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Dengue Lurks During Coronavirus Disease-19 Pandemic in Indonesia: A Narrative Review

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Abstract

BACKGROUND: Most attention and healthcare resources in Indonesia have been geared toward battling the coronavirus (CoV) disease (COVID)-19 pandemic, and less overture has been given to the looming risks of dengue that has been endemic in many areas of Indonesia. Despite related constraints, the Primary Health Cares (PHC) in Indonesia plays an important role in the face of emergency situations.

AIM: This study aimed to review the dengue and COVID-19 infection, clinical manifestations in children and adults, clinical pathology findings, as well as the prevention strategies that could be applied in PHC.

METHODS: This study is a narrative review based on the research articles and reports that were published between 2010 and 2020. A total of 70 articles and reports were obtained and after careful consideration, 58 articles and reports were used as references of this study.

RESULTS: Both dengue virus (DENV) and severe acute respiratory syndrome-CoV (SARS-CoV-2) share the similarity of antigenic structure, common symptoms, and laboratory findings. The immune response in SARS-CoV-2 may cause a cytokine storm, which can increase vascular permeability and organ damage. Secondary infection of DENV with different strains may allow the occurrence of antibody-dependent enhancement. The cross-reactions between SARS-CoV-2 antibodies and DENV antigens may cause false positive on rapid dengue infection serological tests.

CONCLUSION: PHC as the front line of health services has a fundamental role in the crisis situation. The prevention and control of DENV and SARS-CoV-2 infections are based on the mode of transmission and need compliance to the related health protocols.

Introduction

The Indonesia's healthcare system has been overwhelmed by the sudden struck of coronavirus (CoV) disease (COVID)-19 pandemic. After the first two confirmed cases of COVID-19 in Indonesia were reported in March 2, 2020 [1], the disease has spread rapidly to almost all parts of Indonesia that were totally unprepared for the crisis. Being the world's fourth most populous nation [2], Indonesia might suffer immensely compared to less-populous countries [3]. Based on the rising cases, fatalities, and a large-scale socioeconomic impact, on April 13, 2020, the President declared COVID-19 as a national disaster in Indonesia [4].

Most attention and healthcare resources in Indonesia have been geared toward battling the COVID-19 pandemic, and less overture has been given to the looming risks of dengue, despite the fact that dengue has been endemic in many areas of Indonesia and around the period of 1968-2009, Indonesia had a history of the highest cases of dengue hemorrhagic fever (DHF) in South East Asian region [5]. As of 9 July 2020, the Ministry of Health of the Republic of Indonesia revealed that five provinces with high cases of DHF also reported a high case fatality rate (CFR) of COVID-19, namely East Java (5948 DHF cases and COVID-19 CFR 7.3%), Special Capital Region of Jakarta (4227 DHF cases and COVID-19 CFR 5.0%), Central Java (2846 DHF cases and COVID-19 CFR 4.3%), West Java (10,772 DHF cases and COVID-19 CFR 3.8%), and Bali (8930 DHF cases and COVID-19 CFR 1.3%) [6], [7].

Both DHF and COVID-19 battle on two fronts of healthcare need. The heterogeneity of 514 districts in Indonesia by geographical features, demographical characteristics, cultures, local living styles, health-seeking behaviors, and community participations [8] creates challenges in the prevention and control strategies to combat the double burden of diseases. The introduction of universal health coverage with a single-payer system in 2014 that currently covers around 203 million people makes the Primary Health Care (PHC) Centres play

a significant role in the face of emergency situations. Accordingly, this study aimed to review the dengue and COVID-19 infection, clinical manifestations in children and adults, clinical pathology findings, as well as the prevention strategies that could be applied in PHC.

Search Strategy

This study is a review based on the research articles and reports related to dengue virus (DENV), pathogenesis of dengue, epidemiology of dengue in Indonesia, dengue prevention, COVID-19 virology and pathogenesis, COVID-19 and DHF clinical findings, COVID-19 and DHF clinical pathology findings, epidemiology of COVID-19 in Indonesia, and COVID-19 prevention that were published between 2010 and 2020. References from published articles were also included in the review, as long as they were published between 2010 and 2020. We excluded expert's point of views. A total of 70 articles and reports were obtained and after careful consideration, 58 articles and reports were used as references of this study.

Epidemiology of DHF and COVID-19 in Indonesia

In Indonesia, DHF was first reported in Surabaya in 1968, with a high CFR of 41.38%. Dengue has spread to many areas in Indonesia and has become a public health concern since then [5]. DHF usually reaches its peak around March and diminish in the following months, which are the transition months between rainy and dry season. Nonetheless, during the COVID-19 pandemic, DHF cases in Indonesia have still been escalating with reports of more than 71,663 cases and 459 deaths from January to July 2020, even though the recorded cases and deaths were lower compared to reports from January to July 2019 with 112,954 cases and 751 deaths [6].

The incidence rate of DHF in Indonesia (red curve in Figure 1) seemed to increase in a span of half a century, from around 0.05 cases per 100,000 person-years in 1968 to around 77.96 cases per 100,000 person-years in 2016; with a peak of cyclic pattern occurring nearly 6–8 years. In contrast, the annual CFR of DHF has decreased afterward (green curve in Figure 1), from more than 20% in 1968 to 0.79% in 2016 [9].

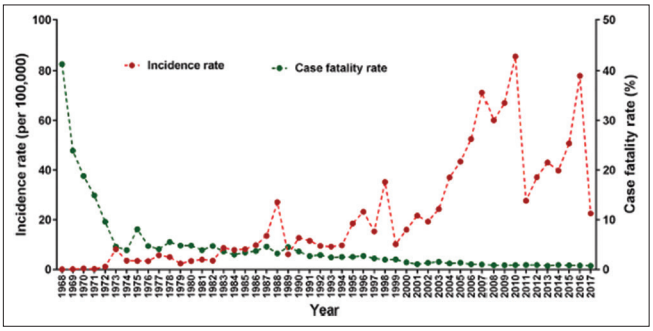

Figure 1: Incidence rate (per 100,000 person-years) and case fatality rate (%) of dengue hemorrhagic fever in Indonesia from 1968 to 2017 [9]

In the meantime, the Ministry of Health of the Republic of Indonesia recorded the increase number of COVID-19 confirmed cases from the first two cases reported in March 2, 2020, to 365,240 confirmed cases reported on October 19, 2020 (Figure 2). There was a sharp increase in attack rate (AR = percentage of confirmed cases by population size per 100,000 people) from 0.7% in March 2, 2020, to 136.4% in October 19, 2020. The calculation was based on the estimated current population of Indonesia in 2020 (267,700,000 people). There was a decrease of case positivity rate (CPR = percentage of confirmed cases by number of specimens tested) from 24.1% in April 2, 2020 to 14.3% in October 19, 2020; an increase of case recovery rate (CRR = percentage of recover cases by confirmed cases) from 6.3% in April 2, 2020 to 79.2% in October 19, 2020; and a decrease of (CFR = percentage of death cases by confirmed cases) from 9.5% in April 2, 2020 to 3.5% in October 19, 2020 [10]. Yet, the recorded COVID-19 data might not represent the number of actual infections, which could be undetected due to several factors, including lack of proper tracing and diagnoses [3].

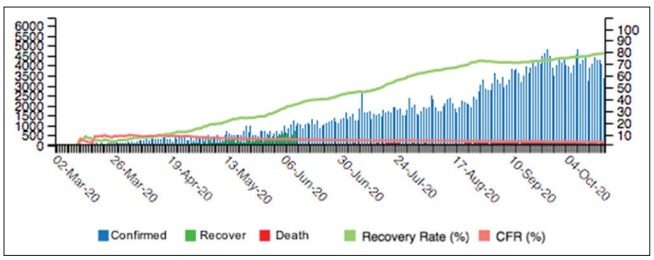

Figure 2: Number of coronavirus disease-19 confirmed cases, recover, death, RR, and CFR as of October 19, 2020 [10]

Epidemiological studies of COVID-19 may provide an insufficient representation of pediatric population. A study involving 582 children conducted in 25 European countries reported a CFR of 0.69%. Conversely, CFR in infants less than a month old to adolescents with COVID-19 reach 1.1% in Indonesia [11].

Dengue and severe acute respiratory syndrome-CoV (SARS-CoV-2) viruses

DENV belongs to the *Flaviviridae*, a family of positive, single-stranded, enveloped RNA viruses [12]. The transmission of DENV is mediated by mosquito vectors, *Aedes* spp. DENV consists of four serotypes, namely, DEN-1, DEN-2, DEN-3, and DEN-4 [13].

Dengue viral genome component (Figure 3) comprises genes that encode structural proteins and non-structural proteins. The structural protein genes contain codes to form protein M (membrane), C (capsid), and E (envelope), and these outer proteins

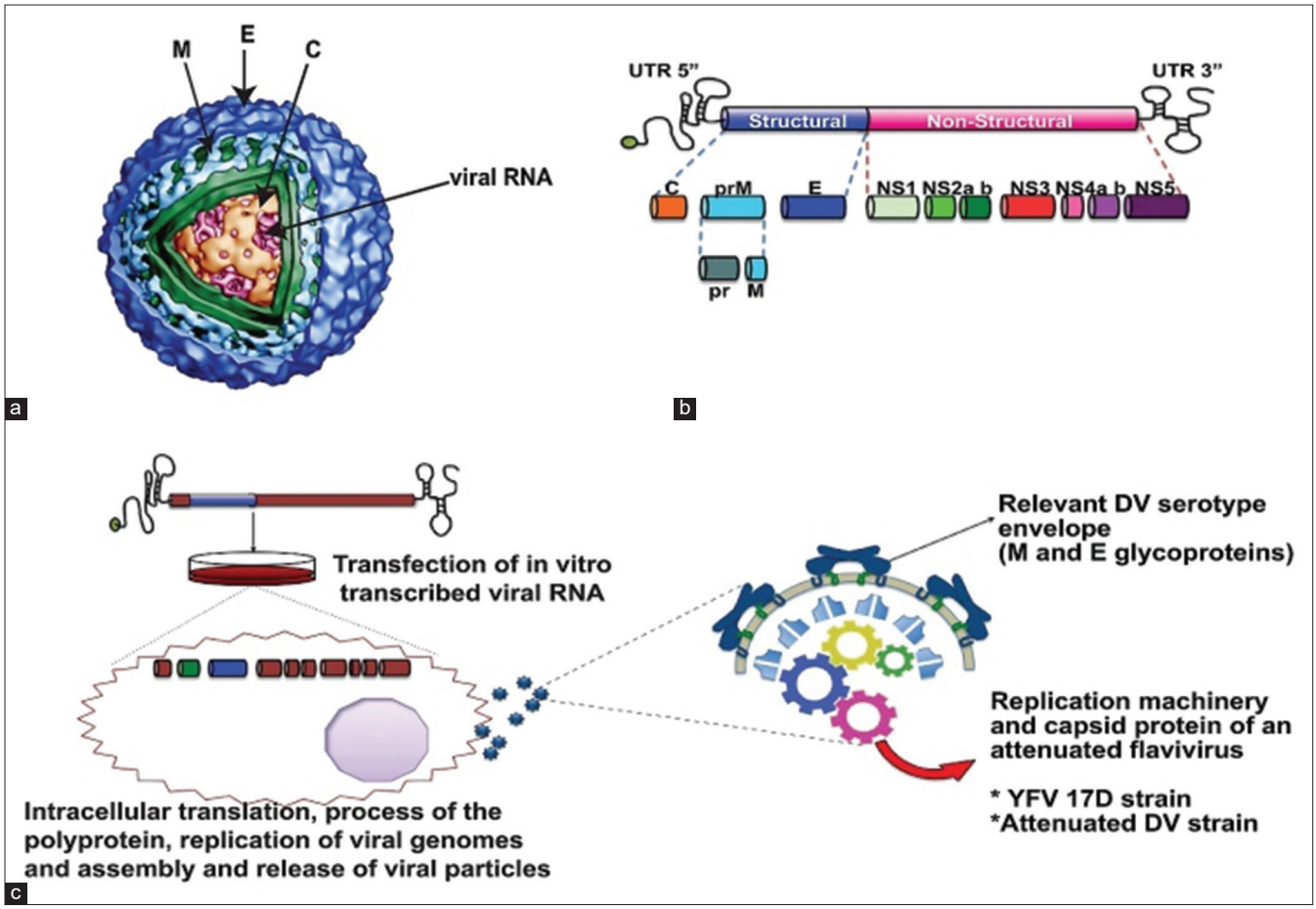

Figure 3: (a-c) Dengue viral genome component [14]

will bind to human antibodies. In contrast, the non-structural protein genes contain codes to form enzymes that are needed for virus replication [14].

Virus that causes COVID-19 (SARS-CoV-2) is one of the *Corona* strains that infect humans (Figure 4). The CoV genome encodes four main proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E). S protein is responsible for the entry of viruses into cells that express angiotensin-converting enzyme 2 (ACE2) receptors. Approximately 75% of the SARS-CoV-2 genome is identical to the SARS-CoV genome, in which both viruses use ACE2 receptors to infect epithelial and endothelial barrier cells of the airway mucosa [17].

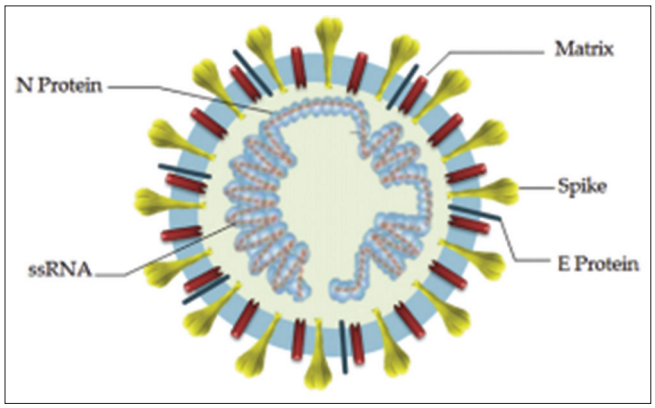

Figure 4: SARS-CoV-2 structure [15], [16]

DENV Infection

Following infection, DENV replicates in the skin cells, including keratinocytes and Langerhans cells [18], which then trigger various host innate immune responses, including macrophage [19], [20], [21]. The bonding complex between receptors on the surface of cytotoxic T cells, major histocompatibility complex I (MHC I) molecules, virus peptides, and macrophage cells will act as antigen-presenting cells. After the bonding complex occurs, CD8 cells will produce cytokines, which will cause macrophage to undergo apoptosis [22], [23], [24]. Dengue may also infect mast cells, causing degranulation and release of several inflammatory mediators, which can increase vascular permeability and vascular leakage [25], [26].

The innate and adaptive immune response phases will determine the clinical symptoms that appear in infected patients. If both systems successfully kill the DENV, then there will be a low viremia or no virus so that the patient does not show clinical symptoms (subclinical). However, if the virus remains in moderate amounts (moderate viremia), then the clinical symptoms appear as dengue fever. If the virus escapes from the immune system and lead to severe viremia, then the clinical symptoms appear as dengue hemorrhagic fever, with life-threatening emergency symptoms, such as bleeding, shock, and death [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27].

DENV is also able to infect endothelial cells (Figure 5). The demise of endothelial cells by apoptosis will increase blood vessel permeability and cause plasma and red blood cell leakage, which is clinically seen as bleeding [28].

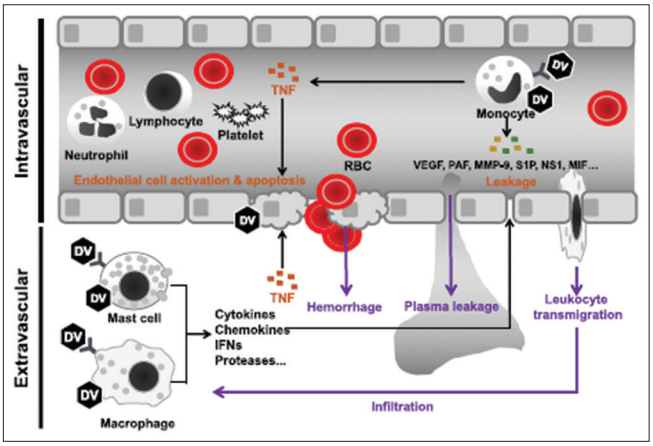

Figure 5: Pathogenesis of extra and intravascular bleeding [28]

Antibodies in dengue infection are produced by plasma cells derived from differentiation of B lymphocytes, by activation of CD4 cells through the intermediary molecule MHC II. Anti-dengue antibodies, part of host humoral pathways, are specific to DENV and will bind as lock and key to neutralize the virus [13]. The mechanism occurs in the first infection by DENV and secondary infection from the same serotype. However, if a secondary infection is caused by a different serotype of DENV (Figure 6), the antibodies assembled from the previous infection are not able to neutralize the virus from the second infection but will cause the fragment crystallizable region (Fc) antibody fragment to attach to antibody receptors on the macrophage cell surface. This attachment causes the entry of DENV into these cells and causes massive viral replication, increase in viral load, and release of several inflammatory mediators, which is referred to as antibody-dependent enhancement (ADE). Clinical manifestations that occur are dengue hemorrhagic fever, dengue shock syndrome, or death [29], [30].

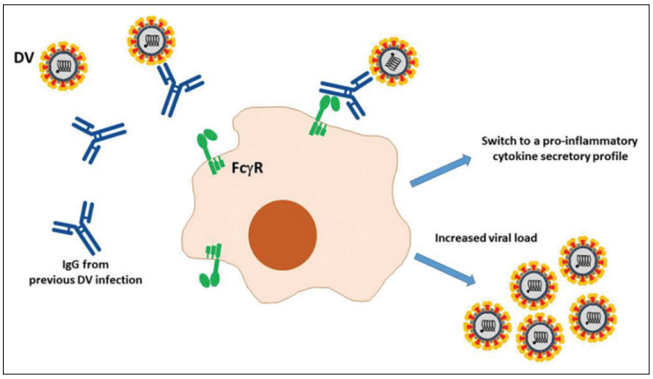

Figure 6: Pathogenesis of ADE in secondary dengue infection with different serotype [29]

SARS-CoV-2 Infection

When a CoV infects macrophage cells (Figure 7), NK cells as part of the innate immune system lyse both the infected macrophage cells and the viruses inside them. If macrophages fail to lyse the virus, they will activate CD4 cells. CD4 cells will differentiate into Th2 and Th1. Th1 cells will release inflammatory mediators to strengthen the role of macrophage cells. Whereas Th2 cells will help differentiate B lymphocyte cells into plasma cells and produce specific antibodies for this virus and then act as neutralizing antibodies [31], [32].

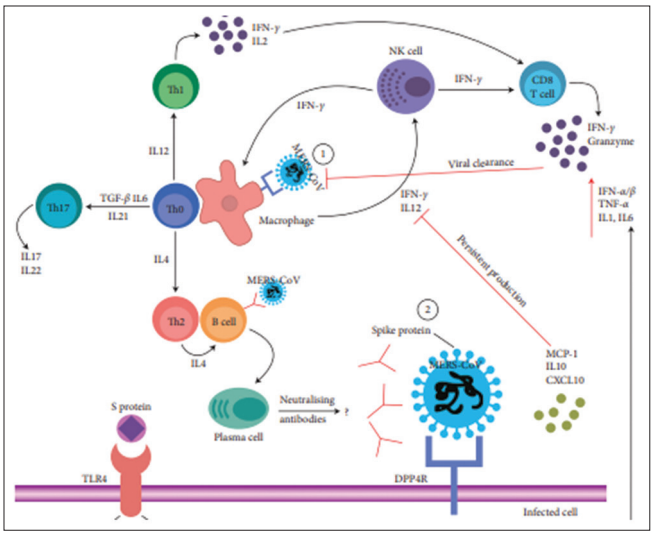

Figure 7: Immune response to coronavirus infection [32]

One of the main features of SARS-CoV-2 infection is the emergence of cytokine storms that produce an uncontrolled systemic inflammatory response from the release of pro-inflammatory cytokines and chemokines by immune cells. Cytokine storms trigger severe inflammatory responses that cause acute respiratory distress syndrome, multiple organ failure, and death [17].

Dengue Fever and COVID-19 Infection

Previous research [33] proposed a possibility of viral interference mechanism [34] of SARS-CoV-2 over DENV. SARS-CoV-2 has a high virulence and pathogenicity, and both SARS-CoV-2 and COVID-19 have a tropism toward endothelial cells [35], [36], which could lead to competitive inhibition. Dengue fever and COVID-19 may have similar clinical symptoms in the early stages and similar laboratory features [37], [38]. COVID-19 cases may be misdiagnosed as dengue, especially when relying on DENV IgM, which can remain positive months after infection [39]. Some common symptoms observed in COVID-19 and dengue patients may include fever, malaise, myalgia, headaches, and weakness [40]. COVID-19 may also produce symptoms such as cough, dyspnea and dysgeusia, sore throat, anosmia, and diarrhea, whereas adult patients with dengue may also suffer from retro-orbital pain, nausea/vomiting, rashes, and arthralgia [39].

It is still puzzling why children with COVID-19 suffer less severe symptoms than adults. A previous study suggested that children might be less sensitive to SARS-CoV-2 due to the maturity and function (e.g., binding ability) of ACE2 in children may be lower than that in adults. Further, the developing immune system in children may respond differently to pathogens [41].

Some common hematological findings in COVID-19 are lymphocytopenia, neutrophilia, eosinopenia, mild thrombocytopenia, and rarely thrombocytosis [42]. Neutrophil-lymphocyte ratio (NLR) in dengue fever is inversely correlated with the degree of severity, whereas NLR in COVID-19 is in line with the severity of the disease [43]. The increase in the inflammatory factor that occurs in COVID-19 may cause a decrease in erythrogenesis and cause erythrocyte destruction, which results in anemia [44]. In addition, coagulation abnormalities often occur in COVID-19, namely an increase in prothrombin time and d-dimer [45].

In dengue-endemic areas, there is also a possibility of false-positive results in serological tests for dengue fever. Due to the similarity of antigenic structure, SARS-CoV-2 can trigger the production of anti-DENV antibodies from immunological memory of T and B cells derived from previous exposure to the DENV virus. The anti-DENV antibodies against dengue may cause a false positive result of rapid dengue test and fail to consider COVID-19 infection, which leads to serious implications for both patients and public health [37]. Moreover, in patients with chronic co-morbidities, overlapping infections may increase the number of the patient requiring intensive care unit and mechanical ventilation [33].

Preventing DENV and SARS-CoV-2 Transmission

A vaccine to prevent dengue is available in some countries for people ages 9–45 years old with confirmed prior DENV infection [46]. DHF prevention and control focus on breaking the life cycle of *Aedes* spp. mosquito vectors with biological, physical, and chemical approaches that have been part of national health programs and have been introduced to the community since 1968 [47]. The popular physical approach of DHF prevention in the community is to eradicate mosquito's breeding place by draining water reservoirs once a week, covering water reservoir, and recycling used containers [48]. The application of biological agents, which are directed against the larval stages of dengue vectors, include fish (e.g., *Gambusia affinis*), bacteria (e.g., *Bacillus thuringiensis*), Cyclopods, and autocidal ovitraps. The chemical control may include chemical larviciding, insect growth regulators, and space sprays with organophosphate insecticides [49].

In contrast, SARS-CoV-2 may be transmitted primarily through contact, respiratory droplet (>5–10 μm in diameter), and droplet nuclei (aerosol, ≤5 μm in diameter) [50] when an infected person talks, coughs, sings, or sneezes [51]. However, it may also be possible to be transmitted through airborne [52], fomite (contaminated services) [53], fecal-oral [54], bloodborne, mother-to-child, and animal-to-human [55].

Many countries apply lockdown strategies to reduce the impact of COVID-19 pandemic [56]. PHC as the front line of health services has a fundamental role in the crisis situation, related to its knowledge of the catchment areas, accessibility, following up on suspected and mild cases that are directed toward restraining the pandemic and preventing the spread of the disease, as well as preventing the disease progression [56].

The prevention of COVID-19 may include washing hands with soap and water or an alcohol-based hand sanitizer; maintaining physical distance between persons; avoid going to crowded places; and avoid touching eyes, nose, and mouth [57], [58]. The health protocols to prevent the transmission of SARS-CoV-2 have been applied in workplaces, schools, health-care facilities, homes, and other public places in Indonesia [58], and compliance to the health protocols is needed.

Conclusion

Both DENV and SARS-CoV-2 share similarity of antigenic structure, common symptoms, and laboratory findings. The immune response in SARS-CoV-2 may cause cytokine storm, which can increase vascular permeability and organ damage. Secondary infection of DENV with different strains may allow the occurrence of ADE. The cross-reactions between SARS-CoV-2 antibodies and DENV antigens may cause false positive on rapid dengue infection serological tests. DENV is transmitted by *Aedes* spp., whereas SARS-CoV-2 may be transmitted through contact, respiratory droplet, aerosol, and other modes.

The sudden struck of COVID-19 pandemic and the surge of dengue causes a huge impact on health-care system in Indonesia. PHC as the front line of health services has a fundamental role in the crisis situation in restraining the pandemic and preventing the spread of the disease, as well as preventing the disease progression. The prevention and control of DENV and SARS-CoV-2 infections are based on the mode of transmission and need compliance to the related health protocols.

Authors' Contributions

Study design: WD and RB. Data acquisition: WD, RB, PAN, MFI, and VB. Drafting of manuscript: WD and RB. Critical revision of the manuscript: WD, RB, PAN, MFI, and VB.

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