

# INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE



NEWSLETTER

August 2022

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HEALTH POLICY AGENCY  
MINISTRY OF HEALTH REPUBLIC OF INDONESIA

2022

# INA-RESPOND newsletter

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Adhella Menur, Eka Windari R., Herman Kosasih, I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Mila Erastuti, Nurhayati, Nur Latifah Hanum, Risky Dwi Rahayu, Riza Danu Dewantara, Ungke Anton Jaya.

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## INA-RESPOND Secretariat

Badan Kebijakan Pembangunan  
Kesehatan, Gedung 6, Lantai 3.

Jl. Percetakan Negara no.29,  
Jakarta 10560

[www.ina-respond.net](http://www.ina-respond.net)

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## FEATURES

# INA-RESPOND Newsletter

## TRIPOD, PROACTIVE, & ORCHID Study Updates

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

### INA102

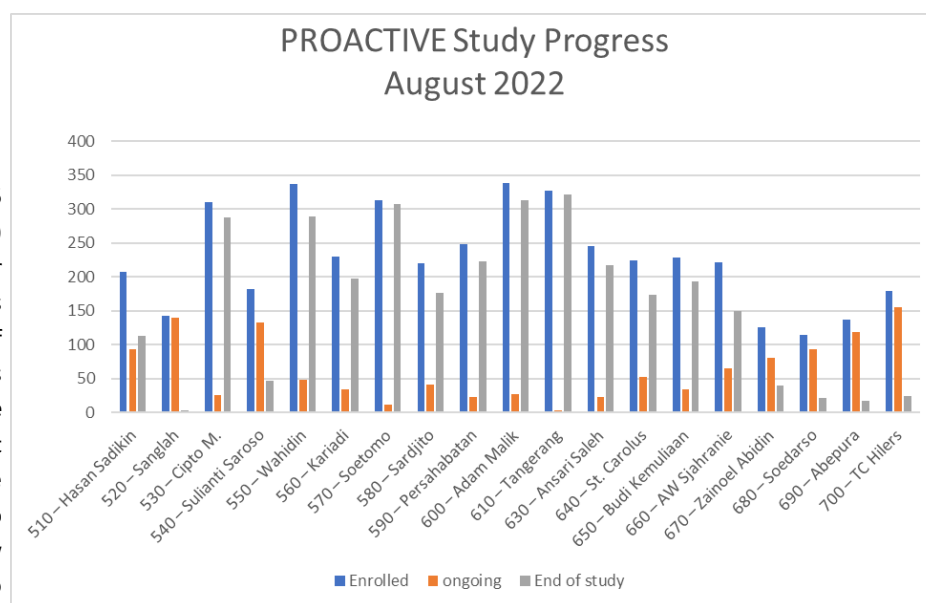
One of two papers from the TRIPOD study submitted for "The Characteristics of Drug Sensitive and Drug Resistant Tuberculosis Cases in Indonesia" to the American Journal of Tropical Medicine and Hygiene on 22 February 2022 was accepted on 18 August 2022. Meanwhile, the other paper, "Performance of Xpert TB/RIF and Sputum Microscopy Compared to Sputum Culture for Diagnosis of Tuberculosis in Seven Indonesian Hospitals," was submitted to the Frontiers in Medicine - Infectious Diseases - Surveillance, Prevention, and Treatment on 31 March 2022. We just received comments from 1 reviewer for paper #2.

The Bandung BBLK has completed the work on subculturing the TRIPOD Isolates sample on the baseline and was extracted for the mTB DNA. Twenty-five did not grow, and 276 samples have been shipped to the INA-RESPOND's Reference Laboratory.

The young investigator winner for REPORT is dr. Myrna Evanda Adeline from site Soetomo's Hospital, Surabaya. She will present the abstract at the upcoming Annual RePORT International meeting in Cape Town, South Africa, on 7-8 September 2022 for Young Investigators.

### INA104

As of 8 August, from 4,336 subjects enrolled, 3,122 (72 %) subjects have ended their study, and 1214 (28 %) subjects are still ongoing. For the end of study subjects, 2559 subjects had already completed the study until the follow-up visit month 36, 242 subjects are death, 249 subjects were lost to follow up, 32 subjects withdrew consent, 33 subjects moved to the city without PROACTIVE Site, 5 subjects with HIV negative, and 2 subject suspended (imprisoned). The study progress from each site is described in Figure 1, while the detailed information on the end of study participants is available in Table 1.



For the monitoring activity, two on-site monitoring visits are already scheduled for August 2022. The Wahidin Hospital, Makassar (site 650) was completed on 1-3 August 2022. The Dr. Soedarso Hospital, Pontianak (site 680) will be conducted from 26-28 August 2022.

**Table 1.** Subjects' end of study reasons

No	Site	End of Study Duration/Complete	Withdrew Consent	HIV negative	Moved	Death	Investigator Discretion	Lost to Follow Up	Other	Total
1.	510 – RSUP Dr. Hasan Sadikin	104	1	0	2	4	0	2	0	113
2.	520 – RSUP Sanglah	1	0	0	0	3	0	0	0	4
3.	530 – RSUPN Dr. Cipto Mangunkusumo	260	0	0	0	17	0	11	0	288
4.	540 – RSPI Dr. Sulianti Saroso	36	0	0	2	7	0	2	0	47
5.	550 – RSUP Dr. Wahidin Sudirohusodo	208	0	0	5	24	0	52	0	289
6.	560 – RSUP Dr. Kariadi	168	1	3	0	15	0	11	0	198
7.	570 – RSUD Dr. Soetomo	256	13	0	4	21	0	14	0	308
8.	580 – RSUP Dr. Sardjito	136	1	0	5	5	0	30	0	177
9.	590 – RSUP Persahabatan	168	0	1	0	37	0	17	0	223
10.	600 – RSUP Dr. H. Adam Malik	242	3	0	2	21	0	45	0	313
11.	610 – RSU Kabupaten Tangerang	272	6	0	4	20	0	18	2	322
12.	630 – RSUD Dr. M. Ansari Saleh	200	1	0	1	7	0	9	0	218
13.	640 – RS St. Carolus	166	0	0	0	1	0	7	0	174
14.	650 – RSU Budi Kemuliaan Batam	158	3	0	5	9	0	19	0	194
15.	660 – RSU A. Wahab Sjahranie	130	0	0	2	6	0	12	0	150
16.	670 – RSUD Zainoel Abidin	29	0	0	0	11	0	0	0	40
17.	680 – RSUD Soedarso	11	0	0	0	11	0	0	0	22
18.	690 – RSUD Abepura	6	2	1	1	7	0	0	0	17
19.	700 – RSUD TC Hillers	8	1	0	0	16	0	0	0	25
Total		2559	32	5	33	242	0	249	2	3122

## INA107

Based on uploaded CRFs as of 10 August 2022, a total of 185 participants were enrolled in the ORCHID-COVID-19 study, with 115 from site 610 (RSU Kabupaten Tangerang, Tangerang) and 70 from site 521 (RS Universitas Udayana, Denpasar). This study had 174 (94%) participants who completed the visits, six (3%) participants decided to discontinue their participation in the study (categorized as other), and five (3%) participants died during the study (figure 1). In terms of deaths, 2 participants from site 610 died because of COVID-19 and heart failure, while three from site 521 died from pulmonary embolism; non-ST-segment Elevation Myocardial Infarction; and non-hemorrhagic stroke & thromboembolism.

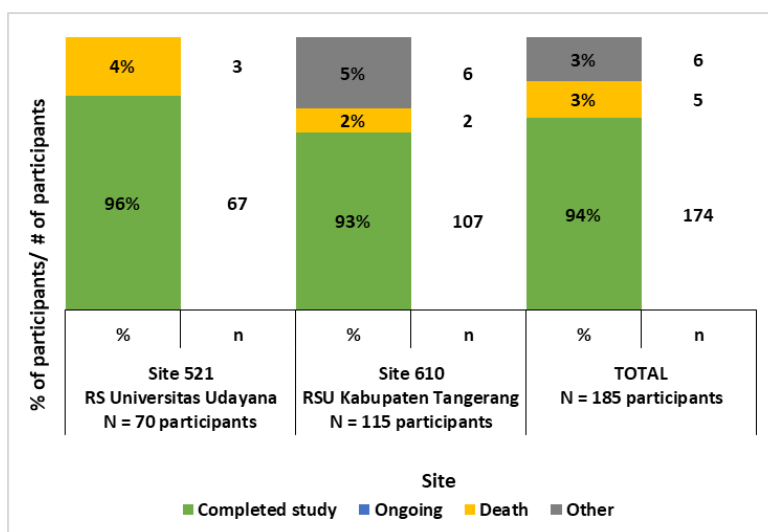


Figure 1. Participant status per site based on uploaded CRF as of 10 Aug 2022

As of 10 August 2022, 153 (83%) participants were positive for COVID-19, while 32 (17%) participants were negative for COVID-19. At site 610, the number of participants with positive COVID-19 was 105 (91%), and 10 (9%) participants were negative for COVID-19. On the other hand, in site 521, there were 48 (69%) participants with positive COVID-19, and 22 (31%) participants were negative COVID-19 (figure 2).

Based on the pathogen identification data, in site 521, SARS-CoV-2 was identified in 47 (69%) participants. SARS-CoV-2 and Dengue (confirmed by PCR SARS-CoV-2 and RDT Dengue IgM) co-infections were identified in 1 (1%) participant. Among negative COVID-19 participants, dengue (confirmed by RDT Dengue NS-1) was also identified in 3 (5%) participants. Meanwhile, based on the data from site 610, SARS-CoV-2 was identified in 103 (90%) participants. SARS-CoV-2 and dengue (confirmed by PCR SARS-CoV-2, RDT Dengue NS-1, and RDT Dengue IgM IgG) co-infection were identified in 2 (2%) participants. Among negative COVID-19 participants, influenza (confirmed by PCR) was identified in 2 (2%) participants. Dengue (confirmed by RDT Dengue NS-1 and RDT Dengue IgM IgG) was also identified in 1 (1%) participant. Overall, the pathogens among 26 (14%) negative COVID-19 participants (19 participants from Site 521 and 7 participants from site 610) were still unidentifiable (figure 3).

Because the enrolment period stopped on 15 July 2022, the secretariat is now preparing for the study close-out before switching to the ORCHID general study. The medical record review was completed on the 2nd week of August, and the Data Quality Assurance Plan (DQAP) document was finalized by the statistician team on the 4th week. Currently, the Data Management Team is conducting a data audit as planned in DQAP.

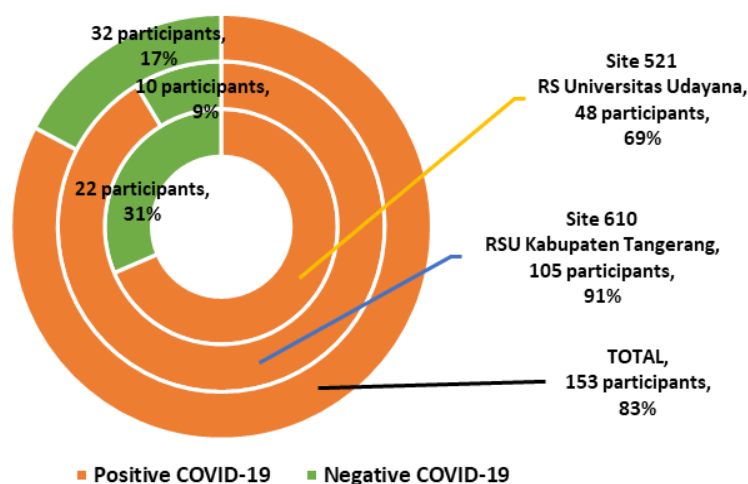


Figure 2. COVID-19 cases at enrolment based on uploaded CRF per 10 August 2022

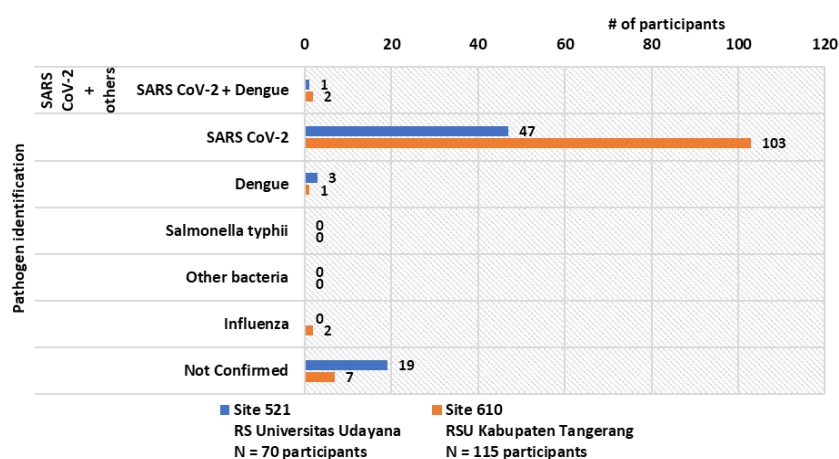


Figure 3. Pathogen identification based on uploaded CRF per 10 August 2022

In parallel, the ethical clearance submission for ORCHID General protocol was processed at the new EC/IRB, namely the Health Research Ethic Commission of Health Polytechnic Jakarta II, on 15 July 2022. After coordinating with the IRB, the ORCHID General protocol was approved on 4 August 2022. Our team will discuss the ORCHID General study plan with the network steering committee to better understand the research's urgency and the sponsor's financial support.

The core team has shared a preliminary data based on available variables on the FLU-PRO questionnaires with John Power and NIAID team. The meeting to further discuss the FLU-PRO manuscripts with these groups will be planned on September 1, 2022. Several discussions through online meetings and email will be conducted by appointment after the session.



# INA-RESPOND Newsletter

## NETWORK STEERING COMMITTEE MEETING

By: Dedy Hidayat, Nurhayati



REPORT

The 2nd INA-RESPOND Steering Committee meeting of 2022 was held on August 24-25 and attended by almost all members of the INA-RESPOND Steering Committee (SC), partners, and the INA-RESPOND Secretariat. The meeting, which was held for two days, discussed the challenges faced by the network, such as emerging issues related to research activities, bureaucracy/permit, funding, and communication. One of the topics that became an interesting discussion was which direction the INA-RESPOND network would go, especially regarding its position in the bigger picture related to the Directorate General at the Ministry of Health, Republic of Indonesia. The SC members recommended placing INA-RESPOND under the Director General of Health Services (*Dirjen YanKes*). This decision is made by considering that the hospitals which are the research site of the INA-RESPOND network are also under the Ministry of Health, especially Dirjen YanKes. Thus, communication and bureaucracy among institutions will be more accessible because all institutions are under the same roof.

In addition to the INA-RESPOND position, SC members listened to the latest research, data processing/analysis, and manuscript writing developments. Everyone in the meeting was dedicated to finding the best solution for any issues raised. The INA-RESPOND network has proven its worth, and all stakeholders are doing what they can to contribute. The INA-RESPOND network is also working on updating/revising its Strategic Plan for the next five years, considering all the changes it has had so far. The development of the Strategic Plan document will later consider the inputs from external parties such as representatives from the DG of Health Services.

Other discussion topics were whole genome sequence testing and capacity building by INA-RESPOND Reference Lab, candidates and requirements for the Doctoral program at UNSW (Biostatics), and a statistics workshop (planned for February 2023). Subsequent meetings were planned and scheduled to discuss the matters further.

The next NSC meeting is planned for the first week of December 2022.

# INA-RESPOND Newsletter

## METAGENOMIC NGS (mNGS) TO DETERMINE THE ETIOLOGY OF INFECTION

By: Ungke Anton Jaya

In March 2022, cases of severe acute hepatitis of unknown etiology occurred in many countries beginning in the UK and reported in other countries, including Indonesia. Interestingly, those cases turned out negative after a series of testing to diagnose hepatitis A-E and other common pathogens related to hepatitis infection. In some cases, the preliminary test gave a positive result for SARSCoV2, HHV-6, HHV-7, and Adenovirus. Due to the uncertain etiology of the outbreak, an untargeted metagenomics attempt was made, resulting in the most abundant reads of Adeno associated virus2 (AAV2). The findings were confirmed by PCR specific assay. (1) This was an excellent example of metagenomics sequencing as an important tool to identify the etiology of infection. Here we will explore further the potential of this method.

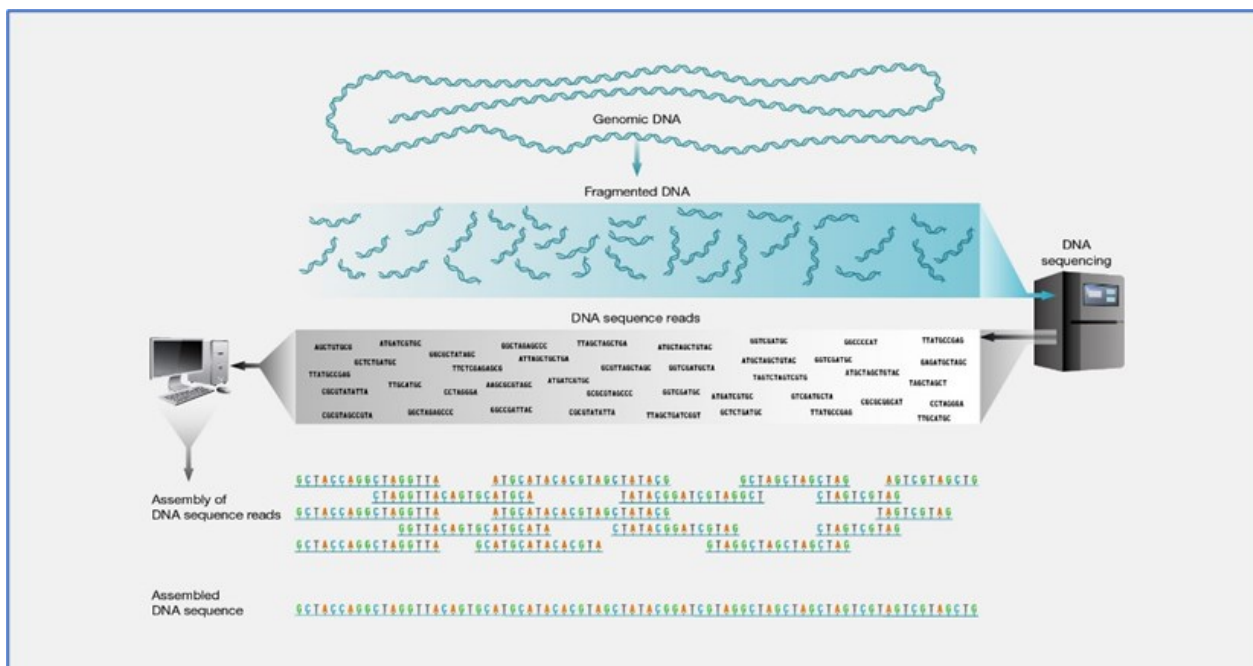
### Metagenomics Next Generation Sequencing (mNGS)

DNA sequencing is the method to identify the order of nucleotide sequence of an organism's genome. This sequence is

unique for each organism and can be used to identify a particular organism. If we can identify a piece of DNA fragment sequence and compare it to the GenBank DNA database, we can identify the organism to which the DNA fragments belong. This method can be developed as a tool to diagnose the etiology of infection.

Shotgun sequencing is a laboratory technique for determining the DNA sequence of an organism's genome. The method involves randomly breaking up the genome into small DNA fragments that are sequenced individually. Later, a computer program looks for an overlapping sequence in the DNA fragments, using them to reassemble the fragments in their correct order to reconstitute the genome

(picture 1). Primer is not always required in sequencing with the shotgun method, in contrast with conventional Sanger sequencing which primer is always needed. This shotgun approach is the basic principle for metagenomics sequencing.



Picture 1. Shotgun sequencing (Courtesy: National Human Genome Research Institute. <https://www.genome.gov/genetics-glossary/Shotgun-Sequencing>)(2)



mNGS is a powerful technique that enables the detection of the full spectrum of pathogens present in any specimen in a single test. mNGS can also provide information on the relative abundance of the organism in the sample containing a community

In contrast to metagenomics NGS, the conventional Sanger sequencing requires a primer to start the sequencing process and generates a sequence of 500 to 1000 nucleotide bases length in one direction, forward or reverse only (Picture 2). To sequence a long fragment of a genome, many primers are pre-designed using a reference sequence of the target organism. Sanger sequencing requires both forward and reverse primers to obtain complete sequencing of the targeted genome. Sanger sequencing requires a DNA template that is homogeneous and abundant from a targeted organism that is usually generated through PCR amplification. If DNA templates contain DNA mixtures from many organisms, the Sanger sequencing reaction will generate an unspecific sequence peak that is uninterpretable. The condition that makes metagenomics sequencing using the Sanger method will be extremely difficult. Sanger sequencing is more suitable to sequence targeted specific pathogens from PCR products.

The metagenomics NGS platform has strong advantage and power to be used as a diagnostic tool for the etiology of infec-



tion, including bacterial, fungal, and viral. In reality, it remains a very challenging process until now. The clinical sample is overwhelmed by human cells with a genome size of 3.200 Mb (Mega base) per cell that outnumber compared to microbes, viruses (4 kb to 1.3 Mb), bacterial (0.6 to 8.0 Mb), or fungal (8.97 - 177.57 Mb). The throat swab specimen always contains both human epithelial cells and commensal bacteria that make detection of the viral genome as potential etiology like finding a "needle-in-a-haystack" situation. The effort will be less complicated if clinical samples come from sterile body sites such as serum and cerebrospinal fluid, which normally contain no pathogen. In the attempt to detect the viral genome, following nucleic acid extraction, human genomic can further be depleted by enzymatic reaction, leaving the viral RNA more exposed for detection.

Application of metagenomics NGS for diagnosis of bacterial infection can be conducted by targeted sequencing using PCR amplification targeting universal bacterial 16s ribosomal RNA (rRNA) gene to increase sensitivity and specificity. This method is not unbiased sequencing but a targeted metagenomics NGS. It is very common that mNGS output normally detects multiple bacterial genome. To determine the etiology of infection, complex bioinformatics analysis and algorithm will be followed, such as whether the bacterial is known as a human pathogen or not and the relative abundance of certain bacterial genomes reflected as the abundance of sequence read/fragment. A similar approach can be used to identify suspects of fungal infection using universal PCR amplification targeting 18s rRNA and the internal transcribed spacer (ITS) gene.

The more challenging process is identifying viral infection with unknown etiology since virus does not have a universal sequence. The viral metagenomics approach can be made by PCR amplification using multiplex primer followed by an mNGS assay. For example, mNGS used 285 and 256 primer pairs to identify 46 virus species causing hemorrhagic fevers. (3) or sequencing whole genome virus SARSCoV2 using ARCTIC primer set from clinical respiratory sample. Another approach is using random primer PCR approach that was successfully used to identify viruses in samples from Sepsis cases with unknown etiology. (4) Another viral metagenomics approach is using capture probe enrichment VirCap Seq-VERT that employs ~2 million probes covering the genomes of members of the 207 viral taxa known to infect vertebrates, including humans. The probe set has been commercially available. (5) All approaches apply untargeted or unbiased high throughput sequencing.

Development of metagenomics NGS for detection of infection improves very fast along with the growing capacity to do NGS and the decrease in the cost of NGS reagents and consumables. Metagenomics NGS still faces major challenges to becoming a reliable diagnostic tool, with main challenges like assay validation, reproducibility, high cost, long turnaround time, and ob-

taining regulatory approval. In fact, several groups have successfully validated mNGS in Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratories for diagnosing infections, including meningitis or encephalitis, sepsis, and pneumonia, and these assays are now available for clinical reference testing of patients.

In Indonesia, metagenomics NGS for bacteria has been initiated in researching the human gut microbiome and antibiotic resistance gene of *Mycobacterium tuberculosis*. Recently NGS has been used in massive efforts for targeted sequencing of genomic surveillance of SARSCoV2. The activity has provided the country with the infrastructure capacity, instrument, reagent, bioinformatics skills, and experience in NGS application. The NGS capacity has the potential to switch to metagenomics NGS if needed to identify the diagnosis of infection, such as in the diagnosis of acute hepatitis cases with unknown etiology in Indonesia.

Clinical metagenomics NGS application for identification of infection still faces many challenges in becoming a diagnostic tool for patient treatment. However, referring to the promising potency, the development of mNGS is currently on the fast track to becoming a powerful tool for diagnosing infection.

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# INA-RESPOND Newsletter

## EXERCISE IS A SELF-CARE FOR A BREASTFEEDING MOTHER

By: Risky Dwi Rahayu



dr. Risky Dwi Rahayu, M.Gizi

SPORTS & LIFESTYLE

Breastmilk is the gold standard for infant feeding and nutrition. It provides all nutrients adjusted to the needs of the infant. Mothers are recommended to breastfeed their infants exclusively until six months old and continue to two years of life. Not only is breastmilk physically beneficial for infants, but it

also provides psychological benefits through connection and bonding during the action. Mothers also benefit from it due to the release of oxytocin and prolactin, which reduce stress and increase positive feelings.

However, breastfeeding could be overwhelming for mothers. Their priority is their infants' health, and they spend most of their time caring for the baby. They lack time to consider proper food intake and physical activity. Moreover, they could feel fatigued and often face more barriers than a supportive environment for their health. About 6-13 % of mothers have postpartum depression. On the other hand, pregnancy causes physiological changes and weight gain, which contribute to the development of overweight and obesity. One birth increases the risk of mothers being overweight by 60% and obese by 110% due to postpartum weight retention. Lactation only is not enough to bring back the mother's body weight to the pre-pregnancy level. Although it is known that breastfeeding reduces postpartum weight retention

by six months, it should meet the condition that mothers breastfeed exclusively, with approximately 12 kg gestational weight gain.

It is proven that exercise during the postpartum period will help reduce mothers' body weight. It is the easiest and cheapest intervention to create optimal health and wellness during the postpartum period and beyond. Exercise will boost the breastfeeding mother's energy level. They will feel better, reduce stress, and sleep better after one exercise session. Their muscles are stronger, especially core muscles. Mothers should consider exercise as relaxation, me-time or time break from taking care of the baby, and time to focus on their health in the transitional period. No study successfully proves that exercise during pregnancy will reduce postpartum depression risk. However, exercise is an effective adjuvant therapy to manage postpartum depression.

### Physical Activity Recommendation

WHO recommends that breastfeeding mothers, without complications, regularly do physical activity as part of their work, domestic chores, transportation (walking, cycling), and recreation/leisure (play, exercise, sports). It is also recommended for the mothers to do moderate-intensity aerobic physical activity for at least 150 minutes per week. Any muscle-strengthening activities and gentle stretching will also be beneficial for their health. There is a dose-response relationship in exercise. It means that doing any exercise, even in the shortest duration and lower frequency, is still better than doing nothing. So, how soon could mothers start?

Some physiologic changes due to pregnancy stay for 4-6 months, i.e., weak lower back and core muscles, flexible ligaments and joints, and increased breast size. Therefore, exercise should be started gradually and consider-

ing several factors such as delivery method, ease of delivery, and physical activity level before and during pregnancy. Those with normal delivery could start physical activity earlier than those with caesarian delivery. Mothers who were engaged in regular exercise before and during pregnancy will also find it easier to do physical activity/exercise postpartum. It is advisable to consult with the obstetric consultant in weeks 6-8 to do a careful examination.

During the first six weeks, the physical activity aims to promote healing and weight reduction and provide a time break with the baby. Options for the mothers are walking or strolling with the baby. They should stop if they feel pain or uncomfortable and have heavier or color changes in postnatal bleeding. After six weeks, the goal of physical activity is to fulfill the recommendation. If mothers become stronger, cycling (if there's no stitching that would be aggravated) can be performed. They could also participate in post-natal exercise classes with the baby (if accessible). Online exercise is also a good choice.

### **Impact of exercise on breastfeeding**

Mothers may worry if exercise negatively impacts breastmilk quality and infant growth. This is logical because both exercise and breastfeeding require considerable energy. Women lose water in the form of sweat and burn 300-600 kcal/hour. However, regular exercise with moderate-vigorous intensity will not change breastmilk volume and quality. Meanwhile, intense anaerobic exercise could change breast milk taste due to lactic acid formation, which then changes breastfeeding behavior. It is believed that breastfeeding will not interfere infant's growth. Mothers could fulfill these conditions: (1) calorie intake is not less than calorie expenditure (intake is not < 20-25% calorie expenditure); (2) mothers should consume at least 1500 kcal per day; and (3) weight loss of no more than 350 – 450 gr per week. A good indicator of exercise and breastfeeding going well is when the baby looks healthy, full, and has normal growth.

### **Additional Consideration**

**Maintain good hydration** – Due to increased energy requirements, mothers commonly increase their calorie intake but forget hydration. It leads to the risk of decreased breastmilk volume, especially if the exercise vol-

ume is increased. There is no recommended amount of fluid, but the general hydration guideline is that the clearer the urine color, the better the hydration

**Extra breast support** – Breast size and mobility are increased after pregnancy. Use cotton material to decrease the risk of abrasion, a sports bra, or a crisscross bandage over the chest and shoulder to reduce discomfort. Schedule exercise after breastfeeding to reduce breast weight and feel more comfortable, especially if mothers want to do more vigorous exercise or jumping activity.

**Pay attention to the baby's cue** – If the baby is reluctant to breastfeed after exercise, there is a possibility of an increased lactic acid level. Lower the exercise intensity to bring back the baby's enthusiasm to breastfeed.

**Look for support** – Join a support group or birth club may help to maintain exercise compliance. The family can offer to babysit while the mother does the exercise. That is the least form of support for breastfeeding mothers in taking care of themselves.

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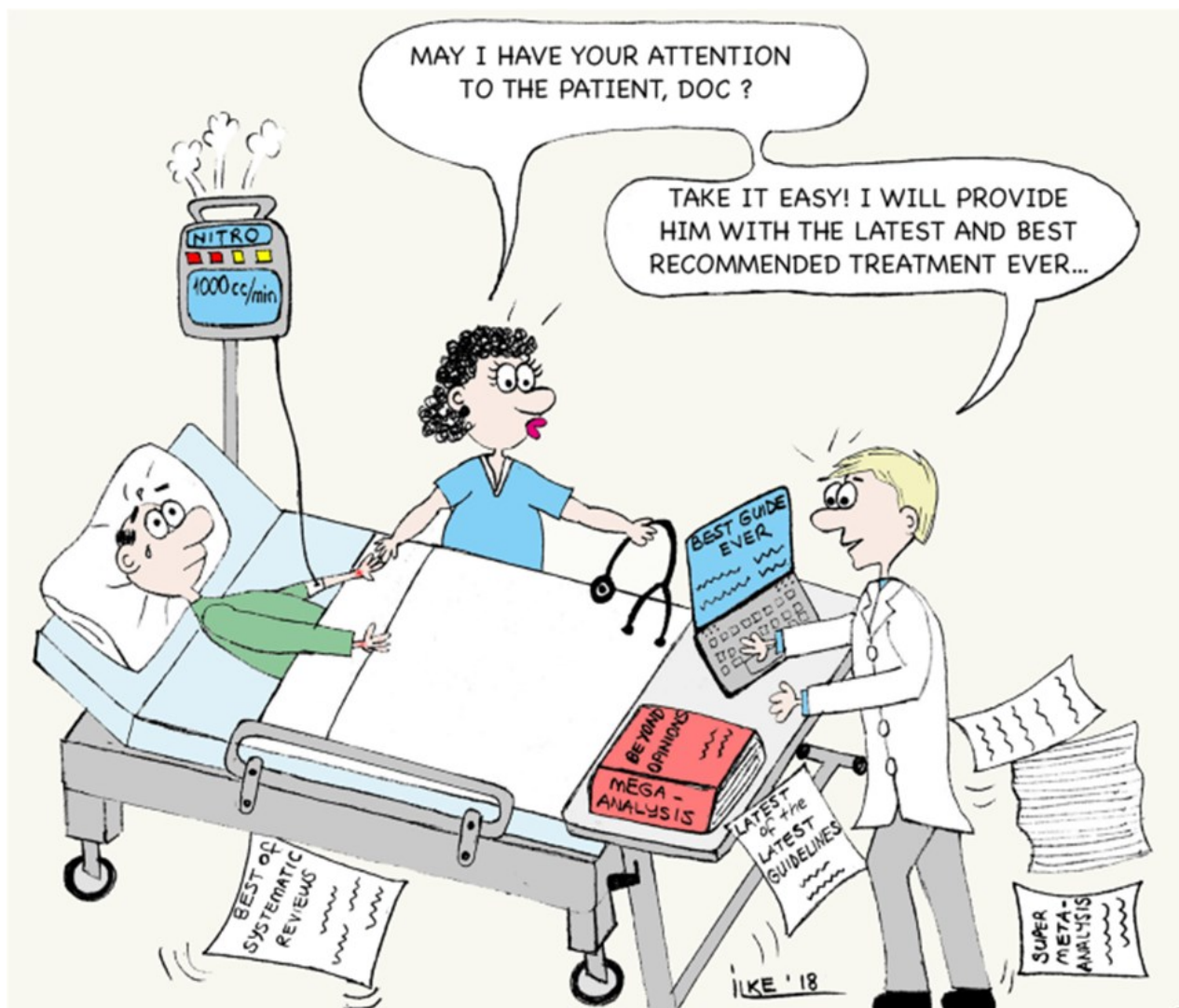
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# INA-RESPOND Newsletter

## NARRATIVE REVIEW, SYSTEMATIC REVIEW, AND SCOPING REVIEW: A BRIEF SUMMARY

By: Aly Diana

COMIC CORNER



In general, narrative review, systematic review, and scoping review are probably the most common review conducted in the scientific field, with scoping review gaining more and more popularity lately. In brief, let's see about the "definition" of these three reviews and then learn a bit more about the different indications for the systematic and scoping review.

A narrative review is a summary of previously published articles on a topic, with the possibility of introducing modifications. Most book chapters are narrative reviews of the literature. Generally, traditional narrative reviews are informal and do not follow a set structure. As such, they can be subjective or less comprehensive. Be careful, though, as some journals no longer accept narrative literature reviews for publication. In contrast, a system-



atic review is performed by systematically evaluating good-quality quantitative evidence to answer a specific clinical question. At least three authors are required for a systematic review: two authors independently screen and evaluate the literature, and the third author adjudicates any conflicting opinions. This methodology minimizes the biases that can be introduced with non-systematically conducted reviews. Systematic reviews must be registered in PROSPERO, an international database of prospectively registered systematic reviews.

A relatively new type of review is the scoping review. Scoping review is a precursor to a systematic review, probing wide-ranging questions. A scoping review is a preliminary assessment of the available literature to identify the nature and extent of the evidence (usually including ongoing research); it's also called mapping the evidence. It is done when the literature is complex or diverse or when a topic has not been extensively examined. A scoping review's results help determine whether a systematic review is warranted. Unlike narrative reviews, a scoping review is structured, rigorous, transparent, and reproducible. Yet, it does not include a risk of bias assessment of the studies included and is therefore not free from potential biases. The results of a scoping review can be used to shape future research, but they cannot be used to recommend clinical practice or treatment. As for now, no registration to PROSPERO is required.

Authors deciding between the systematic review or scoping review approach should carefully consider the indications for each synthesis type and determine precisely what question they are asking and what purpose they are trying to achieve with their review. Broadly, indications for systematic review are: 1) uncover the international evidence; 2) confirm current practice/ address any variation/identify new practices; 3) identify and inform areas for future research; 4) identify and investigate conflicting results; and 5) produce statements to guide decision-making. And the indications for scoping review are: 1) identify the types of available evidence in a given field; 2) clarify key concepts/ definitions in the literature; 3) examine how research is conducted on a specific topic or field; 4) identify key characteristics or factors related to a concept; 5) as a precursor

to a systematic review; and 6) identify and analyze knowledge gaps.

Scoping review is a valuable tool in the ever-increasing arsenal of evidence synthesis approaches. Although conducted for different purposes/indications compared to systematic reviews, scoping reviews still require rigorous and transparent methods to ensure that the results are trustworthy. Contrary to what some may believe, scoping review is not easier/faster than a systematic review, so please bear this in mind when we decide to conduct a scoping review.

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## INA-RESPOND Newsletter

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

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