FAQ COVID-19 in Indonesia

by Muhammad Miftahussurur

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Frequently Asked Questions of Novel Corona Virus: A review of the evidence

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Isna Mahmudah[1], Langgeng Agung Waskito[1], Muhammad Miftahussurur[1,2]*

[1]Institute of Tropical Disease, Universitas Airlangga, Surabaya 60115, Indonesia

[2]Gastroentero-Hepatology Division, Department of Internal Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya 60286, Indonesia

Corresponding author

Muhammad Miftahussurur, MD, PhD

Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya 60286, Indonesia

Jalan Mayjend Prof. Dr. Moestopo No. 6-8 Surabaya 60286, Indonesia.

Tel: +6231-502-3865; Fax: +6231-502-3865

E-mail: muhammad-m@fk.unair.ac.id

Abstract

The corona virus outbreak has become a global pandemic. This situation triggers a sense of crisis in the community. Massive flow of information makes people confused due to the information might be incorrect. Therefore, summary in a review to answers some questions that commonly asked among community is necessary. Information related to sunbathing habits during the daytime is becoming popular, vitamin D is believed by the public to come from sun exposure. However, excessive ultra violet (UV) light from sun exposure could be dangerous. Therefore, it needs to consider several things in applying sunbathing habits. The controversy over the outcome of angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) has an adverse effect on coronavirus infection. In contrary, recent studies of the drug have a protective effect against lung tissue damage caused by this virus infection. Therefore, it not necessarily to stop this medication. In addition, there were findings that a high viral titer of coronavirus was found in asymptomatic or pre-symptomatic patients. Therefore, it could contribute to high transmission rates in the community. It is necessary to do precaution in order to stop the transmission. The existence of massive information flow though needs to filter information based on scientific to prevent the misleading information. Break the chain of infection with appropriate diagnostic tests then isolate the positive person is the best way to resolve this pandemic.

Keywords: COVID-19, SARS-CoV-19, Indonesia, FAQ

1. Introduction

In the last two decades, there have been two major pandemics caused by coronaviruses, in 2003 there was severe acute respiratory syndrome (SARS) and the middle east respiratory syndrome (MERS) in 2012 [*Raoult D et al., 2020*]. In the end of 2019, the world was surprised by the emersion of a new virus caused pneumonia which was at reported by the Chinese Government on December 31, 2019. This new emerge disease first hit Wuhan, a city in the center of China. The death cases from this new novel viral infection were first reported in Wuhan China on 9th January 2020. The virus was then known as new species of the coronavirus family, which is well known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease is known as Coronavirus Disease (COVID-19) [*Raoult D et al., 2020*]. This new virus has attribute to spread quickly and by now had reached more than 150 countries. WHO stated that this COVID-19 is a global pandemic on March 11, 2020 [*Morens DM et al., 2009*]. In Indonesia, COVID-19 cases were first reported on March 2, 2020 from Jakarta, in 2 women aged 64 and 31 years.

During the outbreak of this virus, there were several unclear information about COVID-19 circulating in the community. Since this disease is massively spread worldwide, there are several assumptions how actually this virus is transmitted among human, and what the best way to prevent this transmission. Is wearing mask, physical distancing was the best way to break the transmission chain? In addition, a relative cheaper option of immunoassay-based test to screen infected individual is still debatable. Indeed, a caution is necessary to interpret the result of this immunoassay-based test. As this viral infection which most likely to be a self-limiting disease, reinforcing the immune system is one way to prevent contracting the COVID-19. Sunbathing was reported may enhance immunity by producing vitamin D to give a beneficial in the role of immunity [*Maruotti N, Cantatore FP, 2010*]. However, sunbathing also has an adverse effect on triggers the development of skin cancer due to UV

radiation [*D'Orazio J et al., 2013*]. Therefore, it is important to understand how this virus actually spread, what test is adequate to determine infected individual and how actually we can do to prevent the transmission.

It is familiar that SARS-CoV 2 used angiotensin converting enzyme 2 (ACE2) receptor which is one of target therapy for hypertension patients [*Zhang H et al., 2020*]. Hypertension itself remains a problem in Indonesia with prevalence of 33.4 % (95 % CI: 32.7-34.0) [Peltzer K, Pengpid S, 2018]. Therefore, it makes anxiety in patients with hypertension whose been controlled with anti-hypertensive drug therapy group ACE inhibitors (ACEI) or Angiotensin 2 Receptor Blockers (ARB). In addition, smokers were generally considered a group with a high risk of becoming infected with lung disease. According to a study, smokers usually suffer from a more severe and prolonged form of the disease, which then causes COVID-19, compared to the nonsmokers group [*Russo P, et al., 2020; Zhou F, et al., 2020*]. However, the nicotine contained in cigarettes was recently known to have a therapeutic effect for COVID-19 [*Wittebole X et al., 2007; Mabley J et al., 2011*].

The global case fatality rate (CFR) of COVID-19 was approximately 1.78 % (95% CI: 1.34- 2.22) [*Maitra S et al., 2020*], depends on the how fast is detected and treated and comorbid condition. Delayed disease discovery may increase the CFR. Therefore, the effective drugs are needed in the community. The discovery of a treatment that was developing at this pandemic was chloroquine (and hydroxychloroquine) can also be used also for COVID-19 therapy. This drug has been known as a malaria drugs [*Meo SA et al., 2020*]. However, this drug that has not been used for a long time because of malaria parasite resistance to this drug in Indonesia [*Sutanto I et al., 2010*]. It use was still often used in autoimmune disease [*Mehra MR et al., 2020*] .

Those issues are most commonly asked in Indonesia, in the general community or even among medical practitioners. Here, we summarize the current understanding regarding

most frequently asked questions about COVID-19. It is necessary to underline that the answers to the questions below were temporary answers that may change any time along with the development of the latest scientific evidence related to COVID-19.

Is the sunbathing has benefit to prevent COVID-19?

Sunlight is source of light, heat and energy essential for life on the earth. It consists of various types of light, ultraviolet (UV) light is one of them. UV has multiple and complex benefit for human health. One of the UV benefit for human that it mediates natural synthesis of endorphins and vitamin D [*Trummer C et al., 2016*]. Atrophy, wrinkles, pigment changes, and malignancies, such as squamous cell carcinoma (SCC) and malignant melanoma (MM) are skin disorders influenced by the role of UV as risk factors [*González Maglio DH et al., 2016*].

UV fall in the midst of the wavelengths of visible light and gamma radiation (approx. 100 nm-400 nm) [*Rahman Tamuri A et al., 2014*] . Based on the electro physical properties, UV light divided into UV-A, -B and -C photons, with UV-A has the longest wavelengths (315-400 nm), UV-C has the shortest wavelengths (200-280 nm) and UV-B is falling in between UV-A and UV-C. Based on those different wavelengths, there are diverse effects on cell biology of the skin along with the immune system [*Maruotti N, Cantatore FP, 2010; D'Orazio J et al., 2013*] . Sunlight reaching earth's surface was dominated by UV-A (95% - 99%) and UV-B (1% - 5%) because the atmospheric ozone layer absorbs UV-C [*D'Orazio J et al., 2013*]. The low amount UV-B reaching earth's surface mostly due to the 99% of UV-B radiation is absorbed by the ozone layer [*D'Orazio J et al., 2013; Wacker M, Holick MF, 2013*].

Vitamin D in humans is obtained orally through food and synthesized in the skin. UV-B radiation exposure in the skin triggers the synthesis of vitamin D. During sunlight exposure, radiation of UV-B is absorbed by the skin and transformed 7-dehydrocholesterol to pre-

vitamin D_3 and will be finalized as a vitamin D3 [*Holick MF et al., 1981*]. Phosphate and calcium metabolism are useful for the maintenance of metabolic functions is also obtained from UV-B radiation which is absorbed by Pre-vitamin D3 and vitamin D3 and converted into various of the two main photoproducts; lumisterol3 and tachysterol3 [*Holick MF, 1994*]. Enhancing calcium homeostasis and improving bone health are also functions of vitamin D [*Maruotti N, Cantatore FP, 2010*].

The kidneys and liver metabolize Vitamin D in into 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D as the major circulating and biologically active form, respectively. Many organs are able to produce 1,2-dihydroxyvitamin and have a vitamin D receptor. Therefore, several of biological pathways and association studies related to vitamin D deficiency are influenced by 1,25-dihydroxyvitamin D with increased risk for disease of cardiovascular, cancers, autoimmune diseases, schizophrenia, diabetes mellitus type 2, and infectious disease [*Hoel DG et al., 2016*].

B-, T-, and antigen presenting-cells as immune cells express vitamin D receptors, so vitamin D can modulate innate and adaptive immune responses. Many studies showed auto-immune diseases is associated with vitamin D deficiency although an increasing infection susceptibility [*González Maglio DH et al., 2016*]. Report between 1988 and 1994 using nearly 19,000 subjects showed individuals with <30 ng / ml (low) vitamin D level were more likely to be infected with upper respiratory infections than those with adequate levels [*Ginde AA et al., 2009*]. Other prospective study, double blind placebo study showed that administration of vitamin D resulted in a statistically significant decrease was generated in incidence of influenza infection [*Urashima M et al., 2010*].

In vivo studies showed the important role of vitamin D in immune response [*Liu PT, 2006; Liu PT et al., 2009; Greiller CL, Martineau AR, 2015*]. Vitamin D receptor (VDR) and the CYP27B1 enzyme expressions by most immune cells has extensive and varied effects on

the immune system. The increase of the 1-α-hydroxylase and the VDR expressions is provoked by toll like receptor (TLR) binding [*Liu PT, 2006*]. Then, induce binding of the 1,25 D-VDR-RXR heterodimers to the VDREs of the genes for cathelicidin, beta defensin 4 and subsequent transcription of these proteins. Transcription of cathelicidin is absolutely dependent on sufficient 1,25-hydroxyvitamin D [*Liu PT, 2006*]. It is now clear that beta defensin 4 transcription requires NF-κB binding to appropriate response elements on the beta defensin 4 RNA [*Liu et al., 2009*]. Translocation of NF-κB to its binding site is generated via TLR 2-1 signaling facilitating the IL-1 receptor [*Liu et al., 2009*]. Therefore, the effects of vitamin D metabolites in the pathogenesis of viral or bacterial in the adhesion to the respiratory epithelial cells.

Synthesis of sunlight that induced vitamin D is exceedingly influenced by many factors, including season, time, latitude, altitude, air pollution, sunscreen utilization, skin pigmentation, and aging [*Maruotti N, Cantatore FP, 2010*]. Study in Alaska showed in early morning before 10 a.m. and late afternoon after 3 p.m any vitamin D_3 can be released in the skin [*Kenny DE et al., 2004*]. Sunlight exposure at that time will produce vitamin D which can lasts twice as long in the blood compared to the digested vitamins [*Haddad JG et al., 1993; Kenny DE et al., 2004*]. A clinical study from Sweden comparing full body irradiation with UV-B lamps 3 times a week for 6 weeks to a vitamin D_3 daily supplement of 1,600 IU daily for 6 weeks found UV-B therapy to be more effective in incrasing serum into 25-hydroxyvitamin D concentration [*Bogh MKB et al., 2012*]. However, various studies on the effect of light exposure UV-B to a concentration of vitamin D, generally performed on white populations and uses artificial UV-B rays. UV-B rays from sunlight in the tropical country, including Indonesia showed the highest intensity in the sun exposure between 11 a.m and 11 p.m [*Setiati S, 2008*]. However, there are several factors that can decrease vitamin D_3 production in the skin, including increased skin pigmentation, aging, and the topical

application of a sunscreen [*Bogh MKB et al., 2012; D'Orazio J et al., 2013*] .

Vitamin D levels in the form of 25-hydroxyvitamin D are maintained by the body at least 30 ng / mL [*Hoel DG et al., 2016*]. Large capacity of vitamin D is produced through the skin, 15,000-20,000 IU of vitamin D is equivalent to 1 erythema minimum (MED) is one time exposure to sunlight throughout the body. Therefore, the body surface needs to be exposed to 0.5 MED (50%) to produce 4000 IU of vitamin D a day. Body surface exposed to 0.5 MED with a duration of 2-3 times a week is equivalent to consuming 2000 IU of vitamin D a day to reach a minimum level of 30 ng/mL in the blood [*Hoel DG et al., 2016*]. The exposure time required at an intensity of 1 MED/hour is 1/4 x 60 minutes or equal to 15 minutes [*Setiati S, 2008*]. Therefore, duration needed to sunbathe in Indonesia at an optimal hour is about 7.5 minutes between 11 a.m. to 1 p.m. 2–3 times a week but it is still debatable because MED among individuals was varies especially depend on the skin pigmentation.

As mention above, sunlight exposure especially those that are sufficiently able to provide vitamin D has an impact on the immune system which can prevent various infections, may including the COVID-19. However, there was no research evidence about the benefits for killing the SARS-CoV-2. In addition, there are several considerations need to addressed prior sunbathing, including increasing risk for skin cancer, possibility of heat-stroke and dehydration after the sunbathing.

How effective was the use of rapid immunoassay-based tests in Indonesia?

Polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), enzyme-linked immunosorbent assay (ELISA) and rapid diagnostic test (RDT) or lateral colloidal gold immunochromatography are some of the methods used to detect SARS-CoV-2 [*Green K et al, 2019*]. Currently, the frequently use two types of examination tests for COVID-19 infection, including RDT and PCR. Indonesian government using RDT for

screening method [*Intan G, 2020*].

Direct detection by the presence of virus via quantitative reverse transcriptase (RT-qPCR) is the recommended test for detecting SARS-CoV-2. Therefore, it is considered the best method for diagnosing COVID-19. Collection of specimens was taken from nose, throat of both using either swabs. Test recommendations to detect the most sensitive SARS-CoV-2 with samples collected from both upper and lower respiratory and Broncho alveolar lavage fluid (BAL). This recent study reported that more RNA from SARS-CoV-2 was detected via nasopharyngeal swab (NP) than an oropharyngeal (OP) swab, 63% and 32%, respectively. [*Ramanathan K et al., 2020*]. Purulent sputum production due to pneumonias viruses is typically not produced. Therefore, the NP specimen collection method is usually used in daily. The US CDC also recommends only the NP swab [*Centers for Disease Control and Prevention, 2020*]. However, sputum collection and especially via bronchoscopy is a procedure that requires trained staff, high-cost equipment and has the potential to increase a safety risk for healthcare workers through the production of aerosol droplets. Therefore, BAL was not used routinely. It should be noted that a patients with pneumonia should not be assumed that each of these (e.g., NP swab specimen, sputum, BAL) will have an equal chance of detecting SARS–CoV-2; the detection rate in each specimen type varies in every patient and may change in individual clinical condition. Thus far, the gold standard diagnosis method for COVID-19 is the detection of nucleic acid by NP (nasal) and OP (throat) swab sampling or other respiratory tract samplings with RT-qPCR and further confirmed by sequencing.

RDT or lateral flow assays use the same mechanism usually used for pregnancy tests. This particular method detects the antibody of virus from patient blood (e.g. vein or from a small finger prick) indicating the COVID-19 infection. It yields to the detection of antibody response instead of the virus itself. There are several factors increasing the performance of

antibody-based test, including time of the test (how long from the symptoms), age and patients immunology status. Early studies suggest that most patients seroconvert approximately 7 to 21 days after exposure to the virus, although some patients develop antibodies more rapidly [*Lisboa Bastos M et al., 2020; Patel R, 2020*]. It may yield a negative or non-reactive result if tested too early. In addition, recent systematic reviews and meta-analysis studies on accuracy of COVID-19 serological diagnostic tests showed the biochemical technique sensitivity of enzyme-linked Immunosorbent Assay (ELISA), lateral flow immunoassay (LFIA) and chemiluminescent immunoassay (CLIA) were 84.3% (95% CI:75.6-90.9%), 66.0% (95% CI:49.3%-79.3%) and 97.8% (95% CI:46.2%-100%) respectively [*Lisboa Bastos M et al., 2020*]. Therefore, a caution is necessary to interpret the result of the RDT.

There are several brands of RDT were circulating in Indonesia. Each brand may have different their own quality control (QC) prior distribution of the products. This different leads to major problem due to it may yield a different result. Many countries have returned rapid test products to factories due to the tests was not work properly or fake [*Grady D, 2020*]. Therefore, WHO has issued a list of NRAs that have been received through independent QC conducted by other countries.

RDT is one option to detect COVID-19 in the community. However, since COVID-19 is a global pandemic with massively spread among community, the best approach is to detect the sick person using standard diagnose method. Indeed, it need a huge amount of resources to test all of 'person at risk' and isolate them. However, it is currently the best option to slow down or even stop the pandemic. In addition, RDT accuracy is very dependent to the patients' clinical condition, time of test, target population and QC of the RDT itself. There was no validation study conducted to the RDT that circulating in Indonesia. Therefore, it is necessary to conduct a validation study for the available RDT. As for usage, RDT is more suitable for

screening instead of diagnostic.

How to understand silent spreaders in COVID-19 transmission?

The SARS-CoV 2 has a feature of quickly spread among community with almost 80% of the infected individuals are asymptomatic [*Rothe C et al., 2020*]. This leads to a difficulty to detect infected person unless they showed a *cardinal sign* of COVID-19 and confirmed by PCR test. In addition, asymptomatic person doesn't know if they were asymptomatic carriers of SARS-CoV-2. Finding and testing in persons who had close contact with the patient in some cases confirmed asymptomatic carriers [*Pan X et al., 2020*]. The asymptomatic carrier may has a main contribution to the quickly spread of the SARS-CoV 2.

Pre-symptomatic people are a group of people who have been infected. However, do not yet show symptoms. SARS-CoV 2 transmission occurred predominantly after several days of illness and was associated with modest viral loads in the respiratory tract at the onset of the disease, with viral loads peaking about 14 days after symptom onset [*WHO, 2020*]. A study from 23 January to 16 March in Singapore involving 243 cases of COVID-19 identified seven groups of cases where secondary case explanations occurred pre-symptomatic transmission [*Wei WE et al., 2020*]. Pre-symptomatic transmission was performed on contact tracing including the period before the onset of symptoms. These findings suggest even limiting the symptomatic person only may not enough to control the pandemic, since the asymptomatic individual may transmit the virus as well [*Kimball A et al., 2020*].

High viral titers of SARS-CoV-2 are reported in the saliva of COVID-19 patients. This high viral titers are just as high in asymptomatic or pre-symptomatic patients [*Maclntyre CR et al., 2009*]. Many COVID-19 patients are asymptomatic, and nearly all have a pre-symptomatic incubation period ranging from 2 to 15 days, with a median length of 5.1 days [*WHO, 2020*]. The early course of infection as a route of transmission was also found in

previous reports [*Rna Z et al., 2017*]. Therefore, attention to asymptomatic patients and during the incubation period needs attention to prevent people from being infected.

Do mask really reduce coronavirus spread?

The route of transmission of SARS-CoV-2 is likely via small droplets that are ejected when speaking, coughing or sneezing [*Duguid JP, 1946*]. The most common droplet size threshold has a minimum at 5 μm to 10 μm [*Morawska L et al., 2009*]. Recent analysis shows that speaking can be an important vector of transmission, transmission with a higher viral load is associated with an increase in the number and size of droplets created with louder speech [*Howard J et al., 2020*].

Recommendations on masks in the community vary across countries during the COVID-19 pandemic. In many Asian countries, face mask is used as hygienic habit. In contrast in European and North American countries as something only people who are unwell induced stigmatization and racial aggravations [*Feng S et al., 2020*] . The use of face masks in general, including healthy people, can prevent discrimination individuals who wear masks when feel unhealthy [*Feng S et al., 2020*]. A prospective study using a cluster-randomized trial comparing surgical masks, P2 masks that were not properly tested, and no masks in prevention of influenza like illness (ILI) in households suggests that face masks should have some effect on viral transmission such as distraction on hand-nose contact [*MacIntyre CR et al., 2009*].

Based on their filtering capability, mask can be made of different design and materials. N95 or FFP_2 respirators and face masks (surgical mask) are examples of personal protective equipment (PPE) used to protect the user from airborne particles and from fluids that contaminate the face. N95 (the American standard) was equivalent with FFP_2 (the Europe standard) respirators are recommended for health workers conducting aerosol-generating

procedures during clinical care of COVID-19 patients [*Howard J et al., 2020*]. While it has been shown that N95 or FFP_2 respirators and surgical mask perform well as PPE and can become a scarce resource during a pandemic. Therefore, cloth fabric face mask come into place to reduce the demand of N95 or surgical mask as general PPE. Particle sizes for speech are on the order of 1 μm while typical definitions of droplet size are 5 μm- 10 μm [*Davies A et al., 2013*]. Generally, available household materials have a filtration rate between 49% and 86% for 0.02 μm exhaled particles whereas surgical masks filtered 89% of those particles [*Davies A et al., 2013*]. In a laboratory setting, household materials had 3% to 60% filtration rate for particles in the relevant size range, finding them comparable to some surgical masks [*Rengasamy S et al., 2010*]. In summary, the filtration capacity in the droplet size involved in household masks is laboratory proven to be effective at blocking droplets from the user [*Papineni RS, Rosenthal FS, 1997*].

Since the COVID-19 pandemic spread so quickly around the globe and the cure of COVID-19 has not been discovered yet, the best strategy to overcome is by preventing to infect more people. Due to evidence shows COVID-19 can be transmitted before symptoms onset, the use of face masks in community can reduce the level of community transmission if everyone including people who are infected but without symptoms (asymptomatic) wear a face mask.

Is it necessary to stop taking ACEI or ARB during the Covid-19 Pandemic in hypertensive patients?

It is well known that SARS-CoV 2 interact with ACE receptor in human respiratory tract. In the human physiology, ACE has a major function to regulate body fluid, blood electrolyte and blood pressure. Currently, ACE inhibitor and angiotensin receptor blockers (ARB) drugs are commonly as therapeutic agent in the supervision of hypertension,

myocardial infarction in post treatment, heart failure and to prevent the progression of diabetes-related kidney disease rapidly [*Rico-Mesa JS et al., 2020*]. Since there is an intersect of receptor between COVID-19 and cardiovascular disease, it is interesting to understand the relationship between those diseases.

Physiologically, plasma sodium concentration is maintained by the renin-angiotensin-aldosterone (RAAS) system by the way of feedback from baroreceptors, blood pressure, and sodium as well as potassium levels. Initially, the metabolism of angiotensinogen to angiotensin I was played by renin released from the kidneys. Furthermore, the lungs and kidneys produce ACE, which changes angiotensin I to angiotensin II. Angiotensin II stimulates the cardiovascular response, vasoconstriction, aldosterone production and antidiuretic hormone (ADH), which lead increases the volume of body fluids through sodium, potassium, and water resorption resulting an increase of blood pressure [*Sparks MA et al., 2014*]. The homolog of the ACE2 receptor is ACE, a transmembrane aminopeptidase that express in many organs such as lungs, artery, kidney, and heart [*Kuba K et al., 2010*]. Reversal of RAAS activation due to ACE2 receptors by lowering angiotensin II and increase angiotensin 1/7 [*Sparks MA et al., 2014; Rico-Mesa JS et al., 2020*]. Angiotensin 1/7 acts on the receptor to have a vasodilation effect [*Sparks MA et al., 2014*]. Thus, the role of ACE2 and ACE was opposite in regulating blood pressure (Figure 1.).

SARS epidemic in 2002-2003 found that the SARS-CoV virus can enter host cells mediated through ACE2 receptors [*Patel VB et al., 2014*]. ACE2 bonds in humans have a strong affinity with the surface of the SARS-CoV virus as shown from crystal analysis studies and biochemical interactions on virus spike protein interactions. [*Li F et al., 2005*]. These bonds helped the SARS-CoV virus enter host cell. SARS CoV virus had 76.5% similarity in amino acid sequence with SARS-CoV 2 [*Xu X et al., 2020*]. A study showed that SARS-CoV2 virus was more efficient at recognizing ACE2 receptors in humans [*Wan Y et al.,*

2020]. Therefore, it has higher human to human transmission rate than SARS as we are experiencing now.

The important factor in infectivity is strongly suspected by the interaction between SARS-CoV and ACE2 , considering the SARS-CoV affinity for ACE2 receptors was high. ACE inhibition by ACE inhibitor reduce angiotensin I levels causing negative feedback; hence it may increasing the number of ACE2 receptors to interact due to low amount of available angiotensin I [*Rico-Mesa JS et al., 2020*] . Therefore, it may increase SARS-CoV 2 binding sites. Increasing binding sites is observed among patients with diabetes and/or hypertension, due to they are taking ACE inhibitor or ARB regularly [*Fang L et al., 2020*]. In addition, there were findings patients using ARB especially Olmesartan had an upregulation of ACE2, showed by an increasing of ACE2 secretion in urinary secretions [Furuhashi M *et al*., 2015]. In concordance, another study showed that Lisinopril could increase ACE2 levels by 5-fold and losartan increased ACE2 levels by 3-fold [*Ferrario CM et al., 2005*]. These findings suggest the use of ACE inhibitor and ARB may increase risk for severe COVID-19 infection. However, despite the hypothesis of an increase in ACE2, until now there is no correlation showed between usage of ACE inhibitor and ARB to the mortality or morbidity among COVID-19 patients [*Rico-Mesa JS et al., 2020*].

One study analyzed association between discontinuation of ACE inhibitor and ARB among 112 COVID-19 patients showed poor outcomes in cardiovascular mortality. This poor outcome mostly due to lactic acidosis, thrombotic states and fulminant inflammation [*Rico-Mesa JS et al., 2020*]. This finding suggests the usage of ACE inhibitor and ARB in COVID-19 patients with cardiovascular disease did not affect the COVID-19 progression. Therefore, several related professional organizations such as the Heart Failure Society of America (HFSA), the American College of Cardiology (ACC), and the American Heart Association (AHA) still recommend to not stop the use of ACE inhibitor and ARB drugs in COVID-19

patients who have used it before, due to the benefits of the drug were greater for preventing complications due to uncontrolled hypertension [*ACC, 2020; Guan W et al., 2020*]. In addition, ASEAN Federation of Cardiology (AFC) and Indonesian Heart Association (PERKI) also rejected that reasoning of the harmful of ACEI or ARB pertinent to COVID-19 infection (AFC, 2020). Therefore, those drugs still important for patient with cardiovascular disease and it not necessarily to stop the usage in this COVID-19 pandemic.

Does smoking protect us against coronavirus?

There was a lot of presumption about the smoking effects on COVID-19. The nicotine, primary components of tobacco smoke, may increase the risk of COVID-19 [*Russo P et al., 2020; Vardavas CI, Nikitara K, 2020*]. Recent study reported that current smokers and those with chronic obstructive pulmonary disease (COPD) has a higher expression of the ACE-2 epithelial cells [*Leung JM et al., 2020*]. As SARS-CoV 2 use ACE2 receptor as binding site, the up-regulation of ACE-2 caused by smoking could be harm for COVID-19 patients [*Cai G, 2020*]. However, many studies showed different result that seems up-regulation of ACE2 may become protective against disease severity [Reynolds HR *et al.*, 2020].

Angiotensin II side effects are neutralized by ACE2 by cutting angiotensin I and angiotensin II to angiotensin based on the renin-angiotensin-aldosterone axis. Recently, expression of ACE2 decreased in the lungs and other tissues is found in smoking and nicotine [*Farsalinos K et al., 2020; Zhang H et al., 2020*]. Nicotine modify the of the equilibrium RAAS by upregulating the destructive ACE/angiotensin (ANG)-II/ANG II type 1 receptor axis and downregulating the compensatory ACE2/ANG-(1-7)/Mas receptor axis, contributing to the development of cardiovascular and pulmonary diseases (CVPD) [*Lazartigues E et al., 2018*]. A study showed ACE2 protects the development of ARDS in mice [*Guo YR et al.,*

2020]. The recently observed up-regulation of ACE2 may be provoked as a defense way to neutralize the effects of angiotensin II in smokers [*Farsalinos K et al., 2020*]. Experimental data showed that organ damage and disease severity can be due to the continuous replication and infection of SARS-CoV-2 causing up-regulation of ACE2 regulation [*Reynolds HR et al., 2020*]. Therefore, increasing of ACE2 does not due define an increase in disease susceptibility or severity and may in fact be worthwhile. In addition, there are conflicting findings about smoking in the literature, reports that smoking and nicotine reduce ACE2 were widely published before the COVID-19 pandemic [*Durmus N, Grunig G, 2018; Lazartigues E et al., 2018*]. Whereas, several studies published during the pandemic reported upregulation of ACE2 [*Cai G, 2020; Farsalinos K et al., 2020; Russo P et al., 2020*]. Therefore, it can be assumed that there are no strong conclusions concerning the result of nicotine or smoking on ACE2.

Recent study showed a series of 150 cases in COVID-19 patients, a high of cytokines IL-6 are predictors of mortality [*Ruan Q et al., 2020*]. In concordance, result also was found in study using 191 patients that increased IL-6 was found to be increased in patients who did not survive compared to patients who survived [*Zhou F et al., 2020*]. However, releasing a large of cytokine IL-6 in SARS-CoV-2 infection is activated by the innate immune system, which causes increased vascular permeability resulting in the process of alteration of fluids and blood cells to the alveoli, resulting in clinical appearance of dyspnea and respiratory failure [*Green K et al., 2019; Farsalinos K et al., 2020*] . The infection respons that develops into ARDS was caused by an increase in the release of pro-inflammatory cytokines known as the cytokine storm phenomenon or cytokine release syndrome [*De Jonge WJ, Ulloa L, 2007; Farsalinos K et al., 2020*]. Therefore, cytokine suppression effects are needed to against cytokine-mediated diseases, including endotoxemia and septicemia, which lead organ damage and death.

Nicotine agonists with cholinergic that regulate immunity through inflammatory responses and anti-inflammatory pathways [*Kevin J. Tracey, 2010*]. In vitro studies conducted on animal models, acute respiratory distress syndrome can be prevented and expression of TNF in airway epithelial cells can be suppressed by nicotine [*Mabley J et al., 2011*]. In addition, in vivo studies conducted in humans unprotected to endotoxins, nicotine also showed anti-inflammatory effect [*Wittebole X et al., 2007*]. IL-6, IL-1 and TNF as pro-inflammatory cytokines are inhibited production but IL-10 as anti-inflammatory cytokines is not inhibited [Ulloa L, 2005].

Hypotheses regarding nicotine potential based on RAAS complex interactions and immunomodulatory effects can be explained. Measurable evidence regarding the risk of smokers with SARS-CoV-2 infection in some literature has not been proven. Thus, a population-based study is require to answer it. Clinical trials regarding cytokine strom as a therapeutic target are still being developed in COVID-19 patients. Recently, the US FDA approved a phase III clinical trial of IL-6 inhibitors as a reduction in the intensity of cytocone storms in nicotine utilization [*Farsalinos K et al., 2020*].

Will the antimalarial drug effective to combat COVID-19?

Nowadays, there was no definite and recommended therapy for COVID-19 due to the disease was still new. However, all antivirals used in COVID-19 therapy in almost all countries were still in trial and error. Like in other part of the world, there were no definitive guidelines to cure COVID-19 in Indonesia. As the COVID-19 outbreak began in China, Indonesia tried to refer to China regarding the drugs used, including Chloroquine. Chloroquine is well-known drug to treat malaria as an anti-plasmodium. Autoimmune diseases, including rheumatoid arthritis and lupus erythematosus also use chloroquine as

therapy agent; hence it might have a potential to be a broad-spectrum antiviral drug [*Meo SA et al., 2020*]. Increased pH of endosomes for viral fusion into cells and inhibition of cellular receptor glycosylation is known to be a way to inhibit SARS-CoV infection by Chloroquine [*Guo YR et al., 2020; Zhou F et al., 2020*]. A study of more than 100 COVID-19 patients showed usage of Chloroquine decrease the pneumonia exacerbations, long of symptoms and accelerated viral clearance without serious side effects [*Gao J et al., 2020; Mehra MR et al., 2020*] . In addition, in vitro study showed hydroxychloroquine in the SARS outbreak was previously inform to have anti-SARS-CoV [*Madrid PB et al., 2016; Retallack H et al., 2016*].

Hydroxychloroquine was a chloroquine analogue that reduces concern about drug interactions [*Jallouli M et al., 2015*]. In addition, hydroxychloroquine showed a stronger and less toxic. A study proves hydroxychloroquine has stronger antiviral activity shown by the EC_{50} value for hydroxychloroquine was smaller than the EC_{50} value for chloroquine [*Li C et al., 2017; Yao X et al., 2020*]. Hydroxychloroquine is a more soluble and safer metabolite of chloroquine, which causes less side effects [*Yao X et al., 2020*]. Indeed, both have immunomodulatory effects by suppressing the immune response which is resulted by SARS-CoV 2 infection and reducing the cytokine storm of IL-6 and IL-10; hence it may prevent the multi organ failure [*Huang C et al., 2020; Schrezenmeier E, Dörner T, 2020*]. Therefore, some consensus and research outcomes include Chloroquine and/or hydroxychloroquine as a drug-of-choice in preventing and treating COVID-19 (Table 1).

Current research data showed chloroquine-based therapy has promising result to combat COVID-19. Nonetheless, age, disease severity and clinical presentation are important to consider regarding the benefits of using chloroquine [*Touret F, de Lamballerie X, 2020*] . If clinical data confirm the biological results, chloroquine and hydroxychloroquine may be used in prophylaxis as well as curative treatment for individuals exposed to SARS-CoV-2 [*Meo SA*

et al., 2020]. Therefore, in future assessments of chloroquine dosage trials include high-quality clinical and safety data are required.

Table 1. Studies report of hydrocloroquine and chloroquine in COVID-19 treatment.

Type of study	Strategies	Intervention	Outcome	Ref
Clinical trial sample	30 patients	Hydrocloroquine, 400 mg per day for 5 days	• 86.7% of cases negative for virus nucleic acid on throat swabs specimen • Radiological progression in 33,3% cases	[Doudier B, Courjon J, 2020]
Clinical trial sample	100 patients	Chloroquine phosphate, dose not mentioned	• Chloroquine phosphate was important effect of clinical outcome and viral clearance • Exacerbation of pneumonia, improvement of lung image on radiological examination, negative virus examination and limitation of disease progression can be inhibited by chloroquine phosphate.	[*Gao J et al., 2020*]
Clinical trial sample	20 patients	Hydrochloroquin, 600 mg daily combined with azithromycin	• Hydrochloroquin was associated with the decrease and disappearance viral load of SARS-CoV-2 and azithromicin strengthens this effect	[*Doudier B, Courjon J, 2020*]
Expert Study Group Discussion	Expert consensus	Multicenter collaboration group	• It was recommended that chloroquine phosphate 500 mg twice per day for 10 years acceptable safety in treating COVID-19 associated pneumonia.	[*Meo SA et al., 2020*]

Figure Legend

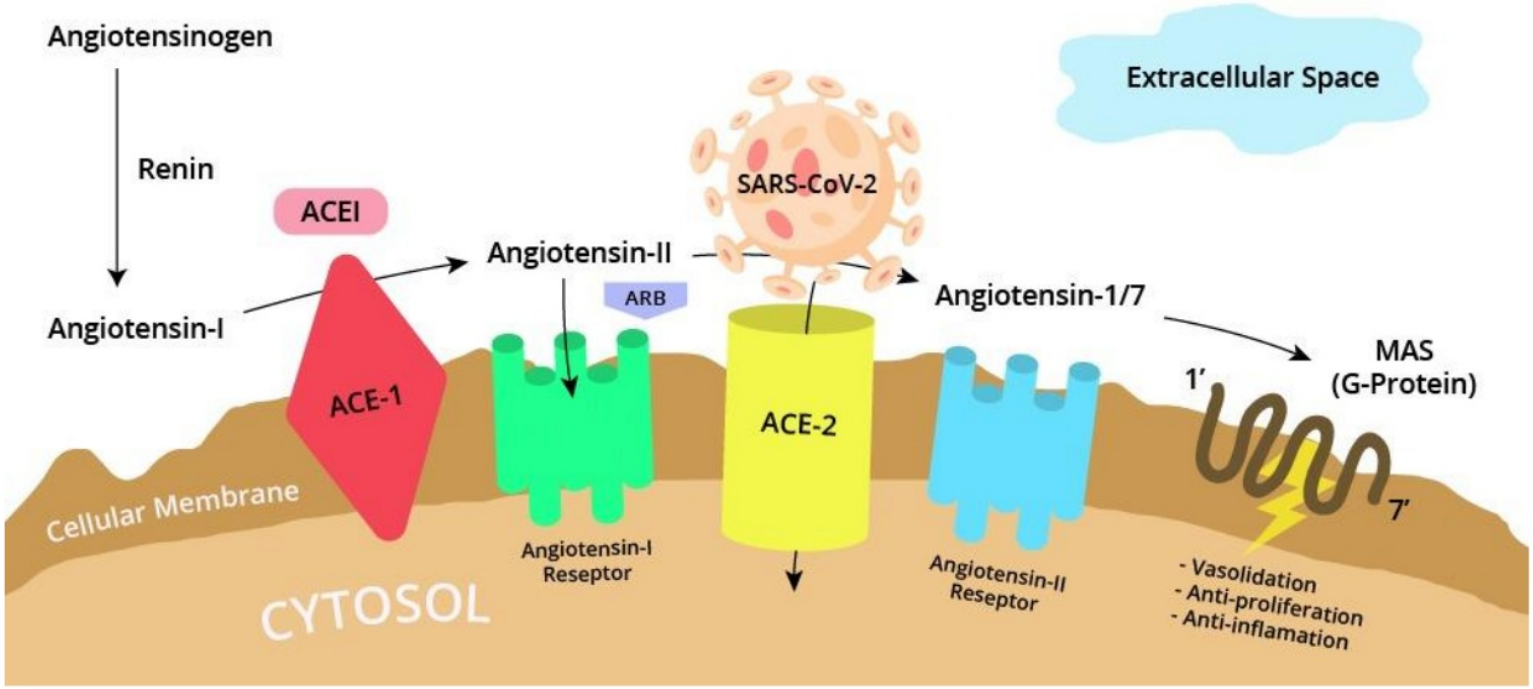

Figure 1. RAAS pathway showing mechanism of action ACEI/ARB and SARS-CoV-2 infectious mechanism by ACE2 receptors

5. Conclusions

The COVID-19 is not only global health pandemic, but also multi sectoral issue. A massive sense of crisis towards COVID-19 leads to massive information flow among community which may leads to misleading information. Scientific paper should be become a basis for every people to answer the commonly asked question among society. With the current state of pandemic which the finish line seems to be long way ahead, the best way to encounter the pandemic is by massive appropriate diagnostic test then isolate them; hence it may break the infection chain.

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