INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

July 2020

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NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
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2020

INA-RESPOND newsletter

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FEATURES

INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, M. Ikhsan Jufri, Venty Muliana Sari

STUDY UPDATES

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PARTICIPANT STATUS

Per 30 Jun 2020, the total ongoing participants in the TRIPOD study are 34 out of 490 enrolled participants. From those 34 ongoing participants, 16 are still on TB treatment while 18 are waiting for a 6-month post-treatment visit. Two hundred and twenty-two participants have completed the study, while 234 participants are terminated early (including death). Therefore, there are still 6.9% of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participant from site 520 and 570 have been completed the study, while there are 1 participant from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar) who still need to be followed up, 20 participants from site 560 (RSUP dr. Kariadi Semarang), 6 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 6 participants from site 590 (RSUP Persahabatan Jakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

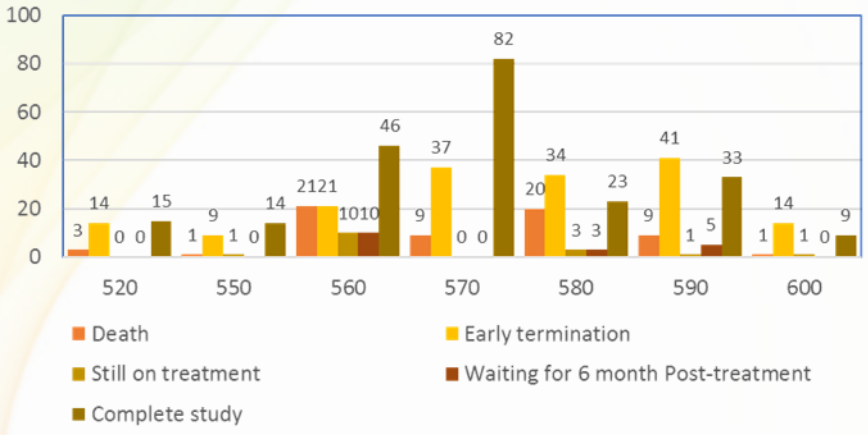

Figure 1.Participant status per site based on uploaded CRF per 30 June 2020

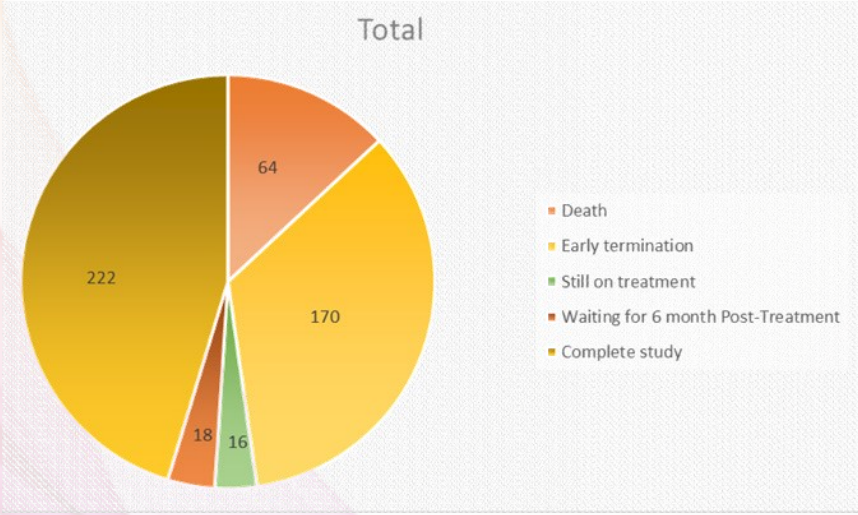

Figure 2. Total participant status based on uploaded CRF per 30 June 2020

RiCC Annual Meeting

RePORT International Coordinating Center Update (RICC) is calling for Young Investigators Abstract that will be shared on RiCC Annual Virtual Meeting, 28-30th September 2020.

All Research assistants in INA-RESPOND expected to submit the abstract not later than 30 Jul 2020, and the result will be notified to participants by the end of August 2020.

Guidelines and requirements for the submission have been shared by site specialists through email, and abstracts need to be reviewed and signed off by the respective Principal Investigators before submission.

Due to the pandemic situation, this event will be held virtually. However, if there will be an in-person meeting in the future (early 2021), the competitive abstract winners will likely have support to travel to the meeting, depending on the availability of funds.

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Currently, the screening, enrollment, and follow up activity of INA-PROACTIVE study are still on halted until further notice. However, to avoid any missed visit for the subject who have reached maximum window period or the subject who might have difficulties to go to the site caused by PSBB (large scale social restriction), the site may continue to arrange subject follow up with prioritizing safety and following the coronavirus disease prevention and control protocol.

Furthermore, the three last activated sites have finished their enrollment period on 30 Jun 2020, which are site 520 (Sanglah Hospital in Bali), site 700 (TC Hillers Hospital in Maumere), and site 690 (Abepura Hospital). As of 30 Jun, a total of 4,336 subjects was enrolled, which consisted of 4,148 adults and 188 pediatrics from a total of 7,364 subjects screened. Details are shown in figure 1. below:

Total Screened and Enrolled subjects:

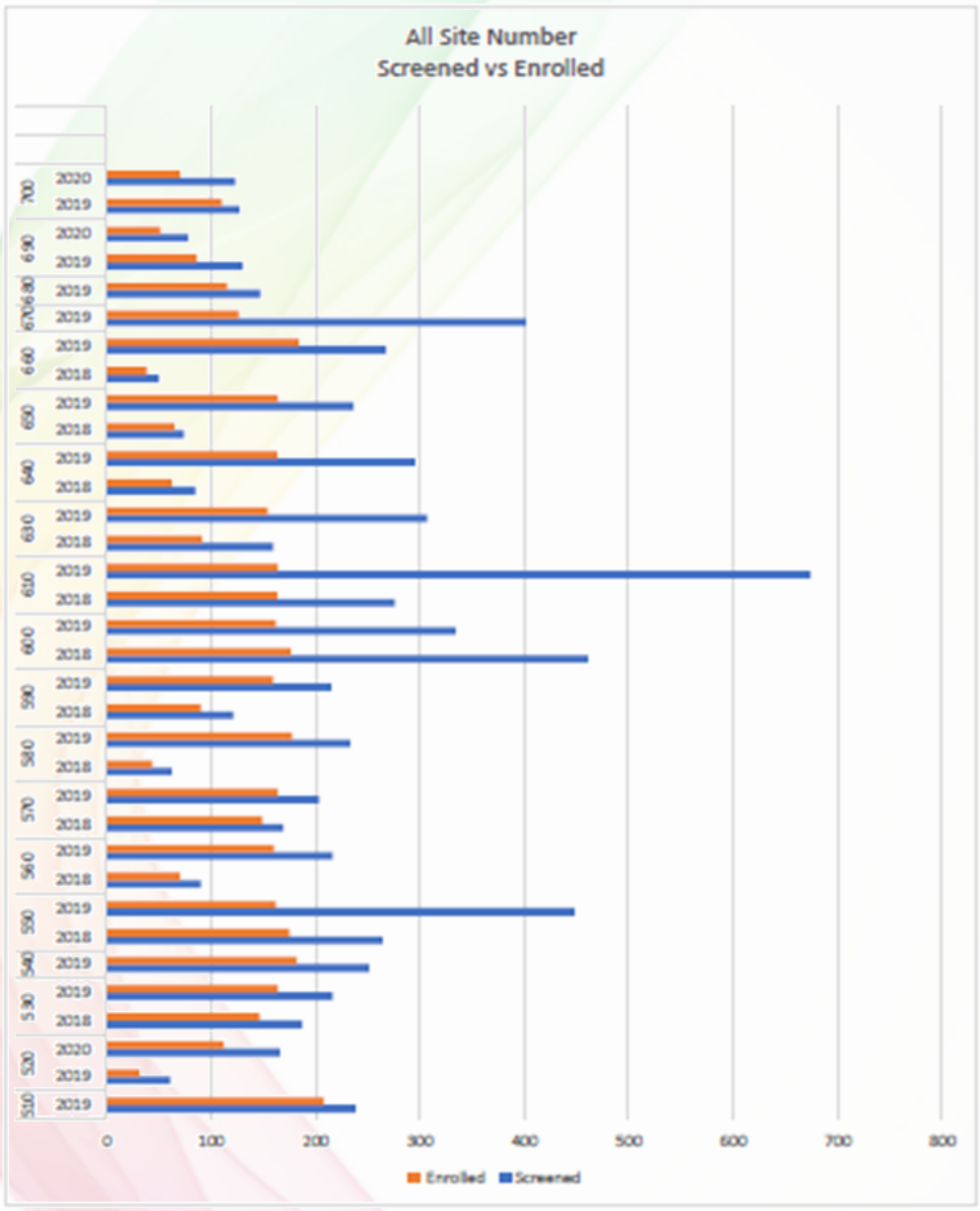


Figure 1. All Site Number Screened vs Enrolled

During the enrollment and follow up halt, some sites are working on completion of study data such as missing logs, syntax data, and study disposition status. Meanwhile, remote monitoring is still being conducted. The remote monitoring that was completed in June is for Site 650 (Budi Kemuliaan Hospital, Batam) on 22-24 Jun 2020, following by Site 600 (Adam Malik Hospital) on 25-26 Jun 2020 and Site 640 (St. Carolus Hospital) on 29-30 Jun 2020. For the sites which have been monitored remotely, the sites will work on the monitoring action item resolution.

During July, the 3rd SMV was conducted for Site 540 on July 21-22, 2020. In August, the 3rd Remote SMV for Site 510 was planned for August 12-13, 2020.

INA-RESPOND Newsletter

SITE PROFILE: RSUD. DR. ZAINOEL ABIDIN

By: Muhammad Abrar Azhar

From bottom left:
Mr.Muslim, dr. Mulya Safri, dr. Kurnia F. Jamil, dr. Hafni, dr. Vivi Keumala, Mrs.Arfajah, dr. Abrar, Ms. Lia, Mrs. Vera, Mrs. Nurul, Mr. Ikhsan

RSUD dr. Zainoel Abidin is a general hospital in Aceh Province and an educational hospital for medical students of Universitas Syiah Kuala (FK-Unsyiah). It survived the 2004 Indian ocean earthquake and tsunami but severely damaged. The province's biggest hospital took almost five years to revive its operation normally after the rehabilitation and reconstruction finished in Januari 2010 with the cooperation between Indonesian and Germany government.

The hospital, known as site 670, officially joined PROACTIVE as the site's first INA-RESPOND Study in April 2019. The Principle Investigator of Site 670, Dr. dr. Kurnia F. Jamil, Sp.PD-KPTI wishes to have sustainable innovative and collaborative INA-RESPOND Research on the site.

Principal Investigator:

Dr. dr. Kurnia F. Jamil, M.Kes, Sp.PD-KPTI, FINASIM

Known as a valuable and respected expert in the site, he is a conceptual and robust lecturer in the Faculty of Medicine of Syiah Kuala University. His experience as a researcher in the Eijkman Molecular Biology Institute and the number of his research publications made him trusted as the Head of the Doctoral Program (Ph.D.) of the Faculty. As a Senior Consultant of Infectious and Tropical Disease in RSUD dr. Zainoel Abidin, he also chairs the Indonesian Association of Tropical Disease and Infection Researchers Association (PETRI Chapter Aceh). He held several important positions in the Regional Organization due to the breadth of his networking such as the Chairperson of the Alumni of the Universitas Indonesia (ILUNI UI Chapter Aceh), Chair of the Health Department in the Indonesian Red Crescent (PMI Aceh) and Chair of the Indonesian Society of Infection Control (PERDALIN Aceh).

Co-Principal Investigator:

Dr. dr. Mulya Safri, M.Kes., Sp.A(K)

Dr. Mulya Safri is a Senior Lecturer in the Faculty of Medicine Universitas Syiah Kuala and a Paediatrician in Zainoel Abidin General Hospital. His excellency in providing high-quality care has lead team members to believe that the goals or objectives of medical care are unattainable without examples of attitudes. Since 2007, He has been a pediatrician consultant in allergy and immunology in the hospital, and the Head of the Paediatric Residency Program of The Faculty since 2010.

Co-Principal Investigator:

Dr. Vivi Keumala Mutiawati, M.Kes, Sp.PK

Dr. Vivi Keumala Mutiawati is a Lecturer and an Education Coordinator in the Faculty of Medicine of Universitas Syiah Kuala and Clinical Pathologist in Zainoel Abidin Hospital. She pays attention to the details and develops the team to focus on quality and performance improvement by strengthens the team's ability to prepare the samples, operating the devices, and reviewing the laboratory results. Thus, the team can make a conscious effort to understand causes instead of just the results. Since 2014 she's been trusted as an internal and external quality coordinator of the Hospital and Chairs the regional association of clinical pathology specialists (PDS PatKlin Banda Aceh) since 2017. Her research interest and the number of journal publications have led her to be speakers in several regional and national symposiums.

Research Assistants

RA 1: Dr. Hafni Cia Masyithah

Born on September 22, 1990, dr. Hafni, a.k.a. dr. Cia, is the first RA of Site 670. Her full dedication to the study leads her to be the most favorite RA for our patients to confide, 24 hours a day. She loves cats, cooking, and gardening.

RA 2: Dr. Muhammad Abrar Azhar

Born on July 29, 1991, dr. Abrar has joined several poster competitions and oral presentations in regional dan national scientific events. The PROACTIVE study is his first experience in multicenter research.

RA 3: Dr. Ika Novita

Born December 26, 1991, dr. Ika is the 3rd RA of Site 670. Despite joining the team at the latest, Dr.ika is the most energetic and uplifting Research Assistant of Site 670.

Research Nurse: Arfajah, SKM, SST

Mrs. Arfajah, usually Called "Kak Ar," is an amiable and humble person to the staff and patients. As the Head of the VCT since 2010, she can remember all the patients, thus with her help, RA can gain the trust from patients since the first approach.

Laboratory Technician 1: Muslim A.Md.Ak

Mr. Muslim, is an expert on Laboratory Testing for HIV since 2008. His experience has made sure the team that the patients will be treated in private and confidential.

Laboratory Technician 2: Nurul Husna A.Md,Ak

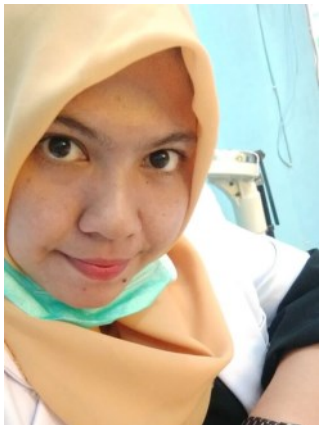
Mrs. Nurul is a fast learner, adaptable with new programs and devices, and a calm technician. She starts and finishes her job full of commitment and enthusiasm.

Site Administrator: Chairun Nisyah, A.Md

Ms. Chairun Nisyah was born on November 15, 1994. She is usually called "Icha." She is a highly trained and skilled lady. Her working experience in a private bank and an insurance company made her accustomed to a bunch of documents. As the "women behind the scenes," she tidies the files calmly and is still able to smile at the end of every day, awesome!









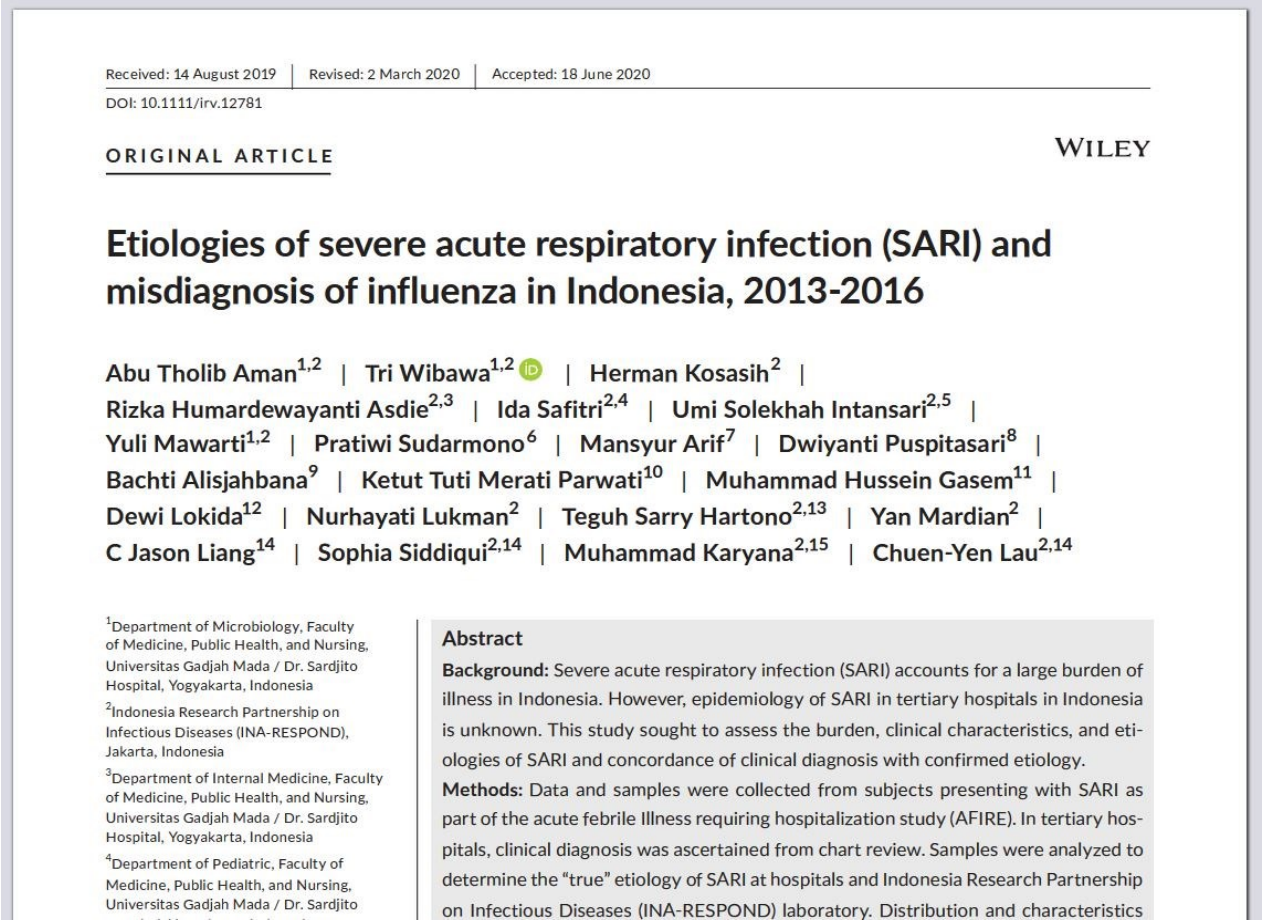

From top to bottom, left to right:

dr. Kurnia F. Jamil, dr. Mulya Safri, dr. Hafni Cia Masyithah, dr. Vivi Keumala Mutiawati, dr. Ika Novita, dr. M. Abrar Azhar, Ms. Arfajah, Mr. Muslim, Ms. Nurul Husna, Ms. Chairun Nisyah

INA-RESPOND Newsletter

BEAUTIFUL JOURNEY TO THE PUBLICATION OF "SEVERE ACUTE RESPIRATORY ILLNESS" (SARI)

By: Yuli Mawarti



Received: 14 August 2019 | Revised: 2 March 2020 | Accepted: 18 June 2020
DOI: 10.1111/irv.12781

ORIGINAL ARTICLE

WILEY

Etiologies of severe acute respiratory infection (SARI) and misdiagnosis of influenza in Indonesia, 2013-2016

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[2]Indonesia Research Partnership on Infectious Diseases (INA-RESPOND), Jakarta, Indonesia

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[4]Department of Pediatric, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada / Dr. Sardjito

Abstract

Background: Severe acute respiratory infection (SARI) accounts for a large burden of illness in Indonesia. However, epidemiology of SARI in tertiary hospitals in Indonesia is unknown. This study sought to assess the burden, clinical characteristics, and etiologies of SARI and concordance of clinical diagnosis with confirmed etiology.

Methods: Data and samples were collected from subjects presenting with SARI as part of the acute febrile Illness requiring hospitalization study (AFIRE). In tertiary hospitals, clinical diagnosis was ascertained from chart review. Samples were analyzed to determine the "true" etiology of SARI at hospitals and Indonesia Research Partnership on Infectious Diseases (INA-RESPOND) laboratory. Distribution and characteristics

SARI is one of INA-RESPOND's publications written by the INA-RESPOND team from site 580, Yogyakarta, with the support of INA-RESPOND's Secretariat and Steering Committee. It has been an honor for me to be part of the team. This paper was submitted to Influenza and Other Respiratory Viruses in August 2019 and was accepted on 18 July 2020. However, it took a long time to come to this point. It has been seven years since the first enrolment in mid-August of 2013. In the first two weeks of screening, we stayed in until late at night, and we did not get any patients to be enrolled. The AFIRE / INA101 study has strict enrolment criteria. My fellow Research Assistant and I sat in the hospital's alley, watching the nurses taking patients away from the emergency room of Sardjito hospital until they were gone from our sight. We felt desperate and lost at first, but we were able to observe and learn the flow and pattern of patients in the hospital. We realized that we had to be more patient, and this publication is proof of that.

SARI is a paper that describes a subpopulation of subjects with respiratory symptoms from the AFIRE study, which recruited hospitalized patients with acute fever, no prior hospitalization within the last three months, and no previous invasive medical intervention. The paper elaborated on the burden, clinical characteristics, and etiology of SARI, as well as the concordance of clinical diagnosis with confirmed etiology. The main finding was that influenza accounted for 12.1% of SARI patients, but it was

never diagnosed in this group. During their hospitalization, influenza was misdiagnosed as other diseases, in the setting of tertiary hospitals. The study showed that 28.7% of the total of 1,464 AFIRE subjects presented with SARI.

In the 420 subjects who presented with SARI, only 242 (57.6%) subjects' etiology was confirmed, including 121 (28.8%) viruses and bacteria associated with systemic infections, 70(16.7%) respiratory bacteria and viruses other than influenza virus, and 51 (12.1%) influenza virus cases. This publication highlighted that none of the Influenza patients were accurately diagnosed as having influenza during hospitalization. These findings are beneficial for developing public health strategies to address the high burden of influenza and improving the diagnosis capacity of hospitals in Indonesia. This paper also suggested that clinical practice should be guided by known epidemiology of the related diseases in Indonesia. Implementation of SARI criteria in a hospital setting and other health care facilities would help clinicians and epidemiologists in effectively and systematically screen the population who might be infected with Influenza viruses.

SARI is a simple approach defined by the WHO in 2011 for global surveillance. SARI definition has been revised to be more implementable by dropping "shortness of breath" and "breathing difficulty" and adding a "history of fever" and increasing the onset of symptoms to 10 days. SARI is now defined as an acute respiratory illness with a history of fever or measured fever of ≥38°C and cough, with onset within the past ten days and requiring hospitalization. The approach has surprisingly filtered subjects who were clinically diagnosed as having non-respiratory diseases along with those who were diagnosed with respiratory diseases at discharge. It gave a picture that patients were often misdiagnosed in tertiary hospitals in Indonesia. Influenza viruses and other respiratory pathogens were confirmed to be the etiologies of some cases from the group of subjects who were clinically diagnosed as having non-respiratory diseases at discharge.

On the other hand, we found that subjects who presented with SARI and were clinically diagnosed as having respiratory disease had etiology, which commonly not considered to be the culprit of respiratory diseases. We identified pathogens such as Leptospira, Dengue viruses, Chikungunya viruses, and Salmonella that caused diseases with respiratory symptoms. The SARI approach should also be useful to screen emerging diseases, such as severe acute respiratory syndromes (SARS) or other emerging novel pathogens.

The paper showed that various and multiple diagnostic tools were used for establishing a diagnosis, but still, the etiology of 42.4% of SARI subjects were unknown. This finding hints at the urgent demand for improving clinical guidelines, the support for point-of-care tests, and the refining of laboratory diagnostic capacity in Indonesia.

For further information about this article, please read the original article at https://doi.org/10.1111/irv.12781 or https://onlinelibrary.wiley.com/doi/10.1111/irv.12781

INA-RESPOND Newsletter

WELCOMING NEW LEIDOS COLLEAGUES

By: Amelia Hayward, Jayda Jones, and Katie Watkins

Please join Leidos Biomedical Research and NIAID in welcoming two new team members who will be supporting the INA-RESPOND network: Amelia Hayward, MPH, and Jayda Jones, MPH, MBA.

Amelia Hayward was born and raised in the Lowcountry of coastal South Carolina. She attended Emory University for her undergraduate studies, completing her Bachelor of Science in Neuroscience and Behavioral Biology with a minor in German Studies in 2015. She then graduated from Emory University's Rollins School of Public with her Master of Public Health in Behavioral Sciences and Health Education in 2017. Her public health interests include social determinants of health, health disparities and inequities, and social epidemiology.

Amelia is the newest Senior Program Coordinator for the Collaborative Clinical Research Branch (CCRB), Division of Clinical Research, NIAID, and will be providing administrative and programmatic support to the NIAID team for their collaboration with the Secretariat. She is most excited about how she can assist in contributing to the enhancement of Indonesia's clinical research infrastructure. Currently, her focus is understanding as much as she can about INA-RESPOND in hopes that she may expand in her auxiliary role and can help in other facets of this collaboration beyond her duties and capabilities now. She is very much looking forward to working with everyone on the team.

Jayda Jones, a Louisiana native, attended the Xavier University of Louisiana, where she completed her Bachelor of Science in Chemistry with a minor in Biology. She then completed her Master of Public Health in Epidemiology and Master of Business Administration in 2010 and 2016, respectively from Tulane University. She has over ten years of clinical research experience serving in numerous capacities. Jayda has served as a Clinical Research Coordinator at Tulane University and Ochsner Medical Center, focusing on public health, pulmonary, infectious disease, and reproductive health research. Prior to joining Leidos Biomedical

Research, Jayda served as a clinical project manager at the Henry M. Jackson Foundation in support of Walter Reed Army Institute of Research's Emerging Infectious Disease Branch. In this capacity, she managed Phase I-II infectious disease clinical trials and bio-surveillance protocols in East and West Africa.

Jayda joins the team as a Clinical Project Manager I for the CCRB and will be providing clinical operations support to the NIAID team. She is most excited about working with the team at INA- RESPOND, learning about their infrastructure and contributing to the growth and success of clinical research in Indonesia.

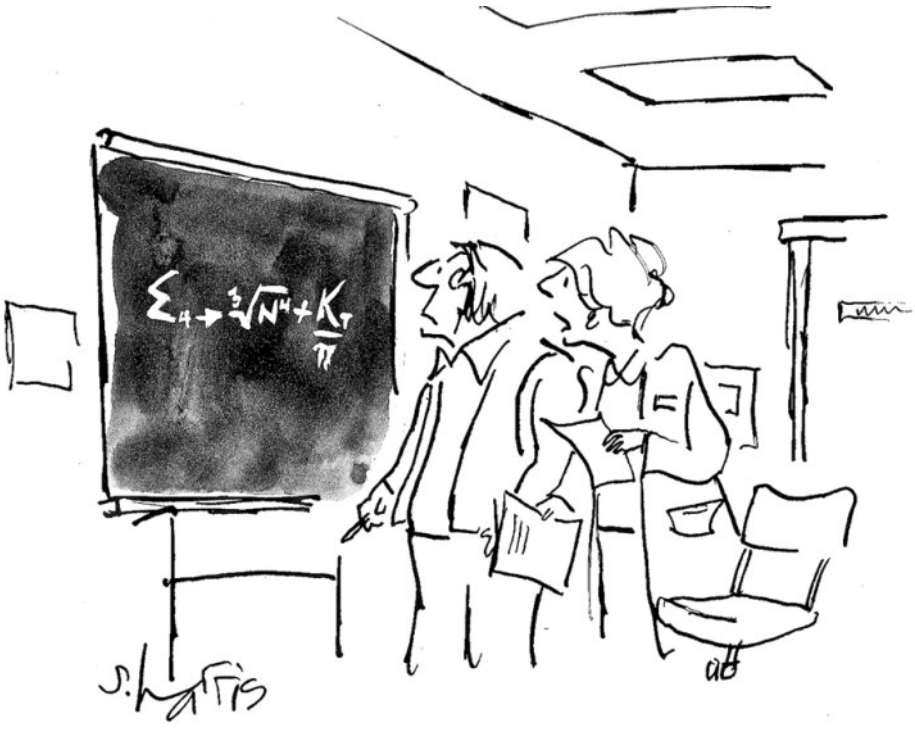
We are very excited to have Amelia and Jayda on the team!

INA-RESPOND Newsletter

THE ARTS OF INTENTION TO TREAT AND PER-PROTOCOL ANALYSIS

By: Aly Diana

COMIC CORNER



When we are conducting a clinical trial, it is not uncommon to have protocol violations or an inability to assess intended outcomes. These "protocol violations" can be of various types: 1) subjects do not receive the assigned treatment, 2) subjects receive the wrong treatment assignment, 3) subjects die before treatment is given, 4) subjects do not adhere to or comply with the study protocol, or drop out of the study. One potential solution to this problem is a statistical concept called intention -to-treat (ITT) analysis. ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores non-compliance, protocol deviations, withdrawal, and anything that happens after randomization.

However, during the analysis of the trial results, some researcher is tempted to exclude such "nonconforming" participants, which called per-protocol analysis. The motivation is to ensure that comparisons are made between those participants in each trial arm who strictly adhered to the planned treatment so that the true EFFICACY of one intervention over the other can be assessed.

However, such exclusion poses multiple problems, such as:

It violates the principle of randomization. In a 2-arm study, randomization ensures comparability of the two groups, i.e., balanced for known and unknown confounders or prognostic factors. When some participants in either or both groups are excluded, the remaining participants in the two groups can no longer be considered as balanced.

At times, the non-compliance is related to a particular intervention or disease severity. For instance, the inability to complete the scheduled treatment or appearance of unacceptable side effects may be more frequent in patients with severe disease. Hence, exclusion of the participants who do not complete the treatment or follow-up as planned would lead to the differential exclusion of patients with severe disease in the treated group, with the residual group unlikely to resemble the original group obtained at randomization. This may make the treatment look better than it is.

The exclusion of participants in one or both groups, particularly if their number is large, may lead to a significant reduction in sample size and hence in study power.

Exclusions can introduce a bias. Often the decision to exclude a particular participant is controlled, at least to some extent, by

the investigator, who may be tempted to exclude patients who are not doing well in a specific arm.

The proportion of responders among those who complete treatment provides an exaggerated estimate of treatment effect – this does not accurately reflect the beneficial effect that may be expected in clinical practice among those who are prescribed this particular treatment.

Therefore, to obviate (or minimize) these problems, it is recommended that "intention-to-treat (ITT) analysis" be used. The principle of ITT analysis is that all participants should be analyzed in the group to which they had been randomized, i.e., as if they had received the intervention which they were supposed to receive, irrespective of the treatment received. ITT analysis is usually described as "once randomized, always analyzed."

ITT analysis reflects the practical clinical scenario because it admits non-compliance and protocol deviations, dealing with the EFFECTIVENESS of the intervention rather than "efficacy." ITT analysis maintains prognostic balance generated from the original random treatment allocation. It gives an unbiased estimate of the treatment effect. If non-compliant subjects and dropouts are excluded from the final analysis, it might create important prognostic differences among treatment groups. Moreover, subjects may be non-compliant or may drop out of the study due to their response to treatment. ITT analysis limits inferences based on arbitrary or ad hoc subgroups of patients in the trial and emphasizes greater accountability for all patients enrolled in the study. Also, it minimizes type I error due to a cautious approach and allows for the greatest generalizability.

The CONSORT guidelines for reporting of "parallel-group randomized controlled trials" recommend that both ITT and PP analyses should be reported for all planned outcomes to allow readers to interpret the effect of an intervention. Although the validity of the ITT strategy is mostly accepted in superiority RCTs, there is no general agreement on the application of this method in equivalence and non-inferiority RCTs. Because non-compliance and cross-over tend to attenuate the between-arms differences, the ITT approach often favors the study hypothesis in equivalence and non-inferiority RCTs, which aim at demonstrating the similarity between two drugs. Consequently, in a non-inferiority trial, both the ITT and PP analyses have equal importance, and that their results should lead to similar conclusions for a robust interpretation.

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INA-RESPOND Newsletter

EXERCISE PRINCIPLE DURING COVID-19 PANDEMIC

By: Septia Mandala Putra

SARS-CoV-2 (COVID-19) is a new virus causing respiratory illness outbreak. Nowadays, COVID-19 has spread to several countries around the world and is presently a major global concern. It appears that no certain effective pharmaceutical agent is currently available for it

In the previous newsletter, we have discussed how to stay active at home during the pandemic. In this article, we would like to discuss a little about how to keep exercising during this pandemic.

Recommendations issued by American College of Sports Medicine (ACSM) and American Heart Association (AHA)[1] for primary physical activity for all adults aged 18-65 years were to participate in moderate-intensity aerobic physical activities for a minimum 30 minutes five days/week, or vigorous-intensity aerobic physical activities for a minimum 20 minutes three days/week. The question is, how can we apply this recommendation during this pandemic? As we know, the government has issued several large-scale regulatory restrictions, which prohibit gymnasium/sports centers from operating and people to do some outdoor activities. Despite that, people try to do their best to maintain or improve their immune system by paying attention to their nutrition and exercise. Exercise has been proven to have many benefits for our health, especially maintaining and improving our immune system.

People who are engaged in regular moderate-intensity exercise maintain a reduced risk of self-reported respiratory symptoms [2]. Multiple studies [3] in humans and animals have demonstrated the profound impact exercise can have on the immune system. There is a consensus that regular bouts of short-lasting (i.e., up to 45 minutes) moderate-intensity exercise is beneficial for the host's immune defense, particularly in older adults and people with chronic diseases. In contrast, prolonged[4] periods of intensive exercise training can depress immunity.

Moderate intensity[5] exercises can act as a preventive therapy to bring down the further incidence of COVID-19. A randomized controlled trial evaluating the preventive effect of aerobic exercises on acute respiratory illness found that participants in the exercise group reported lesser episodes of illness compared to participants with sedentary lifestyles.

This moderate intensity of aerobic activity can be accumulated to total the 30 minutes minimum by performing bouts, each lasting ≥ 10 minutes. This way, we can modify the duration of the exercise. How about intensity? There are some tools we can use, like measuring heart rate or talk to sing test.

Talk - Sing Test

Exercise Intensity	Talk	Sing
Low	Easy	Easy
Moderate	Easy	Difficult
High	Difficult	Difficult

For heart rate, we usually use the formula HRmax = 220 – Age, and adjust it to 50 – 70% of HRmax for moderate intensity. It is useful when we can calculate and count the heart rate while exercising, but to do this, we must have tools like heartbeat monitor/pulse oximeter/smartwatch that can measure heart rate. However, these devices may be expensive. There are two simple tests that we can use easily without spending much money. They are not very accurate, but they can still help us to measure the intensity.

Using this talk-sing test, we can measure the intensity of exercise. When jogging, running, cycling, etc., and we feel difficult to talk or sing, we have to reduce our pace/speed. It means we are already in high intensity.

Perhimpunan Dokter Spesialis Kedokteran Olahraga (PDSKO) has already made a recommendation for doing exercise in public places, and a stratification of risk groups.

When you have to exercise outdoors, please keep in mind the following points:

- Keep your physical distance with others (2 meters while running/ jogging and 20 meters if cycling).
- Keep your mask on. The Centre for Disease Control and Prevention6 (CDC) recommends everyone wear a mask or face-covering cloth in public area/places where maintaining physical distance is difficult.
- Bring your equipment, like a towel, exercise mat, drinking bottle, etc
- Don't rub/wipe your face too often
- Wash your hands frequently with soap or hand sanitizer.

If we do not have dedicated equipment for training, the following options can be done as an exercise:

Resistance training through bodyweight exercises. For example, squats while holding a chair, sitting and getting up from the chair, going up and down steps, transporting light-to-moderate-weight items (vegetables, rice, water, etc.)

Aerobic exercises like walking inside the house, dancing, or balance exercise. For example, walking on a line on the floor, walking on the toes or heels, walking heel-to-toe, and stepping over obstacles [7].

With this recommendation, and while still complying with the health protocols regulated by the government, we can again exercise regularly and safely.

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