INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

INA-RESPOND Secretariat

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Newsletter
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In This Issue

Active Case Finding for TB

Although it can be a real challenge to get rid of TB from the world, medical staffs believe that the vision can be achieved especially after we have made great progress toward this goal in the last quarter of a century. Mortality rate has dropped by 45 percent since 1990, and TB prevalence has been reduced by 41 percent. Since 2000, 37 million people have been cured of TB.

In spite of the great progress we have achieved, there are still so many things to do to eliminate TB as a global health threat. TB still poses great threat among people living with HIV and AIDS and is responsible for approximately one quarter of all HIV-related deaths. So, how can the government and we do to help reduce the number of TB cases? Find out here in this edition.

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Litter-ature or Literature: Decide Before You Start

As researchers, do you know how to write a good literature for your study? Make sure you start with the right foot. Find out what they are here on

Page 4

Save The Date

We have some meetings and events planned up to meet our network's goals. One of the upcoming meetings is the Reference Lab Coordination Meeting (Sepsis). We are also going to hold the Network Steering Committee Meeting this month, where the SC members will discuss important issues related to our network, INA-RESPOND. Here are the dates:

17 March	Reference Lab Coordination Meeting
18 March	Adjudication Meeting (Sepsis Study)
23 - 24 March	Network Steering Committee Meeting

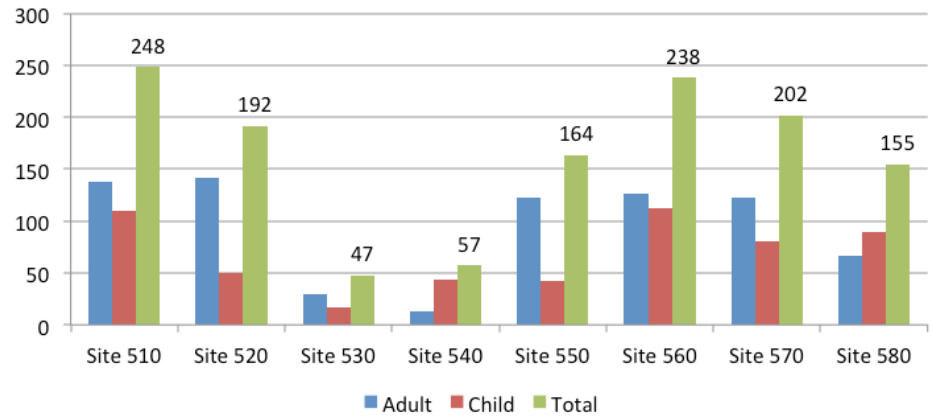
March Birthday

11 Mar	Ms. Eni Yuwarni	NIHRD
20 Mar	Mr. Antonius Pradana	INA-RESPOND Secretariat
24 Mar	Ms. Yayu Nuzulurrahmah	INA-RESPOND Secretariat
27 Mar	Mr. Andi Arahmaniar, Amd, AK	Lab Tech Site 42
28 Mar	dr. Tri Wibawa, Ph.D	INA101 Site PI Site 580
30 Mar	dr. Iman Teguh Badaruzzaman	INA101RA Site 530

INA-RESPOND Study Updates

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

Graph 1. Enrollment progress at each site



AFiRE Study (INA101) Updates

Up to February 22, the study has screened 4,564 patients. 1,303 subjects have been enrolled (759 adults and 545 children). Congratulation to Site Team at Site 510 as the Top recruiter.

The enrollment progress at each site is available in graph 1.

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

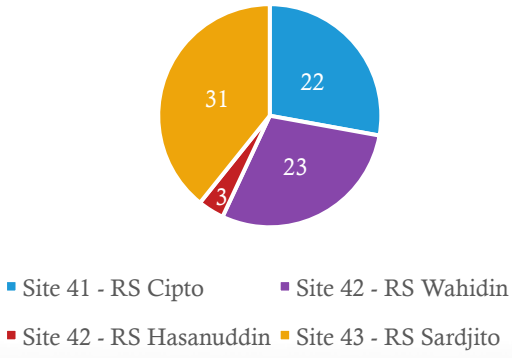
Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: https://ina-respond.s-3.com/EdmFile/getfile/797233

Sepsis Study (SEA050) Updates

Here we are in the 3rd month after enrollment at all sites ended. There were some findings from our Monitors after their Site Close Out Visits last January. One of the main changes is the enrollment number. Unfortunately, there are 3 subjects who are ineligible for the study, consequently they have to be removed from our study and thus **reducing the final enrollment number on December to 79 subjects**. Here is the data of how many subjects were actually diagnosed as severe septic or septic shock:

- 620 patients were screened (391 adults and 229 pediatric).
- A total of 79 subjects (65 adults and 14 pediatrics) were enrolled to the study according to the prior screening number.
- 9 subjects (6 adults and 3 pediatric) were diagnosed as severe septic or septic shock as initial diagnosis.
- 25 subjects (20 adults and 5 pediatric) were diagnosed as severe septic or septic shock as final diagnosis.

Final Enrollment number



Now all sites from Indonesia, Thailand, and Viet Nam are busy with data cleaning process. The data will be used for manuscript writing. For Indonesia, the data cleaning process has finished, and we are waiting for release of Data Transfer Agreement document before we can go ahead.

Cartoon Corner Litter-ature vs Literature: Decide before We Start

By:

dr. Aly Diana

Most researchers usually start their studies with some big goals in mind: to share the results to the government in order to improve policy, to fellow researchers to enrich knowledge, or to community to increase their quality of life to some extends. However, the ugly truth is the results may not even see the shed of light; and end up as a litter-ature and not a literature.

To produce a high quality literature is not only about writing it perfectly, but also about putting a strong foundation on every step of it, including the study design and data collection process. Once the method went wrong or data collection was done without following the protocol, the researchers no longer have any chance/rights to produce a publication out of the results. Violation to the protocol means that your final works can hardly be trusted.

No matter how senior we are or how much experiences we have, planning the study carefully is a key factor to success. We need to define our main objectives clearly and not be swayed away by too many unfocused and minor objectives. Select the samples based on necessity by considering the benefits and disadvantages of each sampling method; and the risks that may occur to the subjects. Develop a clear protocol and make sure that everybody involved in the study following it strictly. Do a proper training for enumerators/ data collector, and check whether the inter- and intra-examiner technical errors are between the acceptable limits. Use valid and reliable measurement tools and calibrate the equipment regularly. Avoid bias in every way that we could and make sure that we collect the highest quality data possible.

Please bear in mind that there is no statistical procedure that can safe our data from their flaws, once they were collected in a bad manner. If we follow the protocol that we have been developed cautiously, then we have the rights to publish the results and pursue our big goals. The last step is writing the study well and then share it through policy brief, article in journals, news, or other mass-media communications.

This may sound very simple, and many of you most likely have done it through the years. Unfortunately, people still make mistakes and forget about details quite easily. Therefore, we hope that this can be a sweet reminder that a good publication is not only decided by our ability to write about our study, but also depends on how we have started and accomplished it. Hopefully, all of our studies will end as the LITERATURE and give benefits to our communities.

Active Case Finding to Eradicate TB

By
Dr. Retna Mustika Indah

March 24 is chosen as World TB Day to commemorate the date when Robert Koch announced his discovery of *Mycobacterium tuberculosis.* "Unite to End TB" has been selected as the theme for 2016 TB day. This is in accordance with a resolution passed by the WHO in May 2014 to fully support post-2015 Global TB strategy targets. The strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and to reduce new cases by 90% between 2015 and 2035, as well as to ensure that no family is burdened with catastrophic expenses due to TB. Unite means that all sectors such as governments, affected communities, civil society organizations, health-care providers, and international partners join together to roll out this End TB strategy and to reach, treat, and cure all those who are ill.

Indonesia as the second country in the world with the highest TB incidence has been fighting TB for many years. A comprehensive approach is needed to end TB in high burden country such as Indonesia. Salman Keshavjee from Department of Global Health, Harvard Medical School said that we could still use the comprehensive approach we have already had to get much closer to zero death of TB than we are today. In his opinion, the methods for controlling TB by active case finding, treatment of latent disease, treatment of all disease form, and patient support should be fully implemented in low-income country. Like many other developing countries, the focus of TB control strategy in Indonesia is more on diagnosis and treatment by passive case finding. However, the policy on TB case finding is about to be shifted to a more aggressive one i.e. active case finding. This is reflected on the national theme of

(continued)

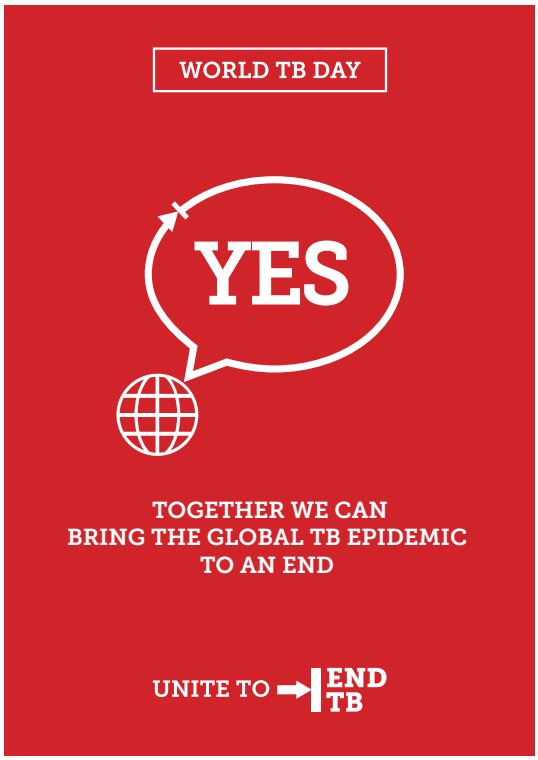
TAKE ACTION:

GOVERNMENT

MUST CONTINUE TO RAMP UP EFFORTS TO IMPROVE THE QUALITY OF DIAGNOSIS, CARE, AND TREATMENT OF TB TO PREVENT THE DEVELOPMENT OF DR-TB, AND DEVELOP NEW TOOLS TO ADDRESS THIS DEADLY EPIDEMIC

EVERYONE

MAKES SURE YOUR FRIENDS AND FAMILY MEMBERS WHO ARE UNDERGOING TB TREATMENT COMPLETE THEIR MEDICATION TO PREVENT THE DEVELOPMENT OF DRUG RESISTANCE.



2016 TB day "*Gerakan Keluarga Menuju Indonesia Bebas TB melalui aksi gerakan TOSS TB (Temukan dan Obati TB Sampai Sembuh)*" (family movement towards TB-free Indonesia through case finding and treating the patients until they are cured).

Finding individuals with TB and promptly initiating the correct treatment are crucial to stopping the transmission. Trying to eliminate TB without stopping the transmission would be like trying to empty a basin full of water without first turning off the tap that fills it. Active case finding is the provider initiated pathway to TB diagnosis. It requires systematic screening and clinical evaluation of persons who are at high risk of developing TB. One of the active case finding strategies is by targeting TB high-risk groups which may vary between different settings (Table 1). Thus, identifying the TB high risk groups within a particular setting is a useful prerequisite to the active case finding activities. People who are contacts of someone who was diagnosed with TB or people living with HIV are the high risk groups that should always be screened for active TB in all settings.

The effectiveness of active case finding in TB patients with limited access to DOTS facilities has been tested with a mathematical model which highlighted the potential. One example to overcome limited access in Indonesia is by involving private health providers to refer suspected TB patients to DOTS facilities. However, this intervention is difficult to be seen in reality since most TB cases from private health providers have not been reported yet. Other interventions to improve access to TB care might be needed.

The acceptability of screening for TB is another issue that needs to be addressed carefully for active case finding to work. The WHO conducted a qualitative assessment of the evidence on the acceptability of screening for TB. The results suggested that acceptability is influenced by several factors, which includes the screening test used, particularly whether it is invasive or noninvasive; the time required for the test and follow-up visit; the perceived negative consequences of screening (such as, legal, social, political and economic consequences); the incentives offered; the quality of the interaction with the person doing the screening; and the number of times screening is repeated.

To make sure that active case finding activities can be implemented, health care facilities as well as the human resources must be prepared to serve this program. It is important to have a separate and

Tuberculosis Risk Groups	
Community	Geographical areas with a high prevalence and subpopulations with poor access (poor populations, urban slums, remote areas, refugees, homeless, etc.)
Hospital outpatient and inpatient departments, and primary health-care cantres	People previously treated for TB People with untreated fibrotic lesion People living with HIV and people attending HIV testing People with diabetes melitus People with chronic respiratory disease and smokers Undernourished People with gastrectomy or jenjunoileal bypass People with alcohol- or drug-use disorder People with chronic renal failure People with immunocompromising treatments Elderly people People in mental health clinics or institutions
Residential institutions	Prisoners and prison staff People residing in shelters Other congregate settings (such as the military)
Immigration and refugee services	Immigrants from settings with a high prevalence of TB People in refugee camps
Workplaces	Health-care workers Miners or others who are exposed to silica Other workplaces with a high prevalence of TB

Table 1. Tuberculosis risk groups *with*in different settings
(Source: WHO Factsheet, 2013)

well-ventilated area to screen individuals with TB symptoms to protect them from nosocomial infection and to prevent the transmission to other populations. The health-care workers involved in this program should protect themselves from the infection and be checked/screened regularly for TB. When screening activity is held outside health-care facility such as in remote areas with difficult access, it is important to ensure that the individuals suspected of having TB can present themselves to the appropriate health-care facility for a confirmatory TB diagnosis and prompt treatment.

Another essential issue is making sure that TB diagnostic tool with sufficient sensitivity and specificity is readily available for screening activity. Some centers in Indonesia already have Xpert MTB/Rif to detect *Mycobacterium tuberculosis* (MTB). However, many centers still rely on sputum smear microscopy, which has several limitations. We urgently need rapid diagnostic tests with greater sensitivity than conventional method i.e sputum smear microscopy, chest X-rays, etc, which can also be used to identify drug resistance. The delay to detect drug resistant TB can result in inadequate treatment that might prolong both illness and infectiousness.

Addressing the above-mentioned issues needs to be made national priorities in TB control strategies. We need to involve private health provider in reporting and referring TB cases to the appropriate TB centers, in order for the patient to get proper care. Family and community support to remove the stigmatization of TB patients should be improved by efforts to explain TB disease through mass media campaign. TB day celebration is a suitable event to ask more people to join and care more about TB by providing free screening and early detection of TB at strategic public facilities or local events. Hopefully, this will be a good step towards TB-free Indonesia.

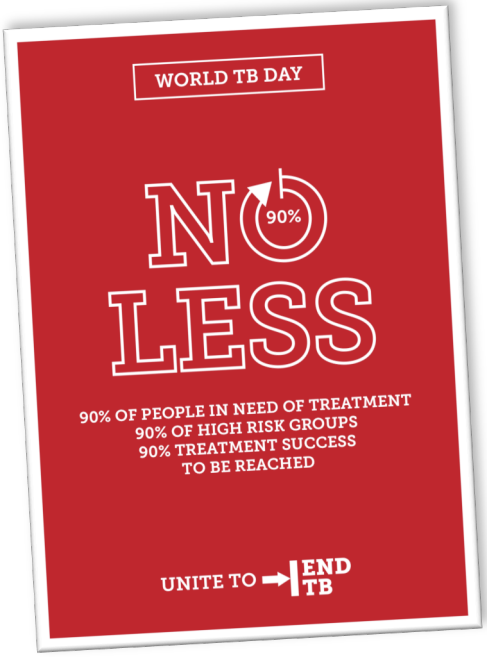
Selected references:

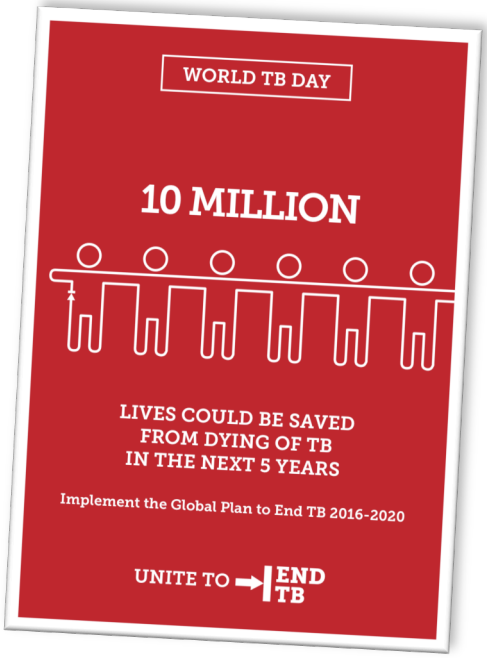
1. WHO. Systematic screening for active tuberculosis - Principles and recommendations. Geneva: World Health Organization; 2013.

2. WHO. Improving early detection of active TB through systematic screening. Geneva: World Health Organization; 2013.

3. Watts G. Salmaan Keshavjee: tackling tuberculosis (without rocket science). Lancet 2015;386:2247.

4. Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. Lancet 2015;386:2334-43.





Site Closeout Visits

By
Ms. Mila Erastuti
Ms. Neneng Aini

With the sepsis study closing at the end of December 2015, the INA-RESPOND monitors have quickly conducted the site closeout visits (SCV) to meet the timelines for data analysis which is currently underway. With the AFIRE (INA101) study closing at the end of June 2016, we thought it would be a good time to review the SCV processes. Per the INA-RESPOND standard operating procedures, SCVs are scheduled at a clinical study site once subjects are no longer being enrolled, enrolled subjects are no longer receiving investigational product (IP) and/or have completed the study, all clinical study procedures and follow-up have ceased, and all required clinical study data collection is complete. In some cases when subject follow-up is ongoing for an unexpected event (e.g., serious adverse event that occurred earlier in the study but is not resolved), exceptions may be made and the SCV could be conducted before all follow-up is completed and before the site is in a position to close with their IRB.

A SCV generally is the last visit to the clinical study site for a specific study. The SCV may occur under any of the following circumstances: The principal investigator (PI) has completed the clinical study in accordance with the protocol, the study sponsor and/or client (heretofore referred to as "sponsor") has decided to terminate the clinical study for all PIs involved, the sponsor, the Contract Research Organization (CRO) in consultation with the sponsor, or the institutional review board/independent ethics committee (IRB/IEC) has decided to terminate a PI from participating in the clinical study or the PI has decided to terminate participating in the clinical study.

Usually, at this point in the conduct of the study, the site's contributions to data collection are over so the monitor returns for one final visit to close out the study at the site. The whole concept behind a SCV is to ensure that everything is "neat and tidy" at the study site. This means the documentation from the study is well organized and will remain intact and accessible if needed in the future for additional research related questions or regulatory requirements.

Once the clinical study data collection is complete and the SCV can be scheduled, the monitor contacts the site staff to arrange a mutually convenient date and time, when the PI is available, to conduct the study close out visit. It is important for the PI to meet with the monitor during the SCV. In preparation for the SCV, the PI needs to ensure that all regulatory documentation and case report forms are complete and available for review, ensure that all data queries received to date have been resolved to the extent possible, ensure that the

appropriate patient medical records, including all laboratory results, needed to verify study data will be available for review at the time of the SCV, inform the Pharmacy, if applicable, of the scheduled visit so that the study drug can be inventoried and drug accountability records can be completed.

During an SCV, the monitor is responsible for final review and verification that the PI's obligations have been met and that all applicable clinical study and regulatory requirements have been fulfilled at the conclusion of the study. The following components, as applicable, are reviewed during the SCV to ensure that all remaining issues are brought to an acceptable resolution. The PIs obligations, clinical study site personnel remaining at the end of the study, and continued adequacy of facilities. The monitor verifies that the Authorized Signature and Delegation Log has been completed in its entirety (to document all delegated duties, with all required printed names, initials, and dates) and asks the PI to provide the final signature and date on the form. The Monitor also verifies the PI understands their regulatory obligations and records retention requirements, the process for audit or inspection notification, source document data verification and case report form review, investigational product and clinical study supplies disposition, project-specific requirements and any serious and/or continuing noncompliance with the protocol or Good Clinical Practice (GCP) standards will be documented as Protocol Deviations or Violations.

After completion of a SCV, the monitor will sum up the findings from the visit in a SCV Report and Follow-up letter. This will include a summary of the monitor's activities and findings during the visit, including significant items reviewed and discussed during the visit and any actions that require follow-up.

Monitors from INA-RESPOND Secretariat have conducted the SCVs for SEA050 sepsis study in January 2016 at three sites including: RSUPN dr. Cipto Mangunkusumo, RSUP dr. Wahidin Sudirohusodo, and RSUP dr. Sardjito. The PIs and clinical study site personnel were very cooperative to ensure all study requirements were fulfilled. The Clinical Research Site Specialist (CRSS) team from INA-RESPOND Secretariat are actively following-up with the PI and clinical study site personnel to ensure all action items are completed and resolved. If you have any questions about SCVs you may contact one of the INA-RESPOND monitors.

INA-RESPOND Newsletter

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Thanks to : INA-RESPOND Network and Partners

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