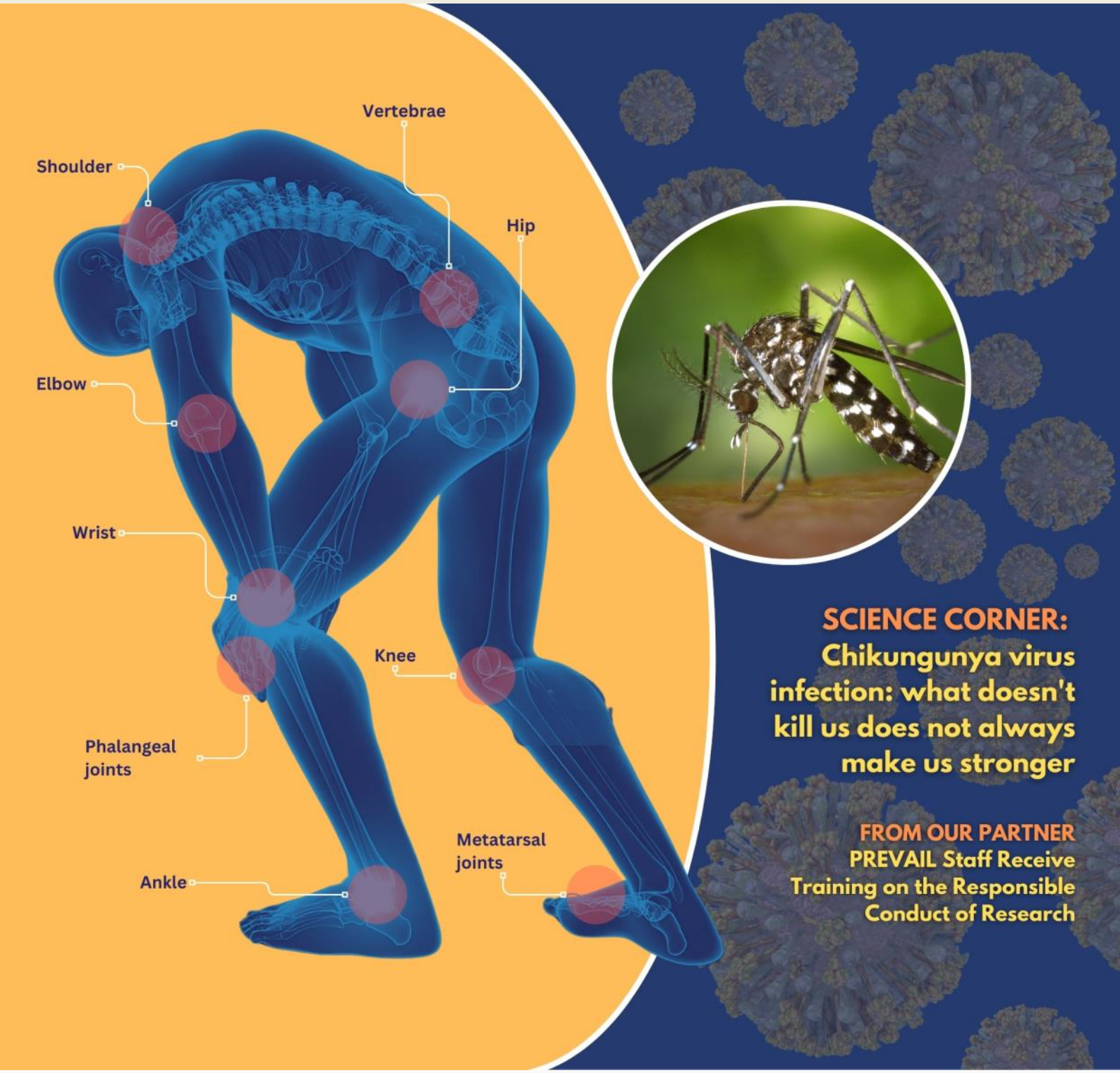
INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

August 2024



SCIENCE CORNER:
Chikungunya virus infection: what doesn't kill us does not always make us stronger

FROM OUR PARTNER
PREVAIL Staff Receive Training on the Responsible Conduct of Research

HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2024

INA-RESPOND newsletter

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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, Natalia Regina, Nur Latifa Hanum, Restu Amalia, Riza Danu Dewantara

InVITE

The Indonesia InVITE study is currently undergoing random quality assurance (QA) by the local Data Management team. Once this process is completed, the Sites team will prepare for a site close-out visit (SCV). The Secretariat and Sites team are coordinating to ensure the completeness of study documents and the necessary supplies for SCV activities. Additionally, designated serum specimens will be shipped to the Central Laboratory in two batches scheduled for September and October 2024 using the World Courier service. The Secretariat team is in ongoing discussions with the US-NIAID team to finalize the shipment preparations.

This month, the Secretariat bids farewell to dr. Natalia Regina M. Kes, a bright and dedicated research assistant (RA) from Site 02 (TC Hillers Hospital, Maumere, East Nusa Tenggara). She will be departing from the InVITE study as her contract has come to an end. In this newsletter, dr. Natalia shares her experiences working as an RA at Site 02 for almost 2.5 years. Site 02 was initially selected for the InVITE study due to its endemicity of malaria, which is one of the sub-groups of interest in the protocol for evaluating immunogenicity after COVID-19 vaccination.

Dr. Natalia was supervised by the Site Principal Investigator (PI) dr. Asep Purnama, Sp.PD, FINASIM, along with Co-PIs dr. Mario B. Nara, Sp.A, and dr. Dwi Kurniawan Nugroho, Sp.PK. She expresses gratitude for the enthusiastic and supportive nature of her supervisors. Dr. Asep, with extensive research experience in malaria, HIV, and rabies, was deeply interested in the InVITE study to gain insights into the immunological properties of the COVID-19 vaccination. Dr. Mario, Sp.A, was particularly helpful in networking with primary health care and enrolling pregnant women in the study. Dr. Dwi, Sp.PK, was always ready to resolve any laboratory issues that arose during the InVITE study.

Dr. Natalia shared the challenges she faced during the preparation for the InVITE study. Having

Figure 1. Site 02 research team (left to right) :
dr. Mario B. Nara, Sp.A, dr. Natalia Regina, M. Kes, dr. Putri Nur Indah Sari, dr. Ulul Azmiyah Riawan, dr. Asep Purnama, Sp.PD, dr. Dwi Kurniawan Nugroho, Sp.PK

prior experience as an RA in the Tanjungsari Cohort Study (2016-2018), she found her new role in the INA-RESPOND study both unique and exciting. With the national COVID-19 mass vaccination schedule set to begin in August 2021, dr. Natalia had to quickly prepare for the InVITE study. She underwent RA training, participated in enrollment mock sessions, and coordinated with laboratory technicians Daniel Fremidon Ndoa, Amd.K, Elisabeth Nona Stefani, S.ST, and study nurse Wahyuni, Amd. Keb. She also managed study logistics and soon initiated subject enrollment. The first enrollment period targeted TC Hillers Hospital health workers who received their second vaccination booster with Moderna. Her diligence and bravery impressed us, especially considering she was new to the hospital. The RA from the INA104-PROACTIVE study also assisted her in successfully recruiting 228 subjects in approximately four months. Dr. Natalia also faced challenges related to administration and bureaucracy. She and her team had to secure permission from The National Unity Politics and Community Protection Agency (Kesbangpol) to collaborate with primary healthcare, allowing for expanded subject recruitment in satellite locations. Thanks to their efforts, Site 02 achieved a high enrollment rate, contributing 32% of the total subjects for the InVITE study in Indonesia.

The subject recruitment process posed significant challenges, especially when potential participants were not health workers. Socioeconomic and educational limitations heavily influenced their willingness to participate. It was difficult to explain the study's purpose to these individuals, particularly since they did not perceive any direct benefits from participating. Many subjects from rural areas were also apprehensive about repeated blood draws. Even those enthusiastic about participating faced logistical barriers such as the long distance between their homes and the healthcare facilities where follow-up visits were conducted. However, some subjects were motivated to join the study because they were interested in learning about their SARS-CoV-2 antibody levels over time. The varying education levels among the subjects provided dr. Natalia and the team with an opportunity to refine their communication skills, ensuring that all participants received clear and consistent information. Sample collection was also challenging due to the lack of a freezer for temporarily storing specimens at the blood draw location. The team addressed this by using a cool box with ice packs and taking turns to promptly transport the samples to the laboratory.

Figure 2. Laboratory Activities

The follow-up period for InVITE study subjects was extended by one year from the original timeline, increasing the number of follow-up visits to eight. Every two weeks, dr. Natalia would contact subjects to inquire about COVID-19 symptoms and remind them of their scheduled follow-up visits. However, economic circumstances made it difficult to reach all subjects as some did not have cell phones. To address this challenge, dr. Natalia and the study nurse began visiting the subjects' homes directly, which not only facilitated communication but also helped them build a good rapport with the subjects and adapt to the local community's customs. During the study, rumors circulated in Maumere that hospitals or healthcare workers were diagnosing patients with COVID-19 for financial gain. This created an additional challenge as some subjects hesitated to disclose their symptoms. The discrepancy between subjective data obtained from interviews and objective data from antibody-level results provided the research team with valuable insights on how to analyze and interpret the collected data accurately.

Research activities are always closely tied to data documentation. In remote areas, supportive tools such as printers, scanners, and reliable internet connections are critical to ensure smooth document uploads. We recall several instances where dr. Natalia had to go to the hospital in the evening to upload documents because the internet connection was sometimes unreliable during the day. Additionally, the availability of spare parts for laboratory equipment and technicians' readiness also posed challenges during the study at Site 02. Another significant obstacle at Site 02 was related to specimen delivery to the INA-RESPOND Reference Laboratory. The lack of airlines willing to ship specimens with dry ice, the absence of direct flights from Maumere to Tangerang, the infrequent flight schedules, and the long travel time combined with strict temperature monitoring requirements complicated the specimen shipping process. However, these challenges were overcome through coordination and teamwork, with one effective solution being the use of Crēdo Cube, a reusable cold chain shipper, for specimen shipping.

Dr. Natalia and the team gained extensive experience from the InVITE study, including systematically organizing documentation, participating in a well-designed study, and coordinating with various parties from different backgrounds. Their unexpected challenges brought the team closer together as they worked hard to cover any gaps. The strict division of tasks between dr. Natalia and the laboratory technicians gradually disappeared, and they all collaborated happily. Follow-up visit days became something they looked forward to, as it was a chance to meet, work together, and share laughs.

Dr. Natalia and the team successfully completed the study activities at Site 02 according to the timeline, thanks to the excellent collaboration of all parties involved and the support of the PI and co-PIs from start to finish. They are now preparing for the SCV, including organizing the shipment of documents from Site 02 to the INA-RESPOND Secretariat and inventorying INA-RESPOND-owned equipment at the site.

The InVITE study at Site 02 was a success, and the INA-RESPOND Secretariat gained invaluable insights from the experience. We extend our deepest gratitude and appreciation to the Site 02 team for their cooperation. **Words of thanks and apologies might not be enough to express our gratitude for the Site 02 research team's patience, flexibility, and hard work during the study.** We're excited to work with TC Hillers Hospital on more INA-RESPOND projects in the future and wish the entire Site 02 research team continued success. **A special thanks to dr. Natalia — we are truly grateful for your dedication and responsiveness throughout the InVITE journey, even beyond office hours. Our hectic moments and communication ups and downs will indeed become fond memories. We wish you happiness and success in your next endeavor, and we hope our paths will cross again.**

***Epang gawang*!** ("thank you" in Sikka language).

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The INA-PROACTIVE investigators, Secretariat, and partners are currently working on both primary and additional manuscripts. The first manuscript, titled "A Prospective Observational Cohort Study of HIV Infection in Indonesia: Baseline Characteristics and One-Year Mortality," was submitted to BMC Infectious Diseases, and the team is now awaiting feedback following its submission on August 7, 2024. Meanwhile, the Scientific, Data, and Site teams are engaging in extensive discussions to finalize the subsequent manuscripts.

The second manuscript, expected to be finalized in the coming months, will focus on the trends and characteristics of late presenters (LP) in the INA-PROACTIVE cohort. LP is defined as a person living with HIV who presents for care with a CD4 count below 350 cells/µL or with an AIDS-defining event, regardless of their CD4 count. The INA-PROACTIVE study collected demographic and clinical data from patients at the time of their first positive HIV test across 19 sites in Indonesia. This allows the team to analyze changes over time in the proportion of LP and identify associated factors. Addressing LP is crucial due to its association with high morbidity and mortality, as well as the potential delays in anti-retroviral therapy (ART) initiation that could hinder the achievement of the UNAIDS 95-95-95 targets.

The INA-PROACTIVE team also highlights the opportunity to focus on a vulnerable population in the study: children living with HIV (CLWH). In 2022, an estimated 18,000 CLWH were in Indonesia, yet only 29% received ART, a rate lower than that of adults. This population deserves equal access to appropriate programs and services. In collaboration with INA-RESPOND Warm-Based Research Assistants (RAs), the Secretariat conducted a scoping review of CLWH research in Indonesia, covering all fields since the first HIV case was reported in 1987. The team aims to provide scientific summaries for this age group and promote HIV control efforts in Indonesia. This scoping review will also sup-

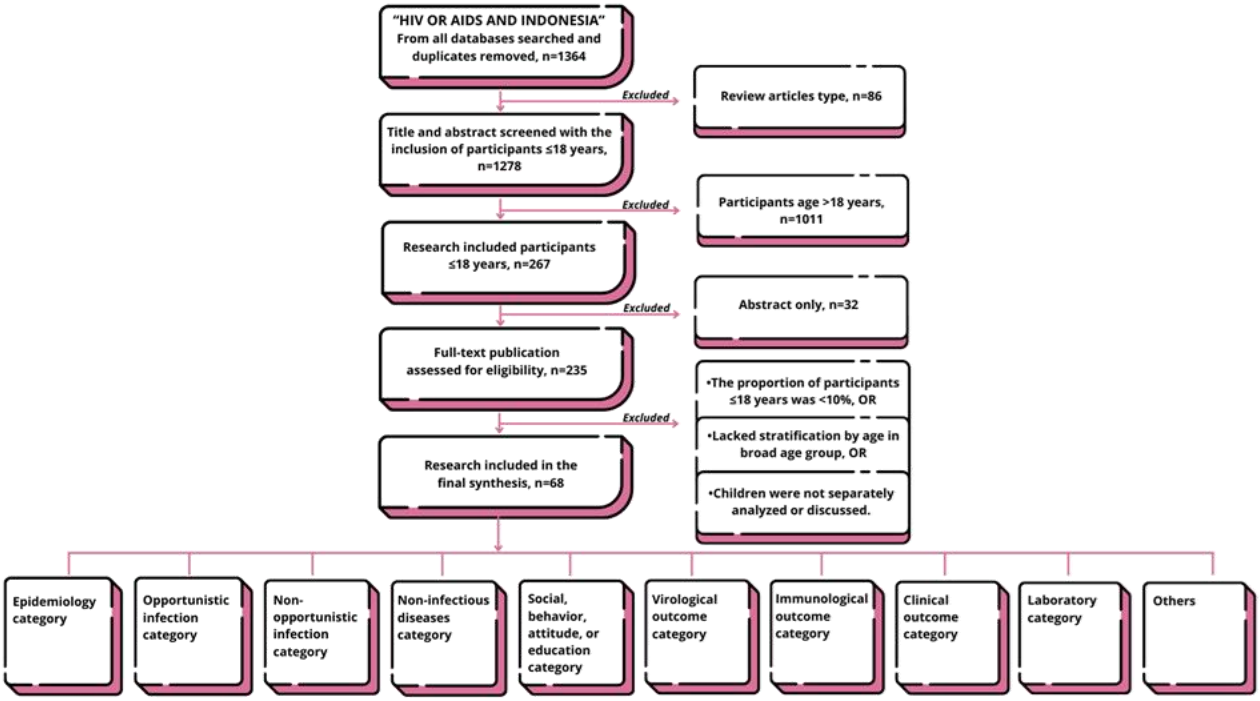

Figure 1. Flowchart of the scoping review in children living with HIV researches

port the preparation of a PROACTIVE manuscript focused on pediatric subjects.

The scoping review followed the Arksey and O'Malley approach, which consists of five stages: (1) formulating research questions, (2) identifying relevant studies, (3) selecting eligible studies, (4) charting the data, and (5) collating, summarizing, and reporting the results. The team developed two key research questions: "**What CLWH research is available in Indonesia?**" and "**What are the research gaps regarding CLWH in Indonesia?**" They established eligibility criteria for articles and conducted a comprehensive search in online electronic databases using keywords found throughout the text of potentially relevant publications. The search terms included: "(HIV OR AIDS) AND INDONESIA AND (NEONATE OR INFANT OR CHILD OR CHILDREN OR PEDIATRIC OR ADOLESCENT OR YOUNG)." The search included original papers written in English and published from 1987, when the first HIV case was reported in Indonesia, to February 2024. Multinational studies involving CLWH in Indonesia were also included. Duplicate journal titles were removed from the search results.

Several articles were excluded due to having less than 10% of participants aged 18 years or younger, lacking age-specific stratification, or not providing separate analyses or discussion for children (Figure 1). The Secretariat team conducted further searches to identify research specifically related to CLWH. Lead authors were available for consultation during the finalization of records. Following the final assessment, the selected articles were categorized into ten categories: **epidemiology, opportunistic infections, non-opportunistic infections, non-infectious diseases, social/behavioral/ attitude/education, virological outcomes, immunological outcomes, clinical outcomes, laboratory,** and **other** categories.

The full text of categorized articles was reviewed independently by assigned groups consisting of six groups with two authors in each. To ensure accuracy, the articles were then swapped between two groups for a second review. Any discrepancies were discussed with the lead authors, who made the final decision when consensus could not be reached. In line with scoping review guidelines, the team did not appraise the methodological quality or risk of bias of the included articles.

A data charting form in Microsoft Excel was used to capture the details of the selected studies. The team then developed a table and narrative synthesis to map and summarize the existing knowledge on research about CLWH in Indonesia. This was an exciting part of the scoping review process. Authors were required to provide a summary of the research, noting similarities and differences among articles within the same category, highlighting key findings, and presenting any unique results.

As the team was still learning together, they held small, active, and productive discussions within each pair of groups. Following these discussions, the next step is to finalize the review report draft and discuss it with the entire team. The scoping review draft will also be consulted with US-NIAID partners, pediatricians, HIV experts, and members of the Health Policy Agency of the Ministry of Health. The team hopes to complete the scoping review draft soon.

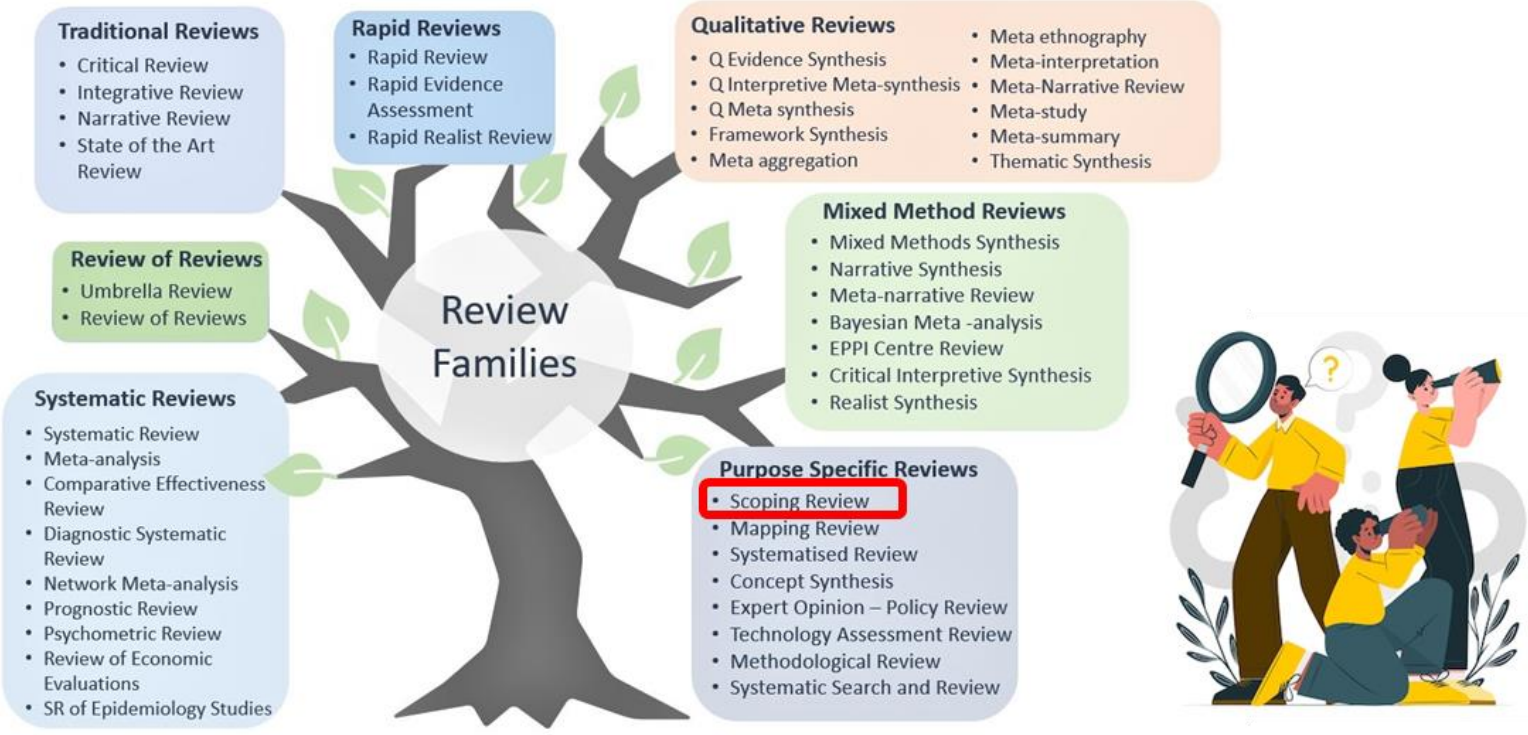

Figure based on the work of Sutton et al., (2019) on 'Review Families' and downloaded from https://unimelb.libguides.com/whichreview.

INA-RESPOND Newsletter

CHIKUNGUNYA VIRUS INFECTION: WHAT DOESN'T KILL US DOES NOT ALWAYS MAKE US STRONGER

By: Ni Luh Putu Ariastuti, Adhella Menur

CHIKV: The neglected bending virus

Chikungunya virus (CHIKV) infection might not be as famous as dengue virus (DENV) or Zika virus (ZIKV) infection due to the low mortality rate compared to other infections. But don't let that fool you; its high morbidity rate and long-lasting health issues create significant economic and social burdens. The virus was first identified in human serum back in 1952 on Tanzania's Makonde Plateau, which is also how it got its name. "Chikungunya" comes from the Makonde word for "that which bends up," describing the stooped posture and severe joint pain sufferers endure. Transmitted by Aedes mosquitoes (Ae. albopictus and Ae. aegypti), CHIKV is a public health threat based on several records of CHIKV outbreaks across Africa, Asia, Europe, and the Americas and sporadic non-outbreak cases. Numerous CHIKV re-emergences have been documented with irregular intervals of 2–20 years between outbreaks. In 2000, a massive outbreak of CHIKV infection resurged in Congo, followed by global emergence in 2004. By 2005-2006, the outbreak had reached the Indian Ocean Island of La Réunion, part of France, affecting an estimated 300,000 people and causing 237 deaths. In Sri Lanka and India, CHIKV infected more than 100,000 and 1.3 million persons, respectively, then subsequently spread to Southeast Asia, including Indonesia. In 2007, a localized outbreak occurred in Italy, traced back to a traveller from India. The virus spread further through international travellers. By 2015, CHIKV was officially recognized as a notifiable disease by the US-CDC. During the past 20 years, over 10 million cases of chikungunya have been reported in more than 125 countries. The latest outbreak was reported in the Malé and Hulhumalé regions of the Maldives during March-May 2024.

In Indonesia, the first recognized CHIKV outbreak occurred in Samarinda, East Kalimantan, in 1973, and the first virologically confirmed cases were detected in Jambi in 1982. Since then, isolated outbreaks have been reported more frequently, peaking during a nationwide epidemic in 2009-2010 with 137,655 cases and a smaller outbreak in 2013 with 15,324 cases. Thence, annual CHIKV cases have returned to pre-epidemic levels (<10,000). A recent suspected local outbreak occurred in Nagasepaha Village, Buleleng, North Bali, from December 2015 to January 2016. Moreover, Indonesia has been identified as a potential source of CHIKV transmission abroad, with studies highlighting infected travelers returning from Indonesia to Taiwan (2006-2009) and Japan (2006-2016) as common sources of imported cases. Unfortunately, CHIKV

infection often goes neglected and is sometimes thought of as the "nicer" sibling of DENV infection. This edition aims to shed light on CHIKV infection and its implications for public health.

Getting to know CHIKV

CHIKV belongs to the Togaviridae family - the Alphavirus genus, and it's part of the Semliki Forest virus antigenic complex, which also includes O'Nyong Nyong, Mayaro, and Ross River viruses. This virus is an enveloped positive-strand RNA virus with the genome encoding four nonstructural proteins (nsP1 to nsP4) and five structural proteins (C-E3-E2-6k-E1). Genetic analysis based on the E1 envelope glycoprotein sequences showed three distinct lineages: West African, Asian, and East/Central/South Africa (ECSA). The Indian Ocean lineage (IOL) is a sub-lineage evolved from the ECSA lineage. In Indonesia, sequencing and evolutionary studies have primarily identified Asian genotypes, with some isolates matching the ECSA genotypes. Notably, the ECSA isolates first identified in Indonesia in 2008 were closely related to the viruses causing significant outbreaks in Southeast Asia around that time.

CHIKV transmission occurs through both urban and sylvatic cycles. In the sylvatic cycle, primarily observed in Africa, CHIKV is transmitted among arboreal forest Aedes mosquitoes and diverse amplifying hosts (mammals including primates, sheep, rodents, bats; as well as birds). Humans are incidental hosts in this cycle, typically infected when they venture into forested areas or are bitten by infected vectors. In the urban cycle, transmission involves humans and urban mosquitoes like Ae. aegypti and Ae. albopictus. CHIKV can be transmitted horizontally in Aedes mosquitoes, aiding in maintaining the infection cycle. Additionally, vertical transmission from mosquitoes to their offspring has been noted, potentially allowing the virus to persist under harsh environmental conditions. Once a mos-

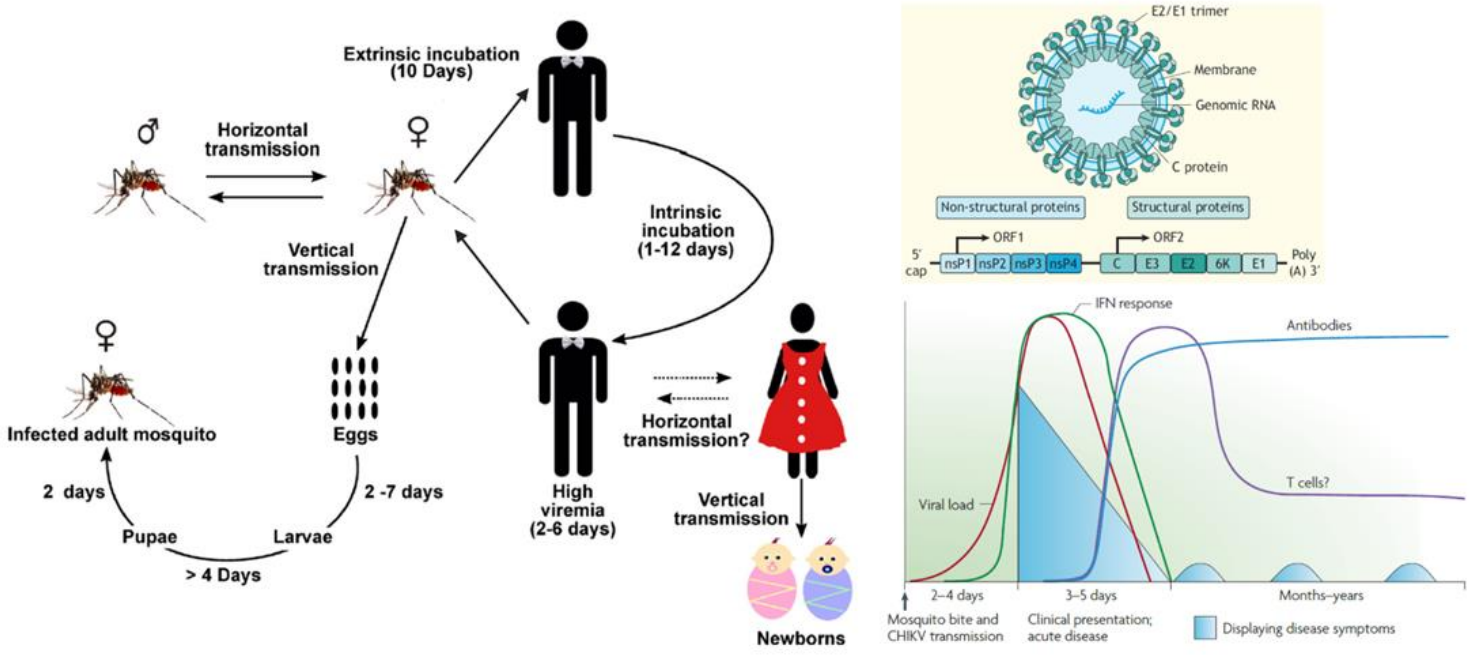

Figure 1. Chikungunya virus, transmission, and immune responses. Sources: Schwartz, O & Albert, M.L. (2010), Silva, J.V.J. et al. (2018), and Henderson Sousa, F., et al. (2023).

quito carrying CHIKV bites a human, the virus replicates at the bite site, with skin fibroblasts serving as the primary amplification points. The virus then spreads to other peripheral organs via the bloodstream. The incubation period varies from one to twelve days, and individuals can exhibit viremia for up to ten days. CHIKV infects various cell types, including myoblasts, skeletal and synovial fibroblasts, and joint macrophages. It also has been detected in epithelial and endothelial layers of lymphoid organs, the liver, and the brain. However, monocytes, B cells, T cells and monocyte-derived dendritic cells may not be susceptible to CHIKV infection. Maternal-fetal transmission has been observed, although there's no evidence of transmission through breast milk. While CHIKV RNA has been detected in semen up to 30 days post-symptom onset, suggesting potential sexual transmission, direct human-to-human transmission has not been documented.

Humans serve as the primary host of the virus during epidemics. Anyone with suspected chikungunya infection should avoid mosquito exposure for at least 7 days after the onset of illness to reduce the possibility of transmitting the virus to mosquitoes, which could then transmit to other humans. The complete transmission cycle from human to mosquito and back to another human can take place in less than a week. Once a mosquito is infectious, it may be capable of transmitting the virus for the remainder of its lifespan (about 2 weeks). Infection with chikungunya virus confers long-lasting, possibly lifelong, immunity.

Acute CHIKV infection

CHIKV disease in humans is typically marked by two phases, an acute phase and a chronic phase. The acute phase of CHIKV disease lasts typically <21 days after the onset of infection. It is divided into two different stages, the viraemic stage (5-10 days), marked by abrupt high fever (>38.9°C) and polyarthralgia/ arthritis (usually symmetrical and primarily involves peripheral joints), myalgia,

Symptoms	CHIKV	DENV	ZIKV
Fever	>38 °C (2–3d[a])	>38 °C (4–7d)	≤38 °C (1-2d)
Rash	++ (d2-d5[b])	+ (d4[c])	+++ (d1-d2[d])
Pruritus	+/++	+/+++	++/+++
Myalgia	+	+++	++
Arthralgia	+++	+	++
Retrorbital pain	+/-	+++	+/-
Conjunctivites	+	+/-	++/+++
Skin bleeding	+/-	++	+/-
Joint swelling	++/+++	+/-	+
Headache	++	+++	++
Diarrhea	+/-	++	+/-
Neurological impairment	++	+	+++
Lymphadenophaty	++	+	+++
Hemorrhagic dyscrasia	+	++	-

Table 1. Overlaping symptoms of Dengue, Chikungunya and Zika virus infection

References: Silva, J. V. J. et all. (2018); PAHO (2017). aDuration of fever in days. bOnset of rash in 50% of cases. Onset of rash in 30–50% of cases. dOnset of rash in 100% of cases.

headaches and skin rashes; and the post-viraemic stage (6-21 days), characterised by a lack of fever, polyarthralgia/arthritis and, to a lesser extent, myalgia, fatigue and anorexia. Preliminary diagnosis relies on the individual's clinical presentation and a thorough travel history. However, CHIKV manifestations overlap with those of other endemic infections such as dengue virus (DENV) and Zika virus (ZIKV). Confirming the diagnosis requires laboratory testing. The more widely available tests include polymerase chain reaction (PCR) to detect viral RNA in the first 8 days of illness, or acute-phase serology to detect IgM, IgG, and neutralizing antibodies toward the end of the first week of illness (>4 days post-onset) paired with a convalescent-phase serology; although possible, viral cultures in the first 3 days of illness are less frequently used. Unfortunately, cross reaction with another arbovirus can happen on antigen-based test thus make some test less sensitive in detecting CHIKV. Additionally due to limited resources, this laboratory test might not be available in certain countries.

In the INA-RESPOND AFIRE study (2013-2016), CHIKV emerged as a significant cause of fever among hospitalized patients, yet it often went unrecognized by clinicians. Out of 40 cases of acute CHIKV infection, none were correctly diagnosed by the attending clinicians at the study sites. Eleven patients were misdiagnosed with DENV, eight with typhoid fever, and one with leptospirosis. The other 20 cases were misdiagnosed to various other conditions: unspecified fever (6), respiratory infections (5), nonspecific viral infections (4), fever with rash (2), enteritis (2), and endocarditis (1). Currently CHIKV IgM rapid diagnostics are plagued by low sensitivity. Performance is better for the ECSA genotype, but suboptimal for the Asian genotype circulating in Indonesia. And since IgM is usually detectable 5 days after fever onset, utility of IgM in acute specimens is minimal. Additionally, persistence of IgM for CHIKV more than a year after infection may confound interpretation of positive results. These challenges highlight the need for CHIKV RNA, or antigen based rapid diagnostic testing to guide clinical decision making.

Surviving the acute phase: weakening in the chronic

For many individuals with chikungunya, the disease is benign and self- limiting. However, after the acute phase of the illness, some patients develop long-term symptoms, known as the chronic phase, that can last from several weeks to months or years (>1 year). Studies vary widely in terms of the percentage (14-43%) of patients that experience the chronic disease and the disease longevity. The primary symptoms for chronic disease in patients with chikungunya are arthralgia and/or arthritis. CHIKV-induced arthritis resembles rheumatoid arthritis (RA), but, unlike RA, there is no evidence that CHIKV-associated arthropathies are caused by autoimmunity. Rather, it is thought that the persistence of viral antigens could be a contributing factor to the development of chronic CHIKV induced arthritis. Chronic arthralgia generally involves the same joints affected during the acute phase and the arthropathy is not usually overtly erosive. Fatigue, depression, mood and sleep disorders, neurological disorders, and alopecia were also common chronic symptoms. Factors predisposing to chronic disease included comor-

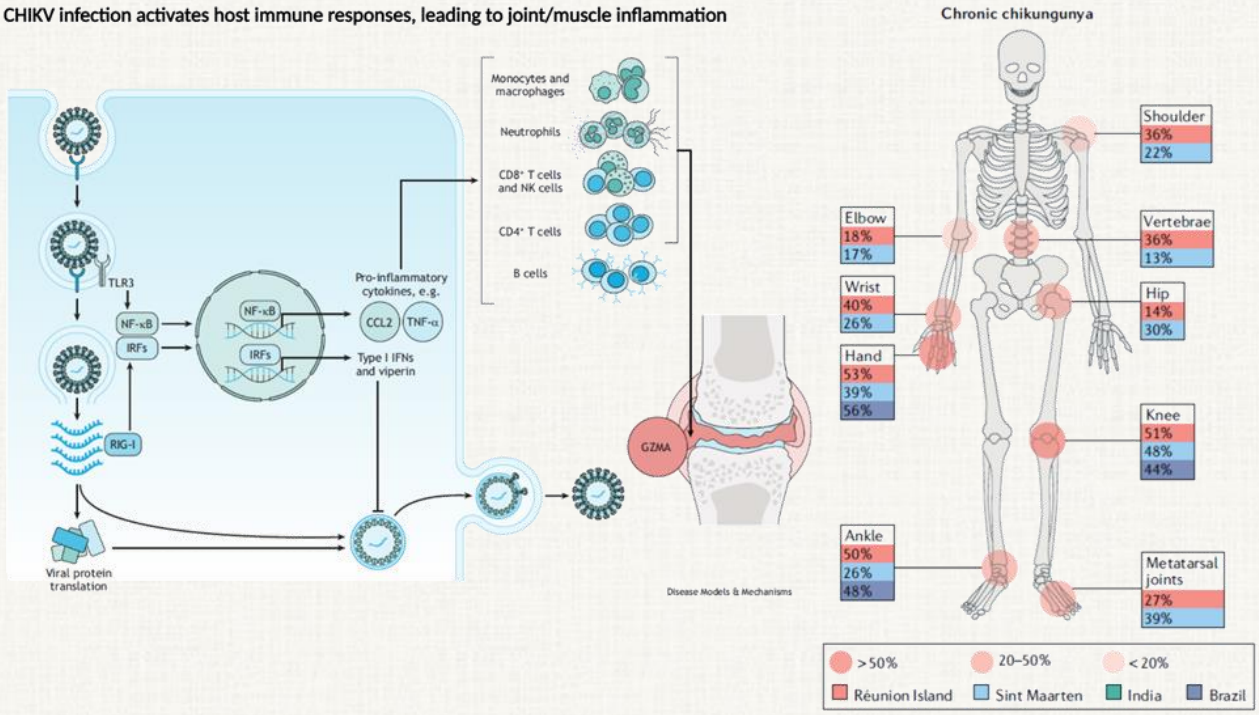

Figure 2. Host inflammatory responses to CHIKV infection, which can affect joints/muscles (source: Henderson Sousa, F., et al. (2023)). Documented joints with arthralgia in patients with chronic chikungunya (source: Suhrbier, A., (2019)). CCL2, chemokine ligand 2; CHIKV, chikungunya virus; IFN, interferon; IRF, interferon regulatory factor; GZMA, granzyme A; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NF-κB, nuclear factor kappa B; NK, natural killer; OAS, 2'-5'-oligoadenylate synthetase 1; RIG-I, retinoic acid-inducible gene I; TLR, Toll-like receptor; TNF-α, tumour necrosis factor alpha.

bidities (such as osteoarthritis and diabetes), older age (>35 years), and high viraemia and severe disease during the acute stage.

A recent study from Brazil investigated the mortality risk between individuals exposed to CHIKV and those not exposed, examining both the timing and causes of death. The findings are concerning. CHIKV disease is associated with an increased risk of all-cause natural mortality, as well as an increased risk of death from cerebrovascular disease, ischaemic heart disease, diabetes, and kidney disease within 84 days of symptom onset. Notably, the study also highlights that CHIKV diseases can exacerbate underlying diseases, further elevating the risk of severe outcomes. A greater understanding of both the acute and chronic phases of CHIKV disease and the role of host immune responses in the pathobiology of the disease is required to develop therapeutic approaches to enhance early viral clearance and limit the development of chronic disease.

Chikungunya – outbreak and non-outbreak, and public health efforts

As previously mentioned, chikungunya can present in outbreak and non-outbreak settings. Often, non-outbreak cases go unnoticed, while those occurring during outbreaks tend to exhibit more severe symptoms. This observed difference in symptom severity could be due to increased awareness during outbreaks or may reflect actual variations in clinical presentation. A

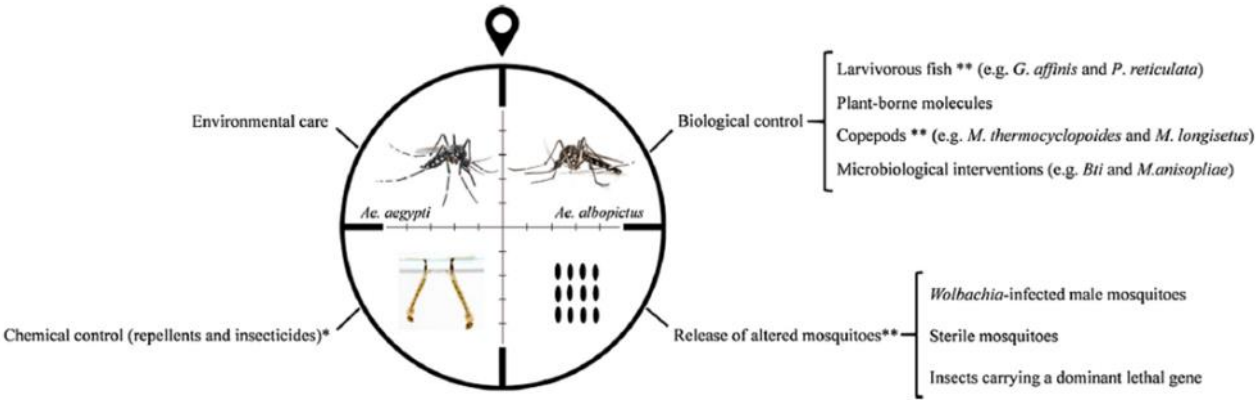

Figure 3. Management for an integrated Aedes vector control. It is important to consider and evaluate the influence of these interventions on ecosystem balance. Source: Silva, J. V. J. et al. (2018).

thorough analysis comparing viral, vector, host, and environmental factors between outbreak and non-outbreak cases would provide valuable insights into these dynamics. Moreover, outbreak recurrences are often preceded by long periods spanning several years or decades with minimal or no cases. Several factors contribute to these recurrences. For instance, the emergence of new virus variants can play a significant role; the ECSA genotype with the A226V mutation of the E1 protein, for example, enhances vector competence in Ae. albopictus but not in Ae. aegypti. Additionally, the absence of pre-existing immunity, particularly in younger populations who have not been exposed during silent epidemiological periods, can facilitate the spread of the virus. Environmental and host-vector interactions might also trigger outbreaks, as demonstrated by the 2010 outbreak in North Kayong, West Kalimantan, where farming activities in forested areas combined with poor vector control were significant risk factors.

The expanding geographical range of chikungunya is attributed to factors such as increased urbanization, international travel, and global warming, which contribute to the proliferation and migration of mosquito vector populations. While the disease itself is rarely lethal, its acute phase can be intensely painful and debilitating. Moreover, the long-term effects of chikungunya can severely restrict daily activities and significantly reduce the quality of life, impacting them both psychosocially and economically. Therefore, public health efforts are crucial to control CHIKV infection.

In addressing CHIKV infection, promising new or repurposed antiviral compounds have been developed. Yet, most require validation through in vivo studies and clinical trials, and they face potential issues with antiviral resistance. Antibody-based therapies, only effective in the acute phase and are costly. Treatment primarily focuses on supportive care—rest, hydration, and pain relief. For chronic cases, treatment strategies emphasize pain management, anti-inflammatory medications, and supportive physical and rehabilitation therapies. After decades, a single-shot chikungunya vaccine, VLA1553/ IXCHIQ®, manufactured by Valneva, was approved in the U.S. in November 2023 and recommended for adults: travellers at high risk, laboratory workers, and those at increased risk of severe disease. However, its distribution remains limited, particularly in endemic regions where it is most needed.

Effective prevention of chikungunya hinges on robust vector control, which is challenged by ram-

pant urbanization, inadequate sanitation, and increasing insecticide resistance in mosquitoes. An integrated approach to virus control is essential, combining epidemiological surveillance, environmental management to eliminate mosquito breeding sites, chemical control using repellents and insecticides, and biological controls targeting mosquito eggs, larvae, and adults.

To effectively combat CHIKV, a virus that can significantly bend and weaken us, it's essential to maintain strong public health awareness, engage in comprehensive research for new treatments and vaccine development, and conduct thorough serological and genomic surveillance to predict and prepare for future outbreaks. Keep being strong and proactive in these efforts!

References

Arif, M., et al. (2020). Chikungunya in Indonesia: Epidemiology and diagnostic challenges. PLoS Neglected Tropical Diseases.

Bartholomeeusen, K., et al. (2023). Chikungunya fever. Nature Reviews Disease Primers.

Cerqueira-Silva, T., et al. (2024). Risk of death following chikungunya virus disease in the 100 Million Brazilian Cohort, 2015–18: A matched cohort study and self-controlled case series. The Lancet Infectious Diseases.

Hapuarachchi, H., et al. (2021). Transient transmission of Chikungunya virus in Singapore exemplifies successful mitigation of severe epidemics in a vulnerable population. International Journal of Infectious Diseases.

Harapan, H., et al. (2019). Chikungunya virus infection in Indonesia: A systematic review and evolutionary analysis. BMC Infectious Diseases.

Henderson Sousa, F., et al. (2023). Evolution and immunopathology of chikungunya virus informs therapeutic development. Disease Models & Mechanisms.

Huang, Y.S., et al. (2017). Biological control strategies for mosquito vectors of arboviruses. Insects.

Khongwichit, S., et al. (2021). Chikungunya virus infection: Molecular biology, clinical characteristics, and epidemiology in Asian countries. Journal of Biomedical Science.

Mourad, O., et al. (2022). Chikungunya: An emerging public health concern. Current Infectious Disease Reports.

PAHO. (2017). Tool for the Diagnosis and Care of Patients with Suspected Arboviral Diseases. Retrieved from https://iris.paho.org/bitstream/handle/10665.2/33895/9789275119365_eng.pdf

Panning, M., et al. (2009). No evidence of chikungunya virus and antibodies shortly before the outbreak on Sri Lanka. Medical Microbiology and Immunology.

Sari, K., et al. (2017). Chikungunya fever outbreak identified in North Bali, Indonesia. Transactions of the Royal Society of Tropical Medicine and Hygiene.

Schwartz, O., & Albert, M.L. (2010). Biology and pathogenesis of chikungunya virus. Nature Reviews Microbiology.

Silva, T., et al. (2018). A scoping review of chikungunya virus infection: Epidemiology, clinical characteristics, viral co-circulation complications, and control. Acta Tropica.

Sitepu, F.Y., et al. (2020). Epidemiological investigation of chikungunya outbreak, West Kalimantan, Indonesia. Clinical Epidemiology and Global Health.

Stubbs, S. C. B., et al. (2020). An investigation into the epidemiology of chikungunya virus across neglected regions of Indonesia. PLoS Neglected Tropical Diseases.

Suhrbier, A. (2019). Rheumatic manifestations of chikungunya: Emerging concepts and interventions. Nature Reviews Rheumatology.

WHO. Regional Office for South-East Asia. (2009). Guidelines for prevention and control of chikungunya fever. World Health Organization.

WHO. (2016). Monitoring and Managing Insecticide Resistance in Aedes mosquito Populations-Interim Guidance for Entomologists.

WHO. (2018). Chikungunya. Retrieved from https://www.who.int/news-room/fact-sheets/detail/chikungunya

INA-RESPOND Newsletter

FROM OUR PARTNER

PREVAIL STAFF RECEIVE TRAINING ON THE RESPONSIBLE CONDUCT OF RESEARCH

By: Chris Worthington, Caeul Lim, Jestina Doe-Anderson

Imagine a world where everything is done right. There would be little room for demonstration of integrity.

We don't live in that kind of world. In our world, things that were once done wrong can be done right; things that could be done wrong can be avoided; and things that have been done right can be done better. That is the thinking behind the Responsible Conduct of Research (RCR), which is defined by the National Institutes of Health (NIH) as "the practice of scientific investigation with integrity."

Research organizations worldwide require researchers to receive training and oversight in the responsible and ethical conduct of research. NIH also mandates it for anyone conducting NIH-sponsored research. PREVAIL, too, is committed to conducting research ethically and with integrity, as demonstrated by its inaugural training on RCR principles and practices.

Inaugural RCR Training

In April 2024, over 100 PREVAIL staff received RCR training. This training was intended primarily for staff who:

a. had access to study participant data or samples and

b. were likely to develop and author manuscripts for publication and/or develop abstracts and presentations based on PREVAIL data or activities.

The 7-hour, 2-module course was delivered in-person by RCR experts who also had experience as trainers. Guidance on instructional design for adult learning was provided by the Leidos Learning and Professional Development team and based on the National Institutes of Health's Responsible Conduct of Research training. Content was developed from learning objectives provided and approved by Leidos Biomed's Ethics and Compliance team and FHIC management (the sub-contractor responsible for oversight and management of PREVAIL activities at the time).

The training included Authorship and Peer Review, Understanding and Preventing Research Misconduct, and the Research Misconduct Allegation Process. It was tailored to research activities performed by PREVAIL, with real-world examples. 'Pulse checks' were used to gauge participants' understanding throughout the course.

To successfully complete the training, participants had to achieve a minimum score of 80% in a multiple-choice assessment of each module. Individuals who did not achieve the required score could re-take the exam.

Out of 101 researchers who took the training, 77 passed the assessments after one attempt. By the end of May, all participants had successfully completed both modules. A further 36 non-research PREVAIL staff also took the opportunity of RCR training. Despite not having a research background, they were all fully engaged in the training, and more than 60% satisfactorily completed it, illustrating the depth of interest in research integrity across the organization. Participants were also invited to anonymously evaluate the training, and they provided overwhelmingly (>90%) positive feedback.

Plans for Training Continuity

Training updates are important to reinforce competence in any subject. Indeed, the Good Clinical Practice standard from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use requires retraining every 2-3 years. To support retraining, five PREVAIL staff who had completed RCR training and who also held Train-the-Trainer certification for Good Clinical Practices or Good Participatory Practices—both internationally accredited courses—were identified and evaluated for their knowledge of RCR and their ability to effectively transfer knowledge to others. Four are now recognized as Qualified Trainers for the RCR course.

Going forward, PREVAIL's Qualified Trainers will offer full RCR training or an abbreviated 'refresher' RCR course for researchers who need to re-certify. With these training offerings, PREVAIL continues to fulfill its commitment to staff development and the achievement of clinical research excellence.

INA-RESPOND Newsletter

SPORTS-RELATED SUDDEN CARDIAC ARREST: ARE WE WELL PREPARED?

By: Risky Dwi Rahayu

In July 2024, the world was shaken by the death of a 17-year-old Chinese badminton player who collapsed on the court while competing in a junior championship.[1] This incident sparked widespread debate about the best ways to prevent such tragedies. Unfortunately, sudden deaths in sports are not new, with most linked to sudden cardiac arrest (SCA). Studies have found that the incidence of SCA in athletes varies globally depending on the methodology used.[2,3] Despite its rare occurrence, the current rate of 2:100,000 athlete-years for athletes under 35 years old is 4-5 times greater than the 1995 estimate of 0.33:100,000 athlete-years.[2]

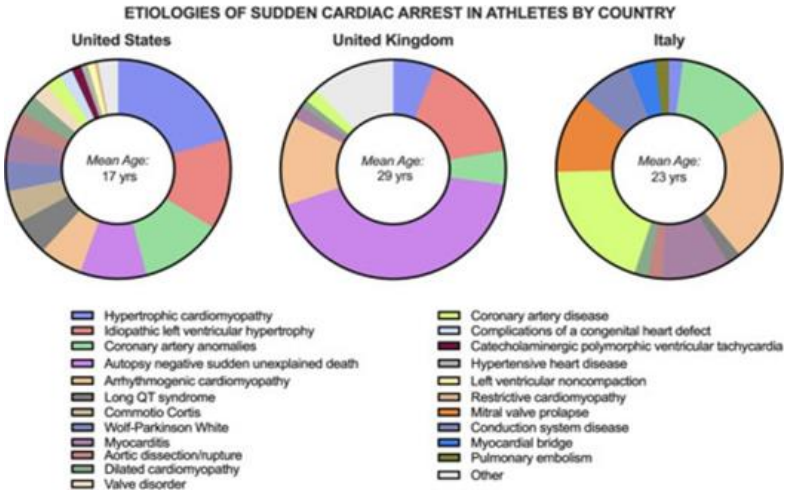

Figure 1. Etiologies of SCA by countries
(Clin Cardiol. 2023 Sep;46(9):1059-1071. doi: 10.1002/clc.24095)

Common causes of SCA in athletes include a wide range of cardiac diseases, such as autopsy-negative sudden unexplained death (AN-SUD), idiopathic left ventricular hypertrophy, arrhythmogenic right ventricular cardiomyopathy (ARVC), congenital coronary artery anomalies, Long QT syndrome (LQTS), Wolff-Parkinson-White syndrome, Marfan syndrome, and myocarditis.[3] A large portion of AN-SUD cases are caused by cardiac ion channelopathies, including LQTS, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (VT). However, other underlying conditions, such as commotio cordis or aortic dissection, may also lead to SCA. Male athletes, Black athletes, basketball players, and football players are populations at higher risk of SCA.[3,4] Compared to adults, younger athletes in high school and college face a higher risk.[4]

Approach to Sports-Related SCA

Any athlete who experiences a non-contact collapse followed by unresponsiveness and abnormal or absent breathing should be assumed to have SCA. Seizure-like movements may occur due to reduced blood flow to the brain. Given the location when the events occur, sports-related SCA is managed according to the American Heart Association's out-of-hospital chain of survival (Figure 2).[5]

Figure 2. Out-of Hospital Chain of Survival (https://cpr.heart.org)

Out of these six components, three are performed on the court or sideline. Most SCAs respond to AED shocks due to the underlying arrhythmia, such as ventricular tachycardia (VT) and ventricular fibrillation (VF).[3] The patient's survival rate increases to 74% when defibrillation is performed within three minutes, compared to 49% when defibrillation is performed after three minutes.[2-4] Studies also highlight the importance of bystanders initiating resuscitation. Without resuscitation, the survival rate is 7%, which increases to 9% if the patient receives only CPR. The survival rate quadruples to 38% when AED shock is administered.

Who Are The Bystanders on The Field?

The nearest bystanders are other players/ athletes, referees/umpires, and team physicians or medical teams. We should also consider people accredited to be on the field, such as coaches, event organizers, match commissioners, photographers, and ball boys. It is crucial to train them appropriately on how to recognize the symptoms of SCA and to activate the emergency response system. By doing so, they can clear the environment of any barriers to help the patient, declare the emergency status, and ask other bystanders to call for an ambulance and bring an AED. They should then secure the airways, check the breathing, and initiate high-quality CPR by placing the hands in the middle of the patient's chest, pushing fast (100x/min), pushing hard (5-6 cm), allowing full recoil after each compression, and giving ventilation with a 30:2 compression-to-ventilation ratio, with minimal interruption. When the AED arrives, CPR should continue until the AED is ready to analyze the rhythm and give shock instructions. CPR should continue until the advanced medical team arrives and takes over or the patient starts to breathe, move, and react.

Preventing Sports-Related SCA

Pre-participation screening is assumed to play a significant role in preventing sports-related SCA. The screening guideline was developed from a 14-item questionnaire targeting high-risk individuals, followed by additional ECG screening. Despite the recommended guidelines, SCA events in sports still occur. Moreover, the financial, psychological, and feasibility aspects of its implementation should also be considered. Therefore, the focus should be more on having readily accessible AEDs and appropriately trained bystanders to optimize the chain of survival.

There are several reasons why bystanders do not initiate CPR during an episode of SCA, such as the inability to recognize cardiac arrest, not knowing how to perform CPR, fear of causing harm, and legal consequences. The provision of AEDs in sporting venues has a specific strategy.

Figure 3. Types of AED signage (Arrhythm Electrophysiol Rev. 2023 Jan;12:e03. doi: 10.15420/aer.2022.30.)

Clear and noticeable signage will increase staff, athletes, and spectators' awareness of its location (Figure 3).

FIFA has recommended that all members provide medical emergency bags during football training and competition.[6] These bags are intended for use by team physicians, field of play medical teams, or other medical professionals on duty. The contents of the medical bag include personal protection, airway management tools, breathing and circulation tools, wound dressing tools, evacuation tools, fracture splints, general medical tools, and medications. Although the study recommended the bag for use in football/soccer events, the prepared contents might be adaptable for other sports.

Lastly, a well-written emergency action plan is needed. The document should state how the facilities and manpower are organized, such as who is responsible for contacting emergency medical services, who has the key to unlock the gate, who will identify the specific training for each responder, and who will check the need for calibration of emergency equipment.

It may seem overwhelming that we have to do so much for a three-minute effort to save the life of an athlete on the court. However, knowing the fatality of SCA, this is the least we can do, and everything becomes easier if the stakeholders work together.

Reference:

1. Outcry over teen athlete's fatal collapse during match https://www.bbc.com/news/articles/cd19xnxdvlko
2. Bassi MD, Farina JM, Bombau J, Fitz Maurice M, Bortman G, Nuñez E, Márquez M, Bornancini N, Baranchuk A. Sudden Cardiac Arrest in Basketball and Soccer Stadiums, the Role of Automated External Defibrillators: A Review. For the BELTRAN Study (BaskEtbaLl and soccer sTadiums: Registry on Automatic exterNal defibrillators). Arrhythm Electrophysiol Rev. 2023 Jan;12:e03. doi: 10.15420/aer.2022.30. PMID: 36845166;
3. Malik A, Hanson J, Han J, Dolezal B, Bradfield JS, Boyle NG, Hsu JJ. Sudden cardiac arrest in athletes and strategies to optimize preparedness. Clin Cardiol. 2023 Sep;46(9):1059-1071. doi: 10.1002/clc.24095. Epub 2023 Jul 26. PMID: 37493125.
4. Denq W, Oshlag B. Cardiac Emergency in the Athlete. Clin Sports Med. 2023 Jul;42(3):355-371. doi: 10.1016/j.csm.2023.02.003. Epub 2023 Apr 7. PMID: 37208052.
5. Out of hospital chain of survival https://cpr.heart.org/en/resources/cpr-facts-and-stats/out-of-hospital-chain-of-survival
6. Dvorak J, Kramer EB, Schmidt CM, et al. The FIFA medical emergency bag and FIFA 11 steps to prevent sudden cardiac death: setting a global standard and promoting consistent football field emergency care. Br J Sports Med 2013;47:1199–1202. doi:10.1136/bjsports-2013-092767

INA-RESPOND Newsletter

BEHIND THE SUPERPOWER OF ORANGE AND GREEN AND TOOLS TO MEASURE IT!

By: Aly Diana

Source: https://www.vecteezy.com/vector-art/5084750-set-of-fruit-and-vegetable-with-various-activity-in-cartoon-character-vector

Carotenoids, the colorful pigments found in fruits and vegetables, are emerging as key players in infectious disease research. These compounds offer more than just dietary benefits; their antioxidant and immune-supporting properties can have significant impact on disease outcomes. As interest in carotenoids grows, so does the need for effective measurement tools to study their effects. The Veggie Meter®, a non-invasive device designed to measure skin carotenoids, is one such tool with great potential, but it requires accurate and standardized application to realize its full benefits. This article explores the role of carotenoids in infectious diseases and considers how the Veggie Meter® can help advance research in this crucial area.

The Role of Carotenoids in Infectious Disease

Carotenoids, including beta-carotene, lutein, and zeaxanthin, are recognized for their antioxidant and anti-inflammatory properties, which play a significant role in immune function and disease management. Here's how carotenoids impact various infectious diseases:

1. **Respiratory Infections**: Carotenoids, especially beta-carotene, enhance immune responses and mitigate oxidative stress during infections like the common cold and flu. By modulating the immune system, carotenoids help the body fend off infections more effectively, and they are associated with reduced severity and duration of respiratory infections.
2. **HIV/AIDS**: In the context of HIV/AIDS, carotenoids have shown promise in improving immune function and slowing disease progression. Carotenoids, particularly beta-carotene, have been linked to better immune responses and overall health in HIV-infected individuals, suggesting their potential in long-term disease management.
3. **Tuberculosis**: Carotenoids may also offer protective benefits against tuberculosis (TB). Low serum carotenoid levels are associated with an increased risk of developing TB. The antioxidant effects of carotenoids could help reduce oxidative stress and inflammation related to TB, supporting their use in prevention and management strategies.

The Need for Accurate Measurement Tools

Accurate measurement of carotenoid levels is essential to understanding their impact on infectious diseases. Traditional methods, like blood tests, are invasive and may not be practical for large-scale studies. Non-invasive tools like the Veggie Meter® present a viable alternative. The Veggie Meter®, developed by Longevity Link Corporation, uses reflection spectroscopy (RS) technology to assess carotenoid levels in the skin. The device shines a light onto the skin and measures the reflected light to determine carotenoid concentration. This process is quick and non-invasive, providing results in about 15–20 seconds.

While the Veggie Meter® is promising due to its non-invasive nature and ease of use, its accuracy and reliability must be verified using established methods. Studies have shown that its results correlate well with serum carotenoid levels and other spectroscopy-based methods, such as Raman resonance spectroscopy (RRS). However, the device's effectiveness can be influenced by factors such as calibration, measurement site, and data documentation. Standardized protocols are crucial to ensure consistent and reliable results.

To realize the full potential of the Veggie Meter®, standardized protocols must be developed and followed. Variations in calibration, measurement sites, and data collection practices can affect accuracy. Uniform guidelines will enhance the reliability of carotenoid measurements, supporting more effective research and enabling better comparisons across studies.

Conclusion

Carotenoids are crucial in supporting immune function and improving outcomes in infectious diseases. Accurate measurement of these compounds is vital for understanding their effects and optimizing treatment strategies. Non-invasive tools like the Veggie Meter® offer a promising approach, but their effectiveness relies on standardized practices. As research into carotenoids and infectious diseases progresses, reliable measurement tools will be key to unlocking their full potential and improving health outcomes.

References

- Aibana O, Franke MF, Huang CC, Galea JT, Calderon R, Zhang Z, Becerra MC, Smith ER, Ronnenberg AG, Contreras C, Yataco R, Lecca L, Murray MB. Impact of Vitamin A and Carotenoids on the Risk of Tuberculosis Progression. Clin Infect Dis. 2017 Sep 15;65(6):900-909. doi: 10.1093/cid/cix476. PMID: 28531276; PMCID: PMC5848231.
- Bhatt T, Patel K. Carotenoids: Potent to Prevent Diseases Review. Nat Prod Bioprospect. 2020 Jun;10(3):109-117. doi: 10.1007/s13659-020-00244-2. Epub 2020 May 13. PMID: 32405969; PMCID: PMC7253555.
- Crupi P, Faienza MF, Naeem MY, Corbo F, Clodoveo ML, Muraglia M. Overview of the Potential Beneficial Effects of Carotenoids on Consumer Health and Well-Being. Antioxidants (Basel). 2023 May 10;12(5):1069. doi: 10.3390/antiox12051069. PMID: 37237935; PMCID: PMC10215867.
- Eggersdorfer M, Wyss A. Carotenoids in human nutrition and health. Arch Biochem Biophys. 2018 Aug 15;652:18-26. doi: 10.1016/j.abb.2018.06.001. Epub 2018 Jun 6. PMID: 29885291.
- Khalil A, Tazeddinova D, Aljoumaa K, Kazhmukhanbetkyzy ZA, Orazov A, Toshev AD. Carotenoids: Therapeutic Strategy in the Battle against Viral Emerging Diseases, COVID-19: An Overview. Prev Nutr Food Sci. 2021 Sep 30;26(3):241-261. doi: 10.3746/pnf.2021.26.3.241. PMID: 34737985; PMCID: PMC8531419.
- Radtke MD, Poe M, Stookey J, Jilcott Pitts S, Moran NE, Landry MJ, Rubin LP, Stage VC, Scherr RE. Recommendations for the Use of the Veggie Meter® for Spectroscopy-Based Skin Carotenoid Measurements in the Research Setting. Curr Dev Nutr. 2021 Jul 29;5(8):nzab104. doi: 10.1093/cdn/nzab104. PMID: 34476333; PMCID: PMC8405124.

Gregorgia Mariska Tunjung Berhasil Meraih Medali Perunggu di Olimpiade Paris 2024

Foto CNBC Indonesia: Atlet angkat besi Indonesia Rizki Juniansyah yang turun di nomor 73 kg pada Olimpiade Paris 2024 sukses menyabet medali emas.

Foto detikbali: Veddriq Leonardo menyumbang emas pertama untuk Indonesia. (REUTERS/Benoit Tessier)

Dirgayahu Indonesia ke 79

Foto bersama Presiden Joko Widodo (Jokowi) dengan 76 nama pelajar yang tergabung dalam Paskibraka Nasional 2024 di Istana Garuda IKN

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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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