INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

February 2022

From Our Partner

Today's Logistical Challenges in the World of International Clinical Research

Comic Corner

Xenotransplantation: Believe it or not?

Let's spread love not SARS CoV-2

Science Corner

Potential Zoonotic Bat-Borne Disease in Indonesia (part 2)

BADAN KEBIJAKAN PEMBANGUNAN KESEHATAN
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2022

INA-RESPOND
newsletter

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FEATURES

INA-RESPOND Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

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

STUDY UPDATES

INA102

After the site closure in November, the TRIPOD team is finalizing the study report for NIHRD. Meanwhile, 2 manuscripts from baseline data are still being reviewed by the TRIPOD team and the US team. We are analyzing clinical and laboratory data for the 3rd manuscript on clinical TB and preparing concept plans to utilize specimens for further sub-studies.

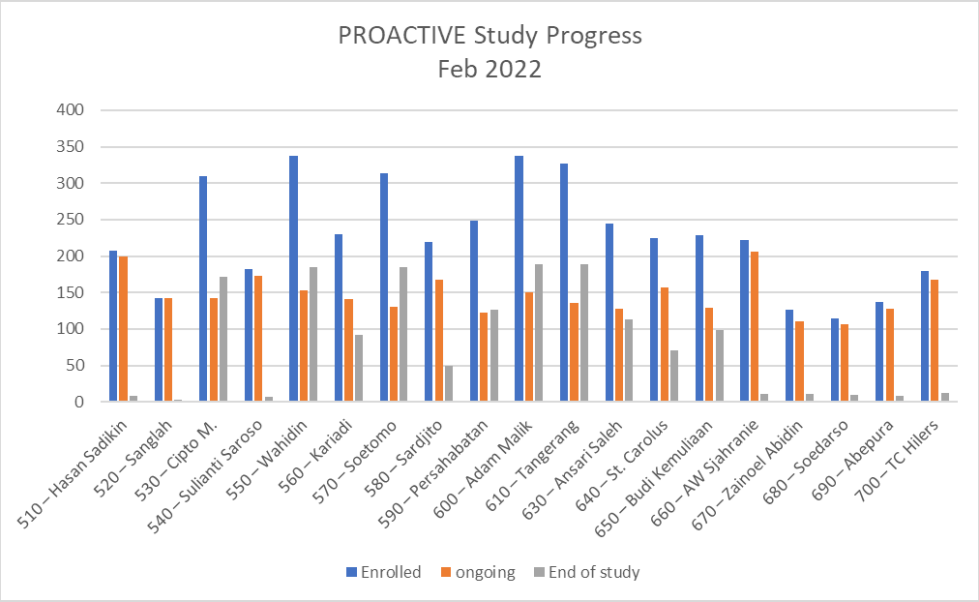
Other ongoing activities regarding TRIPOD are summarized below:

1. Fifty-Two isolates sent to BSL 3 Facility, Central Lab Padjajaran University, Bandung for sub-cultured have grown, 3 isolates did not grow. The 49 isolates were extracted (DNA) and 32 isolates were done (DST). The next 30 isolates for subculture are in process.
2. Collaboration within the RePORT network on Epidemiology of TB Progression and Outcomes Study, using the TRIPOD data
3. Manuscripts writing: TRIPOD 1st manuscript is in progress to be re-submitted to American Thoracic Society Journal, 2nd manuscript is being reviewed by the 1st author and will be circulated to the US author.
4. Data harmonization protocol with RePORT network has got ethical approval from the Universitas Indonesia's IRB, and both documents for the agreement between IRB and INA-RESPOND for RePORT study and the Bioethics Form have been signed by the director of INA-RESPOND and the staff from IRB
5. Working on TRIPOD sub-study, using specimens from baseline to diagnose histoplasmosis.
6. Inviting the network to submit the Ideas on TRIPOD specimens used. Per protocol, there are 8 types of specimens collected on TRIPOD study for future use. Status for Repository specimens is provided in figure 1.

Site	Specimen Type	Whole blood (EDTA) - DNA	Whole blood (Heparin) - PBMCs	Whole blood (Heparin) – Plasma	Whole blood (PAXgene) - RNA	Urine	Saliva	Sputum	MTB Isolate
520 (n=32)	BL (32)	90	22	91	27	125	62	19	36
	M1 (24)	NA	18	64	21	99	NA	16	12
	M2 (24)	NA	22	68	24	93	NA	11	0
	EOT (15)	NA	28	45	15	60	30	2	0
560 (n=108)	BL (108)	382	204	328	102	440	216	131	272
	M1 (95)	NA	188	285	94	381	NA	107	60
	M2 (87)	NA	172	261	86	348	NA	91	20
	EOT (73)	NA	142	219	73	292	146	75	20
570 (n=128)	BL (128)	438	177	380	121	519	254	119	196
	M1 (104)	NA	162	311	103	416	NA	43	92
	M2 (97)	NA	162	294	98	392	NA	22	38
	EOT (80)	NA	162	243	81	320	160	4	12
580 (n=83)	BL (83)	235	130	210	67	308	147	26	42
	M1 (44)	NA	70	102	38	156	NA	18	6
	M2 (38)	NA	54	81	36	148	NA	16	0
	EOT (29)	NA	50	71	27	124	61	8	0
590 (n=89)	BL (89)	340	170	255	84	344	147	78	55
	M1 (59)	NA	98	147	49	196	NA	17	8
	M2 (56)	NA	80	120	41	164	NA	8	0
	EOT (40)	NA	46	72	24	96	46	9	0
600 (n=25)	BL (25)	100	50	75	25	100	50	50	30
	M1 (13)	NA	26	39	13	52	NA	26	4
	M2 (11)	NA	22	33	11	44	NA	22	4
	EOT (9)	NA	20	30	10	40	20	20	0
550 (n=25)	BL (25)	95	48	72	24	100	51	10	27
	M1 (20)	NA	36	54	19	68	NA	7	7
	M2 (20)	NA	36	54	17	72	NA	6	4
	EOT (15)	NA	26	39	13	52	25	0	2

INA104

Per 8 Feb 2022, from 4,336 subjects enrolled, 36% of the subjects have ended their study and 64% of the subjects are still ongoing. The picture on the right shows the study progress from each site.



1,169 subjects already completed the study until follow up visit month 36, 216 subjects died, 90 subjects were lost to follow up, 30 subjects withdrew consent, 29 subjects moved to the city without PROACTIVE Site, five subjects were HIV negative, and one subject was suspended (imprisoned). The list of participants end of study status from each Site is shown in the table below:

No	Site	End of Study Duration	Withdrew Consent	Participants with HIV negative	Moved	Death	Investigator Discretion	Lost to Follow Up	Other	Total
1.	510 – RSUP Dr. Hasan Sadikin	1	1	0	2	4	0	0	0	8
2.	520 - RSUP Sanglah	1	0	0	0	2	0	0	0	3
3.	530 – RSUPN Dr. Cipto Mangunkusumo	149	0	0	0	17	0	5	0	171
4.	540 – RSPI Dr. Sulianti Saroso	0	0	0	2	5	0	0	0	7
5.	550 – RSUP Dr. Wahidin Sudirohusodo	129	0	0	5	19	0	32	0	185
6.	560 – RSUP Dr. Kariadi	72	1	3	0	12	0	4	0	92
7.	570 – RSUD Dr. Soetomo	143	13	0	3	21	0	5	0	185
8.	580 – RSUP Dr. Sardjito	36	0	0	3	4	0	7	0	50
9.	590 – RSUP Persahabatan	84	0	1	0	35	0	6	0	126
10.	600 – RSUP Dr. H. Adam Malik	145	3	0	2	20	0	19	0	189
11.	610 – RSU Kabupaten Tangerang	151	6	0	3	19	0	9	1	189
12.	630 – RSUD Dr. M. Ansari Saleh	101	1	0	1	7	0	3	0	113
13.	640 – RS St. Carolus	70	0	0	0	1	0	0	0	71
14.	650 – RSU Budi Kemuliaan Batam	82	3	0	5	8	0	0	0	98
15.	660 – RSU A. Wahab Sjahranie	5	0	0	2	4	0	0	0	11
16.	670 – RSUD Zainoel Abidin	0	0	0	0	11	0	0	0	11
17.	680 – RSUD Soedarso	0	0	0	0	10	0	0	0	10
18.	690 – RSUD Abepura	0	1	1	1	6	0	0	0	9
19.	700 – RSUD TC Hillers	0	1	0	0	11	0	0	0	12
Total		1169	30	5	29	216	0	90	1	1540

INA107 PARTICIPANT STATUS

Based on uploaded CRFs as of 7 February 2022, 160 participants were enrolled in the ORCHID-COVID-19 study, which consisted of 105 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 55 participants from site 521 (RS Universitas Udayana, Denpasar). There were 151 participants (95%) who had already completed this study, 4 participants passed away during the study, and one subject from site 610 died because of COVID-19, while three subjects from site 521 with the cause of death pulmonary thromboembolism, non-ST-segment Elevation Myocardial Infarction, and thromboembolism. On the other hand, 5 participants decided not to continue the study (categorized as other) (figure 1).

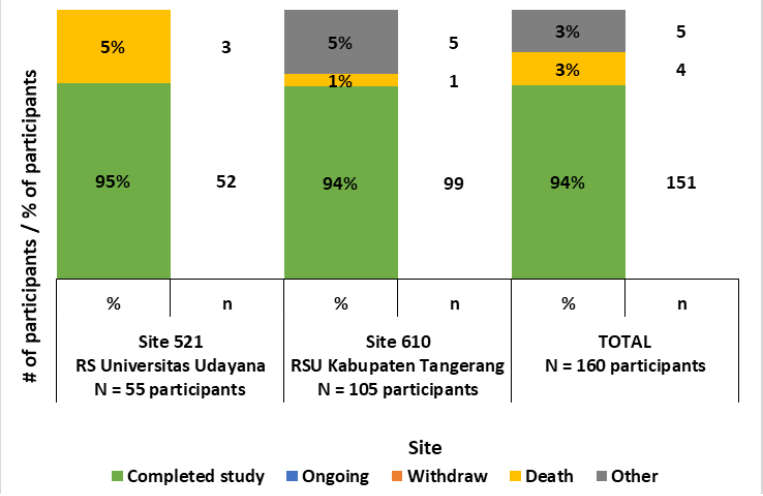


Figure 1. Participant status per site based on uploaded CRF as of 7 Feb 2022

Up to 7 February 2022, a total of 132 participants (82%) were identified as positive COVID-19, and only 28 participants (18%) identified as negative COVID-19. In site 610, the number of participants identified as positive COVID-19 was 95 participants (90%) and 10 participants (10%) as negative COVID-19. While in site 521, there were 37 participants (67%) identified as positive COVID-19, and 18 participants (33%) identified as negative COVID-19 (figure 2).

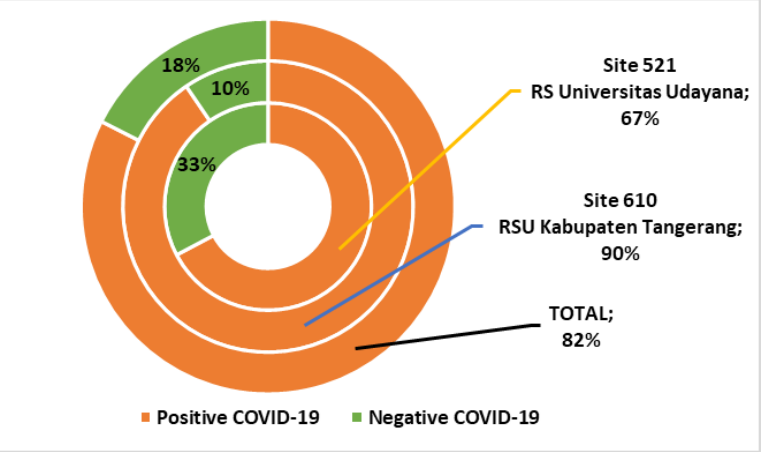


Figure 2. COVID-19 identification at enrolment based on uploaded CRF per 7 Feb 2022

In site 521, SARS-CoV-2 was identified in 32 participants (58%) based on pathogen identification data. SARS-CoV-2 and influenza B (confirmed by RDT Antigen Influenza) co-infections were identified in 5 participants (9%). Influenza B infection (confirmed by RDT Antigen Influenza) was identified in 2 participants (4%). Dengue (confirmed by RDT Dengue NS-1) was also identified in 2 participants (4%). While in site 610, SARS-CoV-2 was identified in 94 participants (90%). SARS-CoV-2 and dengue (confirmed by RDT Dengue NS-1) co-infection was identified in 1 participant (1%). Within 24 participants (15%), the pathogen cannot be identified, who were 14 participants in Site 521 and 10 participants in site 610 (figure 3).

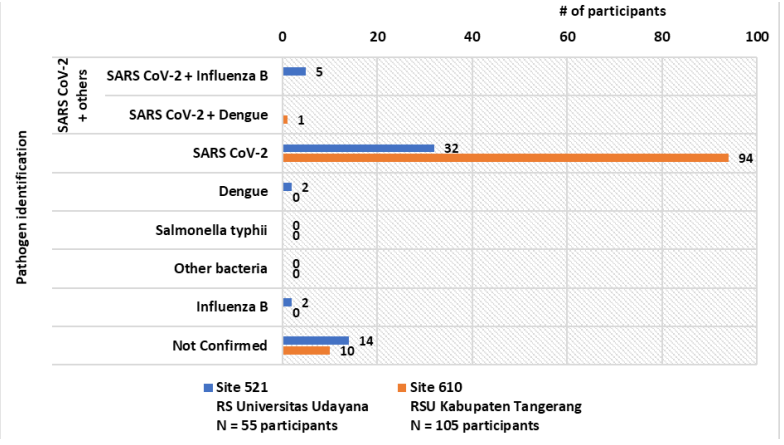


Figure 3. Pathogen identification based on uploaded CRF per 7 February 2022

INA-RESPOND Newsletter

SC PROFILE: DR. AARON NEAL & DR. ERLINA BURHAN

By: Aaron Neal, dr. Erlina Burhan, Putri Permata Sari

PROFILE

Dr. Aaron Neal

Aaron Neal, D.Phil., serves as a Clinical Research Specialist and the Indonesia Partnership Lead in the Division of Clinical Research of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health (NIH). He is an internationally trained infectious disease scientist working at the intersection of science, medicine, public health, and diplomacy. He is particularly interested in research study design, data analysis, and molecular laboratory applications.

Dr. Neal is a native of Huntsville, Alabama, and completed undergraduate studies at the University of Alabama at Birmingham, graduating with a B.S. in Molecular Biology and Honors in Science and Technology. While at UAB, he conducted research on blood-stage *Plasmodium falciparum* surface antigens in the laboratory of Julian Rayner, PhD. Dr. Neal's work included malaria immunogenicity field studies in the remote Peruvian Amazon, which ignited his interest in global health and infectious diseases as a career. He continued on to obtain a D.Phil. in Tropical Medicine from the University of Oxford through the NIH Oxford-Cambridge Scholars Program. Under the guidance of Rick Fairhurst, M.D., Ph.D., and Chris Newbold, Ph.D., Dr. Neal conducted research at NIAID and Oxford focused on understanding molecular mechanisms underlying blood-stage pathogenesis and antimalarial drug resistance in *P. falciparum*. Following a postdoctoral fellowship at NIAID and fieldwork in Cambodia and Mali, he transitioned to a Presidential Management Fellowship (PMF) appointment at NIAID. Dr. Neal served in various science management roles as a PMF, including as a Health Diplomat to Taiwan CDC in Taipei, before joining the NIAID Division of Clinical Research as an International Health Scientist in 2018. He initially provided scientific and laboratory support to NIAID government-to-government research partnerships in Mali, Guinea, and Indonesia before becoming the Indonesia Partnership Lead in 2020.

Currently, Dr. Neal leads the NIAID contribution to INA-RESPOND and represents NIAID on the Network Steering Committee. He works closely with the Secretariat and Reference Lab on all matters affecting the Network and its research. Since his first visit to Indonesia in February 2017, Dr. Neal has been excited to work with the dedicated members of INA-RESPOND on significant disease threats. He has contributed to the Network's research since the end of the AFIRE study, and he continues to enthusiastically support its important research and capacity-building activities. Dr. Neal believes that increasing international scientific cooperation and enhancing research capacity globally are critical to protecting all of us from infectious disease threats. He is thankful to be a part of INA-RESPOND and its work to fulfill these goals, and he looks forward to the Network becoming the premiere research organization in the region.

DR. dr. Erlina Burhan, Sp. P(K), MSc is one of the NSC members of the INA-RESPOND network. She was born in Padang on May 15, 1966. She completed her general medical education (dr.) at Andalas University, Padang, in 1989, then continued her education at Sheidelberg University, Germany, and earned a master of science degree (M.Sc.) in 1995. She obtained a pulmonary specialist (Sp.P) degree from Universitas Indonesia, Jakarta, in 2004. Since she graduated as a pulmonary specialist, she has been a lecturer at the Faculty of Medicine, Universitas Indonesia (2005 until now). Her dedication as an educator led her to a consultant degree (Sp. P(K)) in the field of lung infections in 2010. Two years later, in 2012, she managed to get a Doctorate (DR) degree from Universitas Indonesia.

As a lecturer, Dr. Erlina is very famous and friendly. She is thrilled to share her knowledge and loves encouraging her students to be better doctors. She is also not reluctant to involve her students in scientific activities and introduces her students to famous people and experts in various sciences. She still serves as the head of Infection Division Department of Pulmonology and Respiratory Medicine Faculty of Medicine Universitas Indonesia (DPRM-FMUI). Apart from being a lecturer, she is also actively involved in various research and has produced many scientific writings, both nationally and internationally.

She is also active in scientific activities and professional organizations. She has joined various organizations such as the Coalition of Professional Organizations (KOPI)-TB as head of professionals, has served as chairman of the TB Assembly on Asia-Pacific Society of Respirology (APSR) since 2017 until now, member of the Board Director of the International Union of Tuberculosis and Lung Disease (IUTLD), and a member of the guideline development group of the World Health Organization (WHO), which is a council of international experts for the preparation of the WHO guidebook and together with ATS (American Thoracic Society) to make international standard guidelines for TB care (ISTC).

The COVID-19 pandemic is closely related to her expertise in pulmonary infection disease. She is very active in providing education and information to the public regarding the development of COVID-19 through various social media such as television, radio, etc. As an expert on COVID-19,

DR. dr. Erlina Burhan, Sp. P(K), MSc

she is one of the most frequently asked for opinions. She provides education to the public and is actively involved in providing views on government policies. She also conducts research on COVID-19, both clinical trials and non-trials. As an appreciation for her contribution in handling COVID-19, she received various awards. One of them, she got Tokoh Perubahan Republika 2020, which was given directly by the Minister of Health Budi Gunadi Sadikin.

As one of the network's Steering Committee members and PIs, Dr. Erlina realizes that every doctor should be active in medical services, actively contribute to research, and produce valuable manuscripts for science. This message is consistently conveyed to all research assistants as she involves pre and post-internship doctors in conducting good clinical practice. She formed SATURATE forum (Respiratory & Tuberculosis Research & Training Centre), joined by more than 20 research assistants in RSUP Persahabatan to promote and facilitate research. Dr. Erlina hopes that INA-RESPOND will continue to support research in Indonesia and encourage doctors to involve and produce quality research that is beneficial for all.

INA-RESPOND Newsletter

SCIENCE CORNER

POTENTIAL ZOONOTIC BAT-BORNE DISEASE IN INDONESIA (PART 2)

By: Yan Mardian

As an archipelago, Indonesia's seas and oceans, in theory, may have historically. Globalization and resulting changes in human activities, including wildlife trade, are increasing across and beyond the country, heightening the risk of cross-species transmission and the spread of pathogens. In addition, the potential for diseases to "spill-back" into animals from humans also enables greater potential pathogen spread and poses concerns for biodiversity conservation (1–5).

Given Indonesia's abundant biodiversity of natural reservoir hosts for viruses (e.g., non-human primates, rodents, and bats), high tropical deforestation rates, wildlife trade and hunting networks, and growing human population, the risk for zoonotic disease emergence is high. These rapid ecological changes are bringing humans into close contact with wildlife species that were previously rarely seen (6). It is probable that those factors may increase the risk for zoonotic disease emergence, and therefore the country should become a hotspot in targeting surveillance to identify spillover events.

In the last edition, we have explained the potential presence of coronavirus circulating in Indonesia, which may have spilled over into human populations several times within the region but are either not reported or otherwise missed by clinical surveillance (17). This edition will focus on other virus families that can also be a threat to become zoonotic outbreaks in Indonesia.

Filovirus

To date, 12 distinct filoviruses have been described. The seven filoviruses that have been found in humans belong either to the genus Ebolavirus (Bundibugyo virus (BDBV), Ebola virus (EBOV), Reston virus (RESTV), Sudan virus (SUDV) and Taï Forest virus (TAFV) or to the genus Marburgvirus (Marburg virus (MARV) and Ravn virus (RAVV)). Among the filoviruses family, the filoviruses Ebola virus (EBOV) and Marburg virus (MARV) are defined as category A pathogens by the NIH (https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens) and the Centers for Disease Control and Prevention (CDC; https://emergency.cdc.gov/agent/agentlist-category.asp). There were two major EBOV outbreaks in the last decade. The 2013–2016 epidemic was primarily in West African countries, infecting ~30,000 individuals with a mortality rate of 40%. There was a second large outbreak in the Democratic Republic of the Congo from 2018 to 2020, with around 3,500 infections and a mortality rate of 65%. Until 2020, ~33,604 EBOV infections in humans, including 14,742 deaths (average CFR 43.8%) are on record. Bats are the primary reservoir for EBOV, and the virus can transmit either directly to humans or through intermediate zoonotic hosts. It is thought that fruit bats of the Pteropodidae family are natural EBOV hosts. Once in the human population, EBOV can spread through blood and bodily fluids or sexual transmission (7).

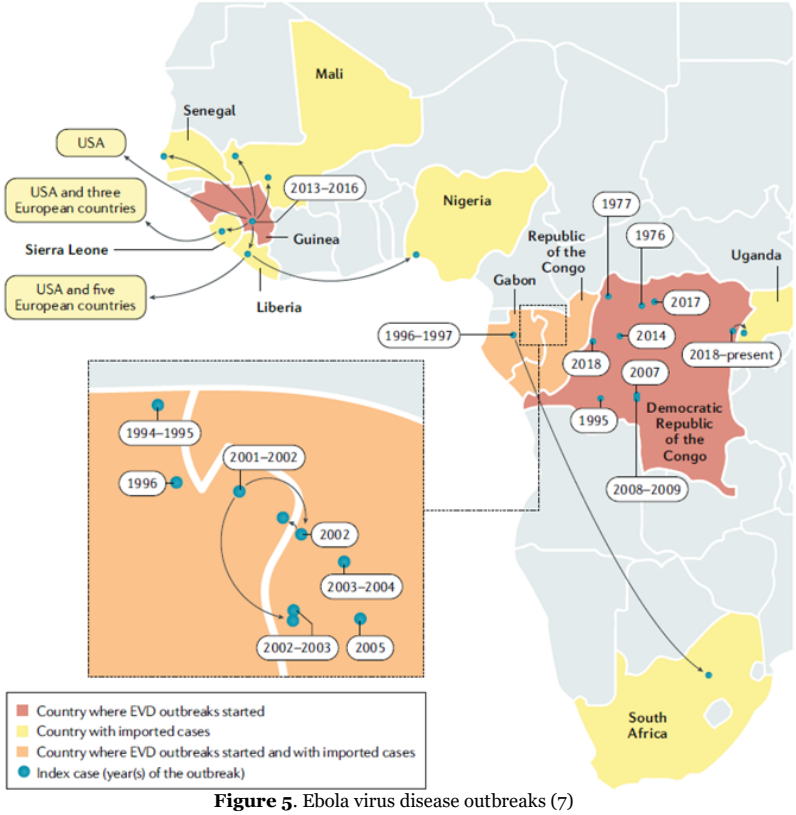


Figure 5. Ebola virus disease outbreaks (7)

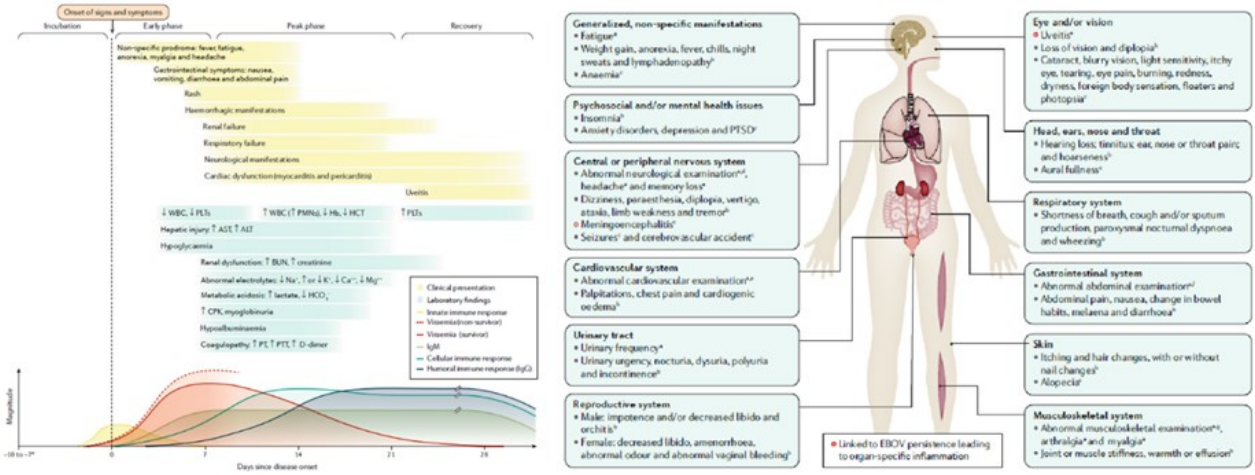


Figure 6. Ebola virus disease clinical course and presentation (7)

It can be difficult to clinically distinguish EVD from other infectious diseases such as malaria, typhoid fever and meningitis. Ebola is vastly less contagious (compared to SARS), evidence to date suggests that transmission of Ebola occurs only through direct contact with bodily fluids, and furthermore, only after an individual has become symptomatic. EVD has a high case–fatality rate (about 50%); it is characterized by fever, gastrointestinal signs and multiple organ dysfunction syndrome (7).

Despite the discovery of EBOV (Reston virus) in nonhuman primates and domestic pigs in the Philippines and the serological evidence for its infection of humans and fruit bats, information on the reservoirs and potential amplifying hosts for filoviruses in Asia is lacking. In a study, serum samples collected from 353 healthy Bornean orangutans (Pongo pygmaeus) in Kalimantan Island, Indonesia, during the period from December 2005 to December 2006 were screened for filovirus-specific IgG antibodies using a highly sensitive enzyme-linked immunosorbent assay (ELISA) with recombinant viral surface glycoprotein (GP) antigens derived from multiple species of filoviruses (5 EBOV and 1 MARV species). They showed that 18.4% (65/353) and 1.7% (6/353) of the samples were seropositive for EBOV and MARV, respectively, with little cross-reactivity among EBOV and MARV antigens. In these positive samples, IgG antibodies to viral internal proteins were also detected by immunoblotting. Interestingly, while the specificity for Reston virus, which has been recognized as an Asian filovirus, was the highest in only 1.4% (5/353) of the serum samples, the majority of EBOV-positive sera showed specificity to Zaire, Sudan, Cote d'Ivoire, or Bundibugyo viruses, all of which have been found so far only in Africa. These results suggest the existence of multiple species of filoviruses or unknown filovirus-related viruses in Indonesia, some of which are serologically similar to African EBOVs, and transmission of the viruses from yet unidentified reservoir hosts into the orangutan populations (8). These findings point to the need for risk assessment and continued surveillance of filovirus infection of human and nonhuman primates, as well as wild and domestic animals, in Asia.

Henipavirus

In henipaviruses, a genus in the family Paramyxoviridae, >350 human fatalities from Hendra (HeV) or Nipah virus (NiV) disease outbreaks have been reported. Nipah Virus (NiV) was discovered in 1998 during the first reported outbreak in the Sungai Nipah village in Malaysia. During that initial outbreak, 283 human cases of acute encephalitis were diagnosed (mainly in farmers), with 109 deaths. Clinical features of NiV disease include acute respiratory distress and severe encephalitic symptoms, including seizures, convulsions, and coma. The onset of disease is very abrupt, and the course of the severe phase is very brief. Since that first outbreak, no other outbreaks of NiV disease have been detected in Malaysia. However, 2 years later, NiV was detected in both Bangladesh and India. Since 2001, sporadic outbreaks have occurred in Bangladesh almost every year, mainly detected retrospectively by the established countrywide encephalitis surveillance program. NiV encephalitis is still a rare disease, involving <5% of the total number of reported encephalitis cases investigated in Bangladesh. NiV is a single-stranded, negative-sense RNA virus of approximately 18.2 kb long, belonging to the family Paramyxoviridae. NiV can be transmitted to humans from animals (such as bats or pigs), or contaminated foods and can also be transmitted directly from human-to-human. The animal host reservoir for NiV is the fruit bat (genus Pteropus), also known as the flying fox (9–11).

Sequence analyses of the viral genomes from the Malaysian and Bangladesh/India outbreaks showed that NiV separates into 2 distinct lineages/genotypes: Nipah-Malaysia (NiV-M) and Nipah-Bangladesh (NiV-B). In addition to differences in genetics and geographic distribution, the viral lineages differ in several other important ways. First, while infected pigs acted as the intermediate host for NiV-M, no intermediate host has been identified for NiV-B. In contrast to NiV-M, the primary source of NiV-B human infections is the consumption of raw date palm sap contaminated by virus shed by infected fruit bats. Human-to-human transmission was not clearly observed during the NiV

-M outbreak but was well documented in a number of NiV-B outbreaks. In addition, case-fatality rates for NiV-B outbreaks have been much higher (range, 60%–100%) than those caused by NiV-M (39%). However, differences in mortality rates may be attributable to differences in healthcare support in the different countries and the fact that Bangladeshi outbreaks are usually identified retrospectively. Finally, in addition to the encephalitic symptoms seen during NiV-M infection, acute respiratory distress symptoms are also seen in cases of NiV-B infection (9–11).

Compared to other viruses, research on the Nipah virus has been limited in Indonesia because attributable disease outbreaks have not been reported. One study reported the detection of Nipah virus genome in in P. vampyrus in Sumatera, Indonesia, between 25 and 29 May, 2009, using real time PCR. A total of 215 samples (71 oro-pharangeal swabs, 71 blood samples, 32 pooled urine samples and 41 urinary bladder samples) were collected from 71 P. vampyrus flying-foxes from two locations (Kota Medan and Deli Serdang Kampung) in the Indonesian province of North Sumatera. Four samples yielded Nipah virus genome - an oro-pharangeal swab and a bladder sample from DS 21 (an adult female), and two pooled urine samples containing urine from DS 21. Virus isolation was not undertaken. Nipah virus is categorized as a BSL 4 agent, and Indonesia does not currently have a laboratory with BSL4 facilities. Realtime PCR and RT- PCR represent a practical and robust alternative to detect Nipah virus from field samples in this situation. Their analyses showed that the Indonesian and Malaysian nucleotide sequences were more closely aligned that sequences with each other than they were with the Bangladesh or Indian sequences (12). This is not unexpected given the demonstrated movement of flying-foxes between peninsular Malaysia and Sumatera across a sea distance of less than 50 km. Other study identified unique paramyxovirus sequence from three species of fruit bats (Pteropus vampyrus, Pteropus hypomelanus and Acerodon celebensis). Fruit bats were captured in:

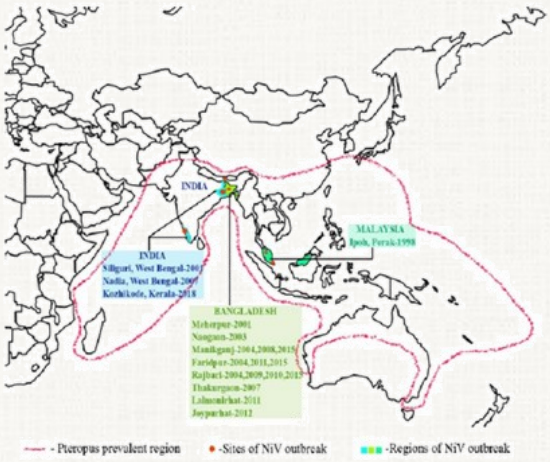


Figure 2. Map of NiV outbreaks and Pteropus fruit bats distribution. In the map, the sites of NiV outbreaks in India, Bangladesh and Malaysia are depicted in different colors. Pteropus bat (the major carriers of NiV) prevalent regions are demarcated by red-dotted line.

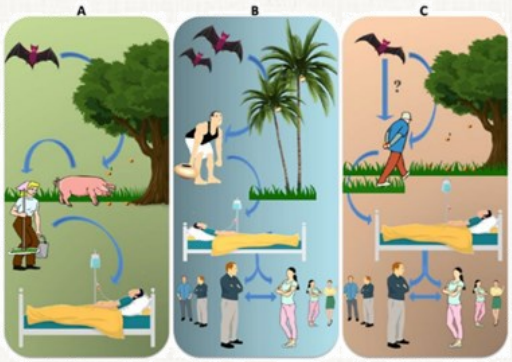


Figure 3. Routes of NiV transmission. Different locations have different routes of transmission. (A) In Malaysia, bat bitten fruits contaminated with NiV-M were consumed by pigs and workers handling the pigs were infected with NiV-M. (B) In Bangladesh, bat saliva- and excreta-contaminated palm sap consumption lead to NiV-B infection in humans and was spread further via nosocomial mode. Infected bats shed the virus in their urine, excreta and saliva. (C) In India, the possibility of direct bat-to-human transmission has been reported in Kerala state, but this was not supported by adequate evidence. Nosocomial spread of NiV-B have been reported in two different states—Kerala and West Bengal.

TABLE 1 Epidemiological and clinical features and outcomes in Nipah virus infections[a]

	Region	
Feature or outcome	**Malaysia-Singapore**	**Bangladesh-India**
Age and occupation	Mainly adult pig farm workers	Adults, children, and health care workers
Spread	Bat-to-pig, pig-to-human	Direct bat-to-human infection by consumption of date palm juice and fruits contaminated by bats; possibility of bat-to-domestic animal-to-human spread
Transmission	Human-to-human occasional	Human-to-human spread
Respiratory involvement	Malaysian cases (14–29%); 2 out of 11 patients in Singapore had pneumonia without encephalitis	Cough (62%) and respiratory difficulty (69%); chest radiographs with acute respiratory distress syndrome in some patients
Encephalitis	Segmental myoclonus seen in 32–54% of cases	Segmental myoclonus not reported
MRI	Disseminated small, high-signal-intensity lesion hallmark of MRI	Confluent high-signal brain lesion in limited MRI
Relapsed and late-onset encephalitis	About 5–10%	Delayed-onset neurological abnormalities in 4 out of 22 patients in a follow-up study
Persistent neurological deficits	About 20%	About 30%
Mortality	32–41%	70%

[a]Adapted from Sherrini and Tan (6).

Figure 7. Epidemiological and clinical features and outcomes in Nipah virus infections (9,11).

Panjalu District, West Java Province during February, 2010 (n = 26); Lima Puluh Kota District, West Sumatra Province during February, 2011 (n = 20). Their findings are potentially representing three new henipaviruses and two new rubulaviruses among fruit bat populations in Indonesia (13).

Other studies have demonstrated anti-Nipah virus antibodies in flying-foxes in Indonesia. One study nonrandomly sampled 106 P. vampyrus bats from market sellers on the Indonesian islands of Java and Sumatra during a 12-day period from July 23 to August 3, 2002. Serum samples from 32 bats neutralized NiV (median titer 20, range 5–160), samples from 52 bats did not, and samples from 20 bats caused toxic reactions in the cell sheet at dilutions <10 (n = 7), <20 (n = 9), or <40 (n = 4), precluding a definitive test outcome. The detection of antibodies that neutralized NiV at all 3 sampling locations indicates that infection with NiV (or a cross-neutralizing virus other than HeV) is widespread in P. vampyrus in Sumatra and Java. These findings, in conjunction with earlier findings in peninsular Malaysia, suggest that NiV infection is likely to be found in P. vampyrus across its entire range (14). Other group conducted study of farmer interviews and a serologic survey of 610 pig sera and 99 bat sera from West Kalimantan province. Farmers reported no recent or historic encephalitic or respiratory disease in themselves, their families, workers or pigs. The survey found no evidence of exposure to Nipah virus in pigs. However, serological evidence Nipah virus was detected in 19% of the 84 Large Flying-foxes (Pteropus vampyrus) from West Kalimantan, Borneo. Another study provides evidence for the presence of NiV east of Wallace's Line in East Timor (Sulawesi, Sumba or New Guinea) (15). This study, in combination with the serological evidence of henipavirus infection in P. vampyrus from Sumatra, Java and Borneo has shown that henipaviruses occur in fruit bats widely across the Sunda Shelf, Wallacea and New Guinea (16).

NiV emerged as a new virus exactly 20 years ago, causing severe morbidity and mortality in both humans and animals and destroyed the pig-farming industry in Malaysia, and it continues to cause outbreaks in Bangladesh and India (11). However, serology survey data on evidence NiV exposure to Indonesian people were scarce, although the moderate endemic of NiV in P. vampyrus in Indonesia had been shown by several above studies. As the reservoir host Pteropus bat is widespread, and NiV has been found in bats in various countries, the potential for outbreaks to occur in new regions remains significant (17). Ongoing surveillance is required to detect indicative changes in infection dynamics in fruit bats or the early introduction of infection to the pig and human population.

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INA-RESPOND Newsletter

TODAY'S LOGISTICAL CHALLENGES IN THE WORLD OF INTERNATIONAL CLINICAL RESEARCH

By: Allison Eyler, Jen Sandrus, and Elfrida Cline-Cole, Frederick National Laboratory for Cancer Research

FROM OUR PARTNER

Managing the procurement and shipping logistics for international clinical research is no easy feat these days as the COVID-19 pandemic and tumultuous political climates have brought logistical support to a whole new level. The pandemic has caused worldwide delays in sourcing and shipping, as well as labor shortages that have trickled down to commerce sectors. The Frederick National Laboratory has supported international clinical research for the National Institute of Allergy and Infectious Diseases (NIAID) for many years, and though working through these more recent challenges has not been easy, it has taught us to be more organized, flexible, innovative, efficient, and collaborative. The following examples detail logistical challenges we have encountered over the past few years and our responses to them.

Once a clinical research team determines study supply needs, they share this information with the administrative support team for procurement. Personal protective equipment (PPE) encompasses many items on such clinical research supply lists and, as we well know, is also needed to protect health care workers and the general population. The additional demand for items like gloves, masks, and lab coats has made sourcing these materials difficult for international clinical research sites. Specific brands or materials from usual sources are often unavailable or must be backordered, causing administrative teams to spend a significant amount of time searching for alternative suppliers and products that are of similar quality and price. Federal Emergency Management Agency regulations on supplying these types of items to international sites when there were critical shortages in the United States also had to be followed, while still meeting the requirements of our international research study protocols. These shortages were not just in PPE, but also encompassed general laboratory, office, and industrial supplies. A pipette tip or laptop that used to arrive within a few days of placing an order now takes months. To assist administrative teams in navigating these supply chain issues, the Frederick National Laboratory purchasing department has dedicated staff who will reach out to reliable vendors to help source hard-to-find items as quickly as possible. Study teams have also worked with in-country staff to find local suppliers for items that cannot be sourced from the United States.

Once supplies have been procured and prepared for shipping, other types of challenges arise. The Mali University Clinical Research Center (UCRC) project at the University of Bamako has dealt with such challenges. Before the pandemic, most shipments to Mali UCRC were sent via Cargolux, a cargo-only airline that provided affordable weekly flights into Bamako. Cargolux

was the ideal carrier for sending items classified as dangerous goods such as laptops, equipment containing lithium batteries, or certain biologicals and chemicals. Shortly after the pandemic began, Cargolux suspended all flights into Bamako and has not (and may never) resume these flights. Many shipments are now sent via passenger aircraft, which must comply with different volume and dangerous good regulations than cargo-only aircraft and have a higher risk of being delayed during a layover.

Another challenge arose when a frequently used passenger airline halted flights into Mali due to political sanctions that caused border closures. Once again, this created the need to exercise flexibility and collaborate with other project teams and government colleagues to find alternatives. Long-standing relationships with reliable international freight forwarders have been instrumental during these types of challenges.

We have relied on freight forwarders even more since in-person travel has not been an option for the past two years. It used to be common to send a replacement laptop, a part to repair lab equipment, or even reagents or test kits in a traveler's luggage or carry on when Frederick National Laboratory, NIAID, and subcontractor staff were regularly traveling to international clinical research sites. The halt in travel has had quite an impact on many aspects of procurement.

The key when dealing with international logistics is strong lines of communication. United States staff faces a time difference of anywhere from 4–12 hours at various international sites, so flexibility and creativity are imperative when it comes to planning Zoom or Microsoft Teams meetings. The time difference also can mean delayed responses to and from our colleagues and international vendors, so simple tasks take longer than normal.

Another logistical challenge resulting from the pandemic is inventory management. In many cases, the supply cycle has broken because of the other challenges previously mentioned. Order lists are created using an Excel formula based on current inventory and minimum stock quantities. When physical inventory is completed and an order list is compiled, order quantities may be inaccurate if previously purchased supplies are still on backorder or awaiting shipment, resulting in more time spent following up on outstanding procurements and making adjustments.

The increase and fluctuation of costs between procuring goods or services and managing shipping logistics has created the need for more innovation, efficiency, and communication among all stakeholders than ever before. Nevertheless, resilient and dedicated staff members continue to provide the best support possible to valuable international partners so that important clinical research can move forward.

Pallets of supplies have different size requirements depending on the carrier.

Equipment over a certain height, such as low-temperature freezers, may need to ship on a cargo-only carrier, which can be hard to find and may result in equipment or supplies spending weeks in transit.

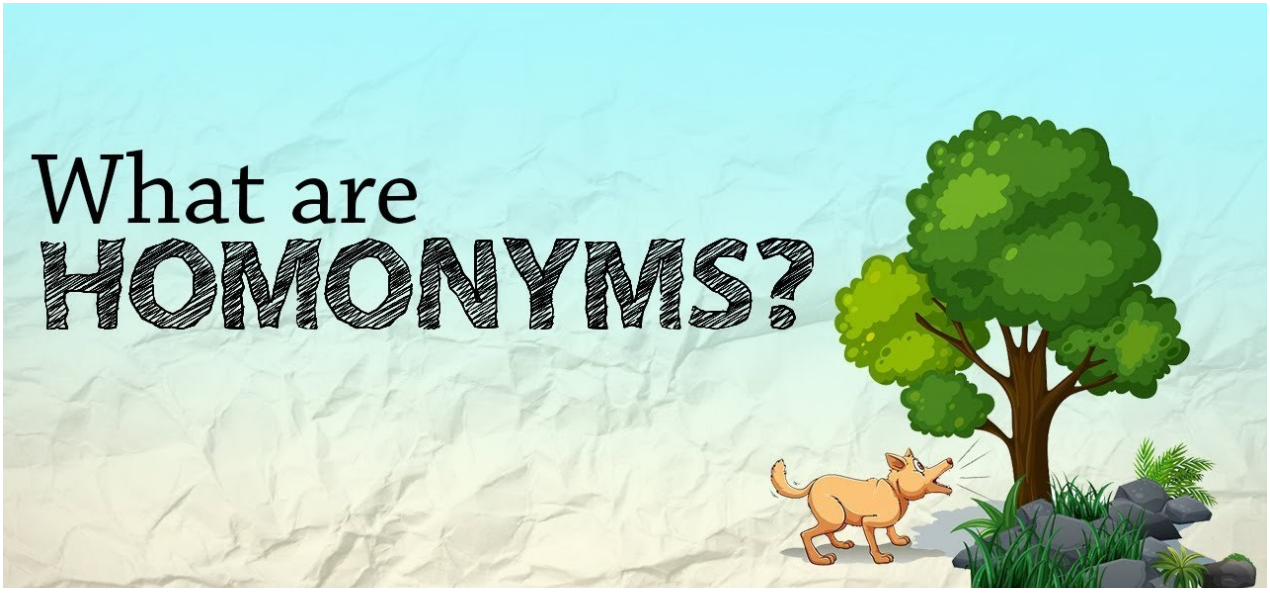
A supply storage room at the Mali University Clinical Research Center.

INA-RESPOND Newsletter

LANGUAGE

DIFFERENTIATING YOU'RE/YOUR, THEY'RE/THEIR/THERE, WHO'S/WHOSE, AND UNDERSTANDING HOMONYMS

By: Amelia Ghani



When we read articles, posts, or literary works in English, we would encounter people misusing the words you're, your, they're, their, there, who's, and whose. These words are called homophones or homonyms: words that sound like other words, but have different meanings or spellings – and they can be tricky. One example that the writer would encounter a lot is the usage of the word 'your' when they meant to say 'you're' or vice versa. This is one of the most common errors in writing articles, posts, or literary works in English, especially if English happens to be your second language, and these errors would create confusion for those who do not speak English fluently. This could also be a typo, but it still would make the readers confused. But those who speak English fluently would be able to notice the errors, especially if the errors are in written form. So, in this article, we would like to explain more how these words should be used and their meanings.

You're vs your

'You're' is a contraction of 'you are', while 'your' indicates possession and defines that something belongs to you.

Examples of mistakes:

Your running late!

CORRECTION: You're running late!

Can I have you're documents submitted to my e-mail?

CORRECTION: Can I have your documents submitted to my e-mail?

Explain how your feeling.

CORRECTION: Explain how you're feeling.

Here is you're book.

CORRECTION: Here is your book.

They're vs their vs there

The same case as you're/your, 'they're' is a contraction of 'they are'. It is used to describe a group of objects while 'their' indicates a possession. Meanwhile, in a more abstract sense, 'there' is about location. It can be used as the first word in sentences that have the subject after the verb and it can also be used with the verb 'be' at the beginning of sentences and questions. ("How to Use They're, There, and Their," n.d.)

Examples of mistakes:

Their working too hard.

CORRECTION: They're working too hard.

They're papers are being examined.

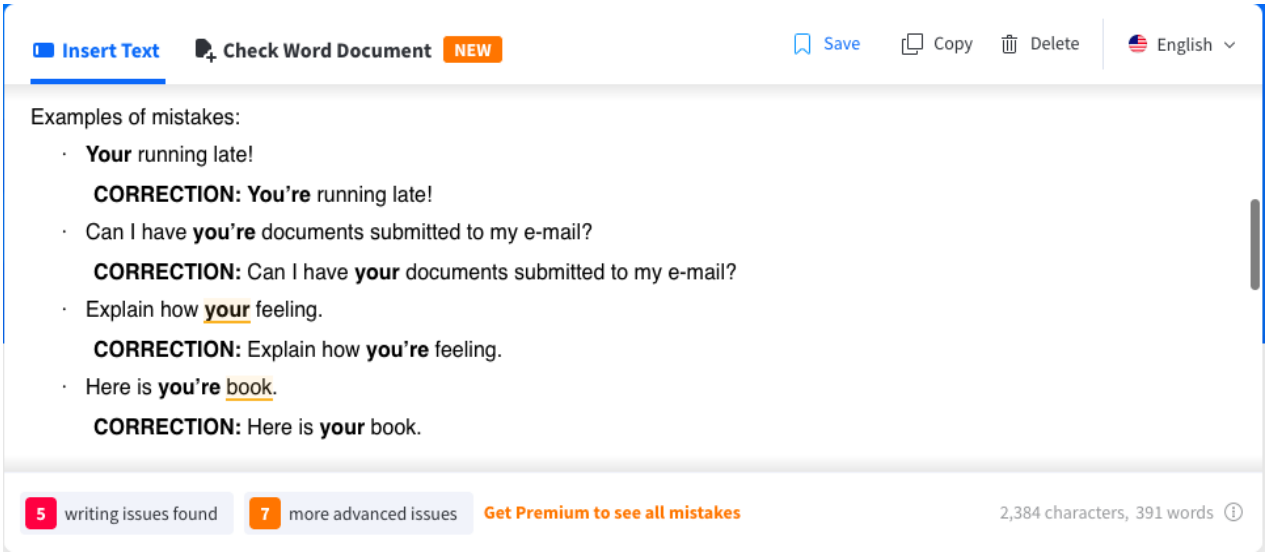


Figure 1 Proof that grammar checkers are not reliable enough in detecting the "you're/your" error. Here, the grammar checker does not detect the first two examples. This is a screenshot of LanguageTool (languagetool.org)

CORRECTION: Their papers are being examined.

Their conducting research on COVID-19 vaccines.

CORRECTION: They're conducting research on COVID-19 vaccines.

They're symptoms were so severe that they had to be hospitalized.

CORRECTION: Their symptoms were so severe that they had to be hospitalized.

Are their other things you'd like to say?

CORRECTION: Are there other things you'd like to say?

Who's vs whose

'Who's' is a contraction of 'who is' or 'who has' while 'whose' is the possessive case of 'who'.

Examples of mistakes:

Who's laptop is this?

CORRECTION: Whose laptop is this?

Whose gotten vaccinated?

CORRECTION: Who's gotten vaccinated? (Who has)

He is the doctor who's wife works as a nurse at the new hospital.

CORRECTION: He is the doctor whose wife works as a nurse at the new hospital.

Whose going to conduct the research?

CORRECTION: Who's going to conduct the research? (Who is)

Based on the explanations and examples above, we would also like to explain further the meaning of contraction. A contraction is a shortened form of two or more words where the omitted letter/letters is/are replaced by an apostrophe ("Whose vs Who's," 2017).

So, how to prevent these errors from happening? Honestly, we would recommend using grammar checker apps or websites such as Grammarly or LanguageTool after you have done writing your works, but we also should not rely on them because based on the writer's experience, they would sometimes be unable to detect the errors (see Figure 1). So, how to really prevent these errors from happening? The best and easiest way to do it is by rechecking your works carefully, or maybe you can ask someone who is more of an expert in English to help proofread them for you.

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INA-RESPOND Newsletter

VIRTUAL EXERCISE IN COVID-19 PANDEMIC

By: Septia Mandala Putra

Source: https://www.tech-critter.com

Decreased physical activity and exercise and increased psycho-physical stress are associated with excessive weight gain in the COVID-19 pandemic. Recently, it has been highlighted that a healthy lifestyle is an effective strategy to improve health and reduce the incidence of non-communicable diseases (NCDs), like type 2 diabetes or cardiovascular diseases.1 The protective effect of physical exercise against NCDs depends on the dose, and in this sense, the World Health Organization (WHO) proposes general recommendations for the promotion of physical activity (PA) worldwide in 2020 to prevent NCDs.2

Given that many are experiencing stressful life challenges under the COVID-19 pandemic crisis, it is imperative to develop innovative and effective PA intervention programs that reduce stress and promote health and wellbeing.

Interventions based on physical exercise through digital platforms have been shown to be appropriate to reach the PA recommendations of the WHO in some populations. Another advantage of virtual interventions is that they have lower costs, greater time flexibility, and higher time savings by not having to travel, compared to face-to-face interventions, favoring adherence.3

One intervention strategy which has shown promise for promoting healthy aging is VR-integrated exercise. Virtual Reality (VR) exercise is a novel and innovative technology, which immerses individuals in a computer-generated, multi-sensory, three-dimensional world where they interact with the virtual environment using either a headset and/or exercise equipment.4

VR has also been shown to be effective in exercise promotion, which led to multiple health benefits, including reduced obesity and anxiety, as well as improved cognition.5 Virtual exercise using website/application seems easy to use and most people tend to use it regarding buy/rent VR devices. People found that virtual training, be that online classes or video tutorials, allowed them to learn new exercises and perform movements safely.

Some examples of interactive health home fitness apps that require home fitness equipment include Mirror, Zwift, Tonal, Peloton, iFit, and Nordic Track, each of which has different membership and pricing structures. These interactive platforms use real-time personalized health data to encourage users to take a more active interest in their own health; but, just as importantly, they provide a social connection with friends and other users of the platform, which can make these types of exercise modalities enticing for those who need social motivation and accountability. Importantly, the data provided by interactive home gym equipment can be combined with the latest wearable tech such as Apple watches, Garmin devices, and Fitbits to track activities over time.6

In a survey that was launched in May 2020, a total of 390 participants was given some questions to know their response about physical activity in the COVID-19 pandemic:7

⇒ Online exercise videos help the participants set the individual target and make them feel motivated, as they would not have to design their own exercise program. This allowed people to not only continue with exercises they were previously doing but also give easy access to new kinds of activity.

⇒ Online exercise videos offered a way to stay connected with people during the lockdown. Not only for socialization and staying in touch with friends but added back the social commitment people used to motivated them to exercise.

There are some important points that must be considered before doing virtual exercise:

1. Set a comfortable space: a comfortable space doesn't have to be spacious, the important thing is that you can move without any limitations.
2. Don't just join any random exercise class: you must know the type of exercise because you do that in your home; maybe you do it alone without any supervision, so don't push yourself too hard.
3. Is the intensity/tempo too high? Can you follow the movement? Is the duration of the exercise too short or too long? Ask yourself honestly.
4. Use a larger screen, don't strain your eyes and body by trying to do the class on your phone.
5. Stick to a schedule: Find and make time that is conducive to you for work out.
6. Stay on track. Don't forget to warm up before you do the exercise and cool down after exercise. Performing warm-ups increases muscle temperature and blood flow, which contributes to improved exercise performance and reduced risk of injuries to muscle and tendons.8

The use of online tutorials/classes and fitness apps was significantly more prevalent during lockdown than before lockdown. Online classes and groups allowed people to both continue accessing knowledge from trainers and stay connected with their exercise communities.

So, despite the COVID-19 pandemic generally limiting the movement of people, we can still use technology to keep our body moving, to do physical activity, to exercise; because our body is created to move, not to stay still!

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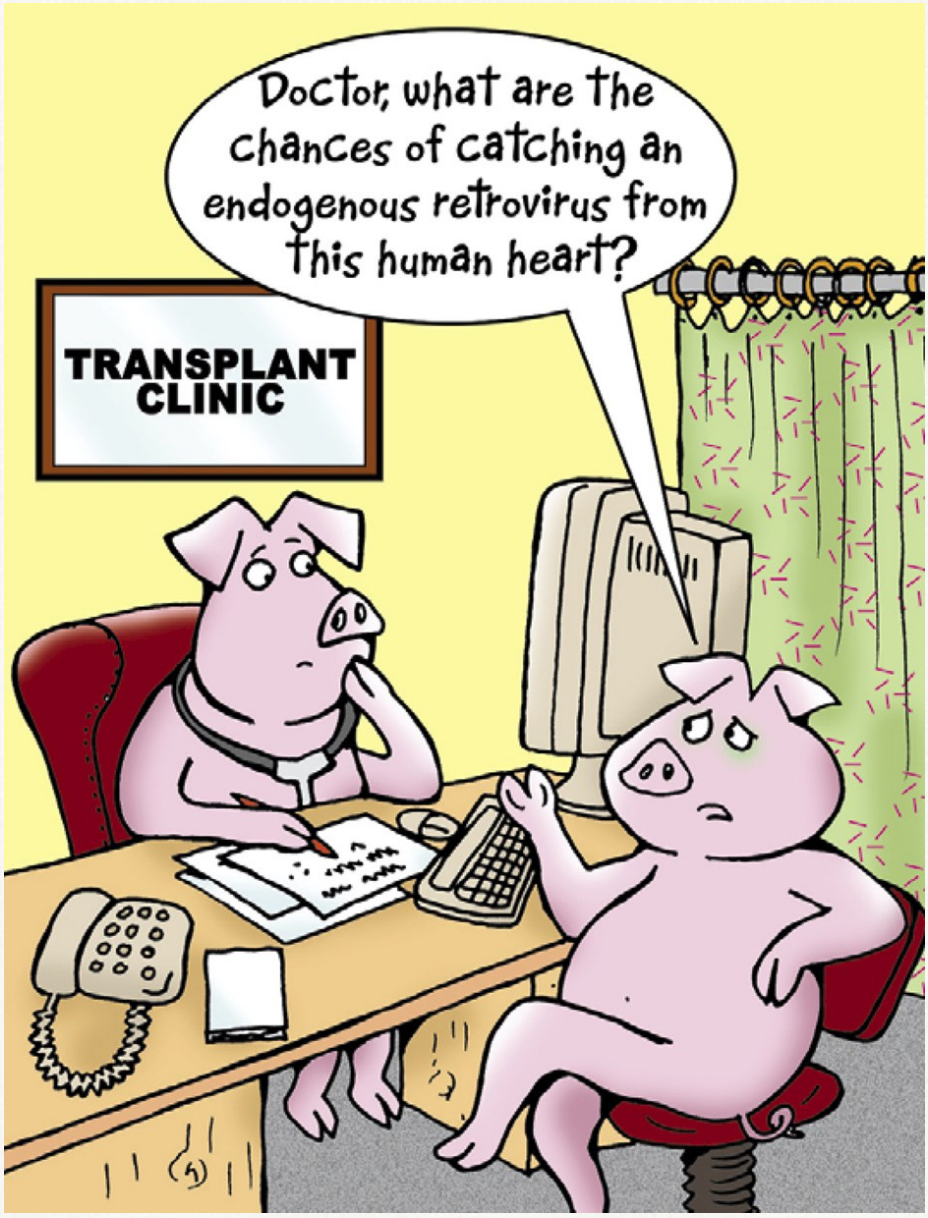
INA-RESPOND Newsletter

XENOTRANSPLANTATION: BELIEVE IT OR NOT?

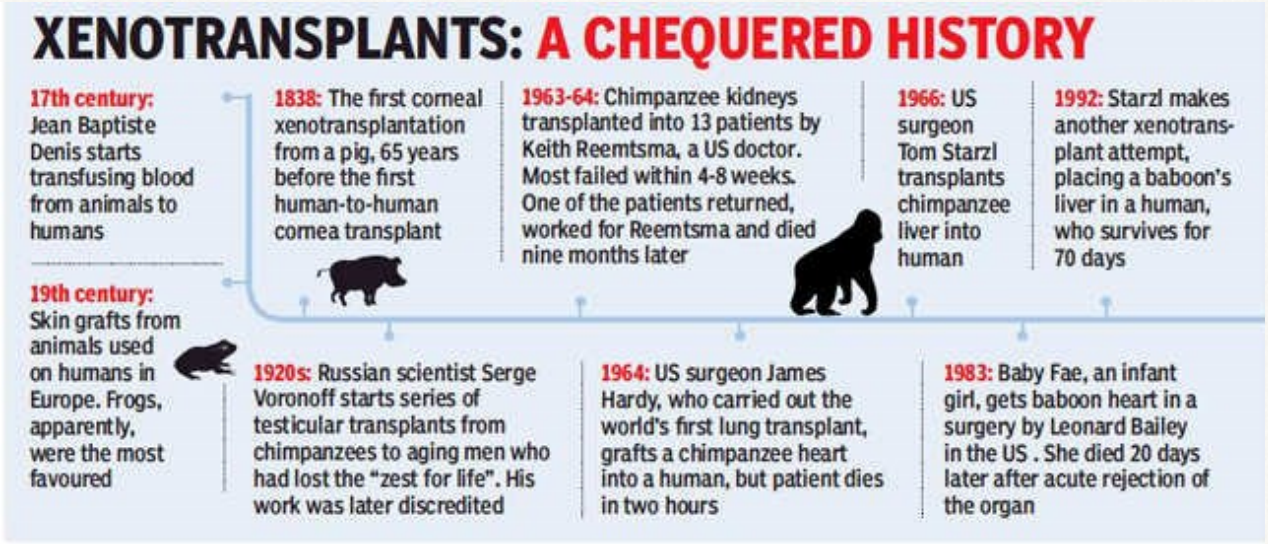
By: Aly Diana

COMIC CORNER



Some of us may have heard the news about the first pig-to-human heart transplant that was conducted on 7 January 2022 in Baltimore, Maryland, USA. A new history has been made! However, this is not the first experience of transplanting animal organs to humans. Truth to be told, the attempt for doing xenotransplantation started many centuries ago. Before talking about the history and the steps leading to the success of this first pig-to-human heart transplant, let's start with the definition. Again, this time, we will avoid discussing the ethical issues and public acceptance of such a procedure; let it be discussed on another day.

Based on Food and Drug Administration (FDA), xenotransplantation is defined as any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs. Xenotransplantation has a long history going back to blood transfusions across species in the 17th century. Following the pioneering surgical work of Carrel, who developed the technique of blood vessel anastomosis, numerous attempts at nonhuman primate (NHP) organ transplantation in patients were carried out in the 20th century. In 1963–64, one patient returned to work for almost 9 months supported by a pair of chimpanzee kidneys. In 1964, the first (unsuccessful) heart transplant utilized a chim-



Source: https://timesofindia.indiatimes.com/

panzee as the 'donor'. A patient with a baboon liver transplant survived for 70 days in 1992. And many more….

However, there are several disadvantages with the use of NHPs as sources of organs and, with the advent of genetic engineering and cloning technologies, pigs are currently considered the animals most likely to resolve the problem of donor organ shortage. Some of the advantages: pigs have good breeding potential, short period to reproductive maturity (4-8 months), a decent number of offspring (5-12), adequate size of adult organs, significantly lower cost of maintenance, a distant relation of the immune system to human, considerable knowledge of tissue typing and experience with genetic engineering in pig, and low risk of transfer of infection.

The pathobiological barriers to successful pig organ transplantation in primates include activation of the innate and adaptive immune systems, coagulation dysregulation, and inflammation. The immunologic barriers to successful xenotransplantation are primarily related to the presence of natural anti-pig antibodies in humans and NHPs that bind to antigens expressed on the transplanted pig organ (the most important of which is galactose-α1,3-galactose [Gal]),5 and activate the complement cascade, which results in rapid destruction of the graft, a process known as hyperacute rejection.

Significant advances in recent years have been achieved with the advent of CRISPR–Cas9 genome editing, which made it easier to create pig organs that are less likely to be attacked by human immune systems. This first pig-to-human heart transplant used an organ from a pig with ten genetic modifications. The company that provided the pig heart knocked out three pig genes that trigger immune attacks and added six human genes that help the body to accept the organ. A final modification aims to prevent the heart from responding to growth hormones, ensuring that it remains human-sized.

Until today (11 February 2022), there is no bad news heard from the heart recipient. Let's hope that he has a long and fruitful life. And let's hope that xenotransplantation has a wonderful future as well.

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