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# Symptomatic similarity, co-infection and cross-reactivity in dengue and Covid-19 disease

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### Abstract

The Corona pandemic, brought about by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is pronounced international public health crisis with shocking health impacts. The Covid-19 disease has created the symptoms misdiagnosis complicacy in tropical and subtropical areas of the world, that are dengue endemic regions too to the population. The dengue is cause by dengue virus (DENV). Initially, there is similarity in the sign and symptoms of patients with Covid-19 and dengue, namely fever, headache, myalgia associated with thrombocytopenia, leukopenia, and abnormal liver function tests. The similarity in clinical symptoms in Covid-19 and dengue fever has to raise the issue of co-infection and symptoms misleading. In addition, co-infection followed by cross-reactivity between antibodies against DENV and SARS-CoV-2 serology tests has been recorded in reports. Furthermore, cross-reactivity of the immune reaction in these infections is an emerging issue, Covid-19 through counteracting agent subordinate upgrade as pre-existing DENV-antibodies may possibly influence Covid-19 through antibody-dependent enhancement. Some studies have proposed that Covid-19 disease and transmission might be slower in dengue-endemic locales of the world. This review deals with the concern of misdiagnosis challenges due to Covid-19 and dengue fever, co-infection, cross-reactivity between SARS-CoV-2 and DENV antibodies. Simultaneous pandemics of dengue and Covid-19, just as the chance of co-contamination, add to the generally significant burden on healthcare services.

**Keywords:** Corona pandemic, co-infection, SARS-CoV-2, dengue endemic, misdiagnosis, cross-reactivity

### Introduction

The vector borne diseases are spread by the bite of hematophagous contaminated arthropods including mosquitoes, triatomine bugs, ticks, and fleas. They cause more than 17% of the entire infectious diseases for instance Dengue, Malaria, Chikungunya, Rift Valley fever, Zika, yellow fever, Japanese encephalitis, Lymphatic filariasis, West Nile fever, Rickettsia diseases, Trypanosomiasis, Leishmaniasis etc. [1]. These diseases increase mostly in the tropical and subtropical regions affecting excessively the poorest population. Since 2014, the major outbreaks of malaria, dengue, chikungunya, Zika and yellow fever have affected human populations and inundated health structures in many countries of the world [2]. According to National Vector Borne Disease Control Program (NVBDCP), Ministry of the government of India, there are vectors borne diseases like Dengue, Malaria, Japanese encephalitis, Kala-Azar and Chikungunya and Lymphatic filariasis, have appeared as serious public health issues in India [3]. Among them, epidemic forms occurred chiefly of dengue, chikungunya fever, Japanese encephalitis and malaria, which cause significant morbidity and death [4].

Dengue is a mosquito vector borne (*Aedes aegypti*) major viral disease, occurs in tropical and sub-tropical regions worldwide occupying both urban and semi-urban parts [5]. According to a recent WHO report (2021), over the last two decades, there is eight-time increase in the number of dengue cases i.e. 505,430 cases in 2000, 2.4 million cases in 2010 and 5.2 million cases in the year 2019 were reported [8]. The dengue has spread as endemic over 100 countries where South East Asia, America, and Western Pacific regions were the most critically affected. About 70% of total dengue infections prevail in Asia only. It is caused by dengue virus (DENV) of the Flaviviridae family, having four closely related but distinct serotypes which enhance the four-time possibility of being infected. S. Bhatt and his associates handled a formal modelling structure to plot the global distribution of dengue threat and they have estimated 3.9 billion dengue virus infections of which 96 million manifests clinically with any type of severity of disease [6].

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O. J. Brady and his associates formulated an evidence consensus map of dengue status of nations and provided a list of 128 countries which are at a high risk of dengue infection [7]. India has all the four strains of the dengue virus, active in almost the entire country and throughout the year. Thus, WHO has labelled India as a hyper-endemic for dengue [9]. However, numerous promising dengue vaccines have been undergoing development for few decades, none have verified to be successful [10]. The only obtainable WHO-approved vaccine for dengue is Dengvaxia® till date, developed by Sanofi, the French multinational company. But it also has controversial status at present due to the deaths of 10 children in the Philippines, linked to this vaccine [11].

Recently, Covid-19 or Corona virus disease is an infectious disease caused by the virus named severe acute respiratory syndrome coronavirus (SARS-CoV-2). It was firstly identified in Wuhan, Hubei Province, China at the end of 2019, after that it is rapidly extended throughout the world affecting human life and the world economy terribly [12]. WHO announced Covid-19 as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020 and declared it as a current pandemic on March 11, 2020 [14]. SARS-CoV-2 is one of the seven types of corona viruses that cause Middle East Respiratory Syndrome (MERS) and Sudden Acute Respiratory Syndrome (SARS) [15]. It can cause a problem in upper respiratory tract that includes sinuses, nose, throat, or lower respiratory tract including windpipe and lungs. The SARS-CoV-2 causes pneumonia, heart problems, respiratory failure, liver problems, septic shock and severity of infection leads to death. Like other coronaviruses, it appears to pass among people through respiratory droplets. This pandemic is causing devastating effects leading to dramatic loss of life, disruptions in public health sector, food system, economic sector and social life.

The demands for disposal of the Covid-19 virus have stressed healthcare structure worldwide. Covid-19 pandemic is also over shading the handling of other dangerous viral outbreaks simultaneously. In this regard, health services for dengue especially in dengue endemic nations, are also adversely affected because of (1) limited access to dengue testing and treatment during Covid-19 pandemic, (2) the difficulty of distinguishing between Covid-19 and dengue infectious cases due to similarity in symptoms at early stages of infection. Both dengue and Covid-19 infections share a major similarity in early clinical symptoms and even many laboratory findings lead to misdiagnosed of each other suspecting immunological cross-reactivity between both viruses [15]. Both dengue infection and Covid-19 cause mild to critical illness and need early and accurate detection and timely treatment otherwise may cause life-threatening complications. Cases of co-infection of dengue virus and Covid-19 are being reported alarming the high threat of death in patients. However, dengue infected patients in the last few years were found to be less susceptible to novel corona infection. In this article, we reviewed the available data on similarities between symptoms of dengue and Covid-19 infections, immunological cross-reactivity of both viruses, development of somewhat level of immunity for corona infection in previously dengue infected patients and raising cases of co-infection of both diseases, particularly in high-risk countries for dengue.

### Similarities between dengue infection and Covid-19 symptoms

Henrina and colleagues described the clinical similarities

between dengue and Covid-19 such as fever, myalgia, headache, cough dyspnoea, vomiting, abdominal pain, skin rashes etc. [15]. They also found similarities in laboratory investigations of haematological abnormalities and coagulopathy i.e., thrombocytopenia, lymphopenia, leukopenia, increased D-dimer after comparison of both infections. Fever is found most common symptom in both cases of infection. In dengue, fever shows high temperature lasts for 6 days with two temperature peaks (saddle back pattern) [16]. Fever in corona infection is noted generally lasts for 7-8 days and does not follow a definite pattern. However, two patterns of fever were observed, fever persisting up to the second week of illness or saddleback pattern of fever as similar in dengue [17]. Headache can complain in both diseases, but it is more observed in dengue fever than Covid-19 [18]. Patients in both infections may experience cough in the early days of their illness. 21.5% of patients were reported with cough in dengue fever, while in Covid-19, 76% patients were found experiencing cough [19, 20]. Gastrointestinal symptoms such as vomiting and abdominal pain are the common symptoms in dengue infection presenting in 30-55% and 16-25% patients based on different studies [16, 18, 21]. These symptoms are also being reported in Covid-19 patients but only 2-5% of patients [21, 22]. Cutaneous manifestations like skin rashes symptoms have been reported in 15-20% of patients of Covid-19 [23], which is a very common phenomenon in dengue fever [16, 24]. A case was reported from Thailand in which a patient was misdiagnosed for dengue because of having a skin rash with petechiae and had a low platelet count [25]. Later, he is diagnosed Covid-19 positive is an infection that was confirmed by RT-PCR and experienced respiratory problems.

In consideration of haematological abnormalities, thrombocytopenia is very common in dengue fever. In one observational study, 69.51% dengue patients (358/515) developed thrombocytopenia, whereas, in another study, all 184 dengue infected patients experienced thrombocytopenia [18, 26]. Covid-19 patients were also reported exposing thrombocytopenia as well. A recent systematic review with 19 studies and 3383 patients with severe Covid-19 had an important level of thrombocytopenia [27]. Lymphopenia has been developed among a large percentage of severe Covid-19 patients and it is also a common finding in dengue patients [28, 29]. Mild to marked elevations in D-dimer level is observed in milder to severe form of the Covid-19. In a cohort study from China, 260 out of 560 (46.4%) Covid-19 patients represented elevated levels of D-Dimer (DD) [30]. Sequential analysis of D-Dimer showed higher levels at all stages of dengue infection in one study involving 41 dengue patients [31].

### Misdiagnosed cases explaining cross-reactivity between DNEV and SARS-Co-2 viruses

Numerous cases are being accounted for last year which gave evidence of cross-reactivity between DNEV and SARS-CoV-2 deriving false-positive Covid-19 patients serology among dengue patients or vice-versa.

Two cases were accounted from Singapore having a probability of serological cross-reactivity between SAR-CoV-2 and DNVE. At first, they were believed to be contaminated with dengue infection because of false-positive outcomes from rapid serological testing for dengue, yet later they were discovered positive just to the trial of Covid-19 disease. Both patients had symptoms like cough, fever, myalgia, dyspnoea

and also experienced thrombocytopenia, lymphopenia, so misunderstood with dengue serology<sup>[32]</sup>. For another situation detailed from Thailand, a 35 years of age female nurse got infected with SARS-CoV-2 infection during the blood inspecting of a patient, who was recently found with dengue contamination because of gentle thrombocytopenia and positive dengue IgG and IgM, further, he was determined to have Covid-19 disease following 3 days of hospitalization<sup>[33]</sup>. In another track down, a Pakistani clinical understudy was at first determined to have Covid-19 disease because of serious indications of fever, hack, chills, myalgia, the runs and had head out history to urban areas with Covid-19 transmission. Be that as it may, his SARS-CoV-2 tests were negative and following 3 days of hospitalization, determined to have corresponding dengue and measles infections<sup>[34]</sup>. Three instances of suspected Covid-19 and dengue co-infection were accounted for in Bali, Indonesia. Patients with positive outcomes for dengue infection NSI antigen, were likewise showed reactivity to Covid-19 rapid antibody tests, suspecting dengue-Covid-19 co-infection. Afterward, two patients were discovered to be negative for SARS-CoV-2 contamination by q-RT-PCR test. It is recommended a conceivable cross-reactivity of hostility to dengue and against Covid-19 antibodies in the serological test<sup>[35]</sup>.

The cross-reactivity among dengue and Covid-19 antibodies was evaluated in Indonesia by testing five Covid-19 RDTs (Rapid indicative tests) on 60 RT-PCR affirmed dengue tests and 95 RT-PCR affirmed Covid-19 examples on dengue RDTs<sup>[36]</sup>. They noticed cross-responses, false-positive outcomes and surprisingly co-infection cases among dengue and Covid-19 disease. Serological cross-reactivity between SARS-CoV-2 and dengue infections may defer convenient laboratory diagnosis and proper treatment which may cause the fast spread of Covid-19 contaminations due to lacking disengagement precautionary measures, especially in dengue inclined areas.

### Covid-19 patients with previous dengue infection

In Rio Branco, Acre, a municipality in the Brazilian Amazon basin, 2351 participants were infected with coronavirus disease in the year 2019, in which 1177 (50%) patients were reported with previous dengue infection. The study observed decreased mortality among covid patients who had previously experienced symptomatic dengue infection (hazard ratio: .44; 95%, confidence interval: .22–.89;  $P = .023$ ) in a 60-day record. It is suggested the possibility that dengue might encourage immunological safety against severe SARS-CoV-2 virus infection<sup>[37]</sup>. Nicolelis *et al.* Observed an inverse relationship between Covid-19 and dengue cases in the regions around Asia, islands in the pacific, Latin America, and Indian oceans. They found that an elevated percentage of people who had suffered from dengue fever in 2019-20, later reported lower Covid-19 cases and deaths<sup>[38]</sup>. This finding also supports the idea of an immunological reactivity of DENV and SARS-CoV-2 serotypes. In conformity with this hypothesis, the study of Himadri *et al.* Can be considered, who found five of 13 dengue antibody-positive serum samples which were collected from dengue patients in the pre-pandemic period gave fake-positive results in SARS-CoV-2 rapid strips test (IgM/IgG)<sup>[39]</sup>. They had suggested that dengue antibodies can cross-react with SARS-CoV-2 antibodies or vice-versa, as both viruses may represent antigenic similarity. Biswas and Shukla observed global

harshness maps of in progress dengue epidemic and Covid-19 pandemic and concluded that countries with a high rate of dengue (>1.5 million cases/year) as endemic appeared to be less sensitive towards Covid-19 infection and transmission<sup>[40]</sup>.

The aforementioned tropical and sub-tropical nations record dengue epidemics regularly. Therefore, it is assumed that populations experienced to usual dengue virus epidemics are comparatively signify resistant to Covid-19 transmission and pathogenesis. Consequently, pre-existing immunological memory to dengue exposure, presenting antibodies against DENV and memory cells (B and T cells), may found to be harmful transmission, harshness and pathogenesis of Covid-19 infections. Standard exposure to dengue infection (germ hypothesis) is likewise prone to signal the natural insusceptibility in individuals in the exceptionally dengue-endemic areas towards a prepared reaction to striking viral diseases like SARS-CoV-2.

### Co-infection cases of dengue and Covid-19 disease

There is also recording a rapid surge in cases of co-infection, Covid-19 with dengue infection. Khalid *et al.* reported four cases of co-infection of dengue and Covid-19 in Jeddah, Saudi Arabia. Patients had indications and blood tests reminiscent of dengue fever and had radiological reports reminiscent of Covid-19 chest contamination with positive PCR tests<sup>[41]</sup>. Saddique and associates directed an examination to explore the job of dengue co-infection on the seriousness of Covid-19 patients in Pakistan<sup>[42]</sup>. Among 20 patients examined, 40% of patients contaminated with just SARS\_CoV-2, were completely recovered. But 60% of patients co-infected with dengue and Covid-19 infection, could not survive indicating a high mortality rate in co-infected cases. This finding highlights the adverse consequences of co-infection of Covid-19 and dengue infection, mainly in dengue-endemic countries and suggests timely investigations, prevention, efficient clinical management and public awareness manage co-epidemics. For a situation report, 18 years of age male, who went back from epicentre area for Covid-19 and following 15 days, was tested positive for SARS-Cov-2 infection by RT-PCR introducing the chance of asymptomatic incubation period. It uncovered that dengue contamination is probably going to more serious in co-infection with Covid-19<sup>[43]</sup>. In another study, Lusting *et al.* detected 12 dengue-positive cases out of 55 (21.8%) Covid-19 patients by using the dengue lateral-flow rapid test and based on in-silico analysis, they revealed possible similarities between SARS-CoV-2 epitopes in HR2 domain of spike proteins and dengue envelop proteins<sup>[44]</sup>. Lokesh *et al.* reported the first paediatric case (14-year-old girl) of Covid-19 encephalitis with dengue shock syndrome (positive for dengue NS1 antigen and IgM antibody)<sup>[45]</sup>.

In a recent study, Hilmy *et al.* Described two reports of co-infection of dengue and Covid-19 depicting symptoms of dengue fever in the first case and further showed symptoms of Covid-19 after 5 days<sup>[46]</sup>. In the second case, there were mild symptoms of Covid-19 due to progressive turn down in leukocyte and thrombocyte counts but reported tested positive for dengue fever. They concluded that viruses may alter the dynamics and natural account of disease succession, one virus can restrain or expand the other one, leading to a classic appearance in the case of dengue infection and Covid-19.

## Conclusion

Current worldwide battles to look at the destruction of the Covid-19 pandemic, dengue-endemic regions are confronting the possibility of a double pandemic that could obliterate medical care services. Corona pandemic and dengue covering represents a challenge for exact analysis of the symptoms and diagnosis since both contaminations share similar signs and lab highlights in the beginning stage. Numerous confirmations estimated comparative infection antigenic structure and movement of the antibodies inspired by DENV disease and their effect on Covid-19 and the other way around. The cross-reactions between SARS-CoV-2 antibodies and DENV antigens may cause false positives on rapid dengue infection serological tests. Symptomatic similarity and cases of co-infection of dengue and Covid-19 making it a danger that patients might be wrongly analyzed right off the bat throughout the illness. The avoidance and control of DENV and SARS-CoV-2 diseases depend on the method of transmission and need consistency to the connected health services.

**Conflict of interest:** The authors declare that they have no competing interests.

**Author Contributions:** All the authors have equal contribution in this paper. All the authors conceived the study, conceptualized the paper, prepared, critically read and revised the manuscript, and gave final approval for publication.

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