INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

July 2024

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FROM OUR PARTNER

NIAID/DCR Study: Investigation of Immune Amnesia Following Measles Infection in Select African Regions

HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2024

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MASTHEAD

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FEATURES

INA-RESPOND Newsletter

InVITE & PROACTIVE Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Restu Amalia, Riza Danu Dewantara

InVITE

The Indonesia InVITE study is currently undergoing data cleaning by the Secretariat and the InVITE Global Team. Once this process is completed, the Study Sites team can prepare for a site close-out visit (SCV). The Secretariat and Sites are discussing the completeness of study documents and the necessary supplies for the SCV activities. Additionally, specimens for central laboratory testing can be shipped, with the estimated shipment of serum specimens taking place in August 2024. The Clinical Research Associate (CRA) is conducting a quality assurance (QA) of the study specimen inventory for all sites. For now, the QA process is completed for Site 2 and still ongoing for Sites 1 and 3.

The InVITE study, which stands for the International Study on COVID-19 Vaccine to Assess Immunogenicity, Reactogenicity, and Efficacy, is unique for INA-RESPOND as it is the first study involving a healthy population who received the COVID-19 vaccine. The study's objective is to characterize the immunogenicity of available COVID-19 vaccine regimens in each participating country two months after completing the initial full vaccination regimen or a booster vaccination regimen. This study is being conducted at three sites: Tangerang Hospital (Site 1), TC Hiller Hospital (Site 2), and Ansari Saleh Hospital (Site 3). In this activity report, we will reflect on the operational challenges faced by the Secretariat.

The study's preparation period was packed and shorter than that of previous INA-RESPOND studies, driven by a commitment to meet the enrollment target, which needed to adapt to the aggressive national COVID-19 vaccination program that began in August 2021. The study also involved primary health care (PHC) and vaccination centers as satellite sites for subject enrollment. The protocol, case report form (CRF), informed consent form (ICF), and other documents were prepared and reviewed swiftly by the InVITE Global Team, US-NIAID, and the INA-RESPOND Secretariat. Fortunately, the Ethics Committee approved shortly after submission, as they supported the accelerated approval process for COVID-19-related studies. After obtaining ethical approval, the site preparation visit (SPV) was conducted remotely due to COVID-19 travel restrictions. The Secretariat found that online training was challenging and less effective than on-site training, as the Site team needed more interaction, hands-on training, and study simulation before the study started. Additionally, the study team at the Hospital Sites had to provide training to the PHC Sites team due to their limited research experience. During the brief SPV period of about one month, intensive communication was maintained between the Secretariat and Sites via calls and WhatsApp groups to ensure the study adhered to the protocol. The Secretariat also communicated regularly with the InVITE Global Team.

INA-RESPOND believes that the spirit of collaboration is crucial for a fruitful study. Therefore, the Secretariat worked with the NIHRD and Site Hospitals to provide local serology testing for participants. This strategy not only enhanced participant enrollment and retention but also generated scientific insights and strengthened the Reference Lab's capacity in serology testing. The large number of subjects enrolled in a short period affected the completion and upload of the CRF into the DF Sent application by the Research Assistants (RAs). After discussing with the InVITE Global Team, the Secretariat decided to suspend enroll-

ment from 28 September 2021 until 21 October 2021. This suspension allowed the site to focus on completing the CRF uploads to 100%.

Specimen management and shipment presented challenges in the InVITE study. Specimens were collected from each site using kits prepared according to the Laboratory Manual. These kits, containing vials, tubes, Whatman cards, and a unique identifier label (KID), were shipped as whole packages by the InVITE Global Team. The Secretariat had to organize, prepare, and label each specimen kit for each subject. Due to the rapid study initiation, the KID labels had not yet been shipped, requiring the Secretariat to use temporary labels. The INA-RESPOND Reference Laboratory replaced these temporary labels with the official KID labels once they arrived. The InVITE Global Team provided freezer tape to ensure the KID labels were securely attached to the frozen specimen vials. Additionally, at the beginning of the study, Whatman cards for collecting were also not yet available. Instead, specimens were collected using vials, with the required specimen volume specified in the Laboratory Manual.

Figure 1. The InVITE study faced challenges in subject enrollment and specimen management that required the Secretariat's suggestion and resolution.

Occasionally, labels could peel off or become damaged due to temperature fluctuations during specimen shipment. To address this issue, the InVITE Global Team recommended using nitrile or powder-free gloves instead of bare fingers when wrapping labels around empty vials. They also advised preparing kits at room temperature and pressing firmly throughout the rotation of the vials to ensure a smooth application and minimize the formation of bubbles or wrinkles during kit preparation. Additionally, the InVITE Global Team suggested using freezer tape over the labels to prevent damage due to extreme temperatures during freezer storage.

The shipment of specimens from the sites to the INA-RESPOND Reference Laboratory in Tangerang posed unique challenges, particularly for Site 2. While Site 1 is co-located with the Reference Lab and Site 3 had no issues with biospecimen flights, Site 2 faced difficulties due to limited direct flights from Maumere to Tangerang. Additionally, Maumere Airport regulations prohibited the use of dry ice during shipment. Several delivery trials were conducted to find the most efficient and fastest way to ship the specimens without dry ice. These included hand-carrying the specimens by the study team or sending them to the laboratory partner in Surabaya before shipping them to the Reference Laboratory in Tangerang. Still, there were temperature excursions during these shipments, reaching 10°C on November 18, 2021, and 5.6°C on February 9, 2022, far from the targeted receive temperature below -65°C. Above this is the temperature at which the Central Laboratory saw fluctuations or impacts in the performance of some serology testing.

Figure 2. Specimen shipment challenges and the Credo Cube as a cold chain solution.

To address this issue, the Secretariat explored a feasible shipping route with a transit through Denpasar, Bali. Specimens were shipped from Maumere to Denpasar using ice packs, and then the ice packs were replaced with dry ice during transit in Denpasar. However, the transit process in Denpasar also encountered challenges, with temperature records showing an increase in specimen temperature above -60°C during the replacement of the ice packs. After extensive and careful consideration, the InVITE Global team and the Secretariat agreed to use a Credo Cube as a packaging solution. The Credo Cube can stabilize and maintain a shipping temperature of -60°C for three days without using dry ice, thus minimizing the risk of temperature excursions during specimen shipment. The Credo Cube usage was also a new experience for INA-RESPOND.

Currently, the subject visit period has been completed, and the focus is now on data cleaning, specimen management for the repository, and shipment to the Central Laboratory. Since the InVITE study is a multi-country initiative, the InVITE Global Team will perform a global database lock (DBL) after all participating countries have completed their study visits. The Site Closeout Visit (SCV) is scheduled to occur one month after the global DBL, which is planned for February 2025. All operational activities managed by the RAs are expected to be completed by December 2024 (Site 1), August 2024 (Site 2), and October 2024 (Site 3). The RAs and the Secretariat must ensure that all administrative activities are finalized before the SCV, which will involve only the Principal Investigator (PI) and co-Principal Investigator (co-PI).

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Currently, INA-PROACTIVE investigators, along with the Secretariat and partners, are preparing the primary and additional manuscripts. The first manuscript, "A Prospective Observational Cohort Study of HIV Infection in Indonesia: Baseline Characteristics and One-Year Mortality," was submitted to The Journal of International AIDS Society on June 13, 2024. Unfortunately, the editor informed us that after editorial appraisal, it was decided that the manuscript could not proceed further. The team is now exploring alternative Q1 journals for submission. Additionally, the Scientific, Data, and Site teams are engaged in extensive discussions regarding the subsequent manuscripts.

In collaboration with INA-RESPOND Warm-Based Research Assistants (RAs), the Secretariat conducted a scoping review on HIV research in Indonesia, covering all fields since the first HIV case was reported in Indonesia in 1987. The first topic of this scoping review project focuses on children living with HIV (CLWH) in Indonesia, aiming to identify gaps in current research. The team hopes to provide scientific summaries for this age group and promote HIV control in Indonesia. This scoping review will also support the preparation of a PROACTIVE manuscript on pediatric subjects.

Apart from that, INA-RESPOND Secretariat and RAs are also active in journal club activities. The sixth journal club meeting was held on February 2, 2024, with an article entitled "Immunological Outcomes after 6 Months with First-Line Antiretroviral Therapy: A Lesson from Yogyakarta, Indonesia." The article was presented by Dr. Rifa'ah from site 570 / RSUD Dr. Soetomo, Surabaya, and Dr. Fransisca from site 610 / RSUD Kabupaten Tangerang, Banten. Below is the summary of this article:

In 2016, there were more than 1,300 CLWH aged 0-14 years in Indonesia. Adequate antiretroviral therapy (ART) has proven to be highly effective in increasing nutritional and immunological status and reducing the incidence of opportunistic infection and mortality caused by HIV infection. During the writing of the article, ART was given to CLWH less than five years old and to CLWH older than five who were in clinical stages 3 and 4 based on the WHO clinical staging. ART was also given to CLWH older than five who were in clinical stages 1 and 2 if their CD4+ absolute count was below age-related thresholds.

After ART initiation, monitoring CLWH's treatment responses and drug side effects is essential. WHO (2013) recommends evaluating CD4+ cell counts every six months and Viral Load (VL) testing six months after ART initiation and every 12 months after the first VL evaluation. Immunological response after ART initiation occurs within the first six months and continues for three years thereafter. In resource-limited settings, clinical and immunological parameters can be used to evaluate ART outcomes. No data have been reported on immunological responses in CLWH who are treated with first-line ART in Yogyakarta. The study aimed to determine the immunological status of CLWH after six months of ART at Dr. Sardjito Hospital in Yogyakarta, Indonesia.

The study design was retrospective, conducted at Dr. Sardjito Hospital Yogyakarta from January 2010 to May 2016. CLWH aged 0-18 years who were given first-line ART for at least six months were included in this study. Data collected from medical records included age

Immunological outcomes after six months with first line antiretroviral therapy: a lesson from Yogyakarta, Indonesia

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Published in final edited form as: JIDC (The Journal of Infection in Developing Countries). 2018 Jun; 12(5): 385–389.

Age (months)	Immune status after six months of ART			
	No immunosuppression (immune recovery)	Mild immunosuppression	Advanced immunosuppression	Severe immunosuppression
£11	NA	NA	NA	NA
12-35	1	1	1	8
36-59	NA	3	1	8
≥60	4	2	4	2

Table 1. Immune status after six months of ART in CLWH with severe immunosuppression status before ART. NA= not available

at ART initiation, gender, residence, nutritional status, clinical staging based on WHO criteria, incidence of hospitalization, baseline CD4+ cell count, CD4+ cell count after six months of therapy, tuberculosis treatment, and ART regimens. The CD4+ absolute cell count analyzed was the one closest to the 6-month evaluation after starting ART. Immunosuppressive status of CLWH aged >59 months was grouped according to absolute levels of CD4+ cell count. Severe immunodeficiency was defined if the CD4+ T cell percentage was <25%, <20%, and <15% for children aged ≤11 months, 12-35 months, and 36-59 months, respectively. For children aged >5 years, severe immunodeficiency was defined if the absolute CD4+ cell count was ≤ 200 cells/mm^3. Nucleoside Reverse Transcriptase Inhibitors (NRTI) regimens used were zidovudine (AZT) and lamivudine (3TC) or stavudine (d4T) and 3TC. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) regimens were nevirapine (NVP) or efavirenz (EFV). Adherence assessment was based on monthly outpatient clinic visits. During this period, VL examination was unavailable, so it was not used to monitor the patient's condition.

This study included 35 subjects, of whom 62% were male. The median age at ART initiation was 45.0 (IQR 18-102) months. Most subjects were in WHO clinical stages 3 and 4. Sixteen subjects were undernourished, and ten subjects were severely malnourished. All subjects were in severe immunodeficiency conditions. The median CD4+ T cell percentage increased from 3.16% (IQR 1-18) to 11.0% (IQR 2-32) after six months of therapy, while the median CD4+ absolute cell count increased from 9.5 cells/mm^3 (IQR 3-176) to 419.5 cells/mm^3 (IQR 202-1428). No serious adverse effects were found, but three subjects' regimens were switched to a d4T and 3TC backbone due to anemia.

In this observational study, immunological improvements were observed following six months of ART, even in subjects with initially very low levels of CD4+ T cell percentage and CD4+ absolute cell count. CD4+ cell counts exhibited a more than two-fold increase, leading to immune recovery in five subjects within six months. This immune recovery is associated with thymus activity in children, so CLWH with severe immunodeficiency conditions can still achieve normal values when they start ART. Almost half of the subjects received tuberculosis therapy, but this immunological status change was not affected by tuberculosis therapy. ART initiation may reduce the incidence of opportunistic infections, directly reducing the incidence of rehospitalization. In this study, most subjects (68.6%) had only one hospitalization period. Worryingly, more than half of the subjects were categorized as non-adherent.

There were several limitations in this study. While the study approach was descriptive, it was the first of its kind conducted in Yogyakarta, providing an early reference for future studies. Some subjects could not be included due to incomplete data. Additionally, there was no standardized method to assess adherence in CLWH on ART, so this study measured adherence only through observations of outpatient clinic visits. In conclusion, ART can improve immunologic conditions even in CLWH with very low CD4+ T cell percentage levels and CD4+ absolute cell count. Monitoring the immunologic conditions and adherence of CLWH on ART is essential to improving treatment outcomes.

INA-RESPOND Newsletter

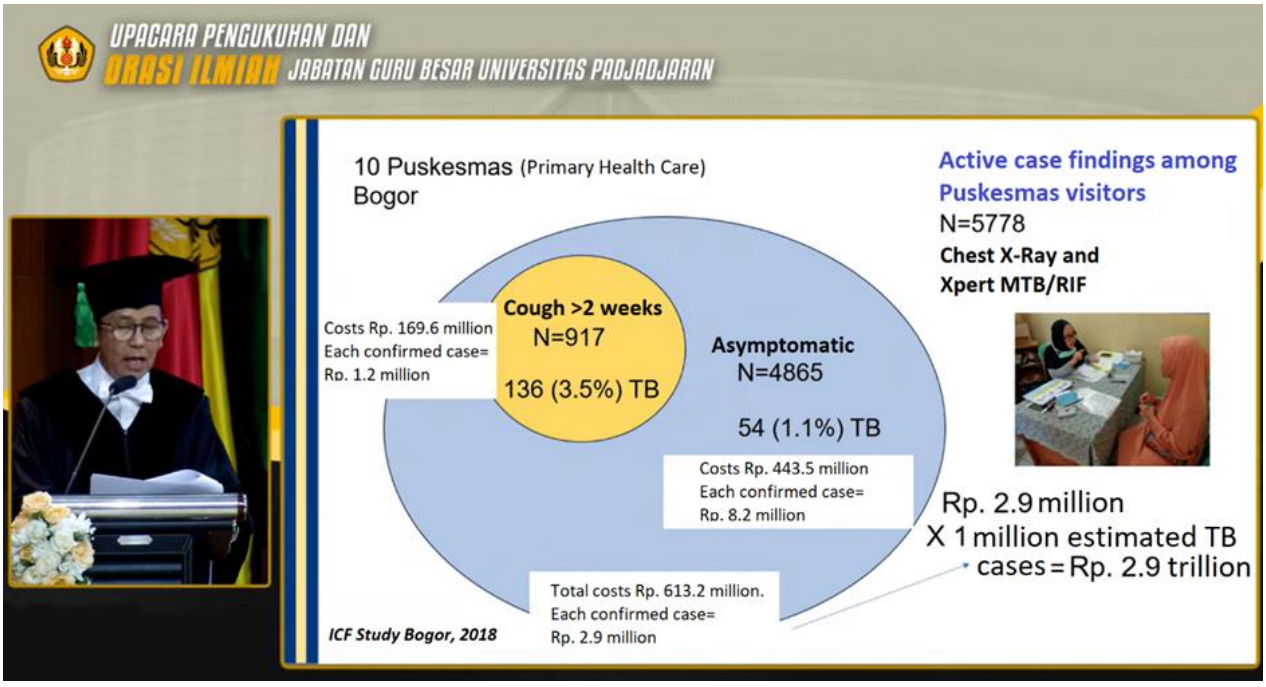
EVENT

INAUGURATION OF PROFESSOR BACHTI ALISJAHBANA: EFFORTS TO IMPROVE ACCESS TO TUBERCULOSIS DIAGNOSIS FOR ELIMINATING TB IN INDONESIA

By: Dedy Hidayat, Adhella Menur

Congratulations to Prof. Bachti Alisjahbana, MD, SpPD-KPTI, PhD, FINASIM, on the formal inauguration of his professorship on July 24, 2024, at *Universitas Padjadjaran* in Bandung. This inauguration recognizes Prof. Bachti's extraordinary dedication and contributions in the fields of internal medicine and tropical infections, as well as his efforts to enhance access to diagnosis and eliminate tuberculosis (TB) in Indonesia. May this achievement continue to inspire and motivate further contributions to the health sector.

Prof. Bachti Alisjahbana, born in Bandung on December 6, 1963, is a well-known expert in internal medicine and tropical infections in Indonesia. He earned his medical degree from the Faculty of Medicine at *Universitas Indonesia* in 1990 and his specialization in internal medicine from the Faculty of Medicine at *Universitas Padjadjaran* in 1998. Prof. Bachti continued his education and received his PhD from Radboud University Medical Center in the Netherlands in 2007. Prof. Bachti has exten-



sive experience in the health sector, including serving as the Head of Bokondini Health Center in Papua and as a staff member in the Department of Internal Medicine at Hasan Sadikin Hospital-FKUP. He also led the Infectious Diseases Study Center at UNPAD from 2014 to 2020 and currently serves as the Head of the Center for Infectious Disease Research (RC3ID) at *Universitas Padjadjaran*.

Prof. Bachti's activities are not limited to the national level but extend internationally as well. He has served as the Chair of the TB Operational Research Group (TORG) and Secretary of the TB Expert Committee (KOMLI TB) at the Ministry of Health. Additionally, he is a member of the Steering Committee of INA-RESPOND and a member of the Indonesian Academy of Sciences. His contributions to research and development in vaccines and diagnostics at the ASEAN Center for Research and Development of Vaccine Therapeutic and Diagnostic are significant. With more than 221 scientific publications indexed by Scopus and several intellectual property rights, Prof. Bachti continues to play an active role in global research and health.

In his speech at *Universitas Padjadjaran*, Prof. Bachti Alisjahbana emphasized the importance of efforts to improve TB diagnosis access for TB elimination in Indonesia. He explained that TB, caused by the *Mycobacterium tuberculosis* (MTB) bacteria, remains a significant disease burden in Indonesia, with around 1 million new cases and 140,000 deaths annually. Prof. Bachti highlighted that TB can be prevented and cured if diagnosed accurately and treated with a combination of anti-TB drugs. However, Indonesia still faces significant challenges in detecting and managing TB cases, influenced by various factors, including poverty, poor nutritional conditions, and limited access to healthcare services. He pointed out that 75% of TB patients initially seek treatment at private clinics, but MTB diagnosis tools such as Xpert MTB/RIF are often only available in public health services. This leads to delays in diagnosis up to 30-60 days and a broader potential for TB transmission. Prof. Bachti stressed the need to integrate private and public healthcare services to improve diagnosis access.

dr. M. Karyana, Prof. dr. Ida Parwati, dr. Dewi Lokida, and dr. Sindy Siahaan

He presented research findings highlighting the effectiveness of active case finding through routine healthcare examinations, which can identify both symptomatic and asymptomatic TB cases. In his survey, primary healthcare using clinical examination, chest X-ray, and Xpert MTB/RIF identified 3.5% (136 out of 917) active TB cases and 1.1% (54 out of 4,865) subclinical TB cases. A cost analysis revealed that Indonesia would need at least 2.9 trillion rupiahs to diagnose the country's estimated 1 million TB cases. With the national budget for overall TB management around 3 trillion rupiahs, it's not surprising that the country continues to experience a gap in TB diagnosis.

He emphasized the need for further research and development of more effective and efficient diagnostic tools using non-sputum-based samples such as blood, saliva, tongue swabs, and urine. He also highlighted the importance of collaboration between the health and technology sectors to eliminate TB in Indonesia. His ongoing study, called EVIDENT, aims to examine and validate potential near and point-of-care testing (POCT) assays for diagnosing TB. Prof. Bachti urged biotechnology and biomedical engineering experts to continue developing innovative solutions to support this effort.

Prof. Bachti Alisjahbana concluded his speech by thanking the various parties who helped him achieve his professorship. He also thanked INA-RESPOND (Indonesia Research Network for Infectious Diseases) for its significant contribution to much-needed research in Indonesia. He was grateful to dr. M. Karyana, dr. Herman Kosasih, and dr. Dewi Lokida, who represented the INA-RESPOND network. Prof. Bachti emphasized the importance of collaborative research in developing effective solutions to Indonesia's urgent health issues.

This professorship inauguration is not only a personal achievement for Prof. Bachti but also a significant step forward in the collective effort to advance science and health in Indonesia.

INA-RESPOND Newsletter

REPORT INTERNATIONAL: TB RICC BIOMARKER – JUNIOR INVESTIGATOR TRAINING

By: Gustiani Salim

Figure 1: Participants and Rutgers team

PART THREE

TRAINING AT RUTGERS UNIVERSITY

The final session of the Junior Investigator training took place at Dr. Padmini Salgame's Laboratory, located in the International Center for Public Health (ICPH), Public Health Research Institute (PHRI), Rutgers New Jersey Medical School, Newark, NJ, USA. This training continued to focus on discovering transcriptomic signatures for tuberculosis, using the advanced nanostring technology to study gene expression and identify potential biomarker candidates.

The wetlab training covered hands-on activities such as extracting RNA from blood samples collected in PAXgene RNA tubes, hybridizing RNA samples, loading samples into cartridges, and operating the nanostring machine. Unfortunately, the participants had to use dummy cartridges from the training kit instead of real cartridges, as the ordered cartridges were unavailable during the training. Despite this, participants gained a clear understanding of the process. Additionally, the facility provided training on analyzing nanostring data, including data cleaning, quality control (QC), and visualization for presentation purposes.

1. Nanostring Technology for Gene Expression Study

Unlike the Fluidigm Biomark© platform, which primarily uses RT-qPCR methods, nanostring is a nucleic acid hybridization technique that allows for simultaneously examining up to 800 targets from 12 samples. Nanostring can be seen as a variation of the microarray method, but with the advantage of hybridizing directly with RNA samples, eliminating the need for reverse transcription, library preparation, or amplification that could introduce bias. Another benefit is that the nanostring system can work with various types of nucleic acid samples, including blood fluids, cell lysates, fresh tissues, and FFPE sections.

Participants learned to manually isolate total RNA from blood samples preserved in PAXgene Blood RNA Tubes (BRT) using the PAXgene® Blood RNA kit by PreAnalytiX (Qiagen). BRT contains an RNA stabilization reagent that protects RNA molecules from degradation and minimizes ex vivo changes in gene expression. The PAXgene® Blood RNA kit is column-based RNA isolation. After the lysis and protein digestion process, RNA selectively binds to the silica membrane as it passes through the spin column.

The quantitation of mRNA transcript expression was conducted using the Nanostring nCounter® SPRINT profiler instrument available in Dr. Padmini Salgame's laboratory. Nanostring technology provides digital, multiplexed measurements of gene expression, offering simultaneous counts of hundreds of mRNA transcripts following solution-based hybridization with target-specific probes. The system utilizes three main components:

1. Capture probe: A 50 base pairs single-stranded sequence complementary to the mRNA target, conjugated with biotin.
2. Reporter probe: A single-stranded sequence complementary to the mRNA target, labeled with a fluorescent barcode specific to each mRNA target. The target-specific reporter and capture probes are collectively referred to as a CodeSet.
3. Cartridge: A microfluidic chamber system containing a streptavidin-coated imaging surface.

During hybridization, the capture probe and reporter probe bind to the target mRNA at adjacent positions, forming an mRNA-probe complex (Figure 2).

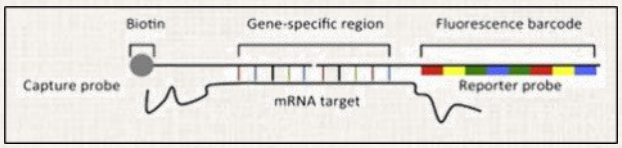


Figure 2: mRNA target - Probes complex

When hybridized samples are loaded into a cartridge and run in the nCounter instrument, the fluidic processing system removes excess probes, unbound targets, and other extraneous material. Purified target mRNA-probe complexes are deposited onto a streptavidin-coated imaging surface and immobilized via the biotinylated capture probe. Immobilized reporters are aligned, stretched, and immobilized again to create parallel fluorescent barcodes that can be imaged. An automated fluorescence microscope in the Digital Analyzer scans the cartridge, identifying each target molecule of interest. The number of detected fluorescence signals reflects the amount of a specific mRNA target in the sample.

The general steps of sample processing with the Nanostring nCounter for gene expression are summarized in the chart on page 13).

The nCounter SPRINT Profilers operate a multichannel epifluorescence scanner and digital analysis system, designed to image samples processed

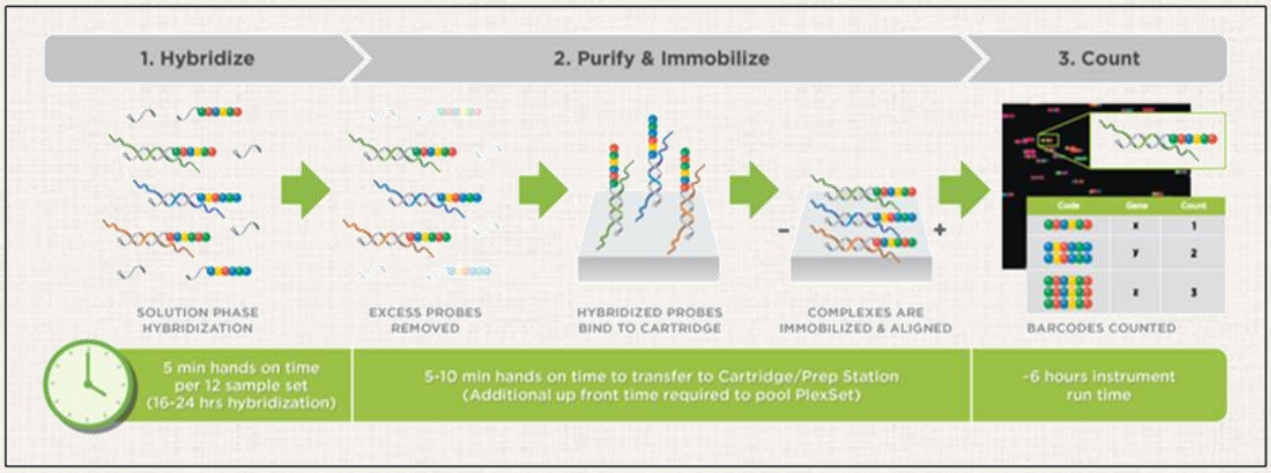


Figure 3: Nanostring nCounter Workflow for Gene Expression Assay

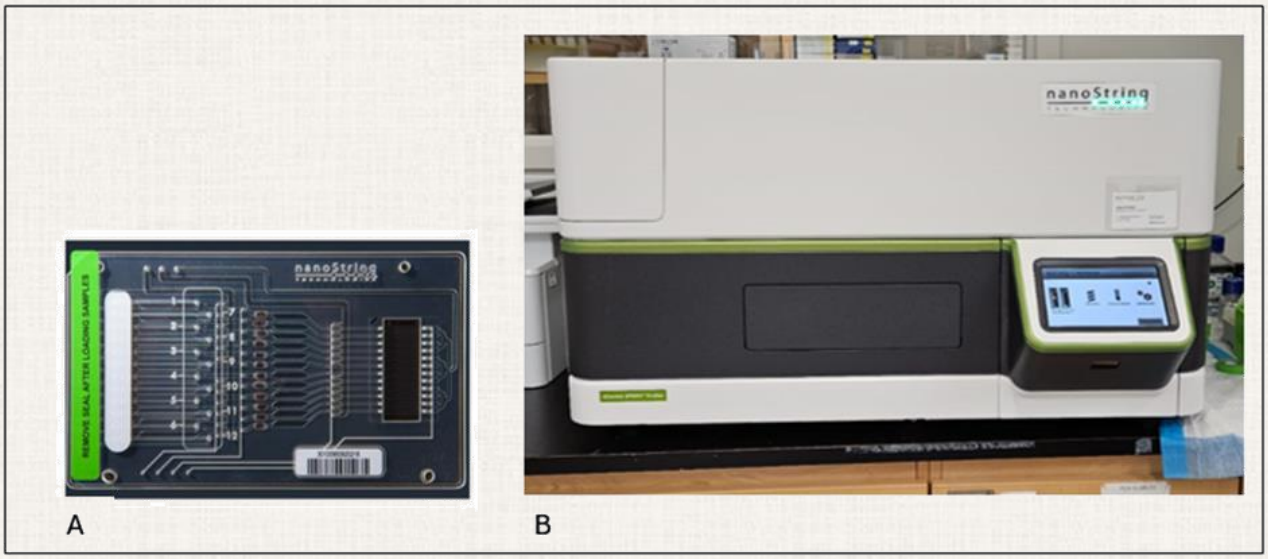


Figure 4: A. Nanostring nCounter cartridge; B. Nanostring nCounter® SPRINT profiler instrument

within cartridges. The digital analysis system collects data by taking images and counting the number of each fluorescent reporter tag, tabulated as CSV files. There are two types of files generated by the system:

1. Reporter Library File: Unique to each custom CodeSet, containing information used during image processing to assign target identities to the barcodes.
2. Reporter Code Count File: Contains data for one of the twelve flow cells (assays) in a cartridge, detailing the counts for each target in an assay.

For analyzing and visualizing Nanostring data to measure the fold difference in gene expression, trainees received training on quality evaluation (QC/normalization) of nCounter data, basic statistical outputs, and publication-quality figures, using the following software options:

a. nSolver analysis software: An integrated analysis platform for basic and advanced analysis.
b. ROSALIND Platform: A cloud-based software platform for data visualization and pathway enrichment.
c. R software packages for differential expression.

2. Public Health Research Institute Facility

Dr. Padmini Salgame's laboratory is part of the Rutgers Regional Biocontainment Laboratory (RBL) under the Public Health Research Institute (PHRI), Rutgers New Jersey Medical School, Newark, NJ, USA. PHRI's mission is to help eliminate infectious diseases worldwide through fundamental and translational research. The RBL is a specialized facility for safely and efficiently studying infectious diseases with highly transmissible agents. Located in the International Center for Public Health, participants were given a tour of the RBL's facilities, including the most advanced laboratories for studying biological agents under biosafety level 3 (BSL 3) conditions. Additionally, the building houses an animal facility laboratory to accommodate research using trial animals such as mice and rabbits.

TB RiCC BIOMARKERS – JUNIOR INVESTIGATOR TRAINING, AN INSPIRING PROGRAM

Being selected as one of the participants for the TB RiCC Biomarkers – Junior Investigator Training was an invaluable opportunity. Participants learned directly from the world's top experts in TB research. With only five participants, each received hands-on laboratory training, making the program highly effective and efficient. The training covered not only lab work but also the upstream and downstream processes conducted in RePORT member countries for TB biomarker research. Participants visited clinical sites to learn about patient recruitment, specimen collection, storage, examination, and data analysis, culminating in presenting results for publication.

Despite using advanced lab equipment unavailable in their home countries, participants gained essential insights and skills to apply in developing TB research or other infectious diseases. The diverse backgrounds and the extended training period fostered close relationships among participants, allowing them to exchange ideas and experiences from their respective countries. They learned to understand the challenges and solutions in TB research under the RePORT consortium. It is hoped that participants will continue to communicate and collaborate to advance TB research and the RePORT consortium.

INA-RESPOND Newsletter

DIAGNOSING TUBERCULOSIS: TO END IS TO BEGIN

By: Adhella Menur

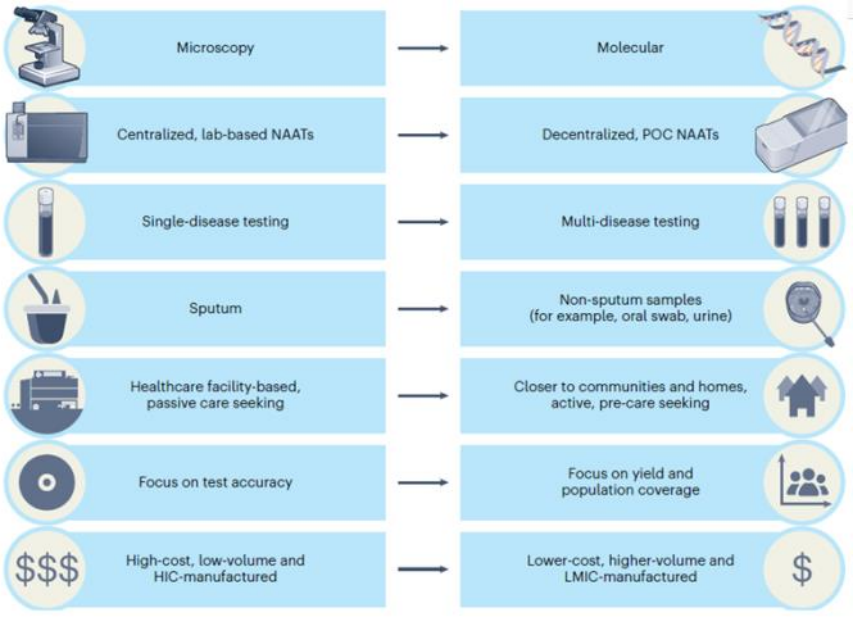
Watching the record of Prof. dr. Bachti Alisjahbana, Sp.PD-KPTI, Ph.D.'s scientific oration and reading Gustiani's report of her TB biomarker laboratory training in Brazil brought me back to my time as a Research Assistant (RA) for the TRIPOD study (Tuberculosis Research of INA-RESPOND on Drug Resistance). In 2017, I transitioned from working as a general practitioner in a remote district hospital and a part-time private clinic to a top-tier referral hospital in Central Java. The difference was striking, with complete laboratory facilities and a full team of specialized doctors—luxuries not often found in remote areas. In TRIPOD, we enrolled presumptive TB patients and performed a range of microbiological tests, including acid-fast bacilli (AFB) staining, Xpert MTB/RIF assays, Mycobacterium tuberculosis (MTB) cultures, and phenotypic drug susceptibility testing (pDST). As an RA responsible for enrolling and following study

participants and collecting biological samples, I gained firsthand insight into the complexity of TB diagnosis.

For many patients, the journey to a TB diagnosis was tiresome even before treatment began. Most came from moderate to low socioeconomic backgrounds, relied on national insurance, and lived far from our hospitals. They had to undergo hospital administration, meet insurance requirements, and wait in long queues with many other patients. Often, a single visit consumed an entire day, and further visits were needed for additional examinations. Even though medical costs were covered, non-medical expenses could still be a burden, especially for the family's breadwinner. When family and work environments lacked support, patients usually felt overwhelmed and sometimes abandoned the diagnostic process. Many opted for private clinics or alternative medicine to relieve their symptoms. Collecting sputum was also difficult for some patients. Sometimes, the nurse would give patients a container and mucolytic drugs, instructing them to bring back a morning sputum sample. Unfortunately, if patients couldn't produce a sample or faced difficulties, they often didn't return. Additionally, with limited knowledge about TB, some patients hesitated to provide sputum, fearing a confirmed diagnosis would lead to long-term treatment, lost jobs, and social stigma.

I also observed the high workload clinicians, nurses, and laboratory technicians face. The unbalanced ratio of clinicians to patients often led to limited engagement. Nurses had to work hard to care for and counsel patients. The limited TB referral laboratories and technicians contributed to long turnaround times for testing results. In 2017, Xpert MTB/RIF testing was still limited to referral hospitals and was primarily used only when there was suspicion of drug-resistant (DR) TB. Additionally, at that time, Indonesia had only 11 certified laboratories for TB culture and nine for phenotypic drug susceptibility testing (pDST) to serve the large number of TB cases across the country. Fortunately, with the commitment to End TB, the government has enhanced case-finding and early TB diagnosis efforts. As AFB testing is less sensitive and specific for diagnosis and cannot detect drug resistance, Xpert MTB/RIF has now become the frontline tool for TB diagnosis. By 2023, there were over 2,000 Xpert MTB/RIF nationwide, with around 1,200 available at primary healthcare centers (Puskesmas). Also, there were 22 certified laboratories for MTB culture, 13 for pDST, and seven for line probe assays (LPA).

However, the diagnosis gap remains significant. In 2023, out of the estimated 1,060,000 people who developed TB in Indonesia, only around 820,000 were diagnosed and reported to national TB programs, leaving 23% undiagnosed. While there are promising advancements in short oral anti-TB drug regimens, these breakthroughs cannot reach their full potential without effective diagnosis. I came across an insightful commentary by Madhukar Pai et al. in Nature Microbiology in 2023, which discussed seven critical



transitions needed to close the TB diagnostic gap. These transitions are interlinked, and their integration could have a significant impact. The commentary aligns well with Prof. Bachti's views, who emphasized the importance of molecular-based TB assays, active case finding, embracing private services in diagnosing and managing TB, discovering more convenient samples than sputum, and innovating point-of-care testing (POCT).

Speaking about non-sputum biomarkers for TB diagnosis, intensified research and innovation in this field have been identified as essential components of the World Health Organization's (WHO) End TB Strategy. Excellent biomarkers will be highly beneficial for diagnosing TB in challenging populations, such as children, people living with HIV, those with extrapulmonary TB, and individuals with subclinical TB. A promising advancement in this field is the use of the host transcriptome as a biomarker to detect disease states. This involves measuring the expression levels of mRNAs derived from blood samples, reflecting the genes actively expressed at a given time. Several studies are underway to discover and validate transcriptomic signatures in clinical trials.

In 2016, Sweeney et al. identified a TB score based on blood mRNA expression levels of three expressed genes: guanylate binding protein 5 (GBP5), dual specificity phosphatase 3 (DUSP3), and Krüppel-like factor 2 (KLF2), which are highly diagnostic for active tuberculosis. Excitingly, these three-gene signatures have been incorporated into an automated qPCR test using the GeneXpert platform (Cepheid, USA). This Xpert MTB Host Response (MTB-HR) prototype quantifies the expression of the three transcripts in a whole-blood sample and computes a TB score based on cycle threshold (Ct) values using an in-built algorithm. Even more exciting is the development of the test using a fingerprick whole blood sample of only about 200 µL, rather than pricier whole blood in PAXgene RNA tube samples. In 2022, Sutherland et al. for the TrENDx-TB Consortium published interim results indicating that the Cepheid MTB-HR cartridge meets the minimal target product profiles for a TB triage POCT using fingerstick blood, regardless of geographic area or HIV infection status. I hope the full results of the study will bring great news and help close the TB diagnosis gap.

With our valuable stored samples, such as whole blood in PAXgene RNA tubes from TRIPOD, and the biomarker assay training gained by Gustiani, I hope INA-RESPOND can collaborate and make significant contributions to biomarker diagnostic research in the fight against TB. I believe that setting a solid start for TB diagnosis is essential to Ending TB. In the spirit of the 2024 Olympics, with the slogan "Games Wide Open," let's race towards the finish line and achieve victory together!

Can't wait for the 2024 Olympics running schedule!

INA-RESPOND Newsletter

NIAID/DCR STUDY: INVESTIGATION OF IMMUNE AMNESIA FOLLOWING MEASLES INFECTION IN SELECT AFRICAN REGIONS

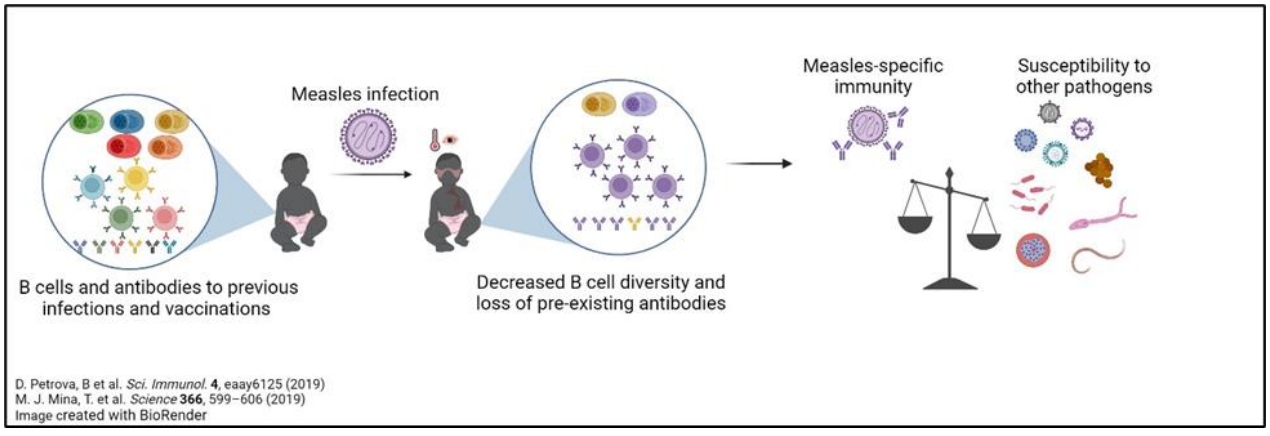
By: Katy Shaw-Saliba

Measles virus (MeV) is one of the most contagious infectious agents; thus, despite having a highly safe and effective vaccine available, sustained high vaccine coverage (>90%) is required to interrupt transmission [1]. Infection with MeV is diagnosed clinically by the presence of a characteristic fever and maculopapular rash, potentially accompanied by coryza, cough, conjunctivitis, and small white spots in the oral mucosa known as Kolpik's spots. Laboratory confirmation is needed using PCR to detect the MeV nucleic acid and/or ELISA to detect anti-MeV IgM as other febrile rash illnesses have overlapping symptoms (with perhaps the exception of Kolpik's spots). MeV can cause serious complications both in the acute phase of the infection and up to 2-3 years after the infection [2].

This prolonged effect of MeV is due to its fascinating dual impact on the immune system termed "immune amnesia." The immune system generates a very robust response to MeV resulting in lifelong immunity to the virus. This robust immune response, however, comes at a cost. The MeV infects lymphoid cells resulting in lymphopenia. Lymphopenia is common in many infections; however, MeV is unique in that it results in a very specific depletion of memory B cells with incomplete reconstitution of naïve B cells [3]. The depletion of memory B cells also leads to an almost complete loss of pre-existing antibodies generated in response to previous infections and/or vaccinations [4]. The loss of memory B cells and antibodies leaves children highly susceptible to other infections.

Vaccine misinformation, disruption in cold-chain, and disease outbreaks such as Ebola and the COVID-19 pandemic have decreased vaccine coverage [5] and continual MeV outbreaks occur in West Africa [6]. Studies on immune amnesia have largely centered around European populations and macaque models. Given this, the NIAID/DCR Special Projects in Guinea (PREGUI) and Mali (UCRC) worked alongside NIAID/DCR members to develop a protocol to study measles immune amnesia in their local context (clinicaltrials.gov NCT06153979).

This study, Investigation of Immune Amnesia Following Measles Infection in Select African Regions or the



Measles study, is an observational, longitudinal, prospective study with specific research questions aimed at enhancing the understanding of measles immune amnesia outside of Europe and animal models. The primary objective is to use a global antibody assay (MIPSA) that includes antigens to all known human viruses with the addition of malaria, typhoid, and tuberculosis antigens to see if the phenotype in conserved in this population. In addition to looking at the immune amnesia phenotype in this population, the other primary objective of the study is to determine if there is any difference in the ability of a child following MeV to respond to a controlled immune stimulus (a rabies vaccine) at an early timepoint compared to a late timepoint (using a neutralizing antibody assay).

Exploratory aims will address the number of hospital encounters in MeV infected children compared to healthy controls, the MeV genomes circulating in West Africa (via whole genome sequencing of the virus), and the etiology of in children who present with signs and symptoms consistent with measles but test negative in the laboratory (via viral capture sequencing, VirCapSeq -VERT). Immune cells (PBMC) are being collected in Mali to investigate the cellular immune response both to MeV and the rabies vaccination. Findings from this study will be additive to the current literature and may be important when considering vaccination following MeV infection.

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INA-RESPOND Newsletter

WALKING AFTER A MEAL: ITS EFFECT ON BLOOD GLUCOSE CONTROL

By: Edrick Purnomo Putra

Walking is a form of physical activity that can be easily done by most people. It is a part of our daily life and does not require specific equipment or a special environment. Walking has become popular as a form of physical activity to gain health benefits, even leading to the well-known recommendation of 10,000 steps daily. However, a recent study shows that it does not have to be 10,000 steps per day to be healthier. A meta-analysis published in 2022 provides an evidence-based threshold for the optimum number of steps per day associated with lower all-cause mortality risk, which varies by age. This is the first

study to do so, including a total of 47,471 adults and 3,013 deaths from 15 studies across Asia, Australia, Europe, and North America. Mortality risk progressively reduced with around 6,000-8,000 steps per day in adults aged 60 years or older and 8,000-10,000 steps per day in adults under 60 years old.

While the studies showed evidence about the number of steps, timing might also play an important role. It is true that "every move counts," just like WHO's latest recommendation on physical activity, but timing might make a bigger impact on our health, especially in controlling blood glucose levels. Blood sugar will increase after every meal, reaching its peak 30-60 minutes after a meal and later dropping to its lowest 2-3 hours after a meal in healthy humans. These blood sugar spikes, or repeated postprandial hyperglycemia, cause hyperinsulinemia, which can contribute to insulin resistance over the long term. This is detrimental to our health, especially for people with diabetes mellitus, those at risk of diabetes, and those with obesity. Exaggerated blood glucose spikes increase oxidative stress, endothelial dysfunction, pro-inflammatory factor levels, and the risk of developing cardiovascular pathologies. Postprandial hyperglycemias also interfere with long-term glycemic control, marked by elevated glycated hemoglobin (HbA1c) levels. These glycemic exposures put diabetics at risk of cardiovascular disease, including micro and macrovascular complications. In healthy humans, glycemic excursions, even in the non-diabetic range, pose a relevant risk of low-grade inflammatory and cardiovascular diseases. Therefore, suppressing postprandial hyperglycemia and maintaining long-term glycemic control is crucial.

One effective way to manage hyperglycemia is to engage in physical activity close to food intake. Research has been conducted to determine whether physical activity done before or after a meal is more beneficial. A study with type 2 diabetes patients compared a single bout of 20 minutes of self-paced treadmill walking done immediately before a meal and 15-20 minutes after a meal. Postprandial walking appeared to be more effective in controlling glycemic impact in evening meals compared to premeal or no exercise. Another study with type 1 diabetes patients using hybrid closed-loop delivery systems (HCLS) compared a single bout of 20 minutes of self-paced walking done within 30 minutes before dinner and 30 minutes after dinner. This study suggests that premeal walking may be more effective at attenuating blood glucose levels after dinner compared to postmeal walking in type 1 diabetes patients with good glycemic management using HCLS.

Walking after a meal is proposed to prevent a rise in blood sugar because walking consumes blood sugar. Studies have discussed whether exercise should be performed directly after a meal or after a certain time. A case report with two Japanese elderly women

showed that walking after a meal flattened the blood sugar curve and resulted in weight loss after a month of walking right after meals. A meta-analysis released in 2022 concluded that walking has a greater effect on postprandial hyperglycemia attenuation when undertaken directly after a meal compared to after a longer interval or before a meal. Some people might feel discomfort while walking directly after a meal; however, for those without such problems, walking directly after a meal brings no adverse events. Moreover, a study showed that 10-15 minutes of slow walking after a meal could be effective in relieving bloating due to abdominal distention.

It is clear that physical activity in the form of walking can be a potential part of diabetes management. A study in New Zealand compared different walking timings in patients with type 2 diabetes. Patients were divided into two groups: one group was advised to walk 30 minutes each day, and the other group was advised to walk 10 minutes after every meal each day, starting within 5 minutes after finishing the meal. This study showed that even though both groups fulfilled the current physical activity recommendation, patients who walked after meals daily had better improvements in postprandial hyperglycemia compared to those who walked at unspecified times. It was also discussed that postprandial activity might avoid the need for additional total insulin doses or mealtime injections. Therefore, the study recommended at least 10 minutes of walking after every meal, especially meals with high carbohydrate content. Another study on the elderly at risk for impaired glucose tolerance compared 15-minute bouts of walking after every meal performed 30 minutes after each meal with a single bout of 45 minutes of walking at different times. This study concluded that both sustained morning walks and postmeal walks significantly improved 24-hour glycemic control. However, postmeal walks were significantly more effective in reducing 3-hour postprandial blood glucose levels. Therefore, short intermittent bouts of walking after a meal were effective in controlling postprandial hyperglycemia in the elderly.

An interesting meta-analysis published in 2022 made interesting comparisons of prolonged sitting to intermittent standing breaks and intermittent walking breaks. This study revealed that intermittent standing breaks significantly improved postprandial blood glucose levels compared to prolonged sitting. While light-intensity walking showed a superior effect in attenuating postprandial hyperglycemia and insulin levels, this study showed that standing can still be a beneficial form of physical activity for glucose control compared to being sedentary.

Walking can be done indoors or outdoors, but some people might be reluctant to get out of the house to walk or may live in limited spaces that prevent them from walking around the house. Spot marching or walking in place can be a safe and feasible alternative for individuals with such problems. A study in Thailand compared post-meal spot marching exercise with standard treatment in type 2 diabetes patients. In the intervention group, patients were asked to do 3 sets of 15-minute spot marching after a meal per day, 4 times per week, for 8 weeks. The movements included shoulder flexion ≥90° and hip flexion ≥70° with an 80-90 beats per minute rhythm. The study concluded that spot marching after meals can be a home-based exercise to improve glycemic control, demonstrated by improvements in HbA1c. Moreover, it also improves exercise tolerance, leg muscle strength, and quality of life in patients with type 2 diabetes.

In diabetes management guidelines, initiating basal insulin is recommended for type 2 diabetes patients who fail on oral hypoglycemic drugs. When the HbA1c target is not yet achieved, controlling postprandial hyperglycemia is advised. Using rapid-acting insulin or GLP1 agonists in combination with basal insulin or switching to premixed insulin are options; however, these options require the patient to have multiple injections daily. Moreover, GLP1 agonists are not cheap and also come with gastrointestinal side effects. Therefore, physical activity after exercise could be a better option. A study in Thailand compared post-meal walking with standard medication

treatment in type 2 diabetic patients who failed basal insulin by comparing one prandial insulin injection and post-meal walking on glycemic control. Patients were asked to walk as fast as possible for 15-20 minutes after at least one meal per day, every day. The study concluded that there were no significant differences in HbA1c and fructosamine reduction between the post-meal walking and prandial insulin groups after 6 weeks. Although post-meal walking might be as effective as prandial insulin, the magnitude of reduction was small; therefore, a longer study with a bigger sample size and different walking protocols is still needed in the future.

Walking causes muscles to contract. After a meal, with blood sugar rising, insulin will also rise. Both insulin and muscle contraction will stimulate the translocation of the GLUT4 transporter protein on the cell membrane of muscle. Muscle contraction itself will start glucose uptake without relying on insulin; thus, exercise can help insulin in people with aging-related reduced insulin secretions and those with insulin resistance. Increased GLUT4 translocation of glucose on the plasma membrane during muscle contraction also contributes to the decrease in HbA1c in type 2 diabetic patients.

Walking after a meal has a significant impact on our health, especially in attenuating blood sugar levels. However, the important thing to note is not just about the number of steps or the timing, but to consider the latest recommendation on physical activity. The 2020 WHO Guidelines on physical activity recommend all adults to do at least 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic physical activity per week. It is also recommended to do moderate or greater intensity muscle-strengthening exercises on 2 or more days per week. Recommendations for people with diabetes are not far different, yet special considerations need to be made, and consultation with sports medicine specialists should be sought. In the end, walking is just a form of physical activity, and with perfect timing, we can optimize its health benefits. So next time after you finish your meal, don't forget to stay active and move to lower your blood sugar.

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INA-RESPOND Newsletter

LOT QUALITY ASSURANCE SAMPLING (LQAS) IN PUBLIC HEALTH: A PRACTICAL OVERVIEW

By: Aly Diana

COMIC CORNER

In the realm of public health and development, ensuring the quality and effectiveness of interventions is paramount. Lot Quality Assurance Sampling (LQAS) is a powerful yet straightforward tool that offers a robust method for assessing quality and coverage in various programs. Originally developed in the manufacturing industry, LQAS has been adapted for use in public health, particularly in evaluating immunization coverage, monitoring healthcare services, and assessing the quality of educational programs, making it invaluable for health program managers and policymakers.

Recently, I encountered terms of reference (TOR) for a study using LQAS, and I was unaware of this method. To my surprise, the World Health Organization has introduced the technique since 1991. So, this is my attempt to briefly understand LQAS and share what I have learned.

Lot Quality Assurance Sampling is a statistical method used to determine if a specific "lot" or batch meets the defined quality standards. A "lot" could refer to a geographic area, a time period, or any other defined grouping relevant to the assessment. The core principle of LQAS is to classify these lots

into two categories: acceptable or unacceptable, based on the quality criteria set before the sampling process.

The essence of LQAS lies in its ability to classify geographical areas or population segments based on whether they meet predetermined health standards. For example, LQAS can be applied to monitor immunization coverage or evaluate the effectiveness of public health interventions in specific regions. The methodology entails several steps: defining the lot and quality standard, selecting an appropriate sample size, conducting the survey, and then classifying the results to ascertain whether the lot meets the quality criteria.

One significant application of LQAS is in infectious disease research. Consider a tuberculosis (TB) control program aiming to ensure that at least 90% of TB patients complete their treatment. By employing LQAS, health officials can define each district as a lot and select a sample of TB patients for data collection. For instance, in a district with 1,000 TB patients, a sample size of 20 patients might be chosen. Health workers would then check these patients to determine if they completed their treatment. If 18 out of the 20 sampled patients completed their treatment, the district could be classified as meeting the 90% completion target. Conversely, if fewer than 18 completed their treatment, the district would need targeted interventions to improve adherence. This rapid identification process facilitates immediate action to enhance program effectiveness and allocate resources efficiently.

In addition to its practical applications, LQAS offers several advantages. It is cost-effective, requiring fewer resources than traditional survey methods, and provides timely insights that facilitate quick decision-making. The methodology is also scalable, making it suitable for a range of health programs and geographical contexts. However, successful implementation necessitates proper training for health workers and careful calculation of sample sizes to ensure accurate classification.

In conclusion, Lot Quality Assurance Sampling is not merely a statistical tool; it is a strategic approach that enables health practitioners to conduct rapid assessments and implement targeted improvements in public health programs. By effectively leveraging LQAS, health officials can ensure that resources are directed toward the most critical needs, ultimately contributing to better health outcomes across populations. This methodology's role in public health continues to expand, promising innovative solutions to pressing health challenges.

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