INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

November 2020

Sport & lifestyle

Postpartum Exercise: What You Need to Know

Reinfection with SARS-CoV-2

Comic Corner

Covid-19 Vaccine Race: Roar to the Top for Saving the World

Science Corner

The Riddle Behind High-Risk Severe COVID-19 Group – A High Priority for Vaccine Recipient?

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

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WORLD AIDS DAY

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FEATURES

INA-RESPOND Newsletter

TRIPOD & PROACTIVE Study Updates

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

STUDY UPDATES

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PARTICIPANT STATUS

Per 09 Nov 2020, the total ongoing TRIPOD study participants are 21 out of 490 enrolled participants. Of those 21 ongoing participants, two are still on TB treatment while 19 are waiting for a 6-month post-treatment visit. Two hundred and thirty-five participants have completed the study, while 234 participants are terminated early (including death). Therefore, there are still 3.9 % of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, all participant from site 520, 570, and 590 have been completed the study, while there are 1 participant from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar) who still need to be followed up, 13 participants from site 560 (RSUP dr. Kariadi Semarang), 5 participants from site 580 (RSUP dr. Sardjito Jogjakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

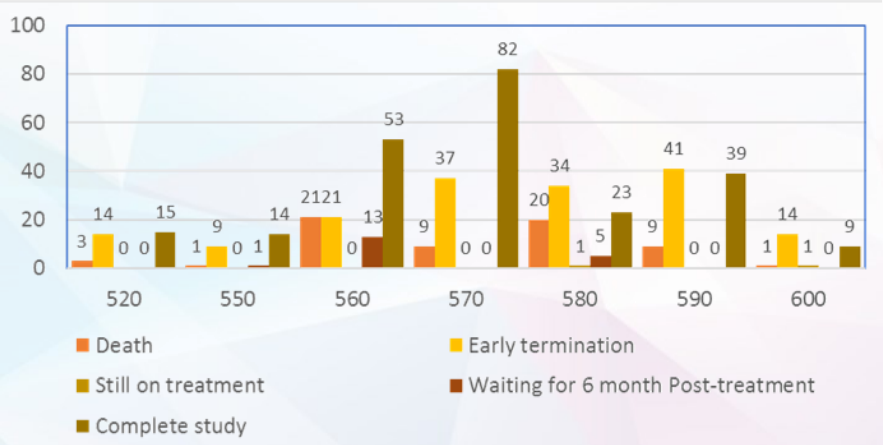

Figure 1. Participant status per site based on uploaded CRF per 9 November 2020

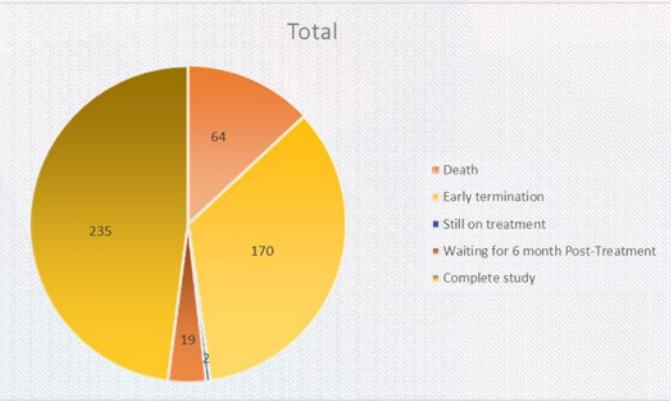

Figure 2. Total participant status based on uploaded CRF per 9 Nov 2020

TRIPOD MANUSCRIPT

Authors for the TRIPOD manuscript has been selected. A meeting with NIH will be performed to initiate the progress. The following are several manuscripts that being planned: a) focus on the baseline findings; b) treatment outcome and the related affected factors; c) related factors of TB and DM co-morbidity.

The authors will be sorted according to enrolled participants. A discussion will be set up during the Clinical Research Protocol Writing Workshop .

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

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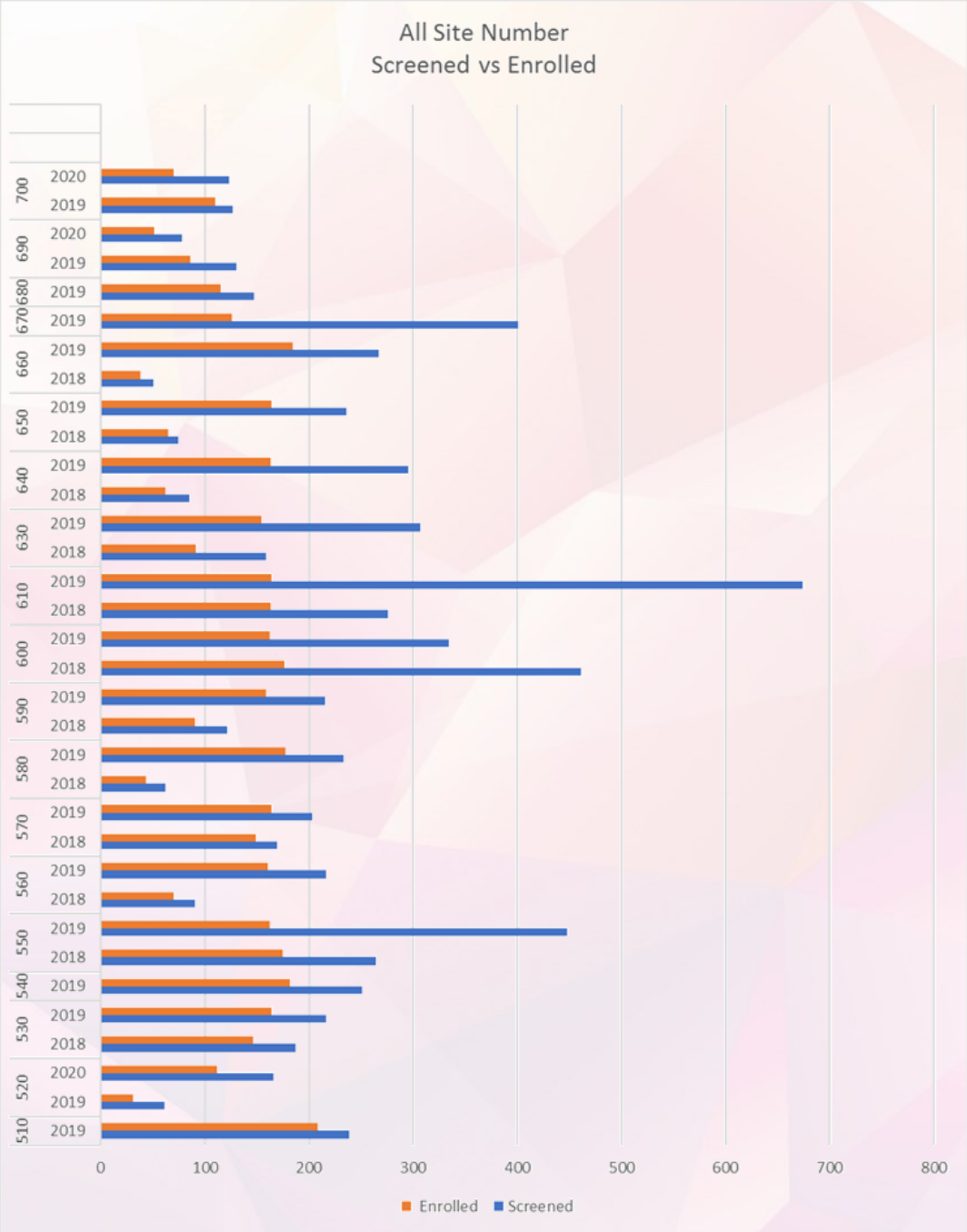
INA-PROACTIVE study has entered its 2.5 years since the first activated site. Thus some of the INA-PROACTIVE sites have conducted 30 months follow-up visits of their subjects. They are site 530 – Dr. Cipto Mangunkusumo Hospital, 550 – Dr. Wahidin Sudirohusodo Hospital, 570 – Dr. Soetomo Hospital, 600 – H Adam Malik Hospital, 610 – Tangerang Hospital, and 650 – Budi Kemuliaan Hospital.

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



All Site Number Screened vs Enrolled

As of 24 Nov 2020, 184 participants ended the study because of various reasons such as death or moving to another city with no site or far from INA-PROACTIVE study site hospital. Thus, there were 4.152 active participants of INA-PROACTIVE to date.

In November 2020, two Site Monitoring visit (SMV) were been done remotely on 11 – 12 Nov 2020 for site 510 – Dr. Hasan Sadikin Hospital as its 3rd SMV, Bandung and on 18 – 19 Nov 2020 for site 700 – TC Hillers Hospital, NTT as its 2nd SMV.

INA-RESPOND Newsletter

FROM OUR SPONSOR

THE RIDDLE BEHIND HIGH-RISK SEVERE COVID-19 GROUP – A HIGH PRIORITY FOR VACCINE RECIPIENT?

By: Adhella Menur

According to unpublished Chinese government data related to 'patient zero' of coronavirus disease-19 (COVID-19), severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) already circulated in mid-November 2019 in Hubei, China. In its one-year milestone, this killer baby already infected and killed more than 54 million and 1,3 million people worldwide. Despite unresolved terror in COVID-19, vaccine development's promising progress brings about new hope for ending this pandemic.1,2

In this November 2020, we received several great updates from vaccine candidate trials. Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) announced their mRNA-based COVID-19 vaccine candidate, BNT162b2, met all of the study's primary efficacy endpoints in ongoing Phase 3 trial with 41,135 subjects already received its second dose as per November 13, 2020. The data analysis indicates a vaccine efficacy rate of 95% ($p<0.0001$) in participants without prior SARS-CoV-2 infection and participants with and without prior SARS-CoV-2 infection. Efficacy was consistent across age, gender, race, and ethnicity demographics. The observed efficacy in adults over 65 years of age was over 94%. 3

A week after the delightful news from Pfizer and Biontech, other mRNA-based COVID-19 from the Massachusetts-based company Moderna, mRNA-1273, also reported a promising result from their first interim analysis of the Phase 3 trial. Based on 95 cases, 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.5% ($p<0.0001$). The 95 COVID-19 cases included 15 older adults (ages 65+) and 20 participants identifying as being from diverse communities (including 12 Hispanic or LatinX, 4 Black or African Americans, 3 Asian Americans, and 1 multiracial). The British-Swedish company AstraZeneca and the University of Oxford, which developed a vaccine based on a chimpanzee adenovirus, ChAdOx1 nCoV-19, also known as AZD1222, jointed to cheer up the world with their preliminary analysis of their Phase 3 trial based on a study of the 131 COVID-19 cases in the United Kingdom and Brazil. The volunteers all got two doses, but in some cases, the first dose was only half strength. Surprisingly, an initial half-strength dose led to 90 percent efficacy, while two standard-dose shots led only to 62 percent efficacy. The researchers speculated that the lower

Figure 1. Next plan for the three vaccine candidates.4

first dose did a better job of mimicking the experience of infection, promoting a stronger immune response. The preliminary analysis also indicated that the vaccine reduced COVID-19 cases with symptoms and reduced the number of asymptomatic cases.5,6 Better days are coming; we believe it.

During a health crisis, the US food and drug administration (FDA) can loosen its normal scientific standards to allow a vaccine's emergency use. In October 2020, FDA decided that vaccine makers should have two months of safety follow-up from half of the

people enrolled in their studies before requesting emergency authorization. That data is expected to be enough for the FDA to allow vaccinations of certain high-risk groups. As we know, the disturbing fact for COVID-19 is while almost confirmed cases are asymptomatic, mild, to moderate; 14% are severe, and 5% are critical, leading to the death attributed to the high-risk group. Since the group appears to be at higher risk of serious disease progression and increased mortality, they should be prioritized in vaccination against the infection. The Advisory Committee on Immunization Practices (ACIP) is considering four groups to recommend for early COVID-19 vaccination if supply is limited possibly, i.e., healthcare personnel, workers in essential and critical industries, people 65 years and older, and people at high risk for severe COVID-19 illness due to underlying medical conditions.7

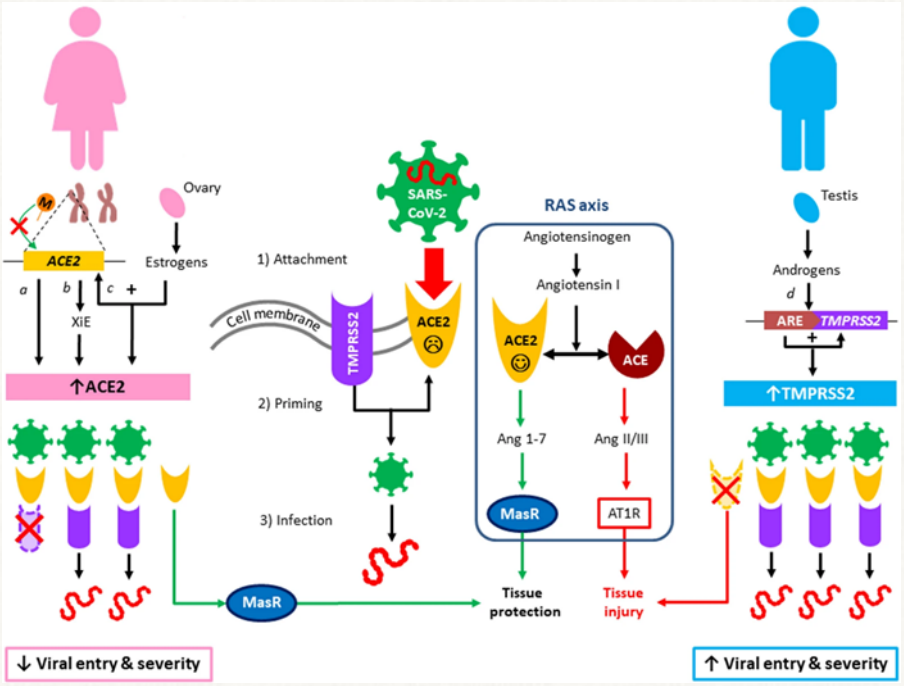


Figure 2. Proposed mechanisms of sex-related susceptibility to COVID19.12

By continuously caring for COVID-19 patients, healthcare personnel has a high risk of being exposed to and getting sick with COVID-19. Healthcare personnel accounts for 10-20% in COVID-19 cases. The war against COVID-19 burdens healthcare personnel with working hours, fatigue, and extreme psychological stress that lead to susceptibility to getting infected. The greatest risk to healthcare personnel is their colleagues or patients in the early stages of unsuspected infections when viral loads are high. The repeated exposure to the virus may lead to extreme viral load and, therefore, to worse clinical outcomes. Moreover, inadequate personal protective equipment (PPE) is also associated with a subsequent increased risk of COVID-19. Healthcare personnel who get COVID-19 can also spread the virus to their patients and increase their patients' risk for severe COVID-19 illness.8,9

Medical and healthcare, telecommunications, information technology systems, defense, food and agriculture, transportation and logistics, energy, water and wastewater, and law enforcement are considered essential and critical industries. Current data show that many workers in those industries are at increased risk of getting COVID-19, particularly men workers. Men are more involved in those industries, combined with their various risky behaviors, such as smoking, alcohol consumption, sitting together with other people, and removing their masks.10,11

In line with many studies of COVID-19, the predominance of being infected and severe is men. Studies suggest that men express more angiotensin converting enzyme-2 (ACE2) receptor in their lungs and heart, potentially explaining the male predilection for more severe disease. Interestingly, ACE2 gene is located on the X chromosome (location: Xp22.2; nucleotides 15 494 402–15 602 148, GRCh38.hg38 version), which raises the possibility that differences in sex chromosome dosage (2X versus 1X) could impact ACE2 activity due to escape from X-inactivation on the second X or differences in parental imprinting. The X chromosome also contains several important genes related to immunity and immune regulation that are extensively involved in shaping sex-specific innate and adaptive immune responses. An example relevant to coronavirus infection is the X chromosome gene coding for the protein called Toll-like receptor 7 (TLR7). TLR7 helps control the innate immune response by recognizing single-stranded RNA of viral origin, like an RNA coronavirus that might be overexpressed in women and contribute to clearing the SARS-CoV-2 faster. The transmembrane serine protease 2 (TMPRSS2), as one of the host proteins that promote the invasion of SARS-CoV-2 to cells, is an androgen-regulated gene whose gene expression is stimulated by testosterone, causing an increased susceptibility of men for severe SARS-CoV-2 infection. An alternative explanation for the male/female difference for severe COVID-19 is that the female hormone estrogen may be protective. In a new study, 10.2% of 987 blood samples from gravely ill patients worldwide found to have auto-antibodies that attacked and neutralized the patients' type I interferon with male predom-

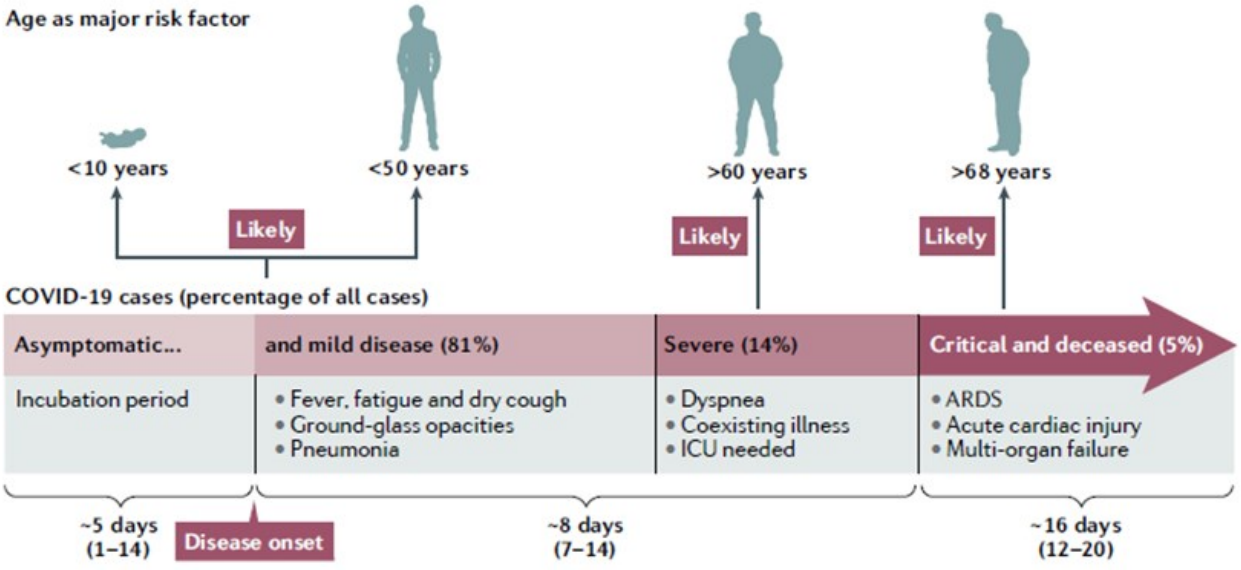


Figure 3. Elderly is the risk factor for developing severe, critical, and deceased in COVID-19.17

inance (95%). Regarding smoking behavior, a meta-analysis showed that ever-smoking significantly increased pulmonary ACE2 expression by 25% and upregulated furin. It may suggest an increased risk for viral binding and entry of SARS-CoV -2 in the lungs of smokers.11-16

Older age is undoubtedly the known risk factor for developing severe COVID-19. Adults older than 60 years may have at least 5 times increased odds of hospitalization and mortality from COVID-19 compared to those aged less than 45 years. This increased risk appears to magnify at least to some degree even for those older than 60 years, with those aged over 80 years having double the mortality risk of those aged 65-69 years. The number of cilia, ciliated cells in the airway, and upper airway size decrease with aging, which jeopardize successful clearance of virus SARS-CoV-2 particles in older adults. Aging is associated with 2 profound biological changes in the immune system; immunosenescence is a gradual decline in the host's ability to mount robust immune responses to pathogens, while inflammaging is a chronic increase in low-grade inflammation arising from an overactive yet ineffective alert system. In older age, the viral alert signals are much slower, giving a great chance for viral replication. A negative correlation between CD4/CD8 T-cell ratio and severity of frailty in the elderly has been reported. The number of circulating 'competent' B cells also significantly decreases with age. The interplay between immunosenescence and inflammaging has been hypothesized to be responsible for the phenomenon of COVID-19 "cytokine storm" in the elderly. D-dimer, a fibrin degradation product and prognostic of disseminated intravascular coagulation (DIC), and elevated levels of the cytokine, IL-6, are associated in the clinic with increased fatality. Multiple age-related comorbid conditions such as heart and lung disease, diabetes, and dementia contribute to poor outcomes in COVID-19 elderly patients. The fact that a lot of older people are taking analgetic and anti-inflammatory medications may reduce antivaccine immunity as well.18-20

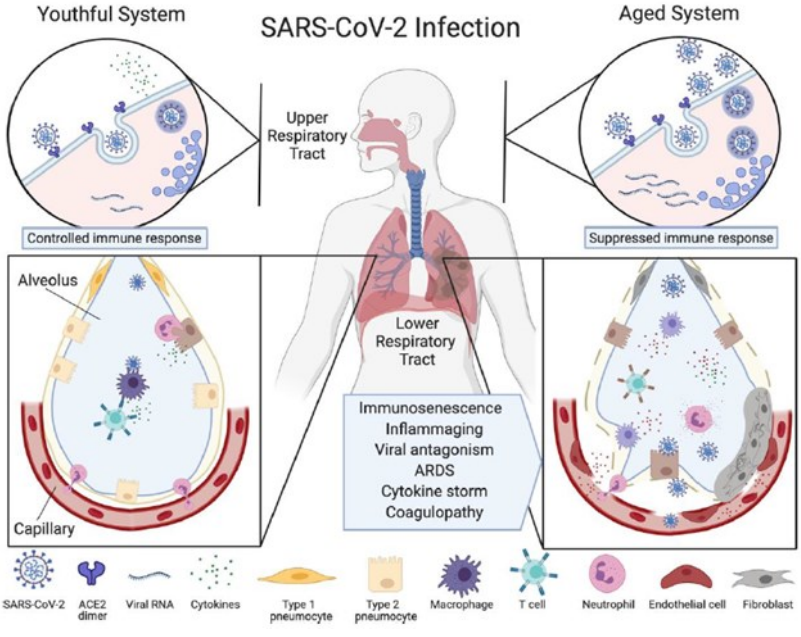


Figure 4. Ineffective clearance of SARS-CoV-2 infection in the aged respiratory system.20

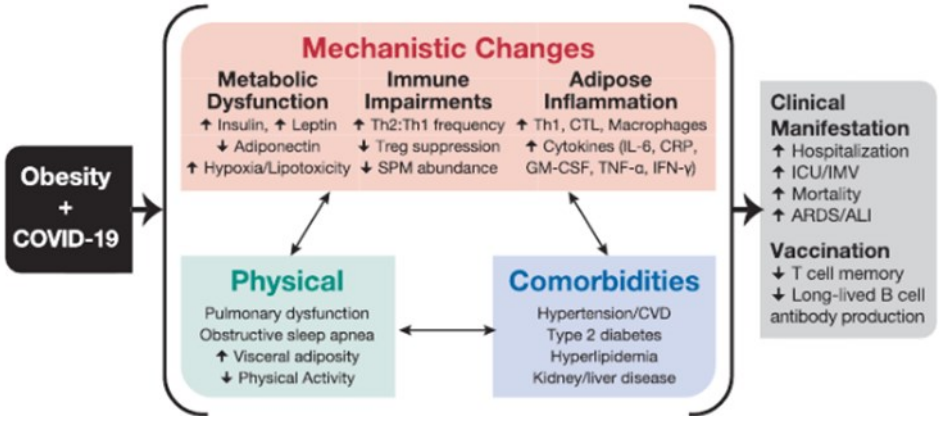


Figure 5. Clinical manifestations and mechanisms for COVID-19 risk in individuals with obesity.22

Studies and clinical experiences suggest that patients with certain comorbidities are more susceptible to COVID-19 infection and lead to a poor prognosis. Obesity, cardiovascular disease (CVD), mainly hypertension, diabetes, chronic kidney disease, liver disease, malignancy, cerebrovascular disease, respiratory diseases, and immunocompromised states are found to have a significantly higher prevalence in fatal cases of COVID-19. Chronic comorbidities can cause dysregulation of the immune system leading to the accumulation of pro-inflammatory cytokines. As a result of the imbalance in immunity, these individuals become very susceptible to severe complications of SARS-CoV-2 and death.21

Body mass index (BMI) of 35 to 40 could increase a person's chances of dying from COVID-19 by 40%, while a BMI greater than 40 could increase the risk by 90%. Blood insulin disturbance acquired from fat accumulation is associated with a range of abnormalities, including increases in inflammatory cytokines and a reduction of adiponectin that directly protects the lungs. In individuals with obesity, diabetes, or CVD, the expression of ACE2 is upregulated, thus increasing the susceptibility to SARS-CoV-2 infection.18,22 Pulmonary physiological abnormalities and microangiopathy associated with obesity and diabetes have been shown to increase viral diversity and titers and to prolong viral shedding. SARS-CoV-2 could also bind to ACE2 in the liver and pancreatic islet, with a potential role in the development of insulin resistance and impaired insulin secretion, further causing acute diabetes or worsening the diabetes prognosis.23

Direct viral-induced myocardial damage and indirect myocardial injury through viral-mediated cytokine storm are proposed mechanisms for the increased cardiac morbidity in COVID-19. SARS-CoV-2 infected mice demonstrated a downregulated ACE2 protein expression, which mediates increased pulmonary vascular permeability resulting in pulmonary oedema and respiratory failure. CD8+ T lymphocyte dysfunction is linked to hypertension which may not only decrease the ability to combat viral infections but also a possible dysregulation of cytokines which play a role in the systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS).24

Chronic obstructive pulmonary disorder (COPD) is characterized by increased ACE2 expression, which provides more receptors for viral entry, possibly increasing viral load and leading to more severe disease. Increased viral load coupled with baseline hypoxia in COPD may lead to worsening pulmonary compromise in

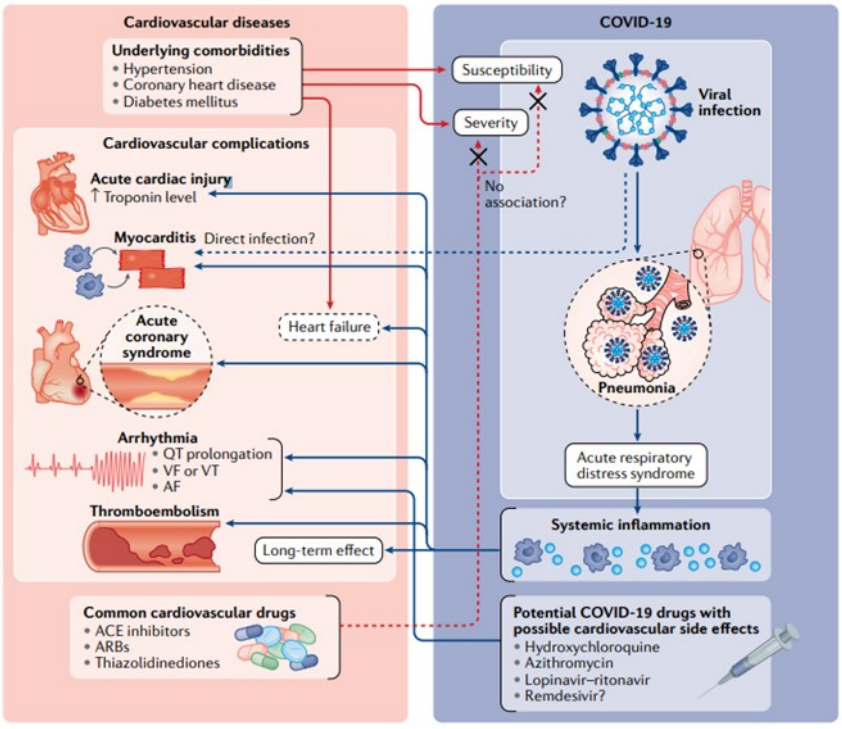


Figure 6. Bidirectional interaction between cardiovascular diseases and COVID-19.25

affected patients. In the immunocompromised patients, lack of immune responses even undetected SARS-CoV-2 antibodies potentiate for persistent infection and accelerated viral evolution. Other comorbidities are under investigation related to its interaction with SARS-CoV-2 infection.24,26

"It is important to identify high-risk severe COVID-19 group as targeted public health vaccination intervention. This group is contributing high numbers in fatal COVID-19 cases. Although the percentage looks small, losing is still losing, grief is still grief."

REFERENCES

1. Ma J. Coronavirus: China's first confirmed Covid-19 case traced back to November 17 [Internet]. 2020; Available from: https://www.scmp.com/
2. Pfizer and biontech conclude phase 3 study of covid-19 vaccine candidate, meeting all primary efficacy endpoints [Internet]. 2020; Available from: https://www.pfizer.com/
3. COVID-19 coronavirus pandemic [Internet]. 2020; Available from: worldmeters.info/
4. Johnson CY, Steckelberg A. What you need to know about the AstraZeneca, Moderna, and Pfizer vaccines [Internet]. 2020; Available from: https://www.washingtonpost.com/
5. Moderna's work on a COVID-19 vaccine [Internet]. 2020; Available from: https://www.modernatx.com/
6. Oxford University breakthrough on global COVID-19 vaccine [Internet]. 2020; Available from: https://www.vaccitech.co.uk/
7. Centers for Disease Control and Prevention. How CDC is making vaccine recommendations [Internet]. 2020; Available from: https://www.cdc.gov/
8. Nguyen LH, Drew DA, Joshi AD, et al. Risk of COVID-19 among frontline healthcare workers and the general community: a prospective cohort study. medRxiv [Preprint]. 2020 May 25. Update in: Lancet Public Health. 2020 July 30.
9. Karlsson Ulf, Fraenkel Carl-Johan. Covid-19: risks to healthcare workers and their families. BMJ 2020; 371: m3944.
10. Cybersecurity & infrastructure security agency. Guidance on the essential critical infrastructure workforce [Internet]. 2020; Available from: cisa.gov/
11. Lipsky MS, Hung M. Men and COVID-19: A Pathophysiologic Review. Am J Mens Health. 2020 Sep-Oct;14(5):1557988320954021. doi: 10.1177/1557988320954021.
12. Foresta, C., Rocca, M.S. & Di Nisio, A. Gender susceptibility to COVID-19: a review of the putative role of sex hormones and X chromosome. J Endocrinol Invest. 2020. https://doi.org/10.1007/s40618-020-01383-6.
13. Abate BB, Kassie AM, Kassaw MW, et al. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. BMJ Open 2020;10:e040129. doi:10.1136/ bmjopen-2020-040129.
14. Wiese O, Zemlin AE, Pillay TS. Molecules in pathogenesis: angiotensin converting enzyme 2 (ACE2). J Clin Pathol. 2020 August 5: jclinpath-2020-206954. doi: 10.1136/jclinpath-2020-206954.
15. National Institute of Health. Scientists discover genetic and immunologic underpinnings of some cases of severe COVID-19 [Internet]. 2020; Available from: https://www.nih.gov/
16. Cai G, Bossé Y, Xiao F, et al. Tobacco Smoking Increases the Lung Gene Expression of ACE2, the Receptor of SARS-CoV-2. Am J Respir Crit Care Med. 2020 June 15;201(12):1557-1559. doi: 10.1164/rccm.202003-0693LE.
17. Hu, B., Guo, H., Zhou, P. et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2020. https://doi.org/10.1038/s41579-020-00459-7.
18. Mahase E. Covid-19: Why are age and obesity risk factors for serious disease? BMJ. 2020 Oct 26;371:m4130. doi: 10.1136/bmj.m4130.
19. Perrotta F, Corbi G, Mazzeo G, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res. 2020 Aug;32(8):1599-1608. doi: 10.1007/s40520-020-01631-y.
20. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging (Albany NY). 2020 May 29;12 (10):9959-9981. doi: 10.18632/aging.103344.
21. Ssentongo P, Ssentongo AE, Heilbrunn ES, et al. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS ONE. 2020; 15(8): e0238215. https://doi.org/10.1371/journal.pone.0238215.
22. Popkin BM, Du S, Green WD, Beck MA, et al. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. Obes Rev. 2020 Nov;21(11):e13128. doi: obr.13128.
23. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. Int J Infect Dis. 2020 Oct;99:47-56. doi: 10.1016/j.ijid.2020.07.029.
24. Gold MS, Sehayek D, Gabrielli S, Zhang X, McCusker C, Ben-Shoshan M. COVID-19 and comorbidities: a systematic review and meta-analysis. Postgrad Med. 2020 Jul 14:1-7. doi: 10.1080/00325481.2020.1786964. Epub ahead of print.
25. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020 Sep;17(9):543-558. doi: 10.1038/s41569-020-0413-9.
26. Choi B, Choudhary MC, Regan J, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised Host. N Engl J Med. 2020 November 11. doi: 10.1056/NEJMc2031364.

INA-RESPOND Newsletter

REINFECTION WITH SARS-COV-2

By: Katy Shaw—Saliba

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to rage on with 51.6 million cases and 1.27 million deaths globally as of 11 November 2020 (1). Since the start of the pandemic, concerns have arisen about the prospect of reinfection as reinfections impact public health control measures. Infection with some viruses offers life-long immunity, while reinfection with other viruses is common, including seasonal human coronaviruses (2-10).

Initial reports of SARS-CoV-2 reinfections

In February 2020, news reports from Japan indicated a female tour bus guide was had tested positive for SARS-CoV-2 for a second time, indicating possible reinfection (11). Other media reports have indicated potential cases of reinfection in China, Malta, and Catalonia (11-13), including one where the second infection was more severe than the primary infection (13).

Following these reports, larger reviews of medical records or diagnostic laboratory databases in France (14), Mexico (15), and the UK (16) also identified potential cases of reinfection. These studies all used a case definition of reinfection as laboratory confirmed symptomatic SARS-CoV-2 (by RT-PCR) followed by a period of recovery and then a second SARS-CoV-2 positive RT-PCR at least 21 days after the first test. Most of the studies used day 28 as it has been demonstrated to be the time that most hospitalized patients have minimal or no virus shedding (17).

A review of 133,266 cases in Qatar used a reinfection case definition as a positive test ≥ 45 days from the first and then evidence ranked based on the RT-PCR cycle threshold (Ct), which can be used as a proxy for viral load as high viral load and has been correlated with infectious virus (18). A total of 243 (0.81%) cases met the definition for strong evidence of reinfection. Of those, 23 had paired specimens available for viral genomic analysis of which 4 had conclusive variation to conclude reinfections. From this, the study concluded the risk of reinfection to be quite low at 0.04% (95% CI: 0.03-0.05%) and calculated the incidence rate of reinfections to be 1.09 (95% CI: 0.84-1.42) per 10 000 person-weeks.

Location (ref)	Age	Sex	Comorbidities	Days between	First infection			Second infection		
					Symptomatic	RT-PCR Ct (target)	Clinical disease	Symptomatic	RT-PCR Ct (target)	Clinical disease
India (35)	25	M	No	108	No	36 (nd)	N/A	No	16.6 (nd)	N/A
	28	F	No	111	No	28.16 (nd)	N/A	No	16.92 (nd)	N/A
Hong Kong (28)	33	M	No	142	Yes	30.5 (E)	Mild	No	26 (E)	N/A
Belgium (33)	51	F	Asthma (corticoid steroids)	93	Yes	25 (N)	Non-severe, Hospitalized	Yes	32.6 (N)	Milder
Belgium (38)	30s	F	No	185	Yes	13 (E)	Mild	Yes	19 (E)	Milder
Ecuador (34)	46	M	No	61	Yes	36.85 (ORF3a)	Mild	Yes	nd	Worse
US military (30)	42	M	No	51	Yes	nd	Mild	Yes	nd	Worse
Nevada, USA (29)	25	M	No	48	Yes	35.24 (N)	Mild	Yes	35.31 (N)	Worse, Hospitalized
Washington, USA (31)	60s	nd	Emphysema & hypertension	140	Yes	22.8 (N, E)	Severe, Hospitalized	Yes	43.3 (N, E)	Less Severe, Hospitalized
Netherlands (32)	89	F	Waldenström macroglobulinemia & B cell depleting therapy	59	Yes	26.2 (E)	Non-severe, Hospitalized	Yes	25.2 (E)	Severe, Died

Table 1. Adapted and updated from (ref). Reports of reinfection with confirmed viral genomic evidence as of 11 November 2020
nd = no data. M = male, F = female. Ct = cycle threshold from diagnostic RT-PCR. E = envelope, N = nucleocapsid

How do you confirm reinfection versus prolonged viral shedding?

These larger reviews provide a comprehensive overview and demonstrate that reinfections are not occurring at an obviously high rate. However, using these definitions, it is not entirely possible to distinguish reinfection from prolonged viral shedding. Two recent reports of an immunocompromised patients found asymptomatic shedding of infectious virus can occur up to 70 days and shedding of viral RNA for 105 days (19). Furthermore, in the second case, there were periods that were relatively symptom-free followed by recurrence and infectious was isolated up to 143 days after the initial onset (20). In both of these cases, viral sequencing confirmed the prolonged positivity and distinct disease episodes were due to SARS-CoV-2 recurrence rather than reinfection (19, 20).

Therefore, the most definitive evidence for reinfection is based on viral genomic analysis. Whole genome sequencing can either reveal different virus clades and/or enough nucleotide differences to conclude that two episodes are not caused by the same virus. The SARS-CoV-2 genome is estimated to accumulate about 2 nucleotide differences per month, which is about one-fourth of the rate of HIV and half of the rate of influenza (21), thus if the clade is the same but there are ≥2 nt/month, there is moderate evidence for reinfection.

The US Centers for Disease Control and Prevention has developed a protocol and guidelines for investigation of reinfection protocol to be used both passive reporting and those found through active surveillance (22). These guidelines and protocol combine descriptive epidemiology with genomic viral evidence.

According to the protocol, ideally the descriptive epidemiology and viral genomic evidence is also coupled with other evidence of infectious virus to distinguish the second episode from prolonged viral shedding of only viral RNA. Examples include positive viral culture, low Ct values (indicating high viral load and correlated with infectious virus (18, 23)), or presence of subgenomic messenger RNA (sgmRNA) indicating potential active viral replication (24-27).

In-depth analysis of reports with genomic evidence

With these guidelines in mind, a review of pre-prints, peer-reviewed manuscripts, and review articles revealed 9 reports with genomic and virologic evidence for reinfection (28-37). These reports are from Hong Kong (28), India (35), the Netherlands (32), Belgium (33, 38), USA (29-31), and Ecuador (34). Table 1 summarizes the basic demographics and characteristics of the two episodes (episode 1 = primary infection. episode 2 = reinfection). All reports are from adults with the median age of 37.5 years, the majority of whom were otherwise healthy. The median duration between the two infections was 100.5 days (range 48-185).

With the exception of the report from India (35) and the second infection in the report from Hong Kong (28), all of the individuals were symptomatic with the reinfection. The asymptomatic reinfections were picked up during routine surveillance of healthcare workers at a COVID-19 unit in a tertiary care hospital in Northern India (35) (both infections were asymptomatic) and during travel screening in Hong Kong (28) (asymptomatic reinfection). These examples illustrate how important routine surveillance is in identifying reinfection events in asymptomatic individuals (36).

Using these studies, we can begin to ask question some of the outstanding questions surrounding immunity and the consequences of reinfection.

Are reinfections the result of waning immunity?

The essential interaction for infection is the interaction of the receptor binding domain of the spike protein with the ACE2 receptor on the target cells and therefore the antibodies that target this interaction are assumed to be protective (39). Studies on SARS-CoV-2 infected individuals have shown that IgM

and IgG appear concurrently 10-14 days post symptom onset, IgG then peaks during the convalescent period of 21-40 days, and then starts to decline but remain detectable 6 months post onset (reviewed in (39, 40)).

With the exception of one case (32), all of the individuals appear to be immunocompetent and most do not report any comorbidities, therefore, we would expect an intact immune response.

Location (ref)	After the first infection (time of assay after first positive RT-PCR)	After the second infection (time of assay after second positive RT-PCR)	Assay (target)
India (35)	HCW1: nd HCW2: nd	HCW1: nd HCW2: nd	N/A
Hong Kong (28)	Negative (10 days)	IgG+ (5 days)	Abbott Architect (N)
Belgium (33)	Nd	Nd	N/A
Belgium (38)	Total Ig+ IgG+ nAb+ (94 days)	Total Ig+ IgG+ nAb+ (7 and 21 days)	Luminex (N) Luminex (RBD) Neut assay
Ecuador (34)	IgM+IgG- (4 days)	IgM+IgG+ (26 days)	1st infection: SafeCare Biotech (S) 2nd infection: Novatech NovaLisa (N)
US military (30)	nd	IgG+ (8 days)	Unknown (S)
Nevada, USA (29)	nd	IgM+IgG+	Roche Elecys (N)
Washington, USA (31)*	nd	IgA+ IgM+ IgG+ nAb+	Inhouse ELISA (N, S, RBD) Pesudovirus (614G and 614D)
Netherlands (32)	Nd	Total Ig- IgM- (4 and 6 days)	Wantai (RBD)

Table 2. Serological assays in individuals with SARS-CoV-2 reinfections
HCW = healthcare worker. nd = no data . N = nucleocapsid, S = spike, RBD = receptor binding domain. nAb = neutralizing antibodies. Neut = neutralization. * = longer discussion in text about kinetics

Table 2 summarizes the serological assays that were done in the 9 reports. While detection of IgG indicates presence of antibodies, the gold standard for functionality is a neutralization assay which demonstrates the antibodies that are present are capable of blocking infection.

Five of the reports had serological data only after the second infection (28-32). In the immunocompetent individuals, SARS-CoV-2-specific antibodies were detected following the second infection (28-31). While IgM was detected after the first infection in the case in Ecuador, the test was shortly after the first infection and no details were available for the development of IgG (34).

In one study, PBMCs were collected following the second infection. Single cell analysis revealed no new clones were present, indicating that either there was prior immune recognition or a deficiency in developing response and therefore, in this case, the immune response either poorly developed after the first infection or waned immune response was not protective from reinfection (31).

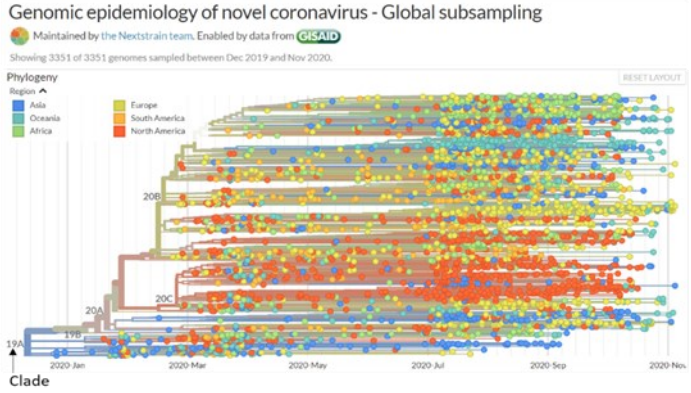
In one case serological assays were conducted after the first and second infections. A healthcare worker had developed neutralizing antibodies following a primary infection were still detectable at 94 days (38) and serology conducted at 7 and 21 days after the second infection demonstrated substantial boosting of both serum IgG and neutralizing titers (38). Given the 185 days between the first and second infections, it is possible that the response had waned. However, it is worth noting that the second infection was much milder than the first.

The results indicate that reinfection likely can occur even in the presence of a proper immune response, but without measurements just prior to the second infection, it is impossible to determine if these were a result of waning immunity.

Are reinfections the result of antigenic variation?

In the case of other viruses such as influenza, reinfections are often the result of viruses that have undergone antigenic drift in response to selective pressure exerted by antibodies. While 5/9 reports demonstrated that the reinfection was caused by a different clade (Figure 1 and Table 3), but so far there have not been variants of SARS-CoV-2 that have naturally arisen due to immune evasion (36, 41). Interestingly, in one of the cases reported, a mutation in the spike protein N440K has been shown in vitro to allow for escape from neutralizing antibodies (42). Continual monitoring of the of SARS-CoV-2 genomes globally coupled with laboratory studies will help elucidate if immune evasion and antigenic variation emerges.

Figure 1. SARS-CoV-2 phylogeny from NextStrain.



Location (ref)	First infection	Second infection
India (35)	HCW1: nd HCW2: nd	10 nt 9 nt (Spike N440K)
Hong Kong (28)	19A	20A
Belgium (33)	20B	19B
Belgium (38)	19A	20A
Ecuador (34)	20A	19B
US military (30)	nd (Spike 614D)	20C (Spike 614G)
Nevada, USA (29)	20C	20C (7 nt)
Washington, USA (31)	19B	20A
Netherlands (32)	Not reported	10 nt

Table 3. SARS-CoV-2 virus clades or nucleotide differences between the first and second infections.
Ct = cycle threshold from diagnostic RT-PCR. HCW = healthcare worker. nd = no data
Virus clade based on NextStrain nomenclature

Does reinfection protect from severe symptoms or clinical disease course?

For the 7 reports of symptomatic reinfections, we can examine if a previous infection can protect from severe symptoms and/or clinical disease course. Only one case reinfection occurred in a patient who had severe disease in the first infection (31) and that resulted in a less severe reinfection. All others occurred in patients who had mild or moderate disease, of those, 2 were reported as less severe on reinfection and 4 were reported as more severe. In the case of the healthcare worker who demonstrated antibody boosting, the second infection was milder (38).

For the 4 individuals that had more severe symptoms and disease course, one occurred in a patient from the Netherlands who had Waldenström macroglobulinemia and had been treated with B cell depleting therapy as well as chemotherapy prior to the reinfection (32). For the 3 of the cases in otherwise healthy individuals where the second infection was more severe, all had a close household contact that was SARS-CoV-2 positive prior to their symptom onset in the second episode indicating potentially viral load could also be playing a role (29, 30, 34).

Taken together, there's not a clear-cut answer about severity during reinfection. It does not appear that reinfection causes major disease enhancement, nor does it indicate that a primary infection will prevent symptomatic reinfections.

Can individuals with reinfections transmit SARS-CoV-2?

Only one report discussed potential transmission to others (38). In that case, a healthcare worker was reinfected during a nosocomial outbreak. She was the only link between other cases in the outbreak indicating she may have transmitted the virus, but none of her close household contacts tested positive (38).

In the other cases, we can speculate based on viral load as indicated by proxy using the cycle threshold (Ct) on the diagnostic RT-PCR. Lower Cts, indicating higher viral load, have been consistently correlated with infectious virus (18, 23). While the Ct values can vary based on assay and target type, in two studies, it was demonstrated that in cases where the Ct was ≥35, infectious virus was only sporadically isolated (23). Apart from 2 cases (Table 1), all of the second infections had Ct values less than 35 indicating likely infectious virus in the nasal cavity. Interestingly, in the case of the three asymptomatic reinfections, all had higher viral load than the first infection (28, 35).

Well controlled cohort studies and animal transmission models may shed more light on the dynamics of reinfection and transmission.

Conclusions

The confirmed reports of reinfections have begun to answer some of the outstanding questions with SARS-CoV-2. It does not appear reinfections are occurring at a dramatic rate at the moment. For certain, it illustrates that we cannot rely solely on natural immunity for herd immunity. Further detailed studies will be informative.

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. The Lancet Infectious Diseases. 2020;20(5):533-4.
2. Kiyuka PK, Agoti CN, Munywoki PK, Njeru R, Bett A, Otieno JR, et al. Human Coronavirus NL63 Molecular Epidemiology and Evolutionary Patterns in Rural Coastal Kenya. J Infect Dis. 2018;217(11):1728-39.
3. Gorse GJ, Donovan MM, Patel GB. Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illnesses. J Med Virol. 2020;92(5):512-7.
4. Galanti M, Shaman J. Direct Observation of Repeated Infections With Endemic Coronaviruses. J Infect Dis. 2020.
5. Schmidt OW, Allan ID, Cooney MK, Foy HM, Fox JP. Rises in titers of antibody to human coronaviruses OC43 and 229E in Seattle families during 1975-1979. Am J Epidemiol. 1986;123(5):862-8.
6. Aldridge RW, Lewer D, Beale S, Johnson AM, Zambon M, Hayward AC, et al. Seasonality and immunity to laboratory-confirmed seasonal coronaviruses (HCoV-NL63, HCoV-OC43, and HCoV-229E): results from the Flu Watch cohort study. Wellcome Open Research. 2020;5.
7. Reed SE. The Behaviour of Recent Isolates of Human Respiratory Coronavirus In Vitro and in Volunteers: Evidence of Heterogeneity Among 229E-Related Strains Journal of Medical Virology. 1984;13:172-92.
8. Macnaughton MR. Occurrence and Frequency of Coronavirus Infections in Humans as Determined by Enzyme-Linked Immunosorbent Assay. Infection and Immunity 1982;38(2):419-23.
9. Callow KA. Effect of specific humoral immunity and some non-specific factors on resistance of volunteers to respiratory coronavirus infection. Journal of Hygiene. 1985;95:173-89.
10. Callow KA, Parry HF, Sergeant M, Tyrrel DAJ. The time course of the immune response to experimental coronavirus infection of man. Epidemiology and Infection. 1990;105:435-46.
11. Stanway D, Kelland K. Explainer: Coronavirus reappears in discharged patients, raising questions in containment fight. Reuters. 2020.
12. Recovered COVID-19 patient tests positive again, in first for Malta [press release]. Times of Malta2020.
13. McMurtry A. COVID-19 reinfection lands Spanish doctor in ICU 2020 [Available from: https://www.aa.com.tr/en/europe/covid-19-reinfection-lands-spanish-doctor-in-icu/1973309.
14. Gousseff M, Penot P, Gallay L, Batisse D, Benech N, Bouiller K, et al. Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound? J Infect. 2020;81

(5):816-46.

15. Murillo-Zamora E, Mendoza-Cano O, Delgado-Enciso I, Hernandez-Suarez CM. Predictors of severe symptomatic laboratory-confirmed SARS-COV-2 reinfection medRxiv. 2020.

16. Tomassini S, Kotecha D, Bird PW, Folwell A, Biju S, Tang JW. Setting the criteria for SARS-CoV-2 reinfection - six possible cases. J Infect. 2020.

17. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-9.

18. Gniazdowski V, Morris CP, Wohl S, Mehoke T, Ramakrishnan S, Thielen P, et al. Repeat COVID-19 Molecular Testing: Correlation of SARS-CoV-2 Culture with Molecular Assays and Cycle Thresholds. Clin Infect Dis. 2020.

19. Avanzato VA, Matson MJ, Seifert SN, Pryce R, Williamson BN, Anzick SL, et al. Case Study: Prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised cancer patient. Cell. 2020.

20. Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. New England Journal of Medicine. 2020.

21. Callaway E. Making sense of coronavirus mutations Nature. 2020;585(10 September 2020).

22. Prevention CfDCa. Common Investigation Protocol for Investigating Suspected SARS-CoV-2 Reinfection 2020 [updated 27 October 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html.

23. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill. 2020;25(32).

24. Wu HY, Brian DA. Subgenomic messenger RNA amplification in coronaviruses. Proc Natl Acad Sci U S A. 2010;107(27):12257-62.

25. Sztuba-Solinska J, Stollar V, Bujarski JJ. Subgenomic messenger RNAs: mastering regulation of (+)-strand RNA virus life cycle. Virology. 2011;412(2):245-55.

26. Alexandersen S, Chamings A, Bhatta TR. SARS-CoV-2 genomic and subgenomic RNAs in diagnostic samples are not an indicator of active replication. medRxiv. 2020.

27. Perera RAPM, Tso E, Tsang OTY, Tsang DNC, Fung K, Leung YWY, et al. SARS-CoV-2 virus culture from the upper respiratory tract: Correlation with viral load, subgenomic viral RNA and duration of illness. medRxiv. 2020.

28. To KK, Hung IF, Ip JD, Chu AW, Chan WM, Tam AR, et al. COVID-19 reinfection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis. 2020.

29. Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. The Lancet Infectious Diseases. 2020.

30. Larson D, Brodniak SL, Voegtly LJ, Cer RZ, Glang LA, Malagon FJ, et al. A Case of Early Reinfection with SARS-CoV-2. Clin Infect Dis. 2020.

31. Goldman JD, Wang K, Roltgen K, Nielsen SCA, Roach JC, Naccache SN, et al. Reinfection with SARS-CoV-2 and Failure of Humoral Immunity: a case report. medRxiv. 2020.

32. Mulder M, van der Vegt D, Oude Munnink BB, GeurtsvanKessel CH, van de Bovenkamp J, Sikkema RS, et al. Reinfection of SARS-CoV-2 in an immunocompromised patient: a case report. Clin Infect Dis. 2020.

33. Van Elslande J, Vermeersch P, Vandervoort K, Wawina-Bokalanga T, Vanmechelen B, Wollants E, et al. Symptomatic SARS-CoV-2 reinfection by a phylogenetically distinct strain. Clin Infect Dis. 2020.

34. Prador-Vivar B, Becerra-Wong M, Guadalupe J, Marquez S, Gutierrez B, Rojas-Silva P, et al. COVID-19 ReInfection by a Phylogenetically Distinct SARS-CoV-2 Variant, First Confirmed Event in South America. SSRN 2020;3 September 2020.

35. Gupta V, Bhoyar RC, Jain A, Srivastava S, Upadhayay R, Imran M, et al. Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. Clin Infect Dis. 2020.

36. Iwasaki A. What reinfections mean for COVID-19. The Lancet Infectious Diseases. 2020.

37. Control ECfDPa. Reinfection with SARS-CoV: considerations for public health response: ECDC; 2020. 2020;21 September 2020.

38. Selhorst P, van Ierssel S, Michiels J, Mariën J, Bartholomeeusen K, Dirinck E, et al. Symptomatic SARS-CoV-2 reinfection of a health care worker in a Belgian nosocomial outbreak despite primary neutralizing antibody response. medRxiv. 2020.

39. Stephens DS, McElrath MJ. COVID-19 and the Path to Immunity. JAMA. 2020;324(13):1279-81.

40. Kellam P, Barclay W. The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection. J Gen Virol. 2020;101(8):791-7.

41. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2020.

42. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JCC, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. bioRxiv. 2020.

INA-RESPOND Newsletter

POSTPARTUM EXERCISE: WHAT YOU NEED TO KNOW

By: Maria Lestari

SPORT & LIFESTYLE

For more than 20 years, many studies have found many beneficial things about physical activity during and after pregnancy for both mother and baby. It is hard for some mothers to get their body back pre-pregnancy (postpartum weight retention). Usually, it is because of inadequate physical activity, poor nutrition, and probably excessive weight gain during pregnancy. After some time, weight retention, physical inactivity, and poor nutritional choices can lead to many chronic health conditions, including obesity.1 Thus, after pregnancy, physical activity and exercise are one of the best things you can do for yourself.

Although the postpartum period is an important time for transition, returning to a physically active lifestyle or starting a new habit can be challenging for many mothers. For some mothers, motherhood challenges can be found in physical or mental symptoms. Fatigue and sleep disturbance are the most common things present in nearly two-thirds of women 12 months after delivery. The lack of movement due to fatigue, newborns' sleep and feeding schedules, other duties as a wife, or working schedules can be too much and can negatively affect mom's ability or desire to exercise consistently. In some cases, it can lead to depression.2

Exercise in the Postpartum Period

Several studies reported that the level of participation in exercise for women after delivery is decreasing, which can lead to overweight or obesity. The postpartum period is an opportunity for sports medicine doctors and other health care to introduce a healthy lifestyle. Returning to exercise or making a new exercise habit after childbirth is important to sustain a lifelong healthy habit. Exercise routines may be resumed gradually after pregnancy as soon as it is medically safe, depending on the delivery mode (vaginal or cesarean birth) and the presence or absence of medical complications.3

Some women can resume their physical activities within days of childbirth. Pelvic floor exercise can be started as a basic reintroduction to exercise during the postpartum period. Abdominal strengthening exercises, such as abdominal crunches and the drawing-in exercise (a maneuver that increases abdominal pressure by pulling in the abdominal wall muscles), have been shown to decrease the interectus distance and decrease the incidence of diastasis recti and urinary incontinence in women who give birth vaginally or by cesarean delivery. Regular aerobic exercise in lactating women has been proven to increase their

cardiovascular fitness without negatively affecting milk production, composition, or infant growth.4, 5

Benefits of Postpartum Exercise

Although conventional wisdom might suggest that exercise will accentuate fatigue, the opposite is generally true. Prolonged rest/physical inactivity contributes to fatigue, promotes increased body weight and decreased vigor and mental acuity, and increases the risk of developing future chronic health conditions.6 An emerging body of evidence indicates that exercise in the postpartum period:

- Reduces fatigue and increases vigor
- Improves mood states and mental acuity
- Improves fitness
- Promotes return to pre-pregnancy weight
- Decreases the risk for developing future chronic health conditions
- Provides important mom time and social interactions

Return to Exercise Safely

Many guidelines are based on common sense and not evidence-based on scientific literature. In a recent statement from the American College of Obstetricians and Gynecologists (ACOG), pre-pregnancy exercise routines may be resumed postpartum slowly, as soon as it is medically and physically safe.7 However, there are no conclusions and recommendations for postpartum exercise listed in the document. In Canada, the current recommendations suggest that if pregnancy and delivery are uncomplicated, a mild exercise program consisting of walking, pelvic floor exercises, and stretching of all muscle groups may begin immediately. However, if delivery was complicated or included a Cesarean section, a medical caregiver's consultation should be given before resuming physical activity, usually after the first postpartum checkup (6–8 weeks). In general, physician approval is indicated before starting a moderate aerobic exercise program, and vaginal bleeding from delivery should be minimal.8

Other activities, including walking up and down the stairs, lifting heavy objects, and performing muscle-toning activities, can begin without delay after uncomplicated vaginal delivery. After cesarean section delivery, maternal activities at home for the first week should be limited to personal care and care of the infant, and by the third to fourth week, most activities at home can be resumed. Care must be given to the incision site, and stretching exercises should be avoided until the incision is healed.9

Those who had exercised before pregnancy consistently and remained physically active throughout pregnancy often can return to their pre-pregnancy routines faster once given medical clearance. But for those who were inactive need to start and progress more gradually.6 Following are some tips to consider when restarting your exercise routine:

- Check your health and get a medical clearance from your health provider.
- Begin with low-intensity activity and gradually increase to a moderate one.
- Try to use a pedometer to count your steps.
- Gradually introduce various resistance training and/or functional training activities. A sports medicine can provide exercise prescription and guidance on appropriate activities, form, and intensity.

Conclusion

There are numerous benefits to being physically active after pregnancy, including reducing fat mass, increased lean mass, improved lipid profiles, and enhanced mental outlook and acuity. All women are encouraged to begin exercising as soon as medically appropriate and to remain physically active throughout their lifetimes.

References

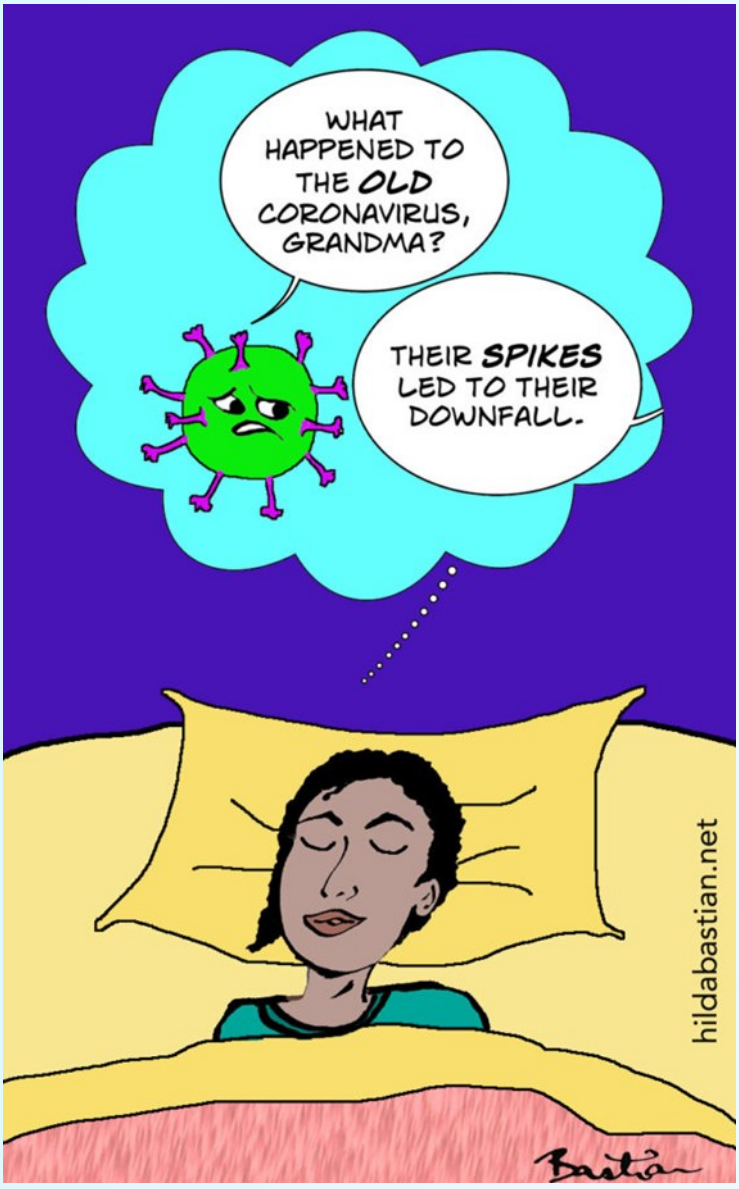
1. Davies G, Wolfe L, Mottola M, MacKinnon C, Arsenault M-Y, Bartellas E, et al. Exercise in pregnancy and the postpartum period. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstétrique et gynécologie du Canada : JOGC. 2003;25:516-29.
2. Roy BA. Postpartum Exercise. ACSM's Health & Fitness Journal. 2014;18(6).
3. Ashrafinia F, Mirmohammadali M, Rajabi H, Kazemnejad A, Sadeghniiat Haghighi K, Amelvalizadeh M. Effect of Pilates exercises on postpartum maternal fatigue. Singapore Med J. 2015;56(3):169-73.
4. Cary G, Quinn T. Exercise and Lactation: Are They Compatible? Canadian journal of applied physiology = Revue canadienne de physiologie appliquée. 2001;26:55-75.
5. Mota P, Pascoal AG, Carita AI, Bø K. The Immediate Effects on Interrectus Distance of Abdominal Crunch and Drawing-in Exercises During Pregnancy and the Postpartum Period. The Journal of orthopaedic and sports physical therapy. 2015;45(10):781-8.
6. Roy BA. Postpartum Exercise. ACSM's Health & Fitness Journal. 2014;18(6):3-4.
7. Artal R, O'Toole M. ACOG Committee Opinion. Exercise in pregnancy and the postpartum period. Number 267, January 2002 ACOG. American College of Obstetricians and Gynecologists Int J Gynecol Obstet 2002 77 79 81 10.1016/S0020-7292(02)80004-2. British journal of sports medicine. 2003;37:6-12; discussion
8. Davies GA, Wolfe LA, Mottola MF, MacKinnon C. Joint SOGC/CSEP clinical practice guideline: exercise in pregnancy and the postpartum period. Can J Appl Physiol. 2003;28(3):330-41.
9. Milani HS, Amiri P, Mohseny M, Abadi A, Vaziri SM, Vejdani M. Postpartum home care and its effects on mothers' health: A clinical trial. J Res Med Sci. 2017;22:96-.

INA-RESPOND Newsletter

COMIC CORNER

COVID-19 VACCINE RACE: ROAR TO THE TOP FOR SAVING THE WORLD

By: Aly Diana



This very morning (16th November 2020), Moderna Inc. has announced that mRNA-1273, its vaccine candidate against COVID-19 in the first interim analysis which is based on 95 cases (90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group), resulting in a point estimate of vaccine efficacy of 94.5% (p <0.0001). A secondary endpoint analyzed severe cases of COVID-19 and included 11 severe cases in this first interim analysis. All 11 cases occurred in the placebo group and none in the mRNA-1273 vaccinated group. The interim analysis also included a concurrent review of the available Phase 3 safety data by the Data Safety and Monitoring Board, which did not report any significant safety concerns. The majority of adverse events were mild or moderate in severity. Grade 3 (severe) events greater than or equal to 2% in frequency after the first dose included injection site pain (2.7%), and after the second dose included fatigue (9.7%), myalgia (8.9%), arthralgia (5.2%), headache (4.5%), pain (4.1%) and erythema/redness at the injection site (2.0%). These solicited adverse events were generally short-lived.

Moderna has conducted a Phase 3 trial, a randomized, 1:1 placebo-controlled study testing mRNA-1273 at the 100 µg dose level in 30,000 participants in the U.S., ages 18 and older. This study enrolled more than 30,000 participants in the U.S., which includes more than 7,000 Americans over the age of 65, more than 5,000 Americans who are under the age of 65 but have high-risk chronic diseases, and more than 11,000 participants from communities of color that have historically been underrepresented in clinical research and have been disproportionately impacted by COVID-19. Alongside with the effectiveness of the mRNA -1273 vaccine, Moderna has announced that the vaccine candidate remains stable at 2° to 8°C (36° to 46°F) for 30 days, at -20° C (-4°F) for up to six months, and at room temperature for up to 12 hours.

A week before Moderna (9th November 2020), Pfizer Inc. and BioNTech SE has announced their mRNA-based vaccine candidate against SARS-CoV-2, BNT162b2, has demonstrated evidence of more than 90% efficacy against COVID-19 from evaluable 94 positive cases, based on the first interim efficacy analysis from the Phase 3 clinical study. The Phase 3 clinical trial of BNT162b2 has enrolled 43,538 participants, 38,955 of whom have received a second dose of the vaccine candidate as of 8th November 2020. Approximately 42% of global participants and 30% of U.S. participants have racially and ethnically diverse backgrounds. The trial is continuing to enroll and is expected to continue through the final analysis when a total of 164 confirmed COVID-19 cases have accrued. The study also will evaluate the potential for the vaccine candidate to provide protection against COVID-19 in those who have had prior exposure to SARS-CoV-2, as well as vaccine prevention against severe COVID-19 disease.

Both vaccine candidates are using mRNA technology, which has been extensively studied in the last decade, but no approved vaccine has used this technology until today. In case the U.S. Food and Drug Administration has approved the Emergency Use Authorization (EUA) of these two vaccines, mRNA-1273 and/or BNT162b2 will be the first available mRNA vaccine in history. Upon vaccination, the mRNA vaccine encoding the viral spike protein packaged in a lipid nanoparticle enters the cell, translated in the ribosome into protein. This protein is either broken into smaller pieces (peptides) by the proteasome or transported via the Golgi apparatus to the outside of the cell. The smaller pieces remaining in the cell are then presented as a complex with an MHC (major histocompatibility complex) class I protein on the cell surface. This complex is recognized by CD8+ T cells generating cell-mediated immunity.

On the other hand, the spike proteins outside the cell can be taken up by different immune cells and broken into pieces in the endosome. These pieces are presented on the cell surface as a complex with an MHC class II protein, which is recognized by CD4+ T cells facilitating B cells to make antigen-specific antibodies. The production of these foreign antigens within the body prepares the immune system to recognize and memorize this viral antigen, so it is ready to fight off future infections caused by a virus with the same antigen.

There are so many breakthroughs lately, sparking some hopes for the future. University of Oxford/AstraZeneca, Sinovac, and Sinopharm seem to follow soon, reporting their interim analysis results. As people in Indonesia most likely will get access to these three vaccine candidates, let's hope that we will hear the same good news soon. Nevertheless, this is just an interim report. Let's hope that the final report will also show the same great results. Again, just a sweet reminder, we don't just need COVID-19 vaccines to end this global crisis. We also need to ensure that everyone in the world has access to the vaccine and get vaccinated – "No one is safe unless everyone is safe"—best wishes for all of us.

References:

Li Y. 2020. Meet the mRNA Vaccine Rookies Aiming to Take Down COVID-19. CAS – A Division of the American Chemical Society.

Moderna Press Release. 16th November 2020. Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study.

Moderna Press Release. 16th November 2020. Moderna Announces Longer Shelf Life for its COVID-19 Vaccine Candidate at Refrigerated Temperatures.

Pardi N, Hogan MJ, Porter FW, Weissman D. 2018. mRNA Vaccines – A new Era in Vaccinology. Nature Reviews Drug Discovery. doi:10.1038/nrd.2017.243.

Pfizer Press Release. 9th November 2020. Pfizer and Biontech Announce Vaccine Candidate against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study.

World Health Organization. 12th November 2020. Draft Landscape of COVID-19 Candidate Vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

World Health Organization. 2020. Covax: Working for Global Equitable Access to COVID-19 Vaccines. https://www.who.int/initiatives/act-accelerator/covax.

Zhang C, Maruggi G, Shan H and Li J. 2019. Advances in mRNA Vaccines for Infectious Diseases. Frontiers in Immunology 10:594. doi: 10.3389/fimmu.2019.00594.

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INA-RESPOND Newsletter

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

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