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Coronavirus infections in childhood and vaccine studies

Deniz Aygün, Pınar Önal, Gözde Apaydın, Haluk Çokuğraş

Department of Pediatrics, Division of Pediatric Infectious Diseases, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

ABSTRACT

In late December 2019, a new coronavirus (CoV) called the severe acute respiratory syndrome CoV 2 (SARS-CoV-2), which had not been detected in humans before, caused a worldwide pandemic. Owing to the highly infectious nature of this virus, it spread rapidly from person to person despite the warnings of the World Health Organization and all the measures taken by the governments. Although it has been reported that SARS-CoV-2 is more likely to infect the elderly, all age groups are susceptible to this virus, including newborns. CoV disease 2019 (COVID-19) symptoms seem to be less severe in children than in adults, but similar to the 2003 severe acute respiratory syndrome epidemic, in the COVID-19 pandemic, the number of cases and the risk of serious diseases increase as age increases. The treatment of COVID-19 is still challenging, especially in children, and the virus continues to cause death worldwide. The safest and most controlled way to effectively and sustainably prevent COVID-19 in a society is to have an effective and safe vaccine and to successfully vaccinate the majority of the population. It is possible that vaccines with safety and efficacy that have been proven in phase III trials will be effective in handling COVID-19.

Keywords: Children, coronavirus disease 2019, vaccine

Introduction

Coronaviruses (CoV) are enveloped, positive-strand RNA viruses that primarily infect humans and animals such as birds, bats, and camels. Coronaviruses are classified under the order Nidovirales and family Coronaviridae and are organized into four groups, namely alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus. Animal CoVs and human CoVs have been known since late 1930s and 1960s, respectively, and are capable of causing mild and moderate upper and lower respiratory tract infections (1-3).

However, new CoVs have been identified that are transmitted from animals to humans, causing severe illness and death, such as severe acute respiratory syndrome (SARS) in 2003 and middle east respiratory syndrome (MERS) in 2012 (4).

In late December 2019, the seventh and a new CoV (SARS-CoV-2), which had not been detected in humans before, caused a worldwide pandemic by rapidly spreading from person to person owing to the highly infectious nature of the virus despite the warnings of the World Health Organization (WHO) and all the measures taken by the governments. The latest data change day by day, but the number of infected people worldwide has exceeded 60 million, and approximately 1.5 million people have died because of CoV disease 2019 (COVID-19) (5-7).

Although it has been reported that SARS-CoV-2 is more likely to infect the elderly, all age groups are susceptible to this virus, including newborns (8, 9). The mean age of children with COVID-19 has been reported to be 6.7 years (range: 1 day to 15 years) (10). The COVID-19 symptoms seem to be less severe in children than in adults. Although 69% of infected adults

Corresponding Author:
Deniz Aygün
✉fdenizaygun@gmail.com
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turkarchpediatr.org

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have clinical findings, only about 21% of children manifest obvious findings (11). In a systemic review and meta-analysis in which Viner et al. (12) evaluated 41,640 children and adolescent cases, it was reported that children aged between 10 and 14 years were less sensitive to SARS-CoV-2, but clinical findings in the adolescent age group were similar to the adults.

The most common complaint of children is usually nonspecific symptoms of upper respiratory tract infection, such as fever and cough. Fever is usually mild to moderate. Other clinical symptoms include sore throat, nasal congestion and runny nose, weakness, myalgia, headache, and respiratory distress. Gastrointestinal system complaints such as abdominal pain, vomiting, and diarrhea can also be seen (13-15). In the study by Önal et al. (16) from Turkey, cough, fever, and weakness were reported as the most common complaints, and the majority of patients had mild to moderate signs of illness. Children are also less infectious as they have a lower viral load, but in children aged >15 years, the infectiousness is similar to the adults.

There is no clear data in the literature on why children are less affected by COVID-19. Owing to the fact that children have frequent viral respiratory tract infections, their likelihood of being recently infected with one of the other common CoV strains in the community vaccination with live vaccines, including Bacillus Calmette–Guérin, are assumed to protect the children from COVID-19. High levels of angiotensin converting *enzyme* (ACE-2) activity in children could also protect them against COVID-19, leading to less severe disease in this age group. Children are less likely to develop severe illness, to be hospitalized, to require mechanical ventilation, and to die than the adults. Similar to the 2003 SARS epidemic, in the COVID-19 pandemic, the number of cases and the risk of serious diseases increase as age increases. However, severe COVID-19 may develop in children with underlying chronic diseases such as immune deficiency, hematological or oncological malignancy, and asthma because of the continuation of systemic inflammation.

Severe COVID-19 is characterized by hyper-responsiveness of the immune system. In viral infections, type 1 interferon (IFN), which is released in the early immune response, promotes intracellular RNA degradation and virus clearance, induces tissue repair, and triggers a prolonged adaptive immune response. It is suggested that the delay in the release of type 1 IFN causes impairment in virus control and paradox hyperinflammation in severe COVID-19. An uncontrolled and abnormal production of cytokines has also been observed in critically ill patients, which leads to exacerbation of symptoms and disease. Inflammation caused by the cytokine storm disrupts the pulmonary vascular and alveolar barrier and causes alveolar interstitial thickening, vascular leakage, pulmonary fibrosis, and death (17-19).

In April 2020, cases similar to Kawasaki disease or toxic shock syndrome were reported in children and adolescents who tested positive for SARS-CoV-2 infection or who had a contact history. These clinical findings, which include high fever, severe abdominal pain, cardiac dysfunction, and circulatory disorder, were considered as hyperinflammation syndrome associated with excessive cytokine release. The clinical pictures, which were later named as multi-system inflammatory syndrome in children (MIS-C), are seen in an increasing number of children (20). MIS-C is defined as patients under the age of 21 with fever longer than 24 hours, laboratory evidence of inflammation, severe illness that requires hospitalization, involvement of more than two organ systems, and positive SARS-CoV-2 infection (reverse transcription polymerase chain reaction, serology, or antigen test) or exposure to a patient with COVID-19 in the 4 weeks before symptom onset.

Molecular structure of SARS-CoV-2 and vaccine studies

CoV has the largest known RNA genome that is encoded by nearly 29,000 ribonucleotides. This virus contains four main structural proteins, including the envelope (E), membrane (M), spike (S), and nucleocapsid (N) proteins, all of which are encoded within the 3' end of the viral genome. The S protein mediates the binding of SARS-CoV-2 to ACE2 on the host cell, which leads to virus entry and pathogenesis. The E protein is considered to be a major virulence factor and plays a role in the secretion of inflammatory factors. The N protein forms the nucleocapsid and is responsible for mRNA transcription and RNA replication. The M protein plays a role in the assembly of the virus. Because of the large genome, the virus is less host-dependent during replication and is able to replicate without being integrated into the host genome. Furthermore, the RNA-dependent RNA polymerase gene, that is, *RdRp,* enables the virus to replicate its genome in the host's cytoplasm. After binding to its receptor, SARS-CoV-2 enters the cell through endocytosis, releases the viral RNA into the cytosol, and exploits the cell machinery for replication. As a final step, viral proteins and RNA genome combine within virions in the endoplasmic reticulum and Golgi body and are released out of the cell by exosomes.

SARS-CoV-2 enters cells by binding its S protein envelope to the human ACE2 after S protein priming by host transmembrane protease serine 2. Approximately, 80% of all human ACE2-expressing cells are located in type II alveolar cells, the rest of which are in nasal mucosa, upper respiratory tract, endothelium, heart, kidney, and intestine cells (21-24). Therefore, to be effective against systemic viral infections seen outside the respiratory system, the vaccine should protect the receiver from the systemic spread of the virus by ensuring immunoglobulin (Ig) G production.

Historically, the coronavirus vaccine development process has been troublesome. As with natural CoV infection, there is concern that vaccination will not provide long-lasting immunity, and reinfection may be possible. The use of previous SARS-CoV and MERS-CoV vaccines in some animal models and T helper (Th) 2 cells–mediated immunopathology has also raised vaccine-related safety concerns.

Vaccine development during a global pandemic is a difficult process that requires extensive and detailed research such as preclinical testing, staged clinical trials, approval, quality control, production, and distribution stages. The varicella vaccine development process took 25 years, human papillomavirus vaccine took 15 years, and influenza vaccine took 28 years. The scientific world appears to have been forced into an unusually accelerated process to develop a vaccine for the new CoV. However, the safest and most controlled way to effectively and sustainably prevent COVID-19 in a society is to have an effective and safe vaccine and successfully vaccinate the majority of the population.

The difference in individual immune responses during COVID-19 infection reveals that a single immune strategy will not be sufficient to provide long-acting immunity in all individuals when developing the vaccine. Vaccines need to replicate specific immune responses that elicit viral clearance, rapidly and reliably. The most important questions to be answered include whether cellular immune response or humoral response to the virus should be induced and which type of Th cells are more effective or which antibody isotype is more effective (25-27). Most of these questions have been answered during laboratory studies in serum and cellular analysis of recovered patients. Unfortunately, there is no guarantee that a vaccine can provide permanent immunity against SARS-CoV-2, although the studies have reached the advanced clinical phase because of the different immune responses of the patients (28).

Another issue that should be taken into account when developing a vaccine is the difference in T cell structure and T cell response; neutralizing antibodies are effective in affinity formation as well as in the elimination of infected cells (29). Immune memory is the main element of long-term immune protection, and studies have shown that the antibody titers of patients infected with the first SARS-CoV were high during the 3 years after infection (30).

The lower respiratory tract is thought to be mostly protected by IgG, and the upper respiratory tract is thought to be mostly protected by secretory IgA. Natural infection with respiratory viruses induces both systemic immune response and a mucosal immune response that is dominated by IgG and by IgA, respectively. Intramuscular or intradermal vaccination leads in many cases to a strong induction of serum IgG but not to an induction of mucosal IgA. Intranasal vaccination can efficiently induce mucosal antibody responses, thereby potentially providing sterilizing immunity in the upper respiratory tract. However, systemic immune responses are often low after this type of vaccination. Currently, all SARS-CoV-2 vaccine candidates in clinical development are administered intramuscularly and focus is on the response to IgM, IgG, or total Ig in the blood (31-34).

Vaccine efficacy should also be evaluated well. According to the WHO, an ideal SARS-CoV-2 vaccine should have an excellent safety profile for multiple population groups, including children, older adults, pregnant women, and immunocompromised individuals with minimal adverse events that are mild and transient. Vaccine should also induce protective immunity ideally after a single dose with at least 70% efficacy.

Because of the urgent need for a vaccine, WHO accelerated the vaccine development processes, and currently more than 234 preclinic and 69 clinic vaccine studies are ongoing on nine different platforms. These platforms are DNA and RNA vaccines, live CoV vaccines, inactivated virus vaccines, subunit vaccines (predominantly S protein), vectored vaccines (vesicular stomatitis virus, adenovirus, measles virus), and protein subunit vaccines (35-40).

Inactivated vaccines

Inactivated vaccines are produced by growing SARS-CoV-2 in cell culture, followed by chemical inactivation of the virus. Because the whole virus is presented to the immune system, immune responses are likely to target not only the spike protein of SARS-CoV-2 but also the matrix, envelope, and nucleoprotein. They can be produced relatively easily; however, their yield could be limited by the productivity of the virus in cell culture and the requirement for production facilities at biosafety level. These vaccines are usually administered intramuscularly and can contain aluminum hydroxide or other adjuvants. Examples of inactivated vaccine candidates include CoronaVac that is under development by Sinovac Biotech in China. Approximately, 247,113 dosages of the Sinovac Vero Cell vaccine have been administered to 178,940 volunteers.

Live attenuated vaccine

Live attenuated vaccines are produced by generating a weakened version of the virus that replicates to a limited extent, causing no disease but inducing immune responses that are similar to that induced by natural infection. Live attenuated vaccines have the ability to stimulate the toll-like receptors (TLRs), TLR 3, TLR 7/8, and TLR 9, of the innate immune system that involves B cells and CD4 and CD8 T cells. An important advantage of these vaccines is that they can be given intranasally, which induces mucosal immune responses that can protect the upper respiratory tract. They can be derived from "cold adapted" virus strains, reassortants, and reverse genetics. However, disadvantages of these vaccines include safety concerns and the need to modify the virus. Only three live attenuated vaccines are currently in preclinical development. Codagenix Inc. and the Serum Institute of India are developing a live attenuated vaccine based on their CodaVax technology that uses codon deoptimization to attenuate viruses.

Nucleic acid vaccines

Nucleic acid vaccines can be inexpensively and rapidly produced and contain no live virus. DNA vaccines require complicated delivery systems and are more difficult to produce. DNA vaccines stimulate both humoral and cell-mediated immune responses but show low immunogenicity and have to be administered through delivery devices to make them efficient. They do not require the handling of the infectious viral particle; however, the insertion of a foreign DNA into the host genome may cause abnormalities in the cell.

Similar to DNA vaccines, in RNA vaccines, the genetic information for the antigen is delivered instead of the antigen itself. RNA based vaccines have a good safety profile and low manufacturing costs. The mRNA-1273 (Moderna TX, Inc.) is a vaccine composed of synthetic mRNA encapsulated in a lipid nanoparticle, which codes for the prefusion stabilized, full-length S protein of SARS-CoV-2. This vaccine by Moderna is considered to be relatively safe as it is neither made of the subunits of the live pathogen nor of the inactivated pathogen.

Pfizer Inc. and BioNTech SE have developed four mRNA-based formulations, including two nucleoside-modified mRNAs, a uridine-containing mRNA, and a self-amplifying RNA. The vaccine elicited receptor binding antibody (RBD)-binding antibody at similar titers to those seen in convalescent patients with COVID-19. The vaccine also elicited modest increases in SARS-CoV-2 neutralizing antibody titers. BNT162b2 developed by BioNTech and Pfizer is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike pro-

tein. The efficacy and safety of the vaccine has been confirmed in laboratory studies (41).

Vectored vaccines

Vector-based vaccines are a form of live attenuated vaccines that adapt existing safe viral vectors such as adenovirus and measles to express CoV proteins on immunization. Their effectiveness stems from their ability to infect cells, which allows them to trigger robust immune responses. However, prior immunity to the vector may be present, and only a small number of CoV antigens may be presented to the host immune system. Integration into the host genome may lead to cancer, and redeveloped immunity problem against the vector is a handicap. They are also not recommended in pregnancy and immunodeficiency. They offer a long term and high level of antigenic protein expression. Oxford University has partnered with AstraZeneca to produce vectored vaccines that is in phase III study.

Protein subunit vaccines

Protein subunit vaccines consist of viral proteins or protein fragments and rely on eliciting an immune response against the S-spike protein to prevent its docking with the host ACE2 receptor. They do not contain viral particles and thus are safe with fewer side effects. They exhibit low immunogenicity and require auxiliary support of an adjuvant to potentiate the vaccine-induced immune responses.

Among all the vaccine subtypes, mRNA-based vaccines are more effective because they are safer, can stimulate a stronger immune response, and have the ability to mimic the natural infection. The need for special storage and transport conditions is a handicap of mRNA vaccines. Inactive vaccines can be prepared easily; however, because they contain the entire virus cell, their side effects are high, and a booster dose is required for immunity. The types of vaccines with their potential advantages and disadvantages are listed in Table 1.

Among the vaccines being developed, Sinovac (China, inactivated vaccine), Oxford (United Kingdom, vector vaccine), Moderna (United States, mRNA), and BioNTech SE (Germany, mRNA) vaccines have reached the phase III trials, but none of these vaccines have yet been approved in peer-reviewed journals. Inactivated virus vaccine at Erciyes and Selçuk University, DNA-based vaccine at Ege University, codon optimized live attenuated vaccine at Acibadem Mehmet Ali Aydinlar University, adenovirus-based vaccines at Erciyes and Ankara University, protein subunit vaccines at İzmir Biomedicine and Genome Center and Boğaziçi University, mRNA vaccine at Selçuk University, and virus-like particle vaccine at Bezmialem Vakıf University and Middle East Technical University are the vaccine studies ongoing in Turkey, all of which are on the WHO's list.

Conclusion

Vaccine production is a process that requires a lot of time and money and has a high failure rate. As with natural CoV infection, there is a concern that vaccination will not result in long-lasting immunity, and reinfection might occur. The fact that the protection provided by the CoV vaccines studied in the past has not yet been determined supports this concern.

Despite all the challenges, it has been experienced in pandemics throughout the history of the world that the most effective and scientific method of ending the pandemic with the least possible loss of life is to provide social immunity with vaccines. It is possible that vaccines with safety and efficacy that have been proven in phase III trials will promise to be effective in handling COVID-19.

However, along with vaccination, taking the necessary isolation measures and using masks and personal protective equipment are the most effective and cheapest protection methods against SARS-CoV-2.

Table 1. The types of vaccines with their potential advantages and disadvantages

	Advantages	Disadvatages
Live Attenuated Vaccine	Ability to stimulate the immune system by inducing the toll-like receptors It can be derived from 'cold adapted' virus strains and reverse genetics	Requires an extensive accessory testing to establish efficacy and safety Probability of nucleotide substitution during viral replication
Inactivated vaccines	Can be easily produced Express conformation dependent antigenic epitopes Can be used along with adjuvants to increase their immunogenicity	Needs the biosafety level 3 Require the booster shots to maintain the immunity Large amounts of viruses need to be handled and the integrity of the immunogenic particles must be maintained
DNA Vaccines	Enhances humoral and cellular immune responses Stable Easily prepared in large quantities	The safety and efficacy remain unknown
RNA Vaccines	Can be rapidly developed Low-cost manufacture	The properties of mRNA may influence its cellular delivery and organ distribution
Subunit vaccines	Do not have any live component of the viral particle. Safe with fewer side-effects	May have limited efficacy Make immune responses unbalanced
Vector vaccines	Can infect APCs directly Physically and genetically stable Has been used widely for MERS-CoV with positive results from the trials	May induce prior immunity to the vector May lead to cancer due to the integration of the viral genome into the host genome

APC, Antigen-presenting cell; DNA, Deoxyribonucleic acid; MERS-CoV, Middle East Respiratory Syndrome, RNA; Ribonucleic acid

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