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Antibiotics and Antimicrobial Resistance in the COVID-19 Era: Perspective from Resource-Limited Settings

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Perspective

Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings

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A B S T R A C T

The dissemination of COVID-19 around the globe has been followed by an increased consumption of antibiotics. This is related to the concern for bacterial superinfection in COVID-19 patients. The identification of bacterial pathogens is challenging in low and middle income countries (LMIC), as there are no readily-available and cost-effective clinical or biological markers that can effectively discriminate between bacterial and viral infections. Fortunately, faced with the threat of COVID-19 spread, there has been a growing awareness of the importance of antimicrobial stewardship programs, as well as infection prevention and control measures that could help reduce the microbial load and hence circulation of pathogens, with a reduction in dissemination of antimicrobial resistance. These measures should be improved particularly in developing countries. Studies need to be conducted to evaluate the worldwide evolution of antimicrobial resistance during the COVID-19 pandemic, because pathogens do not respect borders. This issue takes on even greater importance in developing countries, where data on resistance patterns are scarce, conditions for infectious pathogen transmission are optimal, and treatment resources are suboptimal.

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Antibiotics and antimicrobial resistance in the COVID-19 era

Increased antibiotic use leads to the emergence and dissemination of antimicrobial resistance (AMR), which is a major global health challenge. One of the main recommendations to combat this problem is to optimize antibiotic use by ensuring that the appropriate antibiotic is administered at the correct dose, for the correct duration, and in a manner that ensures the best outcome and limits side effects and AMR. These are, in fact, hallmarks of antimicrobial stewardship programs (Dryden et al., 2011). Nevertheless, since the beginning of the COVID-19 pandemic, there has been growing concern for a potential rise in AMR secondary to increased antibiotic prescription for COVID-19 patients (Rawson et al., 2020a). The aims of this article are to describe how this viral pandemic has caused increased antibiotic use and also the risk of increasing AMR, particularly in low and middle income countries (LMIC).

Antimicrobial resistance

AMR is a grave and pressing public health problem. It has been estimated that by 2050, AMR will be responsible for the death of 10 million people and, furthermore, will cost as much as US$ 100 trillion (O'Neill, 2016). The spectrum of resistance varies widely from region to region. For example, using data from the 2019 Global Antimicrobial Resistance and Use Surveillance System (GLASS), it can be seen that resistance to ciprofloxacin for urinary tract infections ranges from 8.4% to 92.9% for *Escherichia coli*, and from 4.1% to 79.4% for *Klebsiella pneumoniae* (World Health

Organization, 2020a). In high income countries (HIC), AMR is a serious challenge. In the US, 2.8 million antibiotic-resistant infections are reported each year, with more than 35 000 deaths (US Centers for Disease Control and Prevention (CDC), 2019). Estimating the extent of AMR in LMIC is hampered by limited data: AMR data are unavailable for 42.6% of countries in Africa (Tadesse et al., 2017).

Bacterial co-infection and COVID-19

A study conducted in January 2020 in an adult infectious disease unit in China, found that 71% of the patients hospitalized for COVID-19 had received antibiotics despite a confirmed bacterial co-infection rate of only 1% (Chen et al., 2020). Another study in two hospitals in China reported that 95% of COVID-19 patients had been placed on antibiotic regimens even though a secondary bacterial infection was only found in 15% of the patients (Zhou et al., 2020a). However, in a study in the UK, blood cultures in early 2020 were positive in 3.2% of cases during the first 5 days of admission, and beyond this, the rate increased to 6.1%. In respiratory samples, a pathogenic bacterium could be identified in 34.8% of cases (Hughes et al., 2020). all 19 patients had a bacterial infection: *Acinetobacter baumannii* for 90% and *Staphylococcus aureus* for 10% (Sharifipour et al., 2020). It appears, therefore, that the prevalence of bacterial infection may vary depending on the country in question and also on the time after the onset of symptoms at which the samples are obtained. It seems clear that decisions on antibiotic therapy must be informed by regional epidemiological trends and the specific circumstances of the patient treated.

The initial impression of high antibiotic consumption during this viral pandemic was influenced by early reports from Wuhan, China indicating that 50% of patients who died from COVID-19 had a secondary bacterial infection (Zhou et al., 2020a). This phenomenon is consistent with reviews of autopsy series and post-mortem cultures from the 1918 influenza pandemic, revealing that most victims had concurrent bacterial pneumonia (Morens et al., 2008). Some preliminary findings of studies focusing on co-infections in COVID-19 patients showed that the bacteria most frequently isolated from induced sputum and/or bronchoalveolar lavage from COVID-19 patients were *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*. This suggests a difference in the co-infecting pathogens of COVID-19 patients from those commonly observed in co-infected patients with influenza (e.g., Streptococcus pneumoniae, S. aureus, and Streptococcus pyogenes) (Lansbury et al. 2020). Growing evidence suggests, therefore, that antimicrobial stewardship measures specific for COVID-19 patients should be preferentially followed, rather than relying on existing empiric treatment guidelines for influenza patients with secondary bacterial infections.

However, in the face of this evolving pandemic, lessons can be drawn from previous severe outbreaks of coronavirus (severe acute respiratory syndrome coronavirus (SARS-CoV)) to inform antimicrobial management of secondary co-infections in COVID-19 patients, as well as infection prevention control measures based on AMR. For example, the term super-spreader has been used for settings like hospitals, cruise ships, etc.; i.e., for events where there is an important movement of the population leading to high rates of transmission (Cave, 2020). Past SARS-CoV outbreaks have shown that hospitalized patients with bacterial co-infections can be super-spreaders of resistant bacteria, each individual possibly infecting more than 10 other people (Wi et al., 2020). In the case of COVID-19, it has been demonstrated that 80% of contaminations are related to 20% of subjects. It remains unknown whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with the same pattern of spread of resistant bacteria

as SARS-CoV (Cave, 2020). Nonetheless, this is an important observation to keep in mind to reduce the risk of AMR infections and hospital transmission, particularly in LMIC where hospital infection prevention and control measures are often sub-optimal (Alp and Damani, 2015).

Challenges of bacterial identification in patients with pneumonia

As in the case of most infections, the initial choice of antibiotics in COVID-19 patients is often empiric (Huang et al., 2020). Huang et al. reported that while 98% of COVID-19 patients had bilateral lung involvement on chest X-ray, only 28% of patients had enough sputum production to perform a Gram stain or culture (Huang et al., 2020). This scarcity of sputum production in these patients is further complicated by the fact that the identification of pathogens from sputum samples in patients with pneumonia is overall modest and yields results in only 23% of cases (Saldías Peñafiel et al., 2018). Moreover, concerns about aerosol-generating procedures (i.e., deep airway suctioning or bronchoalveolar lavage) further limit the ability to obtain satisfactory sputum samples for bacterial identification and other microbiological studies (Van Doremalen et al., 2020). However, if personal protective equipment is adequate, the proscription of important diagnostics or therapeutic procedures should be reconsidered (Ağalar and Engin, 2020).

Synergy between viral and bacterial pathogens

Despite some preliminary evidence, it is still unclear whether similar synergies exist between SARS-CoV-2 and specific bacterial infections as exist with influenza (Rowe et al., 2019). It has been shown that respiratory viral infections may alter innate immune function in affected pulmonary tissue, promoting bacterial growth: macrophages are overwhelmed by this increased burden of apoptotic cells and thus become limited in their capacity to phagocytose bacteria (Morgan et al., 2018). It has also been observed that both dendritic cells and macrophages have diminished antigen-presenting ability following bacterial and viral infections, which is linked to an immunosuppressive microenvironment involving T (Treg) cells and the cytokine transforming growth factor beta (TGF-β) – a form of immunoparalysis (Roquilly et al., 2017). In addition, the initial immune response to a viral lung infection modifies the respiratory tract microbiome, which can, in turn, undermine immune defenses against infectious pathogens (Hanada et al., 2018). Other inciting mechanisms following viral illnesses include altered epithelial cells that disrupt the mucocilliary clearance and mucus thickening impairing the movement of immune cells (Manohar et al., 2020). In the particular setting of SARS-CoV-2 infection, fluid and pus-filled pulmonary alveoli create a nutritive environment for bacteria such as *P. aeruginosa* and *S. aureus* (Manohar et al., 2020) [Au?1].

If such synergy is proven, the administration of antibiotics would be useful and understandable. In fact, treatment with an antibiotic (azithromycin) and antimalarial (hydroxychloroquine) showed in vitro effectiveness against SARS-CoV-2 and these agents have been used (Andreani et al., 2020). However, although this combination therapy showed early promise, the results of subsequent clinical studies have been equivocal: some have found no beneficial effect (Magagnoli et al. 2020), while others have indicated that hydroxychloroquine yields a mortality reduction of 66%, rising to 71% when used in combination with azithromycin (Arshad et al., 2020). Furthermore, while some studies have found potential cardiac toxicity of hydroxychloroquine combined with azithromycin (Nguyen et al., 2020), others have found no report of torsade de pointes or fatal dysrhythmias, and have commented

that clinicians have seldom needed to discontinue therapy (Saleh et al., 2020). Currently there is no definitive evidence on the clinical benefits of chloroquine or hydroxychloroquine, while there is evidence of the potential harm (Tang et al., 2020).

Clinical trials are underway that may provide answers to the potential contribution of different therapies in the treatment of COVID-19. An example is the Solidarity Trial, an international study conducted by the World Health Organization (WHO), which is based on the principle of repurposing drugs previously used for other indications: remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon (Anon, 2020b) . Nevertheless, on October 15, 2020, the WHO published interim results of the Solidarity Trial, which showed that the four treatments evaluated had no benefit on overall mortality, the initiation of ventilation, or the duration of hospital stay in hospitalized patients (Anon, 2020c). The results from other clinical trials should help guide the choice of treatment and reduce the use of antibiotics and other drugs that have not been proven to be effective for COVID-19 patients.

Challenges of the choice of antibiotics for COVID-19 patients in LMIC

If the use of antibiotics to treat nosocomial bacterial co-infections is justified by the risk of requiring invasive mechanical ventilation (Rawson et al. 2020b), the paucity of ventilators in LMIC minimizes this risk and should therefore greatly reduce unnecessary antimicrobial use (Losonczy et al., 2019). However, even as short-term peripheral venous catheters can be associated with higher rates of bloodstream infections in LMIC than in HIC (Rosenthal et al. 2020), there is a risk that the increasing number of hospitalized patients with COVID-19 may lead to increased reliance on antibiotics to fight nosocomial catheter-associated infections. The implementation of infection prevention and control measures could help mediate this risk, as well as antimicrobial consumption (Phan et al., 2020). It would be revealing to conduct studies on bacterial co-infections in COVID-19 patients in LMIC, since previous studies have revealed that, for the same bacterial pathogens, differences exist between HIC and LMIC regarding populations at risk, clinical manifestations, frequency of pathogen distribution, and antibiotic susceptibility (Aston, 2017). The threat of COVID-19 may, in fact, offer opportunities in LMIC to implement antimicrobial stewardship programs in line with WHO guidelines: education and training of an antimicrobial stewardship team, development of clinical guidelines, surveillance of resistance and antibiotic use (World Health Organization, 2019).

Optimization of antibiotic use in COVID-19 patients from LMIC

LMIC might be more impacted by COVID-19-associated antibiotic resistance for a number of reasons, including reliance on empiric therapy due to the lack of clinical microbiology laboratory capacity, deficiencies in infection prevention and control measures, and systemic stress making the implementation of new practices more difficult. There are a number of possible strategies to reduce excessive antimicrobial use and the resultant antibiotic resistance. The straightforward strategy promoted by most ministries of health could limit antibiotic use: if you have a fever or symptoms similar to flu, stay at home, drink liquids, and take paracetamol. Aside from the obvious public health benefit of this approach, such behavior could reduce antibiotic consumption, since patients seeking care for acute respiratory illnesses may receive unnecessary antibiotics in 41% of cases (Havers et al., 2018). Rapid viral testing could also further reduce the unwarranted prescription of antibiotics in LMIC, as it has been shown that those who test positive for influenza are 50% less likely to receive antibiotics (Tillekeratne et al., 2015). Unfortunately, in developing

countries, antibiotics are often sold in the street without prescription, allowing people to purchase them with the intent of preventing or self-treating COVID-19 or other viral infections, leading to inappropriate use in the setting of non-bacterial infections.

As bacterial co-infection in COVID-19 patients may be less than 15% (Zhou et al., 2020b), it would be prudent to reserve antibiotics for patients with suspected or severe COVID-19 manifestations. Testing for COVID-19 in respiratory patients may therefore be an effective way to limit antibiotic use during the pandemic (Getahun et al., 2020). This approach is recommended by the WHO to combat the pandemic. However, this policy assumes that the country has the capacity to conduct testing and the means to enforce the isolation of infected patients.

Challenges of the traditional measures of the test and isolate strategy in LMIC

Mass viral testing and timely screening has proven challenging even for HIC, and it is even more so in LMIC ("Coronavirus Testing Labs Again Lack Key Supplies" – The New York Times). The fierce and unfair competition between LMIC and HIC for limited stocks of reagents and protective equipment has created additional disparities and barriers to implementing strategies to prevent spread, especially in LMICs ("In Scramble for Coronavirus Supplies, Rich Countries Push Poor Aside" – The New York Times"). In addition, fragile healthcare infrastructure in many limited resource countries makes it difficult to apply basic preventive measures such as inpatient hospital isolation. Isolation rooms are severely limited in 41% of hospitals in LMIC, thereby creating the risk of exposure for patients without COVID-19 (Alp et al., 2011). In addition, the crowded home environments found in LMIC make any attempt to isolate infected patients at home illusory ("Tracking Improvement in the Lives of Slum Dwellers" Prepared by the PSUP Team Nairobi. Printing: UNON, Publishing Services Section, Nairobi, ISO 14001:2004-certified D1 No: 15-02822/200 copies/jw). The inadequate resources for testing for COVID-19 and the limited capacity to isolate those infected raises the question of the practicality of adopting a mass testing strategy in developing countries.

In this case, it is important to develop alternative response strategies. Aggressive screening of suspected cases, contact-tracing, and the creation of emergency ad hoc isolation sites, etc., are very costly and complex undertakings requiring high levels of funding. Furthermore, contact-tracing is probably more useful at the beginning of an outbreak than later and can be very difficult to execute when there is a high number of daily community transmissions. However, these measures can be effective at limiting the number of people infected by SARS-CoV-2, and hence, possibly receiving unnecessary antibiotics. The development and validation of treatment algorithms incorporating clinical signs and possibly selected biological markers as well, could help clinicians decide on antibiotic use.

Discrimination between viral and bacterial co-infection to avoid unnecessary antibiotics

While the symptomology described in COVID-19 generally overlaps with other respiratory infectious diseases, some specific symptoms/signs described can be used to support the diagnosis of COVID-19 (e.g., anosmia). The presence of other clinical hallmarks such as fever, persistent cough, diarrhea, fatigue, abdominal pain, and loss of appetite can further support this diagnosis (Menni et al., 2020). While some common biomarkers, such as C-reactive protein (CRP) and procalcitonin, have not proven helpful at discriminating between patients presenting with COVID-19 and those with

additional bacterial co-infection, they provide some value in assessing disease severity, and could be useful for predicting the prognosis (Hu et al. 2020). Ongoing research is continuing to define the role of these tools in clinical decision-making (Rawson et al. 2020a; Lansbury et al., 2020).

Contribution of antimicrobial stewardship programs and infection prevention control to fight antimicrobial resistance in LMIC

The WHO has developed guidelines for the clinical management of COVID-19 that do not endorse the prescription of antibiotics for patients with suspected or confirmed mild COVID-19 with a low suspicion of a bacterial infection. However, for suspected or confirmed severe COVID-19, the use of empiric antimicrobials is recommended in order to treat all likely pathogens (Anon, 2020b). Finally, although there is not yet an optimal strategy for combating global COVID-19, providers in LMIC should try to establish and/or strengthen antimicrobial stewardship as well as infection prevention and control programs to reduce the emergence and dissemination of AMR (Septimus, 2018).

The type of antimicrobial stewardship program that will work will be very context-specific, but could include education about AMR, the development of guidelines, infection prevention and control guidelines, contributions from an infectious disease consultant at the hospital level, intravenous to oral switch therapy, rules and regulations for antibiotic quality control, upgraded microbiology laboratory capacity, the development of a national action plan, and the implementation of an infection prevention control program (Cox et al., 2017). The choice of measures to enact will depend greatly on local factors, such as available human and economic resources, and infrastructure. Whatever the choice, interventions must be evaluated to demonstrate improvement and also guide further decisions. Ultimately, the choice must have an impact on the real world of people living in the resource-constrained countries, because sometimes there is a gap between the development and implementation of public health policy and the actual benefits accruing to the population. Dialogue between researchers and policy-makers could help fill this gap. In this perspective, the scope of research undertaken, as well as the researchers themselves, must recognize the financial constraints and limitations in human resources, bureaucratic support, and infrastructure that political leaders and decisions-makers in LMIC face, and these realities should be integrated into their work and recommendations. It is also essential to evaluate the cultural environment in which the policies are being implemented. That is why it is very important to facilitate a transparent and honest dialogue between research, political, and executive teams (Cave, 2020).

Ultimately, the strategies discussed here could contribute to saving lives and reducing the economic costs of healthcare. In addition, an unanticipated but beneficial consequence of the COVID-19 pandemic is a heightened awareness about general infection prevention and control measures, such as hand hygiene, surface disinfection, and social distancing, which may help reduce the long-term dissemination of AMR. Finally, it is of the utmost importance in LMIC to continue to conduct studies on antimicrobial consumption and the prevalence of bacterial co-infection, with susceptibility profiles whenever possible, to follow the evolution of AMR in these countries during the COVID-19 pandemic. The results of these studies could help to define the best strategies to use in settings with limited laboratory capacity in order to choose rational empiric antimicrobial therapy.

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Ethical approval

This is a perspective article and no ethical approval was required.

Conflict of interest

None.

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