INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

INA-RESPOND Secretariat

Badan Litbangkes, Kemenkes RI,
Building 4, 5th Floor,
Jl. Percetakan Negara No. 29,
Jakarta, 10560.
Phone: +62 21 42879189
Email: INA.Secretariat@ina-respond.net
Website: www.ina-respond.net

Newsletter
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In This Issue

Zika Virus Alert!

Zika virus is a mosquito-borne flavivirus transmitted primarily by *Aedes aegypti. Aedes albopictus* mosquitoes might also transmit the virus. Outbreaks of Zika virus have been reported in Africa, Asia, and islands in the Pacific.

About one in five people infected with Zika virus become symptomatic. Characteristic clinical findings include acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis. Clinical illness usually is mild with symptoms lasting for several days to a week. Severe disease requiring hospitalization is uncommon and fatalities are rare.

Seeing that the Zika virus poses a real threat to people, especially for pregnant women and their babies. We should learn how to prevent and take action so that the threat will not become bigger. Learn how by reading the complete article in this edition.

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Hitting The Bulls-Eye: Accuracy & Precision for Researchers

As researchers, do you know the difference between accurate and precise? Make sure you've got the right understanding. Find the answer here on

Page 4

Save The Date

The 2016 is starting quite nicely. We have some meetings and events planned up to meet our network's goals. One of the upcoming meetings is the HIV protocol core meeting. We are also preparing sites for the TB study. Hopefully, the site activation will be conducted this month (date to be determined).

18 February	HIV Meeting Double Tree Hotel, Jakarta
24 March	World TB Day

Announcement

To promote greater autonomy and independence in day-to-day functioning so that our network can move towards its self-sustainability, INA-RESPOND network went through a transition period that was completed last month on 13 January 2016. Some changes that entail this transition are changes in the address of our email and portal, as well as the OpenClinica. Our current email's domain is @ina-respond.net. Therefore, all our email address have been changed accordingly. As for portal and OpenClinica, below are their new address:

https://oc.ina-respond.net/OpenClinica

https://portal.ina-respond.net

February Birthday

2 Feb	Dr. Indri Hapsari Putri	INA101 RA Site 560
3 Feb	dr. Gandhi Anandika Febryanto	SEA050 RA Site 43
7 Feb	dr. Anandika Pawitri	INA-RESPOND Secretariat
17 Feb	Dwi Astuti Purwaningsih	Lab Tech Site 580
28 Feb	dr. Khie Chen, SpPD-KPTI	INA101 Site PI Site 530
28 Feb	dr. Achmad Harun	SEA050 RA Site 42

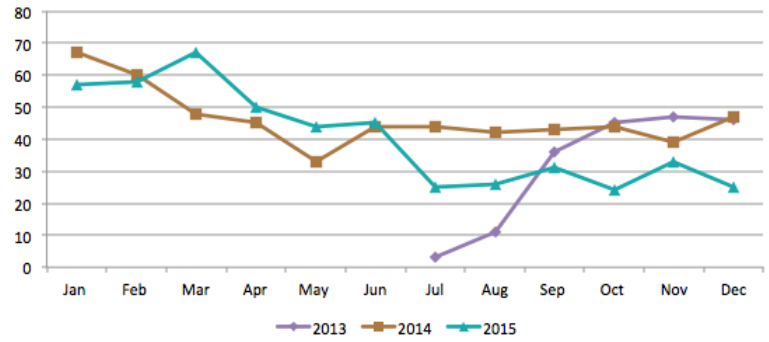
INA-RESPOND Study Updates

By dr. Anandika Pawitri,
dr. Nurhayati,
Ms. Novitasari

AFiRE Study (INA101) Updates

Site Number – Name	Date 1st enrollment	Number screened patients	Number of Enrolled Subjects (adult/child)
510 - RSUP dr Hasan Sadikin	04 Sep 2013	381	241 (133/ 108)
520 – RSUP Sanglah	18 Jul 2013	1224	188 (138 / 50)
530 – RSUPN dr Cipto Mangunkusumo	27 Nov 2014	275	44 (29 / 15)
540 – RSPI Prof dr Sulianti Saroso	08 Dec 2015	190	56 (13 / 43)
550 – RSUP dr Wahidin	16 Oct 2013	339	146 (108 / 38)
560 – RSUP dr Kariadi	19 Aug 2013	626	235 (125 / 110)
570 – RSUD dr Soetomo	03 Jan 2014	568	195 (117 / 78)
580 – RSUP dr Sardjito	26 Aug 2013	827	149 (62 / 87)
Total		**4,430**	**1,260 (728 / 532)**

Description of Monthly Enrollment progress can be seen in the figure below:



Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: https://ina-respond.s-3.com/EdmFile/getfile/797233

Since July 2013, the study has screened 4,430 patients. 1,260 subjects have been enrolled (728 adults and 532 children). Site 510 is our top recruiter with 241 subjects recruited, and site 560 is the runner-up with 235 subjects. It's a tight competition!

Screening and enrollment progress at each site is available in table 1. Screening and enrollment progress at each site.

Sepsis Study (SEA050) Updates

The Site Close Out (SCO) visits to all sites were conducted in the 2nd and 3rd week of January 2016. All sites' team members are being made busy by the Secretariat! The team still needs to answer queries, send specimens, complete documents, and many other things for this study. They still need to push forward with the study at a fast pace, hoping to complete the project on time. We expect to close all data for analysis at the end of March.

Specimen testing will be started in INA-RESPOND assigned reference lab. The results will be very valuable for the manuscript writing.

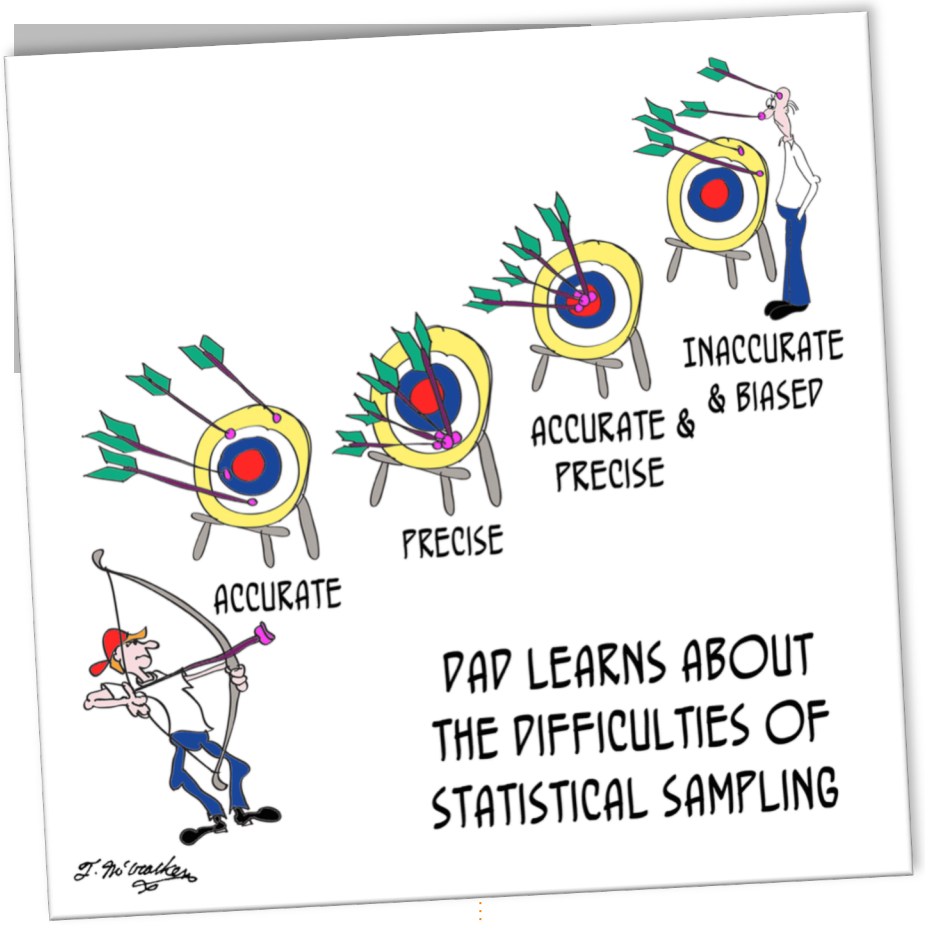
	Site 41 – RS dr. Cipto Mangunkusumo	Site 42 – RS dr. Wahidin Sudirohusodo & RS Universitas Hasanuddin	Site 43 – RS Sardjito
Number of Screened Patients	Adult : 132 Pediatric : 78 Total : 210	Adult : 92 Pediatric : 38 Total : 130	Adult : 166 Pediatric : 113 Total : 279
Number of Enrolled Patients	Adult : 17 Pediatric : 6 Total : 23	Adult : 24 Pediatric : 4 Total : 28	Adult : 25 Pediatric : 6 Total : 31
Enrollment Expectation	Adult : 15 Pediatric : 15	Adult : 25 Pediatric : 25	Adult : 20 Pediatric : 20
Number of days after enrollment	Day 151 (activation date: 6 August 2015)	Day 312 (activation date: 26 February 2015)	Day 256 (activation date: 23 April 2015)

Screening and Enrollment Progress up to 31 December 2015

Cartoon Corner
Let's Hit The Bulls-Eye: Accuracy and Precision for Researchers

By:

dr. Aly Diana



The terms accuracy and precision are often be used interchangeably, as they somehow sound quite the same especially for a layperson. Many people ask the same questions. First, what is the main difference between these two terms? Second, why is it important? Nevertheless, before answering these two most common questions, I think it is better to see the context where accuracy and precision are used.

Researchers use accuracy and precision for describing the ideal measurement tool. When we are collecting data, we always aim for the best data possible. We would love a tool that can really measure the true picture of what we are measuring. After all, if we cannot trust our measurement tool, nobody will trust the data that it produces.

So, what is the difference between these two terms? ***Accuracy*** refers to how close measurements are to the "true" value, while ***precision*** refers to how close measurements are to each other. In other words, accuracy describes the difference between the measurement and the actual value, while precision describes the variation you see when you measure the same part repeatedly with the same device.

The closer your measurement with the target means that your measurement is more accurate; and the closer your measurement with other measurements means that your measurement is more precise.

Why is it important? It is simply because you need both of them to collect good data. I know that we need an example for making it clearer. Let us talk about the diameter of basketball. The accurate (but not precise) measurements of the diameter may result in 24.1, 23.8, 25.9, and 26.2 cm. In this case, the measurements have a larger variance, but the average of the measurements is very close to the target value of 25.0 cm. The precise (but not accurate) measurement of the diameter may result in 27.1, 27.3, 26.7, and 26.9 cm. In this case, the measurements have a smaller variance, but the average of the measurements is quite far to the target value. Therefore, we need to combine accuracy and precision together; and save our dad from being a victim of our mistake.

Zika Virus Alert!

By
Dr. Dona Arlinda

Another virus has re-emerged and quickly garnered attention for its association with severe birth defect and its spread across the Americas.

Zika virus (ZIKV) is a mosquito-borne ssRNA virus in the family Flaviviridae and genus *Flavivirus*. It is related to yellow fever, dengue, West Nile, and Japanese encephalitis viruses. Zika virus was first isolated in 1947 from a blood sample taken from a sentinel Rhesus monkey. Initially, researchers were investigating the high incidence of immunity to yellow fever virus among monkeys in Zika forest in Uganda. When one of the monkey developed fever, its blood samples were taken daily and were inoculated into mice. Further isolations of the mice tissues lead to the discovery of the new virus, which then named after the forest. As an arbovirus, ZIKV has been isolated from *Aedes africanus*, Ae. albopictus, *Ae. apicoargenteus*, Ae. *luteocephalus*, *Ae. aegypti*, *Ae. vitattus*, and *Ae. furcifer* mosquitoes.

Sporadic infections of ZIKV were reported in Africa and Asia. In 1954, ZIKV was isolated from a jaundice patient suspected of having yellow fever in Nigeria, this finding marked the first ZIKV infection in human. Between 1964 and 1970, ZIKV was identified as one of the causative agents in an epidemiological study in Nigeria. In Southeast Asia, several ZIKV infections were reported from Indonesia. The virus was serologically confirmed in acute fever patients in Central Java, Indonesia in 1977. In an arboviral antibodies survey in Lombok 1982, ZIKV was serologically identified in selected samples. Australian citizens were reported of contracting the virus following a brief travel to Jakarta 2013 and Bali 2015. A sample

(continued)

TAKE ACTION:

PROVIDERS

COLLABORATE AND PARTNER UP WITH AGENCIES TO GET READY TO TEST PATIENTS FOR THE ZIKA VIRUS; AND MAKE PREPARATION TO EDUCATE PEOPLE.

EVERYONE

MAKE SURE YOUR YARD IS TIDY. PICK UP ALL THE CANS, ALL THE DEBRIS, ANY LITTER, KEEP YOUR LAWN MOWED SHORT. DON'T LET THE AEDES MOSQUITOS BREED AROUND HOUSES.

obtained from a dengue outbreak patient in Jambi 2015 was positively confirmed by RT-PCR for ZIKV. More incidental reports from Cambodia, the Philippines, and Thailand between 2010 and 2014 were later confirmed the sporadic spread of ZIKV in Asia.

The first ZIKV outbreak occurred in Yap State, Micronesia in 2007 with 49 confirmed cases. Other outbreaks occurred between 2013 and 2014 in four Pacific countries (French Polynesia, New Caledonia, Cook Islands, and Easter Island). In March 2015, a dengue-like illness outbreak occurred in Bahia, Brazil with 7 out of 24 serum samples from the patients were positively confirmed by RT-PCR for ZIKV. As of 23 January 2016, the US CDC reported active transmission of ZIKV is occurring in 25 countries in the Americas, Oceania/Pacific Islands, and Africa (Fig. 1).

Mode of transmission is mainly through an infected Aedes mosquito bites. Non-vector routes include mother to child transmission (during pregnancy or birth), blood transfusion, or sexual contact. ZIKV has been detected in breast milk, however transmission through breastfeeding has yet been reported. The incubation period is currently unknown. Typically, a ZIKV infection would causes mild symptoms and self-limiting dengue-like illness. An infected patient may experience symptoms for 2-7 days. The symptoms were characterized by low-grade fever, maculopapular rash, conjunctivitis, arthralgia, myalgia, and headache. Hospitalizations or deaths are uncommon. However, possible complications following co-infections of ZIKV with dengue virus may include Guillain-Barré syndrome, other autoimmune diseases, neurological syndrome, as well as ophthalmologic and cardiac complications. In addition, ZIKV infection is likely to be associated with congenital anomaly, such as microcephaly in newborn babies.

The unusual occurrence of microcephaly babies in Brazil and its possible association with ZIKV outbreak in 2015 has generated concerns since vertical infection during pregnancy resulting in fetal brain abnormality is relatively rare. Microcephaly is a birth

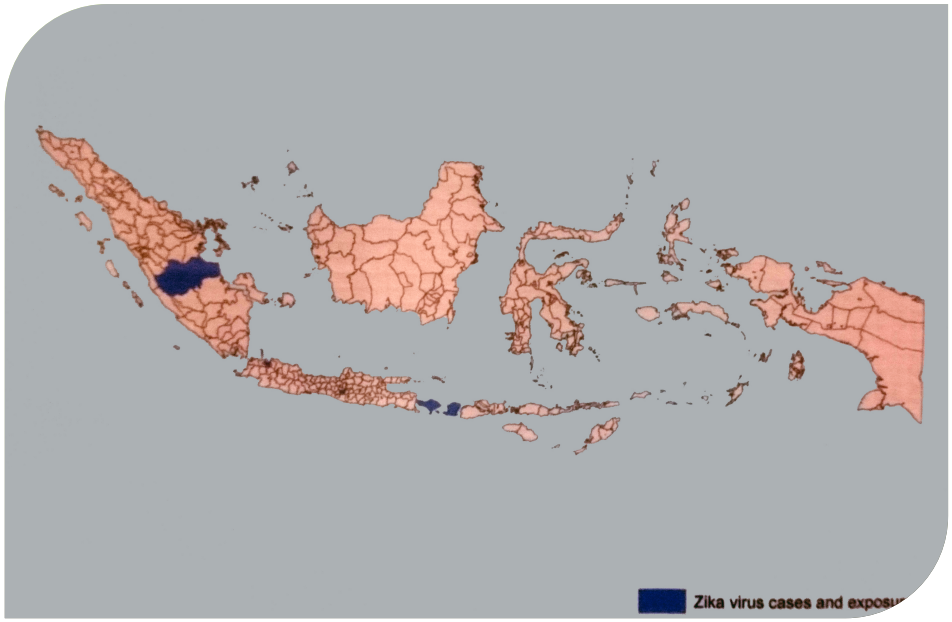


Fig.1 Zika virus cases and exposure in Indonesia

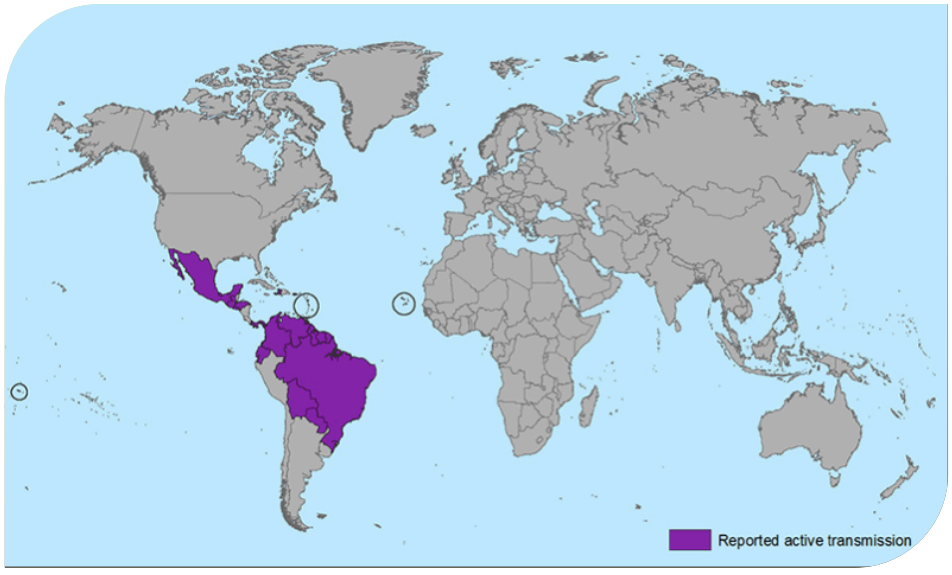


Fig.2 Zika-affected areas as of 23 January 2016 (Source: US CDC, 2016)

defect where a baby's head is smaller than expected when compared to babies of the same sex and age (Fig. 2). In the year 2000, the prevalence of microcephaly in Brazilian newborns was 5.5 cases /100,000 live births. Ten years later, the prevalence was only slightly increased to 5.7 /100,000 live births. As of 30 November 2015, there were twentyfold increase of the prevalence to 99.7 /100,000 live births or 1,248 cases of microcephaly. Brain atrophy and intracranial calcifications are among the prominent abnormalities observed through fetal ultrasound examination. During the outbreak in Brazil, ZIKV RNA has been identified in specimens (brain tissue, placenta, and amniotic fluid) collected from several infants with microcephaly and from fetal losses in women infected with ZIKV during pregnancy. Cerebrospinal fluids from 35 infants with microcephaly from suspected ZIKV-infected mother are currently under investigation.

Clinical diagnoses of ZIKV infection based on signs and epidemiological data are sometimes unreliable because of their similarity with dengue or chikungunya virus infection. Variations on complete blood count (CBC) profile in ZIKV patients were reported. Some showed patterns of leukopenia and thrombocytopenia, which are also commonly found in dengue or chikungunya virus infections. Other reports revealed normal CBC results.

Laboratory confirmations for ZIKV infection are made through serological tests for the presence of specific antibodies, molecular assay using reverse-transcription PCR (RT-PCR), or virus isolation (gold standard) for virus detection. Blood samples for serologic tests should be collected approximately 5 days after the onset of symptoms. Note that ZIKV specific IgM and neutralizing antibodies may cross-react with other flaviviruses, such as dengue, West Nile, and yellow fever virus. Cross-reacting antibodies may be differentiated through plaque-reduction neutralization test.

For RT-PCR assay or virus isolation, blood samples should be collected during the first 3-5 days after the onset of symptoms. RT-PCR may also be performed with urine or saliva samples. A study demonstrated that ZIKV was detected with RT-PCR at higher titers in urine and stayed positive there for a longer period (>10 days) than in blood. Other study revealed that with RT-PCR, ZIKV was detected in saliva within the same time window as in blood. However, saliva should not be used to replace blood samples since negative saliva does not necessarily mean negative ZIKV.

There are no definitive treatments or vaccines for ZIKV infection yet. Infected people would generally be given supportive or symptomatic treatment. They should get plenty of rest, drink enough fluids, and treat pain and fever with common medicines. Take medicine such as acetaminophen to relieve fever and pain. Do not take aspirin or other non-steroidal anti-inflammatory drugs

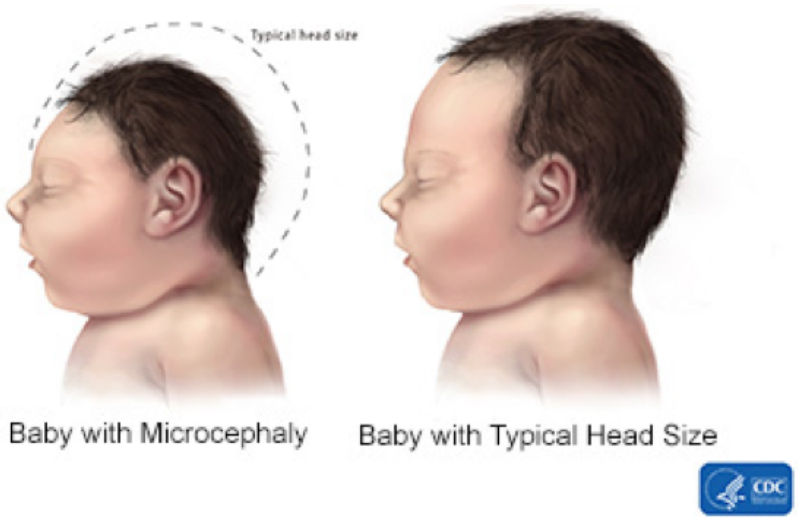


Fig.3 An illustration of a baby with and without microcephaly (Source: US CDC, 2016)

(NSAIDs), such as ibuprofen and naproxen. Aspirin and NSAIDs should be avoided until the possibility of having dengue infection is excluded.

Unfortunately, the performance of diagnostic tools to distinguish the two diseases, especially rapid tests, is still not satisfying. Moreover, there is still much to learn about the signs, symptoms, and pathogenesis of ZIKV infection.

The patients should also prevent further transmission by protecting themselves from mosquito bites during the first week of illness by using repellent or physical barriers such as clothes, screens, mosquito nets, etc. These prevention methods are applicable as well for those who wish to stay uninfected. Other preventative measures to reduce mosquito-breeding sites as suggested for dengue vector control are also recommended. During an outbreak, health authorities may conduct insecticides spray. Pregnant women and women trying to become pregnant are advised not to travel to Zika-affected areas. Some countries even advised women to delay pregnancy up to two years following the outbreaks.

Selected references

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INA-RESPOND Newsletter

Advisors : dr. M. Karyana, M.Kes, dr. Herman Kosasih
Art & Language : Dedy Hidayat S, S.Kom, Dona Arlinda, MD
Columnists : dr. Anandika Pawitri, dr. Nurhayati, Ms. Novitasari, dr. Aly Diana. Dona Arlinda, MD

Thanks to : INA-RESPOND Network and Partners

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