INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

November 2024

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HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2024

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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, Wahyu Nawang Wulan, Nur Latifa Hanum, Restu Amalia, Riza Danu Dewantara

InVITE

Preparation for the Site Close-out Visit (SCV) has been completed for TC Hiller Hospital (Site 02) and Ansari Saleh Hospital (Site 03). The Site Regulatory Binder and Source Document Worksheet for both sites have been stored with the archiving vendor, *Indo Arsip*. Study documents, such as the final Authorized Signature and Delegation Log (ASDL) and Site Visit Log, will be archived after the SCV, which is expected to take place in February 2025.

The Central Laboratory team has received 2,099 serum specimens from main visits (visits 1, 2, and 3) and symptomatic visits. Meanwhile, the Material Transfer Agreement documents for the mid-turbinate swab specimen shipment are still being finalized, as the team plans to ship the extracted RNA from the mid-turbinate swabs as part of global polio control efforts.

The InVITE study involves seven countries examining the immunogenicity and efficacy of various vaccine regimens. While the primary objective is to assess specimens across all seven countries, the InVITE Publication Committee encourages additional publications from country members. One independent analysis, conducted by four country members from sub-Saharan Africa (Democratic Republic of Congo, Guinea, Liberia, and Mali), focused on estimating previous SARS-CoV-2 infections by testing pre-vaccination baseline samples from participants who were COVID-19 vaccine-naive. The results were published this year in the International Journal of Infectious Diseases under the title "SARS-CoV-2 Seroprevalence in Vaccine-Naïve Participants from the Democratic Republic of Congo, Guinea, Liberia, and Mali" (https://doi.org/10.1016/j.ijid.2024.106985). This InVITE study update will also summarize the findings from this publication.

During the first year of the COVID-19 pandemic, while high rates of SARS-CoV-2 infections were reported globally, initial reports suggested that infection rates were significantly lower in sub-Saharan Africa than in other parts of the world. Subsequent studies revealed that although seroprevalence was rapidly increasing in sub-Saharan African countries during the start of the pandemic, it was estimated that less than 1% of infections were detected.

The number of samples shipped and assayed for this study from each country were as follows: 1,016 from the Democratic Republic of Congo (DRC), 375 from Guinea, 663 from Liberia, and 776 from Mali, collected during the enrollment period of August 2021 to June 2022. The pre-vaccination baseline serum samples were tested for anti-Spike IgG antibody levels using the Quanterix anti-Spike IgG semi-quantitative antibody assay (Quanterix, Billerica, MA, USA) and for anti-nucleocapsid (anti-N) antibody levels using the Bio-Rad Platelia SARS-CoV-2 Total Ab assay (Bio-Rad, Hercules, CA, USA). Testing was conducted at the Frederick National Laboratory in Frederick, Maryland, USA.

In this study, participants were asked about the history of COVID-19 during their visit 1. Only 0.8% (22/2830) of study participants self-reported having had a prior positive SARS-CoV-2 test; 18 were in DRC, one from Guinea, two from Liberia, and one from Mali. Hospitalizations occurred in five of the self-reported positive tests. Low rates of reported COVID-19 history can be attributed to several factors:

- High rate of asymptomatic infection
- Limited access to and availability of SARS-CoV-2 detection kits
- Limited access to health care in general
- Inadequate surveillance systems
- Lack of testing in Africa during the 2020-2021

Overall, SARS-CoV-2 seroprevalence, defined as positive for anti-S or anti-N, was 86% over the accrual period, with no difference among the four countries. 86% of the participants were positive for at least one assay with concordance of results for most tested specimens, indicating that only 14% of enrollees had no evidence of prior SARS-CoV-2 infection at the time of vaccination. These estimates align with surveys conducted in Guinea and DRC that were conducted close to the time participants were recruited into this study. There were discordant results in 22% of enrollees (mainly anti-S positive and anti-N negative).

While this could be explained by differences in assay sensitivity (the digital ELISA system used for anti-S antibody capture reportedly has a lower detection threshold), reports indicate that Nucleocapsid-targeting antibodies are more short-lived, and this may also be a factor in this discordance. Another factor contributing to this discordance is antibody tests with assays that use the receptor binding domain or the S1 subunit of the Spike protein, which may have reduced sensitivity after Omicron infection. If the Quanterix assay also had decreased sensitivity, this would lead to an underestimate of the baseline seroprevalence; however, validation of this is beyond the scope of this study.

This paper also examined seropositivity in subgroups, finding no significant differences based on BMI, age, or antibiotic use. However, seropositivity based on anti-N was lower in participants using anti-inflammatory medications compared to those not using them (P=0.009), while no difference was observed in anti-S levels. Due to limited sample sizes, comparisons in other subgroups were not possible. Additionally, a higher seropositivity rate was observed in females, possibly due to a faster decline of Spike-specific antibodies in men, which may explain the difference biologically.

Based on this and other reports, infection rates in many African settings were likely much higher than officially reported. Had this seroprevalence been confirmed by timely, well-conducted surveillance, more accurate infection rates in this region may have been used to understand the pandemic epidemiology and inform the global

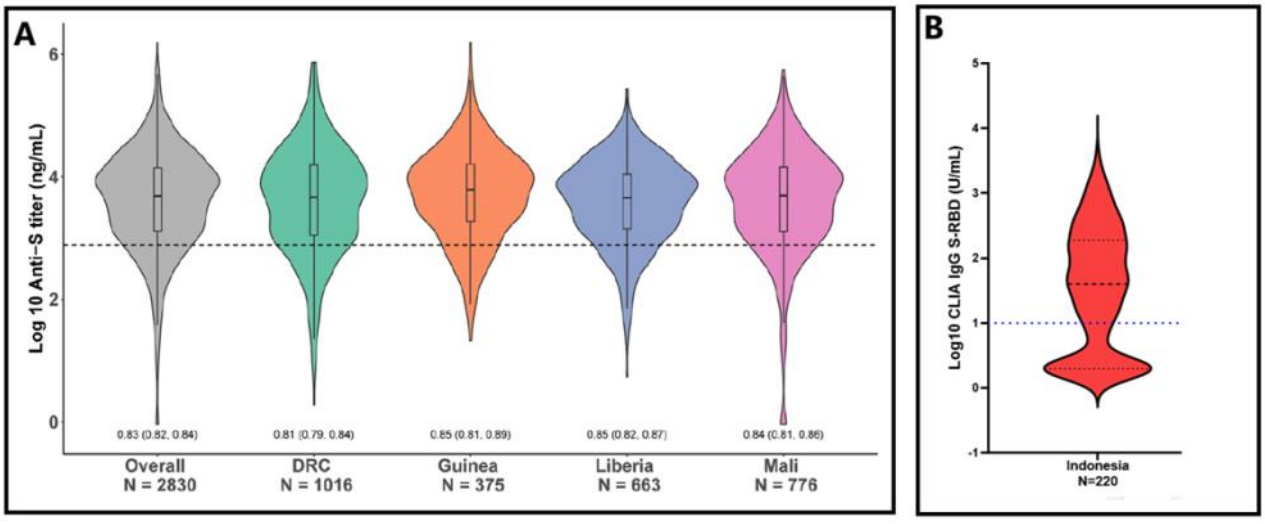

Figure. (A). Distribution of levels and proportion positive (95% CI) for the anti-Spike serology assay; dotted line represents the 770 ng/mL positivity threshold (https://doi.org/10.1016/j.ijid.2024.106985). (B). Local anti-S-RBD antibody results from COVID-19 vaccine-naive samples in Indonesia; the blue dotted line represents the 10 U/mL positivity threshold.

and local COVID-19 responses. However, the limitations of this study have influenced the results and discussion. For instance, vaccination status was self-reported, and some participants may have received prior COVID-19 vaccinations. Furthermore, the seroprevalence rates were derived from a convenience sample and may not reflect the general population. Therefore, these findings should not be seen as a substitute for robust surveillance efforts.

These findings were also reflected in the local IgG anti-S-RBD antibody results from the InVITE Indonesia samples, analyzed using the Mindray SARS-CoV-2 IgG (CLIA) assay. Among 220 COVID-19 vaccine-naive participants, only 8.6% (19/220) self-reported a history of SARS-CoV-2 infection prior to vaccination. In contrast, seroprevalence data revealed that 67.3% (148/220) were positive for anti-S-RBD antibodies. The low rates of reported COVID-19 history are likely due to reasons similar to those highlighted in the publication. Additionally, some participants may have been reluctant to undergo COVID-19 testing early in the pandemic due to fears of isolation and stigma, which could have impacted their ability to work and socialize.

The team eagerly anticipates the results from the Central Laboratory testing and hopes Indonesia's findings will contribute to international publications and strengthen global pandemic efforts.

INA104

As INA104-PROACTIVE progresses through data analysis and publication preparation, the repository specimens offer a valuable resource for HIV research in Indonesia. An opportunity to explore these specimens arose through the 13th Joint Call for Proposals by the e-ASIA Joint Research Program (e-ASIA JRP) in the field of "Health Research," focusing on "Infectious Diseases and Immunology (including Antimicrobial Resistance)." On March 28, 2024, the INA-RESPOND team submitted a proposal titled *"Investigating the Role of HIV-Infected Cell Populations in Persistent Immune Activation during Effective Antiretroviral Therapy."*

The e-ASIA JRP is a multilateral initiative involving public funding organizations from East Asia Summit (EAS) member countries. The initiative consists of 10 ASEAN nations and 8 additional countries (Australia, Japan, New Zealand, China, India, South Korea, Russia, and the U.S.). The program operates on a "Co-funding" model, with research projects selected through open calls for proposals. Each selected project receives financial support of up to approximately $350,000 USD over three years. The objectives of the e-ASIA JRP are to foster a collaborative research community in science and technology, promote innovation, support economic development in the region, and establish equal partnerships through multilateral cooperation. For Indonesian researchers, funding applications are submitted through the National Research and Innovation Agency (BRIN) via their official website: https://www.brin.go.id/.

The Health Research Call aimed to identify opportunities in biomedical and public health research, foster collaborations, promote sharing knowledge, expertise, and resources, and expand the global knowledge base to address the region's infectious disease priorities and challenges. Projects encompassed the full spectrum of health research, including basic science, clinical studies, and applied public health research directly related to human health. Potential research topics in infectious diseases and immunology included, but were not limited to:

- Intersections between chronic and infectious disease, including co- and multi-morbidities
- Novel vaccine immunogens for combatting emerging and re-emerging infectious diseases
- Utilization of microfluidics for discovery of antibody-based therapeutics against antimicrobial resistance
- Pandemic preparedness and response
- Multi-OMICS approach towards discovery and innovation – Host immune responses to infectious diseases

- Novel antibody therapeutics and vaccine immunogens for combatting antimicrobial-resistant pathogens
- Effective public health infection control and prevention methods

The proposal will be evaluated by each relevant Member Organization within the project consortium based on the following criteria:1) **Regional Relevance:** The research should contribute to scientific discovery, the development of science and technology in the region, and address significant issues relevant across the region; 2) **Mutual Benefits:** Projects should leverage unique opportunities provided by the e-ASIA JRP, which cannot be achieved through bilateral or individual research but require multilateral collaboration; 3) **Effectiveness of Exchange:** The project should include activities to nurture early-career researchers, engage female researchers in areas needing capacity strengthening, and enhance overall research capacity in the region. The final decision will be made at a joint panel meeting of the participating Member Organizations, followed by approval at the e-ASIA JRP Board Meeting.

The proposal submitted to the e-ASIA JRP is a collaborative initiative led by Prof. Dr. dr. Evy Yunihastuti, SpPD,K-AI from the Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia. The team includes researchers from **Indonesia** (Udayana University, Hasan Sadikin Hospital/Padjadjaran University, and INA-RESPOND Secretariat), **Japan** (AIDS Research Center of the National Institute of Infectious Diseases, The University of Tokyo, and Hokkaido University), and **the United States** (National Cancer Institute [NCI] and National Institute of Allergy and Infectious Diseases [NIAID]). The collaboration combines expertise in HIV genetics, viral reservoirs, and microbiome analysis to advance the understanding of HIV persistence and immune responses in diverse populations. As the Lead Principal Investigator, Prof. Evy submitted the proposal to BRIN and the e-ASIA JRP Program Secretariat. Dr. Wahyu Nawang Wulan, an INA-RESPOND laboratory technologist and early-career researcher, played a pivotal role in this collaboration. She significantly contributed to the development of the project concept and coordinated the proposal writing process, organizing multiple discussions

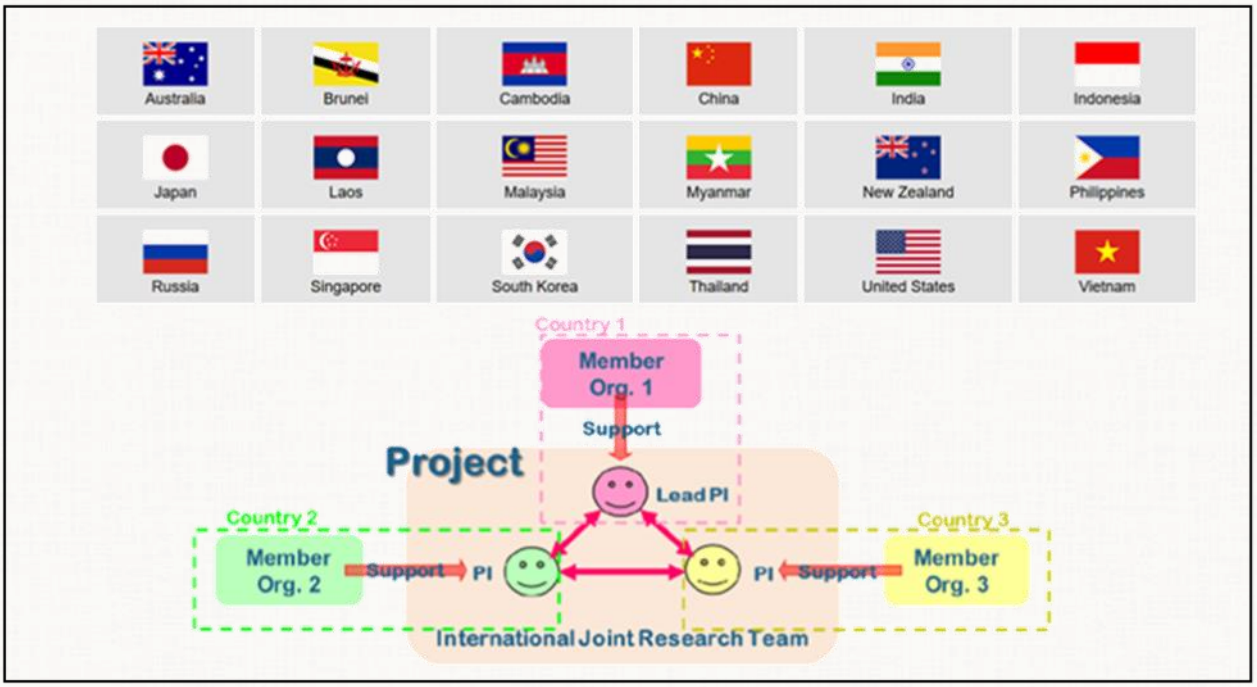

Figure 1. The East Asia Summit (EAS) member countries and joint call for proposals mechanism and process. (source: https://www.the-easia.org/jrp/generaldescription.html)

Table 1. The collaborative team

Indonesia	
Prof. Dr. dr. Evy Yunihastuti, Sp.PD-KAI (Lead)	Cipto Mangunkusumo Hospital/ Faculty of Medicine, *Universitas Indonesia*, Central Jakarta, Indonesia
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	INA-RESPOND Secretariat
dr. Rudi Wisaksana, PhD, Sp.PD-KPTI	Dr. Hasan Sadikin General Hospital/Faculty of Medicine, *Universitas Padjadjaran*, Bandung, Indonesia
	INA-RESPOND Secretariat
Dr. Wahyu Nawang Wulan, S.Si., M.App.Sc	INA-RESPOND Secretariat
dr. Herman Kosasih, PhD	INA-RESPOND Secretariat
dr. Dewi Lokida, Sp.PK(K)	Tangerang District Hospital, Tangerang, Indonesia
	INA-RESPOND Secretariat
dr. Dona Arlinda, M.Sc	Indonesia, Ministry of Health
	INA-RESPOND Secretariat
Deni Pepy Rentina Butarbutar, SSi	INA-RESPOND Secretariat
Rizki Amalia Sari, STrKes	INA-RESPOND Secretariat
USA	
Frank Maldarelli, MD, PhD (Lead)	National Cancer Institute
Aaron Neal, DPhil	National Institute of Allergy and Infectious Diseases
Japan	
dr. Lucky Ronald Runtuwene, PhD (Lead)	National Institute of Infectious Diseases
Prof. Yutaka Suzuki, PhD	Graduate School of Frontier Sciences, The University of Tokyo
Prof. Junya Yamagishi, PhD	Center for Zoonosis Control, Hokkaido University
Tadashi Kikuchi, MD, PhD	National Institute of Infectious Diseases

with the researchers involved. If the funding is granted, she will continue the coordinating efforts, particularly on the Indonesia side. Her responsibilities will expand to include specimen testing, results analysis, data management, and other collaborative activities, including manuscript preparation, where she will serve as the lead and corresponding author. More details on the team involved in the proposal is presented in Table 1.

The proposal addresses a major challenge in curing HIV infection: the virus's ability to integrate into the host's DNA, forming a persistent reservoir of infected cells that remain unaffected by antiretroviral therapy (ART). Effective ART suppresses viral replication and reduces the number of HIV-infected cells to improve health outcomes and lower mortality, but it does not eliminate the virus. Continuous low-level expression of HIV proteins during effective ART can lead to chronic immune activation that negatively impacts on health. Most studies on this immune activation have focused on HIV subtype B in Western populations, leaving gaps in understanding other prevalent subtypes like CRF01_AE, common in Southeast Asia.

This trilateral collaboration aims to investigate persistent HIV levels and immune activation markers in Indonesian patients on long term (over three years) ART, leveraging specimens and data from the INA104-PROACTIVE study. The focus of the study will be viral reservoirs, immune respons-

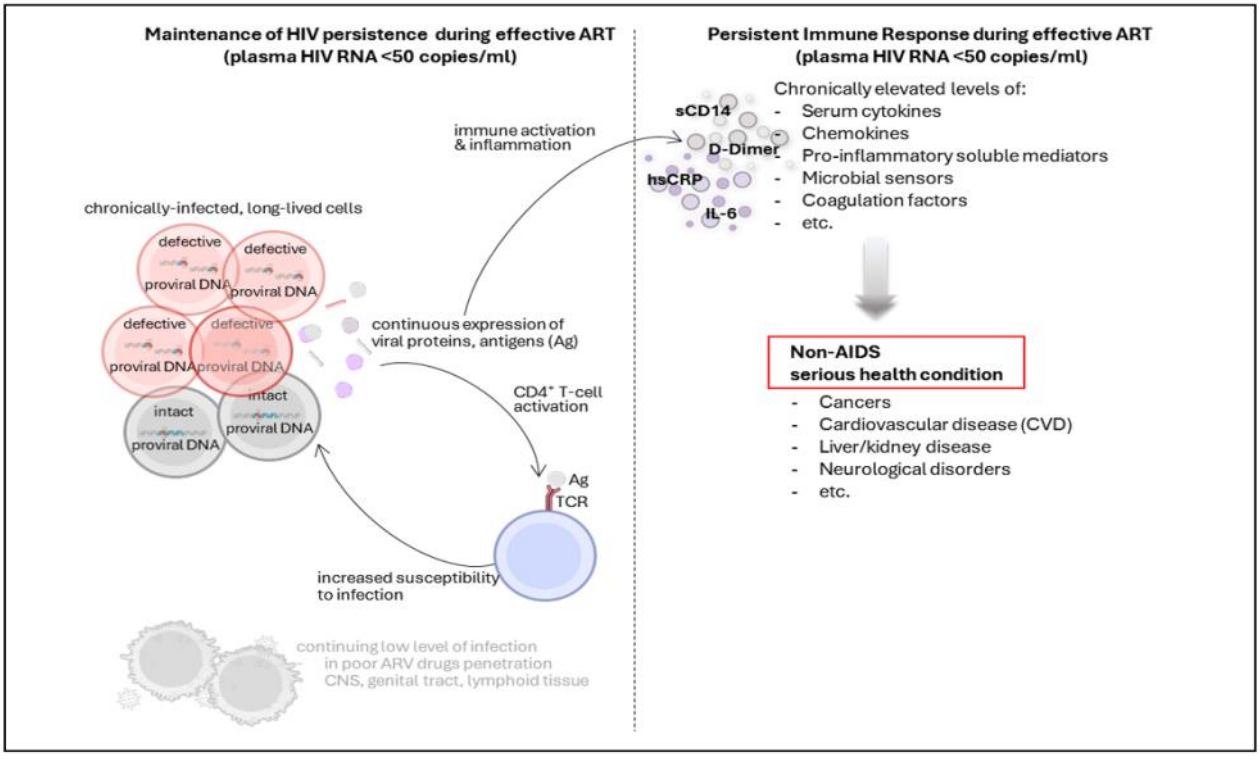

Figure 2. Theoretical framework of the proposal. HIV-infected cells play a role as a driver of immune activation during effective ART, although the majority (>98%) contains defective proviral DNA. People undergoing effective ART, shown by plasma HIV RNA <50 copies/ml have continuing immune activation and inflammation. Chronically elevated levels of immune activation / inflammatory markers, such as IL-6 or sCD14, have been linked to morbidity and all-cause mortality during effective ART.

es, and the distribution of HIV and host genetic variants in Indonesia. Plasma and buffy coat specimens from 199 adults with HIV at 15 sites (across 13 cities) in Indonesia, a subset of 4,329 participants meeting inclusion criteria, will be analyzed.

Specimen testing will be conducted in Indonesia, the USA, and Japan under the Material Transfer Agreement. In Indonesia and the USA, testing will examine associations between HIV concentrations (as provirus or cell-associated RNA copies) and immune activation markers in virologically suppressed individuals on long-term ART. It will also quantify the frequency of HLA I allele in the Indonesian population and analyze cytotoxic T-lymphocyte (CTL) epitopes (escape vs. wild type) in proviruses and cell-associated HIV RNA. Initially, a subset of specimens will be tested in the USA to optimize and validate methods; subsequently, all specimens will be tested in Indonesia. In Japan, testing will focus on quantifying the frequency and distribution of HIV genetic variants.

Data coming from this collaboration will be owned by the participating countries. The collaboration aims to produce 4-5 publications in international journals, with the e-ASIA JRP acknowledged as the funding source.

The Lead PI will be notified of the final decision by the e-ASIA JRP Secretariat once all Member Organizations have approved it. The notification is expected by the end of November 2024. Fingers crossed for this submission—wishing the team the best of luck!

INA-RESPOND Newsletter

FNL GLOBAL CLINICAL RESEARCH EDUCATIONAL MODULES

By: FNL Leadership

The Clinical Monitoring Research Program Leadership are excited to share that we have launched a new virtual training series aimed at describing the essentials of rapid response clinical research in unique, resource-constrained environments.

The Frederick National Laboratory Global Clinical Research Educational Modules (FNL GCREM) is a series of virtual training modules developed by FNL's Clinical Monitoring Research Program Directorate (CMRPD) in partnership with the National Institute of Allergy and Infectious Diseases (NIAID) Division of Clinical Research to share our collaborative approach to rapid response clinical research.

Conducting clinical research amid an infectious disease outbreak brings many challenges, but experience shows us clinical study results can improve patient outcomes. The training series is designed to show you how our teams remediate difficult conditions, and our recommendations and strategies to enhance clinical research preparedness for emerging and re-emerging infectious disease outbreaks.

FNL GCREM uses a mix of clinical research education and lessons learned from actual experiences in facilitating the conduct of clinical trials to assist clinical researchers in the conduct of their own clinical trials.

Current topics include:

- Clinical research in resource-challenged and health emergency settings
- Applying project management to global clinical research
- Navigating regulations, guidelines, and oversight
- Protocol development and complex trial designs

This virtual curriculum is **FREE** and open to all. After completion, individuals can earn continuing education units (CEUs) or continuing medical education (CMEs) units.

We invite you to experience the training or share this with anyone you think could benefit from it and watch for more modules as they become available.

INA-RESPOND Newsletter

SCIENCE CORNER

BACTERIOPHAGE: AN OLD FRIEND RETURNS TO BATTLE SUPERBUGS IN THE POST-ANTIBIOTIC ERA

By: Rizki Auliah Bakri, Dhiny Reskita Ayu, Muhammad Fiqhi Hardiansyah, Adhella Menur

The growing threat of antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) has been acknowledged to be one of the top three major public health threats by the WHO. AMR is potentially the greatest public health threat of our time, surpassing COVID-19 due to its ongoing and escalating impact. AMR affects not just human health but also animals, crops, and the environment. In 2019 alone, it was estimated that 1.27 million deaths worldwide were directly linked to AMR. The O'Neill Review on AMR estimates that 10 million people will die from AMR each year by 2050. The review also estimates that the economic impact of AMR could reach $100 trillion or reduce the global gross domestic product by 3.8% by 2050.

Antibiotics, a specific class of antimicrobials, are primarily used to treat bacterial infections and are far more commonly used than other antimicrobial classes. Antibiotic resistance, however, is a natural phenomenon that predates human use of antibiotics. In their shared ecological niche, bacteria and antimicrobials have evolved side by side, with bacteria developing mechanisms to defend against the effects of antibiotic molecules. Antibiotics typically target one of four critical components of a bacterial cell: the cell wall, cell membrane, protein synthesis, or nucleic acid synthesis. To evade these effects, bacteria employ various strategies.

The rapid global spread of "superbugs"—microorganisms resistant to most known antimicrobials—has elevated the threat of drug-resistant

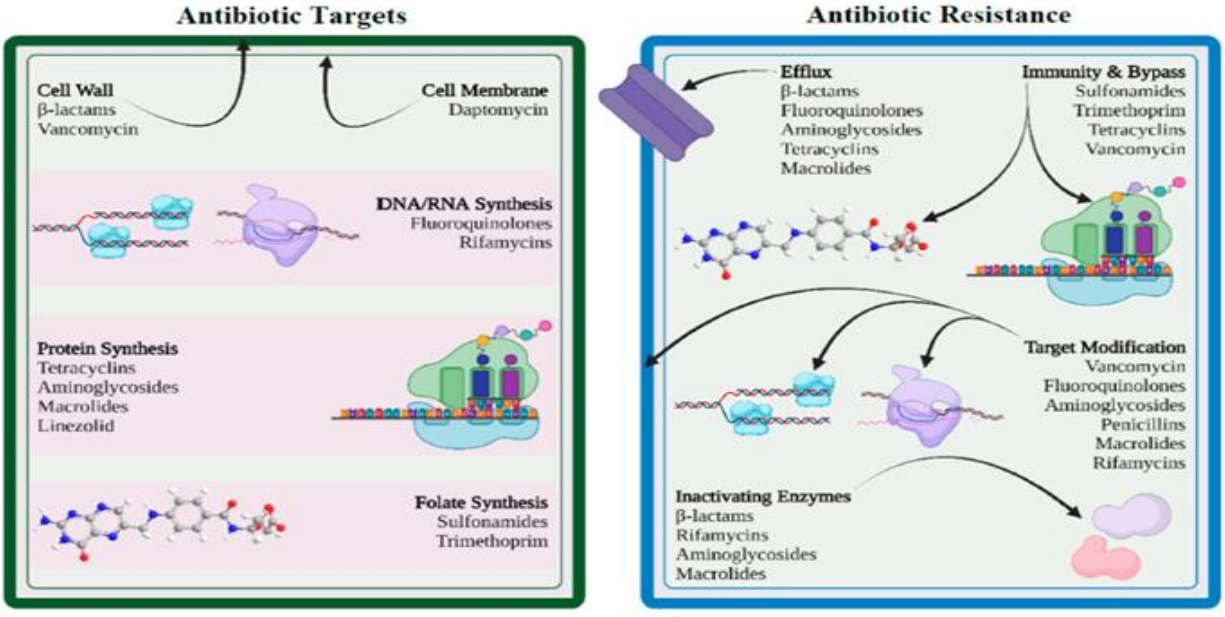

Figure 1. Antibiotic targets and mechanisms of drug resistance (source: Salam MA, et al. 2023. https://doi.org/10.3390/healthcare11131946).

pathogens to a critical and alarming level. The term "ESKAPE" is an acronym representing six highly drug-resistant bacteria: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter*. These pathogens include some of the most dangerous superbugs encountered today, such as vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant S. aureus (MRSA), carbapenem-resistant K. pneumoniae (CRKP), multidrug-resistant (MDR) *Acinetobacter, MDR P. aeruginosa*, carbapenem-resistant *Enterobacterales* (CRE), and ESBL-producing *Enterobacterales*. Moreover, MDR tuberculosis (MDR-TB) and extensively DR-TB (XDR-TB) further amplify the challenges facing public health efforts worldwide.

Over the decades, the surge of antibiotic resistance has been largely fueled by human activities. These include the misuse and overuse of antibiotics in medicine, the food industry, and animal husbandry. The dwindling antibiotic pipeline further exacerbates this issue as pharmaceutical companies increasingly opt out of antibiotic research and development.

The dry pipeline of novel antibiotic development

Ninety-six years ago, Alexander Fleming returned from holiday to find Penicillium growing on Petri dishes in his basement laboratory at St. Mary's Hospital in London. This serendipitous discovery marked the beginning of the "golden age" of antibiotics, which started in the 1940s and lasted over four decades. Over 40 antibiotics were discovered and introduced into clinical practice during this time. Resistance to individual antibiotics was not a major concern, as newer drugs with enhanced pharmacokinetic and pharmacodynamic properties were rapidly developed, fuelling a cycle of discovery, use (and overuse), and the inevitable emergence of resistance. By the 1990s, however, the damaging effects of this cycle had become apparent. The introduction of truly novel antibiotics had slowed significantly, giving rise to what is often described as a "dry pipeline" in antibiotic research and development. Most antibiotics introduced in recent years are either modified versions or combinations of existing compounds, highlighting the increasing difficulty of discovering entirely new classes of antimicrobial agents.

So, why is it so challenging to develop new antibiotics despite technological advancements? Sadly, the obstacle is not just scientific but also regulatory and economic. Novel drugs must go through the challenging process of proving their efficacy, safety, favorable pharmacokinetic profile, and cost-effectiveness. This process is lengthy, expensive, and often fails, making pharmaceutical companies hesitant to invest in antibiotic research. Antibiotics are typically prescribed for short treatment durations, must be regulated under strict stewardship programs, and are constantly threatened by the emergence of resistance— all factors that reduce their profitability. Additionally, antibiotics must be used sparingly to limit the development of resistance and cannot be sold in large quantities. Compared to other, more expensive treatments, they are also relatively low in price. This combination of low sales volumes and low prices has significantly limited profit potential, leading many pharmaceutical companies, including Novartis, Sanofi, AstraZeneca, and GSK, to exit antibiotic research. However, a 2022 WHO report provided some optimism, noting 80 new antimicrobial drugs in the clinical pipeline, including 46 traditional and 34 non-traditional agents. While this offers hope, it will take time for these drugs to reach patients in need, with risks of failure, limited advantages over

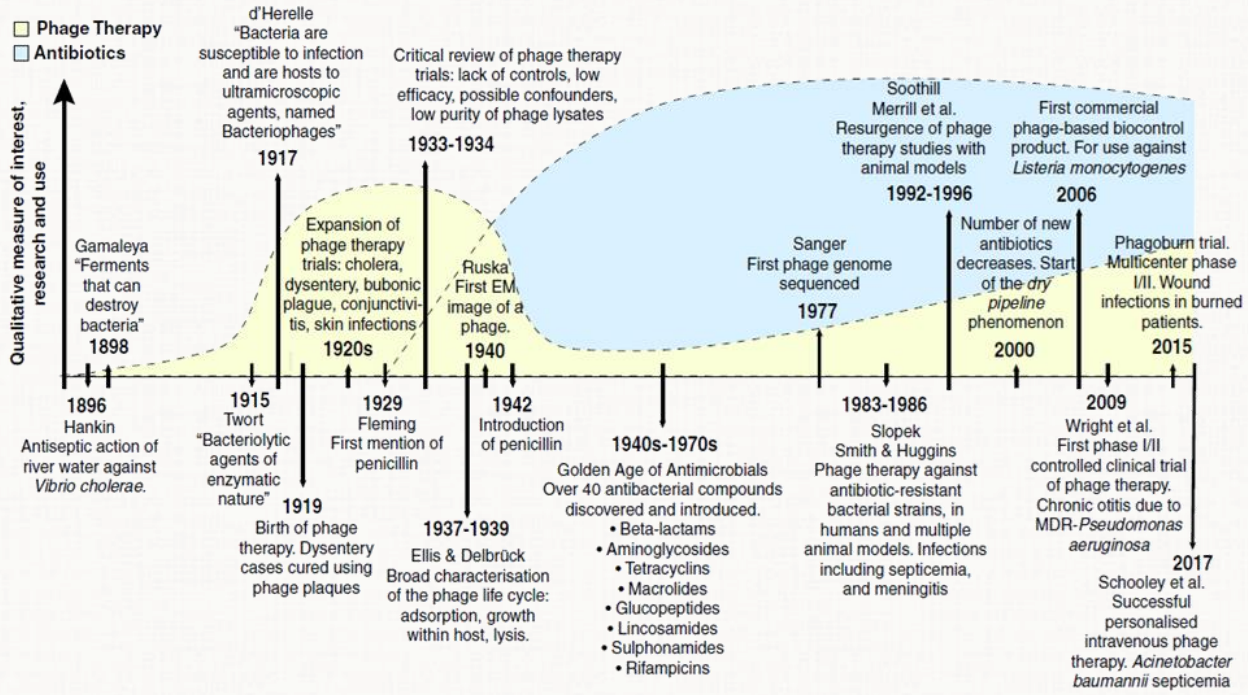

Figure 2. Timeline of major events in the history of research on phages, phage therapy, and antibiotics. Background curves represent a qualitative measure of the overall interest, research, and use of phage therapy (yellow) and antibiotics (blue), showing how the introduction of antibiotics and the critical review of the early phage therapy studies coincided to bring phage therapy research and development to an almost complete standstill around the 1940s (source: Gordillo Altamirano FL, Barr JJ. 2019. https://doi.org/10.1128/CMR.00066-18).

existing antibiotics, and the persistent challenge of drug resistance. Therefore, there is an urgent need for alternative therapeutic strategies to battle resistant bacteria. One promising option is revisiting an old friend: bacteriophages, or phages.

Bacteriophages: An alternative weapon against drug-resistant bacteria

In early 1896, British bacteriologist Ernest Hankin observed antibacterial activity in the Ganges and Jumna rivers in India. He found that an unknown substance seemed to possess antibacterial properties, reducing the spread of cholera in nearby villages. The "official" discovery, however, is partly credited to British pathologist Frederick Twort, who, in 1915, described a similar phenomenon while studying Staphylococcus bacteria. He published his findings in a letter to *The Lancet* but mistakenly identified the agent as a "dissolving substance" secreted by bacteria. Two years later, French microbiologist Felix d'Herelle published a paper that accurately described the viral nature of this invisible anti-Shiga microbe. He isolated it from the feces of recovering dysentery patients and named it a "bacteriophage"—from the Greek "bacteria" and "phagein" (to eat)—meaning "bacteria eater."

Bacteriophages, or phages, are defined as viruses that exclusively target, infect and replicate within bacterial cells, leading to cell death and lysis. They are the most abundant and widespread organisms on Earth, with estimates suggesting over 10^{31}. Like other viruses, phages are obligate intracellular parasites that depend on the bacterial host's machinery for reproduction. According to the International

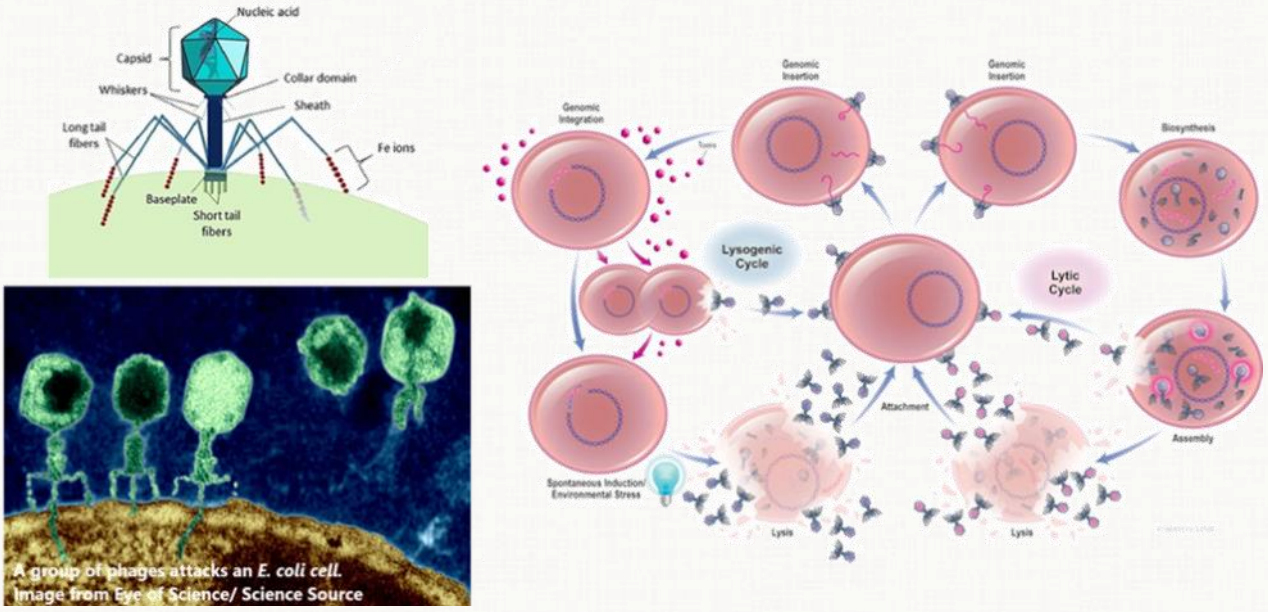

Figure 3. Lytic phages replicate within bacteria and lyse the host cell immediately after assembly. In a lysogenic cycle, phages integrate their genome into that of the host cell (sources: https://asm.org/articles/2022/august/phage-therapy-past,-present-and-future, https://www.newyorker.com/tech/annals-of-technology/phage-killer-viral-dark-matter).

Committee on the Taxonomy of Viruses, phages are classified into one major order, 19 families and 31 genera. Notably, the majority (96%) of identified phages are tailed dsDNA phages belonging to the families *Myoviridae, Podoviridae*, or *Siphoviridae*, which resemble miniature lunar landers.

Phages have complex relationships with their bacterial hosts. They can be classified as virulent or temperate based on their life cycles. Virulent phages follow the lytic cycle, destroying the bacterial cell directly, while temperate phages follow the lysogenic cycle, integrating their genetic material into the bacterial DNA without immediately killing the host. Temperate phages may carry resistance or toxin genes, protect their host from additional phage attacks, and modify bacterial traits. For therapeutic applications, virulent phages—those undergoing exclusively lytic cycles—are the primary and most suitable choice. However, researchers have proposed that genetically engineered temperate phages could serve as gene delivery vehicles, enabling the development of programmable, gene-specific antimicrobials. Further studies are needed to ensure that temperate phages can be considered an option for phage therapy. Since the promising initial reports in 1919-1940, enthusiasm for phage therapy declined with the advent of antibiotics, though treatment centers have persisted in Eastern Europe and the former Soviet Union. However, it is now regaining interest in the post-antibiotic era.

While antibiotics generally exert broad-spectrum effects, phages are highly specific, attacking only their designated bacterial hosts. This precision, combined with their ability to co-evolve with bacterial populations, positions phages as a promising tool in combating antibiotic-resistant infections. A phage initiates its attack by using tail fibers to attach to specific receptors on the bacterial cell wall. It then injects its genetic material into the host, hijacking the bacterial cellular machinery to produce new phages. As replication proceeds, the bac-

terium becomes filled with newly formed phages until it eventually bursts (lysis), releasing 50–200 new phages. These newly released phages infect nearby bacteria, continuing the cycle. Once the bacterial host is eradicated, phages naturally cease functioning, making them a self-limiting therapeutic option. Since phages are primarily composed of nucleic acids and proteins, they are inherently non-toxic. However, their interactions with the immune system warrant careful evaluation. Additionally, bacterial debris and endotoxins released during lysis must be managed to prevent potential adverse events.

To address the limitations of narrow-host-range phages, phage cocktails have been developed. These cocktails combine multiple phages with different receptors and characteristics, allowing them to complement each other in targeting the same bacterial species and strains. By employing diverse phages, these cocktails enhance efficacy and help slow the emergence of phage-resistant bacteria. Uniquely, although phage resistance may occur, it often has a beneficial effect, as bacteria, in their effort to defend against phages, can become re-sensitized to antibiotics they were previously resistant to.

Applications and research on phage therapy for MDR bacteria

Phage therapy has been employed under compassionate use through emergency investigational new drug applications or temporary use authorizations. It is typically considered a last-resort treatment for patients with prolonged infections who have not responded to multiple courses of antibiotics. Several centers worldwide are dedicated to phage therapy research and applications. These include the Eliava Institute (Tbilisi, Georgia), Queen Astrid Military Hospital (Brussels, Belgium), Centre Hospitalier Universitaire de Lyon (Lyon, France), Westmead Institute for Medical Research (Sydney, Australia), HUJI-HMC Phage Therapy Institute (Jerusalem, Israel), and the Center for Innovative Phage Applications and Therapeutics (IPATH) in San Diego, US. Other institutions in the US, such as Baylor College of Medicine, Mayo Clinic, and Johns Hopkins University, have also established clinical phage therapy centers.

The typical process of phage therapy begins when a clinician takes a bacterial sample from the patient, isolates the pathogenic strain, and sends it to a specialized institution or laboratory to request phages. The laboratory conducts a phagogram to test the activity of different phages against the

Table 1. Advantages, disadvantages, and similarities of phage therapy compared to antibiotic therapy (source: Gordillo Altamirano FL, Barr JJ. 2019. https://doi.org/10.1128/CMR.00066-18).

Advantages	Similarities	Disadvantages
Specificity: does not kill the microbiota	Administration requires a neutralized-pH environment	Specificity: causative bacterium must be identified beforehand, narrow spectrum of action
Self-limitation: once the bacterial host is killed, it ceases to function	Therapeutic success depends on variables such as time of treatment initiation	Induction of phage-neutralizing antibody production (clinical relevance to be determined)
Available for patients with antibiotic allergies	Activity is influenced by the immune system of the patient	Significantly smaller body of evidence and correctly designed clinical trials supporting its effectiveness
Safety: no effects on mammalian cells	Versatility in routes of administration	Lack of a specific regulatory framework, and legal issues regarding intellectual property
Exponential reproduction allows for lower doses	Occurrence of bacterial resistance to the therapeutic agent	
Evolution: if resistance arises, phages mutate alongside bacteria		
Antibiofilm activity		
Simple and inexpensive to produce		
Ubiquity		

bacterial strain. If one or more phages prove effective, they are produced, purified, and sent to the clinician for administration. If no active phages are found in the existing collections, they may initiate phage hunting, exploring environments such as wastewater, sewers, or treatment plants to identify new phages. These are then produced and provided for treatment. Globally in 2021, at least 137 phage targets were identified across 135 academic and commercial phage facilities, along with 92 organizations, including phage banks and biotechnology companies. Due to this individualized process, there is often a delay between the request and patient administration. The encouraging news is that several institutions have reported promising outcomes, demonstrating both the safety and efficacy of phage therapy in local and systemic administration based on their experiences.

Adding to the good news about phage therapy, in 2016, Paul E. Turner, a Professor of Ecology and Evolutionary Biology at Yale University, and his team isolated a lytic phage called OMKO1 from a Connecticut pond. OMKO1 targets MDR *P. aeruginosa* by attaching to its cell membrane at the site of an efflux pump mechanism, which the bacteria evolved to expel antibiotics. Experimental evolution revealed a trade-off: when *P. aeruginosa* developed resistance to OMKO1, it altered its membrane, reducing the pump's efficiency. This change rendered the bacteria more susceptible to several classes of antibiotics. Two years later, OMKO1 was used to treat a 76-year-old patient with a MDR *P. aeruginosa* mediastinal and aortic graft infection. Combined with the antibiotic ceftazidime, a single phage application successfully resolved the infection without recurrence, highlighting the therapeutic potential of phage-antibiotic combinations.

Despite the promising results, it is important to recognize that available case studies are often biased toward positive outcomes. Small sample sizes, inconsistent study designs, and the absence of standardized treatment protocols limit the current

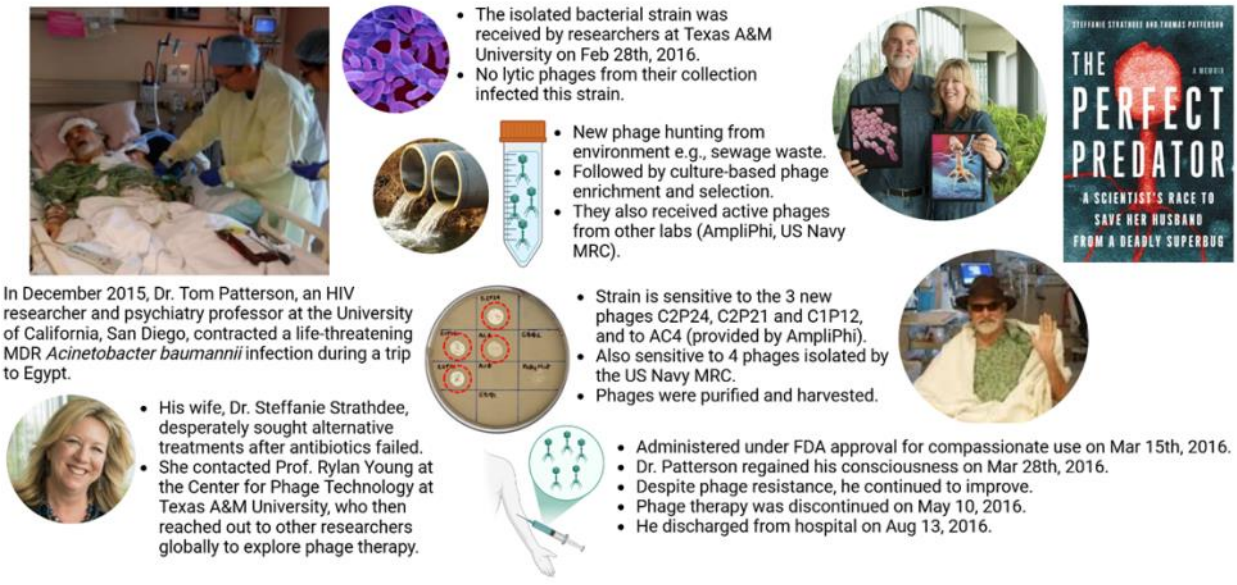

Figure 3. The first patient in the U.S. to receive intravenous phage therapy for a systemic multidrug-resistant infection (source: https://www.bbc.com/news/stories-50221375, https://www.sciencefocus.com/the-human-body/scientist-who-defeated-worlds-worst-bacteria-save-husband, presentation slides from Jason J. Gill, PhD, Center for Phage Technology, Texas A&M University in https://sites.nationalacademies.org (pga_197251.pdf)).

evidence. To establish phage therapy as a widely accepted treatment option, larger-scale clinical trials are essential to confirm its safety, efficacy, and applicability to various infections. Additionally, these trials should focus on developing standardized guidelines for phage selection, dosing, and administration, which are currently lacking in the field. From 2015 to 2017, the *Phagoburn* study evaluated a 12-phage cocktail for treating burn wound infections caused by *P. aeruginosa* in 25 patients. It was the first phage therapy trial conducted under GMP and GCP standards. The study reported no adverse effects of the phage cocktail and demonstrated a significant reduction in pathogen load within the wounds. However, this reduction occurred at a slower rate than in the control group, which received standard care with 1% silver sulfadiazine cream. The study's limitations included small sample size, reduced phage titers after manufacturing - leading to lower-than-intended doses being administered, and bacterial resistance to low phage doses. The authors highlighted the need for further research to address these issues. As of November 2024, ClinicalTrials.gov lists 52 clinical trials investigating phage therapy. These include 28 Phase I or Phase II trials, 16 combined Phase I/II trials, and eight Phase III trials.

The future of bacteriophage therapy in the post -antibiotic era

It's a sentimental story of an old friend from the pre-antibiotic era, shedding light on our battle against superbugs in the post-antibiotic era. The success of phage therapy relies on carefully selecting specific bacteriophages, making rapid and accurate pathogen detection and extensive phage libraries essential. Co-administration of antibiotics as adjuvants is recommended to prevent infections by non-target bacteria and to aid in eliminating bacteria already weakened by phages. With a greater understanding of phage biology, advancements in technology, and higher medical standards, the future of phage therapy looks bright.

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INA-RESPOND Newsletter

STRENGTH TRAINING IN MIDDLE AGE: UNDERSTANDING THE BENEFITS, PREPARATION, AND RECOMMENDED EXERCISES.

By: Caleb Leonardo Halim

Introduction: Understanding Middle Age

Middle age typically refers to the stage of life between 40 and 60 years old, marking the shift from early adulthood to the later stages of life. During this time, the body undergoes natural physical and psychological changes that can impact strength, stamina, and overall health.

While these changes are a normal part of aging, middle age also presents an important chance to prioritize health and fitness. By recognizing and understanding the changes that occur during this period, individuals can take active steps to maintain their health and enhance their quality of life. Strength training is one of the most effective ways to achieve this goal.

Physiological Changes in Middle Age[1]

As people age, several physiological changes tend to occur, including:

1. Loss of Muscle Mass (Sarcopenia)

Sarcopenia, or the gradual loss of muscle mass and strength, typically begins around the age of 30. It becomes more pronounced by middle age, with individuals potentially losing around 3-8% of muscle mass per decade. This loss of muscle not

only impacts physical strength but also mobility, balance, and the ability to perform daily activities without fatigue.

2. Decreased Bone Density

Changes in bone density are also common in middle age. For postmenopausal women, the reduction in estrogen levels accelerates bone loss, increasing the risk of osteoporosis. Men also experience a gradual reduction in testosterone, which affects bone density. Weaker bones are more susceptible to fractures and injuries, making this a crucial health consideration.

3. Decline in Metabolic Function

Metabolic function slows down with age, contributing to a reduction in calorie burning and an increase in fat storage. This often leads to weight gain, particularly around the abdomen, which is linked to higher risks of cardiovascular disease, type 2 diabetes, and hypertension.

4. Cardiovascular Changes

The heart and blood vessels also undergo changes with age. A reduction in arterial elasticity can lead to higher blood pressure and increased risk of heart disease. A weakened cardiovascular system can also impact stamina and the body's ability to handle more strenuous physical activity.

5. Reduced Joint Flexibility and Mobility

Loss of flexibility is another common change associated with middle age. Joints may lose some of their synovial fluid, which lubricates them, and the decrease in collagen can lead to stiffness. As a result, joints are more prone to injury and inflammation, which can impact mobility and physical performance.

Given these physiological changes, strength training stands out as an effective solution for mitigating and even reversing the effects of aging in middle-aged adults.

Benefits of Strength Training in Middle Age[2]

1. Increase and Maintain Muscle Mass

Strength training has been shown to slow or even reverse sarcopenia. By engaging in resistance exercises, the body is stimulated to build muscle fibers, which helps preserve muscle mass and physical strength. A consistent exercise program allows individuals to maintain the essential muscle required for mobility, daily function, and reduced fatigue.

2. Enhance Bone Strength and Density

Decreased bone density is a major cause of fractures in later life. Strength training stimulates the production of new bone cells and increases bone density, which strengthens the skeletal system and lowers the risk of osteoporosis. Exercises beneficial for bone health include weight-bearing movements such as squats, deadlifts, and other resistance exercises.

3. Optimize Metabolism and Reduce Body Fat

Higher muscle mass requires more energy for maintenance, which boosts basal metabolic rate. This helps reduce excess body fat, particularly around the abdomen, which poses a risk factor for various chronic diseases. Strength training also helps reduce insulin resistance, helping regulate blood sugar levels and decreasing the risk of type 2 diabetes.

4. Improve Cardiovascular Health

While strength training does not replace cardiovascular exercise, it provides additional benefits for heart health. Resistance exercises, performed at appropriate intensities, help improve arterial elasticity, lower blood pressure, and promote blood circulation. Gradually, these improvements enhance the body's ability to handle daily physical activities.

5. Increase Flexibility, Joint Health, & Mobility

When performed with proper technique, strength training can improve joint range of motion and muscle flexibility. Healthier joints are maintained when strong muscles support and stabilize them, which reduces the risk of injuries. Exercises such as leg presses, curls, and extensions strengthen muscles around the joints, promoting greater mobility.

6. Enhance Balance and Coordination

Strengthening core and lower body muscles aids in improving balance and coordination, which tend to decline with age. Improved balance also reduces the risk of falls, which are common injuries in later life stages and impact overall stability.

Pre-Exercise Medical Assessments for Strength Training[3]

1. Health History Review and Physical Examination

A comprehensive review of medical history is essential before beginning a strength training regimen. Physicians evaluate any pre-existing health conditions such as high blood pressure, diabetes, heart conditions, or others that could impact exercise. A physical exam may include checking vital signs, joint conditions, and baseline strength to identify any weaknesses or areas needing additional focus.

2. Cardiovascular Function Tests

Cardiovascular testing is especially important for individuals with a higher risk of heart disease. Tests like treadmill stress tests assess how the heart responds to physical activity. The results help establish safe exercise intensities.

3. Body Composition Measurements

Body composition assessments include muscle mass, body fat percentage, and bone density measurements. This evaluation is crucial for understanding initial physical condition and setting realistic goals for strength training progress.

4. Flexibility and Muscle Strength Testing

These tests measure the strength of major muscle groups, including arms, legs, and core muscles, as well as overall flexibility. Understanding baseline flexibility aids in designing a program that supports muscle and joint health without increasing the risk of injury.

5. Joint Function and Mobility Testing

Joint mobility tests allow physicians to identify any limitations or pain points that might impact training. For example, individuals with knee issues may need to modify certain exercises or avoid specific movements to prevent injury.

Safe and Effective Strength Training Recommendations for Middle Age

1. Start with Light Weights and Gradually Increase Intensity

In the initial stages, use light weights around 15-20 repetitions per set to focus on proper form and technique. Starting light minimizes injury risk and allows the body to adapt gradually. Once the body feels comfortable, increase weights or repetitions gradually to provide the muscles with a suitable challenge.

2. Focus on Exercises that hit Big muscle groups

Prioritizing exercises that target larger muscle groups can maximize results and efficiency. Working on these muscle groups — such as the chest, back, legs, and core — offers multiple benefits, from building overall strength to supporting metabolic health. Larger muscles also play a central role in daily functional movements and contribute significantly to stability, balance, and endurance, which are crucial as one ages.

Here are some effective exercises that focus on major muscle groups:

Squats

Squats primarily engage the quadriceps, glutes, and core muscles. They mimic natural movements like sitting and standing, making them ideal for functional strength. Squats can be performed with body weight or by adding resistance through dumbbells or a barbell, depending on individual strength levels.

Lunges

Lunges work the quadriceps, hamstrings, glutes, and calves while also engaging the core to maintain balance. They're excellent for leg and lower-body strength and are beneficial for improving mobility and balance.

Deadlifts

Deadlifts work multiple large muscle groups, including the glutes, hamstrings, lower back, and core. This exercise not only strengthens these areas but also helps improve posture and stability.

Bench Press

The bench press targets the chest, shoulders, and triceps. This classic upper-body exercise builds strength and improves muscle definition in these areas. If you want, you can always replace it with either push up or perhaps dips.

Lat Pulldowns or Pull-Ups

Both exercises focus on the latissimus dorsi (the large muscles in the back) as well as the biceps and shoulders. Strong lats and shoulders enhance posture and support the upper back, which is essential for daily lifting and carrying tasks.

Core Stability Exercises (e.g., Planks)

Core exercises like planks target the abdominal muscles, obliques, and lower back. A strong core is essential for nearly all functional movements, as it stabilizes the body and reduces the risk of falls or injuries.

3. Prioritize Correct Technique and Form

Proper technique is crucial for safe and effective training. Perform movements slowly and with control, paying attention to body posture to avoid injury to joints or muscles. If needed, consult a certified trainer who understands the unique needs of middle-aged individuals.

4. Allow Adequate Recovery Time

Recovery is essential in middle age, as the body takes longer to recover post-exercise. A rest day or two between strength training sessions allows muscles to repair and grow stronger. Strength training three times a week with rest days in between is a suitable approach.

5. Incorporate Flexibility and Cardiovascular Exercises

For optimal results, combine strength training with flexibility exercises like stretching, yoga, or Pilates, as well as cardiovascular activities such as walking, cycling, or swimming. This approach enhances overall fitness, including joint health, heart health, and endurance.

Conclusion

Strength training in middle age is about more than just building strength; it's a powerful tool for slowing the aging process and improving overall quality of life. By preserving muscle mass, strengthening bones, and supporting cardiovascular health and metabolism, individuals can stay healthier, more energetic, and active well into later years. Regular strength training also helps improve posture, balance, and flexibility, reducing the risk of falls and injuries that become more common with age.

For those new to strength training, it's important to start on the right foot. A medical evaluation and guidance from sports medicine physicians or certified trainers can ensure a safe and effective program tailored to individual needs and abilities. Whether beginning with bodyweight exercises, resistance bands, or weightlifting, the key is to start gradually and focus on consistency.

Committing to a regular strength training routine not only enhances physical capabilities but also boosts mental well-being by reducing stress and promoting a sense of accomplishment. Middle-aged individuals who embrace strength training are better equipped to handle daily activities, maintain independence, and enjoy a higher quality of life in the years ahead.

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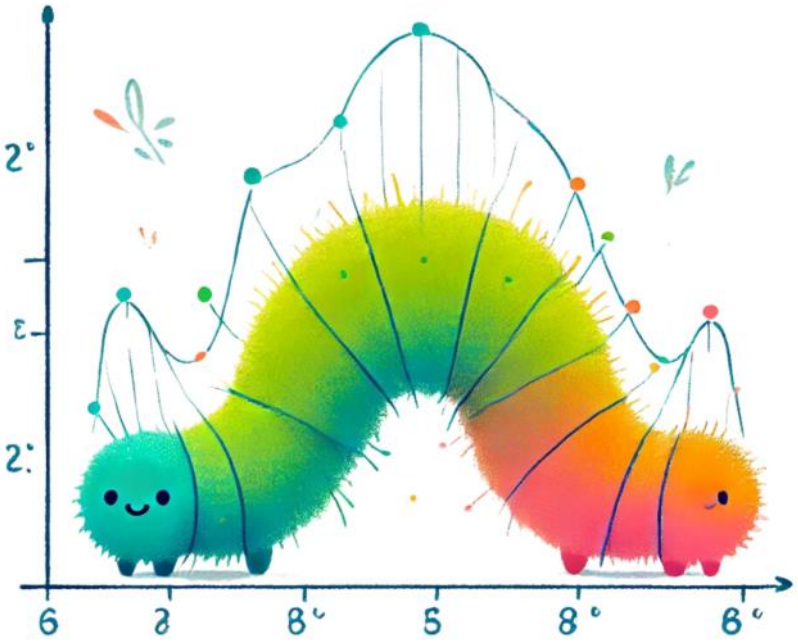
EXPLORING BAYESIAN INFERENCE: A TOOL FOR UNDERSTANDING UNCERTAINTY

By: Aly Diana



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The time has come for me to delve into Bayesian inference—a topic I've managed to avoid for years. Although I'm far from an expert, I've started scratching the surface of this fascinating concept. Here's my attempt to share what I've learned: basic, but hopefully useful.

Bayesian inference is a powerful statistical tool that combines what we already know (prior knowledge) with new evidence to refine predictions and make better decisions. Unlike traditional frequentist methods, which rely solely on observed data, Bayesian inference dynamically updates our understanding as new data becomes available. This adaptability makes it invaluable in fields like healthcare, artificial intelligence, and environmental science, where managing uncertainty is crucial.

At its core, Bayesian inference involves three main components: prior knowledge, new data, and updated beliefs. It begins with a **prior distribution**, which represents our initial understanding or assumptions about a parameter. Then, the **likelihood** measures how well the observed data fits these assumptions. Finally, the **posterior distribution** combines the prior and likelihood, offering an updated perspective on the parameter after considering the new data.

This approach provides a more intuitive understanding of probabilities. For instance, instead of making binary decisions like rejecting a null hypothesis, Bayesian methods allow for statements such as, "There's an 85% probability that this treat-

ment is effective." This nuanced view is particularly useful when decisions involve high stakes or require careful handling of uncertainty.

One of the more whimsical yet essential aspects of Bayesian analysis is the "hairy caterpillar," a term describing traceplots generated during **Markov Chain Monte Carlo (MCMC)** simulations. MCMC is a computational method used to estimate posterior distributions when direct calculations are too complex. Instead of providing simple analytical solutions, MCMC relies on random sampling to explore the parameter space, generating a sequence of values (a "chain") that approximates the posterior distribution over multiple iterations.

Traceplots visualize the sampling behavior of these chains and serve as diagnostic tools for assessing convergence. A well-behaved traceplot resembles a "hairy caterpillar," with stable, wiggly lines indicating that the chains are mixing well and effectively exploring the parameter space. This suggests the simulation is functioning as intended, producing reliable posterior distributions. In contrast, traceplots with trends, stickiness, or irregular patterns highlight convergence issues, requiring adjustments like longer runs, better initialization, or alternative sampling methods.

Bayesian inference has practical applications across various fields. In healthcare, it is used to evaluate treatment effectiveness and dynamically refine predictions during clinical trials. For example, incorporating new patient data into existing models can enhance outcome predictions. In artificial intelligence, Bayesian methods handle uncertainty and incomplete data in tasks like spam filtering. A spam filter uses Bayesian inference to calculate the likelihood that an email is spam based on features like keywords or unusual formatting. These probabilities update as the system processes more emails, improving its accuracy over time. Similarly, autonomous driving systems use Bayesian methods to estimate the positions and movements of surrounding objects, ensuring safe navigation even with noisy or incomplete sensor data.

Despite its many strengths, Bayesian inference does come with challenges. Choosing a prior distribution can be subjective and sometimes controversial. Additionally, the computational demands of Bayesian methods can be significant, especially for large datasets or complex models. However, advances in algorithms like MCMC have made these methods more accessible and scalable, addressing many of these limitations.

This overview offers a glimpse into Bayesian inference and its workings. While it's only a starting point, I hope it sparks curiosity and inspires a deeper exploration of this compelling topic.

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