INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN
REPUBLIK INDONESIA

NEWSLETTER
JANUARY 2018

CEREMONY TO COMMEMORATE THE SIGNING OF IMPLEMENTING ARRANGEMENT BETWEEN NIH AND MINISTRY OF HEALTH, INDONESIA.

INA-RESPOND ACTIVITIES
INA-RESPOND UPDATES
CONFERENCE, TRAINING & WORKSHOP
SCIENCE COMIC CORNER

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
TAHUN 2018

from

INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

Secretariat

Editorial

Editorial in Chief

Editors/Authors

COVER :
dr. Siswanto, MHP, DTM and H. Cliff Lane, M.D.

Greetings

Chair of INA-RESPOND
M. Karyana

2017 was an awesome year for INA-RESPOND. With the signing of the Implementation Arrangement, INA-RESPOND was able to carry on some postponed agendas in the previous years. One of the network's most interesting moments was when our Tuberculosis Research of INA RESPOND on Drug Resistance (TRIPOD) enrolled its first participant in February. This excitement was followed by the activation of Tangerang hospital for a study sponsored by PEER health, Implementing a Combination of Clinical Parameters (Rapid Diagnostic Tests, Biomarkers, and Standard of Care Procedure) for The Etiology Diagnoses of Pneumonia in Pediatric Patients to Improve Clinical Management in Indonesia. By the end of the year, National Institute of Health Research and Development (NIHRD) ethical committee gave their approval for our study, A Prospective Observational Cohort Study of HIV Infection and Its Risk-Related Coinfections/Comorbidities in Indonesia (INA-PROACTIVE).

In addition, INA-RESPOND has published a book titled Panduan Penulisan Ilmiah (Manuscript Writing Guidelines) as our contribution for raising the motivation of researchers in Indonesia, so they will be more productive in writing and publishing scientific papers in prestigious journals, especially international ones. We will continue to pursue our long-term vision of becoming the premier research network in the region, providing evidence to inform policy makers, minimizing the impact of infectious diseases, and improving human well-being. It is our mission to improve the health of the people in Indonesia and to benefit the international community by conducting high-quality infectious disease research through a collaborative, sustainable, and well-recognized research network.

Now, in 2018, our first major challenge is to publish the results of our first study, The Etiology of Acute Febrile Illness Requiring Hospitalization (AFIRE) in a high impact journal. The second challenge is to start the participant enrollment of INA-PROACTIVE. We hope that everything will go well and have a good influence in the development of health and research in Indonesia. Of course, there's still a lot of work ahead we intend to fast-track our steps to accomplish what we have started.

Finally, I wish that our commitment to strengthen our existing partnership will continue to guide our work in 2018. We look forward to new ideas, strong motivation, and never-ending support from all INA-RESPOND members.

Please accept my very best wishes to you and your family for a prosperous 2018!

Contents

kaleidoscope 2017

NSC MEETING
INA-RESPOND MINI SYMPOSIUM

The INA-RESPOND Steering Committee meeting and the Mini Symposium, which were held on 2 – 3 August 2017, were a success. The Steering Committee members were given updates regarding the network's activities, including some of the issues related to the enrollment of the network's study, TRIPOD. More than 100 people attended the mini symposium and many of them were interested in learning what the speakers have to say.

One of the most exciting moments in the event was the ceremony to commemorate the signing of Implementing Arrangement between NIH and Ministry of Health, Indonesia.

AFIRE Manuscript

Writing Week

The INA-RESPOND network's 2nd Manuscript Writing Week (MWW) was held from 25-29 September 2017 at Double Tree Hotel and Convention, Cikini, Jakarta. AFIRE study enrollment ended in June 2016 with the total of 1,486 subjects included in the final analysis. The objective of this MWW is to prepare papers from AFIRE study results for publications. More than 53 participants from INA-RESPOND network, including representatives from NIHRD and US-NIAID attended the event. the MWW was a big success and went smoothly. The Scientific Coordinator, dr. Herman, was very excited seeing the tremendous enthusiasm of the participants in writing the manuscripts. Thank you to all participants for the dedication, cooperation, and support. Hopefully, we will have good-quality papers to publish after this MWW.

As we previously mentioned in the past newsletter editions, AFIRE study enrollment ended in June 2016 with the total of 1,486 subjects included in the final analysis. In light of this, INA-RESPOND network held a Manuscript Writing Week (MWW) for five days, starting from 25 to 29 September 2017 at the Double Tree Hotel, Jakarta. The event aimed to prepare papers from AFIRE study results for publications and was attended by 53 participants from INA-RESPOND network, including representatives from NIHRD and US-NIAID.

The AFIRE MWW was opened with a speech by Dr. Siswanto, MPH, DTM, followed by a presentation on Publication Policy by Prof. Dr. M Hussein Gasem, Ph.D., SpPD, KPTI. In the presentation, Prof. Gasem emphasized on how to arrange and decide authorship

and what each author was responsible for in INA-RESPOND publications. Dr. Herman Kosasih briefly explained about AFIRE Dataset. Afterwards, Dr. Chuen Yen Lau and Dr. Aaron Neal from NIAID-NIH, shared about what should be included in a manuscript and the process of publication. They also gave a few examples of published papers to give a better understanding of the audience. In the next session, the participants were asked to sit in their designated groups. During the last steering committee meeting in August 2017, it was decided that the MWW participants would be grouped based on their interests. There were nine writing groups at AFIRE MWW. Seven groups focused on seven different pathogens (one pathogen per group): Dengue virus, Rickettsia, Salmonella typhi, Chikungunya virus, Leptospira, Seoul virus, and Influenza virus and other respiratory pathogen groups. One group focused on the Algorithm for Diagnostic Prediction in Six Most Common Diseases, and the last one focused on Increasing Diagnostic Capacity in Fever Management.

On the first day, each group was asked to determine the public health significance of their paper and potential target journals where the paper of interest should be submitted. On the second day, each group was scheduled to discuss statistics, tables, and figures. In addition, they were also asked to edit their first manuscript draft and do some data cleaning. The first draft was expected to be finished on the third day so that the next day, each group could practice peer reviewing other groups' paper and gave feedback to each other. On the last day, each group was supposed to present the work they had been working on for the last four days and then finalized it for submission.

During those five days of AFIRE MWW, the Dengue, Chikungunya, Salmonella typhi, and Leptospira groups were able to complete and gave comprehensive, descriptive data regarding epidemiology, clinical and virological/bacteriological aspects of the pathogens. It was very interesting to see the discrepancies between clinical diagnoses in the hospitals compared to the confirmed diagnosis from INA-RESPOND reference laboratory. For instance, none of the Chikungunya infected subjects have the initial diagnosis as Chikungunya infection and apparently, the missed diagnosis also occurred in Rickettsial infection.

Another interesting discussion was spotted in the Salmonella typhi group. There was a lively discussion on how to analyze results from the subjective semi-quantitative Tubex test and the Salmonella typhi IgM and IgG ELISA assays.. Regarding leptospira, although the AFIRE study did not perform Microscopic Agglutination Test (MAT), which is the gold standard for leptospira diagnosis, AFIRE study did capture several subjects with leptospira by observing seroconversion of IgM and IgG antibodies and detecting leptospira genome in blood and urine samples. We propose alternative method for detecting leptospira infection as MAT is not possible to be conducted at the hospitals.

Seoul virus, a member of Hantaviruses, was found from two subjects in two different cities with hemorrhagic and liver disturbances with

mild renal involvement. The finding of Seoul virus, which is rodent-borne, highlights the important fact that rodents in Indonesia could carry other diseases than leptospira.There was another interesting finding from the Influenza and Other Respiratory Pathogen groups; clinicians in Indonesia should also pay attention to influenza virus as it was prevalent and caused severe illness or death particularly in younger and older age group. Other pathogens such as Bordetella pertussis, measles virus, adenovirus, Human Herpesvirus 6 (HHV-6), Respiratory Syncytial Virus (RSV), and human metapneumovirus (HMPV) were not captured since the diagnostic panels for those pathogens were not included in routine diagnostic panels in the hospitals.

The last two groups finished last because they had to combine all parameters from signs and symptoms to laboratory workup to create an algorithm for fever and to increase the diagnostic capacity for fever patients in the hospital. The fever algorithm was developed from rigorous statistics to distinguish dengue fever from the other five common diseases in the AFIRE study. As an alternative, another fever algorithm was developed to distinguish viral and bacterial infection using those clinical parameters, aimed at the rational use of antibiotics. The last group is preparing a recommendation on what kind of diagnostic tests are needed to be installed at the hospitals for a better clinical management that may reduce hospitalization days and mortality.

Group discussion during MWW

Quoting from the Scientific Coordinator, dr. Herman Kosasih, the MWW was a big success and ran smoothly. He was very surprised seeing the tremendous enthusiasm of the participants in writing the manuscripts. Thank you to all participants for the dedication and cooperation. Also, thank you to dr. Siswanto, Head of NIHRD Indonesia, Dr Cliff Lane, dr. Karyana, SC members, INA-RESPOND Secretariat, and US-NIAID (Aaron, Chuen-Yen, Jessy, Jason and Sophia) for the support and contributions. Hopefully, we will have good-quality papers to publish after this MWW.

-dr. M. Helmi Aziz-

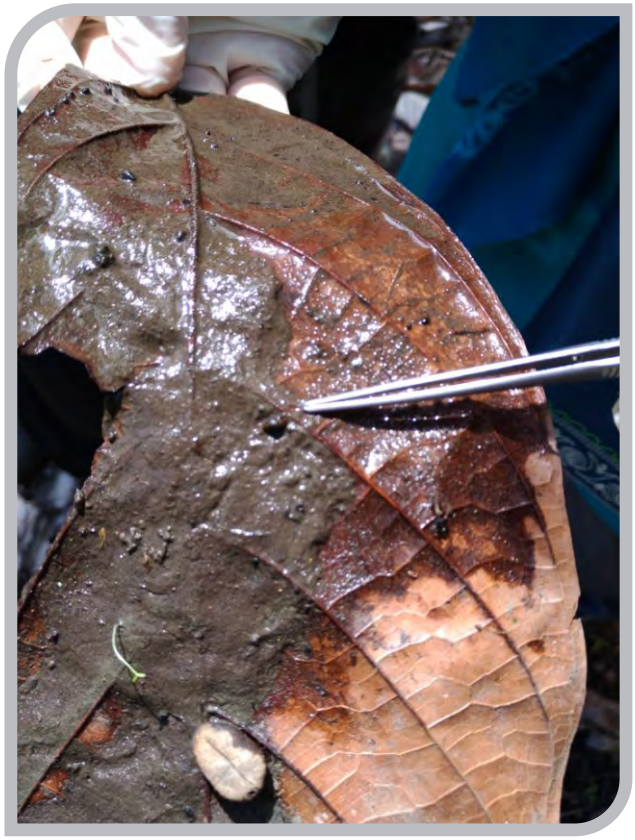
INA-RESPOND goes to Central Sulawesi

A field trip meeting towards Schistosoma elimination

It is well known that Schistosomiasis is caused by trematode *Schistosoma japonicum*. The disease is endemic in three areas in Central Sulawesi, Indonesia. The problem with Schistosoma infection has been recognized since 1932 in three villages in Lindu valley, where its prevalence was 56%[1]. Later, Napu valley (1972) and Bada valley (2008) were also labeled as Schistosoma endemic areas[1]. To combat Schistosomiasis, Indonesia Ministry of Health (MoH) has been implementing several strategies since 1971, such as mass drug administration (MDA); intermediate-snail (*Oncomelania hupensis lindoensis*) elimination; human-mammal Schistosoma surveillance; environmental modification; provision of clean water and sanitary facilities; and relocation of local population[1]. The Schistosoma

prevalence in human, rats, and intermediate snails decreased during the program, but it has been increasing (>1%) in the last five years, making 28,451 population at risk from Schistosoma infection(2). Indonesia MoH has a target to eradicate Schistosoma in 2020 using several strategies during the acceleration phase (2018-2019)[2]. To achieve this, a cross-sectoral collaboration, including research collaboration is needed. Representing INA-RESPOND, dr. Caleb Leonardo Halim, dr. Dona Arlinda, dr. M. Karyana, and Ms. Meity Siahaan conducted a 3-day field trip/meeting to several Schistosoma endemic areas from December 4-6, 2017. On the first day, INA-RESPOND team arrived in Palu and attended a cross-sectoral collaboration meeting with the local BAPEDDA (*Badan Perencanaan dan Pembangunan Daerah*). Shortly after the meeting, the INA-RESPOND team went to P2B2 Donggala Research and Development Center (*Balai Litbang P2B2 Donggala*). Here, we met Mr. Fauzan, the head of Balai Litbang P2B2 Donggala, and observed the laboratory equipment routinely used to diagnose Schistosoma infection. Polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) based test are available only for research purpose, not as routine diagnostic tool of Schistosoma infection. The team also saw the intermediate snails, rats, and the adult Schistosoma worms for the first time. The size of the intermediate snails was surprisingly smaller than we had thought (see Figure). On the second day, the team rendezvoused with *Balai Litbang P2B2 Donggala* team, NIAID team, Dr. Evan Secor from the United States CDC, dr. Patricia Tauran, and *Pencegahan dan Pengendalian Penyakit* (P2P) team. The schedule for the second day was to visit Sigi district, Napu valley, and Balai Litbang P2B2 Donggala. At Sigi district, the team visited Tora Belo district hospital and met dr. Graf Ronald, the Director of Tora Belo hospital. He mentioned that it is hard to diagnose both acute and chronic Schistosoma because their symptoms are non-specific and the hospital doesn't have the capability to do the diagnosis. He also mentioned that the hospital, as a secondary health care, was not involved in the Schistosomiasis elimination program, and it hardly receives referral patients from primary health centers.

Shortly after the hospital visit, the team went to Dodolo and Wuasa villages in North Lore, Napu. In Dodolo village, the team visited the hotspot of the intermediate snails. To our surprise, the hotspot of the snails is located at a cocoa farm which is on a dryland. The team noticed that the behavior of people in Dodolo makes them more susceptible to Schistosoma infection. Although personal protective equipment (PPE), such as boots is widely distributed, people in Dodolo are reluctant to wear them to protect themselves from cercariae penetration. Later, the team went to Wuasa laboratory and Wuasa primary health center. We found that although the staff there have the essential skills and capability to diagnose Schistosoma, the data are not stored electronically. At the end of the visit, the team received a free demonstration of Kato Katz technique to



see the Schistosoma eggs from the Wuasa laboratory officer. The last agenda of the second day was to introduce the NIAID and CDC team to *Balai Litbang P2B2 Donggala*.

On the third day, all participants along with other cross-sectoral participants attended the Schistosoma meeting held at Swiss Bel Hotel, Palu. The meeting was opened by the Head of

Palu Provincial Health Department, and there were presentations/discussion on how to tackle Schistosoma problem in the endemic areas. The conclusion from this meeting is that, it is necessary to harmonize and integrate cross-sectoral efforts to eliminate Schistosoma; laboratory strengthening is urgently needed; and accurate and reliable data to estimate the Schistosoma burden is needed before and after the praziquantel MDA which will be done in 2018.

The next day after the field trip, a meeting was held in Jakarta to discuss the result of the field trip with all related institutions and Schistosoma experts. After three presentations, there was a very intense and enlightening discussion on how we should solve the Schistosomiasis problem. Dr. Evan Secor shared several ideas of research as well as action plan recommendations related to Schistosoma that could be implemented in the upcoming years. At the end of the meeting, all related institutions are committed to help in Schistosoma elimination towards the goal of Schistosoma eradication in 2020.

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- dr. M. Helmi Aziz -

INA-RESPOND
UPDATES

TRIPOD STUDY INA102

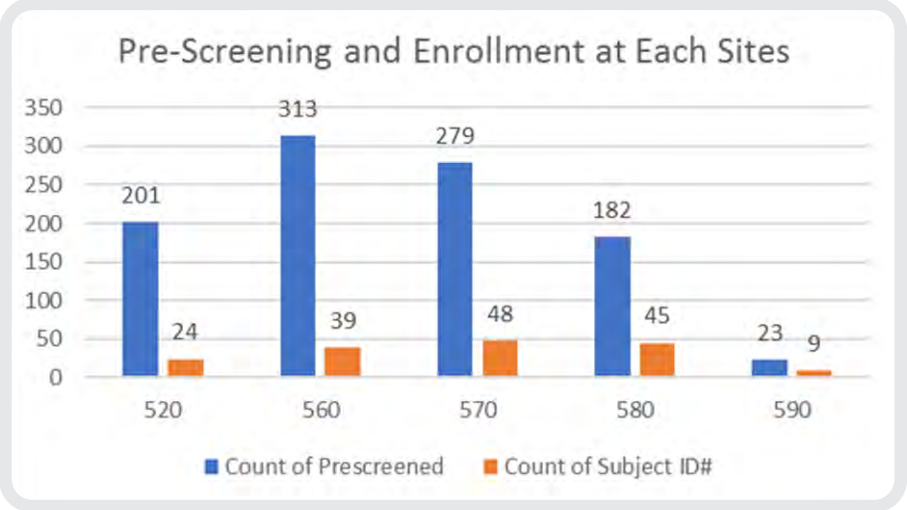
Pre-Screening, Screening and Enrollment

A total of 167 subjects had been enrolled out of 998 patients screened until the end of December 2017. The top recruiter is still site 570 – RSUD dr. Soetomo with 48 participants, followed by site 580 – RSUP dr Sardjito with 47 participants. We have some good news from our new site, site 590 – RSUP Persahabatan, which by the end of December 2017 had enrolled 9 participants since its first enrollment date on 20 November 2017, meaning it achieved 90% of its December enrollment target.

The study will enroll another 1,190 subjects and will stop enrolling patients 2 years after the first site is activated, which will be at the end of January 2019. Fortunately, now we have site 600 – RSUP H. Adam Malik Medan to help us with the enrollment. The site was activated on 27 December 2017 after its activation request was approved by protocol PI, Co-PI, sponsors, and the Chair of INA-RESPOND. The study team then started socializing the TRIPOD study to relevant departments in the hospital, and it was ready to start the enrollment on 3 January 2018. Hopefully, we will get more good news from Medan in the future.

Site 510 – RSUP dr. Hasan Sadikin, Bandung

In order to comply with the requirement of contract agreement between INA-RESPOND and Director of RSUP dr. Hasan Sadikin Bandung, we have submitted our latest protocol TRIPOD version 5.0 through the NSC member. We hope after the contract agreement is signed, we can make arrangement to activate site 510 – RSUP dr. Hasan Sadikin Bandung as one of the TRIPOD study sites. We are excited to welcome the site 510 to join TRIPOD study as they treat a large number of TB patients.



Site 520-Denpasar, Site 560-Semarang, Site 570-Surabaya, Site 580-Yogyakarta, Site 590-Persahabatan, Jakarta

INA-PROACTIVE INA104 STUDY

Local IRB approval from RSU Kabupaten Tangerang was received on 15 December 2017. Site Preparation Visit (SPV) and Site Initiation Visit (SIV) at site 610, RSU Kabupaten Tangerang have been done, and Site 610 will be the first activated and the pilot site for PROACTIVE study. The revised documents for PROACTIVE study were submitted to the NIHRD IRB on December 20, 2017. The study will start to recruit subject on the second week of January 2018 while other sites are preparing their study team and required documents.

INA 104.01, a sub-study of PROACTIVE, will be done at site 610. This study is conducted to evaluate the performance of GeneXpert cartridge Xpert® HIV-1 in measuring HIV-1 viral load. Result Comparison between the national standard from Dharmais Hospital and the INA-RESPOND reference lab will be done for 58 subjects. Local IRB approval was obtained on 5 January 2018, and the study will begin to recruit subjects on the second week of January 2018. User acceptance test (UAT) and the CRF electronic database have been developed by the data manager. CRF version 1.0 and CRF-CG version 1.0 are waiting for external approval.

On 23 January, the first PROACTIVE Investigator meeting, as well as NSC, GCP training, and HIV-update training, will be held at Double Tree by Hilton Hotel, Jakarta. PROACTIVE core team and all research team members from 11 sites will attend this meeting.

CONFERENCE

TRAINING & WORKSHOP

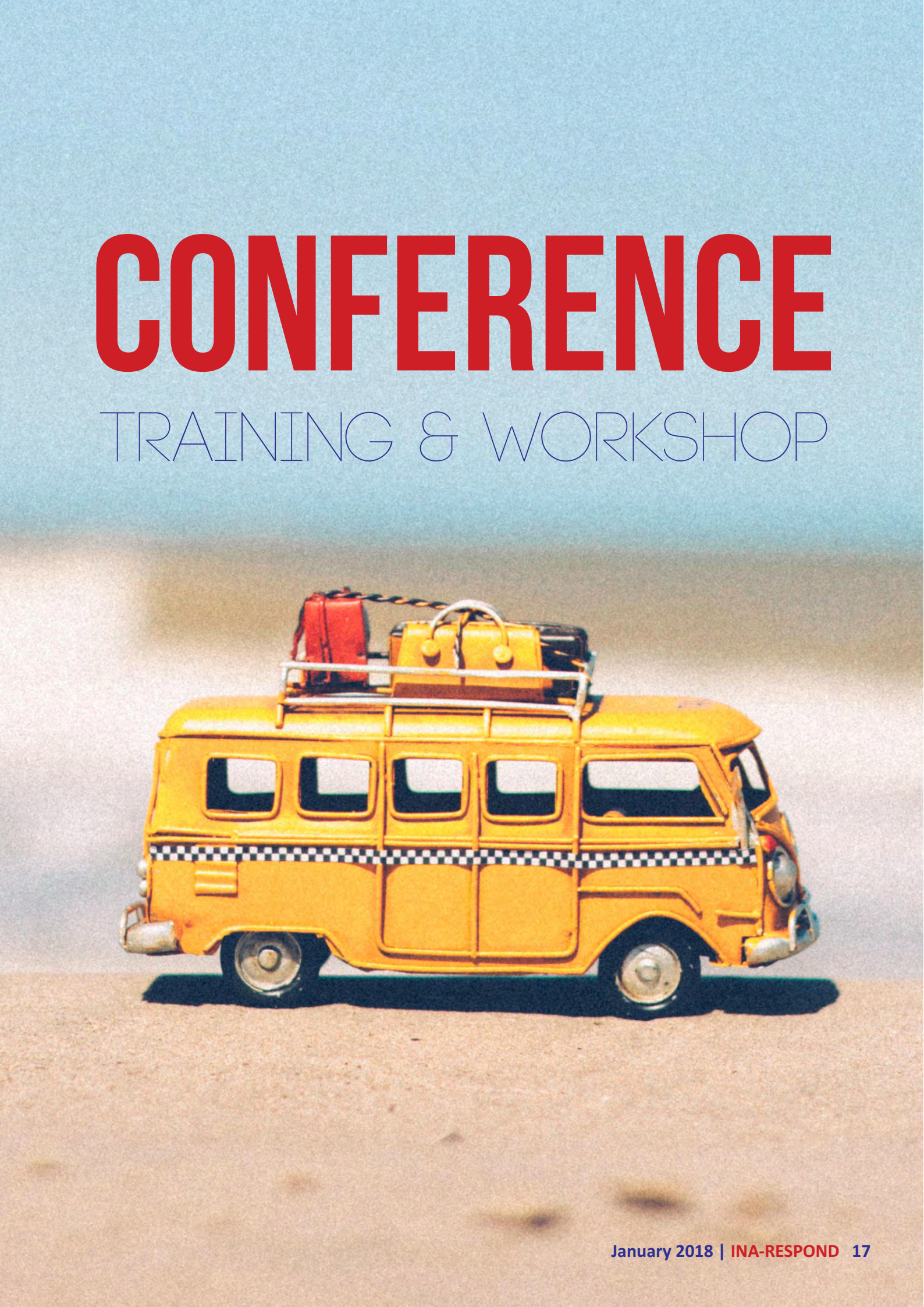


Figure 1. From left to right: dr. Dona Arlinda (NIHRD, Jkt), Dr. Rudi Wisaksana (RS Hasan Sadikin, Bdg), Dr Evy Yunihastuti (RSCM, Jkt)

CROI2017 & INA-PROACTIVE

INTENSE is the one word that can describe the Conference on Retroviruses and Opportunistic Infections (CROI), held on 13-16 February 2017 in Seattle, Washington, USA. Dr. Rudi Wisaksana (Hasan Sadikin Hospital, Bandung), Dr. Evy Yunihastuti (Cipto Mangunkusumo Hospital, Jakarta), and myself were the three delegates from Indonesia attending the conference (Fig. 1).

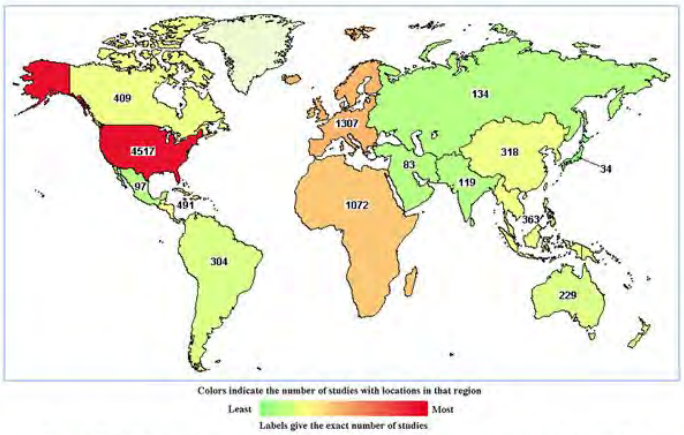


Figure 2. The distribution of HIV studies worldwide (Source: clinicaltrials.gov [accessed on 21 Feb 2017])

CROI is a scientific forum to exchange the latest research findings on HIV/AIDS and its complications, as well as selected other emerging infections. This annual meeting brings together up to 4000 researchers and leaders in the field of HIV/AIDS from all over the world. The goal is to facilitate translation of laboratory and clinical research findings into actionable strategies to fight the HIV pandemics.

This year, CROI accepted over 1,000 abstracts covering the topics from basic molecular virology to implementation researches, HIV prevention, diagnostics, and the latest therapeutics development, clinical pharmacology, HIV cure, antibodies and reservoirs, HIV complications, HIV cost modelling, and Zika virus as the selected topic for emerging infection.

Interestingly, 56.5% of those abstracts originated from the America, 22.5% from Europe, while only 14% from Africa and 7% from Asia and Australia.

Knowing that in 2015, Africa and Asia Pacific were the top 2 regions with the highest number of people living with HIV (30.6 million in Africa and 5.1 million in Asia Pacific), that distribution seemed awfully imbalanced. HIV is by far the most extensively studied virus, so are we not having enough HIV studies in Africa and Asia Pacific? Probably so, the distribution of HIV studies worldwide from clinicaltrials.gov showed that Africa and Asia Pacific are lagging behind the Americas (Fig. 2). Then there is also the question whether we don't have enough (internationally acknowledged) publications of the available studies. That is something that we must address on the upcoming Prospective Observational Cohort Study of HIV Infection and Risk Related Coinfections/ Comorbidities in Indonesia (INA-PROACTIVE) i.e. the HIV study in INA-RESPOND network.

The three of us would like to thank Dr. M. Karyana for his endless encouragement and INA-RESPOND Secretariat for their dedication and support. We look forward to five years (or more) of INA-PROACTIVE and hopefully, another experience in CROI as oral speakers presenting fascinating findings from INA-PROACTIVE.

HIV and Chimeric Antigen Receptors for Cancer Treatment

By: Dr. Dona Arlinda

Alongside with the advancement of personalised medicine, anticancer drug development is currently directed towards targeted therapies. While standard cancer chemotherapies kill both fast-growing cancer cells and the healthy ones, targeted cancer therapies work with specific molecular targets that are involved in the growth, progression, or spread of cancer. There are many types of targeted therapies that have been approved for cancer treatment, such as hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies, and toxin delivery molecules. Immunotherapies in particular, gained much attention at the Conference on Retroviruses and Opportunistic Infections (CROI) 2017. Monoclonal antibodies can be used to recognize specific molecules on the surface of cancer cells and subsequently kill them. Another usage involves linking monoclonal antibodies to other immune cells in order to help them kill cancer cells.

Dr. Carl H. June from the University of Pennsylvania presented the use of targeted immunotherapy using Chimeric Antigen Receptors Lymphocyte T-cells (CAR T-cells) for cancer treatment. CAR T-cells consist of antigen-binding region of a monoclonal antibody linked to intracellular T-cell signalling domains. CAR T-cells have antibody specificity that exert cytotoxic effects when bind to their target. In this case, Dr. June used CD19, a tumour-specific antigen found in normal and malignant B cells and B-cell precursors (CART19).

Although chimeric antigen receptors-based therapies are relatively new, clinically significant antitumor activity is shown in neuroblastoma, chronic lymphocytic leukemia, and B-cell lymphoma, as well as other adult and paediatric malignancies. Currently, China and the USA are two leading countries with clinical trials on chimeric antigen receptors in cancer (Fig. 1).

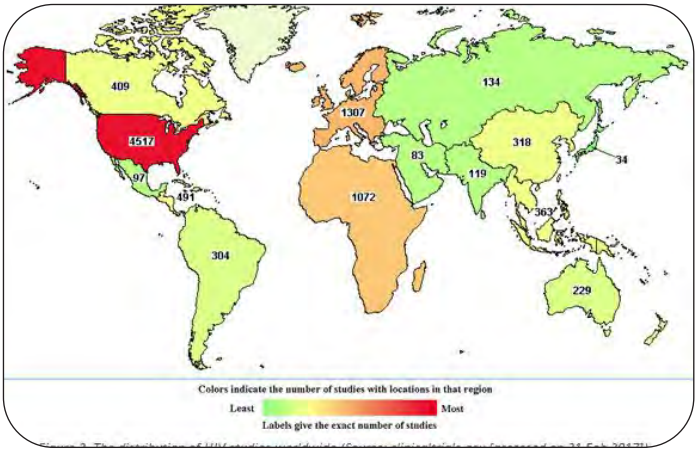


Fig Country Distribution of Clinical Trials on Chimeric Antigen Receptors in Cancer

Dr. June and his team first used CART19 in 2012 on a 7-year-old girl with relapsed and refractory pre–B- cells acute lymphoblastic leukemia (ALL). Dr June initially took out the patient' own lymphocyte T-cells and fused them together with HIV viruses to induce the expression of chimeric antigen receptors. The CAR T-cells were designed to target CD19 molecules on the cancer cells. The CART19 cells were

then grown in the laboratory and were infused back to the patient.

At first, the patient experienced severe toxic effects consistent with cytokine-release syndrome, which manifested as hypotension, acute vascular leak syndrome, and acute respiratory distress syndrome that required intubation. Laboratory findings include elevated levels of ferritin, triglycerides, aminotransferases, bilirubin (primarily conjugated), and soluble interleukin-2 receptor α-chain and decreased levels of fibrinogen. This cytokine-release syndrome appeared to be reversible and was rapidly cleared following the administration of anticytokine therapy. After 180 days of CART19 treatment, the patient came out cancer free and has remained so for five consecutive years.

After the success of the first patient, they continue to CART19 phase 1 clinical trial involving 60 pediatrics/young adults ALL patients which showed 93% complete remission rate. These remarkable results were submitted to the FDA and they anticipated approval in 2017.

In summary, CART19 is a fine example of engineering T-cells for cancer therapy. Although at some point HIV viruses were used as vectors to introduce the chimeric antigen receptors, Dr. June was convinced that the virus would not be able to infect the patient or cause disease. The one thing that he was not sure at that time was whether this treatment could cure the cancer itself. We look forward to the results of bigger and well defined cohort studies of CART19 in the near future.

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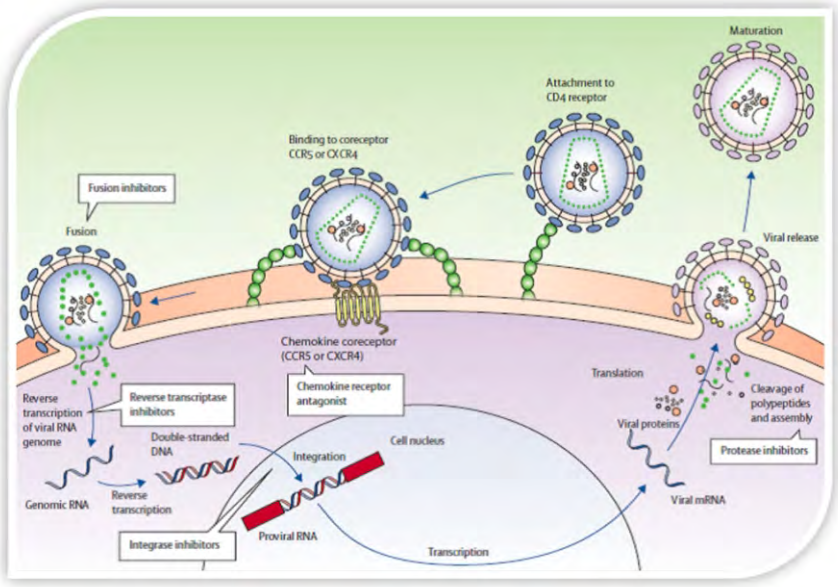
Advances in Anti-HIV Drugs

By: Dr. Dona Arlinda

The pipeline of anti-HIV drugs has developed considerably over the past 20 years. New drug classes and newer generation of the existing antiretroviral offer more options to optimise antiretroviral therapy (ART) regimens, especially for treatment-experienced people with resistant viruses.



Currently, there are more than 25 anti-HIV drugs from six known classes based on their mechanism of action of blocking HIV replication (most are shown in Fig. 1), i.e. entry inhibitors, fusion inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (IIs), protease inhibitors (PIs), and pharmacokinetic enhancer/booster. An ART regimen would generally use 2 NRTIs + 1 NNRTI or 2 NRTIs + 1 PI or 2 NRTIs + 1 IIs.

The Conference on Retroviruses and Opportunistic Infections (CROI) 2017 discussed several advances in the anti-HIV drug pipeline. Novel drug classes are being tested in various stage of clinical trials, including capsid inhibitors in early studies and monoclonal antibodies now in late-stage human trials. Newer-generation drug candidates of the existing antiretroviral classes are also being explored for long-action potential, such as elsulfavirine (NNRTI), MK-8591 and GS-9131 (NRTIs), cabotegravir (IIs), and GS-PI1 (Pis)

Capsid Inhibitors with Long Action Potential

Capsid encloses HIV genetic materials. Capsid inhibitors are a novel mechanism of anti-HIV drugs that impaired capsid function at multiple point during HIV core assembly, disassembly, and nuclear translocation of pre-integration complex. Dr. Winston Tse from Gilead Sciences presented GS-CA1 as the selected candidate of capsid inhibitors to enter pre-clinical studies. GS-CA1 binds to a highly conversed site resulting in high barrier to resistance. It showed highly potent EC50 of 140 picomolar in peripheral blood mononuclear cells and has high metabolic stability resulting in low efficacious dose of once a month. Toxicology studies and phase 1 clinical trials are projected in 2018.

Long acting monoclonal antibodies

Long acting monoclonal antibodies (Ibalizumab and PRO 140) offer new treatment options for people with highly resistant virus and limited treatment options. A phase 3 trial evaluating 2000 mg Ibalizumab intravenous infusions every two weeks in combination with optimised background ART in 40 heavily treatment-experienced participants, which most had exhausted all available drugs in at least three classes, showed modest antiviral activity and was generally safe and well tolerated.

PRO 140 blocks CCR5, one of the two co-receptors HIV uses to enter cells. In 42 HIV-positive adults with exclusively CCR5-tropic HIV on a stable ART with undetectable viral load (<40 copies/ml), weekly 350 mg subcutaneous injections of PRO 140 maintained viral suppression for more than two years in a majority of responders and was generally safe and well-tolerated.

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The 9th International AIDS Society Conference on HIV Science

By: Dr. Dona Arlinda

The 9th International AIDS Society (IAS) Conference on HIV Science (IAS 2017) was held on 23-26 July 2017 at Palais des Congrès, Paris, France. The conference brought together over 6,000 HIV-related professionals worldwide and presented more than 1,800 abstracts selected through blind peer-review process. Three delegates from INA-RESPOND, namely Prof. Dr. dr. Tuti Parwati Merati, Sp.PD-KPTI., (Sanglah Hospital, Bali), Dr. Dewi Lokida, Sp.PK (Tangerang Hospital, Banten), and dr. Dona Arlinda (NIHRD, Jakarta) had the opportunity to join the conference.

The conference topics were divided into four categories, i.e basic science, clinical science, prevention science, and implementation science. Basic science symposiums highlighted innovative strategies to tackle HIV reservoir and identify host factors and mechanisms for viral persistence. Although not all of these studies have clinical applicability, they provided pieces of evidences to our understanding. Two case reports add to the shortlisted examples of HIV “cure”. The first was a patient with hyper acute HIV-1 infection treated for three years of antiretroviral therapy (ART). He stopped treatment and did not rebound until 210

days later. Second, a perinatally HIV-infected infant in South Africa who was treated with one year of ART and maintained 8 years of undetectable viral loads without ART.

Clinical science symposiums highlighted the need for dual or mono ART over triple therapy. Dual therapy showed a devastating gap that 95% of HIV-positive incident TB cases were not in care, 89% of notified TB cases had unknown HIV status, 79% HIV-positive TB cases were not started on ART, and 98% of PLHIV newly enrolled in HIV care did not received isoniazid preventive therapy (IPT). Indonesia was also listed

such as Darunavir/r + 3TC (Cahn), Dolutegravir + 3TC (ACTG 5353 & PADDLE Study), Cabotegravir + Rilpivirine (LATTE 2) appeared to sustain viral suppression in adult patients. Reduced dose of Efavirenz and Atazanavir also appeared to be effective and cost-saving. Early detection of tuberculosis (TB) among people living with HIV (PLHIV) remained a challenge. WHO's estimate in Indonesia in 2015 among the lowest countries with only 62 sites having Xpert MTB/Rif as a diagnostic test for TB (ranging from 1 site in Angola to 1,024 sites in China).

Prevention science symposiums highlighted comprehensive HIV testing and prevention methods to achieve 90:90:90 targets, including pre-exposure prophylaxis (PreP), rapid ART initiation and prioritizing key populations. In addition to oral and

long-acting injectable agents, several topical formulations were tested to deliver PrEP such as vaginal rings and rectal gel. On-demand PrEP was found to be an adequate alternative to daily PrEP for high risk men who have sex with men (MSM) with infrequent sexual intercourse. Raltegravir can be used for prevention of mother to child transmission (PMTCT) for late-presenting pregnant women, despite the high cost.

Implementation science symposiums addressed the need to improve testing uptake and linkage to care (the 'first 90'). HIV self-testing has the potential to reach 'hard-to-reach' groups. Usage of mobile technologies as well as differentiated care and service delivery showed promising impact on HIV/AIDS response, with regards to confidentiality and security issues of the electronic platforms.

Other than attending the symposiums, we also had the opportunity to join abstract and manuscript writing workshop held by the Editors of Journal of the International AIDS Society (JIAS). With impact factor of 6.296, JIAS wished to provide platform for dissemination of HIV research, to encourage submissions from low- and middle-income countries and to provide capacity building opportunities for less-experienced authors. They also provide abstract writing online course at www.healthefoundation.eu and abstract mentor program for the upcoming AIDS 2018 ceonference.

We thank INA-RESPOND Secretariat and Prodia DiaCRO, especially dr. M. Karyana, M.Kes, Ms. Yayu Nuzulurrahmah, Ms. Meity Siahaan, and Ms. Katherine Nadia for their support and hard work.

Report:

IT Specialist Visit to Uganda

By: Dwi Arie Pramanto

A couple of months ago I got the opportunity to visit Uganda Virus Research Institute (UVRI) in Entebbe and Rakai Health Sciences Program (RHSP) in Kalisizo, Uganda. I stayed in Uganda for 12 days to observe, study, and help with some of the IT-related activities together with the IT team and the IBRSP/ICER team.

On the first day, I was taken to Uganda Virus Research Institute (UVRI) in Entebbe. UVRI is one of the most important facilities related to the Rakai Health Sciences Program. This is where some of RHSP's operational activities, especially those related to Network and Data management, are done. The internet is a crucial facility to have in data management. Unfortunately, it is really difficult to get a good Internet Service Provider (ISP) in Kalisizo, where RHSP is located. As a solution, the provision of Internet is distributed

directly through the Data Center at UVRI in Entebbe to RHSP in Kalisizo via fiber optic cable.

The next day, I was taken around to see RHSP's facilities. RHSP has several rooms for operations such as finance, IT, data management, PI's office, and storage. It even has a guest house, where I stayed in for 9 days. The compound also has laboratory for specimen testing and clinic for examining and treating (outgoing) patients. In addition, RHSP has several fields outside of the premises to reach more patients. Patients can visit these fields to get checked and their samples taken. Research Assistants will take the CRF and samples to RHSP on the same day.

As an IT specialist, I was involved in some of RHSP's IT activities. One of them was meeting with the IBSRP/ICER team, where I learnt how the team members work to solve some of their issues and how they inform the latest updates in their fields of expertise. I was also shown and explained about their IT Support Ticketing System: how it works, how to manage, make request, report, and plan each change, correction, and solutions made –all recorded in the system. In addition, I was shown their monitoring system which maps all connected device in the network, so IT staff can easily monitor and find out its location.

On day 11-12, I was back at UVRI in Entebbe. This time, I was trusted to help with some IT-related tasks such as changing, installing, and configuring device (router, PDU, and solar panel.) In addition to the scarceness of good ISP in Uganda, stable/reliable source of electricity is also a big concern. Power is often off and for a long time. To resolve this issue, solar panels are installed as a back-up power after UPS.

Overall, my trip to Uganda was rewarding and worthwhile. I learned many interesting things, and hopefully, some of them can be applied to our INA-RESPOND's network to improve the quality of the IT Support Management.

Report.

TREAT

Asia Network Annual Meeting

dr. Dona Arlinda|dr. Caleb L. Halim | Ms. Lois E. Bang |Ms. Kanti Laras

On 12-13 October 2017, INA-RESPOND's delegates namely dr. Dona Arlinda, Ms. Kanti Laras, and dr. Caleb Leonardo Halim had the opportunity to attend the Annual Meeting of the Therapeutics Research, Education, and AIDS Training in Asia (TREAT Asia) Network in Conrad Hotel, Bali. The TREAT Asia Network is a collaboration of clinics, hospitals, research institutions, and civil society on HIV in adults and children across Asia-Pacific, established in 2001. The purpose of our visit to their meeting was to gain insights from their experience in managing long term study in multiple sites, as well as in handling data and publications.

The two-day meeting was attended by representatives from 14 countries in the TREAT Asia Network, i.e. Australia, Cambodia, China, India, Indonesia, Japan, Malaysia, New Zealand, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam. The first day was dedicated for updates from the TREAT Asia Adult Network and on the next day, the meeting was joined by members from the TREAT Asia Pediatric Network.

Annette Sohn, M.D., the Director of TREAT Asia Network, gave an opening speech and was followed by a presentation on the TREAT Asia HIV Observational Database (TAHOD) adult data summary. TAHOD is an HIV database created in 2003 to assess the natural history of HIV disease in treated and untreated patients. Dr. Cipto Mangunkusumo Hospital, Jakarta, and Sanglah Hospital, Denpasar, were the two participating sites from Indonesia.
By March 2017, the TAHOD adult had collected data from 9,160 participants. The median age was 35 years (IQR 30-42) and 30% were females. Thais, Chinese, Indians, and Indonesians accounted for 71.4% of participants. It was very interesting to notice that the data supported the need to scale up HIV viral load testing, as it was not done in about 40% of TAHOD participants.

Subsequent presentation was on updates from TAHOD study spin-offs, i.e. TAHOD Low Intensity Transfer

(TAHOD-LITE) and TREAT Asia Studies to Evaluate Resistance to Second-line Antiretroviral Therapy (TASER-2). New concepts for data analysis and special projects were also presented, such as Study on Pregnancy Rate and Birth Outcomes among women living with HIV in Asia-Pacific, Prospective Liver Cancer Case-Control and Outcomes Study, and Hepatitis B and Hepatitis C Continuum of Care Cascade. Then, the participants were given updates on the TREAT Asia publications and disseminations.

To engage the meeting participants' attention, there was a lively debate on the pros and cons of HIV self-testing, whether it should be available to all adults in Asia-Pacific. Before the debate started, 4 people disagreed with it. Interestingly, after the debate, a lot of people who agreed at first changed their opinion to disagree. These people probably became more aware that there was no single formula which would work for everybody. Implementation of a recommendation on HIV need to be tailored to local situation, and every country, even in the same region of Asia-Pacific, has different backgrounds and characteristics which need to be carefully considered.

Another interesting ice-breaking method was an online and interactive quiz on TREAT Asia history using a web-based application accessible at www.kahoot.it There were 8 multiple-choice questions, and participants were scored based on how many and how fast they gave correct answers. Prizes were given to the highest score, calculated based on the highest number of correctly answered questions and the fastest time.

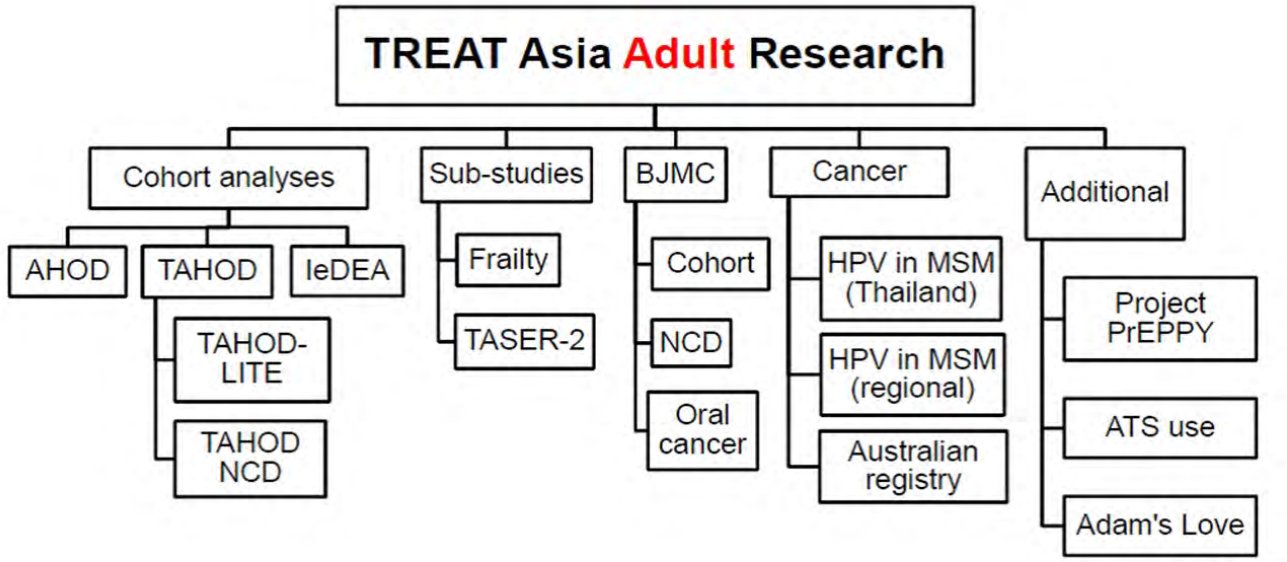
TREAT Asia's Visit to INA-RESPOND Secretariat and Meeting with HIV Program.

On 17th October 2017, it was TREAT Asia's turn to visit INA-RESPOND Secretariat. Jeremy Ross, Boondarika Petersen, and Chuenkamol Sethaputra were the three representatives who came all the way from Bali to Jakarta. They were scheduled to have a meeting with the Head of HIV Program, INA-PROACTIVE Team, and INA-RESPOND

Secretariat.

Dr. M. Karyana, the Chair of INA-RESPOND. opened the meeting and was followed by a presentation on the National HIV Control Policy by the Head of HIV Program, dr. Endang Budi Hastuti. Dr. M. Karyana and dr. Dona Arlinda gave overview presentations on INA-RESPOND and HIV study in INA-RESPOND's Network or INA-PROACTIVE, respectively.

was managed by the Kirby Institute, University of New South Wales, Australia. All participating countries in TREAT Asia Network were required to enter and transfer their data to Kirby twice a year. Most of the countries used Microsoft Access for data entry and transfer, while a small number were still using Microsoft Excel. Kirby then ran QC and QA procedures to the transferred data to ensure the quality. The main



The last session was Jeremy Ross, who introduced us to the portfolio of HIV-related researches in TREAT Asia Network since established in 2001. Aside from TAHOD adult and pediatric, they were interested in HIV drug resistance, non-communicable diseases, and human papilloma virus (HPV)-related cancers in men who have sex with men (MSM). In pediatric HIV population, they were mainly interested in studying the transition of adolescent to adulthood.

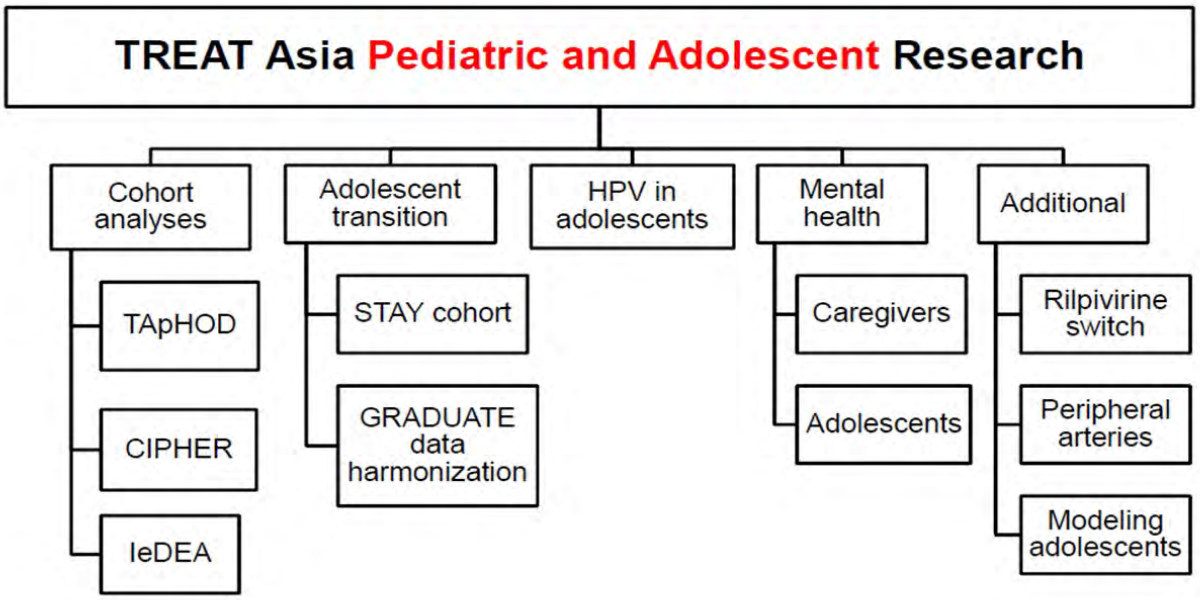
Jeremy also explained about TREAT Asia data management, which

difference from what we did in all INA-RESPOND's studies was that they chose to conduct remote monitoring activities instead of on-site monitoring visits. Cost was probably one of their major considerations, in addition to limited number of clinical research associates (CRAs).

There was a lively discussion when Jeremy explained how they manage data usage, analysis, and publication. The procedures were listed in their Management Guidelines. In short, those who are interested to publish were asked to gather 4-6 persons as

their core writing team. First, they must propose a concept sheet explaining the purposes and methods of the analysis. Upon approval from the Network Steering Committee, they may coordinate with Kirby Institute for the actual analysis. Subsequent presentations or publications are subject to the Authorship Guidelines. A specific concept sheet may be re-assigned or withdrawn if the writing team failed to produce the manuscript within one year after data analysis had been completed. These procedures allowed them to track who and what was being published from their studies, and ensured related parties were being properly acknowledged.

Overall, both meetings were successful. We were inspired to develop our own network management guidelines and publication/authorship guidelines for INA-PROACTIVE Study. We also look forward to establish good relationship with another Network. We hope that INA-RESPOND Network can grow to represent Indonesia and provide accurate national level HIV data for the National HIV Control Policy.



The 60th Annual Biological Safety Conference

dr. Nurhayati | Ms. Wahyu Nawang Wulan

The 60th Annual Biological Safety Conference is a biosafety conference held by ABSA International: The Association for Biosafety and Biosecurity. ABSA International was founded in 1984 to promote biosafety as a scientific discipline and serve the growing needs of biosafety professionals throughout the world.

The goals of the association are to expand biosafety awareness; promote development of safe work practices, equipment, and facilities; and reduce the potential for occupational illness and adverse environmental impact.

ABSA International accomplishes these goals by releasing a quarterly journal, offering various educational biosafety courses, and holding annual Biological Safety Conference to keep its members updated on the latest biosafety issues and regulatory initiatives.

Currently, ABSA International has 1,620 members registered from various discipline societies. The 60th Annual Biological Safety conference was held on October 13-19, 2017, in Albuquerque Conference Center, Albuquerque, New Mexico.

Two of INA-RESPOND Secretariat personnel, Ms. Wahyu Nawang Wulan and Ms. Nurhayati, had the opportunity to attend the conference. Their trip was sponsored by the Biosecurity Engagement Program (BEP), United States Department of State (administered by CRDF Global, Arlington, VA).

More than 650 biosafety/biosecurity professionals and researchers of various disciplines from around the world attended the conference.

The conference started with pre-conference courses for three days to educate and inspire the participants, and they were then followed with various keynotes highlighting the current best practices for biosafety and biosecurity professionals for four days. There were many interesting topics that could be chosen during the pre-conference course, such as risk assessment, BSL-3 operations and management, design high impact educational training activities, Institutional Biosafety Committee, biocontainment laboratory operations, human gene transfer, bio toxins, OSHA regulation, infection control, etc. After the courses, the conference presented a

broad spectrum of biological, pharmaceutical, biotechnology research development and clinical organizations. Some of the topics covered in the conference were enhancing compliance, international biosafety, Inactivation and decontamination, biosafety program management, current regulatory issues, dual use research concern, emergency response, human gene transfer, biosafety promotion and development, etc. In addition, many posters from national and international academia were presented and competed in the event to get awards.

ABSA honors those who contribute significantly for biosafety and biosecurity with Annual Recognition Awards. In the conference, four award recipients presented their work in a series of lecture awards. The first lecture award, "The Next Pandemic: On the Front Lines Against Humankind's Gravest Dangers" (Ali Khan, MD, recipient of Arnold G Wedum Memorial Award) was presented on the fourth day. On the fifth day, there were two lecture awards: "A Journey of Biological Risks Between Compliance and Risk Optimization" (Uwe Mueller-Doblies, PhD, recipient of Elizabeth R Griffin Research Foundation Lecture Series Award) and "Dark Life: The Microbiology of Extreme Cave Environments" (Hazel Barton, PhD, recipient of Eagleson Lecture Series Award). The last lecture award presented was "Shedding Risk with Intracerebral Inoculation of Theiler's Murine Encephalomyelitis Virus: Informing a Risk Assessment" (David Pawlowski, PhD, recipient of Richard C Knudsen Publication Award). These lectures highlighted the achievements of researchers and professionals whose works require lofty standards of biosafety principles. This inspires others

to commit to biosafety and biosecurity standards in different fields that apply.

From the many lectures, there is a take-home message that is relevant to the work of INA-RESPOND. Indonesia is a tropical region that houses emerging/reemerging infectious diseases. These diseases and increased human traffic are the root cause of modern pandemics. Biosafety regulations/principles protect experts, authorities, and public health practitioners to work safely in order to overcome the pandemics. Since pandemics know no border, global biosafety standards need to be set at a certain uniform level that ensures practitioners to work safely in all parts of the world. One of ABSA's achievements is the Twinning Program which was set to help knowledge transfer from countries already having high standard of biosafety practice to places where pandemics are potential to occur (e.g having a high transmission rate of zoonoses).

Overall, the conference is interesting and valuable. A lot of latest information was shared during the meeting, which broadens our knowledge in biosafety practices. In addition, we had some opportunities to talk and introduce our network. It is our hope that we can share the knowledge and information obtained in the conference to improve/increase the capacity of our network and its stakeholders.

The XIV Working Conference PAPDI Report

Malang 13-16 July 2017

dr. Nurhayati | dr. Venty Muliana Sari Suroso | Ms Neneng Aini

PAPDI is *Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia* (Indonesian Society of Internal Medicine). Every three years PAPDI held a series of organizational activities for working conference. Results from this congress will be ratified during the PAPDI national congress. The XIV working Conference event was held on 13 - 16 July 2017 and located at Hotel Ijen Suites Resort & Convention Malang-East Java. The conference was attended by more than 850 symposium participants and more 200 participants in the organization of PAPDI. Three delegates from INA-RESPOND, namely dr. Nurhayati, dr. Venty Muliana Sari Suroso and Ms. Neneng Aini had the opportunity to join the conference.

The main topic of the conference is "The Role of PAPDI in Increasing the Competence and Competition of Indonesian Doctors in the era of National Health Insurance and ASEAN Economic Community." This conference consists of two activities, the organization and scientific activities. Many experts from the internal medicine were invited to talk about interesting topics and novel treatment

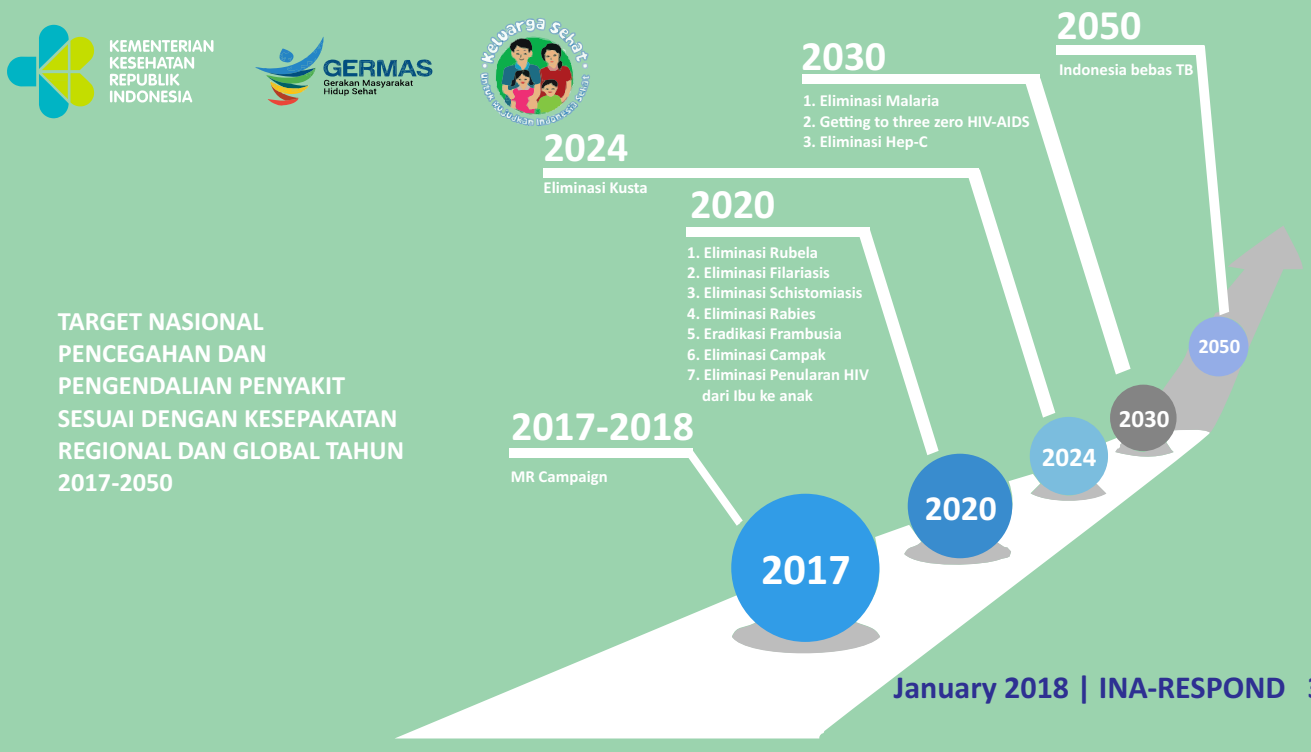
at the conference. The conference started by talking about the role of internist in the era of *Jaminan Kesehatan Nasional*/ National Health Insurance (JKN), and was followed with many interesting topics about new management and treatment on gastro intestinal disease, thromboembolism, asthma, hypertension, diabetes mellitus, hepatitis C, Leukemia Granulocytic Chronic, arthritis rheumatoid, sepsis, chronic kidney disease, DHF, heart failure, and pneumonia and ulcus diabetic in geriatric.

During the conference, the presenter provided us with the current and applicative scientific materials emphasizing on interactive discussions that actively involved the participants. In order to complete a comprehensive knowledge of the participants, there were also several sessions of integrated case discussion about case management in daily practice such as management for rheumatoid arthritis, sepsis, diabetic foot, and pneumonia in geriatric patients setting. These sessions were held after symposium in each day.

At the organizational meeting, the delegates from 36 PAPDI branches (five delegates per branch) discussed the programs that had been implemented and the latest issues in the field of medicine. The results of the XIV PAPDI Working Conference will be endorsed at PAPDI National Congress (KOPAPDI XVII) on 11-15 July 2018 in Surakarta.

This meeting also discussed inputs and corrections for all activities that had been or will be done in the future, including addressing and managing follow-up plans for health problems and health rules or regulations in Indonesia:

- Problems that are encountered during the implementation of National Health Insurance, and suggestion or inputs to the government through the Indonesian Social Security Administrator (Badan Penyelenggara Jaminan Kesehatan/BPJS)
- The government's plans, rules, and



regulation for the upcoming ASEAN Free Trade Area (AFTA) related to foreign doctors

- Ethical issues especially gratuities, sponsorship of doctors to attend scientific events

The Chairman of Indonesian Society of Internal Medicine, Prof. DR. Dr. Idrus Alwi SpPD, K-KV, FACC, FESC, FAPSIC, FINASIM, FACP, stated that the profession of internal medicine has an important role in the optimization of tiered services in the National Health Insurance era through a holistic and comprehensive approach. PAPDI participates in the National Health Insurance era by continuing to hold various professionalism development activities and preparing National Guidelines for Medical Services.

In addition to attending the symposiums, we also had the opportunity to join Tuberculosis workshop. The General Director of Disease Prevention and Control, Ministry of Health, Republic of Indonesia (Direktur Jenderal Pencegahan dan Pengendalian Penyakit Kementerian Kesehatan RI), Dr. H. Mohamad Subuh, MPPM, presented the 2017-2050 National target for Disease Prevention and Control as agreed in the Regional and Global assembly.

By 2030, we're targeting to eliminate Malaria, to get the Three Zero HIV-AIDS (zero new HIV infections, zero discrimination, and zero HIV-related deaths), and to eliminate Hepatitis C. Indonesia also targets to be free of TB in 2050.

Dr. H. Mohamad Subuh, MPPM said that the government expects the PAPDI and its members to participate in the detection and management of TB and HIV cases especially in primary health care facilities, private clinics, and hospitals. He also said that Indonesia is a country with dual burden of TB, TB-HIV and MDR-TB. Therefore, every TB case that is found needs to be tested for HIV, and any HIV case found needs to be screened for TB. During workshop, there were also updates about the latest laboratory examination of TB and TB-HIV treatment.

It was a very informative workshop, and we thank INA-RESPOND Secretariat for giving us the opportunity to take part in it.

The Emerging and Re-emerging

Infectious Disease Workshop

Tainan, Taiwan

The Emerging and Reemerging Infectious Disease Workshop-Dengue, Enterovirus, and Intestinal Parasites was held on 21-25 August 2017 at College of Medicine, National Cheng Kung University (NCKU), Tainan, Taiwan. The workshop was organized by the Center of Infectious Disease and Signaling Research, NCKU, to build a future network and join experts together to enhance infectious disease research in the region. Participants include clinicians and researchers from Taiwan, Myanmar, Thailand, Vietnam, Malaysia, Singapore, the Philippines, Indonesia, and Sri Lanka. From INA-RESPOND, Dr. Yuli Marwati (Gadjah Mada University, Yogyakarta), Mr. Ungke Anton Jaya (Secretariat), and Ms. Wahyu Nawang Wulan (Secretariat) attended the workshop. Lectures, laboratory practice, and field visit were meticulously arranged for 5 days as part of the workshop. Topics discussed, as mentioned in the workshop title, consist of Dengue, Enterovirus, and intestinal parasites.

Dengue lectures were held on day 1 and 4. The speakers shared their experiences in real-time surveillance, pathogenicity, and unmet criteria for Dengue diagnosis. There was a notable update from Malaysia in relation to the well-known consensus that outbreaks are strongly associated with the shift of circulating serotypes or genotypes due to the lack of neutralizing antibodies in population against the prior serotype(s) or genotype(s) circulating. The new evidence shows that antibody against DENV-1 genotype I neutralizes DENV-3 genotypes I and III, thus suppressing the outbreak incidence that was anticipated to happen in mid 2000s due to the shift of DENV-1 to DENV-3 in circulation. In other words, herd immunity plays a role in shaping future outbreaks. The finding is highly relevant to Dengue circumstances in Indonesia since both countries share similar hyperendemicity of all Dengue serotypes, in which serotype or genotype shifts may trigger outbreak at any time. In addition to lectures, participants also shared experiences

from their countries. Most countries, including Indonesia, have increased alertness to the emergence of Zika virus within Dengue surveillance. In addition, some countries have initiated attempts to look at the possible implication of Dengue mass vaccination to the future diversity of Dengue virus.

The Enterovirus family may not draw as much attraction as Dengue does in the tropical region; however Enteroviruses remain important since the clinical presentation of the disease range widely from self-limiting to fatal, and thus discussed in day 2 and 5. The large diversity within the Enterovirus family contributes to the various clinical presentations, from the self-limiting rash herpangina and hand, foot, and mouth disease (HFMD) to the severe meningitis, myocarditis/ pericarditis/ pleurodynia, and encephalitic paralysis. The Enterovirus group of NCKU gave evidence that the great diversity is caused by recombination between the structural and nonstructural genes, resulting in the emergence of new genotypes. Reports from participating countries reveal that EV-71 is the major circulating Enterovirus, with shift to CA-6 is observed in Thailand and the Philippines. Indonesia, represented by INA-RESPOND and Eijkman-OUCRU, reported the identification of EV-71 from HFMD cases in Borneo and EV-68 from an acute respiratory infection (ARI) case in the AFIRE study. EV-68 is an important cause of ARI and is associated with accute flaccid paralysis (AFP) outbreak in the US in 2014.

Updates on intestinal parasites were discussed on day 3. A notable lecture presents the integration of "omics" (genomics, transcriptomics, proteomics, metabolomics) in Trichinella vaginalis, an important sexually-transmitted pathogen. Results can be used as a model to fight against other parasitic infection. Lectures also highlighted the emergence of parasitic protozoa that are often neglected but infection can be acute and fatal, such as

Cryptosporidium hominis and Neigleria fowleri.

For field trip, workshop attendees visited the Taiwan Center of Infectious Disease Control and Prevention (CDC), southern branch, where a tour was arranged to demonstrate the procedure of imminent response against outbreak incidence. Another tour was arranged in the mosquito and the National Mosquito-Borne Diseases Control Research Center, to demonstrate attempts done by the government to eliminate Dengue by vector control.

Outside of the science program, the organizer arranged cultural programs. Tainan is the ancient capital of Taiwan, therefore rich in cultural heritage. Participants visited the Natural History Museum, the Chimei Museum, and Historical Sites, consisting of Anping Tree House, and the temple of the guardian of the policemen, accountant, and students. Last but not least, participants were allocated some time to shop in the Old Streets of Tainan, where local souvenirs and specialty snacks, such as dried fruits and prawn crackers are offered.

Ms. Wahyu Nawang Wulan
Mr. Ungke Anton Jaya

The 17th Indonesian Congress of Pediatrics

KONIKA XVII JOGJA

KONIKA is the largest meeting in Indonesian Pediatric Society which is held every three years. It is an excellent forum to learn, discuss evidence-based knowledge in child, and share experiences, expertise, results of studies. The 17th Indonesia Congress of Pediatrics (KONIKA) was held in Yogyakarta from 6 to 11 August 2017. This congress was also held in conjunction with the 11th International Congress of Tropical Pediatrics. There were more than 1,000 participants who joined the congress, and from INA-RESPOND, Ms. Maria Mila Erastuti, Ms. Salfia Dian Lastari, and Ms. Maria Intan Josie, joined this congress from 8 to 11 August 2017.

The congress theme addresses the importance of "Implementing Advances in Pediatrics for Better Child Health". Topics related to sustainable development goals such as stunting, the first 1,000 days of life, immunization, adolescent health, and non-communicable diseases were discussed here. The congress had breakfast meeting, plenary session, breakthrough symposia, parallel symposia, lunch symposia, and best research presentation/poster presentation. We decided to join the infectious disease because it was related to our studies such as Tuberculosis, Pneumonia, and HIV. Currently, the Indonesia Pediatrics still have some burden in children infectious disease like HIV. New cases of HIV infecting young children are still increasing as presented by Dr. Aman B. Pulungan. Dr. Yulia Iriani said that WHO recommended universal Antiretroviral Therapy (ART) in all HIV-positive children and adolescents (<19 years)

ART has been given to all children below 5 years since 2014 in Indonesia. ART should be initiated in all children (<10 years) living with HIV, regardless of WHO clinical stage or at any CD4 cell counts. In adolescents (10-19 years), ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 and 4) and adolescents with a CD4 count <350 cells/mm3. The other recommendation is that ART should be started in all TB patients living with HIV, regardless of CD4 cell count, and ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of anti-tuberculosis treatment of the CD4 cell count and clinical state.

The goals of antiretroviral therapy are to prevent and reduce morbidity and mortality, restore and/or preserve immune function as reflected by CD4-cell measures, suppressing viral replication maximally and durably, prevent viral drug-resistance mutations, to minimize drug-related toxicity, to maintain normal physical growth and neurocognitive development, and to improve quality of life, as presented by Dr. Ketut Dewi Kumarawati. She said that treatment failure is identified when persistently detectable viral load exceeds 1000 copies/ml in 2 consecutive viral load measurements with 3 months interval with adherence support after at least 6 months using antiretroviral drugs. Clinical failure is a new recurrent WHO stage 3 or 4 condition after 6 months HAART. Immunologic failure is one of the four categories. Once a diagnosis of treatment failure is made, based on either virologic or nonvirologic criteria, patients are switched to second line therapy.

Dr. Aman B Pulungan said that TB affected 9.6 million people in 2014 in Indonesia, causing 1.2 million deaths. Indonesia ranked 2nd for the highest number of TB infection; meaning it accounts for 10% of all TB patients worldwide (WHO Global Tuberculosis Report, 2015). The prevalence dramatically increased from 272/100.000 population in 2013 to 647/100.000 population in 2014. There were some challenges in pediatric TB, such as less portion of funding compare WOT adult in National TB Program, difficult diagnosis of Pediatric TB (tuberculin, molecular rapid test and CXR are not always accessible), TB prevention (NIH prophylaxis) is not well implemented, comorbidities with HIV and other chronic illness, underreporting in private sectors and underestimating increased number of new TB cases.

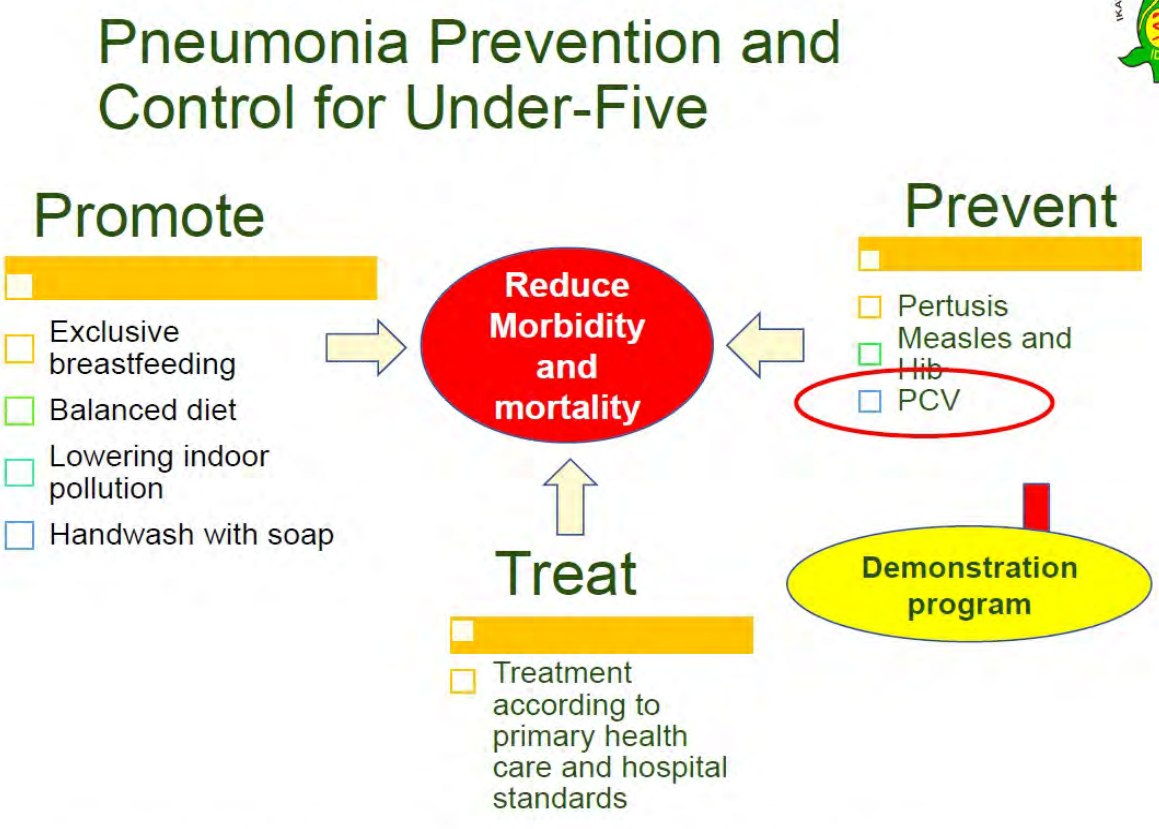
Dr. Rina Triasih presented the update on the diagnosis and management of tuberculosis in children. She presented the new algorithm for TB in pediatrics. Children with at least one symptom of TB are asked to collect their sputum for rapid molecular test (Xpert MTB/RIF). Anti-Tuberculosis Drug (ATD) can be given to the patients if the result of Xpert MTB/RIF is positive, or when the pediatric TB score is more than 6. If the score is less than 6, the patient won't receive TB treatment unless they have been in contact with other TB patient or their TST is positive.

Professor dr. Cissy B. Kartasasmita,

SpA, MSc, PhD presented "New Vaccines Introduction Into The National Immunization Program". She explained based on the United Nations Children's Fund (UNICEF) Committing to Child Survival: A Progress Renewed. Based on Progress Report 2015 (UNICEF, September 2015), there are 5.9 million under five deaths in 2015, 13 % mortality in post neonatal, and 3% mortality in neonatal caused by pneumonia. She also said Pneumonia is the main killer for children under five. Indonesia is one of the 10 countries with the highest number of under-age-of-five deaths in 2015, and 17% (25,000) of the number is due to Pneumonia.

Based on the data, Prof. Cissy said that we need pneumonia prevention and control for children under five. The Indonesian government, through the Ministry of Health, has developed a long-term, conservative plan aimed at preventing and reducing the death caused by pneumonia. The figure below shows the comprehensive multiyear plan for Pneumonia Diseases prevention:

One of the preventive measures the government will take to decrease the mortality rate of pneumonia in children under five is to provide PCV vaccination (Pneumococcal vaccine). Based on the recommendations by WHO on Report Meeting, April 2012 and Indonesia Technical Advisory Group on Immunization in 2016 recommend: "PCV vaccination should be included in national immunization program to increase child life survival, especially in countries with high under-five mortality rate." The government will demonstrate



Comprehensive Multi Year Plan Ministry of Health Indonesia for Pneumococcal Disease Prevention. Presented in Indonesia Pneumococcal Disease Summit, Legian, 21 January 2017

PCV 13 vaccine program on October 2017 at Primary Health Care (PHC), government and private hospitals, and private practices in West and East Lombok, with children of 2, 3, and 12 months age as the target populations.

The congress was very informative and proved to be such a successful meeting in Indonesian Pediatric Society. Topics are useful for research development in future especially for Ina-RESPOND such as HIV, pneumonia and TB especially in pediatrics. And the top of that, we could establish some networks with our PI and PI candidate for our promising studies.

We thank INA-RESPOND for giving us the opportunity to take part in it. We hope we could join another congress in the future.

Ms. Maria Intan Josie - Ms. Maria Mila Erastuti - Ms. Salfia Dian Lastari

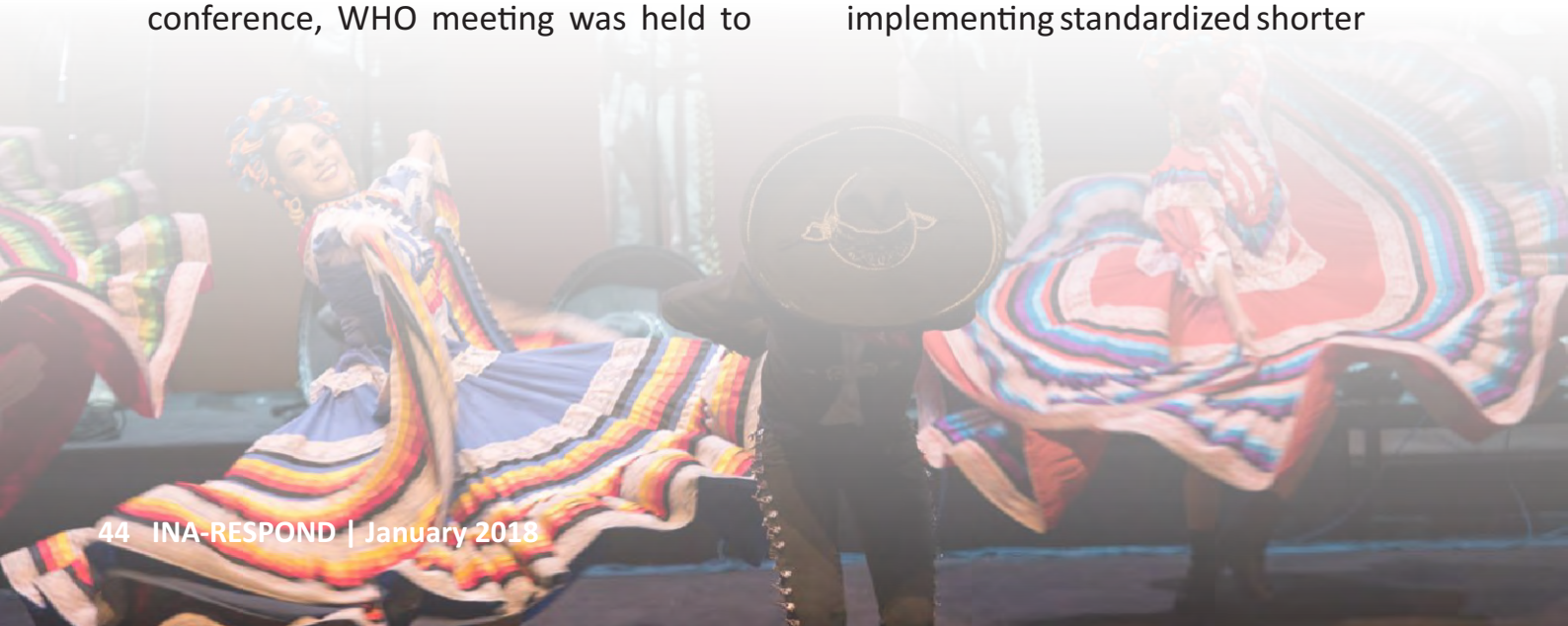
THE 48TH Union World Conference

Guadalajara, Mexico

The 48th Union World Conference was held in Guadalajara, Mexico on Oct 11-14, 2017. Guadalajara is a city in Western Mexico, the capital and largest city of the Mexican state of Jalisco, and the seat of the municipality of Guadalajara. The city is in the central region of Jalisco in the Western-Pacific area of Mexico. This conference was organized by International Union Against Tuberculosis and Lung Disease (The Union). It united researchers, global advocates, civil society, scientists, healthcare professionals, and students working on all aspects of lung health, under the 'Accelerating Toward Elimination' theme. It focused on how to accelerate toward elimination on multiple fronts including tuberculosis (TB) and its co-infections, improving tobacco control, and reducing air pollution. There were approximately 1,600 submitted abstracts from countries around the world, and 850 abstracts were presented in oral or poster sessions.

On October 10, one day before the conference, WHO meeting was held to review End TB progress that had been made in the last year including actions taken and the plan to hold the first United Nations High Level Meeting on tuberculosis, which will take place in 2018. To inform the High-Level Meeting on the current situation, WHO and the Russian Federation are holding the first WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era: A Multisectoral Response. This Conference in November 2017 is bringing together Ministers of Health and representatives from other ministries from across the globe. The meeting is expected to have outcomes on: (1) Advancing the TB response within the SDG and antimicrobial resistance (AMR) Agendas; (2) Sufficient and sustainable financing; (3) Science, research, and innovation; and (4) Multisectoral accountability.

One of the sessions that we followed addressed the issue of implementing standardized shorter



MDR-TB regimen with seven drugs and treatment duration of 9-12 months in more countries. The current 20-24 month regimen used globally in many countries is costly. It also has significant side effects, and the length of the regimen makes it hard for both patients and the health system. The regimen has an average treatment success rate of approximately 50 percent when used in many real-world treatment settings. Therefore, in 2016, WHO recommended the shorter regimen for MDR-TB, and the results from STREAM clinical trial stage 1 showed that the nine-month treatment regimen being tested for multidrug-resistant tuberculosis achieved favorable outcomes in almost 80 percent of those treated and was very close to the effectiveness of the 20-24 month regimen recommended in WHO's 2011 guidelines, when both regimens are given under trial conditions. Indonesia hopefully will start implementing this shorter regimen recommendation this year.

An innovative technology to improve the treatment adherence was introduced; Wireless Observed Therapy (WOT), an ingestible sensor made of minerals which break down in the body, releasing a sensor the size of a grain of sand that sends data to a patch worn on the patient's chest. The patch stores the data until it comes into contact with a mobile device (a tablet or mobile phone) with Bluetooth technology. The mobile device encrypts the data and sends it via wireless Internet to the patients' healthcare provider, facilitating remote monitoring and greatly relieving the burden of treatment on the patient. This sensor confirmed over 50% more doses than DOT. The results presented today reflect phase one of the trial, which must prove the accuracy and clinical utility of the digitized medicines before phase two is started and testing against a control is done. The results of phase 2 cannot be shared yet. This invention is considered as an optimistic strategy to monitor the treatment.

Last but not least, the conference also talked about the TB diagnostic tools development and the strengthening of laboratories capacity. Xpert® MTB/RIF Ultra cartridge which has higher sensitivity is hoped to replace the old cartridge next year. Other rapid tests to detect drug resistance, such as Line Probe Assay (LPA) are starting to be implemented in many countries, and they are constantly being improved especially now that the concern is to rapidly detect the pyrazinamide resistance.

In this occasion, we also joined the RePORT consortium session and had a reunion with colleagues from RePORT meeting in Brazil. We also had a productive discussion with Dr. Carol Hamilton about the implementation of TRIPOD study in Indonesia such as the data management and biorepository management. We also shared our challenges during the study.

- dr. Retna Mustika Indah, Ms. Meity Siahaan -

ASTMH 66TH Annual Meeting

The American Society of Tropical Medicine and Hygiene (ASTMH) 66th Annual Meeting was held on November 5-9, 2017 at Baltimore Convention Center, Baltimore, Maryland, USA. The ASTMH is a non-profit organization of scientists, clinicians, students, and program professionals whose longstanding mission is to promote global health through the prevention and control of infectious and other diseases. The annual meeting was attended by 4,400 delegates from 100 countries. They include researchers, professors, government and public health officials, military personnel, travel clinic physicians, practicing physicians in tropical medicine, students, and all health care providers working in the fields of tropical medicine, hygiene, and global health. INA-RESPOND's representatives attending the meeting were dr. Bachti Alisjahbana, PhD, Sp.PD-KPTI; Prof. dr. Pratiwi Sudarmono Ph.D, Sp.MK; dr. Dona Arlinda; and Ms. Wahyu Nawang Wulan.

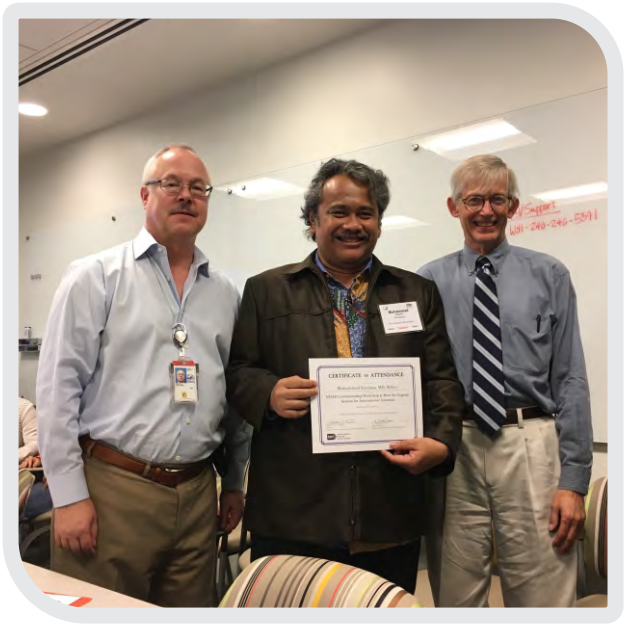
Numerous subjects representing interests in tropical disease research were presented in the scientific sessions, symposiums, plenary sessions, poster sessions, as well as late breakers. The subject categories include clinical tropical medicine, diarrhea and bacterial illness, ectoparasite-borne diseases, entomology, filariasis, global health, HIV and tropical coinfections, integrated control measures for neglected tropical diseases (NTDs), intestinal and tissue helminths, cestodes, kinetoplastida, malaria, molecular parasitology, one health: interface of human health/animal disease, opportunistic and anaerobic protozoa, pneumonia, respiratory infections and tuberculosis, schistosomiasis-helminths, virology, water, sanitation, hygiene, and environmental health. In addition, the meeting organization also included pre-meeting courses in parasitology, arbovirology, and global health; and awards session, namely the Young Investigator and Clinical Research Awards.

INA-RESPOND presented 6 abstracts at the 66th ASTMH Annual Meeting to showcase its achievements. Five abstracts were presented during the poster sessions, and the other one was an oral presentation during the HIV and Tropical Co-Infections symposium session. The posters were (1) Rickettsial Infection: An Unexpected Cause of Fever in Patient Hospitalized with Acute Febrile Illness in Indonesia, (2) The Dynamics of Dengue Virus Infection in Indonesia: Observations from a National, Multicenter Study of Acute Febrile Illness Among Hospitalized Patients, (3) The Etiologies of Fever Requiring Hospitalization in Indonesia, (4) Clinical, Serological, and Molecular Diagnosis of Typhoid Fever, A Significant Cause of Acute Febrile Illness among Hospitalized Patients in Indonesia from 2013 – 2016, (5) Building the Infectious Disease Diagnostic Capacity of a Developing Nation: Experience from the Indonesia Research Partnership on Infectious Diseases (INA-RESPOND). The talk, Unfavorable Tuberculosis Outcome Associated with HIV, Drug Resistance, and Previous Treatment in Indonesia, was presented by dr. Dona Arlinda. The

abstracts, presented in both poster and symposium sessions, drew attention from fellow attendees who visited the poster booth/talk session and gave comments or asked questions.

An interesting talk about the use of Wolbachia to control Aedes aegypti transmitted viruses was delivered by Dr. Scott O'Neill from Monash University, Australia. Wolbachia can be found in over 60% of all insects worldwide and is able to disrupt pathogens' replication in their hosts. Due to cytoplasmic incompatibility, when an infected male mosquito mates with an uninfected female, no eggs are viable. However, when an infected male mates with an infected female or an infected female mates with an uninfected male, all resulting eggs are also infected; and Wolbachia spread through the population. In Indonesia, the effectiveness of Wolbachia is being tested in Yogyakarta. We look forward to the results of this exciting intervention study.

Aside from all the “common” science events, there were also scientific works presented in a more “modern” way. The Project Zero (Huffington Post) is 360-degree virtual reality (VR) films about the untold stories of the victims and health workers battling elephantiasis, river blindness, and sleeping sickness in the most remote and underdeveloped regions of the world. Under the Net (United Nations Foundation) there is another VR story of refugees in Nyarugusu Camp, Tanzania, who struggle to survive without protection from mosquitoes that carry malaria. The films were created to raise awareness around



neglected tropical diseases and increase efforts to fight them.

All in all, attending the ASTMH annual meeting is a valuable experience as we could meet experts in tropical disease research and get updates on the latest achievements in the field. The experience have broadened our knowledge and raised our inspiration in infectious disease research, which would hopefully be valuable for INA-RESPOND's activities. We are thankful for the sponsorship to attend the meeting and present the abstracts.

NIAID Grantsmanship Workshop & Meet the Experts Session for International Scientists

This two-day workshop was held on November 2-3, 2017 at NIAID Office in Rockville, Maryland, USA. Prof. dr. Pratiwi Sudarmono Ph.D, Sp.MK, dr. Dona Arlinda, and dr. M. Karyana attended this workshop on behalf of INA-RESPOND. It was a workshop to provide overview on how to develop and apply for successful NIH extramural grant application. Although the application submission process and registration requirements for NIH extramural grant application are quite strenuous, the take home message of the workshop was researchers need to layer their funding sources to ensure the continuity of the study, and the NIH extramural grant application is a great alternative for research funding source. Having multiple funding sources would allow researchers to have better success in their research career.

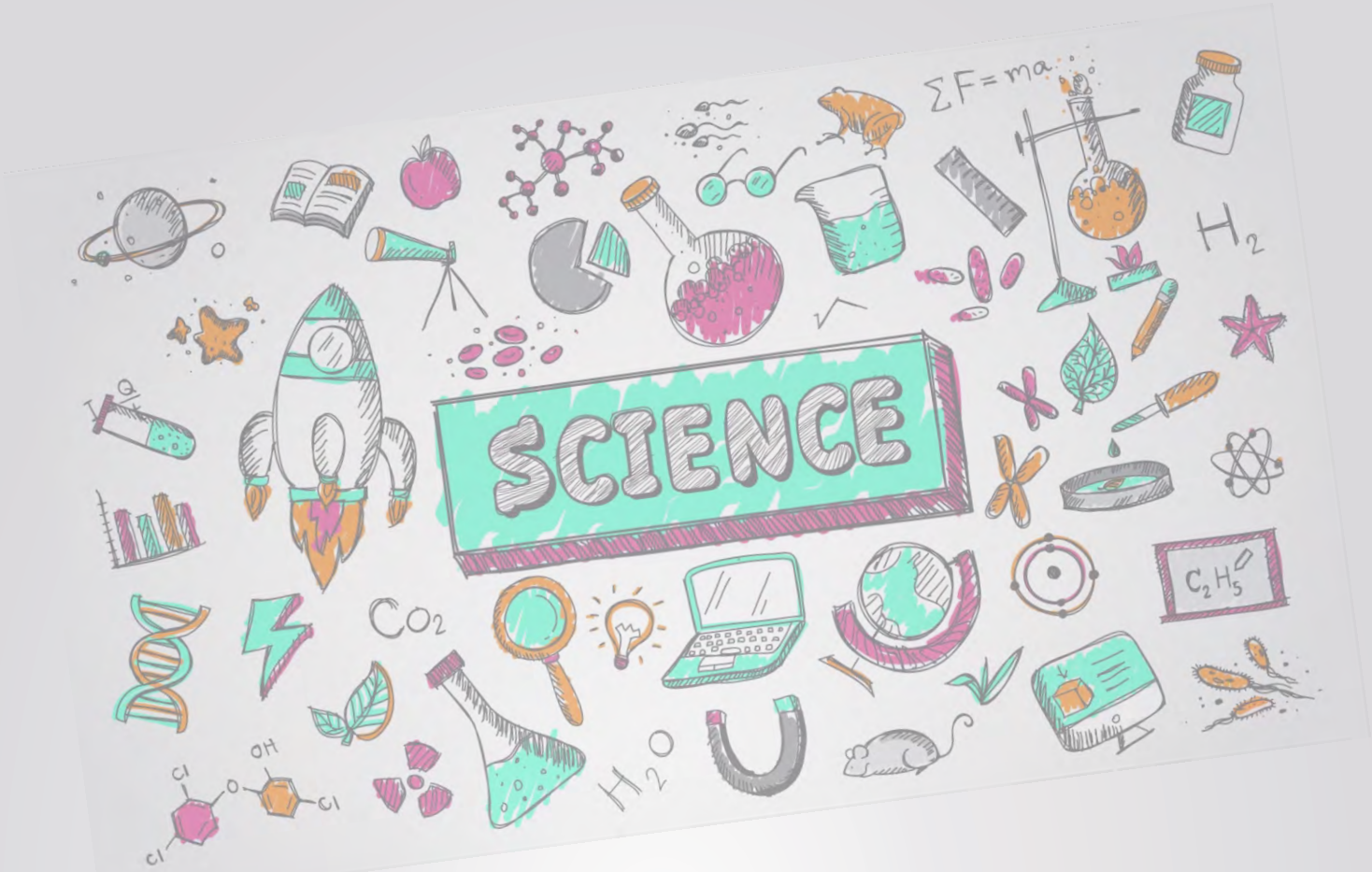
NIAID/DCR Symposium: International and Domestic Collaborations for Clinical Research

This half-day symposium was held on November 3, 2017 at NIAID Office in Rockville, Maryland, USA. The Chair of INA-RESPOND, dr. M. Karyana, gave his talk on the establishment and achievements of INA-RESPOND. There were also other representatives from the University Clinical Research Center (UCRC), Mali; the Mexican Emerging Infectious Disease Clinical Research Network, Mexico (La Red); Partnership for Research on Ebola Virus in Liberia (PREVAIL); and Infectious Disease Clinical Research Program (IDCRP), U.S. Department of Defense. These were the international and domestic collaborations under NIAID Special Projects.

- dr. Dona Arlinda
- Ms. Nawang Wulan Sari

SCIENCE

COMIC CORNER



Randomized Controlled Trials:

Is it a magic spell?

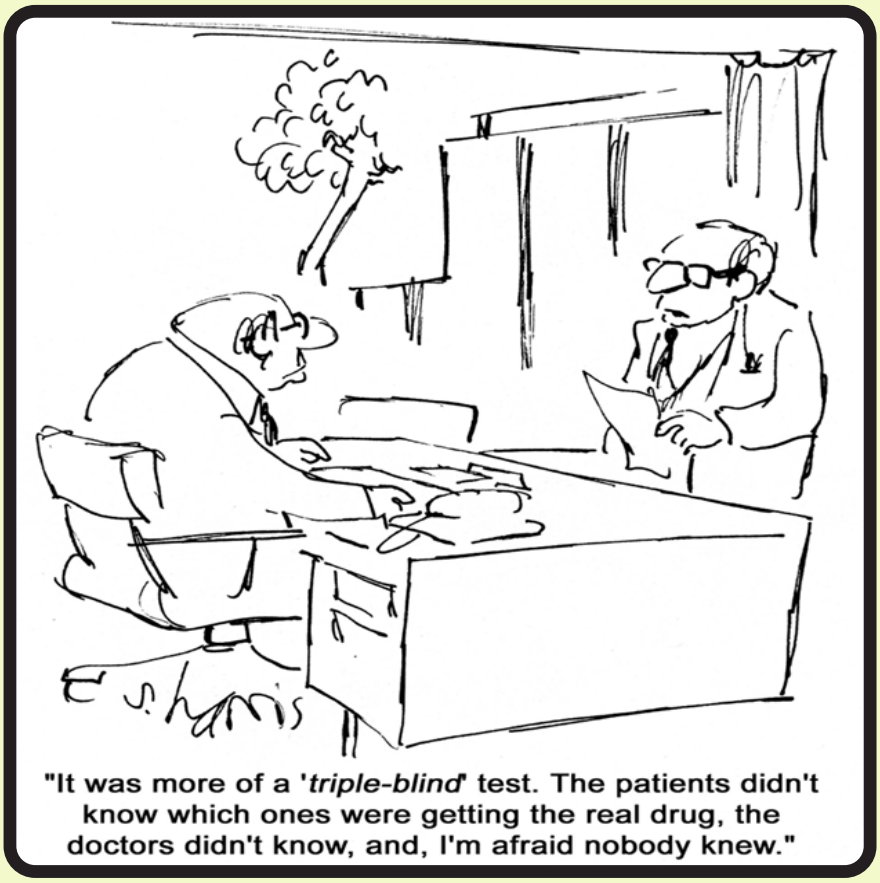
Randomized controlled trial (RCT) is the best way to study the safety and efficacy of a new treatment. It does make RCT the best candidate for doing clinical trials. However, just because you find RCT written in the method section does not mean you get your magic words and everything about the study is acceptable/reliable. Trusting or not trusting the study relies on the quality of RCT, which mainly depends on an appropriate study question and study design, prevention of systematic errors, and the use of proper analytical techniques. The quality of any RCT must be critically evaluated before its relevance to patient or wider community can be considered. So, let us see some little tricks to critically appraise a RCT.

First, the reporting of RCT must follow CONSORT (Consolidated Standards of Reporting Trials) guideline. The checklist items are available and can be seen in the reference list below. In general, the minimal requirements for a publication reporting a RCT should consist of: study design, study population, treatments/interventions, objectives, endpoints, sample size, randomization, blinding, analysis population, results, adverse events, interpretation, and generalizability of the results. Anyway, if a published study misses some of these points, we can consider to stop reading the full paper as it may bring us nowhere.

RCT needs to follow a strict protocol that describes the scientific background, the risks: benefit assessment, study design, study methods, overall planning, conduct, and analysis of the study. Nowadays, RCT must be registered before executed, and the registered protocol is usually accessible. To answer the primary study question, a primary endpoint is required, and it must be stated clearly. Based on the primary endpoint, the study should present the sample calculation to answer the primary question. From the statistical viewpoint, it is vital to distinguish between the primary and secondary study questions, because the number of study subjects usually depends solely on the primary endpoint. So, when a study does not mention about sample calculation correctly, we can be more aware that the study most probably could not answer its primary objective/question.

Next thing to consider is the study design; and the two most important and common factors are randomization and blinding. Respondents must be randomly assigned to different study groups to ensure that all potential confounding factors are divided equally among groups. We need to be sure that we can do a fair comparison between intervention groups, which means the different study groups must be truly comparable (have a structural equivalence). If the potential confounders are known or can be predicted, structural equivalence can be obtained by stratified randomization. In addition, blinding is also usually used to avoid bias. Double-blind study is especially advantageous if knowledge of the treatment might influence the course and therefore the results of the study.

Lastly, please look at the statistical analysis. In general, the analysis in RCT will use the intention-to-treat (ITT) principle. This kind of analysis includes all patients who were randomized, including patients whose treatment was interrupted, prematurely discontinued, or did not take place at all; and the patients will represent the groups where they were randomized into to retain the advantages of randomization as a structural equivalence. The alternative strategy is to restrict analysis to the data using the per-protocol (PP) principle, but this alternative is less


"It was more of a '*triple-blind*' test. The patients didn't know which ones were getting the real drug, the doctors didn't know, and, I'm afraid nobody knew."

favorable as the results may be distorted. The ideal of all is to do both ITT and PP analysis and results comparison. Similar results of PP and IT indicate the results are reliable enough.

Closing remark: Please don't be blinded with the magic words of RCT. Critical thinking and evaluation are absolutely needed before we trust results of any study. Following the guideline to evaluate a publication will be a very smart decision, especially for a beginner.

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Beneficial and **R**esponsive to the research neeeds of Indonesia and the international community.

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High-Quality in conducting scientifically sound and ethical infectious disease research.

Trust and **T**eamwork with respect, transparency, communication, collaboration and shared responsibility.

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