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Literature Review

The difference in severity and management between children and adult's cases of COVID-19

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ABSTRACT

COVID-19 (Coronavirus Disease 2019) has been started in Wuhan, China, and spread worldwide and resulting in many cases of death. COVID-19 attacks the respiratory tract acutely and infected both children and adults. The number of cases in children is less than in adults. By seeing from the clinical aspect, the COVID-19 case in children is milder. There are differences in immunology responses in children and adults where children have higher immunology response of COVID-19 than adults. Meanwhile, if the immunology response is slow in adults, it may cause them infected by COVID-19 with severe symptoms. There are some relations between immunization with immunology response to SARS-CoV-2 where children who already have BCG vaccination has lower infection rates of acute respiratory tract case. This study aims to know the difference between COVID-19 cases that infected adults and children seen in various aspects.



INTRODUCTION

The COVID-19 (Coronavirus Disease 2019) pandemic situation consists of a collection of severe acute respiratory diseases that threaten human health in the world (Rothan and Byrareddy 2020). Covid-19 infection in children under 15 years old is less than that of the adult, and the symptoms are milder. The epidemiological evidence stated that the number of deaths in pediatric cases is also lower than the adult, and there is a biological difference between children and adults (Sighn et al., 2017).

The case number COVID-19 in the world at the date of 27 November 2020 has reached 60.264.241 cases with many deaths of 1.420.306 patients (World Health Organization (WHO), 2020). The Indonesian Ministry of Health reported 522.581 cases of COVID-19 on 27 November 2020 (KEMENKES, 2020). COVID-19 case in children is fewer than in adults. 72.314 recorded positive COVID-19 in China, with 2% of the patients under 19 years old. Italy is one of the countries that experienced the pandemic's impact, with 1,2% of all children. Italy also has higher cases than China (7,2% vs 2,3%), but there is no mortality rate for children (Liguoro et al., 2020). It is recorded that 535 out of 113.368 COVID-19 cases are infected children under 18 years old in Spain (Melgosa et al., 2020). Not only in Italy, China, and Spain but also in children and Africa and America. From March until April 2020, there are 5,2% cases of children infected by SARS-CoV-2 out of 474 recorded cases (Bandi et al., 2020).

The number of deaths caused by COVID-19 in China is 2,3% (1.023 death cases out of 44.672 confirmed cases). There were no cases of death in 9 years old group and younger, but the case was found in 70 until 79 years old group, which has a death rate of 8.0%, and the case in 80 years old group or older has a death rate of 14,8% (Wu dan McGoogan, 2020).

Total number positive COVID-19 cases in Indonesia up until November 2020 reach 522.581. Active cases 68.604, recovered cases 437.456 and number of death cases 16.521. in a children, below 5 years reach 13.587 (2,6%), 6 until 8 years reach 45.987 (8,8%), 9 until 18 years reach 45.466 (8,7%) 19 until 30 years reach 129.077 (24,7%), 31 until 45 years reach 159.387 (30,5%), 46 until 49 years reach 120.716 (23,1%), over 60 years reach 54.348 (10,4%) (Satgas COVID-19, 2020; IDAI, 2020). However, the number of the adult is still higher in Indonesia, reach 79,9 % and 20,1% cases for children (Kementerian Kesehatan RI, 2020; SATGAS COVID-19, 2020).

LITERATURE REVIEW

Virology of SARS-CoV-2

The SARS-CoV-2 is an RNA (*ribonucleic acid*) virus with a small 120-160 nm size. 6 types of coronavirus can infect humans; they are alphacoronavirus 229E, alphacoronavirus NL63, betacoronavirus OC43, betacoronavirus HKU1, Severe Acute Respiratory Illness Coronavirus (SARS-CoV), and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Brooks et al., 2013).

The SARS-CoV-2 is included as one of the beta coronavirus genus, and many reports of phylogenetic stated that SARS-CoV-2 has the same subgenus with SARS virus component, which included as Sarbecovirus genus (Zhu et al., 2020). The SARS-CoV-2 also has similarity with SARS-CoV-2 gained from a bat and isolated, so there was a suspicion that SARS-CoV-2 is from mutated bats and infected humans (Zhou et al., 2020).

The computer test stated that the SARS-CoV-2 virus has a 3 dimension structure, including protein spike receptor-binding, and has a very strong affinity for angiotensin-converting-enzyme 2 (ACE2) (Zhang et al., 2020).

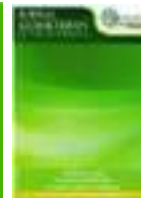
The SARS-CoV-2 has S-protein or spike protein



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in its surface that has a function to attach and enter the viruses into the human body (Z. Wang et al., 2020); the in-vitro data allows the virus to infect inside the human body by using the ACE-2 receptor (Susilo et al., 2020)

The Epidemiology of COVID-19 in pediatric and adults

China has reported that there are 44.762 cases of COVID-19, where 416 cases (1%) and 549 cases (1%) are children under ten years old and 10-19 years old (Z dan JM, 2020). In the United States, there are 32.437 positive cases where 168 cases (0,5%) and 425 cases (1,3%) are children from 0-4 years old and 5-17 years old (CDC COVID-19 Response Team, 2020). Indonesia reported that 522.581 cases of COVID-19 is 105.040 pediatric cases (20,1%), with the rate of deaths 528 cases (3,2%) (Satgas COVID-19, 2020).

The Center for Disease Control and Prevention (CDC) reported that children patient who is treated in hospital and Intensive Care Unit (ICU) is 5,7%-2,0% (0-4 years old) and 0,58%-2,0% (5-17 years old). Meanwhile, the number of adults who are treated in hospital and Intensive Care Unit (ICU) is 33% (CDC COVID-19 Response Team, 2020).

The case of children in China until N reached 2143 positive cases. The asymptomatic case in children (94), mild case (1091), moderate case (831), severe case (112), and critical case (13) (Dong et al. 2020). The severe case found in China and Italy reached 19% and 26% for adults older than 60 years old (Istituto Superiore di Sanità 2020a; Wu and McGoogan 2020). The death rate of children in Indonesia until mid-July 2020 is 2,06% for 0-5 years old and 0,50% for 6-17 years old (Setiabudi 2020).

From the report mentioned above, the number of adult's cases are higher than pediatric cases.

Pathogenesis and pathophysiology of coronavirus in pediatric and adults

The SARS-CoV-2 passes the respiratory tract and is attached to Angiotensin-Converting Enzym-2 (ACE-2) using the spike protein structure of SARS-CoV-2. The ACE-2 receptor can also recognize SARS-CoV (Dhochak et al., 2020; Hoffmann et al., 2020). The ACE-2 can be found in many organs, including oral mucosa, nasal, nasopharynx, lung, stomach, small intestine, large intestine, skin, thymus, bone marrow, spleen, liver, kidney, brain, pulmonary alveolar epithelial cells, small

Table 1. SARS-CoV-2 confirmed patient cases in children and adults.

Characteristics	Children	Children	Children	Adults	Adults	Adults
Number of patients	2572	171	105.040	113.985	1099	417.541
Age	<18 years old	<16 years old	<18 years old	18-64 years old	>15 years old	>18 years old
Region	United States	China	Indonesia	United States	China	Indonesia

Source: CDC COVID-19 Response Team, 2020; IDAI, 2020; Lu et al., 2020; Wu & McGoogan, 2020; SATGAS COVID-19, 2020



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intestinal enterocyte cells, endothelial cells venous arteries, and smooth muscle cells (PDPI, 2020).

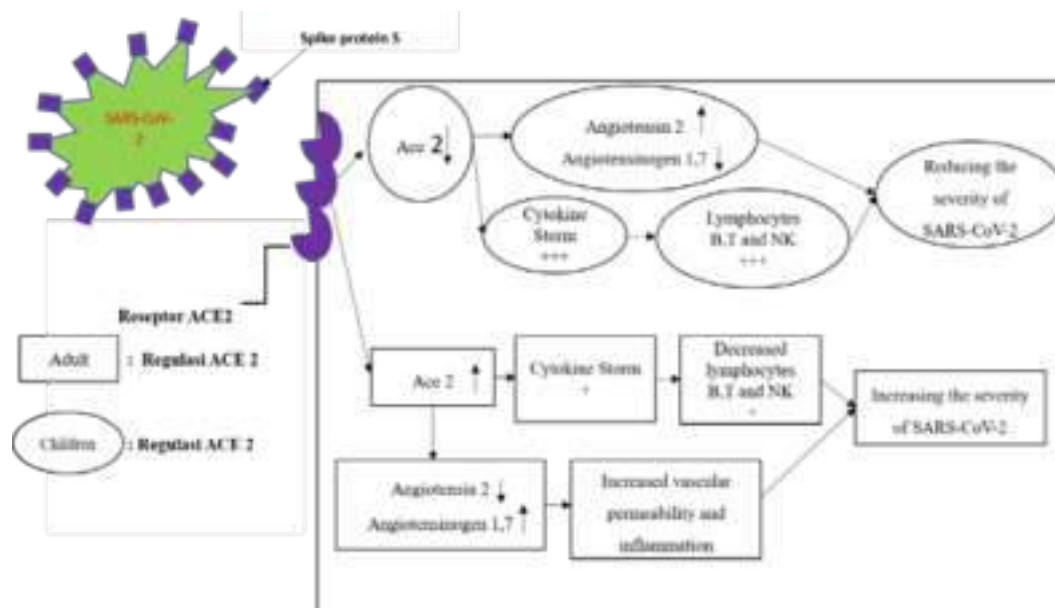
The SARS-CoV-2 enters the cell facilitated by proteolytic breakdown ACE-2 by transmembrane serine protease-2 (Dhochak et al., 2020; Hoffmann et al., 2020). Inside the cell, the RNA genome virus is released to the cytoplasm and then translated into two polyprotein and structural proteins. After being translated, the virus genome begins to multiply itself. The new glycoproteins which are formed on the virus's surface, started to go inside the endoplasmic reticulum membrane and the virus started to grow and forms nucleocapsid. In the last stage, the vesicles that already contain the virus start to combine with plasm membranes that have the purpose of releasing the new virus components (Susilo et al., 2020; de Wit et al., 2016).

Patients infected by SARS-CoV-2 experiencing a decrease of ACE-2 regulation that results in increased vascular permeability and inflammation. The ACE-2 activity in children is very high to give protection

from SARS-CoV-2 infection manifestation and reduce the severity level case (Cristiani et al. 2020; Dhochak et al. 2020; de Wit et al. 2016). The result from recent studies, it is still hard to predict that ACE-2 activity in the lungs is more important than SARS-CoV-2 because the infection of SARS-CoV-2 is more severe clinically in infants rather than the older children (Dhochak et al. 2020).

The difference between adults and children case is related to living habits and host factors. Children are tended to play at home and are taken care of by the parents, so they have a lower chance of infected by the pathogens. Meanwhile, adults have a responsibility to work, etc., which have a higher chance of infected by the pathogens. Children are also less sensitive to SARS-CoV-2 because of the maturity, function, and number of the ACE-2. Besides the ACE-2 factor, children often experience respiratory tract infections that might have a higher antibody level to the virus, and the immune of children still develops and might recognize the pathogens differently than adults (Dong et al. 2020).

Figure 1. The difference of ACE-2 expression in pediatric and adults infected with SARS-CoV-2 (Cristiani et al. 2020; Dhochak et al. 2020; de Wit et al. 2016).





The clinical symptoms of pediatric and adult cases

The clinical symptoms of children infected by SARS-CoV-2 now are milder than the adult infected by SARS-CoV-2. More studies in pediatric SARS COV-2 was conducted; it is now clear that children of any age can be infected. But the case is more difficult to detect since they are likely to be asymptomatic and the possibility to get tested is small (Dong et al., 2020; Lu et al. 2020; Sighn et al. 2017).

The main SARS-CoV-2 symptoms are fever and cough. Some patients experience dyspnea, vomit, diarrhea, myalgia, and fatigue. The fever symptoms in children are only 51,6%, cough 47,3%, and sore throat 17,9%. A few children are infected with SARS-CoV-2 who experienced dyspnea and decreased oxygen levels (7,7% and 9,7%) (Liguoro et al., 2020; Lu et al., 2020; Sun et al., 2020). Other symptoms outside the respiratory are found in children infected by SARS-CoV-2, which is diarrhea (9,7%), vomit (7,2%), and fatigue (10,6%) (Liguoro et al., 2020).

The most common symptoms in adult infected by SARS-CoV-2 is fever (98%), cough (76%), dyspnea (55%), and muscle ache or fatigue (44%). In another study, the symptoms in an adult patient of 70 years old or older are also found shortness of breathing (76%), fever

(52%), and cough (48%). The adult case with covid-19, a 86% had comorbid diseases such as chronic kidney disease (48%), congestive kidney failure (43%), chronic obstructive pulmonary disease (33%), and diabetes (33%) (Shahid et al., 2020)

Total calculation of a (n=1016), Total calculation of b (n=2.572), Total calculation of c (n=113,985), and calculation of d (n=41).

The COVID-19 classification in pediatric

COVID-19 cases classification consists of asymptomatic cases, mild cases, moderate cases, severe cases, and critical cases.

- A. Asymptomatic case : test results were positive with no clinical signs and symptoms
- B. Mild case : Has symptoms of an upper respiratory tract infection such as fever, fatigue, myalgia, cough, sore throat, cold, and sneezing. In some cases, it may have no symptoms of an upper respiratory tract infection and is only accompanied by gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea, or other non-respiratory symptoms.
- C. Moderate case : sign and clinical symptoms of pneumonia. Fever, cough, tachypnea, can be accompanied by rhonchi or wheezing in lung auscultation without respiratory distress and hypoxemia.

Table 2. Clinical symptoms of SARS-CoV-2 in the case of pediatric and adults

	Pediatric	Adults	Pediatric	Adults
Fever	163 (56) ^b	7.794 (71) ^c	503 (51,6) ^a	40 (98) ^d
Cough	158 (54) ^b	8775 (80) ^c	461 (47,3) ^a	37 (76) ^d
Sore throat	71 (24) ^b	3.795 (35) ^c	174 (17,9) ^a	
Dyspnea	39 (13) ^b	4674 (43) ^c		22 (55%) ^d
Diarrhea	37 (13) ^b	3.353 (31) ^c	94 (9,7) ^a	
Vomiting	31 (11) ^b	1.746 (16) ^c	70 (7,2) ^a	
Headache	81 (28) ^b	6.335 (58) ^c		3 (8) ^d
Myalgia / Limp	66 (23) ^b	6.713 (6,9) ^c	103 (10,6) ^a	18 (44) ^d

Source: CDC COVID-19 Response Team, 2020; Huang et al., 2020; Liguoro et al., 2020



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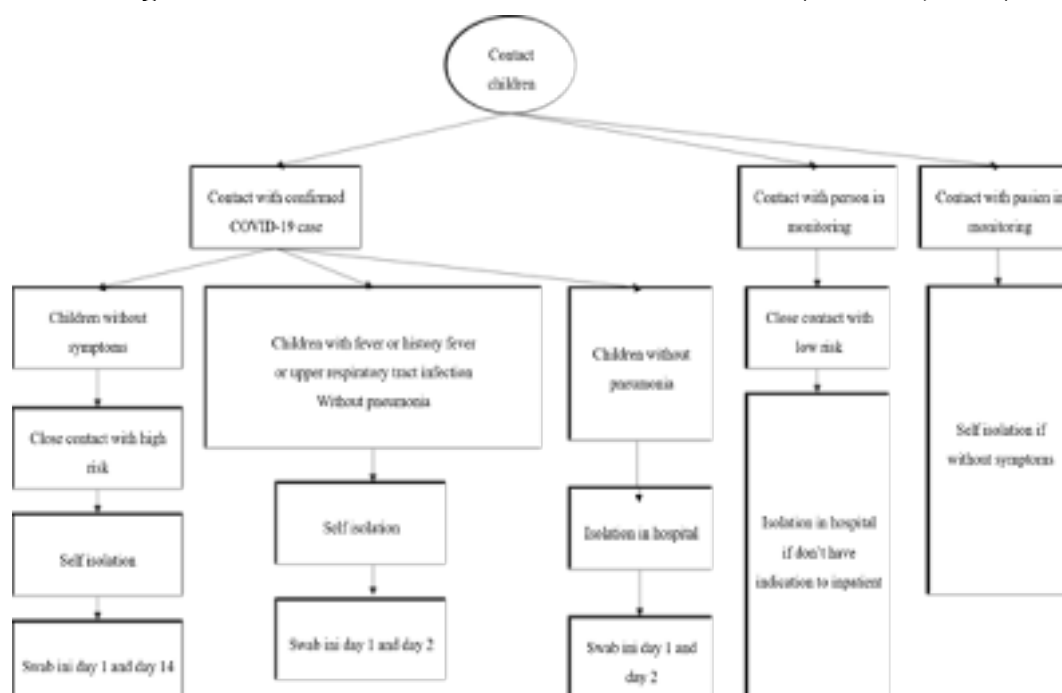
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- D. Severe case : Has clinical symptoms of severe pneumonia such as nostril breathing, cyanosis, subcostal retraction, desaturation (oxygen saturation <92%). In some cases, it may have common dangerous clinical symptoms such as seizures, decreased consciousness, profuse vomiting, and unable to drink, with or without respiratory symptoms.
 - E. Critical case : Patients rapidly experience Acute Respiratory Syndrome (ARDS) or respiratory failure, or experienced shock, encephalopathy, myocardial damage, coagulopathy, acute renal failure, and multiple organ dysfunctions or other manifestations of sepsis
 - F. Multisystem inflammatory syndrome: children and adolescent aged 0-19 years old with 3 days fever, accompanied by minimum 2 of the following:
 - a. Rash or bilateral non-purulent conjunctivitis or sign of oral, hand, or foot mucocutaneous inflammation
 - b. Hypotension or shock
 - c. Myocardial dysfunction, pericarditis, vasculitis, coronary abnormality (consists of abnormality in echocardiography, an increase of troponin/NT-pro BNP)
 - d. Proven coagulopathy (Increase in PT, APTT, D-Dimer)
 - e. Acute symptoms of gastrointestinal (diarrhea, vomiting, or abdominal pain)
- AND increase in inflammatory markers such as LED, CRP, or procalcitonin.
- AND no prove of involvement of bacterial etiology as the cause of inflammation (bacterial shock, shock due to staphylococcal or streptococcal)
- AND with confirmed case COVID-19 infection (RT-PCR, positive antigen test, or positive serology) or high probability of contact with the confirmed case (IDAI, 2020).

Chart 1. Algorithm of Classification COVID-19 case on adult (Andriani, 2020)





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The severe and critical case of SARS-CoV-2 patient relates to another disease experienced by the patient (such as, Hypertension) (Dong et al. 2020). The number of COVID-19 case with comorbidity in Indonesia reach 1881 with hypertension 52,2%, diabetes mellitus 35,2%, heart diseases 18,4% and others. (Satgas COVID-19, 2020).

Laboratory findings on adult and pediatric of COVID-19 cases

The laboratory findings of child cases in Indonesia have been compared with laboratory findings in Wuhan China. There are 4 studies conducted on lymphocyte range and two studies reported that there is a decrease in lymphocytes for 10 of 214 cases. Based on two other studies which reported there was an increase in lymphocytes for 18 of 43 cases. Besides changes in the number of lymphocytes, there was also a change in the amount of C-Reactive protein

that increased ($> 5\text{mg/L}$) in 70 of 271 pediatric cases infected with SARS-CoV-2 (Lee-Archer and von Ungern-Sternberg, 2020).

Blood test findings in adult cases infected with SARS-CoV-2 include lymphocyte range, neutrophil count, total cell T, total CD4^+ , CD8^+ , total cell B, total cell NK (Natural Killer), and CRP total (C-Reactive Protein). Based on some studies conducted in Wuhan, it is found that there is a decreased amount of white blood cells is ($< 4 \times 10^9$) from 10 of 40 adult cases. Not only the decrease amount of white blood cells, but there is also a decrease amount of lymphocytes in adults from 26 of 40 cases reported the number of lymphocytes is $< 1.0 \times 10^9/\text{L}$ (Huang et al., 2020). Other studies also compared the immune profile between children and adults that in adults is found a lower amount of cell T, cell T CD8^+ , and cell B (Chen et al., 2020).

Table 3. Laboratory results of COVID-19 in pediatric and adults

	Pediatric (n=12)	Adults (n=20)	Pediatric (n=38)	Adults (n=41)
Neutrophil ($\times 10^9/\text{L}$)			5,6-6,6	3,3-8,9
Lymphocyte range ($\times 10^9/\text{L}$)			4,33-6,13	0,6-1,1
Hemoglobin (g/L)			114-140.15	118.0-140.0
Cell T total ($\times 10^9/\text{L}$)	$2.13 \pm 0,72$	$1.06 \pm 0,53$		
CD4^+ cell T (cell/ul)	598.10 ± 215	425.50 ± 278.10		
CD8^+ cell T (cell/ul)	442.50 ± 117.50	246.80 ± 144.10		
Cell B Total ($\times 10^6/\text{L}$)	194.70 ± 75.42	120.9 ± 57.89		
NK Cell ($\times 10^6/\text{L}$)	208.2 ± 117.4	191.2 ± 87.91		
CRP (mg/L)	11.51 ± 2.39	$23.34 \pm 2,84$		

Source: Chen et al., 2020; Huang et al., 2020; Liu et al., 2020



Radiological findings in adult and pediatric with COVID-19

Radiological examinations that are often conducted on children infected with COVID-19 are chest x-rays and chest CT scans, both of which often reveal unilateral or bilateral cloudiness. Based on the chest x-rays showed abnormalities in 24 of 46 cases. These abnormalities were in the form of unilateral changes that occurred in 15 of 46 pediatric cases and there were also bilateral changes in 7 of 46 pediatric cases. Besides chest x-rays, there are also chest CT-scans. Based on this examination, it is reported normal from 89 of 267 cases and there were unilateral changes in 63 of 267 cases, and 112 of 267 cases had bilateral changes. Wuhan Children Hospital reported that from 20 pediatric cases of COVID-19, all of them reported sub-pleural changes on chest CT-scans (Lee-Archer dan von Ungern-Sternberg, 2020; Xia et al., 2020).

Some studies also mentioned chest CT-scans and chest x-rays changes reported from 6 of

8 cases that showed bilateral pneumonia and unilateral pneumonia. The changes of image showed there is more than one shadow like a patch in 7 of 8 cases, Ground- Glass opacity in 6 of 8 cases, pleural effusion in 1 of 8 cases, and a white pulmonary appearance was found in 1 of 8 cases (Sun et al., 2020). Based on these results, it is recommended to conduct a CT-scan examination for children infected COVID-19 (Lee-Archer and von Ungern-Sternberg 2020; Xia et al. 2020).

The radiological findings in adult COVID-19 cases were the same as in cases of children. The examinations that are often conducted on adults are x-rays and CT-scans, in 101 cases there were abnormalities on CT-scans such as GGO (86,1%), mixed GGO and consolidation (64%), dilation of blood vessels in the lesion (71,3%), and bronchiectasis (52.5%). There is some lesion that found in CT-scan image in an adult patient that is the peripheral distribution (87%), bilateral (82,2%), and also found multifocal (54,5%) (Zhao et al., 2020).

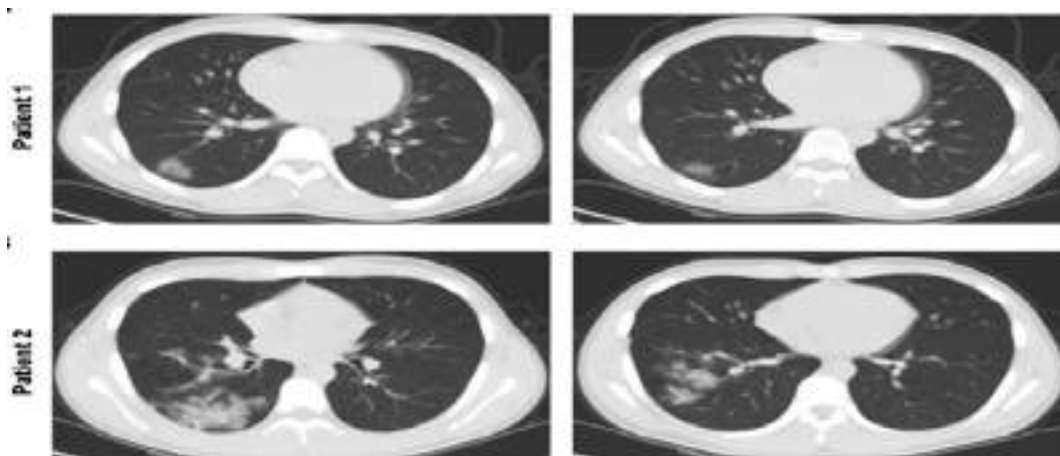


Figure 2.CT-Scan image of two children patients. (A) patient 1 is a 16 years old male with cough symptoms. Based on chest CT-Scan appear GGO image (Ground-Glass Opacity) on the right lungs. (B) patient 2 is a 14 years old female with fever and cough symptoms. Based on CT-Scan appear GGO image (Ground-Glass Opacity) and shadow on the left lungs (Chen et al., 2020).



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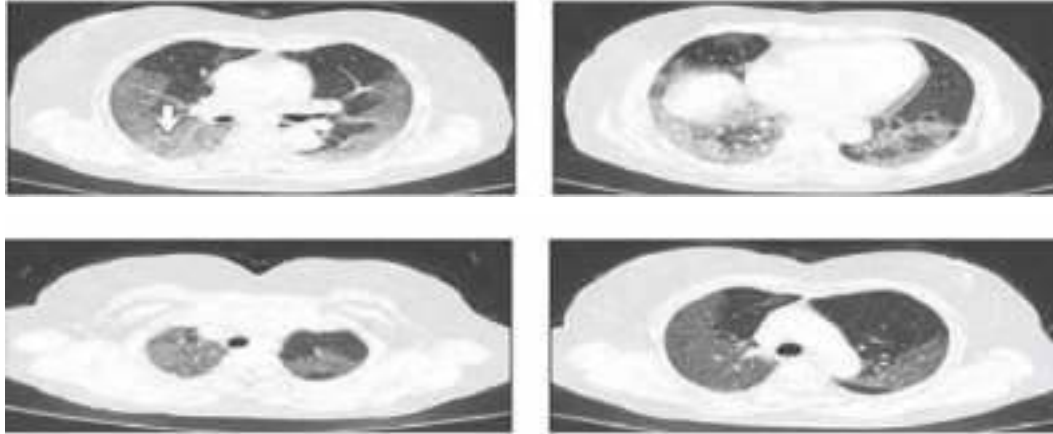


Figure 3. Chest CT-Scan image of an adult patient 63 years old with fever and cough symptoms. The CT-Scan showed diffusion bilateral image GGO (Ground-Glass Opacities) (Zhao et al., 2020).

Immunological response in adult and pediatric cases to COVID-19

SARS-CoV-2 can be high in the lower respiratory tract in early stage. Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes and neutrophils. SARS-CoV-2 induce host immune response (Wiersinga, Rhodes, Cheng, Peacock, & Prescott, 2020). Immunization is a way to increase the innate immune function, aiming to make the condition more active after fighting antigens (infection or vaccination) by increasing the Krebs cycle and epigenetic changes such as the transcription of IL-1 β , IL-6, and TNF- α genes. The process can affect the progenitor cell lines from myeloid cells and monocyte also local cells such as macrophages in the lungs and dendrite cells (Netea et al., 2020).

Some countries with a BCG vaccination program routinely were reported to have lower morbidity and mortality rates (Aaron et al., 2020; Dhochak et al., 2020). The BCG vaccination is often associated with a decrease in acute upper respiratory tract infection in adults and decreased child mortality, but

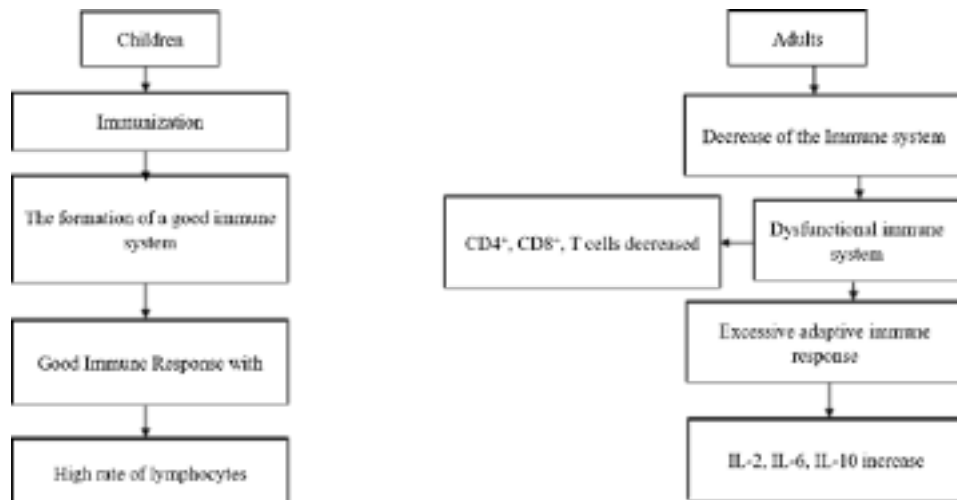
the BCG effect can only stay in 1-2 years (Dhochak et al., 2020; Wardhana et al., 2011). The immunization conducted in children is measles, rubella, and influenza can give them protection to SARS-CoV-2 infection (Dhochak et al., 2020).

The adaptive immune response also has an essential effect on the patient infected with COVID-19. The number of lymphocytes in pediatric cases COVID-19 were reported varied, it can be decreased or increased, and healthy children had more lymphocytes than adults. The level of lymphocytes can be found more in children's cases who are often infected with viruses and result in a robust immune system (Cristiani et al. 2020).

It was found that the total lymphocytes, CD4⁺ and CD8⁺, T cells helper and T cells memory of patients with severe cases decrease significantly, and as well as severe cases in adults. There is an increase in the number of cytokines, namely IL-2, IL-6, IL-10, and the neutrophil amount, indicating the dysfunctional and excessive adaptive immune response that causes damage to the lungs (Dhochak et al., 2020).



Chart 2. Immunology response in children and adults case of COVID-19
(Cristiani et al 2020; Dhochak et al. 2020; Wardhana et al. 2011)



Management of adult and pediatric case infected with COVID-19

Tabel 4. Management of COVID-19 in adult and children based on severity

	Adult	Children
Asymptomatic	a) Self isolation at home or prepared public facility for 10 days will monitor primary health care officers by telephone. b) Non-acidic Vitamin C tablets 500 mg / 6-8 hours orally for 14 days and to consume multivitamin (vitamin C, B, E, and zinc) c) If the patient has comorbidities, it is recommended to continue taking regular medication. d) Other supportive/complementary medicine registered by BPOM may be given with consideration to patient clinical condition	a) Self isolation for 14 days monitored by health care facilities b) Adequate nutrition c) Practicing health protocol d) Supportive pharmacotherapy; vitamin C (400 mg/day for age 1-3, 600 mg/day for age 4-8, 1200 mg for age 9-13, and 1800 mg for age 12-18 years old. Zinc 20 mg/day or other supplementation may be considered.
Mild	a) Self isolation for maximum of 10 days since the course of illness up to 3 days since the symptoms resolved. They will be monitored by primary health care officers.	a) Outpatient care, Self isolation for 14 days monitored by health care facilities b) Adequate nutrition and practicing health protocol c) Symptomatic treatment



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- b) Patients are advised to take 500 mg/6-8 hours of non-acidic Vitamin C tablets orally for 14 days, multivitamin
- c) Chloroquine phosphate 500 mg/12 hours orally for 5-7 days or Hydroxychloroquine 400 mg/24 hours orally for 5-7 days
- d) Azithromycin 500 mg/24 hours orally for 5 days, and one of the following antivirals drugs (Oseltamivir, alluvia, or favipiravir).
- e) Other treatment based on existing comorbid and complication.
- f) Other supportive/complementary medicine registered by BPOM may be given with consideration to patient clinical condition

Moderate

- | | |
|--|--|
| <ul style="list-style-type: none"> a) Isolation in hospital b) Non pharmacological treatment; adequate nutrition, fluid maintenance, oxygen therapy, laboratory and radiology monitoring c) Pharmacological treatment:
Vitamin C 200 -400 mg/8 hours in 100 ml normal saline given through 1 hour intravenously d) Chloroquine phosphate 500 mg/12 hours orally for 5-7 days or Hydroxychloroquine 400 mg/12 hours in 1st day followed by 400mg/24 hours orally for 5-7 days
WITH | <ul style="list-style-type: none"> a) Isolation in hospital b) Close monitoring c) Symptomatic treatment (Such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration) d) Intravenous antibiotic. Ceftriaxone 50-100 mg/kg/day and/or azithromycin 10mg/kg if atypical pneumonia is suspected e) Oseltamivir if there is suspicion of co-infections with influenza virus
<1 years : 3 mg/ kg/ every 12 hours
>1 years :
Give 30 mg every 12 |
|--|--|



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- e) Azythromycin 500 mg/24 hours intravenously or orally (5-7 days) OR levofloxacin WITH
 - f) One of the following antiviral; Oseltamivir, alluvia, favipiravir, remdesivir
 - g) Anticoagulant LMWH/UFH
 - h) Other symptomatic treatment
 - i) Other therapy based on existing comorbid and complications
- hours for children with weight under 15 kg
 Give 45 mg/ 12 hours for children with weight 15 until 23 kg
 Give 60 mg/ 12 hours for children with weight 23 until 40 kg
 Give 75 mg/ 12 hours for children with weight over 40 kg.
- e) Vitamin C
 - 1 until 3 years 400mg/day
 - 4 until 8 years 600 mg/day
 - 9 until 13 years 1,2 gram/ days
 - 12 until 18 years 1,8 gram/ days
 - f) Zinc 20 mg/day or other supplementation may be considered.

Severe or critical and MIS-C in children	a) Isolation in hospital	a) Intensive care unit with negative pressure
	b) Full bed rest, adequate nutrition, monitoring for electrolyte level, fluid maintenance, and oxygen	b) Close monitoring and serial laboratory/imaging examination
	c) Close monitoring of laboratory parameter and serial thorax imaging	c) Oxygenation, fluid, and adequate nutrition
	d) Monitoring for critical condition; respiratory failure, shock, or multi organ failure that need intensive care.	d) Supportive treatment
	e) Oxygen therapy; NRM, HFNC, NIV, invasive mechanical ventilation, ECMO	e) Intravenous antibiotic
	f) Pharmacotherapy: vitamin C, vitamin B1, phosphate chloroquine or hydroxychloroquine, azithromycin or levofloxacin, antibiotic based on focal infection, antiviral, anticoagulant, dexamethasone, comorbid and complications management, and other supportive treatment	f) Potential antivirus and hydroxychloroquine may be considered.
	a) Oseltamivir in suspected co-infections with influenza virus	
	g) Vitamin C, zinc, and other supplementation	
	h) Plasma convalescens, corticosteroid, anticoagulant, other antiinflammation such as anti IL-6 may be given with careful consideration.	



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- g) Additional therapy based on individual consideration;
1. Convalescent plasma
 2. Anti IL-6 (tocilizumab)
 3. Mesenchymal stem cell (MSCs)

Source : Andriani, 2020; IDAI,2020; WHO,2020, KEMENKES SEPT 2020

Table 5. COVID - 19 in pediatric and adults review

No	Source	Design	Sample	Variable	Outcome	Conclusion
1.	(Liguoro et al., 2020)	Systematic Review	Pediatric n= 7480	SARS-CoV-2	Risk lower than adult	SARS-CoV-2 infected children is milder
2.	(Dhochak et al., 2020)	Review Article	Pediatric and adults	Pathophysiology of COVID-19	Children fare better the adults	Immunization in children provides stronger protection against the SARS-CoV-2 virus so that it can reduce comorbid rates
3.	(Huang et al., 2020)	Cohort	Adults n= 41	Clinical Features	Risk on adults	Adults have a rapidly increasing and very high number of cases of death
4.	(Chen et al., 2020)	Full length article	Pediatric and adults n=32	The clinical and immunological on COVID-19 patient	Features of pediatric COVID-19 patient	The immune response to SARS-CoV-2 differs between children and adults. The immune response in children is better than in adults.
6.	(Dong et al, 2020)	Article Journal	Pediatric n=2143	Epidemiology pediatric	Characteristics of 2149 patient COVID-19	The clinical manifestations of SARS-CoV-2 which infect children are not as severe as in adult cases



7.	(Shahid et al, 2020)	Article Journal	Adults	COVID-19 in older adults	What we know on older adults	The SARS-CoV-2 pandemic had a significantly higher mortality rate in older adults with certain comorbid factors.
8.	(CDC COVID-19 Response Team, 2020)	Weekly Report Coronavirus	Pediatric and adult n=116.557	Corona virus in children	Risk corona virus on all age	Severe COVID-19 disease often occurs in adults in the high age range, and therefore cases in young adults may be more similar to those of children.

DISCUSSION

The differences in severity in children’s cases compared to adult were the number of ACE-2 receptor, ACE-2 activation, immunization, and the immune system. The number of ACE-2 receptors in children is lower than adult, and activation of ACE-2 in pediatric stimulation of cytokines stroms (Lymphocytes B, T and natural killer cell) is very high than in adult cases it can protect against the virus (Dhochak et al. 2020). Immunizations given to children can increase the immune system and provide better ability to work against different pathogens (Cristiani et al. 2020) There were fewer cases of children than adults, with milder symptoms in children (CDC COVID-19 Response Team, 2020). Laboratory tests have shown that the number of white blood cells in children is more than normal. Whereas, in adult patients, there is a decrease in the number of white blood cells (Huang et al., 2020; Liu et al., 2020), and the number of T cells and B cells in children is better than in adult cases (Chen et al., 2020).

COVID-19 in children is often caused by infection from family members who live in one house (70-80%) (Setiabudi, 2020). Infected cases are divided into high-risk close contact cases and low-risk close contact cases. The high-risk close contact cases if you have been in contact with a patient OF COVID-19 and the close low-risk contact if you have been in contact with a patient under surveillance (Andarini, 2020).

The treatment given to patients with confirmed of COVID-19 depends on the severity of the case and for cases of children with confirmed of COVID-19, there are several differences where negative pressure isolation, IFN nebulization, and antibiotics and antivirals based on WHO (Andarini, 2020). Treatment antiviral in adult can be given Chloroquine phosphate with dose 500 mg/12 hours orally for 5 days but in children can be given Oseltamivir with dose according to age and weight. Treatment in the critical case may be different with other classification cases. In the critical cases, we should recognize septic shock and ARDS (*Acute Respiratory Distress Syndrome*); children with critical cases should



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receive emergency airway management and oxygen therapy during resuscitation to target $SpO_2 \geq 94\%$. Once the patient stable, the use of nasal prongs or nasal cannula is preferred for children. Adult with critical case should receive emergency airway management and oxygen therapy during resuscitation to target $SpO_2 \geq 94\%$ (WHO, 2020).

There are more positive confirmed COVID-19 in children in Indonesia with a higher mortality rate than other countries in Asia in particular and the world in general (IDAI, 2020). This leads to the need for comprehensive measures to overcome global pandemic of COVID-19 to reduce the rate of transmission in children and short and long-term adequate treatment. A serious cooperation is needed in every aspects of life from health, education, family, and the environment regarding the dangers and awareness of COVID-19. Studies with COVID-19 confirmed case of children in Indonesia is also needed so can be identified in a more detailed map of transmission, symptoms and long-term treatment.

CONCLUSION

Based on this study, it can be concluded that the case in adults is more severe and have more cases. COVID-19 case happens in a patient who has another medical history such as hypertension and diabetes mellitus. The pediatric case is milder because of the immunization effect and ACE-2 rate, so the difference can be seen from the pathophysiology. The management of pediatric cases and adults have differences in the way of isolation and drug dosage.

REFERENCES

- Andarini, I. (2020). *Diagnosis dan Tata Laksana Kasus COVID-19 pada Anak dan Bayi*. 1–22. Jawa Tengah.
- Bandi, S., Nevid, M. Z., & Mahdavinia, M. (2020). African American children are at higher risk of COVID-19 infection. *Pediatric Allergy and Immunology*, *pai.13298*. <https://doi.org/10.1111/pai.13298>
- Castagnoli, R., *et al.* (2020). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatrics*, *174(9)*, 882. <https://doi.org/10.1001/jamapediatrics.2020.1467>
- CDC COVID-19. (2020). Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. *MMWR. Morbidity and Mortality Weekly Report*, *69(14)*, 422–426. <https://doi.org/10.15585/mmwr.mm6914e4>
- Chen, J., *et al.* (2020). The clinical and immunological features of pediatric COVID-19 patients in China. *ScienceDirect*. <https://doi.org/10.1016/j.gendis.2020.03.008>
- Cristiani, L., Mancino, E., Matera, L., Nenna, R., Pierangeli, A., Scagnolari, C., & Midulla, F. (2020). Will children reveal their secret? The coronavirus dilemma. *European Respiratory Journal*, *55(6)*, 2001617. <https://doi.org/10.1183/13993003.01617-2020>
- de Wit, E., van Doremalen, N., Falzarano, D., & Munster, V. J. (2016). SARS and MERS: recent insights into emerging coronaviruses. *Nature Reviews Microbiology*, *14(8)*, 523–534. <https://doi.org/10.1038/nrmicro.2016.81>



- Dhochak, N., Singhal, T., Kabra, S. K., & Lodha, R. (2020). Pathophysiology of COVID-19: Why Children Fare Better than Adults? *The Indian Journal of Pediatrics*, 87(7), 537–546. <https://doi.org/10.1007/s12098-020-03322-y>
- Dong, Y., *et al.* (2020). Epidemiology of COVID-19 Among Children in China. *Pediatrics*, 145(6), 20200702. <https://doi.org/10.1542/peds.2020-0702>
- Frieden, T. R., & Lee, C. T. (2020). Identifying and Interrupting Superspreading Events—Implications for Control of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerging Infectious Diseases*, 26(6), 1059–1066. <https://doi.org/10.3201/eid2606.200495>
- Hoffmann, M., *et al.* (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2), 271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>
- Huang, C., *et al.* (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- IDAI. (2020). *Panduan Klinis Tata Laksana COVID-19 pada Anak IKATAN DOKTER ANAK INDONESIA*. <https://www.idai.or.id/about-idai/idai-statement/panduan-klinis-tata-laksana-covid-19-pada-anak>
- Istituto Superiore di Sanità. (2020). *Epidemia COVID-19 Aggiornamento nazionale: 19 marzo 2020*. roma: Istituto Superiore di Sanità.
- Jawetz, E., Melnick, J. L., & Adelberg, E. A. (2013). *Jawetz, Melnick & Adelberg's medical microbiology* (28th ed.). United States: McGraw-Hill.
- Kementerian Kesehatan RI. (2020). Pedoman Pencegahan dan Pengendalian COVID-19. *Kementerian Kesehatan Republik Indonesia*, 0–115.
- Lee-Archer, P., & von Ungern-Sternberg, B. S. (2020). Paediatric Anaesthetic implications of COVID-19 - A Review of Current Literature. *Paediatric Anaesthesia*. <https://doi.org/10.1111/pan.13889>
- Liguoro, I., *et al.* (2020). SARS-COV-2 infection in children and newborns: a systematic review. *European Journal of Pediatrics*. <https://doi.org/10.1007/s00431-020-03684-7>
- Liu, K., *et al.* (2020). Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *Journal of Infection*, 80(6), e14–e18. <https://doi.org/10.1016/j.jinf.2020.03.005>
- Lu, X., *et al.* (2020). SARS-CoV-2 Infection in Children. *New England Journal of Medicine*, 382(17), 1663–1665. <https://doi.org/10.1056/NEJMc2005073>
- Melgosa, M., *et al.* (2020). SARS-CoV-2 infection in Spanish children with chronic kidney pathologies. *Pediatric Nephrology*, 35(8), 1521–1524. <https://doi.org/10.1007/s00467-020-04597-1>
- Miller, A., *et al.* (2020). Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. *MedRxiv*, 03(24), 085201. <https://doi.org/10.1101/2020.03.24.20042937>
- Netea, M. *et al.* (2020). Defining trained immunity and its role in health and disease. *Nature Reviews Immunology*, 20(6), 375–388. <https://doi.org/10.1038/s41577-020-0285-6>



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- PDPI (Perhimpunan Dokter Paru Indonesia). (2020). Panduan Praktik Klinis: Pneumonia 2019-nCoV. In *PDPI* (p. 5). JAKARTA: PDPI.
- Rothan, H. A., & Byrareddy, S. N. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of Autoimmunity*, *109*(February), 102433. <https://doi.org/10.1016/j.jaut.2020.102433>
- Satgas COVID-19. 2020. *Situasi Virus COVID-19 di Indonesia*. Retrieved from [Peta Sebaran | Satgas Penanganan COVID-19](#)
- Setiabudi, D. (2020). *Dampak Pandemi COVID-19 terhadap Kesehatan Anak*. JAWA BARAT.
- Shahid, Z., *et al.* (2020). COVID-19 and Older Adults: What We Know. *Journal of the American Geriatrics Society*, *68*(5), 926–929. <https://doi.org/10.1111/jgs.16472>
- Singh, T., *et al.* (2020). Lessons From COVID-19 in Children: Key Hypotheses to Guide Preventative and Therapeutic Strategies. *Clinical Infectious Diseases*, *22*(3), 282–289. <https://doi.org/10.1093/cid/ciaa547>
- Sun, D., *et al.* (2020). Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World Journal of Pediatrics*, *16*(3), 251–259. <https://doi.org/10.1007/s12519-020-00354-4>
- Susilo, A., *et al.* (2020). Coronavirus Disease 2019: Tinjauan Literatur Terkini. *Jurnal Penyakit Dalam Indonesia*, *7*(1), 45. <https://doi.org/10.7454/jpdi.v7i1.415>
- Wang, Z., Qiang, W., & Ke, H. (2020). A Handbook of 2019-nCoV Pneumonia Control and Prevention. In *Hubei Science and technology press*. Retrieved from http://fpmpam.org/files/Handbook_2019nCoV.pdf
- Wardhana, Datau., *et al.* (2011). The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. *Acta Medica Indonesiana*, *43*(3), 185–190. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21979284>
- Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA - Journal of the American Medical Association*, *324*(8), 782–793. <https://doi.org/10.1001/jama.2020.12839>
- World Health Organization (WHO). (2020). *Clinical Management of COVID-19 Interim Guidance*. Retrieved from. [Clinical management of COVID-19 \(who.int\)](#)
- World Health Organization (WHO). (2020). *Coronavirus disease COVID-2019* (Vol. 8). Retrieved from https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200607-covid-19-sitrep-139.pdf?sfvrsn=79dc6d08_2
- Wu, Z., & McGoogan, J. M. (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. *JAMA*, *323*(13), 1239. <https://doi.org/10.1001/jama.2020.2648>



- Xia, W., *et al.* (2020). Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatric Pulmonology*, 55(5), 1169–1174. <https://doi.org/10.1002/ppul.24718>
- Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine*, 46(4), 586–590. <https://doi.org/10.1007/s00134-020-05985-9>
- Zhao, W., Zhong, Z., Xie, X., Yu, Q., & Liu, J. (2020). Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *American Journal of Roentgenology*, 214(5), 1072–1077. <https://doi.org/10.2214/AJR.20.22976>
- Zhou, P., *et al.* (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798), 270–273. <https://doi.org/10.1038/s41586-020-2012-7>
- Zhu, N., *et al.* (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, 382(8), 727–733. <https://doi.org/10.1056/NEJMoa2001017>