inflammatory cytokine levels (e.g. interleukin-2, soluble interleukin-2 receptor, interleukin-6, tumour necrosis factor-alpha), higher levels of anti-inflammatory cytokines (e.g. interleukin-4, interleukin-10), lower CD4 and CD8 cell counts, and decreased expression of interferon-gamma by CD4 cells when compared with those experiencing moderate disease.[50,51,65] These changes in inflammatory response are likely to contribute to lung damage that may predispose patients to the abovementioned superinfections.

Initial studies found that 1%–10% of COVID-19 patients developed a secondary bacterial infection.[66] However, later studies from several hospitals in Wuhan, China, found that secondary bacterial or fungal infections occurred in 8.5%–42.2% and coinfections occurred in up to 45.4% of COVID-19 patients.[67] In a study conducted at two hospitals in New York City, the hospitals reported an associated bacteraemia in 6% of all COVID-19 patients, and in 12% of patients that were on mechanical ventilation.[63] Similarly, Zhou *et al.*[68] recruited 191 patients and reported secondary bacterial infections in 28 patients admitted to hospitals in China, with 27 out of 28 patients that developed secondary bacterial infections dying.

The respiratory system has been reported to be the most affected system associated with COVID-19 related secondary infections, e.g. bacterial and fungal pneumonia, especially ventilator-associated pneumonias.[69] Bloodstream and urinary tract infections appear to be less frequent. Most of the bacterial pathogens isolated were found to produce antibiotic-degrading enzymes such as carbapenemases and ESBLs, which confer resistance to the carbapenem and cephalosporin groups of antibiotics, respectively. Among pathogens causing secondary infections, the pandrug resistant (PDR) *A. baumannii*, carbapenemase- and ESBL-producing *K. pneumoniae*, ESBL-producing *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Serratia marcescens*, *Mycoplasma species* and *H. influenzae* were the bacterial pathogens most often observed, whereas *Aspergillus fumigatus*, *Aspergillus flavus*, *Candida albicans*, *Candida glabrata*, and *Candida auris* were the most common fungal pathogens reported.[17,60,67,70–73]

Although it is widely debated as to when a blood culture should be requested in patients with lower respiratory tract bacterial infections such as bacterial pneumonia, microbiological studies using sputum microscopy and culture, pleural effusion microscopy and culture, blood culture, urinary antigen tests and serology are all included in the management of bacterial pneumonia.[74] Blood culture reports offer additional information regarding whether an antibiotic treatment should be implemented or not. De-escalation of the antibiotic prescription in special cases plays an important role in decreasing AMR. However, among several studies conducted to evaluate secondary bacterial pneumonia in COVID-19 patients, only a few included blood culture processing.[67] Despite this fact, it has been widely recognized by the medical community that antibiotics have been overprescribed for the management of COVID-19 patients.

There is currently a paucity of data on the association between increased respiratory bacterial and/or fungal respiratory coinfections and the frequent use of broad-spectrum empirical antimicrobial medications in patients with COVID-19 infections. Data from such studies are required in order to generate scientific evidence to support the development of (inter)national antimicrobial stewardship practices and policies targeted to COVID-19 and future pandemic infections.[75]

## 2. Inappropriate prescribing and use of antimicrobials

Inappropriate prescribing and use of antimicrobials are the most common factors fuelling the development of AMR across the globe. It is estimated by experts that at least 50% of the antimicrobial medications currently used to treat infectious diseases

worldwide are unnecessary or inappropriate.[76] In this respect, the COVID-19 pandemic may be contributing to worsening the scope of AMR globally through the non-rational use of antibiotics as part of preventive and therapeutic management of COVID-19. In fact, repeated warnings have been raised about the role of the COVID-19 pandemic causing an increase in antimicrobial drug resistant bacteria which is an additional burden on already overwhelmed healthcare systems.[77,78] In this line, WHO released guidance discouraging the use of antibiotics in the treatment of patients with mild or moderate symptoms of COVID-19 unless indicated by established laboratory culture susceptibility testing protocols.[79]

In the face of the COVID-19 pandemic the tendency to prescribe antimicrobial medications by healthcare workers is very high. This is partly due to the difficulty in distinguishing the symptoms of COVID-19 from those of other respiratory diseases or even hospital-acquired or ventilator-associated pneumonia, particularly among hospitalized patients.[1,68,71,80] Several studies have observed a comparative increase in the use of antibiotics while treating COVID-19 patients, despite relatively low number of confirmed cases of secondary bacterial or fungal infection. For example, the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) reported that 62% of COVID-19 patients in their study had received antimicrobial therapy.[81] Other studies have also found widespread use of antibiotics (80%–100%) and antifungals (7.5%–15%) in critically ill COVID-19 patients admitted to ICUs in China.[15,16,61,70,71,82] Another study highlighted the administration of antibacterial therapy to 72% of COVID-19 patients even though only 8% of patients were confirmed to have bacterial or fungal infections.[83] In this respect, the most common antibiotics prescribed for empirical therapy in Chinese hospitals were fluoroquinolones, cephalosporins, carbapenems, azithromycin, vancomycin and linezolid.[46,61,70,71,84] However, the extensive and widespread use of antimicrobials to treat COVID-19 patients was also reported outside the Asian continent. A study conducted in France highlighted the use of antimicrobial medications for the treatment of COVID-19 patients, with the use of various combinations of meropenem, tigecycline, levofloxacin, aerosolized colistimethate, voriconazole and/or isavuconazole being reported.[72] In a meta-analysis of 154 studies (30 623 patients), Langford *et al.*[67] found a prevalence of antibiotic prescribing of 74.6% (95% CI 68.3%–80.0%). A Dutch retrospective observational study conducted in four hospitals also reported high prevalence of antimicrobial use (60.1%; range 33.3%–73.4%) in the absence of corresponding level of laboratory confirmed bacterial coinfection (1.2%).[85] One option to address this high level of non-rational antimicrobial use is to expedite the prompt and accurate diagnosis of viral/bacterial coinfection. For example, triage (based on clinical symptoms) combined with the measurement of inflammatory biomarkers such as C-reactive protein (CRP),[86,87] procalcitonin (PCT) or commercially available assays[88]—e.g. the FebriDx rapid test (Lumos Diagnostics, The Netherlands)[89]—could be more efficiently implemented. In 2020, Mason *et al.*[90] concluded that the absence of both elevated baseline white cell counts and antibiotic-related decrease in CRP in COVID-19 infections could help exclude bacterial coinfection. A recent systematic review and meta-analysis of 26 studies showed that the use of PCT to guide initiation and duration of antibiotic treatment reduces the risk of mortality, lowers antibiotic consumption and decreases the risk of antibiotic-related side effects.[91] A study conducted in England evaluated the usefulness of PCT in antimicrobial stewardship. The study reported reduced antibiotic consumption (without an increase in mortality) and a reduction in admission-related carbapenem prescribing for COVID-19 patients presenting with a negative PCT test.[92]

Undoubtedly, antimicrobial therapy is important in the management of suspected or confirmed cases of bacterial or fungal coinfections or secondary infections whether community-acquired or nosocomial infections.[93] However, determining the role of antibiotic treatment in the efficient management of COVID-19 patients still requires more evidence-based research.

### 3. Increased use of biocides

Significantly less is known about the mechanisms and extent of microbial resistance to biocides than is known about microbial resistance to antibiotics. In this respect, the word 'biocides' refers to compounds with antiseptic, disinfectant or preservative activity.[94] Due to the current COVID-19 pandemic, the use of biocides has hugely increased in private, community and hospital settings. Interestingly, improved hygiene practices involving biocides may actually reduce the transmission of antimicrobial-resistant pathogens that are found on our hands, but paradoxically may at the same time select for antimicrobial-resistant pathogens, thereby having an unknown impact on global AMR.[95–99] Additionally, the intensive use of surface disinfectants and household cleaners contribute to an increased concentration of these substances in wastewater treatment plants and receiving waters, altering the normal ecosystem and potentially favouring the emergence of AMR due to biocide-related selection pressure.[100,101] Moreover, in densely populated countries, where the use of disinfectants was mostly confined to the clinical/healthcare settings, the increased use of hand sanitizers and disinfectants might potentially impact on the human microbiome, which contributes to maintaining homeostasis in and on its host. According to the Scientific Advisory Board of the British Institute of Cleaning Sciences, the killing activity of alcohol-based sanitizers for SARS-CoV-2 has not yet been proven. The overuse of these sanitizers may assist alcohol-resistant organisms, in particular the spore-forming *Bacillus* spp. found on the hands, to escape and survive antibiotics, leading to creation of even more harmful resistant microbes.[102] Furthermore, the increased use of disinfectants may induce organisms to a viable but non-cultivable state, becoming undetectable using standard culture-based detection methods.[103,104] These conditions may alter the isolation and antimicrobial susceptibility patterns of microbial pathogens, potentially giving rise to new AMR traits.

In this context, evidence-based data are required to evaluate the impact of the intensive use of sanitizers during the COVID-19 pandemic on the selection and acquisition of AMR genes, as well as on the viability, detection and transmission of antimicrobial-resistant microorganisms in private, community, hospital and environmental situations. This approach should take into consideration a One Health approach and not just focus on hospital-based AMR.

### 4. The impact of compromised healthcare services on the rise of COVID-19

Regular surveillance and monitoring of AMR through antimicrobial stewardship has provided insights into some of the

key mechanisms associated with the increasing prevalence of antimicrobial-resistant organisms. In turn, this knowledge permits the development of targeted AMR guidelines and strategic plans to combat the further emergence and transmission of AMR.[105] Unfortunately however, the COVID-19 pandemic has disrupted healthcare services in many countries and potentially impacted on the microbiological diagnostic laboratory systems that conduct routine screening and surveillance for antibiotic-resistant organisms.[106] This disruption in services is further worsened by the excess pressure on the existing workforce and competing manpower needs. The impact of these changes on the maintenance of antimicrobial stewardship and antibiotic resistance monitoring programmes is likely to contribute to the further transmission of AMR in affected healthcare settings.[107] The impact of the COVID-19 pandemic in many hospitals, across the UK, was a reduction in antimicrobial stewardship activities, with 64% (61/95) of respondents reporting that COVID-19 had a negative impact on routine antimicrobial stewardship activities.[108] Further, the COVID-19 pandemic may interrupt the routine healthcare services associated with antimicrobial stewardship and infection control practices, including the isolation and treatment of patients infected/colonized with AMR bacteria, for example, patients infected with MDR TB or HIV.[75,109] Knock-on effects may also be experienced via the disruption of infectious disease vaccination programmes and services.[109] The use of technology may assist in reducing some of the difficulties being encountered by antimicrobial stewardship teams during the COVID 19 pandemic, as virtual meetings and ward rounds are increasingly being used in stewardship activities in the UK.[75]

## Opportunities for controlling AMR in the COVID-19 era (including in LMICs)

Although the emergence of AMR is a great challenge, the implementation of the following strategies could potentially help minimize the emergence of AMR during the COVID-19 pandemic era (Figure 3).

### *1. Antimicrobial stewardship*

To decrease the spread of AMR, it is necessary to discourage and curtail inappropriate prescribing and use of antimicrobials in COVID-19 patients with mild symptoms (see also sections 2 and 4 above). This is achievable through the application of properly articulated and carefully implemented hospital-wide antimicrobial stewardship programmes such as drug, dose, duration, de-escalation and diagnosis protocols.[110] In this respect, the most accurate antimicrobial (such as the antimicrobial with the narrowest spectrum), at the right dose adjusted for patient weight and assessed with its renal toxicity, should be prescribed by all clinicians. Likewise, the correct duration of antimicrobial prescribing (e.g. successful treatment within the shortest amount of time) is also the most important factor for effective antimicrobial stewardship programs.[110] The de-escalation of antimicrobial medication during the treatment of COVID-19 should not only be encouraged among clinicians/therapists, but medical personnel should also be regularly updated on this practice by AMR taskforces across the globe. The use of broad-spectrum antimicrobials and combination therapy are likely to be more prevalent among critically ill patients. However, it is necessary to carefully de-escalate the use of broad-spectrum antimicrobials and combination therapy in order to focus treatment towards using narrow-spectrum antimicrobials and monotherapy and minimize the emergence of AMR.[111,112] There is no sufficient evidence to favour the use of combination therapy over monotherapy for the management of ventilator-associated pneumonia. Moreover, combination therapy has apparently no beneficial effects in decreasing superinfections or the emergence of AMR in pathogens.[113–117] Additionally, lower rates of superinfections have been observed using monotherapy rather than combination antibiotic therapy.[118]

### *2. AMR awareness, perception and education campaigns*

Public and clinician awareness, perceptions and education are important interventions in promoting behavioural change towards the use of antibiotics in order to prevent AMR, also during periods of viral-related pandemics.[119] There should be continuous educational campaigns to educate healthcare workers and patients on the need for the appropriate prescribing and use of antimicrobial medications. Such campaigns targeting the general public and the healthcare workers have been organized and implemented using different approaches and methodologies, although mainly involving high-income countries.[120]

In most LMICs, lack of national policies and poor regulation of the distribution and use of antimicrobials means that many antibiotics can easily be purchased 'over the counter' without a prescription. Further, the relatively high rates of HIV infection, TB and malaria among patients of LMIC hospitals means that antibiotics may be intensively administered as a proactive preventive measure to try to avoid bacterial or fungal infections.[121–123] Also, in LMIC settings there may be poor levels of healthcare and limited antimicrobial stewardship programmes, which are often linked to lack of resources such as trained personnel and to under-equipped diagnostic laboratories.[124,125] Faced with the above-mentioned challenges, physicians may find it difficult to follow evidence-based antimicrobial prescribing practices,[126,127] the consequence of which may be higher AMR prevalence in affected LMIC settings.[128,129]

Sustained public awareness campaigns on the ineffectiveness of antibiotics to treat viral infections (including pandemic respiratory viruses, respiratory infections caused by 'common cold' viruses and viral diarrhoea) should be instigated and implemented in order to reduce unnecessary antimicrobial prescription, self-medication and potential unwanted side effects.[130,131] Medical professionals themselves also need to be educated about the non-rational use of antibiotics. For example, a randomized controlled trial conducted within primary care environments in 12 European countries recruited 1023 patients with acute cough syndrome—the result indicated no clear advantage of the use of amoxicillin over placebo.[132] For both public and medical professionals, scientific-based evidence is essential in the development of appropriate health educational campaigns.

### *3. Diagnostics and laboratory surveillance*

Diagnostic and laboratory surveillance systems are crucial components of the AMR mitigation response. Robust diagnostic and laboratory surveillance systems are needed to guide the accurate

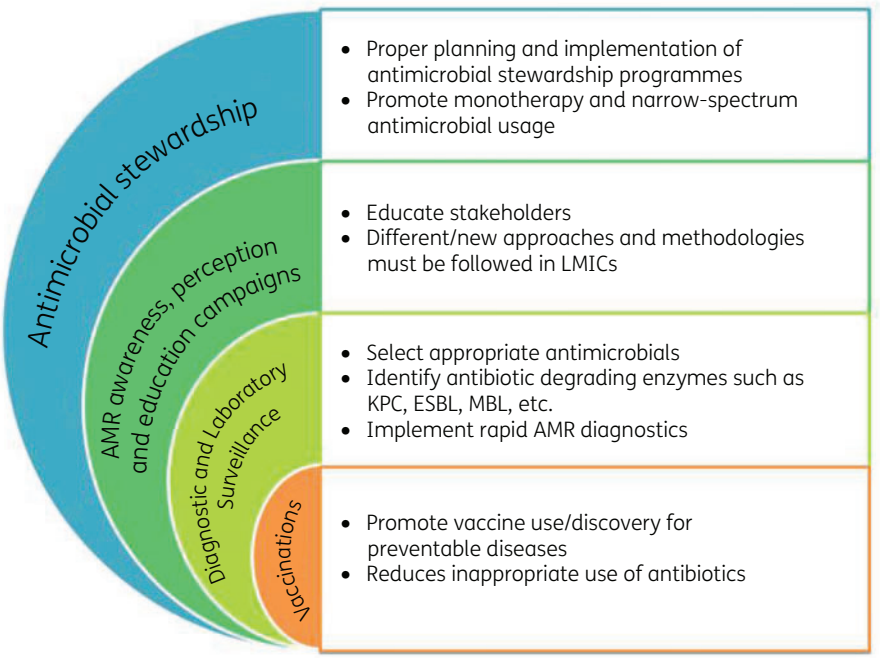


**Figure 3.** The key points to AMR control strategies in the age of COVID-19.

diagnosis of infectious diseases, ensure proper selection of antimicrobial medications (targeted therapy) and monitor the performance of antimicrobial stewardship programmes within the healthcare system. In order to attain the United Nations Sustainable Development Goals to achieve universal health coverage and access to quality healthcare, countries globally need to have access to diagnostics.[133] The CEO of the Foundation for Innovative Diagnostics (FIND), Catharina Boehme, describes comprehensive diagnostic services as a requirement to strengthen the function and efficiency of health systems.[134] The COVID-19 pandemic has served to highlight the lack of access to diagnostics in many LMICs; with research showing that LMICs have lower rates of COVID-19 testing per 100 000 of their population, compared with COVID-19 testing rates in higher-income countries.[135] The lack of diagnostics in LMICs in general is also apparent in the limited participation of LMICs in WHO's GLASS surveillance programme for monitoring AMR.[28]

Finally, the willingness of healthcare authorities to develop, fund and implement rapid diagnostic testing [including point-of-care (POC) testing] against COVID-19 should be matched by a concerted effort to develop, fund and implement rapid bacterial infectious disease and POC testing to combat AMR. This effort, can be augmented via the use of a 'mix and match' implementation package directed at the individual stakeholders involved in the development and use of rapid diagnostics.[136]

### 4. Vaccinations

One of the main focuses for stopping the spread of infectious diseases, including SARS-CoV-2 is vaccination. The use of vaccines (viral and bacterial) has a clear positive impact on global health, as mass vaccination helps reduce the prevalence of infectious diseases and subsequently the number of infections that are unnecessarily treated using antibiotics. Vaccination can have a major impact on the spread of AMR.[137] For example, several studies have found decreased incidence in antibiotic-resistant *S. pneumoniae* isolated from acute otitis media and acute bacterial rhinosinusitis since the introduction of 7-valent pneumococcal vaccine.[138,139] Other studies have found a reduced incidence of penicillin resistance in *S. pneumoniae* strains when collected before and after the use of a 7-valent pneumococcal vaccine.[140,141]

The successful implementation of vaccination against SARS-CoV-2 will help reduce the global prevalence of COVID-19 disease, thereby reducing the (inappropriate) use of antibiotics and potentially reducing the global burden of AMR. Additionally, there may be knock-on effects on the willingness of the public to accept vaccination even among 'anti-vaxers'.[142] For example, there is evidence to suggest that a high influenza vaccine uptake may lead to fewer COVID-19 deaths.[143] Also an increased acceptance of influenza vaccination is being reported with potentially fewer respiratory tract infections and (inappropriate) antibiotic use likely.[144] Currently more than 100 COVID-19 vaccines are at various stages of their development and several candidates have been approved for emergency use. Among the COVID-19 vaccines that have been approved, the adenovirus-vectored ChAdOx1 nCoV-19 vaccine (AZD1222)—which is a replication-deficient chimpanzee adenoviral vector (ChAdOx1) that contains the structural surface glycoprotein (spike protein) gene of SARS-CoV-2—showed an efficacy of 70.4% with an acceptable safety profile.[145] An mRNA-based vaccine, i.e. the Pfizer-BioNTech COVID-19 (mRNA-BNT162b2) vaccine (Pfizer Inc, Philadelphia, PA, USA)—which is a lipid nanoparticle based nucleoside-modified mRNA vaccine that encodes the pre-fusion spike glycoprotein of SARS-CoV-2—was approved for emergency use by FDA on 11 December 2020 and has been shown

to be 95% effective.[146,147] Another mRNA-based vaccine, mRNA-1273 (Moderna Inc., Cambridge, MA, USA)—which is a lipid nanoparticle-encapsulated mRNA-based vaccine encoding the pre-fusion stabilized full-length spike protein—has been found to be 94.1% effective in preventing COVID-19 related illnesses including severe disease.[148] Unfortunately however, it is not yet obvious what the effects of new COVID-19 variants (including the UK, Brazilian and South African variants) will be on the success of COVID-19 vaccination campaigns and ultimately on the development and spread of AMR.[149]

## Conclusions

WHO has placed AMR among the top 10 most urgent global health threats of the 21st century and provided advice on how to tackle the problem. However, the emergence of the COVID-19 pandemic has further complicated the current and future landscape of global AMR. To confront this issue, there is a need for global coordination, especially in developing relevant guidelines for the management of COVID-19 using diagnostics, novel antimicrobials, biocides and vaccines. In addition, continuing education of all stakeholders (healthcare workers, the general public and politicians) about the dangers associated with inappropriate use of antimicrobials and biocides should be made mandatory. The role of antimicrobial stewardship cannot be overemphasized; mechanisms should be instituted to commence stewardship programmes where lacking and made more functional when the implementation of such programmes is suboptimal. Finally, there is a need for LMICs to invest in diagnostics (including rapid and POC diagnostics) and to ensure vaccination of a significant proportion of their population within the shortest possible time frame.

### *AMR Insights Ambassador Network*

The first author and all co-authors are members of the Global AMR Insights Ambassador Network. The AMR Insights Ambassador Network consists of an integrated global and cross-professional community discussing, devising and driving actions to combat AMR. The Network aims to inspire, connect and empower the Ambassadors to take individual and collective actions to curb AMR. For more information about the Network: https://www.amr-insights.eu/about-us/ambassadors.

## Acknowledgements

We would like to express our sincere thanks to the following members of the Global AMR Insights Ambassador Network for supporting us in preparing this manuscript: Herman W. Barkema, Steffanie Strathdee, Emmanuel Benyeogor, Uzairue Leonard Ighodalo, Kurcheti Pani Prasad, Carlos M., Yoshiaki Gu, Sabiha Essack, Dilan de Silva, Akke Vellinga, Wagih Mommtaz Ghannam, Najib Auwal Tsoho, M. H. F. Sakeena, Rhoda Ilenwabor, Dhanuraj (Raj) Shetty, Arnold Ayebare, Zoumana Isaac Traore, Ola Henry, Amritanjali Kiran, Rhoda Ilenwabor, Luisa Fernanda Toro, Adil Smail, Anne Amulele, Luria Leslie Founou, Prathamesh S. Sawant, Esther Buregyeya, Enrique Castro-Sanchez, Javier Moreno-Morales, Mina Izadjoo, Andrea Gori, Debra Goff, Arielle Blocker, Giovanna Forte, Muhammad Farooq Tahir, Mathew Diggle, Dipanjan Chakraborty, Anita E. Asamoah and Humphrey Aberi.

## Funding

This study was supported by internal funding.

## Transparency declarations

None to declare.

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