An Algorithm-Based Computational Method for Overcoming Worldwide Antimicrobial Resistance Exacerbation in COVID-19 Pandemic Era

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Abstract

The use of antibiotics in COVID-19 pandemic era will inevitably exacerbate antimicrobial resistance (AMR) and could ultimately lead to more deaths and morbidity as an unintended consequence of this long-term pandemic. Although AMR was already spreading rapidly before the emergence of COVID-19, the impact of the pandemic may be more pronounced. The wider implications of the pandemic for health and social care systems must be characterized and these data must be gathered to inform and update national strategies that address the long-term challenges of AMR while preserving access to effective drugs. Thus, world needs such level of dedication to reverse the trajectory of AMR by ensuring that research continues to develop antimicrobial drug pipeline, sustainable investment in health systems, and strengthening of antimicrobial stewardship.

Keywords: Antibiotics, COVID-19 Pandemic, Antimicrobial Resistance (AMR), Multi-Drug Resistant (MDR), Health Systems, Antimicrobial Stewardship

Abbreviation: Coronavirus Disease-19 (COVID-19); Antimicrobial Resistance (AMR); Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2); Multi-Drug Resistant (MDR); Chronic Obstructive Pulmonary Disease (COPD); Antimicrobial Stewardship (AMS); Angiotensin-Convert- ing Enzyme (ACE); Acute Respiratory Distress Syndrome (ARDS); Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV); Quantum Universal Exchange Language (Q-UEL).

Introduction

COVID-19 pandemic has changed the focus of healthcare around the globe and antibiotics may be indicated in patients with COVID-19 due to suspected or confirmed bacterial superinfection [1-3]. Many studies reporting on patients hospitalized with COVID-19 have been revealed widespread use of antimicrobial therapies as part of the package of clinical care in some countries [4-7]. Although antibiotic treatment of secondary bacterial pneumonia associated with influenza is accepted clinical practice, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not influenza. In patients with COVID-19 who have co-infections, antibiotic or antiviral treatment is appropriate but those patients may be in a minority. Before the SARS-CoV-2 pandemic, overcoming antimicrobial resistance (AMR) already demanded urgent global action. Now that we are in the midst of a pan- demic, understanding the pathogenesis of SARS-CoV-2 infection, and the potential for bacterial co-infections, is imperative. Until then, efforts to prioritize antibiotic

stewardship around the world must be redoubled for potential long-term impact on antimicrobial resistance. The COVID-19 has placed huge strains on health and social care systems and resources globally. It is important to con- sider the short and longer-term consequences that COVID-19 may have on antimicrobial use and drug-resistant infections. A concerning potential consequence of the COVID-19 pandemic is the long-term propagation of AMR in the acute care setting, resulting from increased patient exposure to antimicrobials, often sub-optimally or inappropriately used [8,9]. However, the simultaneous disruption of routine care and access to health care in acute and community settings for the non- COVID-19 population could potentially reduce the overall use of antimicrobials. The wider implications of the pandemic for health and social care systems must be characterized, and data must be gathered to inform and update national strategies that address the long-term challenges of AMR while preserving access to effective drugs. The emergence of SARS-CoV-2 has required an un- precedented response to control the spread of the infection and protect the most vulnerable within society. Whilst the pandemic has focused society on the threat of emerging infections and hand hygiene, certain infection control and antimicrobial stewardship policies may have to be relaxed. It is unclear whether the unintended consequences of these changes will have a net-positive or -negative impact on rates of antimicrobial resistance. Furthermore, the urgent focus must be on controlling this pandemic and sustained efforts to address the longer-term global threat of antimicrobial resistance should not be overlooked. Antimicrobials have several roles during the pandemic at the individual and organizational impact. Agents are being explored in clinical trials as potential direct therapies for SARS-CoV-2 such as azithromycin and antivirals such as lopinavir [10,11] and ritonavir [10,11], and remdesivir [12]. Antimicrobials are commonly prescribed for the management of presumptive or confirmed bacterial co-infection directly related to COVID-19, co-occurring at the time of infection, or associated with health care, such as prolonged admission to critical care. Combined with a lack of rapid diagnostic and decision support tools to support the clinical management of COVID-19, increased unnecessary antimicrobial use occurs [13-15]. Direct risks to the patient include side effects and adverse drug events. Increases in unnecessary antimicrobial use potentiates future risk of AMR through driving selection of multi-drug resistant (MDR) organisms and car-bapenemase producing Enterobacteriaceae [16,17]. Meanwhile, the impact of the pandemic on antimicrobial prescribing and AMR in the community remains largely unknown. Sustained public campaigns on the role of antibiotics in viral infections as well as the increased use of telemedicine may also reduce antimicrobial prescribing and AMR, but this is yet to be described [18]. In addition to the service changes, some routine infection control practices may have been compromised, including isolation of patients with MDR organisms as well as the redeployment of diagnostics to focus on SARS-CoV-2

in place of routine screening and surveillance for resistant bacteria, other respiratory viruses and healthcare-associated infections. However, emphasis on the role of hand hygiene may reduce transmission of AMR and diseases that would drive antibiotic use [3]. Moreover, the pressure on finite resources, such as medications (including antimicrobials) and high volume needs such as personal protective equipment for patients with COVID-19 may deplete availability of resources for the prevention and management of other infectious diseases. Following the initial global surge in COVID-19 cases, further surges are expected until control measures, such as vaccination, are introduced.

Methods

This study was performed following WHO guidelines using an online tool for evidence synthesis and was conducted to identify common bacterial/fungal co-infections reported in patients diagnosed with coronavirus infections since January 1st 2020. The MEDLINE and EMBASE databases were searched from 1st January 2020 to 2nd October 2020 using a combination of broad-based (and wildcard) search criteria including, coronavirus, COVID-19, SARS-1, MERS, bacterial, co-infection, antibiotics, AMR, MDR. Given the rapidly evolving nature of the literature on SARS-COV-2, journal advanced articles in leading infection journals and bibliographies of relevant articles were also reviewed. Covidence review gets out of the way so that we can bring the best evidence to the world, more quickly.

Results

Ongoing antimicrobial stewardship for co-infection and antimicrobial usage

We strongly believe co-infections play a significant role during COVID-19. Chronic obstructive pulmonary disease (COPD) is one of comorbidities associated with severe COVID-19. COPD patients are colonized by bacterial pathogens even at the stable phase of the disease, making it likely that SARS- CoV-2 infection occurs in patients already colonized with bacteria. Secondly, the very likely possibility exists that severe COVID-19 patients could be subsequently or co-incidentally infected by bacteria. The median hospital stage of COVID-19 patients is 7 days but can reach up to 14 days or even longer, and the risk of a hospital-associated pneumonia increases significantly the longer the hospitalization period. As shown in Figure 1, SARS-CoV-2 virulence factors interact with the lungs and evoke an immune response. Co-infection may result in an exuberant inflammatory response. It is also plausible that the type of immune response induced by SARS-CoV-2 may enable bacteria to flourish in the lungs. On the other hand, bacterial colonization may predispose to SARS-CoV-2 infection because the innate immune host defenses may be down-regulated enabling virus survival, growth and pathology. Co-infection may exacerbate the tissue damage; and the exuberant inflammatory response may

further amplify the lung damage triggered by SARS-CoV-2. Addition to it, we demonstrate that NHC potently inhibits the divergent -CoVs MHV and MERS-CoV [19]. These data are consistent with a mode of action, as evidenced by a decrease in specific infectivity and an increase in G: A and C: U transition mutations present at low frequencies across the genome after treatment with NHC. We also demonstrate that robust resistance to NHC is difficult to achieve in both MHV and MERS-CoV as shown in Figure 2.
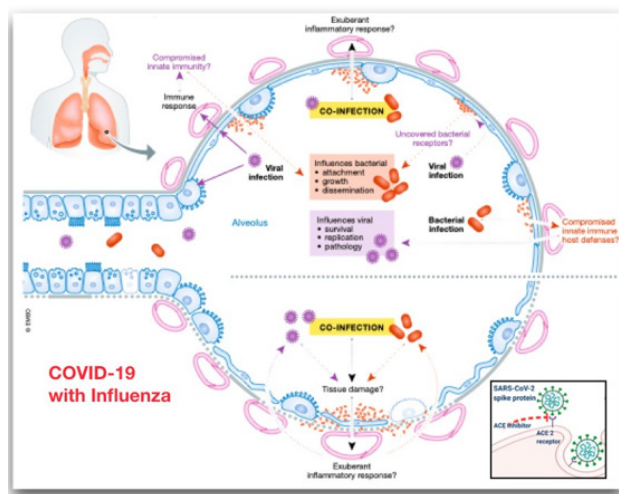

Figure 1: The interplay between SARS-CoV-2, bacteria, and the host in co-infections.
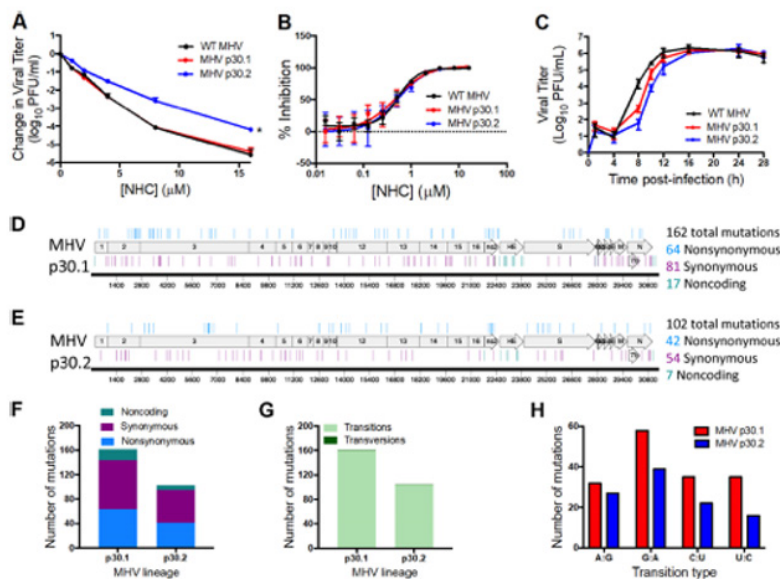

Figure 2: Resistance and mutational profiles of MERS-CoV after 30 passages in the presence of NHC.

Consequently, bacterial respiratory co-infection in the setting of SARS-CoV-2 infection remains poorly described. A description of co-infection and antimicrobial usage is needed to guide ongoing antimicrobial stewardship [20-23]. The rate of bacterial co-infection in SARS-CoV-2 is low. De- spite this, prolonged courses of antimicrobial therapy were primary required in further cohort study. We recommend active antimicrobial stewardship in COVID-19 cases to ensure appropriate antimicrobial prescribing. This study reflects antimicrobial prescribing practices during the COVID-19 pandemic in the absence of an active AMS team.

We demonstrate prolonged duration of antimicrobial treatment despite an alternative diagnosis and absence of evidence for bacterial co-infection as presented in Table 1. We suggest that AMS interventions are required in any ongoing COVID-19 infections, particularly focusing on discontinuing empirical therapy in the setting of negative cultures. Furthermore, the latest update of WHO's interim guidance on the clinical management of COVID-19 incorporates antibiotic stewardship principles with specific recommendations [24]. The guidance further states that empiric antibiotic bacterial pneumonia treatment can be considered in

older people residing in long-term care facilities. As these are non-hospitalized patients, antibiotics within WHO's AWaRe (access, watch, reserve) classification of antibiotics categorized as access, such as co-amoxicillin, should preferably be administered.

Table 1: Characteristics of treatment groups, antimicrobial choice and antimicrobial treatment duration.

Classification	Gender		Age	CFS	Antimicrobial agent	
Specification	Male	Female	Years	Median	Choice(N)	Duration(days)
Non-severe					*	
cephalosporin					4	
amoxicillin/clavulanic acid					20	
piperacillin/tazobactam	29	15	66 (26–90)	3 (1–7)	18	6 (2–14)
meropenem					1	
anidulafungin					1	
amoxicillin/clavulanic acid + clarithromycin					6	
Severe					*	
cephalosporin					2	
amoxicillin/clavulanic acid					18	
piperacillin/tazobactam	29	11	66 (21–92)	3 (1–7)	19	7 (1–14)
meropenem					3	
anidulafungin					1	
amoxicillin/clavulanic acid + clarithromycin					1	

*Comparison of non-severe and severe respiratory infection groups. Demographics, antimicrobial prescription and antimicrobial treatment duration are shown. No significant difference between groups is noted.

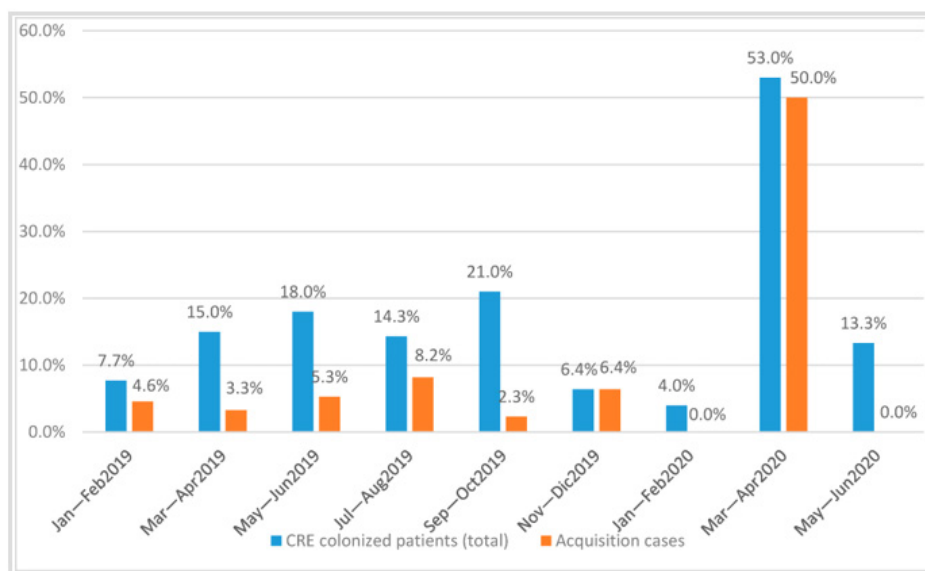## Potential long-term impact of COVID-19 on antimicrobial use and AMR

Figure 3: The trend of incidence of primary Carbapenem Resistance Enterobacteriaceae (CRE) and acquisition CRE in intensive care unit (ICU).

Consideration needs to be given to the impact of the COVID-19 pandemic and vaccination has been identified as a potential key intervention for reducing antimicrobial usage and therefore drug-resistant infections. There is a risk that the pandemic will lead to major disruptions to immunization services, with major long-term consequences, including secondary outbreaks of vaccine-

preventable diseases. The impact on control of MDR tuberculosis as a result of demands on health resources is likely to disproportionately impact low-income and middle-income countries, placing strain on fragile and overstretched health-care systems [25-27]. Particular attention was given to infection control practices with hand hygiene intervention, definition by checklist and continuous training on contact precautions for CRE carriers [28]. We also recommend active surveillance through systematic screening with rectal swab and clinical culture to search patients colonized by CRE, performed on all new ICU admissions and tested again on the seventh day of hospitalization (see Figure 3). The surveillance test to detect CRE on rectal swab was a culture-based method with a direct inoculation into specific selective chromogenic media. It was reported that growing colonies were identified by Vitek-MS, matrix-assisted laser desorption [29]/ionization time-of-flight (MALDI-TOF, bioMeriéux) [30], and tested for carbapenems resistance [31,32] and antibiotic susceptibility using the Vitek 2 system (bioMerieux, Marcy-L'Étoile, France) [33]. Enterobacteriaceae colonies [34] were also analyzed by immunochromatography test, for the identification of OXA-48-like, OXA carbapenemase (OXA-163) [35], Klebsiella Pneumoniae [36], Carbapenemase (KPC) [37], New Delhi Metallo-beta-lactamase (NDM) [38], and Verona Imipenemase (VIM) carbapenemases [39].

To mitigate the potential long-term impact of COVID-19 on antimicrobial use and AMR, health and social care systems must act to ensure that knowledge and evidence are effectively gathered to rapidly shape understanding and inform action. Evaluation of the impact of the pandemic on antimicrobial usage, AMR and access to effective antimicrobial treatments is essential to support the development of mitigation strategies. Clinical treatment guidelines to limit unnecessary antimicrobial exposure, measures to maintain routine surveillance of AMR and review of national policies that do not neglect essential public health programs in tuberculosis control and immunization delivery are essential. These strategies need to be supported by responsive national and international action plans that embed AMR as a priority in the post-COVID-19 era. At the national level, diagnostics and decision support should be developed to differentiate secondary bacterial infection during COVID-19. The role of specific biomarkers such as procalcitonin warrants further investigation [40]. Linkage of data to artificial intelligence-driven decision support software may provide added benefit. Antimicrobial stewardship should become an essential part of the individual clinical teams practice. Broader stewardship engagement will promote wider adoption of interventions designed to optimize treatment and reduce inappropriate antimicrobial use. Within primary care, data are urgently required to evaluate the impact of COVID-19 on antimicrobial prescribing, antibiotic access and clinical outcomes of infection. Novel approaches to stewardship and optimizing prescribing including telemedicine must be explored. Rapid progress has been made globally in basic sciences, epidemiology, diagnostics and clinical research in tackling COVID-19. There is also a societal opportunity to capitalize on the experience and learning from the pandemic to improve existing infection control and to sustain the raised awareness of the importance of vaccines and effective antimicrobial therapy. Coordination at the national level is required to gather evidence on the complex consequences of COVID-19 to inform necessary actions to reduce the potential longer-term impact on AMR and access to effective antimicrobials. For future study it will be investigated that the ex- acerbation of antimicrobial resistance (AMR), viral persistence and hyper-activation of the immune system by COVID-19 may be linked to inactive anti-aging genes. In the developing world plasma bacterial lipopolysaccharides (LPS) have increased and associated with repression of the anti-aging gene Sirtuin 1 the COVID-19 viral persistence and hyper-activation of the immune system is possibly extended with Sirtuin 1 gene inactivation. Activators of Sirtuin 1 may be critical to prevent the severity of the COVID-19 infection and exacerbation of AMR [41-43].

Future design of synthetic vaccines as antagonists of COVID-19 infection

In the midst of the SARS-CoV-2 or COVID-19 outbreak the need for research into the development of antiviral agents is brought into sharp focus worldwide for scientists, governments and the public alike [44]. This special issue includes primary research into new antiviral agents with activity against a range of clinically and economically important viruses. SARS-CoV-2 is a newly emerged β-Coronavirus [45] with sustained human-to-human transmission via the respiratory tract. Influenza viruses are another group of respiratory viruses, which account for 300–600 K deaths annually and represent an ever-present pandemic threat. Emergence of drug-resistant influenza strains is driving research into new anti-influenza drug candidates with different modes of action additionally [46].

Computational Methods

The main methods are essentially standard bioinformatics approaches as used and some methods,

e.g. rules for epitope prediction, are best discussed in this study context [47-49]. The Q-UEL methods (see Figure 4) specifically for bioinformatics are discussed [50-54], and those for computational chemistry and docking of compounds are those using KRUNCH as described in Figure 5. They are somewhat unorthodox by focusing on heuristics to handle the multiple energy minimum problem, but the end effect is probably similar to that of long runs using high grade molecular dynamics calculations, given opportunities for calibration. Epitope predictions lie in more traditional one dimensional bioinformatics, and in this paper but briefly, it is in part because sections predicted with runs of tendency to be immunogenic even if they are incorrect as structure predictions.

However, charged residues in α-helices and β-sheets are believed to be occasionally B-epitopes, and short sections extended chain can effectively imply loops. The core and initial rules for B-epitope prediction used in the present study [55,56]. A main conclusion is that peptide KRSFIEDLLFNKV remains of special interest as well conserved across coronaviruses. Some modifications of the RS-FIEDLLFNKV motif in CoVids of mammalian hosts summarized in Table 2. Other sites and other proteins of the virus may, of course, emerge as the solutions to this formidable problem. All aspects of the virus must be considered. However, even the ACE2 binding domain is significantly more prone to accepted mutations (see Figure 5). The recurrence of the core features of the KRS- FIEDLLFNKV motif over so many diverse species reminds us of zoonotic origins, and it might be recalled that we consider that many and perhaps all plagues of mankind might ultimately be of ani- mal origin (see Table 2).
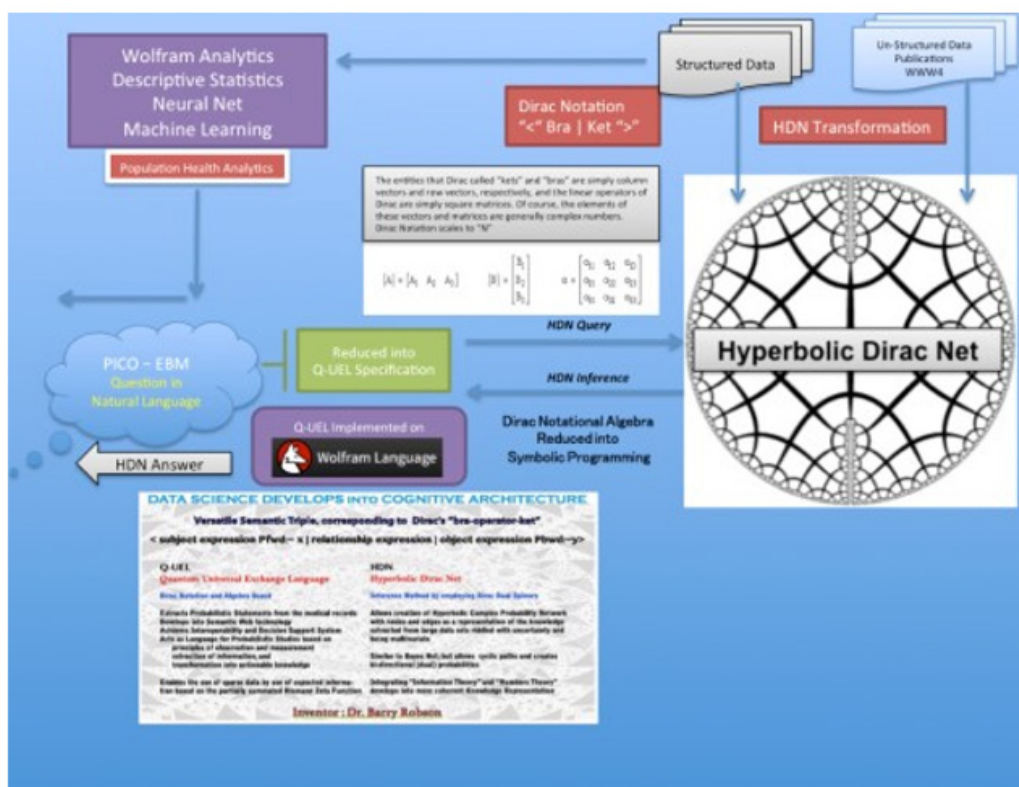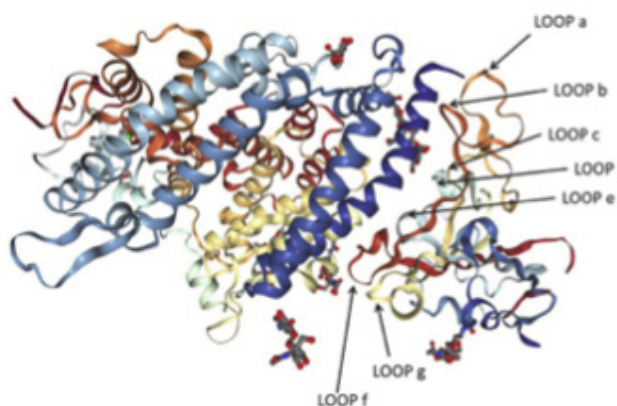

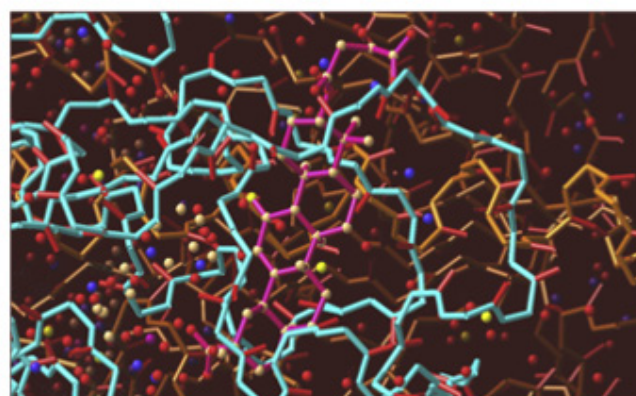**Figure 4:** Generative transformation process of the uploaded data set to activate the automated statistical studies.

ACE2 interacting with spike glycoprotein

Carbenoxolone Analogue

Figure 5: Structure of ACE2 interacting with spike glycoprotein receptor domain and Carbenox- olone Analogue In Situ in the 11β-hydroxysteroid dehydrogenase type 1 Steroid Binding Cavity which is the strongest binder in the KRUNCH Modeling System.

Table 2: Coronaviruses from mammalian hosts modified in RSFIEDLLFNKV motif of epitopes.

Origin	Coronavirus	Motif	Reference
Bat, civet, pig	SARS-CoV-2 and related coronaviruses	RSFIEDLLFNKV	MN908947.3
Kenya/Bat KY22/2006	Chaerephon bat coronavirus	RSFFEDLLFDKL	ADX59495.1
Bat	NL63-related bat coronavirus	RSFVEDLLFDKV	APD51483.1
	229E-related bat coronavirus	RSAIEDILFSKV	ALK28767.1
	Bat - [BtNv-AlphaCoV/SC2013]	DNRGSFIEDLLFDKV	YP_009201730.1
	Western Australian microbat	DNRGSFIEDLLFDKV	QGX41957.1
	Bat-CoV/P.kuhlii/Italy/ 3398-19/2015	ENKGSFIEDLLFDKV	AZF86124.1
Rat	Lucheng Rn rat coronavirus	RSFIEDLLFDKI	YP_009336484.1
Shrew	Wencheng Sm shrew coronavirus	RSVLEDLLFDKI	ASF90465.1
Dog	Canine Coronavirus	RSAIEDLLFNKV	AAP72150.1
		RKYRSAIEDLLFDKV	ADU17734.1
Pig	Porcine coronavirus (transmissible gastroenteritis of pigs, TGEV).	RSAIEDLLFSKV	ASV64340.1
Cat	Feline coronavirus	RSAVEDLLFNKV	ADC35472.1
		RSAVEDLLFDKV	ABI14448.1
		RKYRSAIEDLLFDKV	BAN67909.1
		RKYRSTIEDLLFDKV	BAP19067.1
		RKYGSAIEDLLFDKV	AAY32596.1
Human	Human HCoV-HKU1 "Flu-ish" cold	RSFFEDLLFDKV	NC_006577.2

An algorithm-based method for overcoming resistance to antiviral agents

COVID-19 disease pathogenesis is characterized by an initial virus-mediated phase, followed by inappropriate hyper-activation of the immune system leading to organ damage. Targeting of the SARS-CoV-2 viral receptors is being explored as a therapeutic option for these patients. In previous paper, we summarize several potential receptors associated with the infectivity of SARS-CoV-2 and discuss their association with the immune-mediated inflammatory response [57]. In addition to it, this paper is presented the potential for the development of resistance towards antiviral drugs. An algorithm-based platform to improve the efficacy of and overcome resistance to viral receptor blockers through the introduction of personalized variability is described in Figure 6. This method is designed to ensure sustained antiviral effectiveness when using SARS-CoV-2 receptor blockers [58]. The introduction of personalized variability to counter resistance to antiviral treatments. Regular, fixed dosing using an antiviral agent with robust and rapid effects is expected to lead to viral clearance, while fixed dosing regimens of moderately effective drugs may lead to drug resistance, viral persistence, an augmented hyper-activation of the immune system, and severe disease. The introduction of an algorithm-based dosing method based on quantified variability patterns derived from disease and host parameters improves the response to antiviral drugs.

Figure 6: Regular fixed dosing using antiviral agents with moderate effect against robust rapid effect.

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Discussion

One dimension we feel has not received the necessary attention is the impact of COVID-19 on AMR. Globally, the COVID-19 pandemic is superimposed on the ongoing pandemic of multi-drug resistant bacteria. While we do not argue against this practice, we stress that it is important to note that some of them may content additional chemicals that do not add much in terms of protection but instead may fuel bacterial antimicrobial resistance. Bacteria exploit efflux pumps to develop resistance against disinfectants, and these same efflux pumps contribute to AMR. In any case, it is essential that the public adhere to proper use to avoid the selection of bacteria with increased tolerance/ resistance to antimicrobials. Thus, the development of antiviral agents is brought into sharp focus worldwide against MDR and AMR.

Conclusion

Many studies reporting on patients hospitalized with COVID-19 reveals widespread use of antimi- crobial therapies as part of the package of clinical care in some countries. Recent letter highlighted a need to prospectively monitor co-infections in patients with COVID-19 to understand whether co- infection affects disease progression, and to enable antimicrobial stewardship. It is of the utmost importance that the potential of the global pandemic to increase AMR is taken seriously. Therefore, new drug discovery for COVID-19 should be taken into consideration.

Transparency Declarations

None to declare.

Acknowledgment

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