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# HOSPITAL- AND COMMUNITY- BASED SURVEILLANCE OF ZIKA AND DENGUE VIRUSES IN INDONESIA

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## Abstract

**Background:** Zika virus remained silent for few decades after its first recognition in 1947. Recently, Zika drew global attention due to the outbreak in Pacific island and Latin Americas. The concern was escalating given the shared vector of Zika and dengue with possible deleterious complications. Surabaya as one of the largest cities in Indonesia with high mobility of people is endemic to dengue. This study was aimed to detect Zika infection during dengue outbreaks in Surabaya.
**Materials and Methods:** This was a surveillance study involving patients visiting 4 public hospitals and 8 primary health care centres (PHCs). Patients were recruited if they were suspected to have dengue infection based on WHO guidelines (1997). The recruitment was based on the attendance of the patients at the healthcare facilities until the maximum quota was fulfilled. Dengue serological diagnostic confirmation was based on non-structural protein 1 (NS1) and/or immunoglobulin M (IgM) detection. Zika virus infection was examined using real time polymerase chain reaction (RT-PCR) test.
**Results:** Between February and April 2016, 100 patients consented to participate in this study - 54 females and 46 males. Furthermore, 55 patients were recruited from PHCs and the other 45 patients were from hospitals. Median age was (median (IQR)) 28.6 (14.6) years (range15 to 65 years). Of 100 patients examined, there was no Zika infection detected, but 11 patients were identified to have positive dengue infection with varying clinical and laboratory presentations.
**Conclusion:** Serosurveillance of Zika and dengue infection in Surabaya City found no evidence of Zika infection among those presented to healthcare facilities.

**Keywords:** Zika, dengue, Surabaya, surveillance, RT-PCR

## Introduction

Zika virus was first identified in rhesus monkeys during a yellow fever serosurveillance at Zika forest near Lake Victoria of Uganda in 1947 (Dick et al., 1952). This virus belongs to flaviviridae family together with dengue and Yellow fever virus. Zika currently is drawing global concern due to the outbreaks of Zika cases in several Latin American and Pacific countries with associated increased risk of Guillain-Barre syndrome and teratogenicity effect in newborn babies including brain and macular abnormality (Franca et al., 2016; Petersen et al., 2016; Ventura et al., 2016; Zumla et al., 2016). The global awareness of the infection has been escalating given the shared vector of Zika and dengue virus, *Aedes (stegomyia)* genus, that warns the dengue-endemic countries. Moreover, the similarity of the symptoms and signs of Zika infection to other viral illness makes it difficult to detect the infection early based merely on clinical presentation.

In Southeast Asia, where most of its countries are tropical-disease endemic and located close to Zika outbreaks in Yap Islands of Micronesia in 2007, Zika infection has been reported in several countries including Singapore, Thailand, Cambodia, Malaysia and Philippines with diverse clinical and virus origin (Wiwanitkit, 2016). In Indonesia, the first report was published in 1981 during in-hospital investigation of leptospiral infection in Central Java (Olson et al., 1981). Zika cases was also recently reported in Jambi province of Sumatera island in a patient visiting local hospital during dengue surveillance (Perkasa et al., 2016), following the earlier report of infection in returned traveller to Australia (Kwong et al., 2013), and case of Zika infection suspected from monkey bite (Leung et al., 2015).

Nevertheless, epidemiological data, either hospital or PHCs surveillance data, on Zika virus infection in Indonesia is still limited following recent global epidemic. This study was intended to detect Zika infection through serosurveillance in Surabaya City, as one of dengue-endemic region in East Java, Indonesia. In addition, detection of Zika virus would contribute to the understanding of viral diversity of this virus and vaccine development. Moreover, Surabaya also serves as second largest city and trading hub in Indonesia with high mobility rate of people either from harbour or airport entrance.

## Materials and Methods

This study has been reviewed and approved by Research Ethics Committee of Universitas Airlangga Hospital. All patients participating in this study were provided with informed consent. Participants who were above 21 years old or had married provided self-consent while those who were below 21 years old had their parents or their guardians provide informed consent on their behalf. The authors asserted that all procedures contributing to this work had complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

### Patients and Population

This was a surveillance study to detect the Zika virus infection during dengue outbreak in Surabaya in early 2016. The participants in this study were recruited from patients who visited four public hospitals and eight primary health care centres (PHCs). The four public hospital were Universitas Airlangga Hospital, Dr. Soewandhie Hospital, Bhakti Dharma Husada Hospital, and Haji Public hospital. Menawhile, the eight PHCs, each of which covered one district area, included those in Sawahan, Tambakrejo, Jagir, Dupak, Medokan Ayu, Semampir, Sememi, and Mulyorejo District. Consecutive sampling method based on patients' attendance at health care facilities was used to recruit participants until the decided number of samples was fulfilled (n = 100 participants).

This surveillance was initiated by Airlangga Health Science Institute (AHSI) in respond to the recent re-emerging of Zika virus infection. In addition to detect the possibility of Zika virus spread, this survey was also intended to isolate the virus for vaccine research and development. Screening for those participating in the study was done by general practitioner (GP) in each PHC and emergency physician or internal medicine specialist in hospital. They were responsible for eligibility assessment and case reporting. The data were recorded in standardized forms and used throughout the study. Data processing and management was done by trained personnel and study protocol was coordinated centrally at Universitas Airlangga Hospital.

### Case Definition

The subjects of this study were patients who visited healthcare facilities and who were suspected to have dengue infection based on WHO guideline year 1997 (WHO, 1997). They were approached to participate in this study and to have blood examination. Those whose clinical presentation consistent with the guideline and met the inclusion criteria were offered to participate. The inclusion criteria were male or female above 15 years old, had fever of less than 7 days, and consented to participate in the study. Meanwhile, those who were pregnant, in critically ill condition, had dengue fever confirmed with circulatory shock, or refuse to participate were excluded from this study.

Dengue infection was confirmed when the clinical presentations showed typical dengue infection as per WHO guideline with NS1 and/or IgM-antidengue detected on serological examination. Zika virus infection was defined when real time polymerase chain reaction (RT-PCR) examination was positive.

### Laboratory Testing

Patients who were recruited to the study had 5 millilitres of their venous blood taken which were divided for NS1, serological dengue test (IgG and IgM anti-dengue), routine blood examination, and RT-PCR for Zika virus. Routine blood testing (Sysmex® XT-1800i), NS1 (The Panbio® Dengue Early Rapid) and serological dengue (SD BIOLINE® Dengue IgG/IgM) examination were conducted at the Clinical Pathology laboratory of Universitas Airlangga Hospital; whereas, RT-PCR (PrimeScript™ PLUS RT-PCR kit TaKaRa) was measured at Airlangga Institute of Tropical Disease laboratory.

### Statistical Analyses

The variables were presented as continuous and categorical data. The continuous data was written in forms of median and interquartile range (IQR) while the categorical data was displayed in forms of frequency and percentage. We used Microsoft Excel 2010 (Microsoft Corp., CA, USA) for data management and coding, and SPSS version 22 (SPSS Inc., Chicago, IL, USA) for statistical analysis.

## Results

### Surveillance System

The Surveillance was carried out between February and April 2016 when dengue virus outbreak emerged in Surabaya city. Prior to the study, all general practitioners and health care practitioners involved were briefed on the study protocol and recruitment process.

At the end of the recruitment, there were 100 patients consented to participate in this study; 54 were female and 46 were male. Fifty five percent of the participants were recruited at PHCs and 45% of them were from the hospitals. The median age of participants was (median (Interquartile range)) 28.6 (14.6) years ranging from 15 to 65 years old. More than half of the participants were below 40 years old and at about 9% of the participants aged 50 years or above. All patients presented to healthcare facilities had fever history of less than 7 days. In addition, there was no participant who was in critically ill conditions or needed to have immediate critical treatment at the time of recruitment. Table 1 shows the demographic distribution of the participants.

**Table 1:** Demographic Distribution of the Participants, n= 100

| **Demographic Features** | **(*n*)** | **(%)** |
|---|---|---|
| **Age, median (IQR)** | 28.6 (14.6) | |
| **< 20** | 20 | 20% |
| **20 - 29.99** | 33 | 33% |
| **30 - 39.99** | 27 | 27% |
| **40 - 49.99** | 11 | 11% |
| **50 - 59.99** | 7 | 7% |
| **>= 60** | 2 | 2% |
| **Gender** | | |
| **Male** | 46 | 46% |
| **Female** | 54 | 54% |
| **Recruitment site** | | |
| **Hospital** | 45 | 45% |
| **Primary Health Care** | 55 | 55% |

IQR, Interquartile range, Age, (Years)

### Laboratory Testing

### Zika virus detection

For Zika virus detection, there were 100 blood samples eligible for examination. There was no sample detected for Zika virus by RT-PCR method. The detail of the serologic and RT-PCR test is presented in Figure 1.

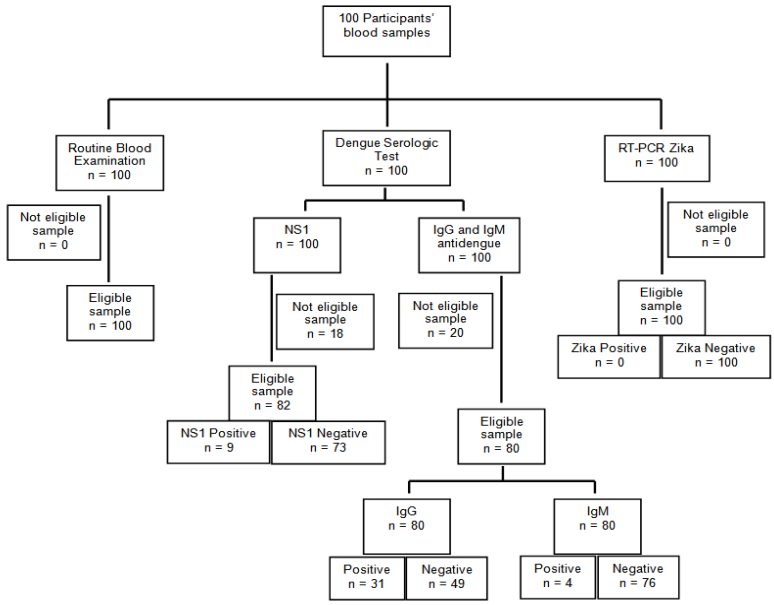


**Figure 1:** Flowchart of Blood Examinations

IgG Immunoglobulin G, IgM Immunoglobulin M, NS1 non-structural protein 1, RT-PCR Real Time Polymerase Chain Reaction

**Serological and routine laboratory test results**

Of 100 patients' blood samples taken for serological examination, 20 (20%) samples were ineligible for IgG and IgM antidengue testing and 18 (18%) samples could not be used for NS1 test due to blood lysis [Figure 1]. The results of the serological examination showed that 39% (31/80) samples positive for IgG anti-dengue indicating previous dengue infection with 61% (49/80) of them were negative. In addition, four patients were detected positive for IgM anti-dengue and nine patients were positive for NS1 antigen.

Furthermore, Table 2 describes the routine laboratory test results of all patients. All of the examination parameters were within normal range, except for monocyte percentage which was above the normal range and leukocyte percentage which was slightly below the reference range.

**Table 2:** Routine Blood Test Results, n= 100

| Variables | Median (IQR) | Reference Range |
|---|---|---|
| **Haemoglobin** | 13.8 (2.5) mg/dL | 13.2 - 17.3 mg/dL |
| **Leucocyte** | 5.9 (4.5) x 10^3/µL | 6.0 - 12.0 x 10^3/µL |
| **Erythrocyte** | 5.1 (0.9) x 10^6/µL | 4.4 - 5.9 x 10^6/µL |
| **Haematocrit** | 40.9 (5.9) % | 40 - 52 % |
| **Thrombocyte** | 183.5 (166) x 10^3/µL | 150 - 440 x 10^3/µL |
| **Leukocyte Differential Count** | | |
| **Lymphocyte** | 28.3 (22.3) % | 25 - 40 % |
| **Basophil** | 0.3 (0.4) % | 2 - 8 % |
| **Monocyte** | 8.3 (6.1) % | 2 - 4 % |
| **Eosinophil** | 0.7 (1.8) % | 0 - 1 % |
| **Neutrophil** | 61.3 (30.6) % | 50 - 70 % |

***IQR, Interquartile Range***

**Dengue Infection**

There were 11 patients identified with dengue infection based on positive IgM and/or NS-1 antigen. Of those, 7 patients had positive results only on NS-1, 2 patients had positive results only for IgM, and 2 patients had both NS-1 and IgM positive. The predominant clinical presentations were headache, myalgia, fatigue and arthralgia. The other minor symptoms were vomiting, minor bleeding including epistaxis, gum bleeding, melena, maculopapular rash and conjunctivitis. The clinical presentations for the patients were summarized in Table 3. Routine laboratory test results of these patients were presented in Table 4. The results were consistent with virus infection with leukopenia except for Patient 3 and Patient 6 who had normal leukocyte level, and Patient 11 with slightly high leukocyte count. In addition, haematocrit level was generally within normal range. However, two patients showed early sign of hemoconcentration indicated by haematocrit level reaching 49.3 % in Patient 4 and Patient 8 with haemoglobin level at 16.4 and 16.8 mg/dL respectively. Moreover, thrombocyte level was below 100,000 count/µL in seven patients. Minor bleeding signs such as melena, appeared in Patient 1 (Thrombocyte 101,000 count/µL) and epistaxis occurred in Patient 4 (Thrombocyte 20,000 count/µL).

**Table 3:** Clinical Profiles of Patients with Positive NS-1 and/or IgM antidengue

| ID | Case Origin | Age | Headache | Conjunctivitis | Fatigue | Maculopapular Rash | Myalgia | Arthralgia | Vomiting | Abdominal Pain | Minor Bleeding | Body Temp |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient 1** | Hospital A | 16.9 | + | - | + | - | + | - | - | - | + | 39.2 |
| **Patient 2** | Hospital A | 21.5 | + | - | - | - | + | + | - | - | - | 39.2 |
| **Patient 3** | PHC A | 32.9 | + | - | + | - | + | + | + | - | - | 38 |
| **Patient 4** | Hospital B | 20.1 | + | - | + | - | + | + | - | - | + | 38 |
| **Patient 5** | Hospital B | 15.0 | + | - | + | - | + | + | + | - | - | 37.8 |
| **Patient 6** | Hospital B | 20.9 | + | - | + | + | + | + | + | - | - | 37.8 |
| **Patient 7** | Hospital C | 18.8 | - | - | - | - | + | - | + | - | - | 38.1 |
| **Patient 8** | Hospital C | 31.0 | - | - | - | - | - | - | + | - | - | 39.2 |
| **Patient 9** | PHC B | 19.9 | + | - | + | - | - | - | + | - | - | 38 |
| **Patient10** | Hospital A | 17.9 | + | - | - | - | + | - | - | - | - | 36.5 |
| **Patient11** | PHC C | 26.9 | + | + | - | - | - | + | - | - | - | 37.2 |

NS-1 Non-structural 1 dengue antigen, IgM Immunoglobulin M, Age (Years), Body temperature (Celsius), PHC Primary Health Care

**Table 4:** Laboratory Profiles of Patients with Positive NS-1 and/or IgM antidengue

| ID | Case Origin | Age | Haemoglobin | Leucocyte | Erythrocyte | Haematocrit | Thrombocyte | IgM antidengue | NS-1 |
|---|---|---|---|---|---|---|---|---|---|
| **Patient 1** | Hospital A | 16.9 | 14.2 | 2.65 | 5.11 | 42.1 | 101 | + | + |
| **Patient 2** | Hospital A | 21.5 | 12.5 | 2.43 | 5.06 | 38.6 | 35 | - | + |
| **Patient 3** | PHC A | 32.9 | 13.8 | 7.63 | 4.7 | 40 | 139 | - | + |
| **Patient 4** | Hospital B | 20.1 | 16.4 | 2.44 | 6.25 | 49.3 | 20 | + | + |
| **Patient 5** | Hospital B | 15.0 | 15.7 | 2.68 | 5.8 | 46.9 | 55 | - | + |
| **Patient 6** | Hospital B | 20.9 | 16.1 | 6.02 | 5.59 | 45.2 | 35 | - | + |
| **Patient 7** | Hospital C | 18.8 | 12.3 | 2.48 | 4.55 | 37.4 | 42 | - | + |
| **Patient 8** | Hospital C | 31.0 | 16.8 | 3.13 | 6.57 | 49.3 | 14 | - | + |
| **Patient 9** | PHC B | 19.9 | 14.7 | 4.39 | 5.05 | 43.4 | 174 | - | + |
| **Patient 10** | Hospital A | 17.9 | 13.6 | 3.81 | 4.99 | 40.5 | 44 | + | - |
| **Patient 11** | PHC C | 26.9 | 13.3 | 13.63 | 4.88 | 40.4 | 234 | + | - |

NS-1 Non-structural 1 dengue antigen, IgM Immunoglobulin M, Age (Years), Body temperature (Celsius), Haemoglobin (mg/dL), Leucocyte (10^3 count/µL), Erythrocyte (10^6 count/µL), Haematocrit (%), Thrombocyte (10^3 count/µL), PHC Primary Health Care

## Discussion

In this dengue and Zika surveillance which involved hospitals and primary health care centres in Surabaya city, no evidence of Zika virus infection was found. This study mainly screened patients who had fever of less than 7 days and were suspected to have dengue infection based on clinical presentation. It was done because Indonesia is still endemic to dengue and its infection shared similarities to the signs and symptoms of Zika (Plourde & Bloch, 2016). The serosurveillance results also indicated that 11 patients had dengue infection showed by NS-1 and IgM test. The clinical and laboratory presentations were varying among patients despite typical viral disease signs and symptoms. The prominent laboratory concern among dengue-positive patients was low platelet count increasing the risk of spontaneous bleeding or, more severely, internal organ bleeding and plasma leakage.

This study was in odds with the recent dengue surveillance in Jambi Province of Sumatra Island (west of Java island), Indonesia. Perkasa and colleagues (Perkasa et al., 2016) reported that there was one case of Zika infection in 27-year-old male patient. The case was found incidentally and was initially suspected for dengue infection. Moreover, the patient did not share typical signs of Zika infection, such as maculopapular rash and conjunctivitis. The virus identified had similar genetic properties to Zika virus circulating in Southeast Asia. The other report of Zika infection came from Kwong and associates in 2013 who reported on Zika infection suspected to be acquired from Indonesia and experienced by a returning traveller to Australia (Kwong et al., 2013). The report highlighted a case with typical clinical presentation of viral infection, but showed descending maculopapular rash and conjunctivitis. This case was also initially suspected to be dengue fever before inconsistent laboratory results with dengue infection at day 5 were found.

Both cases mentioned above were found incidentally with initial dengue suspicion. The case detection involved institutions or research groups that were able to perform advanced laboratory test. This fact raises concern of undetected cases in the community where resources are limited. The finding of this study was similar to a retrospective blood survey conducted on 88 stored blood samples in Singapore (Balm et al., 2012). However, the study was limited to only samples collected in hospital from hospitalised patients admitted with dengue-like infection.

Zika virus detection in Southeast Asia including Indonesia has been limited to sporadic surveillance or incidental case discovery during dengue investigation. Despite the relatively fewer case detections compared to Latin American countries, the public health awareness to Zika infection and preventive measures should be encouraged given the possible deleterious effect (Araujo et al., 2016; Brasil et al., 2016; Parra et al., 2016) and multiple transmission mode (Musso et al., 2015).

### Study limitations and suggestions

Several limitations of this study include the relatively small number of patients compared to the annual dengue infection rate in Surabaya city and to the total number of population. Besides, some blood samples could not be measured for serologic test due to technical problem. This study also did not examine the potential of Zika infection of those visiting private health facilities or clinics. Given the clinical presentations of Zika infection that are similar to dengue or might be asymptomatic, further investigation is also necessary to be performed for visitors returning from overseas in the main gate such as airport and harbour.

## Conclusion

No evidence of Zika virus infection or co-infection of Zika with dengue was found during serosurveillance in Surabaya city. Eleven cases of dengue infection were found with diverse clinical and laboratory presentations.

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**Declaration:** Authors declare that there is no conflicting interest in the course of this research.

### Author Contributions

N, S, MA, DPR, ACR, and P conceived and designed the surveillance study. N, ACR, P supervised the recruitment process. MSH coordinated field data acquisition. DPR supervised and coordinated the laboratory testing. ZP, DPR, MSH managed, coded, and analysed the data. ZP, N, S, DPR, ACR, MA, P, and MSH contributed to the writing and editing process of the paper.

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