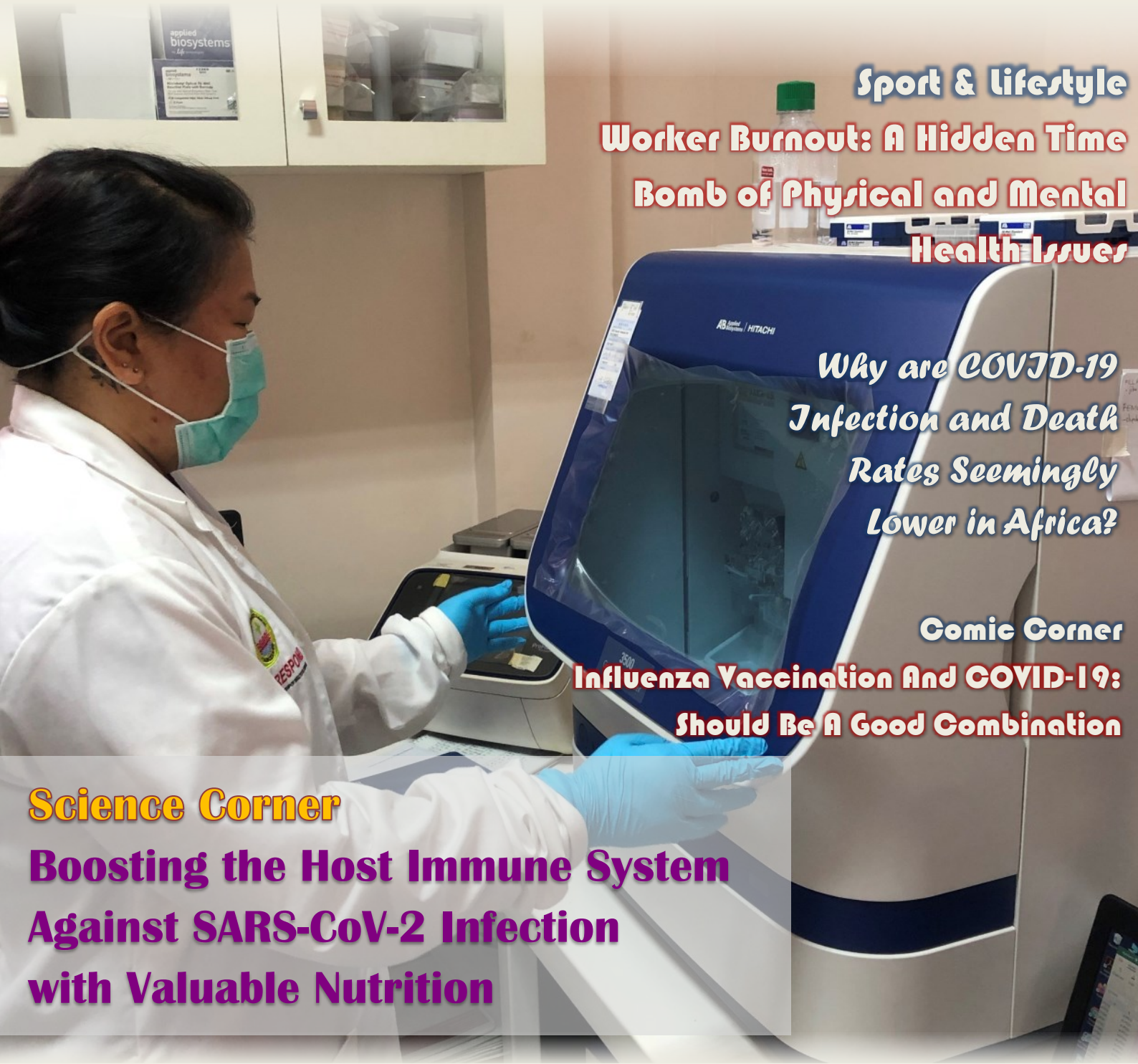
INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

October 2020



Sport & lifestyle Worker Burnout: A Hidden Time Bomb of Physical and Mental Health Issues

Why are COVID-19 Infection and Death Rates Seemingly Lower in Africa?

Comic Corner Influenza Vaccination And COVID-19: Should Be A Good Combination

Science Corner Boosting the Host Immune System Against SARS-CoV-2 Infection with Valuable Nutrition

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2020

Selamat Maulid Nabi Muhammad SAW

INA-RESPOND newsletter

MASTHEAD

EDITOR-IN-CHIEF

M. Karyana

EXECUTIVE EDITOR

Herman Kosasih

CREATIVE DIRECTOR

Dedy Hidayat

ART DIRECTOR

Antonius Pradana

SENIOR WRITERS

Aly Diana, Yan Mardian

REVIEWERS & CONTRIBUTING WRITERS

Dedy Hidayat, Eka Windari R., Herman Kosasih, Kanti Laras, Lois E. Bang, Maria Intan J., Mila Erastuti, Neneng Aini, Nurhayati, Venty M. Sari

THANK YOU

INA-RESPOND Network & Partners

INA-RESPOND Secretariat

Badan Penelitian dan Pengembangan Kesehatan RI, Gedung 4, Lantai 5.
Jl. Percetakan Negara no.29,
Jakarta 10560
www.ina-respond.net

content

October 2020 Edition | issue #85

FEATURES

INA-RESPOND Newsletter

TRIPOD & PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, Venty Muliana Sari

STUDY UPDATES

INA102

PARTICIPANT STATUS

Per 07 Oct 2020, the total ongoing participants in the TRIPOD study are 22 out of 490 enrolled participants. From those 22 ongoing participants, two are still on TB treatment while 20 are waiting for a 6-month post-treatment visit. Two hundred and thirty-four participants have completed the study, while 234 participants are terminated early (including death). Therefore, there are still 4.5% participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participant from site 520, 570, and 590 have been completed the study, while there are 1 participant from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar) who still need to be followed up, 14 participants from site 560 (RSUP dr. Kariadi Semarang), 5 participants from site 580 (RSUP dr. Sardjito Jogjakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

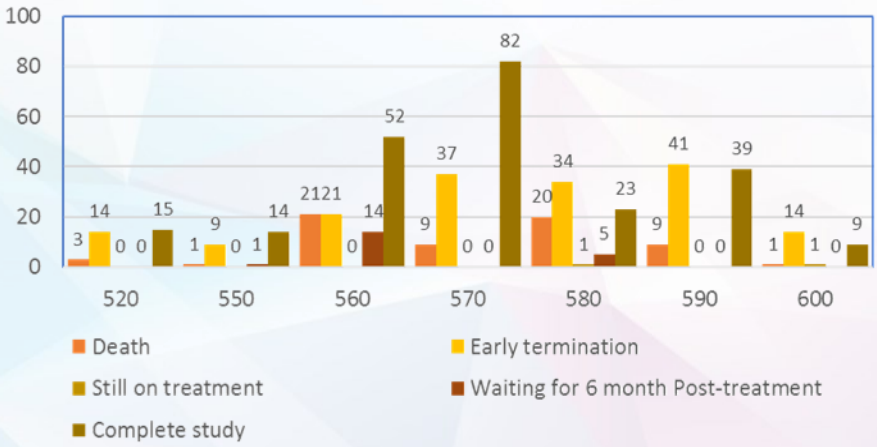


Figure 1. Participant status per site based on uploaded CRF per 7 Oct 2020

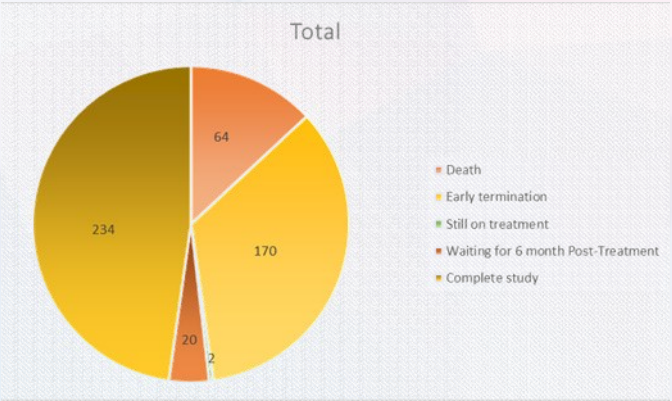


Figure 2. Total participant status based on uploaded CRF per 7 Oct 2020

TRIPOD MANUSCRIPT

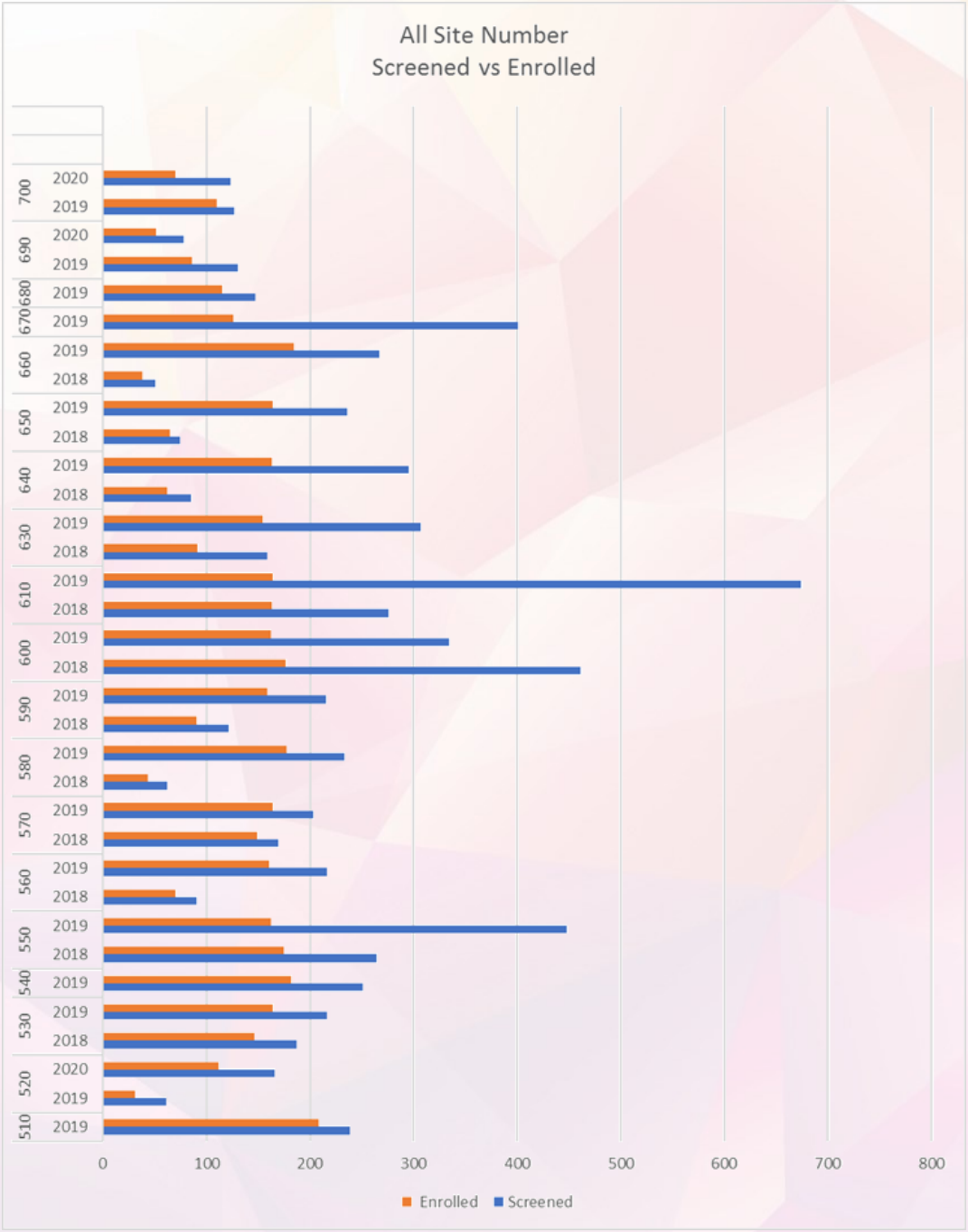
The authors for the TRIPOD manuscript have been selected. A meeting with NIH will be performed to initiate the progress. The following are several manuscripts that being planned: a) focus on the baseline findings; b) treatment outcome and the related affected factors; c) related factors of TB and DM co-morbidity. The authors will be sorted according to enrolled participants. A discussion will be set up during the Clinical Research Protocol Writing Workshop.

Site number	Site name	Author
520	RS Sanglah Denpasar	dr. I Gede Ketut Sajinadiyasa, Sp.PD
550	RSUP dr. Wahidin Sudirohusodo	Dr. dr. Irawaty Djaharuddin, SpP(K)
560	RSUP dr. Kariadi	dr. Banteng Hanang Wibisono, Sp.PD-KP
570	RSUD dr. Soetomo	dr. Tutik Kusmiati, SpP (K)
580	RSUP dr. Sardjito	dr Bambang Sigit Riyanto, SpPD-KP, FINASIM
590	RSUP Persahabatan	dr. Diah Handayani, SpP
600	RSUP H Adam Malik	Dr. dr. Bintang YM Sinaga, M.Ked(Paru), Sp.P(K)

INA104

After the INA-PROACTIVE follow-up activity was reopened on 1 Sept 2020, all study sites continue to conduct subject follow-up, following COVID-19 disease prevention and control protocol. Month 30 follow up visits also have started at some of the sites.

However, due to the COVID-19 pandemic, there is a shortage of cartridge HIV Viral Load supply since the vendor focusing on the production of COVID-19 cartridge. Due to this issue, to prevent the delay of subject follow up visit/ missed visit, for the subjects to still get the benefit of VL test to avoid major protocol deviation, INA-PROACTIVE core protocol team, represented by INA-RESPOND Secretariat, decide that subject can still perform the follow-up visit according to the schedule and collect the specimen as usual including for VL test with the test postponed until the VL cartridges are available. The study team needs to store the VL specimen according to the Secretariat's instructions, and this specimen will be tested once the cartridge is available.



All Site Number Screened vs Enrolled

The screening and enrollment of all 19 INA-PROACTIVE sites ended on 30 Jun 2020. As of 30 Jun, a total of 4,336 subjects were enrolled, consisting of 4,148 adults and 188 pediatrics from a total of 7,364 subjects screened. Details are shown in figure 1.

As of 27 Oct 2020, 180 participants ended the study because of various reasons such as death or moving to another city with no site or far from the INA-PROACTIVE study site hospital. Thus, there were 4.160 active participants of INA-PROACTIVE to date.

INA-RESPOND Newsletter

SITE 520: RSUP SANGLAH, BALI

By: Ni Putu Satriawati

SITE PROFILE

Sanglah Hospital is the most comprehensive type A teaching hospital in Bali with excellent integrated services for heart, cancer, and intensive care. Sanglah Hospital plays an important role, especially for Bali and the eastern part of Indonesia, because it is a referral hospital for Bali, NTB, NTT region.

Principal Investigator (PI)

Dr. dr. I Ketut Agus Somia, SpPD, K-PTI, FINASIM was born in Denpasar in 1968. He is an Internist Consultant for Tropical Diseases and Infections, Internal Medicine Department FK UNUD / Sanglah Hospital, Denpasar. Apart from being a clinician, he has actively participated in the multicenter research TAHOD (Treat Asia Observational DataBase) since 2004. Also, he participated in the MSM-VCT multicenter research in 2011 and the ANSAP study (anal neoplasia study in the Asia Pacific) in 2013 (as a Site Coordinator). Known for being friendly and humble, he has a unique hobby; He fills his spare time painting. He participated in a painting exhibition with the medical community at the Arie Smith museum (HofAS) Ubud Bali in 2019. When talking about an interesting experience as part of the INA-RESPOND research team, he mentioned that it was quite a struggle to get the INA-PROACTIVE research permit at Sanglah Hospital.

Co. PI (1)

dr. Komang Ayu Witarini Sp.A (K) is a pediatrician specializing in pediatric allergy immunology consultants in the Pediatric Division of RSPTN UNUD, Denpasar. She likes traveling and has been actively conducting research. One that she finds memorable was the research of CYD (Chimeric Yellow Fever) -Dengue Vaccine.

Co. PI (2)

dr. Ni Nyoman Mahartini, Sp.PK (K) is a Clinical Pathology doctor, consultant allergy immunology, Clinical Pathology division, RSUP Sanglah. She has a "motherly" hobby, making cross stitches. She is also active as a member of the Central Committee of the PATKLIN PDS (Indonesian Association of Clinical Pathology and Medicine Specialists).

Co. PI (3)

Dr. Ni Nengah Fatmawati, S.Ked. Sp.MK, Ph.D. is the Head of the Department / KSM Clinical Microbiology Faculty of Udayana University/ Sanglah Hospital as well as a lecturer in clinical microbiology, bacteriology, and molecular biology. She is also an active figure in the organization as Chairman of the Bali Royal

Hospital for Infection Prevention and Control Team and Deputy Chair of the Sanglah Hospital's Antimicrobial Resistance Control Committee (KPRA). She likes to spend her spare time gardening and reading. As a researcher, she has produced several research works, one of which is finding the biological activity of proteins (accessory toxins) in Clostridium botulinum type C and D bacteria.

Co. PI (4)

dr. I Made Susila Utama, SpPD, KPTI, FINASIM is a Consultant doctor for Tropical Infectious Diseases in the Department of Internal Medicine, FK UNUD / RSUP Sanglah, Denpasar. He is a disciplined and detailed figure and has a hobby of watching football. He has also participated in previous INA-RESPOND AFIRE study as a Principal Investigator.

Co. PI (5)

dr. Ni Made Dewi Dian, SpPD, FINASIM is a Consultant doctor and a lecturer in Tropical Disease Infection SMF Div, Internal Medicine, FK UNUD / Sanglah Hospital Denpasar. She is a critical and family-oriented figure. She is also active in participating in several studies and as a committee member at international seminars.

Co. PI (6)

dr. Anak Agung Ayu Yuli Gayatri, SpPD, KPTI, FINASIM is a Consultant doctor for Tropical Disease Infection SMF Div, Internal Medicine, FK UNUD / Sanglah. She is a doctor with a beautiful face and kind maternal traits. Also, she is good at singing and dancing. Her hobbies are traveling and cooking. She was the Chairperson of the 2018 APAMT (Asia Pacific Association of Medical Toxicology) congress.

Research Assistants (RA)

RA1

Dr. Ni Luh Putu Ariastuti, MPH was born in Waingapu in 1983. INA-PROACTIVE is the third study she participated in after AFIRE and TRIPOD. Because she is the longest RA at site 520, she truly understands and recognizes implementation, licensing, and research flow rules.

RA2

dr. Ni Putu Satriawati, S.Ked, who loves singing and cooking, was born in Denpasar in 1983. She graduated from Udayana University, and now she works as a General Practitioner and an HIV counselor. She also works as an emergency unit doctor in a private clinic. Working for INA-RESPOND as a Research Assistant is her first experience working in health research, and she is enthusiastic about learning everything that she can learn through the many interesting experiences.

RA3

dr. Ni Ketut Lestari is a doctor who is very interested in research and public health, especially in HIV/AIDS. Because of this interest, and armed with experience working in a VCT clinic, she joined as one of the Research Assistants at site 520. She likes traveling and culinary tours. Her goal is to become an expert doctor in the field of public health.

Laboratory technicians

LT 1

Ni Nyoman Setiani. AMD. AK, born in July 1973, works in the structural section of the clinical pathology division of Sanglah Hospital daily. She runs the equipment and helps take blood samples from patients

LT 2

Ni Wayan Desi Jumiati is a Clinical Pathology Service Staff at Sanglah Hospital. She has good expertise in blood sampling. Desi is in charge of running the equipment and supervising the implementation of sample inspection.

LT3

I Gede Purinawa, AMD. AK is a service staff in the microbiology section of Sanglah Hospital, and he is in charge of sample storage monitoring and recording in the freezer.

LT4

Desak Putra Astini S.Si is a service staff in the microbiology section of Sanglah Hospital, and he is in charge of assisting the patient during blood sample collection.

Research Nurse

Ni Nyoman Seri Sutarni is a nurse who supervises the VCT clinic at Sanglah Hospital. She helps provide information about patients who will be participating in the research.

-oOo-

LT Team in front of Clinical Pathology laboratory

INA104 team from site 520 in front of VCT Policlinic, Sanglah hospital

INA-RESPOND Newsletter

TB RePORT Annual Meeting

By: Maria Intan Josi

RePORT International began in 2012 as a cooperative strategy between the US DAIDS/NIAID/NIH and interested governments to address TB's threat, affecting people's lives and well-being across the globe and poses an increased risk for people living with HIV and AIDS. The initial RePORT International collaboration included TB research investigators from India collaborating with U.S.-based TB research investigators, followed soon by a newly formed Vanderbilt University (US) and Brazil consortium. Subsequently, a South Africa Medical Research Council TB research consortium was added (2016), and an Indonesia-NIAID endeavor (INA-RESPOND) started enrolling in 2017. China signed a memorandum of understanding (MOU) in 2017 and planned to enroll later in the year. The bylaws are written to set clear guidelines and expectations for current and future groups to work together on a broad set of common goals.

RePORT International is a federation of independent RePORT consortia enrolling research participants according to an agreed-upon set of standards outlined in a Common Protocol that describes eligibility criteria, endpoint definitions, and the timing and methodologies for collection and storage of data and specimens. Each RePORT consortia is designed to support local, in-country TB-specific data collection, specimen bio-repositories, and local research. The standardized approach is expected to result in greater ease in sharing data and specimens across geographic regions, which should spur advances in important biomarker and two other TB and TB-HIV research while also building clinical research capacity in high-burden settings and increasing local access to quality data and specimens for members of each network and their domestic and international collaborators. Additional consortia and networks are expected to be added, helping to spur TB treatment and prevention research around the world

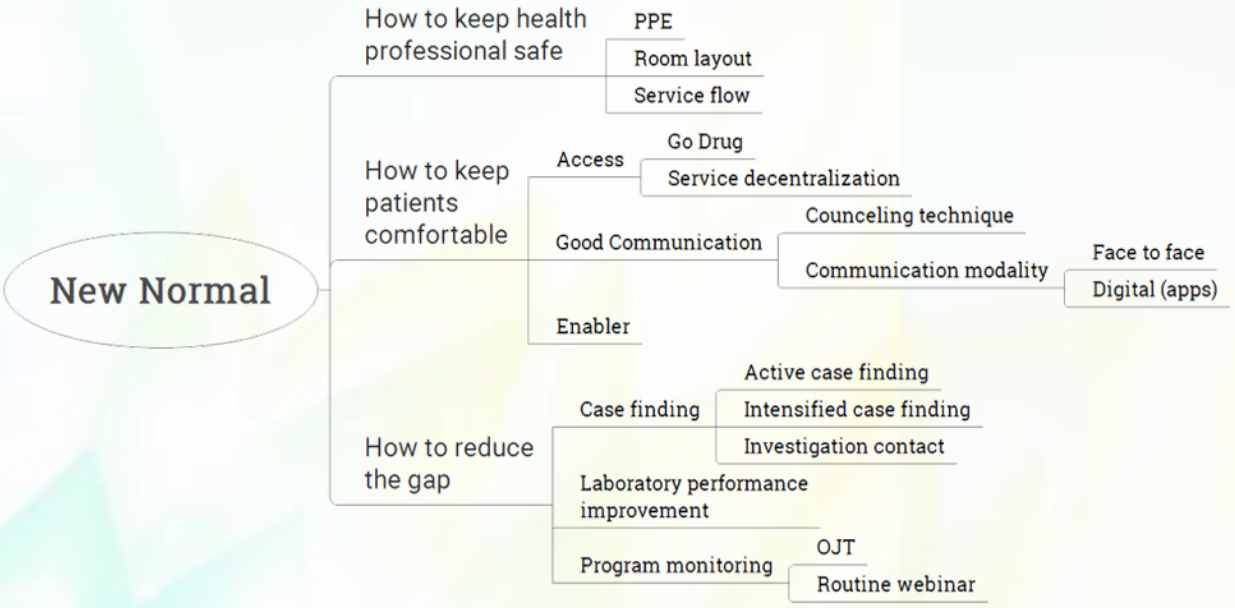
RePORT consortia each have their leadership structures, committees, and scientific priorities. Also, there are several RePORT International committees, including the Executive Committee, TB-Diabetes Working Group, TB-Pediatrics Working Group, and RePORT Cross-consortium Proposal Teams

The purpose of Regional Prospective Observational Research for Tuberculosis (RePORT) International is to advance regional tuberculosis (TB) science that is also relevant in a global context; strengthen TB research capacity and infrastructure in high TB burden settings; and serve as an entity to foster research collaboration within each country and internationally, to carry out a wide range of basic and clinical research that can lead to clinically important TB biomarkers, vaccines, drugs, and diagnostics. Many of the RePORT consortia include explicit partnerships with US TB scientists to facilitate capacity-building and cross-fertilization of ideas.

Each RePORT Consortium is responsible for working toward the following expectations: affirm the commitment to the RePORT International bylaws and principles, store and be prepared to share samples and data specified in the Common Protocol, work with the RiCC to harmonize relevant study protocol, laboratory and biorepository procedures, data element, data management, and other key processes to align with the Common Protocol, participate in the annual RePORT International meeting, seek opportunities and cooperate with other partner consortia members, to do cross-consortium research including utilizing data and specimens collected to further TB biomarker and other areas of interest.

This year, TB Annual Report is handled virtually for three days from 28 August 2020 until 30 August 2020. The three-day annual meeting was divided into three sessions. The first topics discuss comorbidities, the second session is about Biomarkers, and the third session is related to treatment outcomes.

On the first day, talking about the comorbidities that were closely related to tuberculosis, we listened to new updates regarding tuberculosis in diabetic patients delivered by Bruno Andrade from Brazil. He spoke about diabetes associated with a higher risk of TB and a higher risk of adverse TB treatment outcomes. The increase in the number of people with DM may further complicate TB's care and control, especially in the many areas with a high burden of both diseases. Considering that RePORT is well-positioned to study TB-DM since its members (Brazil, South Africa, India, China, Indonesia, and Philipines) are high in TB and diabetic numbers, a couple of efforts must be made to make



more relevant contributions on TBDM, such as harmonizing data collection, standardizing clinical definitions and endpoints, and centralizing laboratory assessments for the immunology /omics studies.

In the next interesting topic regarding smoking habit, alcohol, air pollution, and TB, DJ Christopher from India gave insight that smoking substantially increases the risk of TB (2.5 times) and death from TB. More than 20% of global TB incidence may be attributable to smoking. Therefore, controlling the tobacco epidemic will help control the TB epidemic itself.

Besides its relations with DM, TB is also closely related to HIV incidence. Greg Bison from the University of Pennsylvania delivered facts about TB-HIV, where 10 million people developed, and around 1.5 million people died from TB. About 8.6% of all TB cases occur among HIV-positive from data of Global TB in 2019. The eradication of TB is a must, or HIV patients will suffer more.

The next presenters were from Indonesia. Dr. Erlina observed the Impact of COVID-19 & TB Epidemiology in Indonesia. Her presentation was then followed by remarks from dr Irmansyah, the Head of Centre for Research and Development of Health Resources and Services, Ministry of Health, Republic of Indonesia.

Dr. Erlina brought an issue about the adaptation to the new habit of TB patient's care during the COVID-19 pandemic and why it is important to maintain TB services during the COVID-19 pandemic. TB case detection decreases by 25% in 3 months, and it is predicted that it will give a 13% increase in TB mortality and thus reducing the good progress of TB programs from like five years ago. It is estimated that there will be an additional 1.4 million deaths coming from TB patients due to the consequences of COVID-19 in 2020-2025.

There are adjustments to the service for TB patients. For MDR-TB inpatients, they will be given injection drug, need ECG on follow up, and are supposed to be monitored every day. For oral drug administration, patients do not need to come daily for monitoring. However, patients in the intensive phase will have to be monitored daily and take drugs every two weeks. For the MDR-TB outpatient clinic, sputum pots are delivered by the patients or family members, and a hematology routine will not be done if the patients do not show any symptoms.

However, we have some solutions to ensure patient's adherence in TB treatment, such as the utilization of VOT technology (Video -Observed Therapy), the use of tracker applications such as "Sembuh TB" Application, the utilization of rapid molecular testing for COVID-19 and TB detection, and the creation of TB Group Network.

The second-day topics are related to biomarkers and its development such as Metabolomics, results from CORTIS trial in South Africa, PBMC-based T cell biomarkers of recent infection and progression, and abstracts presentations from RePORT India and South Africa

The third-day topics are interesting regarding outcomes in clinical trials and the relation of malnutrition and TB. There is also a discussion about biomarkers of Mycobacteria resistance and targeted NGS in TB diagnosis.

Joining TB RiCC Virtual Annual Meeting from TB-RePORT International is an incredible experience, and although delivered virtually, the benefit from sharing and discussions may create an impact in TB management in the future.

INA-RESPOND Newsletter

BOOSTING THE HOST IMMUNE SYSTEM AGAINST SARS-COV-2 INFECTION WITH VALUABLE NUTRITION

By: Adhella Menur

"Until the day we have a medical vaccine, food is the best vaccine against chaos," – The United Nation's World Food Programme[1]

The world war against the COVID-19 global pandemic is already passed for seven months. While the first country which spreads the Severe Acute Respiratory Syndrome Coronavirus type-2 (SARS-CoV-2) is calmly surfing down the waves of COVID-19 cases, other countries are still struggling to face the never-ending waves. The world is now focusing on strengthening the COVID-19 preventive health protocol, finding effective drugs, and producing vaccines as fast as possible. Thus, the 2020 Nobel Peace Laureate's statement is strong enough to remind us that we also have to focus on the well-being of the host.[1]

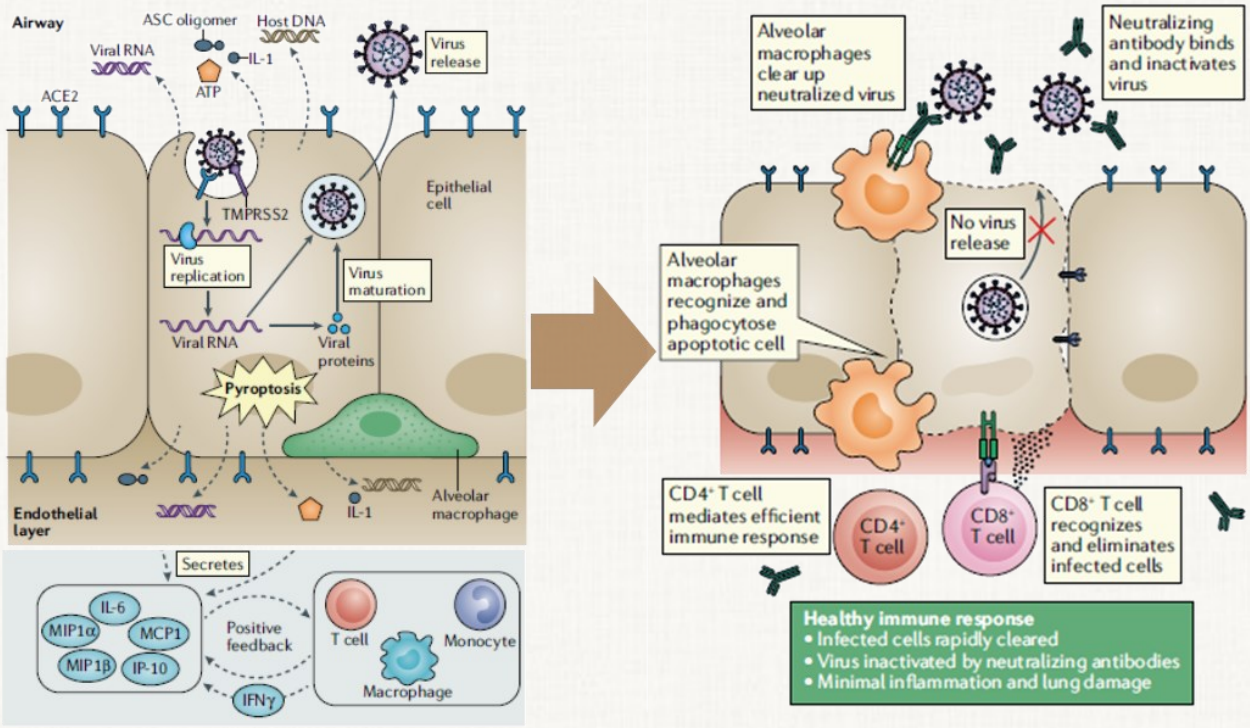
Food is crucial to every human being, and the COVID-19 pandemic threatens food security. It affects both supply and demand side of the food system.[2] The regulation to lockdown complicates the situation related to the distribution restriction and the low buying capacity. If we do not give attention to food security, the world will face the other horrific pandemic; the hunger pandemic.[2] Sadly, it won't stop because hunger will lead to an undernourished host and impairing the immune system. On the other hand, we are facing the undernourished threat and the malnourished in regards to overweight and obesity because of un-appropriate diet during the lockdown. There is evidence that unbalanced nutrition, lack of physical activity, and the sudden lifestyle changes during lockdown can cause physicochemical and psychological stress.[3] These factors may impair the immune system. As one of the pillars of the infection triangle (host, agent, and environment), a weakened host will more susceptible to many infectious agents and may lead to another pandemic. We will share the information about the healthy host immune response against SARS-CoV-2 infection and the valuable nutrition needed to boost it.

The Healthy Host Immune Response Against SARS-CoV-2 Infection

Recognizing the nature of the culprit is the first step to explore how the body defense against it. SARS-CoV-2 belonged to the beta-coronavirus genus. It is a positive sense single-stranded RNA virus characterized by two groups of proteins. First, structural proteins such as Spike (S) proteins which give the virus appearance of having crowns and bind to receptors on the host cell, Nucleocapsid (N) that protects the genetic information of virus, Matrix (M), and Envelope (E); Second, replicase complex encoding non-structural proteins such as proteases (nsp3 and nsp5) and RdRp (nsp12). Like any other creature, the virus only wants to live, and it needs a house to replicate and continue its life-cycle. SARS-CoV-2 has its key (the S-protein) to open the door, and some of the human cells have its matching lock (angiotensin-converting enzyme 2/ ACE2 receptor). The S-protein has two domains of S1 and S2 responsible for invasion, attachment, and entry into human cells via the ACE2 receptor. ACE2 receptor is highly expressed in some organs, like lung epithelial cells; especially type II pneumocytes, cardiovascular tissue, kidneys, gastrointestinal tract, liver, and bladder.[4,5]

The trial to enter a human cell is not only depending on ACE2 receptor, but also the priming of S-protein by host cell transmembrane protease serine type 2 (TMPRSS2). It can cleave the S-protein and stimulates it to induce the fusion of the virus to enter the host cell. Besides TMPRSS2, a type I transmembrane protein namely with Furin also has a role to pre-cleavage at the S1/S2 site and encourage consequent TMPRSS2-dependent entry and spread of infection. Following entry of SARS-CoV-2 into the cell, the viral RNA genome is transferred from the envelope into the cytoplasm and is translated into two structural proteins and poly-proteins, which help in viral replication. Then, new viral particles are formed by incorporating part of the host cell membrane in the new viral envelope and prepare to infect other cells as a readily lysed SARS-CoV-2 buds.[4,5] The invasion of SARS-CoV-2 activates rapid and harmonized orchestra of our body's personal armies; the innate immune response and adaptive immune response.

Innate immune response as the first line of defense against viral infection comprises a set of pattern recognition receptors (PRRs), including Toll-like receptors (TLR3, TLR8, TLR7, and TLR9) which are present in endosomes, the endosomal single-stranded (ss)RNA sensor, the cytosolic double-stranded (ds)RNA sensor, RIG-I/MDA5, the secretory type PRR like Mannose-binding lectin (MBL), and C-reactive protein (CRP) that can recognize viral RNA as pathogen-associated molecular patterns (PAMPs). Upon recognition, these sensors recruit the adaptor proteins, MyD88 and MAVS, respectively, and induce down-



stream signalling. Ultimately, this leads to the activation of the signalling pathways and transcription factors, such as Janus kinase transducers (JAK/STAT), nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and interferon response factor-3/7 (IRF3/7). This signalling cascade leads to increase secretion of pro-inflammatory cytokines like IL-1, IL-6, monocyte chemoattractant protein-1 (MCP-1), MIP-1A, tumor necrosis factor-α (TNF-α), and ultimately interferon 1 (IFN1). IFN1 activates a potent innate immune response to suppress viral replication and acts as an immune modulator to promote phagocytosis of antigens by macrophage, as well as natural killer (NK) cell mediates restriction of infected cells. Furthermore, neutrophils are rapidly recruited to sites of infection, where they kill viruses by an oxidative burst, defensin secretion, and neutrophil extracellular traps (NETs).[4,5]

In conjunction with those innate immune responses, antigen presentation subsequently stimulates the body's specific adaptive immunity; both cellular immunity which are antigen-specific T-cells that kill virus-infected cells and activated B-cells that secrete virus-specific antibodies that culminates in approximately 7–14 days after infection.[5]

The T-cells mediated immune response play a predominant role in adaptive immunity against viral infections. CD8+ T-cells are important for directly attacking and killing virus-infected cells, whereas CD4+ T-cells are crucial to prime both CD8+ T-cells and B-cells. CD8C cytotoxic T-cells (CTLs) secrete a cluster of molecules such as granzymes, perforin, and IFN-g which are essential in the eradication of virus infected cells. CD4C Helper T-cells facilitate the overall adaptive response by assisting cytotoxic T-cells. Additionally, Th17 cells, neutrophils, and granulocytes secrete IL-17, which in turn stimulates the production of IL-1, IL-6, IL-8, MCP-1, Gro-a, GCSF, GM-CSF, TNF-α, and PGE2. All these mediators can increase the recruitment of neutrophils, monocytes, and other immune cells. All these immune signaling pathways are designed to create an inflammatory environment with the goal of eradicating SARS-CoV-2. The good news from a study revealed that individual who recovered from SARS- CoV-2 infection developed coronavirus- specific memory T-cells.[4,5,6]

The B-cells mediated humoral immune response which are assisted by T-cell don't want to miss the war. They play a protective role by differentiating into plasma cells to produce the neutralizing antibody that can block viral infection. A neutralizing IgG plays a major role in the patient recovery and control of infection. IgG reaches its peak in the serum during the convalescent phase and tend to wane after recovery, but memory B-cells could still survive to offer long-term protection (under intensive studies). Knowledge from patients with SARS-CoV infection revealed that the primary target of neutralizing antibodies is the receptor-binding domain (RBD) in the S-protein, which can independently bind to the host target ACE2 receptor. Although a few previously identified monoclonal antibodies to SARS-CoV also bind to or neutralize SARS-CoV-2, the majority do not because of significant differences in the RBDs. Most of SARS-CoV patients develop neutralizing antibodies by week 3 and given the fact that SARS-CoV-2 viral titers peak earlier than for SARS-CoV, antibody responses may also arise earlier. However, it seems that a subset of SARS-CoV-2 patients may not develop long-lasting antibodies to SARS-CoV-2. Efforts are under way to develop therapeutic monoclonal antibodies to

SARS-CoV-2, using approaches including phage library display, traditional mouse immunization and hybridoma isolation, and cloning of B-cell sequences from convalescent human patients.[4,5,6]

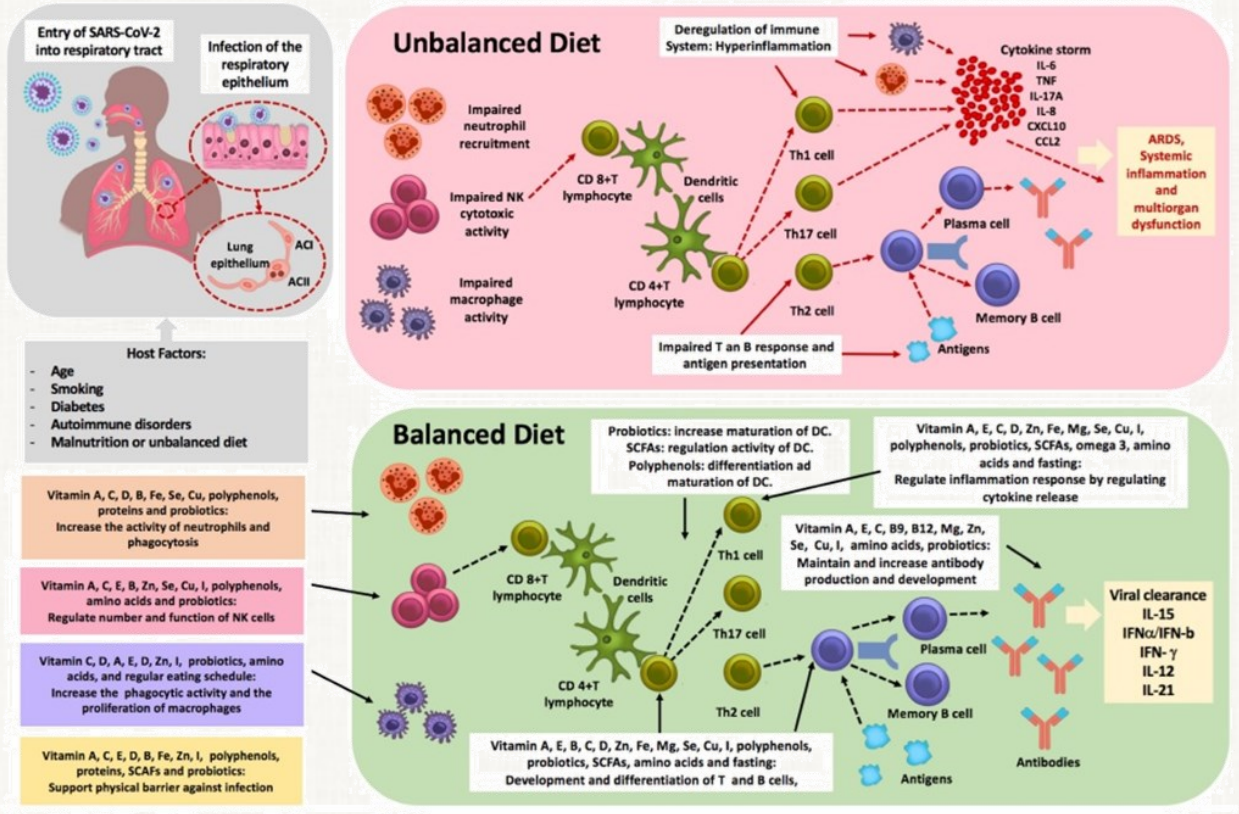
The Valuable Nutrition that Boosts the Host Immune System

Our body's personal armies exactly need a valuable fuel in the form of nutrition to maintain their power. Both macronutrients and micronutrients are optimally required for the development, maintenance, and expression of the immune response. There is a bidirectional interaction among nutrition, infection, and immunity; the immune response is impaired when nutrition is poor, predisposing individuals to infections, and a poor nutritional state may be exacerbated by the immune response itself to an infection.[3,7]

Table 1. Summary of valuable roles played by selected adequate nutrition (macronutrients and micronutrients) in boosting the host immune system[7,8,9,10]

REFERENCE

1. World Food Programme. World Food Programme to assist largest number of hungry people ever, as coronavirus devastates poor nations [Internet]. 2020; Available from: https://www.wfp.org/news/world-food-programme-assist-largest-number-hungry-people-ever-coronavirus-devastates-poor
2. Nordling L. Pandemic of hunger [Internet]. 2020; Available from: https://www.nature.com/immersive/d41586-020-02848-7/index.html
3. Chaari A, Bendriss G, Zakaria D, McVeigh C. Importance of dietary changes during the coronavirus pandemic: how to upgrade your immune response. Front Public Health. 2020 Aug 27; 8: 476. doi: 10.3389/fpubh.2020.00476. PMID: 32984253; PMCID: PMC7481450.
4. Chatterjee SK, Saha S, Munoz MNM. Molecular pathogenesis, immunopathogenesis and novel therapeutic strategy against COVID-19. Front. Mol. Biosci. 2020; 7: 196. doi: 10.3389/fmolb.2020.00196
5. Yazdanpanah F, Hamblin MR, Rezaei N. The immune system and COVID-19: Friend or foe? Life Sci. 2020 Sep 1; 256: 117900. doi: 10.1016/j.lfs.2020.117900. Epub 2020 Jun 2. PMID: 32502542; PMCID: PMC7266583.
6. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020 Jun;20(6):363-374. doi: 10.1038/s41577-020-0311-8. Epub 2020 Apr 28. PMID: 32346093; PMCID: PMC7187672.
7. Maggini S, Pierre A, Calder PC. Immune Function and Micronutrient Requirements Change over the Life Course. Nutrients. 2018 Oct 17;10(10):1531. doi: 10.3390/nu10101531. PMID: 30336639; PMCID: PMC6212925.
8. Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. Diabetes Metab Syndr. 2020 Jul-Aug;14(4):367-382. doi: 10.1016/j.dsx.2020.04.015. Epub 2020 Apr 16. PMID: 32334392; PMCID: PMC7161532.
9. Chowdhury MA, Hossain N, Kashem MA, Shahid MA, Alam A. Immune response in COVID-19: A review. J Infect Public Health. 2020 Jul 14:S1876-0341(20)30567-0. doi: 10.1016/j.jiph.2020.07.001. Epub ahead of print. PMID: 32718895; PMCID: PMC7359800.
10. Singh N, Suthar B, Mehta A, Pandey A. Immune response towards COVID-19: a review on host body. J Infect Dis Diagn. 2020; 5: 134. doi: 10.35248/2576-389X.5.134.
11. Dunn EW, Aknin LB, Norton MI. Spending money on others promotes happiness. Science. 2008; 319. doi: 10.1126/science.1150952



Adequate Nutrition	The Roles in the Host Immune System
Carbohydrate	• The most important fuel source and are necessary for the normal function of immune cells • Prevent the decrease of the number of cells conjoint to apoptosis Note: A diet based on overconsumption of simple carbohydrates can lead to metabolic syndrome, an increase in abdominal fat, hyper-glycemia, and type 2 diabetes, as well as dysregulation in the immune responses
Fat	• Dietary fats are important for absorption of lipo-soluble vitamins A, D, E, and K, as well as permeability and stability of immune cell membranes • Short chain fatty acids (SCFAs) exert anti-inflammatory properties; reduce the production of TNF-α, IL-1β, and IL-6; and enhance the production of IL-10 • SCFAs present immunomodulatory properties; regulate the activation, recruitment, and differentiation of immune cells, including neutrophils, dendritic cells, macrophage, and T-cells • Palmitoleic acid (a mono-saturated fatty acid belonging to omega-7 group) decrease Th1 and Th17 response • Omega-3 fatty acid (one of poly-unsaturated fatty acids) can reduce influenza virus replication in mice model study • Omega-6 fatty acids are precursors of potent lipid mediator signalling molecules, termed "eicosanoids," which have important roles in the regulation of inflammation Note: it has been shown that there is strong association between severity of COVID-19 disease and obesity. High fat diet downregulates ACE2, allows easier entrance of the virus and leads to the increased angiotensin II release. In turn, this can cause vascular (endothelial) trauma and micro-thrombo-embolism in various organs, leading to multiple organ failure
Protein and amino acids	• Protein are considered the building blocks of life and their monomeric component, the amino acids, are considered key regulators of various pathological and physiological processes • Many amino acids like glutamine, arginine, tryptophan, cystine/cysteine, glutamate, histidine, and branched-chain amino acids can regulate the activation of T and B-cells, macrophages, NK cells, and the production of antibodies and cytokines
Vitamin A	• Helps maintain structural and functional integrity of mucosal cells in innate barriers (e.g., skin, respiratory tract, etc.) • Important for normal functioning of innate immune cells (e.g., NK cells, macrophages, neutrophils) • Necessary for proper functioning of T and B-cells, and thus for generation of antibody responses to antigen • Involved in development and differentiation of Th1 and Th2 cells and supports Th2 anti-inflammatory response • A study revealed that persons with low vitamin A status showed an increased risk of lung dysfunction and respiratory disease • Dietary supplementation with vitamin A in humans improves antibody titer response to various vaccines
Vitamin B	• Vitamin B2 and B5 regulate fatty acid oxidation and therefore control the differentiation and function of immune cells • Vitamin B3 plays an important central role in aerobic respiration. It induces the differentiation of Treg and inhibiting the production of the pro-inflammatory cytokines IL-1, IL-6, and TNF-α by macrophages and monocytes. It should be used immediately after the coughing begins or having lung CT image abnormalities because it is highly lung protective • Vitamin B6 helps regulate inflammation, has roles in cytokine production and NK cell activity, and required in the endogenous metabolism of amino acids. It helps to restore cell-mediated immunity and has been shown to improve lymphocyte maturation and growth and increases the number of T-cells • Vitamin B9 or folate, similar to vitamin B6 and B12, plays an important role in protein synthesis. A deficiency in vitamin B9 decreases the resistance to infections by inhibiting the proliferation and circulation of CD8+ CTL and impairs NK cytotoxicity • Vitamin B7 has a crucial role in immunometabolism. It is an essential co-factor for acetyl-CoA carboxylase and fatty acid synthase. It has anti-inflammatory effects and inhibits the activation of the transcription of NF-kB and thus inhibits the secretion of pro-inflammatory cytokines such as TNF-a, IL-1, IL-6, and IL-8 • Vitamin B12 has roles in NK cell functions, facilitates the production of T-cells, and involved in humoral and cellular immunity and one-carbon metabolism (interactions with folate)

Vitamin C	• Effective antioxidant that protects against reactive oxygen species (ROS) when pathogens are killed by immune cells • Promotes collagen synthesis, thereby supporting the integrity of epithelial barriers • Stimulates production, function, and movement of leukocytes (e.g., neutrophils, lymphocytes, phagocytes) • Increases serum levels of complement proteins • Has roles in antimicrobial and NK cell activities and chemotaxis • Involved in apoptosis and clearance of spent neutrophils from sites of infection by macrophages • Can increase serum levels of antibodies • Has roles in lymphocyte differentiation and proliferation
Vitamin D	• Vitamin D receptor expressed in innate immune cells (e.g., monocytes, macrophages, and dendritic cells) • Increases the differentiation of monocytes to macrophages • Stimulates immune cell proliferation and cytokine production and helps protect against infection caused by pathogens • One study has reported an inhibitory effect of the active vitamin D metabolite in human nasal epithelial cells infected with SARS-CoV-2
Vitamin E	• An important fat-soluble antioxidant • Protects the integrity of cell membranes from damage caused by free radicals • Enhances IL-2 production and NK cell cytotoxic activity • Enhances T-cell-mediated functions and lymphocyte proliferation
Zinc	• Antioxidant effects protect against oxidative stress • Helps modulate cytokine release and induces proliferation of CD8+ T-cells • Helps maintain skin and mucosal membrane integrity • Central role in cellular growth and differentiation of immune cells that have a rapid differentiation and turnover • Essential for intracellular binding of tyrosine kinase to T-cell receptors, required for T-cell development and activation and supports Th1 response
Selenium	• Selenium plays an important role in antioxidant defence, by regulating ROS and redox status in tissues • Selenium supplementation resulted in a dose-dependent increase in T-cell proliferation, IL-8 and IL-10
Iron	• Involved in regulation of cytokine production and action; maintaining a certain level of IL-6 and IFN-g production • Important in the generation of ROS that kill pathogens • Important in the differentiation and proliferation of T-cells; helping to regulate the ration between CD4+Th and CD8+CTL • Essential for cell differentiation and growth, component of enzymes critical for functioning of immune cells (e.g., ribonucleotide reductase involved in DNA synthesis)

A psychology study by Dunn et al. revealed that spending money on other people may have a more positive impact on happiness than spending money on oneself. It may be worthwhile in the service of translating increased national wealth into increased national happiness.[11]

So, how about spending some of our money for charity or food donation in this COVID-19 era?

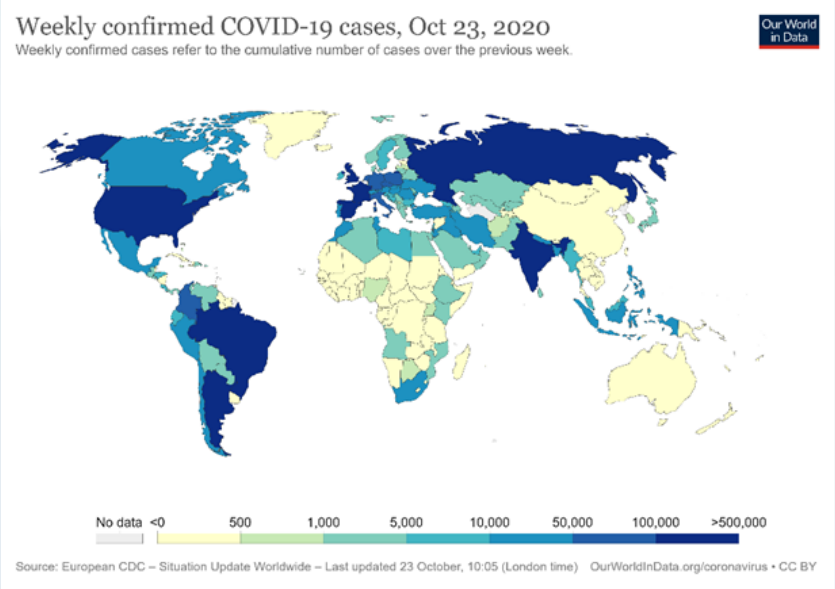
INA-RESPOND Newsletter

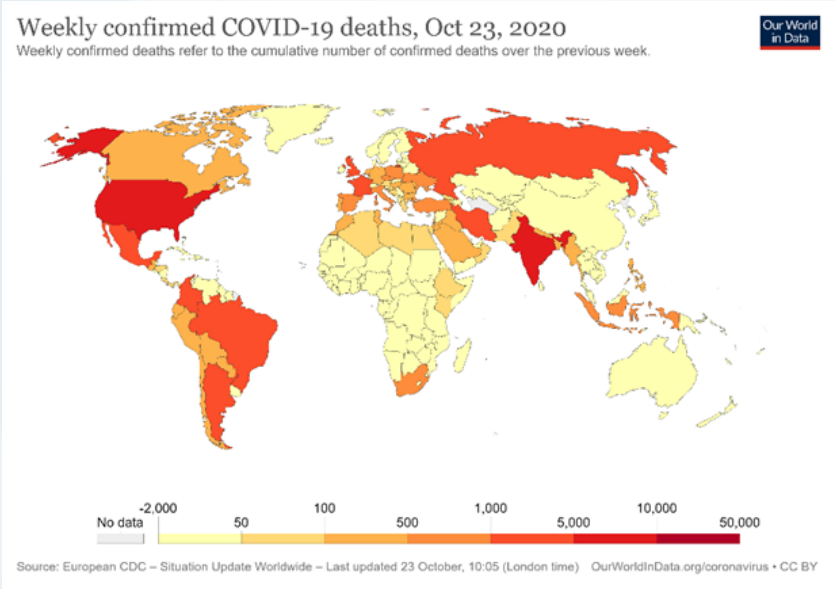
FROM OUR SPONSOR

WHY ARE COVID-19 INFECTION AND DEATH RATES SEEMINGLY LOWER IN AFRICA?

By: Kyle Landers

In late 2019, the first recorded cases of COVID-19 were diagnosed in Wuhan, China. Within three months, the World Health Organization declared this respiratory infection a global pandemic threat, and the disease has since upturned all aspects of daily life. As of October 18, there have been nearly 40 million confirmed cases and 1.1 million deaths globally[1]. Surprisingly, the disease burden varies significantly between countries and continents, with seemingly lower rates of infection and death in Africa than the rest of the world. Are there truly fewer cases and deaths in Africa, and if so, what factors may explain this anomaly? Many theories have arisen to account for these observations, each worth their own consideration in light of current evidence.





Early in the pandemic, international health officials were extremely concerned that COVID-19 would substantially impact Africa, yet approximately seven months later, this has not been the case[2-4]. To date, there have only been 1.4 million cases and 35,000 deaths across the continent. By comparison, the U.S. has seen 8.2 million confirmed cases and nearly 220,000 deaths among a population of 328.2 million, almost four times smaller than Africa. In Indonesia, which has a population six times smaller than Africa, there have been over 370,000 confirmed cases and 13,000 deaths. The differences between Africa, the U.S., and Indonesia are most striking when viewed as ratios of deaths per population and deaths per confirmed cases: 1/35,000 and 1/40 in Africa, 1/1,500 and 1/37.3 in the U.S., and 1/21,000 and 1/28.5 in Indonesia.

The hardest hit African nation, South Africa, has seen a similar case fatality rate as the U.S. (2.6% vs. 2.7%, respectively), but the number of deaths per 100,000 population is less than half of that in the U.S. (31.86 vs. 67.03, respectively)[1]. There has been speculation that these low numbers are simply due to a lack of

COVID-19 testing[2]. An average of 3.5 in 10,000 people are tested each day in South Africa, while in Kenya, it is 1 in 10,000, which almost certainly means that a significant number of infections are going unreported[2,5]. However, the Kenyan healthcare system has not seen a sharp increase in mortality, COVID-19-related or otherwise, implying that COVID-19 infections are somehow less severe if the disease is circulating in the population[2,6].

If infected individuals are going undetected due to a lack of COVID-19 testing and/or generally less severe disease, and if disease transmission dynamics are similar to those seen globally, then much of Africa's population should have anti-SARS-CoV-2 antibodies. Kenya, as well as Malawi, Mozambique, and Cameroon, has conducted large scale seroprevalence studies to estimate the percentage of the population that has been exposed to SARS-CoV-2. Preliminary analysis from these studies suggests that anywhere from 3% to 10% of participants have anti-SARS-CoV-2 antibodies[2]. While it is generally assumed that the presence of anti-SARS-CoV-2 antibodies is due to that specific infection, a recent seroprevalence study among nearly 2,000 COVID-19-naïve evacuees from Hong Kong and Wuhan saw a positivity rate of 2.73%[7]. A similar pre-existing seroprevalence may exist in Africa, which could be due to routine exposure to related mild coronaviruses such as OC43 and HKU1. Globally, seasonal coronaviruses are the cause of approximately 5% of respiratory infections. A metanalysis and bioinformatics mapping project of 157 studies found the highest detection rate for low pathogenic coronaviruses in Oceania (14.40%), followed by Africa (6.64%)[8]. Infection with the highly pathogenic coronaviruses MERS-CoV and SARS-CoV-1, which are most closely related to SARS-CoV-2, may elicit a strongly cross-reactive antibody response. Multiple studies have identified antibodies to these coronaviruses in individuals one to three years following infection[9]. If low pathogenic coronaviruses elicit an antibody response of similar duration, this could explain the apparently less severe and asymptomatic COVID-19 seen in Africa.

Besides antibody-mediated immunity, previous research has found $CD4^+$ T cells reactive to SARS-CoV-2 in 40% to 60% of unexposed individuals[10]. This further strengthens the hypothesis of cross-reaction between SARS-CoV-2 and other low pathogenic coronaviruses[11]. Other studies have suggested that prior exposure to low pathogenic coronaviruses may decrease the susceptibility and severity of SARS-CoV-2 infection[11], but with this paradigm comes the possibility that seroreversion of low pathogenic coronavirus antibodies may occur.

African seroprevalence studies have also indicated that approximately 80% of participants infected with COVID-19 were asymptomatic. This finding, in addition to the lack of mortality spikes in many African countries, suggests that the severity of COVID-19 infections is less extreme compared to the rest of the world, where asymptomatic rates of 40% to 50% are typically seen[3]. While this could be explained by higher levels of pre-existing cross-reactive immunity, another potential theory focuses on the relationship between age and disease severity. In total, African citizens over the age of 65 make up approximately 3% of the population. In contrast, citizens over the age of 65 in Canada and the U.S. comprise 18% and 16% of the population, respectively[3,12]. South Africa has one of the largest senior populations in Africa (6%), which could directly explain why it is the hardest hit country on the continent.

The overall younger demographic seen in Africa may result in less severe COVID-19 symptoms since children and young adults are less likely to develop severe infections and die[13]. The varying extent of urbanization, infrastructure, and close-contact opportunities between populations may also shape the COVID-19 pandemic in Africa. Interestingly, many sub-Saharan African countries see older retirees depart from urban centers to return to their rural hometowns, thus reducing their general exposure to COVID-19. This cultural component, in addition to an underdeveloped transportation network, is another potential explanation for the significantly low mortality rate since transmission would be decreased among high-risk populations[14-16].

Aside from age and location, there may be host genetic factors that are partially or entirely protective. Recent molecular analyses have linked COVID-19 respiratory failure to genotypes within a gene cluster at 3p21.31[17]. This same study discovered that blood typing plays a role in COVID-19 susceptibility, where blood type A individuals are the most susceptible, and blood type O individuals are the least susceptible. Others have linked severe COVID-19 cases to the loss of function of the X-chromosomal TLR7 gene[18]. It has also been shown that individuals who carry a Neanderthal genome segment are at greater risk for COVID-19 infection and hospitalization. This genome segment is prevalent in 50% of South Asians and 16% of Europeans yet surprisingly absent in Africans[19]. The lack of this Neanderthal genome segment in Africans may also play a critical role in the increased asymptomatic rate seen throughout the continent.

Other studies have investigated the SARS-CoV-2 genome itself to explain the lower mortality rate in Africa. Several major global outbreaks have been traced back to four genetic clusters of SARS-CoV-2. One of these "super spreader" events, predominant super spreader 4, was observed in Africa with origins from Europe[20]. This finding suggests that the SARS-CoV-2 virus present in both continents would be of the same origin and should result in similar rates of infection and death. Since this has not been the case for Africa, it is unlikely that the genetic profile of circulating SARS-CoV-2 strains accounts for the low disease burden on the continent.

The dynamics of the COVID-19 pandemic in Africa are complex and likely shaped by many of the observations described above. Continued research during and after the pandemic will help identify what aspects of the disease in Africa led to reduced infections and deaths, hopefully providing tools and strategies to control COVID-19 and future diseases in the rest of the world.

References

1. "Mortality Analyses." *Johns Hopkins Coronavirus Resource Center*, coronavirus.jhu.edu/data/mortality.
2. Linda Nordling, et al. "The Pandemic Appears to Have Spared Africa so Far. Scientists Are Struggling to Explain Why." *Science*, August 12 2020, www.sciencemag.org/news/2020/08/pandemic-appears-have-spared-africa-so-far-scientists-are-struggling-explain-why.
3. York, G. (2020). Africa's low COVID-19 death rate has multiple causes, WHO says. https://www.theglobeandmail.com/world/article-africas-low-covid-19-death-rate-has-multiple-causes-who-says
4. Mwai, P. (2020, October 16). Coronavirus: What's happening to the numbers in Africa? https://www.bbc.com/news/world-africa-53181555
5. Ritchie, research and data: Hannah. "Coronavirus (COVID-19) Testing - Statistics and Research." *Our World in Data*, ourworldindata.org/coronavirus-testing.
6. Ojal, John, et al. *Revealing the Extent of the COVID-19 Pandemic in Kenya Based on Serological and PCR-Test Data*, 2020, doi:10.1101/2020.09.02.20186817.
7. To, K. K., Cheng, *et al.* (2020). Seroprevalence of SARS-CoV-2 in Hong Kong and in residents evacuated from Hubei province, China: A multicohort study. *The Lancet Microbe, 1*(3). doi:10.1016/s2666-5247(20)30053-7
8. Li P, Ikram A, *et al.* (2020) Global Prevalence and Clinical Features of Low Pathogenic Human Coronaviruses with Potential Impact on COVID-19: Systemic Review, Meta-Analysis and Bioinformatic Mapping. https://dx.doi.org/10.2139/ssrn.3612057
9. Huang, A.T., Garcia-Carreras, B., Hitchings, M.D.T. *et al.* A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. *Nat Commun* **11,** 4704 (2020). https://doi.org/10.1038/s41467-020-18450-4
10. Grifoni A, Weiskopf D, *et al.* (2020) Targets of T Cell Response to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. https://doi.org/10.1016/j.cell.2020.05.015
11. Sagar M, Reifler K, *et al.* (2020) Recent endemic coronavirus infection is associated with less severe COVID-19. *J Clin Invest.* 2020. https://doi.org/10.1172/JCI143380
12. McPhillips, D. (2019). Aging in America, in 5 Charts. https://www.usnews.com/news/best-states/articles/2019-09-30/aging-in-america-in-5-charts
13. McPhillips, D. (n.d.). Aging in America, in 5 Charts. Retrieved October 21, 2020, from https://www.usnews.com/news/best-states/articles/2019-09-30/aging-in-america-in-5-charts
14. Zimmermann P, Curtis N. (2020) Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. *Pediatr Infect Dis J.* 2020;39(5):355-368. doi:10.1097/INF.0000000000002660
15. Ezeh AC, Chepngeno G, Kasiira AZ, et al. (2006) The Situation of Older People in Poor Urban Settings: The Case of Nairobi, Kenya. In: National Research Council (U.S.) Committee on Population; Cohen B, Menken J, editors. Aging in Sub-Saharan Africa: Recommendation for Furthering Research. Washington (D.C.): National Academies Press (U.S.); 2006. 6. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20309/
16. Soy, A. (2020, October 07). Coronavirus in Africa: Five reasons why Covid-19 has been less deadly than elsewhere. Retrieved October 22, 2020, from https://www.bbc.com/news/world-africa-54418613
17. Ellinghaus, et al. (2020) Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *New England Journal of Medicine*, vol. 383, no. 16, 2020, pp. 1522–1534., doi:10.1056/nejmoa2020283.
18. van der Made CI, Simons A, Schuurs-Hoeijmakers J, et al. (2020) Presence of Genetic Variants Among Young Men With Severe COVID-19. *JAMA.* 2020;324(7):663–673. doi:10.1001/jama.2020.13719
19. Zeberg, H., Pääbo, S. (2020) The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. *Nature* (2020). https://doi.org/10.1038/s41586-020-2818-3
20. Yang, X., Dong, N., Chan, E. W., & Chen, S. (2020). Genetic cluster analysis of SARS-CoV-2 and the identification of those responsible for the major outbreaks in various countries. *Emerging microbes & infections*, *9*(1), 1287–1299. https://doi.org/10.1080/22221751.2020.1773745

Kyle Landers

Intramural Research Training Award Fellowship program

INA-RESPOND Newsletter

WORKER BURNOUT: A HIDDEN TIME BOMB OF PHYSICAL AND MENTAL HEALTH ISSUES

By: Edrick Purnomo Putra

Working is an essential part of modern human life to earn money and meet living needs. Working is not merely a source of livelihood; for many, work fulfills intrinsic needs such as motivation, belonging, and accomplishment.[1] Ironically, workers may spend up to 8 hours a day in their workplaces, which means most adults devote one-third of their lives to work. Such work time, combined with the large workload and inconducive working environment, may induce a high-stress level at work. When this condition is not managed well, it may cause a problem called burnout syndrome.[2] While it may seem like burnout cause mental issue only, recent studies prove that burnout can also become a risk factor for greater health problems such as chronic diseases, cardiovascular diseases, and metabolic syndrome in the future.[3] Sadly, most workers, including office workers, spend their work time sitting at their desks. This contributes to low physical activity level and sedentary behavior in office workers, which could further impact the worker's health.[4]

Burnout is included in the 11th Revision of the International Classification of Diseases (ICD-11) as an occupational phenomenon. It is not classified as a medical condition but rather described as factors influencing health status or contact with health services', which includes reasons people contact health services but are not classed as illnesses or health conditions. Burnout is a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed. It is characterized by three dimensions: feelings of energy depletion or exhaustion; increased mental distance from one's job, or feelings of negativism or cynicism related to one's career; and reduced professional efficacy.[2]

Maslach Burnout Inventory (MBI) is the most studied instrument used to measure burnout symptoms. MBI is modified to several versions according to profession categories.[5] Healthcare and medical professions are the most studied population regarding burnout. A systematic review in 2018 studied the prevalence of burnout syndrome in physicians using MBI. The prevalence found in this study is substantially varied and ranged from 0 – 80.5% across 182 studies included, with an overall burnout prevalence of 67.0%. This study also found a prevalence of burnout dimensions: 72.0% on emotional exhaustion, 68.1% on depersonalization, and 63.2% on low personal accomplishment.[6]

Another study in Poland investigated the frequency of burnout syndrome in office workers. In this study, the frequency of burnout syndrome concerned 4.15% of subjects, more frequently females (4.5%) than males (2.97%).[7]

With such a great number of burnout syndrome in workers, its impacts have to be understood. Logically speaking, a worker experiencing burnout will be impaired in doing their works. Professional outcomes were identified: job dissatisfaction, absenteeism, new disability pension, job demands, job resources, and presenteeism.[3] These kinds of issues will reduce workers' efficiency, focus, and performance. Eventually, companies' productivity will also be affected.[1]

However, deeper than occupational consequences, a bigger threat comes with burnout syndrome, and it involves the workers' health. Researchers figured out that burnout takes effect on both physical and mental health. Burnout significantly increases the risk of many health outcomes, such as hypercholesterolemia, type 2 diabetes, coronary heart disease, hospitalization due to cardiovascular disorder, musculoskeletal pain, changes in pain experiences, prolonged fatigue, headaches, gastrointestinal issues, respiratory problems, severe injuries, and mortality below the age of 45 years. Burnout also took a toll on workers' psychological health. Many outcomes were observed, such as insomnia, depressive symptoms, psychotropic and antidepressant medications use, hospitalization for mental disorders, and psychological ill-health symptoms.[3] Burnout is also found to be correlated with increased alcohol consumption and smoking habit.[8] Another study found that burnout brings a detrimental impact on the well-being of workers.[1]

As mentioned before, things got worse for office workers who spend most of their working time sitting at their desks. These types of workers are prone to physical inactivity and sedentary behavior. By definition, physical inactivity is not the same as sedentary behavior. Sedentary behavior is defined as any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture. Meanwhile, physical inactivity refers to people who are performing insufficient amounts of moderate and vigorous-intensity activity. Physical inactivity is described as not meeting specified physical activity guidelines, which is recommended by WHO. WHO suggested that adults aged 18–64 years should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate and vigorous-intensity activity. WHO defined moderate-intensity physical activity as any activity with a MET value between 3 and 5.9 and vigorous-intensity physical activity as ≥6 METs.[9] A systematic review and meta-analysis in 2019 comparing device-measured physical activity across occupations revealed that working adults spent around 60% of their working and waking time engaged in sedentary behavior. Office and call center workers had the lowest daily step count compared to other occupations. Office workers had the greatest sedentary time and the lowest time in light intensity physical activity both at work and during the wakeful time. However, office workers had the greatest minutes sent in moderate to vigorous-intensity activity during waking hours.[4] While definitions may differ, both had the same negative impact on health. Both physical inactivity and sedentary behavior increase the risk of cardiovascular disease, high blood pressure, diabetes, obesity, lipid disorders, depression, anxiety, and even some types of cancer.[9]

Therefore, by learning the consequences of worker burnout on the physical, psychological, and occupational aspects, burnout may become a complex syndrome in the workplace, and companies should take burnout syndrome seriously. It is the companies' ethical responsibility leaders to protect the well-being of employees in the workplace.[1] The focus of the companies should be to change the workplace, not the workers. Companies should make rules and policies that will create a conducive environment in the workplace for workers. Workplaces with a high level of job support and workplace justice are protective against emotional exhaustion.

Meanwhile, high demands, low job control, increased workload, low reward, and job insecurity increase exhaustion risk. In clinical settings, burnout on healthcare workers may increase human error, which ultimately affects patient safety.[11] workload needs to be adjusted by improving workflow efficiency, teamwork, and good leadership.[10] In return, companies will get better produc-

tivity and performance out of their workers, which are beneficial for the companies themselves.[1]

Strategies need to be done by companies to tackle burnout syndrome in their workers. A well-studied yet least applied approach to managing worker burnout is to promote and encourage physical activity in the workplace. A systematic review of 10 studies in 2017 found moderately strong evidence for a negative relationship between physical activity and one of burnout key components, exhaustion, in longitudinal studies. Meanwhile, in intervention studies, the study also found strong evidence for physical activity in reducing fatigue.[12] In contrast, a meta-analysis of 4 studies in 2018 did not find any clear evidence.[13] Both the systematic review and meta-analysis stated a lack of high-quality research to be analyzed. Both expected more high-quality longitudinal and intervention studies, which also specify the efficacy of different exercise modalities.[12,13]

However, some other studies showed promising results. A randomized control trial on 49 participants with four weeks of exercise intervention showed that both cardiovascular and resistance exercises have potential as an effective burnout intervention in different ways compared to control.[14] A newer study in 2019 of 44 workers consisting of physicians and teachers concluded that better cardiovascular fitness seems to be associated with decreased burnout symptoms and better ability to cope with occupational stress.[15] The result proved that regular exercise habit represented by good physical fitness is protective against burnout syndrome.

Companies wishing to reduce burnout proactively can encourage workers to stay physically active during working hours and provide access to structured and regular exercise programs for their workers.[14] Not only exercise will protect workers from burnout, but it will also tackle physical inactivity and sedentary behavior, and therefore, the risk of physical and mental health issues in the future can be reduced.[16] The current recommendation of physical activity for adults by the American College of Sports Medicine (ACSM) includes aerobic exercise, which is the same as WHO guidelines, mentioned previously, and resistance training involving major group muscles for a minimum of 2 times each week.[17] All in all, it is necessary to highlight that a healthy company should always care for their workers' health and well-being.

REFERENCES

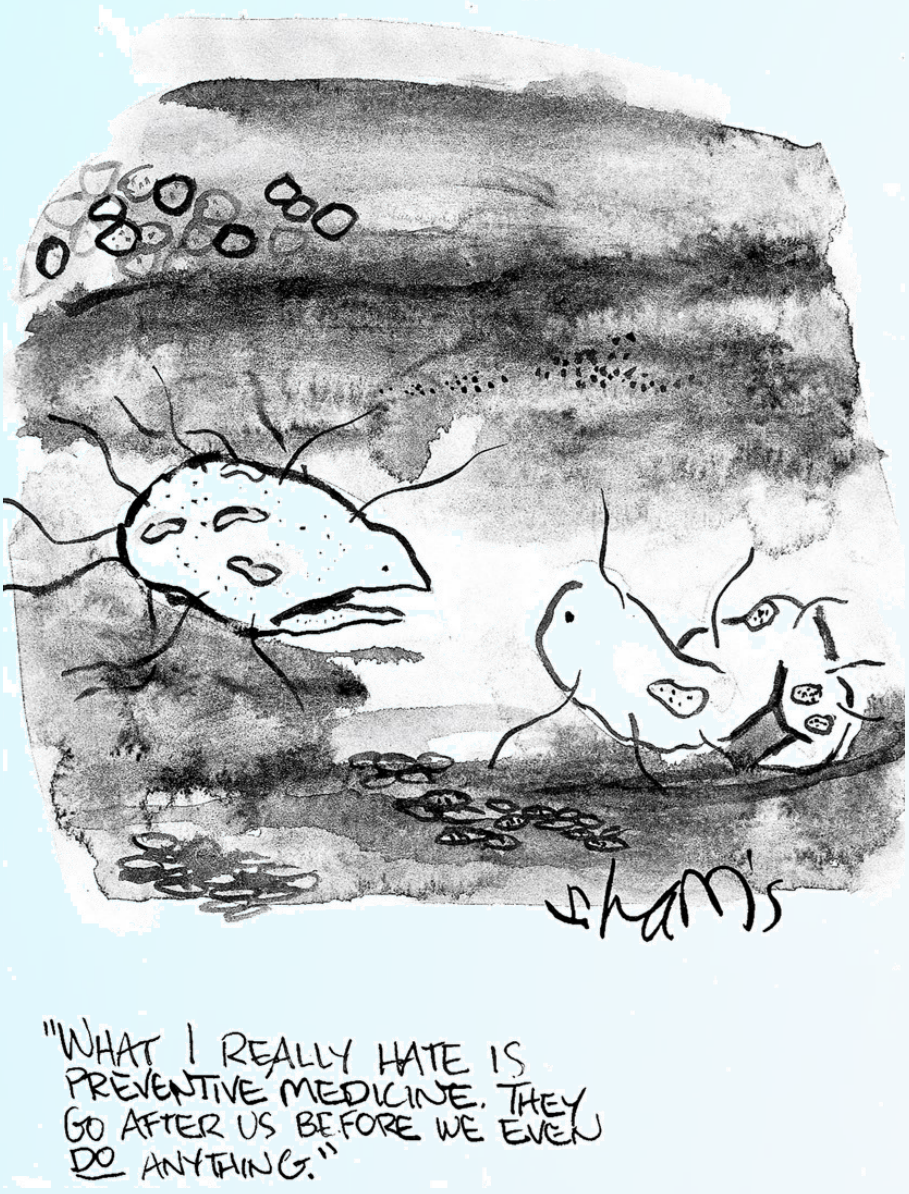
1. Lizano EL. Examining the Impact of Job Burnout on the Health and Well-Being of Human Service Workers : A Systematic Review and Synthesis. Hum Serv Organ Manag Leadersh Gov [Internet]. 2015;39 (3):167–81. Available from: http://dx.doi.org/10.1080/23303131.2015.1014122
2. WHO. Burnout an "occupational phenomenon": International Classification of Diseases [Internet]. Available from: https://www.who.int/mental_health/evidence/burn-out/en/
3. Salvagioni DAJ, Melanda FN, Mesas AE, Gonzalez AD, Gabani FL, Andrade SM de. Physical , psychological and occupational consequences of job burnout : A systematic review of prospective studies. PLoS One. 2017;12(10):1–29.
4. Prince SA, Elliott CG, Scott K, Visintini S, Reed JL. Device-measured physical activity , sedentary behaviour and cardiometabolic health and fitness across occupational groups : a systematic review and meta- analysis. Int J Behav Nutr Phys Act. 2019;16(30):1–15.
5. Shirom A. Burnout and Health Review: Current Knowledge and Future Research Directions. In: Houdmont J, Leka S, editors. Contemporary Occupational Health Psychology: Global Perspectives on Research and Practice Volume 1. Wiley-Blackwell; 2010. p. 59–76.
6. Rotenstein LS, Torre M, Ramos MA, Rosales RC, Guille C, Sen S, et al. Prevalence of Burnout Among Physicians A Systematic Review. JAMA. 2018;320(11):1131–50.
7. Kowalska M, Bugajska J, Zołnierczyk-Zreda D. Frequency of burnout syndrome in office worker. Med Pr [Internet]. 2010;61(6):615–23. Available from: https://pubmed.ncbi.nlm.nih.gov/21452564/
8. Useche SA, Montoro L V., Ruiz JI, Vanegas C, Sanmartin J, Alfaro E. Workplace burnout and health issues among Colombian correctional officers. PLoS One. 2019;14(2):1–20.
9. Ploeg HP Van Der, Hillsdon M. Is sedentary behaviour just physical inactivity by another name ? Int J Behav Nutr Phys Act. 2017;14 (142):1–8.
10. Aronsson G, Theorell T, Grape T, Hammarström A, Hogstedt C, Marteinsdottir I, et al. A systematic review including meta-analysis of work environment and burnout symptoms. BMC Public Health. 2017;17(264):1–13.
11. Hall LH, Johnson J, Watt I, Tsipa A, Connor DBO. Healthcare Staff Wellbeing , Burnout , and Patient Safety : A Systematic Review. PLoS One. 2016;11(7):1–12.
12. Naczenski LM, Vries JD De, Hooff MLM Van, Kompier MAJ. Systematic review of the association between physical activity and burnout. J Occup Health. 2017;59:477–94.
13. Ochentel O, Humphrey C, Pfeifer K. Efficacy of Exercise Therapy in Persons with Burnout . A Systematic Review and Meta-Analysis. J Sport Sci Med. 2018;17:475–84.
14. Bretland RJ, Thorsteinsson EB. Reducing workplace burnout : the relative benefits of cardiovascular and resistance exercise. PeerJ. 2015;1–18.
15. Moraes MGDE, Calais SL, Verardi CEL. The influence of physical fitness on the symptoms of burnout. J Phys Educ Sport. 2019;19 (3):945–51.
16. Mann S, Hamad A, Kumbhare D. The Problem of Sedentary Behaviour in the Office Workspace : A Structured Exercise Program for Primary Prevention Journal of Novel Physiotherapies. J Nov Physiother. 2018;8(3).
17. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 9th editio. Lippincott Williams & Wilkins; 2014.

INA-RESPOND Newsletter

INFLUENZA VACCINATION AND COVID-19: SHOULD BE A GOOD COMBINATION

By: Aly Diana

COMIC CORNER



Seasonal influenza (flu) is a major cause of morbidity, mortality, and the use of healthcare services globally. Based on the World Health Organization, worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths. Although flu viruses are detected year-round, seasonal peaks occur during winter (December-February) in the United States (US) and during the rainy season (December–January) in Indonesia. As the potential of SARS-CoV-2 unfolds, it is highly likely that a second pandemic wave will also occur starting this October-December. With the pandemic, the demand imposed on healthcare systems is expected to far exceed that of medical care demands during the influenza seasons alone. Current influenza-COVID-19 coinfection reports suggest that coinfection rates are as high as 57% when influenza is circulating. Therefore, a looming threat of concurrent influenza and COVID-19 epidemics is a major concern for public health officials and clinicians.

SARS-CoV-2 and influenza are vastly different pathogens, but there are important areas of overlap. Both viruses are primarily transmitted by respiratory droplets. Thus, the adoption of non-pharmacologic interventions (NPIs), such as mandated face coverings in public, closure of schools and retail spaces, and restrictions on movement, would be expected to influence both infections' incidence to varying degrees. Studies have consistently shown a pattern of decreased influenza incidence in 2020 (January through May) after adopting NPIs com-

pared with prior seasons. Nevertheless, caution should be taken when interpreting these data because the rates of testing for non–SARS-CoV-2 respiratory viruses were greatly curtailed during the initial pandemic wave.

The expectation that the pattern of decreased influenza transmission will endure through the next influenza season presumes ongoing adherence to NPIs. Continued use of face coverings and reinstating local lockdowns during periods of increased transmission could substantially reduce the rates of infection for both diseases, but as restrictions on movement relax, the transmission of both influenza and SARS-CoV-2 can be expected to increase.

Therefore, in addition to NPIs, there is a heightened importance for seasonal flu vaccination to minimize the viral reservoir in the population. Influenza has a variable basic reproduction number (R0), but seasonal influenza is estimated as having an R0 of 0.9–2.1. Herd immunity is reached at 1-1/R0. For the upper R0 value of 2.1, this implies that herd immunity would be acquired if 52.3% of the population were to be immune. If the influenza vaccine were to be effective in 50% of cases given, herd immunity would almost be reached if all of the population were to take it.

Moreover, the anti-flu immune responses can induce bystander immunity that is expected to augment immunity against other viral infection such as SARS-CoV-2 non-specifically. Furthermore, influenza vaccination itself would generate sustained immunity that overall enhances immunity against SARS-CoV-2. It might be possible also that individuals who received prior flu vaccination might show mild severity of COVID-19 because of the flu-induced bystander effect of the generated immune responses, which itself might cross-react against SARS-CoV-2. Due to this cross-reactivity between flu and SARS-CoV-2, it has been suggested that the flu-induced bystander immunity is more beneficial effects on COVID-19.

Given the flu vaccine safety in adults, it has been recommended the use of flu vaccine to minimize the severity of COVID-19 disease, especially in the at-risk groups. An almost universal uptake may engender herd immunity and thus protect those in who the vaccine is ineffective. In addition, influenza vaccination plays an important role in protecting the elderly, which is a group that is particularly vulnerable to COVID-19. Furthermore, a decrease in hospital visits and admissions will alleviate hospitals and allow services to better cope with COVID-19 complications as lockdowns are inevitably relaxed.

REFERENCES:

Behrouzi B, Araujo Campoverde MV, Liang K, et al. Influenza Vaccination to Reduce Cardiovascular Morbidity and Mortality in Patients With COVID-19: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;76 (15):1777-1794. doi:10.1016/j.jacc.2020.08.028

Grech V, Borg M. Influenza vaccination in the COVID-19 era. Early Hum Dev. 2020;148:105116. doi:10.1016/j.earlhumdev.2020.105116

Kosasih H, Roselinda, Nurhayati, et al. Surveillance of influenza in Indonesia, 2003–2007. Influenza Other Respir Viruses. 2013;7(3):312-320. doi:10.1111/j.1750-2659.2012.00403.x

Maltezou HC, Theodoridou K, Poland G. Influenza immunization and COVID-19. Vaccine. 2020;38(39):6078-6079. doi:10.1016/j.vaccine.2020.07.058

Marín-Hernández D, Schwartz RE, Nixon DF. Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy [published online ahead of print, 2020 Jun 4]. J Med Virol. 2020;10.1002/jmv.26120. doi:10.1002/jmv.26120

Ozaras R, Cirpin R, Duman H, Duran A, Arslan O, Leblebicioglu H. An open call for influenza vaccination pending the new wave of COVID-19 [published online ahead of print, 2020 Jul 8]. J Med Virol. 2020;10.1002/jmv.26272. doi:10.1002/jmv.26272

Paget J, Caini S, Cowling B, et al. The impact of influenza vaccination on the COVID-19 pandemic? Evidence and lessons for public health policies. Vaccine. 2020;38(42):6485-6486. doi:10.1016/j.vaccine.2020.08.024

Salem ML, El-Hennawy D. The possible beneficial adjuvant effect of influenza vaccine to minimize the severity of COVID-19 [published online ahead of print, 2020 Apr 22]. Med Hypotheses. 2020;140:109752. doi:10.1016/j.mehy.2020.109752

Solomon DA, Sherman AC, Kanjilal S. Influenza in the COVID-19 Era [published online ahead of print, 2020 Aug 14]. JAMA. 2020;10.1001/jama.2020.14661. doi:10.1001/jama.2020.14661

Aly Diana
INA-RESPOND

INA-RESPOND website: www.ina-respond.net

INA-RESPOND Newsletter

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

The INA-RESPOND newsletter welcomes all network members and stakeholders to contribute by submitting articles related to the network's studies and interests. Send your articles or subscribe to our latest newsletter by sending an email to INA.Secretariat@ina-respond.net