INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

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Newsletter August 2016

In This Issue

We have determined the dates for the Steering Committee Meeting and the AFIRE Study meeting. Steering Committee members, Site PI, and one Research Assistant from each AFIRE site are invited to the meeting. Find out when they are going to be held on page 2.

Save the date and do come to these important meetings. For further information, please contact the Secretariat.

Dengue Prevention Breakthrough: Could Dengue Vaccine Be the Answer?

Dengue is one of the most devastating mosquito borne diseases in the world. Plaguing mostly the developing countries, Dengue is a health hazard that takes scores of lives every year.

Asian countries spend an estimated 6.5 billion USD annually in both direct and indirect medical costs due to Dengue. The situation gets murkier because of the absence of any kind of preventive medicines for the same. But as they say where there is a will there is a way and we humans have proved it time and again that we, with the help of technology and resources can overcome even the most difficult of problems.

Vaccination is the emerging hope that leads many scientists to conduct vaccine invention research. Researchers have been in a long journey to find the ideal vaccine for Dengue. So, are we there yet? Find out in this month's newsletter.

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Multitasking in A World of Focus

Have you ever felt that you have amazing skills at multitasking? Is it really possible for a person to successfully multitask in his/her job? Is there any repercussion? Find out in this newsletter.

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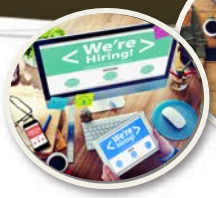
Save The Date

Important Events & Meetings

17 August	Indonesia Independence Day
14 September	Network Steering Committee Meeting
15 September	AFIRE Study Meeting



August Birthday

2 Aug	Mr. Agus Dwi Harso	NIHRD
11 Aug	dr. Patricia M. Tauran	Secretariat
	Ms. Agnita Triyoga	Secretariat
12 Aug	Prof. Dr. Suharto, SpPD, KPTI	SC Member Site 570
	Mr. Junediyono	NIHRD
14 Aug	dr. Caleb Leonardo Halim	RA SEA050 Site 41
17 Aug	Ms. Libertha Clara M.	LT SEA050 Site 42
21 Aug	dr. Rizka H. Azdie	PI SEA050/ INA101 Site 580
	dr. Retna Mustika	Secretariat
26 Aug	dr. Yenni Risniati	NIHRD

Announcement

The INA-RESPOND network is going to hold its second Network Steering Committee (NSC) meeting in September. The meeting is scheduled on 14 September, and we are inviting all Steering Committee members from sites.

In addition to the Steering Committee Meeting, our network is going to hold the AFIRE Study meeting, which will take place at Double Tree Hotel, Jakarta on 15 September 2016. SC members, Site PIs, and INA101 RAs are invited to attend the meeting.

INA-RESPOND Study

By dr. Anandika Pawitri, dr. Nurhayati

AFIRE Study (INA101) Updates

Site Number - Name	Enrolled Subject		
	Total	Adults	Pediatric
510 – RSUP dr Hasan Sadikin	152	117	269
520 – RSUP Sanglah	161	53	214
530 – RSUPN dr Cipto Mangkusumo	41	26	67
540 – RSPI Prof dr Sulianti Saroso	16	75	91
550 – RSUP dr Wahidin Sudirohusodo	147	54	201
560 – RSUP dr Kariadi	136	122	258
570 – RSUD dr Soetomo	136	85	221
580 – RSUP dr Sardjito	75	96	171
Total	**1,492**	**864**	**628**

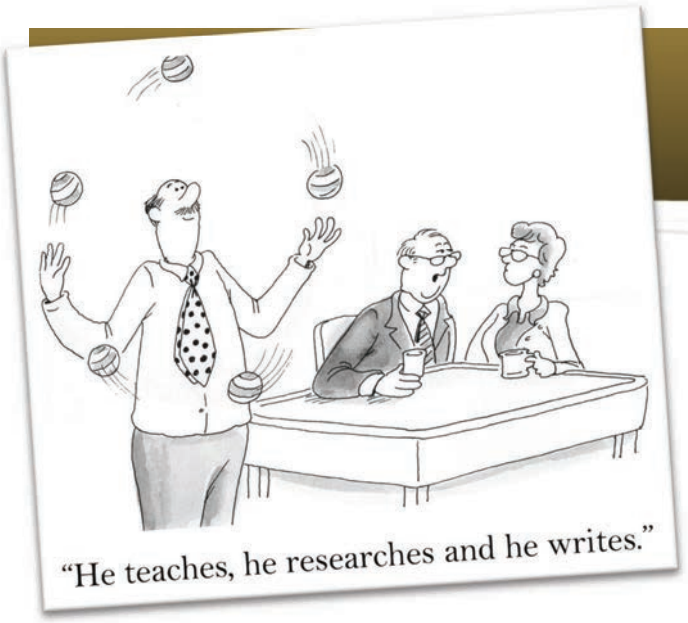
The recruitment process for all sites finished on 30 June 2016. 1,492 subjects were recruited for this observational cohort study. While waiting the follow-up visit for each subject, the site team is preparing to complete and upload the case report form. Site team and secretariat staffs are preparing some manuscripts based on interim data analysis. A meeting to discuss AFIRE study will be held on 15 Sept 2016. Details of subject enrollment at each site can be seen in the table.

A – Site 510 – RSUP dr Hasan Sadikin, Bandung
B – Site 520 – RSUP Sanglah, Denpasar
C – Site 530 – RSUPN dr Cipto Mangunkusumo, Jakarta
D – Site 540 – RSPI Prof Dr Sulianti Saroso, Jakarta
E – Site 550 – RSUP dr Wahidin Sudirohusodo, Makassar
F – Site 560 – RSUP dr Kariadi, Semarang
G – Site 570 – RSUD dr Soetomo, Surabaya
H – Site 580 – RSUP dr Sardjito, Yogyakarta

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

Sepsis Study (SEA050) Updates

The final report to NIHRD IRB and local IRB will be submitted after all outstanding items from site monitoring close-out are completed. From February 2015 to 31 December 2015, 79 subjects (65 adults and 14 children) were enrolled from 619 screened patients. The male to female ratio was 1.4:1 and the median (range) of age was 42 year old (3 month old – 83 year old). Most subjects came to the hospitals on day 4 of their illnesses. The median (range) day duration of hospitalization was 7 (1 – 29 days) days. From 35 death subjects, 94% (33 subjects) died during hospitalization and 2 subjects, who were discharged before day 28 against medical advice, died at home.



Multitasking Jobs in the World of Focus

By:

dr. Aly Diana

Calling this world a world of focus may sound exaggerating, but in terms of expectations, somehow it's the truth. Many of you are lecturers, researches, analyst, managers, event organizers, etc. How many of you have felt overwhelmed by the tasks given? This article is not aiming to provoke you to start a strike saying that your supervisors are damaging your brain by making you multitask different jobs. This article simply aims to give you some tips to survival in this crazy world of focus.

Although some of us may accuse that the world is not fair and the tasks given are unrealistic and never ending, somehow we also drive ourselves to a worse condition, by incorporating media into our lives, becoming heavy media multitaskers. Media multitaskers are us, who watch online videos, surf the web, talk or text on our smart phones, check e-mail, read journal, and at best try to write a scientific article, all at the same time. These changes to the media addiction are actually placing new demands on cognitive processing, and especially on attention allocation.

So, what is happening to our brain, the brain of high media multitaskers? Generally, the high multitaskers (especially the chronic one) have a worse performance when being compared to the low multitaskers in three main areas. First is filtering: the ability to ignore irrelevant information and focus on relevant information. In fact, multitaskers are sucker for distraction and the irrelevant. Therefore, the more irrelevant information they see, the more they're attracted to it. Second is the ability to manage our working memory, keeping it organized, so we know where to search when we need the information. Multitaskers are also much worse at that. Finally, multitaskers are even slower and worse at switching from one task to another, surprisingly!

Research shows that multitasking contributes to cognitive overload through too much information supply and demand, interruptions, and inadequate infrastructure, thus increasing needs for planning, monitoring, reminding, and reclassifying information.

Many multitaskers tend to rate their own ability to multitask as higher than average. In fact, their perceived ability and actual ability to multitask are inversely related. A study suggests that overconfidence, rather than skill, drives the proliferation of multitasking. So, we have to realize that sometimes our confidence can be very deceiving.

If you feel that it's **ME** who is having all signs and symptoms of heavy multitasker when you are reading this (just like me when I am discovering facts about multitasker from the scientific journals and trying to write at the same time, while listening and singing to random songs, and keep checking my Facebook and WhatsApp); we still have hope. The cognitive function can go back to normal when we deteriorate from our super busy world and do fewer things at one time. Spending more time for one task before switching to others will also help. Some scientists suggest having specific time to check e-mail and time for media fasting.

Yes, it's easier said than done. However, let's not give up. Let's go back to the world of focus, and try to do one thing at a time; and give our better performance for our many roles and jobs.

Dengue Prevention Breakthrough: Could Dengue Vaccine Be the Answer?

By
dr. Luthvia Annisa
dr. Yuli Mawarti

Dengue is a global, major vector-borne *Arboviral* disease causing huge pressure on health system due to costly resources straining and its socio-economical impacts on society.[1] Alleviating dengue infections remain the major health priority in most Latin American and Asian countries where epidemics inevitably occur regularly and contribute as one of the most frequent reasons of hospitalization.[1] Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.[1]

The Epidemiological patterns of dengue are demonstrated by its high incidence and other features including hyper-endemicity of multiple dengue virus serotypes in many countries.[1] Dengue is considered the most rapidly spreading mosquito-borne viral disease in the world.[2] By 1970, there were only 9 countries that had experienced severe dengue epidemics, but now it is endemic in more than 100 countries.[1] The number of cases is increasing as the disease spreads to new areas, some with explosive outbreaks resulting dramatically grown global incidence of dengue. A study of dengue prevalence estimates that 3.9 billion people (more than half of the world's population) of 128 countries are at risk of dengue infection.[1]

In Indonesia, Dengue Hemorrhagic Fever (DHF), the severe form of dengue infection, was first reported in 1968, in Surabaya and Jakarta, with a total of 58 cases of which 24 died during the outbreak (CFR 41%).[2] The annual DHF incidence increased from 0.05/100,000 in 1968 to 35-40/100,000 in 2013, with the highest epidemic occurring in

(continued)

TAKE ACTION:

GOVERNMENT

SOCIALIZE THE GUIDELINES FOR INTEGRATED VECTOR MANAGEMENT FOR CONTROL OF DENGUE FEVER TO HEALTHCARE PROVIDERS AND SOCIETY.

EVERYONE

USE INSECT REPELLENT ON EXPOSED SKIN TO PREVENT POSSIBLE MOSQUITO BITES DURING OUTDOOR ACTIVITIES.

2010 (85.70/100,000; $p < 0.01$).[2] The incidence is thought to be higher because the actual dengue cases number are often underreported, and many cases are misclassified due to their broad spectrum of clinical symptoms and because of the surveillance systems limitations.[3]

Dengue is typically found in urban and semi-urban areas, and in tropical and sub-tropical climates worldwide.[4,5] There are 4 distinct - but closely related- virus serotypes, which cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4).[6] Dengue viruses are primarily maintained in a human-to-mosquito-to-human cycle with *Aedes aegypti* mosquito as the primary vector.[7]

Aedes aegypti is highly adapted to human habitations. It lives in urban habitats and breeds mostly in man-made containers.[8] Indonesia is a tropical country with relatively constant high temperature and humidity, conducive for *Aedes Aegypti* perpetuation.[9,10] *Aedes albopictus*, a secondary dengue vector in Asia, has spread to North America and arrived in more than 25 countries of the European region.[11] Its spread is due to its tolerance to below freezing temperatures, hibernation ability, and proficiency to shelter in microhabitats.[11]

Demographic, climate, and social changes also play an important role in increased incidence and geographical spread of dengue virus.[12]

The WHO has set the target to reduce dengue mortality by 50% and reduce morbidity by 25% by 2020 (using 2010 data as the baseline).[1] At present, there is no specific treatment for dengue disease and the renowned strategy on its prevention is the vector control, which comprises:

- preventing mosquitoes from accessing egg-laying habitats by environmental management and modification
- disposing solid waste properly
- covering, emptying, and cleaning domestic water storage containers on a weekly basis
- applying appropriate insecticides to water storage
- using personal household protection
- improving community participation and mobilization
- applying insecticides as space spraying during outbreaks as one of the emergency vector-control measures;
- active monitoring and surveillance of vectors.[1]

However, this approach is thought to be less effective due to the cosmopolite and highly adaptive characteristics of the vectors and vector resistance to some insecticides.[1] Eventually, vaccination is the emerging hope that leads scientist to conduct vaccine invention research. Researchers have been in a long journey to find the ideal vaccine for Dengue, which should be affordable, 4 serotypes effective, giving effective long-term immunity, safe, storage friendly, and genetically stable.[13]

There are candidates for dengue vaccine that have been in either preclinical or clinical trials. First is tetravalent live attenuated which is made of conventionally attenuated virus.[13] The second one is chimeric vaccine that is similar to live attenuated vaccine, but specifically went through genetic engineering process by inserting the genetic membrane of Dengue virus to *yellow fever* virus (YF 17D).[13] The YF17D is chosen because it is genetically related to Dengue virus and is proven safe.[13] Other candidates are the sub-unit vaccine that is made of microorganism certain parts (i.e. recombinant protein E) and the DNA vaccine that is designed by inserting some genetic materials of the virus to the plasmid vector. [13]

After two decades of research, in late 2015, the world had its first

ever WHO-approved Dengue vaccine called **Dengvaxia** (CYD-TDV).[14] It is a recombinant, tetravalent (of DEN-1, -2, -3 from Thailand, and DEN-4 from Indonesia), live-attenuated vaccine that has been licensed in four countries—Mexico, Brazil, El Salvador and the Philippines.[14] Its phase 3B clinical trials have been held in 5 countries in the Asia Pacific region, assessing 10,275 healthy children aged 2–14 years with its primary objective to estimate protective efficacy against symptomatic, virologically confirmed dengue after the completion of three doses of CYD-TDV given 6 months apart (at months 0, 6, and 12).[15]

The trial result is translating into an overall protective efficacy of 56·5% (43·8–66·4%). The vaccine efficacy was somewhat serotype specific. Efficacy against serotypes 3 and 4 was consistently more than 75% and was 50% for serotype 1, but low for serotype 2 (35%), with wide range of confidence interval (95% CI is 9·2 to 61·0) in the per-protocol analysis; and 34·7% (10·4–52·3) in the intention-to-treat analysis.[15] That efficacy in younger age groups was far lower than that in older children (33·7% in children aged 2–5 years in contrast to 74·4% in those aged 12–14 years) is a finding which is of concern, because younger children have a higher incidence of dengue than older children, and are often at higher risk for more severe disease.[15]

Furthermore, CYD-TDV is associated with increased risk of hospitalized and severe dengue illness in the 2–5 year age group; WHO then recommends CYD-TDV use only in population of 9-45 years of age.[14,15] Another concern is the relative lack of vaccine efficacy in participants who were dengue-virus naive (35·5%, 95% CI –26·8 to 66·7), suggesting that this vaccine boosts and broadens pre-existing immunity rather than raising protective immunity.[16] Therefore, the vaccine might be of limited use in countries with low dengue endemicity, or for international travellers from non-dengue-endemic countries.[16]

Dengue immunity is serotype specific. The lifelong immunity gained after recovered from one serotype infection is specifically against it.[14] A cross-immunity to the other serotypes after recovery is only partial and temporary and subsequent infections by other serotypes is more likely to increase the risk of developing severe dengue, a phenomenon known as *Antibody Dependent Enhancement* (ADE).[14] Sasmono reported that a vaccine of different genotype virus from some geographical setting might result in a non-optimum/different immunity response when implemented in different geographical setting, depending on the detail of dengue virus nucleotide genomic sequences.[17] The Indonesian Dengue Vaccine Consortium is conducting preclinical phase, a research in genetic characteristics of local dengue viruses strain from different areas in Indonesia and in choosing the most appropriate virus prototype for the vaccine material suits best for Indonesian setting.[18]

An ideal Dengue vaccine may signify the dawn of the new era in Dengue control, although for now, the low vaccine efficacy (56.5 %) is suggesting continuous support for other novel strategies development. WHO recommends that countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings where epidemiological data indicate a high burden of disease and it should be a part of a comprehensive dengue control strategy, including well executed and sustained vector control, evidence-based best practices for clinical care for all patients with dengue illness, and strong dengue surveillance.[14]

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INA-RESPOND Newsletter

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