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Review article

COVID-19 and antibiotic resistance; parallel pandemics, different intercessions

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ABSTRACT

Coronavirus virus disease 2019 (COVID-19) is one of the challenges to the global public health. With COVID-19 impacts across all sectors, the most glaring one is its impact on antibiotic resistance, another silence pandemic. Antibiotic resistance is at a crossroads of becoming a major killer and the emergence of COVID-19 pandemic aggravate the threat, due to excessive and extensive use of antibiotics in the treatment package of COVID-19 despite being a viral pneumonia and for prophylaxis to prevent bacterial co-infection. Low bacterial co-infections were associated with COVID-19, but large antibiotics were employed, this challenged the principles of antibiotic stewardship, thus, further complicate the antibiotic stewardship guidelines. This review revolves to highlight the effect of COVID-19 pandemic and its impacts on bacterial co-infections as well as how it fuels the already existing silent pandemic; antibiotic resistance which is waiting to unleash its effect on public health and socioeconomic sectors. While there is increased focus on COVID-19 pandemic, the review urged that focus should not be taken off on antibiotic resistance.

Introduction

Coronavirus virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel virus originated in Wuhan region of China, 2019, is a member of family of virus, coronaviredea. It is enveloped virus with long strand RNA genome, with projections of glycoproteins, which aid in spread via large droplets-route [1,2]. The whole genome sequencing showed that the virus is significantly related to SARS-COV, an agent of SARS, which caused an outbreak in 2002 in south China and spread across the world. There are seven members of coronavirus family that infect humans in varying degree. Worthy to note, SARS-CoV, MERS-CoV and SARS-CoV-2 are associated with severe disease than other members such as HKU1, NL63, OC43 and 229E [1,3]. These viruses are distributed among humans, mammals, birds and other animals, thus a potential spilled over of diseases is possible between these species [4].

COVID-19 pandemic has dramatically changed the world across many sectors, from health to socioeconomic, making it one of emergencies of recent history. The COVID-19 led to total shut down of world's travels, aviation, economic activities as well as social interactions and tourism. The total economic burden is difficult to be estimated across the globe, especially in low and middle income (LMICs) countries with defective surveillance system [5]. An important sector that the pandemic unleashed significant effect is public health causing multidimensional crisis. The pandemic became no respecter of borders and

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health systems of the countries, as even developed nations with effective healthcare systems were challenged and burdened by the rapid spread of the infection as well as late respond of countries due to underestimation and political will that encircled the outbreaks [5,6].

This multisystemic viral infection has no definative treatment or vaccines currently, however, billions of dollars have been injected into the research and development (R&D) of drugs and vaccines across the globe. The therapeutic drugs and vaccines candidates are at different stages, funded by governments and other partners coordinated by the World Health Organizations (WHO) under its Solidarity trials to finding treatment of COVID-19 [7]. However, to achieve this feat, it will take longer than expected while the virus continues to ravage the world in an unprecedented manner. In fact, at some point it became a burning issue where experts tend to skip or hasten standard protocol in the discovery of the candidate drug or vaccine, thusbrought concern of safety issue of any potential agent in this time [8]. As ealier affirmed by studies [9-11] the time-lag from initial potential candidate drug to final product through policy to clinic, that would be an avarage of a decade, however, **Hannery et al.** [8] argued that the timeframe can be holistically reduced to accelarate development of therapeutic agents or vaccine for SARS-COV-2, a novel coronavrius. The authors suggested massive increase in resources to fast track development of therapeutic agents and reduced delay in R&D, moreover, available resources mean parallel research could be conducted at evidence-based interphase. Furthermore, the study suggested a way which might not be accepted by the scientistworking at risk of safety and finance, for example shorten time interval of Phase I-III trials of drug development as seen in development of HIV/AIDS drugs [8,12,13]. In the quest for finding treatment for the pandemic, and the uncertainty surrounding the clinical outcome, necessitate the use of antibiotics in the treatment package, however, this tend to speeds up occurrence of another pandemic; antibiotic resistance.

Here, we review the impact of COVID-19 on emergence of antibiotic resistance, bacterial infections associated with COVID-19, the likely implications of COVID- 19 pandemic on antibiotic resistance interventions and antibiotic stewardship which is being ignored in the times of COVID-19 times.

It is evidenced that the emergence of COVID-19, the world focuses on finding a therapeutic candidate and vaccine for the SARS-COV-2 in effort to mitigate the COVID-19 pandemic, however, these efforts tend to affect other health care interventions. Of great concern is antimicrobial resistance, an area believed to have fuel the emergence of infections caused by antibiotic resistant bacteria, in short and long term run. With millions of confirmed COVID-19 infections, significant number are hospitalized and requiring treament of the symptoms, however, there are reports of wide spread applications of antibiotics in the treatment package of COVID-19, eventhough there is no evidence that some of the patients needing them [14-17]. While the former receiving so much attention, the later is off the radar, largely ignoring antibiotic stewarship approaches to ensure that antibiotics are judiciously used. Interestingly, increased application of emperical broad spectrum antibiotics was reported in countries that were hit most by COVID-19. Forinstance, study conducted in Catalonian region of Spain reported significant increased of antibiotic usage at the peak of confirmed cases of COVID-19 compared to the previous year [17]. In USA, another country with high infection with COVID-19, study confirmed early antibiotic therapy to over half of 17,000 hospitalized patients in Michigan, with only 3.5% (59/1705) reported to have bacterial coinfection [18]. Similar pattern was reported elsewhere, In Wuhan, the epidcentre of the pandemic, almost all hospitalized pateints were given antibiotics, this was due to clinical uncertainty of the hospitalized patients and wether they have community-acquired bacterial infections [19]. Across the globe, increased use of antibiotics in times of COVID-19 pandemic was reported, a study from Asia showed significant increased upto 70% of patients received antibiotics despite that only less than 10% of the patients has bacterial co-infection [16], in Africa, a region where excessive use of antibiotics has been a norm, the emergence of the COVID-19 only aggravated further the situation [20]. It is interesting to note that, the bacterial co-infections associated with COVID-19 is minimal, thus, use of antibiotics in the treament package is unnecessary. It is established that excessive use of antibiotics in both clinical and community settings due to emergence of new

infectious diseases and resurgence of many, fumes the emergence of antibiotic resistance.

Regardless of the emergence of COVID-19, global use of antibiotics have significantly increased, a report of antibiotics consumption in 76 countries covering span of 15 years (2000-2015) shows the increase of 65% on daily basis, this account for increase in consumption rate of about 39% in recent years [21]. Furthermore, **Klein et al.** [21] projected the increase in antibiotic consumption worldwide in a decade to come, provided the present parameters used remain constants, which is correlated with population growth. Interestingly, this coincided with the recent projection of worldwide increase of deaths due to infections with antibiotic resistant bacteria; these studies further revealed that COVID-19 pandemic may perhaps result in a serious disruption to the gains at tackling antibiotic resistance threat [22,23]. With the present challenge of the use of antibiotics in COVID-19, this scenario could only get to worrying level to the global public health. The use of the antibiotics in the treatment of COVID-19 has weakened antibiotic stewardship even in developed nations with strict adherence of guidelines and could be at devastating level at low and middle income countries with weak stewardships adherence, as it is previously projected that the antibiotic consumptions in those countries may increase by 200% in 2030 [20,21]. With the recent increase in antibiotics use for COVID-19 treatment, the estimations of antibiotic resistance machinery could substantially increase in short period of time.

Apart from the documented reports of antibiotic use in LMICs, there is widespread access to watch and reserved antibiotics which have drastically increased in recent times, agents that ought to be used for life-threatening conditions are now employed in common infections [24]. In a systematic review which described the global access to antibiotics without prescription across 24 countries, found that 62% of countries mostly in South America freely have access, this trend could be similar in most African countries where antibiotics regardless of the classifications are found on street vendors [25]. This easy supply of antibiotics in many countries could lead to overuse and fuel the emergence of antibiotic resistance especially in times of pandemic like this, with uncertainty in treatment protocols.

Conversely, antibiotic resistance as a pandemic has not been receiving serious attention as COVID-19 despite posing substantial burden to the global health sector. Unlike COVID-19 that is caused by single virus, antibiotic resistance is emerging in vast array of bacterial pathogens. Research and development of new antibiotics has been on slow pace and lack of interest in pharmaceutical industries and partners in investing for the discovery of new class of antibiotics has been a glaring challenge pushing the world to the post-antibiotic era. It is established that the global antibiotics consumptions have skyrocketed and the association with the rise in antibiotic resistance, however, there is slow discovery of new antibiotics to tackle the threat, putting the global public health in a danger [26,27]. Since the birth of penicillin that marked the golden era of antibiotics in the early 1940s, few antibiotics have been introduced after the roaring period of antibiotic manufacturing in 1960s and currently there are very few new antibiotics in the pipeline of development [28]. In fact, only limited classes have been traded in the last two decades and few are in the pipeline of development, yet resistant bacteria are at exponential growth pace. The lack of new class of antibiotics is compounded by decrease in number of pharmaceutical industries that are involved in antibiotic discovery and lack of funding that can match with the rise in antibiotic resistance [29]. With these challenges and steep regulation in approving new agents by the regulatory agencies has led to increase cost of discovery of antibiotics, hence most industries counted lost.

The key antibiotic widely used in the course of COVID-19 treatment is azithromycin, other macrolide, and ceftriaxone in combination with hydroxychloroquine, with little evidence to support the argument of their activity against SARS-COV-2 [30,31]. The rationale use of antibiotic prophylaxis is to tame secondary bacterial infection induced by the viral infection. However, this treatment package is not recommended by WHO for prophylaxis and in mild to moderate COVID-19, unless confirm case of bacterial infection indicated. Recent study confirmed the earlier skepticism of the claim of azithromycin activity on COVID-19 treatment, because there was no clinical improvement [31]. Therefore, it is argued that the number involved in clinical trials and relying on previous data on activity of azithromycin on some viruses such as Ebola, Zika, H1N1, rhinovirus and respiratory syncytial virus is not enough to incorporate

antibiotic in the treatment process [32]. The debate surrounding whether azithromycin show antiviral activity has substantially increase the pressure on use of antibiotic in the treatment of COVID-19, thus, more employing antibiotics, more facilitating selection pressure for antibiotic resistance. While COVID-19 swept the world and receiving serious intervention, on contrary, antibiotic resistance as a slow-burning pandemic with a potential to cause more deaths in near future, if not tackled, is largely ignored. This complex scenario may worsen due to difference among countries on the guidelines of when to start application of antibiotic to treat suspected bacterial co-infection associated with confirmed COVID-19 patients, hence standard recommendation is not abided.

COVID-19 and bacterial co-infections

Microbial infection associated with COVID-19 is possible, and it complicates the management of COVID-19, thus aid the progression of SARS-COV-2 infections and result to mortality. The uncertainly on co-infections associated with COVID-19 have tremendously affected the treatment of this global health challenge. Among the critically ill patients, bacterial co-infection is reported to be more common than other microbial co-infection. Co-infection in SARS-COV-2 infection was reported to be mild; however, this may expose patients to severe disease conditions due to the combined effects of the microbial pathogens and their ability to overcome host immunity that lead to disease progression [33].

Early data revealed that COVID-19 associated with either fungal, other viruses or bacterial co-infection is minimal in hospitalized patients while higher among those that succumbed to the virus. Several studies reported low rate of bacterial co-infection associated with COVID-19 ranging from 3.5 to 10% contracted secondary bacterial infections; conversely, the amount of broad-spectrum antibiotic use is unprecedented ranging from 65-90% of confirmed COVID-19 cases [33,34]. Worthy to note, bacterial co-infection upon admission tend to be low than bacterial secondary co-infection in confirmed COVID-19 cases. There are studies which investigated the association of other microorganisms due to infection with SARS-CoV-2 [35-37]. In a study by **Guet et al.** [37], it was observed that gastrointestinal disorder caused by SARS-COV-2 may affect the gut microbiota, by increasing the number of opportunistic pathogens such as *Actinomyces*, *Streptococcus spp*, *Veillonella* and subsequently facilitate bacterial opportunistic infection. This impact, in turn would affect the abundance of the beneficial microbes in guts such as *Bifidobacterium* and *Collinsella*. The situations of COVID-19 coupled with bacterial superinfection may have a significant increase on the severity of the infections and rise in mortality. Previous studies also reported bacterial co-infection in respiratory viral infection as most common [38,39]. In SARS-CoV-2 infection, up to 20% of positive case reported bacterial co-infection, with Gram negative bacilli ranked highest among the vast microbial pathogens [38]. This scenario might confirm the initial report of more bacterial co-infection in SARS-CoV-2. For instance, in a particular study, a total of 221 patients comprising of 55 severe cases of COVID-19 and 166 non-severe, overall result indicated that bacterial co-infection was higher than fungal co-infection, 7.7% and 3.2% respectively [39].

In a similar trend, early co-occurring bacterial infection in COVID-19 patients was investigated in Lyon, France; early bacterial co-infection was found to be 27.7% (13/47) among the subjects recruited for the study [40]. Like the previous study, the common bacterial pathogens were *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa and Haemophilus infuenzae* [37,40]. Another set of important pathogens reported in COVID-19 patients include *Escherichia coli* and *Enterococcus spp* and they are known to have multidrug resistance patterns [41].

The presence of multi-pathogens co-infections may be explained due to immune status interference by the COVID-19 which expose patients to secondary bacterial infections. This background could allow early antibiotic treatment, however, confirmed culture report is needed to avoid unnecessary empiric broad spectrum antibiotic treatments. In a living meta-analysis and rapid systemic review by **Langford et al.** [42], acute bacterial co-infection was reported to be 3.5% of the 3338 patients with COVID-19 while secondary bacterial co-infection was found to be 14.3% of the patients; the proportion of patients received antibiotic treatment was 71.8% in 24 studies included. With these data, the prevalence of bacterial co-infections is indicated to be low, and some of the patients may not require broad

spectrum antibiotic treatment such as fluoroquinolones and third generation cephalosporins. This reflects similar data on bacterial co-infections in similar study [43] and in relation with other viral respiratory infections reported previously [44].

In immunological context, increase in proinflammatory cytokines such as IL-6, IL-12 and TNF-α was observed, and this may contribute to the mortality rate by two-fold in COVID-19 patients [45]. The complex microbial interactions may provoke complex immunological response, especially the roles of lymphocytes such as B Cells, T cells and NK cells, this in turn can impair the immune functions and increase host susceptibility to opportunistic infections and increase the severity of the disease and this may lead to receiving invasive procedure in severely ill COVID-19 patients and more chance of secondary bacterial infections [45,46]. Understanding the immune response to SARS-CoV-2 infections is significant in determining degree progression and possibility of co-infection [47]. **Shi et al.** [47] alarmed that cytokine storm and subsequent lung damage are as the result of immune response to the virus, thus leading to the severe life-threatening condition.

The degree of clinical status is important factor in determining use of antibiotic treatment, because there is high possibility of bacterial infection in critically ill patients. However, this guiding principle is overlooked, and extensive antibiotic treatment is deployed. Given that the available data show that the bacterial mixed infection with COVID-19 is direct opposite to the extensive and excessive antibiotic use in the treatment is a cause for concern, with already high use of antibiotics, this will have future impact on the emergence of antibiotic resistance. In an evidence-based guideline for antibiotic therapy for COVID-19 patients, **Sieswerda et al.** [48] recommend that restrictive antibiotic use should be apply especially to early presenters during admission and to be decided by the outcome of sputum and blood for confirmation of bacterial co-infections. The authors suggest discontinuing use of antibiotics treatment when cultures show no sign of bacterial pathogens after 48 hours. This would go a long way in minimizing antibiotic use in COVID-19 patients. Furthermore, the study recommended that five days antibiotic regimen should be employed for suspected secondary bacterial respiratory infection [48].

Antibiotic stewardship in the times of COVID-19 pandemic

Steep antibiotic applications during this pandemic interfere with antibiotic stewardship, as global antibiotic prescriptions increase among hospitalized patients, in some cases even among not critically ill patients. From the evaluations of the studies, bacterial co-infections are less but high use of broad spectrum is applied, hence, strong antibiotic stewardship principles should be re-enforced by assessing the presence of bacterial co-infections before commencement of antibiotic treatments. **Sieswerda et al.** [48] consider immune status to a guiding principle in employing empiric antibiotic treatment in COVID-19 case; in this case, patients with already dilapidated immune systems such as those on cancer chemotherapy, HIV/AIDS patients or those on prolonged use of immunosuppressive drugs can be placed on empiric antibiotic therapy while waiting for laboratory results. Overall, the authors suggest that empirical broad spectrum for appropriate de-escalation in COVID-19 patients, in order to reduce unnecessary antibiotic use as much as possible and further recommend the need for updating the guidelines regularly as new evidence data on bacterial co-infection, secondary infections and general COVID-19 treatment package emerged.

The implementation of antibiotic stewardship during COVID-19 is necessary in mitigating the exacerbation of antibiotic resistance. A study on the impact of COVID-19 on antibiotic stewardship in emergency unit shows the need for improving stewardship in prescription of antibiotics in emergency department (ED) of hospitals [49]. Initial data reveal that there is increase in antibiotic use in ED and this may breach the traditional stewardship principles due to condition of the patient presented, coupling with time pressure and diagnostic uncertainty [49]. Overall, the overuse of antibiotics in ED has been complicated in times of COVID-19 pandemic due to lack of established guidelines in most cases, and early presentations of COVID-19 resemble other acute respiratory conditions which allow use of antibiotics.

Regardless of the hospital units, antibiotic stewardship is been challenged by COVID-19 pandemic. Mitigation of antibiotic overuse should not be overlooked while treating bacterial infection associated with COVID-19. The proportion of antibiotic consumption in ICU is huge, as most patients are expected to be vulnerable to bacterial

co-infection; however, available data has shown that bacterial co-infection in COVID-19 patients is less than other viral pneumonia like the case of influenza [43]. Therefore, it is important to be conscious of empirical antibiotic use while been alert to microbial co-infections in hospitalized patients. While it is challenging in practice to distinguished on initial presentation of early-stage COVID-19 and bacterial infection acquired in community, and on disease progression of COVID-19 such as presentation of hyperinflammatory condition, which is being confused with secondary bacterial infection, the use of biomarkers such as procalcitonin (PCT) and C-reactive proteins (CRP) levels is suggested for the diagnosis of bacteria causing lower respiratory infections[50]. On a study to suggest biomarkers for antibiotic use for COVID-19, PCT and CRP levels were used as predictive measures for possible bacterial co-infection. It is observed that CRP levels tend to increase while PCT often low in COVID-19 patients on presentation [50]. The authors though have reservations on the clarity of these biomarkers, the levels of both PCT and CRP decreased in patients without secondary bacterial infections, conversely significant increase in levels of both PCT and CRP were reported in patients with secondary bacterial infections [50]. Therefore, these variables can be used in COVID-19 patients in ICU as clues to when to start empirical antibiotic therapy with a suggestion of further research to standardize the predictive values with the aim of judicious use of antibiotics in the treatment of COVID-19.

Across the globe, there has been call on antimicrobial stewardship among COVID-19 patients, as they are given antibiotics unnecessarily. In a cohort study in Korea, of the 6871 subjects hospitalized with COVID-19, 35.21% (2419/6871) were given antibiotics, which suggest high deployment of antibiotic use considering large number of the patients 86.28% (5928/6871) had mild to moderate case of COVID-19 cases [51]. Even before the advent of COVID-19, high use of antibiotics is reported in LMICs, with little or no antibiotic stewardship enforcement. Thus, the emergence of COVID-19 pandemic is expected to increase significantly despite low cases of COVID-19 in some of the countries. For example, in African context, indiscriminate use of antibiotics is used for the treatment and prophylactic purpose of possible bacterial co-infection in COVID-19 cases for longer duration due to delay in bacterial culture results from patients, in fact, some were given antibiotics without confirmation of microbiological results [52]. Data available from Asia, on the dangers of COVID-19 poses on antibiotic stewardship program has shown that more than 70% of patients received antimicrobial treatment despite less than 10% developed microbial co-infections [16]. It is evident that use of antibiotics surge in the era of COVID-19 pandemic and this could affect antibiotic stewardship and could lead to another pandemic, antibiotic resistance.

Conclusion

In summary, emergence of novel infectious disease could affect global health sector, and COVID-19 pandemic is no different. The rapid spread of the virus and with definitive treatment and overlapping of the symptoms made the management of the disease a difficult one. In the light of that, excessive antibiotics use in the treatment package was reported across the globe, despite no clinical evidence of clinical outcomes and less bacterial co-infection in confirmed cases of COVID-19 patients. The key driver of antibiotic resistance is overuse of antibiotics, which could further fuel the antibiotic resistance by impacting on the antibiotic stewardship. Since no one side solution to this global health issues; COVID-19 pandemics and antibiotic resistance, there is need for standard antibiotic guideline in the treatment package of COVID-19 with clear evidence of bacterial co-infection. Further methods of infection control methods in both hospital and community should be re-enforced through surveillance and public enlightenment. Extensive epidemiological studies need to be conducted to assess and profile bacterial co-infection in COVID-19 patients so that antibiotics would not be given when not needed.

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All authors declare no conflicts of interest in this paper

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AD conceived the idea of the review and written the first draft of the manuscript. JN and TI critically revise the manuscript and added valuable contents. All the authors reviewed the final version of the manuscript and agreed to its submission.

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