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Immunopathogenesis of dengue virus and Salmonella typhi coinfection

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Literature Review

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ABSTRACT

Typhoid, malaria, leptospirosis, dengue virus (DENV), and other arboviruses are endemic in Indonesia. Therefore, it is more likely that DENV and other infectious diseases could be coinfected. More severe symptoms, delayed identification, and ineffective treatment of the illness can all result from *Salmonella typhi* coinfection. To serve as a principle for clinicians' considerations while diagnosing and prescribing, we aim to examine the immunopathogenesis of dengue associated with *Salmonella typhi* coinfection. Dengue virus has the potential to increase both susceptibility and incidence of this coinfection, leading to dengue haemorrhagic fever (DHF) with more severe clinical symptoms. This is explained by regulating impact of coinfection in the presence of gram-negative membrane endotoxin, DENV replication, and lipopolysaccharide (LPS). If *Salmonella typhi* coinfection is not treated promptly, both dengue and *Salmonella typhi* can affect several organs and result in significant morbidity and death. Dengue and typhoid immunopathogenesis coinfection are unclear. When dengue monoinfection compared with Salmonella dengue dual infections are related to higher fatality and morbidity rates.

INTRODUCTION

During the COVID-19 pandemic, DENV infection remains a severe health concern. The symptoms of DENV infection range from asymptomatic dengue fever to dengue haemorrhagic fever and dengue shock syndrome.[1] Acute undifferentiated fever illness is the most prevalent disease symptom among patients admitted to hospitals in poor nations.[2] The increased risk of the dengue epidemic's spreading is attributed to several factors, such as the shifting distribution of the vector, *Aedes aegypti*, particularly in areas where dengue was previously prevalent. Another factor is also effects of climate change, which include increased temperatures, humidity, and rainfall. Furthermore, the next factor is the weak health system in nations dealing with complex humanitarian crises and significant population movements. These factors also raise questions about the how the pandemic spreads to other nations and how we respond to it, even in endemic nations.[3] Typhoid, dengue fever, and malaria are the most prevalent acute febrile infections. For main part, they have comparable seasonal patterns and can coexist, leading to a diagnostic challenge for doctors.[4] The diagnosis of DENV may be challenging based on non-specific symptoms. The primary symptoms are non-specific and difficult to distinguish from a variety of febrile infections. Dengue coinfections with typhoid, malaria, leptospirosis, and other arboviruses are possible in endemic locations.[5] The most

frequent illnesses in the tropical and subtropical countries were dengue fever and typhoid fever. The condition is related to poverty and slow growth.[6]

A study has shown that bacterial and DENV infections at the same time can increase mortality from dengue infection.[7,8] Concurrent bacteraemia can also cause longer hospital stays and death. Lipopolysaccharide, as a constituent of bacteria, is known to be associated with the severity of DHF and the increase in platelet-activating factor (PAF) and other inflammatory mediators. Infections caused by DENV and *Salmonella typhi* infections were reported to frequently occur with overlapping symptoms, making difficult to diagnose.[9] The same symptoms and almost similar results in physical and laboratory examinations are also difficult to be diagnosed. It is necessary to know clearly how the pathogenesis of DENV and *Salmonella typhi* occur when they infect the same host.[10]

Salmonella typhi is known as a bacterium that lives in cells, which is thought to aggravate DENV infection. It infects the host via Toll-Like Receptor (TLR4), which is also recognized by the non-structural-1 (NS1) protein DENV while infecting the host.[11] To provide clinicians with a principle to diagnose early and promptly to lower morbidity and mortality, we examine the immunopathogenesis of dengue co-infection with *Salmonella typhi*. Additionally, physicians can consider the immunopathogenesis of *Salmonella typhi* and dengue virus infections while deciding to recommend pharmacotherapy or non-pharmacotherapy. Considering the development of symptoms and the occurrence of problems in patients, dual infections were difficult to detect, particularly in endemic locations during the rainy season. So, this article compare clinical and pathogenesis data about mono-infection of dengue and coinfection of dengue with *Salmonella typhi.* The path of immunopathogenesis can also serve as the basis for selecting a patient's treatment options to reduce the severity and avoid fatalities. It can also be a topic for more biomolecular studies.

Dengue virus

Dengue virus belongs to the family Flaviviridae and antigenically consists of four different serotypes variant, namely DENV-1, DENV-2, DENV-3, and DENV-4.[12-15] Anyone of the four dengue virus serotypes (1-4) can cause dengue fever; an Aedes mosquito-borne illness can range in severity from mild or asymptomatic to severe disease with vascular leakage that can result in shock and viral haemorrhagic syndrome.[16] However, genotypically, the virus variant has 3% and 6% similarities in amino acid and nucleotide sequences respectively.[17] This genetic variation influenced the interaction between these four serotypes with the immune system which in turn will affect the effectivity of the host immune response against DENV.[12,17] Genetic variation between DENV viruses in the same serotype could be done by nucleotide sequence analysis. Using sequence analysis, it is possible to compare amino acids to nucleotides from DENV patients with different clinical manifestations as an approach to studying the pathogenesis of DENV.[18]

Dengue virus, an enveloped virus, has a spherical shape, and it has positive ss-RNA. Dengue virus has a genome of 11 kB and one open reading frame (ORF) encoding a single polyprotein. The protein then will be cleaved into three structural proteins, capsid (C), pre-membrane (pr-M), and envelope (E) (Figure 1), which are the component of the viral virion, and seven non-structural

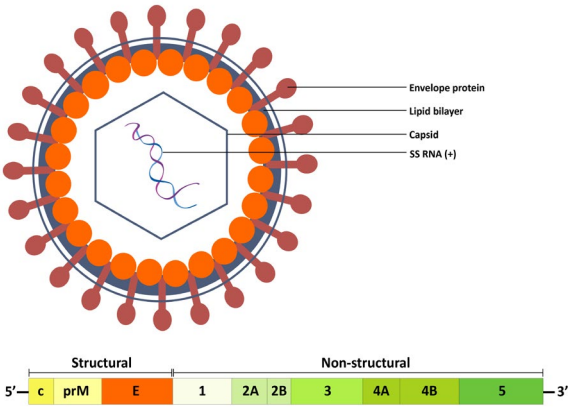

Figure 1. Structure of dengue virus

proteins. There are NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 which involved in viral replication.[18]

Dengue virus pathogenesis

The pathogenesis mechanism in DHF or dengue shock syndrome (DSS) is sophisticated and has not been fully understood until now. Various theories have been put forward regarding DENV pathogenesis, such as pathogenesis caused by viruses and pathogenesis caused by the host (immunopathogenesis).[15] Host factors that cause the pathogenesis of DENV are physiology and immunology (cellular and humoral), which will determine the occurrence of the infection and or re-infection as well as the severity of the disease due to infection.[19]

Cells that are primarily infected by the dengue virus in cases of acute dengue infection are monocytes and macrophages. When enhancing antibodies are present, it has also been demonstrated that monocytes infected with the DENV contribute to endothelial dysfunction. We aim to study whether monocyte-derived macrophages undergo antibody-dependent enhancement (ADE) and PAF production when infected with the DENV, as monocytes and macrophages are known to produce PAF and are a main target of the virus. We also investigate whether the LPS levels reported in DHF patients encourage PAF synthesis from DENV-infected macrophages since LPS has been demonstrated to operate on monocyte-derived macrophages and to activate PAF in a bi-phasic manner. When exposed to ADE or the DENV alone, DENV-infected macrophages did not create PAF; however, LPS and the DENV appeared to work in concert to cause the production of PAF and other inflammatory cytokines by the macrophages.[20]

Cell and tissue tropism also have a significant influence on DENV infection. Langerhans cells are the main target of DENV infection after mosquito bit, followed by macrophage/monocyte infection, and then DENV will enter the circulatory system. In vitro studies showed that CD14+ and CD1c+ were found in dendritic cells, Langerhans cells, and dermal macrophage cells infected with DENV, and the highest DENV titters were found in Langerhans cells. After replication at the site of infection, DENV could attack other body organs such as the liver, spleen, kidneys, bone marrow, lungs, thymus, and brain in severe DENV infection.[21]

The range of cells and tissues that can be infected with DENV suggests that the DENV receptor is diverse. The affinity of DENV for these receptors may influence infectivity and virulence of DENV. In conclusion, the factors that cause the number of DENV-infected cells at a particular site influence the pathology of DENV.[9] The viral components that are related to disease severity in DENV infection include viral proteins, virion structure, viral genotype, and serotype.

Virus protein

Dengue virus, a virus with a genome size of 11 kb encodes 3 structural proteins (C, E, and pr-M), 7 non-structural proteins, and 2 untranslated regions (UTR). The UTR region functions as a regulator of gene translation and replication, while structural proteins E and pr-M are the main targets of the immune system. Protein E roles in the attachment and entry of DENV into the body. Protein E consists of 3 domains; domain I (DI) and domain II (DII) are dimerization domains that role in membrane fusion, and domain III (DIII) is an immunoglobulin domain associated with receptor attachment. Antibodies to DI and DII are cross-reactive among all DENV serotypes and the family Flaviviridae, while antibodies to DIII are specific to the DENV serotype.[22]

Among these four DENV serotypes, it is known that each serotype causes different levels of disease severity.[7] The incidence of DHF/DSS cases varies in primary or secondary infections, but on average DHF/DSS occurs in secondary infections, and in infants, DHF/DSS occurs in primary infections with a history of birth from mothers who have immunity to DENV.[21] The results of a study in Thailand (1992-2002) showed that primary infection by DENV-1 and DENV-3 could cause DHF in patients, while DENV-2 and DENV-4 could only cause DHF at the time of secondary infection.[23] Several theories have been put forward regarding the incidence of DHF/DSS during secondary infection. One of them was antibody-dependent enhancement (ADE) where antibodies from primary infection failed to eliminate DENV with different serotypes in secondary infection.[24]

Viremia

The severity of the disease due to DENV infection is related to the viral load seen from the viremia titer.[13] A study conducted by Vaughn

et al. revealed that the viremia titters of patients with secondary infection by DENV-1 and DENV-2 demonstrated that there was an association between viremia at the onset of symptoms and disease severity.[4] Viremia titters are 100 to 1,000 times higher in patients with DHF/DSS than those in DENV-3 patients.[13]

Immunopathogenesis dengue

Autoimmunity

Autoimmunity associated with viral infections has been found, for example, in Ebola virus (EBV) infections. Autoantibodies represent another factor that contributes to disease severity in DENV infection. Molecular mimicry of platelets, endothelial cells, and blood coagulation molecules by NS1, pr-M and E causes a cross-reaction among anti-NS1, anti-prM, and anti-E antibodies with proteins, which may eventually lead to platelet dysfunction, endothelial cell apoptosis, blood coagulation disorders, and macrophage activation. Dysfunction of these cells can cause plasma leakage, bleeding, and thrombocytopenia (Figure 2).[15]

Cytokine storm

One of the hypotheses stated the pathogenesis of DENV is the occurrence of a cytokine storm characterized by excessive activation of pro-inflammatory cytokines such as TNF-α and IL-1β. Even though the mechanism is not fully understood, but the interaction between the immune system and other types of cells such as endothelial cells is clear.[25] These cytokines will activate other pro-inflammatory cytokines such as IL-6 and anti-inflammatory cytokines such as IL-10 which causes vascular permeability and blood clotting disorders. One theory states that cytokine storms in severe DENV infection are caused by ADE as non-neutralizing antibodies increase the entry of DENV into monocytes through the Fc receptor.[26]

Other theories causing cytokine storms are mediators (IL-6; IL-8; and IL-10), cytokines (interleukin-1 receptor antagonist/IL-1RA; soluble interleukin 2 receptor (sIL-2R), chemokines (monocyte chemoattractant protein-1/MCP-1); interferon γ-induced protein/IP-10, monokine induced by interferon-γ/MIG, regulated upon activation, normal T-cell expressed, and secreted (RANTES), and growth factors (hepatocyte growth factor/HGF; epidermal growth factor/EGF); granulocyte-colony stimulating factor/G-CSF, and vascular endothelial growth factor/VEGF). The IL-10 and MCP-1 have role in plasma leakage, IL-15 and IP-10 have a role in Natural Killer cell response, and G-CSF is involved in the development and differentiation of neutrophils. High concentrations of IL-6 and IL-8 are thought to be the cause of plasma leakage and shock.[23,27] In addition, a study also reported that high concentrations of LPS can also be a cause of DENV pathogenesis because LPS

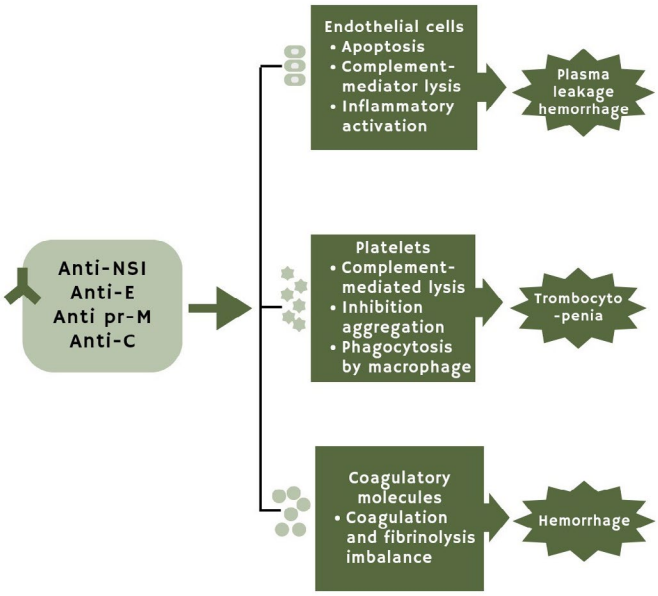

Figure 2. Autoimmunity scheme as a cause of DENV pathogenesis

is an immunostimulatory cytokine storm. The LPS stimulation is known to induce the production of IL-6, IL-8, tumour necrosis factor-α (TNF-α), and IL-1 as well as growth factors of VEGF and HGF.[26,28]

Soluble factor

Several studies have shown that levels of cytokines, chemokine and other mediators increase during DENV infection. Interleukin-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-18, MCP-1, macrophage migration inhibitory factor (MIF), transforming growth factor-β (TGF-β), TNF-α, and interferon-γ (IFN-γ) are found in patients with severe DENV symptoms. These mediators have an important role in regulating the immune response against DENV. In addition, TNF-α also contributes to endothelial permeability and bleeding during infection in animal models. Several studies have also pointed out that IL-8, MCP-1, MIF and metalloproteinases cause endothelial permeability in vitro. Furthermore, IL-6 and IL-8 are also known to be associated with the activation of coagulation and fibrinolysis. IL-8 levels are known to be elevated in DENV infections and are associated with neutrophil degranulation. In addition, IL-10 is also associated with decreased platelet count and platelet function abnormalities.[15]

The T cell response

Memory T cells, which can produce immunity to viruses, can also cause immunopathology.[15,19] This is because T cells have a surface and functional phenotype activated by antigens found in the convalescent phase of severe cases of DENV infection. In addition, CD8+ T cell epitopes are found in many non-structural proteins, especially NS3 and NS5. Although the effect of these CD8+ T cells on plasma leakage is still unknown, the original antigenic sin theory suggests that it occurs in the CD8+ T cell population during secondary infection. In contrast to CD8+ T cells, CD4+ T cell epitopes are more dominantly found in the structural proteins (the capsid and envelope) and NS1 protein as these three proteins are also targets of antibodies. The CD4+ T cells circulation during the early convalescent phase has surface and phenotype of helper T cells, related to their role in assisting antibody production.[19]

Salmonella typhi pathogenesis

Salmonella is a gram-negative bacterium with flagella, anaerobicity, and no spores. Salmonella has three major antigens, namely H (flagellar), O (Somatic), and Vi antigens. The A antigen exists in two forms, known as Phases 1 and Phases 2. The O antigen is found on the membrane's surface and can be identified by the sugar sequences found on the cell surface. The Vi antigen is an antigen's surface that conceals the O antigen, and it is only found on a few serovars.[29]

Polysaccharides, flagella, and peptidoglycans are among the pattern-associated molecular patterns (PAMPs) seen in Salmonella typhi.[30] In case, Salmonella typhi interacts with human cells, and flagella control a key role, particularly during the inflammatory process. Flagella expression in Salmonella typhi is influenced by SPI-1 and polysaccharide Vi components.[31] Polysaccharide Vi capsules including anti-inflammatory components reduce complement component CR3 deposition on bacterial cell surfaces, limit immunological activation, and boost serum killing. Capsule Vi also influences the interaction of LPS and TLR4 and increases the levels of the cytokine IL-10 regulation in infected tissues.[32]

Several immunological studies of typhoid fever that use antigens to measure specific responses. The IFN-γ response has been observed considerably in cells stimulated with diverse antigens, including fimbriae and outer membrane proteins, utilizing poly mononuclear cells from typhoid fever patients' blood. When blood was stimulated with LPS, the amount of TNF-α released was lower than that in treated typhoid fever, indicating immunological suppression against infection and nucleotide-binding oligomerization domain containing 2 NOD2, which both of them generate the cytokines Il-6 and TNF-α.[32]

Dengue coinfection with _Salmonella typhi_

In clinical practice, DENV and bacterial coinfection are often found. Lee et al. observed that 5.5% of 774 patients presenting with DHF indicated bacteraemia. A previous study described that it emphasized the clinical and scientific significance of dengue and bacterial co-infection, which had been proven to exacerbate the outcome of dengue illness.[33] Dengue virus can enhance the incidence of this coinfection as well as increase susceptibility, resulting in DHF with more severe clinical signs. Their regulation impact in the presence of LPS, gram-negative

membrane endotoxin, and DENV replication supports this finding. Chen et al. discovered that DENV replication became more frequent and sustained, and a similar finding was obtained in the investigation with Aedes aegypti culture when LPS was added to in vitro cultures of monocytes and macrophages following DENV infection.[7,9]

Myeloid or plasmacytoid dendritic cells and monocytes in humans can promote the production of various co-stimulator molecules and TLRs, proteins that have critical functions in the innate immune system. Expression of TLR can be modulated not only by the establishment of a specialized immune response against viruses but also by dendritic cell activation, which influences the immunological response against bacteria. Its outcome also depends on the severity of DENV infection, and it is consistent with other studies which found that the presence of sub-neutralizing antibodies induced by previous exposure to different DENV serotypes was associated not only with a high risk of developing severe dengue but also with downregulation of TLRs expression and upregulation of NF suppression. The NF-Kb signalling pathway is significant in cytokine production.[9]

Because LPS can activate the immune system via signals emanating from the CD14 or TLR4 cell membrane complex, Its is an essential immunological stimulant. The LPS will be modulated, and the transfer of LBP (LPS binding protein) and soluble CD14 will be accelerated by the system that secretes LPS into the circulation.[26] A study showed elevated circulating levels of the fungal product-β (1-3)-D-glucan and confirmed study demonstrating that circulating bacterial LPS was increased in DENV infection and correlated with severity.[34]

The possibility of a worse result in dengue co-infection due to bacterial co-infection can be explained by immunological mechanisms. Cytokines can be responsible for immunological mechanisme. The cytokines that are known as secreted during dengue infection include tumour necrosis factor, interferon, IL-1, IL-8, IL-12, MIP-1, RANTES, migratory inhibitory factor, and human cytotoxic factor.[34] These cytokines are produced by macrophages and other immune system cells. Greater levels of soluble tumour necrosis factor receptor-II and plasma IL-10 were shown by connecting with the degree of thrombocytopenia in one study, whereas higher levels of hepatic transaminases were found that correlated with an increase in Il-2. It demonstrates the role of cytokines charge in the pathophysiology of dengue.[35]

Gram-negative bacteria produce LPS, which mediates increasing cytokine production and synergistic IFN production as well as increasing viral replication.[7] A study by Nugraheni et al. mentions that the levels of IL-6, TLR-4 and TLR-6 in the single infected and coinfected groups indicated significant differences. Based on several analyses of cytokines presence in the blood, there was a significant relationship between certain cytokines and the incidence of single infection and coinfection. Cytokine Il-6 increased in the coinfected and mono-infected groups. In addition, TLR-4 and TLR-6 receptor components also increased in the coinfected group.[36] Dengue dual infections are associated with increasing mortality and morbidity when they are compared to dengue without concurrent bacterial infections, as demonstrated by See et al. Primary gram-negative bacteraemia might be caused by a breakdown of the intestinal mucosal barrier in severe dengue infections.[4]

Clinical manifestation

The clinical similarity of two distinct infections complicates difficulties in a diagnose. Both dengue fever and typhoid fever are characterized by body pains, myalgias, abnormal bowel habits, and sore throats. Typhoid fever and dengue fever have similar test results and physical symptoms, including rash, moderate splenomegaly, relative bradycardia, and neutropenia, making distinction clinical symptoms nearly impossible.[37] Other febrile diseases should be investigated, particularly when a patient's clinical history departs from the usual disease course or when a patient is refractory to standard therapy.[4]

Coinfection should always be considered in endemic regions while treating individuals with protracted acute nonresponsive febrile illness. In every febrile patient, common infections should be investigated using a history, clinical exams, and logical investigations. Dengue and typhoid, if they are not treated promptly, can cause multi-organ involvement with considerable morbidity and death. Because of the variety of clinical manifestations, some disorders are frequently

underreported or misdiagnosed.[2]

There is a paucity of data on dengue-typhoid coinfection, the probable influence of one illness on the progression of regression of the other, and the severity of sequelae if both co-exist or if one disease predates the other. Dengue and typhoid fever occur periodically in India, particularly during the monsoon season when mosquitoes multiply and feck-oral transmission is rampant. Coinfection may introduce a whole new layer of problems, portending disaster for the individuals as well as the concerned civil authorities and health programs. More research on this subject is required.[2]

Symptoms and severity of coinfection dengue

Dengue fever is sometimes known as breakbone fever because of its symptoms, which include fever, severe myalgia, skin rashes, retro-orbital pain, and bone pain. Compared to patients with first dengue virus infection, those with secondary dengue virus infection more frequently complain of abdominal pain.[4] It is clinically challenging to confidently differentiate DENV infection from a wide range of other infectious disorders, including *S. typhi*, at this stage of the illness. Though it is difficult to predict whether the patient will progress to the critical phase, which is marked by a rapid onset of a severe capillary leak, circulatory collapse, and haemorrhage with thrombocytopenia, an accurate diagnosis during the acute phase of the febrile illness is necessary for prompt intervention. Hospitalization, careful hydration and platelet transfusions (if needed) are required for these patients.[38]

The clinical similarity of the co-occurrence of two distinct infections exacerbates the diagnostic problem. Both dengue fever and typhoid fever are characterized by the presence of body pains, myalgia, abnormal bowel habits, and sore throat. It is nearly impossible to distinguish between typhoid fever and dengue fever due to similar test results and physical symptoms, such as rash, mild splenomegaly, relative bradycardia, and neutropenia. Other feverish conditions must be taken into account, particularly if a patient's clinical course deviates from the course of the disease naturally or if the patient does not improve with conventional therapy.[37]

A case study by Amin et al. reported about coinfection with DENV and extensively drug-resistant *Salmonella typhi*, as found in a young boy with coinfection dengue fever and *Salmonella typhi*. On the 8th day after symptoms onset, his platelet count increased to 54,000/mcL, but he remained febrile (40^{o}C) and toxic, with abdominal pain and diarrhoea. Serology testing for hepatitis viruses A, B, C and E and repeated thick and smears for malarial parasites and human immunodeficiency virus antibodies were negative, but blood culture indicated growth gram negative bacteria rods. The final report of the study revealed an XDR (Extensively-Drug Resistant) *Salmonella typhi* strain. Considering from culture report, meropenem was continued, and the patient's condition improved over time. This case emphasizes the importance of considering other possibilities when a clinical course of patients with dengue fever differs from the natural course of the disease.[4]

CONCLUSION

The clinical similarity of two distinct infections complicates the diagnosis. Immunopathogenesis of coinfection with dengue and typhoid is not well known. Because it may activate the immune system via signals emanating from the CD14 or TLR4 cell membrane complex, LPS is an essential immunological stimulant. The clinical similarity of the co-occurrence of two distinct infections exacerbates the diagnostic problems. Both dengue fever and typhoid fever are characterized by the presence of body pains, myalgia, abnormal bowel habits, and sore throat. Dengue dual infections are associated with increased mortality and morbidity when compared to dengue without concurrent bacterial infections. The clinical symptoms or complications that arise in patients with dual infections can be explored using the new ideas from this paper with high and varied infection rates.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

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AUTHOR CONTRIBUTIONS

EN: Conceptualization, writing, methodology; TMS: original draft preparation, LN: supervision, FF: review and editing; BED: supervision, corresponding. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

ADE: Antibody-Dependent Enhancement; DENV: Dengue Virus; DHF: Dengue Haemorrhagic fever; DSS: Dengue Shock Syndrome; EGF: Epidermal growth factor; EV: Ebola Virus; G-CSF: Granulocyte-colony stimulating factor; HGF: Hepatocyte growth factor; IL: Interleukin; IP-10: Interferon γ-induced protein; IL-1RA: Interleukin-1 receptor antagonist; LPS: Lipopolysaccharide; LBP: LPS binding protein; MCP-1: Monocyte chemoattractant protein-1; MIF: Migration inhibitory factor; MIG: Monokine induced by interferon-γ; ORF: Open reading frame; PAF: Platelet Activating Factor; RANTES: Regulated upon activation normal T-cell expressed and secreted; sIL-2R: Soluble interleukin 2 receptor; TGF-β: Transforming growth factor-β; TLR: Toll-like Receptor; TNF: Tumour Necrosis Factor; VEGF: Vascular Endothelial Growth Factor; XDR: Extensively-Drug Resistant

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