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INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

April 2018

The 25th Conference on RETROVIRUSES and OPPORTUNISTIC INFECTIONS

GLOBAL VACCINE & IMMUNIZATION RESEARCH FORUM 2018

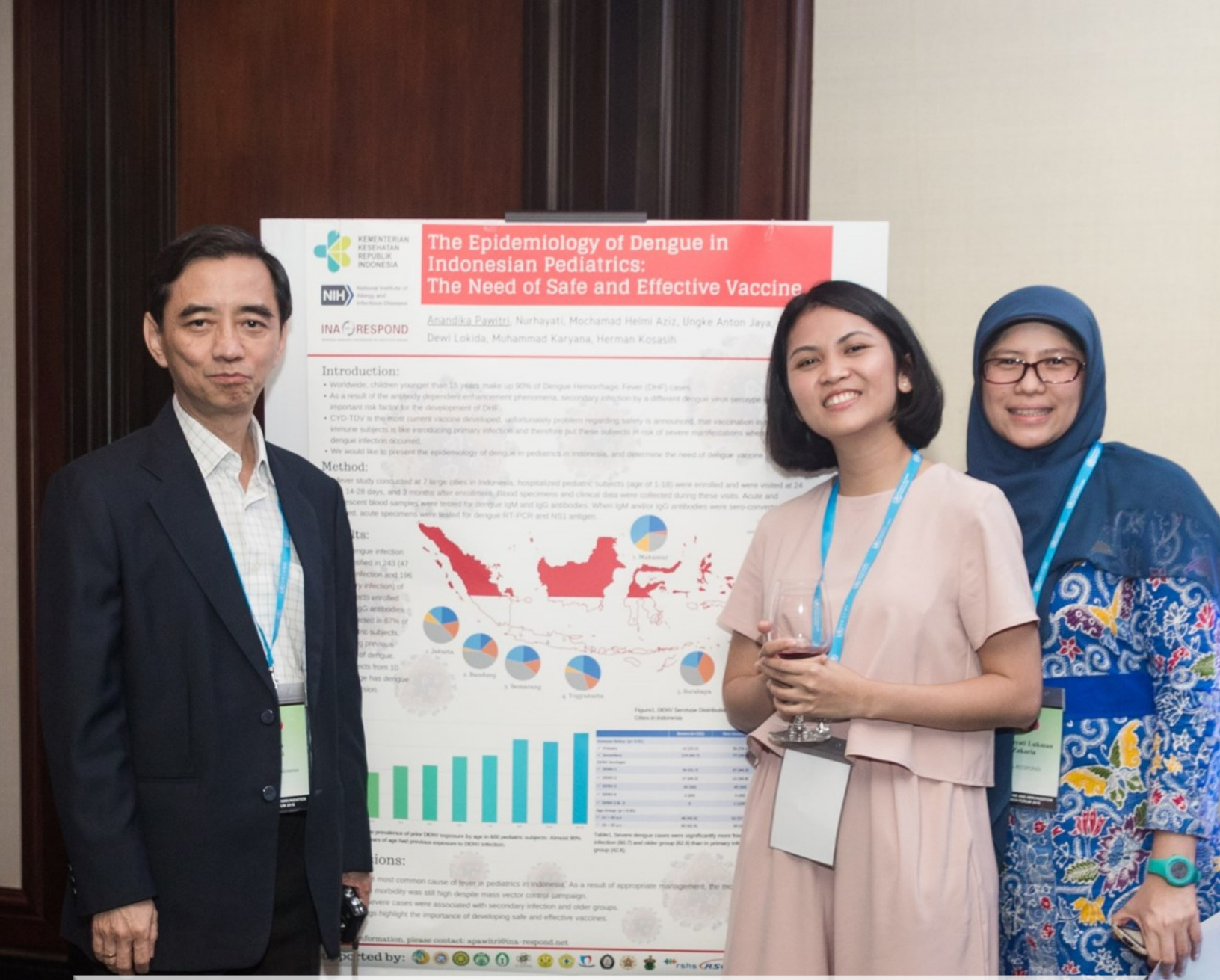
BCG VACCINATION: INEFFECTIVE AND NEEDS TO BE SUBSTITUTED?

Lost in Translation: Are YOU an Alien?

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT

MINISTRY OF HEALTH REPUBLIC OF INDONESIA

2018



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Badan Penelitian dan Pengembangan Kesehatan, RI
Gedung 4, Lantai 5

Jl. Percetakan Negara no.29, Jakarta, 10560

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TRIPOD & INA-PROACTIVE Study Updates

BY: ANANDIKA PAWITRI, CALEB L. HALIM, LOIS E. BANG, MARIA INTAN, M. IKHSAN JUFRI

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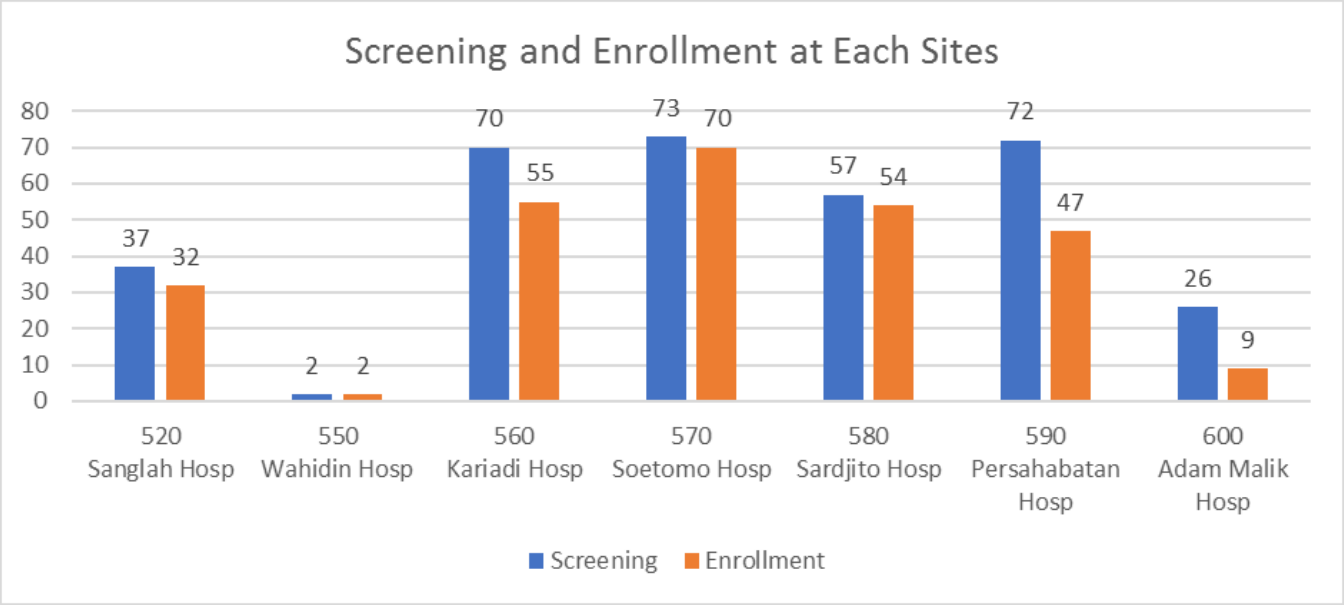
Screening and Enrolment

Up to 27 March 2018, sites have enrolled 269 subjects. Site 570, RSUD dr Soetomo, is still the top recruiter with 70 subjects. Enrolment by site 520, RSUP Sanglah, is temporarily stopped until the study permission is cleared. Enrolment progress until the end of March 2018 can be seen in the graphic below.

NIH/Leidos Visit to INA-RESPOND Secretariat

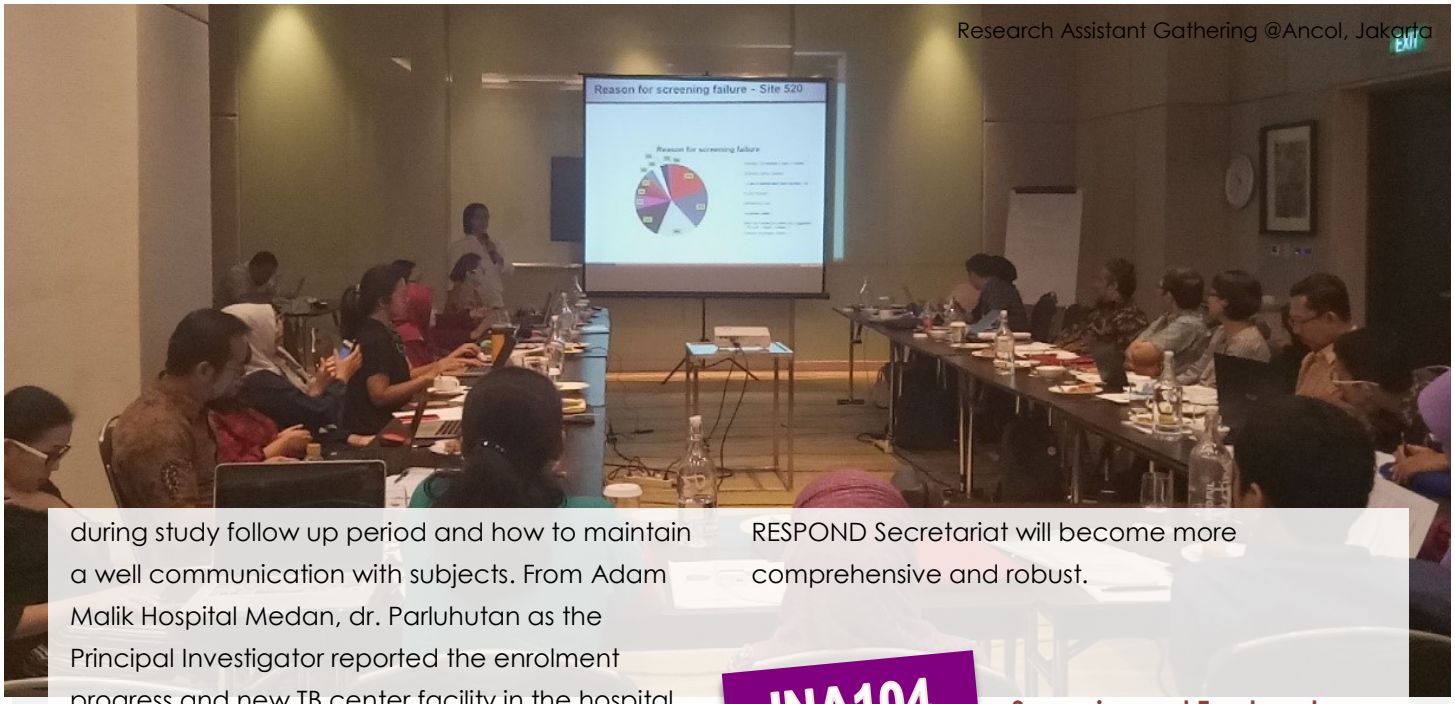
2nd TRIPOD Interim Analysis Meeting was successfully held on 3 April 2018 in Jakarta. The meeting was attended by Principal Investigators, Co-Principal Investigators, and Research Assistants from seven sites. This meeting began with presentation of data and screening/enrolment progress which was delivered by The Secretariat followed by presentations from sites.

dr. Ari, Research Assistant from Sanglah Hospital, reported that the permission for the site is now in agreement process. From Dr. Wahidin Sudirohusodo Hospital, Makassar, dr. Ira as the Principal Investigator gave updates and talked about the possibility of next enrolment. From site 560, 570, 580, and 590, each Research Assistant reported the ongoing enrolment process and challenges to maintain the subjects in study. They also shared subject management and retention



*Site number:

520 – RSUP Sanglah, Denpasar
560 – RSUP dr Kariadi, Semarang
570 – RSUD dr Soetomo, Surabaya
580 – RSUP dr Sardjito, Yogyakarta
590 – RSUP Persahabatan, Jakarta
600 – RSUP H Adam Malik, Medan



Research Assistant Gathering @Ancol, Jakarta

during study follow up period and how to maintain a well communication with subjects. From Adam Malik Hospital Medan, dr. Parluhutan as the Principal Investigator reported the enrolment progress and new TB center facility in the hospital, which will be opened in near future.

Besides showing preliminary results of TRIPOD study to site team, the purpose of this meeting is to elicit ideas that can be developed from TRIPOD study data for the next study. Site team also propose ideas for future publication plan. One of them is publishing the study in national and international conferences such as Respina in Jakarta, Congress of the Asian Pacific Society of Respirology in Taipei, and Union World Conference on Lung Health in The Netherlands.

Also In this occasion, an in-depth discussion took place between the national PI (dr. Erlina) and PIs from every site about the study result and management of TB patient in the field. The discussion brought up interesting ideas such as how TRIPOD study would benefit health regulation.

By the end of the interim analysis meeting, dr. Lidya from Universitas Padjadjaran Bandung explained about future specimen testing that can be done for TRIPOD sample, and dr. Adriansjah from Microbiology University of Indonesia Jakarta shared about Line Probe Assay for molecular testing of TB sample. can be finalized and used for TRIPOD reporting. From the meetings, it is expected that the Data Management and Statistics of INA-RESPOND Secretariat will become more comprehensive and robust.

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Screening and Enrolment

Four months have passed since INA-PROACTIVE study enrolled its first subject. Per 16 April 2018 a total of 62 subjects has been enrolled. Tangerang Hospital has enrolled 34 participants for INA-PROACTIVE study while Adam Malik Hospital and Wahidin Hospital have enrolled 28 participants (14 participants each). The subjects comprises 53 adult subjects and 9 pediatric subjects.

Currently, eight study sites have signed the INA-PROACTIVE study contract and agreement. They are Tangerang Hospital, Adam Malik Hospital, Wahidin Sudirohusodo Hospital, Cipto Mangunkusumo Hospital, Soetomo Hospital, Kariadi Hospital, Gatot Soebroto Hospital, and Sardjito Hospital.

The Secretariat conducted Site Preparation Visit (SPV) for site 570 Soetomo Hospital on 20-21 March 2018 and Site Initiation Visit on 4-5 April 2018. SPV was also conducted for site 560 Kariadi Hospital on 11-13 April 2018. The next SPV is for site 580 Sardjito Hospital on 18-20 April 2018.

Since last month, several hospitals (Ansari Saleh Hospital in Banjarmasin, Budi Kemuliaan Hospital in Batam, St. Carolus Hospital in Jakarta, Wahab

Site Preparation Visit at RSUD. Soetomo, Surabaya

Site	SPV	SIV	Activation	Enrolled Subjects
Site 610 (Tangerang Hospital)	19-20 Dec 2017	22 & 27 Dec 2017	09 Jan 2018	34
Site 600 (Adam Malik Hospital)	7-8 Feb 2018	12-13 Feb 2018	12 Mar 2018	14
Site 550 (Wahidin Hospital)	13-14 Feb 2018	19-20 Feb 2018	13 Mar 2018	14
Site 530 (Cipto Hospital)	21-22 Feb 2018	13-14 Mar 2018	-	-
Site 570 (Soetomo Hospital)	20-21 Mar 2018	4—5 Apr 2018	-	-
Site 560 (Kariadi Hospital)	11—13 Apr 2018	23 –24 Apr 2018	-	-
Site 580 (Sardjito Hospital)	18—20 Apr 2018	17—18 May 2018	-	-

Sjahranie Hospital in Samarinda, Kandou Hospital in Manado, Jayapura Hospital in Jayapura) have replied our collaboration invitation letter. We conducted site assessment at Ansari Saleh Hospital on 9 April, and the hospital management gave positive respond to our study network and to our HIV Study. As for the other five hospitals, we will conduct site visit within these two months.

INA-RESPOND Newsletter

GLOBAL VACCINE & IMMUNIZATION RESEARCH FORUM 2018

BY: NURHAYATI, ANANDIKA PAWITRI, VENTY MULIANA SARI SOEROSO, M HELMI AZIZ

On 20–22 March 2018, four INA-RESPOND representatives have a great opportunity to attend the invitation as poster presenters and participants on the third Global Vaccine and Immunization Research Forum (GVIRF) supported by The World Health Organization (WHO). The GVIRF was held by WHO, the National Institute of Allergy and Infectious Diseases (NIAID), and the Bill & Melinda Gates Foundation (BMGF). Vaccine scientists, developers, and public health officials from around the world discussed scientific and technical challenges in discovery, development, decision making, and delivery for three consecutive days in Shangri-La Hotel, Bangkok, Thailand. This report summarizes and highlights what we learned at the GVIRF meeting.

Progress Towards in Vaccine Development

HIV, TB, and Malaria vaccines

The HIV Vaccine Trials Network (HVTN) launched another study called HVTN702, phase IIb/III clinical trial, a part of series from Uhambo (Journey) study. Before the HVTN702, the HVTN100 was conducted in smaller studies to 210 people in South Africa as the I/IIa phase trial to evaluate the safety of the vaccine. The study vaccines, called ALVAC-HIV (vCP2438) and Bivalent Subtype C gp120/MF59, were given to seronegative participants during HVTN100 and HVTN702. Interim results from HVTN100 showed that the vaccine components are safe to give and it has comparable immunogenicity result with its predecessor fa-

GLOBAL VACCINE AND IMMUNIZATION RESEARCH FORUM 2018

Photos credit to WHO (http://www.who.int/immunization/research/forums_and_initiatives/gvirf/en/)

mous trial, RVV144. The aim of the HVTN702 trial is to evaluate the efficacy aspect (whether this vaccine could prevent new HIV infection), and the results will be shared in late 2020.

Bacille Calmette-Guerin (BCG), the famous TB vaccine, has variable and inconsistent results of TB protection. Therefore, replacing BCG or boosting BCG was the main interest in TB vaccine development. Despite a lot of TB vaccine candidates such as MTB-Vac, VaccaeTM, VPM1002, and M72/AS01E, the main focus during this forum was how to develop pipeline for TB vaccination that is useful for decision making. For Malaria vaccine, up until now no malaria vaccine has reached phase 3 development except for the RTS,S/AS01 (Mosquirix™). Blood stage vaccine targeting PfPh5 and transmission blocking vaccines for malaria were discussed during this meeting as the next candidates for malaria vaccines.

Enteric vaccines

Enteric diseases caused by rotavirus, enterotoxigenic Eschericia coli (ETEC), and Shigella raise concern towards vaccine development. Rotavirus, ETEC, and Shigella are the most common pathogen among infants and young children, causing severe diarrhea which leads to acute dehydration. Thus, several rotavirus vaccines were licensed with different strains, doses, and dosage. The introduction of rotavirus vaccines has decrease the mortality rate due do rotavirus diarrhea in several countries. While for ETEC and Shigella, the vaccine candidates are still in clinical study phase, and concern has been raised whether combination of ETEC/Shigella or single vaccine should be prioritized or not.

Pneumococcal vaccines: Lessons learned and the Road Ahead

Pneumococcal Conjugate Vaccine (PCV) is recommended by WHO as a priority in childhood national immunization program worldwide, particularly where mortality is high. This vaccine aims to complement other pneumonia-control measures such as case management, exclusive breast feeding, or reducing risk factors. Since its introduction in 2000 in the U.S., PCV7 has been administered in 134 countries including in some of the high-burden countries, such as Sudan, Tanzania, Nigeria, Afghanistan, India and Bangladesh. After 15 years introduction of PCV, mortality and antibacterial resistance related to pneumonia have decreased in those countries. However, the coverage varies highly among the 10 countries that have introduced PCV (e.g. 13% in Nigeria to 95% in Tanzania). Since 2011, the PCV administrations schedule has changed from PCV10 to PCV13 while the dosing schedule differs among countries (3 + 0 or 2 + 1). The research showed that there is no difference between PCV10 and PCV13 efficacy, and there is no difference of PCV13/ 2+1 administration among malnourished and non-malnourished children. However, it should be noted that there is im-

portant difference between HIV and non-HIV patient. To achieve and sustain a high level of equitable vaccine coverage and improve the utility of PCV, challenges remain with the high cost of the vaccine and the vaccine serotype replacement.

Introduction of New Vaccine Pipeline

Trial of formalin inactivated Respiratory Syncytial Virus (FI-RSV) vaccine in the late 1960's hampered the development of RSV vaccine. Currently, there is no approved RSV vaccine available. Four RSV vaccine candidates are still on trial to combat the RSV infection which is the leading cause of hospitalization in infants and young children. The following are new RSV vaccine candidates on trials: Novavax GSK RSV pre-F vaccine, VRC317, and MEDI8897.

Human hookworm infects more than 470 million people and ranks number one in terms of Years Lost from Disability (YLDs). It is prevalent worldwide, causing anaemia, malnutrition, physical, and developmental delays, hence the potential to cause future global problem. Current treatments using small molecule drugs do not prevent re-infection, have low cure rates and varied efficacy; which increases the drug's failure rate. Moreover, after massive drug administration (MDA) which aimed to prevent hookworm infection, the infection rate almost unchanged thus the urgently needed vaccine against hookworm. Human Hookworm Vaccine (HHV) initiative, led by Texas Children's Hospital Center for Vaccine Development, is developing pipeline prioritization and evaluation for hookworm vaccine candidates. Indonesia, Brazil, and India are the initial target markets since these three countries have the highest number of children at risk of hookworm infection. A series of Phase I clinical trial were conducted in the USA, Brazil, and Gabon in 2015 to test the recombinant protein based vaccine (Na-GST-1 and Na-APR-1), and it was found to be safe and well-tolerated. Currently, HHV is also running Controlled Human Hookworm Infection (CHHI) model which is at phase 2 trial.

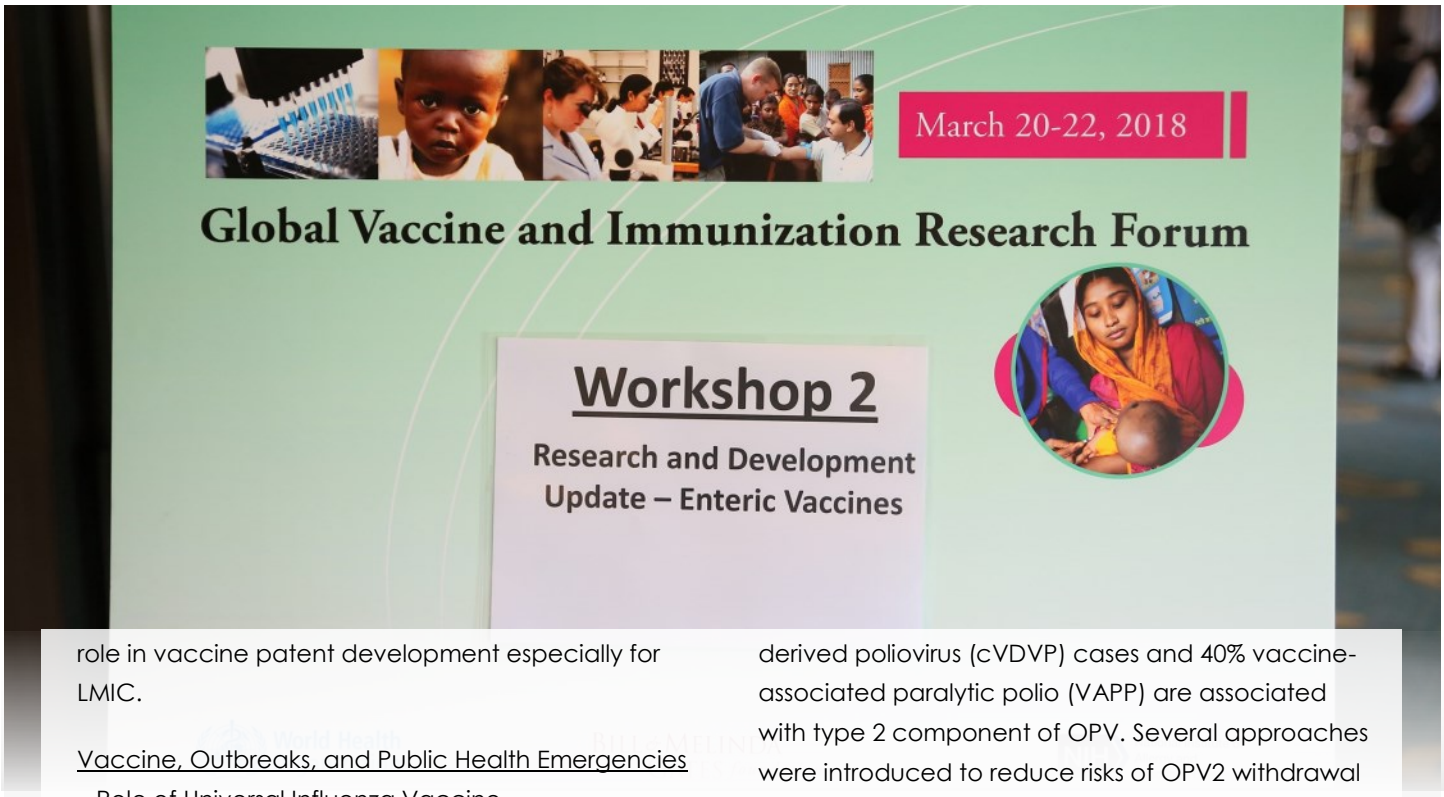
Vaccination Challenges and Regulatory

Vaccine Delivery Strategies for Equitable High Vaccine Coverage and Role of Regional Capacity in Vaccine Development-Biotechnology

Several strategies were discussed in GVIRF related to achieving and sustaining equitable high vaccination coverage. Guest speakers from India, China, Nigeria, and Ukraine shared their vaccination strategies such as strengthening government commitment like Mission Indradhanush in India; using social media platform like WeChat as vaccination reminder in China; and using social media to discuss health issues and counter vaccine hesitancy group in Ukraine. Not only did it make commitment on vaccine delivery, India also advance its technology in vaccine development. India has three institutions that are responsible for novel design of several new vaccines (ICGEB, THSTI, IISER), and ROTAVAC was one of the success vaccines that was developed based on local circulating strain in India.

Perspective of Vaccine Manufacture in Developing Countries

It is well known that there is a gap in population, disease burden, and vaccine sales aspect between vaccine markets in low- and middle-income countries (LMIC) and developed countries . Developing Countries Vaccine Manufacturers Network (DCVMN) mentioned that LMIC are the emerging vaccine market, but only 64 of 145 WHO prequalified vaccines are manufactured in LMIC. Therefore, vaccine development in LMIC could be a significant investment although the gestation period of vaccine investment is up to 5-7 years. The VMPA study, a study performed in 54 Africa countries by UNIDO, showed that vaccine development in Africa needs a large capital investment. Therefore, African government should create a policy and plan to better promote vaccine production in Africa. Kate Elder, a MSF representative, mentioned that the high price of new vaccine, shortages of supply, refusal to sell, and ill-adapted products are the main problems of delivering vaccine in LMIC. In addition, MSF strengthens its



role in vaccine patent development especially for LMIC.

Vaccine, Outbreaks, and Public Health Emergencies – Role of Universal Influenza Vaccine

Influenza pandemic has been around since 1918, and the latest pandemic occurred in 2017. These influenza pandemics has made influenza a constant ongoing global threat to public health. Despite the availability of the seasonal influenza vaccine, influenza pandemics do occur. It has been thought that current seasonal influenza vaccines have different efficacy between strains, thus a universal influenza vaccine is greatly needed. Overall, universal influenza vaccine development has challenges related to safety, scalability, vaccine component (including carriers and adjuvants), formulation, potency determination, and funding. To overcome these problems NIAID has developed a strategic plan for universal influenza vaccine starting from basic research to clinical trials.

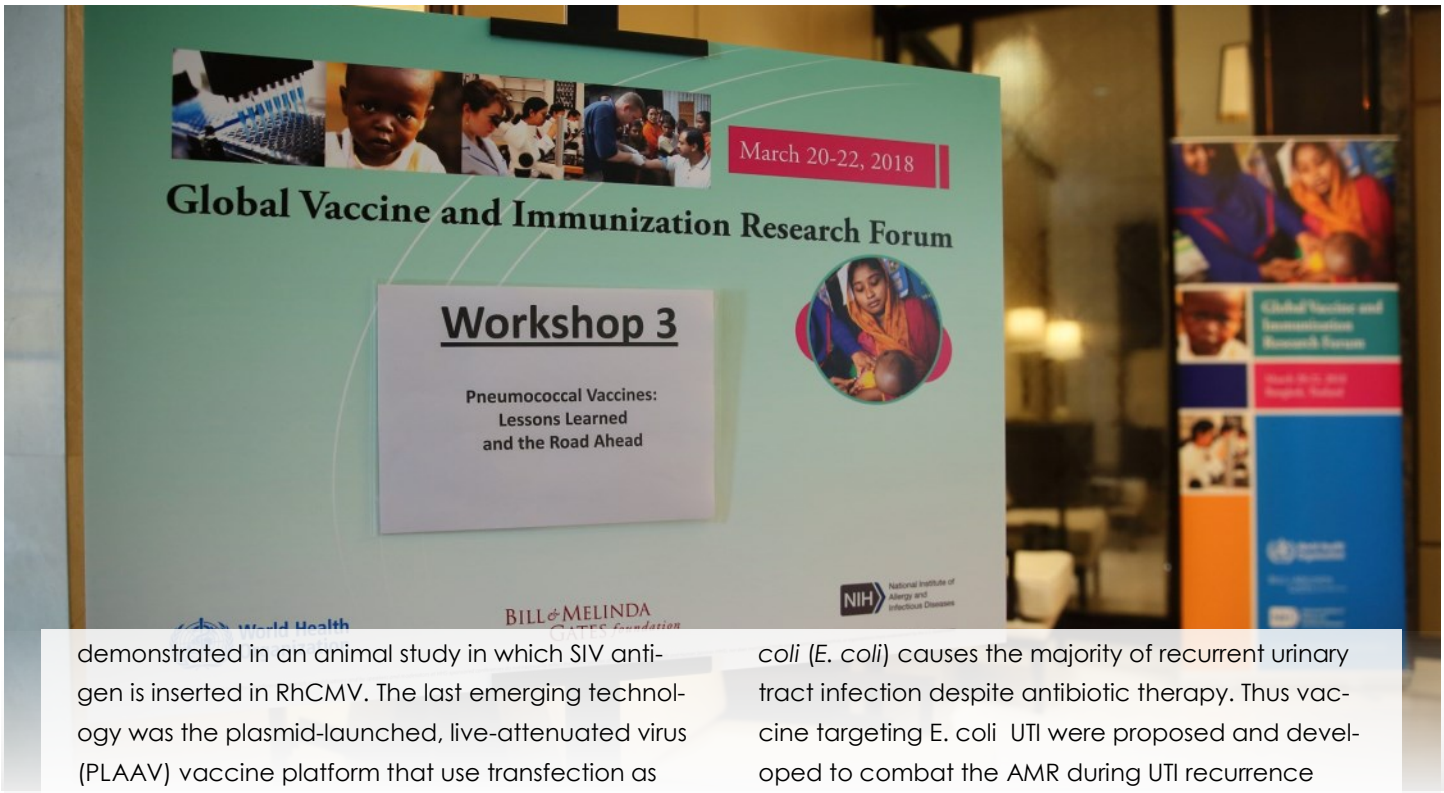
Polio Endgame Strategic Plan

The withdrawal of oral polio vaccines (OPV) began in April 2016 by removing Sabin type 2 component (OPV2) from immunization programs (switched from trivalent OPV (tOPV) to bivalent OPV (bOPV). The switch was done because the wild poliovirus type 2 (WPV2) had been eradicated (the last case occurred in 1999) but almost 90% circulating vaccine-derived poliovirus (cVDVP) cases and 40% vaccine-associated paralytic polio (VAPP) are associated with type 2 component of OPV. Several approaches were introduced to reduce risks of OPV2 withdrawal such as introduction of inactivated polio vaccine (IPV), use monovalent OPV2 in case of outbreaks, and develop new polio vaccine formula such as new adjuvant for IPV, fractional dose administration of IPV, and novel vaccines for OPV2.

Updates on Vaccine Research and Technologies

Emerging Technologies on Vaccine Development

Several emerging technologies to improve vaccine success rate during pre-clinical test were discussed in GVRIF. MIMIC™ (Modular Immune In Vitro Construct) technology, established by Sanofi Pasteur VaxDesign, could evaluate the immune response aspect of new vaccine candidate. The automatic process of MIMIC™ ensures the precision and quality of the result while the diverse donor pool ensures the immunological diversity of human immune system. Cytomegalovirus (CMV) vectored vaccines were discussed as the new vector vaccine candidates. But why use CMV as the new vector for vaccines? It has been well known that in human, CMV develops lifelong latency and has immune evasion mechanism, thus enabling CMV to re-infect efficiently. Not only that, CMV has been proven as an excellent inducer of CD8+ T-cells response which is useful for vaccination response. This mechanism has been



demonstrated in an animal study in which SIV antigen is inserted in RhCMV. The last emerging technology was the plasmid-launched, live-attenuated virus (PLAAV) vaccine platform that use transfection as route of administration. Other advantage of PLAAV is that this platform does not need cold chain maintenance like the traditional vaccine.

Immunological Updates on Vaccination Principle

The problem with several available pediatric vaccines is that antibody titer does not reflect the correlate of protection, thus understanding protective responses will accelerate vaccine development. RTS,S/AS01 vaccine study showed that anti-CSP titers correlated with protective response of malarial vaccine, since CSP is responsible for immobilizing malarial parasites. Several approaches were discussed to elaborate the immunological vaccine response using the latest technologies such as mass spectrometry, T-cells repertoire analysis, and organoid system.

Vaccines and Antimicrobial Resistance

The emergence and spread of antimicrobial resistance (AMR) does not only limit the effective treatment option for infectious diseases but also increases the costs of health care systems. Several vaccines were developed to reduce antibiotic selective pressure. An alga based platform vaccine for oral delivery was developed to counter the antimicrobial resistance in aquaculture. Uropathogenic *Eschericia coli* (*E. coli*) causes the majority of recurrent urinary tract infection despite antibiotic therapy. Thus vaccine targeting E. coli UTI were proposed and developed to combat the AMR during UTI recurrence treatment.

Monoclonal Antibody for Prevention and Treatment (HIV, Rabies, and Influenza)

Passive immunization using antibody has been applied in several diseases such as tetanus, rabies, and diphtheria. Several monoclonal antibodies were developed to prevent HIV infection, to replace rabies immunoglobulin in order to reduce cost of pst-exposure prophylaxis (PEP) and to combat influenza infection.

Despite the emerging technologies in vaccine development, new innovative vaccine design, and new approaches to ensure vaccine delivery, vaccine preventable diseases are still a major challenge especially in LMIC. Investing in vaccine development and ensuring vaccines delivered to those who are in need will have an impact on socio-economic benefit.

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All materials are obtained from GVIRF 2018, Bangkok, Thailand.

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INA-RESPOND Newsletter

BCG VACCINATION: INEFFECTIVE & NEEDS TO BE SUBSTITUTED?

BY: MYRNA EVANDA ADELINE & M. HELMI AZIZ

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Every year we commemorate World Tuberculosis (TB) Day on March 24. TB Day is designed to increase public awareness about public health impact of TB. In 2016, it was estimated that 10.4 million people were infected with TB, and 56% of them were from five countries, including Indonesia, which ranked number two for the highest incidence of TB [1]. To cope with that problem, Indonesia has running Bacillus Calmette–Guérin (BCG) vaccination program for newborn since 1956 and directly observed treatment short-course for TB treatment since 1995. Data from 2007 showed that Indonesia BCG vaccination coverage was up to 75%, and the latest data on 2016 the BCG coverage was 93% for the newborn [2, 3]. Despite the high and increased coverage of BCG, TB incidence in Indonesia still increased from 183/100,000 (2013) to 395/100,000 (2016) [2, 3]. Therefore, this month article will review the protective effect, BCG re-vaccination, BCG side effect, and latest development on TB vaccine research.

The BCG vaccine was developed from 230 passages attenuated strain of *Mycobacterium bovis*

by Cammille Calmett and Albert Guerin at the Pasteur Institute between 1906−1919 [4]. BCG has been proven to have protective effect against serious forms of tuberculosis (meningeal and miliary) but the protective effect was ranged from zero and 80% for pulmonary TB at any age [4-6]. But, why does the efficacy of BCG vaccination have a wide variation for lung TB protection? Several factors including exposure to mycobacteria, genetic of the population, virulence of *M. tuberculosis*, nutritional status, and different BCG strains play a role in determining BCG vaccination effects [4, 5].

Since 1921, BCG vaccine has been administered and distributed worldwide more than any other available vaccine nowadays [4, 7]. In 1921 it was impossible to freeze-dry (lyophilize) or store BCG at -80ºC. Therefore, the original BCG no longer exists. At the Pasteur Institute BCG was continually produced using the same technique until 1173 passages and stopped until lyophilization technique was found in 1961 and at the same time to keep up the BCG demand several laboratories develop their own BCG (daughter strain) [7]. The different laboratories using different method to cultivate BCG, thus promoted genetic modification, affecting the immunogenicity, and reactogenicity of BCG [4, 5]. It has been shown that BCG derived before 1930 or 1940 may have better immunogenicity than the widely used variants [5].

But how do we prove that the different methods of cultivation affect genetic modification of BCG? Thanks to the development of molecular genomic tools which allowed us to determine the molecular differences between BCG strains and tracking the genetic events. Several studies have showed that there are molecular differences between BCG strains which are restriction-fragment-length polymorphism (RFLP), different numbers of IS986 (previously IS6110), *mpt64*, *mma3,* and three deleted regions (RD1−3) [7, 8]. Additionally, the genomic tools are able to demonstrate the molecular events between the first BCG until the last passage of BCG Pasteur (Figure1) where three deletions, three duplications, and one-point mutations occurred during passage [8].

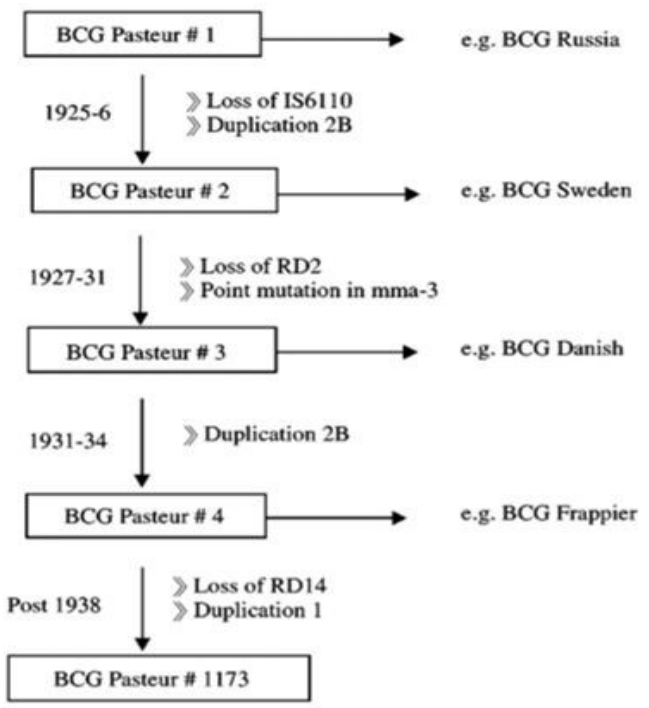

Figure 1. Molecular events of BCG Pasteur from the first BCG Pasteur to the last BCG Pasteur 1173.

Now that we know there are genetic events in BCG vaccine, the next question is, "what is the impact of these changes?" For a live attenuated vaccine such as BCG, the vaccine component must survive long enough after inoculation to provoke the targeted immune response [7]. Methoxymycolic acid, encoded by *mma3*, is the component of bacterial cell wall that is responsible for the survival of BCG inside the host [7, 8]. The BCG strains after 1931 did not produce methoxymycolic acids, thus dividing BCG into two groups, virulent and avirulent form [7, 8]. During the genetic changes, the BCG antigens such as *mpt64* also altered, affecting the immunologic response of BCG vaccination [7]. Moreover, result from BCG trials using BCG−Pasteur 450 and BCG−Pasteur 575 had an efficacy about 80% and 77% respectively, while BCG−Pasteur 1173 showed no pro-

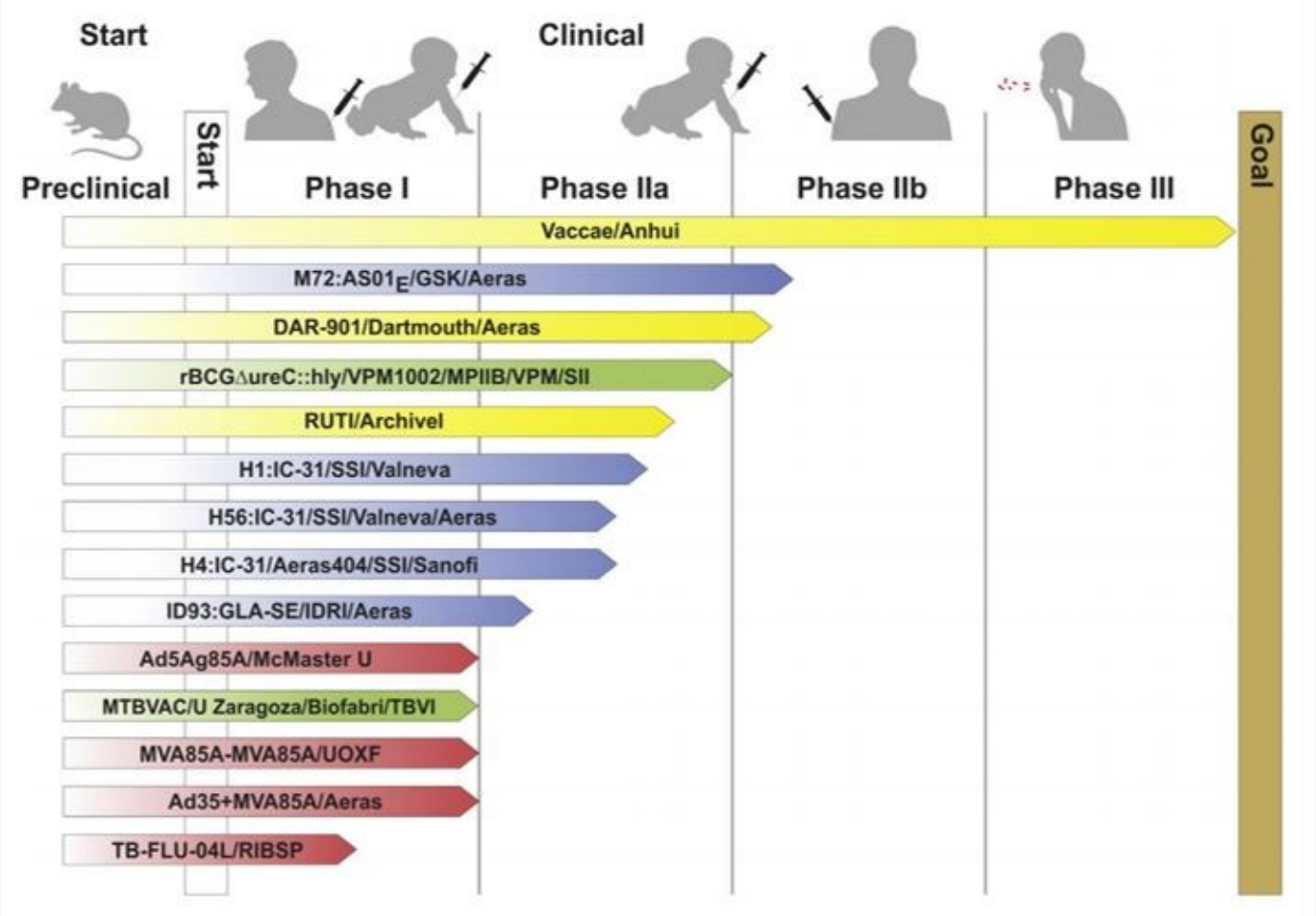

Figure2. TB vaccine candidates that were made into clinical trials [6]

tection at all [8]. While the genomic tools have gave us insight regarding molecular differences, the phenotypic result of this genetic events remains to be determined.

Related to the various efficacy of BCG, several policies related to BCG vaccination have been applied in different countries to increase the BCG efficacy. Globally, BCG is administered to a newborn baby as a single dose, but in several countries BCG revaccination policy for school children or older with negative tuberculin test or negative BCG scar or for higher risk groups is applied [4]. The success story of BCG revaccination came from Hungary, where 4-times BCG revaccination to negative tuberculin children lowered the pulmonary TB incidence from 83/100,000 to 21/100,000 [4]; while in Malawi, Chile, and Brazil BCG revaccination had no effect on TB protection [4]. The different methods between those studies in different countries are thought to be the cause of the variation of BCG protective effect.

Despite the controversy on BCG efficacy, there is also a controversy related to BCG safety. Adverse events due to BCG administration ranged from local reaction up to systemic infection [4]. The famous case related to BCG safety was the Lübeck disaster in 1930 which destroy the belief in BCG administration [9]. The BCG was supplied from Pasteur, prepared at Lübeck laboratory, and administered orally [9]. From 250 vaccinated people, there were 73 deaths, and 135 people were infected but recovered due to the contamination of virulent tubercle bacilli in the Lübeck laboratory [9]. Nowadays, BCG also poses a serious threat in HIV

infected individual since BCG is a live attenuated vaccine. The BCG administration could induce BCG-itis (BCG-osis). This is why several countries postpone BCG administration in this population [4]. This data is supported by study cases in Canada and South Africa where BCG administration leads to death of HIV+ individuals despite the anti-retroviral medication [4].

All those controversies on BCG efficacy and safety raise concern to new TB vaccines development. Several attempts have been made for new TB vaccine development, and some have been tested in clinical trials (Figure2) [6]. Currently, the new TB vaccine candidates are divided into three big groups: preventive pre-exposure vaccines, preventive post-exposure vaccines, and therapeutic vaccines [6]. The preventive vaccines are further divided into three generic types: 1) the subunit vaccines (including viral vectored (e.g MVA85A) and adjuvant-based (AERAS-402/ Crucell Ad35)), 2) viable whole-cell vaccines (VPM1002), and 3) inactivated whole-cell vaccines (SRL172) [6, 10]. The antigens for the pre-exposure vaccines are most likely the antigens that are expressed during the stages of active replication; while for the post-exposure vaccines, the targeted antigens are expressed during latent infection or dormant stage [6]. The ideas of developing therapeutic vaccines, such as Mw (*M indicus pranii*) and RUTI, were to improve treatment outcome in active TB. Stimulation with mycobacterial antigens was hypothesized to enhance immune response and improve bacterial killing in active TB infection. Despite all the rigorous attempt on TB vaccine development, none of them has been licensed to replace BCG due to the lack of compatible animal models in vaccine development and ineffective methods to measure the correlates of protection [10].

In conclusion, although BCG is not an ideal vaccine for preventing TB, but it is still widely used and plays a role to prevent severe forms of TB. Several attempts to increase BCG efficacy and to replace BCG have been made by health policy maker and scientist with diverse results. In the future we hope that there will be new methods or vaccines that are safe and could prevent or eliminate TB infections.

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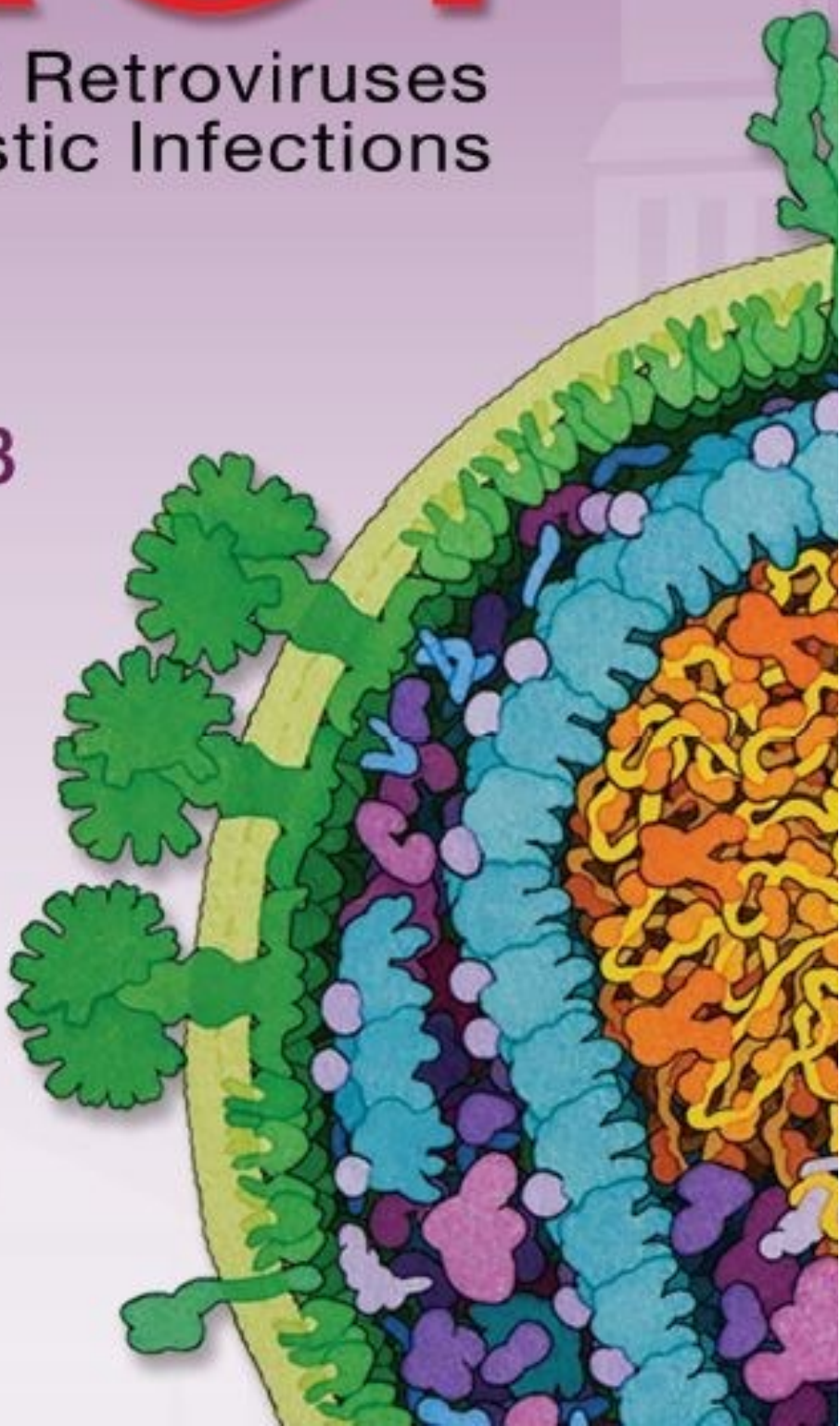

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CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS

BY: DONA ARLINDA & NENENG AINI

THE CONFERENCE

Each year for the past twenty-five years, thousands of HIV scientists gather at the United States–based Conference on Retroviruses and Opportunistic Infections (CROI) to share important scientific findings with their peers. This year's conference, held in Boston on March 4th to 7th, is the 25th anniversary of the CROI. As always, the conference aimed towards better treatment for HIV, as well as finding a cure someday. Three delegates from INA-RESPOND, namely dr. Endang Budi Hastuti (Head of the Sub-directorate of HIV AIDS and STIs of the Ministry of Health of Indonesia), Prof. Dr. dr. Ketut Tuti Parwati Merati, Sp.PD-KPTI (Udayana University) and Ms. Neneng Aini (INA-RESPOND Secretariat) had the opportunity to join the conference.

The year's CROI conference assembled more than 4,000 HIV researchers in Boston, bringing together top basic, translational, and clinical researchers from 76 countries to share the latest studies, important developments, and best research methods in the ongoing battle against HIV/AIDS and related infectious diseases (visit the conference website for abstracts, webcasts, and other materials being released over the conference). The conference' topics range from HIV therapies to issues that intersect with HIV care. This year, CROI also broadened its lens from the lab to different strategies that might have impact to the people's complex lives.

Limiting the Gap Between ARV Prophylaxis and ART Initiation may Limit the Size of HIV Reservoir in Children

At the 2013 CROI, a presentation about the so-called Mississippi Baby spurred worldwide excitement and fanfare. It seemed at the time, an atypically aggressive ARV regimen given to the infant immediately after birth had possibly led to a functional cure of the virus. But the child's HIV ultimately rebounded, raising many important questions about how early treatment may limit the size of the viral reservoir, but not eliminate it.

A new study presented at this year's conference found that starting HIV-positive infants on ARVs very early is indeed associated with the establishment of a smaller reservoir. The researchers' findings also indicate that the wider the gap between prophylactic use of ARVs and the initiation of a traditional ARV regimen in an HIV-confirmed infants is linked to the establishment of a larger reservoir. To view a webcast of the conference presentation, click here.

DTG Versus LPV/r in Second Line (DAWNING): Outcomes by WHO-Recommended NRTI Backbone

DAWNING is a non-inferiority study comparing dolutegravir (DTG) vs lopinavir/ritonavir (LPV/r) when both were combined with 2 nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-1 infected adults failing first-line therapy (HIV-1 RNA ≥400 copies/mL). In DAWNING, response rates were highest in subjects receiving DTG + 2 NRTIs. Furthermore, within each arm, subjects receiving WHO-recommended 2 NRTIs had higher response rates suggesting resistance testing to guide NRTI selection may not be necessary in this population. DAWNING provides important information to help guide second-line treatment decisions in resource-limited settings. To view the abstract, click here.

New TB prevention treatment

In what has been described as a 'game changing' new finding, researchers have discovered that effective tuberculosis (TB) prevention can be delivered in one month. The current preventative treatment being

offered, isoniazid, must be taken every day for nine months, and in high TB/HIV burden countries the World Health Organization recommends that it is taken for 36 months.

A one-month antibiotic regimen to prevent active tuberculosis (TB) disease was at least as safe and effective as the standard nine-month therapy for people living with HIV, according to the results of a large international clinical trial. Adults and adolescents in the trial were more likely to complete the short-course regimen — consisting of daily doses of the antibiotics rifapentine and isoniazid for four weeks—than the standard nine-month regimen of daily isoniazid. This ultra-short course therapy could become an important tool to control HIV -related tuberculosis and has the potential to transform global tuberculosis control efforts. To view the abstract, click here.

Pre-exposure prophylaxis (PrEP)

As PrEP has rolled out across the United States—Gilead Sciences estimates that more than 150,000 people are currently taking it—it has become increasingly apparent that uptake of Truvada as prevention is quite uneven. A collection of studies presented at CROI sought to more clearly identify various disparities in the use of PrEP.

Access to PrEP was woven throughout the CROI program, as data on PrEP programs and use continues to accumulate. Findings from San Francisco and Australia both showed a significant uptick in PrEP use and reduced infections (primarily in men who have sex with men) but across both of the studies racial and ethnic disparities in access remained largely unchanged. A new analysis from the US Centers for Disease Control and Prevention (CDC), also presented at CROI, found that two-thirds of those who could benefit from PrEP are African-American or Latino and yet prescriptions for these populations remain stubbornly low. Gaps in access were seen across racial groups but were most stark among non-white populations. To view the abstract, click here

Looking for future forms of pre-exposure prophylaxis (PrEP), scientists conducted a study in monkeys that showed that a new class of ARV was so effective at a low dose that humans could possibly take just 0.25 milligrams of the drug MK-8591 once a week and still achieve good protection against HIV. By comparison, Truvada (tenofovir disoproxil fumarate/emtricitabine) contains a cumulative 500 mg of ARV medications.

DAPIVIRINE RING

The biggest conference news in the field of so-called biomedical prevention of HIV—using antiretrovirals (ARVs) among HIV-negative individuals to prevent acquisition of the virus—came from a pair of studies that have followed up on previously announced research about the ARV-infused vaginal ring. To view a webcast of the conference presentation, click here.

The dapivirine vaginal ring is a silicone ring containing an antiretroviral that is released slowly over time. It's been designed to be worn by women for around a month. Two years ago, at CROI 2016, the ASPIRE and Ring Study results showed that the dapivirine vaginal ring is safe and reduces the risk of HIV infection by around 30 percent overall among women enrolled in the study. At CROI 2018, interim data from the open-label extension (OLE) trials of the ring—HOPE and DREAM—showed that the ring reduced risk by 50 percent. Final data from HOPE and DREAM, including findings on how well it works in those who use it consistently, will be available in late 2018/early 2019.

The European Medicines Agency (EMA) is reviewing available data on the ring under a framework that allows it to provide regulatory guidance for developing countries. Its decision is expected in late 2018.

PREGNANT AND POST-PARTUM WOMEN NEED HIV PREVENTION

A presentation from Renee Heffron (University of Washington) provided more evidence that pregnant and post-partum women are at increased risk of HIV infection. She and colleagues analyzed data from two studies of over 2,700 serodifferent couples. They found that women who were pregnant or post-partum were 3-4 times more likely to acquire HIV. Implications for care and prevention include counselling, more testing, treatment for male partners and woman-controlled prevention options like oral PrEP. A new HIV infection during pregnancy or postpartum not only has negative consequences for the woman's health, but also carries the risk of perinatal HIV transmission to her fetus or to her new-born through breastfeeding. Better understanding HIV acquisition risk during and after pregnancy is critical to ensuring that women receive the best HIV prevention counseling and tools at all stages of their lives. Read the study abstract ; view the presentation.

Discussions of pregnancy, contraceptives and HIV risk rise as many stakeholders prepare for data from the

ECHO trial. ECHO is looking at three different methods (DMPA, copper IUD and Jadelle implant) to see if any have an impact on women's HIV risk. These data are an essential reminder that HIV risk is driven by many things-including pregnancy. Advocates need to push for PrEP in the ante- and post-natal context, contraceptive choice, programs that diagnose male partners and link them to effective ART-and more. Data and global and national guidelines on the use of oral PrEP (e.g., the WHO technical brief on preventing HIV during pregnancy and breastfeeding in the context of PrEP) and the dapivirine ring for pregnant and post-partum women are essential.

UNDETECTABLE=UNTRANSMITTABLE

In the meeting, conversations about the Undetectable=Untransmittable campaign and its role in reducing stigma were frequent and welcomed. For the first time there was a plenary session on mental health at which presenter Robert Remien (HIV Center for Clinical and Behavioral Studies, Columbia University) called for stepped up mental health services to achieve the 90-90-90 goals.

Pre-treatment HIV Drug Resistance in START Study Using Next Generation Sequencing

In START study, an international trial comparing immediate versus deferred ART initiation among ART-naïve HIV-infected persons with CD4 counts >500 cells/ µL, study entry HIV-1 was characterized by next generation sequencing (NGS); a sensitive assay capable of detecting low-frequency variants associated with pre-treatment HIV-1 drug resistance (PDR). The START trial represents one of the largest global cohorts with NGS characterization of PDR. Overall prevalence of PDR using the ≥2% detection threshold was 19.7% for RT-PR DRMs, while only 8.3% using the 20% threshold and varied by region. INI DRMs were detected in 0.9% of the study cohort primarily as minor variants. NGS would be expected to detect a substantially higher prevalence of PDR than traditional Sanger sequencing, particularly for DRMs occurring predominately as minor variants. To view the abstract, click here

Antiretroviral drug levels in hair strongly predict viral suppression

Antiretroviral drug levels in a sample of hair were the strongest predictor of response to HIV treatment, and this method also holds promise for monitoring adherence to pre-exposure prophylaxis (PrEP). Antiretroviral drug levels in hair samples are a reflection of adherence over time. Drug levels can be measured in blood and in some cases in urine, but this only gives information about levels shortly before testing. Measuring drug levels within cells – where antiretrovirals must reach to be effective – is more complex.

Hair testing avoids the "white coat" effect, in which an individual could take their medication inconsistently but do so before a medical appointment. In addition, hair is easy and cheap to collect and samples can be stored and shipped at room temperature without biohazard precautions. However, hair testing currently must be performed in a lab and cannot be done in "real time" while a patient waits.

The researchers concluded that further study is warranted to see whether early monitoring of hair drug levels, followed by targeted adherence interventions for those with low levels, could help reduce virological failure. View the presentation.

PRODUCTS IN THE PIPELINE

While there was an increased focus on implementation work this CROI, data from early-stage research were also being presented. Among the hundreds of posters and oral abstract presentations a couple stood out including a non-ARV vaginal insert-designed to prevent HIV, HSV-2 and HPV infection-from PopCouncil and the long-acting ARV from Merck (MK-8591) to prevent HIV. Given favorable animal data, both products are being considered for clinical development.

We thank INA-RESPOND Secretariat, especially dr. M. Karyana, M.Kes and NIH-NIAID, for the support and hard work all the way.

"The Doctor will see you now. Here's your medical jargon dictionary."

INA-RESPOND Newsletter

LOST IN TRANSLATION: ARE **YOU** AN ALIEN?

BY: ALY DIANA

Communication between patient and practitioner is essential, but it may not be happening as often as health professionals think it is. We have installed another set of dictionaries containing medical jargon; and through times, unconsciously, we started to speak alien language. Communicating with a different language may lead to miscommunication, and the results of the miscommunication can be benign or disastrous. Ill-informed patients tend to neglect timely or appropriate examination/treatment which can lead to very bad outcomes. In contrast, for patients who understand their conditions/health status, the aims and potential of their treatment are likely to experience superior outcomes.

In the Institute of Medicine (IOM) report on health literacy, as reported by US Department of Health and Human Services, IOM finds that there is a major mismatch between the health information people receive and what they understand. But this lack of understanding is not primarily the fault of individuals receiving the information; nor is it solely the result of poor or limited literacy skills. People can be very well educated and highly literate in their area of expertise, and still not fully understand complex medical information. Virtually everyone has experienced receiving health information about themselves or a loved one that caused confusion and uncertainty. Regardless of one's literacy level, when a healthcare provider uses unfamiliar, technical language or delivers bad news, it is difficult to fully comprehend what is being said, especially when these individuals are made more vulnerable by their poor health.

First thing first: as medical professionals, we need to remember that we are humans before we are aliens. We also need to understand that plain language is not a "dumbing down". Sometimes, we are concerned that using plain language will oversimplify information to the point where it is inaccurate or worthless. However, plain language is not anti-intellectual, unsophisticated, or drab. Plain language is about clear and effective communication—nothing more or less. When we are thinking that communicating with our patients who has low health literacy is really hard, please remember that in the past we communicated in the same way they do now.

The patient-practitioner relationship should be two-way and mutually beneficial. One important shared concept is that people should be able to both understand and use the information presented. A meta-analysis shows that good communication in medical care is highly correlated with better patient adherence, which lead a better success of the treatment. Looking at this fact through the perspective of researchers who conducting and evaluating RCT, when we are seeing a negative result(s) of the treatment due to non-compliance, what do we think we will blame first then?

Closing remarks: There are a lot of useful materials and trainings available to improve our communication skills. We just need to put in some efforts to improve our skills. Hopefully, this article can give us a slight motivation to move in the right direction.

'*The patient will never care how much you know, until they know how much you care.*' (Tongue, et al., 2005).

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INA-RESPOND website: www.ina-respond.net

INA-RESPOND Newsletter

The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

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