



Dengue, Chikungunya, and Zika: Differences in Similarities

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ABSTRACT

Arbovirus (arthropod-borne virus) outbreaks have become a major problem in recent decades. Dengue, Chikungunya, and Zika outbreaks are part of the main focuses currently as they share similar vector, symptoms, and environment. Reported cases of these viruses have occurred in epidemic areas with low mortality rate at the same time. This condition complicates diagnosis. Despite those similarities, each virus has their unique viral characteristics, transmission, symptoms, and complications of the disease. These unique characteristics can improve understanding of the diseases and be used to prevent and to diagnose the disease.

Keywords: Chikungunya, Dengue, Zika

ABSTRAK

Arbovirus (virus arthropod-borne) merupakan wabah yang menjadi masalah besar dalam beberapa dekade terakhir. Wabah Dengue, Chikungunya, dan Zika termasuk fokus utama saat ini, karena memiliki vektor, gejala, dan lingkungan yang sama. Kasus di daerah epidemi dengan angka kematian rendah yang dilaporkan pada saat yang sama, kondisi ini mempersulit diagnosis penyakit. Meskipun mempunyai kesamaan, masing-masing virus memiliki karakteristik, transmisi, gejala, dan komplikasi yang unik. Karakteristik unik tersebut dapat digunakan untuk diagnosis, serta dapat meningkatkan pemahaman tentang penyakit dan cara-cara pencegahannya. **Dias Rima Sutiono, Jeremy David Gunawan. Dengue, Chikungunya, dan Zika: Perbedaan dalam Kemiripan**

Kata kunci: Chikungunya, Dengue, Zika,

INTRODUCTION

In the 21st century, arbovirus (arthropod-borne virus) outbreaks have become a global problem. Among these arboviruses, Dengue, Chikungunya, and Zika outbreaks have been the main focuses as infection of these viruses occurs in similar environment, with similar vector and symptoms. Dengue, Chikungunya, and Zika viruses primarily infect tropical and sub-tropical areas in equatorial regions, such as South-East Asia, the Americas, the Pacifics, and Africa.^{1,4} They can travel and spread rapidly due to urbanization and technological advances of vehicles. In addition, their incubation period, which last for several days; and their symptoms, which is similar to normal febrile illness make them more effective to be transmitted.^{1,5} There have been millions of cases reported with low mortality rate.^{1,3} Even so, diagnosis of these diseases is proven to be difficult. Infection shows similar symptoms and occurs in similar areas; also cross-reactivity of the antibodies could give false positive results.^{1,3-5} Lack of knowledge also adds to the

difficulties to make diagnosis. Furthermore, no vaccine or specific medication has been introduced. Thus, it is important to understand their differences among their similarities.

Dengue

Dengue fever is caused by Dengue virus (DENV) from *Flavivirus* genus in *Flaviridae* family. Dengue has become a major infectious disease since 20th century, and its cases has increased dramatically in 21st century.^{1,2} Before 2013, there were only 4 serotypes of Dengue (DENV-1, DENV-2, DENV-3, and DENV-4). Additional serotype, DENV-5, was announced in 2013.¹ The virus has enveloped spherical shape with 40-50 nm in diameter. Its genome is positive single-stranded RNA with 11kb length. The genome has single open reading frame (ORF), which encode 3 structural proteins [capsid (C), membrane (M), and envelope (E)] and 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5).² Dengue is mainly transmitted by genus *Aedes* mosquitos, such as *Aedes*

aegypti, *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes scutellaris*¹. Dengue fever shows its symptoms in 3-14 days after exposure, starts with high-onset fever, headache, body pain (muscle and joint), and rash. In acute phase, Dengue fever can resolve by itself, while in critical phase, Dengue needs to be treated with immediate care.^{1,2} Some cases become more severe, characterized with bleeding, thrombocytopenia, ascites, vomiting, and abdominal pain. This condition creates dengue shock syndrome (DSS) and dengue hemorrhage fever (DHF). During this stage, patients show reduction of fever.

Chikungunya

Chikungunya virus (CHIKV) comes from *Togaviridae* family and *Alphavirus* genus. It is 60-70 nm diameter enveloped spherical virus with positive single-stranded RNA genome. Its length is approximately 12 kb long and has 2 ORF. One ORF encode for 5 structural proteins (C, E3, E2, 6K, E1) and another one encode for 4 non- structural proteins (nsP1, nsP2, nsP3,

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nsP4). Chikungunya virus is divided into 3 genotypes based on geographical origins: The Asian, the West African, and the East, Central, and South African (ECSA).^{3,5} Similar to Dengue, Chikungunya virus is transmitted by *Aedes* genus mosquitoes, specially *Aedes aegypti* and *Aedes albopictus*.^{5,6} Exposure to CHIKV-infected mosquito's bite can cause Chikungunya fever. It takes 2-12 days' incubation period before showing symptoms.⁶ The acute onset is said to be "Dengue-like" with high fever, severe joint pain, muscle pain and rash. Headache and back pain has also been reported in many cases.^{3,5,6} In most cases, acute phase lasts for several days to couple of weeks. However, joint and muscle pain can persist for years, which might develop into chronic arthritic syndrome.³

Zika

Similar to Dengue virus, Zika virus (ZIKV) comes from *Flavivirus* genus and *Flaviridae* family. It is positive single-stranded RNA with approximately 11 kb in length. It has spherical shape with diameter of 40-60 nm and contained in envelope.^{4,7,8} The genome contains an ORF which encodes for 3 structural proteins [capsid (C), premembrane (prM), and envelope (E)] and 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5).^{7,8} Zika virus is divided into 2 major lineages, Asian and African.^{4,8,9} It has same main transmission vector as Dengue and Chikungunya, which is *Aedes* genus mosquitoes (*Aedes aegypti*, *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes hensilli*). Zika fever onset appears after a few days of ZIKV-infected mosquito bites.⁴ Its clinical appearance is fever, headache, body pain (muscle and joint pain), rash, edema of extremities, retro-orbital pain, and conjunctival hyperemia.^{4,7-9}

DIFFERENCES IN SIMILARITIES

Dengue, Chikungunya, and Zika are transmitted with *Aedes* genus mosquitos and circulate in the same area. Dengue, which has become medical problem since World War II, has been more studied.^{1,7} These viruses give similar febrile illness, thus, difficult to differentiate and diagnose them. As a result, misdiagnosis and under-reported cases could happen.^{4,7,8} Despite these similarities, each virus has its uniqueness in its viral characteristics, transmission, symptoms, and complications.

Viral Characteristics

Dengue, Chikungunya, and Zika show high similarities, they have spherical shape with 40-70 nm diameter and genome size between 11-12 kb.^{2-5,7,8} Since Chikungunya comes from difference family and genus compared to Dengue and Zika, it has distinct viral proteins (as shown in table I). Even so, E2 and E1 proteins in Chikungunya have similar function as E proteins in Dengue. These proteins are used as receptor binding and antibodies neutralization.^{2,5} There are high possibilities that E protein in Zika have similar function.

Dengue has shown 4 serotypes for decades until the appearance of 5th serotype on 2013. These serotypes differ in serum reactivity (antigenicity).¹ Secondary infection from other serotypes of Dengue can increase risk of severe Dengue.^{1,2} This showed the effectiveness of Dengue mutation to infect their host. Just like Dengue, Chikungunya is also considered as one successful mutant virus. CHIKV, which is mainly transmitted with *A. aegypti*, has lower ability to affect *A. albopictus*. Yet, a mutation occurred in Asian and Indian Ocean increased its transmission

ability to *A. albopictus*.⁵ On the other hand, Zika has been considered as benign virus as its infection often misdiagnosed and under-reported until its outbreak in 2007 in Yap Island, Micronesia.^{4,7,9}

Transmission

Aedes genus mosquito is the main vector for Dengue, Chikungunya, and Zika virus. These viruses infect mosquito for life without detrimental effect.^{1,3,4} *A. aegypti* and *A. albopictus* are the main vectors for all viruses. Several other species, such as *A. scutellaris*, *A. polynesiensis*, and *A. hensilli* can also transmit the diseases.^{1,4} These viruses circulate in blood, while transmission through blood donor and organ transfusion is possible.^{1,5,6,8} For Zika case, another horizontal transmission can be through sexual route as reported in United States.^{8,10} Vertical transmission of these diseases also has been reported, due to trans-placental transmission or during delivery.^{1,6,8}

Signs and Symptoms

There are many misdiagnoses of Dengue, Chikungunya, and Zika ever since World War II. During World War II, these 3 diseases are

Table 1. Comparison of Dengue, Chikungunya, and Zika virus characteristics

Virus Characteristic	Dengue	Chikungunya	Zika
Name	DENV	CHIKV	ZIKV
Family	<i>Flaviridae</i>	<i>Togaviridae</i>	<i>Flaviridae</i>
Genus	<i>Flavivirus</i>	<i>Alphavirus</i>	<i>Flavivirus</i>
Shape	Spherical	Spherical	Spherical
Diameter	40-50 nm	60-70 nm	40-60 nm
Serotypes	5	1	1
Genome	Positive ssRNA	Positive ssRNA	Positive ssRNA
Genome Size	11 kb	Approximately 12 kb	Approximately 11 kb
Viral Proteins	C,M,E (structural) and NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5 (non-structural)	C, E3, E2, 6K, E1 (structural) and nsP1, nsP2, nsP3, nsP4 (non-structural)	C,M,E (structural) and NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5 (non-structural)

*Abbreviation: DENV (Dengue virus); CHIKV (Chikungunya virus); ZIKV (Zika virus); Positive ssRNA (Positive single stranded ribose nucleic acid)

Table 2. Similarities and differences of symptoms for Dengue, Chikungunya, and Zika

Symptoms	Dengue	Chikungunya	Zika
Fever	√	√	√
Rash	√	√	√
Muscle and Joint Pain	√	√	√
Retro-Orbital Pain	√	√	√
Edema of Extremities	-	-	√
Conjunctivitis	-	√	√
Lymphadenopathy	√	√	√
Hepatomegaly	-	√	-
Leukopenia/Thrombopenia	√	√	-
Hemorrhage	√	-	-



just considered as Dengue; malaria, or other known diseases, as febrile illness appears. Chikungunya and Zika were not known at that time. When Chikungunya was known, there were confusions in differentiating Dengue and Chikungunya. Currently, the confusion repeats itself in Zika cases.⁷ Furthermore, asymptomatic cases of Dengue reach 80% and Zika is also known to be asymptomatic.^{1,4} More than 75% to 97% of Chikungunya cases show symptoms.⁶

Dengue, Chikungunya, and Zika share similar symptoms that appear between 2 to 14 days.^{1,2,4,6} Fever, muscle and joint pain, rash, retro-orbital pain, and lymphadenopathy are the most common shared symptoms, with several unique symptoms in addition for each infection.⁴

Fever in Dengue is the highest among these infections, which can reach above 40°C. Fever in Chikungunya is also high and can reach above 38.9°C, while Zika gives milder fever.^{1,4,6} Even though Zika gives only mild fever in 62% - 65% cases, rash occurrence in Zika is high (90% - 96%) which spread from face to limbs.⁸ High rash occurrence also can be found in Dengue (50% - 80%), shows measles-like rash, often called as "islands of white in sea of red."¹ Rash can also occur in Chikungunya, appears in trunk and extremities⁶ but it is not reliable sign for Chikungunya. Muscle and joint pain are

the most noted symptoms in Chikungunya; joint pains in wrists, elbows, fingers, knees, and ankles can lead to joint swelling. Muscle and joint pain also can occur in Dengue and Zika but not as severe as in Chikungunya. There are no specific differences of retro-orbital pain and lymphadenopathy among those 3 diseases.^{1,4,6}

There are specific symptoms which only occur in each disease. In Dengue, mild bleeding from mouth and nose's mucous membrane can happen during acute phase. It might lead to hemorrhage in critical phase and other severe impairment.¹ In Chikungunya infection, high levels of viremia can be found which lead to hematomegaly.⁶ In Zika, edema of extremities and conjunctivitis are the specific symptoms.⁴

FURTHER COMPLICATIONS

Dengue and Chikungunya virus are associated with neurological manifestation.^{1,5} Encephalitis, meningitis, and febrile seizures can be manifested in Chikungunya cases; neurological, alongside with hemorrhage and myocardial disease can be transmitted to the infants during delivery.^{5,6} Unlike Chikungunya, which transmit the complication vertically, Dengue develops its complications to the patients by infects the Langerhans cells and travel to the lymph nodes carrying viruses. Dengue patient can have encephalitis, impairment of organs, and neurological

disorders, such as transverse myelitis and Guillain-Barré syndrome. In rare cases, myocarditis and acute liver failure can happen.¹

On the other hand, Zika virus connection to neurological disorders is still unknown. During Zika outbreaks, microcephaly and Guillain-Barré syndrome cases suddenly increased in newborn. Suspicion of Zika connection with neurological disorders has been arisen and preventive cautions have been alarmed.⁸

CONCLUSION

Similarities between Dengue, Chikungunya, and Zika have created misinterpretation among population. Even so, there are unique characteristics. During infection, Dengue gives bleeding, Chikungunya gives severe muscle and joint pain, and Zika gives rash, edema of extremities, and conjunctivitis. These viruses have many similarities in characteristics and their transmission. Understanding these diseases helps the development for diagnosis, vaccination, and medication; a single prevention action can get rid of these three threats.

In the future, awareness of these viruses' unique characteristics needs to be increased, especially among people in epidemic areas and travelers to hot spots.

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