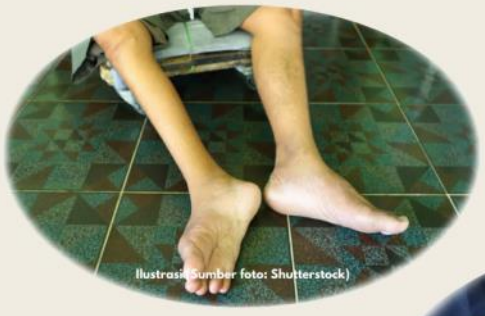
INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

March 2024



SCIENCE CORNER

Poliovirus Outbreaks: Throwing A Curveball Into The Polio-free World Endgame

HEALTH POLICY AGENCY

MINISTRY OF HEALTH REPUBLIC OF INDONESIA

2024

MASTHEAD

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, Nur Latifa Hanum, Retna Mustika Indah, Restu Amalia, Riza Danu Dewantara

InVITE

Out of the 700 (100%) participants who enrolled in the study, all have ended their participation, so the InVITE study has entered its final phase. Almost all specimens have been sent to the INA-RESPOND Reference Laboratory, with only one more shipment of specimens from site 03 to the Reference Laboratory INA-RESPOND remaining. After all specimens are received at the Reference Lab, INA-RESPOND will prepare a subset of specimens to be sent to the Central Laboratory.

In the final phase of the study, the research team at each site must ensure that the documents completed in the Case Report Form (CRF) are consistent with the source document. Next, Source Document Verification (SDV) of several Critical Variable data will be carried out by the INA-RESPOND secretariat team, to confirm the continuity between the data in the CRF and the source documents. This SDV is expected to be completed before the special Global data cleaning for Indonesia starts in June 2024.

The global database lock for all countries involved in the InVITE study will be carried out after the Last Patient Last Visit (LPLV) is completed at all sites, which is in January 2025. After the Global database lock, a Site Close Out Visit (SCV) will be conducted in February 2025.

Details regarding the timeline for the InVITE study from each site are listed in Table 1.

Site Number	Last Patient Last Visit (LPLV)	Last Site Monitoring Visit	Local Database Soft Lock	Global Data Cleaning (Indonesia)	Global Database Lock (All country)	Site Closeout Visit (SCV)
01	24 Jan 2024	09 - 11 Apr 2024	Early May 2024	Jun 2024	Jan 2025	Feb 2025
02	24 Nov 2023	Not done	20 Feb 2024			Feb 2025
03	04 Jan 2024	30 Apr - 02 May 2024	Early May 2024			Feb 2025

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The preparation of PROACTIVE primary and additional manuscripts is still ongoing. At the same time, we are still performing a scoping review on HIV research in Indonesia since the first HIV case was reported in Indonesia (1987). Our first focus of this scoping review project is research on children living with HIV in Indonesia. This review will support the preparation of a PROACTIVE manuscript on pediatric subjects. Besides that, INA-RESPOND Secretariat Staff and Research Assistants (RAs) are also active in journal club activities. The second journal club meeting was held on January 16, 2024, with an article entitled "*Association between human immunodeficiency virus infection and arterial stiffness in children*". The article was presented by dr. Cintya Naya Danastri from Tangerang Site and dr. Ni. Luh Putu Ariastuti from Denpasar Site. Below is the summary of this article:

Cardiovascular disease (CVD), in particular, has emerged as an essential cause of morbidity and mortality in HIV-infected patients since the introduction of Antiretroviral therapy (ART). Despite the nature of pro-atherosclerotic properties in HIV, treatment with ARV, especially protease inhibitors (PIs), may accelerate the development of atherosclerosis by enhancing dyslipidemia or affecting macrophages, endothelial or smooth muscle cells. Given

HIV Journal Club – 2nd

Original scientific paper

Association between human immunodeficiency virus infection and arterial stiffness in children

Justin S Kuilder[1], Nikmah S Idris[1,2,3], Diederick E Grobbee[1], Michiel L Bots[1], Michael MH Cheung[3,4], David Burgner[3,5], Nia Kurniati[2] and Cuno SPM Uiterwaal[1]

Published in European Journal of Preventive Cardiology, 2017, Vol. 24(5) 480-488

the rising prevalence of CVD in HIV-infected people on ART, the question of whether HIV causes vascular alterations is becoming increasingly important. The study investigated vascular stiffness in HIV-infected children using pulse wave velocity (PWV) and aortic augmentation index (Aixao) to indicate early vascular functional changes. As a result, it may provide information about the relationship between HIV infection and early vascular abnormalities, as well as the potential effects of early life inflammation on future cardiovascular risk in HIV as a chronic inflammatory disease.

This cross-sectional study comprised 51 vertically acquired HIV-infected children and 52 healthy children (ages 3.2–14.5 years, 49 boys). HIV-positive children were recruited from Cipto Mangunkusumo Hospital and Koja District Hospital in Jakarta. Healthy children were randomly recruited from the Cipto Mangunkusumo Hospital and the Bekasi neighborhood. PWV and Aix_{ao} were measured with the non-invasive oscillometric arteriograph equipment to determine arterial stiffness. PWV and Aix_{ao} are then calculated automatically using the arterial pulse waveform. The stiffer artery wall and vessel led to increased PWV velocity and Aix_{ao}. All children were measured in a supine posture (92 children) or a sat upright position (11 children) if they were restless, agitated, or uncomfortable. At least two valid measures were made for every kid, although, for 15 children, only one good measurement was achieved because the child became uneasy.

Potential confounders included the subjects' age, height, weight, socioeconomic status, secondhand smoke exposure, heart rate, and recent infection. Socioeconomic status, body weight, and smoking exposure are all risk factors for CVD, and they are likely to be linked to HIV infection and/or ART. The data were gathered by measurements, questionnaires, and laboratory tests. This study used multivariable general linear models to assess the connection between HIV infection and arterial stiffness, with additional adjustments for confounders and potential intermediary variables. The findings show mean group differences with 95% confidence intervals and p-values.

Based on the study's findings, HIV-infected children had lower body weight and height than healthy children, were slightly younger, and were more likely to have been exposed to maternal smoking while pregnant. Acute infections were more common in HIV-infected youngsters, and hsCRP levels were elevated. The median (range) duration of ART treatment was 3.4 years (0.1-9.2). Among the HIV-infected children, 11 (21.6%) were on PI, with a median (range) treatment duration of 3.6 (0.1-5.1) years.

There were no significant changes between groups in blood pressure and heart rate, total cholesterol, LDL, or HbA1C levels. The mean PWV values for HIV-infected and healthy children were 6.28 (SD 1.13) and 6.13 m/s (SD 0.67), respectively. There is no significant mean group difference in PWV. The Aix_{ao} groups had mean values of 29.0% (SD 9.4) and 20.0% (SD 8.2), respectively. HIV-infected children had a higher mean Aix_{ao} (crude difference 9.0%, $p<0.001$) than healthy children, even after controlling for confounders (adjusted difference 6.1%, $p<0.001$). Further adjustments for blood pressure, pulse pressure, LDL, hsCRP, or HbA1C did not alter these correlations.

This study demonstrates that HIV infection in ART-exposed children is related to higher Aix_{ao} levels than in healthy children. This link was not mediated by brachial blood pressure, inflammatory severity, or lipid or HbA1c levels. There was no significant association between HIV infection in ART-exposed children and PWV. This result differs from the previous study, which found that HIV-infected children had considerably higher PWV than controls. Because the study participants are younger children, the investigator hypothesizes that the change in PWV is more subtle and hence requires a more extensive study population to detect, as PWV increases with age. The HIV-infected youngsters in this study may be a "fitter" population with a milder form of HIV infection; the impact of HIV infection on PWV may be under- or overestimated.

INA-RESPOND Newsletter

REPORT INTERNATIONAL: TB RICC BIOMARKER – JUNIOR INVESTIGATOR TRAINING

By: Gustiani Salim

Enhancing Laboratory Skills and Capacity in TB Biomarker Research

For the first time, RePORT International held a Junior Investigator Training program aimed at enhancing the capacity and laboratory skills of staff from RePORT International member countries. This training provides participants the opportunity to learn not only from expert scientists directly but also by using the latest advanced laboratory equipment and techniques that can be used as assays for research such as biomarkers, immune mechanisms, and transcriptomics, metabolomics, advanced host-pathogen interactions in high-throughput associated with tuberculosis (TB) disease. From this program, participants are also expected to engage in relevant research, including RePORT International study projects and to build collaborative relationships between countries.

The Junior Investigator Training in 2024 was attended by five participants from three RePORT member countries: one person from Indonesia, two from India, and two from the Philippines. The training was conducted in three central laboratories located in three different countries where participants specifically learned techniques and laboratory methods that support research focusing on the search for host biomarkers associated with TB treatment failure. The three laboratories are:

1. SATVI Laboratory at the University of Cape Town, South Africa, directed by Prof. Thomas Scriba. Participants learn and receive hands-on training on multiplex quantitative PCR assay methodology (Fluidigm/Microfluidics). The training was held for two weeks from February 5 – 16, 2024.
2. RiCC Luminex Referral Laboratory, Salvador, Bahia, Brazil, directed by Dr. Bruno Andrade. Participants learn and receive hands-on training on protein quantification assays using Luminex technology. The training was held for two weeks from February 19 – March 1, 2024.
3. Rutgers - New Jersey Medical School (NJMS) Laboratory, Newark, New Jersey, United States of America, led by Dr. Padmini Salgame. Participants learn and receive hands-on training on the digital Nanostring platform. The training will be held for two weeks from May 6 – 17, 2024.

Photo: Training participants

In addition to wet lab training, the trainees also received virtual training through online webinars by Dr. Evan Johnson, an informatics specialist. He provided training to the group in the use of R Studio – a software package intended for the analysis of complex biology and informatics data. This training serves as a foundation for analyzing the results that will be obtained from the three laboratory assays above.

Training at SATVI Laboratory, University of Cape Town, South Africa

The South African Tuberculosis Vaccine Initiative (SATVI), is a world leader in TB vaccine clinical research located within the Health Sciences Faculty at the University of Cape Town.

The research conducted at the SATVI laboratory mainly focuses on immunology in TB, TB vaccine development, biomarker development, and deepening understanding of pathogenesis and immunity related to risk and protection against TB. Specifically for this training program, SATVI focuses on providing material regarding gene expression studies aimed at finding and developing specific biomarkers for TB disease by performing microfluidic RT-qPCR using the Fluidigm Biomark© platform.

Photo: Participants and SATVI team

1. Gene Expression Study

What is Gene Expression Study

Gene expression is the determination of the pattern of genes expressed at the level of genetic transcription, under specific circumstances or in a specific cell. Gene expression works by measuring levels of mRNA, the intermediary between DNA and protein. It is well-known that to activate a gene, a cell must first copy the DNA sequence of that gene into a piece of mRNA known as a transcript. Thus, by determining which mRNA transcripts are present in a cell, it can be determined which genes are expressed in that cell. However, gene expression can also be analyzed by directly measuring protein levels. When studying gene expression, researchers usually investigate changes, increases, or decreases, in the expression of a particular gene. The investigation monitors the response of a gene to treatment with a compound or a drug of interest, under a defined set of conditions.

There are several laboratory methods that can be used to measure gene expression such as quantitative polymerase chain reaction (qPCR), DNA microarray, and RNA-sequencing by measuring mRNA levels. For protein levels, techniques such as Western blot, ELISA, or bead-based immunoassay (Luminex) can be used.

Quantitative Polymerase Chain Reaction (qPCR) for Assessing Relative Quantification of Gene Expression

Quantitative Polymerase Chain Reaction (qPCR), also known as real-time PCR using the Taqman primers/probes platform, is a commonly used assay when studying gene expression. This platform allows us to relatively quantify dif-

ferences in the expression level of a specific target gene between different samples. The data output is expressed as a fold-change or fold-difference of expression levels, for example, the change in expression of a particular gene over a given time period in treated versus untreated samples.

One of the analysis methods for relative quantification of gene expression from qPCR data is known as the comparative C_T or double delta C_T ($\Delta\Delta C_T$) method. This method requires the quantification of two different genes: the target gene and the housekeeping gene as a reference gene. The reference gene is used to normalize the quantification of targets for differences in the amount of total nucleic acid added to each reaction. $\Delta\Delta C_T$ analysis assumes that:

- There is equal primer efficiency between primer sets (i.e., within 5%),
- There is near 100% amplification efficacy of the reference and the target genes,
- The internal control genes are constantly expressed and aren't affected by the treatment.

Calculating Gene Expression Using the $\Delta\Delta C_T$ Method and Interpretation

In general, there are several main components required when performing the relative quantification $\Delta\Delta C_T$ method:

- Target gene: The gene of interest whose expression we are determining.
- Endogenous control gene: The housekeeping gene whose expression is regulated.
- Calibrator sample: The sample or group of samples used as a control.
- Test sample: The sample or group of samples treated or tested for differences.
- Expression fold change/Relative gene expression: The ratio of the target gene expression in the test sample over the calibrator sample.

The arithmetic formula needed to measure the amount of target, normalized to an endogenous control and relative to a calibrator, is given by:

$$RQ=2^{-\Delta\Delta CT}$$

Where:

$\Delta\Delta C_T$ = ΔCT (test samples) − ΔC_T (calibrator samples)

ΔC_T (test samples) = CT value (target gene in test) – C_T value (endogenous control gene in test)

ΔC_T (calibrator samples) = CT value (target gene in calibrator) – C_T value (endogenous control gene in calibrator)

The value obtained from the calculation represents the fold change of the gene of interest in the test condition, relative to the control condition, after normalization to the housekeeping gene. For example:

- A fold change of 1 indicates that there is 100% as much gene expression in the test condition as in the control condition, meaning there is no change between the experimental group and the control group.
- A fold-change value above 1 indicates upregulation of the gene of interest relative to the control (e.g., a 1.2-fold change equals 120% gene expression relative to control, 5 equals 500%, 10 equals 1,000%, etc.).
- Values below 1 indicate gene downregulation relative to the control (e.g., a fold change of 0.5 equals 50% gene expression relative to control, meaning there is half as much expression as in the control, etc.).

Microfluidic RT-qPCR using the Fluidigm Biomark© platform for Gene Expression Study

In the SATVI laboratory, the trainess learn about gene expression using the Fluidigm Biomark© platform, an automated, high-performance PCR/ qPCR system that utilizes microfluidics technology to process samples at nanoliter-scale volumes. This

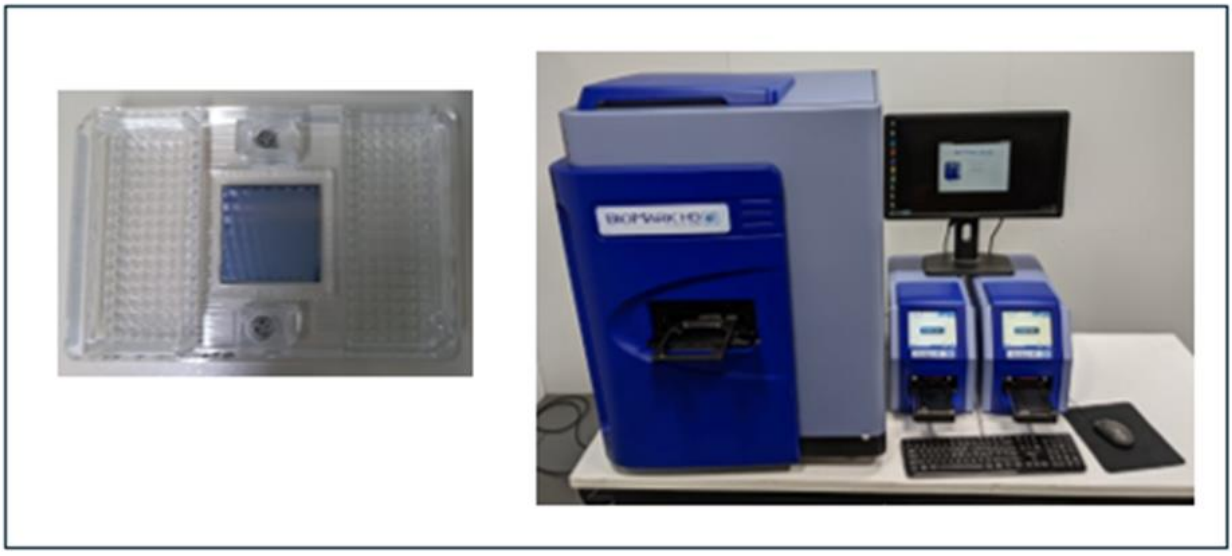
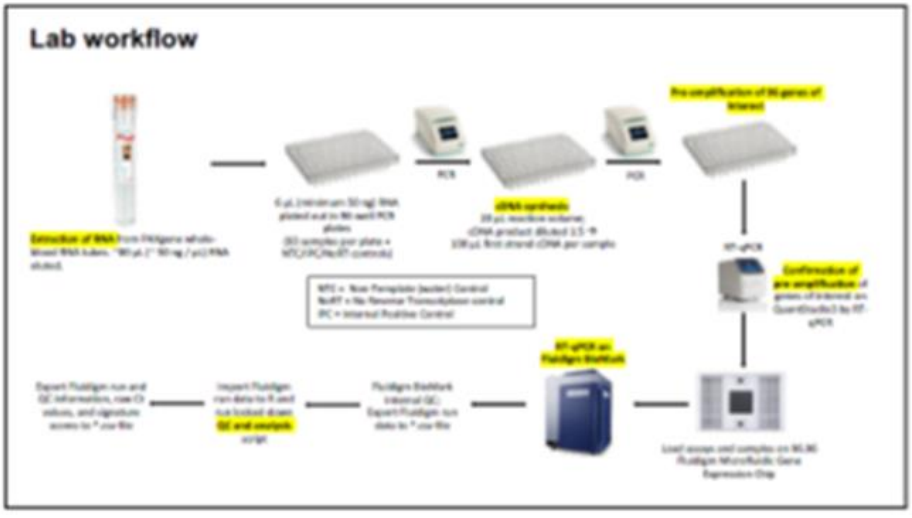


Photo: Dynamic ArrayTM IFC and Biomark HDTM Fluidigm System

machine features Dynamic Array™ integrated fluidic circuits (IFCs) that allow us to test up to 96 individual cells against 96 genes in a single experiment. The Dynamic Array™ combines cDNA material from individual cells with reagents to create individual quantitative PCR (qPCR) reactions.

Before performing qRT-PCR on the Fluidigm system, it is necessary to conduct reverse transcription and specific target amplification using a thermocycler suitable for 96-well plates. The overall process for processing blood samples for gene expression is summarized in the following chart.



When running the samples, upon completion, the Fluidigm qPCR analysis software calculates and provides results displayed as a table, an image view diagram, or a heat map. The results table presents the numeric CT values for the different samples for each gene. The image view option graphically plots the fluorescence intensity as it increases during qPCR amplification. The heat map represents the results according to a color range, with each color tone indicating a CT value. In the heat map display, individual assays (X-axis) are plotted against individual samples (Y-axis). The software can also use a housekeeping gene included in the array to normalize the CT values, thereby correcting differences in the CT values due to slightly varying starting amounts of RNA—these are known as ΔCT values, which are then converted to fold change values. Furthermore, the resulting data are analyzed using R software for quality control, statistical analysis, and presentation purposes.

2. Visiting Field Site

During the training opportunity at SATVI, the trainess were also invited to visit clinics and sites for TB patients' recruitment, located in Worcester city, approximately a 2-hour drive from Cape Town. From this visit, we were able to observe how patients are screened, consented, and recruited to participate in TB studies. For patients who agree to participate, the team should visit their homes and transport them to the clinics when it is necessary to draw their blood. Once collected from the patients, the blood samples are then processed in the clinic's laboratory before being sent to the SATVI laboratory in Cape Town.

After two weeks at SATVI, the trainees proceed to Salvador, Brazil, for Luminex technology training. Due to lab capacity limits, they are split into two groups. The first group, comprising one participant from Indonesia and one from the Philippines, attends from February 19 to March 1, 2024. The second group, with one participant from the Philippines and two from India, has their session from April 15 to 26, 2024. Details of their experiences in Brazil will be featured in the April 2024 edition of our INA-RESPOND newsletter.

World TB Day 2024: Yes! We Can End TB!

March 24 marks a significant day in the global health calendar: World TB Day. This date was chosen to commemorate the discovery of the bacterium Mycobacterium tuberculosis by Dr. Robert Koch in 1882, which opened a new chapter in the fight against tuberculosis (TB). Over a century later, the battle against this deadly disease continues with concerted efforts from organizations worldwide, including our network, INA RESPOND.

Indonesia remains at the forefront of the TB epidemic, ranking as the country with the second-highest number of TB cases globally. As of 2024, Indonesia has only made little progress, with a 68% treatment coverage and an 86% TB treatment success rate. The country still faces challenges in meeting the Global TB Elimination targets set for 2030, which include reaching over 90% in treatment coverage, treatment success rate, and preventive treatment coverage.

The path to these ambitious goals is filled with obstacles, including stigma, delayed diagnosis, and treatment, lengthy and complex treatment regimens, co-infections with HIV, and drug-resistant TB strains. Addressing these issues requires a multifaceted approach, focusing on improving TB management and increasing awareness and support at both the community and government levels.

While World TB Day 2024 brings hope and determination, it also serves as a reminder of the journey ahead. It is a call to action for governments, organizations, and individuals to unite in the fight against TB. By working together, sharing knowledge, and committing to sustained efforts, we can look forward to a future where TB is no longer a threat to global health.

As we commemorate World TB Day, let us remember that each step taken towards TB control is a step towards a healthier, TB-free world. *Yes! We can end TB!*

Source: Instagram *@inarespondsecretariat*

INA-RESPOND Newsletter

POLIOVIRUS OUTBREAKS: THROWING A CURVEBALL INTO THE POLIO-FREE WORLD ENDGAME

By: Putri Permata Sari, Titin Dani Martiwi, Adhella Menur

SCIENCE CORNER

Brief history of polio, outbreaks, and towards a polio-free world

When we hear "polio" or "poliomyelitis," we might imagine a child with a small and floppy, one-sided leg, emblematic of the spectrum of disabilities caused by poliovirus infection that has plagued humanity since ancient times. Evidence of polio was identified in an Egyptian painting from 1403 BC, depicting children with limb deformities relying on walking sticks. It wasn't until 1789 that the English physician Michael Underwood provided the first clinical description, labeling polio as a "debility" of the lower extremities, primarily afflicting children under five. Its most severe consequences were permanent disability and even death, due to paralysis of the breathing muscles. The virus itself was successfully isolated by Karl Landsteiner and Erwin Popper in 1909. In 1931, Sir Macfarlane Burnet and Dame Jean MacNamara identified the three serotypes of the poliovirus: 1, 2, and 3.

By the mid-20th century, poliovirus infections were prevalent worldwide, causing paralysis or death in over half a million people annually. In the United States, localized paralytic poliomyelitis outbreaks began to appear around 1900. Poliovirus outbreaks became increasingly common in the late 19th and early 20th centuries, particularly in summer. One of the most notable early poliovirus outbreaks occurred in New York City in 1916, resulting in thousands of cases and deaths. This outbreak drew widespread attention due to the severity of the disease and fueled public fear. The United States experienced one of its worst poliovirus outbreaks in 1952, with over 50,000 reported cases and thousands of deaths. With no cure and increasing epidemics, a vaccine became urgent. Thomas Weller and Frederick Robbins successfully cultured the poliovirus in 1948, and David Bodian's description of the three antigenic serotypes in 1952 paved the way for significant progress in vaccine development. Jonas Salk's inactivated polio vaccine (IPV) in 1955 and Albert Sabin's oral polio vaccine (OPV) in 1961 marked pivotal milestones, leading to widespread deployment in mass vaccination campaigns. Consequently, the number of polio cases steadily declined, and by 1985, polio had largely disappeared in developed countries. However, in developing countries, polio continued to cripple a child on average every 90 seconds, prompting global commitments and concerted efforts to immunize populations against the poliovirus.

In 1988, the World Health Assembly (WHA) adopted a resolution for the worldwide eradication of polio, marking the launch of the Global Polio Eradication Initiative (GPEI) - a collaborative effort led by various entities, including national governments, the WHO, Rotary International, the US CDC, UNICEF, and later, the Bill & Melinda Gates Foundation and Gavi, the Vaccine Alliance. Since its establishment, the GPEI has made remarkable progress, with a 99.9% reduction in global polio incidence. Wild poliovirus serotypes 2 and 3 (WPV2 and WPV3) were declared eradicated in 2015 and 2019, respectively. However, the endemic transmission of WPV1 persists in Afghanistan and Pakistan. The endgame effort was also tempered by the emergence of circulating vaccine-derived polioviruses (cVDPVs) from OPV. In 2023, 12

cases of WPV1 in Afghanistan and Pakistan and 374 cases of cVDPV in several countries in Africa and Asia were reported.

To achieve a polio-free world in 2026, the GPEI has re-envisioned the endgame pathway with an urgent call for collective ownership and accountability across the GPEI partnership and with governments, communities, and all other stakeholders. The Polio Eradication Strategy for 2022–2026 outlines the plan for achieving a world free from all polioviruses. Efforts are also focused on transitioning and post-certification initiatives to ensure that the infrastructure established for polio eradication will continue to support broader public health initiatives even after polio is eliminated. The GPEI will transform its approach in each region and country with two elemental goals: *Goal One* to permanently interrupt all poliovirus transmission in the final WPV-endemic countries of Afghanistan and Pakistan, and *Goal Two* to stop cVDPV transmission and prevent outbreaks in non-endemic countries. Failure to implement strategic approaches results in continued virus transmission and could lead to a global resurgence of the disease, emphasizing the importance of achieving complete eradication.

Understanding polio

Poliovirus is a member of the genus Enterovirus, belonging to the Picornaviridae family. Human beings are the only known reservoir of poliovirus infection. The infection spreads through the fecal-oral route, and the virus is disseminated in feces, contributing to its highly contagious nature. The highest amount of virus excretion occurs 2 to 3 days before and up to 1 week after symptoms appear. The virus also presents in urban sewage, which may then serve as a source of direct or indirect transmission through flies or contaminated water used for drinking, bathing, or irrigation. Transmission is remarkably rapid in areas with poor sanitation, especially among children and individuals lacking immunity.

The clinical manifestation of poliovirus infection is categorized based on the severity of symptoms. Approximately 95% are asymptomatic cases. Symptomatic cases may present as mild illness (abortive poliomyelitis), aseptic meningitis (nonparalytic poliomyelitis), and paralytic poliomyelitis. Abortive poliomyelitis, which accounts for 4% to 8% of cases, may lead to symptoms like gastroenteritis, flu-like illness, and mild respiratory problems that usually resolve within a week. Aseptic meningitis accounts for about 1% of

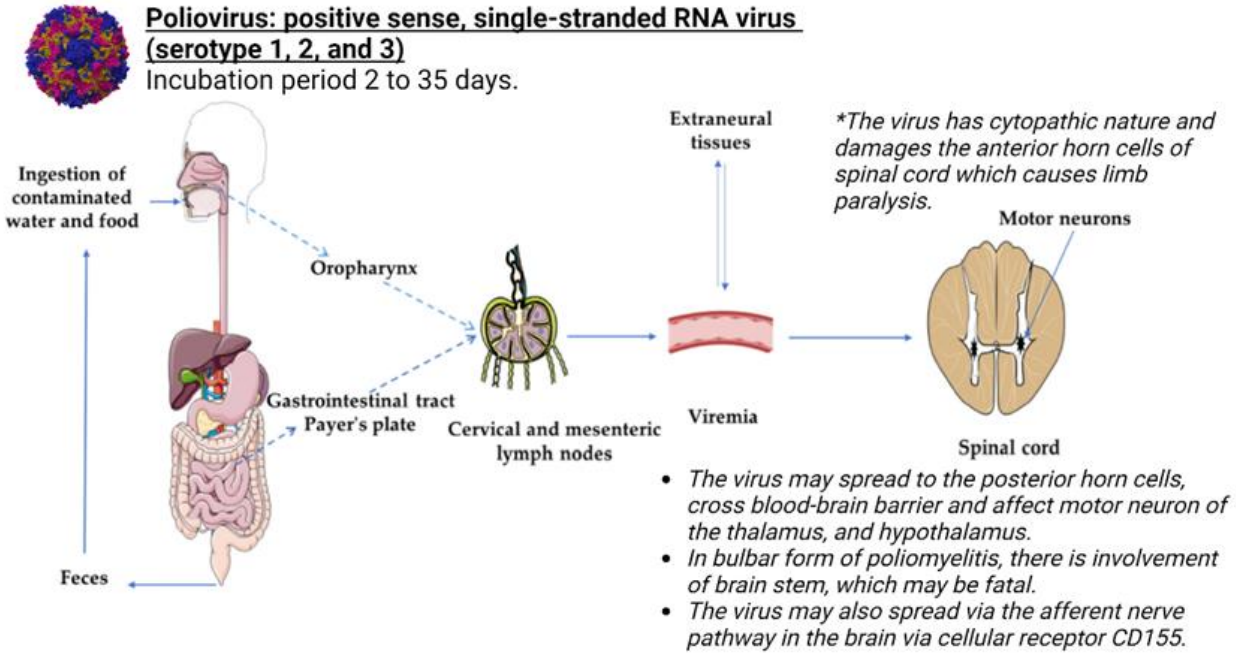


Figure 1. The polio pathogenesis (Mehndiratta MM et al., 2014, doi: 10.1177/1941874414533352). Created with Biorender.com

clinical cases and is characterized by severe muscle spasms in the neck, back, and lower limbs following a brief prodrome like abortive poliomyelitis. Complete recovery usually occurs within ten days. The most severe manifestation is paralytic poliomyelitis, which affects less than 1% of patients. There are three forms of paralytic poliomyelitis: spinal poliomyelitis (most common), bulbar poliomyelitis (2%), and a combination of the two, bulbospinal poliomyelitis (19%). Bulbar poliomyelitis carries the highest fatality rate due to the involvement of the brain stem. In children, the disease may have a biphasic presentation—a prodromal period followed by a brief symptom-free interval of 7 to 10 days, then the onset of asymmetrical limb flaccid paralysis. While some patients may experience complete recovery, lifelong disability may occur if motor function loss persists beyond 12 months. Post-polio syndrome (PPS) can occur 25 to 40 years after the initial paralytic attack and is characterized by progressive muscular weakness, joint deterioration, and increasing skeletal deformities.

Poliovirus infection can be diagnosed by detecting the virus through culture in cell lines and polymerase chain reaction (PCR) from stool, throat swabs, blood, and cerebrospinal fluid (CSF) samples. A 4-fold rise in serum antibody titer can also confirm the infection. Neutralizing antibodies appear very early in the disease process and persist for life. While there is currently no cure for polio, treatment strategies aim to alleviate symptoms and manage complications. During the acute phase of the illness, medical interventions focus on relieving pain and muscle spasms, ensuring adequate respiratory function and hydration, minimizing the risk of skeletal deformities, and addressing any secondary effects of paralysis. In the recovery phase, physiotherapy, appropriate orthotic devices, and surgical management may improve outcomes.

Polio vaccines and the emergence of vaccine-derived polioviruses

Preventing and eradicating polio is certainly possible with the deployment of polio vaccines to maintain high rates of population immunity. As mentioned above, there are two types of polio vaccines, OPV and IPV, which have their particular advantages and flaws, but both continue to play an essential role in polio control (Table 1).

	Oral Polio Vaccine	Inactivated Polio Vaccine
Preparation	Live attenuated.	Inactivated (killed) virus with formalin, adsorbed into adjuvants.
Valency	Monovalent (type 1, 2, or 3) OPV (mOPV), bivalent (type 1 and type 3) OPVs (bOPVs), and trivalent OPVs (tOPVs).	Trivalent only.
Administration	Through mouth as drops	Intramuscularly into the upper arm or anterolateral thigh.
Pathogenesis	Produce a local immune response in the intestines. Mucosal immunity decreases the replication and shedding of the virus. Also induce humoral immunity.	Serum antibodies provide humoral immunity, thus decreasing the replication of the virus.
Vaccine efficacy	OPV produces excellent gut and humoral immunity, and the immunity is probably lifelong.	Highly effective in producing immunity to poliovirus and protection from paralytic poliomyelitis. No gut immunity. The duration of immunity is not known with certainty.
Adverse effects	Vaccine-associated paralytic poliomyelitis (VAPP) (sporadic and rare), and vaccine-derived poliovirus (VDPV).	Adverse events following administration of IPV are very mild and transient.

Table 1. Oral Polio Vaccine (OPV) and Inactivated Polio Vaccine (IPV)

The OPV has many benefits, but it carries a risk. Sometimes, the weakened polioviruses in the vaccine can genetically mutate to vaccine-derived poliovirus (VDPV) and revert to neurovirulent forms, spread among low-immunized individuals and cause paralysis. There are three types of VDPV, which are: (1) circulating VDPV (cVDPV), which is spread from person to person in a community with a low level of polio immunization coverage; (2) immunodeficiency-associated VDPV (iVDPV), which is isolated from people with primary immunodeficiency disease (PID); and (3) ambiguous VDPV (aVDPV). Among these, cVDPVs pose the most significant public health concern as they resemble wild polioviruses, have the potential to cause outbreaks, and require similar control measures. Since 2000, cVDPV outbreaks have occurred in 18 countries, with the majority (87.1%) associated with type 2 cVDPV. A global resurgence of cVDPV2 began in 2016, linked to the switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) for routine vaccination, creating immunity gaps to type 2 poliovirus. Type 1 cVDPVs (11.1% of cases) caused outbreaks in Hispaniola in 2000–2001 and Indonesia in 2005, while type 3 cVDPVs are relatively rare, accounting for only 1.8% of known cases. Since January 2020, cVDPV has sprung up in more than 50 countries and hampered the endgame of a polio-free world.

Poliovirus outbreaks and government responses in Indonesia

The journey towards polio eradication in Indonesia has been long and challenging. The government has committed to providing free polio vaccines, including IPV (given twice before one year) and OPV (given four times at 1, 2, 3, and 4 months of age). However, in 2021, the national average OPV vaccination rate was only 80.2% (target 95%). Alarmingly, 19 out of 34 provinces had vaccination coverage lower than the national average, with West Papua and Aceh having the lowest coverage rates (West Papua: 43.3% of 19,200 and Aceh: 50.9% of 101,520 infants born). The WHO assesses the polio risk to be high at the national level due to low polio vaccination coverage in some provinces in Indonesia. The population is susceptible to poliovirus type 2 after switching from tOVP to bOPV in 2016, combined with low uptake of

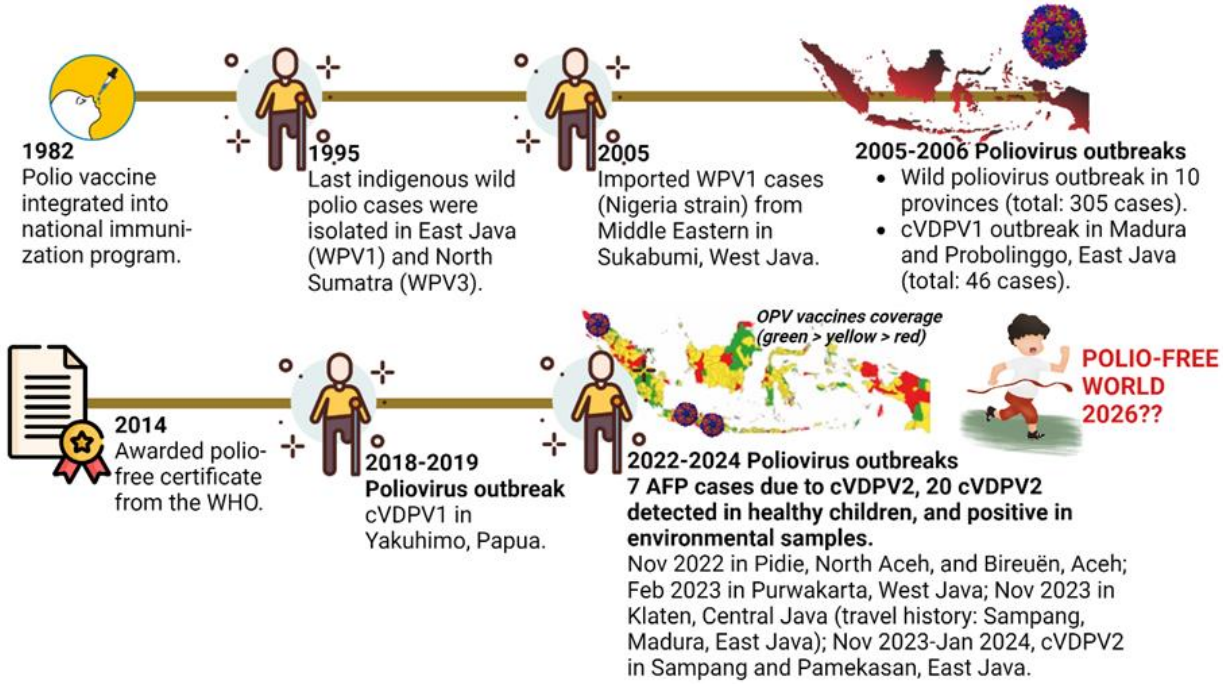


Figure 2. Poliovirus outbreaks timeline in Indonesia. Created with Biorender.com.

IPV, sub-optimal acute flaccid paralysis (AFP) surveillance capacity, and vaccine hesitancy among the at-risk population. Additionally, in some regions, there are still issues with open defecation, diapers discharged to the river, and children playing in contaminated rivers, increasing the risk of polio transmission.

When there's a poliovirus outbreak, two main strategies are used: (1) **Outbreak Response Immunization (ORI)**: this involves giving OPV to all children and toddlers at risk of being exposed to the virus, especially in the area where the case was found and nearby. Vaccines are administered as soon as possible (within 3x24 hours), no later than the first week, regardless of the child's immunization status; (2) **Mopping Up**: this strategy covers a broader area by administering OPV to all children under five years, regardless of their immunization status. Mopping Up is carried out nationwide namely National Immunization Week (Pekan Imunisasi Nasional/ PIN) or in specific provinces namely Sub-National Immunization Week (Sub-PIN) or supplementary immunization activities (SIA). Recent outbreaks of cVDPV2 underscore the importance of maintaining high levels of routine vaccination coverage everywhere to reduce the risk and consequences of poliovirus circulation. It's also crucial to ensure quality AFP surveillance for early detection.

The primary responses to recent cVDPV2 outbreaks have included enhancing AFP case finding and surveillance, routine immunization, Sub-PIN/ SIA campaigns with novel OPV2 (nOPV2; more genetically stable) and promoting proper hygiene and sanitation practices. Great news! The polio vaccination coverage during the Sub-PIN/ SIA in Central Java, Yogyakarta, and East Java provinces has surpassed 95%. This vaccination campaign was conducted in two rounds (January 15th to 21st, 2024 and February 19th to 25th, 2024) targeted 8.6 million children 0-7 years. This high coverage is a significant achievement in the fight against polio. It inspires us to strive for even greater success in expanding routine polio immunization coverage across all provinces in Indonesia. By ensuring that more children receive the necessary vaccinations, we can effectively protect them from the threat of polio and contribute to a healthier future for all towards polio-free world in 2026.

Concluding remarks

Poliovirus outbreaks are like throwing a curveball into the polio-free world endgame. For every child paralyzed by poliovirus infection, there are approximately 200 asymptomatic cases, meaning that a single reported case is just the tip of the iceberg. As long as polio exists in any country, even polio-free nations remain at risk. Enhanced AFP surveillance is crucial for early detection and intervention in polio cases. Eradicating polio will also require discontinuing OPV to prevent a resurgence of VDPVs in a polio-free world. New, safe, and effective polio vaccines, such as currently developed poliovirus virus-like particles (VLPs) and new-generation IPV, are urgently needed. However, until the new vaccines are available, conventional and novel OPVs must continue to be used. Sequential immunizations with IPV and OPV have been proven to increase population immunity and stop the spread of cVDPV.

Acknowledging the significant progress made in the fight against polio is essential. To date, an estimated 16 million people today are walking who would otherwise have been paralyzed by the disease, and more than 1.5 million people are alive whose lives would otherwise have been lost. The GPEI stated: "Achieving and sustaining a polio-free world has proven harder – and taken longer – than anyone could have imagined. **But making history is never easy, and we are confident that together we can eradicate** a second human disease after smallpox from this earth and build stronger, more resilient health systems along the way."

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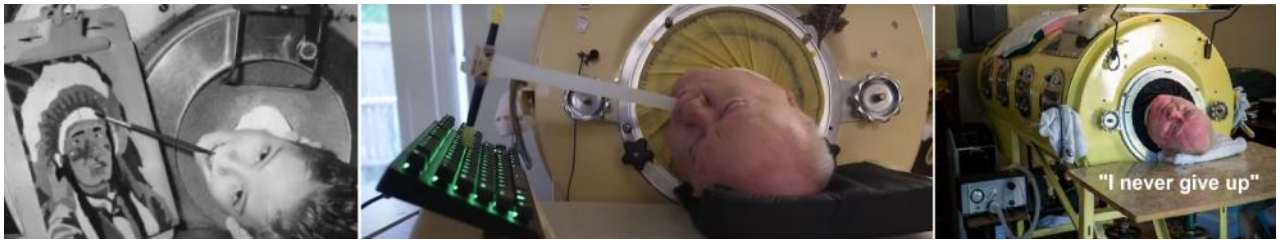
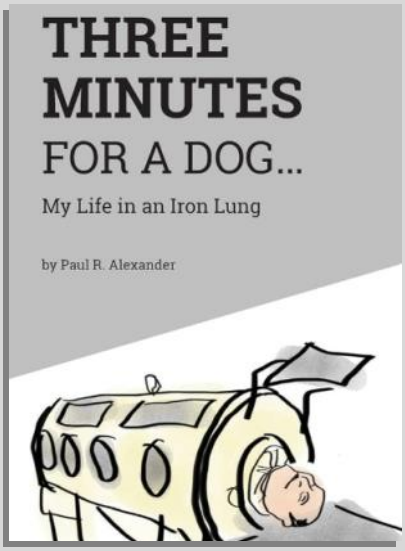


A moment to silence – Paul Richard Alexander "man in the iron lung" (January 30, 1946 – March 11, 2024)



Paul Alexander, a polio survivor who was paralyzed from six years old in 1952 and spent almost his life in an iron lung (a traditional negative pressure ventilator), died at 78 years old. His story was amazing and inspiring. Despite his disability, he became a practicing lawyer and writer and lived life to the fullest. His memoir, "Three Minutes for a Dog: My Life in an Iron Lung," tells his story. The title comes from a promise made by his therapist, Mrs. Sullivan, who said she'd give him a dog if he could breathe independently for three minutes. To do so, he learned to breathe like a frog, using his throat muscles to push air into his lungs, allowing him to leave the iron lung temporarily. He said, **"No matter where you're from, what your past is, or the challenges you may be facing, you can truly do anything. You have to set your mind to it and work hard."**

Rest in peace, Paul Alexander, our iron lung man, we love you 3000

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INA-RESPOND Newsletter

MAXIMIZING PHYSICAL ACTIVITY DURING RAMADAN FASTING

By: Marco Ariono

SPORTS & LIFESTYLE

Healthy Muslim adolescents and adults who have reached puberty are obliged to fast from sunrise to sunset during the ninth month of the Islamic calendar. During this time of fasting, one must abstain from all forms of food and alcohol consumption, smoking, and sexual activity.[1] Nonetheless, throughout this month of Ramadan, one should not neglect their health. Although there are health benefits associated with fasting, this does not imply that one should abstain from physical exercise, remain inactive, and hope that their health will improve solely through fasting. It is necessary to combine fasting with physical activity, such as exercising, because missing 30 days of exercise during Ramadan is equivalent to missing four months of exercise.[2]

Best Times to Exercise During Ramadan

Exercise timing throughout Ramadan is an important aspect that can be adjusted to fit the pattern of daylight fasting. Iftar, or breaking the fast, is the evening meal eaten shortly after sunset, whereas Sahur is the final meal eaten before the fast begins. When planning exercise times, there are four options[3-5]:

Performing Exercise Sessions 2-3 hours after Sahur: This is generally not recommended due to the extended recovery period needed between this workout session and Iftar time. Our bodies will be under stress, and the lack of food and liquids will affect our recovery periods. If this session is scheduled, it should consist of low-intensity exercises focusing on specific skills, tactics, and techniques, rather than activities that demand long-term, high-level physical exertion. Under such circumstances, complete relaxation in a cool setting is necessary, as prolonged exposure to heat and/or humidity will increase physiological stress.

Performing Exercise Sessions 1-2 hours before Iftar: Scheduling exercise sessions one to two hours before Iftar allows for early completion and quick replenishment of fluids and nutrients post-workout. It is recommended to engage in resistance training or low-to-moderate aerobic exercises at this time. Since fasting leads to dehydration, this is also the best time to perform intensive workouts, albeit at a volume that is 10-15 –30% lower than before Ramadan.

Performing Exercise Sessions 2-3 hours after Iftar: This time allows for maintaining a suitable nutritional and hydration state during the workout. It is a good time for long-term, high-intensity training activities. However, exercising during this period could negatively affect our sleep-wake cycle and sleep quality, potentially leading to sleep deprivation and affecting physical and psychological functions.

Situation with Multiple Exercise Sessions in a Day: As stated earlier, we can exercise before and after Iftar.

Exercise Adjustment: Frequency, Intensity, Time, and Type

Although professional athletes typically exercise twice a day, doing so during Ramadan can be taxing on the body and mind. However, coaches could replace a physical exercise session with a non-physical one, such as a session focused on technical or tactical skills, before the first pre-Iftar exercise session.[5]

To adjust to exercise while fasting, a progressive loading strategy should be employed, gradually increasing the exercise intensity and varying the loading throughout the month of Ramadan.[5]

Avoiding high-intensity exercise sessions during Ramadan could lead to detraining, especially in elite athletes accustomed to such intensity. Exercise should start off easy to moderate during the first week of Ramadan and gradually become more challenging.[5]

Pre-Iftar exercise sessions should last no more than sixty to seventy-five minutes, including warm-up and cool-down phases, to prevent hypoglycemia, which could result from depleted muscle glycogen stores. This could impair physical performance later in the exercise session and increase the risk of musculoskeletal injuries.[5]

Maintaining a healthy metabolism, preventing muscle breakdown, and preserving strength and endurance are all benefits of exercising during Ramadan. Being active and less fatigued also benefits the soul, making it easier to perform salah prayers and rituals with enthusiasm. According to published research, a basic exercise regimen including warm-up, aerobic, weight training, stretching, and cool-down exercises should be followed during Ramadan. A minimum of 150 minutes should be allocated each week for exercise.[6]

Exercise Environment

Adverse environmental factors, such as heat and/or high humidity, add to the physiological stress that raises body temperature and causes significant sweating. Therefore, the exercise environment should be cool and ideally indoors during the day. To minimize excessive sweat loss, exercise should be performed in a shaded area if possible.[5]

Persons with Acute or Chronic Disease

Individuals with chronic illnesses should consult their doctor for a comprehensive assessment to determine if fasting is advisable. When planning to exercise during the fasting month, people with chronic conditions like diabetes should exercise with caution. They should first consult with their respective medical professionals to determine if they are fit to exercise.[2,5]

Conclusion

Even though we are fasting during the month of Ramadan, it is still necessary to exercise. We can safely achieve positive health outcomes by exercising at the right times and with the right intensity.

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INA-RESPOND Newsletter

ELEVATING RESEARCH WITH PHOTOVOICE: AMPLIFYING VOICES TO BE HEARD

By: Aly Diana

Photovoice, a participatory action research methodology, represents a significant evolution in how data is collected, analyzed, and utilized in various fields, including healthcare. This approach empowers participants to capture images reflecting their personal experiences, insights, and environments, offering a rich visual narrative that complements traditional research methods. The essence of Photovoice lies in its ability to provide depth and context to research topics, making it an invaluable tool for scientists and researchers across disciplines.

The Core of Photovoice

At its heart, Photovoice is grounded in the belief that everyone has a story to tell and that these stories can drive change. Developed with a focus on empowerment, education, and action, this methodology enables participants to document their lives through photographs and share their narratives, thereby contributing to a broader understanding of community issues, health concerns, and social conditions. The approach is deeply democratic, valuing the perspectives and voices of all participants, particularly those from marginalized or underrepresented groups.

Methodological Framework

Photovoice follows a structured yet flexible methodology that includes several key stages: participant recruitment and training, thematic photography assignments, reflective discussions, and the dissemination of findings. This process begins with equipping participants with cameras and basic photography skills, followed by the task of capturing images that reflect specific themes or questions. Subsequent group discussions or interviews provide a platform for participants to share the stories behind their photographs, offering qualitative insights that are both personal and profound.

The methodology's strength lies in its ability to elicit detailed, context-rich information that quantitative methods might overlook. By analyzing the visual and narrative data generated through Photovoice, researchers can uncover patterns, themes, and insights that inform policy, practice, and further research.

Example of How Photovoice Is Used to Affect Policy in Clinical Settings

Photovoice has showcased its influence on policy within clinical settings, particularly during the tumultuous times of the COVID-19 pandemic. A study utilizing this method captured the firsthand experiences of health professionals battling the crisis. The emotive imagery and personal narratives generated through Photovoice provided an authentic account of the front-line challenges, highlighting the urgent need for policy reforms. This included enhancing resource allocation, improving access to personal protective equipment, and ensuring

the well-being of healthcare workers. As a result, these visual accounts went beyond storytelling, triggering administrative and structural changes within healthcare institutions, thereby underscoring the power of Photovoice as an agent for policy change and advocacy in healthcare.

Advantages and Disadvantages

Photovoice offers several advantages: it enables a non-traditional needs assessment that can reveal overlooked or neglected concerns and fosters community storytelling, enhancing the assessment process. Moreover, it builds social networks and raises awareness of community needs. However, there are disadvantages, including the potential for self-censorship by participants due to fear of retribution and the complexity of analyzing the abundant information contained within photographs. Group dynamics can also pose challenges, with stronger personalities potentially dominating discussions.

Ethical Considerations

Photovoice necessitates careful ethical consideration. Issues of privacy, consent, and public exposure must be addressed thoughtfully to ensure participants' rights and the implications of their contributions are fully understood and respected.

Conclusion

Photovoice is an exceptionally unique and potent research methodology that values all participants' perspectives and experiences. It enables individuals to express and share their realities through photography, leading to a more profound understanding of complex issues, enhancing the research process, and encouraging actionable change. The adaptability of Photovoice and its potential to provide meaningful insights further enhance the sense of community and collaborative spirit within research ventures.

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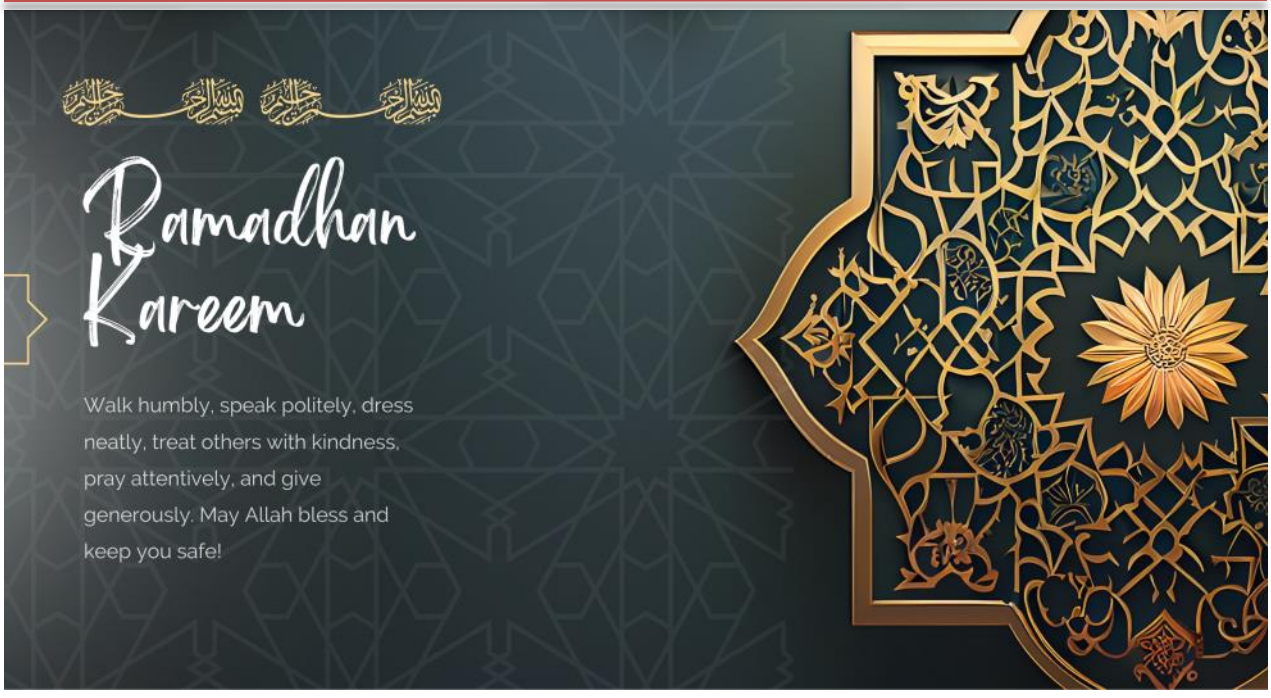

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