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THE SURGE OF DENGUE CASES DURING COVID-19 IN INDONESIA

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Abstract

Most healthcare resources in Indonesia have been engulfed by COVID-19 pandemic, and less attention has been given to the rising cases of dengue that has been endemic in many areas of Indonesia.

Present study aimed to review the immunopathogenesis of dengue and COVID-19 infection, as well as their prevention strategies.

This study is a narrative review based on the research articles and reports published between 2010-2020. A total of 60 articles and reports were obtained and after careful consideration 49 articles and reports were used as references of this study.

The immune response in Dengue virus and severe acute respiratory syndrome coronavirus 2 infections aims to eliminate the virus, but it causes an increase in inflammatory mediators (cytokine storm) which can increase vascular permeability and organ damage. Secondary infection of Dengue virus with different strains may allow the occurrence of antibody-dependent enhancement. The possibility of antibody-dependent enhancement in severe acute respiratory syndrome coronavirus 2 infection has been studied in vitro and in animal studies. Dengue virus and severe acute respiratory syndrome coronavirus 2 infections have antigenic similarities and trigger memory B cells. The cross reactions between severe acute respiratory syndrome coronavirus 2 antibodies and Dengue virus antigens may cause false positive on rapid dengue infection serological tests.

The prevention and control of Dengue virus and severe acute respiratory syndrome coronavirus 2 infections are based on the transmission mode, and people should comply to the related health protocols

Keywords: *Dengue, COVID-19, antibody-dependent enhancement.*

Introduction

On March 2, 2020, the first two confirmed Coronavirus Disease (COVID-19) cases were registered in Indonesia [*MH RI, 2020e*]. On March 11, 2020, WHO declared COVID-19 as a pandemic, after more than 118,000 cases had spread to more than 110 countries [*VERTIC, 2020*]. The disease has spread fast to almost all parts of Indonesia, causing a massive strain on Indonesia's healthcare system along with a surge of COVID-19 cases and deaths. Based on the rising fatalities and extensive socio-economic impact, on April 13, 2020, the President declared COVID-19 as a national disaster [*Cahya G, 2020; WHO, 2020a*].

While most healthcare resources in Indonesia have been engulfed by COVID-19 pandemic, less attention has been given to the rising cases of dengue, despite a history that Indonesia had the highest cases of dengue hemorrhagic fever (DHF) in South East Asian region from 1968-2009 [*Soepardi J, 2010*]. Dengue fever has been originally reported in Surabaya in 1968 in Indonesia, with 58 people being

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affected and 24 dead, resulting in 41.38 percent case fatality rate (CFR). Dengue has spread to many areas in Indonesia and has become a public health concern since then [*Soepardi J, 2010*].

In Indonesia, DHF usually reaches its peak around March and dwindles in subsequent months, which are transition months between rainy season and dry season. However, during COVID-19 pandemic, DHF cases in Indonesia have still been increasing 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 [*MH RI, 2020g*].

As of July 9, 2020, ten provinces reported highest number of DHF cases in 2020: West Java (10,772 cases), Bali (8,930 cases), East Java (5,948 cases), East Nusa Tenggara (5,539 cases), Lampung (5,135 cases), Special Capital Region of Jakarta (4,227 cases), West Nusa Tenggara (3,796 cases), Central Java (2,846 cases), Special Region of Yogyakarta (2,720 cases), and Riau (2,255 cases) [*MH RI, 2020g*]. As of July 9, 2020, five of the ten provinces that reported highest cases of DHF also reported highest cases of COVID-19, i.e., East Java (CFR 7.3%), Special Capital Region of Jakarta (CFR 5.0%), Central Java (CFR 4.3%), West Java (CFR 3.8%), and Bali (CFR 1.3%) [*MH RI, 2020f*]. The double burden of diseases has baffled health workers as both DHF and COVID-19 viruses might have similar symptoms in early stages and both battle on two fronts of healthcare need. Therefore, this study aimed to review the immunopathogenesis of dengue and COVID-19 infection, as well as their prevention strategies.

Search Strategy

This study is a narrative review based on the research articles and reports related to dengue virus, immunopathogenesis of dengue, epidemiology of dengue in Indonesia, dengue prevention, COVID-19 virology and pathogenesis, epidemiology of COVID-19 in Indonesia, and COVID-19 prevention that were published between 2010-2020. References from published articles were also included in the review, as long as they were published between 2010-2020. We excluded expert's point of views. A total of 60 articles and reports were obtained and after careful consideration 49 articles and reports were used as references of this study.

Table 1

Number of DHF cases, deaths and CFR from January to April (four months)

Cases	Years			
	2017	2018	2019	2020
Number of cases	39,213	26,441	83,059	45,256
Number of deaths	206	218	625	297
CFR	0.53%	0.82%	0.75	0.66%

Epidemiology of Dengue Hemorrhagic Fever in Indonesia

Around half a century (1968-2017), there was an annual increase of incidence rate (IR) of DHF in Indonesia (Fig. 1, red curve), 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 peak of cyclic pattern prevailing nearly 6-8 years [*Harapan H et al., 2019*]. In contrast, the annual case fatality rate (CFR) of design history file (DHF) has decreased subsequently (Fig. 1, blue curve), from more than 20% in 1968 to 0.79% in 2016 [*Harapan H et al., 2019*].

From 2011 to 2020, West Java had the highest average number of DHF cases annually [*Harapan H et al., 2019; MH RI, 2020c*]. The four months' data from January to April 2017 to 2020 revealed the highest number of DHF cases was in 2019, while the highest DHF CFR was in 2018 (Table 1) [*MH RI, 2020c*].

Dengue Virus

Dengue virus (DENV) is one of Arthropod-borne viruses (arbo virus), in which its transmission is mediated by mosquito vectors, *Aedes* spp. Dengue virus belongs to the *Flaviviridae*, a family of positive, single-stranded, enveloped RNA viruses [*Westaway E et al., 1985; Choumet V, Desprès P, 2015*], consists of four serotypes, namely DEN-1, DEN-2, DEN-3 and DEN-4 [*Martina B et al., 2009*]. Further, dengue virus is endemic in more than 100 tropical and subtropical

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

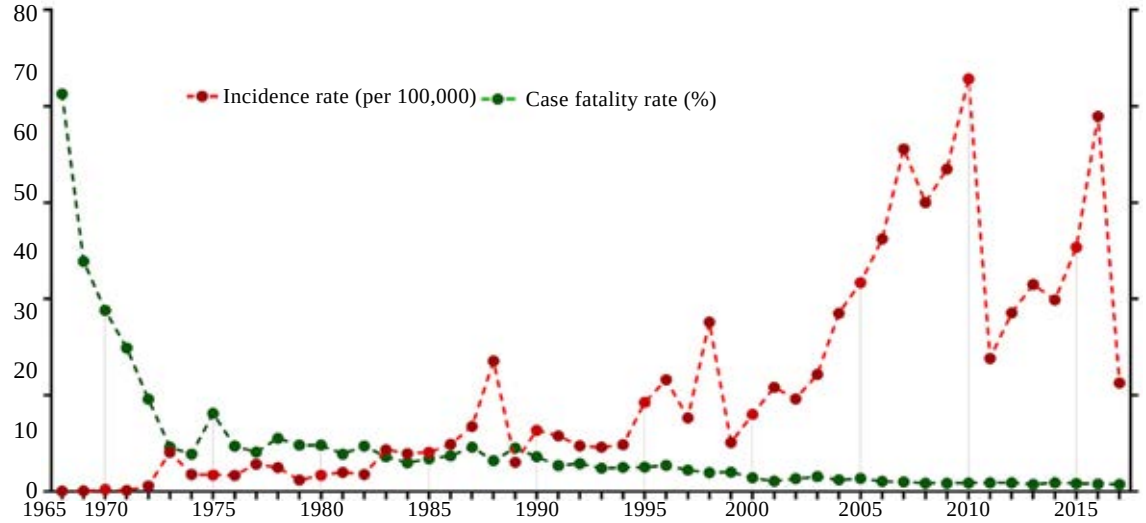

Figure 1. *Incidence rate (per 100,000 person-years) and case fatality rate (%) of dengue hemorrhagic fever in Indonesia from 1968 to 2017 [Harapan H et al., 2019].*

countries where its vectors reside [*Uno N, Ross T, 2018*], with around 100 million symptomatic cases being reported every year [*Messina J et al., 2014*].

Dengue viral genome component comprises of 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 will bind to human antibodies. In contrast, the non-structural protein genes contain codes to form enzymes that are needed for virus replication [*Angel R, Valle J, 2013*].

Immunopathogenesis of Dengue Virus

Dengue viruses, including keratinocytes and Langerhans in cells, are replicated in the skin cells after infection [*Garcia M et al., 2017*]; which then trigger various host innate immune responses, including macrophage, Natural Killer cells (NK cells), as well as the secretion of interferon 1 (IFN 1) by infected cells, that prevent the entry of viruses into other cells [*Samuel C, 2001; Cha L et al., 2014; Shereen M et al., 2020*]. When the innate immune system fails to destroy the virus, the adaptive or specific immune system, including CD4 T lymphocytes (T helper cells), CD8 T lymphocytes (cytotoxic T cells) and B lymphocyte cells will take a role. Macrophages that unable to kill the virus will present the virus peptide component on the surface of the cell to cytotoxic T cells through Major Histocompatibility Complex I (MHC I). The bonding complex is formed between receptors on the surface of cytotoxic T cells, MHC molecules, virus peptides and macrophage cells, which acts as APC (antigen presenting cells). After the bonding complex occurs, CD8 cells will produce cytokines, such as perforin, granzime, granulosin, IFN 1 and tumor necrosis factor alpha (TNFα), which will cause macrophage to undergo apoptosis [*Pulendran B et al., 2013; Mak T et al., 2014*].

In addition, macrophages also present viral peptides to T helper cells, where the bonding complex that occurs between APC cells, MHC molecules and T helper cells will cause T helper cells to differentiate into Th1 and Th2 to produce mediator cytokine inflammation IL-4, IL-5, IL-10, IL-12, and IFN γ. The cytokines will help the macrophages to kill the virus. CD4 cells will also differentiate B lymphocytes to proliferate into plasma cells, in which plasma cells will produce anti-dengue antibodies that will neutralize the virus [*Pulendran B et al., 2013*].

Dengue may also infect mast cells, causing degranulation, which may activate melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene I (RIG-I). Both MDA5 and RIG-I will activate the transcription of nuclear factor kappa-light-chain-enhancer of activated B cell (NFκB) and produce IFN 1. Therefore, IFN 1 is a natural antiviral as described above. Moreover, mast cell degranulation will cause these cells to release several inflammatory mediators, such as chymases, leukotrienes, tryptases and vascular endothelial growth factor (VEGF), which can increase vascular permeability and cause vascular leakage [St. *John A, 2013; Hasan S et al., 2016*].

The innate and adaptive immune response phases will determine the clinical symptoms that appear in infected patients. If both systems successfully kill the dengue virus, 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 [*Martina B et al., 2009; Rothman A et al., 2014*].

Dengue virus is able infect macrophage cells, dendritic cells and mast cells. The virus is also able to infect endothelial cells. The infected endothelial cells will activate NFκB, which will cause apoptosis in these endothelial cells. 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 a bleeding [*Wan S et al., 2018*].

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 dengue virus and will bind as lock and key to neutralize the virus [*Martina B et al., 2009*].

The above mechanism occurs in the first infection by dengue virus and secondary infection from the same serotype. In the case of a secondary infection, however, which may be caused by a particular Dengue virus serotype, the antibodies formed from the prior infection may not neutralize the second, but cause the fragment crystallisable region (Fc) antibody fragment on the macrophage cell surface to be bound to the antibody receivers. This attachment causes the entry of dengue virus 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). The occurring clinical manifestations are dengue hemorrhagic fever, dengue shock syndrome or death [*Negro F, 2020; Ulrich H et al., 2020*].

Epidemiology of COVID-19 in Indonesia

Figure 2 depicts number of COVID-19 confirmed cases, recover, death, recovery rate (%) and case fatality rate (%) reported from March 2, 2020 to July 28, 2020. There was an increase in the number of confirmed cases from the first cases reported on March 2, 2020 to July 28, 2020 following the increase number of people that have been tested with reverse transcription polymerase chain reaction. There was a decrease in attack rate (AR = percentage of confirmed cases by population size per

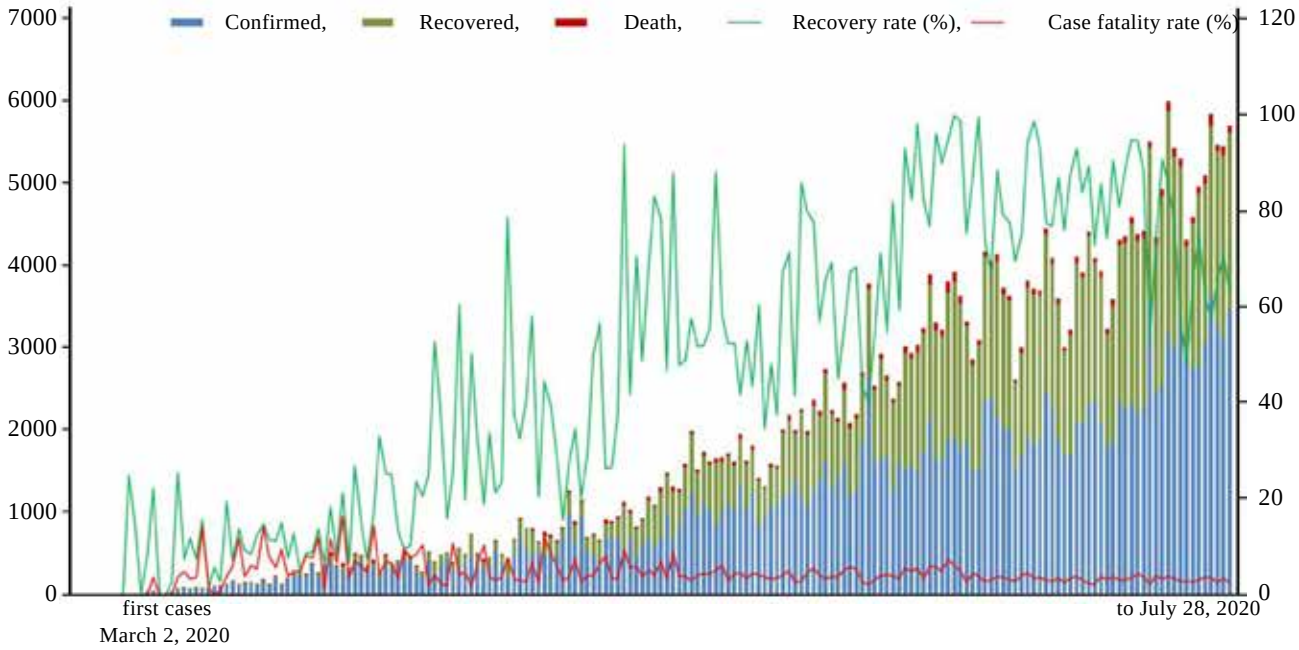

Figure 2. *Number of COVID-19 confirmed cases, recover, death,* **recovery** rate (*RR) and* case fatality rate *(CFR) [MH RI, 2020b].*

100,000 people) from 0.7% on March 2, 2020 to 22.2% on July 2, 2020. The estimated current population of Indonesia in 2020 is 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% on April 2, 2020 to 11.7% on July 2, 2020. There was an increase of case recovery rate (CRR = percentage of recover cases by confirmed cases) from 6.3% on April 2, 2020 to 45.4% on July 2, 2020. There was a decrease of case fatality rate (CFR = percentage of death cases by confirmed cases) from 9.5% on April 2, 2020 to 5.0% on July 2, 2020 [*MH RI, 2020b*].

SARS-CoV-2

Virus causing COVID-19 (SARS-CoV-2) is Corona strains affecting humans following severe acute respiratory syndrome-related coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The genome of the coronavirus occupies four large protein areas: spike (S), nucleocapsid (N), membrane (M), and envelope (E). S protein is responsible for the entry of viruses into cells which express the enzyme 2 (ACE2) receptors that convert angiotensin. About 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 [*Nile S et al., 2020*].

The SARS-CoV outbreak that emerged in 2003 and MERS-CoV outbreak in 2012 were originated from bats [*Hu B et al., 2015*]. Over time, mutations occur that cause possible transmission between bats to camels and other intermediate hosts, then transmission continues from animals to humans (zoonotic transmission) and finally from humans to humans [*De Wit E et al., 2016*].

Immunopathogenesis of SARS-CoV-2

The immune response to SARS-CoV-2 is not much different from dengue infection, in which the innate immune system collaborates with the cellular immune system to kill the virus. When a virus infects macrophage cells (Fig. 3A), 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 IFN γ and IL2 as well as granzyme and several other inflammatory mediators to strengthen the role of macrophage cells. Meanwhile, Th2 cells will help differentiate B lymphocyte cells into plasma cells and produce specific antibodies for this virus and then act as neutralizing antibodies [*Mubarak A et al., 2019; Merad M, Martin J, 2020*].

One main feature of a SARS-CoV-2 infection is the emergence, by the release of proinflammatory cytokines and chemokines by immune cells, of cytokine storms that create an unregulated systemic inflammatory response. High levels of cytokines and chemokines have been detected in COVID-19 patients, including interleukin IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, basic TNFα, and VEGFA. Cytokine storms cause extreme inflammatory responses causing ARDS, multiple organ failure, and death [*Nile S et al., 2020*].

Is there a role of ADE in COVID 19 infection?

There are no available clinical data to date showing the mechanism of ADE for SARS-CoV-2. However, previous coronavirus infections that heal with different types of SARS-CoV-2 may indicate the possibility of ADE, based on in vitro and animal models infected with SARS-CoV and MERS-CoV. The non-neutralizing antibodies recognize the S protein of the virus and bind it to the receptor. The non-neutralizing antibody-Fc receptor complex will then cause viruses to enter cells that express IgG Fc receptors [*Ulrich H et al., 2020*]. Furthermore, it was proposed that anti-MERS-CoV specific antibodies and SARS-CoV specific antibodies may mediate the attachment of the SARS-CoV to monocyte cells that express Fc receptors (FcR), thereby triggering structural changes in MERS-CoV antibodies that allow the virus to enter the monocyte cells, replicate and increase the amount of virus [*Wan Y et al., 2019*].

Other studies suggest that the antibodies produced from the SARS-CoV vaccine actually increase the infection process in B lymphocyte cells from animal models of hamsters [*Negro F, 2020*]. In SARS-CoV infection, ADE can be mediated by the involvement of FcR expressed by immune cells, such as monocytes and macrophages. SARS-CoV specific antibodies may allow viruses to enter cells that express FcR. This FcR-mediated process is different from the cellular pathway for virus entry mediated by the ACE2 receptor. However, macrophage infection through ADE does not produce a productive virus in replication. In contrast, the internalization of the viral immune-antibody complex via FcR

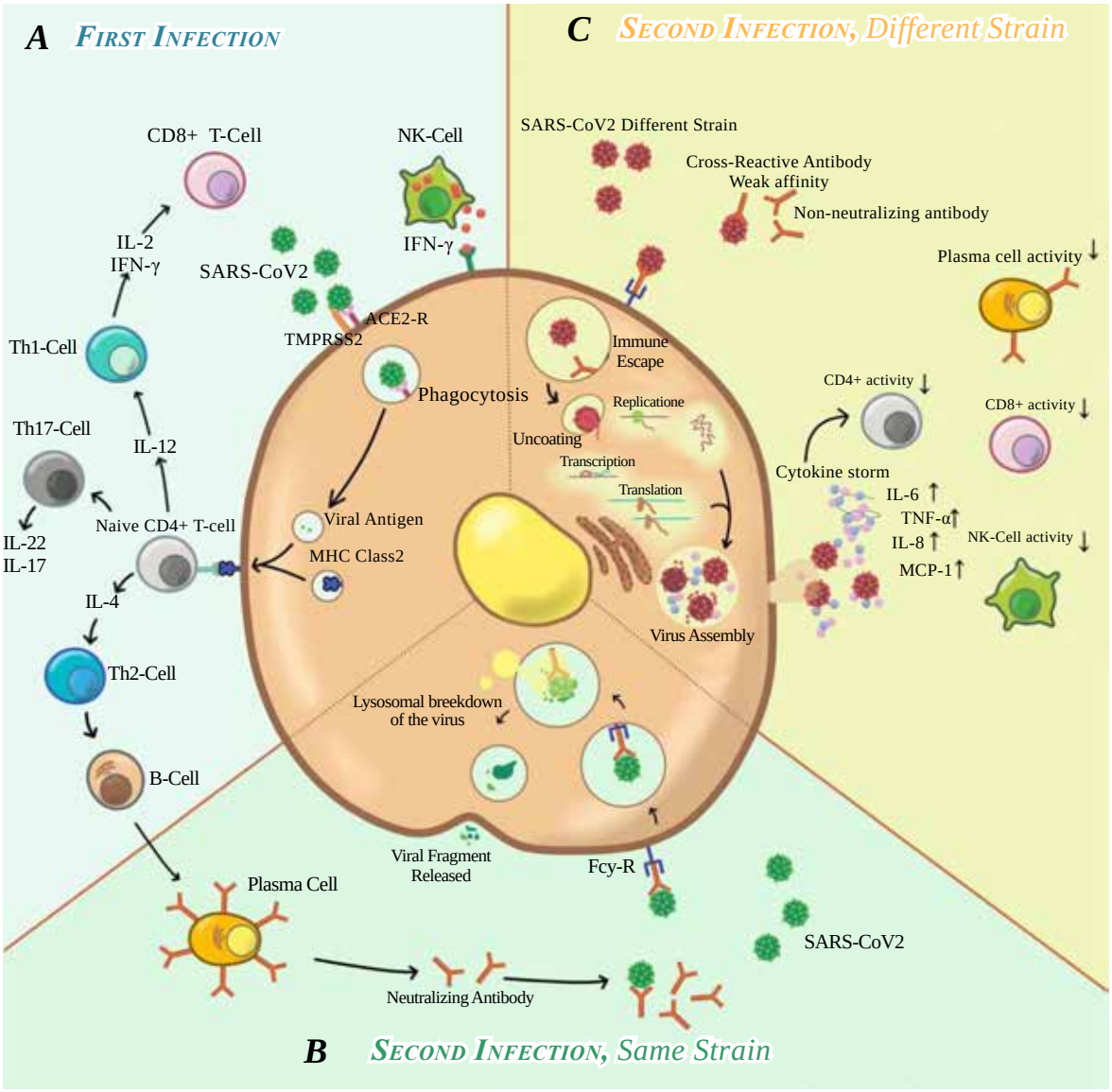

Figure 3. *Potential role of Antibody-Dependent Enhancement (ADE) during SARS-CoV-2 infection.*
A. *When SARS-CoV-2 infects macrophage cells, their S protein binds to angiotensin-converting enzyme 2 receptor (ACE2-R) and transmembrane serin protease 2 (TMPRSS2) and leading them into the macrophage cytoplasm. NK cells then lyse both the SARS-CoV-2 infected macrophage cells and the viruses itself. Macrophages also activate naïve CD4⁺ T-cells, which differentiate into Th2 and Th1. Th1 cells will release IFN-γ and IL2 as well as granzyme and several other inflammatory mediators. Whereas Th2 cells will help B lymphocyte cells differentiation into plasma cells and produce specific antibodies.*

B. *On second infection of the same strain, the high titre of specific antibodies will neutralize the virus.*

C. *However, in reinfection cases of different SARS-CoV-2 strain or from immunization settings, the non-neutralizing antibodies recognize the S protein of the virus and bind it to the receptor. The non-neutralizing antibody-Fcγ receptor complex will then let the virus to enter cells that express IgG Fcy receptors without binding to ACE2 receptor. After engulfing into the cells, the virus will be separated from the non-neutralizing antibody/SARS-CoV-2 complex because of the weak affinity and the virus will escape from lysosomal breakdown. Furthermore, the virus will replicate more and prompt further pro-inflammatory response*

in macrophages causes an increase of TNF and IL-6 production, which can increase inflammation (Fig. 3C) [*Iwasaki A, Yang Y, 2020*].

Dengue Fever and COVID-19

Dengue fever and COVID-19 may have similar clinical symptoms in early stages and similar laboratory features [*Yan G et al., 2018; Chen N et al., 2020*]. A rapid serological test for dengue (IgG anti-dengue) has been shown in two patients in Singapore to be false positive, and they were later reported to have a SARS-CoV-2 positive reverse transcription polymerase chain reaction [*Yan G et al., 2020*]. False-positive results in serological tests for dengue fever are possibly due to antigenic similarities between dengue virus and SARS-CoV-2, so they are able to form antibodies that will be detected by rapid serological tests for dengue virus. In addition, 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 lead to serious implication for both patients and public health [*Yan G et al., 2020*].

Preventing DENV and SARS-CoV-2 Transmission

DENV is primarily transmitted by female *Aedes aegypti* and *Aedes albopictus*, which are endemic almost in all areas of Indonesia [*Kraemer M et al., 2015*]. DHF prevention and control focus on breaking the life cycle of 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 [*Kusriastuti R, Sutomo S, 2005*]. 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 [*MH RI, 2020a*].

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) [*WHO, 2014*] when an infected person talks, coughs, sings or sneezes [*Liu J et al., 2020*]. However, it may also be possible to be transmitted through airborne [*WHO, 2020b*], fomite (contaminated services) [*Van Doremalen N et al., 2020*], fecal-oral [*Wang W et al., 2020*], blood borne, mother-to-child, and animal-to-human [*WHO, 2020*].

The prevention of SARS-CoV-2 are based on the mode of transmission and the approaches have been introduced to the community. The health protocols to prevent the transmission of SARS-CoV-2 have been applied in the work places, schools, health care facilities, homes, and other public places in Indonesia [*MH RI, 2020d*], and it is expected that people will adhere to the health protocols.

CONCLUSION

The immune response in DENV and SARS-CoV-2 infections aims to eliminate the virus, but it causes an increase in inflammatory mediators (cytokine storm), which can increase vascular permeability and organ damage. Secondary infection of DENV with different strains may allow the occurrence of ADE. The possibility of ADE in SARS-CoV infection has been studied in vitro, and in animal studies. DENV and SARS-CoV-2 infections have antigenic similarities, and trigger memory B cells. The cross reactions between SARS-CoV-2 antibodies and DENV antigens may cause false positive on rapid dengue infection serological tests. The prevention and control of DENV and SARS-CoV-2 infections are based on the mode of transmission, and people should comply to the related health protocols.

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