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**REVIEW**

Covid-19 and dengue: Double punches for dengue-endemic countries in Asia

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Summary

The coronavirus disease 2019 (Covid-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an international public health crisis with devastating effects. In particular, this pandemic has further exacerbated the burden in tropical and subtropical regions of the world, where dengue fever, caused by dengue virus (DENV), is already endemic to the population. The similar clinical manifestations shared by Covid-19 and dengue fever have raised concerns, especially in dengue-endemic countries with limited resources, leading to diagnostic challenges. In addition, cross-reactivity of the immune responses in these infections is an emerging concern, as pre-existing DENV-antibodies might potentially affect Covid-19 through antibody-dependent enhancement. In this review article, we aimed to raise the issue of Covid-19 and dengue fever misdiagnosis, not only in a clinical setting but also with regards to cross-reactivity between SARS-CoV-2 and DENV antibodies. We also have discussed the potential consequences of overlapping immunological cascades between dengue and Covid-19 on disease severity and vaccine development.

Abbreviations: 2019-nCoV, 2019 novel coronavirus; ACE2, angiotensin converting enzyme 2; ADE, antibody-dependent enhancement; Covid-19, coronavirus disease 2019; CRP, C-reactive protein; CTL, cytotoxic T lymphocyte; DENV, dengue virus; DHF, Dengue hemorrhagic fever; DIC, disseminated intravascular coagulation; FcγRII, Fc gamma (γ) receptor II; IFN-γ, interferon gamma; IL-6, interleukin-6; irAE, immune-related adverse events; MIF, macrophage migration inhibitory factor; NS1, nonstructural protein 1; PAIgM or PAIgG, platelet-associated immunoglobulin; PHEIC, Public Health Emergency of International Concern; RBD, receptor-binding domain; RDT, rapid diagnostic test; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; WHO, World Health Organization.

KEYWORDS

ADE, Covid-19, cross-reactivity, dengue, SARS-CoV-2

1 | INTRODUCTION

In December 2019, pneumonia cases of unknown etiology were reported in Wuhan district of Hubei Province, China.¹ By January 7, 2020, the causative agent of the disease was identified as the 2019 novel coronavirus (2019-nCoV).² The virus was later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and hence the disease was termed coronavirus disease 2019 (Covid-19).³ On January 30, 2020, the World Health Organization (WHO) announced Covid-19 as a Public Health Emergency of International Concern (PHEIC), and 2 months later, on March 11, it was declared as a global pandemic.³⁻⁵ SARS-CoV-2 is primarily transmitted from person-to-person through droplets while coughing and sneezing, enabling the virus to disperse up to 1 to 2 m.⁶⁻⁸ The transmission occurs not only from symptomatic and pre-symptomatic patients but also probably from those who are asymptomatic,⁹⁻¹³ with the incubation period ranging from 2 to 14 days.^{3,6} There is no specific antiviral for Covid-19 but multiple drugs are being assessed in clinical trials.¹⁴⁻¹⁷

Dengue is a major public health problem throughout tropical and sub-tropical regions.¹⁸ This disease is caused by any of the four serotypes of dengue virus (DENV), transmitted by mosquitoes, primarily the *Aedes aegypti* species and the development of a efficacious vaccine still remains a challenging task.^{19,20} Dengue is also a rapidly increasing problem among international travelers²¹⁻²⁴ and it is the leading cause of febrile illness in returning travelers from Asia.^{25,26} In Asia, dengue is endemic and there has been a 400% increase in the number of dengue cases over the last 13 years (2000-2013), with the World Health Organization (WHO) estimating there to be 100 million symptomatic cases and 300 million asymptomatic cases, annually.²⁷ Singapore, a Southeast Asian country, is experiencing a dengue outbreak that has been ongoing since April 9, 2020; there were 5091 cases with 98 active clusters.²⁸ Dengue outbreaks also occurred in Indonesia where 68 000 dengue cases have been reported across the nation as of June 21, 2020, resulting in 446 deaths.²⁹ The dengue cases were reported in 460 districts in Indonesia of which 439 of them have also reported cases of Covid-19.³⁰ Dengue outbreaks have occurred in other Asian countries as well.³¹

Clinical symptoms of Covid-19 include cough, muscle aches, fatigue, skin rash, and petechiae, making it challenging to differentiate Covid-19 from other endemic viral infections in the region, such as dengue,³² and thus potentially leading to misdiagnosis.³³ In addition, a study in Singapore reported the possibility of serological cross-reactivity between SARS-CoV-2 and DENV,³⁴ raising the question of overlapping immunological cascades between Covid-19, dengue, and other arboviruses. This article aims to: (a) provide evidence of Covid-19 and dengue misdiagnosis in clinical settings and the possibility of cross-reactivity between SARS-CoV-2 and DENV; (b) discuss the

possible consequence of immune response overlapping on enhancement or protective effect, disease severity and vaccine development; and (c) provide insights for further studies that are urgently needed in the region.

2 | COVID-19 PANDEMIC AND ITS EFFECT ON DENGUE IN ASIA

Co-infection and co-occurrence of Covid-19 and dengue have introduced a significant burden on healthcare systems in dengue-endemic regions.³⁵⁻³⁹ The complexity of diverse disease severities, prolonged infectious periods, and shared clinical manifestations and pathogenesis have made their diagnosis, treatment, and resource allocation challenging, particularly in developing countries in Asia with high prevalence of dengue and other arboviruses.

2.1 | Misdiagnosis between dengue and Covid-19

A study consisting of more than 44 000 Covid-19 cases in China found that 81% of the cases exhibited mild to moderate symptoms.⁴⁰ Some patients reported complaints of fever, cough, muscle aches, or fatigue with normal chest radiography, resembling other viral infections, thereby making it difficult for doctors to differentiate Covid-19 from dengue, which leads to primary examination misdiagnosis.^{32,41} Further, clinical manifestations on the skin, such as rashes and petechiae, have been reported in Covid-19 patients,⁴² which are also commonly found in dengue.³³ A study in Italy found that Covid-19 patients presented with skin erythematous, rash, urticaria, and vesicles.⁴³ Skin manifestations have also been reported in Madrid.⁴⁴ Such skin manifestations, including rash or petechiae, increase the challenge in differentiating between dengue and Covid-19 in dengue-endemic regions.^{33,45} Misdiagnosis between Covid-19 and dengue based on clinical presentation was also reported in Thailand, where patients presented with petechiae and thrombocytopenia, were diagnosed as dengue but were later diagnosed with Covid-19 after developing respiratory symptoms and undergoing reverse transcription polymerase chain reaction (RT-PCR) testing.^{33,46} In addition, a study of 41 Covid-19 patients reported the occurrence of hematological disorders, such as leukopenia, decreased platelet count⁴⁰ and prothrombin time.⁴⁵

Beyond the similar clinical manifestations of Covid-19 and dengue, misdiagnosis may be due to serological cross-reactivity between SARS-CoV-2 and DENV. It was hypothesized that patients with previous exposure to DENV possess anti-DENV antibodies that are cross-reactive with SARS-CoV-2 antigens.³² Alternatively, there may be antigenic similarities between SARS-CoV-2 and DENV, such that upon

SARS-CoV-2 infection, the body is triggered to generate anti-DENV antibodies derived from memory B cells.³² These possibilities might have caused the false-positive phenomena in rapid dengue serology tests.

Misdiagnosis due to serology cross-reactivity between Covid-19 and dengue was first reported in Singapore where patients were initially confirmed to have dengue through dengue IgM and IgG rapid serological testing, but were later found to be positive for Covid-19 using RT-PCR testing.³⁴ Subsequent RT-PCR analysis were failed to detect DENV in both urine and blood samples, confirming the absence of dengue infection in the respective patients. This suggests the possibility of serological cross-reactivity between DENV and SARS-CoV-2, in particular when using rapid serology-based test, that could lead to significant challenges in dengue-endemic countries in Asia. In Indonesia for example, there have been no reports of misdiagnoses between Covid-19 and dengue in the literature. However, there has been an increase in dengue cases in the country; 68 000 cases have been reported as of June 21, 2020.²⁹ In Indonesia, most dengue cases were exclusively diagnosed with IgM and IgG rapid serological testing, if not clinically diagnosed.^{47,48} Therefore, it is possible that there were

Covid-19 cases among these dengue-diagnosed patients. In addition, it remains challenging to access Covid-19 testing in Indonesia, as reported early in the pandemic.⁴⁹ The lack of adequate laboratories across the country and low testing rate could hamper the diagnosis and management of Covid-19 patients.

The wide range of Covid-19 clinical symptoms and lack of a specific and affordable test to differentiate Covid-19 and dengue have led to serious impacts on community health in the dengue-endemic countries. The WHO has reported that the antigen-based rapid diagnostic test (RDT) for Covid-19 has a sensitivity of 34% to 80%.⁵⁰ Therefore, there is an urgent need for an affordable and accurate diagnostic method to prevent misdiagnosis of Covid-19 and dengue in Asian countries with limited resources.

2.2 | Shared pathophysiology between Covid-19 and dengue

Covid-19 and dengue exhibit some pathophysiological similarities, such as capillary leakage, thrombocytopenia, and coagulopathy

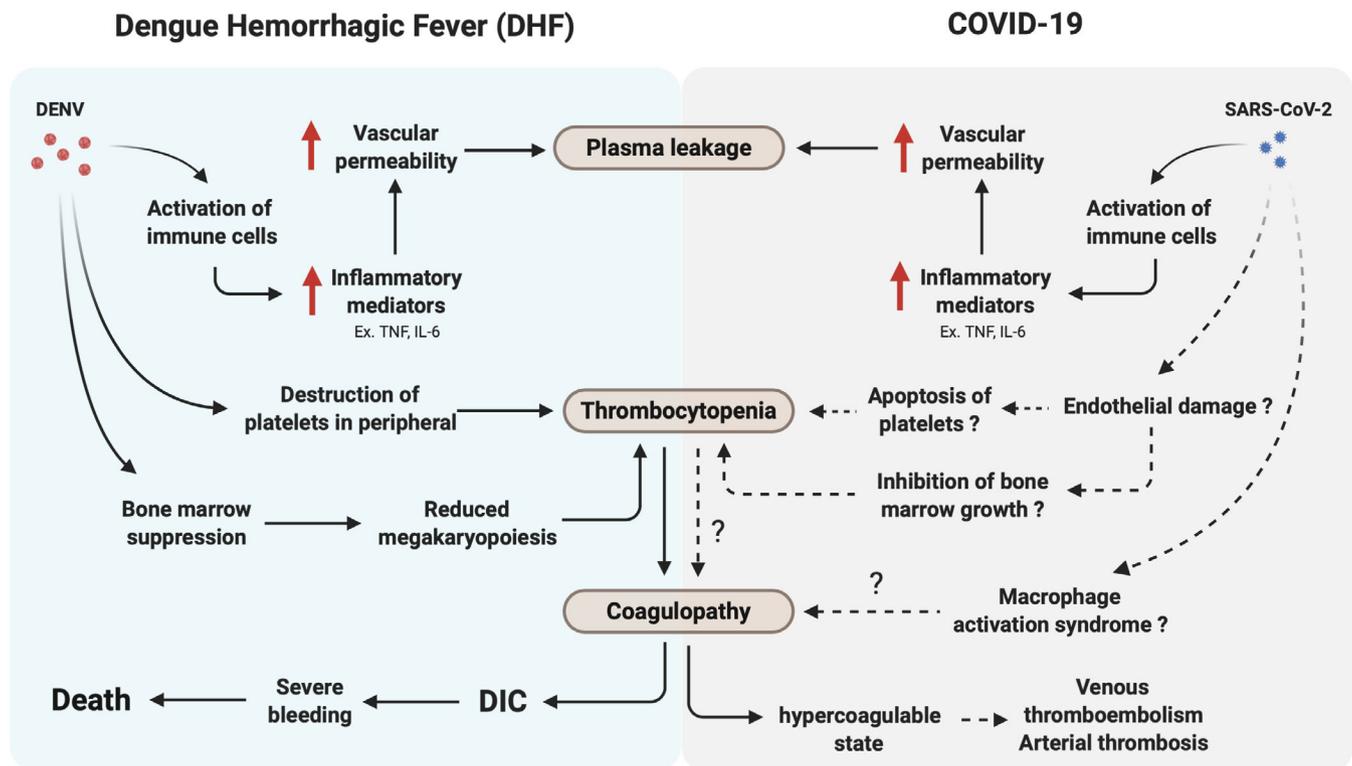


FIGURE 1 Pathophysiological similarities between DHF and Covid-19. Plasma leakage, thrombocytopenia, and coagulopathy are the hematological hallmarks of DHF and Covid-19. Both DENV and SARS-CoV-2 induce the activation of immune cells leading to the release of pro-inflammatory cytokines such as TNF and IL-6. This event promotes increased vascular permeability that leads to plasma leakage. In DHF cases, the destruction of platelets in the peripheral region by DENV has been suggested as the cause of thrombocytopenia which in the end culminates as coagulopathy, disseminated intravascular coagulation, and in some cases, resulting in the death. While thrombocytopenia was also evident in Covid-19 patients, pathophysiological mechanisms on how such event has occurred remain to be elucidated. Current data indicating that endothelial damage coupled with platelet apoptosis and impaired bone marrow growth might be the drivers of thrombocytopenia and coagulopathy in SARS-CoV-2-infected patients. The sequential pathophysiological process leads to the occurrence of DIC and the death of Covid-19 patients remains to be demonstrated

(Figure 1).³⁹ Plasma leakage is a crucial factor for dengue pathophysiology and is primarily mediated by the host immunological response. Several immuno-mediators, including pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), interferon gamma (IFN- γ), and chemokines such as macrophage migration inhibitory factor (MIF), are associated with plasma leakage.^{51,52} Altered platelet function⁵³ and increased C-reactive protein (CRP) levels^{54,55} are also responsible for plasma leakage. Covid-19 is characterized by over-activation of effector T-cell function and increased inflammatory cytokine production, especially IL-6, often leading to a cytokine storm.⁵⁶ IL-6, along with other inflammatory mediators, such as IL-1, TNF, and IFN- γ , contribute not only to plasma leakage but also to other vascular disorders, including vascular permeability and disseminated intravascular coagulation (DIC).⁵⁷ In dengue, plasma leakage is associated with the interaction between nonstructural protein 1 (NS1)-specific antibodies and proteins expressed on endothelial cell surfaces, that may pave the way for the elevated rate of viral replication and inflammatory cytokine secretion.⁵⁸⁻⁶⁰ However, the mechanism of capillary leakage in Covid-19 is not well understood and further studies are required to elucidate it.

Recent studies have demonstrated that the severity or progression of Covid-19 is positively associated with plasma CRP levels.⁶¹⁻⁶³ CRP is also important for dengue progression and may potentially be used as a prognostic biomarker.⁶⁴⁻⁶⁷ Hepatocytes primarily synthesize CRP upon stimulation through inflammation. CRP then binds various pathogens and activates the complement system through the classical pathway.⁶⁸

Thrombocytopenia is one of the main characteristics of DENV infection.⁶⁹⁻⁷³ In dengue, NS1 induces complement-mediated pathways, which cause platelet lysis.⁷⁴ DENV infected endothelial cells exhibit higher expression of E-selectin and P-selectin and increase the interaction of platelets with monocytes, leukocytes, and endothelium, which contribute to thrombocytopenia.⁷⁵⁻⁷⁸ In addition, elevated levels of platelet-associated immunoglobulin (PAIgM or PAIgG) are reported in dengue cases and are also correlated with thrombocytopenia.⁷⁴ Thrombocytopenia is also observed in Covid-19 patients.⁷⁹⁻⁸¹ A meta-analysis found that thrombocytopenia is associated with the severity of Covid-19.⁷⁹ SARS-CoV-2 infection has been speculated to lead to endothelial damage and interfere with the activity of certain receptors to inhibit bone marrow growth and induce apoptosis, leading to abnormal hematopoiesis and ultimately resulting in thrombocytopenia.⁸² Moreover, immune system-mediated specific destruction of platelets has also been observed in Covid-19 patients, which may arise from the elevated levels of immune complexes and autoimmune antibodies.⁸³ It is hypothesized that the cytokine storm damages the bone marrow hematopoietic progenitor cells, resulting in a decline in primary platelet production and a decline in platelet count in peripheral blood.⁸³ However, these speculations must to be investigated and verified in the context of SARS-CoV-2 infection.

Coagulopathy is one of the main pathologies associated with DENV infection^{84,85} and is also presented in cases of Covid-19.⁸⁶⁻⁸⁸ Both SARS-CoV-2 and dengue infections exhibit prolonged prothrombin time and partial thromboplastin time.^{89,90} Surprisingly, the activity

of coagulation factors, including prothrombin, factors V, VII, VIII, IX, and X, antithrombin, and α 2-antiplasmin, was markedly reduced during the acute febrile stage of dengue; while in contrast, it appears to increase in the Covid-19 patients.⁹¹ Growing evidence suggests that hypercoagulable state was evident in Covid-19 patients. This condition leads to the increasing incidence of venous and arterial thromboembolic diseases such as pulmonary embolism, venous thromboembolism, myocardial infarction, stroke, and other microvascular thrombosis (Figure 1).^{2,92-96} The pathobiology of coagulopathy in Covid-19 is not well understood. A recent study reported the presence of antiphospholipid antibodies in Covid-19 patients, including anticardiolipin IgA antibodies and anti- β 2-glycoprotein I IgA and IgG antibodies, which abnormally target several phosphoproteins.⁸⁹ The presence of these antiphospholipid antibodies is considered associated with coagulopathy.⁹⁷ However, several critical illnesses and other infections also elevated the levels of these antibodies; therefore, it is speculated that the presence of these antibodies might be less associated with the occurrence of any severe coagulopathies.⁹⁸ Studies have also reported the presence of DIC pre-terminally in Covid-19 patients.⁸⁶⁻⁸⁸

2.3 | Dengue and Covid-19: The role of antibody-dependent enhancement in disease progression

The pathogenesis of Covid-19 may include antibody-dependent enhancement (ADE).⁹⁹ Mechanistically, ADE involves the cross-linking of virus and antibody or virus and activated complement component complexes through interactions with cellular molecules, such as Fc and complement receptors or cell surface molecules, to promote internalization of the virus and increase the infection of monocytic and granulocytic cells.¹⁰⁰⁻¹⁰² Although the role of ADE has been reported in numerous contemporary viral diseases affecting humans and animals,¹⁰³⁻¹⁰⁵ dengue is arguably the best disease model to study this phenomenon.¹⁰⁶ DENV homotypic infection confers long-lasting and even life-time immunity. However, cross-neutralizing antibodies against re-infection of different serotypes are short-lived.^{107,108} At sub-neutralizing concentrations, these heterotypic antibodies may trigger ADE and are associated with higher odds of more severe forms of secondary infection when present at relatively low levels in children.¹⁰⁹ This condition affects the development of a dengue vaccine, given that vaccination is considered to mimic a primary infection. Indeed, the diminishing levels of antibodies may pose a serious risk of ADE occurrence in children with secondary infections¹¹⁰ and may cause alert for vaccine-induced enhancement of viral infection.¹¹¹⁻¹¹³

Approximately 40-45% of SARS-CoV-2 infection may be asymptomatic,¹¹⁴ despite clinical findings explaining the pathological mechanism of Covid-19 as both directly cytotoxic and immune-mediated.¹¹⁵ SARS-CoV-2 infection induces an exuberant inflammatory response, known as a cytokine storm,¹¹⁶ which subsequently results in uncontrolled pulmonary inflammation primed by rapid viral replication, cellular damage, virus-induced downregulation of angiotensin converting enzyme 2 (ACE2), viral shedding, and ADE.¹¹⁷ In

coronaviruses, ADE may function through the interaction of Fc, or other receptors in susceptible cells, with the complex between virus and anti-spike (S) protein-neutralizing antibodies, thereby facilitating both inflammatory responses and persistent viral replication in the lungs.^{102,117,118} ADE have been reported in severe acute respiratory syndrome coronavirus (SARS-CoV) infection and has been observed in vaccine-induced infections by a SARS-CoV vaccine through an Fc gamma receptor II (FcγRII)-dependent mechanism.¹¹⁹ Polymorphic FcγRIIA on monocytes has been reported to favor ligation of non-neutralizing antibody-virus complexes in both dengue and Covid-19. In dengue, this ligation activates the expression of negative regulators of dihydroxyacetone kinase and autophagy proteins (cascade of down-regulatory pathways) to decrease production of type I IFN-activated antiviral molecules and suppress the capacity of macrophage antiviral mechanisms, leading to enhanced viral replication.¹²⁰ FcγRIIA-mediated enhancement has been reported in SARS-CoV in a study of 180 people from Hong Kong who were infected with SARS-CoV. Moreover, it was found that FcγRIIA polymorphism affects disease severity.¹²¹

ADE of SARS-CoV is thought to utilize a novel cell entry mechanism for entry into immune cells, wherein antibody-mediated infection is dependent on FcγRII but does not utilize the endosomal/lysosomal pathway through the ACE2 receptor.¹²² Viral neutralization was demonstrated with concentrated antisera against the S protein, although higher dilutions failed to neutralize the infective virus and even induced apoptosis caused by increased viral infection. In contrast, anti-nucleocapsid (N) protein antibodies neither neutralized the virus, nor caused ADE. However, nucleocapsid proteins have been observed to induce cytotoxic T lymphocyte (CTL) immune responses that are specifically SARS-CoV-2 protective.¹¹⁸

The modulation of pathogenesis among diseases caused by viruses from the same family has been previously described, such as between Zika and dengue.^{113,123} Prior infections with other coronaviruses, ranging from those that cause the common cold to SARS, are thought to have primed Covid-19, and might lead to the development of severe SARS-CoV-2 infection.⁹⁹ However, the molecular and immunological host response to SARS-CoV-2 infection have not yet been fully elucidated to confirm ADE.¹²⁴ In the tropical areas of the world, the apparent cross-reactivity between antibodies in dengue and Covid-19 serology tests have been reported.¹²⁵ A study in Colombia found that there was a decreasing trend of dengue during increasing reports of Covid-19 and it was speculated it might be due to viral interference of SARS-CoV-2 over DENV.¹²⁶ Studies are needed to identify the interaction between these antibodies against dengue and Covid-19. How will Covid-19 pathogenesis in populations where the immunities to DENV or other arboviruses are present? Furthermore, the mechanism of ADE in viral infection has become a great concern to disease control by vaccination. Therefore, the development of SARS-CoV-2 vaccines has to incorporate approaches to develop the vaccine with minimum or no risk for ADE, if ADE exists in COVID-19.

2.4 | Covid-19 and dengue cross-reactivity: Consequences for Covid-19 vaccine development

Vaccine development must account for safety measures, including immune-related adverse events (irAE) that may result from vaccination. ADE leading to a cytokine storm is a hallmark of SARS-CoV pathogenesis and disease severity,¹²⁷ and of dengue infection.¹⁰⁹ This may also be the case for SARS-CoV-2.²⁸ ADE has been suggested to be caused by pre-existing, non-neutralizing, low-affinity antibodies,¹¹¹ along with neutralizing antibody¹²⁸; therefore, the antigen design of a vaccine must ensure correct antigen conformation¹²⁹ or spike-based subunit vaccines lacking the receptor binding domain (RBD).¹²⁸

A recent study demonstrated that SARS-CoV-2 infection provides protection from re-challenge in rhesus macaques;¹³⁰ however, the phenomenon in humans requires further investigation. Studies on vaccine candidates should examine whether antibodies raised by vaccine administration result in protection or ADE. Pre-clinical trials of several SARS-CoV-2 vaccine candidates have demonstrated protection after challenge in animals,^{131,132} but similar results in humans and the absence of ADE have yet to be observed. Given that anti-SARS-CoV-2 antibodies have been indicated to cross-react with DENV antigens within dengue rapid serological kits,³⁴ there is a possibility that anti-SARS-CoV-2 antibodies raised by a Covid-19 vaccine candidate may also cross-react with DENV antigens. Because ADE in dengue most often results in severe disease progression^{18,133} and ADE have been observed previously in other coronavirus,^{118,119} it would be advisable to also evaluate the possible effect of ADE-induced vaccine in Covid-19.

3 | CONCLUSION, RECOMMENDATIONS AND FURTHER PERSPECTIVE

As dengue-endemic region, some countries in Asia experiencing of overlapping outbreaks of dengue and Covid-19. This poses a challenge for accurate diagnosis and treatment since both infections share similar symptoms and laboratory features in the early phase. In addition, cross-reactivity between antibodies against DENV and SARS-CoV-2 serology tests have been documented in reports. Therefore, a simple and affordable rapid test capable of differentiating SARS-CoV-2 and DENV with high sensitivity, is urgently needed. In addition, there is an urgent need to establish additional laboratories to perform specific RT-PCR testing for SARS-CoV-2 in the region.

Although some studies have speculated the possible interaction between SARS-CoV-2 and DENV¹²⁶ and the possible of ADE in SARS-CoV-2 infection,¹³⁴ no strong evidence yet to support this and further studies are warranted to elucidate this association. There is minimal analysis of the immunological differences in the mechanisms of enhancement and differences in receptor binding viral proteins among two genetically diverse RNA viruses such as DENV and SARS-CoV-2. Detailed receptor sequence analysis would be required to substantiate the possibility of cross-reactivity between DENV and SARS-CoV-2 antibodies and to establish the immunological relations

between the antibodies elicited by DENV infection and their impact on Covid-19 and vice versa.

Other perspectives that need to be explored are the role of vector control and changes of DENV serotype circulating during the Covid-19 pandemic in the region. During the pandemic, vector control measures might have decreased in the community and dengue prevention programs might have been paused in some countries. Therefore, countries that are experiencing or have high risk for dengue outbreak should maintain the vector control measures during the pandemic.¹³⁵ One of the most possible strategies is to improve within-household strategies by encouraging community members to reduce mosquitoes breeding sites in and around the homes. Lastly, displacement of DENV serotypes or genotypes leading to the cyclic pattern of dengue have been reported in several countries in Asia previously.^{47,48,136-138} This could be another possible reason for the observed increase of dengue cases during Covid-19 pandemic. Continuous dengue surveillance needs to be in place to track transmission dynamics of DENV infection in the region.

CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization, Harapan Harapan; validation, Harapan Harapan, Mirza Ryan, Benediktus Yohan, Rufika Shari Abidin, Firzan Nainu, Ahmed Rakib, Israt Jahan, Talha Bin Emran, Irfan Ullah, Kritu Panta, Kuldeep Dhama, and R. Tedjo Sasmono; writing—original draft preparation, Harapan Harapan, Mirza Ryan, Benediktus Yohan, Rufika Shari Abidin, Firzan Nainu, Israt Jahan, Talha Bin Emran, and Kritu Panta; writing—review and editing, Harapan Harapan, Benediktus Yohan, Firzan Nainu, Kuldeep Dhama, and R. Tedjo Sasmono. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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