COVID Vaccination for Children: A Literature Review

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has devastated the world since 2020. The transmission of COVID-19 occurs through droplets from the respiratory system, not through airborne transmission. Caused by SARS-CoV-2, COVID-19 causes a variety of symptoms in patients, including mild, moderate, severe, and even asymptomatic symptoms. COVID-19 can occur in children and adolescents as well as adults undergoing treatment. Children tend to be asymptomatic or have milder clinical symptoms than adults. One way to stop the spread of COVID-19 is through vaccination. COVID-19 vaccines approved for use in children and adolescents include Pfizer, Moderna and CoronaVac. Vaccines cause mild to moderate local and systemic side effects, includes injection site pain (80%), weakness and headache (60%), and fever (20%). Based on the recommendation of the Indonesian Pediatrician Association (IDAI) for the provision of COVID-19 vaccine to children and adolescents, it is recommended to administer the CoronaVac vaccine made by SinoVac at a dose of 3 µg (0.5 ml) by intramuscular injection in the deltoid muscle.

Keywords: Coronavirus disease 2019 (COVID-19), SARS-CoV-2, COVID-19 vaccine.

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease (zoonosis) caused by SARS-CoV-2 and transmitted between animals and humans [1]. WHO stated that COVID-19 was a Public Health Emergency of International Concern (PHEIC) in late January 2020 and was eventually declared a pandemic in March 2020. COVID-19 attacks all ages from children to the elderly with the main transmission route through direct inhalation or contact with patient droplets [2], [3]. The disease has an incubation period of 2 to 14 days and presents with a variety of clinical manifestations. COVID-19 in children generally causes mild or moderate clinical manifestations, rarely causing severe symptoms as in adults [4]. Children infected with COVID-19 may be asymptomatic or experience symptoms including fever, myalgia, upper respiratory symptoms, and gastrointestinal symptoms [5]. WHO stated there were 479,311,589 cases of COVID-19 in March 2022, with 6,122,118 deaths [6]. Meanwhile, Indonesia reported 6,427,764 cases of COVID-19 and 158,076 deaths in September 2022 [7]. Cumulative cases of COVID-19 in children of October 2022 was 14,845,577 cases [8]. Most children will recover quickly from SAR-CoV-2 infection, but abnormalities in the patient's lungs are still found after several months [5].

The survival rate in COVID-19 cases is influenced by COVID-19 vaccinations. However, the effectiveness of vaccination may vary depending on the virus variant. Patients who received the COVID-19 vaccination were protected almost completely from infection with the Delta variant, with reinfection cases approaching 0 for approximately 100 days. However, there are no significant data for the case of the Omicron variant. Vaccination also causes changes in the profile of COVID-19. Post-vaccinated COVID-19 patients who have COVID-19 infection experience milder disease symptoms (such as low-grade fever) compared to patients without the vaccine [9]. The main goals of COVID-19 vaccination are to reduce transmission of COVID-19, reduce morbidity and mortality from COVID-19, and achieve herd immunity in society [10].

II. OVERVIEW OF COVID-19 IN CHILDREN

Coronaviruses are single-stranded RNA viruses that infect animals and humans. This virus is called coronavirus because it has virions that are round in shells with a surface similar to the corona in the sun. Corona comes from the Latin meaning crown [11]. In late 2019, animal-to-human transmission of coronavirus occurred in Wuhan, causing coronavirus disease (COVID-19). The disease is caused by a new type of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [12]. COVID-19 is characterized by the presence of upper and lower respiratory tract infections that can cause serious complications and even death. SARS-CoV-2 infected about 70,000 people and caused 1,800 deaths in 1 week [13], [14].

SARS-CoV-2 is a coronaviruses (CoVs) which are in the subfamily Orthocoronavirinae. SARS-CoV-2 is coated with a spike protein containing multiple receptor binding domains (RBDs). The RBDs then binds with angiotensin-converting enzyme-2 (ACE-2) receptors in the heart, lungs, kidneys, and gastrointestinal tract, facilitating viral entry into target cells [16]. Based on genome sequencing, SARS-CoV-2’s RBDs are lookalike a mutated version of the RaTG13 virus obtained from bat (Rhinolophus affinis).
samples. Therefore, it is believed that SARS-CoV-2 also originated in bats, and that mutations can infect other animals. The mutations that occur increase the affinity of RBDS for ACE-2 in humans and other animals such as ferrets and decrease the affinity of RBDS for ACE-2 in rodent genomes [17]. The genome viruses have a capsid, and they are enveloped by three structural proteins: membrane protein (M), spike protein (S) and envelope protein (E). In addition to structural proteins, SARS-CoV-2 also has sixteen nonstructural proteins (nsp1-16) with different functions. NSPs can mediate effects on splicing, translation, and protein trafficking to inhibit host defenses [18].

The reported incidence of COVID-19 in children <18 years was 2.1%, with a mortality rate of 0.2%. No deaths were reported in children <9 years old. It has been reported that children with the new coronavirus infection have symptoms like Kawasaki disease. Therefore, cardiac complications observed in this case. The best markers for diagnosing disease severity in children are bilirubin and liver enzymes. A high number of ACE-2 receptors on cell surfaces, an ineffective immune system, and high levels of lymphocytes in the blood are reportedly responsible for the low incidence of COVID-19, which causes severe symptoms in children [19].

Coronavirus is generally spread through droplets from the respiratory system, not through airborne transmission. Droplets are larger in size and fall to near an infected host’s gound. Transmission of the droplets is limited to short distances, usually it is less than 2 meters. However, airborne transmission occurs when small droplets travel long distances through air displacement. Airborne droplets can fly within a few hours in favorable humidity and temperature [17]. Droplets from an infected host that land on a surface, can survive and will determine the possibility of transmission by contact. Based on knowledge about other beta coronaviruses such as SARS and MERS, the coronavirus survives and remains infectious on inanimate surfaces such as iron, glass, and plastic for 2 hours-9 days, and virus viability is high in cold, dry conditions. Increases in low-impact environments. Therefore, cleaning surfaces using biocides one of an ethanol or sodium hypochlorite is highly effective in inactivating the coronavirus within 1 minute of exposure [20].

### III. PATHOGENESIS OF COVID-19 IN CHILDREN

Children may asymptomatic or have milder clinical manifestations than adults. Common clinical manifestations that appear in children infected with SARS-CoV-2 include fever, upper respiratory symptoms, and symptoms of the digestive system. Upper respiratory symptoms commonly found in children with SARS-CoV-2 infection are dizziness, fever, and cough. As long as delta and omicron variants predominate, infected children may develop nasal congestion, headache, sore throat, sneezing, and cough-like symptoms. Gastrointestinal symptoms that occur in infected children generally appear without symptoms of upper respiratory, such as diarrhea, vomiting and pain in abdominal [21]. Severe symptoms can also appear in cases of COVID-19 in children, such as hypoxia (oxygen saturation <92%), ARDS (acute respiratory distress syndrome), shock an various organ failures such as, heart failure, coagulation abnormalities, encephalopathy and AKI (acute kidney injury) [22]. Neonates infected with SARS-CoV-2 may asymptomatic or have mild or moderate symptoms such as fever, cough, rhinorrhea, vomiting, or respiratory distress. Neonates can also experience complications due to infected mothers, such as experiencing respiratory distress, pneumonia, low birth weight, experiencing skin rashes, DIC (disseminated intravascular coagulation), asphyxia and death [5].

SARS-CoV-2’s cycle of infections begins with the viral S protein binding to the ACE-2 receptor on type 2 pneumocytes in the lungs. This activates an inflammatory cascade in the lower airways. Protein S is cleaved into two subunits (S1, S2) by the transmembrane protease serine 2 (TMPRSS2) and plays a role in plasma membrane receptor recognition and fusion processes. Subunit’s S1 has a receptor binding domain that recognizes and binds to the host cell's ACE-2 receptor, while the subunit’s S2 mediates fusion of the viral cell membrane and release of the viral genome into infected cells. Viral RNA replication and transcription occur in the cytoplasm to produce a group of viruses that will exit the infected cell by exocytosis and infect other cells through the same cycle [23]-[25].

The entry of the viruses and cell infection will trigger immune responses of the host and antigen presenting cell (APC) will initiate inflammatory cascade. The process begins with APCs presenting foreign antigens to CD4+ T-helper (Th1) cells and stimulate Th1 cells further by secreting interleukin-12. Th1 cells stimulate CD8+ T-killer (Tc) cells which will target all cells that contain the foreign antigen. On the other hands, B cells will stimulate by the activation of Th1 cell to produce antibodies against specific antigens [17]. CARS-CoV-2 infection will result in a response from the immune system and increase levels of cytokines, chemokines in the bronchial tree and result in monocytes, leukocytes, natural killer cells and interleukins’ accumulation. These mediators have high expression induces a reaction that causes cough, fever, and symptoms of pneumonia. Protein S is also reported to bind to ACE-2 receptors located in nerve tissue and endothelium of cerebral capillary which can cause damage of the nerve and deterioration of cerebral capillaries in SARS-CoV-2’s patients [28],[29]. The low number of ACE-2 receptors in children causes limited SARS-CoV-2 that enters cells,
resulting in a lower risk of COVID-19 infection in children and milder symptoms. In addition, the low prevalence of comorbid diseases that occur in children such as diabetes, chronic lung disease, and cardiovascular disease also results in complications that occur not as severe as in adults [5].

IV. COVID-19 VACCINES FOR CHILDREN

The COVID-19 vaccination is one way that to prevent the spread of COVID-19. Vaccines are also a form of protection for people who are vaccinated and stop the spread of disease in a population. The main objectives of the COVID-19 vaccination is to reduce the transmission/transmission of COVID-19, reduce morbidity and mortality caused by COVID-19, achieve herd immunity and protect the community from COVID-19 in order to remain socially and economically productive [30]. There are various types of COVID-19 vaccines available, including [7]:

- **mRNA vaccine**
  This vaccine uses an RNA or DNA genetic engineering approach to produce proteins that themselves trigger an immune response. Take Pfizer for example.

- **Viral Vector (adenovirus)**
  This vaccine uses genetically engineered viruses that it causes disease, but safely generate an immune response instead of produces proteins of coronavirus. Examples include Astra-Zeneca and Johnson & Johnson.

- **Inactivated virus vaccine**
  This vaccine uses a virus that is inactivated or weakened and does not cause disease but will produces response of immune. Take CoronaVac for example.

- **Vaccine subunit proteins**
  This vaccine uses fragments of protein or shells of protein that look alike COVID-19 to generate response of immune. Take Novavax for example.

Various COVID-19 vaccines are based on their safety and efficacy against the formation of an immune response, including [15]:

1. **BNT161B12 (Pfizer-BioNTech)**
   This vaccine is formulated with modified lipid nanoparticles and nucleosides in phase I or II trials. Most of recipients have mild-moderate local systemic symptoms. The concentration of IgG binding to RBD as well as the serum neutralizing SARS-CoV-2 titer increased after first dose and after the second dose.

2. **Coronavac (Sinovac)**
   The Coronavac vaccine, which is denatured with aluminium hydroxide, has been continued into a phase III of clinical trial. The vaccine is well tolerated and stimulates immunity. Immunogenicity, optimal dose, and safety of CoronaVac were tested in 600 healthy patients aged 18 to 59 years who received 2 injections at a dose of 3 g/0.5ml or 6 g/0.5 ml. CoronaVac declared to provide protection for COVID-19 patients was 50%.

3. **mRNA1273 (Moderna)**
   Nucleoside-modified messenger RNA (modRNA) encoding the SARS-CoV-2 S protein is formulated in lipid particles, which allows delivery of RN into host cells for the expression of the SARS-CoV-2 antigen, and stimulates an immune response against the S antigen.

4. **Ad26COV1S (Janssen Vaccine)**
   Ad26COV2S (Janssen Vaccine) is a recombinant transgenic vaccine. A single dose of Ad26COV2S can protect from SARS CoV-2 infection with symptomatic and asymptomatic. It effective against severe to critical conditions. WHO recommends people 18 years of age and older can achieve the Janssen (J&J) vaccine.

Fig. 2. Clinical Manifestations of COVID-19 [26].

Fig. 3. (A) Surface of the coronavirus’s S protein binds to the ACE-2 receptor of the target cell. (B) TMPRSS2 binds to and cleaves the ACE-2 receptor. (C) Virus enters the target cell. TMPRSS2 increases coronavirus uptake [26], [27].

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5. ChAdOx1 nCoV-19 (AstraZeneca)

The AstraZeneca/Oxford product is a vaccine of the viral vector that consisting of a chimpanzee adenoviral vector that has a ChAdOx1 replication deficient and consists of structural glycoprotein antigen of the SARS-CoV-2. ChAdOx1 nCoV-19 has safety profile and effective against symptoms of COVID-19 within 21 days of the first dose. This vaccine is not recommended for people under 18 years.

6. SputnikV (Gam-COVID-Vac)

This vaccine uses a recombinant adenovirus that is heterologous with adenovirus-26 (Ad26) and adenovirus-5 (Ad5) as vectors for the SARS-CoV-2 S protein’s expression. With the exception of rashes and immunological reactions, no severe side effects were reported. There were three identified severe adverse events over 60 years old patients who had renal colic, deep vein thrombosis, and abscess.

7. BBIBP-CorV (Sinopharm)

Local antigenic epitopes produced by inactivated viruses that binds to T and B cell antibodies and appears in a stable mode. This vaccine uses aluminum hydroxide as an adjuvant to increase immune system. WHO approved the use of this vaccine for emergency cases in people over 18 years old.

8. NVX-CoV2373 (Novavax)

This recombinant protein vaccine uses various versions of the S protein as a component of the vaccine antigen. The trimeric NVX CoV2372 nanoparticle produced by Novavax was made of a long S protein. Efficacy of Novavax was 96% in COVID-19 patients in clinical trial. The most usually reported side effects are headache and muscle aches.

V. Effectiveness and Safety of COVID-19 Vaccination in Children

There are various types of COVID-19 vaccines, but only a few are approved for use in children and adolescents, including Pfizer, Moderna, and CoronaVac. The efficacy of the vaccine against COVID-19 that causes symptoms was found after the second dose was indicated by higher antibody titters, especially at the age of 12-15 years compared to the age of 16-25 years. Mild to moderate side effects are common, including injection site’s pain (80%), weakness and headache (60%) and fever (20%) [31]. Following are the COVID-19 vaccines given to children (Table I).

Based on the recommendation of the Ikatan Dokter Anak Indonesia (IDAI) for the provision of COVID-19 vaccine to children and adolescents, it is recommended to administer the CoronaVac vaccine made by Sinovac at a dose of 3 μg (0.5 ml) by intramuscular injection in the deltoid muscle and given 2 times with a distance 1 month. This vaccination is given to children aged 12-17 years with the consideration of adequate clinical trials, high mobility, and the possibility of crowding outside the home and is considered capable of expressing the side effect. The administration of vaccines to children aged 3-11 years is still waiting for the results of studies to assess safety and safe doses. The consideration that underlies the administration of CoronaVac to children in Indonesia is the vaccine that is already available in Indonesia and there have been phase 1 and 2 clinical trials with the results are safe with high seroconversion [3].

Special attention is needed in several cases that need to be considered as having greater benefits than the risks, with the recommendations of treating doctors and vaccinations carried out in hospitals, including [33]:

1. Primary immune deficiency
2. Children with cancer who are undergoing chemotherapy/ radiotherapy
3. Children with fever of 37.5°C or more
4. Uncontrolled chronic disease or congenital disorder
5. Adrenal insufficiency such as congenital adrenal hyperplasia and Addison's disease
6. Bleeding disorders such as haemophilia
7. Liver and kidney transplant patients. Severe allergic reactions such as shortness of breath and generalized urticaria

Although CoronaVac has high safety to be given to children and adolescents, it has contraindications, including [33]:

1. Anaphylactic reactions due to vaccine components in previous administration
2. Guillain-Barre syndrome, transvenous myelitis, acute demyelinating encephalomyelitis
3. Currently on treatment with immunosuppressants
4. The child has been hospitalized in the last 7 days or has experienced emergencies such as shortness of breath, seizures, palpitations, bleeding, hypertension, and severe tremors

VI. Conclusion

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2 that is transmitted between animals and humans (zoonosis). Coronavirus generally spreads through droplets from the respiratory system. The infection cycle of SARS-CoV-2 starts from the binding of the viral S protein to the ACE-2 receptor on type 2 pneumocytes in the lungs. Virus entry and cell infection will trigger host immune response and antigen presenting cell (APC) will initiate inflammatory cascade. The main objectives of the COVID-19 vaccination is to reduce the transmission/transmission of COVID-19, reduce morbidity and mortality caused by COVID-19, achieve herd immunity and protect the community from COVID-19.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Classification</th>
<th>Efficacy</th>
<th>Dose</th>
<th>Post vaccine symptoms (AEFI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SinoVac (CoronaVac)</td>
<td>Inactivated viral vaccine with aluminum hydroxide</td>
<td>50%</td>
<td>2 doses with 2 weeks apart</td>
<td>Pain at the injection site, fever</td>
</tr>
<tr>
<td>Moderna (mRNA1273)</td>
<td>mRNA vaccine</td>
<td>94%</td>
<td>2 doses with 3 weeks apart</td>
<td>Local and systemic symptoms</td>
</tr>
<tr>
<td>BNT161B12 (Pfizer-BioNTech)</td>
<td>mRNA vaccine</td>
<td>95%</td>
<td>2 doses with 3 weeks apart</td>
<td>Injection site’s pain, redness, joint pain, myalgia</td>
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