INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

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NEWSLETTER

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IN THIS ISSUE

Network Steering Committee Meeting

by Dedy Hidayat S.

Picture 1 Opening Remarks. From left to right: Dr. Siswanto, Prof. Dany H., Dr. Bachti A.

The Network Steering Committee meeting was successfully held on October 22 – 23, 2014 in Bandung. Except for a couple of SC members who could not make it, all SC members gathered at *Gedung Fakultas Kedokteran Universitas Padjajaran, Bandung* to discuss important issues related to the network's studies and the future of the network.

The Highlight

A network as big as INA-RESPOND surely has its own challenges. However, with good communication and openness, there is nothing the network cannot resolve. *Badan Litbangkes* is going to hold a meeting with the Ministry of Foreign Affairs, Republic of Indonesia to talk about the network. We are hoping that through this meeting, INA-RESPOND network's activities will gain more support from other departments and ministries.

In one of the discussions in the NSC meeting, every SC member shared and testified to the benefits and acknowledgement received from conducting the AFIRE study, such as:

- becoming the model study in GCI accreditation (because the study meets international standards and requirements),
- improving inter-department communication (because the study involves more than one department),
- developing the infrastructure of clinical research at sites, and
- creating topnotch researchers.

The sharing session proved to be a morale boost for all the meeting participants, including the AFIRE study's site PIs who also attended the meeting.

One Research Assistant (RA) from each site was also invited to give and share their findings. The RAs also participated in the "INA101 Data Introduction and Analysis" training, organized by the Data Management department of INA-RESPOND Secretariat.

ICAAC 2014

The INA-RESPOND network submitted 2 abstracts to the 54th ICAAC, and one of them was included in the meeting book. The network sent four of its researchers to attend the ICAAC meeting on September 5 – 9 in Washington D.C. Find their report in this newsletter.

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Are you interested in health research and dreaming to work with exceptional minds in their field? The Indonesia Research Partnership on Infectious Disease (INA-RESPOND) network is looking for high quality, dedicated, and easy-going people to fill the Publication Specialist position. The candidate will be posted in the INA-RESPOND Secretariat office in Jakarta. Take a look at the description and see if it suits you!

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Studies' Progress and Updates

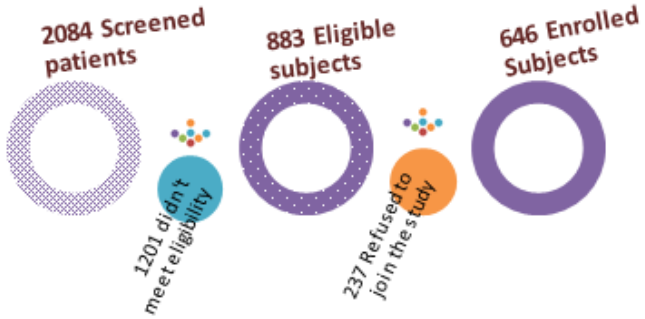
by dr. Nurhayati,
dr. Nugroho Harry Susanto,
dr. Anandika Pawitri,
dr. Herman Kosasih

Picture 2 Research Assistants Briefing at TRIPOD IM

AFIRE STUDY

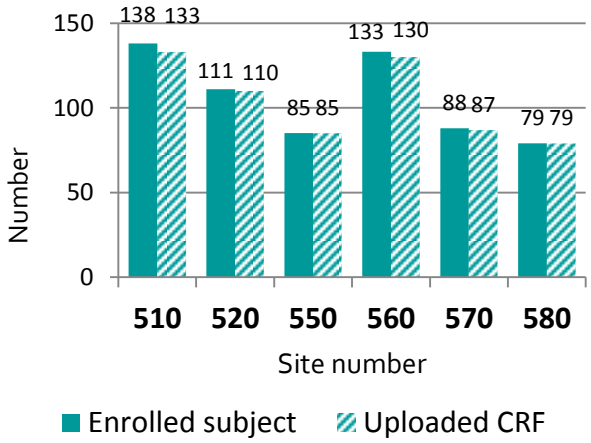
Since July 2013, the study has screened 2,084 patients. 646 subjects have been enrolled (374 adults and 171 children).

Screening Progress Chart up to October 26, 2014



This observational cohort study of hospitalized patients needs to enroll 954 more subjects to complete. Enrollment progress and estimated number to enroll 200 subjects per site up to Oct 26, 2014 can be seen in the table below.

Enrolled Subject and Uploaded Case Report Forms (CRF) Per Site up to October 20, 2014



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

Site no & Name	Total Enrolled (Adult / Child)	Remaining subject to be enrolled	Average number of subject enrolled per month	Estimated number of months to enroll 200 subjects
510 – RS dr Hasan Sadikin	141 (73 / 68)	59	10	5.9
520 – RS Sanglah	113 (73 / 40)	87	7	12.4
550 – RS dr Wahidin	86 (67 / 19)	114	7	16.3
560 – RS dr Kariadi	138 (79 / 59)	62	9	6.9
570 – RS dr Soetomo	88 (48 / 40)	112	9	12.4
580 – RS dr Sardjito	80 (34 / 46)	120	6	20

Table 1 Enrollment Progress and Estimated Number to Enroll

ReDEFINe STUDY

Tuberculous Meningitis (TBM) is the most severe form of TB with high mortality, and the current treatment regimens are not based on clinical trials. Rifampicin is a key drug for TBM, but its penetration into the brain is limited, suggesting that a higher dose may be more effective. Therefore, Dr. Rovina as Principal Investigator and her team at the Department of Clinical Pharmacology, Faculty of Medicine, *Universitas Padjadjaran*, Bandung, Indonesia will conduct a clinical trial titled: **High-dose rifampicin for the treatment of tuberculous meningitis: a dose-finding study (ReDEFINe: Rifampicin DosE FINding Study)**.

This is a double-blinded, 1:1:1 randomized, placebo-controlled, phase IIb trial. Adult TBM patients will be randomized to 450 mg rifampicin (standard dose, ~10 mg/kg), 900 mg rifampicin (20 mg/kg), and 1350 mg (30 mg/kg) rifampicin administered orally for 30 days as part of a standard 4-drug regimen for TBM. The primary objective is to generate pharmacokinetic (PK) data for higher doses of rifampicin in patients with TBM, and the secondary objective are: to evaluate safety and tolerability of higher doses of rifampicin in TBM patients as assessed by liver function, hematology, gastrointestinal intolerance and hypersensitivity; to evaluate efficacy of higher doses rifampicin in patients with TBM by assessing clinical and neurological response and mortality at 180 days; to evaluate the application of GeneXpert TB as a diagnostic test for TBM and to establish a bio repository of blood, plasma and CSF specimens for future research studies related to susceptibility and outcome of TBM. Planned enrolment period will be from April 2014 to April 2016 (2 years) + 6 months follow up.

INA-RESPOND will be involved in the monitoring aspect and set-up of the DSMB team and communication.

SEPSIS

Ethical approval for sepsis protocol was obtained on Oct 7. We are now submitting protocol to local IRB in all 3 sites (Jakarta, Yogyakarta, and Makassar). Currently, sites are preparing the research team so they can start immediately. As facility and capability of each site is different, INA-RESPOND lab specialist will conduct lab assessment to every site. Also, to accommodate site's particular interest in this study, SEAICRN is forming working group for Ebola case preparation.
If members from study sites would like to join in this group, please contact dr Direk to be included, or you can contact us for more information and assistance.

TRIPOD

On October 11, TRIPOD Investigator meeting was held at Hotel Santika, Bogor. TRIPOD core team and research team members from all seven sites attended the meeting. The meeting went really well; there were valuable inputs given, which were then integrated in the latest version of protocol, ICF, and CRF. The revised documents were submitted to the NIHRD IRB on October 29, 2014. One factor that needs to be paid attention to is the HIV test for the TB patients. We will need to give these patients some counseling regarding the issue. Although is sounds simple, the practice poses some challenges. Therefore, training on Provided Initiated Testeing and Counceling (PITC) is needed.

HIV/ AIDS

It has been described that INA-RESPOND study on Prevention of HIV/AIDS Transmission by Increasing Testing and Prompt Treatment (INDONESIA PASTI BISA) will be conducted in randomly selected *Kabupaten* from 76 *Kabupaten* with continuum of care (Layanan Komprehensif Berkesinambungan). According to the previous study that enrolled 1763 seo-discordant couples and was conducted in several countries, this method has shown to be very effective with a reduction of 96% incidence rate. However, population level impact of this intervention remains unknown. Population based study is therefore on-going in South Africa and Zambia where high prevalence rate of HIV is high. INA-RESPOND will conduct a similar study but in areas with lower incidence rate with low mobility. EarlyTest and Treat is one of preventive methods that is very crucial, besides condomization, PMTCT, pre and post exposure profilaxes, male circumcision, microbicides, and of course, vaccine, to stop the epidemics of HIV/AIDS.

Birthdays and Celebrations!

NOVEMBER

- 3 November – dr Bambang Sigit Riyanto, Sp.PD K-P (PI TB site 580)
- 4 November – Prof. Dr. Mansyur Arif, PhD, SpPK (K) (SC Member at site 550)
- 5 November – Rina Sirait, S.Kom (Lab Technician site 560)
- 11 November – Dewi Sriyanti (Lab Technician site 550)
- 16 November – dr. Akbar Fahmi (RA Site 570)
- 28 November – Widoretno (NIHRD)

Data Safety Monitoring Board

The INA-RESPOND network has added a Data and Safety Monitoring Board (DSMB) in its structure. The DSMB is an independent group of experts that advises the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to NIDCR concerning the continuation, modification, or termination of the trial.

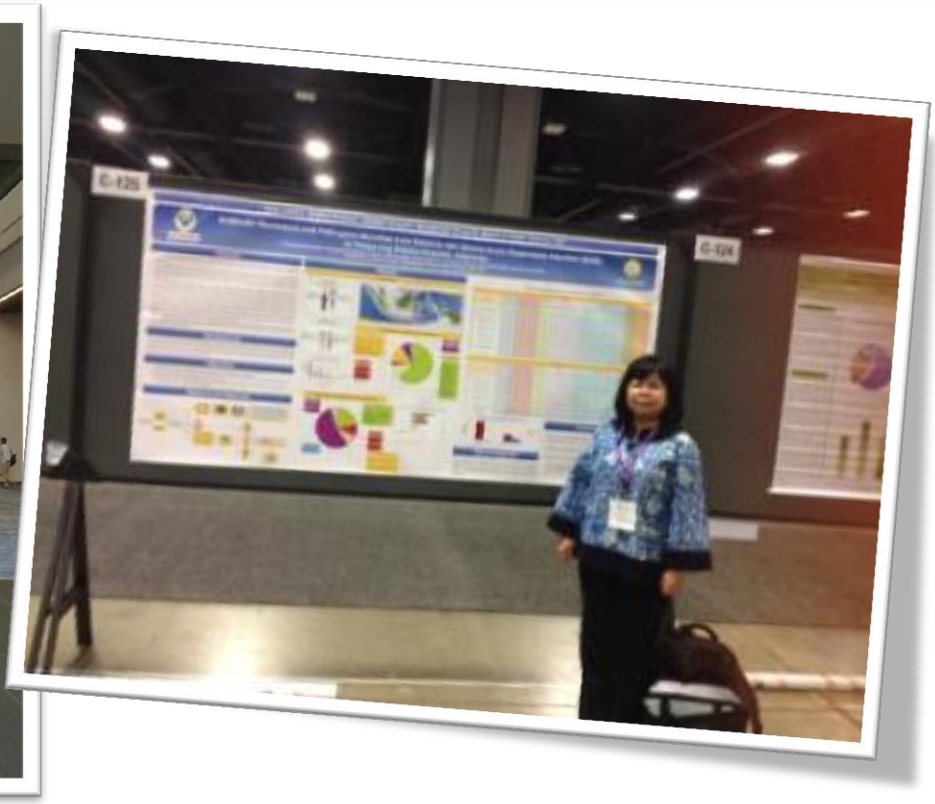
The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DSMB should review each protocol for any major concern prior to implementation. During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include: Data quality, completeness, and timeliness; Performance of individual centers; Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities; Adherence to the protocol; Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and, Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

Since the ReDEFINe study is intended to provide definitive information about effectiveness and/or safety of an appropriate dose of oral Rifampicin for TB Meningitis, the INA-RESPOND network has formed the DSMB to monitor the study. The board will gather in a face-to-face meeting on November 26-27, 2014.

Source: http://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/DSMBGuidelines.htm



Highlights From The 54th ICAAC Meeting

by Dr. Karyana, Dr. Dewi Lokida, Dr. M.H. Gasem, Dr. Bachti

Dr. Karyana, Dr. Dewi Lokida, Dr. M.H. Gasem, and Dr. Bachti, four of INA-RESPOND researchers, had the opportunity to attend the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) on September 5, 2014 in Washington D.C.

The INA-RESPOND network sent two abstracts to this meeting. The AFIRE abstract, titled "Undiagnosed Fever Is a Major Cause of Hospitalization in Patients in Indonesia" was included in the meeting book. This abstract reports that unexplained fever remains a major cause of hospitalization in Indonesia. Blood cultures provides information about the infecting micro-organisms in 16% of the subjects that otherwise would not have been identified by current standard testing at the hospitals.

Dr. Dewi Lokida, the head of INA-RESPOND laboratory, presented the results of her WHO-sponsored study on Severe Acute Respiratory Infection (SARI) in pediatrics and adults at Tangerang hospital. In her presentation, she describes the pathogens that are identified and the pattern of antibiotic resistance.

The most common bacterial pathogen in adults is *Pseudomonas aeruginosa*, and the most common one in pediatrics is *Acinetobacter baumanii*. Influenza virus contributes to 18.7% of SARI cases. In 65% of the cases, the most sensitive antibiotic is Carbapenem. Fatalities in these cases are associated with antibiotics resistance and the presence of underlying diseases.

The Highlights

A study on Moxifloxacin-containing regimen against tuberculosis was presented by Gillespie. This randomized phase 3 trial failed to show non-inferiority of the 4 month-regimens that included Moxifloxacin compared to the standard 6-month chemotherapy. This study was concluded as treatment relapse or failure within 18 months after randomization occurred, which is more frequent in the Moxifloxacin groups (15-20% vs 8%). However, patients in the Moxifloxacin groups converted to culture-negative sputum quicker than patients in the standard 6-month control chemotherapy.

Another study in Japan in 2011 reported that *Legionella pneumophila SG6* was found in five of 17 faucets and seven of 14 dishwashers in hospital staff areas. However, there was no evidence of patient infections during the investigation period. This finding was associated with lower temperature in the pipeline than the central system and the lower chlorine concentration that may cause biofilm growth. Since *Legionella* is one of the causes of fever that is rarely reported, we should consider identifying it for our AFIRE study.

Influenza is sometimes underestimated in Indonesia. However, RSU Tangerang's study shows that influenza is the most prevalent cause of SARI. At the 54th ICAAC meeting, Richard Whitley gave a presentation on a few available and under-development drugs. On the under-development drugs, he talked about a phase 2 and 3 placebo-controlled randomized trial of a single dose intra-muscular Peramivir. The trials involved 427 adults with uncomplicated influenza who were treated within 48 hours of onset of the symptoms. Compared to placebo, Peramivir reduced time of symptoms alleviation by 22 hours of its administration and the resolution of fever by 24 hours. Shedding of influenza virus was also reduced significantly in the first 48 hours after Peramivir administration. These results may argue the recent doubts of the efficacy of neuraminidase inhibitor for influenza infection.

The results from RSU Tangerang's study shows that Carbapenem is still sensitive in more than 60% patients. Although this is alarming, there is good news from the meeting which reports that a newly modified Carba NP test shows high sensitivity (92%) and specificity (100%) in detecting Carbapenem-resistant Enterobacteriaceae (CP-CRE). This test is cheap and fast, providing results in 2.5 hours. Timely detection of CP-CRE is critical to patient care and infection control as this strain has rapidly spread around the globe.

In a few months, INA-RESPOND is going to conduct a new study on sepsis. A test that is commonly performed in sepsis patients is procalcitonin. Ramanathan found that many physicians and residents did not really know how to interpret the results. She and her colleagues used retrospective data to evaluate 171 consecutive patients with a total of 402 procalcitonin tests. Of the 77 patients with negative procalcitionin (less than 0.25 mcg/L), 36 (46.8%) continued antimicrobial therapy. However, they also evaluated that the negative predictive value was only 49.4%. It meant that the chance of infection in patients with negative procalcitonin was still high. Therefore, a negative procalcitonin test should be taken with a grain of salt (skepticism), and other clinical factors like white blood cell count should also be considered. But, if a patient has a positive procalcitonin test, then there is most likely a bacterial infection present and the patient will need antibiotics.

One of the objectives of our studies (AFIRE, TB, or Sepsis) is to evaluate the outcome of treatment. One of the most common treatments is antibiotics administration. Until now, we still use body-weight-based antibiotics dosing. Several studies found that in obese patients utilizing actual body weight is associated with increased serum concentrations or toxicity in morbidly obese patients compared to normal

weight patients. This is primarily as a result of decreased drug penetration into adipose tissue. Researchers from the University of Michigan Hospitals have developed a guideline for weight-based antimicrobial dosing in obese patients using ideal body weight, adjusted body weight, or actual body weight when calculating an antibiotic dosing regimen. This guideline shows significant cost savings, provides general dosing recommendations, and increases prescriber awareness about the differences in antimicrobial pharmacodynamics in obese patients.

Operation Support Team

by Yanti Triswan and Meity Siahaan

Picture 4. Yanti Triswan (left) and Meity Siahaan (right)

In support of the INA-RESPOND Network day-to-day operational activities, the following are members of the team: Yanti Triswan, Meity Siahaan, Yayu Nuzulurrahmah and Budhi Kusnadi.

The team is responsible for the management of the administrative and financial functions; these include ensuring that INA-RESPOND sites are furnished with appropriate equipment to run the clinical trial smoothly e.g. deep freezer, computer, printer, barcode scanner, lock cabinets, etc. Other activities managed by the team involve organizing the logistics of various INA-RESPOND meetings, trainings and workshops, arranging travel plans, and last but not least, ensuring INA-RESPOND sites' finances are transferred in a timely fashion.

Picture 5. Yayu Nuzulurrahmah and Budhi Kusnadi

Approval is the "magic word" before any activity can be executed. No financial funding can be given before approval. ☺ At times, this might prove to be a "challenge", especially when the given approval is close to the start of the event, which could happen in stuations where meetings and events were suddenly created to accommodate the needs of the network.

To reduce any inconveniences that might occur, a sound and meticulous planning is key. Without a solid planning, conducting an event will possess more risks as more interference is likely to happen. In the worst case scenario, an event might be cancelled due to poor planning.

Participants of a meeting or an event can also play their part in making an event go smoothly by reading all travel arrangement information carefully and completing the required documents on time, such as the boarding pass, transportation receipts, and airport tax receipts.

The INA-RESPOND network, a collaborative initiative between United States and Indonesian government institutions formed to promote and conduct high-quality infectious disease clinical research in Indonesia through development of a collaborative, sustainable, and well-recognized research network, is seeking high quality individuals to fill vacant position as a *Publication Specialist*.

Job Description

Candidate is responsible for performing and coordinating a range of publication activities for the Indonesian Research Partnership on Infectious Diseases (INA-RESPOND) Secretariat in Jakarta, Indonesia (managed by the National Institute of Health Research and Development, Ministry of Health, Indonesia and Social and Scientific Systems, Inc.). Candidate must be comfortable working in a fast-paced environment and must be fluent in Indonesian and English.

Duties and Responsibilities

Key duties and responsibilities may include, but are not limited to the following:

- ✓ manage publication activities,
- ✓ provide support in the manuscript submission processes,
- ✓ facilitate manuscript writing team meetings, conference calls, and other communications
- ✓ assist with editorial and quality checks,
- ✓ research international and local journals,
- ✓ provides support and guidance in publication processes
- ✓ assist with protocol development and implementation processes, etc.

Requirements

- ✓ A baccalaureate degree from an accredited college or university. A master's degree or equivalent is preferred.
- ✓ Relevant experience in the arrangement and submission of publications to international and/or local journals.
- ✓ Relevant experience or coursework in microbiology/infectious diseases, public health, biomedical research or other related field.
- ✓ A minimum of 3 years of increasingly responsible, broad and diversified professional management experience relevant to implementing clinical research or biomedical training programs.
- ✓ Fluent in *Bahasa Indonesia* and English, both written and spoken.

To apply, email your Resume/CV to Meity Siahaan at MSiahaan@s-3.com by Nov 14, 2014. Please write down the position that you'd like to apply in the subject line of your email.

For more information about the position, go to the INA-RESPOND website below:
http://www.ina-respond.net/join-us/

INA-RESPOND Newsletter

Advisor : dr. M. Karyana, dr. Herman Kosasih
Chief Editor : dr. Anandika Pawitri
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Columnists : dr. Nurhayati, dr. Nugroho Harry Susanto, Meity Siahaan, SE.,Ak, Yanti Triswan
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