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INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

July 2023

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content

July 2023 Edition | issue #118

FEATURES

INA-RESPOND Newsletter

InVITE & PROACTIVE Study Updates

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

InVITE

As of July 10, 2023, 700 participants were enrolled in the study, out of which 244 (34.86%) have completed their participation, while 508 (65.14%) are still actively involved. The study is being carried out across three different sites, all of which are currently at visits 4 and 5. Detailed breakdowns of these visits for each site are presented in Table 1.

Out of the 244 participants who have finished their involvement, 183 (26.14%) completed the study, whereas 44 (6.29%) withdrew. Reasons for withdrawal varied from personal choice, personal circumstances, to loss of interest. Furthermore, some participants failed to receive the complete vaccine regimen within the first 12 months of enrollment, leading to the exclusion of three (0.43%) subjects. Two (0.29%) subjects were discontinued from the study due to the determination that further participation was not in their best interest. Meanwhile, one (0.14%) participant was non-compliant with study procedures. Regrettably, one (0.14%) participant passed away during the study, and ten (1.43%) participants ended their involvement due to other unspecified reasons.

In addition, the study has been monitoring symptomatic visits among participants. As of July 10, 2023, Table 2 provides information about these visits. It's crucial to understand that having COVID-19 symptoms does not necessarily confirm disease contraction.

The MTA Committee held a monitoring session on June 23, 2023, to oversee research progress and ensure compliance with both the Cooperation Agreement and the Material Transfer Agreement. The committee's conclusion was supportive of the study. The MTA Committee, along with the INA-RESPOND team, gained a better understanding of data and specimen management, including ownership and confidentiality. They also reminded the INA-RESPOND team to ensure knowledge and technology transfer for capacity building throughout the study.

The Standard Operating Procedure (SOP) for the Credo Box for Specimen Shipment was published on July 3, 2023, and was subsequently trained to the Research Assistant on July 10, 2023.

Site	Symptomatic Visit		
	# of visit	Positive	Negative
01	102	61	41
02	14	6	8
03	2	1	1
Total	118	68	50

Table 2. Symptomatic Visit Details per July 10, 2023

Site	Screening / Visit 1	Enrollment Failure	Enrolled	Ongoing	Add. Visit 1	Visit 2	Add. Visit 2	Add. Visit 3	Visit 3	Agree Ext.	Not Agree Ext.	Ext. Visit 4	Ext. Visit 5
01	345	2	343	253	88	326	314	306	315	286	29	249	34
02	228	1	227	108	97	214	191	188	195	151	44	151	42
03	130	0	130	95		130			129	95	35	95	0
Total	703	3	700	456	185	670	505	494	639	532	108	495	76

Table 1. Details of Visits per site per July 10, 2023

INA104

As of June 22, 2023, all 4,336 subjects enrolled in the study have successfully completed their participation. The final site, Site 520, concluded its last follow-up visit in May 2023.

With respect to the end-of-study subjects, 3,485 successfully completed the study up to the 36-month follow-up. However, we faced challenges with 506 subjects who were lost to follow-up, making it difficult to acquire complete data for their entire study period. Furthermore, 248 subjects unfortunately passed away during the study. Due to personal reasons or changes in their circumstances, 32 subjects decided to withdraw their consent. In addition, 38 subjects relocated to cities lacking a PROACTIVE Site, while 5 subjects were found to be HIV negative. Lastly, 2 subjects were suspended due to their imprisonment. The progression of the study at each site is detailed in Figure 1.

To facilitate a systematic and comprehensive close-out process, sites that have finished their follow-up period are currently preparing for their official close-out visit, which signifies the end of their participation in the study. In July 2023, several sites, including 660, 530, and 670, are scheduled for close-out.

As part of the process, sites must complete all items on the close-out visit checklist. This includes, but is not limited to, Case Report Form/Source Documents, all AE/SAE/UP Reports, Data Management, Site Regulatory Binder, Logs, Equipment and Supplies, and Specimens. This extensive checklist ensures proper organization and accountability of all required documentation and data, thereby streamlining the close-out process.

Following a successful close-out visit, sites are then required to archive all study documents within one month. These documents must be retained for a minimum of 5 years following the study's conclusion.

Proactive measures have already been taken by several sites, including 610, 630, and 560, who have sent their study documents to the Secretariat. Furthermore, sites that have concluded their SCV in the forthcoming weeks will follow suit. The Secretariat has partnered with a reliable vendor to ensure the proper archiving and safekeeping of these crucial study documents.

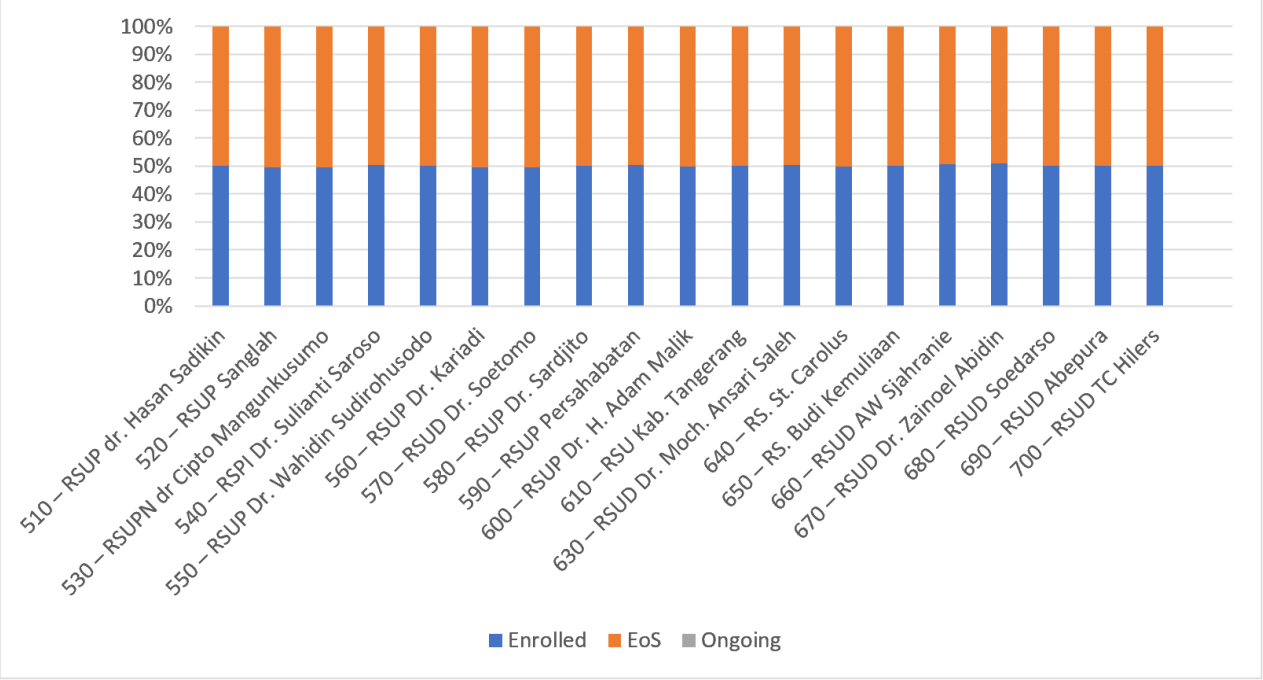

Figure 1. Site's Study Progress

Table 2. Study timeline for Site Close Out Visit (SCV)

Site	Site Name	Site Close Out Visit (SCV)	
		Scheduled	Actual
510	RS Hasan Sadikin, Bandung	Jun-23	15-16 Jun 2023
520	RSUP Sanglah, Denpasar	Sep-23	Sep 2023 (Tbd)
530	RS Cipto Mangunkusumo, Jakarta	Jul-23	31 Jul – 1 Aug 2023
540	RS Sulianti Saroso, Jakarta	Sep-23	Aug 2023 (Tbd)
550	RS Wahidin Sudirohusodo, Makassar	May-23	24-15 May 2023
560	RS Kariadi, Semarang	Mar-23	30-31 Mar 2023
570	RS Soetomo, Surabaya	Apr-23	13-14 Apr 2023
580	RS Sardjito, Yogyakarta	Apr-23	20-21 Apr 2023
590	RS Persahabatan, Jakarta	Jun-23	14-15 Jun 2023
600	RS Adam Malik, Medan	Jun-23	21-23 Jun 2023
610	RSU Kab Tangerang, Banten	Mar-23	08-09 Mar 2023
630	RSUD M. Ansari Saleh, Banjarmasin	Apr-23	05-06 Apr 2023
640	RS St. Carolus, Jakarta	Jun-23	05-06 Jun 2023
650	RS Budi Kemuliaan, Batam	Jun-23	07-08 Jun 2023
660	RSU Wahab Sjahranie, Samarinda	Jul-23	12-14 Jul 2023
670	RSUD dr. Zainoel Abidin Banda Aceh	Jul-23	12-13 Jul 2023
680	RSUD dr. Soedarso, Pontianak	Sep-23	Sep 2023 (Tbd)
690	Abepura	Jul-23	1-2 Aug 2023
700	RSUD Dr. TC Hillers Maumere	Aug-23	9-10 Aug 2023

INA-RESPOND Newsletter

FROM OUR PARTNER

WRITING TIPS: COMMUNICATING SCIENCE TO THE PUBLIC

By: Christopher Worthington

An ongoing conversation between scientists and the public has always been important (think of the polio vaccine rollout and the Apollo moon missions, for instance). The COVID-19 pandemic brought this conversation to a new height of significance and scrutiny—suddenly, people relied on scientists to relay vital, potentially life-saving information.

Therefore, it's not surprising that NIH has a checklist for communicating science and health research to the public. The suggestions on this list can help prospective writers describe their work to the public. Recommendations from the checklist include:

- Provide perspective for the study and explain the context
- Do not overstate the importance or significance of a study, finding, or situation
- Use clear language to describe the science and only use conditional language when appropriate
- Convey information respectfully—do not stigmatize or assign blame
- Provide the original study by linking to PubMed or other reliable sources
- Note funding sources and potential conflicts of interest

Speaking of clear language (the third bullet point above), the Federal Plain Language Guidelines are another resource for any type of writing, including communicating science to the public. Scientific research is often technical and complex, but it is possible to convey meaningful, accurate information to a lay audience without using indecipherable jargon and shoddy constructions.

The University of Oxford has long recognized the importance of communicating science to the public and even has a staff position dedicated to it: the Simonyi Professor for Public Understanding of Science. Marcus du Sautoy, who currently holds this post, told *Scientific American*:

"I think communication should be a fundamental part of any scientist's training as frankly it benefits your own science. Science, in my mind, has always been about two things, discovery and communication. As scientists we have to learn how to emphasize with a public audience for them to fully understand and to acknowledge the ideas we are seeing. The broader audience science can reach, the bigger the benefit in terms of the new ideas you are transmitting as a scientist."

Finally, do not get discouraged. Writing is hard work! A 2021 *Nature Medicine* article titled "How to be a good science communicator" described science communication as more of an art than a science. Like any art, it takes practice.

INA-RESPOND Newsletter

TOP FOUR NEGLECTED RODENT-BORNE PATHOGENS IN INDONESIA

By: Upi Nurhayati, Aly Diana, Dewi Lokida, Adhella Menur

Revisiting the top four rodent-borne pathogens (Yersinia pestis, Leptospira spp., Rickettsia typhi, and Seoul Orthohantavirus) in Indonesia: neglected yet significant *Plus, a report from dr. Dewi Lokida, Sp.PK (K) supervision on the PESTO-RITA research in Pasuruan District, East Java

Each year, infectious diseases kill about 7 million people, devastating global health and creating significant economic losses. Zoonotic infections, which are naturally transmitted from vertebrate animals to humans, account for 70% of emerging infectious diseases. Rodents are well-known hosts and vectors for zoonotic infections, representing about 43% of all mammalian species worldwide. There are around 2,375 living species, spanning mice, rats, squirrels, hamsters, voles, beavers, chipmunks, capybara, and more. Rodents are being introduced from continent to continent along with human migration and trade. They are highly adapted to modified environments, making them one of the best-suited mammals for living in various habitats. Their capability to adapt within a relatively short period is due to their accelerated evolution, where the genomes evolve 4 to 6 times faster than primates. Interestingly, rats and mice are highly intelligent rodents. They are natural students who excel at learning and understanding concepts.

The combination of abundant food, global warming, and deforestation, which drove them to migrate from their natural habitats to human settlements, and a rapid reproduction rate has resulted in rodent's explosion and increasing the risk of human exposure to the pathogens that rodents carry. Rodent-borne diseases can be spread via two different pathways: direct and indirect. Rodents can spread pathogens directly to humans, e.g., by biting them or because humans consume food products or water contaminated with rodent feces. Moreover, humans can encounter surface water contaminated with rodent urine or inhale germs from rodent excrements. Rodent-borne pathogens can also be spread indirectly to humans. They can serve as amplifying hosts of the pathogens and can bring them into contact with humans through ectoparasitic arthropod vectors (ticks, mites, and fleas). The rodent population in Indonesia is growing and becoming more brazen. So far, about 171 species of rodents have been identified in the country. The "commensal rodents" live near human and their surroundings, such as Rattus norvegicus (sewage rat), R. rattus diardii (roof rat), Mus musculus (house mouse), R. rattus brevicaudatus (ricefield rat), R. rattus roquei (wood rat), and R. exulans (polynesian rat). They can carry at least 85 unique zoonotic diseases from bacterial, viral, parasitic, and fungal infections. This article will briefly discuss the top four rodent-borne pathogens: Yersinia pestis, Leptospira spp., Rickettsia typhi, and Seoul Orthohantavirus, which are prevalent in Indonesia.

The first INA-RESPOND study, titled Acute Febrile Illness Requiring Hospitalization (AFIRE) and conducted from 2013-2016, revealed the critical prob-

Figure. Infected rodents serve as an amplifying host for *Yersinia pestis* and *Rickettsia typhi*, and the Oriental rat flea (*Xenopsylla cheopis*) acts as the main vector responsible for the transmission to humans. *Leptospira spp.* infections typically result from both direct and indirect exposure or contact with the urine of infected rodents and spread through water or soil. Seoul Orthohantavirus enters the human body through the biting infectious rodents, inhaling virus-contaminated aerosols, ingesting polluted food or direct mucosal contact with rodents' excreta. *Created with Biorender.com.*

lem of misdiagnosing rodent-borne diseases in Indonesia. The study recruited febrile subjects hospitalized at the country's eight largest hospitals. Of the 156 rodent-borne disease cases identified (103 rickettsioses, 51 leptospirosis, and 2 Seoul orthohantavirus infections), 134 patients (85.9%) were misdiagnosed as other tropical diseases. Consequently, 48 subjects received treatment for Salmonella typhi, 33 for dengue virus, and 53 for other bacterial/ viral infections during their hospitalization.

Yersinia pestis, a member of the family Enterobacteriaceae, causes Plague disease with a case fatality rate (CFR) between 30–100% if left untreated. Plague is one of the most infamous and feared diseases, having caused three pandemics - the Justinian Plague in the 6th century, the Black Death in the 14th century, and another in China in the late 19th century - and resulted in more than 150 million deaths worldwide. People infected with Y. pestis often develop symptoms after an incubation period of one to seven days. Plague manifests itself in three main clinical syndromes: 1) bubonic Plague, 2) septicemic Plague, and 3) pneumonic Plague, which is transmissible from human-to-human. Bubonic Plague is the most common form and is characterized by painful swollen lymph nodes or 'buboes'. Septicemic Plague presents as hypotension and shock without a bubo, and pneumonic Plague patients demonstrate high fever, cough, chest pain, and hemoptysis. Confirmation of Plague requires lab testing (staining, culture, molecular, and serology). The best practice is to identify Y. pestis from a sample of pus from a bubo, blood or sputum. There is a laboratory validated antigen rapid dipstick test now widely used in Africa and South America, with the support of the WHO. Early antibiotics are the cornerstone of effective treatment, with aminoglycosides being considered first-line treatment. Alternative treatments include doxycycline, tetracycline, and levofloxacin. Vaccines to prevent Y. pestis infection exist, especially given concerns about the potential widespread dissemination of Plague via bioterrorism. However, the WHO only recommends vaccination for high-risk groups. Two types of Plague vaccines are currently used in various parts of the world. The live vaccine is derived from a Pgm2 attenuated strain, usually related to EV76, while the killed vaccine uses a formalin-fixed virulent strain of Y. pestis. Natural transmission to humans remains a possibility in many regions of the world, where foci exist in infected rodent populations. Even today, there are an estimated 1000–3000 cases of the bubonic Plague

each year worldwide, mainly in Africa, the Americas, and Asia. The three most endemic countries are the Democratic Republic of Congo, Madagascar, and Peru. In Indonesia, the main areas to monitor for Plague are villages located in the high valley that extends between the summits of two volcanoes. These fall into four foci which are in Selo and Cepogo in Boyolali District, Central Java; Cangkringan in Sleman District, Yogyakarta; Ciwidey in Bandung Regency, West Java; and Tutur Nongkojajar in Pasuran District, East Java.

Leptopira spp. are spirochete bacteria classified into L. interrogans (pathogenic) and L. biflexa (non-pathogenic). Human infections are caused by L. interrogans, of which there are over 300 known pathogenic serovars. It lives in the kidneys of natural hosts, predominantly in mammals, and is excreted with urine. Most infections caused by leptospires are either subclinical or of very mild severity and often overlap with other febrile illnesses such as dengue and typhoid. However, untreated cases are at an increased risk of progression to the severe manifestation of Weil's disease (jaundice, renal impairment, and hemorrhages), or severe pulmonary hemorrhage syndrome (SPHS), which has a 10-70% CFR. Over 60,000 people die due to leptospirosis annually, and nearly one million are reported to be affected. Reliance on the Microscopic Agglutination Test (MAT), which detects serovar-specific antibodies and is the current gold-standard for serology, is impractical due to technical requirements and expense. Since an accurate rapid diagnostic test (RDT) for leptospirosis is not available, molecular tests and ELISAs for IgM can be used to inform medical management in resource-limited settings. Doxycycline and azithromycin are the recommended treatments for leptospirosis, and empirical administration against suspected or probable leptospirosis cases may prevent the disease's progression. Intravenous penicillin should be initiated for clinically severe forms of the disease, which may contribute to decreasing mortality. In most cases, ceftriaxone can be used as an alternative. Even after decades, we still do not have a universal vaccine for leptospirosis because the immune response is mainly dependent on serovar, does not cross-react, and is based on lipopolysaccharide antigens. Several vaccine platforms have been widely used for many years to induce immunity in animals and humans, with limited success. In Indonesia, according to reports from 11 of 38 provinces, there were 1,408 cases of leptospirosis, with 139 fatal cases (CFR 9.87%) in 2022.

Rickettsia typhi is a gram-negative bacterium that causes murine or flea-borne typhus. It is one of the species from the Rickettsia genus. The genus is classified into four categories: the spotted fever group (SFG), the typhus group (which includes R. typhi), the ancestral group, and the transitional group. Murine typhus often goes unrecognized and is perceived as a clinically mild disease. However, untreated patients may have fever for 12–21 days and a 26% complication rate (including lung, central nervous system, and acute renal injury), indicating the pathogen's substantial burden. There is a diverse range of presentations, from mild constitutional and gastrointestinal symptoms to severe sepsis-like physiology with multiorgan involvement. It is characterized by fever, headache, and macular rash, mainly on the trunk, along with a small black scab or eschar at the site of the insect bite, accompanied by local or general lymphadenopathy. The triad of fever, headache, and rash has historically been used as a clinical diagnostic tool; however, the triad is inconsistent and unreliable. Also, the rash appears an average of 5 days after the onset of symptoms, thus an unreliable early indicator. Ideally, laboratories should be equipped with valid diagnostic assays (PCR for molecular detection during acute illness and indirect fluorescent antibody (IFA) as the gold standard for serology). However, PCR and IFA have several disadvantages,

including the need for an expensive thermal cycler or a fluorescence microscope. Therefore, ELISA can be an alternative when both are unavailable. The drug of choice for treating rickettsial infections is doxycycline; chloramphenicol and azithromycin are an option in the case of allergy and severe disease. Prevention relies on avoiding exposure to flea bites, mainly when residing or traveling to endemic areas, because no vaccine or prophylaxis is available. Murine typhus was first identified in Indonesia in 1951 from fever patients in Jakarta. The disease has been identified in Sumatera, Java, Bali, Sulawesi, Muna, Flores, Timor, and Papua. However, the epidemiology of human rickettsioses in Indonesia is still not well characterized.

Seoul Orthohantavirus (SEOV) is a (-) single-stranded RNA-enveloped virus and one of the species from the family Hantaviridae of order Bunyaviridae. SEOV belongs to the "Old World" hantaviruses group along with Hantaan (HTNV), Dobrava -Belgrade (DOBV), and Puumala (PUUV), generally affect blood vessels and kidneys and can manifest as hemorrhagic fever with renal syndrome (HFRS). The other group, the "New World" hantaviruses, is generally associated with lungs and can manifest as hantavirus pulmonary syndrome (HPS). HFRS has become a significant epidemic, primarily in Asia and Europe. SEOV manifests as moderate HFRS and is associated with a mortality rate of ±1%. The disease has a 1 - 5-week incubation period, starting with a fever and influenza-like symptoms. Classically, HFRS occurs in five distinct phases: febrile (3-5 days), hypotensive (few hours to few days), oliguric (3-7 days), polyuric (1-2 weeks), and convalescent (3-6 months). The oliguric stage accounts for approximately one-half of all hantavirus-related deaths. Interestingly, in SEOV infection, gastrointestinal symptoms and elevated liver enzymes are prominent, but kidney dysfunction is mild, imitating the hepatitis virus. Dual infection with Leptospira spp. may occur since they need a similar rodentia as a reservoir. Evidence of viral antigen in tissue by immunohistochemistry (IHC), the presence of viral RNA in blood or tissue, or positive serological test (ELISA or IFA) result, with compatible history of HFRS, is considered diagnostic for the disease. The treatment of HFRS is mainly supportive and dependent on the clinical manifestations. Currently, no antivirals, vaccines, or immunotherapeutics are approved by the U.S. FDA. Several inactivated vaccines have been generated from hantavirus in cell cultures or the rodent brain, and a few of these have been licensed for use in humans in Korea and China. The existence of Orthohantavirus in rodents in Indonesia was confirmed in 29 provinces based on MoH special research on vectors and reservoirs (Rikhus Vektora) in 2015-2018. About 16 Orthohantaviruses infections (by serology and/or molecular testing) in human manifested as HFRS have been reported since 1995. Three patients were confirmed as SEOV infection by sequencing, with one of the cases co-infected with Leptospira spp.

The top four rodent-borne pathogens are often overlooked due to their similar clinical manifestations with other tropical diseases, even though they can potentially cause considerable epidemics in human populations. The underreporting of cases is due to a lack of integrated surveillance, clinicians' unawareness, unreliable RDTs, and limited access to standard diagnostics. Underdiagnoses could engender inappropriate management, treatment delays, prolonged hospitalization, and increased morbidity and mortality. Further comprehensive research is urgently needed in every aspect: epidemiological, diagnosis, treatment, and vaccine. One Health approach includes human, animal and environmental health must be considered to understand better the epidemiology, clinical burden, and transmission of these neglected yet significant diseases.

Supervision on PESTO-RITA research in Pasuruan Regency, East Java

In 2023, The Eijkman Institute for Molecular Biology and The National Research and Innovation Agency (BRIN) granted support from the WHO to conduct research, namely "Development of Detection and Genomic Characteristics and Molecular Epidemiology of Plague, Leptospirosis, Rickettsioses, and Hantaviruses in East Java and Central Java" or PESTO-RITA research. The head of INA-RESPOND Reference Laboratory, dr. Dewi Lokida, Sp.PK(K) is appointed as the Supervisor. The PESTO-RITA research aims to identify the top four rodent-borne pathogens in humans, ectoparasites, and rodents in hot-spot areas in East and Central Java, Indonesia. Dr. Dewi is responsible for assisting in protocol development, specimen handling from collection to testing (molecular and IFA), and results analysis.

One of the PESTO-RITA research sites is Pasuruan District, East Java. There are Plague hot-spot areas under five Puskesmas (primary health centers/ PHCs) in Pasuruan District, i.e., Nongkojajar, Tutur, Tosari, Puspo, and Pasrepan, which are now have been updated as “Low List Extreme” by the WHO. Plague was brought into East Java by infected rats and fleas in cargoes of rice imported from Rangoon (Myanmar) into the eastern seaport of Surabaya in November 1910. From 1910 to 1920, a total of 240,375 Plague deaths were reported in Java. In 1987, there was a Plague outbreak in Tutur Nongkojajar subdistrict, Pasuruan District, in which 248 cases with 21 deaths were reported. In the same district, one case occurred in 1997, and Plague bacilli were isolated from rodents in one of the villages (Sulorowo village). The last human Plague case from Pasuruan District was reported in 2007, which caused one death of 82 suspects. The government collaborates with the people to

Photo: muskitnas.net

dr. Tjipto Mangunkusumo

strengthen rodent surveillance (rodent live-trapping and fleas' identification) and human surveillance (active case finding). Fortunately, until now, there have been no reports of human Plague cases anymore. However, the surveillance should be consistently performed, as the absence of new Plague cases could also be a sign of a 'silent period,' which may last as long as ten years or even longer, after which sudden explosions of rodents or human Plague may occur.

On 26th-28th June 2023, dr. Dewi visited Pasuruan District, East Java. She discussed research preparation with the Pasuruan Health Officials and field team from the PHCs and Hospitals. She had a chance to lecture about the PESTO-RITA briefly and presented INA-RESPOND AFIRE study results emphasizing rodent-borne pathogens detection. She also visited P2P BBTKLPP Surabaya Laboratory in Nongkojajar to supervise research testing preparation. The activity will continue until next years.

A GLIMPSE OF HEARTWARMING HISTORY

During the first Plague outbreak in Malang, East Java, in 1910, the city was in chaos and locked down. Foreign doctors hesitated to treat the poor local people, and many died without proper treatment. At that time, dr. Tjipto Mangunkusumo and dr. Soetomo stepped in to provide free treatment for local people. They went door to door to monitor the patients. In one house, dr. Tjipto found a crying baby lying in her parents' corpses. He adopted the baby and named her, Pesjati.

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INA-RESPOND Newsletter

BIOMECHANICAL AND MUSCULOSKELETAL CHANGES IN OBESE INDIVIDUALS

By: Edrick Purnomo Putra

When discussing obesity, the conversation typically revolves around the metabolic impact on the body. However, the mechanical strain on the musculoskeletal system, due to the extra weight, is often overlooked. Overweight and obesity are independently associated with an increased risk of developing musculoskeletal disorders.[1] For instance, a study involving 150 severely obese participants, with body mass index (BMI) of 35 kg/m2 or higher, indicated a high prevalence of pain in the ankles and feet (68.7%), lower back (62.7%), knees (53.3%), and upper back (52.0%). The pain is predominantly severe. The study also discovered associations between specific conditions and pain in particular sites: type 2 diabetes correlates with hand/wrist pain; hip pain is associated with sedentary time; insomnia with hip and knee pain; edema in the lower limbs with lower back and ankle/foot pain; obesity degree with ankle/foot pain; and percentage of total fat with ankle/foot pain.[2] Yet, the correlation between an increased BMI and various musculoskeletal disorders isn't extensively described for all musculoskeletal issues.[1]

From a physiological standpoint, the human physique interacts with various forces during daily activities, and these forces progressively shift with body weight. The ground reacts to the body's weight by exerting a force back, known as the ground force reaction (GFR). For people of normal weight, the mechanical forces and GFR acting on the body are relatively lower compared to those with a higher BMI. Joint alignment is maintained and loading effect is minimized by adequate muscle strength and low systemic inflammation. However, as weight or mass progressively increases, mechanical stress also increases, especially in weight-bearing joints. With this, the GFR also amplifies, causing further stress on joints, while muscle strength decreases, failing to provide adequate compensation. Systemic inflammation, which tends to increase with obesity, may also induce biochemical reactions in the musculoskeletal system.[3]

The link between obesity and osteoarthritis (OA) has been well established in numerous studies. Obesity exerts both mechanical and systemic effects on the development of OA. Chronic low-grade inflammation, typically induced by obesity, might trigger the

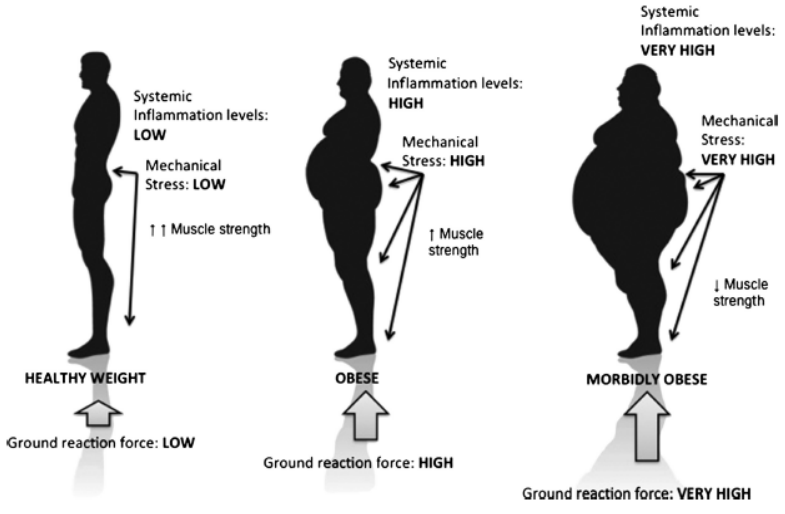

Figure 1. Progressive changes of physiological forces acting on body of people with increased BMI.3

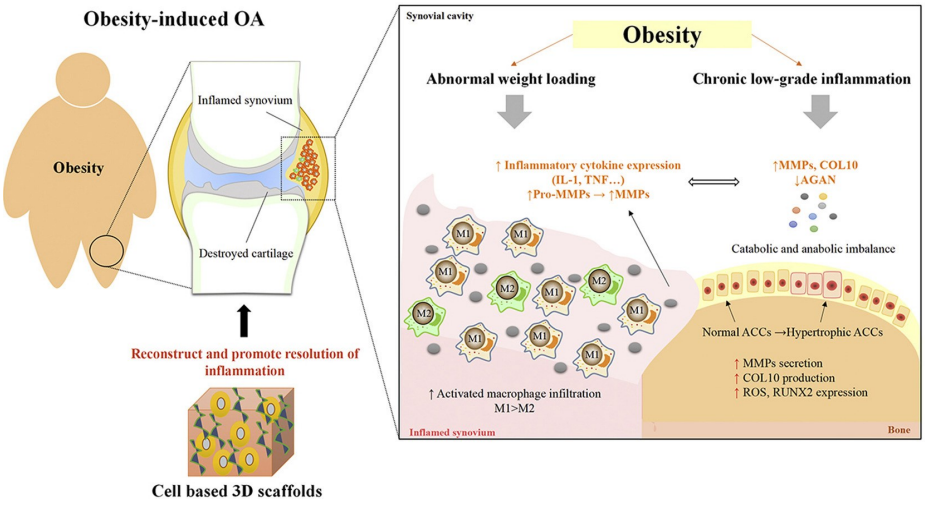

Figure 2. Mechanical and biochemical impact of obesity on the development of OA.4

onset and progression of OA, not only in weight-bearing joints but also in non-weight-bearing ones. Inflammation enhances the production of inflammatory cytokines and might induce macrophage infiltration into the joint synovium, causing local inflammation, pain, swelling, and stiffness in the joint.[4] Recent studies have also linked inflammation in obesity to adipokines from adipose tissue. These adipokines, when in excess, can disrupt cartilage homeostasis, degrade the cartilage matrix, and hinder chondrocyte function.[5] Obesity-associated vascular disease has led to the hypothesis that microvascular changes in the subchondral bone might accelerate the OA process by creating an ischemic effect and altering the nutritional supply to the bone.[5] Furthermore, in diabetes induced by obesity, the formation of advanced glycation end products (AGEs) in the articular cartilage may contribute to increased collagen stiffness.[5]

Excessive and abnormal loading on weight-bearing joints cause shear stress on the knee joint, leading to inflammation and breakdown of articular cartilage. Chondrocytes, the cells within cartilage, have mechanoreceptors sensitive to pressure. Their activation can lead to the expression of cytokines, growth factors, and metalloproteinases, producing mediators that eventually inhibit matrix synthesis and degrade cartilage.[5] Elevated body weight may increase stress on the knee joint, causing malalignment and exacerbating underlying joint issues. Muscle weakness, often associated with obesity, can further impair a joint's ability to absorb stress, given the crucial role muscles play as shock absorbers in joints.[6]

Gait mechanics also change in people with obesity. On the whole, people with a higher BMI typically display slower gait velocity, shorter stride length, slower cadence, and a longer stance period compared to those with a normal BMI. The higher the BMI, the more pronounced the

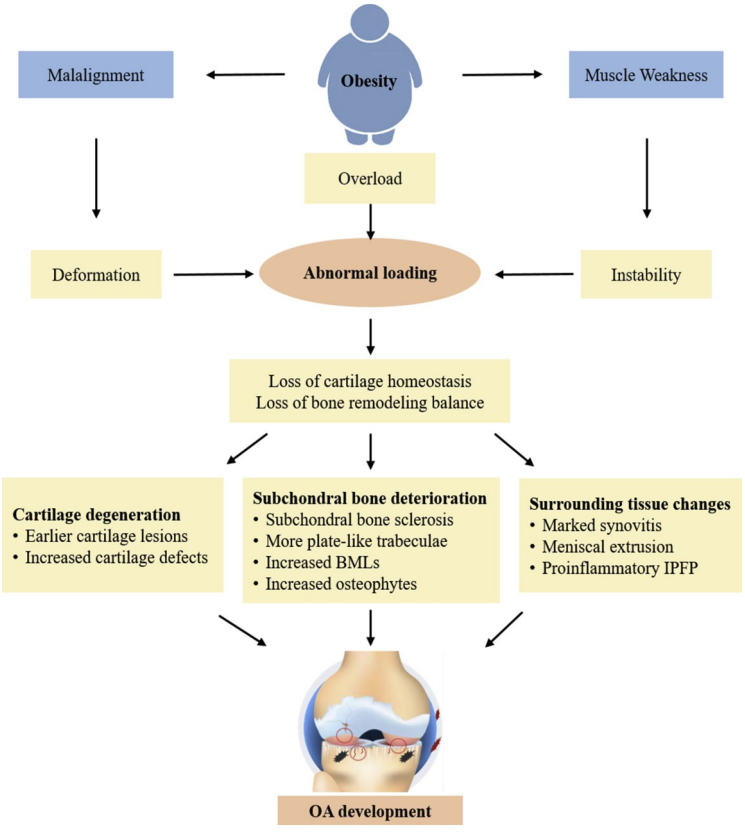

Figure 3. Mechanical changes in weight bearing joints on obesity related

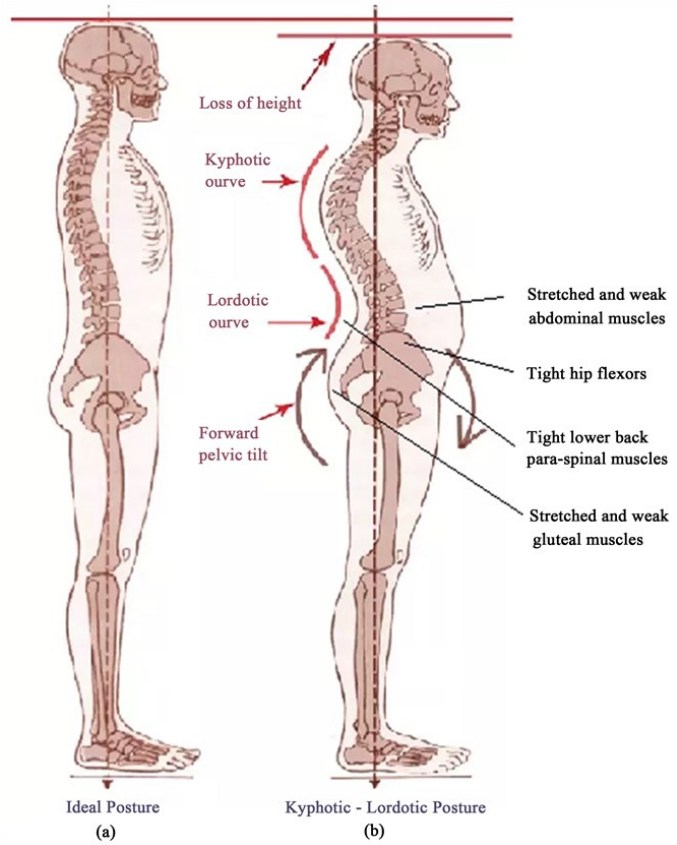

Figure 4. Postural changes in individuals with obesity.[10]

influence on gait energetics and mechanics.[7] A decreased daily activity level is often a result of these walking impairments, as demonstrated by a lower daily step count in obese individuals compared to those of healthy weight.[3] One study found that obese women exhibited a significantly greater touchdown angle, a more extensive total eversion range of motion, and faster maximum eversion velocity, which suggests abnormal rearfoot movement.[8] These differences in walking are associated with an increased risk of musculoskeletal injury and falls in people with obesity.[9]

Another study demonstrated a correlation between a higher BMI and greater peak internal ankle plantar flexion, a lower arch with greater peak ankle eversion and abduction, and knee adduction during walking. Adults with a higher BMI often have lower arches or flat feet, resulting in more flexibility during the propulsive phase of walking and, subsequently, excessive foot pronation. Overpronated feet can lead to lower limb malalignment with excessive loads and a greater toe-out angle during walking, possibly causing foot pain such as chronic plantar heel pain. The combination of walking differences and foot misalignment in obese individuals contributes to musculoskeletal injuries, including posterior tibial tendon dysfunction, ankle sprains, and plantar fasciitis.[9]

Knee adduction also occurs in individuals with obesity. An external knee adduction moment (KAM) during the stance phase of gait is considered indicative of tibiofemoral knee joint loading in the medial compartment and is strongly associated with excessive body mass. One study found a robust association between an increased KAM and the risk of OA progression. Obese individuals often have larger thigh circumferences, necessitating greater hip abduction, a circumferential swing phase, and varus alignment of the knee to prevent thigh touching while walking. This malalignment, particularly in conjunction with a high BMI, intensifies knee OA progression, especially in the medial part of the tibiofemoral joint.[6]

The accumulation of body fat around the waist and hips in individuals with obesity results in an anteriorly tilted pelvis and lumbar lordosis. This tilt is caused by the habitual concentric contraction of the hip flexor, which lengthens the hip extensor eccentrically. Concurrently, abdominal and gluteal muscles weaken and elongate, while paraspinal and flexor muscles shorten. The resulting muscle strain leads to lower back pain (LBP).[10] A study of lumbosacral angles in individuals with obesity concluded that a higher BMI and waist-hip ratio are associated with larger lumbosacral angles, which may increase the incidence of LBP.[1]

Obese individuals with increased abdominal girth experience a ventral shift of the body's center of gravity (COG), which leads to a loss of neutral position and sagittal alignment. This COG shift considera-

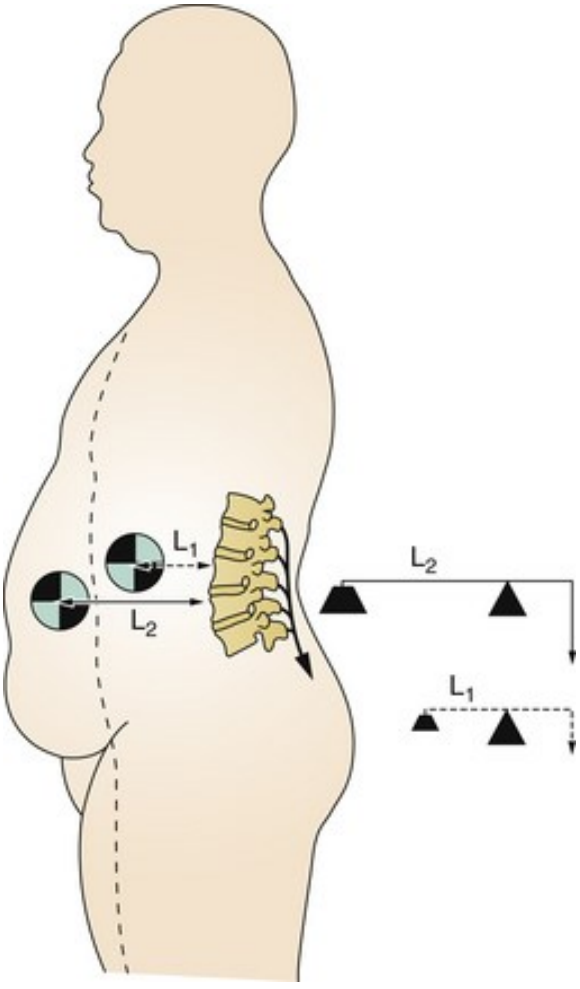

Figure 5. Center of gravity shift in obesity.[11]

bly amplifies the forces experienced by the spine. The extra weight also increases axial loading on the spine. Repetitive and excessive loads on the spine, coupled with a loss of sagittal balance, may initiate degenerative changes in the spine of obese individuals.[11]

The primary management of obesity involves a multidisciplinary approach to promoting a healthy lifestyle to reduce body weight. However, due to the potential for musculoskeletal pain, fear avoidance behavior, or kinesiophobia and functional decline in patients with obesity, encouraging physical activity can be challenging.[3] Therefore, proper pain management is crucial to facilitate patient participation in physical activity. It is important to reassure patients that pain can be managed and to provide a supervised, tailor-made exercise program that accommodates the patients' fitness levels while ensuring their safety.

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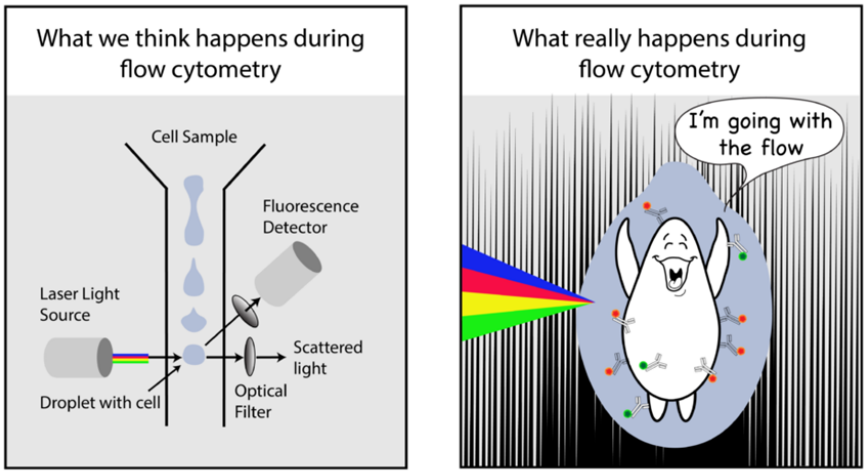
INA-RESPOND Newsletter

COMIC CORNER

LIVING CELL ISOLATION: A GAME-CHANGER IN BIOMEDICAL RESEARCH

By: Aly Diana



Source: https://cellcartoons.net/cartoons-all/

Last week, I knew nothing about living cell isolation. By luck, I attended a Biophysics seminar and realized (once again) how vast the world of science is. Today, I still know almost nothing about living cell isolation, and there may be some errors in this article. I apologize in advance. However, I would like to share what I have heard and read in the past few days, hoping to motivate people who haven't heard about it to explore more.

Living cell isolation, also known as cell separation or cell sorting, is a powerful technique that allows scientists to isolate specific cell populations from complex mixtures. By separating cells based on unique characteristics such as size, density, surface markers, or viability, living cell isolation enables researchers to study and analyze individual cells in isolation, providing valuable insights into their function, behavior, and molecular characteristics. This technique has become increasingly important in biomedical research as it unlocks a deeper understanding of cellular behavior, disease mechanisms, and the development of targeted therapies.

Various techniques are employed in living cell isolation, each with its advantages and applications. These techniques include:

1. Differential Centrifugation: This technique separates cells based on their size and density using varying centrifugal forces. By pelleting cells at different speeds, different cell types can be effectively isolated.

2. Fluorescence-Activated Cell Sorting (FACS): FACS utilizes fluorescently-labeled antibodies or dyes to bind to specific cell surface markers. This enables precise sorting of cells into different populations using flow cytometry, allowing the isolation of specific cell types.

3. Magnetic-Activated Cell Sorting (MACS): MACS relies on magnetic beads coated with antibodies that bind to target cell surface markers. By applying a magnetic field, specific cell populations can be separated effectively, providing enriched cell populations.

4. Microfluidics-Based Cell Sorting: Microfluidics-based sorting employs microfluidic channels to manipulate cells based on their physical properties such as size or deformability. This technique enables precise separation of cells and is particularly useful for isolating rare cell populations.

5. Exosome Isolation and Purification: This technique specifically focuses on the isolation and purification of exosomes, small extracellular vesicles released by cells. Methods such as ultracentrifugation, density gradient separation, immunoaffinity-based capture, and size exclusion chromatography are used to sepa-

rate exosomes from other cellular components and contaminants, resulting in highly enriched exosome populations. Exosome isolation and purification techniques are crucial for studying intercellular communication and exploring the diagnostic and therapeutic potential of exosomes.

Living cell isolation has yielded remarkable success stories across various fields of biomedical research. For instance, in cancer research, single-cell analysis using living cell isolation has provided insights into the heterogeneity of tumor cells within a patient. This understanding has led to advancements in tumor evolution studies, drug resistance mechanisms, and personalized treatment strategies. In neurobiology, living cell isolation has revealed the intricacies of neuronal diversity, contributing to our understanding of neurodevelopmental disorders and the complexities of neuronal function. Stem cell biology, immunology, and developmental biology have also greatly benefited from living cell isolation. By isolating and studying individual cells, researchers can decipher the mechanisms governing stem cell differentiation, immune cell responses, and tissue development. These insights have the potential to advance regenerative medicine, immune system research, and tissue engineering.

While living cell isolation offers immense potential, it is not without its challenges. Sample complexity, maintaining cell viability, preserving cell interactions, minimizing technical variability, isolating rare cell populations, avoiding phenotypic alterations, managing cost and time, and preventing cross-contamination are some of the challenges that scientists face when conducting living cell isolation experiments. To overcome these challenges, ongoing research and development efforts are focused on optimizing isolation techniques, standardizing protocols, and sharing best practices within the scientific community. Collaboration and knowledge exchange will contribute to refining living cell isolation methods, ensuring reproducibility and reliability across experiments and laboratories.

Living cell isolation has transformed biomedical research, providing unprecedented insights into cellular behavior, disease mechanisms, and targeted therapies. As technology advances and challenges are addressed through collaboration and ongoing research, the future of this technique holds great promise for further breakthroughs. Scientists can delve into the intricacies of cellular behavior, unlocking valuable insights for personalized medicine. Overcoming isolation challenges requires collaboration, standardization, and ongoing research. With each advancement, the potential for groundbreaking discoveries expands, offering hope for improved health outcomes and a deeper understanding of life's fundamental building blocks. Personally, I hope that this brief blurb sparks curiosity in people who are unfamiliar with this topic.

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