



Perspective

Dengue virus and SARS-CoV-2 Co-infection dynamics: An emerging threat among African countries

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ABSTRACT

The rising circulation of the vector borne disease such as dengue fever amidst the COVID-19 pandemic in African countries is on the rise, which pose a significant public health threat. In this article, we discussed the co-infection of dengue virus (DENV) (the causative agent of dengue fever) and SARS-CoV-2 (the causative agents of COVID-19) as well as the associated risk factors involved. Our review highlights that the continuous increase in the incidence and disease mortality from the co-infection of dengue Virus and SARS-CoV-2 is as result of inadequate surveillance and limited testing centers. Second, the overlapping clinical features and indistinguishable symptoms from both infections is a major challenge. Third, lack of scientific prudence among stakeholders has played a significant impact on how to contain these diseases. Therefore, there is a need to reassess research priorities in understanding the risk factors involved from the coinfection. Also, the development of accurate point-of-care diagnostics for COVID-19 and dengue fever coupled with community-based health intervention programs is highly essential for control.

1. Introduction

Dengue virus-the causative agent of dengue fever and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-the causative agent of the coronavirus disease 2019, otherwise referred to as (COVID-19) shares a number of laboratories and clinical features. This may be linked with a given co-morbidity and some clinical characteristics which the two diseases share [1]. The co-infection of these two diseases (COVID-19 and dengue fever) is regarded as an emerging public health challenge especially in Africa as they add to the severity and clinical complications of SARS-CoV-2 infected patients [2].

Dengue fever is a viral infection that is mostly transmitted through the bite of female mosquitoes belonging to the genera "Aedes" and species "aegypti". Symptoms of dengue viral infections, ranges from none to serious flu-like symptoms such as chills and high fever. Infections with dengue may be fatal among some few categories of patients, as the disease progress to become severe [3].

Coronaviruses (CoVs) consists of four different genera which include the α , β , γ and δ CoVs. The α - and β -CoVs are known to infect mammals while the γ - and δ -CoVs infect birds. Recently identified δ -CoVs are known to possess a very high antigenic and genetic plasticity adding to their genetic diversity [4]. The SARS-CoV-2 is a non-segmented, enveloped and positive-sense RNA (Ribonucleic acid) virus that belongs to the β -CoVs, (subgenus: sarbecovirus, Orthocoronavirinae subfamily) [4]. SARS-CoV-2 causes a serious illness among the human population, which include respiratory, enteric or systemic disease of which are of varying severity [5]. The virus originates from China in the city of Wuhan, Hubei province, at the end of 2019. The most common symptoms of SARS-CoV-2 infections are loss of sense of taste or smell, cough and fever while some of the less common symptoms include aches and pains, diarrhea, sore throat and skin rashes.

2. SARS-CoV-2 infection and dengue fever

2.1. SARS-CoV-2 infection

In December 2019, the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were discovered in China, after which the virus continue to spread around the globe in a rapid manner which the world has never seen before [6]. Since the initial cases were reported, millions of confirmed cases (about 19.3 million) have been linked to infection with SARS-CoV-2 worldwide, with a case fatality rate of around 4.1 million, as at the time of writing [7]. The COVID-19 pandemic is regarded as one of the diseases with the most debilitating effect on world economies, and has recorded the greatest number of deaths among all the pandemics the world has ever recorded [8]. This has also overstretched many health systems all over the world [9]. COVID-19 has been recorded in almost every country in the world, and out of the 47 African nations, it has so far caused 3,527,876 cases with approximately 88,022 deaths as at the time of writing. In Africa, countries like Egypt, Ethiopia, Morocco and Tunisia are mostly affected, and this might be linked with the poor containment measures, the weak healthcare institutions as well as the social distancing practices put in place during the acute stage of the infection [10]. The common coronavirus symptoms are fever, dry cough, and extreme exhaustion, however, cases of anosmia, aches, rashes as well as conjunctivitis have been reported among many patients [11]. The main route of transmission of SARS-CoV-2 is person to person via aerosols, following the release of respiratory droplets or when infected patient coughs, talks or sneezes [8, 12].

2.2. Dengue fever infection

Dengue fever (DF) is one of the most common acute febrile arboviral infection which is caused by dengue virus (DENV) [6]. Globally, there

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Fig. 1. A typical rash seen in Dengue fever [16].

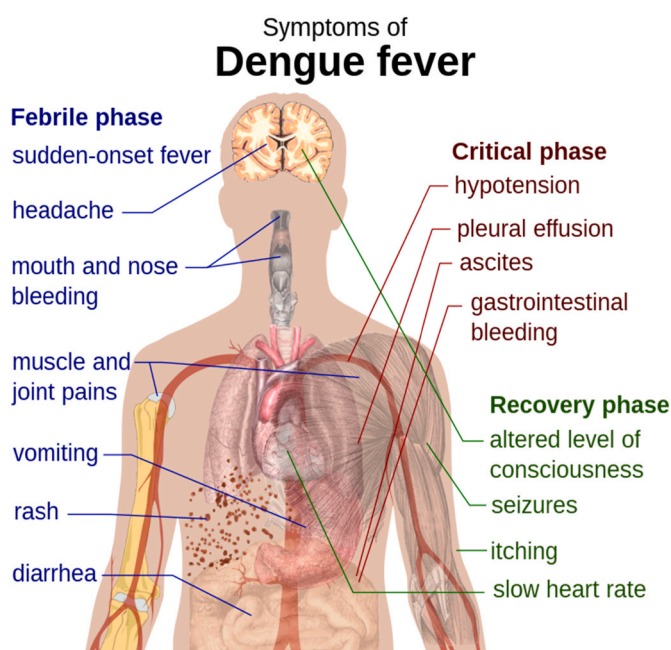


Fig. 2. Schematic depiction of the symptoms of dengue fever [17].

are estimated 390 million cases of DENV infections annually, with 25000 deaths and 500,000 hospitalizations. Majority of DENV infections around 70–80% are asymptomatic. In Africa, DF epidemics have a long history which dates back to the 19th century. At present, the virus is endemic in approximately 34 African nations [11]. In 2021, approximately 13,482 new cases of dengue viral infections were reported in the Africa, with Kenya having the highest number of cases [13]. DENV is usually spread by many different species of female mosquitoes, belonging to the genus “Aedes” and principally Aedes aegypti mosquito, a vector that is predominantly found the tropical and subtropical part of the globe [13]. Tourism and inter-country trade as well as educational trip have contributed to the spread of this disease. Many regions in the tropical world are presenting a hyper endemic form of dengue

infections, with different serotypes in circulation [14]. DENV is a positive-sense, single-stranded RNA encoding virus that encodes seven (7) non-structural and three (3) structural proteins. The virus contains four different serotypes that are referred to as DENV1–4. The serotypes share a similar genetic property but with a distinct antigenic configuration and infection with multiple serotypes increase the risk of severe DENV complications [13]. As the disease develop into a more severe form, this leads to a dengue hemorrhagic fever (DHF) which results in blood plasma leakage, low platelets count and bleeding [15]. DF is characterized by typical rash seen in Fig. 1 while the major symptoms of dengue viral infection are summarized in Fig. 2.

3. Co-infection of dengue virus and SARS-CoV-2

As at the time of writing, SARS-CoV-2 has infected about 179.7 million people in over 210 countries [18]. This includes developing countries where DF is widely spread, such as Africa, Latin America, and Southeast Asia, and co-infection with DENV has generated concerns [19–21]. Even though COVID-19 and Dengue virus are caused by viruses belonging to different families, the symptoms of these diseases are very similar and can be difficult to identify [22]. In Africa, co-infection of SARS-CoV-2 with other VBDs such as DENV infection is at an alarming rate. This has posed a serious health threat to the populace mainly because of the weak nature of most health institutions in Africa [10,23]. More so, the problem arising from such coinfection is compounded by the fact that DENV infection has the ability to showcase a wide spectrum case from severe DHF, mild self-limiting febrile illness, asymptomatic and DF. DHF is characterized by a series of complications such as extensive plasma leakage, thrombocytopenia to acute shock and death [3,24].

The increasing complication of SARS-CoV-2 with DENV infections is as a result of symptoms similarities resulting in misdiagnosis. At present, little is understood regarding the coinfection of SARSCoV-2 with DENV infections and more so, there are limited available literatures explaining these co-infections [1].

A study by Saddique et al. [22] reported that the co-infection of these two viruses (DENV and SARS-CoV-2) poses a significant health threat, especially in dengue endemic countries, the study further examined the specific role played by this co-infection on increasing the overall clinical severity and manifestation of COVID-19 among infected patients. More so, Sebastiao et al. [25] found a 10.3% DENV and SARS-CoV-2 coinfection rate among 105 tested subjects in Angola. This shows that SARS-CoV-2 and DENV are still spreading in tropical areas like Angola [26,27], amidst other arboviral diseases such as Zika, Chikungunya [28, 29].

In Ethiopia, Mohan et al. [30] reported a major public health problem related to a dengue outbreak during the COVID-19 pandemic. These authors reported a high number of new cases of infections. According to epidemiological evidence, dengue outbreaks occurred in Ethiopia in 2017, 2019, and 2021 [31,32], with an approximate 160 new cases, recorded in Warder Woreda of Dolo Zone in February 2021 and 47 number of disease cases reported in same location [32]. The monsoon season provides a shoddy sanitation system that allows Aedes mosquitos to thrive [33], which can lead to a co-epidemic situation for SARS-CoV-2 and DENV [30].

According to a recent data, the majority of symptomatic COVID-19 patients come down with cough, headache and fever, with others presenting with fever cases alone [34]. Patients with DF have high temperature and occasionally a headache [35]. Skin rashes also occurred in COVID-19 patients, which is a frequent sign of DENV infection [35], indicating similar laboratory features. To curtail this menace in Africa, there is a need for accurate understanding of the mechanisms governing these infections to allow for a tailored management of these diseases, timely and accurate diagnosis of these diseases which could offer an insight on the possible containment and prevention measures along with adequate support in severe cases [36].

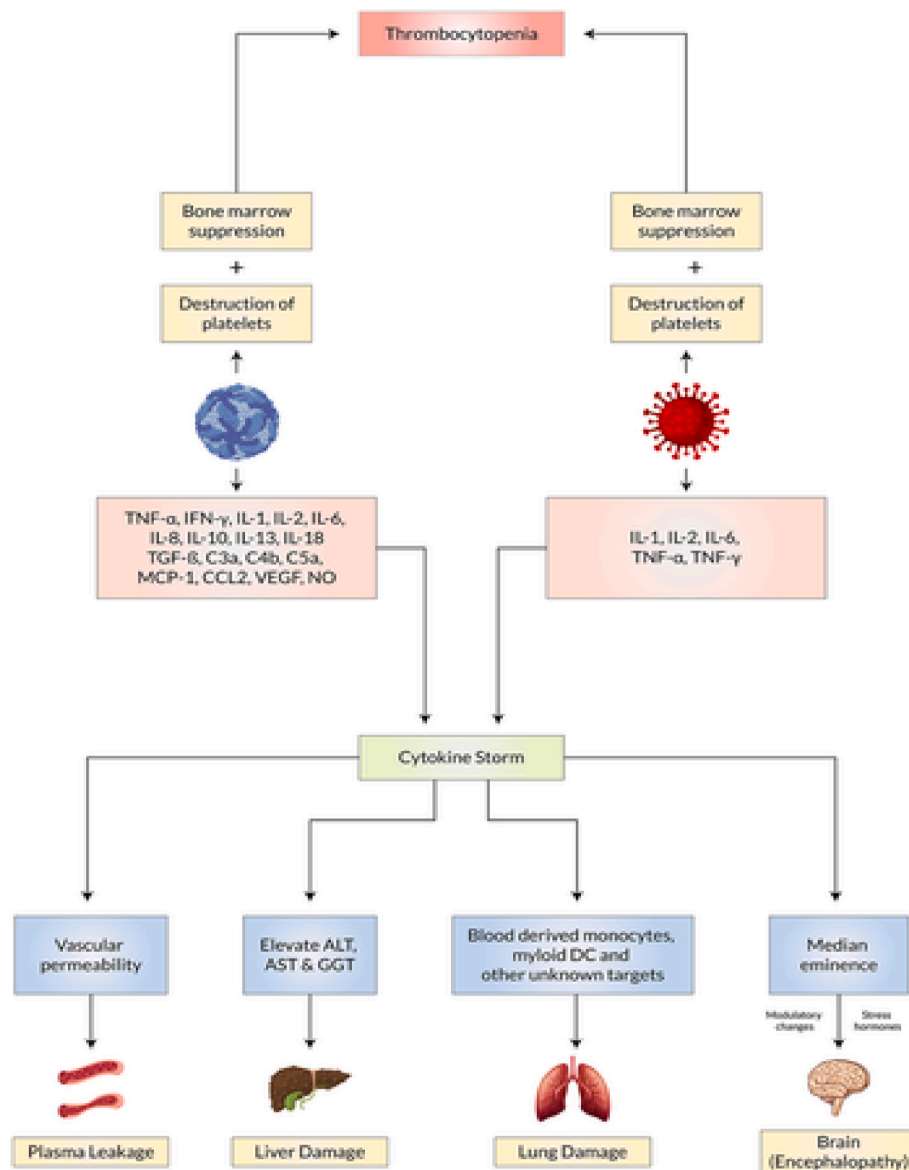


Fig. 3. Mechanism of disease progression in dengue virus (DENV) and SARS-CoV-2 co-infection [42].

3.1. Associated factors involved in co-infection of dengue virus (DENV) and SARS-CoV-2

COVID-19 and Dengue Fever (DF) have similar clinical manifestations thereby making their clinical differentiation difficult, this enables the two diseases to co-exist. This calls for a serious concern as extra care is needed to be observed especially during the diagnosis of the disease as to avoid the risk of misdiagnosis [11]. Furthermore, less attention is giving to DF mainly because the world is more focused on addressing the health threat of COVID-19 pandemic. On the other hand, due to inadequate surveillance and limited testing centers, the overall incidence and disease mortality due to co-infection with these viruses i.e., SARS-CoV-2 and DENV, may rise [37].

Lockdown due to rising cases of COVID-19 pandemic has affected the excellent work and programs of containment of many diseases with VDBs inclusive. However, in the case of VDBs, control programs such as environmental and indoor residual spraying of insecticides have been halted as a result of the restraints enforced due to the COVID-19 pandemic. These have tremendously enhanced the persistence of mosquito vectors in the environment which eventually spread DENV [38]. Lockdown-related disruptions are also likely to have resulted in the

increased mosquitoes' populations over time, as new breeding habitats are formed [39].

The lack of scientific prudence mainly among the political class as well as their advisee and other stakeholders in Africa have had a significant impact on how best an outbreak should be contained. More so, Africa remains without effective disease surveillance mechanisms, as such the control measures as well as action plans for the containment of disease in emergency situations are difficult to be established, which further underscores lack of expertise clarification in the face of diseases outbreak [40,41]. Also, lack of effective drainage systems, which results in stagnant water, is a major factor that aids mosquito growth and transmission of VDBs in Africa. To avoid the development of mosquitoes, the healthcare institutions must embark on a public health campaign on the need for continual community sanitization practices, personal hygiene and the collective effort in reporting all residents who boycott the set environmental sanitization control measures put in place by both the government and other stakeholders [11].

The two viruses, SARS-CoV-2 and DENV both contain a positive sense RNA genome single stranded RNA genome. DENV uses some attachment factors such as the glycosaminoglycans, immunomodulatory proteins receptors, C-type lectins DC-SIGN (CD209) and mannose

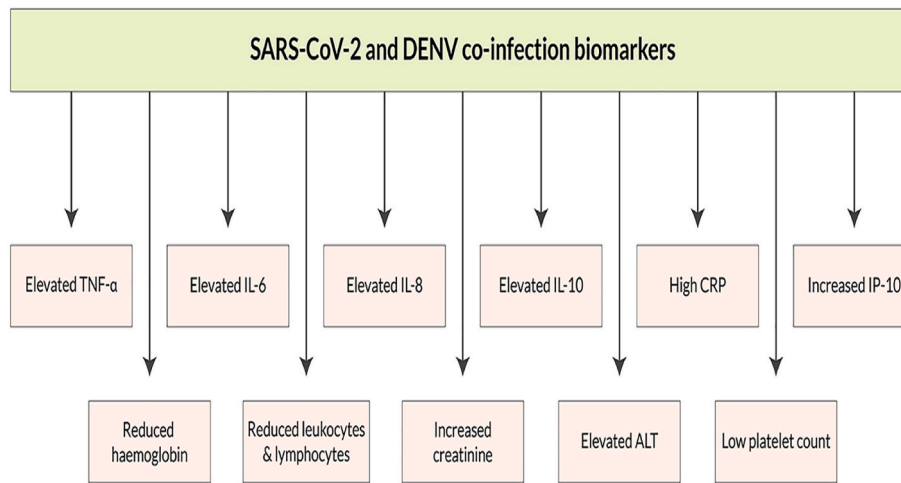


Fig. 4. Increasing and decreasing levels of biomarkers in the dengue virus (DENV) and Sars-Cov-2 co-infection [42].

receptor (CD206), to gain entry into the host cell receptors while the SARS-CoV-2 interact with the host cell receptors via the use of its glycoprotein spikes which in turn interacts with the host angiotensin-converting enzyme-2 (ACE-2) before gaining entry into the host cell. Following the infection with SARS-CoV-2, there is a release of cytokine storms as well as inflammatory immune response. The same cytokine storms are observed following DENV infections and further leads to the production of an increased level of antibody concentrations.

More so, both DENV and SARS-CoV-2 infection disrupt the coagulation system, in exactly the same manner in the case of DENV infections. Furthermore, both DENV and SARS-CoV-2 cases can lead to different organs failure especially the cardiovascular system, the lungs, and the Central Nervous System (CNS). These co-infections are further associated with many complicating symptoms along with lesser prognoses compared to that of a single infection. Both DENV and SARS-CoV-2 have the ability to infiltrate the CNS to cause a severe and multitude cases of different neurologic complications [42]. Fig. 3 further explains the mechanism of disease progression for DENV and SARS-CoV-2 co-infection.

Biomarkers such as neutrophil and leukocytes usually have a higher count in SARS-CoV-2 infection while in DENV infection, the reversed is seen. High platelet, lower Aspartate transaminase (AST) and lower Alanine transaminase (ALT) levels are seen in COVID-19, while in the case of DENV, higher number than normal levels are recorded. However, lower-than-normal levels in the neutrophil-to-lymphocyte ratio (NLR) are seen in the case of DENV while an increased level is seen in SARS-CoV-2 [43,44]. Fig. 4 further explains the increasing as well as the decreasing levels of biomarkers in the case of DENV and SARS-CoV-2 co-infection.

Both DENV and SARS-CoV-2 have some certain type of biomarkers such as Tumor Necrosis Factor Alpha (TNF-α), Interleukin-8 (IL-8), Interleukin-6 (IL-6), Interleukin-10 (IL-10) and C-reactive protein (CRP) that allow for the understanding of the pathogenesis of the two viruses and assessment of therapeutic interventions. These biomarkers act as measurable parameters to indicate the process and progress of pathogenesis and the results of therapeutic interventions.

4. Recommendations and conclusions

Based on the information presented in this article, it is clear that the coinfections of SARS-CoV-2 and DENV has resulted in significant morbidity and mortality in African countries as a result of overlapping clinical features and indistinguishable symptoms which continue to pose a public health challenge regarding diagnosis and treatment of cases. However, while these two viruses are different family, the control

measures to be adapted on them are similar, particularly at local and community level. There is a need for improvement in community health in emerging diseases hotspot coupled with public health education on mode of transmission, prevention and control of these two diseases. Consequently, since it has been established that co-infection of these two viruses is as a result of misdiagnosis, there is a need to invest in research lab and well-equipped with molecular diagnostic tools such as Polymerase Chain Reaction (PCR) that would aid in distinguishing these two viruses accurately. Beyond this, public health professionals should be well trained on proper identification of the differences in COVID-19 symptoms and that of dengue. Development of accurate point-of-care diagnostics for COVID-19 and dengue coupled with community-based public health intervention programs are highly essential for targeted care and prevention of coinfection. Since the usual disease control strategies including insecticide-treated bed-net and indoor residual spraying of repellent-known to be effective against other VDBs remains ineffective against dengue, effort should be directed towards development of effective drug therapy and vector control programs. Effort on COVID-19 drug development should also be improved. While various effective vaccines are available for COVID-19, the Sanofi Pasteur dengue vaccine i.e., dengvaxia has had mixed result due to inability to target the four serotypes in dengue. As a result, this necessitates the need for more effective vaccine that is specific to the four serotypes. Finally, medical centers need more facilities for biosafety purposes to effectively handle patients suffering from COVID-19 co-infection with dengue.

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Author contribution

Habeebullah Jayeola Oladipo, Ismail Rabi, and Yusuf Amuda Tajudeen: Conceptualization, Habeebullah Jayeola Oladipo, Ismail Rabi, Yusuf Amuda Tajudeen: Methodology, Data curation, writing—original draft preparation. Habeebullah Jayeola Oladipo, Ismail Rabi, Yusuf Amuda Tajudeen: Writing—Reviewing and Editing. All the authors contributed equally to this paper and approved it for publication.

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Appendix A. Supplementary data

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