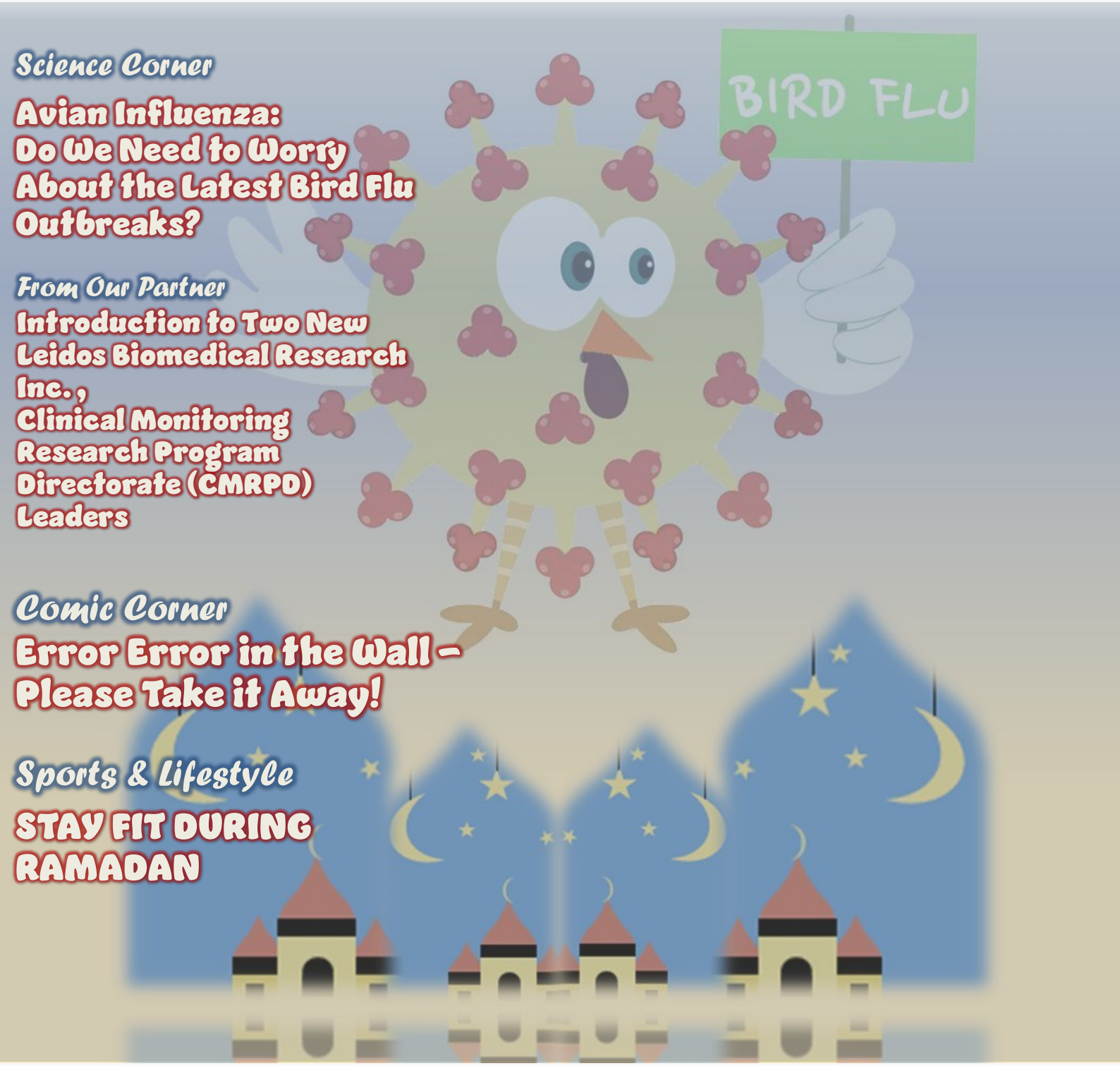
INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

March 2023



HEALTH POLICY AGENCY

MINISTRY OF HEALTH REPUBLIC OF INDONESIA

2023

MASTHEAD

INA-RESPOND newsletter

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THANK YOU

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FEATURES

INA-RESPOND Newsletter

InVITE & PROACTIVE Study Updates

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

InVITE

As of March 6, 2023, out of the 700 participants who have enrolled in the study, 160 (22.86%) have ended their participation, while 540 (77.14%) are still ongoing. The study is being conducted at three different sites. Site 1 and site 2 are on visit 4, while site 3 is still on visit 3. The details of the visits for each site are listed in Table 1.

It is worth noting that the study has encountered some challenges with retaining participants. Out of the 160 subjects who ended their participation, 44 (6.29%) withdrew from the study. Reasons for withdrawal included participant decision, personal reasons, or loss of interest . Additionally, some participants did not receive the complete vaccine regimen within 12 months of enrollment, which resulted in three (0.43%) subjects being excluded from the study. Two (0.29%) subjects were not allowed to continue because continuation was not in their best interest, and one (0.14%) subject was non-compliant with study procedures. Unfortunately, one (0.14%) subject passed away during the study, and nine (1.29%) subjects had other reasons for ending their participation.

Furthermore, the study has been tracking symptomatic visits among participants. Table 2 provides the details of these visits as of March 6, 2023. It is important to note that while some participants have experienced COVID-19 symptoms, this does not necessarily mean that they have contracted the disease.

Site	Symptomatic Visit		
	# of visit	Positive	Negative
01	97	59	37
02	14	6	8
03	2	1	1
Total	113	66	46

Table 2. Symptomatic Visit Details per March 6, 2023

Site	Screening / Visit 1	Enrollment Failure	Enrolled	Ongoing	Add. Visit 1	Visit 2	Add. Visit 2	Add. Visit 3	Visit 3	Agree Ext.	Not Agree Ext.	Ext. Visit 4	Ext. Visit 5
01	345	2	343	288	88	326	314	306	315	287	28	137	0
02	228	1	227	156	97	214	191	188	195	156	39	149	0
03	130	0	130	96		130			128	96	34	6	0
Total	703	3	700	540	185	670	505	494	638	543	94	292	0

Table 1. Details of Visits per site per March 6, 2023

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As of March 10, 2023, the study has enrolled a total of 4,336 subjects, with 2,74% still ongoing and 97% having already completed their participation. To provide a visual representation of the study's progress, please refer to Figure 1. The sites that still have active participants are sites 520, 530, 680, 690, and 700.

Regarding the end-of-study participants, as of follow-up month 36, 3,404 subjects have successfully completed the study, while 442 were lost to follow-up, 248 passed away, 32 withdrew their consent, 38 relocated to an area without a PROACTIVE site, 5 tested negative for HIV, and 2 were suspended due to imprisonment. The status of end-of-study participants for each site is presented in Table 1.

The last patient's last visit (LPLV) was conducted at site 610 in August 2022. Sites 550, 560, 570, 580, 590, 600, and 630 completed theirs in October 2022. Site visits were accomplished in November 2022 at sites 510, 640, and 660, while site 650 completed theirs in December 2022. Sites 670, 680, 690, and 540 finished in January 2023. Meanwhile, site 530 will complete their study visit in March 2023, and sites 520 and 700 will complete their study visits in April 2023.

The close-out study visit activity for site 610, RSUD Tangerang, was conducted on March 9, 2023. Following that, the close-out activity for site 560 will be conducted at the end of March 2023. The upcoming close-out activity will be held next month for sites 570, 630, and 580.

The monitoring activity is scheduled to occur at sites 690 in March 2023 and at sites 520 and 700 in April 2023. This monitoring activity will ensure the study's accuracy and integrity and provide valuable information for future research.

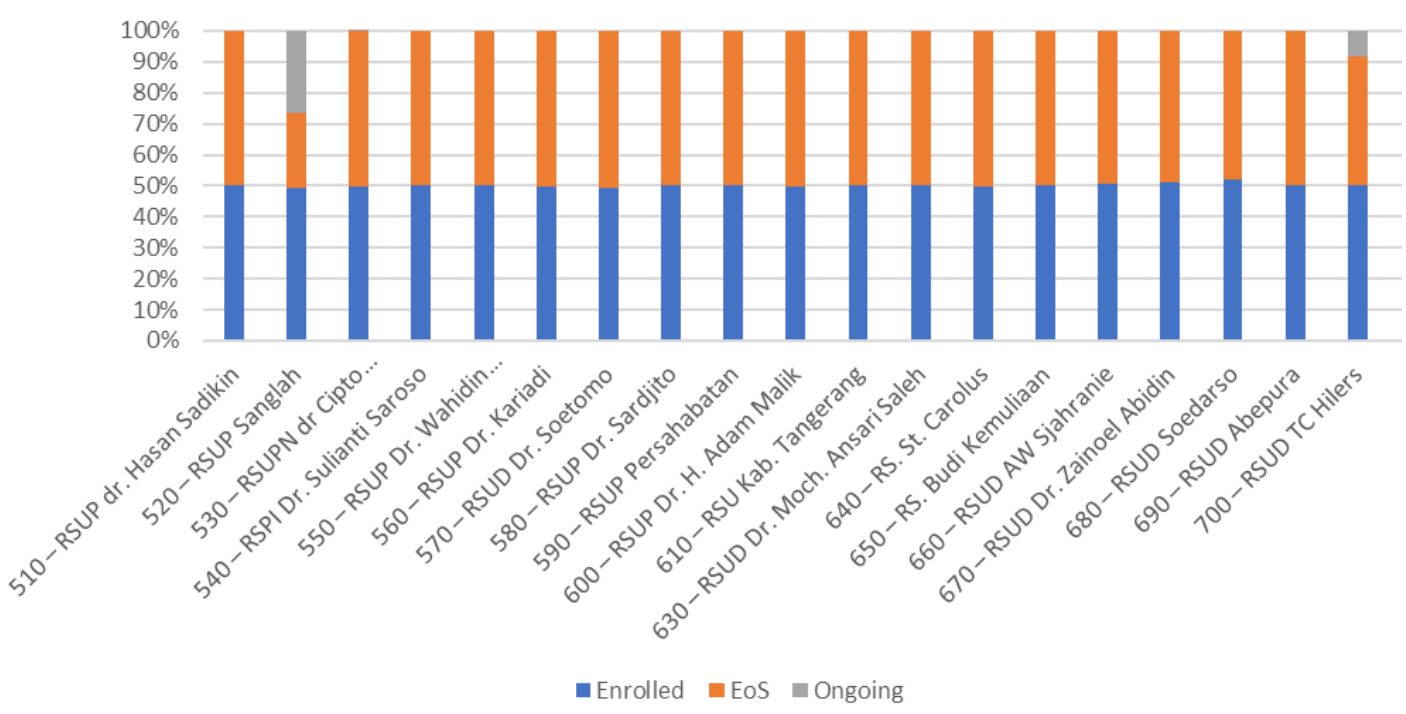


Figure 1. Site's Study Progress

No	Site	End of Study Duration/ Complete	Withdrew Consent	Partici-pants with HIV nega-tive	Moved	Death	Investiga-tor Discre-tion	Lost to Follow Up	Other	Total
1.	510 – RSUP Dr. Hasan Sadikin	189	1	0	5	5	0	6	0	206
2.	520 - RSUP Sanglah	65	0	0	1	4	0	0	0	70
3.	530 – RSUPN Dr. Cipto Mangunkusu-mo	283	0	0	0	17	0	15	0	315
4.	540 – RSPI Dr. Sulianti Saroso	132	0	0	3	8	0	35	0	180
5.	550 – RSUP Dr. Wahidin Sudiro-husodo	240	0	0	5	25	0	67	0	337
6.	560 – RSUP Dr. Kariadi	199	1	3	0	15	0	16	0	234
7.	570 – RSUD Dr. Soetomo	261	13	0	4	21	0	21	0	320
8.	580 – RSUP Dr. Sardjito	168	1	0	5	6	0	38	0	218
9.	590 – RSUP Per-sahabatan	186	0	1	0	37	0	22	0	246
10.	600 – RSUP Dr. H. Adam Malik	253	3	0	2	21	0	61	0	340
11.	610 – RSU Kabupat-en Tangerang	272	6	0	4	20	0	22	2	326
12.	630 – RSUD Dr. M. Ansari Saleh	215	1	0	1	7	0	17	0	241
13.	640 – RS St. Carolus	211	0	0	0	1	0	15	0	227
14.	650 – RSU Budi Kemuliaan Batam	179	3	0	5	9	0	33	0	229
15.	660 – RSU A. Wahab Sjahranie	183	0	0	2	6	0	26	0	217
16.	670 – RSUD Zainoel Abidin	89	0	0	0	11	0	21	0	121
17.	680 – RSUD Soedar-so	68	0	0	0	11	0	28	0	107
18.	690 – RSUD Abepu-ra	84	2	1	1	7	0	42	0	137
19.	700 – RSUD TC Hillers	127	1	0	0	17	0	5	0	150
	Total	3404	32	5	38	248	0	490	2	4221

Table 1. Subjects' End of Study Reasons

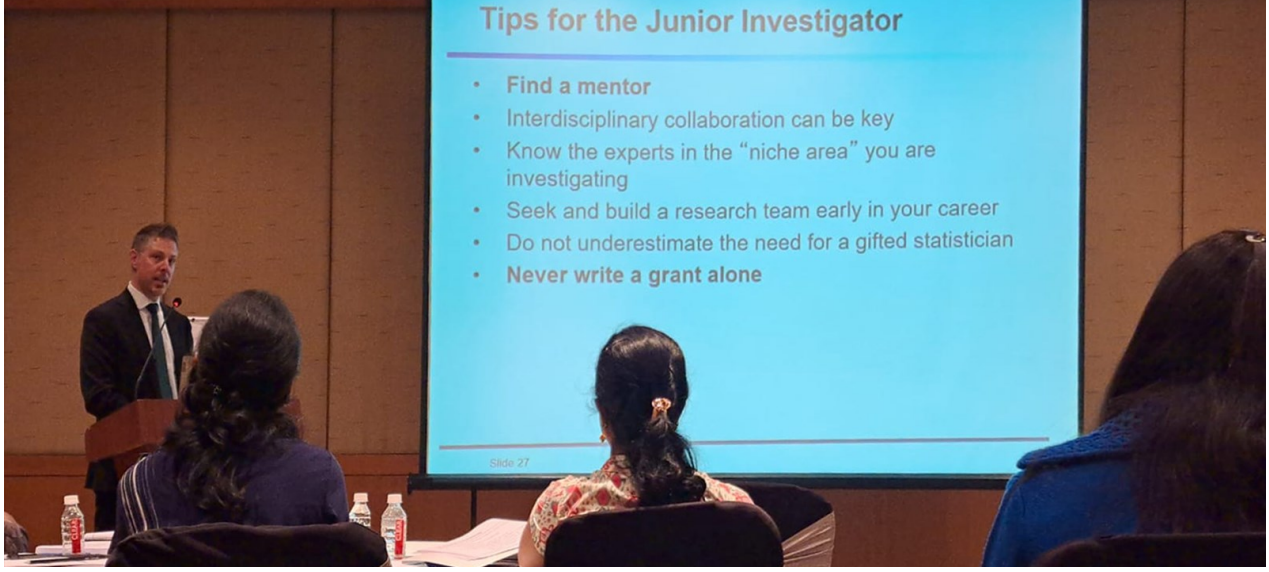
INA-RESPOND Newsletter

JUNIOR INVESTIGATOR WORKSHOP REPORT

By: Adhella Menur and Retna Mustika Indah

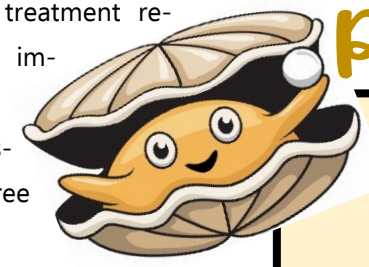
REPORT

On February 5-10, 2023, Adhella Menur, a member of the INA-RESPOND Scientific Team, participated in a two-and-a-half -day grantsmanship workshop and the 12th RePORT India annual meeting in India. The workshop was hosted by CRDF Global in collaboration with the Division of AIDS, NIAID, NIH, to train young investigators in developing successful grant proposals. To participate in the workshop, interested young investigators should fulfill eligibility criteria such as having completed a graduate degree in the last eight years, being affiliated with a current RePORT International network research project, and submitting the required documents (application form, personal statement, proposed research concept, and letter of support). The proposed research concept should include a brief background, rationale, hypothesis, objective, and aims. The concept title from Indonesia was "Applicability of selected host blood transcriptional signatures to assist clinicians in deciding empiric treatment for clinically diagnosed tuberculosis (TB) patients." Twenty-three participants from RePORT International member countries (13 from India, four from the Philippines, three from South Africa, two from Brazil, and one from Indonesia) attended with different and inter-



esting TB concept proposals. Understanding the creation process of a grant proposal and the review criteria is essential. In this workshop, Bradley S. Schneider, Ph.D. (UTMB, Texas) and Luke Daniels, Ph.D. (The College of Idaho) trained the participants on NIH grant application preparation and strategies for producing well-written research proposals.

Sequentially after the grantsmanship workshop, Regional Prospective Observational Research in Tuberculosis (RePORT) India invited the participants to the 12th RePORT India annual meeting. The RePORT India network is well-established and multi-partnered with various institutions from other countries. The network successfully performed the RePORT International Common Protocol research (Cohort A: 3,040 active TB patients and Cohort B: 3,766 household contacts (HHCs)) in Phase I (2013-2018). Their achievements include 106 scientific publications and 64 sub-projects utilizing the collected and stored samples for biomarkers and vaccine trials. They are currently running Phase II trials with specific aims to study TB diagnostics, markers of treatment response, lung injury & impairment, resistance to infection, and progression to disease. The three most exciting projects are: combining rapid next-generation sequencing (NGS) and anti-TB drugs monitoring for personalizing TB treatment, identifying "Resisters" (HHCs who were not progressing to latent or active TB) for biomarker and vaccine development, and a modified BCG vaccine (VPM1002BC) trial that can be used for a healthy person as a primary vaccine, for HHCs to prevent developing active TB, for an adjuvant during anti-TB treatment, or for the post-TB patient to prevent recurrence. The workshop and the RePORT India annual meeting were beneficial experiences for the junior investigator participants across the RePORT consortia. From those experiences, participants gained the skills to develop competitive research proposals, familiarized themselves with applying for international grant funding, discussed and developed collaboration with other investigators, and gained insight and inspiration from the RePORT India presentations. For INA-RESPOND, hopefully, we can explore our archived TB specimens to have a greater impact on TB control in Indonesia and globally.



Pearls!

Keys to a successful grant proposal are:

- A good idea, good science, and good application
- Aligning the project to funding opportunity
- Reaching out to collaborators as soon as possible
- Being careful about administrative requirements
- The budget should detail and rational
- Write, discuss, and revise – repeat!

INA-RESPOND Newsletter

INTRODUCTION TO TWO NEW LEIDOS BIOMEDICAL RESEARCH INC., CLINICAL MONITORING RESEARCH PROGRAM DIRECTORATE (CMRPD) LEADERS

By: Louis Grue and Kristine Nagales

FROM OUR PARTNER

Shelly Simpson, M.S.,
CMRPD Director

After the retirement of the long time CMRPD Director Beth Baseler, Ms. Shelly Simpson was appointed the new CMRPD Director in December 2022. With over two decades of time and experience at Leidos Biomedical Research Inc. (Leidos Biomed), and the Frederick National Laboratory for Cancer Research (FNLCR), and CMRPD, Ms. Simpson is a leader and skilled executive in full-cycle clinical trials management and monitoring of domestic and international clinical research programs. Her leadership drove the CMRPD response to some of the complex healthcare threats of our time, including the Ebola crisis in Africa and most recently, the COVID-19 pandemic. Under her directive, the Clinical Trials Monitoring team received a 2020 NIH's Director's Award, for the DCR/NIAID PALM Consortium, and two FNL Outstanding Achievement Awards in 2020, for outstanding support to NIAID/FDA Inspection for PALM EBOLA study in the Democratic Republic of Congo and for establishment and execution of the COVID-19 master platform protocol. Ms. Simpson was one of the five CMRPD recipients of the 2020 FNLCR President's Award for contributing to the establishment of the international remdesivir COVID-19 clinical trial, travelling to set up sites in South Korea and Japan even as Americans abroad in the early days of the pandemic were returning back to the United States. Ms. Simpson is a very well-respected leader within Leidos Biomed and an integral member of the community who she serves. Ms. Simpson is deeply rooted in her passion and commitment to all around her, Leidos Biomed Government customers, clinical trial partners and participants, and her colleagues and family at CMPRD. She completed her BA at St. Mary's College of Maryland and went on to earn a master's degree in science technology management, with a concentration in biotechnology, at the University of Maryland.

Mike Galcik, MS MT (ASCP),
CMRPD Deputy Director

Mr. Michael 'Mike' Galcik was appointed CMRPD Deputy Director in December 2022. Mr. Galcik has been with FNLCR CMRPD for 20 years and has nearly three decades of experience in cGMP laboratory, clinical research, and information technology. He has served in various roles rising though capacities most recently as Information Technology Manager before becoming CMRPD Deputy Director. He responded to complex matters as the HIPAA/HITECH Privacy and Compliance Officer and provided technical expertise and led rapid response teams to critical crisis needs providing direct on-the-ground support during the Ebola outbreak in Africa in 2014-2016, and in the recent days of COVID-19 response. Mr. Galcik is an outstanding leader, and his tenure thus far is attested in all he has been involved in. He was part of CMRPD teams that received two NIH Director's Awards, first in 2020 as a member of the DCR/NIAID PALM Consortium for the extraordinary contributions of DCR staff in identifying two effective treatments for Ebola virus disease and the second in 2021, as a member of the NIAID Accelerating COVID-19 Therapeutic Interventions and Vaccines Team for outstanding efforts in the pursuit of effective therapeutics to treat COVID-19. In 2019, he received the NIAID Merit Award as a member of the PALM team in helping support a randomized, controlled clinical trial in the Democratic Republic of the Congo and prior in 2011, as a member of the regulatory affairs team that launched an electronic common technical document system for FDA submissions. Most notably in 2015, he received the FNL President's Award as a member of the Ebola emergency response team for extraordinary commitment and selflessness in providing support to the 2014-2015 health care threat in West Africa. Most recently he was awarded the 2021 FNL Special Achievement Award for the NIH COVID-19 treatment guidelines website. Mr. Galcik graduated from The Pennsylvania State University with a Bachelor of Science degree in microbiology, has his Master of Science degree in computer and information sciences from Hood College, and is an American Society for Clinical Pathology (ASCP) certified medical technologist.

CMRPD and collaborators are thrilled to have Shelly and Mike in their new positions and look forward to their unwavering governance in the mission and vision of our directorate! Contact Information: shelly.simpson@nih.gov and mike.galcik@nih.gov

INA-RESPOND Newsletter

AVIAN INFLUENZA: DO WE NEED TO WORRY ABOUT THE LATEST BIRD FLU OUTBREAKS?

By: Yan Mardian

SCIENCE CORNER

An 11-year-old girl has died of bird flu in Cambodia, south-east Asia, and multiple others who live in her area have been sickened, including her father, according to media reports, marking the first known H5N1 human infections in the country since 2014—and potentially setting the stage for sustained human-to-human transmission. The cases raised fears that the virus had acquired the ability to spread among people and may trigger another pandemic. But the World Health Organization said that 11 contacts of the girl, four of whom have flulike symptoms, had tested negative for infection with the H5N1 flu virus. Cambodian authorities said that the deceased girl and survived father was infected with an older viral variant H5 clade 2.3.2.1c which has circulated in Cambodia among birds/poultry for many years and has sporadically caused human infection. The virus is unrelated to the outbreaks in birds caused by a new strain of H5N1, clade 2.3.4.4b, which emerged in 2020, in the United States and Europe. While these avian influenza viruses can cause human infections, it has not been seen to cause human-to-human transmission to date.

Influenza virus

Influenza is an infectious respiratory disease; in humans, it is caused by influenza A (genus influenza virus A) and influenza B (genus influenza virus B) viruses (influenza virus C and influenza virus D genera are also known). All influenza viruses are enveloped negative-sense single-strand RNA viruses with a segmented genome. Influenza A and B viruses contain eight RNA segments, which encode RNA polymerase subunits, viral glycoproteins (namely, haemagglutinin (HA), with its distinct globular 'head' and 'stalk' structures, which facilitate viral entry, and neuraminidase (NA), which facilitates viral release), viral nucleoprotein (NP), matrix protein (M1) and membrane protein (M2), the nonstructural protein NS1 and nuclear export protein (NEP). The HA and NA viral proteins are the most antigenically variable, and in the case of influenza A virus, they are classified into antigenically diverse subtypes. These two viral glycoproteins are located at the surface of the virus particle and are the main targets for protective antibodies induced by influenza virus infection and vaccination.

The segmented nature of the influenza viral genome enables reassortment, that is, interchange, of genomic RNA segments when two viruses of the same type (that is, two influenza A viruses or two influenza B viruses) infect the same cell. A unique characteristic of influenza A viruses is that they circulate not only in humans but also in domestic animals, pigs, horses and poultry and in wild migratory birds (>100 species of ducks, geese, swans, gulls, waders and wild aquatic birds are considered natural reservoirs. These animal reservoirs provide a source of antigenically diverse HA and NA genes that can be exchanged between viral strains by reassortment after co-infection of the same host, increasing virus diversity and in some instances leading to the generation of human pandemic influenza virus strains with HA and/or NA derived from animal strains. By contrast, influenza B and influenza C viruses are not divided into different subtypes and are restricted to humans, with no known animal reservoirs, although limited spillover to seals and pigs has occurred, respectively.

Avian influenza virus

Avian influenza (AI) viruses are highly contagious, extremely variable viruses that are widespread in birds. Wild birds in aquatic habitats are thought to be their natural reservoir hosts, but domesticated poultry and other birds can also be infected. Most viruses cause only mild disease in poultry and are called low pathogenic avian influenza (LPAI) viruses. Avian influenza viruses can occasionally affect mammals, including humans, usually after close contact with infected poultry. While

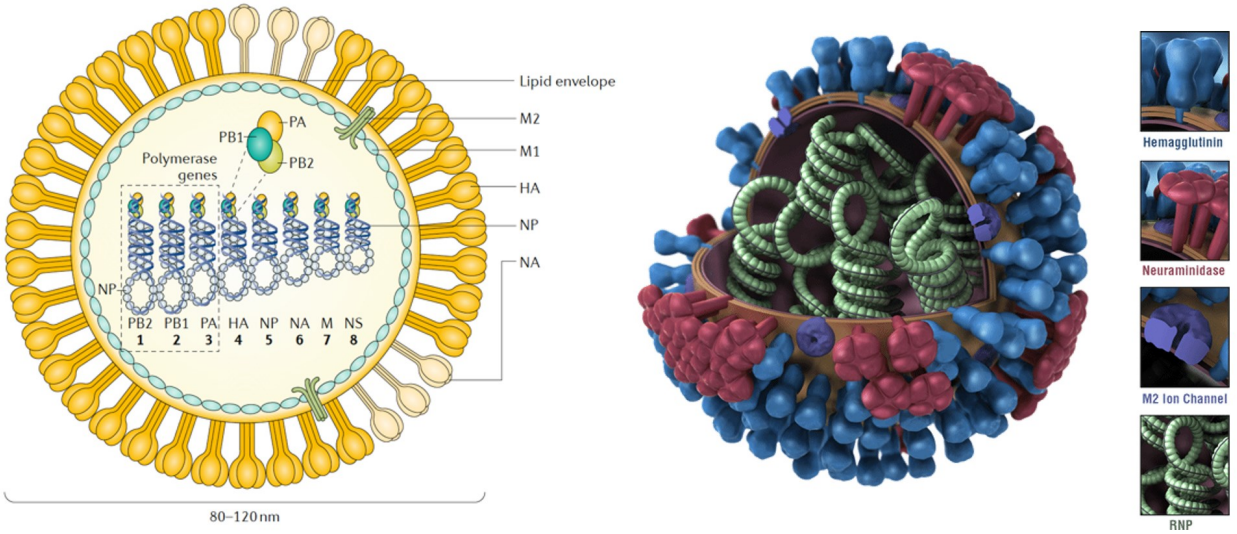


Fig. 1. Influenza A and influenza B. The figure represents an influenza A virus particle or virion. Both influenza A and influenza B viruses are enveloped negative- sense RNA viruses with genomes comprising eight single- stranded RNA segments located inside the virus particle. Although antigenically different, the viral proteins encoded by the viral genome of influenza A and influenza B viruses have similar functions: the three largest RNA segments encode the three subunits of the viral RNA- dependent RNA polymerases (PB1, PB2 and PA) that are responsible for RNA synthesis and replication in infected cells; two RNA segments encode the viral glycoproteins haemagglutinin (HA , which has a 'stalk' domain and a 'head' domain), which mediates binding to sialic acid- containing receptors and viral entry , and neuraminidase (NA), which is responsible for releasing viruses bound to non- functional receptors and helping viral spread. The RNA genome is bound by the viral nucleoprotein (NP), which is encoded by RNA segment 5. RNA segments 6 and 8 encode more than one protein, namely , the matrix protein (M1) and membrane protein (M2) — BM2 in the case of influenza B — and the nonstructural protein NS1 (not shown) and nuclear export protein (NEP). The M1 protein is thought to provide a scaffold that helps the structure of the virion and that, together with NEP, regulates the trafficking of the viral RNA segments in the cell; the M2 protein is a proton ion channel that is required for viral entry and exit and that, together with the HA and NA glycoproteins, is located on the surface of the virus anchored in a lipid membrane derived from the infected cell. Finally, the NS1 protein is a virulence factor that inhibits host antiviral responses in infected cells. The influenza viruses can also express additional accessory viral proteins in infected cells, such as PB1–F2 and PA- x (influenza A), that participate in preventing host innate antiviral responses together with the NS1 protein or NB (influenza B), the function of which is unknown. NS1, NEP, PB1–F2 and PA- x are not present in the virus particle or are present in only very small amounts. NB is a unique influenza B virus surface protein anchored in the lipid membrane of the virus particles.

infections in people are often limited to conjunctivitis or mild respiratory disease, some viruses can cause severe illness. During the last century, such viruses have caused or contributed to at least three pandemics in humans, contributed to the diversity of swine influenza viruses in pigs, and produced one of the two canine influenza viruses now circulating among dogs. AI viruses belonging to the species influenza A virus, genus influenza virus A and family Orthomyxoviridae. Influenza A viruses are classified into subtypes based on two surface proteins, the hemagglutinin (HA) and neuraminidase (NA). A virus that has a type 1 HA and type 2 NA, for example, would have the subtype H1N2. At least 16 hemagglutinins (H1 to H16), and 9 neuraminidases (N1 to N9) have been found in viruses from birds.

Avian influenza A viruses are classified into the following two categories: low pathogenicity avian influenza (LPAI) A viruses, and highly pathogenic avian influenza (HPAI) A viruses. The categories refer to molecular characteristics of a virus and the virus' ability to cause disease and mortality in chickens in a laboratory setting. Highly pathogenic avian influenza (HPAI) viruses can develop from certain LPAI viruses, usually while they are circulating in poultry flocks. HPAI viruses can kill up to 90-100%

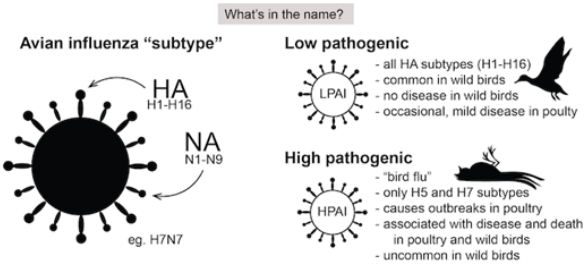
of the flock, and cause epidemics that may spread rapidly. HPAI and LPAI are defined and explained below:

a. Low Pathogenic Avian Influenza (LPAI): Low pathogenic avian influenza viruses cause either no signs of disease or mild disease in chickens/poultry. Most avian influenza A viruses are low pathogenic and cause few signs of disease in infected wild birds. In poultry, some LPAI viruses can mutate into HPAI avian influenza viruses.

b. Highly Pathogenic Avian Influenza (HPAI): Highly pathogenic avian influenza viruses cause severe disease and high mortality in infected poultry. Only some avian influenza A(H5) and A(H7) viruses are classified as HPAI A viruses, while most A(H5) and A (H7) viruses circulating among birds are LPAI A viruses. HPAI A(H5) or A(H7) virus infections can cause disease that affects multiple internal organs with mortality up to 90% to 100% in chickens, often within 48 hours. HPAI A(H5) and A(H7) virus infections in poultry also can spill back into wild birds, resulting in further geographic spread of the virus as those birds migrate. While some wild bird species can be infected with some HPAI A(H5) or A(H7) virus subtypes without appearing sick, other HPAI A(H5) and A(H7) subtypes can cause severe disease and mortality in some infected wild birds/poultry.

HPAI and LPAI designations do not refer to or correlate with the severity of illness in cases of human infection with these viruses; both LPAI and HPAI A viruses have caused mild to severe illness in infected humans. There are genetic and antigenic differences between the influenza A virus subtypes that typically infect only birds and those that can infect birds and people.

The first known human cases of AI were reported in China and Hong Kong in 1997, where transmission from animals to humans led to 18 people being infected, of whom six died. Since then 19 countries have reported more than 860 H5N1 human infections to the World Health Organization from 2003 to 2022. Of these, 53% have resulted in death. Since 2005, HPAI A(H5N1) viruses have undergone extensive genetic diversification including the formation of hundreds of genotypes following reassortment with other avian influenza A viruses. Clade 2.3.4.4b HPAI A(H5N1) viruses emerged in 2020 and were introduced into North America in late 2021 and have spread to Central and South America, resulting in wild bird and poultry outbreaks in many countries. Globally, this 2.3.4.4b clade of HPAI A(H5N1) viruses has become widespread causing record numbers of bird outbreaks. Recently, over 11,300 animal outbreaks of HPAI A(H5N1) viruses were reported by 73 member states to the World Organization for Animal Health since January 2022.

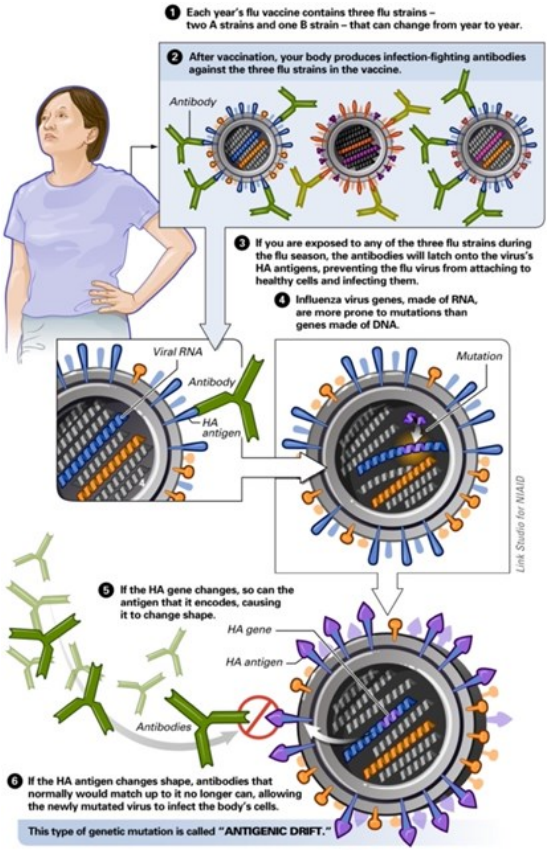


While HPAI A(H5N1) viruses are currently circulating widely in wild birds and poultry in many geographic regions, relatively few human cases of A(H5N1) have been reported in recent years. Between January 2022 and March 15, 2023, only ten sporadic human cases of A (H5N1) were reported from seven countries. All reported cases had recent exposure to sick or dead poultry, and no cases of human-to-human HPAI A(H5N1) virus transmission were identified. Five cases (3 children, 2 adults) had severe disease, and 2 died. Seven cases were associated with clade 2.3.4.4b HPAI A(H5N1) viruses, and two cases were associated with clade 2.3.2.1c HPAI A(H5N1) viruses (the ones mentioned earlier); none of the HPAI A (H5N1) virus genetic sequences contained any known markers of reduced susceptibility to currently recommended FDA-approved influenza antiviral medications.

Antigenic drift

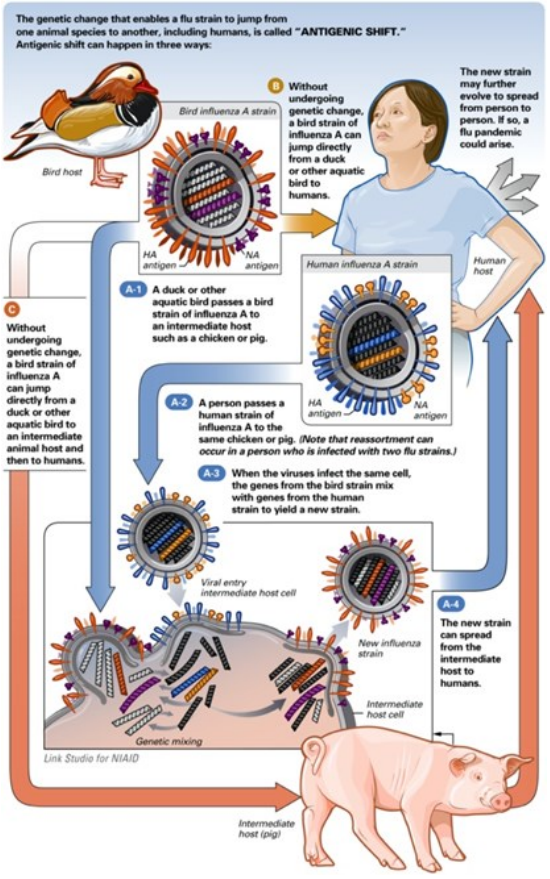
Influenza viruses are capable of evading the antibody mediated immunity induced during previous infections or vaccinations by gradually accumulating mutations in HA and NA. This process, known as antigenic drift, necessitates frequent updates of influenza vaccines to ensure sufficient antigenic relatedness between the vaccine and emerging virus variants. Because HA is current-

ly the main component of the inactivated influenza vaccines, human and animal influenza virus surveillance programmes are in place to monitor antigenic changes of the virus, primarily using the haemagglutination inhibition assay and viral RNA sequence analyses. Increased attention to antigenic drift of NA, measured using neuraminidase inhibition assays, could further increase the antigenic match between vaccines and circulating viruses. The antigenic evolution of influenza viruses was shown to be more rapid in human influenza viruses than in swine and equine viruses, which is presumably related to the size, mixing and age- structure (that is, humans have a longer lifespan than swine and horses) of the host populations.



Antigenic shift

In contrast to antigenic drift, antigenic shift refers to drastic changes in the antigenicity of the HA of circulating influenza A viruses; antigenic shift is associated with influenza A pandemics. The HA — and sometimes the NA — molecules of pandemic viruses are derived from antigenically diverse animal strains of influenza virus, which can be acquired by human influenza strains through reassortment. Viral reassortment is a more complex form of antigenic shift. It occurs when two viruses simultaneously infect the same animal. For example, pigs carry an endemic strain of influenza and can be infected with both human and avian influenza strains. The virus that caused the 2009 pandemic influenza (type A H1N1) is a quadruple reassortment virus. It contains genes from pigs normally found in Europe and Asia, avian–swine influenza genes, and human influenza genes.



Pandemic outbreaks are usually associated with the extinction of the previous circulating strains. However, in 1977, influenza A H1N1 viruses, not seen in humans since the 1957 influenza A H2N2 pandemic, started to co- circulate with influenza A H3N2 viruses. The 2009 influenza A H1N1 pandemic was caused by an influenza A H1N1 virus that was antigenically very different from the seasonal influenza A H1N1 virus circulating at the time and resulted in the extinction of the previous influenza A H1N1 human lineage, but it did not result in the extinction of the influenza A H3N2 viruses. Since 2009, influenza A H3N2 and influenza A H1N1 viruses derived from the 2009 pandemic virus and two lineages of influenza B virus are co-circulating in humans. Human influenza A virus infections with antigenically diverse avian H5N1, avian H7N9, swine H3N2 and other animal influenza viruses are constantly detected in geographical regions where these strains are prevalent owing to the contact of infected poultry or swine with humans.

However, no cases of sustained human- to-human transmission have been associated with these viruses, indicating that further adaptations need to take place for these viruses to become transmissible in humans.

Clinical Picture of avian influenza in Animals and Humans

In birds, fortunately, many avian influenza A viruses exhibit low pathogenicity, causing few signs of disease in infected wild birds. LPAI viruses are either asymptomatic or cause mild/subclinical disease (such as ruffled feathers and a drop in egg production) in chickens and poultry. However, these viruses are primed for continual emergence and pandemic potential, and some low-pathogenic viruses can mutate in poultry into highly pathogenic avian influenza viruses. HPAI viruses often cause severe disease and high mortality in infected poultry. HPAI A(H5) or A(H7) virus infections can cause disease that impacts multi-organ systems with mortality as high as 90-100% in chickens, often within 48 hours. HPAI A(H5N1) is one of the most contagious viruses occurring among birds, and the clinical outcome is typically deadly, especially in domestic poultry. However, ducks can be infected without any signs of illness. HPAI A(H5) and A(H7) virus infections in poultry can also spill back into wild birds, resulting in rapid geographic dissemination of the virus with bird migration. While some wild bird species can be infected with some HPAI A (H5) or A(H7) virus subtypes without appearing sick, other HPAI A(H5) and A(H7) virus subtypes can cause severe disease and mortality in some infected wild birds, as well as in infected poultry.

Table 1. Similarities and differences between seasonal and pandemic influenza.

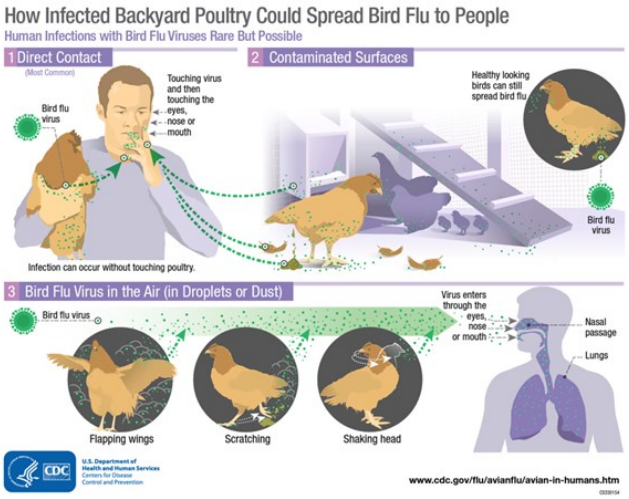
Seasonal influenza A and B	Pandemic influenza A
Occurrence	
Annual (in temperate regions)	Four true pandemics in last 100 years Shortest inter-pandemic interval 11 years, longest interval 39 years
Predictability	
Occurrence: predictable seasonality, but dominant antigenic type/subtypes vary Impact: difficult to predict until dominant type/subtype is known	Occurrence: difficult to predict when it will happen and what the subtype will be Impact: difficult to predict, although historical trend is for major impact, particularly for younger adults and children
Antigenic change	
Antigenic drift (subtle changes in existing HA/NA)	Antigenic shift (major change in HA/NA resulting in new virus and subtype)
Immunity	
Some naturally-acquired immunity is likely in adults, through previous infection and/or vaccination. Antigenic drift facilitates immune escape, leading to recurrent infections. Young unvaccinated children will lack immunity until infected or vaccinated	Specific antibody-mediated immunity is lacking and most of the population will not have significant cross-protective immunity from previous influenza infections The effect of T-cell mediated immunity is largely unknown but could potentially give some cross-reactive protection against severe disease (especially in the mucosa)
Risk groups for severe influenza	
Elderly persons, infants, those with certain underlying health conditions (asthma, COPD, heart disease), obesity, pregnancy	As for seasonal influenza, but there may be over-representation of younger adults and children, and otherwise healthy individuals. Spread depends on absent or low herd immunity
Impact	
Varies season-to-season WHO estimates between 3 and 5 million cases and 290,000 to 650,000 global annual deaths In wealthy countries, most deaths occur in those >65 years of age	Mortality varies between different pandemics and is difficult to predict in advance 1918 H1N1 pandemic believed to have caused at least 50 million deaths globally 2009 H1N1 pandemic is believed to have caused 250,000–500,000 deaths globally
Vaccines	
Readily available in many countries before influenza season begins. Annual vaccine recommendations made for Northern and Southern hemispheres, dependent on predictive algorithms and epidemiology. Recently vaccine effectiveness poor in H3N2-dominated years	Strategic preparedness in some countries for viruses with pandemic potential e.g., avian influenza viruses Pandemic influenza viruses arise from diverse sources and are unpredictable Likely lag-time between a pandemic commencing and vaccine being available lessens the probability that vaccines will have a major impact
Antivirals	
Predominantly neuraminidase inhibitors Other classes of antivirals are in development and may have additional impact alone or in combination	Sensitivity to existing antivirals cannot be guaranteed. Some countries stockpile existing antivirals as countermeasures, but demand may outstrip supply during a higher-impact pandemic. Resistant, highly transmissible pathogenic influenza variants could be devastating

When birds are infected with this virus, they shed bird flu virus through their saliva, mucous and feces. Human infections are likely caused by accidental inoculation of virus into a person's eyes, nose or mouth or via respiratory routes. Inhalation of virus occurs when the virus is in the air (in droplets or possibly dust) and a person breathes it in, or possibly when a person touches a fomite (contaminated object) that has virus on it then touches their mouth, eyes or nose. No human bird flu infections have been reported from proper handling of poultry meat or from eating properly cooked poultry or poultry products. Bird flu transmission from human–to-human is very rare, and when it has happened it has only spread to a few people. Human infections with bird flu viruses have ranged in severity from asymptomatic/mild illness to severe disease resulting in mortality. Despite there being a broad range of AI subtypes, fortunately, only a very select subset of these have been shown to infect humans with highly pathogenic consequences.

Asian lineage H7N9 and Asian lineage H5N1 viruses have been responsible for most human illness from bird flu viruses globally, including the most serious illnesses and illness with the highest mortality. The emergence of the avian-derived H7N9 strain infecting humans was first described in March 2013 in China's Yangtze River Delta. This viral subtype is of a particular concern, as unlike H5N1, which is highly pathogenic in chickens and humans, H7N9 typically presents as an LPAI in chickens, but causes a high mortality rate in humans (40%), similar to that seen for H5N1 infections. H7N9 is one of several LPAI viruses in the H7 family capable of human infections, with viral transmission usually only acquired through close contact with host species. However, for reasons that are still unclear, H7N9 has greater transmissibility and more severe disease outcomes in humans than any other H7 viruses. The reported signs and symptoms of this type of infection in humans range from asymptomatic to mild (e.g., conjunctivitis/red eye) or mild, flu-like (e.g., upper respiratory symptoms), to more severe (e.g., pneumonia requiring hospitalization). Fever (temperature of 100oF [37.8oC] or greater), cough, sore throat, congestion, achiness, headaches, fatigue and shortness of breath or difficulty breathing are common. Diarrhea, nausea, vomiting or seizures may be observed more rarely.

Conclusion

The emergence of avian influenza viruses is of major concern to the avian and human population. The lack of pre-existing antibody immunity and their ability to cause severe



disease through multiple host and viral mechanisms makes these viruses difficult to counter. Currently, these viruses are yet to effectively replicate and transmit between humans, however, experiments in ferrets show that only a few mutations are needed for H5N1 and H7N9 viruses to quickly adapt and become a major pandemic threat. Their ability to pass from birds to mammals commonly in contact with humans requires constant surveillance across all known bird reservoirs to limit the potential threat of an Avian influenza-derived pandemic. While H5N1 has been circulating among birds and poultry in various parts of the world for years, the latest outbreaks have sent warning signals to the scientific community, as the virus seems to be spreading to places previously unreached.

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INA-RESPOND Newsletter

STAY FIT DURING RAMADAN

By: Monica Surjanto

The month of Ramadan involves Muslims fasting for approximately 12-18 hours each day, abstaining from food and drink during daylight hours. Many people experience fatigue and weakness during their fasts and often require long naps during the day. Standing in prayer for extended periods can cause pain in the feet, knees, and lower back and make it difficult to concentrate. Research has shown that fasting for 30 consecutive days without exercise can lead to a decline in strength and fitness. Individuals who skip exercise during Ramadan after training for 11 months are at risk of setbacks in cardiovascular and resistance adaptations.[1] Therefore, it is important for Muslims to maintain their exercise routine and stay fit during Ramadan.

Benefits of Exercise During Ramadan Fasting[2]:

Increased Energy Levels

Exercising can increase energy levels by releasing natural hormones, such as endorphins, which

make you feel happier and relieve stress. During Ramadan, when there are so many goals to accomplish, it is crucial to focus on exercises that do not drain excessive energy. Instead, concentrate on movements that slow down each exercise and focus on building a strong foundation. Even a long walk can help, but it is important to ensure your heart rate rises to gain maximum benefits.

Improved Cognitive Function

It can be challenging to focus for long periods during Ramadan. Physical activity or exercise can enhance focus and help sharpen our minds.

Reduced Aches and Pains

Standing for extended periods and sitting on the floor in different positions can be difficult, especially for those who are not used to it. This can put a lot of stress on the lower back and knees. Most people experience pain in these areas due to a lack of strength and/or mobility. Regular strength and mobility training can prevent this pain.

Weight Loss

Combining fasting with exercise training can lead to effective fat mass and body weight loss.

When is the best time to exercise during Ramadan?[3,4]

It depends on personal preference, but there are advantages and disadvantages to consider for different times of the day.

1-2 hours before Iftar (the first meal to break the fast - at sunset)

- Advantages: You will be able to replenish nutrients and fluids soon after training, and there will be no disturbance to your sleep.
- Recommendation: Low to moderate cardiovascular load or resistance training sessions of relatively short duration. The duration of sessions should not exceed 60-75 minutes to avoid hypoglycemia due to excessive depletion of the fasting individual's muscle glycogen stores.
- Disadvantage: Minimal pre-exercise nutritional support.

In the evening (3 hours after Iftar)

- Advantage: The best option for maintaining acceptable hydration and nutrition levels throughout training.
- Recommendation: Avoid high-intensity/ long-duration sessions as they can negatively affect your sleep-wake cycle/sleep quality, resulting in sleep deprivation.
- Disadvantage: Usually different from the times of training and competitions in many sports.

2-3 hours after Sahur

- Advantage: You may have more energy after a pre-fast meal (Sahoor).
- Recommendation: If you train at this time, do it in a cool environment.
- Disadvantage: You may run the risk of dehydration as there will be no opportunity to refuel until breaking your fast at Iftar.

Tips for Physical Activity during Ramadan[5]

Plan and Prepare

Fasting during Ramadan requires making changes to your daily routine. It is important to plan and prepare ahead of time. It is also recommended to consult with your doctor if you need to adjust medication timings or embark on physical activity during fasting if you have any long-term health conditions.

Adjust Your Routine

Commitments such as prayer, work, and food preparation will need to be adjusted during the month of Ramadan. Try to set aside time to focus on physical activity and make it work around your schedule. It is essential to look after your health during Ramadan by having a balanced diet and staying active as your body adjusts to the new routine.

Make it Interesting

Choose an activity that you enjoy so that you are more likely to stick with it. Being active isn't just about going to the gym or playing a sport. There are many other ways to be active, such as housework and food preparation, which can also be counted as physical activity.

Be Patient

Ramadan is an excellent time to practice patience. Starting a new routine that improves your health and well-being can take time. Slowly increase your activity levels, and your fitness levels will increase accordingly.

Set Goals

Make each goal S.M.A.R.T (specific, measurable, achievable, realistic, time-based) or as detailed as possible. Instead of just saying, "I'm going to do more walking," be specific. Write down when and where you are going to walk, and how often you will walk, and measure it by time or distance.

Keep Track

An excellent way to stay motivated is to see your progress and activity levels increase. By keeping an activity diary, you can look back over previous months and compare how much you have improved.

Listen to Your Body

It is crucial to remember to listen to your body and rest or stop if you feel too tired or weak. People with long-term health conditions should take extra care while doing any form of physical activity during Ramadan.

Good Hydration

Good hydration is essential for our immune system. Drink at least 8-12 glasses of fluids (2 liters) daily between breaking your fast (Iftar) and the pre-dawn meal (Sahoor).

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INA-RESPOND Newsletter

ERROR ERROR IN THE WALL - PLEASE TAKE IT AWAY!

By: Aly Diana

COMIC CORNER

As a disclaimer, I would like to clarify that while I am not an expert in statistics, I am keen on learning and expanding my knowledge. Recently, a professor asked me about the adjustment of multiple comparisons, and my initial reaction was, "Oh noooooo, I totally forgot!" Therefore, I decided to share a brief reminder with all of you in the hope that it might be helpful.

The adjustment of multiple comparisons is a crucial step in many fields of research, such as genetics, medicine, and social sciences. Whenever multiple tests are conducted on a dataset, the risk of making at least one Type I error increases, leading to false discoveries. As a result, the adjustment of multiple comparisons is necessary to control the familywise error rate (FWER).

The FWER refers to the probability of making at least one Type I error across all the tests conducted. In other words, it is the likelihood of rejecting a true null hypothesis in at least one of the tests. For instance, if a researcher performs ten independent tests with a significance level of 0.05, the FWER is not 0.05 but rather 0.401. This implies that there is a 40.1% chance of making at least one Type I error in the ten tests.

To control the FWER, one of the most widely used methods is the Bonferroni correction. This method adjusts the significance level for each test based on the number of tests conducted. For example, if a researcher performs ten independent tests with a significance level of 0.05, the Bonferroni correction would adjust the significance level to 0.005 (0.05/10) for each test. This adjustment ensures that the overall probability of making at least one Type I error across all the tests is less than the desired level of significance.

Another widely used method is the Holm-Bonferroni method, which is more powerful than the Bonferroni correction. This method adjusts the significance level for each test in a stepwise manner, based on the tests' p-values. The tests are ranked from the most significant to the least significant, and the significance level is adjusted starting from the most significant test and proceeding to

the least significant test. The Holm-Bonferroni method is more powerful than the Bonferroni correction because it can detect smaller effects while still controlling the FWER.

There are other methods for controlling the FWER, such as the Sidak correction, the Benjamini-Hochberg (BH), and the Hochberg method. Each method has its strengths and weaknesses, and the choice of method depends on the specific research question and the data's characteristics.

In conclusion, controlling the FWER is a critical concept in multiple hypothesis testing. The risk of making at least one Type I error increases when conducting multiple tests on a dataset, which can lead to false discoveries. To control the FWER, researchers use various methods, including the Bonferroni correction, the Holm-Bonferroni method, and the Benjamini-Hochberg method. These methods adjust the significance level or p-value threshold to ensure that the overall probability of making at least one Type I error across all the tests is less than the desired level of significance. By controlling the FWER, researchers can ensure that their results are reliable and meaningful.

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INA-RESPOND Newsletter

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